advancing the art & science of medicine in the midwest

WMJ

2023 • volume 122 • issue 5

Lessons Learned *from the* Pandemic

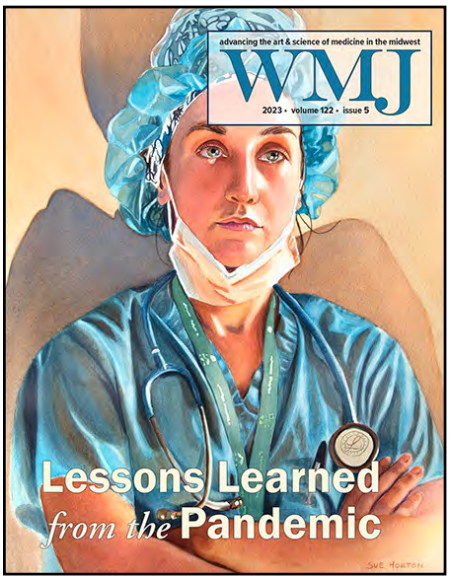
CORONA_A Twisted GUERNICA

Nadia Alkhun

Medium: Acrylic and ink on paper

Artist Statement:

This is a remix artwork of "Guernica" by Pablo Picasso. The artwork documents our chaotic reality during the pandemic. Nowadays, this may be perceived as a comic, but it does remind us of the difficulties we went through and all the loved ones we lost. Now that life is back to near normalcy, we get to appreciate all its small details.



COVER ART

Resolute Angel

Sue Horton

Watercolor

Artist Statement:

"This transparent watercolor portrays my niece, who is employed as a physician's assistant in Milwaukee, Wisconsin. Throughout the COVID-19 pandemic, she cared for seriously ill patients and their families. She consistently displayed her deep commitment and dedication. We could observe the emotional toll and challenges. Among all the tools and medications available to combat the disease, we must always remember the human element is the most important component in patient care and recovery."

The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues. *WMJ* is published through a partnership between the Medical College of Wisconsin and the University of Wisconsin School of Medicine and Public Health.

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WMJ

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Lessons Learned From the Pandemic

Fahad Aziz, MD, FASN, *WMJ* Editor-in-Chief, Tripti Singh, MD; George Morris, III, MD

This double issue of the *Wisconsin Medical Journal* delves deeply into the intricate ramifications of the pandemic, meticulously examining its profound effects on microcultures across diverse levels—from local communities to the global stage. Through an array of comprehensive reports, enlightening studies, thoughtful reflections, and accompanying artwork, this issue sheds light on the myriad challenges and opportunities encountered by various segments of society. The field of health and medicine undergoes a seismic shift in epistemology, leaving an indelible mark on both the patient population and the health care workforce across numerous dimensions. As health care providers, we find ourselves not only fulfilling our professional roles but also navigating the intricate web of complexities that come with being essential employees, managing careers, caring for isolated patients, and serving as "experts" sought after by friends and neighbors as they grapple to comprehend the unprecedented events unfolding worldwide. This special edition serves as a testament to the intricate interplay of effects on individuals, patients, and health care professionals alike.

The issue opens with a report card by Patrick Remington, MD, MPH, reflecting which aspects of our response to the pandemic were successful and which were not.[1] The fields of medicine, bioengineering, and public health services are given our enthusiastic endorsement. And it was back to the drawing board for communication and addressing the many emerging disparities. Although the massive private-government effort "led to significant lives saved" and was deemed by many a great success, it was not without casualties, prompting Remington to advocate for an enhancement of public health data and increased funding.

> All of these reports—and the artwork interspersed throughout—help to illuminate the multifaceted nature of the challenges we faced during the pandemic and the imperative to address these challenges within the broader context of health care delivery.

The other reports included in this journal converged into four overarching themes summarized here.

PATIENT CARE

First, we focus on understanding and responding to the evolving landscape of medical care in light of the virus. The reports cover a wide spectrum of scenarios, including the interconnectedness of violence and COVID-19 in Milwaukee,[2] ocular care during Wisconsin's "Safer At Home Order,"[3] and creativeness in taking care of immunocompromised patients during the pandemic.[4] Another investigation explores the effectiveness of a digital intervention aimed at enhancing the scheduling of annual wellness visits amidst the COVID-19 backlog, revealing challenges in implementing a noncontact version of medical care universally within our system.[5] Even seemingly commonplace observations, such as delirium frequencies in hospital settings[6] and the dynamics of pediatric care during the Omicron surge, emerge as valuable insights for future planning.[7] This collective exploration underscores our capacity to adapt and learn from the multifaceted impact of COVID-19 on various aspects of health care, illuminating the path forward in navigating and enhancing our medical care system.

WORKFORCE

Next, we explore the deep effects of the pandemic on the workforce, revealing the complex function of vital employees and the devastating effects of infectious illnesses. Reflections

on this theme by Vazirnia et al illuminate the pervasive sense of a loss of control and an uncertain future, leaving an indelible mark on clinicians.[8] The personal vaccination decisions made by nurses take center stage in another perspective,[9] and echoes of the crisis reverberate through examinations of the influence on career trajectories, productivity, and the shift to remote work,[10] as well as training experiences during the pandemic.[11]

Indifferent to gender, the virus emerges as a ubiquitous disruptor, affecting workers across various occupations in this moment of chaos. Reports exploring the incidence of COVID-19 and worker's compensation[12] and mortality rates by occupation and industry[13] demonstrate how work, life, and the huge problems caused by the pandemic are all connected in complicated ways.

PUBLIC HEALTH APPROACHES

Our third theme focuses on insights gained in the public health arena, including how specific conditions like breast cancer might influence SARS-CoV2 susceptibility[14] and the concordance of health-related behaviors among romantic partners during the pandemic.[15] In the early days of the pandemic when diagnostic testing was very limited, laboratory-developed tests served as a critical bridge until demand could be met with commercially available tests.[16] Of course, COVID-19 rapid testing eventually was employed outside health care settings, and Temte et al report on the feasibility and functionality of testing in K-12 public school health offices.[17]

INEQUITIES RELATED TO COVID-19

Our final theme delves into the distinctive repercussions stemming from unequal access to health and medicine, further unraveling an already strained health safety net. These consequences manifest in various domains, illustrating the complex challenges inherent in addressing disparities. For instance, a study by Schell et al sheds light on the deleterious effects of inequities in vaccine access among individuals with inflammatory bowel disease in Wisconsin,[18] while another study looks at the inequitable vaccine uptake among rehabilitation patients,[19] and a third reports on the outcomes of a vaccination outreach program targeted at patients without access to their electronic patient portal.[20] These reports and others in this section not only underscore disparities in vaccination rates, they also explore the ways in which COVID-19 affects other health behaviors, from breastfeeding to opioid and other drug use.

All of these reports – and the artwork interspersed throughout – help to illuminate the multifaceted nature of the challenges we faced during the pandemic and the imperative to address these challenges within the broader context of health care delivery. The intersection of research, health care access, and the unique needs of specific patient populations underscores the need for comprehensive and equitable strategies to fortify our health safety net and enhance health care outcomes for all.

We extend our gratitude to the *WMJ* publishing and editorial boards for their unwavering support in bringing this special issue to fruition. Their dedication and collaborative efforts have played a pivotal role in shaping the content and ensuring its quality. Additionally, we express sincere appreciation to our advisory board, whose guidance and insights have been invaluable throughout the entire process. Together, these collective efforts have contributed to the creation of what we hope is a meaningful, insightful special issue.

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The COVID-19 Stress Test: Results and Recommendations

Patrick L. Remington, MD, MPH

The stress test has been a mainstay in medicine for almost a century, aiding in the assessment of patients suspected of having ischemic heart disease. If a patient fails a stress test, such as by having chest pain, shortness of breath, changes in blood pressure, or a heart arrhythmia, then some form of treatment may be prescribed.[1] In March 2020, our society was confronted by a different type of stress test: The COVID-19 pandemic. The global pandemic stressed not only our public health systems, but also nearly every other system in society, ranging from our health care system to our global economic system. In the past 3 years, we have learned a lot about how each system—and society in general—responded to this COVID stress test. In this commentary, I reflect on the results of this stress test, including some notable successes and abysmal failures, and conclude with recommendations for changes for when—not if—the next pandemic comes.

• • •

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STRESS TEST RESULTS: PUBLIC HEALTH, HEALTH CARE, AND BIOMEDICAL RESEARCH

The COVID-19 pandemic stressed the public health system more than ever before.[2] Never had the entire public health system been called into action to respond to a public health crisis. Workers at all levels of government—from the Centers for Disease Control and Prevention (CDC) to state and local health departments—were mobilized to answer questions, test people with symptoms, track cases, make recommendations for isolation and quarantine, and implement "stay-at-home" policies. This "all-hands-on-deck" approach was effective and a sign of the talents and commitment of our public health workforce. But it also led to worker burnout and uncovered a serious lack of capacity needed to respond to a pandemic. This impact may have been even more stressful in Wisconsin, as the state is tied with Nevada for the lowest spending on public health in the nation, at only $72 per capita per year.[3]

The health care system was also stressed, despite the heroic efforts of frontline primary care providers and specialists who cared for seriously ill patients (as shown on the cover art for this special issue). Shortages of masks, COVID-19 tests, nasal swabs, and intensive care unit beds led to delayed diagnoses and treatment.[4] In addition, the pandemic had disparate effects on minority populations – often at higher risk from preexisting chronic conditions and having less access to primary health care services.[5,6] The pandemic also led to the cancellation of routine surgeries and screening tests, further exposing the problems with a fee-for-service health care system, as hospitals and other health care systems lost revenue.[4]

> ...as members of a civil society, we need to respond collectively to improve the capacity of our public health and health care systems to respond to the next pandemic.

Fortunately, our biomedical system responded to the call for a vaccine for a novel virus with incredible speed and success. In the early days of the pandemic, public health strategies, such as social isolation and wearing masks, were intended to "flatten the curve" and delay the spread of the virus, until a vaccine or treatments were developed. Few experts, however, predicted the vaccine would be ready for widespread distribution in less than a year. This success was built on decades of basic research, including research led by Jon Wolff, MD, at the University of Wisconsin School of Medicine and Public Health,[7] and

subsequent research by Katalin Karikó, PhD, and Drew Weissman, MD, PhD, leading to their 2023 Nobel Prize in Medicine.

STRESS TEST RESULTS: COMMUNICATIONS, POLITICS, AND SOCIETY

In addition to the stress placed on the public health and health care systems, the COVID stress test brought to the surface serious problems in our news and social media systems. Leadership and clear communications are critical during a crisis. However, a recent survey showed that those who trust Newsmax, One American News, and Fox News hold more misconceptions about COVID than those who trust network news, local television, CNN, MSNBC, and NPR.[8] Although some credible sources emerged on social media (eg, https://thosenerdygirls.org/), one study showed that a small number of physicians propagated COVID-19 misinformation about vaccines, treatments, and masks on social media with a wide reach.[9] And an investigation by the *Washington Post* showed that doctors who spread misinformation are rarely held accountable.[10]

In addition to a failure in communications, the COVID-19 pandemic further stressed our already divisive political systems. Perhaps the biggest stress on our political system involved views of the role of government during a public health crisis. Our Constitution granted states the right to use "police powers" to constrain the rights of individuals for the collective good. This has been the mainstay of public health departments, used to reduce the risk of infectious disease outbreaks and the transmission of diseases like tuberculosis. These debates have made it harder for our state and local health officers to enforce evidence-based public health policies that reduce the risk of disease transmission.[11]

Finally, the COVID-19 pandemic stressed individuals and families at all levels of society. The pandemic brought to the surface existing disparities in access to health care, prevalence of chronic conditions, and economic security.[12] The early responses to the pandemic were unfair, as low-income workers either lost their jobs or were deemed required "essential workers," exposing themselves and their families to risks. In contrast, high-income workers were able to transition to remote working, with fewer layoffs and losses in income. And the pandemic laid bare an unwillingness among some to follow simple, practical approaches to protect the health of others (eg, social distancing, vaccination, or use of masks).

RECOMMENDATIONS

When a patient fails a stress test, the clinician outlines a treatment plan to address the underlying disease and pathophysiology. The COVID-19 stress test exposed a variety of problems in our public health and health care systems, as well as in society in general. How should we respond?

First, as members of a civil society, we need to respond collectively to improve the capacity of our public health and health care systems to respond to the next pandemic. The CDC has taken a first step in this direction through its "Moving Forward" initiative, identifying ways to improve and institutionalize how it develops and deploys its science, both in pandemic and nonemergency times.[13] A similar approach should be taken at state and local health departments. These changes to improve the capacity of public health and health care systems will require support among our legislators, not only of public health policies but also for the core funding needed to be prepared for the next pandemic.

Second, we need to find better ways to confront the pandemic of misinformation. Gone are the days when we got our news from a small number of highly respected national and local news sources. Given this plethora of news sources, our schools and universities need to develop courses focused on media literacy, enabling the public to discern fact from fiction. Physicians need to be more active in serving as credible sources of information, and our profession needs to do a better job of confronting those who willfully disseminate information that is harmful to the public's health. For the most egregious instances, the state licensing board should revoke a physician's license to practice medicine.[14]

Finally, each of us has a responsibility to act individually as citizens. Many of the failures in our response to the COVID stress test will require political solutions, from better public health laws to more funding for state and local public health departments. It is imperative that we support candidates and elected officials who represent our public health interests through sound, evidence-based programs and policies.[15] The worst of the COVID-19 pandemic may be over, but the lessons learned from this stress test on our society cannot be forgotten.

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Safety in Numbers

Riley Meskin

Digital Illustration

Artist Statement:

"We are safest when we work together to protect each other."

A Milwaukee Syndemic? Penetrative Injury and COVID-19

Alexandra Dove, BS; Kara J. Kallies, MS; Stephen Hargarten, MD, MPH; Carissa W. Tomas, PhD

ABSTRACT

Introduction: This study sought to evaluate injury frequency of penetrative trauma before and after stay-at-home orders were implemented due to COVID-19 in Wisconsin.

Methods: Patients who presented to a level I trauma center from January 2018 through December 2021 with a mechanism of injury of firearm or stab wound were included. The study was split into pre-COVID (January 2018-February 2020) and COVID (March 2020-December 2021) periods. Statistical analysis included chi-square tests and interrupted time series analysis.

Results: A total of 1702 patients met inclusion criteria. The COVID group had a statistically significantly higher proportion of firearm injuries (83.2%) and a significantly lower proportion of stab injuries (16.8%) compared to the pre-COVID period group (70% and 30%, respectively, $P<0.001$). There was no change from pre-COVID to COVID periods in in-hospital mortality or length of hospital stays. There was an increase in firearm incidents in the COVID period in 72% of Milwaukee County ZIP codes and a decrease in stab incidents in 48% of ZIP codes. Interrupted time series analysis indicated a significant increase from the pre-COVID to COVID periods in monthly firearm and stab injuries. Firearm injury significantly increased from pre-COVID to COVID for Black or African American patients but no other racial group.

Conclusions: These findings are consistent with other state and national trends suggesting increasing penetrative injury during the COVID-19 pandemic. The intersection of the COVID-19 pandemic and violence pandemic may yield a "syndemic," imposing a significant burden on trauma systems. Evidenced-based public health interventions are needed to mitigate the surge of firearm injuries.

INTRODUCTION

In December 2019, the first cluster of patients with pneumonia of unknown etiology was reported.[1,2] Over the next 24 months, the novel coronavirus that causes this disease—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19—rapidly spread worldwide.[3–5] In response, local, national, and international agencies implemented measures to reduce the viral transmission. This included travel bans, stay-at-home orders, and the temporary closure of many schools and workplaces. The stay-at-home orders recommended or required that residents stay in their living quarters, with exceptions for essential activities.[6] In the United States, 43 states and the District of Columbia implemented stay-at-home orders between March 2020 and April 2020.[7] Wisconsin issued stay-at-home orders in March 2020.[8] Despite these mitigation measures, the pandemic created many challenges, and by the end of 2021, over 825 000 people had died due to COVID-19 in the United States.[9] Many individuals faced economic hardships, social isolation, and increased stress, and there were national supply chain issues and elevated sociopolitical tension.

Since the beginning of the COVID-19 pandemic, hospitals and health care systems have reported a decrease in total unintentional trauma and an increase in penetrating trauma, largely driven by firearm injuries.[10–13] In the US, gun violence has been a longstanding public health crisis and is now one of the top 5 causes of death among Americans ages 1 to 44 years.[14] In 2020, firearm-related incidents became the leading cause of death among young Americans—those ages 1 to 24 years old.[15,16] This has led to reframing the language around gun violence, recognizing it as an epidemic.[17,18] Violence also has been described as a biopsychosocial disease, requiring a comprehensive approach to prevention

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and treatment.[19–22] Gun violence rates increased by approximately 30% during the first year of the COVID-19 pandemic compared to prepandemic rates in 2019, with variation across states.[13,23] Wisconsin was one of 28 states with a significant increase in gun violence during the pandemic.[13]

The impact of the COVID-19 pandemic and the increase in gun violence may represent a "syndemic."[24] A syndemic is the aggregation or convergence of two or more disease epidemics that negatively exacerbate prognosis and burden of disease.[25,26] Factors such as poverty, unequal access to health care, and underresourced neighborhoods may be important structural facilitators of both morbidity and mortality of the COVID-19 virus.[27] Similar structural factors have been associated with increased violence and firearm injuries.[28] Milwaukee County, in particular, is the largest urban area in Wisconsin, with increased demographic diversity. To evaluate the synergistic associations between the stay-at-home order implementation in response to COVID-19 and the epidemic of violence, we conducted a study to examine penetrative injury trends in the wake of the COVID-19 pandemic.

METHODS

Participants

Data were queried from the trauma registry at Froedtert Hospital, the level 1 trauma center in Milwaukee, Wisconsin. Patients were included in the study if they were adults who sustained a penetrating injury from January 2018 through December 2021 and met trauma registry inclusion criteria. For the purposes of this analysis, penetrating injuries were defined as a mechanism of injury (MOI) of either firearm or stab injuries. The trauma registry adheres to the inclusion criteria as determined by the American College of Surgeons National Trauma Data Bank's (NTDB) Data Standard.[29] The study was approved by the Institutional Review Board prior to conducting any research.

Measures

Variables of interest from the registry included patient demographics (ie, age, sex, race), MOI, injury location ZIP code, and clinical data, including injury severity score (ISS), discharge status (ie, deceased or alive), length of stay in hospital, length of stay in the intensive care unit (ICU), and number of days on a ventilator. Race was defined according to NTDB data standards: American Indian, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other Race, Unknown, and White. Age was categorized into the following age groups: 18-24, 25-34, 35-44, 45-54, 55-64, 65+ years. Injury severity scores were grouped into low (<15), middle (16-25), and high (>25).[30,31]

Data Analysis

In Wisconsin, stay-at-home orders were implemented in March 2020. This time point was used to designate pre-COVID (26-month period from January 2018 through February 2020) versus COVID (22-month period from March 2020 through December 2021) periods. Injury counts were aggregated by month. For all analyses, firearm and stab injuries were examined separately. Demographic and clinical data were compared pre-COVID and COVID using *t* tests for continuous variables and chi-square tests for categorical variables. Changes in the number of incidents by injury location ZIP code also were compared pre-COVID and COVID for only injuries that occurred in Milwaukee County due to small sample sizes of incidents in other counties.

Finally, an interrupted time-series analysis was conducted via segmented quasi-Poisson regression to compare changes in level (intercept) and slope of monthly counts of penetrating injury pre-COVID to COVID periods. A quasi-Poisson model was selected due to modeling counts and to account for overdispersion by freely estimating variance as a linear function of the mean. Interrupted time series analyses were first completed for all patient firearm and stab injuries and then repeated within racial groups. Only Black or African American, White, and Other Race groups were examined in the interrupted time-series analysis due to insufficient sample sizes of remaining racial groups. Bonferroni correction was applied to adjust for multiple tests (2 MOI x 3 racial groups = 6 interrupted time-series analyses; $\alpha = .05/6 = .008$). All data were analyzed using R version 4.3.0 (R Core Team, 2023).

RESULTS

Overall, there were 12 262 patients recorded in the trauma registry during the study period. Of those, 1702 (13.9%) patients met inclusion criteria; 1321 (77.6%) sustained firearm injuries and 381 (22.4%) sustained stab injuries. The COVID period group included a significantly higher proportion of firearm injuries (83.2%) and a significantly lower proportion of stab injuries (16.8%) compared to the pre-COVID group (70% and 30%, respectively) ($\chi^2 = 40.99$, $P < 0.001$). When comparing pre-COVID to COVID periods, there were no differences in sex or age for firearm or stab injuries (Tables 1 and 2). A significantly higher proportion of patients within the highest ISS category was noted during the COVID versus pre-COVID period for firearm injuries only (Table 1). Overall, there was a significant difference in firearm injuries by race from pre-COVID to COVID periods; however, post-hoc tests indicated an increase among those identified as Other Race and a decrease among those whose race was Unknown or White (Table 1). Similarly, there was an overall difference by race for stab injuries, yet in post-hoc tests, only those identified as Other Race had a significant increase in stab injuries from the pre-COVID to COVID period (Table 2). Total hospital days, ventilator days, ICU days, and in-hospital mortality did not change significantly from the pre-COVID to COVID period for firearm (Table 1) or stab injuries (Table 2).

ZIP codes of injury location were reported for 97% of the sample, of which 99% were within Milwaukee County and included in the following results. An increase in firearm incidents

Table 1. Patient Characteristics During the Pre-COVID and COVID Periods Among Those Who Sustained a Firearm Injury

Variable	Pre-COVID (Jan 2018 – Feb 2020) n = 507 n (%)	COVID (Mar 2020 – Dec 2021) n = 814 n (%)	*P* value
Gender			0.99
Female	65 (12.8)	105 (12.9)	
Male	442 (87.2)	709 (87.1)	
Age, years			0.6
18 – 24	161 (31.8)	245 (30.1)	
25 – 34	184 (36.3)	322 (39.6)	
35 – 44	84 (16.6)	147 (18.1)	
45 – 54	48 (9.5)	62 (7.6)	
55 – 64	18 (3.6)	21 (2.6)	
65+	12 (2.4)	17 (2.1)	
Race			**< 0.001**[a]
American Indian	< 5	< 5	ns
Asian	10 (2.0)	< 5	ns
Black or African American	376 (74.2)	647 (79.5)	ns
Native Hawaiian or Other Pacific Islander	< 5	< 5	ns
Other Race	6 (1.2)	53 (6.5)	**< 0.001**[a]
Unknown	< 5	16 (2.0)	**< 0.001**[a]
White	113 (22.3)	91 (11.2)	**< 0.001**[a]
Discharge status			0.626
Alive	449 (88.6)	728 (89.5)	
Dead	58 (11.4)	85 (10.4)	
Injury Severity Score			
Low	333 (65.7)	478 (58.7)	0.212
Middle	121 (23.9)	162 (19.9)	0.777
High	49 (9.7)	151 (18.6)	**< 0.001**[a]
Mean total hospital days	6.15 ± 7.95	6.79 ± 10.0	0.223
Mean total vent days	1.04 ± 4.03	1.48 ± 5.68	0.123
Mean total ICU days	1.77 ± 4.63	2.10 ± 5.54	0.268

[a] ***P* < 0.05**

n < 5 is masked for patient confidentiality.

ns = not significant (*P* > 0.05) on post-hoc tests.

Abbreviation: ICU, intensive care unit.

Table 2. Patient Characteristics During the Pre-COVID and COVID Periods Among Those Who Sustained a Stab Wound

Variable	Pre-COVID (Jan 2018 – Feb 2020) n = 217 n (%)	COVID (Mar 2020 – Dec 2021) n = 164 n (%)	*P* value
Gender			0.98
Female	45 (20.7)	33 (20.1))	
Male	172 (79.3)	131 (79.9)	
Age, years			0.36
18 – 24	42 (19.4)	30 (18.3)	
25 – 34	54 (24.9)	55 (33.5)	
35 – 44	53 (24.4)	29 (17.7)	
45 – 54	36 (16.6)	31 (18.9)	
55 – 64	21 (9.7)	13 (7.9)	
65+	11 (5.1)	6 (3.7)	
Race			**< 0.001**[a]
American Indian	< 5	< 5	ns
Asian	5 (2.3)	< 5	ns
Black or African American	128 (59)	98 (59.8)	ns
Native Hawaiian or Other Pacific Islander	< 5	< 5	ns
Other Race	< 5	15 (9.15)	**< 0.001**[a]
Unknown	< 5	< 5	ns
White	78 (35.9)	47 (28.7)	ns
Discharge status			0.99
Alive	211 (97.2)	160 (97.6)	
Dead	6 (2.8)	< 5	
Injury Severity Score			0.072
Low	185 (85.3)	132 (80.5)	
Middle	25 (11.5)	19 (11.6)	
High	< 5	9 (5.5)	
Mean total hospital days	3.55 ± 4.07	3.5 ± 4.89	0.916
Mean total vent days	0.24 ± 0.72	0.46 ± 2.17	0.148
Mean total ICU days	0.67 ± 1.31	0.67 ± 2.31	0.989

[a] ***P* < 0.05**

n < 5 is masked for patient confidentiality.

ns = not significant (*P* > 0.05) on post-hoc tests.

Abbreviation: ICU, intensive care unit.

occurred in 35 (72%) of the 48 Milwaukee County ZIP codes, and a decrease in stab incidents occurred in 23 (48%) of the 48 Milwaukee County ZIP codes.

Results of an interrupted time-series analysis indicated a significant increase in the level of monthly counts of firearm injuries from pre-COVID to COVID periods (ß = 0.52, z 4.71, $P < 0.001$), but no change in the slope (ß= 0.002, z = 0.31, $P = 0.75$). Similarly, there was a significant increase in the level of monthly counts of stab injuries (ß= 0.41, z = 1.99, $P = 0.04$) but no change in the slope (ß = -0.01, z = -1.17, $P = 0.23$) (Figure 1). Firearm and stab injuries observed for all patients were, on average, 32.6% and 10.2% higher, respectively, than expected during COVID. Further, the interrupted time-series analysis by race showed that from the pre-COVID to COVID periods, Black or African American patients experienced a significant increase in the level of monthly firearm injury (ß = 0.53, z = 4.56, $P < 0.001$) but no change in the slope (ß = -0.002, z = -0.28, $P = 0.77$) during COVID. Observed firearm injuries for Black or African American patients were, on average, 42.5% higher than expected during COVID (Figure 2). There were no other significant changes for firearm or stab injuries by any other racial groups that survived Bonferroni correction (all *P*s > 0.03).

DISCUSSION

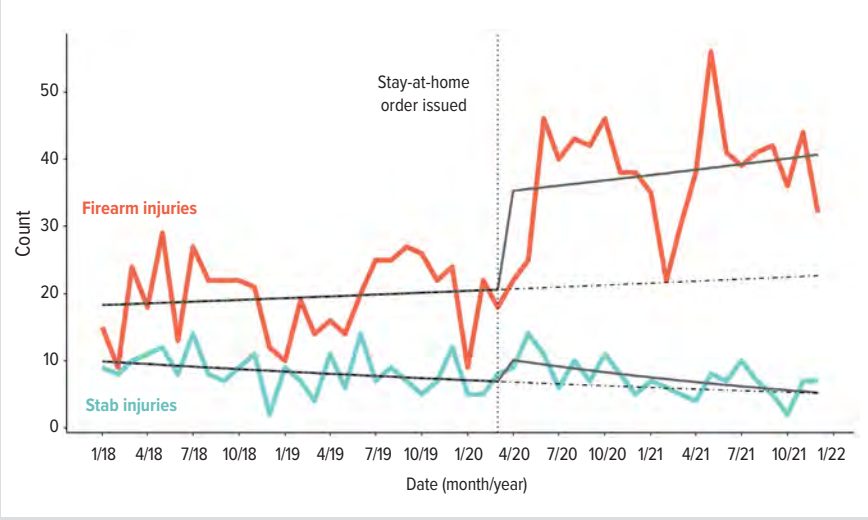
This study is consistent with other literature reporting an increase in penetrating injuries from pre-COVID to COVID, with firearm injuries accounting for much of this increase. Despite the increase in penetrating injury incidents during the COVID period com-

pared to pre-COVID, the mean hospital lengths of stay, ICU days, ventilator days, and in-hospital mortality rates did not change significantly. There was a widespread geographic increase in firearm incidents across Milwaukee County, and the increase in incidents was not isolated to any one ZIP code. Further, the increase in firearm injury during the COVID period was disproportionately shouldered by Black or African Americans underscoring the disparities in the burden of firearm-related injury.

Although this study used data from a single level I trauma center in Wisconsin, it serves as a potential model for other communities to assess local or regional trends in penetrating injury in pre-COVID and COVID time periods. The results of this analysis are consistent with other reports in the literature demonstrating an overall increase in penetrating injuries during the COVID-19 pandemic, increased firearm incidents, and decreased or minimal change in rates of stab injuries. Mokhtari and colleagues completed a multicenter study and noted an increase in penetrating injuries but that they were specific to certain sites rather than attributable to the stay-at-home orders.[32] Chodos and colleagues compared the COVID period March-May 2020 to pre-COVID (March-May 2019) and noted significant increases in penetrating trauma (22.6% vs 15.1%), gunshot wounds (11.8% vs 6.8%), and stab wounds (9.2% vs 6.9%).[11] In looking specifically at intentional, violent traumatic injuries before versus after stay-at-home orders were implemented, Abdallah and colleagues noted increased penetrating trauma from 17.37% to 29.91%, stabbing from 7.0% to 7.92%, and gunshot wounds from 12.61% to 22.92%, respectively.[10] In Wisconsin, relative increases in excess firearm-related incidences, nonfatal firearm injuries, and firearm-related mortality were approximately 38.8%, 60.1%, and 39.5%, respectively.[23] Prior analyses by city or state within the US have noted significant variability, indicating that geographic location and the specific characteristics of those locations are important. In Milwaukee County, firearm injuries increased in most ZIP codes, where stab injuries decreased in nearly half of the county's ZIP codes.

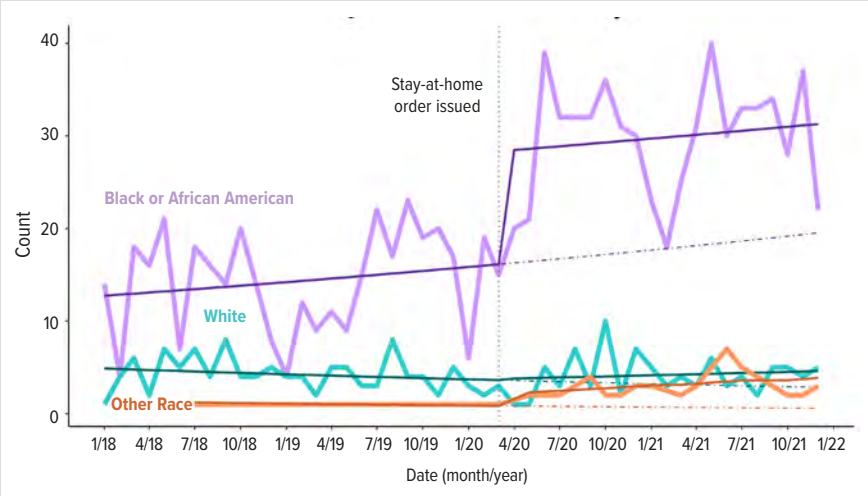
The factors associated with the notable increase in firearm incidents observed in this study and others are likely complex and varied; however, reported increases in gun purchases after the beginning of the COVID-19 pandemic may be a contributing factor.[33,34] Increased saturation of guns within communities may increase the likelihood of firearm-related incidents. In the first 2 months of the COVID-19 pandemic (March and April 2020), there were over 2 million internet searches for gun-related purchasing or removing guns from storage; this was 158% higher than what would be expected without the occurrence of the COVID-19 pandemic.[35] In a nationally representative survey sample, 6% of Americans reported purchasing a gun between March and July 2020; 34%

Figure 1. Interrupted Time Series Analysis of Penetrative Traumatic Injury Counts by Month, 2018-2021



Dotted vertical line depicts March 2020 when stay-at-home orders went into effect in Wisconsin. Solid black lines depict fitted interrupted time series model for each of firearm and stab injuries. Dashed horizontal lines depict the counterfactual prediction of injury without consideration of the stay-at-home order interruption.

Figure 2. Interrupted Time Series Analysis of Firearm Injury Count by Race per Month, 2018-2021



Dashed vertical line depicts March 2020 when stay-at-home orders went into effect in Wisconsin. Solid black lines depict fitted interrupted time series model for each racial group. Only Black or African American, White, and Other Race groups were examined due to insufficient sample size of remaining racial groups. Bonferroni correction was used to adjust for multiple comparisons by race (adjusted $\alpha = 0.008$).

of those were new gun owners, resulting in an estimated 6 million new gun owners in the US.[33] In another national survey, 40% of new gun owners reported having an unlocked gun.[34] Reasons cited for purchasing a gun after the beginning of the pandemic included crime, supply chain disruptions, health, and the economy.[34]

The COVID-19 pandemic brought inequities in health, outcomes, and health care access to the forefront. Health inequities by racial and ethnic groups in COVID-19 mortality have been well documented.[36–38] Additional studies have indicated that people in the lowest socioeconomic position have experienced the highest COVID-19 mortality rates within racial and ethnic groups.[36,39] Nationally, Hispanic people had a 48% higher risk of experiencing a COVID-19 infection compared to White people.[40] Compared to White patients, those identified as Hispanic, non-Hispanic Black, or Asian or Pacific Islander had increased in-hospital mortality from COVID-19 in an adjusted model.[41] On a state level, Illinois reported that Hispanic and non-Hispanic Black patients experienced a disproportionately higher burden of COVID-19-related hospitalizations versus White patients.[42] Similar to the inequities noted in COVID-19 mortality, this study noted an increased burden of firearm injuries among Black or African American patients in the COVID period versus the pre-COVID period.

This unequal distribution of firearm injuries by race and ethnicity may be related to several contributing factors, many of which also contributed to the disparities by race for COVID-19 mortality and hospitalization rates. The social determinants of health (conditions in which one is born, lives, works, and ages) and the broader systemic factors that impact these vary geographically. Communities that experienced poverty, food insecurity, housing instability, and employment barriers at baseline were vulnerable to the changes brought about during the COVID-19 pandemic.[43] These same communities were also those vulnerable to gun violence. Increased distress, unemployment, and uncertainty brought about by the pandemic may have increased violent incidents.[10] In Milwaukee, in particular, historic redlining has contributed to significant inequities that continue to affect the social determinants of health today.[44] This intersection of racism, inequity, COVID-19, and firearm incidents is complex and cannot be ignored.

The unprecedented response to mitigate the spread of COVID-19 including, but not limited to, social distancing and self-isolation may have exacerbated the mental health crisis, contributed to the high rate of unemployment, and increased overall stress and anxiety for individuals. Many of these factors also have been linked to an increase in all types of violence – and the results of this analysis should be contextualized to the multifaceted environment of the pandemic. Further, during the COVID-19 pandemic – particularly in the early months – hospital systems were near or at capacity with COVID-19 patient admissions, while simultaneously attending to those who sustained penetrating injuries. The intersection of COVID-19 infection and penetrating injuries on the burden of hospitals should be examined – particularly with the limited availability of ICU and ventilatory care – to prevent future health crises associated with future and ongoing syndemics.

These data demonstrate a concerning increase in penetrating trauma from pre-COVID to COVID periods with increased firearm injuries. These data are an important component to inform injury prevention efforts. Despite these benefits, this study has several limitations. The data are limited to patients who met trauma registry inclusion criteria within a single level I trauma center and do not include patients who sustained minor or superficial penetrating injuries or patients with penetrating injuries who were treated at other hospitals, nor does it account for incidents where a patient died at the scene of an injury or the patient did not seek medical care. Our results may be an underrepresentation of the overall penetrating incidents in Milwaukee; however, they likely represent the most severe penetrating injuries. These data were retrospectively reviewed and therefore cannot determine any cause-effect or identify any other direct interactions between the stay-at-home orders during the COVID-19 pandemic and the changes in penetrating injury. Local and national sociopolitical events occurring over the same time period also may influence gun violence and are not accounted for in these data. We did not separate injuries by intent because data quality was insufficient, but future work should consider examining self-inflicted injuries and assaultive injuries separately during the pandemic.

CONCLUSIONS

Penetrating traumatic injuries increased during the COVID period compared to pre-COVID. Firearm injuries accounted for much of this increase, while a decrease in stab injuries was noted. The potential syndemic effect of gun violence and the COVID-19 pandemic is crucial for health care professionals, community programs, and policymakers to understand to ensure better care for patients and communities in the event of future natural disasters and disease outbreaks.

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Association Between COVID-19 and Delirium Development in the General Medical Units at an Academic Medical Center

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ABSTRACT

Introduction: Evidence suggests that inpatients who develop delirium experience worse outcomes. Although there is reason to believe that COVID-positive patients may be at a higher risk for developing delirium, little is known about the association between COVID-19 and delirium among hospitalized patients outside the intensive care unit (ICU). This study aimed to examine (1) the independent association between COVID-19 infection and the development of delirium among all non-ICU patients and (2) the risk factors associated with developing delirium among patients admitted with COVID-19, with a special focus on presenting symptoms.

Methods: Using electronic health record (EHR) data of adults admitted to any general medical unit at a large academic medical center from July 2020 through February 2021, we used a cross-sectional multivariable logistic regression to estimate the associations, while adjusting for patients' sociodemographic, clinical characteristics, delirium-free length of stay, as well as time fixed effects.

Results: Multivariable regression estimates applied to 20 509 patients hospitalized during the study period indicate that COVID-19–positive patients had 72% higher relative risk (odds ratio 1.72; 95% CI, 1.31 – 2.26; $P < 0.001$) of developing delirium than the COVID-19-negative patients. However, among the subset of patients admitted with COVID-19, having any COVID-19–specific symptoms was not associated with elevated odds of developing delirium compared to those who were asymptomatic, after controlling for potential confounders.

Conclusions: COVID-19 positivity was associated with higher odds of developing delirium among patients during their non-ICU hospitalization. These findings may be helpful in targeting the use of delirium prevention strategies among non-ICU patients.

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INTRODUCTION

At its emergence, COVID-19 was characterized as an acute respiratory disease. However, as the pandemic unfolded, mounting evidence suggested that other systems in the body could be affected. For example, signs of gastrointestinal, hematologic, and nervous system impairment often accompany respiratory symptoms[1] and may occur in their absence.[2] Of particular interest is the involvement of the nervous system. Documented neurological manifestations of COVID-19 range from stroke, encephalitis, encephalopathy, and Guillain-Barré syndrome[3] to less acute manifestations, such as headache, dizziness, and altered mental status.[4] While incidence varies, several studies estimate that 30% to 90% of cases will experience one or more neurologic symptoms.[5,6]

Delirium has been recognized as a substantially complicating factor among medical inpatients. Inpatients who develop delirium experience worse outcomes, including longer length of stay,[7] cognitive decline,[8] and increased mortality.[9] There is reason to believe that delirium occurs in COVID-19 inpatients,[10] as in persons hospitalized for other medical conditions.[11] Unfortunately, the study of delirium among COVID-19 inpatients has been hampered by the lack of systematic screening using validated assessment tools to identify cases,[12] which is the best practice for such research.

When properly recognized in the inpatient setting, delirium can be mitigated using a delirium prevention program.[13-15] Such programs may be challenging to deliver to all COVID-19 patients

due to the physical isolation measures required for such patients. However, if specific factors present at admission were to convey a higher risk of delirium development, then the targeted use of prevention programs might be more feasible.

This study had 2 main objectives: (1) to examine the independent association between COVID-19 infection and development of delirium among patients admitted to general medical units and (2) to examine potential risk factors associated with the occurrence of delirium among the subset of patients admitted with COVID-19.

METHODS

Setting and Study Design

This cross-sectional study was performed at Froedtert Hospital, a major academic medical center located in southeast Wisconsin serving a population of 1.8 million individuals. The hospital uses a centralized laboratory (Wisconsin Diagnostics Laboratory [WDL]) for COVID-19 testing. All consecutive, unique patients admitted to any general medical unit at Froedtert Hospital from July 2020 through February 2021 were eligible for the study. We excluded patients who were younger than 18 years old, were identified as delirious at admission, did not have their first delirium assessment within 8 hours of admission, were transferred to a general medical unit from an intensive care unit (ICU), or had a history of a psychiatric diagnosis identified via coded diagnosis groups in the electronic health record (EHR). Patients were followed until they developed delirium, died, or were discharged from the general medical unit. The analysis received Institutional Review Board exemption as it was conducted as part of a quality improvement effort.

COVID-19 Status

COVID-19 results were based on a polymerase chain reaction (PCR) test administered to every patient on admission by WDL. COVID-19 symptoms were self-reported as part of a questionnaire that accompanied the order for the COVID-19 test.

Delirium Screening Status

We relied on the Nursing Delirium Screening Scale (NuDESC) to assess delirium positivity in all hospitalized patients. The NuDESC is a validated screening tool that assesses 5 domains: disorientation, inappropriate behavior, inappropriate communication, hallucination, and psychomotor delay.[16] Each domain is scored on a 3-point scale by severity from zero (absent) to 2 (severe). A NuDESC result of 2 or higher is considered a positive screen for delirium. The NuDESC has a demonstrated sensitivity of 77% and specificity of 85% in an assessment of its validity at the study site.[17] Patients were assessed for delirium upon admission and every 8 hours thereafter for the duration of their hospital stay. The NuDESC assessment tool was built directly into the EHR system and documented electronically.

Data Sources and Variable Definitions

Data were drawn from the health system's EHR and included demographics (eg, age, sex, race/ethnicity), comorbidities, and primary health insurance. Based on self-reported data, individuals were classified according to race/ethnicity as non-Hispanic Black/African American, Hispanic (any race), non-Hispanic White, and other race/ethnicity. As a proxy for financial vulnerability, we used uninsured (self-pay) status or enrollment in Medicaid, the public program that provides health insurance to low-income persons. Comorbidities were calculated using the Elixhauser algorithm[18] applied to clinical encounters during the 12 months preceding the patient's index admission.

Statistical Analysis

A cross-sectional multivariable logistic regression was used to estimate the association between COVID-19 status and the odds of developing delirium during the acute care hospital stay. The key explanatory variable of interest was COVID-19 status, a binary indicator set to 1 if the patient tested positive for COVID-19 at admission and zero otherwise. Other covariates included sex (female as the reference), age group (categorical, age 18-30 as the reference), race (non-Hispanic White as the reference), financial vulnerability (1 for uninsured or Medicaid enrollee, 0 for all other payers), comorbidities (0 as the reference), and time fixed effects (month of admission) to capture common temporary shocks across all patients. With the concern that prolonged length of stay may lead to higher odds of developing delirium, we also adjusted for the length of stay before delirium onset, ie, delirium-free length of stay, measured as days elapsed from a patient's hospital admittance to delirium onset, or to discharge from the hospital for patients who did not develop delirium. Recurring visits from the same patient were excluded to avoid serial correlation. Estimates are reported in odds ratios with standard errors robust to heteroskedasticity. The regression analysis was conducted in Stata version 17 (StataCorp LLC, College Station, Texas).

To examine whether presenting with any COVID-19 symptoms acted as risk factors for the development of delirium among COVID-19-positive patients, we conducted a secondary analysis in which the sample was restricted to COVID-19–positive admissions. In addition to the covariates described previously, we included a binary indicator denoting the presentation of any of the following COVID-19–specific symptoms at admission: cough, fever, shortness of breath, others (asymptomatic as the reference). We also included a category of missing symptom information in the regression. Standard errors are clustered at the patient level to account for intrapatient correlation among the COVID-19–positive patients with multiple admissions during the study period.

RESULTS

Table 1 presents the summary statistics for the study population, overall and by COVID-19 status. Among the total 20 509 unique

patient hospitalizations to general acute care units (first encounters), 374 patients (1.8%) tested positive for COVID-19. The average age of the sample was 55.6 years old (SD 19.7), with 9768 (47.6%) over 60 years old. More than half were women (56.3%); 12 918 (63.0%) were non-Hispanic White, 5732 (27.9%) were non-Hispanic Black, 1038 (5.1%) were Hispanic, and 821 (4.0%) were other races. Overall, 4351 patients (21.2%) were considered financially vulnerable. About one-third (n = 6216, 30.3%) had at least 1 comorbidity, although very few (n = 41, 0.2%) had more than 2 comorbid conditions. The average delirium-free length of stay was 3.6 days (SD 4.9), with a median of 2.1 days and an interquartile range of 3 days.

Table 1. Summary Statistics, Overall and by COVID-19 Status

	Total n = 20 509	COVID-19 Positive n = 374	COVID-19 Negative n = 20 135	*P* value
Sex, n (%)				
Female	11 553 (56.3)	202 (54.0)	11 351 (56.4)	0.361
Male	8956 (43.7)	172 (46.0)	8784 (43.6)	
Age, n (%)				
18 < 30	2518 (12.3)	39 (10.4)	2479 (12.3)	0.070
30 – 39	3035 (14.8)	47 (12.6)	2988 (14.8)	
40 – 49	2210 (10.8)	35 (9.4)	2175 (10.8)	
50 – 59	2978 (14.5)	63 (16.8)	2915 (14.5)	
60 – 69	4096 (20.0)	70 (18.7)	4026 (20.0)	
70 – 79	3305 (16.1)	59 (15.8)	3246 (16.1)	
80 – 89	1765 (8.6)	48 (12.8)	1717 (8.5)	
90+	602 (2.9)	13 (3.5)	589 (2.9)	
Race, n (%)				
Non-Hispanic White	12 918 (63.0)	180 (48.1)	12 738 (63.3)	0.000
Non-Hispanic Black	5732 (27.9)	154 (41.2)	5578 (27.7)	
Hispanic	1038 (5.1)	26 (7.0)	1012 (5.0)	
Other race/ethnicity	821 (4.0)	14 (3.7)	807 (4.0)	
Insurance status, n (%)				
All remaining payers	16 158 (78.8)	294 (78.6)	15 864 (78.8)	0.933
Medicaid and self-pay	4351 (21.2)	80 (21.4)	4271 (21.2)	
Comorbidities, n (%)				
0	14 073 (68.6)	247 (66.0)	13 826 (68.7)	0.136
1 – 2	6175 (30.1)	119 (31.8)	6056 (30.1)	
3 – 4	41 (0.2)	0 (0.0)	41 (0.2)	
Missing	220 (1.1)	8 (2.1)	212 (1.1)	
Delirium-free LOS (days), mean (SD)	3.6 (4.9)	4.4 (5.8)	3.6 (4.9)	0.000
Outcome: developed delirium, n (%)				
No	18 231 (88.9)	306 (81.8)	17 925 (89.0)	0.000
Yes	2278 (11.1)	68 (18.2)	2210 (11.0)	

Abbreviation: LOS, length of stay.

Compared to COVID-19-negative patients, COVID-19–positive patients were older (58.1 vs 55.6; $P = 0.008$), more likely to be non-Hispanic Black (154 [41.2%] vs 5578 [27.7%]) or Hispanic (26 [7.0%] vs 1012 [5.0%]; $P < 0.001$) and had a greater mean of delirium-free length of stay (4.4 vs 3.6; $P < 0.001$). The groups did not differ significantly in terms of sex, financial vulnerability, or comorbidity burden. Unadjusted statistics indicated that a higher proportion of patients with COVID-19 developed delirium during their hospital stay compared to non-COVID-19 patients (68 [18.2%] vs 2210 [11.0%]; $P < 0.001$).

COVID-19 Infection, Other Risk Factors, and Development of Delirium

Table 2 summarizes the estimates of the multivariable logistic regression. After adjusting for potential confounders, including delirium-free length of stay, COVID-19–positive patients had, on average, 72% higher odds of developing delirium during the acute care stay than the COVID-19–negative patients (OR 1.72; 95% CI, 1.31-2.26; $P < 0.001$).

Men had 35.7% higher odds of developing delirium than women (OR 1.36; 95% CI, 1.23-1.49; $P < 0.001$). In comparison to adults between 18 and 30 years old, the odds of developing delirium increased with age for patients over 40 years old. Odds of developing delirium for Non-Hispanic Black patients (OR 1.57; 95% CI, 1.40-1.76; $P < 0.001$) and Hispanic patients (OR 1.36; 95% CI, 1.07-1.72; $P = 0.012$) were 57.1% and 35.8% higher, respectively, than non-Hispanic White patients. Financially vulnerable patients had 67.5% higher odds of developing delirium (OR 1.67; 95% CI, 1.44-1.94; $P < 0.001$), all else being equal, and patients with more comorbidity risk factors appeared to have lower odds of developing delirium than those with no comorbidities. The estimates of time fixed effects were statistically significant, with their magnitudes coinciding with the COVID-19 spike in the Milwaukee, Wisconsin area that began in October 2020, peaked in November, and started to wane through February 2021, suggesting a positive impact of COVID-19 prevalence on the odds of developing delirium across the whole population (data not shown).

COVID-19 Symptoms at Admission and Development of Delirium Among COVID-19–Positive Patients

Tables 3 and 4 show descriptive statistics and parameter estimates for the secondary analysis examining the potential association between being symptomatic for COVID-19 (ie, presenting with any of the 3 most prevalent COVID-19-related symptoms) at admission and the development of delirium among the 469 COVID-19-positive admissions.

More COVID-19 asymptomatic patients developed delirium

Table 2. Association Between COVID-19 Status and Delirium Development

	Odds Ratio (95% CI) n = 20 509	*P* value
COVID-19 status		
COVID-19 negative	1 [Reference]	—
COVID-19 positive	1.72 (1.31 – 2.26)	0.000
Sex		
Female	1 [Reference]	—
Male	1.36 (1.23 – 1.49)	0.000
Age		
18< 30	1 [Reference]	—
30 – 39	1.06 (0.82 – 1.37)	0.652
40 – 49	1.50 (1.16 – 1.95)	0.002
50 – 59	2.57 (2.04 – 3.26)	0.000
60 – 69	4.13 (3.28 – 5.20)	0.000
70 – 79	6.83 (5.38 – 8.67)	0.000
80 – 89	12.25 (9.59 – 15.65)	0.000
90+	28.10 (21.52 – 36.69)	0.000
Race		
Non-Hispanic White	1 [Reference]	—
Non-Hispanic Black	1.57 (1.40 – 1.76)	0.000
Hispanic	1.36 (1.07 – 1.72)	0.012
Other race/ethnicity	0.98 (0.74 – 1.28)	0.874
Insurance status		
All remaining payers	1 [Reference]	—
Medicaid and self-pay	1.67 (1.44 – 1.94)	0.000
Comorbidities		
0	1 [Reference]	—
1 – 2	0.64 (0.58 – 0.71)	0.000
3 – 4	0.59 (0.24 – 1.45)	0.250
Missing	1.09 (0.71 – 1.67)	0.681
Delirium-free length of stay	0.88 (0.84 – 0.91)	0.000

Regression also includes month fixed effects. Standard errors are robust to heteroskedasticity.

Table 3. Descriptive Statistics for COVID-19 Symptoms and Delirium Development

	Total COVID-19 Positive n = 469	Asymptomatic n = 247	Symptomatic n = 142	*P* value
Outcome: Developed delirium, n (%)				
No	371 (79.1)	193 (78.1)	117 (82.4)	0.481
Yes	98 (20.9)	54 (21.9)	25 (17.6)	

Eighty out of the 469 admissions were missing COVID-19 symptom-related information.

Table 4. Factors Associated with Developing Delirium in COVID-19-positive Patients

	Odds Ratio (95% CI) n = 461	*P* value
Sex		
Female	1 [Reference]	
Male	2.29 (1.35 – 3.89)	0.002
Age		
18 < 30	1 [Reference]	—
30 – 39	2.39 (0.27 – 20.90)	0.430
40 – 49	2.81 (0.26 – 29.87)	0.392
50 – 59	5.21 (0.66 – 40.41)	0.119
60 – 69	13.10 (1.82 – 94.06)	0.011
70 – 79	24.84 (3.40 – 181.29)	0.002
80 – 89	52.80 (7.18 – 388.52)	0.000
90+	66.22 (7.69 – 570.58)	0.000
Race		
Non-Hispanic White	1 [Reference]	—
Non-Hispanic Black	1.30 (0.70 – 2.39)	0.403
Hispanic	0.79 (0.22 – 2.85)	0.718
Other race/ethnicity	1.55 (0.32 – 7.54)	0.589
Insurance status		
All remaining payers	1 [Reference]	—
Medicaid and self-pay	1.04 (0.46 – 2.35)	0.923
Comorbidities		
0	1 [Reference]	—
1 – 2	1.07 (0.60 – 1.93)	0.815
COVID-19 symptom status		
Asymptomatic	1 [Reference]	—
Symptoms	0.83 (0.39 – 1.73)	0.615
Missing	1.10 (0.45 – 2.67)	0.830
Delirium-free length of stay	0.90 (0.74 – 1.10)	0.299

Regression also includes month fixed effects. Standard errors are clustered at patient level.

(n = 54, 21.9%) than their symptomatic counterparts (n = 25, 17.6%). (See Table 3.) After adjusting for potential confounders, the estimates of the multivariable logistic regression also suggested no associations between having any COVID-19 symptoms at admission and the development of delirium (OR 0.83; 95% CI, 0.39-1.73; $P = 0.615$). (See Table 4). However, COVID-19-positive males were more likely to develop delirium than females (OR 2.29; 95% CI, 1.35-3.89; $P = 0.002$) as were individuals aged 60 years or older. Race, financial vulnerability, and comorbidity scores were not significantly associated with developing delirium.

DISCUSSION

In this study of 20 509 patients hospitalized on general medical inpatient units, delirium was significantly more likely to occur in COVID-19-positive–patients than COVID-19–negative patients (18.2% vs 11.1%; OR 1.72; 95% CI, 1.31-2.26; $P < 0.001$). The elevated risk of delirium among COVID-19-positive patients persisted despite adjustments for demographic and socioeconomic factors, comorbid illness burden, and (delirium-free) length of stay. In the subset of all COVID-19-positive patients, male gender and increased age (over 60 years) were associated with the development of delirium, but initial COVID-19 symptoms were not.

The presentation of delirium in hospitalized patients with COVID-19 likely represents a cumulative insult that is the result of multiple precipitating and potentiating factors. It includes SARS-CoV-2-specific considerations, systemic physiological changes related to infection, pharmacological aspects of management, and environmental factors.[19] COVID-19 may adversely affect the central nervous system through direct neurotoxicity[20]

or through a more systemic inflammatory response.[21] COVID-19 also is associated with hypoxia, hypotension, dehydration, and electrolyte disturbance, all of which may precipitate delirium in a susceptible patient. Isolation's adverse impact on sensory cues, patient contact, and orientation also may contribute to the development of delirium in an individual with COVID-19. In addition, medications commonly utilized in the management of COVID-19, such as sedatives, steroids, and corticosteroids, also may lead to the development of delirium.[22-24]

Our findings are consistent with prior reports that identified COVID-19 as a risk factor for the development of delirium in hospitalized patients. Previous studies that have explored this association have been limited to elderly patients,[25] individuals presenting with neurologic abnormalities,[26] or those admitted to the ICU.[27] In addition to using a validated delirium assessment tool, our study contributes to the literature by demonstrating an association between COVID-19 and delirium among non-ICU hospitalized patients of all ages.

The finding of a negative association between medical comorbidities and the onset of delirium conditional on COVID-19 status merits discussion. Earlier studies have identified the burden of coexisting conditions as a risk factor for delirium in patients with and without COVID-19.[28-29] One explanation for this unexpected finding is that the study focused on non-ICU hospitalized patients. In excluding patients requiring an ICU level of care, we may not have captured the patient population with a high burden of medical comorbidity and, therefore, risk of developing delirium. In addition, patients with delirium, COVID-19, and significant co-occurring illness may have been delirious upon admission to the hospital and thereby excluded from the population studied. Finally, this negative association also could be attributed to the institution-wide delirium prevention program implemented prior to the pandemic, in which patients with multiple comorbidities may have triggered more nonpharmacologic delirium prevention interventions. To the extent that delirium prevention efforts were heterogeneous, such negative associations could dominate any underlying positive association between comorbidity score (at admission) and the odds of developing delirium during the hospital stay.

Also of note was the finding that potential symptoms of COVID-19 infection were not associated with the occurrence of delirium. A possible explanation for this finding is that we studied self-reported symptoms of COVID-19 and not physical signs of illness, such as hypoxia, fever, and hypotension. Objective signs of illness may have corresponded better to the severity of the illness and the probability of developing delirium.

On the other hand, since we have found that the only independent risk factors for development of delirium among COVID-19 patients were male sex and age 60 years and older, if resources do not permit using delirium prevention programs in all COVID-positive patients, we would suggest that health care systems prioritize them on males and those over 60 years old, pending further data.

There are important limitations to our study. Given our focus on the development of delirium during the index non-ICU hospital stay, patients assessed as delirious at admission were excluded from the analyses. It is likely that those patients differ systematically from those who developed delirium during their hospital stay in terms of COVID-19 status and other factors, including the number, type, and severity of comorbid conditions. As mentioned above, we excluded patients transferred from the ICU, as their delirium status could not be consistently ascertained. Finally, the SARS-CoV-2 variants circulating during the months that these patients were hospitalized included only early variants, as delta and omicron variants had not yet been identified in Wisconsin. It is possible that later variants might have different patterns regarding complications, such as delirium.

Finally, even though the study health system had implemented a hospital-wide delirium prevention program meant to be applied to every at-risk inpatient homogeneously, it is plausible that COVID-19-positive patients received fewer interventions delivered in a more isolated treatment environment, potentially overestimating the association between COVID-19 and the development of delirium.

CONCLUSIONS

The results of this study suggested that COVID-19 positivity was positively associated with the odds that patients would develop delirium during their non-ICU hospitalization—even after controlling for known risk factors, including sex, age, race/ethnicity, comorbidities, financial vulnerability, and delirium-free length of stay. For the subpopulation of COVID-19 positive patients at admission, only sex and age placed individuals at particularly higher risk of developing delirium while hospitalized. As more evidence points toward a prolonged coexistence of humans and the SARS-CoV-2 virus and its variations, in addition to using validated tools to assess delirium, hospitals should design delirium prevention interventions and care delivery processes to accommodate patients at higher risk and reduce the onset of delirium among COVID-19-positive inpatients. This would help avoid negative patient care outcomes and the corresponding cost of care following delirium onset, thereby improving value for patients.

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COVID-19 Infection Outcomes and Testing Outreach Efforts Among People Living With HIV in Milwaukee, Wisconsin

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ABSTRACT

Introduction: Since the beginning of the COVID-19 pandemic, the incidence and severity of COVID-19 co-infection in people living with HIV (PLWH) has been an area of investigative research. Clinic databases of PLWH provide opportunities to investigate outcomes of COVID-19 co-infection and efficacy of outreach efforts, which are integral to patient care during health crises.

Methods: All PLWH over 18 years of age who receive care at the Froedtert & Medical College of Wisconsin Adult Infectious Disease Clinic and who had a COVID-19 test performed during May 2020 through March 2021 were included for analysis. All patients received an individualized phone call with COVID-19 testing education and information. Automated data collection and manual chart review were used to acquire information on demographics, outreach efforts, COVID-19 testing results, and COVID-19 clinical course.

Results: Four hundred sixty-two COVID-19 tests completed on 793 PLWH were included, with 40 (8.7%) positive tests and 422 (91.3%) negative tests on a predominantly young, male, and virally suppressed cohort. Most patients had mild to moderate COVID-19 infection (20/27, 74.07%), with 1 patient requiring hospitalization and zero deaths. Three hundred fourteen (39.59%) patients accepted outreach for COVID-19 testing; 171 were tested in our health system, with 72 of those tests occurring within 2 weeks. Outreach efforts demonstrated a statistically significant increase in COVID-19 testing ($P < 0.001$).

Conclusions: In this largely young, male, virally suppressed cohort of PLWH, most COVID-19 co-infections were associated with mild to moderate disease severity, with 1 hospitalization and zero deaths. Individualized patient outreach efforts were associated with a significant increase in COVID-19 testing, most of which occurred after a single phone call. This outreach process could have utility in other public health arenas, though may be limited by larger patient populations.

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INTRODUCTION

In late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and has since spread worldwide, infecting millions of people. As of May 3, 2023, 765 million Coronavirus disease (COVID-19) cases and 6.9 million COVID-19-related deaths have been reported worldwide.[1] COVID-19, the disease caused by SARS-CoV-2, has clinical manifestations ranging from asymptomatic infection to respiratory failure and death.[2] Several studies have demonstrated that biologic characteristics, including older age, obesity, hypertension, diabetes, and chronic kidney disease, are associated with a higher risk of severe disease and death from COVID-19.[3] Also well published is the disproportionate impact COVID-19 has on underserved populations due to differences in race, socioeconomic status, health care accessibility, educational opportunities, housing situations, and prevalence of chronic medical conditions.[4-6]

Similarly, a disproportionate burden of HIV infection exists in this population. The impact of co-infection with COVID-19 in people living with HIV (PLWH) has been an area of research. Generally, PLWH are perceived to be at high risk of developing severe COVID-19 infection due to their characteristic chronic inflammatory state and varying degrees of immune dysfunction.[7] To date, reports on outcomes of COVID-19 infection in this population have been mixed. Most studies have demonstrated no significant differences in disease severity or

mortality in PLWH when compared to the general population.[8-16] However, a smaller number of studies have identified either significant or trends toward significant increases in disease severity and/or mortality rates in this population.[17-21] Electronic medical record registries of PLWH offer opportunities for outreach into communities that may be disproportionately affected by COVID-19. While there are publications that explore the detrimental effect of the COVID-19 pandemic on HIV testing and treatment of PLWH, along with suggestions of ways to improve outreach (including via self-testing HIV kits, increased social media presence, and increased televisits), little information exists about outreach to them with regard to COVID-19 testing.[22-25] We outline one center's experience with outreach efforts to PLWH during the COVID-19 pandemic and add to the current body of work regarding outcomes of COVID-19 infection in this population.

METHODS

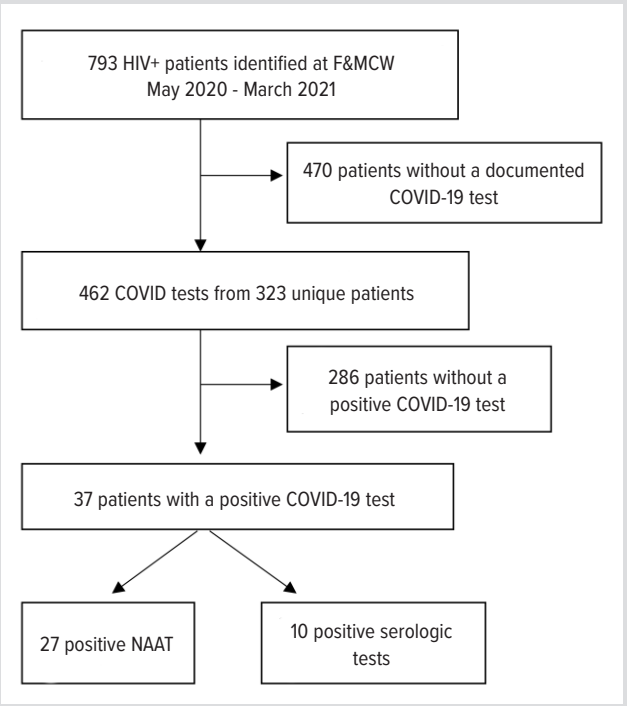
Patient Selection

Cases of co-infection were identified through use of an Epic (Epic Systems Corporation, Verona, Wisconsin) registry. Seven hundred ninety-three patients with HIV infection over the age of 18 who receive care through the Froedtert and the Medical College of Wisconsin (F&MCW) Adult Infectious Disease Clinic were included in the study. Co-infection was defined as those with HIV infection who were diagnosed with COVID-19 infection either by a positive nucleic acid amplification test (NAAT) for SARS-CoV-2 or a positive serology test between May 2020 to March 2021.

Data Extraction

Following patient identification, further data were gathered via use of the CAREWare database. Information regarding patient age at time of diagnosis, sex at birth, current antiretroviral therapy (ART), race, last viral load, COVID-19 test result, and type of COVID-19 test completed were extracted automatically. A suppressed viral load was defined as greater than 200 copies/mL, which is the standard threshold used in guidelines. The most recent viral load prior to the date of a COVID-19 test was used for analysis. Because CD4 counts were not reliably available with proximity to COVID-19 testing—likely given heterogeneity in provider preference following prolonged viral suppression—these values were not included in our analysis. Manual chart review was then performed to identify medical comorbidities, clinical presentation of infection, and outcomes, including severity of infection, need for hospitalization, and death. Obesity was defined as body mass index greater than 30 kg/m^2. Centers for Disease Control and Prevention guidelines were utilized for the definition of severity, with categories of mild to moderate (mild symptoms up to mild pneumonia), severe (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and critical (respiratory failure, shock, or multiorgan system dysfunction), as well as asymptomatic infection. Care Everywhere software Epic Systems, Verona, Wisconsin) was used to review hospitalizations occurring at outside institutions.

Figure. Selection of Patient Inclusion



Abbreviation: F&MCW, Froedtert and the Medical College of Wisconsin
Thirty-seven patients with positive testing were included in analysis; 286 patients with negative testing were included in the control group.

Outreach Efforts

Ryan White emergency funding was applied for and utilized for outreach efforts to PLWH who were active Ryan White recipients receiving their medical care through the F&MCW infectious disease clinic. All 793 patients identified via the institution's Epic registry received an individualized telephone call from a clinic social worker. COVID-19 outreach data were logged and included the date of outreach and number of attempts. If the patient engaged and accepted the service, a template was used to document the conversation, including information regarding patient requests and prior COVID-19 testing results. The completed template was then routed to a staff HIV nurse for COVID-19 test education and scheduling.

Data Analysis

Four main types of analyses were conducted. First, chi-square tests and 2-sample *t* tests were used to assess differences in demographic characteristics and comorbidities between individuals who tested positive and negative for COVID-19. Second, frequencies and percentages of symptoms and severity were calculated for individuals with a positive NAAT test. Third, a pre-post analysis was conducted to assess COVID-19 testing before and after the outreach intervention. The sample for this analysis

included only individuals who received the outreach intervention. McNemar's test was used to test for significance between pre- and post-outreach intervention. Finally, the entire study sample was utilized to compare testing across the number of outreach attempts. Chi-square tests were used to test for significance across the no outreach, post-outreach 1 call, and post-outreach 2 or more calls groups. STATA SE 2013 (StatCorp LP College Station, Texas) was used to accomplish this analysis. Variables used were compiled from electronic medical records. Age was utilized as a continuous variable. Sex at birth was coded as male and female. Current ART was classified as yes or no. Race/ethnicity was categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic, and Non-Hispanic Other. Last viral load was dichotomized into less than 200 copies/mL and greater than or equal to 200 copies/mL. Comorbidities such as obesity, hypertension, type 2 diabetes, chronic kidney disease, and chronic obstructive pulmonary disease were coded as binary variables.

Ethical Approval

This study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Table 1. Demographic Characteristics of People Living With HIV Tested for COVID-19

	Total (n = 323)	COVID positive (n = 37)	COVID negative (n = 286)	*P* value
Age, years, average (SD)	48.98 (13.86)	42.08 (13.15)	49.87 (13.72)	0.001
Sex at birth, n (%)				
Male	258 (79.88%)	31 (83.78%)	227 (79.37%)	0.53
Female	65 (20.12%)	6 (16.22%)	59 (20.63%)	
Race, n (%)				
Non-Hispanic Black	155 (47.99%)	22 (59.46%)	133 (46.50%)	
Non-Hispanic White	132 (40.87%)	12 (32.43%)	120 (41.96%)	
Hispanic	26 (8.05%)	1 (2.70%)	25 (8.74%)	0.23
Non-Hispanic Other	10 (3.10%)	2 (5.41%)	8 (2.80%)	
Current antiretroviral therapy, n (%)				
Yes	302 (93.50%)	34 (91.89%)	268 (93.71%)	0.72
No	21 (6.50%)	3 (8.11%)	18 (6.29%)	
Last viral load, n (%)				
< 200	274 (84.82%)	32 (86.49%)	242 (84.62%)	0.80
≥ 200	48 (14.86%)	5 (13.51%)	43 (15.03%)	
Obesity, n (%)				
No	213 (65.94%)	23 (62.16%)	190 (66.43%)	0.61
Yes	110 (34.06%)	14 (37.84%)	96 (33.57%)	
Hypertension, n (%)				
No	221 (68.42%)	28 (75.68%)	193 (67.48%)	0.31
Yes	102 (31.58%)	9 (24.32%)	93 (32.52%)	
Type 2 diabetes, n (%)				
No	278 (86.07%)	33 (89.19%)	245 (85.66%)	0.80
Yes	45 (13.93%)	4 (10.81%)	41 (14.34%)	
Chronic kidney disease, n (%)				
No	290 (89.78%)	33 (89.19%)	257 (89.86%)	0.78
Yes	33 (10.22%)	4 (10.81%)	29 (10.14%)	
Chronic obstructive pulmonary disease, n (%)				
No	310 (95.98%)	36 (97.30%)	274 (95.80%)	> 0.99
Yes	13 (4.02%)	1 (2.70%)	12 (4.20%)	

RESULTS

Patient Selection

Selection of included patients is outlined in the Figure. Through use of the CAREWare dataset, a total of 793 PLWH who received care at F&MCW were identified. Between May 2020 and March 2021, 360 NAAT and 102 serologic tests were performed for a total of 462 COVID-19 tests. Of these, there were 40 (8.65%) positive tests and 422 (91.34%) negative tests. Of the positive tests, 2 patients had both a positive NAAT and serology, while 1 patient had 2 positive NAATs (performed 4 weeks apart), leaving 37 unique patients who tested positive and were included for analysis. Of the 37 positive cases, 27 (72.97%) were identified by NAAT and 10 (27.02%) by serology. Of the 422 negative tests—after adjusting for multiple tests performed on the same individual—286 unique patients were identified for the control group.

Demographics

Demographic information for the patient cohort is summarized in Table 1. Patients were divided into 2 groups according to the presence or absence of a positive COVID-19 test. Between the two groups, the COVID-postive group was significantly younger that the COVID-negative group (42.08 vs 49.87 years, $P = 0.001$). Most of the total cohort was male (79.88%), were on ART at time of testing (93.5%), and were virally suppressed (85.09%). The most represented races were Non-Hispanic Black (47.99%) and Non-Hispanic White (40.87%). The most common comorbidities were obesity (34.06%) and hypertension (31.58%). There was no statistically significant difference between the groups with regard to sex at birth, race, current ART, last viral load (copies/mL), or medical comorbidity (obesity, hypertension, type 2 diabetes, chronic kidney disease, or chronic obstructive pulmonary disease).

Outcomes and Presentations of COVID-19-Positive Patients

Data regarding presenting symptom(s), severity, and need for hospitalization are summarized in Table 2. Only patients with a positive NAAT test (n = 27) were included in this analysis, as those who tested positive via serologic test generally did not have symp-

Table 2. Outcomes and Presentations of COVID-19-Postive Patients Diagnosed Via Nucleic Antigen Amplification Test, N = 27

	n (%)
Symptoms	
Cough	13 (48.15)
Fatigue	7 (25.93)
Subjective fever	5 (18.52)
Myalgias	5 (18.52)
Congestion	5 (18.52)
Sore throat	4 (14.81)
Diarrhea	4 (14.81)
Anosmia	4 (14.81)
Chills	3 (11.11)
Headache	3 (11.11)
Nausea	3 (11.11)
Shortness of breath	3 (11.11)
Weakness	2 (7.41)
Anorexia	2 (7.41)
Abdominal pain	1 (3.70)
Back pain	1 (3.70)
Rhinorrhea	1 (3.70)
Severity	
Asymptomatic	3 (11.11)
Mild to moderate	20 (74.07)
Severe	4 (14.81)
Critical	0 (0.00)
Hospitalization	
Yes	1 (3.70)
No	26 (96.30)

Figure 2. Flow Diagram of Test Completion and Outreach Efforts

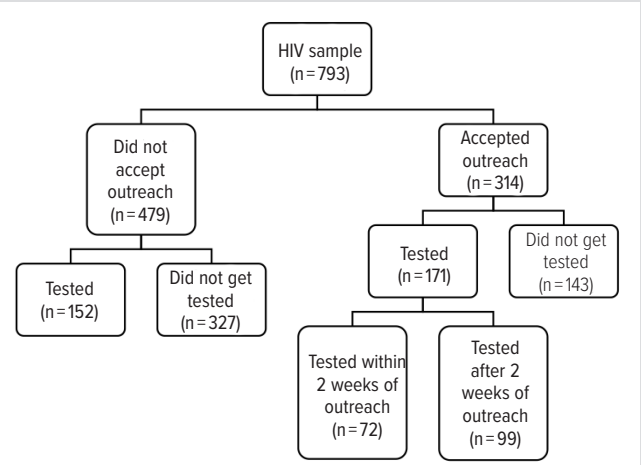


Table 3. COVID-19 Test Completion in Those Who Accepted Outreach Intervention

	Before Outreach (n = 314)	After Outreach (n = 314)	*P* value
COVID-19 tested			
Yes	20 (6.37%)	151 (48.09%)	< 0.001
No	294 (93.63%)	163 (51.91%)	

toms charted due to unknown timing of infection. Most patients (n = 20, 74.07%) had symptoms that correlated with mild to moderate infection, the most common of which included cough (48.15%), fatigue (25.93%), subjective fever (18.52%), myalgias (18.52%), and congestion (18.52%). The remaining symptomatic patients met criteria for severe infection due to dyspnea and/or hypoxia (n = 4, 14.81%). Three patients were asymptomatic, and all were tested following concern for exposure. There were no critical infections. Only 1 patient required hospitalization, and there were no documented deaths.

Outreach Efforts

The number of outreach attempts and subsequent testing is outlined in Figure 2. Of the 793 PLWH identified, 314 (39.59%) accepted outreach and 479 did not (60.40%). Of those who accepted outreach, 171 (54.45%) were tested; 72 of those tests (42.10%) were performed within 2 weeks of outreach, and 20 (6.37%) were tested prior to outreach. Of those who did not accept outreach, 152 (31.73%) patients were tested during the study period. Information summarizing the effect of outreach efforts is included in Tables 3 and 4. Following outreach, 151 tests were performed within the monitoring period, which represented a statistically significant change in the amount of testing. One hundred forty-seven (97.35%) of these tests were performed after 1 call, and 4 were after 2 or more calls (2.65%). In total, regardless of outreach, 323 patients (40.73%) underwent COVID-19 testing out of the 793 identified PLWH.

DISCUSSION

Overall, patients sampled from the F&MCW adult infectious disease clinic were found to be a largely young, male cohort who were virally suppressed on ART. Most patients presented with symptoms correlating to mild to moderate COVID-19 infection, with 1 hospitalization and zero deaths. When compared to other publications investigating PLWH during this time period, the demographics of our study population were similar overall.[8-15] The main difference was an overrepresentation of Non-Hispanic White patients in our cohort, though multiple studies did not report race, and exact numbers varied considerably by location. Additionally, our sample size of 27 PLWH and COVID-19 co-infection was smaller when compared to other studies – most with population sizes between 30 and 80. Patients in our cohort who tested positive were statistically younger, which may be representative of differences in social distancing and may have contributed to milder infections overall.

Hypotheses that PLWH may be at higher risk for severe COVID-19 infection and death have been postulated since early in the pandemic due to immune dysregulation and varying degrees of immunodeficiency, with some existing studies demonstrating this effect in New York, South Africa, and the United Kingdom.[17-20] One review article discussed that several

independent risk factors in PLWH may contribute to a higher risk of mortality overall, including older age, male gender, Black racial background, presence of medical comorbidities, intravenous drug use, and low CD4 cell counts.[21] During our survey of existing publications, most data suggested there was not a significant increase in disease severity or mortality in PLWH with COVID-19 co-infection when compared to the general population – especially when virally suppressed.[8-16] Our data demonstrate a lack of severe co-infection and mortality in this cohort and perhaps is related to immune recovery while virally suppressed on ART. When compared to these publications, our data appear to have lower rates of both hospitalizations and deaths. This may be representative of a lower sample size or that our study timeframe did not include some of the earliest cases of COVID-19 in our population.

Table 4. Outreach Efforts and COVID-19 Testing

(n = 793)	Total (n = 499)	No Outreach/ Pre-Outreach (n = 283)	Post-Outreach 1 call (=11)	Post-Outreach 2+ calls	*P* value
COVID-19 Tested, no. (%)					
Yes	323 (40.73%)	172 (34.47%)	147 (51.94%)	4 (36.36%)	<0.001
No	470 (59.27%)	327 (65.53%)	136 (48.06%)	7 (63.64%)	

Through grant funding, all PLWH who received HIV care at F&MCW received COVID-19 testing outreach with a telephone call from a social worker, which, if accepted, was documented in the patient chart. If testing was declined, the reason was not documented consistently in the chart. Common documented reasons for declining testing included a lack of symptoms, recent testing, or a general lack of interest. Overall, compared to testing that had been performed prior to any outreach, outreach efforts by our team had a statistically significant impact on the number of PLWH who completed testing. The discovery of an effecctive and successful manner of outreach is valuable. Outreach for other public health issues, including vaccination, may be able to follow a similar design. Additionally, given that PLWH represent a highly marginalized population, any outreach efforts that better connect these patients to health care are important. In our population, outreach efforts were possible due to an existing database of PLWH that was small enough to make individualized phone calls feasible; thus, this may not be realistic to expand to larger patient populations.

To our knowledge, there are limited studies examining the results of outreach efforts to PLWH during the COVID-19 pandemic. One such study is a virtual outreach program led by students at Brigham and Women's Hospital in Boston, Massachusetts.[26] This outreach was aimed at identifying areas of social need, such as food and financial insecurity, health education regarding COVID-19, and engagement of individuals struggling with social isolation. Outreach events were thought to have positive effects on students, providers, and patients alike. Overall, this study suggests that direct engagement of PLWH through outreach efforts has more potential benefits than simply those related to physical health and highlights the significant psychosocial impact of the COVID-19 pandemic.

There are multiple limitations to this study. With regards to the COVID-19 data in PLWH, it is possible that patients in the F&MCW database tested positive or were hospitalized at outside institutions. We attempted to mitigate this by using the Care Everywhere software to query various institutions across the city and state but could not capture all regional hospitals or COVID-19 testing sites. The small sample size raises questions about the power of the study, though based on similar studies, the overall demographics appear to be consistent with the notable difference of overrepresenting the Non-Hispanic White population. Our results may not be generalizable to centers that have a patient population with lower rates of viral suppression, with most of our patients being on ART and virally suppressed at the time of COVID-19 testing. Regarding outreach efforts, it is difficult to discern whether COVID-19 testing during our study period was specifically due to the outreach event. However, any patient who accepted the outreach was given information about where and how to test, so there was likely value in the outreach, even if testing occurred several months later.

CONCLUSIONS

In this largely young, virally suppressed cohort of PLWH, COVID-19 co-infection was associated with mostly mild to moderate disease severity, which corresponds with most existing studies. Outreach efforts by the infectious disease department via individualized phone calls to PLWH were shown to have a statistically significant increase in the number of patients who were tested for COVID-19. This type of outreach may have value for further public health efforts, though would likely have limitations expanding to other populations given the one-to-one nature of communication.

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Ocular Emergencies During the Coronavirus Disease 'Safer at Home Order' in Wisconsin

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ABSTRACT

Introduction: The coronavirus pandemic created large shifts in utilization of hospital resources, patient presentations, and delivery of medical care.

Objectives: This retrospective study evaluated the ocular emergencies at a tertiary-care academic hospital in Wisconsin during the COVID-19-related "Safer at Home" order.

Methods: Ophthalmology consultations performed March 23 through May 26, 2020, were compared to the same time period in the 4 preceding years and the subsequent year. Billing codes were obtained to evaluate the diagnoses and procedures performed during this time frame.

Results: In 2020, 155 consultations were performed (42 emergency department, 113 inpatient), compared to a mean of 214 over the 5 other study years. The incidence rate ratio (IRR) of total consultations in 2020 was 0.72 ($P \leq 0.001$) compared to previous years. Significantly fewer emergency department consultations were performed (IRR 0.62, $P \leq 0.001$), while inpatient consultations were similar (IRR 0.88, $P = 0.119$). The most common diagnosis across all study years was fracture of the skull/orbit with injury to the eye/orbit. In 2020, 13% of consultations led to a procedure, compared to a total of 16% in the other years (IRR 0.59, $P = 0.018$).

Conclusions: This study demonstrated a 28% reduction in ophthalmology consultations at a major university hospital in Wisconsin during the COVID-19-related "Safer at Home" order, though the number of consultations leading to surgery were stable. This suggests that while patients with less acute needs may have deferred care, those requiring urgent surgery still presented to the emergency department. These data may help hospitals appropriately allocate eye care resources during future public health emergencies.

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic caused dramatic shifts in the use of hospital resources and personnel. Intensive care units and inpatient wards filled with COVID-19 patients, while concern for contagion and cancellations of elective procedures led to a 70% decrease in outpatient services following the declaration of a national emergency on March 13, 2020.[1] At the same time, voluntary lifestyle changes and "Safer at Home" Orders, such as the state of Wisconsin's Emergency Order #12,[2] led many to spend much more time in their homes. Emergency department (ED) visits declined by 42% in the United States during March-April, 2020, presumably due to a combination of fewer injuries occurring while staying at home and concerns about the risk of COVID-19 exposure while seeking care.[3] While many ophthalmology appointments were deferred during this time, emergency ophthalmic care continued, as eye trauma and other eye emergencies are an important source of morbidity.[4]

Eye injuries account for many ED visits. In the United States in 2017, about 413 000 ED visits were related to ocular injuries.[5] While many of these visits in a typical year are for true emergencies, many are not. Of 12 million eye-related ED visits from 2006-2011 studied using a nationally representative database, only 41% of eye-related ED visits could be categorized as emergent. In this cohort, corneal abrasions were the most common emergent diagnosis, and conjunctivitis was the most common diagnosis overall (28%).[6]

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Little has been published about ocular emergencies during the COVID-19 pandemic due to the recent and ongoing nature of the pandemic. A cohort study conducted in Philadelphia, Pennsylvania, identified a 25% decrease in the daily number of patients presenting for emergency eye evaluation, although the incidence of severe ocular trauma remained similar to that prior to lockdown.[7] Globally, a 68.4% decline in the number of ED visits for eye injuries was reported in Italy, while a tertiary care center in India reported 58.5% fewer ED visits due to ocular trauma.[8,9] Injuries that continued to occur during stay-at-home orders included chemical injuries, injuries due to home improvement projects, and exercise-related injuries.[10,11]

This study aims to compare the ophthalmology consultations in the ED and inpatient settings at a tertiary-care academic hospital in Wisconsin during the 2020 "Safer at Home" order compared to the same period in prior years and the subsequent year. We hypothesized that the incidence of ophthalmology consultations would be lower during the 2020 study period, although the incidence of severe ocular emergencies would be similar compared to previous years. To our knowledge, this is the first study of its kind from the Midwestern United States.

METHODS

This study was submitted to the Institutional Review Board (IRB) and was judged to be exempt from further IRB review given the deidentified nature of the data used for the study. This is a retrospective cohort study comparing the volume of ophthalmology consultations at a single academic Wisconsin hospital that occurred during the Wisconsin "Safer at Home" emergency order, March 23, 2020 through May 26, 2020, versus the same period in the 4 preceding years (2016-2019) and 1 following year (2021). The second year of the pandemic was studied to evaluate any differences in consultations as the pandemic restrictions eased. Consultations were identified by searching institutional billing records and subdivided into location of consultation (ED, inpatient, observation, and outpatient short stay). Observation is commonly used for patients who present to the ED and need a period of treatment or monitoring before further decisions are made and are not expected to stay more than 1 night, and outpatient short stay is used for patients who are not admitted and are not expected to stay overnight.

Additional information gathered via computerized extraction included demographic data (patient age, gender, and race), diagnosis codes, and procedure codes associated with the visit. Codes 2 weeks post discharge were also included to capture any procedures and diagnoses made subsequent, but related to the initial encounter. Ophthalmology-associated diagnosis codes (*International Classification of Diseases, Tenth Revision* [ICD-10]) and procedure codes (*Current Procedural Terminology* [CPT]) were isolated for further evaluation. CPT codes of interest were further categorized as requiring an operating room or as bedside procedures. Many visits had several associated diagnosis codes of interest.

Statistical analysis was performed using R (version 4.2.0). Chi-square testing was used to compare racial and gender differences among study years; *t* testing was used to compare age differences. These comparisons were between a particular year and all other years. Poisson models were used to compare the volume of consults and number of consultations leading to surgical interventions in 2020 compared to other years. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of our cohort was 42 years; 55.3% identified as male and 87% as White. Participant demographics were similar across the years of the study (Table 1), except for a higher proportion of White participants in 2017 and a lower proportion in 2021.

A total of 1227 ophthalmology consults were performed during 2016-2021. During this time frame, a total of 101 941 patients were cared for at this hospital across all studied care locations. The total number of ophthalmology consultations was 155 in 2020 compared to a mean of 214 in the other years evaluated. The plurality of consultations occurred in the inpatient setting, followed by the ED (Figure 1). The incidence rate ratio (IRR) of ophthalmology consults in 2020 derived from the Poisson model was 0.72 ($P \leq 0.001$), meaning that the number of consultations was 72% of what would be expected compared to previous years. When subdivided into different consultation locations, the number of ED consults was significantly fewer compared to previous years (IRR 0.62, $P \leq 0.002$), but the number of inpatient consults was similar (IRR 0.88, $P = 0.254$).

The year 2017 had more consultations than other study years (265 total). When 2017 was removed from the Poisson model in a sensitivity analysis, the decrease in consultations in 2020 remained significant (IRR 0.77, $P = 0.002$). The IRR of consultations in 2020 when comparing to all study years versus all study years except 2017 were 0.62 vs 0.66 ($P = 0.002$ vs $P = 0.010$) for ED, 0.88 vs 0.94 ($P = 0.254$ vs $P = 0.578$) for inpatient, 0.35 vs 0.34 ($P = 0.018$ vs $P = 0.016$) for observation, and 0.47 vs 0.51 ($P = 0.006$ vs $P = 0.017$) for outpatient short stay settings, respectively. Ophthalmology consultation volume returned to normal in 2021, with 198 total consultations (IRR 0.91, $P = 0.206$ when compared to 2016-2019).

The most common diagnosis across all years was fracture of the skull and orbit with injury to the eye or orbit (ICD codes S02 and S05) associated with 840 of 1227 (68.5%) consults. The most common diagnosis in 2020 was the same, with 112 of 155 (72.3%) consults. This was followed by disorders of the eyelid and lacrimal system (279/1227, 22.7%) and retinal detachments and breaks (224/1227, 18.3%) (Table 2). These percentages sum to greater than 100%, as more than 1 diagnosis can be associ-

ated with an encounter – for example, an orbital trauma patient may be diagnosed with both an eyelid laceration and an orbital fracture. The most common procedure across all years was the repair of eyelid laceration, accounting for 104 of 372 (28%) associated CPT codes, followed by repair of retinal detachments and tears, accounting for 103 of 372 (28%) related CPT codes (Table 3).

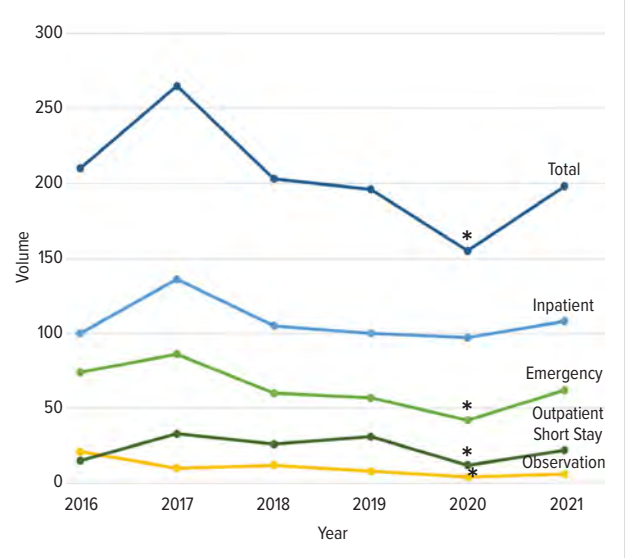
Twenty of 155 (13%) consultations led to a procedure in 2020, compared to a total of 169 of 1072 (16%) in the other study years (IRR 0.59, $P=0.018$) (Figure 2). In 2020, 7 of 155 (5%) consultations led to procedures that require an operating room compared to a total of 46 of 1072 (4%) in other study years (IRR 0.76, $P=0.486$), while 13 of 155 (8%) led to bedside procedures compared to a total of 123 of 1072 (11%) in other study years (IRR 0.53, $P=0.017$).

Table 1. Demographic Information

Variable	Interval	2016	2017	2018	2019	2020	2021	Total
Age	Years (mean)	41.4 $P=0.662$	41.8 $P=0.840$	44.3 $P=0.165$	42.3 $P=0.888$	38.8 $P=0.104$	43.1 $P=0.510$	42
Gender	Male (%)	116/210 (55.2%) $P=0.939$	142/265 (53.6%) $P=0.626$	121/203 (59.6%) $P=0.165$	111/196 (56.6%) $P=0.639$	80/155 (51.6%) $P=0.301$	108/198 (54.5%) $P=0.876$	678/1227 (55.3%)
Race	White (%)	187/210 (89%) $P=0.369$	244/265 (92.1%) $P<0.007$[a]	176/203 (86.7%) $P=0.909$	163/196 (83.2%) $P=0.082$	137/155 (88.4%) $P=0.613$	161/198 (81.3%) $P=0.011$[a]	1068/1227 (87%)
Total consultations		210	265	203	196	155	198	1227

P values are from a *t* test (age) or a chi-square test (gender, race) comparing a particular year to all other years.
[a]Indicates *P* value < 0.05.

Figure 1. Volume of Ophthalmology Consultations by Year and Patient Location



*Indicates a statistically significant difference ($P<0.05$) between 2020 and other years.

DISCUSSION

This study demonstrated that 28% fewer ophthalmology consultations were performed at our large academic hospital during the COVID-19 "Safer at Home" order in 2020 compared to the same period in the surrounding years. This finding is similar to what was observed in a recent cohort study from Philadelphia; however, the magnitudes of change in both studies were smaller than what has been reported in 2 international studies.[7-9] Consultations returned to pre-COVID-19 volumes in 2021, when activity restrictions eased and rates of COVID-19 infections decreased. Variation in the magnitude of decline in ophthalmology consultations may be attributable to regional factors – for example, a starker decrease was observed in Italy,[8] where "Safer at Home" style regulations were stricter than in Wisconsin.

The decline in ophthalmology consultations was largely driven by a significant decrease in ED consultations, rather than those in the inpatient setting. A plausible explanation for this decrease is that outpatients deferred seeking care for their eye symptoms as they wanted to protect themselves from exposures to COVID-19, but those who were already admitted to the hospital had the ophthalmology service consulted on their behalf. Prior work has shown that up to 59% of eye-related ED visits are not urgent,[6] and it is possible that patients with less urgent concerns may have chosen not to seek care during the "Safer at Home" order. Interestingly, another study noted that patients who presented with retinal detachments during the first year of the pandemic were more likely to have a macula-off detachment with proliferative vitreoretinopathy, leading to worse final visual acuity outcomes – likely due to the delay in seeking care.[12] Our data demonstrate that the number of retinal detachments or tears and associated procedures were lower in 2020 compared to other years, suggesting that patients either deferred seeking care (as postulated in the aforementioned study) or actually had fewer retinal tears or detachments. This is somewhat unexpected, since the closure or limited availability of some local practices could have led to more patients seeking care at our ED. Another plausible reason for the lower volume of ophthalmology consultations during the "Safer at Home" order is that many eye-related ED visits are related to trauma occurring outside the home, such as motor vehicle accidents.[13,14] With fewer people leaving their homes, fewer injuries may have occurred, leading to fewer ED visits.

Our analysis showed that consultations leading to procedures that require use of an operating room remained similar to pre-COVID levels in 2020, while procedures that could be performed at bedside were 46% lower in 2020. This is consistent with the hypothesis that patients may have deferred care for less severe

Table 2. Diagnoses Associated With Ophthalmology Consults by Frequency

ICD-10 code(s)	Diagnosis	ICD-10 Descriptions	2016	2017	2018	2019	2020	2021	Total
S02, S05	Orbital fracture	Fracture of skull and facial bones; injury of eye and orbit	161	166	116	97	112	188	840
H00, H01, H02, H04, H05, L03.213	Disorders of eyelid and lacrimal system	Hordeolum and chalazion; other inflammation of eyelid; disorders of lacrimal system; disorders of eyelid, lacrimal system and orbit; periorbital cellulitis	35	65	47	47	35	50	279
H33	Retinal detachment and breaks	Retinal detachments and breaks	38	55	33	50	19	29	224
H53	Visual disturbances	Visual disturbances	42	34	39	31	29	38	213
H25, H26, H27, Z96.1, Z98.41, Z98.42	Cataract and intraocular lens	Age-related cataract; other cataract; other disorders of lens; presence of intraocular lens; cataract extraction status right and left eye	56	37	20	33	26	27	199
H35, H36	Other retinal disorders	Other retinal disorders; retinal disorders in diseases classified elsewhere	33	31	46	28	29	26	193
H43	Vitreous disorders	Disorders of vitreous body	35	38	34	32	19	29	187
E10.3, E10.9, E11.3, E11.9	Diabetes	Type 1 and 2 diabetes with and without complications	32	30	23	19	26	24	154
H10, H11, H15	Conjunctival and scleral disorders	Conjunctivitis; other disorders of conjunctiva; disorders of sclera	21	24	21	14	23	28	131
H16, H17, H18	Corneal disorders	Keratitis; corneal scars and opacities; other disorders of cornea	34	23	9	17	11	18	112
H40, H42	Glaucoma	Glaucoma; glaucoma in diseases classified elsewhere	22	16	26	15	11	11	101
H49, H50, H51	Strabismus	Paralytic strabismus; other strabismus; other disorders of binocular movement	11	27	27	14	5	11	95
H52	Refractive error	Disorders of refraction and accommodation	20	19	16	8	14	13	90
H46, H47	Optic nerve disorders	Optic neuritis, other disorders of optic nerve and visual pathways	13	20	12	14	12	18	89
S01.1	Eyelid and adnexal wounds	Open wound of eyelid and periocular area	20	15	13	16	8	13	85
H20, H21	Iritis	Iridocyclitis, other disorders of iris and ciliary body	9	25	10	13	12	10	79
H57	Miscellaneous	Other disorders of eye and adnexa	10	17	14	14	13	10	78
H54	Blindness and low vision	Blindness and low vision	15	16	12	3	6	18	70
B37.7, B37.89, B37.9, B49	Fungemia consultation	Candidal sepsis; other sites of candida; candidiasis unspecified; unspecified mycosis	16	6	7	11	11	12	63
H30, H31	Choroidal disorders	Chorioretinal inflammation; other disorders of choroid	7	12	11	2	3	6	41
B25.8, B25.9	Cytomegalovirus	Other cytomegalovirus; cytomegalovirus	6	8	5	6	7	4	36
H34	Retinal vascular occlusions	Retinal vascular occlusions	9	2	13	4	0	6	34
H44	Globe disorders	Disorders of globe	3	10	3	9	5	4	34
H59, Z98.89	Postoperative issues	Intraoperative and postprocedural complications, disorders of eye and adnexa, not elsewhere classified, other specified postprocedural states	25	3	1	1	0	2	32
G93.2	Intracranial hypertension	Benign intracranial hypertension	4	6	3	4	2	4	23
T15	Foreign body	Foreign body on external eye	3	5	0	7	2	5	22
T26	Burns	Burn and corrosion confined to eye and adnexa	3	0	3	0	5	10	21
H55	Nystagmus	Nystagmus and other irregular eye movements	5	1	4	1	2	3	16
M31.6	Giant cell arteritis	Giant cell arteritis	3	2	2	0	1	3	11
Z04.72	Pediatric nonaccidental trauma	Encounter for examination for alleged child abuse	0	0	1	0	1	0	2
Total			691	713	571	510	449	620	3554

Abbreviations: ICD, International Classification of Diseases.

ICD-10 codes are grouped into diagnosis categories for simplicity.

Table 3. Procedures Associated With Ophthalmology Consultations by Frequency

CPT Code(s)	Procedure	2016	2017	2018	2019	2020	2021	Total
13151, 13152, 12051-12054, 67935, 12011, 12013, 12015, 67966, 67930, 67921, 10120, 68420, 68815, 68700	Canalicular and eyelid laceration repair	20	25	28	27	8	19	127
67108, 67145, 67113, 67228, 67105, 67107, 67039	Retinal tear or detachment repair	15	23	17	29	7	12	103
65286, 65280, 65285, 65105, 65093, 65755, 65730, 65750	Open globe repair	6	8	5	7	5	8	39
67028	Intravitreal injection	3	4	4	3	2	6	22
65220, 65430, 65222, 65205	Extraocular foreign body removal, corneal scraping	4	3	1	3	3	2	16
21390, 67715, 21406, 67500	Orbital fracture repair	2	3	2	3	3	2	15
65778, 67875	Tarsorrhaphy, placement of amniotic membrane graft	3	5	2	0	1	3	14
65800, 65810	Paracentesis of anterior chamber	3	3	1	3	2	1	13
69990	Operating microscope	2	2	1	3	1	1	10
37609	Temporal artery biopsy	2	1	2	0	1	1	7
67700, 10060	Abscess drainage	1	1	0	1	0	0	3
66761	YAG peripheral iridotomy	0	2	0	0	0	0	2
68200	Injection procedures on the conjunctiva	1	0	0	0	0	0	1

Current procedural terminology (CPT) codes are grouped with similar codes for simplicity.

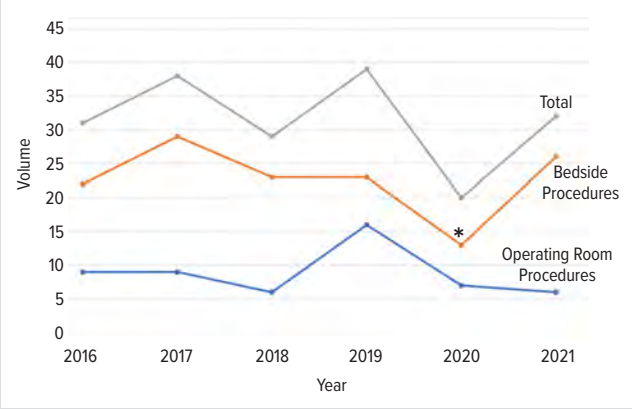
injuries or illnesses in 2020, and/or that patients staying at home engaged in fewer risky activities that might result in injury.

These data provide a useful framework for resource allocation in the event of a future public health emergency—for example, another pandemic requiring strict curfews. Any physician or other health care provider working during the 2020 pandemic will recall the many conversations and questions about reallocation of resources, both human and material: workers were reassigned to less familiar settings, and operating room access was limited to urgent cases in order to preserve ventilators and staff for patients severely ill with COVID-19. A drop in total consultations indicates that an ophthalmology service may be able to operate with slightly decreased staff. This could allow a portion of the service to reassigned to harder hit departments or could simply allow the service to continue to function effectively in the event that some team members become ill or need to quarantine. On the other hand, because the volume of consultations leading to surgery was consistent, operating room access for emergency eye cases would need to be preserved.

Our data revealed an unexpectedly high number of consultations in 2017. We speculate that this is due to the loss of ophthalmology call coverage at another local hospital. Soon thereafter, our center increased urgent outpatient appointment availability, facilitating the return to normal levels in 2018.

In this dataset, the most common reason for consultation was fractures in the orbital region. The most common ocular concern presenting to the ED used to be related to ocular surface disease, but studies have seen an increase in the number of orbital fractures from falls—especially in the elderly—and blunt force trauma.[6]

Figure 2. Volume of Ophthalmology Consultations Associated With Procedures by Year and Patient Location



*Indicates a statistically significant difference ($P<0.05$) between 2020 and other years.

The most common category of CPT codes in this dataset related to the repair of eyelid region lacerations. CPT codes for orbital fracture repair were less frequent, since many orbital fractures can be observed without surgical repair while few lacerations can be. Diagnosis codes for retinal tears and detachments and procedure codes for their repair were among the top 3 most common codes.

While this study was not designed to detect between-year volume differences for specific procedures, there were notably fewer eyelid laceration repairs and retinal detachment repairs in 2020 compared to other study years (7 vs a mean of 19 for both procedure types). Similar drop-offs in the number of eyelid laceration and retinal detachment diagnosis codes were observed. We suspect

this finding is due to decreased trauma among those complying with the "Safer at Home" order (and therefore not engaging in risky activities like driving, sports, and fighting).[15]

Strengths of this study include a large sample size. Additionally, inpatient data were also evaluated in this study, which plays a significant role when considering resource allocation (similar studies have assessed only ED data). While this was a single center study, the University of Wisconsin is one of two level I trauma centers in Wisconsin and a large referral center, so we likely captured many of the emergency eye visits in our region. Limitations include the retrospective nature of data collection. Coding data provided us with a reliable count of ophthalmology consultations; however, it lacks certain details such as mechanism of injury and long-term visual outcomes.

CONCLUSIONS

This study demonstrated a 28% reduction in ophthalmology consultations at a major university hospital in Wisconsin during the COVID-19-related "Safer at Home" order compared to the same period in the years before and after. These findings were similar to those noted in other single center studies[7-9] and are the first to demonstrate a decrease in ophthalmology consultations during the lockdown order in the Midwestern United States. The volume of consultations leading to surgeries performed in the operating room remained consistent, suggesting that patients with severe eye emergencies continued to seek care. Future studies are needed to evaluate differences in mechanism and place of injury during this period. Findings from this study may influence resource allocation and strategic planning during future public health emergencies.

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Incidence and Prognosis of Pneumothorax and Pneumomediastinum in Hospitalized Patients With COVID-19 Pneumonia

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) can cause multisystem complications, with pulmonary involvement associated with the highest mortality. Pneumothorax (PT) and pneumomediastinum (PM) are uncommon complications of COVID-19 that have been reported to occur in the absence of trauma or mechanical ventilation. This study seeks to determine the incidence of these complications in patients with COVID-19 and evaluate clinical characteristics and outcomes.

Methods: We identified 3375 patients admitted to our health system during March 2020 through November 2020 who tested positive for SARS-CoV-2 with a polymerase chain reaction test. Patients were screened for PT or PM and were matched to COVID-19–positive patients without PT and/or PM. Data compared demographics, clinical characteristics, and laboratory values.

Results: Out of a total of 3375 COVID-19 admissions, 33 patients with PT/PM (1%) were compared to 32 matched controls without PT and/or PM. The patients with PT and/or PM demonstrated a significantly higher incidence of concomitant cancer diagnosis than those without PT and/or PM (18% vs 3%, respectively; $P=0.05$). Those with PT and/or PM required significantly more invasive mechanical ventilation than those without PT and/or PM (79% vs 47%; $P<0.01$). Mortality was significantly higher among those patients with PT and/or PM than those without PT/PM (55% vs 25%; $P<0.05$).

Discussion: A significant number of COVID-19 patients with PT and/or PM had a concomitant cancer diagnosis, required supplemental oxygen on admission, and invasive mechanical ventilation during hospitalization. Additionally, the COVID patients with PT and/or PM had significantly higher mortality compared to those without PT and/or PM. However, with all retrospective studies, there are limitations.

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INTRODUCTION

In December 2019, several cases of pneumonia were identified in Wuhan, Hubei Province, China.[1,2] All of these patients were linked to a local seafood market, where live animals were being sold. On January 7, the pathogen for these cases was identified by the Chinese Center of Disease Control and Prevention as a novel coronavirus that belongs to the *Orthocoronavirinae* family and was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease caused by this virus was named coronavirus disease-19 or COVID-19. Novel coronavirus primarily affects the respiratory system but also has demonstrated multisystem dysfunction affecting the heart, kidneys, circulatory system, liver, gastrointestinal tract, and blood cells precipitating hemolysis.[3] Respiratory complications of COVID-19 occur with a wide spectrum ranging from self-limiting mild upper respiratory infection to significant hypoxia secondary to acute respiratory distress syndrome (ARDS).[4]

Barotrauma, which includes pneumothorax (PT) and pneumomediastinum (PM), recently has been observed as an emerging complication in COVID-19 patients. Traumatic pneumothorax results from an injury to the pleura, including iatrogenic cases during medical procedures, whereas primary spontaneous pneumothorax is defined as PT that presents in an otherwise healthy lung without any precipitating external events. Secondary spontaneous pneumothorax is defined as PT that occurs as a complication of underlying lung disease. In prior studies, the reported incidence of PT and/or PM in COVID-19 patients was 1%.[5]

However, in a recent case-control study assessing 601 critically ill intensive care unit (ICU) patients with COVID-19 requiring invasive mechanical ventilation, the reported incidence was up to 12.8%.[6]

There are several proposed mechanisms for the development of PT and PM in patients with COVID-19. Formation of pneumatocele or cysts in the affected lung tissue in the absence of positive pressure ventilation suggests direct parenchymal injury induced by the virus itself and the body's immune system.[7,8] We performed a retrospective cohort study to determine the incidence, risk factors, and outcomes of PT and/or PM in hospitalized patients with COVID-19 over the course of 9 months.

METHODS

Study Design and Population

This was an Institutional Review Board-approved retrospective chart review of patients in the CHI Health Nebraska health system that includes 6 health care facilities serving patients in Nebraska and Iowa. Adult patients age 19 and older admitted during March 2020 through November 2020 who tested positive for COVID-19 via a polymerase chain reaction (PCR) test and who developed spontaneous PT or PM during their inpatient hospital stay were included. This period involved multiple surges of the COVID-19 pandemic prior to vaccine availability. COVID-19–positive patients without spontaneous PT or PM during their inpatient ICU hospitalization served as control patients. Those who had COVID-19–like symptoms but negative COVID-19 PCR testing were excluded, as were patients with PT or PM secondary to trauma without a positive COVID-19 PCR test result.

Data Collection

Electronic medical records (Epic Systems Corp, Verona, Wisconsin) were reviewed retrospectively for demographic, clinical, and laboratory values for all patients who met the inclusion criteria of COVID-19 with PT/PM. These patients were matched by age (±1 year), gender, and recent ICU admission to the admission date with a positive COVID-19 test to a group of patients without PT/PM. If there was more than 1 possible match, the match was chosen at random. One patient could not be age-matched to a COVID-19–positive patient without PT. Admission data included the need for supplemental oxygen and the following commonly performed labs: lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, and procalcitonin. The electronic medical records were further reviewed to assess for comorbidities related to COVID-19 risk and respiratory disease, including body mass index (BMI), hypertension, diabetes, cancer, chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease, and other underlying lung diseases. The course of the disease from symptom onset to PT/PM was measured. Data on vasopressor requirements in the PT/PM cohort were compared with controls. Information on whether a chest tube was placed, initiation of new renal replacement therapy, and initiation of extracorporeal membrane oxygenation (ECMO) during the hospital stay were collected.

The number of days of invasive and noninvasive mechanical ventilation, if applicable, after the PT/PM was recorded. Records were reviewed to determine whether palliative care was consulted during the hospital course. The primary outcomes of this study were mortality and length of hospital stay. Secondary outcomes were vasopressor requirement, laboratory inflammatory markers, need for the palliative care team, and need for invasive mechanical ventilation. All of these variables were compared statistically.

Statistical Analysis

Data were reviewed and entered in SPSS Statistics version 27 (IBM Corp) for statistical analysis. Discrete variables were analyzed by chi-square, and continuous variables were analyzed by *t* test or Mann-Whitney U test. Statistical significance was determined based on a P value ≤ 0.05.

RESULTS

Cohort Demographics

A total of 33 patients with COVID-19 had PT and/or PM out of 3375 COVID-19 admissions, with a calculated incidence of 1%. PT alone was more prevalent than PM alone (61% vs 21%, respectively) and both PT and PM concomitantly (18%). The median age in the study group was 67 years (range 39-98 years) (Table 1). Males were predominantly affected with PT/PM (70%), consistent with the overall COVID-19 pandemic. Twenty-two patients (667%) were White, 5 (15%) were African American, 4 (12%) were Hispanic, 2 (6%) were Asian. Twenty-four patients (73%) had a BMI greater than 25, and 6 patients (18%) had a BMI greater than 35. Among both groups, no statistically significant difference was noted in the comorbidities (BMI, hypertension, diabetes, COPD, asthma, interstitial lung disease, and other underlying lung diseases). PT/PM was more common in patients with a history of cancer (COVID-19 with PT/PM: 18% vs COVID-19 without PT/PM: 3%; $P = 0.05$).

Patient Outcomes

Patients with PT and/or PM required significantly more oxygen support (nasal cannula, high-flow noninvasive ventilation, and invasive mechanical ventilation) on hospital admission compared to patients without PT and/or PM (85% vs 59%, respectively; $P = 0.03$). Similarly, the need for invasive mechanical ventilation was significantly higher among COVID-19 patients with PT/PM than those without PT/PM (79% vs 47%; $P < 0.01$). Among the patients with PT/PM (n = 26), only 10 patients were mechanically ventilated at the time of PT/PM. These patients (n=10) averaged 3.2 (± 4.6) days of mechanical ventilation before PM/PT. No difference ($P > 0.05$) was noted in the laboratory

Table 1. Demographics and Outcomes

Variable	COVID-19 w/ PT/PM (n=33)	COVID-19 w/out PT/PM (n=32)	*P* value
Race			0.09
Asian	1	0	
Hispanic	4	11	
African American	5	7	
White	22	12	
Sex			0.63
Male	23	24	
Female	10	8	
Oxygen requirement (at admission)			0.033
Room air	5	13	
Nasal cannula	13	9	
High-flow nasal cannula	7	1	
NIPPV	3	1	
Mechanical ventilation	5	8	
Comorbidities			
Hypertension	26	25	0.94
Diabetes mellitus	15	18	0.38
Cancer	6	1	0.05
COPD	9	5	0.25
Asthma	4	3	0.72
Interstitial lung disease	1	0	0.32
Other underlying lung disease	5	6	0.69
Hospital course			
Mechanical ventilation	26	15	0.008
Initiation of RRT	4	2	0.41
ECMO	2	1	0.57
Outcome			0.02
Discharge to home	14	24	
Death	18	8	
Palliative care consults	20	8	0.004
Length of hospital stay, days	18.7	15.8	0.75

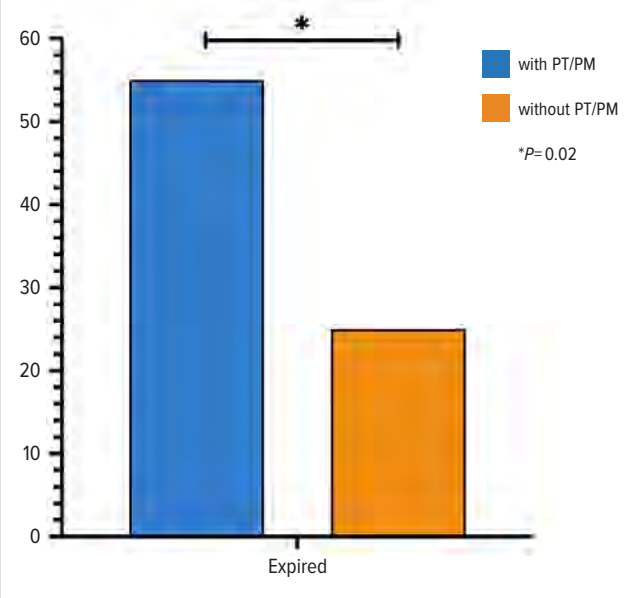
Abbreviations: PT, pneumothorax; PM, pneumomediastinum; NIPPV, noninvasive mechanical ventilation; COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Table 2. Laboratory Tests and Other Parameters

Variable	COVID-19 w/ PT/PM Mean (±SD)	COVID-19 w/out PT/PM Mean (±SD)	*P* value
Admission lab tests			
LDH (U/L)	447.8±13.0	415.6±453.4	>0.05
CRP (mg/L)	144.5±95.3	112.7±91.3	>0.05
Ferritin (ug/L)	1037.6±799.0	1298.3±1868.5	>0.05
Procalcitonin (ng/mL)	1.4±3.2	2.7±8.5	>0.05
Days of symptom onset to PT/PM	11.5±10.3		
Days of vasopressor support	5.9±5.1	3.26±5.8	>0.05

Abbreviations: PT, pneumothorax; PM, pneumomediastinum; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Figure. Significantly Higher Mortality Associated With COVID-19 With Pneumothorax (PT)/Pneumomediastinum (PM) Versus Without PT/PM



tests from admission (LDH, CRP, ferritin, and procalcitonin) between both groups. Mean (±SD) number of days from symptom onset to the development of PT/PM was 11.5 (±10.3). Days of vasopressor requirement averaged approximately 2 days longer for COVID-19 patients with PT/PM (5.9±5.1 days) compared to the group without PT/PM (3.26±5.8 days), which did not reach statistical difference (Table 2). COVID-19–positive patients with PT and/or PM were noted to have significantly higher mortality compared to the control group (55% vs 25%; $P<0.05$). (Figure 1) The palliative care team was consulted more often in PT/PM group than the group PT/PM (61%vs 25%; $P<0.05$). Finally, the length of hospitalization averaged 3 days longer for patients with PT and/or PM (18.7±18.4 days) than the control group (15.9±10.3 days).

DISCUSSION

PT and PM are rare complications of COVID-19, but they are associated with significant morbidity and mortality. To explain this, there are many case series in the literature, but this is one of the few case-control studies that describe the incidence and outcomes of PT and PM in COVID-19 patients with or without use of invasive mechanical ventilation. During the viral replication phase, SARS-CoV-2 causes damage to epithelial cells in the lungs, which produces a surge of cytokines leading to damage of circulatory system and failure of multiple vital organs simultaneously.[9] Damage to this circulation barrier leads to acute respiratory distress syndrome (ARDS) in the lungs that, in turn, alters the static compliance of lungs. The increased pressure gradient across the inflamed alveolar wall can be a cause of increased incidence of spontaneous PT/PM in such a patient population.[10,11]

In addition to SARS-CoV-2, barotrauma is a well-known complication secondary to *pneumocystis jirovecii*, severe acute respiratory syndrome (SARS), and Middle Eastern respiratory syndrome (MERS).[5]

Our results demonstrated that COVID-19–positive patients with PT/PM had higher morbidity and mortality than those who did not develop this complication. Previously published literature demonstrated varying incidence from 1% to as high as 13%.[6,12,13] After analyzing the retrospective charts, we found an incidence of 1% among 3375 COVID-19 admissions. Male sex was predominantly affected, and PT was seen more frequently than PM alone or combined.

Our retrospective review demonstrated more severe hypoxia and increased oxygen demand at the time of admission in COVID-19 patients with PT/PM compared to controls, even before the development of PT/PM. It is plausible that the degree of hypoxia and severity of the disease is associated with the development of barotrauma later. All of the patients were assessed for comorbidities, and among diabetes, hypertension, COPD, reactive airway disease, and interstitial lung disease, only history of cancer was statistically important for the development of PT/PM. Unlike previously published literature, no correlation was found with a history of diabetes or asthma.[4,14]

In our cohort of patients with barotrauma, 21% (7 out of 33) did not require invasive mechanical ventilation during the hospital stay. Nineteen patients (58%) who developed PT/PM required chest tube placement. Percutaneous intervention was used in all except one, who required a surgical thoracostomy tube. Gazivoda et al did not notice changes in mortality with the placement of thoracostomy tube.[4] Similarly, patients with PT/PM required more invasive mechanical ventilation compared to controls, but no difference was seen with initiation of renal replacement therapy or ECMO between both groups. Patients with PT/PM requiring mechanical ventilation (n = 26) were analyzed further, and it was determined that mechanical ventilation preceded development of PT/PM in only 10 patients (38.5%), leaving most of the patient population (61.5%) with no exposure to barotrauma prior to PT/PM development. This supports the idea of direct viral damage to lung tissue causing decreased lung compliance, as described in recent studies.[10,11] The number of days on mechanical ventilation prior to incidence of PT/PM averaged 3.2 (± 4.6) days.

Patients with isolated PM secondary to COVID-19 can be managed conservatively with serial imaging and avoiding high positive end-expiratory pressure (PEEP) during invasive mechanical ventilation.[15,16] In contrast to our results, a large case series from the United Kingdom demonstrated significantly higher mortality in the COVID-19–positive patients with PT/PM compared to COVID-19–positive patients without PT/PM (55% vs 25%).[17] Lung protective mechanisms during invasive ventilation are needed to lower the risk of barotrauma in patients with ARDS.[18]

In the study group of COVID-19 patients with PT/PM, the palliative care team was consulted more often than for the control group, which can reflect the severe overall morbidity secondary to barotrauma in COVID-19–positive patients. No statistical significance was seen in the length of hospital stay and days with vasopressor requirement between the groups, but patients with PT/PM averaged 3 days longer hospitalization and 2 days longer vasopressors, which could be clinically significant.

Limitations

There are limitations to our study. This is a retrospective review of a patient population from the US Midwest. Our institution followed guidelines from the Infectious Disease Society of America for treatment of critically ill COVID-19 patients, but treatment options for COVID-19 were not considered in this study to calculate the incidence and mortality in COVID-19–positive patients with PT and/or PM. Previously published literature demonstrated some benefits with the use of remdesivir and corticosteroids.[4] We did not include patients with isolated subcutaneous emphysema. Excessive positive pressure ventilation in ARDS can be associated with increased occurrence of PT and/or PM, but we did not evaluate the tidal volumes and PEEP for this study.[5] The matching criteria used for this study was retrospective and could suffer from selection bias. We conducted our study prior to the availability of vaccination against COVID-19, which can alter the disease severity in the future and potentially outcomes in patients with barotrauma.

CONCLUSIONS

COVID-19 patients with PT and/or PM required significantly more oxygen on admission, had a higher prevalence of cancer diagnosis, and required more invasive mechanical ventilation support. There was a significantly higher mortality in the patients with PT and/or PM than those without PT and/or PM. Palliative care consultation should be sought sooner when needed.

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Pediatric COVID-19 Hospitalizations During the Omicron Surge

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ABSTRACT

Background: Treatment recommendations for children hospitalized with COVID-19 during the winter 2021-2022 omicron variant surge included remdesivir and dexamethasone for hypoxia and remdesivir for patients at risk of severe illness, including those with comorbidities. The omicron variant caused many otherwise-healthy children without hypoxia to be hospitalized for common viral syndromes like croup. This study aimed to characterize children hospitalized with COVID-19 during the omicron surge and describe their management and clinical trajectory.

Methods: This single-center retrospective study included patients under 19 years old with a COVID-19 discharge diagnosis on the Pediatric Hospital Medicine service in January and February 2022. Hypoxia was defined by sustained oxygen saturation greater than 90%. Primary outcome was return to emergency department or readmission within 14 days. Secondary outcomes were length of stay, multisystem inflammatory syndrome within 6 weeks, and death.

Results: During the study time frame, 111 children were hospitalized with COVID-19, including 35 who had an incidental COVID-19 result. In the remaining 76 patients, the median length of stay was 1.9 days (1.0 – 3.3). Eight patients (11%) returned to the emergency department or were readmitted within 14 days of discharge; 3 of the emergency department visits were related to ongoing COVID-19 infection. Of the 10 patients with croup, 1 received remdesivir due to prolonged illness, and none returned to the emergency department or were readmitted.

Discussion: Most children hospitalized with COVID-19 were young, previously healthy and unvaccinated for COVID-19 due to age-based ineligibility. Hypoxia was the most common indication for use of remdesivir/corticosteroids (25%). Return to the emergency department for ongoing COVID-19 symptoms was uncommon (4%). Patients with croup, a presentation seen more commonly with the omicron variant than previously, appeared to do well without remdesivir.

BACKGROUND

While pediatric patients generally are less severely affected by COVID-19 than adults,[1,1] children with comorbidities, including cardiopulmonary disease, neurologic impairment, obesity, and immunocompromised state may develop more severe illness.[2] The National Institutes of Health treatment guidelines for hospitalized children with acute COVID-19 infection have continued to evolve. At the time of this study, dexamethasone and remdesivir were recommended for hypoxia; remdesivir also was recommended for patients known to be at risk of severe illness.[3]The omicron variant has unique considerations for pediatric patients. First, it preferentially targets the upper airway, thus predisposing otherwise healthy children to illness given the smaller and softer pediatric upper airway.[4] Second, the omicron variant is more transmissible than prior variants, and vaccination against COVID-19 was only available to children older than 5 years during the omicron peak, both of which likely contributed to higher pediatric rates of infection and, proportionally, hospitalization.[5,6]

Literature is emerging regarding the connection between COVID-19 and common pediatric viral syndromes, such as croup and bronchiolitis. Patients with these syndromes may present with hypoxia, and their management typically does not vary by causative virus.[7,8] There has been an increase in croup diagnoses associated with the omicron variant, and prior studies demonstrate good clin-

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ical outcomes with standard croup treatment.[9] Early pandemic isolation resulted in fewer bronchiolitis hospitalizations than in prior years, but less is known about lower respiratory tract illness such as bronchiolitis during the omicron period, and decision-making around COVID-specific treatment in these patients remains variable.[10]

This study aimed to characterize pediatric patients hospitalized with COVID-19 during the winter 2022 omicron peak and describe their management and clinical trajectory.

METHODS

Setting and Population

This was a retrospective study of patients at Children's Wisconsin, an academic freestanding children's hospital in southeastern Wisconsin. COVID-19 nasopharyngeal swabs were performed on all patients at the time of hospitalization during the study time frame. Patients less than 19 years old were included if they received care on the Pediatric Hospital Medicine service in January and February 2022 and had a COVID-19 discharge diagnosis. This included patients who were transferred to or from the pediatric intensive care unit (PICU). To focus on the population cared for by pediatric hospitalists, patients were excluded if they were exclusively cared for in the PICU or emergency department (ED). The study time frame was chosen based on omicron strain predominance from local health department data. If a patient had multiple encounters with a COVID-19 discharge diagnosis during the study time frame, only the first encounter was included in the study.

Variables and Definitions

Patient characteristics collected included sex, race, ethnicity, age, comorbidities (prematurity, heart disease, chronic lung disease, immunodeficiency, neurodevelopmental disorder, other medical complexity including gastrostomy tube), reasons for hospitalization, interventions (including oxygen support and COVID-specific treatments), and clinical outcomes (below). A COVID-19 positive test was defined as incidental if this was specifically noted in the electronic medical record or if the patient lacked symptoms based on the Centers for Disease Control and Prevention definition. Hypoxia was defined by sustained oxygen saturation greater than 90% for more than 4 hours and/or needing nasal cannula or high flow nasal cannula (HFNC) with fraction of inspired oxygen (FiO_2) greater than 21%.

Outcomes

The primary outcome was return to the ED or readmission within 14 days. Secondary outcomes were length of stay (LOS), multisystem inflammatory syndrome (MIS-C) within 6 weeks, and death.

Statistics

Deidentified patient information was stored in Redcap, a secure database. Categorical variables are reported as n (%), and con-

Figure. Age Distribution of Patients

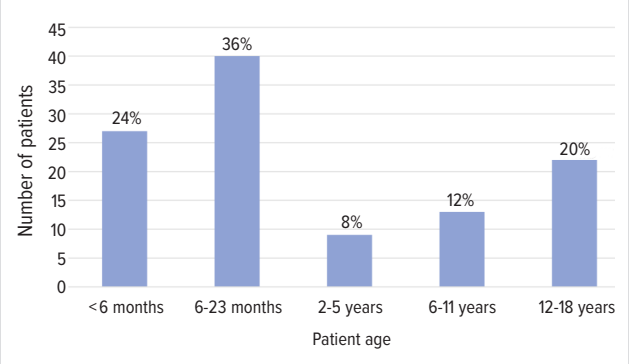

Table 1. Characteristics of Children Hospitalized With Nonincidental COVID-19, N = 76

Age, months (median, IQR)	12.2 (4.7 – 40.0)
Sex, male (n, %)	46 (61%)
Race[a] (n, %)	
White	50 (68%)
African American	19 (26%)
Asian	3 (4%)
Multirace	1 (1%)
Hispanic/Latino[b] (n, %)	12 (16%)
Comorbidities (n, %)	
Previously healthy	47 (62%)
At least 1 comorbidity	29 (38%)
Neurodevelopmental disorder	14 (18)%
Prematurity	11 (14%)
Asthma/bronchopulmonary dysplasia	5 (7%)
Heart disease	3 (4%)
Obesity	1 (1%)
Other complexity[c]	10 (13%)
Additional viral testing (n, %)	45 (59%)
Influenza co-infection[d]	4 (9%)
Other viral co-infection[d]	3 (7%)
Illness severity (n, %)	
Initial pediatric intensive care unit admission	9 (12%)
Hypoxia	19 (25%)
High flow nasal canula	12 (16%)
COVID-specific treatment (n, %)	
Remdesivir	25 (33%)
Corticosteroids	36 (47%)
Clinical course	
Length of stay, days (median, IQR)	1.9 (1.0 – 3.3)
Returned to ED within 14 days of discharge (n, %)	8 (11%)
Returned to ED within 14 days due to illness caused by by COVID-19[e] (n, %)	3 (4%)
Readmitted within 14 days of discharge (n, %)	2 (3%)
Multisystem inflammatory syndrome (n, %)	0 (0%)
Death (n, %)	2 (3%)

Abbreviation: ED, emergency department.
[a]Race available for 73 patients.
[b]Ethnicity available for 74 patients.
[c]Includes immunodeficiency, diabetes, gastrostomy tube, ventriculoperitoneal shunt.
[d]Of patients who had additional viral testing.
[e]None of these patients required readmission.

tinuous variables are reported as median (IQR). Data were analyzed using SPSS version 28 (Chicago, Illinois).

Ethical Considerations

The Children's Wisconsin institutional review board deemed the study to be nonhuman subjects research, and patient consent was not required.

RESULTS

This study included 111 hospitalized children with a median age of 17.2 months (6.4-124.7) (Figure 1). Thirty-five (32%) patients were found to have incidental COVID-19 and were hospitalized for other reasons, including ingestion (23%), behavioral health emergency (20%), and skin/soft tissue infection (14%). Further information on the 76 patients with nonincidental COVID-19 is provided below.

Table 2. Children Who Returned to the Emergency Department Within 14 Days of Discharge for Ongoing COVID-19 Illness

	Patient 1	Patient 2	Patient 3
Demographics	10-year-old male with congenital heart disease, chronic lung disease on home oxygen, baclofen pump, gastrostomy tube	1-month-old previously healthy male	5-month-old previously healthy male
Hospitalization diagnoses	COVID-19 pneumonia, dehydration	Febrile neonate, dehydration	Bronchiolitis
Illness severity	Hypoxia requiring HFNC with FiO_2 60%	No hypoxia or respiratory support	No hypoxia or respiratory support
COVID-specific treatment	5 days remdesivir, 6 days dexamethasone	Supportive	Supportive
Clinical course	LOS 5.99 days; required PICU transfer; returned to ED for irritability, new fever; MIS-C labs negative; not readmitted	LOS 1.52 days; returned to ED for ongoing diarrhea, did not require fluid resuscitation; not readmitted	LOS 3.16 days; returned to ED for fussiness, increased work of breathing; did not require respiratory support; not readmitted

Abbreviations: HFNC, high flow nasal canula; FiO_2, fraction of inspired oxygen; LOS, length of stay; PICU, pediatric intensive care unit; ED, emergency department.; MIS-C, multisystem inflammatory syndrome.

Presentation

Sixty-two percent of patients with nonincidental COVID-19 were previously healthy (Table 1). Only 3% of patients were fully vaccinated against COVID-19, largely due to ineligibility with age less than 5 years (79%). Of the 59% of patients who had additional viral testing, 16% were found to have an additional virus. Of these 7 patients with viral co-infection, 4 had influenza and 1 each had respiratory syncytial virus, parainfluenza, and rhinovirus/enterovirus. The most common nonincidental reasons for hospitalization were dehydration (36%), bronchiolitis (24%), COVID-19 pneumonia (17%), croup (13%), and febrile neonate (12%). Twenty-five percent of patients were hypoxic. The rate of hypoxia in patients with a viral co-infection was not significantly different compared to that in patients who had additional viral testing and were negative for a viral co-infection (57% vs 39%, $P = 0.43$).

Management

All hypoxic patients received corticosteroids and remdesivir treatment. Twenty percent of patients were not hypoxic but received corticosteroids for asthma or croup. Other than hypoxia, reasons for prescribing remdesivir included severity of illness (12%) and complex medical history (8%). Median treatment durations were 3.0 days (2.5–5.0) for remdesivir and 2.0 days (1.0–5.3) for corticosteroids. One patient receiving remdesivir developed transaminitis. No patients received monoclonal antibodies.

Disease Course

The median LOS was 1.9 days (1.0–3.3). Five patients (7%) required transfer to the PICU; 11% of patients returned to the ED within 14 days of discharge, and 2.6% were readmitted. Three of the ED visits were related to ongoing COVID-19 infection (Table 2). Two patients died. The first was a 7-month-old infant with methicillin-resistant *Staphylococcus aureus* septic shock and unclear role of COVID-19 infection. The second was a 5-month-old infant hospitalized for pulmonary hemorrhage who died of nonaccidental trauma 10 days after hospital discharge.

Patients With Croup

Ten patients with a median age of 9.9 months (8.1–16.9) were hospitalized for croup, two of whom had an underlying neurodevelopmental comorbidity. None of them had viral co-infection, hypoxia, or required PICU admission or HFNC. All were treated with dexamethasone, and 1 patient received remdesivir due to prolonged illness course. Median LOS was 1.0 day (0.6–1.2). No patients returned to the ED or were hospitalized within 14 days, developed MIS-C, or died.

DISCUSSION

Presentation

The majority of patients hospitalized for COVID-19-related symptoms were young, previously healthy, and recovered without corticosteroids or remdesivir. Most patients were ineligible for the COVID-19 vaccine due to age at the time of the study, although vaccines are now available to younger children.

Management

At the time of our study, COVID-19 treatment guidelines recommended dexamethasone and remdesivir for patients with hypoxia, as well as remdesivir for patients known to be at risk of severe illness, including those with comorbidities.[2] Our local management guidelines reflected these recommendations and allowed case-by-

case decision-making around the use of remdesivir in nonhypoxic patients. In our study, nearly two-thirds of patients were previously healthy and the majority did not require respiratory support, compared to higher rates of hospitalized patients with comorbidities and rates of respiratory support earlier in the pandemic.[1] As a result, sustained hypoxia was the primary reason for remdesivir treatment. Patients rarely received treatment due to complex medical history or high level of respiratory support alone. Similar to prior studies, only 1 of the 30 patients who received remdesivir in our study developed transaminitis.[2]

Clinical Course

We found a readmission rate of 2.6%, which is similar to both the overall readmission rate of 4.2% during the same time frame for all diagnoses at our institution and the 2.1% COVID-19-associated readmission rate in a large retrospective administrative database analysis.[1] None of the readmissions at our institution were related to ongoing COVID-19 infection, which may reflect a lower severity of the omicron variant.[5] Similar to other reports, mortality was low in our study, with 1 of 2 patient deaths potentially related to COVID-19.[1] None of our patients developed MIS-C, which may reflect our small sample size. Patients with croup appeared to have good clinical outcomes with standard corticosteroid treatment, which is consistent with prior studies.[4,9]

Limitations

This single-site, retrospective study had several limitations including small sample size and potential selection bias as not all hospitalized patients with COVID-19 were cared for on the hospitalist service. Additionally, variant testing was not performed on our patients, so presence of the omicron variant was inferred based on local health department variant reporting. Future studies should include a larger sample size, consider variant testing on all patients to assess variant-specific rates of rare outcomes such as MIS-C, and investigate the rate of bacterial superinfection and antibiotic prescribing in patients with COVID-19.

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Efficacy of a Digital Intervention to Increase Annual Wellness Visit Scheduling Amid COVID-19 Backlog

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ABSTRACT

Background: The Medicare Annual Wellness Visit is a preventive visit that is largely underutilized, a problem further compounded by the COVID-19 pandemic.

Methods: We implemented a digital outreach intervention to improve Annual Wellness Visit scheduling in our health system. Using a bulk outreach functionality in the electronic medical record, we sent a message to patients due for an Annual Wellness Visit and analyzed the efficacy of this message on scheduling rates while also assessing its impact by race.

Results: Patients who read the message were 40% more likely to schedule an Annual Wellness Visit (OR 1.42; 95% CI, 1.34 – 1.50) compared to those who did not read the message.

Discussion: After this intervention, Annual Wellness Visit scheduling rates increased by 50% for White patients and 325% for Black patients versus prepandemic rates in 2019.

BACKGROUND

The Medicare Annual Wellness Visit (AWV) was created in 2011 as part of the Patient Protection and Affordable Care Act.[1] It provides an opportunity for primary care clinicians to create personalized care plans, assess risk factors for illness, update problem and medication lists, and accurately document chronic health conditions. AWVs are associated with better clinical quality outcomes and lower health care spending,[2] making it an important part of closing gaps in care. Medicare beneficiaries incur no out-of-pocket expense for AWVs.

In 2011, the national AWV completion rate was 7.5%[3] and has climbed slowly: in 2017, it was 24%.[4] In 2019, the AWV completion rate in our health system was 30%. In 2020, the health system halted nonessential care due to COVID-19; patients could not be seen for AWVs, creating a backlog. As clinics reopened, we needed to mitigate this backlog. Using a digital bulk outreach (DBO) tool, we sent batches of electronic messages to thousands of patients and evaluated the impact of this tool on the AWV scheduling rate.

METHODS

Prior to implementing DBO, standard-of-care outreach at our organization included calling or sending letters to patients reminding them to schedule AWVs. From August 30 through September 27, 2020, we sent messages to the electronic medical record (EMR) inbox of approximately 3000 patients per week – a 4-fold increase over phone outreach, historically, during the same time frame. The message included an explanation of the AWV, its benefits, and directions on how to schedule an appointment. Messages were sent to Medicare Advantage and Fee-for-Service patients with a primary care clinician in our health system, an activated MyChart account (Epic Systems Corporation, Verona, Wisconsin), and who were due for an AWV. Patients without an activated MyChart account continued to receive standard-of-care outreach.

Our analysis of the effectiveness of DBO was limited to those patients who received it: as our immediate and primary concern was addressing the backlog of AWVs due to clinical disruptions caused by COVID-19, we messaged all eligible patients via DBO. As a result, we had no control group of patients who did not receive it. We instead compared AWV scheduling rates (dependent variable) in patients who read the message vs those who did not (independent variable). We chose this comparison

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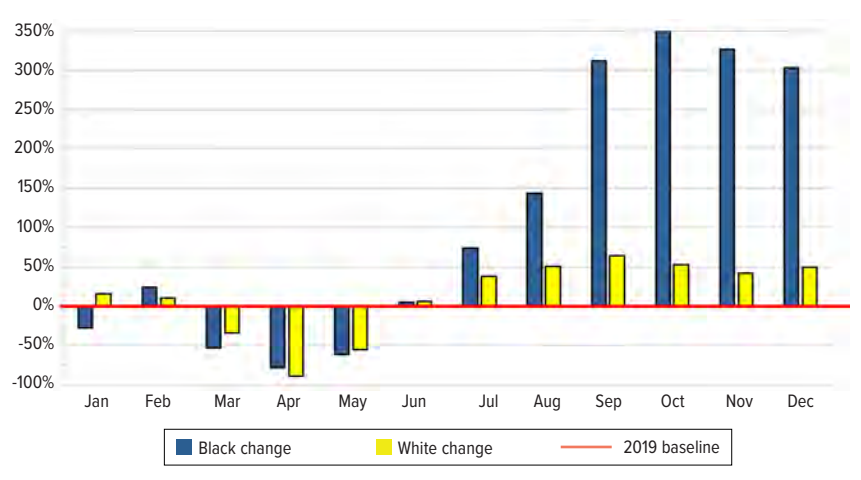
for these reasons: (1) we felt that those who received DBO but who did not open it were conceptually similar to a control group who did not receive the DBO, (2) it was not possible to use a historical control from the months immediately preceding the DBO as they were affected by COVID-19.

To balance our cohort and maximize sample size for matching, we used inverse probability of treatment weighting and evaluated the treatment effect of DBO using a multivariate logistic regression. Our model controlled for age, sex, race, comorbidities (Charlson Comorbidity Index), socioeconomic status (Area Deprivation Index[5,6]), and median income. As we used DBO to overcome the backlog of AWVs, we wanted to examine its effect by race given the evidence of disparities in AWV utilization.[7] To compare the relative increase in AWV scheduling by race, we calculated the unadjusted scheduling rates from September through December, 2020, to the same months in 2019 – the best available baseline. Rates were calculated by dividing the total number of eligible patients, per month, by the number of patients scheduling an AWV.

Figure. Percent Change in Annual Wellness Visit Scheduling Rate for Eligible Patients by Race in 2020 vs Same Months in 2019



RESULTS

Our analysis included 18 106 patients; 75% read the message (Table). People who read the message had fewer comorbidities and a higher median income. Of Black patients who received the message, 51% (n = 663) read it compared to 77% (n = 12 523) of White patients. After adjustment, we found that people who read the message were 40% more likely to schedule an AWV (OR 1.42; 95% CI, 1.34 – 1.50) compared to those who did not read the message. We found a 50% increase in scheduling in 2020 for White patients and a 325% increase for Black patients (Figure).

Table. Summary Statistics

	Total n = 18 106	Read n = 13 616	Unread n = 4490	*P* value
Annual Wellness Visit, n (%)				
Not scheduled	11 400 (63)	8135 (60)	3265 (73)	< 0.001
Scheduled	6706 (37)	5481 (40)	1225 (27)	
Age, median (IQR)	71 (67 – 77)	71 (67 – 77)	72 (66 – 79)	< 0.001
Sex, n (%)				
Female	10 364 (57)	7711 (57)	2653 (59)	0.004
Male	7742 (43)	5905 (43)	1837 (41)	
Race, n (%)				
Asian	202 (1.1)	135 (1.0)	67 (1.5)	< 0.001
Black	1292 (7.1)	663 (4.9)	629 (14)	
Hispanic	259 (1.4)	170 (1.2)	89 (2.0)	
Other	186 (1.0)	125 (0.9)	61 (1.4)	
White	16 167 (89)	12 523 (92)	3644 (81)	
Charlson Comorbidity Index, n (%)				
Mild	15 104 (83)	11 632 (85)	3472 (77)	< 0.001
Moderate	2458 (14)	1636 (12)	822 (18)	
Severe	544 (3.0)	348 (2.6)	196 (4.4)	
Deprivation Index, median (IQR)	0.25 (0.21 – 0.30)	0.24 (0.20 – 0.30)	0.26 (0.22 – 0.33)	< 0.001
Median income quartile,[a] n (%)				
Poorest quartile	4222 (23)	2932 (22)	1290 (29)	< 0.001
Second quartile	4278 (24)	3172 (23)	1106 (25)	
Third quartile	4429 (24)	3406 (25)	1023 (23)	
Wealthiest quartile	5169 (29)	4102 (30)	1067 (24)	

[a]Does not add to column total due to missing data.

DISCUSSION

DBO is an efficient way to contact patients compared to our usual labor-intensive process of mailing letters and making phone calls. After controlling for baseline differences, we noted that those who read the DBO message were 40% more likely to schedule their AWV versus those who did not read the message. DBO has wide-ranging applicability beyond AWVs. We have used it for other prevention-oriented care, such as vaccinations, colonoscopy, and mammography. While read rates of the message were higher than expected, improved strategies are needed to increase the probability of acting on the message. We incorporated several behavioral economics nudges,[8] such as positive framing, into our message but were not able to study the effects of these concepts individually. Other desired improvements include enabling patients to self-schedule directly from the message – a feature added to a subsequent iteration of this intervention in 2021.

Our study must be viewed with several limitations in mind. It is not a true experiment; thus, there is the possibility that our results are affected by unmeasured confounders and selection bias. We do believe that the results of this analysis provide preliminary,

yet compelling, evidence to prompt further rigorous studies incorporating randomization and a true control group to further understand this important topic.

Digital tools may help or further exacerbate structural racial disparities in society, which worsened during the COVID-19 pandemic.[9] We noted a large racial disparity in the rates of reading DBO messages. On the other hand, we also noted that rates of scheduling for Black patients increased far more than for White patients, suggesting that ultimately DBO did not worsen existing disparities. With increasing reliance on technology, we must further understand how to engage with nondigitally enabled patients to ensure that quality improvement efforts do not contribute to existing inequality. Our report shows that DBO is an efficient and effective tool for AWV scheduling that does not worsen disparities of care.

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Early Cutaneous Manifestations of COVID-19: A Systematic Review and Public Health Implications

Abhinav Grover, MBBS, MD, MS; Franchesca Choi, RPh, MD; Sheng-Pei Wang, MD

ABSTRACT

Introduction: Cutaneous manifestations before other symptoms have great potential for early COVID-19 diagnosis to prevent surge.

Methods: We conducted a search of PubMed and Embase databases through April 11, 2021 to include 39 studies reporting skin manifestations occurring prior to any other COVID-19 symptoms in laboratory-confirmed cases.

Results: Ninety-seven patients were included. Urticarial (24.7%) and maculopapular (22.7%) lesions were most common, followed by pernio (17.5%), vesicular (14.4%), papulosquamous (8.2%), and purpuric (5.1%) lesions. Cutaneous to systemic symptom latency ranged from 2 to 20 days in cases that reported it (26%), while skin lesions were the only presentation in 23 cases (23.7%). Skin lesions were the only COVID-19 manifestation in 58.8% of pernio, 40% of vesicular, 16.6% of urticarial, 18.2% of maculopapular, and 12.5% of papulosquamous presymptomatic cases. Although sample size is limited, all purpuric cases developed other symptom(s) later.

Conclusions: Pernio and purpuric lesions have been well-associated with COVID-19, but papulosquamous, vesicular, mild maculopapular, and urticarial lesions can easily be dismissed as unrelated to COVID-19. Pernio lesions are thought to be related to strong immune response and low contagiousness, while purpuric and vesicular cases are speculated to be related to higher SARS-CoV2 viral load, severity, and contagiousness. All rashes, even without other symptoms, should necessitate high level of suspicion for isolation or contact tracing.

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INTRODUCTION

Coronavirus 2019 (COVID-19) vaccination has led to a decrease in cases. However, with the rise of variants of concern and the removal of mask mandates, recent reports have shown increased cases across different countries and concerns about future surges. COVID-19 can have a presymptomatic incubation up to 14 days before common symptoms manifest. Asymptomatic or presymptomatic cases can transmit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Postvaccination breakthrough cases are possible and could present with longer incubation period and atypical nonrespiratory symptoms. Although fully vaccinated people have less severe symptoms, recent reports show that they are equally capable of spreading SARS-CoV-2.[1,2] Early detection of potential asymptomatic or presymptomatic cases is an important preemptive measure to prevent future surges in this postvaccination variant strain era.

It is now known that SARS-CoV2 has high affinity for angiotensin II converting enzyme (ACE2) receptors. ACE2 receptors are found in various tissues, thereby explaining the wide spectrum of systemic symptoms of COVID-19.[3] High ACE2 receptor expression has been found in keratinocytes, explaining the myriad COVID-19 skin lesions.[4] Cutaneous signs can occur before, concurrent, or after other symptoms.[5,6] Many skin complaints are easily dismissed or overlooked; however, cutaneous features that manifest before any other symptoms have great potential for early COVID-19 diagnosis. Therefore, a systematic review of the litera-

ture was conducted to collate and analyze cutaneous manifestations in laboratory-confirmed COVID-19 patients who presented initially or only with a skin lesion.

METHODS

A primary literature search was conducted using PubMed and Embase on April 1, 2023. Three authors independently screened PubMed with the search terms "covid OR SARS-COV-2" AND "skin OR cutaneous OR dermatology" and Embase with the search terms "coronavirus disease 2019" AND "skin disease." PubMed Medical Subject Headings (MeSH) controlled vocabulary; Embase Emtree terms and text words all were utilized to develop the search terms.

Three reviewers independently screened all article titles and abstracts to include cohort studies, case series, cross-sectional studies, or case reports published in English and Chinese on skin manifestations that occurred prior to any other COVID-19 symptoms in polymerase chain reaction (PCR) laboratory-confirmed cases. Articles that described skin lesions concurrent with other symptom(s) were excluded. Subsequently identified studies were subjected to full-text review. Bias risk and methodological quality were assessed. Rationales for exclusion and article appraisals were recorded at every stage. References of included and excluded studies were reviewed for potential studies not identified through initial search strategy.

Included studies were summarized using a data extraction form. Skin lesions were classified into the categories maculopapular, papulosquamous, pernio, purpuric, urticarial, vesicular, and others, according to a modification of Freeman et al's and Galvan-Casas et al's studies.[7,8] Cutaneous signs are also systemic COVID-19 manifestations; however, for simplicity, in this manuscript, we use the term "presymptomatic" to denote cases that presented initially or only with a skin lesion.

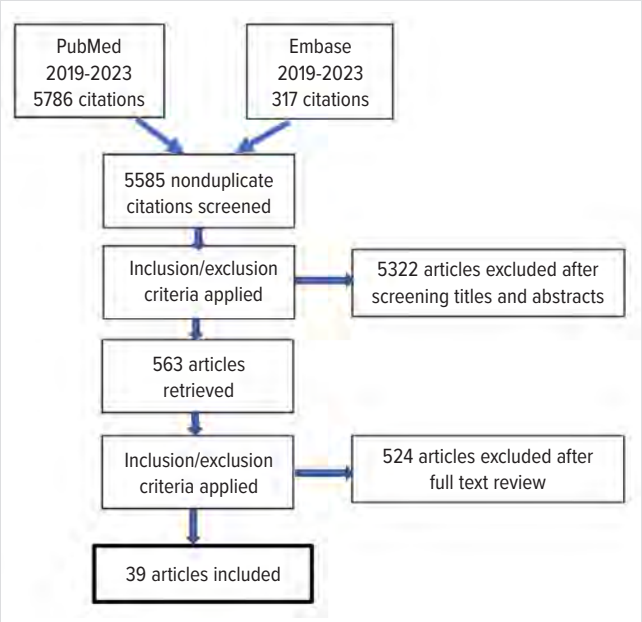
RESULTS

Through full-text screening of 5885 nonduplicate articles, 39 studies including 27 case reports and 12 case series and totaling to 97 patients (6 months to 78 years old; 25 male, 17 female, 55 unknown) were included in this review (Figure).

Cutaneous to systemic symptom latency ranged from 2 to 20 days in 25 patients (2 days in 12 patients, 3-6 days in 3 patients, 7 days in 5 patients, 8-14 days in 4 patients, 20 days in 1 patient, and nondocumented in 49 patients. Skin lesions were the only presentation (no other symptoms) in 23 patients (23.7%) (see Table). COVID-19 symptoms that occurred after cutaneous lesions included anosmia, cough, dyspnea, fever, headache, myalgia, and odynophagia. Skin lesions lasted from 1 to 24 days in cases that reported duration. No cases of mortality were reported; however, mortality/recovery status were unavailable for 28 cases.

Twenty-two cases (22.7%) presented with maculopapular lesions, 17 (17.5%) with pernio, 24 (24.7%) with urticarial, 14 (14.4%) with vesicular, 8 (8.2%) with papulosquamous, and 5 (5.1%) with purpuric lesions. Cases are summarized in subsections below. Noncategorizable lesions were grouped under "Others."

Figure 1. Flow Diagram for the Systematic Review of Cutaneous COVID-19 Lesions That Occurred Prior to Other Symptoms



Most of the 14 hospitalized cases (14.4%) were the eldest cases among each lesion category or patients with preexisting chronic conditions, except for a 6-year-old boy with severe cheilitis along erythema multiforme, 22-year-old man with thrombocytopenia along petechial purpura, and 50-year-old man with recurrent periorbital dyschromia along dyspnea. No hospitalization cases were noted among the pernio and papulosquamous lesion categories, while hospitalization was noted highest in the purpuric group. Twenty-eight cases (28.9%, age 10 months–61 years old) remained as outpatient, and 55 (56.7%) had undocumented hospitalization status (Table). Skin was the only COVID-19 manifestation in 58.8% of pernio, 40% of vesicular, 16.6% of urticarial, 18.2% of maculopapular, and 12.5% of papulosquamous presymptomatic cases. Although sample size is limited, all purpuric cases developed other symptom(s) later.

Maculopapular

No predilection of any body area was noted in the 22 patients (age 10 months–74 years old) with maculopapular presymptomatic lesions.

Papulosquamous

Among the 8 papulosquamous cases (age 26-38 years old), there was 1 case of pityriasis rosea (PR). There was no predilection for any body part, but face was spared in all 8 cases.

Pernio

Pernio lesions were noted in 17 cases (age 14-59 years old; 14

acral, 1 nonacral – auricle, 2 unknown). In acral lesions, the feet were 4 times more likely to be involved than the fingers. The auricle pernio[9] was an incidental case of positive PCR found via contact tracing. It is unclear whether auricle pernio occurred during active COVID-19 or as a long-term sequela.

Purpuric

Four cases presented with reticular purpura on the limbs. One 22-year-old previously healthy male had petechial, purpuric lesions in his bilateral lower extremities and dorsal hands and was hospitalized due to thrombocytopenia and buccal bleeding 2 days after. No trunk involvement was noted in all 3 cases.[10]

Urticarial

Twenty-four urticarial cases (age 6 months–61 years old) did not reveal predilection of any body area. Two cases developed angioedema,[11,12] with 1 progressing to odynophagia.[11] A 61-year- old male showed purpuric evolution from initial urticarial lesions.[13]

Vesicular

Among the 14 vesicular cases (age 19-65 years old), 3 involved diffuse papulovesicular lesions that had a predilection for the trunk. One reported hemorrhagic crusted vesicles in a dermatomal distribution[14] that was later clinically diagnosed as herpes zoster. Four cases clinically ruled out herpes zoster. None of the cases performed a Tzanck test nor herpes PCR.

DISCUSSION

In 1966, microbiologist Mims highlighted an existing lack of knowledge about viral rashes. He speculated blood vessel dilation, vascular injury, extravascular spread to cutaneous layers, hypersensitivity, and direct viral damage as possible pathomechanisms.[15] In 2005, French dermatologists Lipsker and Saurat broadly classified viral eruptions into classic viral (direct cytopathogenic viral interactions with skin) or paraviral (viral-triggered immune reactions). They noted that classic viral eruptions (eg, morbilliform measles rash) usually correlate to active viremia and contagiousness, while paraviral eruptions (eg, parvovirus B19 reticular lacy rash) usually indicate immune response against the virus and lower contagiousness.[16] The concept of linking viral rash pathomechanism to disease contagiousness is intriguing—especially during this COVID-19 pandemic—but not always clear-cut, ie, if immune reaction was partial and the virus remains latent in the body, contagiousness cannot be determined confidently. With COVID-19, more studies are needed to determine relationship of viremia load curve, contagiousness, and skin manifestations. Cycle threshold (Ct) numbers can be reported in future studies for contagiousness determination.

Previous publications analyzing laboratory-confirmed COVID-19 skin manifestations (occurring prior, concurrent, and/or after) showed that maculopapular (35.7%-52.1%) were the most frequent lesion type[7,8] Galvan-Casas et al's study (December 2019–April 8, 2020) showed that other common lesion types in laboratory-confirmed patients included urticarial (20.9%) and pernio (12.4%),[8] while Freeman et al's study (April 8, 2020–May 17, 2020) revealed pernio (18.1%) and urticarial (15.8%) lesions.[7] In our review (December 2019-April 2023) that solely studied skin manifestations occurring prior to any other symptom(s), urticarial (24.7%) and maculopapular (22.7%) lesions were the most reported, followed by pernio lesions (17.5%). These differences could be related to overreporting of pernio lesions due to the chilblain debate that started around April 2020.[7,17] Moreover, patients are likely to dismiss or forget skin lesions during history intake. It is also possible that many cases with only cutaneous signs have gone undiagnosed. It is pertinent to note that alopecia and pernio are the most frequent long-term cutaneous manifestations of COVID-19 in contrast to the early cutaneous signs of COVID-19, which may be due to persistent inflammation and stress.[6,18] Our findings also are limited by our small sample size. In the next subsections, we discuss the various lesion categories in relevance to clinical significance, possible pathomechanisms and public health implications.

Maculopapular

Macules are thought to be secondary to virally induced lasting local dilation of subpapillary dermal vessels. As dilation progresses to edema and cell infiltration, papules then result. All individual maculopapular case reports included in our review were pruritic, while included case series were reportedly 61% to 91% pruritic.[7,8] It is possible that nonpruritic maculopapular lesions are reflected less in the literature since patients are less concerned with seeking medical help if the rash is nonitchy.

Papulosquamous

From dermal vessels, viruses can affect the dermis then epidermis, leading to epidermal changes, such as scales and vesicles.[15] Papulosquamous lesions, such as PR, can be triggered by various viruses, especially Herpesviridae.[19,20] This raises the question on whether PR was triggered by COVID-19 infection or due to co-infection with other viruses. Abadías-Granado et al's study suggested that SARS-CoV-2 could cause reactivation of human herpesvirus 6 (HHV-6), leading to PR; however, authors also highlighted the need for more investigation due to limited sample size and serology limitations.[21]

Vesicular

Similarly, it is interesting to investigate whether vesicles were caused by COVID-19 or by other etiologies, such as varicella, herpes zoster, or pseudovesicular Grover disease.[22] Our review included 1 clinically diagnosed herpes zoster case in a male patient with a positive COVID-19 PCR.[14] It has been speculated that COVID-19-related lymphopenia could predispose to herpesvirus recurrence.[23,24] Some authors have suggested that herpes zoster (reflecting immunosuppression) in an otherwise immunocompetent patient should raise suspicion for subclinical COVID-19 coinfection, especially if lesions are present in various stages of

development at the same time.[24,25] Histologically, Mahé et al reported that SARS-CoV-2 vesicles appear with acantholysis and dyskeratosis with unilocular intraepidermal suprabasal vesicle, distinct from the large multinucleated cells and ballooning degeneration in the basal layer seen in herpes zoster.[26]

Vesicular viral lesions (eg, varicella, herpes zoster) are generally thought to be contagious19 through airborne respiratory droplets and vesicular fluid contact 1 to 2 days prior to the lesions up until the vesicles are crusted.[27] The same questions exist with COVID-19 vesicles. Fernandez-Nieto et al found negative vesicular PCR in 2 patients with nasopharyngeal PCR-confirmed COVID-19; however, more studies are needed.[25] Apart from the systemic vessel-dermis-epidermis route, concerns have been raised on whether SARS-CoV2 can enter through the skin, cause epidermal changes (such as vesicles or scales), then spread into the systemic circulation;[28] however, no studies have been done in this area.

Urticarial

Vesicles and urticarial lesions also can result from hypersensitivity reactions to viral components.[15] Urticaria can be easily overseen and disregarded as idiopathic;[12] however, infections are known triggers for acute and chronic urticaria.[29] Urticaria results from a combination of Types I-IV hypersensitivity reactions.[30] Increased bradykinin production due to activation of contact coagulation cascade and decreased bradykinin breakdown due to viral-ACE2 binding also are implicated in COVID-19-related urticaria and dry cough.[31-33] Coagulation factors also are thought to activate mast cell release of histamine.[34] As with all urticaria, angioedema development must be cautioned.

Pernio

Several scientific groups hypothesize that pernio is due to high production of type I interferon related to innate immune response against COVID-19.[19,35] In fact, in his 1966 review, Mims noted that interferons are likely related to recovery from primary virus infection, while antibodies confer resistance to reinfection.[15] Immune inflammation could then lead to microthromboses.[28] Microangiopathy reflecting COVID-19-related endothelitis[17] has been noted in nailfold capillaroscopy of fingers and toes of COVID-19 patients, even when lesions are visible only in the toes,[36] reflecting a systemic process. The nonacral auricle pernio case included in our review[9] also supports the systemic microcirculatory alterations that underlie pernio development in COVID-19.

Pernio is thought to be associated with younger patients and milder cases.[7,37] Our review reflects the same – presymptomatic pernio cases were found in the age range 22 to 59 years old and all outpatients. The strong innate immune response also explains the mild course in these patients[19,35] and the lack of other systemic symptoms in 58.8% of pernio cases included in this review. Some authors also believe that due to the strong innate immune response, patients with pernio lesions are no longer contagious,[17] which supports Lipsker and Saurat's theory of paraviral eruptions.[19]

Purpuric

Parallel to viral-induced vasodilation, viruses also can cause vessel injury leading to purpura.[15,19] Specifically, retiform purpura is due to vessel occlusion,[8] while petechiae is due to red blood cell extravasation and hemorrhage into the dermis. Purpuric COVID-19 lesions were usually found in elderly, more severe cases.[8,38] Our review included limited purpuric cases (n = 5, 22–66 years old) but did not reflect a more elderly population. In contrast to the strong innate immune reaction that could lead to microthromboses in pernio cases, purpura reflects COVID-19-related macrothrombotic hypercoagulability, possibly due to ineffective defense against the virus,[17,28,38] which supports why increased severity was noted with purpuric cases. Histologic findings of the petechial purpura case included in our review were consistent with viral exanthem,[10] possibly reflecting active viremia alongside the vascular phenomena.

Others

Cutaneous hyperesthesia, along with hyposmia and dysgeusia, belong to viral-induced subjective neurological symptoms found frequently with neurotropic viruses, such as the Herpesviridae.[39] Subjective neurological symptoms in SARS-COV2 are thought to be related to the presence of ACE2 receptors in sensory neurons.[40] Smell and taste abnormalities – often considered as early specific symptoms – frequently have been reported in COVID-19 patients, while cutaneous hyperesthesia, such as that included in our review, rarely has been reported.[41]

Periorbital dyschromia and the subsequent fever and cough in 2 cases recurred for the second time after initial resolution. The authors speculated that periorbital dyschromia was due to coagulation dysfunction of periocular vessels.[42] It is, therefore, intriguing to investigate the pathogenesis of COVID-19 more in depth.

Polymorphic Evolution

Patel et al's case[33] that reported multiple morphologies evolving from concurrent maculopapular, vesicular, and urticarial lesions to purpuric lesions is a good material to explore the sequential pathogenesis of COVID-19 cutaneous manifestations. As the virus proliferates in the bloodstream, dermal vascular dilatation and inflammation-related cell infiltration leads to maculopapular lesions. From dermal vessels, viruses can affect the dermis then epidermis, leading to epidermal vesicular (and papulosquamous) eruptions. Continued viral proliferation brings upon early coagulation dysfunction and hypersensitivity reactions to viral components, leading to urticaria and facial angioedema. Purpura forms as coagulation dysfunction progresses. Patel et al also pointed out the possibility of coinfection with other viruses or multiple viral strains leading to polymorphic presentation,[33] which is supported by reports of coinfection with herpes zoster or HHV-6.[14,21]

Table 1. Summary of Studies Reporting Skin Lesions Prior to Any Other COVID-19 Symptoms

Author(s), Year	Study Design	Age (y), Sex	Comorbidities	Skin Lesion Location and Clinical Features	Latency (days)	Inpatient
Maculopapular (22/97 = 22.7%); 9.1% hospitalized, 72.7% unknown hospitalization status; **18.2% cutaneous symptoms only**						
Altayeb et al, 2020[44]	Case report (n = 1), extracted from n = 2	74, M	AF, FL	Neck, back, and chest; pruritic	-10 (D)	Yes
Hunjan et al, 2020[45]	Case report (n = 1)	64, F	NR	From trunk that rapidly spread to upper thighs and inner arms with associated facial edema; pruritic	-7 (DF)	Yes
Dertlioğlu, 2020[46]	Case report (n = 1), extracted from n = 5	10 mo, M	NR	Widespread: trunk and arm; pruritic	Skin only	No
Freeman et al, 2020[7]	n = 3 out of case series (n = 23)	31 (27–55); 7 M, 16 F	N/A	Macular erythema: back (48%), arms (48%); 61% pruritic, 26% painful/burning	-x (n = 2), skin only (n = 1)	NR (n = 3)
Freeman et al, 2020[7]	n = 4 out of case series (n = 38)	52 (36–66); 19 M, 19 F	N/A	Morbilliform: abdomen (63%), back (61%); 61% pruritic, 61% painful/burning	-x (n = 3), skin only (n = 1)	NR (n = 4)
Galván Casas et al, 2020[8]	n = 4 out of case series (n = 122)	60 (45–77); 63 M, 59 F	N/A	N/A; 91% pruritic, 6% burning, 3% painful	-x (n = 4)	NR (n = 4)
Gianotti et al, 2020[47]	Case report (n = 1), extracted from n = 3	57, M	None	Widespread; pruritic	-2 (CF)	No
Serafini et al, 2020[48]	case report (n = 1)	32, F	None	Sparing face, scalp, and abdomen; pruritic	-7 (C)	No
Ghafoor et al, 2022[49]	n = 5 out of case series (n = 23)	38.9 ± 11.5	None	N/A	-x (n = 5)	NR (n = 5)
Assaf et al, 2021[50]	Case report (n = 1)	26, M	None	Initially appeared on legs, then progressed to affect trunk and arms, sparing the face; pruritic	Skin only	No
Papulosquamous (8/97 = 8.2%); 0% hospitalized, 75% unknown hospitalization status; **12.5% cutaneous symptoms only**						
Chu et al, 2020[51]	Case report (n = 1)	52, M	DM, HTN	Bilateral palms, forearms, and legs; pruritic	-4 (DF)	No
Freeman et al, 2020[7]	n = 4 out of case series (n = 17)	28 (27–38); 10 M, 7 F	N/A	Abdomen (65%), arms (65%), back (65%), legs/buttocks (65%); 94% pruritic, 29% painful/burning	-x (n = 3), skin only (n = 1)	NR (n = 4)
Merhy et al, 2020[20]	Case report (n = 1)	26, F	None	Christmas tree pityriasis rosea pattern preceded by herald annular plaque on right thigh	-9 (CFM)	No
Ghafoor R et al, 2022[49]	n = 2 out of case series (n = 5)	31.4 ± 8.3	None	N/A	-x (n = 2)	NR (n = 2)
Pernio (17/97 = 17.5%); 0% hospitalized, 70.5% unknown hospitalization status; **58.8% cutaneous symptoms only**						
Altayeb et al, 2020[44]	Case report (n = 1) extracted from n = 2	29, M	NR	Fingertips; also had symmetrical painless desquamation	-4 (CF)	No
Freeman et al, 2020[7]	n = 11 out of case series (n = 31)	35 (22–59); 15 M, 16 F	N/A	Feet (84%), hands (32%); 36% pruritic, 71% painful/burning	-x (n = 5), skin only (n = 6)	NR (n = 11)
Galván Casas et al, 2020[8]	n = 1 out of case series (n = 29)	44 (21–67) 11 M, 18 F	N/A	N/A; 47% pruritic, 42% painful, 11% burning	-x (n = 1)	NR) (n = 1)
Guarneri et al, 2021[52]	Case report (n = 1), extracted from n = 3	14, M	NR	Dorsum of toes; progressed to small ulcer on left 5th toes after 7 day	Skin only	No
Guarneri et al, 2021[52]	Case report (n = 1), extracted from n = 3	14, M	NR	Dorsum of toes; some progressed to necrotic blackish crusts	Skin only	No
Proietti et al, 2020[9]	Case report (n = 1)	35, F	None	Lateral right auricle; extremely painful	Skin only	No
Paparella et al, 2022[53]	Case report (n = 1)	14, M	None	Left toes; swollen erythematous; itching	Skin only	No
Purpuric (5/97 = 5.1%); **80% hospitalized; 40% cutaneous symptoms only**						
Freeman et al, 2020[7]	n = 1 out of case series (n = 11)	66 (51–73); 9 M, 2 F	NR	Legs/buttocks (64%), trunk and face spared; 9% painful/burning	-x (n = 1)	Yes
Lobos et al, 2020[10]	Case report (n = 1)	22, M	None	Petechiae in bilateral lower limbs and dorsal hands; gingival bleeding and buccal hematoma after dental	-5 (H)	Yes
Khalil et al, 2020[54]	Case report (n = 1)	34, F	None	Livedo reticularis of bilateral arms and thighs	-2 (M)	No
Brito Caldeira et al, 2021[55]	Case report (n = 1)	44, M	None	Both thighs; large (>15 cm)	Skin only	Yes
McBride JD et al, 2021 [56]	Case report (n = 1)	66, F	HTN, DM, COPD	Bilateral buttocks; nonindurated, retiform purpuric patch	Skin only	Yes

Table continued on page XX

Abbreviations: M, male; F, female; y, years; mo, months; NR, not reported; ICU, intensive care unit; N/A, not applicable; AF atrial fibrillation, FL, follicular lymphoma, DM, diabetes mellitus; HTN, hypertension; PHTN, pulmonary hypertension; OSA, obstructive sleep apnea; CKD, chronic kidney disease; VE, vascular epilepsy; HF, heart failure; HSV, herpes simplex virus; A, anosmia; C, cough; D, dyspnea; F, fever; M, myalgia; O, odynophagia; COPD, chronic obstructive pulmonary disease.

Table 1 continued. Summary of Studies Reporting Skin Lesions Prior to Any Other COVID-19 Symptoms

Author(s), Year	Study Design	Age (y), Sex	Comorbidities	Skin Lesion Location and Clinical Features	Latency (days)	Inpatient
Urticarial (24/97 = 24.7%); 10.7% hospitalized, 58.3% unknown hospitalization status; **16.6% cutaneous symptoms only**						
Naziroğlu et al, 2020[57]	Case report (n = 1)	53, M	Previous smoker	Generalized; pruritic	Skin only	Yes
Pagali and Parikh, 2021[58]	Case report (n = 1)	54, F	Obesity, PHTN, OSA, AF, CKD	Upper/lower limbs and trunk; pruritic, burning	-2 (DM)	Yes
Chen et al, 2020[59]	Case report (n = 1)	6 mo, M	None	Generalized; pruritic	-11 (F)	No
Dertlioğlu, 2020[46]	Case report (n = 1), extracted from n = 5	42, M	NR	Trunk	-7 (CM)	No
Galván Casas et al, 2020[8]	n = 2 out of case series (n = 49)	53 (32–74); 17 M, 32 F	N/A	N/A; 98% pruritic, 2% burning	-x (n = 2)	NR (n = 2)
Freeman et al, 2020[7]	n = 3 out of case series (n = 27)	42 (29–54); 6 M, 21 F	NR	Legs/buttocks (52%), arms (48%), hands (48%); 74% pruritic, 22% painful/burning	-x (n = 2), skin only (n = 1)	NR (n = 3)
Hassan et al, 2020[12]	Case report (n = 1)	46, F	Asthma, hay fever	Upper/lower limbs and trunk, after a day involved face and angioedema of lips; pruritic	-2 (CF)	No
Mendes and Pimenta, 2020[60]	Case report (n = 1)	18, F	None	Trunk, inguinal zone, distal upper/lower limbs, forehead; asymptomatic	-2 (F)	No
Palomo-Pérez et al, 2021[11]	Case report (n = 1), extracted from n = 4	43, F	NR	Gace, progressed to odynophagia	-2 (OM)	No
Quintana-Castanedo et al, 2020[13]	Case report (n = 1)	61, M	NR	Thighs, arms, and forearms; pruritic	Skin only	No
van Damme et al, 2020[61]	Case report (n = 1), extracted from n = 2	39, F	None	Generalized (started from forearms); pruritic	-2 (F), -5 (A)	No
Pangburn J et al, 2023[62]	Case report (n = 1) extracted from n = 2	46, M	None	Bilateral upper and lower exctremities	Skin only	Yes
Ghafoor et al, 2022[49]	Case series (n = 9) extracted from n = 15	40.4 ± 11.5	None	N/A	-x (n=9)	NR (n = 9)
Vesicular (14/97 = 14.4%); 14.2% hospitalized, 42.8% unknown hospitalization status; **0% cutaneous symptoms only**						
Goyal et al, 2021[14]	Case report (n = 1), extracted from n = 3	60s, M	NR	Left T6 dermatome; hemorrhagic	-2 (AFM)	Yes
Marzano et al, 2020[63]	Case report (n = 1), extracted from n = 22	65, M	NR	Trunk, no facial/mucosal involvement; pruritic	-2 (CF)	Yes
Fernandez-Nieto et al, 2020[25]	n = 2 out of case series (n = 24)	45 (19-65), 6 M, 18 F	NR	Widespread: trunk; different stages of the lesions appeared simultaneously	-10 (n = 1), -20 (n = 1)	NR (n = 2)
Freeman et al, 2020[7]	n = 1 out of case series (n = 18)	55 (36-58), 8 M, 10 F	N/A	Abdomen (44%), arms (44%), legs/buttocks (44%); 72% pruritic, 50% painful/burning	-x (n = 1)	NR (n = 1)
Galván Casas et al, 2020[8]	n = 2 out of case series (n = 17)	56 (43-70), 11 M, 6 F	N/A	N/A; 85% pruritic, 15% burning	-x (n = 2)	NR
Ghafoor et al, 2022[49]	n = 1 out of case series (n = 15)	46.7 ± 7.8	None	N/A	-x (n = 1)	NR (n = 1)
Sil et al, 2022[64]	Case series n = 6	58 (34–76) 4 M, 2 F	Diabetes (n = 1)	Facial vesicles; painful; burning sensation	-x (n = 6)	no
Others						
Labé et al, 2020[65]	Case report (n = 1), extracted from n = 2	6, M	None	Severe erosive cheilitis, bilateral conjunctivitis, multiple erythema multiforme target lesions (HSV and *Mycoplasma pneumoniae* ruled out by serology)	-7 (F)	Yes
Patel et al, 2020[33]	Case report (n = 1)	78, F	VE, HF, hypothyroid	Widespread maculopapules with vesicles and urticaria on trunk and malar region; facial angioedema with drooling; progressed to purpuric rash; nonpruritic	-7 (F)	Yes
Kalner and Vergilis, 2020[42]	Case report (n = 1), extracted from n = 3	50, M	None	Dusky red, nonpruritic, nonblanching periorbital dyschromia; skin and systemic symptoms recurred after resolution	-2 (DMF)	Yes
Kalner and Vergilis, 2020[42]	Case report (n = 1), extracted from n = 3	43, F	None	Dusky red, nonpruritic, nonblanching periorbital dyschromia; skin and systemic symptoms recurred after resolution	-2 (CFM)	No
Krajewski et al, 2020[41]	Case report (n = 1), extracted from n = 9	62, F	NR	Cutaneous hyperesthesia	-2 (FM)	NR (n = 1)
Andina-Martínez et al, 2021[66]	Case series (n = 2), extracted from n = 6	5, F; 9, M	None	Hands; mild erythema and desquamation of the fingertips	Skin only	No

Abbreviations: M, male; F, female; y, years; mo, months; NR, not reported; ICU, intensive care unit; N/A, not applicable; AF atrial fibrillation, FL, follicular lymphoma, DM, diabetes mellitus; HTN, hypertension; PHTN, pulmonary hypertension; OSA, obstructive sleep apnea; CKD, chronic kidney disease; VE, vascular epilepsy; HF, heart failure; HSV, herpes simplex virus; A, anosmia; C, cough; D, dyspnea; F, fever; M, myalgia; O, odynophagia; COPD, chronic obstructive pulmonary disease.

Public Health Implications

Somehow similarly with Lipsker and Saurat, Kolivras et al echoed that specific cutaneous lesions develop in specific stages of COVID-19 and reflect different prognosis and contagiousness. For instance, pernio eruptions due to strong innate immune response eradicating the virus are thought to be less contagious,[17,19] while vesicular and purpuric lesions can be speculated to have a higher viral load and thus more contagious. Findings in our review support these hypotheses. Although sample size is limited, all the purpuric and vesicular cases developed a systemic symptom later, while 58.8% of pernio cases did not develop systemic symptoms. Moreover, hospitalization was also noted highest with purpuric cases.

Our review included 6 pediatric cases (6 months, 10 months, 5 years, 6 years, 9 years, and 14 years old), one of which only presented with maculopapular lesions and no further symptoms. At this writing, COVID-19 vaccines were not yet available for children below 12 years old,[43] making them and their caretakers vulnerable, along with the rest of the unvaccinated population. With the opening of daycares, schools, restaurants and large events—along with removal of mask mandates—cluster outbreaks are highly possible, thereby further highlighting the need for early detection of COVID-19 cases.

CONCLUSIONS

In patients who presented initially or only with cutaneous lesions, urticarial and maculopapular were most common, followed by pernio. Skin lesions were the only COVID-19 manifestation in 23.7% of all included cases in this review. Skin lesions were the only manifestation in 58.8% of pernio-like, 16.6% of urticarial, 18.2% of maculopapular, and 12.5% of papulosquamous presymptomatic cases. Pernio and purpuric lesions have been well-associated with COVID-19, but papulosquamous, vesicular, mild maculopapular and urticarial lesions can be easily overlooked and dismissed as unrelated to COVID-19. Pernio lesions are thought to be related to strong immune response and low contagiousness, while purpuric and vesicular cases are speculated to be related to higher SARS-CoV2 viral load, severity, and contagiousness. However, more studies are needed to better understand the link between viral pathogenesis, gross morphology, and contagiousness. Regardless, all presymptomatic skin lesions could serve as a valuable tool for early case identification and spread control. Rashes should necessitate a high level of suspicion, especially if possible COVID-19 contact history is present. Even when skin lesions occur after the patient is no longer contagious (eg, pernio), contact tracing should still be done to minimize asymptomatic spread that potentially could have happened prior to development of skin lesions

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A Review of Morphologic Findings in Peripheral Blood Smears of COVID-19 Patients

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ABSTRACT

Introduction: Peripheral smear examination is a simple and cost-effective test that is routinely performed while monitoring patients diagnosed with COVID-19. We sought to summarize the peripheral blood morphologic findings in patients with COVID-19 infection.

Methods: A systematic review was conducted using a standardized keyword search on Medline database (PubMed), med RXIV, Google Scholar, EMBASE, and SCOPUS for studies discussing peripheral blood smear or morphologic blood findings in patients diagnosed with COVID-19.

Results: A total of 28 studies were included in the review. Normocytic normochromic anemia was the most frequently encountered red blood cell finding. Neutrophilia was seen in most of the studies. A variety of morphological changes were observed in neutrophils, including pyknotic nuclei, variable shapes, toxic granules, and cytoplasmic vacuolization. Hyposegmented neutrophils, pseudo-Pegler Huet forms, and hypogranular forms were common findings reported by many studies. Lymphopenia was reported by most studies. Lymphocytes showed numerous morphological changes, including reactive forms, Downey forms, increased large granular lymphocytes, and plasmacytoid cells. The presence of giant platelets was seen frequently.

Conclusions: The peripheral blood in COVID-19 shows a spectrum of findings, mostly reactive changes in neutrophils, monocytes, lymphocytes, and platelets. Increased neutrophil/lymphocyte ratio and higher neutrophil counts have been associated with poor prognosis, which potentially could help triage patients, but this needs to be confirmed in larger studies.

INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), first emerged in Wuhan, China. The virus spread very rapidly across countries and quickly emerged as a global pandemic, drastically affecting health worldwide. Based on the favorability of viral spread, there have been abrupt surges in cases causing so-called "waves." The omicron and delta variants of SARS-CoV-2 emerged by undergoing mutations and have proven to be highly contagious and deadly. Despite the implementation of various prevention measures, such as social distancing, contact tracing, and mandatory vaccination, COVID-19 remains a major health concern causing a high number of fatalities.[1-3]

Several studies have reported the complex pathophysiology of COVID-19, including immune dysregulations and various hematologic manifestations. Viral infections are known to affect hematopoiesis both quantitatively and qualitatively. HIV infections, cytomegalovirus infections, infectious mononucleosis, SARS, and COVID-19 infection have been associated with atypical lymphocytes.[4-6]

The morphologic changes in peripheral blood have not been studied extensively. To our knowledge, no comprehensive review of the literature describing the peripheral blood morphologic findings in patients diagnosed with COVID-19 has been published. This review aims to summarize the literature to date.

METHODS

Literature Search Strategy

A systemic search of the literature was conducted in the electronic databases following the preferred reporting items for systematic reviews and meta-analysis guidelines. We searched in the Medline database (PubMed), med RXIV, Google scholar, EMBASE, and SCOPUS, with the combined terms "novel coronavirus," "2019 novel coronavirus," "SARS – COV-2," "COVID-19," and "periph-

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eral blood smear" or "morphologic peripheral blood findings." Additional studies were identified by studying the references of the original studies and pertinent review articles. Three researchers examined the databank.

Selection and Exclusion Criteria

Searches were limited to publications before January 31, 2022. Papers published in English were included. Original articles, clinical analysis, and research discussing the peripheral blood smear manifestations of COVID-19 were included. Unavailable articles, medical hypotheses, and duplicate articles were excluded. Cases with the clinical diagnosis of disease were included, in addition to cases of COVID-19 confirmed by viral nucleic acid detection, viral gene sequencing, and serum antibody test. Due to the scarcity of studies reporting peripheral blood morphologic findings in COVID-19, case reports were included. The following exclusion criteria were applied: case reports of other coronaviruses, animal studies, and studies that did not describe the peripheral blood morphologic findings in humans.

Data Extraction

Data extraction was performed independently by two authors and discrepancies were resolved by consensus. Full-text articles were retrieved for detailed review. We used standardized forms that included author, year, study design, age, and gender.

RESULTS

Study details including year, article type, title, and number of smears studied, as well as patient demographics (eg, country, age, and sex) are enumerated in Table 1.[7-31] Morphologic findings of red blood cells, neutrophils, lymphocytes, platelets, and additional findings are enumerated in Table 2.[7-31] and have been summarized in Table 3. These findings are further elaborated in this section.

Red Blood Cells

Anemia was the most frequently encountered red blood cell finding, reported by 8 studies. Luke et al,[17] Mitra et al,[18] and Pozdnyakova et al[21] reported cases with nucleated red blood cells. Pezeshki et al reported a relatively higher number of cases with schistocytes,[20] and Schapkaitz et al reported cases showing red cell fragments.[23] Overall, hemolytic changes were not a predominant finding in most of the studies.

White Blood Cells

Neutrophil counts were reported in 16 of the 28 studies. Twelve studies reported neutrophilia, 1 study documented neutropenia, and 3 studies included some patients with neutrophilia and others with neutropenia. A variety of morphological changes were observed in neutrophils, including toxic granulation (7 studies), pyknosis (2 studies), hyposegmentation (7 studies), hypersegmentation (2 studies), Pelget Huer anomaly (7 studies), and other findings (11 studies). Berber et al saw pyknotic neutrophilic nuclei in their patient group,[6] as did Nazarullah et al in rare cases.[19]

Singh et al reported striking morphologic changes in the neutrophils358– ring-shaped, C-shaped, and fetus-like nuclei; heavily clumped nuclear chromatin; aberrant nuclear projections; and elongated nucleoplasm. They lumped these findings together and described them as COVID nuclei.[24] In addition, they found toxic granules and cytoplasmic vacuolization in neutrophils, which also were seen by Kaur et al14 and Pozdnyakova et al.[21] Cantu et al found only toxic granules without any vacuoles and also reported blue-green inclusions in neutrophils in 6 cases.[10]

Luke et al, the only researchers to study the electron microscopic findings of peripheral blood elements, found multiple aberrancies in all hematopoietic lineages as described in the Tables.[17] Hyposegmented neutrophils, pseudo-Pelger Huet forms, and hypogranular forms were common findings reported by many studies.

Lymphocyte counts were reported in 18 of the 28 studies, and lymphopenia was the predominant finding in all 18 studies. The presence of reactive lymphocytes was documented in 19 studies irrespective of lymphocyte counts. Reactive lymphocytes showed various morphological forms, including Downey forms (7 studies) and plasmacytoid cells (10 studies). Kubik et al described the plasmacytoid lymphocytes, immunoblastic cells, and plasma cells as "covidocytes."[25] Morphological forms, such as smudge cells (2 studies) and apoptotic cells (2 studies), also were seen. Luke et al observed other morphological features, including multilobulated nuclei and large cytoplasmatic granulations in lymphocytes.[17] Bahadur et al reported azurophil granules and prominent nucleoli in lymphocytes.[9] Tummiddi et al found cytoplasmic pods, vacuolations, and nuclear blebbing.[26] Seven studies reported increased large granular lymphocytes. Kubik et al found increased granulation in the large lymphocytes.[25] Luke et al studied the electron microscopic findings of the reactive lymphocytes and found features such as nuclear lobulation and invagination, elongation of lymphocytes, enlarged lymphocytes with basophilic cytoplasm, and undergoing apoptosis with signs of karyolysis.[17]

Monocyte count changes were reported in 5 studies, with two documenting monocytosis and three reporting monocytopenia. Four studies reported an increase in monocyte size, and 12 studies found cytoplasmic vacuolation of the monocytes.

Morphologic findings in eosinophils were reported by only a few studies. One study reported a decrease in eosinophil count with COVID-19 infection,[6] while cytoplasmic vacuoles were seen in eosinophils in studies by Ahnach et al[7] and Pozdnyakova et al.[21]

Platelets

A common morphologic finding in platelets was the presence of giant forms. Platelet counts were documented in 6 of the 28 studies. Thrombocytopenia was reported in 3 studies, thrombocytosis was reported in 1 study, and 2 studies documented both thrombocytosis and thrombocytopenia. Morphological changes documented in platelets included giant forms (11 studies), large forms (1 study), platelet clumps or aggregates (3 studies), platelet

Table 1. Demographic and Clinical Characteristics of Patients in the Included Studies

Author (month, year)	Article Type	Country	Age	Sex	No. of COVID Smears Studied
Ahnach et al (12/20)[7]	Letter	Morocco	N/A	N/A	15
Akçabelen et al (03/21)[8]	Images	Turkey	16	F	1
Bahadur et al (10/21)[9]	Original	India	42.16 ± 15.55 y	M 35, F 15	50
Berber et al (01/21)[6]	Original	Turkey	44 (range 18–88 y)	M 25, F 25	50
Cantu et al (06/20)[10]	Letter	New York, USA	N/A	N/A	6
Chong et al (04/20)[11]	Images	Singapore	N/A	N/A	32
El Jamal et al (06/20)[5]	Correspondence	New York, USA	N/A	N/A	33
Gerard et al (06/20)[4]	Images	France	74	F	1
Gabr et al (01/22)[12]	Original	Egypt	60.68 ± 13.04 (24–89 y)	M 65 (57.5%), F 48 (42.5%)	113
Harris et al (04/21)[13]	Original	Boston, MA, USA	32 to > 89; median, 63 y	M 12, F 8	20
Kaur (02/21)[14]	Original	Danbury, CT, USA	65.1	M 13, F 7	20
Lee et al (08/20)[15]	Images	Singapore	60	M 1	1
Liu et al (11/20)[16]	Letter	China	31–83	F 12	23
Luke et al (06/20)[17]	Original	Germany	58 (21–77 y)	M 30 (67%), F 15 (33%)	45
Mitra et al (04/20)[18]	Images	California, USA	46 y	F 1	1
Nazarullah et al (08/20)[19]	Original	Texas, USA	55 (25–100 y)	M 7, F 5	12
Pezeshki et al (07/21)[20]	Original	Isfahan, Iran	10–90 y	M 54 (60.7%), F 35 (39.3%)	89
Pozdnyakova et al (02/21)[21]	Original	Boston, USA	58.66 (non-ICU group) 64.12 (ICU group)	M/F ratio: 0.56 (non-ICU group) 1.55 (ICU group)	90
Sadigh et al (07/2020)[22]	Letter	Massachusetts, USA	52.6 (28–80 y) COVID+ group	M 17, F 10	78
Schapkaitz et al (12/20)[23]	Letter	South Africa	Median, 49 y	M/F ratio: 1.2:1	59
Singh et al (05/20)[24]	Images	India	55 y	F	1
Kubik et al (01/22)[25]	Original	Canada	Mean, 58 years (20–98 y)	M 30, F 24 (discovery set) M 38, F 21 (validation set)	113 (total)
Tummidi et al (04/21)[26]	Case report	India	58 y	F	1
Weinberg et al (06/20)[27]	Correspondence	Illinois, USA	26–90 y	M 8, F 7	15
Yarali et al (05/20)[28]	Letter	Turkey	8.11 ± 5.71 y (4 m–17 y)	N/A	30 (COVID+ cases)
Yuki et al (09/21)[29]	Original	Japan	61 (46–67 y)	M 30 (75.0%) F 10 (25.0%)	40 (COVID+ cases)
Zhang et al (09/20)[30]	Original	China	N/A	N/A	34 patients
Zini et al (04/20)[31]	Images	Italy	N/A	N/A	40

Abbreviations: F, female; M, male; y, years; ICU, intensive care unit; N/A, not available.

Table 2. Morphologic Findings of Red Blood Cells (RBC), Neutrophils, Lymphocytes, Platelets, and Additional Findings

Author	RBC	Neutrophils	Lymphocytes	Platelets	Other
Ahnach et al[7]	N/A	Hyposegmented, hypogranular	Lymphopenia (46%), reactive forms	Giant forms	Monocytosis (9.5%), large moncytes; eosinophils: vacuoles
Akçabelen et al[8]	N/A	Hypersegmented, pseudo Pelger-Huet forms	Reactive forms	Giant forms	Monocytes: vacuoles
Bahadur et al[9]	Normocytic normochromic (76%)	Toxic changes, hyposegmented forms, nuclear projections 9 (18%), ring nuclei 7 (14%)	Azurophil granules 6 (12%), prominent nucleoli 5 (10%)	Giant platelets 28 (56%)	Monocytes: vacuoles, monocytes clumped nuclear chromatin 6 (12%), cytoplasmic granules 4(8%)
Berber et al[6]	N/A	Neutropenia, pyknotic, hypogranular, pseudo Pelger-Huet: 10 (median), dysplastic neutrophils, pyknosis, karyolysis, karyorrhexis	Decreased counts, reactive forms, Downey forms	N/A	Eosinophils: Decreased counts; monocytes: vacuoles
Cantu et al[10]	N/A	Toxic changes, green blue inclusions	N/A	N/A	N/A
Chong et al[11]	N/A	N/A	Reactive forms, plasmacytoid forms	N/A	N/A
El Jamal[5] et al[5]	N/A	N/A	Reactive forms, Downey forms, plasmacytoid forms	N/A	N/A
Gerar et al[4]	N/A	Increased counts	Downey forms	N/A	N/A
Hala Gabr et al[11]	N/A	Toxic forms, hypogranular, pseudo Pelger-Huet, pyknotic forms w fragmented (karyorrhectic) nuclei w intense basophilic chromatin and broken forms	Reactive, vacuolated forms; plasmacytoidforms	N/A	Monocytes: vacuoles, apoptotic eosinophils. Dysplastic cells of myeloid origin. Mott cells.
Harris et al[13]	Anemia (6 cases)	Increased counts	Decreased counts	Decreased counts,	Plasma cells giant forms

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Table 2 continued. Morphologic Findings of Red Blood Cells (RBC), Neutrophils, Lymphocytes, Platelets, and Additional Findings

Author	RBC	Neutrophils	Lymphocytes	Platelets	Other
Kaur et al[14]	Anemia (17 cases), coarse basophilic stippling, nucleated RBCs	Toxic changes, hyposegmented, pseudo Pelger-Huet forms, hypersegmented forms vacuolization, abnormal nuclear shapes and aberrant nuclear projections; smudged neutrophils	Reactive, Downey, large granular, plasmacytoid forms	Platelet clumps	Smudge cells left shift
Lee et al[15]	N/A	N/A	Decreased counts; reactive, Downey, large granular, plasmacytoid forms	N/A	Plasma cells
Liu et al[16]	N/A	N/A	Reactive, plasmacytoid forms	N/A	N/A
Luke et al[17]	Nucleated RBCs, basophilic stippling, stomatocytes	Hyposegmented, hypergranular (35), pseudo Pelger-Huet (21), LM: hypergranular (35), aberrant nuclear segmentation; EM: early stages of apoptosis, hypercondensed chromatin, nuclear shrinking	36 (80%) abberant forms; 5 (9%) reactive forms. EM: nuclear lobulation and invagination; elongation of lymphocites, enlarged lymphocyte w basophilic cytoplasm, undergoing apoptosis with signs of karyolysis), plasmacytoid forms	Giant forms, platelet clumps	Monocytes w aberrant nuclei (clumped chromatin) and basophilic cytoplasm, plasma cells, left shift
Mitra et al[18]	Normocytic anemia nucleated	Increased count	Decreased count	Large forms	N/A
Nazarullah et al[19]	N/A	Toxic changes (4/12), pseudo Pelger-Huet (12), rare pyknotic forms, apoptotic changes	Decreased count Downey forms (types 1,2,3), large granular and plasmacytoid forms	N/A	Left shift
Pezeshki et al[20]	Schistocytes (24, 27%)	N/A	Reactive and large granular forms	Giant forms	Leucoerythroblastic reaction, left shift, smudge cells
Pozdnyakova et al[21]	Nucleated RBCs	Toxic changes, hypogranular forms, cytoplasmic vacuolization, Howell-Jolly body-like inclusions, and Döhle bodies	Reactive, large granular, plasmacytoid	N/A	Monocytes: large coalescing cytoplasmic vacuoles; eosinophils: cytoplasmic vacuoles
Sadigh et al[22]	Anemia, 13 dysmorphic, 14 normal	Smudged neutrophils	Decreased lymphocyte count, reactive and plasmacytoid forms	Giant forms	Plasma cells
Schapkaitz et al[23]	RBC fragments >1%	Increased counts, hyposegmented forms, hypogranular forms, pseudo Pelger-Huet forms (60/102)	Lymphopenia (49/102), severe lymphocytopenia (19/102), reactive large granular, plasmacytoid forms	Increased counts, giant forms	Monocytes: decreased counts, vacuoles. Plasma cells. Leuko erythroblastic reaction, left shift.
Singh et al[24]	N/A[a]	Increased counts, toxic changes, heavily clumped chromatin, nuclear abnormalities	Decreased counts, large granular forms, apoptotic lymphocytes	Few giant forms	Monocytes: decreased counts, vacuoles
Kubik et al[25]	N/A	Abnormal absolute neutrophil counts (either 2000/IL or 9000/IL)	Absolute lymphopenia, absolute large granular lymphocyte counts >300/IL, enriched in cases w/out lymphopenia; covidocytes (plasmacytoid w/out lympho cytes, immunoblastic cells, plasma cells)	Platelet aggregates	Monocytes: increased count; smudge cells
Tummidi et al[26]	Normochromic normocytic	Hyposegmented, hypogranular, ring shape, club shape, U shape, fetal-like, satellitism	Increased granulation in large lymphocytes, cytoplasmic pods, vacuolations, nuclear blebbing	Platelet satellitism, giant forms	Monocytes: vacuoles, abundant cytoplasm with granulations, nuclear blebbing, irregular cytplasmic membranes; smudge cells
Weinberg et al[27]	Normocytic anemia mild anisopoikilocytosis, no hemolysis	Increased counts predominated	Decreased counts, reactive and Downey 2 forms, plasmacytoid forms	N/A	N/A
Yarali et al[28]	Anemia, 1/70	Increased and decreased counts, hypergranulation/lobulation abnormalities in neutrophils (n = 11; 36.7%)	Decreased counts, reactive forms	Decreased counts, giant forms	Monocytes: vacuoles
Yuki et al[28] `	Polychromatic RBCs, hypochromic RBCs, schistocytes	Increased absolute neutrophil counts; toxic changes, Dohle body, vacuoles, giant forms; neutrophil dysplasia: increased acquired Pelger-Huët anomaly and monolobated neutrophils, degranulation/hypogranulation, and chromatin abnormality	Lower absolute lymphocyte count; vacuoles, reactive forms, granular lymphocyte	Giant forms	Increased neutrophil-lymphocyte ratio
Zhang et al[30]	N/A	N/A	N/A	N/A	Monocytes: increased counts, large forms, with vacuoles
Zini et al[31]	N/A	Increased counts, toxic changes, pseudo Pelger-Huet forms, hypogranular forms, nuclear and cytoplasmic granulation. Preapoptotic and apoptotic cells	Decreased counts, reactive large granular,plasmacytoid forms	Large, hyperchromatic, vacuolated forms	Apoptotic forms, left shift

Abbreviation: N/A, not available.
[a]The study did not report this parameter.

satellitism (1 study), giant forms with clumping (1 study), and large, hyperchromatic, vacuolated forms (1 study). Various other changes also were reported, including leucoerythroblastic reaction (2 studies), left-shifted maturation (8 studies) and apoptotic forms (1 study), and smudge cells (4 studies).

DISCUSSION

Neutrophilic leukocytosis is frequently observed in COVID-19 cases, but the cause remains uncertain. Bacterial or fungal coinfection may play a role secondary to lowered immune function and has been described in a few patients from Wuhan and in additional studies.[32-34] However, Harris et al and others have reported neutrophilia in the absence of superimposed infections, suggesting patients with COVID-19 and no known coinfections can nevertheless develop a pronounced neutrophilic leukocytosis.[13]

Several studies also have found associations between higher neutrophil counts with worse outcomes. Singh et al reported characteristic nuclear findings in neutrophils, along with morphological changes in lymphocytes and monocytes. The neutrophils showed peculiar morphological changes that have not been reported frequently. However, these features were restricted to only 1 case.[24] Cantu et al found that neutrophilic green inclusions were identified more than 20 days after COVID-19 testing and that these patients had acutely elevated transaminases, lactate dehydrogenase, and lactic acid.[10] Prior studies have postulated that these inclusions may be derived from the lipofuscin released from necrotic hepatocytes.[35-37] Due to poor prognosis and death shortly after the identification of these inclusions, Cantu et al red-flagged the presence of these inclusions as a higher risk factor for short-term mortality in COVID cases.[10]

Luke et al studied both the light and electron microscopic findings in 45 cases. They studied their cohort extensively after negative SARS-CoV-2 testing and found that as the infection subsided and systemic inflammation decreased, granulopoiesis showed only mild morphologic changes, such as improvement in the left shift.[17] Thus, to analyze the recovery of the hematopoietic system, follow-up of these patients systematically on a long-term basis will prove beneficial. This would also facilitate the investigation of other parameters, such as higher susceptibility of these patients for immune-related or hematologic diseases, and assess their eligibility for immunosuppressive or cytostatic therapy if the need arises. The aberrations in granulopoiesis and dysplastic changes resembled changes seen in conditions like myelodysplastic neoplasms or myelodysplastic/myeloproliferative neoplasms. These changes can be attributed to hyperinflammation or cytokine release.[17,38] The presence of these dysplastic cells in the blood can jeopardize the host immunity and may lead to secondary infections in these patients. A larger study of COVID patients with secondary infections can help to validate the utility of peripheral smear examination as a potential tool to assess the susceptibility of these patients to secondary infections. This could also help triage patients needing prophylactic antibiotics.[39,40]

Table 3. Summary of the Morphologic Findings of Red Blood Cells (RBC), White Blood Cells (WBC), and Platelets

Cell Type	Significant Findings
Red Blood Cells	Anemia, nucleated red blood cells, schistocytes
White Blood Cells	
Neutrophils	Neutrophilia, toxic granulations, pyknosis, hypo segmentation, hyper segmentation, Pelger-Huet forms
Lymphocytes	Lymphopenia, reactive lymphocytes including Downey forms and plasmacytoid cells/"covidocytes," smudge cells, apoptotic cells, and large granular lymphocytes
Monocytes	Monocytosis, monocytopenia, increase in monocyte size, cytoplasmic vacuolation
Eosinophils	Decrease in eosinophils, cytoplasmic vacuoles
Platelets	Thrombocytopenia, thrombocytosis, both thrombocytosis and thrombocytopenia, giant forms, large forms, platelet clumps or aggregates, platelet satellitism, giant forms with clumping, large, hyperchromatic, vacuolated forms

Many studies reported lymphopenia. Several mechanisms have been postulated for lymphopenia in COVID (42 studies?), including direct infection of T-lymphocytes due to expression of the ACE2 receptor on them, resulting in lymphocyte death,[41,42] and direct viral damage to the thymus and spleen resulting in acute lymphocyte decline.[41] Other studies have postulated that disordered inflammatory cytokines (tumor necrosis factor α, interleukin 6)[41,43] and metabolic molecules elevated blood lactic acid levels can lead to lymphocyte depletion.[41,44] Reactive or atypical lymphocytes are known to be seen in viral infections of various etiologies, such as Epstein-Barr virus, dengue virus, and SARS virus, and recently have been reported in COVID-19 as well with a relatively higher occurrence than seen with previous SARS.[11,27] Downey type II reactive lymphocytes and plasmacytoid forms are reported frequently in various studies and maybe a helpful diagnostic feature, although they are nonspecific and seen in many other conditions.[7,45]

Numerous studies have tried to link the clinical application of lymphocyte morphology or lymphocyte counts to patient prognosis. Berber et al found that lymphopenia was seen in severely ill patients, and pseudo Pelger-Huet anomaly/mature lymphocytes ratio increased in severely ill patients versus the mild stage group ($P < 0.05$).[6] They also found that at the disease onset, patients with an increased number of lymphocytes and monocytes with vacuoles had a short hospital length of stay. Wang et al found that among COVID-19 patients, severely ill cases had a lower level of total lymphocytes, CD4+ T cells, CD8+ T cells, and B cells than the mildly ill cases.[46] Kubik et al postulated that low counts of "covidocytes" that were essentially reactive and plasmacytoid lymphocytes (ie, 0.3%) were classified as "high risk" for a critical outcome.[25]

Viral infections may be associated with monocytes with vacuoles of the peripheral blood smear. Zhang et al reported morphological and inflammation-related changes in monocytes and reported

an increased number of larger, atypical, vacuolated monocytes not seen in healthy individuals' peripheral blood smear, like those seen by Berber et al.[6,30] There is not enough data suggesting an association of these changes in monocytes with prognosis. Similarly, there is not enough evidence reporting a correlation between eosinophilia or its vacuolization with patient prognosis.

Some well-known viral infections that have been associated with lymphomagenesis include Epstein-Barr virus, human T-lymphotropic virus (HTLV-1), hepatitis C virus, human herpesvirus (HHV-8), and HIV.[47] Although coronaviruses have not been associated with the development of lymphomas, long-term follow-up of COVID-19 patients remains essential.

Some limitations of this review include the heterogeneity of the studies, the predominance of case reports, and large variability in the findings. Most of the studies included did not analyze peripheral blood smear changes by SARS-CoV-2 strains or vaccination status, and, thus, the changes could not be evaluated. As new SARS-CoV-2 strains emerge, there is a need to describe the changes seen in the peripheral blood smear related to these specific strains so that any new or unique changes can be evaluated for diagnostic/prognostic significance. Additionally, prolonged pre-analytical time can alter the morphological features of white blood cells. Changes like cytoplasmic vacuolation, hairy projections, nuclear lobulation, vacuolation, and degeneration are observed in white blood cells due to prolonged time intervals between specimen collection and smear preparation.[48] Another limitation is that the effect of prolonged pre-analytical time on white cell morphology was not evaluated by the studies included, and the morphological findings were reported by an single pathologist and were not confirmed by another pathologist or central review.

CONCLUSIONS

There is a spectrum of findings in the peripheral blood in COVID-19--primarily reactive changes in neutrophils, monocytes, lymphocytes, and platelets. Increased neutrophil/lymphocyte ratio and higher neutrophil counts have been associated with poor prognosis, which could help triage patients, but this needs to be confirmed in larger studies.

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Double Trouble: COVID-19 Pneumonia Concurrent With COVID-19-Associated Pulmonary Aspergillosis

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ABSTRACT

Introduction: Severe complications due to COVID-19 are a growing concern. We present a case of COVID-19 pneumonia with development of a superimposed COVID-19–associated pulmonary aspergillosis.

Case Presentation: A 52-year-old unvaccinated male with a history of asthma and sleep apnea presented with progressive dyspnea 10 days after COVID-19 diagnosis. Worsening respiratory function despite broad-spectrum antibiotics and negative cultures prompted a repeat respiratory culture that revealed *Aspergillus*; voriconazole was initiated.

Discussion: The risk of COVID-19–associated pulmonary aspergillosis is highest in patients who are immunosuppressed or who receive corticosteroids to treat COVID-19 infection. Subtle and atypical presentations can be seen; our patient had only mild leukocytosis and progressive dyspnea with a negative initial respiratory culture. COVID-19–associated pulmonary aspergillosis is associated with high morbidity and mortality; thus, prompt diagnosis and treatment may confer a survival benefit.

Conclusions: Despite the subtle presentation and variable radiographic findings in COVID-19–associated pulmonary aspergillosis, a low clinical threshold for workup is crucial to a timely diagnosis and treatment.

INTRODUCTION

Aspergillus is an opportunistic fungal pathogen that historically is known to cause potentially devastating disease in immunocompromised individuals.[1] It also has been established recently that invasive pulmonary aspergillosis (IPA) can cause illness in immunocompetent but critically ill patients with various risk factors. These include, but are not limited to, steroid use, chronic obstructive pulmonary disease, diabetes, and influenza infection.[2,3] Over the last 2 years, IPA increasingly has been reported secondary to severe COVID-19 pneumonia. This phenomenon has been termed COVID-19–associated pulmonary aspergillosis (CAPA). Diagnostic challenges and differing case definitions have made it difficult to assess the true incidence of CAPA; however, it is estimated to affect approximately 10% of mechanically ventilated COVID-19 patients.[4-6] Superinfections like CAPA may not only prolong the acute phase of COVID-19 infection but are associated with significant morbidity and mortality.[7] As the pandemic continues, awareness of rare secondary complications – particularly those that manifest with subtle and nonspecific clinical presentations – becomes exceedingly necessary.

CASE PRESENTATION

A 52-year-old unvaccinated male with a past medical history significant for asthma and uncontrolled obstructive sleep apnea presented to the emergency department (ED) in October 2021, a time when the highly infective delta variant was the dominant strain of the SARS-CoV-2 virus. He presented with worsening dyspnea 10 days after receiving a COVID-19 diagnosis from an at-home test. He also endorsed a nonproductive cough, fever, chills, and nonbloody diarrhea.

Upon initial presentation, his vitals were remarkable for arterial oxygen saturation (SaO_2) of 65% on room air; thus, he was placed on high-flow nasal cannula (HFNC) due to critical hypoxemia. A physical exam revealed scattered bilateral crackles throughout the lung space. Lab workup was significant for leuko penia (white blood cells [WBC] 1.7 K/uL). The initial lab workup was also significant for hyperglycemia (blood sugar 182 mg/dL, hemoglobin A1c 9.6%). A computed tomography (CT) pulmo-

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Figure 1. Repeat Chest Computed Tomography Angiography With Contrast During Initial Admission

Patient's central airways were patent with mild central airway secretions and diffuse bronchial wall thickening. There was mucous plugging in the subsegmental lower lobe. There is a presence of widespread consolidations, widespread ground glass opacities, and subpleural atelectasis in the left lower lobe.

Figure 2. Chest Computed Tomography Angiography Without Contrast 3 Months Posttreatment

At follow-up for COVID-19 pneumonia and *Aspergillus* infection, computed tomography revealed improving bilateral opacities with some areas of residual consolidation and bronchiectasis.

nary angiogram was negative, and a chest x-ray revealed multifocal, bilateral opacities. The patient was initiated on intravenous (IV) dexamethasone 10 mg twice daily and IV remdesivir 100 mg daily and later admitted to the medical intensive care unit for acute hypoxemic respiratory failure. He did not receive oral antivirals or monoclonal antibodies prior to admission. Notably, he had no prior diabetes diagnosis. Given his elevated A1c, he was started on a sliding scale insulin and glargine and followed by the diabetes care team for the remainder of his admission.

Barcitinib 4 mg daily was added to the patient's regimen for 14 days for its anti-inflammatory effects against COVID-19. Linezolid and cefepime were given as empiric antibiotic therapy due to concern for bacterial superinfection but were discontinued after receiving negative blood and sputum cultures. Days later, new leukocytosis (WBC 16.0 K/uL) and worsening dyspnea prompted a repeat standard sputum culture, which grew mold on a preliminary read. Oral voriconazole 600 mg was initiated empirically due to concern for *Aspergillus fumigatus* infection and was continued upon confirmation with a positive serum galactomannan assay.

A repeat CT pulmonary angiogram was negative for pulmonary embolus but revealed left pneumomediastinum, small right apical pneumothorax with associated subcutaneous emphysema, and bilateral ground-glass opacities (Figure 1). Despite ongoing treatment, the patient continued to require nasal cannula (NC) at rest and HFNC with minimal exertion. Nearly 2 months after admission, he was discharged home with instructions to continue voriconazole 400 mg oral twice daily, with close follow-up with pulmonology as an outpatient to monitor the medication's trough levels and assess for potential treatment side effects. He also was discharged home with new oxygen requirements of 3 L NC at rest and 6 L nasal cannula with exertion. On follow-up chart review, he completed 3 months of voriconazole, which was titrated down to 150 mg twice a day after his first follow-up appointment with pulmonology due to a supratherapeutic voriconazole level of 4.5 (reference range 0.5 – 4.0 mg/L). The trough levels became therapeutic following the dose reduction, and he did not report any side effects throughout the treatment course. Four months following discharge, he was no longer requiring supplemental oxygen and a repeat chest CT showed improving bilateral opacities with some areas of residual scarring (Figure 2).

DISCUSSION

The increasing incidence of CAPA in critically ill COVID-19 patients, in addition to regularly emerging new COVID-19 variants, makes the discussion of CAPA worthy of heightened attention. There is wide variability in the reported incidence of CAPA due to numerous factors, including differing diagnostic criteria in the first year of the pandemic, utilization of diagnostic tools with varying degrees of sensitivity and specificity, and improper diagnostic fungal workup. Furthermore, CAPA is associated with high mortality rates. One study assessed severely ill COVID-19 patients in intensive care units (ICU) across Wales and found that the mortality rate in untreated patients defined with CAPA was 57.9%.[8]

Although the risk factors for CAPA are not well elucidated, acutely ill patients in the ICU with comorbidities seem to be at higher risk. Specifically, respiratory comorbidities, such as chronic obstructive pulmonary disease and asthma, hypertension, coronary artery disease, and type 2 diabetes, frequently have been reported in patients with CAPA.[9,10,11] It also been has demonstrated that corticosteroids used to treat critically ill COVID-19 patients are independently associated with increased risk of CAPA.[12] Indeed, the patient presented in our case possessed many of these risk factors.

Similarly, the pathophysiology of CAPA remains ill-defined. It is postulated that the impaired type I and III interferon (IFN) response observed in severe COVID-19 infection contributes to the development of CAPA. Type I IFN drives the production of Type III IFN, which, in turn, causes neutrophils to fight against *Aspergillus*. Type I IFN also plays a critical role in promoting CD4+ Th1 cell activation against *Aspergillus*. Another element to the pathogenesis may lie in the depletion of alveolar macrophages in patients acutely ill with COVID-19. These cells are the front-line defense that inhaled *Aspergillus conidia* encounter.[1] Unfortunately, the treatment for hospitalized COVID-19 patients (ie, corticosteroids) is often one of the culprits in the pathogenesis of CAPA. Of their many effects, corticosteroids cause inhibition of interleukin-6, and this blockade itself is a risk factor for CAPA.[13] Nonetheless, corticosteroids remain the treatment of choice in these patients. Hence, it becomes imperative to have heightened awareness of these risk factors to remind clinicians to consider CAPA as a differential diagnosis. Early recognition and prompt initiation of treatment may confer a survival benefit in these patients.[14]

The typical clinical presentation involves either refractory fever, pleural rub, chest pain, or hemoptysis,[8] but CAPA also can present with subtler signs and symptoms as demonstrated in our case. The patient developed nonspecific symptoms, including mild leukocytosis and worsening dyspnea. Due to the potential for subtle clinical presentations, clinicians should exercise a low threshold for suspicion of CAPA. According to a 2021 task force report on CAPA, it is recommended that a diagnostic workup for CAPA be performed on all mechanically ventilated COVID-19 patients with persistently poor respiratory function and clinical deterioration with no other explanation.[15] Diagnosing CAPA poses a great challenge, as radiological findings can vary widely. Some of the findings reported in the literature include peripheral nodule, air crescent, reverse halo sign, nodular consolidation, ground-glass opacities, crazy paving pattern, pleural effusion, and pulmonary cysts.[16]

Despite nonspecific clinical and radiological signs, a reliable diagnostic tool lies in bronchoscopy and bronchoalveolar lavage, and maximum efforts should be made to perform this procedure.[15] Detecting *Aspergillus* in the sputum or endotracheal aspirate is insufficient due to the inability to distinguish normal colonization from invasion. The first line treatments are voriconazole or isavuconazole and should be initiated immediately upon diagnosis due to the high mortality associated with CAPA.[17] Voriconazole is metabolized by cytochrome P450 enzymes and, therefore, raises the potential for drug-drug interactions. Vigilant monitoring for signs of hepatotoxicity and neurotoxicity is imperative for patients undergoing voriconazole treatment with regular assessment of trough levels. Maintaining trough levels within the 2-6 mg/L range is considered therapeutic. Treatment duration is typically between 6 and 12 weeks, depending on clinical and radiologic severity. In cases where concerns regarding hepatotoxicity arise, isavuconazole is a viable alternative. Its advantages include fewer drug-drug interactions, lower toxicity, and a wider therapeutic window.

Patients in the ICU with CAPA have worse outcomes than those without CAPA. According to a European multinational observational study, patients who received systemic antifungal therapy with voriconazole or isovuconazole, had a survival rate of 52% at ICU discharge, whereas untreated patients had a survival rate of only 10%. CAPA also was found to be a significant negative prognostic factor despite adjusting for other predictors of survival, such as age and comorbidities.[18]

CONCLUSIONS

Early diagnosis and treatment are vital to preventing worse clinical outcomes; thus, it is important to have heightened awareness of the risk of developing CAPA in critically ill COVID-19 patients. Given that it may be heralded by subtle and nonspecific symptoms, as in our patient's case, a high clinical suspicion for CAPA is crucial. Mechanically ventilated patients with continued poor respiratory function and no other explanations for their clinical decline should undergo workup for CAPA; in particular, immunocompromised patients who have received a long duration of corticosteroid therapy are at increased risk. Maximum efforts to perform a bronchoscopy with bronchoalveolar lavage to diagnose CAPA is recommended due to varying clinical presentations and radiologic findings. Voriconazole therapy should be initiated immediately upon diagnosis to combat the high mortality rates in CAPA patients.

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Reactive Infectious Mucocutaneous Eruptions (RIME) in COVID-19

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ABSTRACT

Reactive infectious mucocutaneous eruptions (RIME) is a relatively novel terminology describing postinfectious mucocutaneous eruptions that usually affect 2 or more mucosal sites. To our knowledge, we describe the first case of RIME secondary to COVID-19 infection in an elderly 64-year-old immunocompetent male patient. This contrasts with previous case reports that have identified cases of RIME post-COVID-19 infection among the pediatric population and young adults. Our patient had characteristic mucosal involvement and required hospitalization and treatment with systemic steroids. This report also reviews the clinical features, treatment modalities, and outcome of RIME secondary to COVID-19 infection in other published case reports. We emphasize the need for further prospective studies to better elucidate the use of steroids in the management of RIME.

INTRODUCTION

A wide array of dermatological and mucocutaneous lesions associated with COVID-19 infection have been described in the literature.[1,2] Dermatological manifestations commonly reported were morbilliform eruptions, pernio-like lesions, and urticaria;[1] while mucocutaneous findings were papillitis, aphthous stomatitis, and mucositis.[2] In addition, a few case studies have highlighted erythema multiforme (EM) or EM-like cutaneous lesions in patients with COVID-19.[3] Recently, reactive infectious mucocutaneous eruption (RIME)—a unique and distinct entity signifying mucocutaneous involvement— also has been described in patients with COVID-19.[3]

RIME is a relatively novel term characterized by the clinical presentation of significant mucositis (oral, ocular, and anogenital) affecting at least 2 mucous membranes, with absent to sparse cutaneous involvement.[4] It has been associated classically with *Mycoplasma pneumoniae* (*Mycoplasma*-induced rash and mucositis). However, RIME also can be triggered by adenovirus, influenza virus, parainfluenza virus, metapneumovirus, enterovirus, rhinovirus, and, lately, SARS-CoV-2.[5]

To date, RIME secondary to COVID-19 infection has been described primarily in children and adolescents.[3,6-11] There are only a few case reports of RIME following COVID-19 in young adults.[4-5,11] In this article, we describe a case of suspected RIME secondary to COVID-19 in a healthy, immunocompetent 64-year-old man.

CASE PRESENTATION

A 64-year-old male patient with a past medical history of coronary artery disease presented with blisters in his mouth and irritation in the eyes for 3 to 4 days. He was diagnosed with COVID-19 via polymerase chain reaction testing a week prior to the presentation when he had a sore throat, myalgia, cough, chills, and diarrhea. Of note, he had not received any COVID-19 immunization. At that time, he was symptomatically managed with rest and hydration. However, he sought an alternative therapy through an online telemedicine consultation and received a single dose of 47 g ivermectin 4 days after his COVID-19 diagnosis. Twenty-four hours after receiving ivermectin, he noticed red eyes with constant tearing, dryness, and

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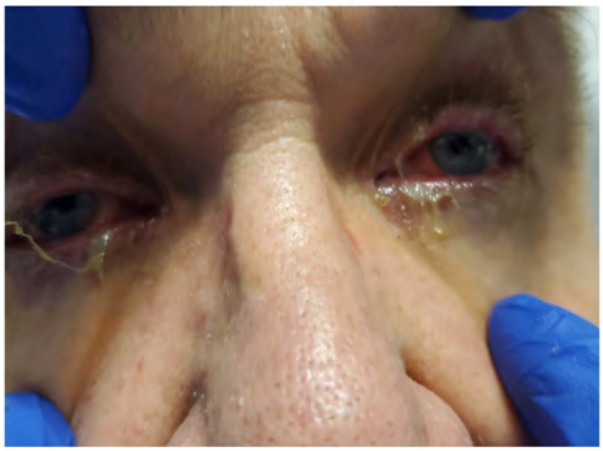
slightly blurry vision. The next day, he noticed blisters in his mouth, particularly underneath his upper and lower lips. He denied any other cutaneous rashes, headaches, chest pain, or consumption of any new medication except ivermectin. Other than ongoing diarrhea, his COVID-19–related symptoms had subsided.

On admission, the patient was febrile and temperature was 101.5 °F with normal heart rate and blood pressure. He was maintaining an oxygen saturation of greater than 95% on room air. His physical exam was significant for confluent superficial erosions with overlying heme crusting on the upper and lower vermillion lips. There were superficial circular erosions on the hard and soft palate. He also had thick discharge matted on his eyelashes bilaterally and conjunctival injection. His other examinations, including the dilated fundoscopy, corneal exam, penile exam, and detailed skin examination, were unremarkable (Figures 1 and 2). Blood tests, including complete blood cell count, basic metabolic panel, and liver function test, were unremarkable. His platelet counts were normal at 277×109/L; ferritin was 850 ng/mL (normal value 30-400 ng/mL), C-reactive protein (CRP) was 1.04 mg/dL (normal value < 0.50 mg/dL), and erythrocyte sedimentation rate was 17 mm/hr (normal value 0-20 mm/hr). His infectious workup, including rapid plasma reagin screening, nasopharyngeal *Mycoplasma pneumoniae* nucleic acid amplification testing (NAAT), herpes simplex virus (HSV) type 1 and 2 NAAT obtained from buccal mucosal lesions, and extended respiratory panel NAAT (adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, human metapneumovirus, influenza A, influenza B, parainfluenza virus 1-4, rhinovirus, respiratory syncytial virus, *Bordetella pertussis/parapertussis, Chlamydia pneumonia*) from nasopharyngeal swab were unremarkable, except for SARS-CoV-2 by NAAT. His chest x-ray revealed subtle densities in the bilateral peripheral upper lobes and the right midlung that appeared to be improving compared to a week prior when he was diagnosed with COVID-19.

The patient was diagnosed with suspected RIME secondary to COVID-19 infection and was managed symptomatically with intravenous (IV) hydration, viscous lidocaine, chloraseptic spray, and acetaminophen. He also received topical erythromycin ointment twice daily, along with preservative-free artificial tears for his conjunctival injection. During the hospital course, he had worsening of his mucocutaneous symptoms, including oral pain and difficulty swallowing. He also had low-grade intermittent fever spikes. His subsequent physical exam revealed a slight worsening of his aforementioned oral erosions with interval development of conjunctival pseudomembranes. His inflammatory markers worsened, with ferritin increasing to 1214 ng/mL (from 850 ng/mL) and CRP rising to 26.32 mg/dL (from 1.04 mg/dL). White blood cell count remained within the normal limits without any left shift. Due to his clinical deterioration, he was started on IV methylprednisolone 48 mg daily for 5 days, along with prednisolone acetate 1% eye drops 4 times daily to each eye. He also received IV ketorolac for pain management alongside "magic mouthwash" (lidocaine, Benadryl, dexamethasone) and nystatin. He reported improvement after treatment escalation as above, and once he

Figure 1. Mucositis With Superficial Erosion and Heme Crusting on the Lips and Buccal Mucosa

Figure 2. Bilateral Conjunctivitis



was able to tolerate soft food, he was switched from IV methylprednisolone to oral prednisone with the following taper schedule: oral prednisone 60 mg daily for 2 days, followed by 40 mg daily for 4 days, then 30 mg daily for 4 days, 2 mg daily for 4 days, and, finally, 10 mg daily for 4 days.

On day 6 to 7 of admission, he started having nonpruritic and painless maculopapular eruption bilaterally on the hands and feet. It started as a few small macules that increased in size and number and became targetoid lesions of approximately 4 to 5 mm (Figure 3). It later evolved to become papules with central clearing. A few of the papules had even coalesced to form larger plaques. He otherwise felt better with the improvement of his mucocutaneous symptoms. He remained afebrile and his CRP had improved to 8.11 mg/dL. His targetoid lesions were thought to be associated with the diagnosis of RIME, and he was continued on oral steroids as above. His mucocutaneous erosions and acral lesions improved prior to discharge.

Figure 3. Targetoid Macules and Plaques on Bilateral Hands and Feet Occurring on Hospital Day 6 to 7.

At a 2-week follow-up visit, the patient reported significant improvement in his oral symptoms and increased oral intake. In addition, his hands and feet lesions also improved without residual scarring. Unfortunately, he continued to have bilateral eye irritation with conjunctival injection and pseudomembranes. He also was noted to have new punctate epithelial corneal erosions bilaterally. He was continued on prednisolone acetate 1% eye drops 3 times daily, along with erythromycin ointment. After 4 weeks, he had a complete resolution of his ocular symptoms.

DISCUSSION

We report the case of a healthy immunocompetent 64-year-old male patient who was diagnosed with suspected RIME secondary to COVID-19 infection. He had oral mucositis and conjunctivitis, with only sparse cutaneous involvement. His mucositis resolved after the initiation of systemic steroids. No recurrence was noted at the 6-week follow-up visit. To the best of our knowledge, this is the first reported case of RIME secondary to COVID-19 in an older patient. Previous reports have identified cases of RIME post–COVID-19 infection in the pediatric population and young adults from age 13 to 39 years.[3-11]

The diagnosis of RIME can be challenging in patients with COVID-19 due to a wide array of dermatologic and mucocutaneous findings associated with COVID-19 infection.[1,2] In addition, erythema multiforme major (EMM) and EM-like lesions also have been reported in COVID-19,[12] which can be difficult to distinguish from RIME and can pose a diagnostic challenge. The criteria for the diagnosis of RIME include an infectious trigger, erosive mucositis affecting 2 or more sites, vesiculobullous lesions or atypical target lesions affecting less than 10% of the body surface area, noncontributory medication history, and prodromal symptoms.[13] It is distinguished from drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis and herpes-related EM due to its predominance of mucosal involvement, relatively sparse cutaneous findings, prevalence among younger patients, and its excellent prognosis.[14]

Stevens-Johnson syndrome was a potential differential diagnosis in our patient due to the consumption of 1 dose of 47g ivermectin 24 hours prior to symptom onset. The short latency period of only 24 hours between ivermectin consumption and symptom onset, along with no cutaneous findings on admission, made Stevens-Johnson syndrome unlikely in our patient. Furthermore, the interval development of acral targetoid lesions later in the hospital course was thought to be more likely related to RIME rather than EMM due to the absence of classic target-like lesions, the appearance of rashes while being on steroids, and the negative HSV type 1 and 2 NAAT. The cutaneous findings of papules, plaques, vesicles, and targetoid lesions on extremities including hands and feet also were described in other cases of RIME secondary to COVID-19.[3,4,8,11] Lastly, multisystem inflammatory syndrome in adults (MIS-A) was a potential differential diagnosis in our patient. The Centers for Disease Control and Prevention has postulated criteria for case definition of MIS-A that include presence of fever, severe cardiac illness, rash, new-onset neurologic symptoms, shock, and thrombocytopenia.[15] Our patient did not meet this case definition.

The onset of mucocutaneous findings after acquiring COVID-19 infection can range from 3 days to 2 weeks post-infection, with the resolution of mucositis occurring after 5 days to 3 months.[11] In

our patient, conjunctivitis developed after 4 to 5 days of COVID-19 diagnosis and rapidly progressed to mucositis. It lasted 4 to 6 weeks, with complete resolution occurring after 6 weeks. This timeline of onset and resolution is consistent with the reported literature. Our patient had mucositis involving lips, buccal mucosa, and conjunctiva, with the absence of urogenital involvement. This is also consistent with the reported literature highlighting consistent involvement of lips, with variable ocular findings and urogenital involvement.[11] Lastly, our patient had fever at the onset of his illness, which also is seen commonly in other reported cases of RIME.[3-6,9,11]

As RIME is considered a self-limiting diagnosis, its treatment is usually supportive—with mucosal care, pain management, and hydration[14]—and most patients require hospitalization.[10] The role of immunomodulators, including steroids, is unclear. In most reported cases of RIME secondary to COVID-19 infection, systemic steroids (oral or IV) with variable doses, duration, and tapering schedules were employed.[3-4,6-11] Concomitant IV immunoglobulin (IVIG) with systemic steroids[6] or systemic steroids followed by cyclosporine were utilized in some published cases.[9,11] Antibiotics and antivirals also have been used sparingly.[6,11,14] In the literature, topical therapies commonly administered were hydrocortisone buccal tablet, dexamethasone oral solution, topical corticosteroid ointment, and viscous lidocaine.[3-11] In our case, we initially utilized supportive therapies, including viscous lidocaine, acetaminophen, and IV hydration. Due to worsening symptoms, a systemic steroid with a tapering schedule as mentioned above was initiated. As the complete resolution of mucositis took around 4 to 5 weeks in our case, it is unclear if improvement represents the therapeutic effects of steroids or the natural resolution of the disease process. Further prospective studies are needed in this regard to elucidate the role of steroids in the management of RIME. In addition, it is unclear if COVID-19 vaccinations have any role in mitigating the severity of RIME. Interestingly, in a large retrospective cohort study done in the United Kingdom, the odds of having cutaneous manifestations of COVID-19 were similar between vaccinated and unvaccinated individuals.[16]

CONCLUSIONS

We report a case of RIME secondary to COVID-19 in an older male patient. To the best of our knowledge, this is the first reported case of RIME post–COVID-19 infection in this age group. Due to the wide-ranging mucocutaneous manifestations associated with COVID-19 and challenging differentiation with the EM or EM-like lesions, the identification of RIME can pose a diagnostic challenge. In the context of the recent pandemic, physicians should consider the diagnosis of RIME in patients presenting with predominant mucositis or mucosal involvement after the COVID-19 diagnosis. Most patients usually require hospitalization and treatment with supportive care and systemic steroids. More studies are needed to create a treatment algorithm to aid clinicians in guiding timely therapy. It is unclear if COVID-19 immunizations can have an impact on preventing the development of RIME.

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A Case of COVID Cholangiopathy and Literature Review

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ABSTRACT

Introduction: With cholangiopathy, the bile ducts become inflamed and have a "beads on string appearance" with elevated bilirubin. It is typically associated with primary sclerosing cholangitis but is now being reported as a post-COVID complication.

Case Presentation: A 65-year-old White male presented with resolved respiratory failure from COVID-19 pneumonia, jaundice, and likely subacute kidney injury. He was diagnosed with COVID-19 cholangiopathy due to clinical picture and magnetic resonance cholangiopancreatography imaging. Unfortunately, due to a massive refractory gastrointestinal bleed, he was transitioned to hospice care.

Discussion: COVID-19 has been shown to have both short- and long-term effects on multiple organ systems. Cholangiopathy is a rare complication of COVID-19. Most of these cases result in severe liver failure and require liver transplant, similar to primary sclerosing cholangitis.

Conclusions: We report this case to increase awareness among clinicians to consider COVID-19 cholangiopathy in patients with unexplained jaundice and a history of severe COVID-19 infection.

INTRODUCTION

COVID-19 is a disease that has short- and long-term effects on multiple organ systems, ranging from classic symptoms of runny nose, cough, and fever to more severe cases that can include acute respiratory distress syndrome and cardiomyopathy secondary to an inflammatory response.[1] Interestingly, hepatic and bile duct involvement after severe COVID-19 infection also have been reported.[2] The 2 leading theories for this cholangiopathy are that a prolonged inflammatory state causes chronic cholangitis resulting in cholangiopathy and ischemic injury of the biliary epithelium causing cholangiopathy.[3] In literature, this has been classified as cholangiopathy secondary to COVID-19—different from primary sclerosing cholangitis (PSC). However, both have the same treatment options with supportive management of hyperbilirubinemia and ultimately require liver transplantation for a cure. Here we report a case of a patient who had a severe COVID-19 infection and developed COVID-19 cholangiopathy, with comparisons to other cases reported in the literature.

CASE PRESENTATION

A previously healthy 65-year-old unvaccinated White male with no significant past medical history presented from an outside hospital after transfer from Brazil. He had contracted COVID-19 in May 2021 and was immediately admitted to an intensive care unit (ICU) in Brazil until mid-June. He had received dexamethasone and mavrilimumab for acute respiratory distress syndrome, was intubated for 10 days, and placed on extracorporeal membrane oxygenation (ECMO) for a week. Records from Brazil were not provided, and the timeline is based on his wife's recollection/in-flight physician handoff. He was then extubated and transferred to the floor until mid-July.

While still in Brazil, the patient developed acute hepatitis with bilirubin to 16mg/dL, elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) to 200s IU/L. According to his wife, jaundice and acute hepatitis developed 4 days prior to transfer. On arrival to the initial admitting hospital in Wisconsin, he was febrile, blood culture was positive for *Stenotrophomonas maltophilia*, and x-ray revealed stage 4 sacral

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ulcer with sacral osteomyelitis. His labs included the following: white blood cell count 26K/uL, hemoglobin 9.8g/dL, AST 219 IU/L, ALT 241 IU/L, bilirubin 14.1mg/dL (direct 12.8mg/dL), alkaline phosphatase 1622 U/L, and creatinine 3.02mg/dL. He was started on cefepime, metronidazole, and vancomycin. He also had not had a bowel movement for 4 days. Given the need for higher level of care, he was transferred to Froedtert Hospital in Milwaukee, Wisconsin.

On arrival, the patient's vitals were as follows: temperature 97.6 °F, pulse 97 beats per minute, blood pressure 118/63 mmHg, 99% oxygen saturation on room air, and fraction of inspired oxygen (FiO2) 21%. Labs were bicarbonate 19 mEq/L, international normalized ratio 1.1, total bilirubin 15 mg/dL, AST 181 IU/L, ALT 200 IU/L, and alkaline phosphatase of 1391 U/L. He initially was evaluated for cholestasis of sepsis, drug-induced liver injury, and acute cholangitis. However, right upper quadrant ultrasound was negative for obstruction/dilation of the common bile duct, and no altered mental status was present. He was started on N-acetyl cysteine and ursodiol due to jaundice, alongside piperacillin and tazobactam given concerns of acute cholangitis. Anti-smooth muscle antibody (ASMA), antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibodies (pANCA), and IgG4 labs were drawn to isolate causes of acute hepatitis and cholangiopathy. The following day, magnetic resonance cholangiopancreatography (MRCP) was significantly motion degraded but showed no evidence of hepatic contour nodularity, with mild multifocal intrahepatic biliary dilation and normally patent hepatic vasculature and mild periportal edema. There was no evidence of portal hypertension. Furthermore, the patient's clinical picture included no history of inflammatory bowel disease and no prior abnormal liver chemistries. Due to the MRCP results, with negative pANCA, IgG4, ASMA, and ANA, he was diagnosed with COVID-19 cholangiopathy (Figures 1 and 2).

Labs showed no changes from the previous day. Due to the patient's relative stability and request, his nasogastric tube was removed. He also underwent an abdominal x-ray due to constipation. It showed large stool caliber in bowels with no obstruction. As such, he was given polyethylene glycol and an enema.

The following morning, the patient passed a large melanotic stool and proceeded to become hypotensive and hypoxic. He was given 1 L of lactated ringer and blood pressure up to 138/73 mmHg. Hemoglobin and hematocrit levels also showed a hemoglobin of 5.7 g/dL – down from 9.0 g/dL on admission – and he was given 2 units of packed red blood cells (pRBC). At this point, due to hemodynamic/respiratory instability and the need for massive transfusion protocol, he was transferred to the ICU.

The patient underwent an esophagogastroduodenoscopy (EGD) and was found to have a large 2-cm ulcer in the distal duodenum bulb, oozing with no portal hypertension. Despite multiple hemoclips and multiple epinephrine injections, the ulcer did not stop bleeding. Interventional radiology was consulted and embolized the duodenal ulcer artery. Computed tomography angiography (CTA) performed the day after the procedure did not demonstrate a place for intervention radiology to intervene. However, given continued bleeding, the day after CTA imaging, an additional EGD was performed and 3 hemoclips were placed.

Figure 1. Magnetic Resonance Cholangiopancreatography Image of Patient's Dilated Intrahepatic Bile Ducts

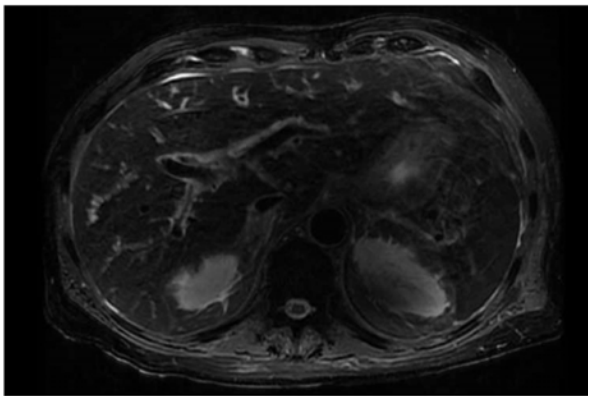
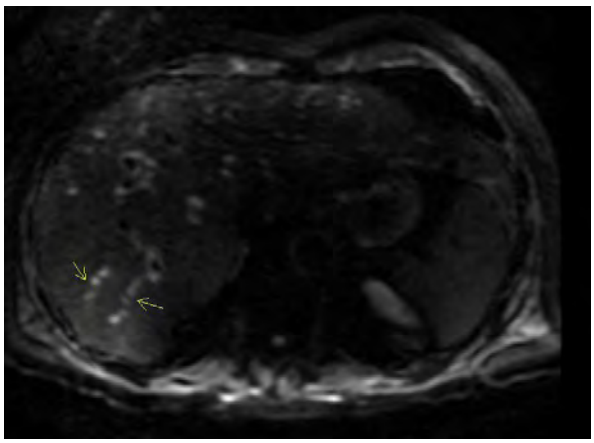


Figure 2. "Beaded" Appearance of Distal Ducts



After the second EGD, the patient was given additional pRBC units due to low hemoglobin and started to develop delirium. He also continued to have melanotic stools and required additional transfusions to keep hemoglobin greater than 7.0 g/dL. Unfortunately, he continued to bleed from the ulcer site and hemoglobin continued to decline.

Despite 2 EGDs and embolization of the gastric duodenal artery, the patient continued to have bleeding and a third EGD was performed in late July. The same duodenal bulb ulcer was treated with epinephrine, gold probe, and hemoclip. After the third EGD, his hemoglobin stabilized, and acute care surgery was

consulted a few days later given the potential need for surgical intervention due to exhaustion of nonsurgical options. However, because of the patient's comorbidities and likely need for long-term hemodialysis or potential organ transplant, acute care surgery did not offer surgical options. As both options were against the patient's wishes, the following day he decided to discontinue treatment and be placed on comfort care.

DISCUSSION

Since COVID-19 was first recognized by the World Health Organization in December 2019, it has infected 219 million people and killed 4.55 million people around the world.[4] At the time of this report, in the state of Wisconsin, there had been over 700 000 cases and over 8000 deaths due to COVID-19.[5] COVID-19 also has developed a multitude of variants and presentations, including the Omicron BA.4 and BA.5 subvariants, which are proving incredibly virulent and responsible for a majority of infections.[6]

While most commonly known for its effect on the lungs, COVID-19 is a disease that affects multiple organ systems and can cause long-term effects, some of which are still unknown. There have been many reports of damage to the vascular endothelial cells, brain, kidneys, intestines, and increased risk of clotting.[7] Many of these are believed secondary to the immense inflammatory response caused by COVID-19, which involves an increase in cytokines and interleukin (IL)-1, IL-2, IL-6, IL-8, IL-17, IL-19, and interferon gamma.[8,9]

We present this case of hepatobiliary involvement as a relatively new and rare discovery. Although there is no current agreement on the exact pathophysiology of COVID-19 cholangiopathy, we agree with Faruqui et al, who suggest that given the similarities of COVID cholangiopathy and secondary sclerosing cholangitis in critically ill patients, the pathophysiology of the diseases are similar.[3,10,11] The main component of this pathophysiology is that the biliary epithelium is vulnerable to ischemic injury due to its singular blood supply from the peribiliary vascular plexus, supplied by hepatic arterial branches. The hepatic parenchyma, on the other hand, has dual blood supply from both the portal vein and hepatic arteries.[3] Should the pathophysiology of COVID-19 cholangiopathy be proven similar to secondary sclerosing cholangitis in critical illness, it could be speculated that it is worsened by SARS-CoV-2 epithelial infection, microthrombi, and/or the magnitude of cytokine release syndrome particular to COVID-19. With these theories, the end result is that there is damage to the biliary epithelium that presents with an elevation in the total bilirubin, elevation in liver enzymes, and inflammation of the bile ducts, diagnosed as cholangiopathy.

Our patient likely had COVID-19 cholangiopathy, supported by his recent severe COVID infection, elevated total bilirubin, elevated liver enzymes, elevated alkaline phosphatase, and elevated inflammatory markers like C-reactive protein. All these pointed towards hepatobiliary involvement. In addition, the right upper quadrant ultrasound was negative for cystic duct dilation or stones, no fever was present during Froedtert Hospital admission, and pANCA, ASMA, IgG4 labs were all negative; this led to COVID-19 cholangiopathy as the most likely diagnosis. MRCP further supported the diagnosis with the classic "beading" patterning of the intra and extra hepatic bile ducts. Due to this presentation 3 months after COVID-19 infection, the lack of major medical histories, and the lack of markers for PSC, the diagnosis of exclusion of COVID-19 cholangiopathy was made. Our case is unique due to the lack of documented cases of COVID-19 cholangiopathy; the Table represents a brief overview of cases presented in literature, including two from our own institution.

In the literature, COVID-19 cholangiopathy has very bleak outcomes, with supportive care being the only management option before definitive treatement.[3,12] As stated by Faruqui et al, because the pathophysiology of COVID-19 cholangiopathy and PSC is so similar, the definitive treatment is also similar: liver transplant and urdoxylic acid used for symptomatic management.[3] However, due to this patient's multisystem organ failure, refractory gastrointestinal (GI) bleed, and recurrence of respiratory failure, liver transplant was not discussed and the patient was managed with urdoxylic acid and hospice care.

Furthermore, due to the patient's severe presentation and rapid deterioration after admission secondary to GI bleed, we believe our case is an excellent teaching case that shows the workup process for COVID-19 cholangiopathy and the potentially fatal outcomes that can result. Additionally, given that refractory bleeding appears to be the cause of death in a number of these patients, if this pattern becomes recognizable, it would be reason for a more emergent referral to liver transplantation. While we were able to identify what was causing this patient's hepatic dysfunction, due to his multisystem organ failure and massive refractory GI bleed, little could be done other than supportive care.

Management of cholangiopathy is supportive only as a bridge to transplant.[12] While hospitalized, it is important to monitor daily labs, including coagulation parameters and hemoglobin. It is also important to monitor for melena or hematochezia. If the patient is otherwise stable, then liver transplantation is the only viable cure in these cases, but the patient can receive supportive treatment with urdoxylic acid treatment to decrease total bilirubin.

In summary, the diagnosis of COVID-19 cholangiopathy should be a diagnosis of exclusion and should only be considered with a prior history of severe COVID-19 infection. It should be worked up with imaging and ruling out PSC and can be confirmed with MRCP that shows "beading" of the intra and extra hepatic bile ducts. Given the continued changes and prevalence of unknown variables from the pandemic, it is imperative for clini-

Table. Additional Cases of COVID-19 Cholangiopathy Reported in Literature

Author	Patient Age	Sex	Medical History	Location	Major Liver Pathology Location	Mode of Diagnosis	Clinical Status
Faruqui, et al[3]	73	M	Diabetes, HTN, HLD, CVA	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	39	M	HTN, HLD, cocaine use	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	64	M	Diabetes, HTN, HLD, CVD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive, had LT
Faruqui, et al[3]	77	M	HTN, HLD, CVD, PD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive on ursodiol
Faruqui, et al[3]	46	M	HTN	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	72	M	Obesity	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased from hemiperitoneum, no LT
Faruqui, et al[3]	38	M	None	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased, listed for LT
Faruqui, et al[3]	60	M	Obesity, HTN, HLD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive on ursodiol, listed for LT
Faruqui, et al[3]	42	M	None	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased from massive GI bleed, no LT
Faruqui, et al[3]	57	M	Obesity, HTN	New York, NY	Unspecified hepatic abnormality	MRCP	Deceased from perforated duodenal ulcer, no LT
Faruqui, et al[3]	68	M	Diabetes, HLD, CVD, HT	New York, NY	Unspecified hepatic abnormality	MRCP	Alive on ursodiol
Faruqui, et al[3]	62	F	Obesity, diabetes, HTN	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Durazo, et al[12]	47	M	Obesity, OSA, HTN, HLD	Milwaukee, WI	Intrahepatic bile ducts	CTAP, ERCP	Alive, had LT
Gourjault, et al[13]	55	M	Obesity	Paris, France	Intrahepatic bile ducts	Hepatic MRI w/ biopsy, ERCP	Alive, listed for LT
Gourjault, et al[13]	45	M	Obesity	Paris, France	Intrahepatic bile ducts	Hepatic MRI	Alive
Gourjault, et al[13]	30	M	None	Paris, France	Intrahepatic bile ducts	Hepatic MRI w/ biopsy	Unknown, had LT
Roth, et al[14]	38	M	None	Manhasset, NY	Intrahepatic bile ducts, terminal hepatic veins, zone 3 region	Hepatic MRI w/ biopsy, ERC	Alive
Roth, et al[14]	25	M	None	Manhasset, NY	Extrahepatic bile ducts, sinusoidal obstruction w/ zone 3 necrosis	Hepatic MRI w/ biopsy, ERC	Alive
Roth, et al[14]	40	F	Diabetes	Manhasset, NY	Severe zone 3 hepatocanalicular cholestasis/focal bile infarcts	Hepatic MRI w/ iopsy, ERC	Alive
Lee, et al[15]	64	M	HTN, HLD, diabetes	St. Louis, MO	Common bile duct, intrahepatic bile ducts	CTAP, ERCP, MRCP	Alive, had LT

Abbreviations: MRCP, magnetic resonance cholangiopancreatography; CTAP, computed tomography of abdomen and pelvis; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; MRI, magnetic resonance imaging; ERC, endoscopic retrograde cholangiography; HTN, hypertension; HLD; hyperlipidemia; CVD, cardiovascular disease; CVA, cerebrovascular disease and/or accident; PD; Parkinson's disease; HT, hypothyroidism; OSA, obstructive sleep apnea; PCR, polymerase chain reaction; LT, lung transplant.

[a]Faruqui, et al report MRCP for all patients; 4 patients underwent hepatic biopsy however unspecified, other tests not specified.

cians to have continued awareness on guidelines of management for cases that may turn severe, such as the COVID-19 cholangiopathy presented here.

CONCLUSIONS

Although COVID-19 cholangiopathy is an uncommon complication of COVID-19 infection, it should be considered in the differential diagnosis of elevated liver enzymes and total bilirubin after severe COVID-19 infection. We report this case and literature review to increase awareness among clinicians treating patients who present with unexplained jaundice and acute hepatitis. Detailed examination and investigation are necessary to make this diagnosis. More reporting of similar cases is essential for attention from clinicians and researchers to develop evidence-based guidelines for the diagnosis and management of this condition.

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Nihilism, Neurocognition, and the Novel Coronavirus: A Case of Acute Onset Cotard's Syndrome

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ABSTRACT

Introduction: The novel coronavirus (COVID-19) is a respiratory illness that may cause neuropsychiatric sequelae, including persistent psychotic symptoms.

Case Presentation: A 70-year-old White man with no prior psychiatric history presented with altered mental status, Cotard's syndrome, and rigid delusions of poverty and homelessness 6 weeks after recovering from a mild case of COVID-19. After extensive medical workup revealed no organic etiology, he was treated for psychotic symptoms with an atypical antipsychotic, an antidepressant, and electroconvulsive therapy, with improvement over time.

Discussion: While COVID-19 is primarily a respiratory disease, some individuals may develop new-onset psychiatric or neuropsychiatric symptoms without prior psychiatric history.

Conclusions: To our knowledge, this is the only published case of post–COVID-19 psychotic symptoms treated with electroconvulsive therapy. As the pandemic continues, the total impact of COVID-19 on psychotic symptoms remains to be seen.

INTRODUCTION

While primarily causing widespread death and devastation as a respiratory illness, several years into the COVID-19 pandemic, we now understand SARS-CoV-2 infection to cause numerous other sequelae, including psychotic symptoms. It has been established previously that other viral infections are associated with neuropsychiatric consequences. Encephalitis was seen during the 1917 Spanish flu pandemic.[1-4] Caused by similar beta-coronaviruses, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were found to have increased risk of manic-depressive disorders, agitation, and delirium.[1,5,6] While coronaviruses are known to be neurotropic, the exact mechanism for neuropsychiatric symptoms is unknown.[7] Proposed theories include hypoxia, exaggerated immune response with "cytokine storm," inflammation, and invasion of the central nervous system; however, inflammatory markers were not obtained in this case.[1,3,5,7-10]

Here, we discuss the presentation and treatment course for post-COVID neuropsychiatric symptoms in a geriatric patient with minimal psychiatric history and highlight possible long-term effects of the novel coronavirus infection that are not yet fully recognized or understood. Few other case reports have demonstrated similar findings following COVID-19 infection,[5,7,9,11,12] and only 1 case report has documented Cotard's syndrome in the clinical presentation.[8]

While some studies using data from similar coronavirus pandemics suggest there is no concern for increased psychotic symptoms following COVID-19 infection,[1,10] a large retrospective analysis by Taquet et al[13] found increased risk of psychotic disorders up to 2 years after recovery. Our intent is to contribute to the limited existing literature describing psychotic symptoms secondary to COVID-19 infection and discuss treatment options, as well as highlight the importance of continued public health efforts in slowing and preventing disease spread.

CASE PRESENTATION

A 70-year-old White male with past medical history of gout, benign prostatic hyperplasia, and insomnia presented to the emergency department (ED) with altered mental status. He was brought in by family due to 2 weeks of erratic behavior, nihilistic delusions, irrational fixations on hospital bills, and delusions of outstanding debt and homelessness. His family reported that he had made statements like "I'm not going to be around very long," "It is judgement day," and "I feel like I'm out of this world." These

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behaviors had been worsening progressively over the 3 weeks leading up to admission. He had no history of substance use, was retired, and was widowed 5 years prior to admission. He reported no psychiatric history, although his mother had schizophrenia.

The patient tested positive for COVID-19 6 weeks prior to admission and recovered without hospitalization. His predominant symptoms of COVID-19 included several weeks of gastrointestinal distress. He did not report taking any medications for his symptoms. In the ED, he had a blood pressure of 122/76 and pulse of 68 beats per minute. His oxygen saturation (Sp02) was 100%, and he was afebrile. Both complete blood cell count and comprehensive metabolic panel were within normal limits. Ammonia, thyroid-stimulating hormone, and salicylate levels were normal. Urinalysis was without infection, and urine drug screen was negative.

The patient was admitted to the inpatient medicine service with differential diagnoses of neurocognitive disorder, post-COVID encephalitis, autoimmune encephalitis, other toxicities, and primary psychiatric disorder. On physical exam, he was fully oriented and cranial nerves II-XII were intact. Both strength and sensation were intact in proximal and distal muscle groups of all extremities. His tandem walking was intact, Romberg test was negative, and he was without asterixis or tremor. He underwent comprehensive screening investigating possible organic cause for his symptoms. Computed tomography (CT) head was negative for mass effect, midline shift, hydrocephalus, or acute intracranial hemorrhage. Due to concern for underlying malignancy given his presentation and history of weight loss over the past year, a CT scan of chest, abdomen, and pelvis was performed without findings suggestive of neoplastic disease. Additional workup for paraneoplastic syndrome included amphiphysin autoantibody, CV2 antibody, and Hu autoantibody—all of which were negative. Combined with imaging, urine metanephrines testing ruled out pheochromocytoma. Magnetic resonance imaging of the brain showed abnormal increased T2/FLAIR signal intensity in the left insular cortex, which was noted to be a nonspecific finding and unclear whether related to psychosis, as well as mild chronic microvascular ischemic white matter changes. Vitamin B12 was normal, and folate was mildly low at 8.0 ng/mL. Screening for lead, mercury, and arsenic was negative. A cerebrospinal fluid examination yielded no abnormalities, which ruled out neurosyphilis and other infectious causes. Inflammatory markers were not obtained.

During initial assessment by the psychiatry consultation liaison team on day 2 of hospitalization, the patient was noted to be perseverative on having died and being in hell, stating he was being punished for the life he lived. He reported, "I wish I could kill myself, but I can't," believing to be already deceased. While his organic workup was unrevealing, his presentation and illness onset were unusual for primary psychiatric illness or neurocognitive disorder. Neuropsychological assessment showed abnormalities in executive function, abstraction, and retrieving new information on the Montreal Cognitive Assessment (MoCA version 8.2), thought to be secondary to active psychosis. He was without evidence of delirium and demonstrated intact attention on exam. He was treated with high-dose intravenous thiamine for 3 days given history of recent weight loss. Olanzapine was started and titrated to address delusions. His nihilistic delusions showed some improvement while other delusions persisted.

On day 13 of hospitalization, the patient was transferred to the inpatient psychiatric unit. He continued to express delusions of impoverishment, stating he did not have a home or family. Escitalopram was added to treat depressed mood. By day 29 of hospitalization, nihilism and Cotard's syndrome had resolved, but other delusions continued, and he noted paranoid ideas of reference regarding peers on the unit. He also struggled with simple grooming tasks, such as showering and trimming nails. As symptoms were most consistent with psychotic depression, electroconvulsive treatment (ECT) was initiated on day 40 of hospitalization and continued for 13 sessions over 5 weeks. He tolerated ECT without significant adverse effects. Olanzapine was transitioned to risperidone to further address delusions. He continued to show improvement and acknowledged owning a home and car and being without financial debts. He was without any acute agitation throughout his hospitalization and cooperative with unit staff and treatment team. Towards the end of his hospitalization, he consistently attended unit programming and group therapies. On day 74, he was discharged home with family.

During the patient's stay, collateral was collected from multiple sources. Several family members confirmed that he had never been diagnosed with psychiatric illness and that he did, indeed, own his home and had no outstanding debts. They also confirmed that prior to onset of unusual symptoms, he had been able to manage a rental property, live independently, and perform all activities of daily living (including grooming and hygiene) without issue.

DISCUSSION

Several other case reports demonstrate similar findings in patients with no prior psychiatric history who developed psychotic symptoms during acute illness or shortly after recovery from COVID-19.[2,7,9,11,12] In many cases, the patients had been treated previously with steroids, antivirals, or antibiotics.[5,11,12] To date, there is one other documented case of Cotard's syndrome following COVID-19 infection. Ignatova et al[8] described a patient with nihilistic delusions about having died (with decomposing organs) shortly after being treated for COVID-19 and pneumonia. He improved with haloperidol and showed complete recovery after several months. The authors suggested that fear of infection and impending doom related to the pandemic may be tied to onset of nihilistic or Cotard's delusions.[8]

While our patient shared some symptoms and characteristics with patients in similar case reports,[8,11] he differed in that he was not hospitalized for COVID-19 and recovered without oxygen, steroids, or antibiotics. Further, to our knowledge, this is the only

published case of post-COVID psychotic symptoms requiring ECT, though there have been other documented cases of Cotard's syndrome successfully treated with ECT.[14]

The etiology of psychotic symptoms secondary to viral illnesses is not fully understood, though several theories have been postulated. Significant inflammatory response to infection or "cytokine storm" is thought to cause cardiopulmonary complications of COVID-19 and also may contribute to neuropsychiatric symptoms.[1,7,10,15] Several previous case reports noted raised inflammatory markers (TNF-alpha, ferritin, and C-reactive protein [CRP]) in patients with similar presentations, suggesting that obtaining cytokine profiles in patients with psychiatric symptoms secondary to COVID-19 may be beneficial to inform management.[2,3,5,7,9] Other possible mechanisms include molecular mimicry and invasion of the nervous system secondary to viral "proteiform" disease.[5,9] Of note, our patient contracted COVID-19 prior to widespread use of coronavirus vaccines, thus it begs the question whether immunization would have affected or even prevented his symptom course.

In a descriptive systematic review of case reports, Smith et al[6] found delusions (92% of patients) to be the most common symptom in adults with psychotic symptoms during or after COVID-19; the authors also encouraged clinicians to acknowledge numerous confounders between COVID-19 and incident psychosis and obtain detailed clinical assessment. Later, in a retrospective analysis, Taquet et al[13] found increased risk of mood disorders, such as anxiety or depression, following COVID-19 infection that returned to baseline after several months. However, increased risk of psychotic symptoms and cognitive deficit persisted up to 2 years after initial infection. Conversely, Watson et al[4] suggested that psychosis may be a potential complication of all viral illnesses, and cases secondary to COVID-19 may seem so prevalent due to the scale of the pandemic.

While we cannot rule out the possibility that this patient's presentation was entirely related to psychological stress, it seems unlikely given the onset of symptoms and lack of psychiatric history. Was he predisposed to psychosis due to family history, coupled with the possible inflammatory insult of COVID-19 illness that led to persistent delusions? According to Watson et al,[4] the possible association between COVID-19 infection and psychotic symptoms does not meet the Bradford-Hill criteria required for determination of causality; however, there is biological plausibility to the association.

Our case describes an interesting clinical presentation possibly secondary to COVID-19, yet is limited by small sample size and lack of additional medical workup (eg, measurement of inflammatory markers such as CRP, IL-6, TNF-alpha, and other cytokines). Additionally, reliance on the patient's report and collateral information may affect the exact timeline of events. As stated by Troyer et al,[3] the neuropsychiatric burden of the COVID-19 pandemic is currently unknown but likely to be significant. This case highlights the importance of research into possible neuropsychiatric sequelae of COVID-19 infection and public health measures for disease prevention.

CONCLUSIONS

While COVID-19 is primarily a respiratory disease, some individuals may develop new-onset psychiatric symptoms without prior psychiatric history, as in this patient. Early intervention and appropriate treatment are of critical importance for effective treatment and recovery; ECT may be considered as an option if antipsychotic medications are not effective. As the worldwide coronavirus pandemic continues, it is likely that additional cases of post-COVID psychosis will manifest, requiring ongoing research into pathophysiology and treatment.

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Ready to Live, Be Prepared to Die

Quratul Ain Aziz, MD

"It was a meditation on life, love, old age, death: ideas that had often fluttered around her head like nocturnal birds but dissolved into a trickle of feathers when she tried to catch hold of them."

—*Gabriel García Márquez,* Love in the Time of Cholera[1]

As a primary care physician for the last 10 years, I take pride in supporting my patients and their families. Every day I see patients and help them control pertinent risk factors that ideally will help them live long and healthy lives. However, with the emergence of the COVID-19 pandemic, I realized what I have lost sight of in the past 10 years is that the reality of life is death. While I build relationships with patients and promise to give them the best insight I have, I have failed to prepare them for end-of-the-life decisions.

During the first couple of weeks of the pandemic, as physicians, we did not really understand how this new disease affected people, and learning how best to treat it was challenging. With COVID-19 and its spectrum of symptoms in different patients, we did not know what the clinical course would look like, and it was difficult to predict a patient's prognosis. These moments broke my heart—when I was uncertain about the patient's prognosis, and they were looking to me for answers I did not have.

For patients, perhaps the hardest part of the pandemic was the isolation they experienced when they were sick enough to be admitted to the intensive care unit. They had to battle the disease alone, without the support of their loved ones. For those who weren't getting better, this was undoubtedly even more difficult as those caring for them questioned their "code status"—something many may never have heard of or considered before.

For families forced to be apart from their loved ones, the stress was even greater if no one was sure of the patient's wishes or even who they would want as their health care power of attorney. For these families, too often they had to leave their family member at the emergency department, and a few weeks later they received a call from the ICU that their loved one was dying. Under "normal" circumstances, a patient's family members would see the day-to-day deterioration. Instead, because they could not be with them, there was a disconnect. They were forced to make difficult decisions, such as withdrawing life support, without having been present to witness the decline or even getting a chance to talk to their loved one. In these instances, family members sometimes turned toward the patient's primary care provider to seek answers—a situation I personally experienced a few times and that had a huge impact on me.

Today, I continue to build relationships with my patients as they pursue a healthy life. But I have changed my view to include the end of their lives. I have started taking my time in their preventive visits to go over medical terms like "full code," "DNR," "health care power of attorney," "guardianship," and "living will." It is important that while our patients are physically and emotionally healthy, they consider what kind of care they want toward the end of their lives. These conversations will give them a chance to think about and share their end-of-life wishes, including who they want to make decisions for them if they cannot.

Fortunately, the pandemic has ended. And while it was a soul-crushing experience for so many patients and clinicians alike, we emerged having learned countless lessons that will hopefully leave us better prepared for the future. As Jay Asher writes in his book *Thirteen Reasons Why*,[2] "After all, how often do we get a second chance?"

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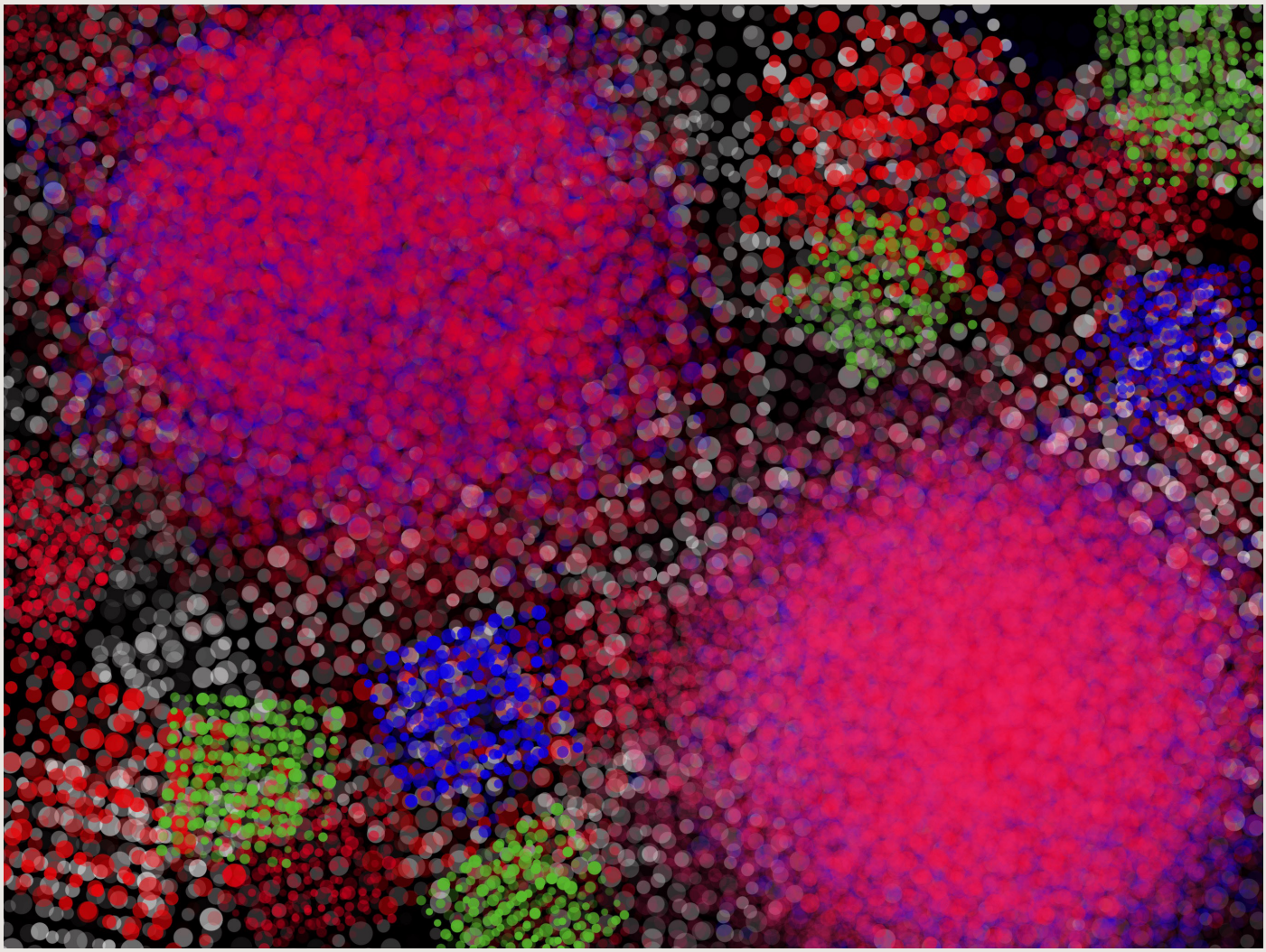

Pandemic

Vincent Cryns, MD

Digital Painting on iPad Pro

Artist Statement:

I am a physician-scientist who turns to painting to explore many topics I encounter every day in my personal and professional life. I work in acrylic, watercolor and digital media. I incorporate vivid colors to portray emotional content and recurring patterns to express the shared features of the natural world and medicine.

Work and Life in the Balance: COVID-19 Mortality by Usual Occupation and Industry in Wisconsin

Paul D. Creswell, PhD; Komi K. S. Modji, MD, MPH; Collin R. Morris, BS; Katherine E. McCoy, PhD

ABSTRACT

Introduction: Work is central to the discourse surrounding the pandemic. Going to work during the COVID-19 pandemic put individuals at risk for both disease and death. This study assesses COVID-19 mortality by industry and occupation for working-age adults in Wisconsin and applies a health equity lens to understand COVID-19, demographics, work, and mortality in the state.

Methods: We used vital records data to evaluate COVID-19 mortality in Wisconsin. We assessed the demographics of working-age decedents using chi-square tests and logistic regression. We also classified decedents by usual occupation with Standard Occupational Classification (2018) and North American Industry Classification System (2017) codes to calculate mortality rates. We then calculated proportional mortality ratios to evaluate if mortality rates from COVID-19 in industry or occupation groups were significantly higher than the overall (ie, average) mortality rate from COVID-19 among all working-age Wisconsin adults.

Results: Both Asian/Pacific Islander and Hispanic individuals in Wisconsin had elevated likelihoods of dying from COVID-19. Lower levels of education also were associated with a higher likelihood of COVID-19–attributable death. Additionally, we found several occupations and industries that had elevated mortality rates from COVID-19. Proportional mortality ratios showed higher than expected mortality for several occupations including Protective Service; Office and Administrative Support; Farming, Fishing, and Forestry; and Installation, Maintenance, and Repair. Moreover, several industries had elevated proportional mortality ratios, including Agriculture, Forestry, Fishing, and Hunting; Finance and Insurance; Transportation and Warehousing; and Public Administration.

Discussion: The lessons of the pandemic are important for public health and worker safety. Understanding who bears disparate risks allows us to prepare, communicate, and mitigate risk.

INTRODUCTION

The SARS-CoV-2 virus (COVID-19 virus) has killed at least 14 469 Wisconsin residents and continues to cause deaths within the state.[1] The COVID-19 pandemic profoundly affected many aspects of society, and work – a key social determinant of health,[2,3] – was not exempt. Rather, work – not only in terms of having or not having employment, but also with regards to the conditions and location(s) where work was being done – was often central to pandemic discourse. As the pandemic captured the national consciousness, we saw discussions about frontline workers,[4,5] working from home,[6] telemedicine,[7] and government interventions (eg, safer-at-home orders,[8] presumption for worker's compensation,[9] and mask or vaccine mandates[10,11]). This list of topics demonstrates how central work was to the unfolding pandemic. Leaving home for work during this period put workers at risk not just for disease, but for death.[12] Additionally, national findings[13] and some early Wisconsin data[5] suggested significant racial disparities in COVID-19 case counts and mortality. While findings on COVID-19 exposure and diagnoses among workers in Wisconsin have been published previously,[14] there is currently no Wisconsin-specific analysis of mortality among working-age adults or by industry and occupation. Given that exposures only tell part of the story, our analysis takes a health equity lens and explores the relationships between demographics and COVID-19 mortality among working-age Wisconsin decedents.

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Moreover, these analyses focus on deaths from COVID-19 by industry and occupation for working-age adults and contribute to our understanding of the relationship between COVID-19, demographics, work, and mortality in the state.

Table 1. Demographic Characteristics of Individuals With COVID-19–Attributable Deaths vs All Other Causes of Death – Working-age Wisconsin Decedents, March 19, 2020-December 31, 2022

	COVID-19 n = 3321		Other Causes n = 36 415		χ^2	*P* value
	Count	%	Count	%		
Age (years)						
16-19	14	0.42	538	1.48	72.06	< 0.0001
20-24	16	0.48	1081	2.97		
25-34	143	4.31	3378	9.28		
35-44	343	10.33	4718	12.96		
45-54	833	25.08	7606	20.89		
55-59	806	24.27	7596	20.86		
60-64	1166	35.11	11 498	31.57		
Race						
American Indian/Alaska Native	77	2.32	794	2.18	85.94	< 0.0001
Asian/Pacific Islander	113	3.40	500	1.37		
Black	410	12.35	4993	13.71		
White	2721	81.93	30 128	82.74		
Ethnicity						
Hispanic	321	9.67	1656	4.55	169.69	< 0.0001
Non-Hispanic	2997	90.24	34 695	95.28		
Unknown	3	0.90	64	0.18		
Sex[a]						
Female	1256	37.82	13 155	36.13	3.78	0.052
Male	2065	62.18	23 259	63.87		
Education						
< High school	431	12.98	5127	14.08	13.50	0.0091
High school graduate	1601	48.21	17 588	48.30		
Some college, associate's or bachelor's degree	1138	34.27	11 840	32.51		
Advanced degree	84	2.53	1229	3.37		
Unknown/missing	67	2.02	631	1.73		

[a]Excludes "Unknown" Sex (n = 1).

METHODS

Data Sources

Analyses were conducted using Wisconsin vital records data from March 19, 2020, through December 31, 2022. This start date was chosen because it was the date that the first official COVID-19 death was reported in the state.[15] In Wisconsin, all deaths are captured by the Vital Records Office at the Wisconsin Department of Health Services. Wisconsin deaths are collected and reported by individual coroners and medical examiners at the county level.[16] The information gathered on decedents includes date of death, cause of death (including contributing causes), and sociodemographic information (eg, race, ethnicity, sex, age, education, and usual occupation). The National Institute for Occupational Safety and Health Industry and Occupation Computerized Coding System (NIOCCS) autocoder was used to convert free-text industry and occupation from vital records into Standard Occupational Classification (SOC) (2018) and North American Industry Classification System (NAICS) (2017) codes.[17] Detailed information about current SOC and NAICS codes is available via the US Bureau of Labor Statistics.[18,19] We obtained the most recent population estimates from the American Community Survey (ACS) (2017-2021)[20] via the Integrated Public Use Microdata Series platform from the University of Minnesota's Institute for Social Research and Data Innovation.[21]

Classification of Deaths Due to COVID-19

COVID-19 mortality was determined with a text search of the immediate cause of death and all contributing cause of death fields. Our definition was based on the Council of State and Territorial Epidemiologists' (CSTE) interim guidance for classification of COVID-19–associated deaths for public health surveillance.[22] However, we found that many of the key terms suggested by this guidance were too specific given the variability in the case note entries in the death records (eg, "severe acute respiratory syndrome coronavirus 2019"). As such, we chose the terms "COVID," "SARS," and "COV2" to create our definition. The term "corona" also was considered but was overly inclusive of non-COVID sources of mortality (eg, "coronary artery disease"). For validation, we compared our cases against the mass casualty indicator created by the Wisconsin Vital Records Office as an internal indicator of deaths due to COVID-19. Validation of our case detection showed that our method detected 209 cases more than the internal indicator. All of these cases were manually reviewed, and all met our classification for COVID-19–attributable death.

Sample

During the study period, 39 736 working-age decedents (ie, aged 16-64 years) were recorded in the vital records data, and 3321 of those (8.36%) had a COVID-19–attributable death. Decedents who had both an unknown industry and an unknown occupation were excluded from our analysis of mortality rates and proportional mortality ratios (PMR) (n = 5903). The sample for our final analyses, excluding those with unknown industries or occupations, was 33 833 decedents, including 2833 (8.37%) who had a COVID-19–attributable cause of death.

Statistical Analysis

In order to evaluate the relative burden of COVID-19 mortality, chi-square tests were used to assess the proportion of COVID-19–attributable deaths compared to all other causes of death by demographic characteristics. Next, we used multivariate logistic regression to assess the likelihood of death from COVID-19 by demographics for working-age decedents. Age-adjusted mortality rates for COVID-19 were then calculated to assess the differences in burden across occupation and industry groups. Age-adjustment was used to compensate for the disproportionate representation by age in certain occupations or industries given that age is also known to be associated with COVID-19 mortality.[1] Finally, PMRs were calculated to assess within-group burden of COVID-19 mortality for occupation and industry groups. PMRs are estimated as the proportion of deaths from COVID-19 within each SOC or NAICS group divided by the proportion of deaths from COVID-19 among all workers multiplied by 100.[12] PMRs evaluate if the mortality rate for COVID-19 in a given group is significantly higher than the overall mortality rate from COVID-19 for the working-age population. PMRs greater than 100 indicate elevated COVID-19, and lower-bound confidence intervals above 100 indicate statistical significance. PMRs were considered unstable if an occupation or industry group had fewer than 15 deaths from COVID-19 or fewer than 100 deaths from all causes during the study period.

RESULTS

Demographic Analysis

Table 1 compares the proportion of COVID-19–attributable deaths to all other causes of death for Wisconsin working-age decedents during the study period. Age, race, ethnicity, and education all were associated with higher proportions of COVID-19 deaths. Those in the 3 highest age categories had significantly higher proportions of death from COVID-19, while those in the 4 lowest age categories had significantly lower proportions of death from this cause ($\chi^2 = 72.1$; $P < 0.0001$). The Asian/Pacific Islander population had more than double the proportion of COVID-19–attributable deaths than deaths from other causes ($\chi^2 = 85.9$; $P < 0.0001$) and the Hispanic population also had more than twice the proportion of COVID-19–attributable deaths as non-COVID deaths ($\chi^2 = 169.7$; $P < 0.0001$). Education was associated with COVID-19–attributable deaths, and those who had the highest levels of educational attainment (ie, advanced degrees) had a significantly lower proportion of COVID-19–attributable deaths than deaths from all other causes ($\chi^2 = 13.5$; $P = 0.0091$).

Logistic Regression Analysis

Table 2 provides the results of the logistic regression analysis, which assessed demographic differences in the likelihood of dying from COVID-19 (compared to dying of another cause) for working-age decedents in Wisconsin during the pandemic. Patterns of association were similar to those found in the cross-tabulations (Table 1). However, logistic regression controls for the variance of other factors within the model and, as such, provides a better estimate of the true associations. Age remained associated with COVID-19 mortality. Among working-age Wisconsin decedents, those in the oldest 4 age categories all had elevated likelihoods of dying from COVID-19 compared to those in the youngest age category. Those in the top 3 age groups had more than 4 times the likelihood of dying of COVID-19 (Table 2).

Asian/Pacific Islander individuals had more than 3 times the likelihood of dying from COVID-19 compared to their White counterparts (OR 3.12; 95% CI, 2.52-3.86) and Hispanic individuals had nearly 3 times the likelihood of dying from COVID-19 compared to non-Hispanic individuals (OR 2.80; 95% CI, 2.46-3.20). Among working-age decedents in Wisconsin, those

Table 2. Logistic Regression Analysis of Individual Characteristics Associated With COVID-19-Attributable Death – Working-age Wisconsin decedents, March 19, 2020–December 31, 2022 (N = 39 736)

	Odds Ratio	95% Wald Confidence Limits
Age		
16-19 years	reference	–
20-24 years	0.53	0.26 – 1.09
25-34 years	1.55	0.89 – 2.72
35-44 years	**2.76**	**1.60 – 4.77**
45-54 years	**4.31**	**2.52 – 7.39**
55-59 years	**4.33**	**2.53 – 7.43**
60-64 years	**4.23**	**2.47 – 7.24**
Race		
American Indian/Alaska Native	1.22	0.96 – 1.54
Asian/Pacific Islander	**3.12**	**2.52 – 3.86**
Black	1.08	0.97 – 1.20
White	reference	–
Ethnicity		
Hispanic	**2.80**	**2.46 – 3.20**
Non-Hispanic	reference	–
Unknown	0.56	0.18 – 1.81
Sex[a]		
Female	reference	–
Male	0.95	0.88 – 1.03
Education		
< High school	1.22	0.95 – 1.55
High school graduate	**1.47**	**1.17 – 1.85**
Some college, associate's, or bachelor's degree	**1.52**	**1.21 – 1.92**
Advanced degree	reference	-
Unknown/missing	**1.53**	**1.09 – 2.15**
Year		
2020	**1.25**	**1.13 – 1.38**
2021	**2.02**	**1.85 – 2.21**
2022	reference	–

[a]Excludes "Unknown" sex (n = 1).

Bold text indicates statistical significance ($P < 0.05$).

with a high school education were 1.47 times more likely to die from COVID-19 than those with an advanced degree (ie, master's degree equivalent or higher) (OR 1.47; 95% CI, 1.17-1.85). Those who had some college, an associate's degree, or a bachelor's degree faired similarly (OR 1.52; 95% CI, 1.21-1.92). Finally, given the changes over time related to COVID-19 (eg, changes in disease detection, definitions, vaccine availability), we included time in years as a covariate in this analysis. The 2021 period was associated with the highest likelihood of COVID-19–related death for this population (OR 2.02; 95% CI, 1.85-2.21), while 2020 also was associated with a higher likelihood of dying from COVID-19 when compared to 2022 (OR 1.25; 95% CI, 1.13-1.38).

Mortality Rates by Usual Occupation and Industry

Table 3 provides counts of COVID-19–attributable deaths, ACS denominator estimates (5-year: 2017-2021), and age-adjusted mortality rates per 100 000 workers for COVID-19 by major SOC code (ie, highest level of classification) in Wisconsin for the study period. The overall age-adjusted COVID-19 mortality rate was 112.50 per 100 000 workers (95% CI, 108.67-116.32) (not shown in Table 3). The occupations with mortality rates significantly above the overall age-adjusted rate were (1) Protective Service (rate 209.55; 95% CI, 167.15-251.96), (2) Transportation and Material Moving (rate 195.86; 95% CI, 178.13-213.59), (3) Installation, Maintenance, and Repair (rate 145.11; 95% CI, 121.06-169.16), (4) Food Preparation and Serving Related (rate 141.45; 95% CI, 122.83-160.07), and (5) Healthcare Support (rate 138.68; 95% CI, 116.66-160.69). Table 3 also provides the age-adjusted COVID-19 mortality rates by 2-digit NAICS code (ie, highest level categorization). The two industries with the highest stable rates compared to the overall age-adjusted average rate were (1) Transportation and Warehousing (rate 158.40; 95% CI,

Table 3. Counts of COVID-19-Attributable Deaths, Amercian Community Survey 5-year Denominator Estimates (2017-2021), and Age-Adjusted COVID-19 Mortality Rates – Working-age Wisconsin Decedents, March 19, 2020-December 31, 2022

Major SOC Code	COVID-19-Attributable Deaths (n = 2786)	ACS Denominator Estimate (n = 2 937 652)	Age-Adjusted Rate	95% CI
Protective Service	**67**	**44,675**	**209.55**	**167.15 – 251.96**
Transportation and Material Moving	**487**	**238,866**	**195.86**	**178.13 – 213.59**
Installation, Maintenance, and Repair	**151**	**96,248**	**145.11**	**121.06 – 169.16**
Food Preparation and Serving Related	**114**	**156,475**	**141.45**	**122.83 – 160.07**
Healthcare Support	**128**	**109,774**	**138.68**	**116.66 – 160.69**
Construction and Extraction	174	137,074	133.86	114.51 – 153.22
Production	395	287,636	128.55	115.46 – 141.65
Personal Care and Service	54	63,848	110.45	84.68 – 136.21
Building and Grounds Cleaning and Maintenance	115	96,016	106.85	86.18 – 127.51
Architecture and Engineering	58	63,682	90.47	67.12 – 113.82
Arts, Design, Entertainment, Sports, and Media	39	48,797	87.32	61.11 – 113.53
Farming, Fishing, and Forestry	18	25,751	84.47	48.99 – 119.95
Sales and Related	**204**	**259,877**	**80.44**	**69.54 – 91.34**
Community and Social Service	**36**	**47,630**	**72.01**	**47.92 – 96.10**
Management	**240**	**297,461**	**68.13**	**58.75 – 77.51**
Office and Administrative Support	**230**	**315,218**	**65.50**	**56.57 – 74.43**
Computer and Mathematical	**42**	**88,202**	**62.00**	**45.57 – 78.43**
Business and Financial Operations	**74**	**157,359**	**44.11**	**33.74 – 54.49**
Healthcare Practitioners and Technical	**82**	**183,165**	**43.96**	**34.36 – 53.56**
Legal[a]	—	16,775	—	—
Education, Training, and Library	**61**	**169,287**	**37.59**	**28.36 – 46.83**
Life, Physical, and Social Science[a]	—	33,836	—	
2-Digit NAICS Code	**COVID-19-Attributable Deaths (n = 2756)**	**ACS Denominator Estimate (n = 2 914 232)**	**Age-Adjusted Rate**	**95% CI**
Mining, Quarrying, and Oil and Gas Extraction[a]	—	4237	—	—
Transportation and Warehousing	**231**	**120 583**	**158.40**	**135.96 – 180.85**
Accommodation and Food Services	**153**	**194 529**	**151.71**	**134.42 – 169.01**
Other Services (except Public Administration)	165	116 031	134.48	113.39 – 155.57
Administration and Support and Waste Management and Remediation Services	121	99 854	128.26	106.06 – 150.46
Manufacturing	705	516 485	119.35	109.93 – 128.76
Construction	216	186 151	116.34	100.85 – 131.82
Agriculture, Forestry, Fishing and Hunting	71	56 420	115.38	87.37 – 143.40
Arts, Entertainment, and Recreation	45	52 200	109.77	81.36 – 138.17
Public Administration	96	103 038	97.29	78.26 – 116.33
Retail Trade	**243**	**311 209**	**91.33**	**80.71 – 101.94**
Utilities	**22**	**21 422**	**86.35**	**47.02 – 125.68**
Information	**34**	**45 778**	**80.90**	**54.85 – 106.94**
Health Care and Social Assistance	**312**	**433 504**	**70.84**	**62.92 – 78.76**
Finance and Insurance	**92**	**143 140**	**61.34**	**48.51 – 74.16**
Real Estate and Rental and Leasing	**25**	**34 396**	**56.97**	**31.75 – 82.19**
Wholesale Trade	**47**	**75 237**	**56.83**	**39.80 – 73.87**
Professional, Scientific, and Technical Services	**80**	**150 250**	**54.66**	**42.84 – 66.48**
Educational Services	**89**	**244 868**	**36.79**	**29.20 – 44.39**
Management of Companies and Enterprises[a]	-	4900	-	—

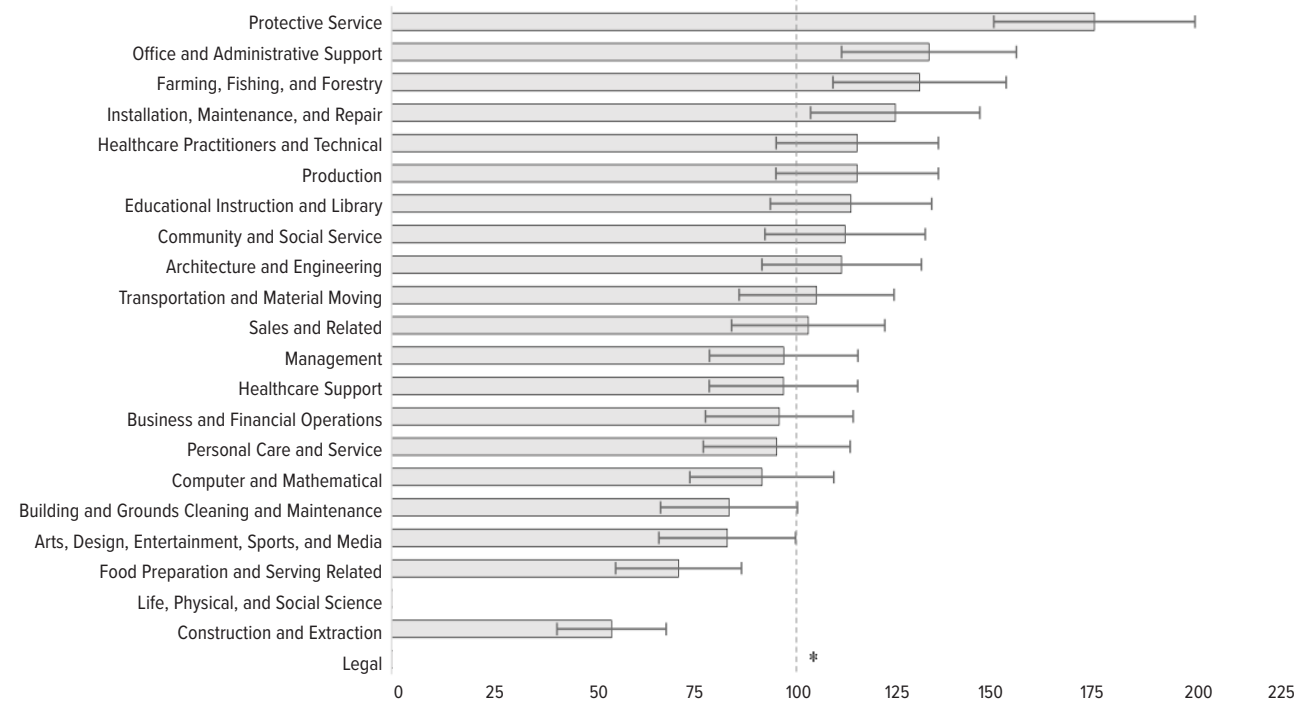
Abbreviations: ACS, American Community Survey; SOC, Standard Occupational Classification; NAICS, North American Industry Classification System

[a]Numerator <15 and/or denominator <100 denoting rate instability. Counts below these thresholds also suppressed in tables for confidentiality.

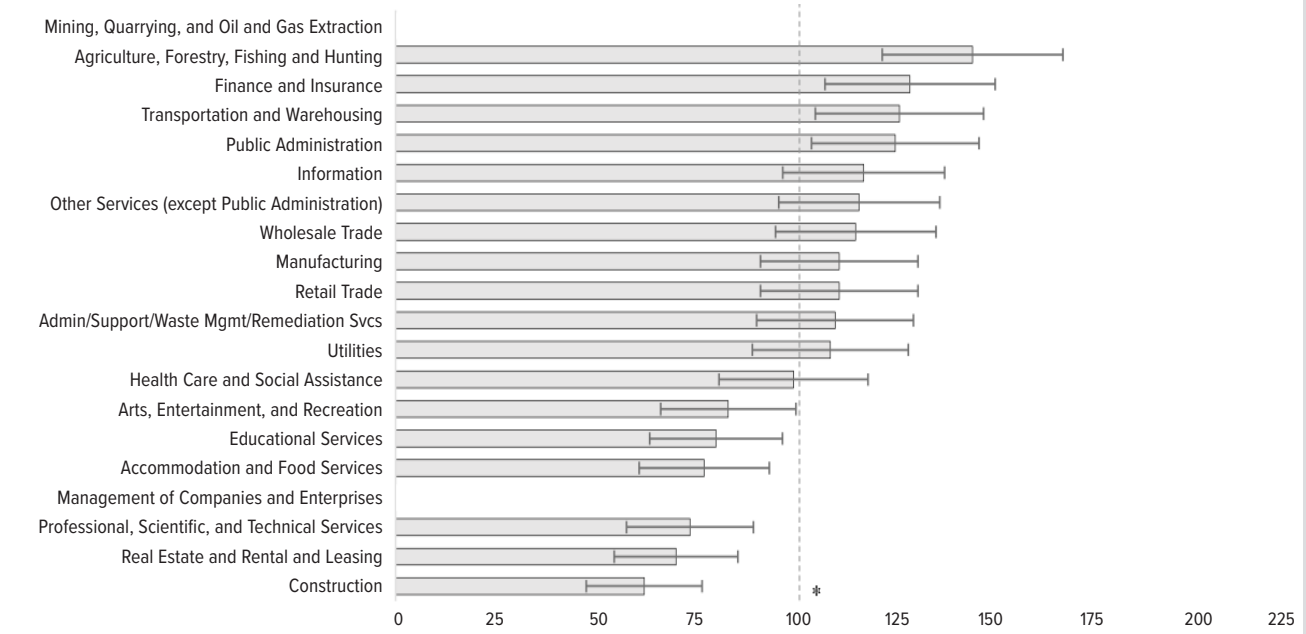
Bold text indicates statistical significance ($P < 0.05$).

Figure 1. Age-Adjusted Proportional Mortality Ratios (PMR) for COVID-19–Related Mortality, Wisconsin, March 19, 2020—December 31, 2022 (1A) by Major Standardized Occupation Classification (SOC) Code and (1B) by Two-Digit North American Industry Classification System (NAICS) Code

1A. Age-Adjusted PMRs for COVID-19–Related Mortality by Major Standardized Occupation Classification (SOC) Code



1B. Age-Adjusted PMRs for COVID-19–Related Mortality by Two-Digit North American Industry Classification System (NAICS) Code



Proportional mortality ratios over 100 indicate elevated COVID-19 mortality for a given group, and lower-bound confidence intervals above 100 indicate statistical significance. The age-adjusted PMRs were suppressed for industries and occupations with fewer than 15 death cases or 100 workers.

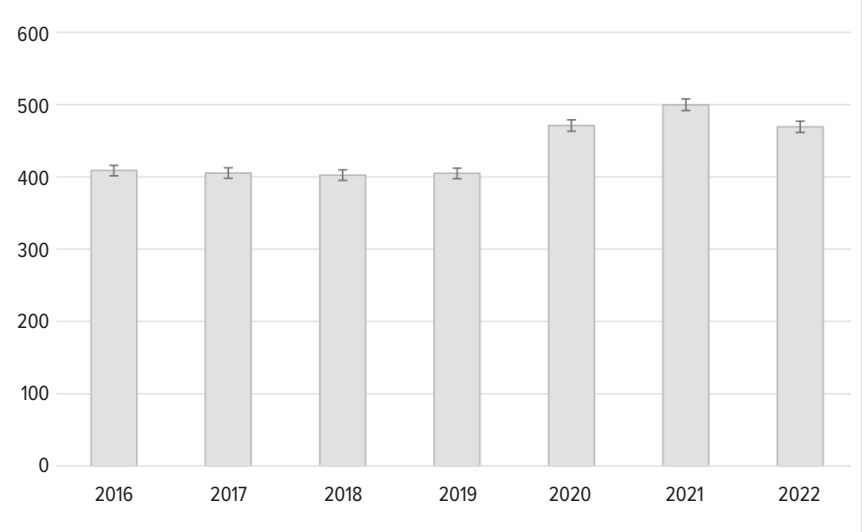
135.96-180.85) and (2) Accommodation and Food Services (rate 151.71; 95% CI, 134.42-169.01).

Proportional Mortality Ratios (PMR)

Figure 1A shows age-adjusted PMRs for occupations in Wisconsin during the pandemic as defined by major SOC codes. Four occupations had significantly elevated COVID-19 mortality during the pandemic: (1) Protective Service (PMR 173.67; 95% CI, 148.80-200.43), (2) Office and Administrative Support (PMR 132.80; 95% CI, 111.18-156.32), (3) Farming, Fishing, and Forestry (PMR 130.47; 95% CI, 109.04-153.79), and (4) Installation, Maintenance, and Repair (PMR 124.48; 95% CI, 103.57-147.28).

Figure 1B shows age-adjusted PMRs for industry sectors in Wisconsin during the study period as defined by 2-digit NAICS codes. Four industries had significantly elevated PMRs: (1) Agriculture, Forestry, Fishing and Hunting (PMR 144.05; 95% CI, 121.49-168.51), (2) Finance and Insurance (PMR 128.45; 95% CI, 107.20-151.60), (3) Transportation and Warehousing (PMR 125.82; 95% CI, 104.79-148.73), and (4) Public Administration (PMR 124.76; 95% CI, 103.83-147.58).

Figure 2. Age-Adjusted All-Cause Mortality Rate per 100 000 Among Working-Age Adults, Wisconsin, 2016-2022



DISCUSSION

Demographic Disparities

These findings expand our understanding of the relationship between demographics, work, and COVID-19 mortality in Wisconsin. Our logistic regression showed that working-age Asian/Pacific Islander individuals in Wisconsin were more than 3 times as likely to die of COVID-19 when compared to their working-age White counterparts. Additionally, working-age Hispanic individuals in Wisconsin had nearly 3 times the likelihood of dying from COVID-19 compared to their non-Hispanic peers. While disparities between Black and White Wisconsin residents were indicated by data early in the pandemic,[5] they were not found in our analysis. While we lacked the statistical power to assess racial and ethnic differences within industry and occupation groups, the literature shows that there are differences in distribution of race by industry and occupation.[12] We may see indications of these relationships in other components of our analyses as well. For instance, Farming, Fishing, and Forestry occupations had a significantly elevated PMR, as did the Agriculture, Forestry, Fishing, and Hunting industry. Both of these classifications tend to have large proportions of Hispanic workers.[12,23]

The relationship between age and COVID-19 mortality is established,[1] but the correlation with education has been less well documented.[24] Certainly, education and occupation are intertwined components of socioeconomic status, and those with the highest levels of education are the most likely to have been able to take precautions to prevent exposure to COVID-19 (eg, working from home, avoiding contact with strangers) and to have had better health pre-infection and better access to care. Such factors are likely to reduce the COVID-19 mortality for these individuals. This is reflected in our findings that, by and large, those with lower education levels had higher likelihoods of COVID-19 mortality than those who had advanced degrees (ie, master's degree equivalent or higher). As education is not an equitably distributed good in society, these differences point to disparities that need to be recognized.

Comparison Between Incidence and Mortality

Our findings on mortality rates differed from what might be expected from previously published findings on work-related incidence of COVID-19 for workers in Wisconsin.[14] While we found high mortality rates for several occupations, including Protective Service, Food Preparation and Serving-Related, and Health Care Support – all of which also had high incidence of COVID-19 – we did not find high mortality among other occupations associated with high incidence (ie, Personal Care and Service, Buildings and Grounds Cleaning and Maintenance). Similar patterns were found with industries. Our findings indicated high mortality rates for Accommodations and Food Service and for Other Services (except Public Administration), which each had high incidence rates – but we did not find elevated mortality rates among other high incidence industries (ie, Health Care and Social Assistance, Public Administration, and Utilities). Resolving discrepancies between incidence and mortality is complicated but potentially

instructive. For instance, individuals in the Health Care and Social Assistance industry may have high incidence and low mortality because while they were more likely to be exposed to the virus, they also were more likely to be tested, to have access to personal protective equipment, and to be among the first individuals vaccinated – all of which may have resulted in lower mortality. Looking for ways to resolve these differences can lead to hypotheses that may be tested with future analyses.

Proportional Mortality Ratios

PMRs provided additional information and indicated the industries with the highest relative burden of COVID-19. Some occupations and industry groups (eg, Protective Service, Transportation and Warehousing) had both elevated mortality rates and elevated PMRs in our analyses, indicating that COVID-19 was a leading cause of mortality for these groups. However, the patterns were not always so consistent. For instance, Farming, Fishing, and Forestry occupations had the lowest incidence in the Pray et al analysis.[14] Our analyses found a slightly below average overall mortality rate for that group (Table 3) but a significant PMR (Figure 1B), suggesting elevated COVID-19–related mortality. These findings were paralleled with a related industry group—Agriculture, Forestry, Fishing, and Hunting—which was the lowest industry in terms of COVID-19 incidence in the Pray et al analysis.[14] In our analyses, we found a somewhat below average mortality rate for this group (Table 3) but a significantly elevated PMR (Figure 2B). While we cannot say for certain why we see these differences, it is possible that individuals in these industries were less likely to be tested for COVID-19 and, therefore, underrepresented in the incidence data, which would, in turn, artificially suppress the incidence rate for these groups. Additionally, as mentioned above, a large percentage of these individuals were likely Hispanic.[23] As such, these workers may have had a harder time getting information due to language barriers or an absence of trusted information sources.[25]

Limitations and Sensitivity Analyses

There are several limitations in our analyses worth noting. First, while we had data on occupation for decedents, this was usual occupation and not necessarily the current occupation. As such, it may be that some individuals were not employed or working in their usual occupation or industry at the time of death. Second, we have no way of knowing if the virus was transmitted via work or not, and while our data show rates of COVID-19 mortality, they do not reveal causation. Rates for each occupation or industry are likely to be affected by social or behavioral risk factors unrelated to the specific work setting. It is also a limitation that we used high-level categories (ie, major SOC and 2-digit NAICS codes) to assess industries and occupations, as this may mask important intragroup differences.

Another potential limitation is how inclusive we were when defining mortality from COVID-19 (ie, including all contributing causes of death). We believe our choice is defensible given CSTE's interim guidance for classification of COVID-19-associated deaths[22] and the novelty of the virus. Still, the risk of our approach is that we may have included some deaths that were not truly attributable to COVID-19. Should that be the case, however, the additional variance would likely make it more difficult to detect an effect. Given that the effects we show are robust to this potential source of additional variance, we believe our estimates are conservative. Moreover, we conducted a sensitivity analysis of mortality rates using a more restrictive definition and found no meaningful differences (data not shown). While the rank order of the mortality rates changed slightly, the same SOC and NAICS codes were associated with elevated rates. That said, it remains possible that we failed to detect effects that were important, and future analyses may consider a different approach to defining mortality from COVID-19.

Finally, it is a limitation that PMRs are estimated relative to the count and distribution of all deaths[12] and, as such, if there was a meaningful decrease in deaths from other causes during the pandemic, COVID-19 mortality could appear artificially elevated (ie, by supplanting these missing deaths). In consideration of this, we inspected the overall age-adjusted mortality rates per 100 000 working-age adults in Wisconsin during 2016-2022, which suggests a relatively stable year-over-year trend in mortality with significant increases during the pandemic (Figure 2). This is consistent with COVID-19 contributing additional mortality.

CONCLUSIONS

This study represents an important step in our continued understanding of COVID-19 and COVID-19 mortality in Wisconsin. Usual occupation and industry were associated with differential mortality, and some groups had a significant burden of COVID-19 mortality. The lessons of this recent pandemic are important for the future of public health and worker safety, though it is important to keep in mind that future pandemics may affect the population differently with regards to demographics (ie, who is at higher risk). That said, understanding who bore disparate risks of death in the COVID-19 pandemic provides a starting place to prepare, communicate, and mitigate risks to workers in the future. It is important to note the inequities that our findings indicate. Many demographically defined populations (eg, older individuals, people who are Hispanic or Asian/Pacific Islanders, and those with lower educational attainment) were found to have higher rates of COVID-19 mortality. These populations should be considered when creating policies, communication strategies, and mitigation or prevention plans.

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Incidence of COVID-19 and Worker's Compensation Utilization Among Food Manufacturing Workers in Wisconsin, October 1, 2020 – December 31, 2021

Komi K.S. Modji, MD, MPH; Katherine E. McCoy, PhD; Paul D. Creswell, PhD; Jonathan G. Meiman, MD

ABSTRACT

Background: The food manufacturing industry is a critical economic sector and has been a high-risk industry for COVID-19. This analysis aimed to describe COVID-19 cumulative case incidence rates among Wisconsin food manufacturing workers and their worker's compensation utilization.

Methods: This was a descriptive analysis of COVID-19 cases among food manufacturing industry workers in Wisconsin from October 1, 2020, through December 31, 2021.

Results: Occupations with the highest cumulative case incidence rate (per 1000 workers) were Packers and Packagers, Hand (275; 95% CI, 252–300), Packaging and Filling Machine Operators and Tenders (266; 95% CI, 254–277), and Laborers and Freight, Stock and Material Movers, Hand (261; 95% CI, 247–276). Two worker's compensation claims were paid to food manufacturing workers.

Discussion: Wisconsin food manufacturing workers were disproportionately affected by COVID-19, with a high cumulative case incidence rate exceeding that of the manufacturing industry overall, statewide non-institutionalized working-age adults, and the ambulatory health care industry. There was also a disproportionately low use of worker's compensation benefits in Wisconsin compared to the high COVID-19 disease incidence. Improved worker protections for occupational infectious diseases with high risk of transmission are needed as well as improvements to the worker's compensation system.

BACKGROUND

The food manufacturing industry represents approximately 15% of the total manufacturing workforce, 1% of US non-farm workers, and has been a major contributor to the economy.[1,2] Many workers in the food manufacturing industry are at high risk of exposure to respiratory pathogens given that tasks are often performed in close proximity to other workers and in poorly ventilated environments without respiratory protection measures.[3] During the COVID-19 pandemic, workers in the food manufacturing sector were categorized as "essential" to maintain operations without the accompanying benefits (paid leave, worker's compensation presumption) and testing privileges afforded other occupations, such as health care workers.

In Wisconsin, the COVID-19 pandemic placed a heavy burden on the food manufacturing industry. It had the highest case incidence (14 cases per 100 full-time equivalents) among manufacturing subsectors,[4] and several fatal cases of COVID-19 occurred among food industry workers, which resulted in Occupational Safety and Health Administration investigations and fines to employers.[5]

Wisconsin did not enact a rebuttable presumption law covering food manufacturing workers who filed worker's compensation (WC) claims for COVID-19, which left the burden of proof on workers to establish the work-relatedness of any infections. Despite widespread attention to COVID-19 risks among food manufacturing workers, no studies have quantified COVID-19 incidence at the detailed occupation level or number of WC claims associated with this specific industry. Understanding which workers within this broader industry were most affected is necessary to advance targeted prevention measures in future outbreaks and also can generate a better understanding of respiratory disease risks in industrial settings more generally.

This analysis aimed to describe COVID-19 case incidence rates among these workers as well as their WC utilization.

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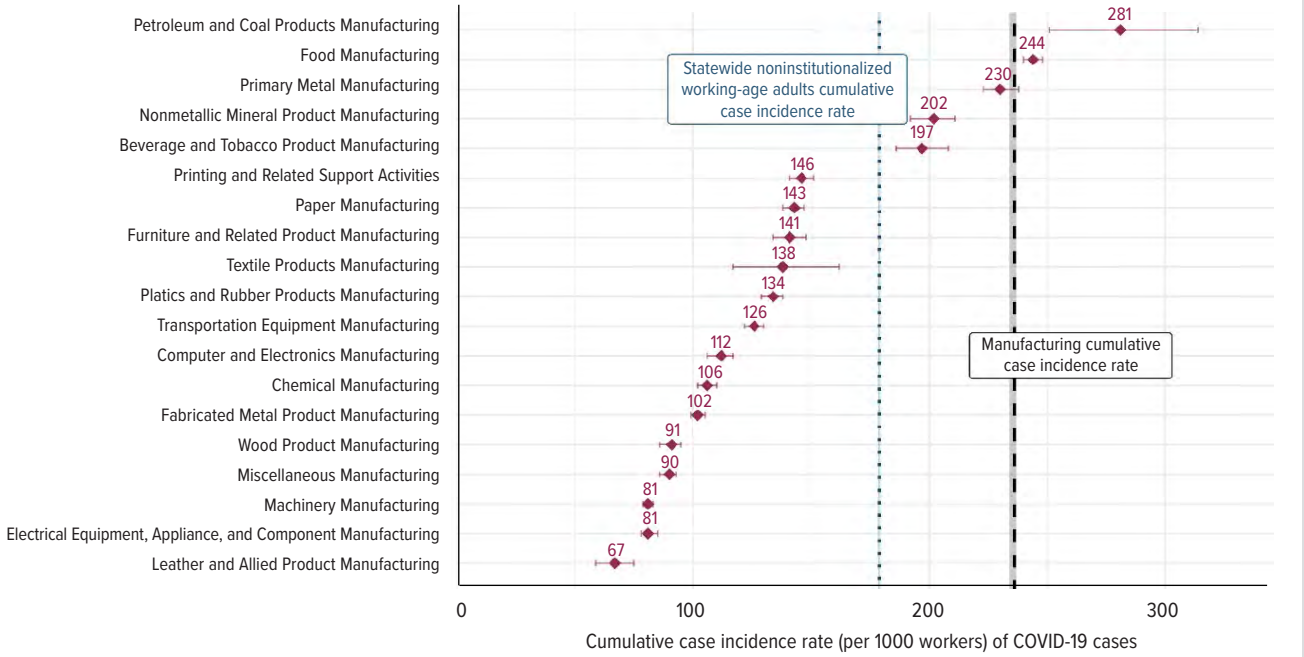
Figure 1. Cumulative Case Incidence Rates of COVID-19 by Manufacturing Subsector, October 1, 2020 – December 31, 2021



The blue dotted line represents the statewide noninstitutionalized working-age adults cumulative case incidence rate and the shaded area around the line represents the 95% CI.

The black dashed line represents the cumulative case incidence rate in the manufacturing industry and the shaded area around the line represents the 95% CI.

METHODS

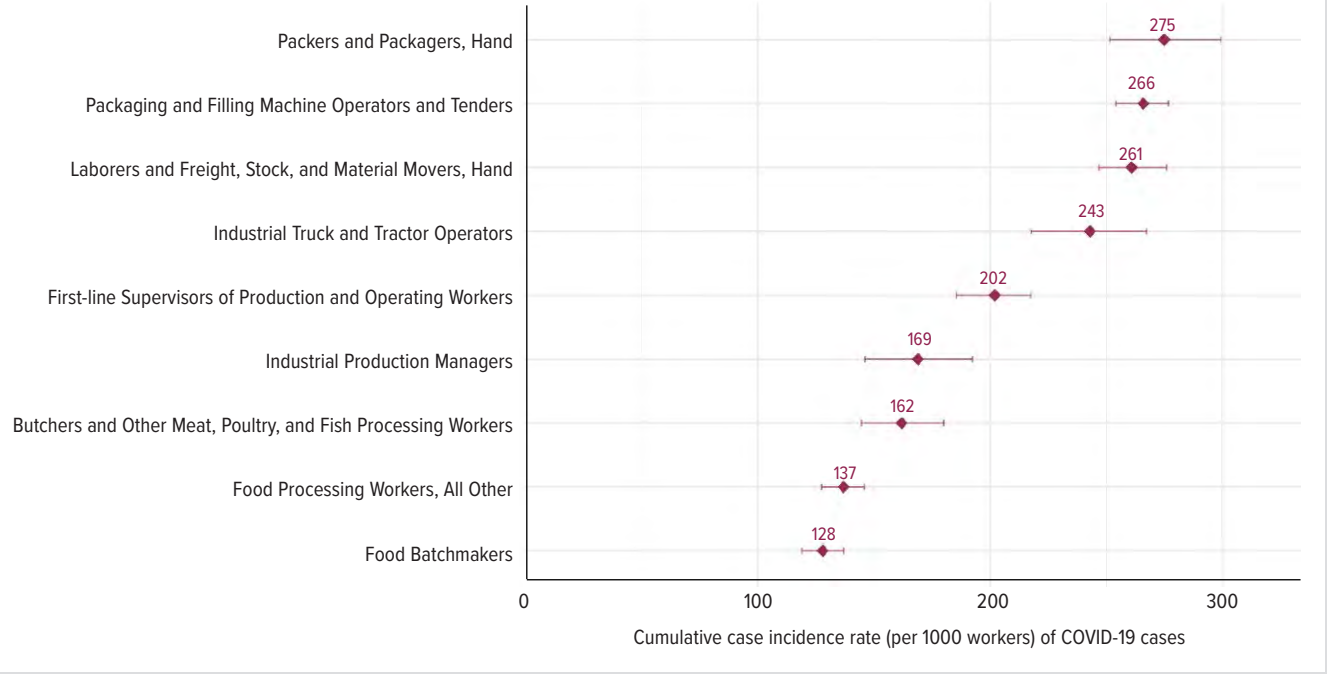
This was a descriptive analysis of COVID-19 cases (positive molecular or antigen-based tests) among food manufacturing workers during October 1, 2020 – December 31, 2021, reported in the Wisconsin Electronic Disease Surveillance System (WEDSS). In WEDSS, we collected industry and occupation information as free text that we coded through the National Institute for Occupational Safety and Health (NIOSH) Industry and Occupation Computerized Coding System (NIOCCS) to obtain standardized industry and occupation codes. For industry, we retained the North American Industry Classification System (NAICS), and for occupation, we retained Standard Occupational Classification (SOC) code. Unemployment insurance data were used to supplement missing standardized industry codes in the surveillance data. Food manufacturing workers were defined by the corresponding NAICS code (311), which represents food manufacturing workers alone without including agricultural workers.

Inverse probability treatment weighting was used to adjust for missing industry and occupation data in a regression model in which the predictors were age, sex race, ethnicity, jurisdiction, and episode date. We conducted a sensitivity check to verify the quality of the adjustment (Appendix 1). These weights were applied to the total number of cases with known industry and occupation to obtain the adjusted total number of cases by industry and occupation as well as all rates computed in this report. Denominators were obtained from the 1-year American Community Survey 2020, and unreliable estimates (relative standard error > 0.3) were excluded. Cumulative case incidence rates by detailed occupations expressed as cases per 1000 workers were computed along with their 95% confidence intervals. The chi-square test was performed to assess the strength of association with a significance threshold of 0.05. The WC data included indemnity claims reported to the state by the insurers. We linked the WC claim data to the unemployment insurance data by the employer's federal employer identification number or the employer's name to obtain the corresponding industry code for each claim. The claims were filtered down to manufacturing claims only (NAICS codes 31, 32, 33). This claim dataset of manufacturing workers was linked to the COVID-19 surveillance data on full name and date of birth to obtain the number of claims that pertained to manufacturing workers. We suppressed lost work time and payment information if the total number of claims was less than 5. For comparison purposes, we compared the number of claims, cumulative case incidence rate, and paid claims in the food manufacturing industry to the health care industry, which includes ambulatory health care services (NAICS 621), hospitals (NAICS 622), and nursing and residential care facilities (NAICS 623).

RESULTS

After adjustment for missing industry and occupation, among

Figure 2. Cumulative Case Incidence Rates of COVID-19 Among Occupations Within Food Manufacturing Industry, October 1, 2020 – December 31, 2021



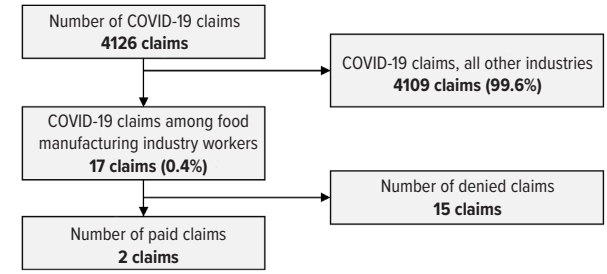
Note: Butchers and Meat Cutters; Slaughterers and Meat Packers; Meat, Poultry and Fish Cutters and Trimmers were grouped into their broad occupation group that is Butchers and Other Meat, Poultry, and Fish Processing workers due to a lack of subcategory denominators for these groups.

non-health care industries, manufacturing was the industry sector with the highest case count (n = 112 733) (Appendix 2), out of which the food manufacturing subsector had the highest case count (n = 17 604, 15.6%) and the second highest cumulative case incidence rate of 244 cases per 1000 workers (95% CI, 240 - 247, Figure 1 and Appendix 3). The food manufacturing industry cumulative case incidence rate was higher than that of the overall manufacturing sector (236 cases per 1000 workers; 95% CI, 234 - 237, Figure 1), non-institutionalized working-age adults (179 cases per 1000 workers; 95% CI, 179 - 180, Figure 1), and ambulatory health care services (220 cases per 1000 workers; 95% CI, 217 - 222, Appendix 3).

COVID-19 rates varied significantly between occupations within the food manufacturing industry (Figure 2), where 5 occupations had a cumulative case incidence rate exceeding that of the statewide non-institutionalized working-age adults. The top 3 occupations with the highest cumulative case incidence rate per 1000 workers were Packers and Packagers, Hand (275; 95% CI, 252 - 300), Packaging and Filling Machine Operators and Tenders (266; 95% CI, 254 - 277), and Laborers and Freight, Stock and Material Movers, Hand (261; 95% CI, 247 - 276) (Figure 2).

During the study period, 4126 COVID-19 claims were reported for all industries and occupations, out of which 70.5% (n = 2909 claims) were denied. The proportion of claims reported by food manufacturing workers represented 0.4% (n = 17) of COVID-19 claims, out of which 2 claims were paid for lost work time (Figure 3). By contrast, 44% (n = 1243) of health care workers' claims were paid for lost work time.

Figure 3. Worker's Compensation Claims of Food Manufacturing Industry Workers



DISCUSSION

We demonstrated that Wisconsin food manufacturing workers were disproportionately affected by COVID-19, with a high cumulative case incidence rate exceeding that of the manufacturing industry overall, statewide non-institutionalized working-age adults, and the ambulatory health care industry. Cumulative case incidence rates varied significantly between occupations within the food manufacturing industry, with the highest rates observed among Packers and Packagers, Hand; Packaging and Filling Machine Operators and Tenders; and Laborers and Freight, Stock

and Material Movers, Hand. These occupations are known to involve close proximity work, as well as group, team, and face-to-face interactions,[6] which may have increased the risk of COVID-19 transmission.

The extremely low WC utilization of food manufacturing worker cases contrasted with relatively high utilization of WC by health care industry workers, despite both industry subsectors having high COVID-19 cumulative case rates. While our data limit our ability to know why claim filing was so low, differences likely were driven by the fact that health care workers were covered by rebuttable presumption while manufacturing workers were not. In addition, it is possible that food manufacturing workers were discouraged by fears of retaliation from employers, including loss of employment during a pandemic where the likelihood of getting another job was small.[7] However, during the pandemic, the federal paid sick leave policy implemented by many companies served as an alternative to filing WC claims for lost work time. Regardless, there was a disparity in workers' protection and a need for food manufacturing workers' protection as illustrated by an article in the *Milwaukee Journal Sentinel*.[8] The underdetection of COVID-19 among food manufacturing workers could also reduce their WC utilization because proof of a positive test result is needed to file a claim. Finally, the low payouts of successful claims may disincentivize lawyers from taking cases disputed by the employer, which during the study period was more likely for food manufacturing workers than those covered by presumption (ie, health care workers and other first responders).

A strength of our analysis was our ability to generate rates at the detailed occupation level, which increases accuracy and allows for cross-occupation comparisons. Another strength was the use of the inverse probability treatment weighting to adjust for missing industry and occupation response in our surveillance data. A limitation was the absence of behavioral data on COVID-19 by industry and occupation, which could affect patterns of exposure, testing, and claiming.

Although the cumulative COVID-19 incidence rate among food manufacturing workers was high, this rate is likely underestimated given that statewide testing goals were not met, and throughout the pandemic, testing priority was given to frontline workers—especially health care workers.[9] Additionally, economic disadvantages and linguistic barriers of this disproportionately temporary, immigrant, and undocumented workforce are well documented barriers to WC claiming and public health outreach.[10] Therefore, it is more likely to result in lower completion of case interviews where industry and occupation are collected.

Overall, our study showed a disproportionately low use of WC benefits in Wisconsin compared to the high COVID-19 disease incidence. There is a need for improved worker protections for occupational infectious diseases with high risk of transmission and the need to strengthen the worker safety net through improvements to the WC system.

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Ethics Approval: The University of Wisconsin Institutional Review Board (UW-IRB) provided written approval for the Wisconsin Fundamental-Plus Occupational Health Surveillance Program (Submission ID number: 2013-0331-CR010) under which this study was performed. The UW-IRB determined that this study met the requirements of public health surveillance as defined in the US Department of Health and Human Services regulations for the protection of human subjects (45 CFR 46.102(l)(2)). This analysis did not require the informed consent of cases as these were administrative data reported to statewide public health surveillance databases.

Appendices: Available at www.wmjonline.org.

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Perception of Burnout and Its Impact on Academic Hospitalists During COVID-19 and Institutional Strategies to Combat Burnout and Improve Wellness

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ABSTRACT

Introduction: Physician burnout has been alarmingly high, particularly among general internal medicine, which displays some of the highest rates. A recent study of academic hospitalists reported a higher level of burnout (62%) than the rates found in similar studies, but with agreement about factors leading to burnout, consequences of burnout, and importance of steps to prevent burnout. This study seeks to expand upon these results by investigating the impact of COVID-19 on burnout among hospitalists and uncovering the perspectives of frontline clinicians to formulate effective mitigation strategies.

Methods: Academic hospitalists were recruited to participate in a series of focus group interviews. The questions focused on contributors to burnout, the impact of COVID-19, and strategies to improve wellness and reduce burnout. The focus groups were audio-recorded, transcribed, and coded for emergent themes using Taguette, an open-source qualitative data analysis software.

Results: Burnout-inducing themes included workload, bureaucratic hurdles, and lack of control. COVID-19-specific themes included fear of exposing family and social isolation. The most common mitigation strategy was to increase social interactions to foster a sense of community. Additional solutions included adhering to a census cap of patients, streamlining clinical work, and providing avenues for two-way communication between leadership and clinicians to share concerns and elicit feedback.

Conclusions: Streamlining clinical work allows more time for patient care. Enhancing community and fostering collaboration in decision-making allows clinicians to feel more empowered. A crucial first step to combat burnout is to encourage a work environment that values clinician well-being and proactively works to increase job satisfaction.

INTRODUCTION

The term burnout was first introduced in 1974 by psychologist Herbert J. Freudenberger, who described it as a state of mental exhaustion in one's career—particularly in the professions dedicated towards helping others, namely health care providers.[1] In 1981, social psychologist Christina Maslach expanded upon Freudenberger's work and conceptualized burnout into the 3 chief components: exhaustion, depersonalization (negative attitudes and cynicism), and reduced sense of personal accomplishment.[2-4] The term burnout is now recognized as an occupational hazard by the World Health Organization's International Classification of Diseases (ICD-11).[1]

Physician burnout is alarmingly high, with one study showing burnout documented in over 50% of practicing physicians and trainees in the United States.[3] Despite already high numbers of physicians experiencing burnout, the problem appears to be getting worse.[2] In a survey study of physicians in 2011 and 2014, 45% reported at least 1 symptom of burnout in 2011 compared to 54.4% merely 3 years later.[4] There is variability among medical specialties, with emergency medicine, general internal medicine, and neurology associated with burnout rates 3 times higher than other specialties.[3] This suggests that there are unique aspects to these disciplines that contribute to the variable rates of reported burnout.

A study of academic hospitalists surveyed in 2018 reported a higher level of burnout (62%) than rates found in similar studies.[5] Another recent study discovered a significant rise in burnout and decline in work-life integration satisfaction in US physicians between 2020 and 2021.[6] Measurements of depression were negligibly different, indicating the primary cause of physician distress was primarily work related. Relatively few pieces of research pro-

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vide comprehensive information about the impact of the COVID-19 pandemic on physician burnout in the United States; in fact, most studies on physician burnout have been conducted in countries outside of the United States.[7] We posit that the COVID-19 pandemic negatively affected provider well-being and requires the unique perspectives of frontline clinicians to formulate effective mitigation strategies to combat this rampant issue.

METHODS

Twenty practicing academic hospitalists at Froedtert Hospital were recruited to participate in a series of qualitative, semistructured focus groups. Froedtert Hospital is a 702-bed academic medical center affiliated with the Medical College of Wisconsin (MCW). All physicians who practice at Froedtert are MCW faculty dedicated to patient care, research, and teaching. Before participant recruitment, prior approval was obtained from the institutional review board.

Recruitment and Focus Groups

An invitation letter with details about the study was emailed to the entire hospitalist group. It highlighted the importance of the study, emphasized voluntary participation, and included the focus group questions. Written by the research team, the questions covered (1) contributors to burnout, (2) the influence of COVID-19 on wellness/burnout, (3) strategies to mitigate burnout and improve wellness, and (4) hospitalists' perceptions during COVID-19. Participants were divided into 4 focus groups composed of 4 to 5 individuals. Each interview was approximately 45 minutes and took place in January and February, 2022. All participants were blinded as to which colleagues would be participating. Focus groups were audio-recorded, deidentified, and transcribed. The researchers utilized Taguette, a validated, free, open-source qualitative data analysis tool, to code the transcripts.[8] The study utilized an inductive approach that allowed patterns and themes to emerge from the data. Each transcript was analyzed line by line in Taguette, and tags were assigned within the software to specific quotes that corresponded to a common theme across all transcripts. Participant quotes were later edited for clarity and brevity.

RESULTS

Discussion centered around 3 topics: (1) perceived contributors of burnout, (2) impact of COVID-19 on burnout, (3) suggestions for institutional wellness initiatives. We have highlighted the emergent themes in the Table.

Perceived Contributors of Burnout

The most common contributors to burnout reported were high workload, numerous bureaucratic hurdles, and lack of control. Participants reported having a high patient census that often required them to work extra shifts due to the increased demand for medical care. While their job hours and number of shifts seemed to increase over the years, job descriptions have remained the same, which is a source of frustration. Additionally, participants indicated that a lack of transparency from leadership contributes to their burnout and that they would like more two-way communication between the administration and health care providers.

> "There is no transparency from leadership…we are left unaware of decisions, which causes confusion and contributes to burnout."

In addition to the high patient census/extra shifts, participants reported having a high workload due to the abundant roles that they play within the academic setting—such as clinician, teacher, researcher, and administrator—while having little protected time to engage in learning activities outside of clinical duties.

> "The responsibility of teaching, taking care of patients, and coordinating care teams all contributes to physical and mental burnout...Even when you're not working, you feel like you are."

Participants also reported that extensive documentation is one of the biggest daily obstacles as they spend more time documenting and writing patient encounter notes than in direct face-to-face contact with patients.

> "Less time is spent with patient care and more time is spent writing the notes for the patient...The medical care of the patient is secondary to documentation as opposed to the primary issue."

Another bureaucratic hurdle that leads to burnout is the numerous additive requests from leadership and colleagues, such as writing a comprehensive discharge summary, discharging at a specific time, and having to consult specific committees about patients' medical histories.

> "Additive requests, such as writing a good discharge, discharging by 10 AM, and consulting a specific committee, take time away from the reason you came into medicine, which is to talk with and care for patients."

Participants further reported that they do not have control over instutional decisions, which further contributes to their feelings of burnout.

> "Burnout is all about how much control you have and your input in the sudden decision-making process."

Impact of COVID-19 on Burnout

Focus group participants reported that COVID-19 introduced new reasons for burnout, including emotional stress. They said they were afraid to expose their families to COVID-19 and took on extra shifts out of sympathy for colleagues who contracted COVID, although they did not have the mental capacity to work those extra shifts.

> "If you don't take the extra shifts, then you feel guilty for not helping the team, but if you overload your schedule, then you pay the price later down the road."

Participants also said that the impact of COVID made it dif-

ficult to find work-life balance—especially when their children were not able to attend school in person.

> "It was especially tough being a woman in hospitalist medicine as it has been difficult juggling clinical work, family, and virtual schooling for my children...My job was doubled both at home and at work."

Additionally, participants said the pandemic created a sense of social isolation, which further contributed to their sense of burnout as there was little face-to-face interaction among colleagues.

> "There was a degree of social isolation that everyone has experienced worldwide...I really miss seeing people and now I work mostly alone when I'm at the hospital."

Table. Themes From Focus Groups

Topics	Emergent Themes
Perceived contributors of burnout	1. High workload/patient census 2. Bureaucratic hurdles 3. Lack of control/transparency 4. Extensive documentation
Impact of COVID-19 on burnout	1. Emotional stress 2. Fear of exposing family 3. Overworked/scheduling demands 4. Difficult work-life balance 5. Social isolation 6. Patient skepticism regarding COVID-19 7. Witnessing patient suffering/dying
Suggestions for institutional wellness initiatives	1. Have a better workroom/space for social interactions at work 2. Increase social gatherings outside of work (retreat, holiday parties, interest groups, etc) 3. Provide avenues for bidirectional communication with leadership and clinicians to better understand and elicit feedback 4. Have a wellness officer 5. Census caps/improved scheduling 6. Better financial incentives

Interestingly, participants reported that the pandemic made them skeptical of patients. They questioned their empathy for patients who were not immunized against COVID despite evidence-based research and available information about vaccinations and treatment.

> "The trickiest part was the strong public perception that the standard quality of care was suspicious...The public often thought we were up to no good even though we are dedicated and committed to serve our patients."

> "This is taking a huge psychological toll…I go to patient rooms and they are not immunized…I'm losing empathy due to so much information available regarding immunizations."

At the same time, participants reported that it was difficult for them to witness many patients dying and suffering from COVID. The combination of patients dying and patients who did not trust health care providers further affected their own mental states.

> "Seeing COVID patients who are dying is not a good feeling and gave a sense of hopelessness, especially at a certain time when there were no treatment options besides oxygen and steroids to just blunt the immune response."

Suggestions for Institutional Wellness Initiatives

The most common suggestion for improving wellness was increasing social interactions to allow clinicians to relax, share feelings, and create more community. This included a better workroom and increasing social gatherings outside of work. There was a desire for a workroom with windows, more space, snacks, coffee, and a couch. It also was noted that existing space constraints have resulted in new hires being scattered—increasing isolation and loneliness.

> "I would love if there was a place for all the providers working that day to have a place to come together and have a cup of coffee for 5 minutes and talk about cases where you need advice…That will let us provide better care and would really brighten our day."

Suggestions for social interactions outside of work included a retreat, arranging activity groups for people to join based on their interests, and holiday parties. It was suggested that these gatherings would make people more comfortable talking to each other and go a long way to help relieve stress.

Another suggestion was to provide avenues for two-way communication between leadership and clinicians to share concerns and elicit feedback; increasing bidirectional communication would allow clinicians to feel more control.

> "It would be helpful, before our administration made decisions, to involve the physicians at the onset so that they can actually be a part of the decision-making and feel as though they have some control."

Additionally, it was suggested that it would be beneficial to have a wellness officer to help clinicians navigate wellness resources.

> "There might be a need to have someone from our section to provide that information to us in a better way so that we know how we should approach those resources…There is info out there, but clarity about resources will be needed… just sending an email doesn't mean that you have completed your responsibility."

Other suggestions included streamlining clinical work, as small tasks by management are burdensome and do not improve quality of care; introducing census caps; improved scheduling; and providing better financial incentives.

DISCUSSION

The key findings in our focus group interviews were consistent with Maslach's interpretation of burnout (exhaustion, depersonalization, and reduced personal accomplishment).[2-4] We found hospitalist exhaustion was exacerbated during the pandemic as they took on extra shifts to cover for colleagues who became ill, while simultaneously having increased duties at home (ie, childcare/home schooling). The pandemic further took a toll on participants' mental health by causing fear of infecting loved ones and inducing social isolation. They experienced depersonalization as they struggled to feel empathy for unvaccinated patients and felt reduced personal accomplishment due to the public's negative perception of health care providers during the pandemic.

Our study also highlighted several strategies hospitals can take to alleviate the causes and consequences of burnout. Focus group participants reported a desire for increased social activities, improved work spaces that foster community, increased communication with leadership, census caps, and streamlined clinical work. They are vulnerable to exhaustion that comes from the combination of a high workload, bureaucratic hurdles, and comprehensive documentation, which were made worse by COVID-19 due to increased scheduling demands, difficult work-life balance, and no time for self-care.

These themes were shown in previous research on how the pandemic exacerbated physician burnout. A May 2021 news article in *BMJ* reported that approximately 6 in 10 physicians reported higher levels of fatigue and exhaustion while working in the pandemic.[9] A *BMJ* tracker survey revealed that more than half (58%, n = 2834 of 4876) of its respondents had worked extra hours relative to the previous month, and 44% (n = 2086) said they felt pressured by their employer to work extra hours.[9] As work demands increased, physicians also had increased demands at home. A 2021 survey of academic medicine faculty at the University of Texas Southwestern reported that faculty had increased time spent on household and childcare duties by an additional 27 hours per week.[10]

This feeling of pressure to take on extra work while already having a full workload also was expressed by our study cohort. A suggested solution to this problem is to cap the number of patients assigned to each team. A 2012 study on internal medicine residents at Mayo Clinic revealed that having a census cap on the number of patients admitted improved resident workload while benefiting their learning.[11] Streamlining clinical work also may help alleviate clinician exhaustion. It has been reported that for every hour spent on patient interaction, a physician spends an additional 1 to 2 hours finishing progress notes, administrative requirements such as ordering labs, prescribing medications, and reviewing results.[4] Thus, by reducing hours spent on nonclinical administrative work, clinicians can spend more time on patient care, which is associated with increased personal accomplishment and reduced burnout.[3]

All of these contributors to burnout, exacerbated by the emotional stress of COVID-19, created a unique burden on hospitalists. During the state of social isolation, the stress of the burden that the hospitalists in our study faced was heightened. In population studies, social support and community belonging have a well-established association with improved mental and physical health.[12] The same principle should be applied to the health care workplace to improve wellness. A survey of Mayo clinic internal medicine hospitalists in 4 states showed that 27% "felt isolated from others" and 2.6% "felt like a stranger to those around me" compared to 0% for both categories prior to the COVID-19 pandemic.[13] Our study suggests that creating spaces for dialogue between colleagues with shared experiences to discuss challenges can alleviate some of this stress. Both increasing workplace social interactions through a better workroom experience as well as gatherings outside of work were persistently highlighted during our focus groups. These findings are consistent with previous research suggesting the importance of cultivating workplace relationships to improve wellness in resident physicians and the importance of social connectedness among health care staff.[14,15]

Leadership and organizations can play a significant role in mitigating burnout in health care workers. Seeking input, informing constituents, and recognizing individuals for their contributions help decrease feelings of burnout and increase career satisfaction among those they lead.[3] Studies have shown that when organizations and leaders provide physicians with increased control over the workplace, lower levels of work-related stress and subsequent burnout are more likely.[3] In a cross-sectional study conducted across 3 emergency departments (ED), frontline employees reported feeling more supported and experiencing less stress and burnout when local leadership communications were effective, consistent, and bidirectional.[16] These results were similar to our findings in that participants wanted avenues for two-way communication between clinicians and leadership to better understand concerns and elicit feedback. Health care organizations previously have prioritized self-resilience and stress management education, which is a tactic that places the perceived blame on physicians.[1] Organizations must foster a culture of wellness and effective procedures that can reduce health care stressors rather than attempting to fix the clinicians.[17] However, a well-being oriented culture can only be established with leadership support. It is necessary for institutional transformation to start at the top. A crucial first step is to encourage a work environment that values clinician well-being and proactively works to increase job satisfaction by lowering burnout.[18]

Our study has a few limitations. Our qualitative data were derived from multiple focus groups. Although widely utilized, this method of data collection has the potential pitfall of groupthink. We attempted to avoid this outcome by having a different participant be the first to answer each question to prevent the conversation from being dominated by a particular person or

idea. Additionally, participation was voluntary, and the topic of the focus groups was disclosed in the invitation letter. Thus, it is likely that hospitalists who were disproportionately affected by factors leading to burnout were more inclined to participate. Furthermore, all study participants belonged to a single academic center, which limits the generalizability of our findings. Our analysis also was limited by the level of detail provided by participants, as some were more detailed in their responses than others.

Future studies can be done that randomly select individuals to participate. Participating sites should include multiple academic centers in order to create universal institutional strategies to mitigate burnout. They also can standardize the level of detail in interviewee responses by asking more follow-up questions targeted towards specific statements.

CONCLUSIONS

Physician burnout remains alarmingly high and should be of concern to academic institutions. The COVID-19 pandemic further increased physician burnout, while both maintaining traditional views and creating unique perceptions of physician burnout. Social isolation and lack of effective communication between clinicians and leadership contribute to fatigue and frustration and worsens burnout. This can be mitigated by enhancing community and fostering collaboration in decision-making, which may alleviate stress and reduce burnout. A crucial first step to combat burnout is to encourage a work environment that values clinician well-being and proactively works to increase job satisfaction.

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COVID-19 Vaccine Acceptance or Refusal Among US Nurses: A Descriptive Cross-Sectional Study

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ABSTRACT

Introduction: Nurse turnover has accelerated during the COVID-19 pandemic. Nurse refusal of mandated vaccines contributes to understaffing and affects patient health outcomes. The purposes of this study were to describe (1) nurse reasons for COVID-19 vaccine decisions and (2) the relationship between vaccine status and nurse characteristics.

Methods: This cross-sectional descriptive study employed a survey of US nurses who worked in nursing during the COVID-19 pandemic. The survey included a free-text question about COVID-19 vaccine uptake rationale, self-reported vaccine acceptance/refusal, and demographic data.

Results: Of the 1682 participants, 11.2% refused the COVID-19 vaccine. Higher education level was correlated with greater vaccine acceptance rates ($P < 0.001$). Themes for vaccine rationale included safeguarding well-being, trust in the science, coercion to vaccinate, perceived immunity, and concern about preexisting health conditions.

Conclusions: The risks of COVID-19 vaccine mandates may be greater than the potential benefits given the potential for compounding workforce attrition during a nursing staffing crisis. Further research is needed to outline the relationships between vaccine education, advocacy, and vaccine uptake among nurses.

INTRODUCTION

Nurses play a critical role in health care delivery across the acute, primary, and community settings that is essential to global universal health outcomes.[1] The present global shortage of nurses—exacerbated by shortfalls in the number of educators and nurses voluntarily leaving the profession before retirement—is concerning given the impact that nurses make on global health.[2] Prior to the pandemic, there was projected to be a shortage of 151 500 licensed practical nurse and 918 232 registered nurses jobs in the United States by 2030.[3,4] The COVID-19 pandemic has accelerated nurse attrition through numerous mechanisms, such as burnout, lack of personal protective equipment, and COVID-19 vaccine refusal in the setting of vaccine mandates.[5,6] In 2021, COVID-19 vaccine refusal for nurses was estimated to be 18.3% globally[7] and approximately 12% in the United States.[8] Potential losses to the nursing workforce secondary to vaccine refusal-related attrition would exacerbate the existing nursing shortage. Therefore, understanding reasons for vaccine refusal is crucial to prevent future losses that would ultimately negatively affect patient health outcomes.

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Vaccine Refusal Among Health Care Workers

Vaccine refusal historically has been an issue among global health care workers, with wide geographic variances in childhood vaccine completion rates for children of health care workers under 5 years old.[9] Vaccine uptake rates also can vary in the same region from year to year. Influenza vaccine uptake among Italian health care workers was 60% in 2019 but only 22% in 2020.[10] There are several predictors for health care worker vaccine uptake. Education level and self-perceived vaccination knowledge are associated with both personal uptake of vaccines and recommendation for patient vaccine uptake.[10] Health care workers are less receptive to receiving vaccines for diseases that they perceive to have low severity.[8,10] Natural immunity from prior infection is sometimes cited as a rationale for vaccine refusal.[8,11,12]

Vaccine Mandates for Health Care Workers

Vaccine mandates for health care workers can effectively increase vaccine uptake rates;[13] however, it is unclear if mandates alone are responsible for improved vaccine uptake. One implementation of a hospital-wide mandatory influenza vaccine policy coupled with a vaccination campaign found that vaccine uptake increased from 54% to 97.6%; however, unionized staff who were exempt from the mandate also achieved 95.8% vaccination.[14]

The impact of vaccine mandates on patient safety outcomes is unknown.[15,16] The COVID-19 vaccine has poor relative efficacy in reducing disease transmission.[17] Proponents of vaccine mandates argue that mandates are a codification of the health care worker's duty to protect the well-being of their patients. Vaccine refusal is perceived as a willingness to spread contagious disease to the vulnerable and, therefore, a refusal to meet the duty of care burden that health care workers inherently shoulder.[18] Breach of the health care worker's duty to their patients' well-being is rationalized as justification for excluding them from patient care duties.[19]

Vaccine mandates also can be seen as a violation of the health care worker's right to personal medical autonomy.[19] Alternatives, such as mandatory personal protective equipment (PPE) use for unvaccinated staff, are often overlooked in the discourse supporting vaccine mandates and were not supported by the Centers for Medicare and Medicaid Services (CMS) COVID-19 vaccine mandate.[20] Health care workers are patients when they undergo medical treatment; however, their autonomy is perceived to be unvalued when a treatment is mandated and without alternatives.[21]

While proponents of vaccine mandates would argue the intrusion into personal autonomy is justified, a consequence of a vaccine mandate may be premature attrition from the profession by vaccine-hesitant health care workers, further exacerbating staffing shortages and compromising the ability to provide patient care.[22] Preexisting workplace stressors, such as demanding working conditions with inadequate resources and perceived poor support from health care institutions, may further diminish a vaccine-hesitant nurse's motivation to remain in the profession.[23,24] There is a dearth of research examining nurse rationale for their decision to accept or refuse the COVID-19 vaccine—particularly in the setting of a new mandate for a vaccine that had emergency use authorization at the implementation of the mandate.[20,25] The purpose of this study is to describe nurses' reasons for accepting or refusing the COVID-19 vaccine and to understand relationships between nurse characteristics and COVID-19 vaccination acceptance status.

METHODS

This cross-sectional study employed an online survey of US registered nurses and licensed practical nurses. Inclusion criteria included nurses currently licensed in any state and working in nursing at any time since the beginning of the COVID-19 pandemic in the United States, defined in this survey as March of 2020. Nurses were recruited via social media, an advertisement through the Wisconsin Nurses Association, and mass email to all actively licensed nurses in Wisconsin. Consent was implied by participating in the voluntary survey. Participants were surveyed via Qualtrics about their perceived reasons for accepting or refusing the COVID-19 vaccine and their vaccine status. This study was reviewed and approved by the Marquette University institutional review board for human research. The survey was open between November 2021 and January 2022. The CMS COVID-19 vaccine mandate took effect at the beginning of this study period and remained in effect throughout the study duration.[20]

Measures

The survey consisted of 2 vaccine questions: (1) "Did you receive the COVID-19 vaccine?" (yes/no) and (2) "Why did you choose to receive or not receive the COVID-19 vaccine?" (free-text answer). Demographic data included age, gender, highest completed nursing education level, years in practice, working with COVID-19 patients, and practice type (eg, direct patient care, manager).

Analysis

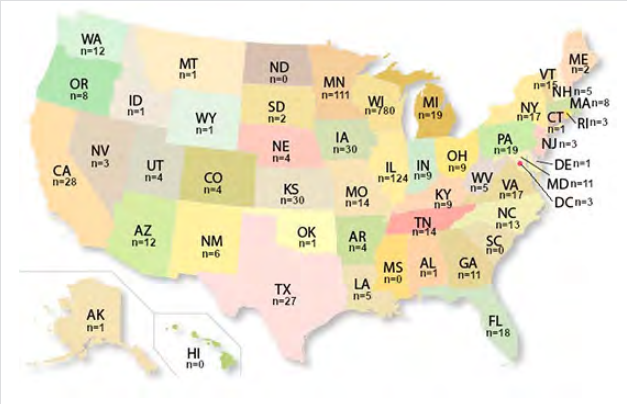
Quantitative data were analyzed with chi-square tests to examine the association between participant characteristics and vaccination status. This analysis was performed using SPSS Statistics version 28.0.0.0.[26] Qualitative data were analyzed using content analysis, a process in which data are coded and analyzed for meaning and abstracted into broader themes.[27] Three investigators (JC, BSO, and MM) independently read the content to identify meaningful themes. A predefined theoretical framework was not utilized for this analysis to preserve the integrity of the messages as they were written by participants. The three investigators met as a team to validate themes and examples within the data. A consensus was reached that the themes and exemplar quotes were accurate representations of the data set (internal validity and credibility). Transferability was enhanced by sample description via demographic data.

RESULTS

Participants

A total of 1682 participants answered the survey; of those, 1445 (85.9%) answered the binary vaccine acceptance/refusal question, 1316 (78.2%) answered the free-text vaccine rationale question, and 1301 (77.3%) answered both questions. Of the participants who answered both questions, 1155 (88.8%) received the vaccine and 146 (11.2%) did not. To create an equal sample of both vaccinated and unvaccinated participants for comparison, a random sample of 146 vaccinated participants were selected for analysis via a random number generator. All three investigators agreed that data saturation was met for both the selected vaccinated participant group and the unvaccinated group. Over 90% of participants (91.7%) were female, and the majority held a baccalaureate degree (54%) (missing data excluded from percentage tabulations).

Figure. Participant Location by State



N = 1428 participants with available location data.

Almost half had been in nursing for less than 10 years (44.9%), 52.7% were ages 25 to 44, and 78.3% were primarily involved in direct patient care (Table 1). A state-by-state participant breakdown is presented in Figure 1.

Vaccination Status and Sample Characteristics, Intention to Leave

A chi-square test was performed to assess the relationships between nurse characteristics, including gender, age, education level, years in nursing, practice type, and whether they worked with COVID-19 patients. This analysis was performed on the total sample (N = 1682). There was a significant correlation between education level and vaccine acceptance; nurses with higher education levels were more likely to accept the COVID-19 vaccine ($P < 0.001$, Table 1).

Table 1. Education Level and Vaccination Status

Characteristic	No Vaccine (%)	Yes Vaccine (%)	*P* value
Gender	155 (10.9)	1273 (89.1)	0.197
Female	147 (11.2)	1162 (88.8)	
Male	1 (0.9)	107 (99.1)	
Nonbinary/other	1 (20)	4 (80.0)	
Age	156 (10.9)	1276 (89.1)	0.215
18 – 24	8 (7.5)	99 (92.5)	
25 – 34	50 (13.2)	330 (86.8)	
35 – 44	45 (12.0)	330 (88.0)	
45 – 54	30 (10.2)	264 (89.8)	
55 – 64	18 (8.4)	197 (91.6)	
65+	5 (8.2)	56 (91.8)	
Education level	154 (10.8)	1272 (89.2)	< 0.001
LPN	17 (21.3)	63 (78.8)	
ADN	44 (15.3)	243 (84.7)	
BSN	70 (9.1)	703 (90.9)	
Graduate[a]	23 (8.0)	263 (92.0)	
Years in nursing	156 (10.9)	1277 (89.1)	0.057
< 10	75 (11.6)	569 (88.4)	
10 – 20	52 (13.1)	344 (86.9)	
21+	29 (7.4)	364 (92.6)	
Practice type	155 (10.8)	1275 (89.2)	0.969
Direct patient care	123 (11.0)	996 (89.0)	
Manager/supervisor	9 (8.0)	104 (92.0)	
Educator	7 (12.5)	49 (87.5)	
Other	16 (11.3)	126 (88.7)	
Worked with COVID patients	156 (10.9)	1276 (89.1)	0.831
Yes	128 (11.0)	1038 (89.0)	
No	28 (10.5)	238 (89.5)	

Abbreviations: LPN, licensed practical nurse; ADN, associate degree nurse; BSN, baccalaureate of science in nursing.

[a]Graduate education level includes master's and doctorate degrees. Within the education level subcategories, the percentage denoted is the percentage within the education level.

Vaccination Rationale

Five themes emerged from the free-text question about rationale for vaccine acceptance or refusal: (1) safeguarding well-being, (2) trust in the science, (3) coercion to vaccinate, (4) perceived immunity, and (5) concern regarding preexisting health conditions. Exemplar quotations for each theme are presented in Table 2.

Safeguarding Well-Being: Among vaccinated participants, the desire to protect oneself, one's family, and one's patients was the most prevalent theme. The desire to end the pandemic was also a prevalent concern expressed. Some participants reported fears about catching COVID-19 or personal experiences of COVID-related loss. On the other hand, some of the unvaccinated participants expressed concerns for their personal safety with regard to the vaccine. Unvaccinated nurses expressed concerns about personal side-effects.

Trust in the Science: Trust in the science around vaccine development was a prevalent theme for all respondents. Vaccinated participants reported trust in the science behind vaccinations. Some cited their education, profession, and perceived duty to comply with evidence-based practice guidelines as a rationale for trust in the science. Many expressed desire to utilize science to end the pandemic, and some recalled the impact of vaccination on past epidemics.

Unvaccinated respondents, on the other hand, discussed their skepticism around vaccine development and deployment, with most giving multiple reasons for their mistrust. Mistrust in health care authorities and concern for misinformation from authorities or pharmaceutical manufacturers was prevalent. Several participants expressed concerns about experimentation specifically, and others discussed concerns about the veracity of vaccine side-effect reporting systems.

Coercion to Vaccinate: Perceived coercion and breach of personal autonomy was a theme among unvaccinated nurses. Some unvaccinated nurses reported frustration due to perceived coercion because of the COVID-19 vaccine mandate. Many reported threatened or actual firing from their jobs if they remained unvaccinated.

Table 2. Exemplar Quotes From Themes

Vaccinated Participants	Unvaccinated Participants
Safeguarding Well-Being	
"I received this [vaccine] before it was mandatory. To first and foremost prevent me from getting sick, second my family, third my patients."	"Chose not to receive due to fear of adverse effects."
"I chose to receive the COVID-19 vaccine because I trust and believe in science and think it is part of a collective effort to end the global pandemic."	"Lack of documentation of long-term side effects."
"Not one of my patients lived for the first three months. That whole time I was terrified I would be the next to die. I would have taken the vaccine as a shot in my eyeball just to decrease the stress of going to work and not bring home COVID to my family."	"It's not a vaccine. It is gene therapy and I do not consent."
Trust in Science	
"I believe in science and it's my duty as a nurse to educate the public on that science."	"Something feels wrong about all of it. Don't feel I need a questionable vaccine for something with a high survival rate."
"I believe in science and the protective power of vaccines. I am an older nurse and lived through polio, etc."	"I have every vaccination known to man, except the COVID vaccine. It is too highly politicized, you are not allowed to question the side effects, it was rushed to the market."
"This is an evidence-based profession; we have a duty to follow the evidence and the evidence is clear – the vaccine has saved lives."	"I chose not to receive the vaccine because I still have major doubts about the amount of time and research put into this vaccine. I do not feel as though I'm ready to be an experiment just because I'm a nurse."
	"I also saw horrible side effects of the vaccine that people received in the ER. And it was even more disgraceful that not one doctor would relate the vaccine to these effects. Therefore, all of the side effects I saw from this vaccine never got reported to VAERS [vaccine associated event reporting system] at the facility I worked at."
Coercion to Vaccinate	
"I do feel like it was pushed on us, and I'm not sure that there will not be long-term side effects."	"I'm not allowing anyone to make my medical decisions for me."
"I felt forced to in order to keep my job."	"[I] did not get [the] vaccine and will lose my job due to this."
"I had to [get the COVID-19 vaccine] as a requirement, otherwise I would not have. I wanted to know more about it (long term studies), and I feel it is not working as they said it would. Way too many politics involved, and I don't trust Fauci or big pharma."	"Nurses were heroes at the start of the pandemic and are now being fired for not taking a vaccine. What happened to living in a free country."
"Nobody cared last year when we didn't have PPE or a vaccine… it is more safe to have more staff than having unvaccinated coworkers."	"Too much media hype and pressure."
Perceived Immunity	
There were no responses from vaccinated participants in this category.	"There is not enough research or evidence to prove efficacy stronger than my own natural immunity to make me want to risk the adverse effects."
	"Epidemiology 101 taught us vaccines are good, but natural immunity infection is better toward herd immunity."
Concern Regarding Preexisting Health Conditions	
"I was in the first group to have the shot. But I had a severe allergic reaction to the shot and cannot get the vaccine. I am frustrated and worried about my own personal health."	"There was not enough clinical studies/research for me to feel comfortable receiving the vaccine while pregnant. I am absolutely disgusted that when I make a decision about my body and the little body I have growing inside of me that I continued to be called out, lectured, and told I was wrong. I will now get the vaccine because I have to in order to return to work from maternity leave."
	"I was pregnant and very nervous to harm my pregnancy. I chose to not get it while pregnant and am hopeful for an exemption to not get it while breastfeeding."
	"I have had health issues and am concerned about my immunity."

Some vaccinated nurses also indicated they felt that they were not presented with a genuine choice regarding their vaccination status. While many expressed frustrations at unvaccinated colleagues for their refusal, some reported they got the vaccine even though they did not want to solely because it was required to continue work. Several voiced disagreement with vaccine mandates due to the effect it had on their unit staffing.

Perceived Immunity: Numerous unvaccinated respondents rationalized that their natural immunity from prior COVID-19 infections was sufficient to protect them. One cited perceived superiority of natural immunity.

Concern Regarding Preexisting Health Conditions: Some unvaccinated respondents reported personal health conditions that made them situationally unable or unwilling to accept the COVID-19 vaccine. Numerous participants expressed possible safety concerns due to their pregnancies. (At the time of this study, the American College of Obstetrics and Gynecology had released a statement recommending COVID-19 vaccination for all eligible persons, including pregnant and lactating individuals.[28]) Two respondents reported anaphylactic or severe adverse reactions to the first vaccination in a 2-dose series and self-identified as unvaccinated despite receiving 1 vaccine dose. Other unvaccinated participants reported concerns for their health following vaccination given preexisting health concerns, such as a family history of adverse vaccine reactions (1 nurse) or witnessing patient side-effects (9 nurses).

DISCUSSION

The purposes of this study were to describe nurses' reasons for accepting or refusing the COVID-19 vaccine and to better understand the relationships between nurse characteristics and COVID-19 vaccination acceptance. While this analysis supports prior findings that vaccination mandates increase vaccination acceptance, 11.2% of our sample declined the vaccine despite mandates, including some who accepted personal consequences due to their refusal.

Prior research has associated vaccination refusal with inadequate staffing due to job attrition, which risks further exacerbating the nursing shortage.[13,23] While COVID-related escalations in attrition from the nursing profession are multifactorial, vaccine refusal is a particularly concerning potential contributor to attrition because it is preventable—particularly if alternatives to vaccination like continuous PPE use for unvaccinated staff were implemented.[21] Research on influenza vaccine mandates have shown that job attrition secondary to vaccine mandates is as low as 0.15%.[14] However, this number may have limited comparison to attrition secondary to COVID-19 vaccination refusal.

Exemption criteria for the COVID-19 vaccine mandate was broadly outlined by CMS; however, implementation of exemption policies were left to the discretion of health care facilities.[20] Participants in this study reported variance in how their facilities treated their exemption requests, which may indicate variance in exemption implementations. Prior recommendations regarding influenza immunization mandates have advised against severe actions, such as termination, due to vaccine refusal; however, several participants in this study reported threatened or actual termination due to COVID-19 vaccine refusal. While it is outside the scope of this study to determine the proportion of nurse attrition attributable to vaccine mandates, further research on this topic may be warranted.

The COVID-19 vaccine was perceived as new and of questionable trustworthiness by unvaccinated participants in this study. Mistrust in COVID-19 vaccine development may have been fueled over evolving knowledge around side-effects, such as coagulopathies associated with adenovirus vaccine vectors (eg, Johnson and Johnson/Janssen vaccine).[29] While the CMS mandate cited concerns for PPE compliance as rationale for a vaccine mandate in lieu of stricter PPE use guidelines, the evidence for N95 mask use to prevent COVID-19 transmission among health care workers was graded as high.[20,30] Policy decisions that may further exacerbate the nurse shortage should be carefully examined for their necessity prior to implementation—particularly considering pandemic-related escalations in nurse burnout and attrition.[23,24,31]

Vaccination and Science Literacy

Education level and attitudes toward the efficacy of government and scientific institutions have been correlated with COVID-19 vaccine acceptability.[10] Participants in this study were divided with regard to trust or mistrust in scientific processes and government health care authorities. Vaccinated participants expressed trust in those institutions as a rationale for vaccine acceptance, whereas unvaccinated participants expressed skepticism in the same authorities. Nonetheless, education efforts have been shown to be effective in past vaccine advocacy campaigns.[7,10] Participants who have high confidence in their vaccine knowledge are more likely to accept vaccines.[10] One vaccinated participant in our study expressed initial hesitancy that improved with education: "Initially highly encouraged and [I] felt obligated, now I stand behind the vaccines with further education."

While experts agree that education programs are effective in increasing vaccine acceptance among health care workers, policy experts disagree on the adequacy of voluntary vaccination programs and education to reach desired health care worker vaccination compliance.[15,19,21] While there was an association between education level and vaccine uptake, it is outside the scope of this study to determine if COVID-19 vaccine education—or education on vaccines in general—is correlated with increased vaccine uptake in nurses.

Limitations

The CMS vaccination mandate went into effect on November 5, 2021, as this study commenced.[20] While some vaccinated nurses

reported they would not have received the vaccine were it not for the mandate, nurse preference for COVID-19 vaccination was not addressed in this study. There may be an unacknowledged discrepancy between desire to become vaccinated and actual vaccination status, and nurses may have had preferences for which vaccine they would rather receive. Additionally, this study did not collect data regarding when nurses made their decision regarding COVID-19 vaccination.

This study took place approximately 1 year after the first COVID-19 vaccine was available for health care workers. Vaccine refusal constitutes an ongoing decision; an unvaccinated nurse can choose to become vaccinated at any time. While some nurses were skeptical about the science of the vaccine and its emergency use authorization, additional evidence has become available and 2 COVID-19 vaccines have been fully approved for use by the US Food and Drug Administration.[25] It is possible that nurses who declined the COVID-19 vaccine at the time of our study have since reconsidered. Vaccinated and unvaccinated nurses were categorized by how they self-identified. However, several nurses self-selected their status as unvaccinated despite writing in free-text that they received a dose (eg, nurses who received 1 dose but did not complete a 2-dose series due to adverse reactions).

There were markedly more vaccinated than unvaccinated nurses; our chosen method of randomly sampling vaccinated participants to include in the analysis may have missed themes despite achieving data saturation. Participants in this convenience sampling may have unique perspectives that prompted them to self-select to participate in this study. This sample was also disproportionately representative of the states of Wisconsin and Minnesota.

CONCLUSIONS

An extensive analysis of the COVID-19 pandemic response is important to improve our response and prevent avoidable missteps during future pandemics. This study highlights the need to consider the ethical and practical implications of vaccine mandates for health care workers. While some vaccinated nurses opted to obtain a vaccine they otherwise would have declined, there is also potential that vaccine mandate-related nurse attrition could exacerbate the pre-existing nursing shortage. Vaccination mandates should be carefully considered in relation to the practical benefits and costs with regard to patient care prior to implementation. Many nurses who declined the vaccine cited skepticism about safety and efficacy; alternatives to mandates such as strict PPE requirements should be considered prior to or in combination with vaccination advocacy to reduce the potential for further disruption of the nursing workforce. Further research is needed to evaluate the effects of vaccine mandates and their impact on both nosocomial disease transmission and workforce attrition. Changes to global health needs during a pandemic may warrant reconsideration of whether vaccine mandates are necessary and pragmatic for all health care workers.

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The Association Between Remote Work During the First Wave of the Pandemic and Faculty Perceptions of Their Productivity and Career Trajectory: A Cross Sectional Survey

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ABSTRACT

Introduction: Early in the pandemic, studies documented that there are gendered differences in many factors related to working during the pandemic, especially for caregivers. This study aimed to focus on the effects of remote work, rather than the pandemic in general, on perceptions of productivity and career trajectory in research and education faculty at an academic health center.

Methods: A questionnaire was developed and distributed to all faculty in the Department of Medicine. We obtained demographic information and asked respondents to report the effect that remote work had on their research or teaching productivity. Those who reported a decrease in productivity were asked to choose a degree of impact. We also asked about the level of concern for the effect remote work would have on their career trajectory in research and teaching and about the impact of remote work on academic wellness.

Results: We received responses from 51.4% of 479 faculty. A little less than half were females, and most were subspecialists. More than half (60.6%) were responsible for providing care to children, parents, or others. Nearly one-quarter of respondents (22.8%) reported a negative effect of remote work on teaching productivity, which was more pronounced in senior faculty versus junior faculty (28.6% vs 16.5%, $P=0.03$). Few faculty (7.4%) were concerned about their career trajectory in teaching; however, those who provided care at home were significantly more likely to be concerned (10.7% vs 2.1%, $P=0.01$). Over half of respondents (56.6%) reported a negative effect of remote work on research productivity; this was significantly higher for tenure faculty than clinician educators (71.9% vs 50.7%, $P=0.01$). Almost half of respondents (39.6%) were concerned about their career trajectory in research, and this concern was significantly higher in specialists than in generalists (42.9% vs 15.8%, $P=0.02$) and in clinician educators versus clinicians (39.7% vs 0.0%, $P=0.007$). A small number of faculty (11.5%) reported a negative impact of remote work on their academic wellness; this impact was higher in specialists than in generalists (13.2% vs 3.7%, $P=0.05$). There were no significant differences in any areas of concern for males versus females or in those with or without leadership roles.

Conclusions: In this single-center study during the first wave of the pandemic, faculty perceived reduced productivity in teaching, research, and academic wellness. Our study found that remote work concerns were overall more evenly distributed across gender and those responsible for caregiving than had been reported previously; however, caregivers were more concerned about their career trajectory in teaching than noncaregivers. The lack of significant differences may have been due to several factors: remote work allowed flexibility when caregiving arrangements were disrupted; remote work was required of all faculty, mitigating concerns that caregivers were singled out; and institutional support offset some of the challenges. Further studies are needed to determine whether social or operational interventions in academic health centers can reduce the negative perception of remote working on academic productivity.

INTRODUCTION

Shortly after a state of emergency was declared in the United States in March 2020 related to the COVID-19 pandemic, academic operations in the Department of Medicine at the University of Wisconsin School of Medicine and Public Health were reduced to essential activities. Physicians, scientists, and educators adjusted their efforts to preserve and promote the future of the academic mission. A large part of this shift was a transition to working from home or otherwise working remotely. This transition was a significant departure from prepandemic norms, and the unique circumstances surrounding this policy change mean that the consequences—both benefits and burdens—may have been experienced differently across groups.

Earlier reports during the pandemic demonstrated gendered differences in burnout, perception of work-life balance, passing up leadership opportunities, and

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planning to reduce hours or leave a job among physicians and scientists, with a greater negative effect on females overall and most markedly on female parents/caregivers of preschool aged children.[1,2] There also have been reports of a gender gap in manuscript submission and, specifically, COVID-19–related research manuscript submission, with an early paper showing only 12% female authors for COVID-19–related research at the time of the analysis. [3] The greater negative effects of the pandemic on female faculty in prior studies have been attributed to exacerbation of prepandemic biases and inequalities compounded by gendered division of domestic labor and caretaking responsibilities.[4]

Studies prior to the pandemic have examined the complexity of the relationship of remote work to wellness and productivity.[5] Work productivity can be negatively affected if a remote worker lacks adequate resources in the remote work set-up[6,7] or if they are expected to take on increased home responsibilities.[8] Historically, remote work has been associated with lower likelihood of promotion and lower wage growth—particularly for women with higher frequency of remote work use.[9] Remote work and requests for more flexible work arrangements may be perceived as signs of less commitment to work and career advancement.[10] Taken together, these factors contribute to individuals' hesitancy to use remote work options[11] and concerns that remote work can be harmful to career prospects.

There is the potential that significant differences in research and education productivity and academic wellness may have emerged between groups, despite a universal policy enacted across all faculty requiring remote work. We conducted a survey of faculty on the effects of remote working on educational and research productivity, as well as overall academic wellness. A distinguishing feature of this study versus other studies is the focus on the impact of remote working—rather than the pandemic in general—on academic productivity and well-being, with attention to differences across subgroups.

METHODS

Survey Subjects

The Department of Medicine consists of 479 faculty whose academic rank includes instructors, scientists, assistant professors, associate professors, and professors. This is a mixture of clinical faculty, clinician educators, clinician researchers, and researchers.

Questionnaire

This survey was developed and administered in collaboration with the University of Wisconsin Survey Center. Informed consent was not obtained because the study was of minimal risk, the survey was conducted anonymously and voluntarily, and it involved no procedures for which written consent would be required outside of the research context. It was approved by the Institutional Review Board.

All 479 Department of Medicine faculty were invited to participate to assess their perception of remote work on their academic productivity and well-being. This invitation was based on university employment records, and an email was sent from a Department of Medicine address, which is excluded from spam filters.

The first section of the survey used multiple choice questions and asked about academic track (Instructor, Scientist, Clinician, Clinician Educator, and Tenure—the latter of which is a heavily research-focused faculty track), rank, subspecialty, area of operation, administrative leadership roles ("Do you currently hold any administrative leadership roles within the department, school or campus?"), area of research and/or education, distribution of work (proportion of effort devoted to clinical/research/education/administration), gender (choices were male, female, or no response), and ethnicity. Data about caregiving responsibilities also were collected where applicable, including a breakdown of care by "full-time" or "part-time" (not further defined in the survey) and by the following groups: "caring for children <5 years old," where enrollment in school is not a given; "caring for children 5-18 years old," where school enrollment is typical; "caring for parents," or "other."

The second part of the survey included questions about research, educational activities, and academic wellness prepandemic and intrapandemic. In the area of research activity, faculty were asked whether remote work had increased, decreased, or had no effect on their productivity. For those respondents who indicated a decrease, they were asked further about the degree of the impact; multiple choice options were "a little," "a moderate amount," "quite a bit," and "a great deal." We also asked how concerned they were that remote work would affect their career trajectory in research. For respondents who indicated a concern, multiple choice options were "not at all," "a little," "somewhat," "very," and "extremely."

In the area of education, faculty were asked whether remote work had increased, decreased, or had no effect on their productivity in teaching. For those respondents who indicated a decrease, they were further asked about the degree of the impact; multiple choice options were "a little," "a moderate amount," "quite a bit," and "a great deal." We also asked how concerned they were that remote work would affect their career trajectory in teaching. For respondents who indicated a concern, multiple choice options were "not at all," "a little," "somewhat," "very," and "extremely."

Faculty also were asked about the impact of remote work on their academic wellness, defined as a faculty member's ability to manage research and teaching workloads while developing skills and preparing for the future in a healthy way.

Data Collection

The survey was sent in August 2020 by email with a Qualtrics link asking participants to complete the survey anonymously.

Second and third reminders were sent to all participants asking for responses if they had not yet completed the survey.

Univariate and bivariate analyses were used for all analyses. Proportions are presented and compared across subgroups by chi-square tests.

RESULTS

A total of 246 faculty members responded to any of the questions in the three areas (teaching, research, or wellness), representing 51.4% of the 479 faculty members (Table 1). The completion rate differs across the specific areas, as not all participants were asked to complete each section (eg, only those participating in research were asked to complete the research-related sections).

Hospitalists and general internists were combined for analysis to group the two divisions more heavily involved in clinical care and education. This group was compared to the other specialties in the department that are generally more research focused. Of all respondents, a little less than half were female, and most were subspecialists (ie, not hospitalists or general internists). More than half were responsible for providing care for children, parents, or others. About half of those providing care did so on a part-time basis.

Table 2 summarizes responses regarding the effect that remote work had on productivity and career trajectory. For respondents who indicated a negative impact on productivity, we report in aggregate the responses that the negative impact was "a moderate amount," "quite a bit," or "a great deal," and we did not include "a little." For the questions regarding concern about remote work affecting their career trajectory in research or teaching, we report in aggregate the responses of "somewhat," "very," or "extremely," and we did not include "not at all" or "a little." Approximately one quarter (22.8%) of respondents reported that remote work had a negative impact on teaching productivity. Senior faculty were significantly more likely to report a negative impact on overall teaching productivity than junior faculty (28.6% vs 16.5%, $P=0.03$). Only 7.4% of respondents reported concern about the effect of remote work on their teaching career trajectory. Those with caregiving responsibilities differed only slightly from their counterparts without caregiving responsibilities in terms of teaching productivity but were more likely to be concerned about their teaching career trajectory (10.7% vs 2.1%; $P=0.01$), though this comparison is based on relatively few respondents. Teaching productivity and concern about the impact of remote work on career trajectory did not differ significantly between generalists and subspecialists, females and males, those in different academic ranks, and those with and without leadership roles.

Over half (56.6%) of respondents reported a negative impact of remote work on research productivity, and almost half (39.6%) were concerned about the effect of remote work on their career trajectory. There were no significant differences across those with and without caregiving responsibilities, females and males, those with and without leadership roles, or junior and senior rank. Significantly more tenure track faculty reported reduced research productivity when compared to clinician teacher faculty (71.9% vs 50.7%; $P=0.01$). Significantly more clinician educator faculty reported being concerned about the impact of remote work on their research trajectory compared to clinical faculty (39.7% vs 0%; $P=0.007$). A nonsignificantly higher proportion of specialists than generalists reported reduced research productivity (57.9% vs 47.4%; $P=0.39$), but a significantly higher proportion of specialists reported being concerned about the impact of remote work on their research career trajectory (42.9% vs 15.8%; $P=0.02$).

Only about 1 in 10 respondents (11.5%) reported a negative impact of remote work on academic wellness. A higher propor-

Table 1. Participant Characteristics

	N (%)
Completed teaching, research, or wellness questions	246
Completed teaching questions	245 (99.6)
Completed research questions	159 (64.6)
Completed wellness questions	227 (92.3)
Gender	
Male	115 (46.7)
Female	97 (39.4)
No response	34 (13.8)
Specialty	
Generalist	55 (22.4)
Other	182 (74.0)
No response	8 (3.2)
Caregiving	
Yes	149 (60.6)
< 5 years old	47 (19.1)
5 – 18 years old	111 (45.1)
Parents/others	35 (14.2)
Part-time	107 (43.5)
Full-time	42 (17.1)
Junior faculty	75 (30.4)
Senior faculty	77 (31.3)
No	95 (38.6)
No response	2 (0.8)
Leadership role	
Yes	86 (35.0)
No	158 (64.2)
No response	2 (0.8)
Rank	
Junior: instructor/scientist	26 (10.6)
Junior: assistant professor	87 (35.4)
Senior: associate professor	69 (28.0)
Senior: professor	61 (24.8)
No response	28 (11.4)
Academic track	
Clinician	71 (28.9)
Clinician educator	93 (37.8)
Tenure	59 (24.0)
Other (eg, instructor, scientist)	23 (9.3)

N (%) of total respondents who completed the teaching, research, or wellness questions.

tion of specialists reported an impact on academic wellness than generalists (13.2% vs 3.7%; $P = 0.05$). This comparison, however, is based on relatively low numbers. Significantly more clinician educator faculty reported a negative impact on their academic wellness than clinicians (14.9% vs 2.9%; $P = 0.01$) The impact on academic wellness did not differ significantly across categories of gender, caregiving, leadership, or rank.

Table 2. Proportion (%) of Respondents With Negative Impact, by Respondent Characteristics

	Teaching		Research		
	Productivity	Concern About Career Trajectory	Productivity	Concern About Career Trajectory	Academic Wellness
Negative impact	22.8	7.4	56.6	39.6	11.5
Generalist					
Yes	20.0	8.2	47.4	15.8	3.7
No	24.0	3.6	57.9	42.9	13.2
P value	0.54	0.25	0.39	0.02	0.05
Caregiving (any)					
Yes	24.8	10.7	55.9	37.5	11.0
No	20.9	2.1	57.1	40.2	12.1
P value	0.48	0.01	0.88	0.74	0.81
Sex					
Male	25.4	8.7	58.7	40.0	11.1
Female	18.8	4.2	53.1	37.5	11.4
P value	0.25	0.18	0.51	0.76	0.96
Leadership role					
Yes	23.3	10.5	53.3	43.3	11.7
No	23.4	5.7	58.2	36.7	11.3
P value	0.98	0.18	0.55	0.41	0.94
Rank					
Junior	16.5	9.2	52.1	43.0	12.3
Senior	28.6	5.4	60.5	35.6	10.7
P value	0.03	0.26	0.29	0.34	0.72
Track					
Clinician	26.8	7.0	25.0	0.0	2.9
Clinician educator	20.4	9.7	50.7	39.7	14.9
Tenure	25.4	6.8	71.9	50.9	20.0
P value[a]	0.34	0.55	0.10	0.007	0.01
P value[b]	0.47	0.53	0.01	0.20	0.45

[a]*P* value = Clinician compared to clinician educator faculty.
[b]*P* value = Clinician educator faculty compared to tenure faculty.

DISCUSSION

Previous studies of the impact of the COVID-19 pandemic on work-life balance, burnout, well-being, and career activities have demonstrated differences in the experience and reactions of physicians and scientists across gender, career focus, and home life factors.[1,2,3,7,12] Prior studies have focused largely on the effect of the pandemic in general on these areas, whereas this study specifically focused on the impact of remote work during the pandemic on the areas of research, education, academic wellness, and concern for career trajectory.

Remote work can negatively affect workers' well-being when it leads to increased professional isolation,[13] which can lead to decreased opportunities for mentorship and knowledge exchange, and productivity can be hampered for highly interdependent work[14]—factors that are important in a large academic department across all faculty. We observed results that likely reflected these collaboration factors—particularly for faculty in the clinician educator and tenure tracks where there were disproportionate effects on research trajectory or productivity.

We found less effect of remote work on caregiver responsibilities than we expected. When integrating family and work, there are ways that work responsibilities complicate home life (work interfering with family [WIF]) and vice versa (family interfering with work [FIW]). Remote work has historically been found to decrease WIF but can increase FIW. For example, removing commuting time leaves more time for home activities, and when remote work is paired with flexible hours, it can further improve abilities to balance work and home life.[15] While our results showed a trend toward greater negative impact on those with caregiving responsibilities across research, education, and academic wellness, these results did not reach statistical significance, with the single exception of where faculty considered their career trajectory in education. This was based on a small number of respondents; however, it is possible these faculty had a different workload that was more affected by caregiving and felt more uncertainty about the future of child care that was scarce early in the pandemic. That the negative impact was more evenly distributed across gender, rank, specialty, and degree of caregiving responsibility may be intuitive when the following factors are considered:

1. The degree to which the pandemic disrupted prior arrangements for caregiving (and education of school-age children) and created an immense need for flexibility, enhancing the benefit of remote work in relation to potential FIW conflicts.
2. The fact that remote work was undertaken as a whole and at the directive of the institution, rather than opted into by individuals, potentially mitigating the concerns about professional isolation and perceived relative dedication to career.
3. The presence of institutional support to provide the necessary equipment and technology to successfully transition to remote work where possible and to provide tools to allow for as immer-

sive an experience as possible for teams to work remotely. This potentially offsets some of the challenges to productivity for those involved in more interdependent work and helping to ensure a more level playing field across all faculty in terms of adequate resources.

Limitations of this study include that we used a single though large department within a single academic institution, which may not represent the perspectives of other departments or institutions. Timing of the survey also may have been a factor, since faculty may have been thinking and hoping that the pandemic would be over soon and that their home and work life would return to its prepandemic state. Participants more affected or concerned about the impact of COVID-related changes to the workplace may be more motivated to complete the survey, potentially resulting in an overestimation of the effect on their research, teaching, or wellness. We do not, however, expect this to bias the associations with other characteristics.

CONCLUSIONS

The COVID-19 pandemic prompted abrupt and dramatic shifts in the working lives of individuals around the world, and faculty in the Department of Medicine were no exception. One of the major changes was the swift transition to remote work for research, teaching, and some clinical work where possible. The shift to remote work had negative effects mostly on research productivity, less so on teaching productivity, and a small effect on academic wellness. This leveled impact may be explained by the complex interplay of factors contributing to the remote work experience and highlights several unique characteristics of remote work during the pandemic. Further exploration of this experience could lead to a greater understanding of ways to improve the remote work experience for faculty and enhance their research and academic productivity, while supporting career development and academic wellness. Further evaluation of the concern for effects on career growth may help us understand the concerns of the most affected groups and help address these with more targeted interventions. This knowledge would be key because of ongoing high levels of remote work and organizational planning for potential future needs.

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Trainee Experiences During COVID-19

Anthony Bui, BS; Samuel Tesch, BS; Margaret Zwick, BA; Kurtis J. Swanson, MD

The COVID-19 pandemic is a generation defining, history-altering event whose impact is still being felt today. One group significantly affected by the pandemic is medical trainees. Peri-COVID trainees have unprecedented experiences in this brave new post-COVID world, exacerbated by policies and proceedings in terms of how the hospital system functioned in the early post-COVID timeframe, quarantines, utilization of virtual and telemedicine modalities not only for patient care but also for trainee education. With COVID – and perhaps future endemic/pandemic events to come – drawing from these experiences can serve to guide educators and mentors alike on how best to address future challenges to foster trainee growth into competent, fulfilled physicians.

For this commentary, I invited three medical students I had worked with to reflect on their experiences training during COVID-19. Their accounts are of particular interest as these students are in the class of 2024 and, thus, have received all of their medical training post-March 2020 when the pandemic truly took hold in Wisconsin.

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COVID-19 has had a vast impact on my medical school experience; in fact, I don't know what medical training is like without it. I entered medical school in 2020, just around when the disease was nearing its peak. As a student originally from California, it was surreal moving across the country to attend medical school in Wisconsin at this time. During our first year of preclinical curriculum, teaching was done almost solely over Zoom, Blackboard, or WebEx where faculty would have to deliver lectures to a lot of blank screens or silent faces. As a learner, it was easy to get distracted when listening to hours upon hours of online lectures all day. Additionally, former in-person activities, such as anatomy and case-based small-group learning, were modified to be online, which made it tough to visualize anatomic structures spatially or participate in quality discussions. During clinical skills sessions with standardized patients, we were told to not perform certain respiratory exam procedures to prevent further risk.

> As we collectively move past the peak of the COVID-19 pandemic, we cannot help but look back and evaluate. Did we miss something? What else ought to have been done?

However, as a byproduct of COVID, many students-- myself included--became close with our assigned learning groups as they were a place to talk and decompress. They also offered an avenue to meet in real life. I also was fortunate because I lived with many roommates who provided friendship and support as I transitioned into medical school.

Although online education was burdensome, one positive aspect of COVID-19 learning was the more efficient use of online meetings and workflow. The summer after my M1 year, I did research in the Department of Human Oncology where many things were streamlined to be virtual. Because of this, I was able to travel back home to California and had time to visit Milwaukee and Chicago. As COVID was finally dwindling and cities were fully reopening, one of my fondest memories will always be watching the Milwaukee Bucks win the NBA championship in person with hundreds of thousands of other fans. It reminded me of the beauty of the human experience and why we needed social interaction, pride, and passion in our lives after COVID.

My medical school journey continued as I entered my second year, and our preclinical studies started transitioning to in-person. It was

a breath of fresh air to be able to interact with more of our classmates in a physical setting and to see all of my peers at once. The lecturers and professors were more enthusiastic and charismatic in person, and it was nice to have more opportunities to interact, spend time, and have fun with my colleagues.

Once we started our clerkships, our education became almost identical to a pre-COVID clinical rotation. One change was that we had to remember COVID-19 as an additional differential diagnosis and vaccine suggestion. We also had to recall certain testing policies and various rules and regulations on COVID precautions. I had never had medical school clerkships before COVID, so masks became a very normal part of the hospital for me. Now that mandates are slowly being lifted, it feels very peculiar but also exciting that we are transitioning to a new era.

As I am writing this, I recently finished STEP 2 and am continuing more clinical rotations before applying for residency. COVID-19 has had a huge impact on my medical school experience, making an already tough curriculum even less forgiving. However, even despite COVID, my time in medical school has been one of the best experiences of my life – meeting, collaborating, and socializing with some of the most intelligent people I've ever met. Bonding through the hardship of medical school has made me grow both professionally and emotionally and there is certainly nothing I would change about it. Even more so, because of COVID, I've learned more about what it means to be human and have found further meaning into why I am excited to eventually be a physician.

–Anthony Bui

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It's hard to describe the differences in studying medicine during the COVID-19 pandemic when you didn't have the opportunity to experience it pre-pandemic, but the biggest overarching theme I felt over the course of my time in medical school has been loneliness. On my first day, I met my classmates through masks – unable to see what their faces looked like--and when I spoke to them about study techniques, everyone truly seemed a bit lost. At first there were some in-person events and classes; however, as COVID cases rose later in our first semester, those brief moments of contact with my peers decreased. Many libraries were closed, and peer study groups were established in secret. I frequently struggled to keep focus in the online learning environment, which was often disturbed by issues with technology. I began watching lectures from previous years to learn material, so I could consume it with higher quality audio, better resolution, and fewer distractions. Being stripped of study environments and peer groups made me fail to realize the volume of medical knowledge I truly needed, and the impact on my first few exams and semester grades was devastating. Over Thanksgiving break, I barely saw my family, instead choosing to study for those 4 brief days in an effort to pass my final exams. Over the following semesters, my grades improved--especially as libraries, coffee shops, and other study locations began to open. But even outside of classes, my medical education was stunted in many ways as I was deprived of nonclinical volunteering experiences and opportunities to connect with attending physicians and mentors in our respective fields of interest.

"Despite COVID, my time in medical school has been one of the best experiences of my life – meeting, collaborating, and socializing with some of the most intelligent people I've ever met."

There were, however, some advantages to this experience. During this time, I was able to train for a half ironman 15 hours a week or more, which was aided by scheduling long indoor bike rides during lecture time. This flexibility was something I took for granted early in my career, but it soon changed.

Over my M1 summer, I participated in the Shapiro research experience at the University of Wisconsin-Madison and was able to generate research that led to two publications and several presentations. At the same time, I was able to meet regularly with my peers and, along with my friend Ryan, helped to teach a group of medical students to become better at tennis. My final semesters of my preclinical year were much easier than the first, aided by the ability to study with my friends and learn what external resources they used to be successful.

As I transitioned into my clinical year, the loss of the flexibility I had come to cherish due to COVID restrictions ended. I was now rounding on the wards at 6 am and grinding out practice questions after work until I passed out from exhaustion. I had to learn work-life balance quickly. I felt like I was chasing a car that was always getting further away, unable to truly understand the clinical nuances of the patients I was caring for. At this point, I again found myself always on opposite schedules from my closest friends. To make matters worse, the OMICRON variant emerged and ripped through the clinicians where I was completing my family medicine rotation. I finally contracted the COVID-19 virus and was absolutely wiped out and exhausted for 10 days. I was pulled off of clinical rotations and lost out on a large chunk of learning. During that time, I participated in telehealth appointments while feverish and sick. However, for some of my classmates on inpatient rotations, a COVID absence meant having to repeat coursework and the possibility of delayed graduation; so, on the whole, I felt lucky.

However difficult COVID has made my medical school experience, I have never let it defeat me or my desire to become a physician. In some ways, it strengthened my resolve, and, in other ways, I found unique ways to adapt and overcome. I believe the biggest impact to my education was the loss of meaningful peer and mentor connections, which would have strengthened my educational experiences and allowed me to feel like a full part of the medical community earlier in my career.

–Samuel Tesch

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I began medical school at the University of

Wisconsin School of Medicine and Public Health (UW SMPH) in August 2020, amid the chaos and uncertainty that accompanied the initial wave of the COVID-19 pandemic. Whether this unsteady start affected our overall success and match rates remains to be seen, as the majority of us are submitting residency applications this fall. What is certain, however, is that--as for most people--the effects of the pandemic permeated nearly all aspects of our personal lives, schooling, and work.

Our classes were almost entirely virtual for the first year of medical school. We had once weekly in-person sessions for case discussion groups and one or two monthly clinical skills sessions to prepare us for Observed Structured Clinical Examinations. All other didactic courses, including our anatomy labs, were held online. Courses transitioned to being held entirely in person in my third semester of school. There was a bit of a catch-up period in anatomy lab, as many of us had not previously worked with cadavers and required instruction on dissection techniques. Although I plan to apply into a nonsurgical residency, several peers applying into surgical fields expressed concern over the impact this course structure had on their anatomy learning prior to starting surgical clerkships.

Meetings for student organizations, including our initial student organization fair, were also held virtually, which contributed to significant social challenges for new medical students hoping to connect with their peers and faculty. Despite this, I, along with many others, joined and led student organizations. It was difficult, however, to form any substantial relationships with peers – including upperclassmen, who previously would have provided guidance about topics such as course selection, test preparation, and tips for residency applications.

Faculty mentorship suffered for the same reason. Informal meet-and-greets between student organization faculty mentors and participants were hindered significantly by the virtual environment. As such, opportunities for students to get to know faculty and develop mentor-mentee relationships were few and far between. Having to seek out these opportunities through setting up a virtual meeting certainly limited my one-on-one and small-group interactions with faculty, and I don't feel that I experienced much in the way of faculty mentorship – especially in my chosen field – until I began clinical rotations. Each student was, however, assigned to a faculty member who served as a "longitudinal teacher-coach" and directed our clinical skills sessions and competency review meetings. In my case, this meant working with Susanne Seeger, MD, an adult neurologist, who both advised her students on academic matters and consistently checked in on our mental health and well-being despite the challenges of virtual meetings. Her stable and caring presence in the lives of her students was (and still is) sincerely appreciated.

Most of the friendships I developed during my first two semesters were sustained largely by group chats and text messages, and I socialized only sparingly in person with a group of 3 to 5 peers. I was lucky to live with my younger brother during this time and, therefore, did not experience too much loneliness, but multiple friends shared how much they struggled emotionally during that first year due to the combined effects of the significant stress of a rigorous medical school curriculum and their social isolation. Several friends required inpatient and/or outpatient behavioral health services for worsening anxiety and depression. Although it is entirely possible that they would have required this support even prior to the pandemic, their stories are a testament to the degree of psychological stress many students experienced during those first few years. The UWSMPH administration made a point of repeatedly communicating the mental health resources available to students, which was a helpful and appreciated effort on their part to mitigate these stressors.

Overall, I don't feel that my medical knowledge or interpersonal skills with patients were significantly affected by beginning medical school in a pandemic, nor have I gathered from faculty that the abilities of our class differ significantly from those prior. But I do feel that my class has, to some degree, been flying by the seat of our collective pants through this whole ordeal. I suspect the faculty and administrative leadership feel much the same, as it was certainly challenging for lecturers and content directors to adjust to virtual teaching. It's frustrating to be the first group to go through any sort of curriculum change, as there are bound to be bumps along the road, and this was a larger change than most. In this case, I really do think the school mostly did the best it could under difficult circumstances. In the end, I'm confident the members of our class will emerge as competent, caring physicians prepared to tackle the challenges of residency despite our rocky start.

–Margaret Zwick

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These three learners have described their experiences as medical trainees during the COVID-19 pandemic. In doing so, several themes/motifs are identifiable – technologic and logistical challenges of virtual medical school curriculum, social isolation, the blessing/curse of virtual engagement, and the impact on work-life balance, as well as resiliency and perseverance.

As we collectively move past the peak of the COVID-19 pandemic, we cannot help but look back and evaluate. Did we miss something? What else ought to have been done? With medical student safety as a priority, options on prevaccination approaches were limited. However, with adherence to guidelines from the Centers for Disease Control and Prevention for masking and social isolation, one could consider having had hybrid medical training in the postvaccination timeframe. Moreover, taking advantage of the low risk of outdoor transmission for community-building events, for exam-

> Hippocrates' famous oath reverberates a call to arms to the medical community to foster meaningful relationships – to uphold and support our community and society of medicine.

ple, could have been utilized early and often to stave off isolation and improve wellness. In my own experience as a medical student, I found being part of a creative writing group to be a breath of fresh air and opportunity to connect with my peers outside of studying. Hopefully, social groups (eg, interest groups, friend groups) will be nimbler and more adaptable to virtual/hybrid or safer meeting styles in future pandemics.

Are we ready as a medical education community to face a new pandemic? Have our experiences in COVID-19 taught us how to better support medical trainees during pandemics? Though specifics regarding transmissibility, virulence, mortality/morbidity are all important considerations for the next pandemic, COVID-19 has identified core issues faced by medical trainees and ought to guide us in the future. Rapid, clear communication, curriculum adaptability across various media/approaches, and multidisciplinary mental health/wellness initiatives will all serve to support medical trainees in their already arduous journey towards becoming health care professionals. In a report of their 2021 survey of 14 medical schools from the Medical Student Well-being Research Consortium, Dagher et al[1] noted that despite vaccination availability and other efforts, the rate of burnout was about the same in 2021 as in 2020 (50% vs 53%, $P=0.06$) and loneliness was actually higher (55% vs 50%, $P<0.001$). Similar to COVID-19, the next pandemic is unlikely to have a panacea or quick fix. Furthermore, as we all know, medical students, let alone the medical community at large, is at high risk for burnout, loneliness, stress independent of pandemics.

In my opinion, healthy relationships are fundamental to building resilience and overcoming the challenges brought on by medical training. Thriving diverse relationships, such as those with peers, upper and underclassmen, mentor-mentee, family and/or friends, as well as a community outside of medicine are vital for support, belonging, and wellness. In a society that has grown ever digitized with various social media platforms, we are engaged in a collective loneliness whereby community and connection give way to façade and illusion.

Kurt Vonnegut, in his work, *Palm Sunday*: *An Autobiographical Collage*, charges us to be bold: " "What should young people do with their lives today? Many things, obviously. But the most daring thing is to create stable communities in which the terrible disease of loneliness can be cured."[2]

As a medical education community, we are called to shepherd and guide. While this is understood as competency training, it should extend beyond this domain holistically. Hippocrates, in his oft-cited and quoted oath, said this well:

"To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the Healer's oath, but to nobody else."[3]

Historical qualifier and quibbles aside, Hippocrates is talking about the practice of the art of medicine beyond competency, evaluations, and test scores. He is talking about a deeper humanistic commitment of relationships and connection. It is like comparing a live orchestral performance to an artificial intelligence-generated quantized song file – though both "play the right notes at the right time," the orchestra ebbs and flows, organic and alive, creating the art of music that captures the mind, body, and soul that notes on a page or digital time signatures cannot. Hippocrates' famous oath reverberates a call to arms to the medical community to foster meaningful relationships – to uphold and support our community and society of medicine.

These three trainees bore their souls and I am grateful to them for sharing their experiences training during COVID. From their stories, I hope we can gain insight into ways we in the field of medicine can adapt in these times to foster strong trainee-mentor relationships--strong relationships that can welcome them into the fold and guide them in their pursuits and growth from trainees to physicians practicing in Wisconsin and beyond.

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The Impact of COVID-19 on Students in the Medical Field

Anjali Patel

The outbreak of COVID-19 changed the "normal" for nearly everyone. As an undergraduate student on a premed track, I believe it has especially affected medical and premedical students—from education and clinical experiences to mental health.

EDUCATION AND EXPERIENCE

Early in the pandemic, schools nationwide were forced to transition classes and clinical rotations to online or hybrid learning formats, and education among pre-med and medical students was greatly altered.

For example, due to "stay-at-home" orders and virtual office visits, many undergraduate students were unable to shadow physicians. Even after the stay-at-home orders were lifted, many physicians refrained from having undergraduate students in their offices. Though necessary for everyone's safety, it may inadvertently have hindered students' understanding of the medical field and particular specialties and limited their ability to reach the "recommended hours" needed to apply to certain medical schools. Additionally, both undergraduate and medical students, who often learn best through hands-on experience, were frequently denied of in-person training. Moreover, those who struggled faced additional barriers, as they could not easily meet with their professors or participate in study groups.

A survey conducted in the US among medical students found that 43.3% felt unprepared for their clinical rotations, and 56.7% felt unprepared for their board exams due to the pandemic.[1] Another cross-sectional survey of 741 medical students from 6 US medical schools showed that 74.9% had their clinical rotations either cut short or canceled, and 93.7% reported not being involved in any clinical rotations that had in-person patient contact.[2]

A survey conducted in the US among medical students found that 43.3% felt unprepared for their clinical rotations, and 56.7% felt unprepared for their board exams due to the pandemic.

MENTAL HEALTH

For many students, success hinges on having mentors for guidance and support. I have been fortunate to have had multiple opportunities to connect and work with the wonderful doctors at UW Health. My mentors have played a pivotal role in my journey, guiding me through significant career decisions, obstacles, and personal hurdles. Yet with the shift to virtual classes and the loss of one-on-one student-teacher interactions, many of my peers have struggled to find and connect with mentors during this period. Furthermore, when students enter college, it is a time to make new connections, learn what the college has to offer, and explore their interests, but the pandemic limited our ability to do this.

Working with people in-person allows students to create their sense of belonging, security, and safety. But for some deprived of this opportunity, lack of support increases the risk of burnout and mental health challenges. Three of my peers discontinued their medical studies due to pandemic-related stress. One recounted the difficulty of balancing academic and work responsibilities while isolated, leading to depression and loss of direction. "As a premed student, I already had a lot on my plate – my classes, CNA (certified nursing assistant) job, research work – but then I had to stay confined in a small dorm room alone. I could not even go home since flights were closed and it got to a point where I was severely depressed. I had no motivation, no ability to focus and no goal in life. I eventually dropped the premed major, and I believe

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the main reason behind that was I had no support."

A survey done in Changzhi Medical College among undergraduates showed a correlation between the pandemic and academic delays and mental health.[1] Similarly, in Hong Kong, due to exam delays, students lost their appetites and developed sleep problems due to stress. In the same survey, out of 757 students, 20% reported stress levels of 10/10 on exam delays.[1] These findings suggest that setbacks and cancellations not only caused educational deficits, but also affected mental health. Further, in a survey of 248 medical students from 13 schools, 48% reported feeling depression and 52% felt lonelier.[1]

In another study, 1139 allopathic medical students from Washington and New York were assessed for depression and anxiety symptoms and self-rated their mental health during versus before the pandemic. Seventy percent of respondents reported their mental health was worse than baseline following the initial months of pandemic; 61% reported experiencing some depressive symptoms (24% meeting criteria for major depression); and 58% reported some symptoms of anxiety (20% meeting criteria for an anxiety disorder).[3] These findings suggest that over two-thirds of the medical students who completed the survey believed that their mental health had deteriorated after the start of COVID-19.

There is no doubt that COVID-19 has had a negative effect on many medical and undergraduate students – myself included, and we have suffered in obtaining a well-rounded experience in the medical field. Fortunately, however, although it has been slow, the recovery to "normal" has begun.

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Thank you!

to the following artists who submitted their work for this special issue

Nadia Alkhun
Acrylic and Ink on Paper

Sue Blaustein
Digital Photo

Vincent Cryns, MD
Digital Painting on iPad Pro

Angela Gifford
Digital Photo

Sue Horton
Watercolor

Claudia Krogmeier
Film

Ryan McAdams, MD
Digital Illustration

Kelly McGregory, DO
Digital Photo

Riley Meskin
Digital Design

Diane Yao
Painting

COVID-19: The Prickly Menace That Made Us Bloom

Kelly McGregory, DO

Digital Photo

Artist Statement:

This golden barrel cactus with santa rita prickly pear grows in the Ventana Canyon in Tucson, Arizona. The COVID-19 virus wreaked havoc costing millions of lives, shuttering businesses, and impacting the education and mental health of our children in previously unimaginable ways. Despite its wretchedness, the pandemic helped us bloom in the worst of circumstances. We survived. We tell our stories. Although still not free, we keep blooming.

Matched Case Control Analysis of Breast Cancer-Specific Factors Affecting Risk of Developing SARS-CoV-2 Infection

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ABSTRACT

Introduction: In this retrospective matched case control study, we aim to identify breast cancer-related risk factors associated with developing COVID-19 and describe outcomes of patients with breast cancer diagnosed with COVID-19.

Methods: Women with breast cancer treated at the Medical College of Wisconsin and diagnosed with COVID-19 from March through December 2020 served as cases, and those without COVID-19 within the same timeframe served as controls. Univariate and multivariate comparisons were performed.

Results: Twenty-five cases and 77 controls were identified. All cases were fully matched by age, obesity, county, and race. Mean age was 54.6 versus 54.9, body mass index 31.0 versus 31.6, 48% lived in Milwaukee County, and 68% were White. Regarding COVID-19 outcomes, 24.0% (n = 6) of cases were hospitalized, median length of stay was 2 days, 8% (n=2) needed oxygen, 4% (n = 6) were intubated, and 4% (n = 6) died. COVID-19 led to treatment delays in 40% of cases. On univariate analysis, there was no statistically significant difference in hormone receptor status or breast cancer stage. Being on active chemotherapy (OR 5.8, *P* = 0.043) significantly increased the likelihood of developing COVID-19.

Conclusions: In this matched case control study of patients with breast cancer, active chemotherapy was significantly associated with an increased likelihood of developing COVID-19, with a trend seen for triple negative disease. These findings support continued strict precautions for those on active chemotherapy and warrant further analysis in those with triple negative disease.

INTRODUCTION

In December 2019, a novel coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in the Wuhan province of China. It rapidly spread across the world, causing a clinical syndrome of viral infection known as coronavirus disease 2019 (COVID-19).[1–3] In addition to the unparalleled toll on global health care systems as a direct result of these infections, COVID-19 has had drastic secondary consequences for routine care of all kinds, including the regular care of patients with cancer.[4] COVID-19 has been shown to disrupt all aspects of cancer care, including screening, surgical management, systemic chemotherapy administration, and routine follow-up.[5–10]

In 2020, breast cancer surpassed lung cancer and is now the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases diagnosed per year.[11] Particularly in the beginning of the pandemic, well-established screening programs for breast cancer were disrupted, leading to fewer women being diagnosed.[6,8,9] It has been reported previously that up to 54% of breast cancer patients have experienced treatment delays as a result of the COVID-19 pandemic.[7] Such treatment delays in breast cancer have been associated with worse overall survival.[5] It is unknown to what extent and what types of treatment delays have occurred in our own center.

Patients with cancer often are more vulnerable to infections due to the immunosuppressive effects of treatment and their underlying malignancy.[12] To date, most published literature on the outcomes of patients with cancer who were diagnosed with COVID-19 do not differentiate based on cancer type. Additionally, there are varying accounts on the association between cancer-specific risks such as recent chemotherapy treatment and patient out comes with COVID-19 infection.[13–20] It is unknown whether the outcomes of patients with breast cancer and SARS-CoV-2 infection differ from the general population.

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The risk of severe illness from SARS-CoV-2 is known to increase with age.[21] This association seems to persist in patients with and without cancer.[14,17,19,20] For patients newly diagnosed with breast cancer, the median age at diagnosis is 62, putting a majority of patients with breast cancer at increased risk of severe illness due to age alone.[3,22] However, data also suggest that women are at decreased risk compared to men of developing severe illness from SARS-Cov-2.[3] We aim to describe the characteristics and outcomes of patients with active breast cancer diagnosed with SARS-CoV-2 infection at our own academic medical center. Our goal is to identify risk factors associated with SARs-CoV-2 infection specific to breast cancer patients.

METHODS

After institutional review board approval, patient data were gathered retrospectively from the electronic medical record. Data collected included tumor pathology, cancer stage, demographic characteristics, comorbidities, types of treatment received (surgery, radiation, chemotherapy and/or endocrine therapy), treatment disruptions (as defined by ≥1 day delay in active treatment), method of determination of SARS-CoV-2 infection, COVID-19 symptoms, hospitalization, and severity of COVID-19 infection (need for hospitalization, need for intensive care unit [ICU] stay, supplemental oxygen, intubation status, disposition from hospital).

Women with breast cancer treated at the Medical College of Wisconsin and diagnosed with COVID-19 from March through December 2020 served as cases. Women with breast cancer with at least one clinic visit from January through July 2020, but without COVID-19 diagnosis within the same time frame were identified as potential controls. Controls were chosen by matching for age (≥60 vs <60), obesity (BMI <30 vs ≥30), county (Milwaukee vs suburban), race (White vs non-White), and diabetes with 3:1 matching planned. These variables were chosen for matching as they have been known to affect outcomes of COVID-19 infection.[1-3,21] The same control could be used for multiple cases. For calculation of summary statistics, controls were weighted by the inverse of the number of matches for the case. Univariate comparisons between cases and controls were done via Rao-Scott stratified chi-square test for categorical outcomes and stratified *t* test for continuous variables. Conditional logistic regression was performed to evaluate the joint effect of multiple characteristics on the odds of being a COVID-19 case. The multivariable analysis included predictors that were significant at the 0.1 level in the univariate analysis.

RESULTS

Twenty-five cases and 77 controls were identified. All cases were fully matched by age, obesity, county, and race. Three cases were not able to be matched for diabetes. Full demographic information is included in Table 1. Mean age at diagnosis of COVID-19 was 54.6 years, mean BMI was 31.0, 48% of cases lived in Milwaukee County, and 68% of cases were in White patients. Breast cancer-specific information is included in Table 2. Fifty-two percent of cases had stage I disease at time of COVID-19 diagnosis, 64% had estrogen receptor (ER)/progesterone receptor (PR) positive cancer, 12% had human epidermal growth factor receptor 2 (HER2) positive cancer, and 28% had triple negative disease. Seventy-two percent were on active treatment at the time of COVID-19 diagnosis, 44% were receiving endocrine therapy, and 20.8% were on active chemotherapy at the time of COVID-19 diagnosis. All patients had received surgery for their breast cancer, 76% had received chemotherapy, and 60% had received radiation therapy.

Of the 25 patients diagnosed with COVID-19, 6 (24%) needed hospitalization, with a median length of hospital stay of 2 days. Two patients (8%) required supplemental oxygen, and 1 patient (4%) required intubation. Of the 6 hospitalized patients, 4 (16%) received only supportive care, 1 patient (4%) received hydroxychloroquine, and 1 patient (4%) received convalescent plasma and

Table 1. Demographic Information of COVID Cases and Matched Controls

Patient Characteristics	Case (n=25)	Control (n=77)
Mean age at diagnoses of COVID, or last follow-up if control (SE)	54.6 (2.4)	54.9 (0.8)
Mean body mass index (SE)	31.0 (1.4)	31.6 (0.7)
Residence		
Milwaukee County	48%	48%
Suburban county	52%	52%
Diabetes	16%	4%
Tobacco use	40%	37.2%

Abbreviation: SE, standard error.

Table 2. Univariate Analysis of COVID-19 Cases and Controls

	Case (n=25)	Control (n=77)	*P* value
Stage at Last Contact			
0 – I	52.0%	66.0%	0.433
II	16.0%	12.7%	
III – IV	32.0%	21.3%	
ER/PR positive	64%	74.7%	0.309
HER2 positive	12%	20.3%	0.340
Triple negative	28%	13.4%	0.103
Active treatment at time of COVID diagnosis, or last contact if control	72%	74%	0.850
On chemotherapy at time of COVID diagnosis, or last contact if control	20.8%	4%	0.007
On endocrine therapy at time of COVID, or last contact if control	44%	52%	0.488
Breast cancer radiation prior to COVID, or at last contact if control	60%	63.3%	0.763

Controls are weighted to match the number of cases.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor.

remdesivir. COVID-19 diagnosis resulted in a treatment delay for 10 patients (40%).

As reported in Table 2, univariate analysis of cases versus controls showed 64% versus 74.7% were ER/PR positive ($P = 0.31$), 12% versus 20.3% HER2 positive ($P = 0.34$), and 28% versus 13.4% triple negative ($P = 0.10$). There was no statistically significant difference in breast cancer stage. At time of COVID diagnosis, or their last contact with clinic if a control, 16% versus 14% had active disease ($P = 0.81$), 72% versus 74% were on active treatment ($P = 0.85$), with 20.8% versus 4% being on chemotherapy ($P = 0.007$) and 44% versus 52% on endocrine therapy ($P = 0.49$). On multivariate conditional logistic regression, current treatment with chemotherapy significantly increased the risk of COVID-19 infection (OR 5.66, $P = 0.044$) as shown in Table 3. There was a trend toward triple negative disease, but it did not cross the boundary of statistical significance (OR 2.69, $P = 0.08$).

Table 3. Multivariate Conditional Logistic Regression for Odds of Being a COVID-19 Case

Predictor	Comparison	Univariate OR (95% CI)	Univariate *P* value	Multivariate OR (95% CI)	Multivariate *P* value
Stage at last contact	II vs 0 – I	1.81 (0.44 – 7.41)	0.4084		
	III – IV vs 0 – I	2.10 (0.67 – 6.61)	0.2052		
Previous radiation	yes vs no	0.86 (0.34 – 2.14)	0.7410		
ER/PR-positive	yes vs no	0.59 (0.22 – 1.58)	0.2963		
HER2-positive	yes vs no	0.50 (0.14 – 1.84)	0.2994		
Triple negative	yes vs no	2.69 (0.88 – 8.20)	0.0813	2.65 (0.78 – 9.03)	0.1186
Active treatment at time of COVID diagnosis, or last contact if control	yes vs no	0.89 (0.32 – 2.43)	0.8143		
Active chemotherapy at time of COVID diagnosis, or last contact if control	yes vs no	7.50 (1.46 - 38.66)	0.0160	5.66 (1.05 – 30.43)	0.0435
On endocrine therapy at time of COVID diagnosis, or last contact if control	yes vs no	0.71 (0.28 - 1.80)	0.4685		

Abbreviations: OR, odds ratio; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor.

DISCUSSION

Existing literature on breast cancer and COVID-19 is limited. We set out to identify and describe breast cancer-specific risk factors for developing COVID-19 infections and to describe our institutional experience. Our cohort of cases was relatively representative in terms of both cancer stage and hormone receptor status, with perhaps triple negative breast cancer overrepresented in comparison to our patient population as a whole. Of all cancer-specific patient factors, we found that only current treatment with chemotherapy was significantly associated with developing COVID-19. One potential mechanism for this finding is the common neutropenia experienced with cytotoxic chemotherapy and more frequent clinic visits.

Chemotherapy has been implicated inconsistently as a risk factor for severe COVID-19 and/or death in previous studies, but to our knowledge, it has not been described as a risk factor for development of COVID-19 itself. Multiple cohort studies have suggested that advanced age and comorbidities are associated with increased mortality from COVID-19 but that recent chemotherapy was not.[14,16] Unfortunately, those studies have included all types of cancer, which can impact cancer-specific attributions. A French cohort study by Vuagnat et al prospectively described breast cancer patients diagnosed with COVID-19 and found that age and hypertension were associated with higher risk of ICU stay and/or death, while current treatment with chemotherapy was not associated with patient outcomes.[15] In contrast to these studies, multiple retrospective cohort studies from China have identified recent chemotherapy as a risk factor for developing severe COVID-19 infection and/or death.[17–19]

Similar to previously reported pandemic-related treatment delays, 40% of our patients experienced cancer treatment delays as a result of COVID-19 infection. A recent population study of the impact of timely treatment on breast cancer-specific survival by Ho and colleagues found that delayed first treatment (as defined by more than 90 days from time of diagnosis) was associated with worse overall survival in both the nonmetastatic and metastatic settings.[5] In addition to the deleterious effect on patient survival, treatment delays can contribute to significantly worse patient-reported outcomes. One study in China found that 46.2% of patients with breast cancer had to modify planned, necessary anticancer treatment, and these changes were associated with significant anxiety, depression, and overall distress.[23] Additionally, a European registry enrolling adult patients with cancer and COVID-19 infection found that as a result of sequelae from SARS-CoV-2 infection, 38.2% of patients required a systemic therapy regimen or dose adjustment, and 15% of patients permanently discontinued anticancer therapy.[24] Thus, COVID-19 infection can have lasting repercussions for cancer patients.

It has been established that cancer patients are at higher risk of developing infections, including COVID-19. We endeavored to elucidate risk factors specific to patients with breast cancer in the development of COVID-19 infection. While our study found no association between hormone receptor status or breast cancer stage with the development of COVID-19, there was an association between COVID-19 infection and recent chemotherapy treatment.

One limitation of our study is that it was conducted prior to widespread availability of COVID-specific therapeutics and

COVID-19 vaccination. However, there are some data to suggest that COVID-19 vaccination in patients with solid tumors receiving cytotoxic chemotherapy results in less immunogenicity and therefore lower immune response.[25-28] Thus, this highlights a continued need for further protective measures for this patient population.

CONCLUSIONS

COVID-19 infection represents a significant risk to the health of patients with breast cancer and a substantial disruption to their routine care. We found that factors specific to breast cancer, such as hormone receptor status and endocrine therapy, had no bearing on the risk of developing COVID-19 but that recent treatment with cytotoxic chemotherapy significantly increased risk of infection. The percentage of patients experiencing treatment delays as a result of COVID-19 infection was similar to previously published values.

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Feasibility and Functionality of SARS-CoV-2 Rapid Testing in K-12 School Health Offices

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ABSTRACT

Introduction: The COVID-19 pandemic created unprecedented opportunities to introduce rapid SARS-CoV-2 antigen testing (RSAT) into kindergarten through 12th grade (K-12) school settings. We evaluated the feasibility and functionality of Sofia Fluorescent Immunoassay Flu + SARS in 1 school district across the 2021-2022 academic year.

Methods: Seven schools in the Oregon School District (Oregon, Wisconsin) were supplied with RSAT analyzers and test kits, along with minimal training of health office staff. We assessed RSAT utilization among schools, rate of invalid results, and comparability to 952 190 reverse transcription-polymerase chain reaction tests performed countywide during the same time period. A feedback survey was distributed to all 13 health office staff to assess respondents' perceptions regarding the feasibility and acceptability of RSAT in the Oregon School District.

Results: Over the school year, 1226 RSATs were performed; SARS-CoV-2 was detected in 103 specimens. Percent positivity was similar to the county level (8.4 vs 9.2%; chi-square = 0.74; $P = 0.39$). Cross-correlation of weekly positive tests between the Oregon School District and Dane County was maximal with no lag ($r_S = 0.69$; $P < 0.001$). Health office staff indicated Sofia2 RSAT was easy to perform, and 92.3% reported interest in continuing to utilize RSAT in the upcoming school year.

Conclusions: Implementing a RSAT protocol is feasible and acceptable for monitoring SARS-CoV-2 cases in K-12 school settings. High rates of compliance and confidence in results demonstrate program effectiveness. Continuing to use RSAT in school settings after the urgency of the pandemic subsides could help address future outbreaks of SARS-CoV-2 and other respiratory viruses within schools and in the larger community.

INTRODUCTION

Increased social contact, through physical proximity and across ages, in kindergarten through 12th grade (K-12) school settings is associated with outbreaks of acute respiratory infection and became a major concern during the COVID-19 pandemic.[1] Although literature describing incidence and clinical presentation of COVID-19 in school-age children is still limited, pediatric infections of SARS-CoV-2 are generally milder than those in adults and often include fever, cough, and fatigue.[2] According to the Centers for Disease Control and Prevention, pediatric infections currently account for approximately 17.2% of diagnosed COVID-19 cases.[3] K-12 schools deployed several tactics to disrupt transmission of SARS-CoV-2 among students and staff, including the use of rapid antigen tests. Federal policy changes and funding created unprecedented opportunities to introduce rapid SARS-CoV-2 antigen testing (RSAT) into the K-12 environment.[4]

Several studies have demonstrated that testing asymptomatic students and staff who were exposed to SARS-CoV-2 was an effective alternative to quarantine and resulted in fewer disruptions in education.[5-7] School and community testing sites also improved the accuracy of disease surveillance by capturing cases that were not seen by a health care provider and may not have been reported otherwise. Little is known about the feasibility and functionality of RSAT for symptomatic children and staff in K-12 schools.

Prior to the pandemic, rapid antigen tests were traditionally

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limited to clinical and public health settings. The SARS-CoV-2 pandemic, however, provided an opportunity to expand the use of rapid diagnostic technologies. K-12 schools are a prime location for rapid testing because of the proximity to students and immediacy of results that enable near real-time decision-making. Continuing to use rapid tests in school settings after the urgency of the pandemic subsides could help address future outbreaks of SARS-CoV-2 and other respiratory viruses that have long-plagued communities.

Drawing on a longstanding relationship with a school district[8] and years of experience evaluating rapid influenza diagnostic tests in clinical and community settings,[9,10] we conducted a retrospective evaluation and quality improvement program to assess (1) the feasibility and functionality of a district-wide rapid testing protocol in 7 schools and (2) whether school testing was correlated with local SARS-CoV-2 trends.

METHODS

The program was part of a Wisconsin Department of Health Services (WDHS) statewide initiative and was originally developed as a nonresearch service to the Oregon School District (OSD) (Oregon, Dane County, Wisconsin). The OSD serves over 4000 K-12 students and comprises 7 schools, including 3 elementary schools (grades K-4), 1 expanded elementary school (K-6), 1 intermediate school (5-6), 1 middle school (7-8), and 1 high school (9-12). The health office at each school was supplied with a Sofia2 Fluorescent Immunoassay (FIA) analyzer,[11] equipped with wireless reporting capability,[10,12] and received Sofia2 Flu + SARS Antigen FIA test kits as needed throughout the school year. Parental consent for rapid antigen testing of students was obtained at the beginning of the academic year during the school registration process. The WDHS provided funding for and oversight of the statewide rapid antigen testing program, thus the institutional review board (IRB) deemed our involvement was restricted to consultation, technical support, and training relevant to specimen acquisition and testing and did not require a formal review. The survey distributed to school nursing staff was granted a waiver from the UW Health and Sciences IRB.

Implementation and Reporting

The OSD health offices were staffed by 13 individuals, including 4 nurses and 9 health aides. Due to our longstanding relationship with the school district, we provided—prior to the start of the 2021-2022 academic year—technical support and trained health office staff on: (1) screening students for rapid testing eligibility, (2) nasal swab collection technique, (3) Quidel Sofia2 FIA analyzer operation, and (4) reporting SARS-CoV-2 results via the COVID Connect platform, the WDHS web-based portal for managing COVID-19 test results.[13] Rapid testing was performed under a Clinical Laboratory Improvement Amendments (CLIA) Certificate of Waiver obtained by the OSD superintendent. Deidentified rapid results were transmitted wirelessly to Virena, a service that collects test results from Quidel instruments and makes them accessible for analysis.[12] For all specimens with a negative SARS-CoV-2 rapid result, health office staff collected a second nasal swab and placed it into a 3 mL tube of viral transport medium, which was labeled appropriately for reverse transcription-polymerase chain reaction (RT-PCR) SARS-CoV-2 molecular testing at Exact Sciences in Madison, Wisconsin, per WDHS protocol. Specimens were transported to Exact Sciences by Fitchburg Pharmacy staff (contracted by the WDHS), and results were communicated to the lead school nurse within 7 days.

Recruitment

Parents/guardians of minor students provided their consent to the school district for on-site testing at the beginning of the academic year. School health office staff selected students and staff for rapid testing according to inclusion criteria that we suggested based on other research activities within the school district. Students and staff were eligible for testing if they presented to the school health office while at school and had at least 2 of the following symptoms: fever, chills, cough, shortness of breath/difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or runny nose, nausea or vomiting, and diarrhea. Students and staff were swabbed and tested in a designated isolation room at each school to reduce the risk of transmission.

RSAT Performance

We used anonymous data obtained from Virena to assess the numbers of tests performed per week; the number of positive, negative, and invalid results; and the utilization across schools. Percent positivity for SARS-CoV-2 within the OSD was calculated as the number of positive tests divided by the total number of valid tests performed. For community comparison, we used SARS-CoV-2 testing data provided by Public Health Madison and Dane County,[14] covering the same time period, with 87 183 positive results out of a total of 952 190 tests.

Feedback Survey

We designed and distributed a 40-question post-program feedback survey as part of a quality improvement effort via Qualtrics XM survey software (Qualtrics; Utah, USA) to school health office staff. The survey was intended to assess respondents' perceptions regarding the feasibility, ease of use, and overall acceptance of rapid testing in the OSD health offices. The survey included basic demographic questions and questions assessing knowledge and experience with Sofia2 FIA analyzer technology, swab collection, specimen preparation for RT-PCR testing, and utilization of COVID Connect. For questions related to potential effects of training, we relied on respondents' recall for the pre- and post-training experiences. The survey was delivered by

email over the course of one week in June 2022.

Statistical Analysis

Descriptive statistics were used to evaluate the rates of invalid tests, percent positivity, and responses to survey questions. Changes in survey responses, pre- and post-training, were assessed using Wilcoxon signed-rank test. The percent positivity of OSD and Dane County data were compared using the chi-square statistic. Spearman rank-based cross-correlation was used to determine an association between weekly counts of SARS-Co-2 detections for Dane County and the OSD. In addition, we accounted for time-dependency using a generalized additive model (GAM) structure, where Dane County counts were the outcome of the model, OSD counts were a covariate, and a smoother was used to estimate and account for the week-to-week time-dependency. We examined 5 scenarios: one where the Dane County/OSD count pairs were from the same week (no lag or lead), 2 versions where the OSD counts lagged the Dane County counts by 1 or 2 weeks, and 2 versions where the OSD counts led the Dane County counts by 1 or 2 weeks. All analyses were performed in R 4.2.0 using the mgcv package and the GAM function defaults for all smoothing parameter settings. Statistical significance was assessed at the 5% level.

Table 1. Enrollment Data and Sofia Rapid SARS-CoV-2 and Influenza Test Results by School

School	Enrollment (2021-22)	Total Tests	Student Tests (≤18 years) n (%)	Staff Tests (>18 years)	SARS-CoV-2 (+) tests n (%)	Influenza (+) tests
Elementary 1 (K-4)	382	139	96 (25)	43	7 (5.0)	5A, 1B
Elementary 2 (K-4)	397	191	129 (32)	62	17[a] (8.9)	9A[a], 6B
Elementary 3 (K-4)	367	82	69 (19)	13	10[a] (12.2)	4A[a], 1B
Elementary 4 (K-6)	426	214	161 (38)	53	15 (7.0)	5A, 4B
Intermediate (5-6)	476	197	160 (34)	37	15[a] (7.6)	4A[a], 6B
Middle school (7-8)	631	109	74 (12)	35	13[b] (11.9)	6A[b], 1B
High school (9-12)	1251	294	251 (20)	43	26 (8.8)	2A, 1B
Total	4159	1226	940 (23)		103 (8.4)	35A, 20B

[a]1 dual SARS-CoV-2/Influenza A positive.

[b]3 dual SARS-CoV-2/Influenza A positives.

Enrollment numbers are for students only. Total tests include those for students and staff. The percentage of students tested (number of student tests/number of students) is provided for each school. The overall percent positivity is shown in the SARS-CoV-2 (+) column, based on the number of positive tests divided by the total number of tests at each school.

Table 2. Comparability of the Temporal Trends in Weekly SARS-CoV-2 Detections From the Oregon School District (OSD) and Dane County, Wisonsin Over the 2021-2022 Academic Year

OSD Lag/Lead	Spearman's Correlation		Generalized Additive Model Results for the OSD Count Relationship With Dane County Count, After Accounting for the Estimated Time-Form		
	Estimated Spearman's rho	*P* value	Estimate	SE	*P* value
2-week lag	0.55	<0.001	-66.2	61.2	0.289
1-week lag	0.66	<0.001	96.8	59.5	0.115
None	0.69	<0.001	247.5	49.6	<0.001
1-week lead	0.63	<0.001	280.6	45.8	<0.001
2-week lead	0.57	<0.001	92.0	66.2	0.176

RESULTS

RSAT Performance

Over the course of the 2021-2022 school year (September 1, 2021 through June 6, 2022), a total of 1226 Sofia2 Flu + SARS rapid antigen tests were performed at the 7 schools in the OSD (Table 1). A total of 940 students (77%) and 286 OSD staff (23%) were tested, and SARS-CoV-2 was detected in 103 specimens (84 students, 19 staff). There were 6 invalid results (0.5%). Influenza was detected in 55 specimens (35 influenza A, 20 influenza B). The average age of a tested student was 10.9 years (SD ± 3.8 years). Although the district's 4 elementary schools enrolled 38% of students, they accounted for 51% of completed rapid tests. The 2 schools with the highest SARS-CoV-2 positivity rates, at 12.2% and 11.9%, also conducted the lowest number of rapid tests (82 and 109, respectively). Six specimens tested positive for both SARS-CoV-2 and influenza A. Families of students who tested positive for COVID-19 or influenza were notified immediately and advised of school policy regarding testing and returning after illness. They were also given information on local testing locations.

While Family Educational Rights and Privacy Act (FERPA) guidelines did not allow us to match RSAT results with corresponding RT-PCR results, the Sofia Flu + SARS Antigen FIA is reported to have a sensitivity of 95.2% for SARS-CoV-2, compared with an average of 50% to 77% for comparable at-home SARS-CoV-2 tests.[11,15]

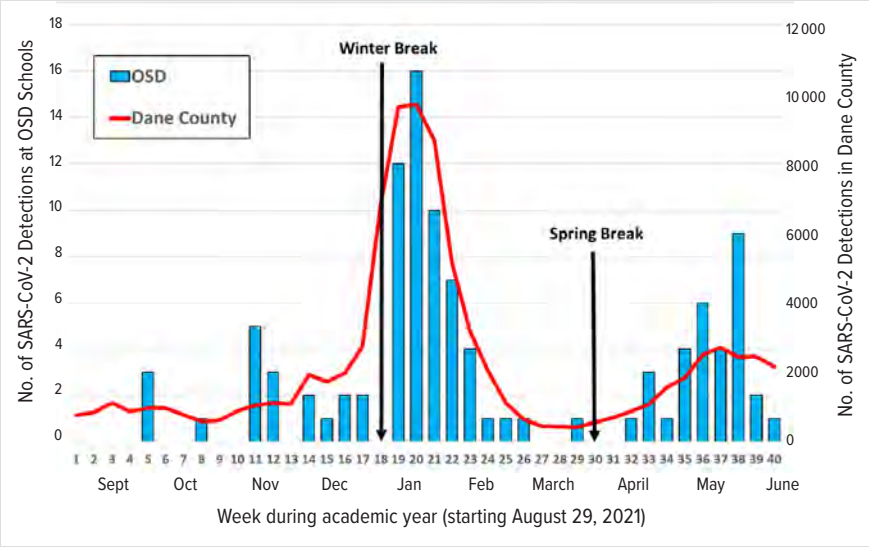
Comparability of Results

The overall percent positivity for RSAT at OSD was 8.4% (103/1220), which compared closely to the overall county-wide percent positivity of 9.2% for RT-PCR (chi-square = 0.74; $P = 0.39$) over the same time period. The temporal patterns of weekly positive specimens from OSD and Dane County demonstrated similar trends (Figure). In the Spearman correlation analyses, all 5 versions displayed statistically significant positive correlations between Dane County and OSD counts, with all estimated Spearman's rho (r_s) tests between 0.55 and 0.69 (Table 2). The analysis without any lag or lead displayed the largest esti-

mated rho and the smallest *P* value, with smaller rho estimates and larger *P* values exhibited for greater leads or lags away from zero. It should be noted that differences in these estimates was not assessed statistically.

In the GAM analyses, both the 1-week lead and the no lag models had statistically significant positive associations between the OSD counts and Dane County counts. Both lag models and the 2-week lead model did not detect a statistically significant association between OSD and Dane County counts. These results are after the models accounted for the nonlinear time-dependent form of Dane County counts. The 1-week lead model had the smallest standard error of the estimate and the smallest *P* value but, similar to the Spearman correlation, the differences in these estimates and *P* values have not been assessed statistically.

Figure. Number of SARS-CoV-2 Detections per Week Within K-12 Schools of the Oregon School District (OSD) and in Dane County, Wisconsin, August 29, 2021-June 4, 2022



Black arrows depict the timing of winter (week 18) and spring (week 20) breaks.

Feedback Survey

The end-of-year feedback survey was completed by 100% (n = 13) of respondents (Table 3). Respondents rated their level of confidence in measures critical to performing and reporting SARS-CoV-2 testing before and after training on a 5-point Likert scale (1 = not at all confident, 5 = very confident). Health office staff reported significant improvement ($P < 0.05$) post-training on the following measures: registering a student in COVID Connect, collecting a nasal swab, performing a Sofia rapid test, and reporting test results to a parent. Staff noted an improvement in identifying COVID-like symptoms, though this change was not significant ($P = 0.054$). On the same Likert scale, respondents rated feasibility measures related to utilization of Sofia rapid testing, PCR testing, and COVID Connect (Table 4). On average, staff reported ease of use for Sofia rapid testing at 4.62/5 and ease of nasal swab collection for Sofia rapid testing and PCR testing at 4.77 and 4.45, respectively. On a scale of 1 (not at all confident) to 5 (very confident), staff reported confidence in the accuracy of Sofia rapid testing and PCR testing results at 4.23 and 4.92 on average, respectively. Respondents rated usefulness of Sofia rapid testing and PCR testing for detecting cases of COVID-19 at 4.54 and 4.85, respectively, on a scale of 1 (not at all useful) to 5 (very useful). A majority of health office staff (12/13, 92.3%) indicated interest in continuing to use Sofia rapid testing and COVID Connect in OSD health offices the following year.

DISCUSSION

Use of RSAT in a K-12 school environment was feasible, acceptable, and performed comparably to county-wide SARS-CoV-2 testing. Individuals collecting specimens and running the rapid tests within school health offices rated the RSAT highly and indicated willingness to continue this service into the following year. A low rate of invalid testing was noted (<1%). In addition, high similarities in percent positivity and temporal patterns of positive results were noted between the RSAT and the reference testing program.

We found that brief, in-person training resulted in improvements in tasks related to testing students for SARS-CoV-2 including (1) registering students in the state's COVID-19 result reporting system, (2) collecting a nasal specimen, (3) performing the RSAT, and (4) reporting results to parents. Most of the health office personnel reported an appreciation for on-site rapid testing, reduction in the need to help families navigate testing elsewhere, and the ability to test staff members. They also noted challenges with time demands required for in-school testing and concerns with false negative results.

We were unable to provide a formal assessment of performance characteristics of Sofia2 in this quality improvement report, as we did not have access to the RT-PCR results from negative RSAT specimens. In addition, we did not assess the utility of testing for influenza. We did note a very low rate of invalid tests in this CLIA-waived environment where tests were performed by non-laboratorians. In addition, the overall percent positivity closely matched that for the surrounding county, and the temporal trends of positive specimens per week closely reflected the ambient level of SARS-CoV-2 in the community.

Compared to screening of asymptomatic students, the testing of symptomatic students appeared to work well. In contrast, a recent report from Wisconsin detailed low yield, high cost, and

high burden of a screening program for asymptomatic individuals in the setting of relatively high student masking compliance and physical distancing.[16]

Table 3. Self-rated Average Level of Confidence in Performing Activities Involved in Testing for SARS-CoV-2 and Reporting Results Before and After Training

	Before Training	After Training	Mean Change	*P* value
How confident are you in your ability to:				
Identify COVID-like symptoms	3.85	4.46	+0.62	0.054
Register a student in COVID Connect	1.54	4.46	+2.92	0.001
Collect a nasal swab	3.54	4.77	+1.23	0.008
Perform a Sofia rapid test	1.69	4.69	+3.00	0.002
Report test results to parent	3.38	4.69	+1.31	0.014

Ratings were reported on a Likert scale (1 = not at all confident, 2 = slightly confident, 3 = somewhat confident, 4 = fairly confident, 5 = very confident).

Table 4. Comparisons Between Use of Sofia Rapid Testing, Polymerase Chain Reaction (PCR) Testing, and COVID Connect (Wisconsin Department of Health Services Reporting Portal)

	Sofia Rapid Testing	PCR Testing	COVID Connect
How easy was this resource to use?	4.62	–	3.46
How easy was it to collect a nasal swab for this test?	4.77	4.45	–
Would you like to utilize this resource next year?	12/13	11/13	12/13
How helpful was in-person training?	4.83	4.58	4.67
How confident were you in the accuracy of these results?	4.23	4.92	–
How useful was this resource for detecting cases of COVID-19?	4.54	4.85	–
How useful was this resource for detecting cases of Influenza?	4.46	–	–
How easy was it to select students and staff for testing?	3.83	–	–

Each question was scored on a 5-point Likert scale, from 1 (very difficult, not at all helpful, not at all useful, or not at all confident) to 5 (very easy, very helpful, very useful, or very confident).

Strengths and Limitations

There were a number of strengths to this evaluation. First, this was a pragmatic assessment of the introduction of rapid antigen testing into a K-12 environment. As such, setup and our review of quality required minimal input. Accordingly, it represents a real-life experience with RSAT in K-12 settings. The health office staff made testing available to students (77% of tests) and staff (23%) who developed symptoms at school and were able to receive accurate test results within 15 minutes. Those who tested positive for SARS-CoV-2 were sent home immediately, thus avoiding the potential for transmission during the school day had testing been delayed until after school. Second, we were able to combine external assessments of performance and staff level experiences. Third, this was conducted within a county that had very active SARS-CoV-2 testing activity. During the evaluation period, almost 1 million SARS-CoV-2 tests were performed, yielding a detailed assessment of background SARS-CoV-2 activity for comparison. Finally, the OSD used an available, easy-to-use, and inexpensive RSAT, enhanced by a wireless reporting system that can be used for public health measures. Accordingly, this approach is replicable elsewhere.

There were also significant limitations. First, we worked with the manufacturer of Sofia to provide the OSD with analyzers and test kits. Other school districts may use other technologies and may not have the same level of support. Second, rapid test results were not labeled as student or school staff, so our staff used the provided age to delineate the tested individual (>18 years old labeled as staff, ≤18 years old labeled as student). Third, because of FERPA guidelines, secondary swabs taken from individuals with a negative rapid test and submitted for RT-PCR testing were unable to be paired with the corresponding rapid results, so study case numbers are based on rapid results without confirmatory testing. Rapid tests generally have high specificity, but only moderate sensitivity, so the true positivity may be greater than reported data suggest.[17] Furthermore, we were unable to evaluate influenza data, as current surveillance for influenza has been disrupted by the pandemic. Fourth, the reasons and process for RSAT testing is clear; however, the reasons and process for individuals seeking testing in the Dane County data are less known and likely more variable. Moreover, we lacked the ability to enumerate invalid tests for Dane County. Fifth, we relied on recall to assess the value of training provided. Finally, this evaluation was conducted in a small school district with an annual enrollment of 4159 students, with a racially and ethnically homogeneous student population (86.1% White non-Hispanic).[18] Accordingly, the findings may not be generalizable.

CONCLUSIONS

We found that implementing a district-wide K-12 SARS-CoV-2 rapid testing protocol is feasible, widely accepted, and reflective of local trends. With minimal training, 13 health office staff members were able to successfully implement a rapid testing protocol for symptomatic students and staff in 7 schools during the 2021-2022 academic year. Testing was performed continuously throughout the school year with an invalid result rate of less than 0.5%, and positive rapid testing data correlated highly with county rates of SARS-CoV-2. Twelve of 13 participating health office staff indicated interest in continuing this program of rapid testing in the coming school year.

Rapid tests are relatively inexpensive and have the added benefit of being performed on-site, with results that are available in

near real-time. Cause-specific illness episode data emanating from K-12 schools has the potential of providing a community-based data stream for more accurate estimates of local SARS-CoV-2 trends, especially when there is a potential for underreporting of at-home tests.[19] The SARS-CoV-2 pandemic has opened the door for the introduction of rapid antigen testing in K-12 schools. In the future, schools may serve as an ideal location for testing and surveillance of other pathogens.

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Testing Similarity in Romantic Partners' COVID-19 Experiences at the Time of a Pain-Related Emergency Department Visit

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ABSTRACT

Background: Research has established associations between romantic partners' health-related behaviors, although links between partners' experiences of the COVID-19 pandemic at the time of an important medical event remain untested.

Methods: The sample was drawn from an existing study of patients who received a new opioid prescription at an emergency department visit for acute pain. We assessed COVID-19 experiences of 97 patients and their romantic partners from April 2021 through June 2022.

Results: Romantic partners reported similar ratings of COVID-19 impact and were likely to agree on their coping with the pandemic by engaging in more time on activities like puzzles or books, using marijuana, and drinking alcohol. Partners also demonstrated high concordance in their COVID-19 vaccination statuses.

Conclusions: These findings extend a robust literature showing romantic partners' concordance in a host of health-relevant behaviors to their COVID-19 experiences.

BACKGROUND

People tend to exhibit health behaviors similar to those around them—especially their romantic partners or spouses.[1,2] In earlier research, Wilson[3] analyzed the interspousal correlation in health status among married couples in later life and reported a tendency to share lifestyle behaviors, such as diet, smoking, and exercise. Comparable patterns have been found in research based on other types of romantic relationships, although marital couples are the most frequently studied. For example, in a sample comprised of nearly all (>90%) dating couples, partners demonstrated similarity in their drinking behaviors and drinking motivations.[4,5]

Emerging research shows that many aspects of adults' health behaviors have been altered in mostly negative directions since the onset of COVID-19, including sleep, physical activity, dietary habits, and relationship aggression.[6] Despite longstanding recognition that romantic relationships play an important role in how individuals' health may change over time in response to the pandemic onset,[7] few studies have been able to test dyadic-informed hypotheses about connections between partners' COVID-19 experiences (eg, coping behaviors, perceived adjustment). Dyadic study designs involving both members of the romantic couple are critical for testing similarity of linked partners' health-related behaviors and experiences.[8] Having this dyadic perspective can reveal insights regarding medical events with potential for surveying or treating both patients and their partners to promote health during the pandemic and beyond.

Here, we draw from a study of patients receiving a new prescription for pain medication during an emergency department (ED) visit for acute pain and their romantic partners. This broader study provided a value-added opportunity to test the links between partners' experiences of the COVID-19 pandemic. We predicted that patients and their partners would report similarities in their COVID-19-related coping and experiences (ie, perceived impact, life satisfaction, coping behaviors, and vaccination status) at the time of this salient medical event.

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METHODS

Study Design and Setting

This report is drawn from a broader study designed prior to the pandemic to investigate romantic partner characteristics as risk factors for an individual's problematic opioid use or misuse at the time of a new opioid prescription. Questions about COVID-19 were incorporated to understand patient (and partner) experiences in the evolving public health situation. Study enrollment and data collection occurred following the pandemic onset from April 2021 through June 2022. Participating patients and their partners received electronic gift card payments (US $50 per participant).

Target individuals were recruited and enrolled by staff members of the BerbeeWalsh Department of Emergency Medicine's Emergency Department Research Coordinator (EDRC) Program at the University of Wisconsin-Madison. Potentially eligible patients were identified using electronic health records and then approached for the study if they were aged 21 years or older, English speaking, able to provide informed consent and sign the HIPAA (Health Insurance Portability and Accountability Act) authorization form, receiving a new opioid prescription for acute pain, and in a committed romantic relationship with a same- or different-sex partner. Romantic partners were required to be at least 21 years old and needed to enroll during the same emergency visit. Potential patients were excluded if their medical chart indicated a cancer diagnosis or opioid prescription in the prior 6 months. Patients and their partners completed informed consent, and all procedures were approved by the university's Institutional Review Board. Trained research coordinators administered surveys to patients using RedCap on EDRC-owned tablets; partners completed the RedCap surveys using the same procedures or on their personal devices at the same time as the patient when the ED needed to enforce restrictions on visitors to comply with public health orders.

Participants completed questions about their demographic characteristics, COVID-19 experiences, and additional measures not included in the current study; all measures were completed during a single survey session. Patients and their romantic partners reported on their COVID-19 experiences via brief scales from the Environmental Influences on Child Health Outcomes (ECHO) Program COVID-19 Questionnaire – Adult Version available from the National Institutes of Health PhenX Toolkit (www.phenxtoolkit.org). Participants rated the extent to which COVID-19 had an impact on their functioning. Instructions stated, "COVID-19 is an emerging respiratory disease caused by a new coronavirus that can be caught by, and spread among, people. Using a scale from 1 (not true of me at all) to 7 (very true of me), please indicate the degree to which each statement below describes you." Items included the following: "Thinking about COVID-19 makes me feel threatened," "I am afraid of COVID-19," "I am not worried about COVID-19," "I am worried that I or people I love will get sick from COVID-19," "I am stressed around other people because I worry I'll catch COVID-19," "I have tried hard to avoid other people because I don't want to get sick," "COVID-19 has impacted me negatively from a financial point of view," "I have lost job-related income due to COVID-19," and "COVID-19 has NOT impacted my financial status at all." Responses were recoded such that higher values for all items indicated greater impact of COVID-19 on adjustment and then averaged (α for patients = 0.78, α for partners = 0.76). Participants also rated a single item from 1 (not at all) to 5 (very often) that asked how often they felt happy and satisfied with their life since becoming aware of the COVID-19 outbreak. Participants completed a checklist of 11 possible behavioral coping responses to manage stress related to the COVID-19 outbreak (behaviors listed in Table 2), along with an option stating, "I have not done any of these things to cope with the COVID-19 outbreak." Participants were instructed to check all that apply (yes/no). Finally, participants reported whether they had received a COVID-19 vaccine (yes/no).

Table 1. Demographics Reported by Patients and Romantic Partners, N = 97 Dyads

Demographic Characteristics	Patients	Partners
Gender		
Man	58	36
Woman	37	60
Nonbinary	0	0
Transgender	0	1
None of these	0	0
Unknown	2	0
Age, years; mean (SD)	52.3 (16.4)	52.0 (15.4)
Married		
Yes	81	
No	15	
Unknown	1	
Race/ethnicity		
White	86	87
Black	4	3
Hispanic/Latinx	4	2
Other or mixed race	2	4
Unknown	1	1
Education		
No high school degree	0	4
High school degree or equivalent	13	13
Some college	32	34
Bachelor's degree or greater	51	45
Unknown	1	1

Age was reported by 87 patients and 83 partners.

Data Analysis

Statistical tests of concordance were conducted using Pearson correlation for continuous outcomes and χ^2 analysis for dichotomous outcomes. Specifically, a positive r indicates a positive association between romantic partners' ratings of a construct, while a significant χ^2 reflects a positive likelihood that a behav-

ior (or response) endorsed by one participant is also likely to be endorsed by their partner. Statistical significance was evaluated at $P < 0.05$.

RESULTS

Descriptive statistics on participant demographic characteristics are shown in Table 1. Ninety-eight patients were enrolled in the study. Romantic partner data were available for 97 patients; these 97 couples formed the analytic sample. Missing data were minimal (99.7% complete across study variables shown in Table 2) and were handled using listwise deletion.

Romantic partners demonstrated a positive link in their ratings of the extent to which COVID-19 had impacted them ($r = 0.21$, $P = 0.042$), whereas there was no reliable association between partners' ratings of their life satisfaction since COVID-19 ($P > 0.05$). See Table 2.

Table 2. Descriptive Statistics and Similarity of Patient and Romantic Partner COVID-19 Experiences, N = 97 Dyads

Variable	Patient	Romantic Partner	Statistical Test
Impact of COVID-19	2.97 (1.16)	3.00 (1.06)	r (96) = 0.21, P = 0.042
Life satisfaction since COVID-19	3.93 (1.00)	3.80 (0.92)	r (95) = -0.13, P = 0.21
Activities to cope with COVID-19			
Meditation and/or mindfulness practices	32 (33%)	27 (27.8%)	χ^2 (1, N = 97) = 1.02, P = 0.31
Talking with friends and family	76 (78.4%)	72 (74.2%)	χ^2 (1, N = 97) = 0.11, P = 0.74
Engaging in more family activities	43 (44.3%)	31 (32%)	χ^2 (1, N = 97) = 0.11, P = 0.75
Increased television watching or other screen time activities (eg, video games, social media	50 (51.5%)	52 (53.6%)	χ^2 (1, N = 97) = 2.92, P = 0.087
Eating more often, including snacking	27 (27.8%)	24 (24.7%)	χ^2 (1, N = 97) = 0.03, P = 0.87
Increased time reading books or activities like puzzles and crosswords	41 (42.3%)	42 (43.3%)	χ^2 (1, N = 97) = 6.72, P = 0.01
Drinking alcohol	14 (14.4%)	13 (13.4%)	χ^2 (1, N = 97) = 12.23, P < 0.001
Using tobacco	9 (9.3%)	3 (3.1%)	Fisher exact, P > 0.99
Using marijuana	11 (11.3%)	3 (3.1%)	Fisher exact, P = 0.033
Talking to health care providers more frequently, including mental health providers	13 (13.4%)	5 (5.2%)	Fisher exact, P = 0.52
Volunteer work	9 (9.3%)	10 (10.3%)	Fisher exact, P = 0.59
None of these things	12 (12.4%)	14 (14.4%)	Fisher exact, P = 0.68
Received COVID-19 vaccination	78 (80.4%)	80 (82.5%)	Fisher exact, P < 0.001

Fisher exact test is reported when 1 or more cell counts (including those not shown) were less than 5 in a given χ^2 analysis.

According to both patients and their partners, the most frequent coping behaviors in response to COVID-19 were "talking with friends and family" and "increased television watching or other 'screen time' activities." Most participants engaged in at least one coping behavior; however, 12.4% of patients and 14.4% of partners did not engage in the behaviors listed. Among those who reported coping behaviors, patients used an average of 3.82 (SD 1.95, range 1-10) and their partners used an average of 3.40 (SD 1.72, range 1-8). As shown in Table 2, results revealed significant associations between patients' and their partner's use of the same coping behavior in response to COVID-19, including engaging in increased time reading or completing puzzles ($\chi^2[1] = 6.72$, $P = 0.01$), engaging in alcohol use ($\chi^2[1] = 12.23$, $P < 0.001$), and engaging in marijuana use ($P = 0.033$). Similarity in romantic partners' use of other coping behaviors was not observed (remaining tests had P values > 0.087; see Table 2).

Most participants (80.4% of patients, 82.5% of partners) reported receiving a COVID-19 vaccine. As reported in Table 2, patients were significantly likely to report being vaccinated if their romantic partner also did ($P < 0.001$), in line with previously documented concordance in health-promoting behaviors.

DISCUSSION

This study extends support for concordance in romantic partners' COVID-19 experiences in the context of critical medical situations. Participants' evaluations of COVID-19 impact and life satisfaction after COVID were assessed; romantic partners reported similar levels of impact but not life satisfaction. Thus, there was mixed support for the hypothesis that romantic partners would rate their adjustment levels following COVID-19 in similar ways.

Additionally, patients and their partners reported a range of coping behaviors (and typically multiple behaviors) in response to COVID-19. Although most coping behaviors endorsed by romantic partners were not interrelated (3 of 11 behaviors tested reached statistically significant levels; see Table 2) and thus did not support our hypothesis, reliable findings emerged for behaviors that are particularly important to patients' health. Specifically, coping through substance use (ie, alcohol use and marijuana use) demonstrated concordance among romantic couples. Longer-term study is needed to understand whether this similarity endures as the pandemic evolves and the extent to which the link holds risks to partners' health and their relationships.[9] Partners also reported reliable concordance in their vaccination statuses.

Strengths, Limitations, and Implications

We utilized a rigorous data collection protocol, including trained researchers in the ED setting and simultaneous survey completion by patients and their partners to collect dyadic perspectives at the time of a new prescription for pain medication—a medical event that commonly precedes longer-term problematic opioid use or misuse.[10] The broader study required romantic partners to participate at the same time during an ED visit, which may have introduced a selection bias towards more supportive partnerships. Results cannot necessarily generalize beyond the current population but do provide initial evidence for partner-related health

behaviors and experiences associated with the COVID-19 pandemic among couples seeking emergency treatment for one partner's acute pain.

In terms of limitations, we acknowledge that survey assessments were collected from couples at a single timepoint and from a single academic ED in a majority-White geographical region. It remains to be tested whether similar interdependence would be observed in different settings and populations; for example, strong positive concordance in partners' vaccination status may not hold among those from locales with lower vaccination rates. The COVID-19 surveys were limited to measures available at the time; in particular, the checklist format of the coping measure included 11 behaviors and did not allow participants to write in other strategies that were likely used and, thus, should be regarded as incomplete. Future research should consider the couple relationship context of the pandemic among samples with more diverse racial-ethnic and geographic characteristics.

By necessity, patient care typically focuses on the individual patient. However, patients experience medical visits oftentimes in the presence of their partner, and these may provide a more thorough and powerful vantage point at which to collect information or share guidance. For example, when sending patients home with guidance for health-promoting behaviors, it may be more powerful to share the information with both partners, when possible, to maximize the benefits.

CONCLUSIONS

These preliminary findings document concordance of some aspects of romantic partners' COVID-19 experiences, including the extent to which they reported being affected by COVID-19 and their likelihood of using substances to cope. Thus, the results encourage additional consideration of romantic relationships as a context for understanding and targeting change in both adaptive and problematic aspects of health-relevant behaviors and experiences.

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Laboratory-Developed Tests: A Critical Bridge During the COVID-19 Pandemic

William M. Rehrauer, PhD; David T. Yang, MD

In February 2020, it was becoming increasingly clear that a global pandemic was fomenting, and diagnostic testing for COVID-19 in the United States was woefully inadequate.[1] Under normal circumstances, diagnostic tests are developed largely by commercial manufacturers and sold to clinical laboratories. The US Food and Drug Administration (FDA) reviews these commercially available tests through an extended and bureaucratic process that manufacturers have necessarily built and staffed with infrastructure to navigate.[2] Alternatively, clinical laboratories certified to perform high-complexity testing can implement laboratory-developed tests (LDT) for use within the institution through a quicker, less bureaucratic process. As long as these tests are performed within the institution and not directly marketed to consumers, the FDA has so far exercised regulatory discretion and allowed oversight of LDTs to fall under the Clinical Laboratory Improvement Amendments (CLIA) clinical laboratory certification process managed by the Centers for Medicare and Medicaid Services (CMS).[3]

Like most clinical laboratories at academic medical centers that serve a referred population of complex and high-acuity patients, UW Health Clinical Laboratories has experience developing LDTs that fill a niche where commercial tests are either unavailable or do not meet clinical needs. Having staff with test development expertise and validation/implementation workflows in place was critical to our ability to design and operationalize a diagnostic COVID-19 LDT in 7 days. In order to appreciate the significance of this rapid implementation, it is important to recall that COVID-19 testing initially could be performed only by the Centers for Disease Control and Prevention (CDC) and local public health departments.[4] As these institutions quickly became overwhelmed with testing demands, turnaround times stretched from days to weeks.[1] Thereafter, the FDA was forced to permit clinical laboratories with high-complexity designation to develop LDTs.[5] When UW Health Clinical Laboratories began test development, essentially no COVID-19 testing was available to our patients. The implications were dire as there was no way to ration depleting stocks of personal protective equipment, reliably isolate infected patients, or implement an employee testing program. The timely implementation of local public health measures, including school closures and limiting gatherings, likely averted an impending disaster at our medical center during the interval of LDT development.[6]

> The ability to develop LDTs was not serendipitous but rather emerged out of a policy that allowed clinical laboratories to address gaps in diagnostic testing—gaps that became strikingly apparent and were pervasive...during the early days of the pandemic.

Laboratory-developed COVID-19 testing at our institution served as a critical bridge for 4 weeks until we transitioned to a high throughput commercial test whose availability was delayed due to reagent and manufacturing supply chain constraints. In addition, LDTs also provided clinical laboratories the opportunity to diversify their testing methodologies to counter these same supply chain constraints and to accommodate alternative specimen sources to meet clinical needs.[7,8] Without LDTs, it is hard to imagine the degree to which patient care may have been compromised. The ability to develop LDTs was

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not serendipitous but rather emerged out of a policy that allowed clinical laboratories to address gaps in diagnostic testing – gaps that became strikingly apparent and were pervasive throughout the entire country during the early days of the pandemic.

Today, expanded regulation of LDTs is being considered in Congress through two competing bills. The Verified Innovative Testing in American Laboratories (VITAL) Act[9] proposes to keep regulatory oversight of LDTs with CMS, while the Verifying Accurate Leading-edge IVCT Development (VALID) Act[10] proposes to establish new FDA authority for regulation of LDTs. The VALID Act would add another layer of oversight and bureaucracy designed for manufacturers who sell commercial tests to be duplicatively imparted on clinical laboratories that already are subject to CMS oversight. Looking back at lessons learned from the pandemic, we reflect on how critical our ability to develop a COVID-19 LDT was and the possible consequences of legislation that might curtail a clinical laboratory's inclination to foster and support expertise in laboratory test development.

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September 2022

Sue Blaustein

Digital Photo

Artist Statement:

Several Binax COVID tests are arranged like flowers in an (empty pill bottle) vase. They document the week in September 2022 when my partner, then I got COVID.

Research During COVID-19: Reflections From an Institutional Review Board Office

Kristin Busse, PharmD; Sara Griffin, MS; Ryan Spellecy, PhD

The COVID-19 pandemic affected clinicians by placing extreme stress on professions that were already facing personnel shortages, burnout, stress, and mental health challenges.[1] In addition to the well-known impact on the entire health care system, clinical research also was affected dramatically by the pandemic. This commentary focuses on the effect of COVID-19 on human research through the lens of an Institutional Review Board (IRB) office. We will highlight how our institution managed the suspension of research, transition to virtual platforms and activities for research, transition of effort to minimal risk research projects, and virtual consenting options, followed by a summary of the changes that have continued since the emergence of the pandemic.

As COVID-19 spread throughout the world and the United States, representatives from the Medical College of Wisconsin Office of Research, including the Human Research Protection Program (HRPP), which includes the IRB, began developing plans to suspend research. On March 13, 2020, senior leadership from the Office of Research issued guidance assuring stakeholders that they were closely monitoring the spread of COVID-19. They noted that research at our institution is mission critical, seeking to continue clinical research whenever possible while balancing safety and mitigating risk. Leadership advised each clinical research department to review its portfolios and categorize studies into three groups, described below. Phase I, described as a "research slow down," was activated when community-based transmission of COVID-19 was detected in Wisconsin in mid-March. For human research, this meant that all nontherapeutic research – research that provides no or minimal benefit to participants (Group 3) and involves direct contact – was suspended. On March 28, MCW leadership took further steps to mitigate the risks of COVID-19. For human research, in-person activities for all studies that offered only moderate benefit to participants (Group 2) were suspended. Only research involving in-person activities for which ceasing study activities could cause immediate and possibly life-threatening risk to subjects (Group 1) was allowed to continue. By the end of March 2020, the framework described above coincided with MCW's mandatory work-from-home directive to limit face-to-face contact and protect both research participants and personnel from exposure to SARS-CoV-2. Leadership provided an avenue for principal investigators to appeal the suspension of specific studies by petitioning the Clinical Research Appeals Group to review the study and determine if in-person research visits could continue.

> Regulations that govern the conduct of research contain a provision that allows researchers to implement a planned deviation without prior IRB review when those changes are "necessary to eliminate apparent immediate hazards to the subject."

As research was suspended, study teams were encouraged to transition to virtual activities whenever possible, which had the potential to inundate the IRB with amendments and possibly delay the review of pending urgent COVID-19-related research. Regulations that govern the conduct of research contain a provision that allows researchers to implement a planned deviation without prior IRB review

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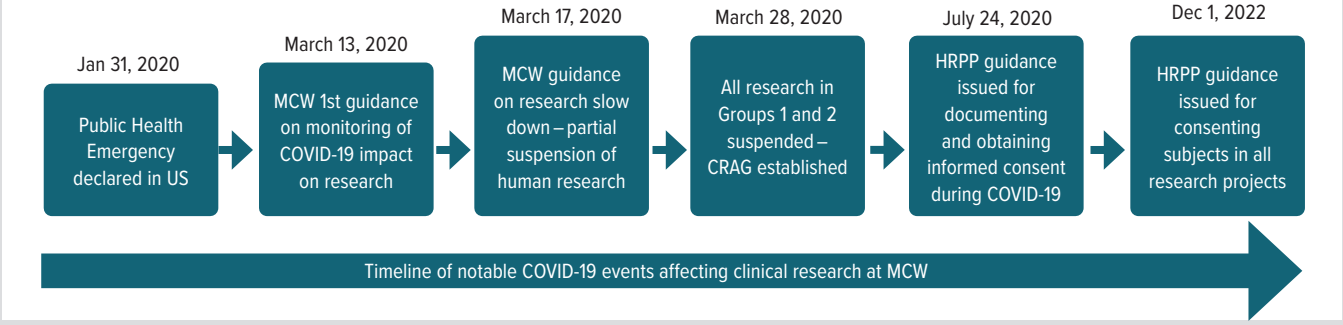
Figure 1. Timeline

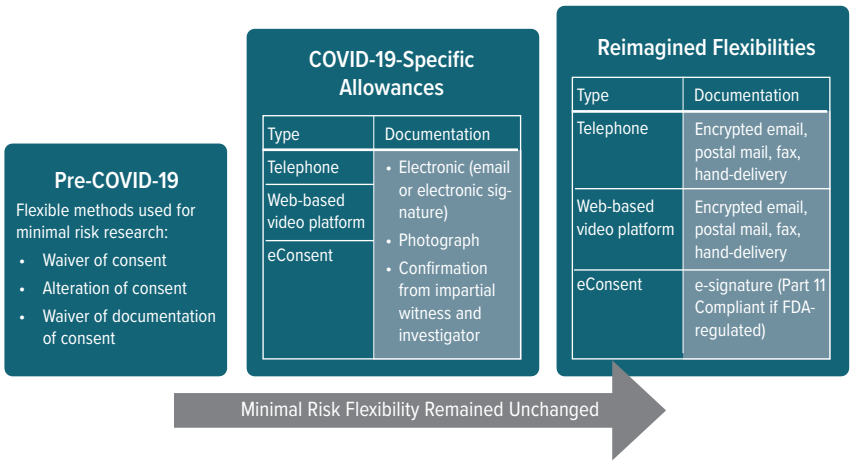


Abbreviations: MCW, Medical College of Wisconsin, CRAG; Clinical Appeals Research Group; HRPP, Human Research Protection Program

when those changes are "necessary to eliminate apparent immediate hazards to the subject."[2] Avoiding exposure to SARS-CoV-2 certainly met that criterion. However, making such changes would still require immediate reporting to the IRB. This, too, could inundate the IRB. When the National Institutes of Health (NIH) Clinical Center deferred all elective admissions and outpatient visits, including research visits, they, too, noted this challenge. The NIH IRB issued guidance that if a change was necessary to assure the safety of the research participant and given the expected volume of reports, only deviations that were "major deviations" needed to be reported immediately.[3] Major deviations are defined as deviations that could negatively impact the rights of research participants or substantively impact the scientific integrity or validity of the study. MCW followed this example and further stated that if the change was expected to be a temporary response to the COVID-19 pandemic and not a permanent change, this could be reported at the time of annual review instead of within 5 days according to institutional policy.

The transition to virtual activities also had implications for obtaining informed consent. Questions about consent were not at the forefront of the minds of researchers nor the MCW IRB committees since most research was suspended and the focus was placed on preventing immediate harm. During this time, the HRPP Office leaned heavily on US Food and Drug Administration (FDA) guidance when drafting its own guidance on how to obtain consent from individuals in quarantine or with suspected or confirmed COVID-19 infection.[4] Flexible methods were encouraged for documenting consent, even for FDA-regulated projects, due to the risk of infection during this early phase.

Figure 2. Evolution of Flexible Consenting Methods



When it became clear that we would be unable to "flatten the curve" and return to some semblance of normal operations in a few weeks, study teams began conducting remote, minimal-risk research. For example, an in-person study related to sickle-cell disease that offered minimal benefit to the participants – and so was suspended – could pivot to surveying their research participants about the impact of the COVID-19 pandemic on their quality of life and sickle-cell disease. For the IRB, this resulted in a massive volume shift from greater than minimal risk research to minimal risk research, which overwhelmed the committee dedicated to reviewing minimal risk research. We believe the ability of our committees to focus and specialize is a strength, but the pandemic prompted us to cross-train IRB staff quickly.

The results were not felt immediately, but we continue the practice of cross-training IRB staff so that they can shift focus as volumes change.

Similarly, another shift occurred in IRB operations to pivot to a remote video platform option for IRB meetings. This solution offered the opportunity to review the usual regulatory submissions (eg, continuing progress reports) without delay. While this shift offered a somewhat easy solution, technical issues encountered by some committee members and a lack of familiarity with social norms of interacting in the virtual space created new barriers to fruitful IRB meeting discussions.

As restrictions began to lift from non-COVID-19-related research, it became clear that consenting methods had changed for most research, whether by choice or necessity. As previously mentioned, the minimal-risk research portfolio grew during this time, and many minimal-risk projects already could employ consent methods not requiring a signature. The stark reality of a changing research enterprise led to a second consent guidance focused on all research rather than only COVID-19. Interestingly, all strategies could have been utilized prepandemic for most research, but as we functioned almost exclusively in-person, resources had not been allocated to pursue alternate strategies. The guidance not only highlighted possible consent methods, but it also detailed institutional requirements relating to embedded HIPAA (Health Insurance Portability and Accountability Act) authorizations for research and discrepancies in documentation resulting from alternate consenting strategies. See Figure 2.

Earlier, it was noted that attention rapidly shifted during the early pandemic toward the reduction of harm to subjects and research staff. During that time, the HRPP recognized that temporary changes were likely being made to research practices, but permanent changes required IRB review. MCW IRB has begun to see an increase in pandemic-related noncompliance being discovered at the time of continuing review and as part of routine reviews by the HRPP Quality Improvement office. One of the most common types of noncompliance is the incorrect application of information within the consent guidance, particularly for FDA-regulated research. Although the HRPP recognizes the hardships experienced throughout the pandemic, the regulations and ethical principles governing human research remain unchanged.

Additional adaptations have emerged from the pandemic experience, including home visits for research procedures and our virtual consent workflow. For some research participants, if a study visit only includes vitals and a physical exam, it is much easier if an in-home health care service visits them instead of traveling to a hospital. What began as a necessity when travel to a hospital was too risky has continued as a welcome convenience for some. We also have retained our guidance and workflow for virtual consent, as this offers convenience for both study teams and potential research participants. While we still seek to create a virtual consent option for FDA-regulated research compliant with the additional requirements for the FDA, this practice continues for non-FDA-regulated research.

Other practices that have continued include remote study monitoring visits, site initiation visits, and IRB meetings. While such visits from study sponsors became virtual at the onset of the pandemic, we have yet to return to in-person visits for this aspect of clinical research. Like many changes made during the pandemic, there are considerable cost savings associated with making these meetings and visits virtual, though the benefits of meeting in person – whether it be relationships established for the work moving forward or the ability to converse face-to-face – are diminished. Time will tell if these visits and meetings will return to in-person.

Overall, clinical research at our institution was able to continue, despite the added stress of COVID-19. Some activities have proven advantageous over previous workflows, including virtual IRB committee meetings, virtual monitoring and site initiation visits, home visits for research procedures, and virtual consenting procedures. While we reimagine the conduct of clinical research post-COVID-19, these activities will likely remain and provide flexible alternatives to research-related work that were underutilized prior to the pandemic.

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New Mourning

Ryan McAdams, MD

Digital Illustration

Artist Statement:

This is a digitally designed art piece aimed to convey the grief, loneliness, death, and division that resulted from the COVID-19 pandemic, an impact that is still being felt throughout America.

COVID-19 Vaccination Telephone Outreach: A Primary Care Clinic Intervention Targeting Health Equity

James F. Wu, MD; Martin D. Muntz, MD; Ann Maguire, MD, MPH; Anna Beckius, BS; Mandy Kastner, MPH; Brian Hilgeman, MD

ABSTRACT

Introduction: Equitable COVID-19 vaccine access is essential to ending the COVID-19 pandemic. In many instances, COVID-19 vaccination notification and scheduling occurred through online patient portals, for which socially vulnerable populations have limited access. Our objective was to reduce disparities in COVID-19 vaccine access for the Black and socially vulnerable populations unintentionally excluded by our health system's patient portal-driven vaccine outreach through a telephone outreach initiative.

Methods: From February 1, 2021, through April 27, 2021, telephone outreach was directed towards patients aged 65 and older without patient portal access at a large urban academic general internal medicine clinic. Univariate and multivariate analyses between those who did and did not receive telephone outreach were completed to assess the odds of vaccination, accounting for outreach status, sex, age, race/ethnicity, payor status, social vulnerability index, and Elixhauser Comorbidity count.

Results: A total of 1466 patients aged 65 and older without active patient portals were eligible to receive the COVID-19 vaccine. Of these patients, 664 received outreach calls; 382 (57.5%) of them got vaccinated compared to 802 patients who did not receive outreach calls, of which 486 (60.6%) got vaccinated (P= 0.2341). Patients who received outreach calls versus those who did not were more likely to be female, younger, non-Hispanic Black, from high social vulnerability index census tracts, and have higher Elixhauser Comorbidity counts. Logistical analysis revealed an odds ratio (OR) with a nonstatistically significant trend favoring higher vaccination likelihood in the no outreach cohort with univariate analysis with no changes when adjustment was made for age, sex, race/ethnicity, payor, social vulnerability index, and Elixhauser Comorbidity count (univariate analysis: OR 0.88 [95% CI, 0.71-1.09]; model 1: OR 0.89 [95% CI, 0.72 – 1.10]; model 2 – 0.89 (0.72 - 1.11); model 3: OR 0.87 (95% CI, 0.70 -1.09)].

Conclusions: While our telephone outreach initiative was not successful in increasing vaccination rates, lessons learned can help clinicians and health systems as they work to improve health equity. Achieving health equity requires a multifaceted approach engaging not only health systems but also public health and community systems to directly address the pervasive effects of structural racism perpetuating health inequities.

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INTRODUCTION

The COVID-19 pandemic has disproportionately affected minority communities, as evidenced by higher rates of infection, hospitalization, and mortality.[1,2] The pervasive effect of structural racism results in worse COVID-19 outcomes in minority communities.[3] Structural racism is embedded in the fabric of our systems of housing, education, employment, earnings, benefits, credit, criminal justice, and health care – ultimately manifesting in the creation and persistence of health and social inequities.[4,5]

With the development of highly effective and safe COVID-19 vaccines, it is imperative that communities of color and social vulnerability have equitable vaccine access. During the beginning of the US vaccine rollout, vulnerable populations – especially racial/ethnic minorities – did not have equitable vaccine access. Per data from the US Centers for Disease Control and Prevention (CDC), racial disparities in vaccination persisted even after July 23, 2021, when more than 187 million people had received at least 1 dose.[6] As reported by the Kaiser Family Foundation, there remained a consistent pattern across states of Black and Hispanic people receiving smaller percentages of vaccinations compared to the percentages of cases, deaths, and total population among these groups.[7]

Non-Hispanic Black populations comprise 7% of the Wisconsin population but, as of September 2021, had received only 3.9% of total vaccinations while representing 8% of cases, 12.2% of hos-

pitalizations, and 7.6% of deaths.[8] Milwaukee County, a county with a history of significant segregation,[9] has a higher percentage of non-Hispanic Black residents (27.2%);[10] however, this population received only 17.4% of total first vaccine doses, and just 43% of residents in high social vulnerability index (SVI) census tracts received at least 1 dose of the vaccine compared to 53.8% of the total population as of September 2021.[11]

Historically, minority communities have experienced lower rates of adult immunization compared to White communities.[12,13] The causes of disparities in adult immunization are multifactorial, and many are manifestations of the downstream effects of structural racism. Barriers to vaccination include, but are not limited to, problems with access and cost;[14,15] differences in knowledge, attitudes, and beliefs, including well-founded mistrust of the medical establishment by minority populations due to a long history of medical discrimination and abuse;[16,17] and poor health literacy; misinformation; and the antivaccine movement.[18,19]

COVID-19 vaccine immunization scheduling through patient portal notification is cost-effective but has the potential to worsen health disparities. People who are older, less educated, economically disadvantaged, and from racial/ethnic minorities are less likely to have access to digital health information[20-22] and, thus, are put at a distinct disadvantage when these notification methods are used.

Leveraging the eagerness to contribute toward combating disparities during the COVID-19 pandemic and building off successful telehealth interventions across the nation,[23-24] our general internal medicine (IM) clinic created a telephone outreach initiative for patients aged 65 and older who lacked patient portal access. Our objective was to reduce disparities in COVID-19 vaccine access for the Black and socially vulnerable populations unintentionally excluded by our health system's patient portal-driven COVID-19 vaccination outreach.

METHODS

Setting and Participants

The study setting is a large urban academic general IM clinic serving over 12 000 patients, with 19 faculty physicians, 7 advanced practice providers, and 45 residents. The clinic employs 2 community health workers (CHW) who assist with community outreach to the most vulnerable patients. It is part of a large nonprofit health system consisting of 1 tertiary care hospital, 4 community hospitals, and nearly 40 outpatient clinics providing 1.1 million outpatient visits per year. The clinic serves a high share of patients who are non-Hispanic Black (32.7%), rely on Medicare/Medicaid (27.8%/15.6%, respectively), and live in ZIP codes with majority high SVI census tracts (36.8%).

The clinic cares for 4296 patients aged 65 and older, including 25.6% who do not have access to their patient portal. For these patients, significant disparities exist in patient portal access between non-Hispanic White and non-Hispanic Black patients (87.9% vs. 42.9%), ZIP codes composing majority high versus low SVI census tracts (51.9% vs. 85.2%), and those with Medicaid and/or Medicare versus those with commercial insurance (89.7%) (Table 1).

Table 1. Patients Age 65 and Older With Portal Access

Demographic	Category	Active Patient Portal
Race/Ethnicity	Non-Hispanic Black	42.9%
	Non-Hispanic White	87.9%
Neighborhood	High social vulnerability index	51.9%
	Non-high social vulnerability index	85.2%
Payor	Medicare only	82.0%
	Medicaid only	51.6%
	Medicare + Medicaid	43.2%
	Commercial	89.7%

Our institution granted this project an Institutional Review Board exemption as a quality improvement project.

Intervention

Beginning January 22, 2021, the health system deployed a COVID-19 vaccination strategy driven by patient portal notification and scheduling, which was supplemented by other means of access for those without portal access. A message with a link to schedule a vaccination appointment electronically was sent to all patients aged 65 and older who receive primary care within the health system. Letters with scheduling phone numbers were sent out via US mail to those without patient portal access.

From February 1 through April 27, 2021, medical students, CHWs, primary care physicians, internal medicine residents, clinic staff, and advanced practice providers provided telephone outreach to patients aged 65 and older without patient portal access. After the first 3 to 4 weeks of phone calls, staff also called patients with patient portal access who had not received their COVID-19 vaccine, when it was believed that the majority of patients without portal access had been called. Of note, in subsequent waves of vaccine allocation, the health system intentionally delayed the release of patient portal messages several days to allow for more high-risk patients to be contacted first.

Medical student volunteers were recruited from clerkships and via mass emails through the Medical College of Wisconsin. Students worked 4-hour shifts from a shared patient list in the electronic health record. A detailed workflow was created to standardize outreach between staff members, and backup support from attending clinicians was available via telephone.

During the calls, project staff discussed vaccination for eligible patients. Unsure patients were counseled about the safety and efficacy of the vaccine using information from evidence-based government and health system websites. Patients who declined vaccination were referred to their primary care provider if they had more questions. CHWs were able to schedule patients for vaccination

directly. For non-CHW callers, if during business hours, a vaccine scheduler from the clinic contacted patients; if after business hours, patients were provided the COVID-19 hotline number to schedule vaccination themselves. Some limited resources were available to provide vaccines to homebound patients, including home visits by emergency medical service personnel.

Data Analysis

A retrospective analysis was conducted on patients completely without or without an active patient portal (ie, portal use within the last year) who received the COVID-19 vaccine from February 1 through April 30, 2021. Patients also had to have a Wisconsin address and have completed a visit (ie, office visit, home health, virtual checkin, telemedicine) with a primary care clinician in our health system within 36 months of February 1, 2021. Descriptive statistics of patient characteristics were assessed between the patient populations that did and did not receive telephone outreach. The odds ratio of vaccination was compared between those who did and did not receive outreach. A univariate analysis was completed, followed by adjusted multivariate models: sex, age, and race/ethnicity in model 1, adding primary payor and SVI in model 2, and adding Elixhauser Comorbidity count[25] in model 3. Complete statistical analyses were performed using SAS statistical software. A P value <0.05 was considered statistically significant. SVI is a measure adopted by the CDC that uses 15 variables to reliably predict a community's risk from a natural or human-caused disaster and that community's potential resource need.[26] The SVI is based on census tract, and geomapping was utilized to determine SVI based on patients' addresses.

RESULTS

Forty medical students volunteered to engage in outreach and signed up for a total of 139 shifts. Two CHWs devoted approximately 50% of their 40-hour workweek to outreach over the initial 3 weeks, then approximately 25% of their workweek thereafter. A total of 2018 patients received outreach calls, the majority of which were completed by CHWs (941 calls) and medical students (863 calls). Some outreach calls were made to individuals with patient portal access as outlined in the program description above, and some of the individuals who received calls had already received vaccination (9%). Intervention outcomes and documented reasons for vaccination denial are in Tables 2 and 3. Overall, 23% of patients were reached and willing to schedule vaccination, 38% could not be reached directly or a message was left, and 13% refused vaccination. Reasons for refusal included the following: no reason (23%), desire to talk with family or primary care clinician (22%), concern about side effects (13%) and physical health effects (10%), location (10%), and lack of trust in the vaccine (10%).

From February 1, 2021, though April 30, 2021, a total of 1466 patients aged 65 and older and without active patient portals were eligible to receive the COVID-19 vaccine. Of these patients, 664 received telephone outreach, including 382 (57.5%) who got vaccinated compared to 486 who got vaccinated out of 802 patients who did not receive outreach (60.6%) ($P=0.2341$) (Table 4). Those who received outreach were more likely to be female (70.2% vs 64.8%; $P=0.03$), younger (age 74.5 vs 76.6; $P<0.0001$), non-Hispanic Black (68.8% vs 49.3%; $P<0.0001$), from a high SVI census tract (68.8% vs 52.7%; $P<0.0001$), and have higher Elixhauser Comorbidity Counts (8.3 vs 7.2; $P<0.0001$) (Table 4).

Logistical analysis revealed an odds ratio with a nonstatistically significant trend favoring higher vaccination likelihood in the no outreach cohort; univariate analysis revealed no changes when adjustment was made for age, sex, race/ethnicity, payor, SVI, and Elixhauser Comorbidity count. (See Table 5.) We examined the impact of the intervention, stratified by the factors in the model, and saw no differences.

Table 2. Outcomes of Outreach Calls

Outcome	% (n = 1205)
Reached, willing to schedule	23%
Did not answer, unable to leave message	20%
Did not answer, spoke with family member, or left message	18%
Reached, refused	13%
Reached, already vaccinated	9%
Reached, unsure, not willing to schedule	8%
Reached, unsure, willing to schedule	3%
Other	3%
Already scheduled	2%
Unknown	

Table 3. Reasons for Refusal of Vaccination

Reasons	% (n = 290)
Adamantly refused, no reason given	23%
Want to discuss with family member or primary care clinician	22%
Side effects and safety	13%
Health concerns	10%
Location (access, convenience)	10%
Don't trust or believe in vaccines	10%
Want more people to get vaccinated	9%
"I'm healthy," "don't go out," or "had COVID already."[a]	6%
Out of state	6%
Waiting for another type of vaccine available (Johnson and Johnson)	4%

[a]Patients may have selected multiple reasons

DISCUSSION

The program described here is a novel method of augmenting modern patient portal outreach with telephone outreach aimed at improving health outcomes for patients without patient portal access. Of note, 802 COVID-19 vaccination-eligible patients without patient portals did not receive outreach calls, which became evident only during our retrospective analysis, indicating a program oversight. Based on the analysis above, the telephone out-

reach did not lead to a higher likelihood of vaccination. However, lessons learned can help clinicians and health systems as they work to improve health equity—a key focus of current population and public health efforts in the United States and in medical education. We learned about the importance of convenience in vaccine scheduling and locations, the importance of trusted messengers, the limitations of telephone outreach, and the multiple structural barriers preventing vaccination.

There are myriad reasons for the outreach program's lack of efficacy. Medical student volunteers could not directly schedule patient vaccinations. If a medical student was able to successfully convince a patient to receive the vaccine, the additional step of waiting for another scheduling call or calling the scheduling number themselves created an additional structural barrier to vaccination. CHWs were able to directly schedule vaccinations, so further analysis could investigate the difference between medical student and CHW outreach in the likelihood of vaccination. Allowing for all callers to have the ability to directly schedule appointments would be an important change for future telephone interventions. Additionally, the general IM clinic itself was not a vaccination site at the time of the telephone outreach initiative; instead, patients were directed to other institutional vaccination sites. The loss of a familiar location to get vaccinated may have contributed to vaccine hesitancy and was noted in 10% of the responses from patients who refused vaccination.

Table 4. Patients Age 65+ Without Patient Portal Access Eligible for COVID-19 Vaccine: Outreach Characteristics

	Received Outreach		
	No	Yes	*P* value
Count (n = 1466)	802	664	
Sex			0.0300
Female	520 (64.8%)	466 (70.2%)	
Male	282 (35.2%)	198 (29.8%)	
Age			< 0.0001
Mean ± SD (minimum–maximum)	76.6 ± 8.4 (65.0 – 100.0)	74.5 ± 7.4 (65.0 – 97.0)	
Median (IQR)	75.0 (70.0 – 82.0)	73.0 (69.0 – 79.0)	
Race/Ethnicity			< 0.0001
Non-Hispanic White	357 (44.5%)	177 (26.7%)	
Non-Hispanic Black	395 (49.3%)	457 (68.8%)	
Hispanic	33 (4.1%)	23 (3.5%)	
Asian/Other	17 (2.1%)	7 (1.1%)	
Primary payor			0.1292
Medicare	722 (90.0%)	602 (90.7%)	
Medicaid	37 (4.6%)	40 (6.0%)	
Commercial	23 (2.9%)	9 (1.4%)	
Other/no insurance	20 (2.5%)	13 (2.0%)	
Social vulnerability index (SVI) status			< 0.0001
Low SVI < 0.75	379 (47.3%)	207 (31.2%)	
High SVI 0.75+	423 (52.7%)	457 (68.8%)	
Elixhauser Comorbidity Count			< 0.0001
Mean ± SD (minimum–maximum)	7.2 ± 4.6 (0.0 – 24.0)	8.3 ± 4.5 (0.0 – 22.0)	
Median (IQR)	6.0 (3.0 – 10.0)	8.0 (5.0 – 11.0)	
COVID-19 Vaccination			0.2341
No	316 (39.4%)	282 (42.5%)	
Yes	486 (60.6%)	382 (57.5%)	

Table 5. General Internal Medicine Patients Age 65+ Without Patient Portal Access Eligible for COVID-19 Vaccine – Vaccination Logistic Analysis (Primary Predictor: Received GIM Outreach)

	Univariate Model		Multivariable Model (Sex, Age, Race/Ethnicity)		Multivariable Model 2 (Model 1 + Payor, SVI)		Multivariable Model 3 (Model 2 + Comorbidity Count)	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Outreach		0.23		0.28		0.30		0.22
No	Ref		Ref		Ref		Ref	
Yes	0.88 (0.71 – 1.09)		0.89 (0.72 – 1.10)		0.89 (0.72 – 1.11)		0.87 (0.70 – 1.09)	

Through a separate qualitative analysis of the medical student experience providing this telephone outreach, medical student volunteers noted the importance of the "trusted messenger" role.[27] An additional hurdle of telephone outreach is that callers were cold-calling patients. Lacking a prior relationship with the patient may dramatically increase the difficulty of changing the mind of a patient who has concerns regarding vaccination.

It is also clear that telephone outreach alone will not eliminate structural barriers preventing vulnerable populations from getting vaccinated. There are many structural barriers to effective care for Black and vulnerable populations—especially in Milwaukee—including, but not limited to, structural racism, historical redlining, medical racism, health literacy, transportation, distance to health care facilities, health insurance, safety, finances, lack of sick and vacation time, and lack of childcare.[28-34] Telephone outreach only serves to create awareness of the vaccination opportunity and improve health literacy, while having minimal effect on the other aforementioned barriers. This would need to be addressed through other interventions.

Similar to our study—which showed that among people who declined the vaccine, 13% were worried about side effects and safety, 10% did not trust or believe in vaccines, and 9% wanted

more people to get vaccinated first—a survey of over 5 million people demonstrated that fear of side effects, not trusting the vaccine, not trusting the government, and waiting to see if vaccinations were safe were the primary reasons to not get vaccinated.[28] For Black, Latinx, Indigenous, and Asian American populations in this country, a long history of medical mistreatment has resulted in a deep-seated generational mistrust of medicine and science.[29] Thus, the role of trusted messengers highlighted above may be minimal in relation to the myriad other structural barriers our patients face toward equitable health care.

For many of our patients, the specific ZIP code in which they live in Milwaukee directly affects their health.[30] Due to historical redlining—discriminatory practices of denying minority populations access to equal loan and housing opportunities—Milwaukee is one of the most segregated metropolitan areas in the United States.[31] Racially hypersegregated neighborhoods in Milwaukee led to lack of investment and infrastructure in predominately Black communities, directly resulting in worse educational opportunities and health care access and food deserts—all leading to worse health outcomes among many other persisting downstream effects. Not only does Milwaukee rank consistently worst or near-worst across 30 indicators of racial inequality and last on a composite index of Black community well-being,[32] inequalities for Milwaukee's Black communities are worse today than they were 40 or 50 years ago.[33]

Ensuring access to transportation or bringing vaccination directly into the communities is vitally important to achieving health equity. The local community did provide a few resources to mitigate these factors. Fire departments provided home visits to vaccinate homebound patients, but significant delays of up to a month reduced the service's efficacy toward lowering disparities. The city health department deployed mobile vaccination clinics and local vaccine clinics at schools throughout metropolitan Milwaukee that likely had an impact. However, more can be done. Improving these structures and systems in the city could have profound effects on population health. During efforts locally and nationally to improve vaccine access, it is crucial to not use vaccine hesitancy as a scapegoat for structural racism and mask the fundamental inequalities of vaccine access, putting the focus on the individual rather than the systems perpetuating inequality.

Successful interventions both in Milwaukee and around the United States took the vaccines directly into the communities where patients live, work, and play. Mobile units, pop-up clinics, and partnering with local faith-based organizations, barber shops, and sports teams all have been shown to be effective. Partnering with trusted individuals and organizations has proven to be an essential component of any community intervention.[34] These are important lessons that should be applied to any future public health equity-focused intervention.

In terms of achieving health equity, a limitation of telephone outreach is the obvious exclusion of patients without telephones. Despite standardization of our outreach and formal training, inter-interview differences in approach may have introduced additional variability in vaccine uptake. Limitations to our logarithmic analysis include a stark difference between the population without patient portal access that did and did not receive outreach—most notably in race/ethnicity ($P<0.0001$) and SVI status ($P<0.001$), with more non-Hispanic Black patients (68.8% vs 49.3%) and high SVI (68.8% vs 52.7%) (Table 4). This, in part, was an intended effect of the telephone outreach as some outreach days were dedicated to call non-Hispanic Black patients and those living in high SVI census tracks. Further, our study was completed at a single institution for a single type of preventive health outreach; thus, data may not be applicable to other health equity focuses or other locations or health systems.

CONCLUSIONS

Our study attempted to address COVID-19 vaccination patient portal health disparities through telephone outreach but was not successful in increasing vaccination rates. Through our outreach program, we discovered vaccination site convenience, vaccine appointment scheduling, and cold-calling and lack of trust as significant barriers for vaccination. Through further reflection, we highlight the various ways in which effects of structural racism creates obstacles to vaccination and suggest solutions to overcome these obstacles. One of the most important lessons learned from our institutional and national efforts to achieve COVID-19 vaccination equity is the necessity of a multifaceted approach engaging not only health systems but also public health and community systems to directly address the pervasive effects of structural racism perpetuating health inequities.

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High but Inequitable COVID-19 Vaccine Uptake Among Rehabilitation Patients

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ABSTRACT

Introduction: There is a paucity of studies evaluating vaccine uptake in adults with neurological and musculoskeletal medical conditions. We sought to evaluate the rates of COVID-19 vaccine uptake in patients seen in an outpatient rehabilitation clinic.

Methods: We conducted a retrospective, single center study of adults seen at an outpatient rehabilitation clinic from December 1, 2020, through June 30, 2021, with an active Wisconsin Immunization Registry record. The primary outcome was completion of a COVID-19 primary vaccine series.

Results: Of 1362 patients, 83.3% completed a COVID-19 vaccination series. Younger patients had increased odds of not completing a COVID-19 vaccination series (mean [SD] 46.7 [14.7] vs 54.3 [15.8]; OR 1.03; 95% CI, 1.02-1.04; $P<0.001$). Those who identified as non-White (1.88; 95% CI, 1.16-3.04; $P=0.010$) or current smoker (1.85, 95% CI, 1.85-2.79; $P=0.004$) had increased odds of not completing a COVID-19 vaccination series. Those who resided in rural ZIP codes (1.81; 95% CI, 1.35-2.43; $P<0.001$), had not received a 2019-2020 influenza vaccine (5.13; 95% CI, 3.79-6.96; $P<0.001$), or had lower comorbidity scores (2.95; 95% CI, 1.98-4.41; $P<0.001$) had higher odds of not completing a COVID-19 vaccination series.

Conclusions: There was a high rate of COVID-19 vaccine uptake among patients seen in a rehabilitation clinic, though racial, ethnic, and geographic differences did exist. Further studies are needed to determine why these disparities exist and investigate interventions to increase vaccine uptake in these populations.

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INTRODUCTION

The COVID-19 pandemic led to important health and social implications for patients with neurological and musculoskeletal conditions, including restricted access to important health care services. Patients with a disability who were admitted with COVID-19 infection had longer hospital stays and higher readmission rates compared to those without disabilities.[1]

Physiatrists and other physicians who treat people with neurological and musculoskeletal conditions across their lifespans form relationships with patients while focusing on preserving and maximizing function and participation in the community. They advocate for their patients, and discuss optimizing health, including being up to date with their health maintenance. Thus, these physicians should play a pivotal role in strongly recommending a COVID-19 vaccine primary series and appropriate boosters to their patients.

The National Institutes of Health (NIH) defines health care disparities as preventable differences in health status and outcomes that adversely affect certain populations. Research on health care disparities examines the influence of environment, social determinants, and other underlying mechanisms leading to differences in health outcomes.[2] Health care disparities are found in patients with neurological and musculoskeletal conditions commonly seen by physiatrists. Racial health disparities disproportionately affect Black persons in access and referrals to rehabilitation, community reintegration, and overall functional outcomes in those with neurorehabilitation and musculoskeletal

conditions in the United States. This may result in worse outcomes in patients with neurological and musculoskeletal diagnoses, including greater physical activity limitations in patients with stroke, more recurrent urinary tract infections and pressure injuries in patients with spinal cord-injured, and greater postoperative complications and mortality after joint arthroplasty and hip fractures.[3]

Racial, ethnic, and socioeconomic disparities in COVID-19 vaccine uptake exist within the general population.[4-6] It also has been shown that geographic disparities exist in COVID-19 vaccine uptake, with people who reside in a rural ZIP code being less likely to have completed a COVID-19 vaccine primary series.[7] Furthermore, a study from the Centers for Disease Control and Prevention (CDC) showed adults with a disability had lower COVID-19 vaccine uptake compared to those without a disability, even though those with a disability reported less hesitancy to vaccination.[8]

There is a paucity of studies evaluating adult vaccine uptake in patients seen in a rehabilitation clinic; one retrospective chart review of 60 patients with spinal cord injury reported that only 55% had received an influenza vaccine, though recommendations for the general population and spinal cord injury guidelines specifically recommend immunization for all patients.[9] Physicians of all specialties often see patients with physical and cognitive disabilities and should be aware of potential barriers to vaccination.

The aim of our study was to evaluate the rates of COVID-19 vaccine uptake in adult patients with neurological or musculoskeletal chronic medical conditions who are commonly seen in a rehabilitation clinic. We hypothesized that racial, ethnic, and geographic disparities in COVID-19 vaccine uptake would exist among our patients.

METHODS

Study Setting

We performed a retrospective, single center study evaluating COVID-19 vaccine uptake among adults seen at an outpatient rehabilitation clinic from December 1, 2020, through June 30, 2021. The study met the requirement for quality improvement as determined by the University of Wisconsin-Madison and, therefore, was deemed exempt from Institutional Review Board review.

Study Population and Design

An electronic health record (EHR) (EPIC Corporation, Verona, Wisconsin) query was performed to identify patients meeting the following inclusion criteria: age 18 years and older and seen by a physiatrist during the study period. Patients were excluded if they had an inactive Wisconsin Immunization Registry (WIR) record and/or residence outside Wisconsin. Unvaccinated patients who died during the study period also were excluded since they may not have had an opportunity to complete a COVID-19 primary series.

Sociodemographic characteristics, Charlson Comorbidity Index (CCI), receipt of influenza vaccine (2019-2020 season), and receipt of COVID-19 vaccine (including vaccine type) were manually abstracted from the EHR. Scores from the CCI are based on a number of comorbidities, each given a weighted integer from 1 to 6 based on the severity of the morbidity.[10] Patients were classified into groups based on their primary rehabilitation diagnosis: stroke, spinal cord injury, brain injury (including traumatic, nontraumatic, and developmental/intellectual disability), multiple sclerosis, and other. Guardianship was determined by the presence of an activated health care power of attorney, which was abstracted from the patient's chart.

Sociodemographic classification included patient age, sex, race, ethnicity, and ZIP code of permanent residence at the time of data collection. Race was defined using the existing structure of the EHR data as self-identified by the patient, where White, Black, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander race are defined categorically, and Hispanic ethnicity is a modifier. Given the small sample size of certain racial and ethnic groups, patients were aggregated into 2 larger cohorts: non-Hispanic White patients and all racial and ethnic groups except non-Hispanic White patients.

Using ZIP codes, the cohort was divided into urban (population ≥10 000) or rural (population <10 000).[11] We excluded ZIP codes that are nonresidential (eg, only post office box or commercial organization addresses), ZIP codes with populations less than 500, or those located outside of Wisconsin. To further investigate disparities within rural and urban communities, we used a novel rural-urban geodisparity model that includes 6 categories (rural underserved, rural, rural advantaged, urban underserved, urban, and urban advantaged) that incorporate information on regional health care capacity and health needs in Wisconsin ZIP Code Tabulation Areas. The categories were determined using rates of poverty, uninsured, Medicaid, educational attainment, access to health care providers, and perceived health status.[11] The Wisconsin ZIP Code Tabulation Areas and their corresponding categories are available at https://www.hipxchange.org/RuralUrbanGroups.

Wisconsin Immunization Registry

The WIR is a statewide computerized Internet database that was developed to record and track immunization records of Wisconsin residents. The WIR is provided by the Wisconsin Department of Health and Family Services and has been available since May 2000.[12] Immunization history was back-loaded from January 1995. Immunizations provided by both public and private providers in Wisconsin are uploaded into the registry, and 98.5% of Wisconsin adults have an active WIR record.[13] Studies have demonstrated that the WIR captures 97% of vaccines administered in Wisconsin.[14] It is directly incorporated into the University of Wisconsin Hospital and Clinics EHR.

The WIR has been used previously in other studies to evaluate influenza and COVID-19 vaccine uptake in other patients seen in specialty clinics.[15,16]

Outcomes

Our primary outcome was to evaluate the rates of completing a COVID-19 primary series in adults with neurological and musculoskeletal conditions commonly seen in a rehabilitation clinic. We considered those who had completed a COVID-19 primary series if they had received 2 doses of an mRNA vaccine – BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) – or 1 dose of Ad26.COV2.S, the Janssen adenovirus vector-based vaccine. Secondary outcomes included evaluating disparities in completing a COVID-19 series in relation to race, ethnicity, guardianship, geographic area of residence, past influenza vaccination uptake, insurance, and diagnosis.

Statistical Analysis

Data for those who were fully vaccinated and those who were not fully vaccinated were summarized by N (%), mean (SD), or median (IQR). Rate of COVID-19 vaccine uptake was estimated by percentage and 95% CI. Secondary outcomes of association between patient characteristics and vaccine status were assessed via univariable logistic regression and summarized by odds ratio (OR) and 95% CI. All analyses were conducted in R for statistical computing version 4.0 (R Core Team, 2020) and a 5% significance level.

RESULTS

We identified 1362 patients who met the inclusion criteria. Most identified as female (55.9%), non-Hispanic (97.1%), and White (91.1%) (Table 1); and most were fully vaccinated: 1134/1362 (83.3%) completed a COVID-19 vaccination series, including 1045 (92.2%) who received an mRNA vaccine.

Predictors for Not Completing a COVID-19 Vaccine Series

Younger individuals had increased odds, per year younger, of not completing a COVID-19 vaccine series (mean 46.7 vs 54.3; OR 1.03; 95% CI, 1.02-1.04; $P < 0.001$). Those with a lower comorbidity score also had increased odds of not completing a COVID-19 vaccine series when compared to CCI greater than 2 (CCI 1-2: OR 2.20; 95% CI, 1.57-3.09; $P < 0.001$ and CCI 0: OR 2.95; 95% CI, 1.98-4.41; $P < 0.001$). There was a significant increase in the odds of not completing a COVID-19 vaccine series in non-White patients compared to White patients (OR 1.88; 95% CI, 1.16-3.04; $P = 0.010$) and current smokers compared to never smokers (OR 1.85; 95% CI, 1.22-2.79, $P = 0.004$). Additionally, the odds of not completing a COVID-19 vaccine series for those who did not receive a 2019-2020 flu vaccine were over 5 times higher (OR 5.13; 95% CI, 3.79-6.96; $P < 0.001$). See Table 2.

Table 1. Baseline Demographics

	Full Cohort (N = 1362)
Age (mean+ SD)	53.0 + 15.9
Female	762 (55.9%)
Race	
American Indian/Alaskan Native	8 (0.6%)
Asian	20 (1.5%)
Black	66 (4.8%)
White	1241 (91.1%)
Native Hawaiian/Pacific Islander	1 (0.1%)
Other	26 (1.9%)
Ethnicity	
Hispanic/Latino	40 (2.9%)
Charlson Comorbidity Index: median (IQR)	2.0 (1.0 – 4.0)
0	225 (16.5%)
1-2	545 (40.0%)
>2	592 (43.5%)
Insurance	
Private/HMO	604 (44.3%)
Medicare/Medicaid	739 (54.3%)
Uninsured	10 (0.7%)
Other	9 (0.7%)
Smoking status	
Never	771 (57.6%)
Former	410 (30.1%)
Current	157 (11.5%)
Guardianship	
Own Guardian	1181 (86.7%)
Urban Area Total (N = 12 excluded) [†]	942 (69.2%)
Urban underserved	48 (3.5%)
Urban	121 (8.9%)
Urban advantaged	773 (56.8%)
Rural underserved	35 (2.6%)
Rural	245 (18.0%)
Rural advantaged	128 (9.4%)
Diagnoses	
Stroke	128 (9.4%)
Spinal Cord Injury	113 (8.3%)
Brain Injury	302 (22.2%)
Multiple Sclerosis	55 (4.0%)
Other	764 (56.1%)
Influenza vaccine uptake (2019-2020)	892 (65.5%)
COVID-19 vaccine uptake	1134 (83.3%)
mRNA vaccine	1045 (92.2% of vaccinated)

[a]12 patients were excluded from the urban-rural subgroupings because they lived in a location with a population <500 or had a post office box as an address.

Geographic Disparities

Most patients resided in urban areas (n = 942, 69.8%) and advantaged areas (n = 901, 66.7%), but geographic disparities in completing a COVID-19 vaccine series existed. Those who resided in a rural ZIP code had an 81% increase in odds of not completing a COVID-19 vaccine series compared to those in an urban ZIP code (OR 1.81; 95% CI, 1.35-2.43; $P < 0.001$). Those residing

in urban, urban underserved, rural advantaged, or rural underserved areas had significantly higher odds of not completing a COVID-19 vaccine series compared to those living in an urban advantaged area ([urban: OR 2.26; 95% CI, 1.40-3.63; $P = 0.001$]; [urban underserved: OR 2.78; 95% CI, 1.42-5.46; $P = 0.003$]; [rural advantaged: OR 1.91; 95% CI, 1.18-3.10; $P = 0.009$]; [rural: OR 2.17; 95% CI, 1.50-3.15; $P < 0.001$]; [rural underserved: OR 3.91; 95% CI, 1.88-8.13; $P < 0.001$]). See Table 2.

Table 2. Predictors of Completion of a COVID-19 Series

	Completed COVID-19 Vaccine Series[a] (n = 1134)	Did Not Complete COVID-19 Vaccine Series (n = 228)	Odds Ratio (95% CI)	*P* value
Age per year younger	54.3 ± 15.8	46.7 ± 14.7	1.03 (1.02 – 1.04)	< 0.001
Female	634 (55.9%)	128 (56.1%)	1.01 (0.76 – 1.34)	0.949
Race				
White	1043 (92.0%)	198 (86.8%)	reference	
Non-White	70 (6.2%)	25 (11.0%)	1.88 (1.16 – 3.04)	0.010
Ethnicity				
Hispanic/Latino	33 (2.9%)	7 (3.1%)	reference	
Non-Hispanic	1091 (96.2%)	215 (94.3%)	0.93 (0.41 – 2.13)	0.862
Insurance				
Private/HMO	490 (43.2%)	114 (50.0%)	reference	
Medicare/Medicaid	634 (55.9%)	105 (46.1%)	0.71 (0.53 – 0.95)	0.022
Uninsured	5 (0.4%)	5 (2.2%)	4.30 (1.22 – 15.10)	0.023
Other	5 (0.4%)	4 (1.8%)	3.44 (0.9 – 13.01)	0.069
Smoking status				
Never	648 (57.1%)	124 (53.4%)	reference	
Former	343 (30.2%)	67 (29.4%)	1.02 (0.74 – 1.41)	0.901
Current	117 (10.3%)	41 (18.0%)	1.83 (1.22 – 2.74)	0.003
Guardianship				
Own guardian	982 (86.6%)	199 (87.3%)	reference	
Not own guardian	152 (13.4%)	29 (12.7%)	0.94 (0.62 – 1.44)	0.781
Influenza vaccination 2019-2020				
Yes	816 (72.0%)	76 (33.3%)	reference	
No	318 (28.0%)	152 (66.7%)	5.13 (3.79 – 6.96)	< 0.001
Diagnoses				
Stroke	107 (9.4%)	21 (9.2%)	reference	
Spinal cord injury	93 (8.2%)	20 (8.8%)	1.10 (0.56 – 2.15)	0.790
Brain injury	253 (22.3%)	49 (21.5%)	0.99 (0.56 – 1.73)	0.963
Multiple sclerosis	51 (4.5%)	4 (1.8%)	0.40 (0.13 – 1.22)	0.108
Other	630 (55.6%)	134 (58.8%)	1.08 (0.65 – 1.79)	0.754
Area of residence				
Urban Advantaged	682 (60.1%)	91 (40.0%)	reference	
Urban	93 (8.2%)	28 (12.3%)	2.26 (1.40 – 3.63)	0.001
Urban Underserved	35 (2.8%)	13 (5.7%)	2.78 (1.42 – 5.46)	0.003
Rural Advantaged	102 (9.0%)	26 (11.4%)	1.91 (1.18 – 3.10)	0.009
Rural	190 (16.8%)	55 (24.1%)	2.17 (1.50 – 3.15)	< 0.001
Rural Underserved	23 (2.0%)	12 (5.3%)	3.91 (1.88 – 8.13)	< 0.001
Urban vs rural				
Urban	810 (71.4%) 71.4%?	132 (57.9%)	reference	
Rural	315 (27.8%) 27.8%?	93 (40.8%)	1.81 (1.35 – 2.43)	< 0.001
Charlson Comorbidity Index (CCI)				
Per unit decrease	2.0 (1.0 – 4.0)	2.0 (0.8 – 3.0)	1.23 (1.14-1.33)	< 0.001
CCI Grouped				
> 2	531 (46.8%)	61 (26.8%)	reference	
1 – 2	435 (38.4%)	110 (48.2%)	2.20 (1.57-3.09)	< 0.001
0	168 (14.8%)	57 (25.0%)	2.95 (1.98-4.41)	< 0.001

Abbreviations: HMO, health maintenance organization.

[a]We considered those who had completed a COVID-19 primary series if they had received 2 doses of an mRNA vaccine (BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna], or 1 dose of Ad26.COV2.S, the Janssen adenovirus vector-based vaccine.

DISCUSSION

To our knowledge, this is the first US study to describe COVID-19 vaccination rates in a rehabilitation population. Although we found high rates of COVID-19 vaccine uptake in our population, there were racial, ethnic, and geographic disparities. This finding is important because it suggests that physiatrists and other physicians who see patients with neurological and musculoskeletal conditions should consider race, ethnicity, and geographic location as important factors when optimizing education around vaccination, as well as when recommending COVID-19 vaccination and counseling on COVID-19 boosters.

Those who had not completed a COVID-19 vaccination series in this study population were more likely to be younger, identify as non-White, be a current smoker, and have a lower CCI. Additionally, patients who did not receive an influenza vaccine during the 2019-2020 vaccine season were less likely to receive a COVID-19 vaccine. Many of these factors are consistent with those reported for the COVID-19 vaccine uptake in the general population, which implies that these disparities are not unique to the rehabilitation population.[7,17]

We also found that geographic disparities existed in vaccination uptake. Patients who lived in rural areas of Wisconsin were less likely to get vaccinated than those living in urban areas. A recent CDC report showed that the prevalence of adults with

a disability in the United States is significantly higher in rural areas versus large metropolitan areas.[18] Studies prior to the pandemic have shown that health care disparities exist among people living in rural and urban areas. Those living in rural areas may have reluctance to seek health care due scarcity of services, lack of trained physicians, insufficient public transportation, or poor availability of broadband internet services.[19]

In addition to those living in rural areas, those living in underserved geographic locations in Wisconsin were less likely than those in urban advantaged areas to be vaccinated. People who live in underserved geographic location – whether rural or urban – may face barriers, such as lower access to transportation or medical care, as well as less flexibility in work schedules to access health care.

Our findings also showed racial and ethnic disparities in COVID vaccination rates in the rehabilitation clinic. Previous studies have shown that racial and ethnic disparities exist in the care provided to patients seen in a rehabilitation clinic.[3] Verduzco-Gutierrez et al addressed the intersection between race and disability during the COVID-19 pandemic and called for more research to identify gaps in care to this vulnerable population.[20] One such area to address the gaps in care may be in ensuring our patients are up to date with recommended adult vaccines, as illness prevention can be as important as treatment. A cross sectional study of over 140 000 patients hospitalized in the United States showed that people from racial and/or ethnic minority groups experienced higher COVID-19–associated hospitalization, intensive care unit admission, or in-hospital death during the first year of the US COVID-19 pandemic.[21] This further highlights the importance of prevention and improved access and education around the COVID-19 vaccination for these groups. These two interventions are key since several studies have shown that health care provider recommendations are strongly associated with a patient's receipt of vaccines.[22]

Our findings showed disparities in patients related to race, ethnicity, and geographic location. We advocate that physicians should be aware of these disparities and be prepared to discuss recommendations for COVID-19 vaccinations. Physiatrists often have ongoing health care relationships with their patients due to the chronic conditions they treat and can initiate the vaccination conversation, advocate for their patients, and address barriers to vaccination.

Bazan and Akgün reviewed racial/ethnic inequalities in COVID-19 illness and vaccination rates.[23] Suggested strategies to improve vaccination rates include improved access to vaccination sites, customized information regarding vaccination, and discussions with trusted community members, including medical professionals.[8,23] In a call to action for influenza vaccination for persons with disabilities, Peacock et al suggested that effective communication with people with disabilities and their caregivers and offering vaccinations in places where people with disabilities spend their time, such as where they live or work – often in congregate settings – may increase vaccination rates.[24] The CDC offers free online materials to ensure that people with disabilities are able to access COVID-19 vaccines, including pictorial storylines communicating about COVID-19 and vaccination, and a Disability Information and Access Line to connect callers to local services.[25] Physicians are familiar with partnering with other specialties, therapies, and community support agencies for their patients' care. Working with these groups to identify any barriers to vaccination, such as communication, scheduling a vaccination appointment, transportation, or discussions with guardians is possible from within a rehabilitation clinic setting.

Strengths and Limitations

Our study has several strengths that make our findings generalizable to other centers. We were able to verify vaccine uptake using a statewide immunization registry, whereas other vaccine coverage studies often rely on participant survey responses.[26,27] We used a novel rural-urban geodisparity model that incorporates information on health care resources and needs in different geographic settings. Utilization of this model showed significant variation in vaccination status both between overall rural and urban areas, as well as within the traditional binary rural and urban categories.

There were also several limitations to our study. Race and ethnicity were defined within the social constructs of the EHR, and some racial ethnic groups had relatively small numbers and, thus, were combined for the analysis. This unintentionally implies a generalized experience and may mask unique differences among various racial and ethnic groups. Other limitations included lack of documentation of whether patients were offered vaccines, reasons for incomplete vaccination schedule, and short study duration. Additionally, our study population likely overrepresented patients with adequate health insurance coverage, as being seen in clinic was among the inclusion criteria.

CONCLUSIONS

We found a high rate of COVID-19 vaccine uptake among patients seen in a rehabilitation clinic. However, we found racial/ethnic and geographic disparities in vaccine uptake. Further studies are needed to evaluate how to address these disparities in order to improve vaccine uptake in these populations.

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Uptake Rates of Three COVID-19 Vaccine Doses and Risk Factors for Incomplete Vaccination Among Patients With Inflammatory Bowel Disease Residing in Wisconsin: A Single-Center Cohort

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ABSTRACT

Introduction: Patients with inflammatory bowel disease on systemic corticosteroids may be at higher risk of adverse outcomes of COVID-19 infection, and vaccination is an essential preventive measure. Uptake of the original 2-dose COVID-19 messenger RNA (mRNA) primary vaccine series was previously high among patients with inflammatory bowel disease, while uptake of subsequent doses based on interval recommendations made by the Advisory Committee on Immunization Practice remains unknown. Herein, we evaluated uptake of 3 COVID-19 mRNA vaccine doses among patients with inflammatory bowel disease.

Methods: We performed a single-center, retrospective study evaluating COVID-19 vaccine uptake among adult patients with inflammatory bowel disease residing in Wisconsin who were seen at the University of Wisconsin Digestive Health Center. Vaccination status as of April 30, 2022, was verified in the Wisconsin Immunization Registry. A multivariable logistic regression was performed with the primary endpoint of receipt of 3 COVID-19 vaccine doses. Secondary outcomes included identification of demographic and clinical variables associated with incomplete vaccination.

Results: A total of 1012 patients were identified; 728 (71.9%) patients received 3 COVID-19 vaccine doses. Multivariable logistic regression revealed that younger age (odds ratio [OR] 1.02; 95% CI, 1.01–1.03; $P=0.001$), rural status (OR 3.44; 95% CI, 2.17–5.56; $P<0.001$), underrepresented minority status (OR 3.85; 95% CI, 1.89–7.69; $P<0.001$), and absence of influenza vaccination (OR 8.17; 95% CI, 5.41–12.33; $P<0.001$) were significantly associated with incomplete COVID-19 vaccination.

Conclusions: Receipt of 3 COVID-19 mRNA vaccine doses is high overall among patients with inflammatory bowel disease. Younger age, underrepresented race/ethnicity, rural status, and lack of influenza vaccination are associated with incomplete COVID-19 vaccination.

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INTRODUCTION

In the United States, 4 safe and effective vaccines are available that reduce incidence of COVID-19–related hospitalization and death: BNT162b2 (Pfizer-BioNTech, messenger RNA [mRNA]), mRNA-1273 (Moderna, mRNA), JNJ-78436735 (Janssen, viral vector), and NVX-CoV2373 (Novavax, protein subunit).[1] Gastroenterologists provide care for patients with varying degrees of immunosuppression, including patients with inflammatory bowel disease (IBD). Patients with IBD on systemic corticosteroids are at higher risk of severe COVID-19 (eg, intensive care unit admission, mechanical ventilation, death), and vaccination is important to prevent such outcomes.[2]

While COVID-19 vaccines are safe and well tolerated among patients with IBD, they are also effective.[3] Patients with IBD have demonstrated a 95% to 99% humoral immune response rate to a 2-dose COVID-19 mRNA vaccine series and a 100% response rate to 3 doses, and this immune response may be relatively blunted by anti-tumor necrosis factor (anti-TNF) therapy.[4–7]

Moreover, receipt of 3 COVID-19 vaccine doses has been shown to reduce risk of COVID-related hospitalization.[8,9] At the time of this study, the Advisory Committee on Immunization Practices (ACIP) had recommended a 3-dose primary mRNA vaccine series, followed by a booster mRNA vaccine dose 3 months thereafter for those who were considered moderately to severely immunosuppressed.[10] For patients with IBD, this definition includes those on antimetabolites (eg, methotrexate, thiopurines),

anti-TNFs, or systemic corticosteroids. For those who do not fulfill these criteria, the ACIP had otherwise recommended a 2-dose primary mRNA vaccine series followed by a booster mRNA vaccine dose 5 months thereafter.

COVID-19 vaccine uptake is an obvious but fundamental prerequisite to realize the benefits of vaccine-induced immunity and prevent adverse outcomes secondary to infection. Prior reports have established suboptimal uptake of non–COVID-19 vaccines within the IBD population.[11] A previous study analyzing a Wisconsin-based cohort of patients with IBD identified an 84% completion rate of the 2-dose primary series – the prior ACIP recommendation.[12] Significant disparities of age, gender, race/ethnicity, geography, and socioeconomic status with respect to vaccine uptake were identified. Vaccination patterns among US patients with IBD have not been formally evaluated since the advent of a 3-dose series and booster dose.

The purpose of this study was to evaluate COVID-19 vaccination patterns among patients with IBD. The primary outcome was receipt of 3 COVID-19 mRNA vaccine doses. We hypothesized that vaccine uptake would be high, with similar disparities as observed with the original 2-dose primary series.[12] Secondary outcomes included identification of demographic and clinical variables associated with incomplete vaccination.

METHODS

Study Design

We performed a single-center, retrospective study evaluating uptake of 3 COVID-19 vaccine doses among adult patients with IBD. Our cohort comprised patients with IBD who were seen initially at the University of Wisconsin Digestive Health Center from November 1, 2020, through April 30, 2021, as first described in our prior report pertaining to the original 2-dose primary series.[12] In-person, video, and telephone visits were considered eligible encounter types. Exclusion criteria included death during study period, inactive Wisconsin Immunization Registry (WIR) record, residence outside the state of Wisconsin, and address listed as a post office box or correctional center.

Data Collection

Manual chart review was performed and completed by April 30, 2022. The following general variables were extracted from the electronic medical record: age, gender, race, ethnicity, address, smoking status, body mass index (BMI), variables of Charlson Comorbidity Index (CCI), and addressal of patient COVID-19 vaccination status by the provider as documented in the encounter note. Disease-specific data included type and duration of IBD, history of IBD-related surgery (eg, incision and drainage, bowel resection), and current IBD-directed therapy.

Underrepresented minority (URM) was defined as Black, Native Hawaiian/Pacific Islander, American Indian/Alaska Native, Hispanic/Latino. ZIP codes were assigned to 1 of 6 rural-urban geodisparity categories using the Health Innovation Program toolkit: urban advantaged, urban, urban underserved, rural advantaged, rural, or rural underserved.[13] Street-level addresses were used to assign 2018 area deprivation index (ADI) using the Neighborhood Atlas.[14] COVID-19 vaccination was considered addressed by the provider if there was documentation of COVID-19 vaccination status in a clinic encounter note (eg, "fully vaccinated against COVID-19," "declines COVID-19 vaccine").

Wisconsin Immunization Registry

Influenza (2021–2022 season) and COVID-19 vaccination (including number of doses, respective dates, vaccine manufacturer), or absence thereof, were verified in the WIR. Vaccination status was assessed as of April 30, 2022. As previously described, the WIR is a statewide, electronic database that documents immunization records of Wisconsin residents.[15] The WIR captures 97% of vaccines administered in the state, including data from both public and private providers, and 98.5% of Wisconsin residents have an active WIR record. The WIR does not capture vaccines administered outside the state of Wisconsin; for this reason, residents of other states were excluded from the study. All vaccine providers are required to enter COVID-19 vaccine administration into the WIR, which is directly incorporated into our institution's electronic medical record. At the time of this study, influenza and COVID-19 vaccines were available at University of Wisconsin clinics through primary care or immunization clinics, in addition to private pharmacies. While influenza vaccines were available, COVID-19 vaccines were not available at the University of Wisconsin Digestive Health Center.

OUTCOMES

The primary outcome was defined as receipt of 3 COVID-19 mRNA vaccine doses or the viral vector equivalent. Three doses may represent completion of the 3-dose primary series in those who are moderately to severely immunosuppressed or completion of the 2-dose series plus booster dose in non-immunosuppressed patients. Moderate-to-severe immunosuppression as defined by the ACIP includes patients on antimetabolites (eg, methotrexate, thiopurines), anti-TNFs, or systemic corticosteroids. Systemic immunosuppression was defined as administration of antimetabolites, anti-TNFs, ustekinumab, tofacitinib, and systemic corticosteroids as previously described.[7] The 3-dose viral vector equivalent was defined as receipt of (1) initial 2-dose mRNA vaccine series followed by a viral vector dose, (2) initial viral vector dose followed by an mRNA vaccine dose, or (3) initial viral vector dose followed by a subsequent viral vector dose. Secondary outcomes included identification of variables associated with incomplete vaccination, such as demographic (eg, age, gender, race/ethnicity, urban-rural status), clinical (eg, duration of IBD, type of IBD-directed therapy), and vaccine-related (eg, influenza vaccination) variables.

Table. COVID-19 Vaccination Status Organized by Characteristic Data

	<3 Doses[a] (n = 284)	3 Doses[a] (n = 728)	*P* value
Demographic Data			
Age [years]: median (IQR)	38 (28 – 52)	49 (36 – 64)	< 0.001
Gender [male]: n (%)	166 (58.5)	369 (50.7)	0.023
Race: n (%)			
American Indian/Alaska Native	0 (0.0)	7 (1.0)	< 0.001
Asian	3 (1.1)	12 (1.6)	
Black	21 (7.4)	14 (1.9)	
Native Hawaiian/Pacific Islander	0 (0.0)	1 (0.1)	
White	250 (88.0)	689 (94.6)	
Unspecified	10 (3.5)	5 (0.7)	
Hispanic/Latino: n (%)	10 (3.5)	9 (1.2)	< 0.001
Underrepresented minority[b]: n (%)	30 (10.6)	29 (4.0)	< 0.001
Rural-urban geodisparity category: n (%)			
Rural	110 (38.7)	192 (26.4)	< 0.001
Underserved	18 (6.3)	39 (5.4)	0.210
Area deprivation index: median (IQR)	4 (2-5)	2 (1-4)	< 0.001
Clinical data			
BMI: median (IQR)	26.6 (23.6 – 31.5)	26.6 (23.4 – 30.8)	0.640
Smoking: n (%)			
Never	188 (66.2)	454 (62.4)	0.310
Current	20 (7.0)	45 (6.2)	
Former	75 (26.4)	228 (31.3)	
Unspecified	1 (0.4)	1 (0.1)	
CCI: median (IQR)	0 (0 – 1)	1 (0 – 3)	< 0.001
Clinic appointments [2021]: median (IQR)	1 (1 – 2)	1 (1 – 2)	0.520
Crohn's disease: n (%)	148 (52.1)	400 (54.9)	0.420
Duration of IBD [y]: median (IQR)	10 (5 – 17)	12 (6 – 22)	< 0.001
Prior IBD surgery: n (%)	73 (25.7)	218 (29.9)	0.180
IBD-directed therapy: n (%)			
No therapy	28 (9.9)	60 (8.2)	0.160
Mesalamine monotherapy	60 (21.1)	207 (28.4)	
Vedolizumab monotherapy	19 (6.7)	56 (7.7)	
Vedolizumab combination therapy	1 (0.4)	4 (0.5)	
Azathioprine or mercaptopurine monotherapy	19 (6.7)	6 (0.8)	
Methotrexate monotherapy	1 (0.4)	2 (0.3)	
Anti-TNF monotherapy	88 (31.0)	194 (26.6)	
Anti-TNF combination therapy	21 (7.4)	50 (6.9)	
Ustekinumab monotherapy	14 (4.9)	30 (4.1)	
Ustekinumab combination therapy	1 (0.4)	3 (0.4)	
Tofacitinib therapy	1 (0.4)	8 (1.1)	
Systemic corticosteroid therapy	31 (10.9)	46 (6.3)	
Vaccination Data			
Influenza vaccination [2021-22]: n (%)	87 (30.6)	582 (79.9)	< 0.001
COVID-19 vaccine provider addressal: n (%)	93 (32.7)	246 (33.8)	0.750

Abbreviations: IBD, inflammatory bowel disease; BMI, body mass index; CCI, Charlson Comorbidity Index; TNF, tumor necrosis factor.

[a]Number of mRNA vaccine doses received, or viral vector equivalent

[b]Black, Native Hawaiian/Pacific Islander, American Indian/Alaska Native, Hispanic/Latino.

Statistical Analysis

In urban-rural analyses, pooled urban advantaged, urban, and urban underserved categories were compared to pooled rural advantaged, rural, and rural underserved categories. In advantaged-underserved analyses, pooled urban advantaged and rural advantaged categories were compared to pooled urban underserved and rural underserved, with urban and rural categories being excluded. Mann-Whitney U test, *t* test, and chi-square test were used for statistical analyses. A multivariable logistic regression was performed with the primary endpoint of receipt of 3 doses, which incorporated the following variables: age, gender, URM status, advantaged/underserved status, urban-rural status, ADI, BMI, smoking status, CCI, type of IBD, duration of IBD, systemic immunosuppression, moderate-to-severe immunosuppression, COVID-19 vaccine addressal by provider, and influenza vaccination. A P value < 0.05 was considered significant. Statistical analysis was performed using IBM Statistical Product and Service Solutions version 27 (IBM Corp, Armonk, New York).

Ethics

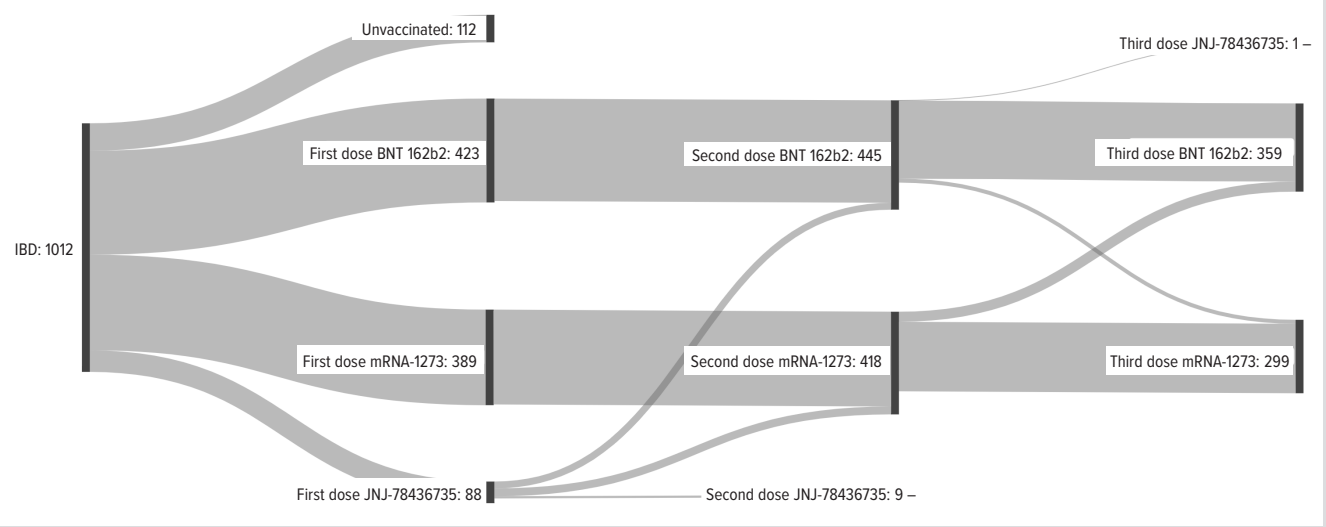
The study met the requirements for quality improvement as determined by the University of Wisconsin-Madison and was, therefore, deemed exempt from Institutional Review Board review.

RESULTS

A total of 1012 patients were identified (Table). Eight hundred ninety-one (88.0%) patients received the equivalent of 2 COVID-19 mRNA vaccine doses, and 728 (71.9%) patients received the equivalent of 3 doses (Figure). Five hundred twenty-nine patients were moderately to severely immunosuppressed. Three hundred sixty-seven (69.4%) immunosuppressed patients and 361 (74.7%) non-immunosuppressed patients received 3 doses ($P = 0.058$). The median time between doses 2 and 3 for immunosuppressed and non-immunosuppressed patients was 207 days (IQR 162-237) and 227 days (IQR 198–248), respectively ($P < 0.001$).

Among those who received more than 3 doses, compared to those who received 3 doses, the median age was lower (38 years [IQR 28-52] vs 49 years [IQR 36-64], $P < 0.001$), and there was a greater proportion of men (58.5% vs 50.7%, $P = 0.023$). Racial demographics were significantly different between both groups ($P < 0.001$), and among those who received less than 3 doses, there was a greater proportion of Hispanic/Latino patients (3.5% vs 1.2%, $P < 0.001$), URMs (10.6% vs 4.0%, $P < 0.001$), and rural patients (38.7% vs 26.4%, $P < 0.001$). The median ADI was higher among those who received less than 3 doses (4 [IQR 2-5] vs 2 [IQR 1-4], $P < 0.001$). Patients who received less than 3 doses had a shorter median duration (years) of IBD (10 [IQR 5-17] vs 12 years [IQR 6-22], $P < 0.001$), lower median CCI (0 [IQR 0-1] vs 1 [IQR 0-3], $P < 0.001$), and lower influenza vaccine uptake (30.6% vs 79.9%, $P < 0.001$). There was no difference in IBD-directed therapy as a whole ($P = 0.160$), but there was a trend

Figure. COVID-19 Vaccination Patterns in Patients With Inflammatory Bowel Disease (IBD)



Of the 88 initial viral vector recipients, 60 patients went on to receive an mRNA vaccine while 9 received another viral vector dose. Of the 803 patients who initially received 2 mRNA vaccine doses, 58 patients went on to do a mix/match strategy, one of whom pursued a viral vector vaccine.

(Figure created using SankeyMATIC.)

towards a greater proportion of patients with moderate-to-severe immunosuppression among those who received less than 3 doses (57.0% vs 50.4%, $P=0.058$). There was no difference in vaccine addressal by provider (32.7% vs 33.8%, $P=0.750$), which was low overall.

Multivariable logistic regression revealed that younger age (odds ratio [OR] 1.02; 95% CI, 1.01-1.03; $P=0.001$), rural status (OR 3.44; 95% CI, 2.17-5.56; $P<0.001$), URM status (OR 3.85; 95% CI, 1.89-7.69; $P<0.001$), and absence of influenza vaccination (OR 8.17; 95% CI, 5.41-12.33; $P<0.001$) were significantly associated with incomplete COVID-19 vaccination. The following variables did not contribute to the model: gender, advantaged/underserved status, ADI, BMI, smoking status, CCI, type of IBD, duration of IBD, systemic immunosuppression, moderate-to-severe immunosuppression, and COVID-19 vaccine addressal by provider.

DISCUSSION

This is the first US study to formally evaluate COVID-19 vaccine uptake in patients with IBD since the inception of the 3-dose series and booster dose. Vaccine uptake was again high, with 71.9% of our patient population receiving 3 doses. However, this rate is slightly lower than the 88% we observed for 2 doses, indicating that a relatively small subset of patients who did not receive interval doses exists, despite updated ACIP recommendations.[12] Moreover, in the approximate 1 year that passed between our initial study and this study, 2-dose uptake increased only from 84% to 88%. This small interval increase may indicate that most patients who intend to get vaccinated have done so already.

Basic statistical analyses identified the following variables as being associated with incomplete vaccination: age, gender, URM status, rural status, ADI, CCI, duration of IBD, and influenza vaccination. However, only the following variables remained significantly associated with incomplete vaccination following multivariable logistic regression: age, URM status, rural status, and influenza vaccination. These determinants of incomplete vaccination are similar to those reported in our initial study evaluating uptake of the original 2-dose primary series.[12] Additionally, these variables mirror risk factors observed at the national level with respect to the general population.[16–18]

While lower CCI and shorter duration of IBD were associated with incomplete vaccination using basic statistical analyses, this finding is likely the effect of confounding—we suspect due to age—given that these variables were no longer associated with vaccination following multivariable logistic regression, while age as a variable maintained statistical significance. Basic analyses also demonstrated a trend toward incomplete vaccination among those considered moderately to severely immunosuppressed; however, neither systemic immunosuppression nor moderate-to-severe immunosuppression significantly contributed to the multivariable logistic regression model. As we described previously, influenza vaccine uptake was again associated with COVID-19 vaccine uptake.[12] Addressal of COVID-19 vaccination status in a clinical note was found in only one-third of cases and was not associated with vaccination status; however, this lack of association may be an issue of statistical power given the relative infrequency of documented vaccine addressal.

While there is not yet published data describing uptake of 3 COVID-19 vaccine doses among patients with IBD in the US, similar work has been carried out elsewhere. Wellens et al

described uptake of a third COVID-19 vaccine dose among 733 patients with IBD receiving infliximab or vedolizumab at their 2 centers.[19] They found an uptake rate of 79.1%, with younger age, Crohn's disease, non-White ethnicity, and low socioeconomic status being associated with incomplete vaccination. These findings are similar to ours in that we both identified age and race/ethnicity to be a predictor of vaccination. However, we did not find type of IBD to be associated with vaccine uptake. Kuenzig et al, analyzing 107 059 patients with IBD residing in Ontario, Canada, reported a third dose uptake rate of 58.3%, with younger age being associated with incomplete vaccination.[20] While a significant strength of this study was the large sample size, it did not include relevant clinical information, such as medications. Finally, it should be noted that differences in vaccine uptake may be related to study timing relative to updated vaccine recommendations.

On September 1, 2022, the Centers for Disease Control and Prevention endorsed the ACIP's recommendation for vaccination with the updated bivalent COVID-19 booster for all adults.[21] Bivalent vaccines have been shown to reduce both incidence of COVID-related infection and death during Omicron circulation.[22] At the time of this manuscript preparation, according to Wisconsin Department of Health Services data, only 20.1% of eligible Wisconsin residents have received the bivalent booster, with similar disparities of age, gender, and race/ethnicity being observed.[23] At the national level, bivalent booster uptake has been reported as disproportionately low among underrepresented minorities and rural dwellers.[24] Some patient-cited reasons for incomplete vaccination have included lack of awareness of eligibility, perceived existing immunity from prior vaccination or infection, and concerns regarding safety, side effects, and efficacy.[25] While income and social vulnerability have been associated with incomplete vaccination, these variables are not associated with vaccine hesitancy, underscoring the importance of eliminating barriers to vaccine access at a structural level.[24] Finally, while provider recommendation is associated with increased bivalent booster vaccination rates, it is important to ensure that vaccine counseling is done consistently and in an equitable, systematic way.[24] In a recent study among unvaccinated adults "open" to vaccination, less than half received a provider recommendation for vaccination, and those who identified as "unsure" were even less frequently recommended vaccination.[24] Provider recommendation for vaccination in a culturally competent manner represents a practical and readily available intervention to increase vaccination rates in our patient population.

Both primary care physicians and gastroenterologists alike should address and strongly recommend COVID-19 vaccination to their patients with IBD, as doing so may improve vaccine uptake.[26] Vaccine addressal by the clinician has been shown previously to be positively associated with COVID-19 vaccine uptake.[27] Clinicians, including those caring for other immunosuppressed patient populations (eg, solid organ transplant, rheumatologic disease), may feel empowered to use our predictors of incomplete vaccination to identify patients who may benefit from additional discussion and education on the benefits of receiving a booster dose. Current trends suggest that implementation of updated boosters will become a regular occurrence, and, as such, integration of consistent and culturally competent vaccine messaging into the clinical workflow is apt to improve health outcomes and equity in our community.

Our study had several strengths. We included a large sample size of patients with IBD with a wide urban-rural geographic distribution, and we were able to confirm their vaccination status using a statewide immunization registry. Moreover, implementation of a multivariable logistic regression model allowed us to identify variables that were associated with incomplete vaccination. The study was limited in that it was a single-center, retrospective study that was not able to determine reasons for vaccine refusal nor accurately determine vaccine recommendations by providers. Moreover, the emphasis placed on vaccination at our center may have contributed to a relatively higher vaccination rate. Our academic center being located in an urban setting also likely contributed to our observed vaccination rate. We were also limited in the relatively small number of URMs in our patient population.

CONCLUSIONS

Receipt of 3 COVID-19 mRNA vaccine doses is high in patients with IBD. Younger age, underrepresented race/ethnicity, rural status, and lack of influenza vaccination are associated with incomplete COVID-19 vaccination. Further work is needed to evaluate uptake of additional doses and bivalent vaccine formulations, and there is a significant need for interventions to address disparities in vaccine uptake. Finally, COVID-19 vaccination, including administration of an updated booster dose, should continue to be addressed and recommended to our patients.

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The Burden of Neonatal Abstinence Syndrome, Opioids, and COVID-19 in Wisconsin

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ABSTRACT

Introduction: Wisconsin experienced overlapping and accelerating epidemics of opioid use and COVID-19 after March 2020. We hypothesized that Wisconsin neonatal abstinence syndrome rates increased after March 2020 alongside other markers of opioid burden.

Methods: Retrospective cohort analysis examined deidentified Wisconsin census, birth certificate, death certificate, hospital discharge, Prescription Drug Monitoring Program, emergency medical service run, and COVID-19 diagnosis records spanning January 1, 2019, through December 31, 2021. January 2019 through March 2020 was considered before the onset of COVID-19 (pre); April 2020 through December 2021 was considered post-onset of COVID-19 (post). Wisconsin Department of Health Services guidelines defined 5 Wisconsin regions. Rates pre- to post-onset were compared with P values < 0.05 considered statistically significant.

Results: From January 2019 through December 2021, 190 072 infants were born in Wisconsin, of which 1205 were diagnosed with neonatal abstinence syndrome. Statewide opioid-associated deaths, emergency medical service runs, and emergency department visits all increased from the pre- to post-onset periods. Per-person Prescription Drug Monitoring Program rates decreased in both the total population and childbearing-age females (15-44 years), and statewide deaths in childbearing-age females increased significantly ($P < 0.001$). Statewide monthly neonatal abstinence syndrome incidence rates did not change significantly (6.68/1000 births to 6.10/1000 births; $P = 0.16$) but decreased significantly in the most populous Southeastern Region (8.13/1000 births to 6.37/1000 births; $P = 0.02$) of the state.

Conclusions: Opioid-associated morbidity and mortality increased in Wisconsin during the study period, including among females age 15 to 44 years. Despite increased opioid burden, neonatal abstinence syndrome incidence decreased in the Southeastern Region. Ongoing neonatal abstinence syndrome and opioid analysis may benefit from region-based contextualization.

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INTRODUCTION

Neonatal abstinence syndrome (NAS) is a clinical syndrome affecting newborns who are prenatally exposed to substances – classically opioids – and who subsequently experience withdrawal symptoms after birth.[1] Rates of opioid use in pregnant people and rates of NAS in infants have increased with the accelerating opioid epidemic in the United States.[2,3] Substance use disorder significantly contributes to pregnancy-associated maternal morbidity and mortality.[4,5] In addition, newborns affected by NAS are more likely to experience prolonged hospitalizations, higher average medical costs, and increased readmission rates within 30 days of discharge.[6-8]

This at-risk population of mother-infant dyads has demonstrated unequal distribution across geography, race, and income, with neonates experiencing NAS presenting disproportionately from rural areas, lower incomes, and with public insurance.[9-11] Recent efforts to identify associations between county-level factors that increase community risk of opioid-associated health care events and NAS suggest associations with higher rates of mental health hospitalizations, mental health professional shortages, unemployment, property crime, and poverty, underscoring the connection between social determinants of health and opioid use.[12,13] This clustering of increased resource needs in areas of higher resource scarcity may amplify inequality in health care accessibility and utilization, thereby potentially compound-

ing the risks of the opioid epidemic – and other epidemics – to mother and infant.

Wisconsin historically has exhibited increasing maternal opioid use and NAS rates similar to trends seen nationally.[14] Wisconsin also has exhibited geographic variation in counties experiencing the burden of both the opioid epidemic and NAS incidence rates.[15] The most recent statewide summary of county rates of NAS was published in 2015, presenting county-level rates of NAS per 1000 births during 2009-2014. In that report, the state's northernmost counties experienced the highest NAS rates, despite the population centers concentrated in the Eastern and Southeastern Regions of the state.

In March 2020, the onset of the COVID-19 pandemic drastically changed how patients sought and received health care, including pregnancy-related care and opioid treatment. Treatment of opioid use disorder relies on regularly scheduled clinician-patient meetings and tight regulation of opioid agonist dispensation, which were heavily affected by social distancing protocols, decreased in-person clinic availability, and the expansion of telehealth.[16,17] COVID-19 also changed the experience of giving birth in the health care setting, including strict visitor guidelines, maternal rooming-in practices, and concerns with viral transmission and breastfeeding.[18,19] A 2022 study by Racine et al demonstrated that after the onset of COVID-19 in Wisconsin, an increased percentage of mothers presented in active labor, presented at or after 41 weeks, and mother-infant dyads had shorter hospital lengths of stay.[20] Nationally, the proportion of infants born outside of a hospital increased.[21]

Wisconsin observed an increase in the suspected opioid burden after the onset of the COVID-19 pandemic in the state.[22] Prior trends would suppose that this would cause an increase in opioid use among childbearing-age females and a subsequent increase in NAS infants. However, no studies have examined whether this association has been disrupted by changes in health care access and delivery caused by COVID-19.

This investigation aimed to identify if regional and statewide NAS incidence rates also changed after the onset of the COVID-19 pandemic in Wisconsin. We hypothesized that the burden of the opioid epidemic in Wisconsin increased after the onset of the COVID-19 pandemic, specifically among childbearing-age females (15-44 years), and that NAS incidence rates also increased.

METHODS

Study Design

This retrospective cohort analysis examined regional disease burdens of NAS and opioid use in Wisconsin before and after the onset of the COVID-19 pandemic. COVID-19 onset was defined as March 2020, corresponding with Wisconsin's first identified positive cases. January 2019 through March 2020 was considered prior to onset of COVID-19 (pre); April 2020 through December 2021 was considered post-onset of COVID-19 (post). This retrospective project was approved and informed consent was waived by the Medical College of Wisconsin Institutional Review Board and the Wisconsin Department of Health Services (DHS) Data Governance Board as there is no identification or interaction with subjects.

Deidentified data from January 1, 2019, through December 31, 2021, were obtained from databases administered by the Wisconsin DHS; totaled by month, year, and associated Wisconsin county; and aggregated by region for analysis. Data were excluded if a county association could not be identified. Five regions (Northern, Northeastern, Southeastern, Southern, and Western) were defined by DHS Region by County guidelines.[23] Regional aggregation prevented unintended identification of individuals when county counts were small, increased statistical reliability, and facilitated compliance with the DHS Data Governance Board recommendation for suppression of case counts less than 5.

Data Sources

Wisconsin Population: Overall population data for Wisconsin were obtained through the Wisconsin Interactive Statistics on Health portal.[24] These data are based on the yearly estimates provided for Wisconsin from the US Census Bureau. Variables of interest included year, county of residence, age, and sex. Childbearing-age females were defined as ages 15 to 44 years to maintain alignment with other maternal and child health literature.[24]

Birth Certificates: The birth certificate database is maintained by the Wisconsin Vital Records Office and includes all finalized birth certificates for Wisconsin residents. Extracted birth certificate variables included infant date of birth, maternal county of residence at time of birth, infant death at birth, and birth outside a health care facility, with less than 1% of records excluded for missing county information. The county of an infant's birth is ascribed to the maternal county of residence at the time of birth.

Death Certificates: The death records database also is maintained by the Wisconsin Vital Records Office, with coding of the underlying and contributing causes of death completed by the National Center for Health Statistics. Variables of interest included date of death, county of residence, age and sex at death, underlying or contributing causes of death, and pregnancy status at time of death. Infant mortality was defined as death prior to 1 year of age. Deaths were ascribed to the county of residence of the deceased. Two percent of records extracted from the death records database were excluded for missing county information.

Hospital Records: The hospital records database collects legally required billing documentation at the time of discharge from Wisconsin inpatient, emergency department (ED), surgery, or observational visits (Wis Stat § 153.05). Hospital discharge data are also collected from Iowa and Minnesota health care facilities for Wisconsin residents. Variables of visit included date of visit, county of residence, date of birth, sex, age at visit, and princi-

Table 1. Change in Wisconsin Population Characteristics Following COVID-19 Onset

Region (% population)	Statewide			Northern (8.4%)			Northeastern (21.6%)			Southeastern (36.6%)			Southern (19.8%)			Western (13.7%)		
Population Characteristics	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***
Population total	5 839 299	5 835 721		490 400	490 272		1 260 328	1 259 054		2 133 382	2 134 136		1 156 110	1 154 363		799 078	797 896	
Birth rate per 1000 persons	0.91	0.90	0.43	0.80	0.77	0.14	0.87	0.85	0.46	0.96	0.92	0.08	0.87	0.87	0.88	0.86	0.87	0.54
Death rate per 1000 persons	0.79	0.89	**0.004**[a]	0.93	1.06	**0.03**[a]	0.82	0.92	**0.03**[a]	0.77	0.88	**0.002**[a]	0.71	0.79	**0.02**[a]	0.78	0.89	**0.004**[a]
% Childbearing population (15-44 F)[b]	16.31%	16.33%	**<0.001**[a]	14.52%	14.54%	0.24	16.23%	16.25%	**0.03**[a]	18.54%	18.57%	0.13	16.23%	16.26%	**0.01**[a]	16.92%	16.93%	0.18
Infant deaths per 1000 births	5.82	5.47	0.38	5.36	5.63	0.84	7.04	4.81	**0.01**[a]	6.54	6.80	0.66	4.28	4.84	0.42	5.27	4.49	0.47
Births occurring outside a hospital per 1000	32.27	37.55	**<0.001**[a]	41.03	47.01	0.12	24.37	31.10	**<0.001**[a]	11.50	14.24	**0.001**[a]	47.19	50.90	0.14	80.89	88.10	0.06

[a]Denotes *P* value < 0.05

[b]Denotes unpaired *t* test with counties as unit (N).

Abbreviations: pre, prior to COVID-19 onset; post, post COVID-19 onsent; *P*, *P* value; y, year-old; F, females.

pal and diagnosis codes, with 4% of records excluded for missing county information. ED visits and hospitalizations were tallied by individual's county of residence.

Prescription Drug Monitoring Program (PDMP): The Wisconsin PDMP is a legally required administrative database that monitors the dispensation of controlled substances from pharmacies to Wisconsin residents (Wis Stat § 153.87). Variables of interest obtained from the Wisconsin PDMP database included date of dispensing, county of residence, age and sex at dispensing, and drug category (this analysis selected for opioids), with 2% of records excluded for missing county data. PDMP dispensations were attributed to the county of residence of the prescription recipient. Of note, buprenorphine- and methadone-containing prescription dispensations were not included. Additionally, monitoring of gabapentin began on September 1, 2021, in the Wisconsin PDMP. However, gabapentin is not classified as an opioid by the Wisconsin PDMP; thus, this change is assumed to have minimal impact on this opioid-focused analysis.[25]

Wisconsin Ambulance Run Data System (WARDS): WARDS gathers "emergency medical service (EMS) run" reports from first responders for all 911 call responses. EMS run reports describe preliminary treatment in the field, whether or not they resulted in transport or hospitalizations. Variables of interest included date of incident, county of incident, age and sex at incident, call type, primary and secondary complaint and impression, and incident narrative, with no excluded records. EMS runs were ascribed to the county where the incident occurred.

Wisconsin Electronic Disease Surveillance System (WEDSS): COVID-19 is a reportable condition in Wisconsin, meaning that all laboratory-confirmed cases and clinical diagnoses are legally required to be reported to WEDSS (Wis Stats § 252.05). These reports are then consolidated at the individual level so that the number of cases may be ascertained. Variables of interest included date of diagnosis, county of residence, and indicator of COVID-19. The county variable was required for receipt of the data, so it is not possible to determine how many cases were excluded; however, since it is a reportable condition, it may be that no cases were missing county information.

Variable Definitions

NAS: NAS cases were identified by querying statewide hospital inpatient discharge records for *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code P96.1 Neonatal Abstinence Syndrome, which is diagnosed within the first 28 days of life. Each unique infant was identified to ensure that infants experiencing multiple hospitalizations for NAS were not counted more than once. NAS cases were tallied by county of birth, which is based on county of residence of the mother listed on the birth certificate. Then, the incidence rate of NAS was calculated for each Wisconsin region by dividing the number of NAS cases by the number of total births occurring within that region within the identified time frame and reported as a rate per 1000 births.

Opioid Burden: The overall population burden of the opioid epidemic was characterized by multiple deidentified measures. PDMP data provided the number of opioid prescriptions dispensed by county of residence of recipient, which was then reported per 1000 persons residing in the county or region. Opioid poisoning or overdose was determined from inpatient and

Table 2. Change in Wisconsin Opioid Burden Following COVID-19 Onset

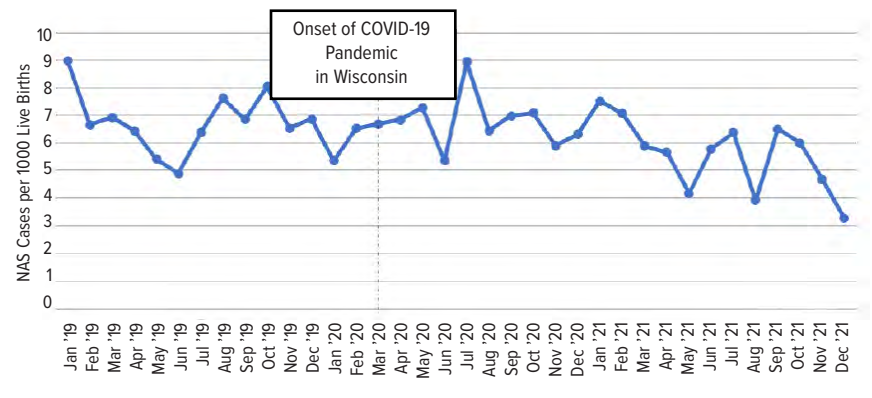
Region (% population)	Statewide			Northern (8.4%)			Northeastern (21.6%)			Southeastern (36.6%)			Southern (19.8%)			Western (13.7%)		
Opioid Burden	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***
Population total	5 839 299	5 835 721		490 400	490 272		1 260 328	1 259 054		2 133 382	2 134 136		1 156 110	1 154 363		799 078	797 896	
Opioid deaths per 1000 deaths	33.96	43.90	**<0.001[a]**	16.87	21.13	0.15	19.43	28.15	**<0.001[a]**	49.90	68.85	**<0.001[a]**	41.63	42.91	0.75	18.39	21.26	0.40
Opioid deaths per 1000 deaths in 15-44 y F	375.34	452.80	**0.03[a]**	249.85	229.61	0.82	230.65	463.43	**0.001[a]**	430.68	530.94	**0.04[a]**	502.09	429.17	0.24	215.46	317.57	0.14
Opioid ED rates per 1000 ED visits	1.47	1.93	**<0.001[a]**	1.00	1.17	0.15	0.90	1.70	**<0.001[a]**	1.78	2.04	0.10	1.97	2.73	**<0.001[a]**	1.00	1.39	**0.005[a]**
Opioid ED rates per 1000 ED visits in 15-44 y F	1.55	2.02	**0.002[a]**	1.56	1.87	0.24	1.04	2.18	**<0.001[a]**	1.67	1.80	0.52	1.99	2.73	**0.01[a]**	1.24	1.61	0.14
Opioid suspected EMS rates per 1000 EMS visits	11.25	14.75	**<0.001[a]**	7.08	9.04	**0.007[a]**	8.55	12.23	**<0.001[a]**	13.10	17.18	**<0.001[a]**	13.25	16.19	**0.01[a]**	7.85	10.55	**<0.001[a]**
Opioid suspected EMS rates per 1000 EMS visits in 15-44 y F	20.21	26.50	**<0.001[a]**	21.35	26.43	0.14	20.57	30.83	**<0.001[a]**	19.42	24.94	**<0.001[a]**	23.59	30.66	**0.004[a]**	18.57	22.83	0.08
Opioid inpatient rates per 1000 hospitalizations	2.04	1.93	0.25	1.60	1.43	0.26	1.65	1.49	0.34	2.49	2.43	0.66	2.24	1.86	**0.02[a]**	1.29	1.51	0.09
Opioid inpatient rates per 1000 hospitalizations in 15-44 y F	2.13	2.07	0.71	2.63	2.30	0.63	1.89	1.57	0.30	2.33	2.46	0.64	1.89	1.97	0.87	1.94	1.61	0.42
Averaged opioid prescriptions per 1000 persons	44.46	40.25	**<0.001[a]**	48.68	41.70	**<0.001[a]**	44.35	40.05	**<0.001[a]**	47.25	42.74	**<0.001[a]**	42.07	38.64	**<0.001[a]**	38.09	35.34	**<0.001[a]**
Averaged opioid prescriptions per 1000 persons in 15-44 y F	27.02	24.03	**<0.001***	29.87	26.60	**<0.001[a]**	28.73	25.65	**<0.001[a]**	28.05	24.55	**<0.001[a]**	25.78	13.32	**0.001***	21.82	19.79	**<0.001[a]**
NAS births per 1000 births	6.68	6.10	0.16	8.57	10.32	0.24	7.17	7.10	0.95	8.13	6.37	**0.02[a]**	4.78	4.74	0.97	4.48	4.54	0.94

[a]Denotes *P* value < 0.05.

Abbreviations: pre, prior to COVID-19 onset; post, post COVID-19 onset; *P*, *P* value; y, year-old; F, females; ED, emergency department; EMS, emergency medical services; NAS, neonatal abstinence syndrome.

ED hospital discharge data (ICD-10-CM code of T40.0-T40.4 or T40.6), death certificates (cause of death code X40-X44, X60-64, X85 or Y10-Y14 and an opioid use code in any of the contributing causes of death fields), and ambulance run data (suspected case defined by presence of key words within the incident narrative). The number of opioid-related EMS, ED, and inpatient visits was tallied by county and reported as a rate per 1000 of their respective events. Death certificates citing opioids were reported as a rate per 1000 death certificates from residents of that county or region.

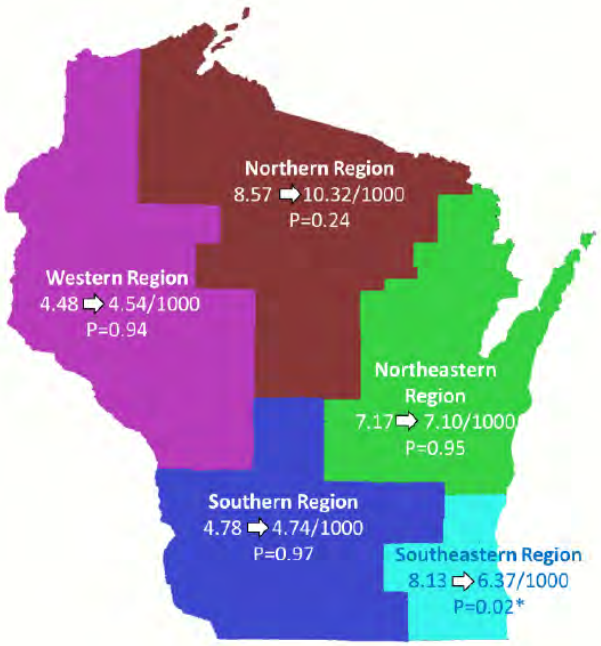
Figure 1. Neonatal Abstinence Syndrome (NAS) in Wisconsin, January 2019 – December 2021



Wisconsin statewide monthly rate of NAS decreased but did not significantly change January 2019 – March 2020 vs April 2020 – December 2021 (6.68 to 6.10 per 1000 births, *P* = 0.16).

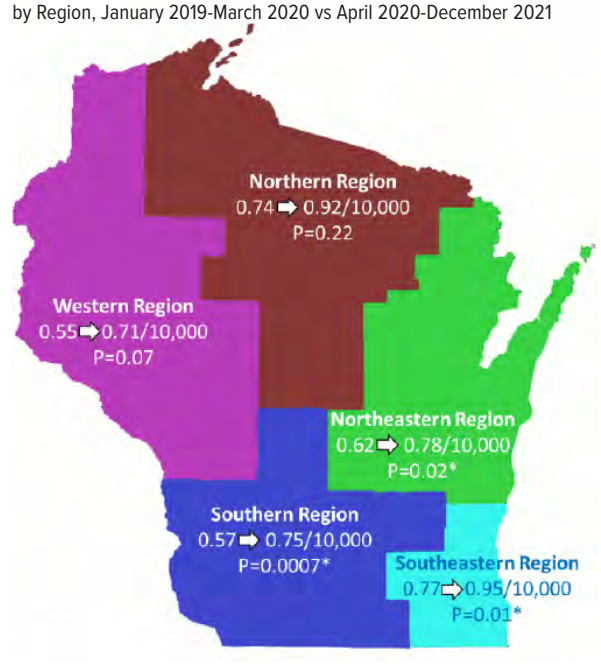
Figure 2. Regional Neonatal Abstinence Syndrome Incidence and All-cause Mortality Rates in Childbearing-Age Females

2A. Change in Regional rates of NAS in Wisconsin per 1000 Births, January 2019-March 2020 vs April 2020-December 2021



The statewide NAS rate did not significantly change (6.68 vs 6.10 per 1000 births $P=0.16$. P values obtained via unpaired t test.
*Denotes statistical significance of $P<0.05$.

2B. Average Rate of Death in Childbearing Age Females (Age 15-45 Years) per 10 000 Females of Childbearing Age in Wisconsin per Month by Region, January 2019-March 2020 vs April 2020-December 2021



Statewide death rates in this population increased from 0.67 to 0.84 per 10 000 ($P=0.0002$). P values obtained via unpaired t test.
*Denotes statistical significance of $P<0.05$.

COVID-19: COVID-19 cases were determined by surveillance reporting of laboratory findings of SARS-CoV-2 genetic material and death certificate coding. COVID-19 deaths were defined as those coded U071 in the underlying or contributing causes of death fields.

Statistical Analysis

Trends in outcomes were plotted over time at statewide and regional levels. Incidence rates of NAS and opioid burden were aggregated and averaged into monthly rates for the two periods (pre- and post-onset of COVID-19). The pre- and post-onset rates were considered independent and were then compared using t test with months as unit of analysis. The exception to this was in the percent childbearing-age population; as they are not completely independent, a paired t test was used with counties as the unit of analysis. P values <0.05 were considered statistically significant. The analysis utilized SAS version 9.4 (Cary, North Carolina).

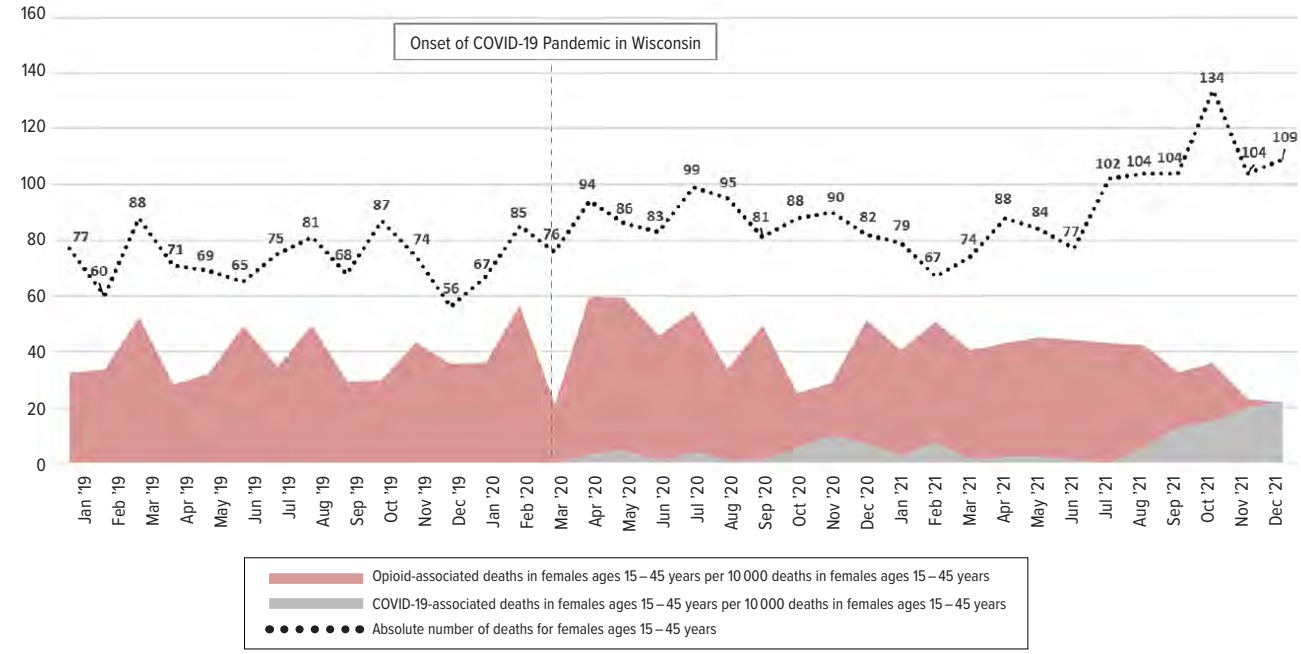
RESULTS

During the study period, 190 087 infants were born in Wisconsin, of which 1205 were diagnosed with NAS. Table 1 summarizes changes in statewide and regional population characteristics and birth rates following COVID-19 onset. Although the statewide birth rate did not change significantly during the study period, an increased proportion of births occurred outside of a health care facility (32.3 vs 37.6 per 1000 births, $P<0.001$).

The statewide total death rate increased significantly (0.79 to 0.89 deaths per 1000 persons, $P=0.004$), as did opioid-associated death rates (33.96 to 43.9 opioid-related deaths per 1000 deaths, $P<0.001$) (Table 2). However, statewide per-person PDMP opioid prescriptions decreased significantly (44.46 to 40.25 opioid prescriptions per 1000 persons, $P<0.001$), while the proportion of opioid-related EMS and ED visits increased (11.25 to 14.75 opioid-related EMS visits per 1000 EMS visits, $P<0.001$; 1.47 to 1.93 opioid-related ED visits per 1000 ED visits, $P<0.001$). Similarly, among the subgroup of childbearing-age, there was a significant increase in statewide opioid-associated deaths (375.34 to 452.8 opioid-related deaths per 1000 deaths in females 15-44 years, $P=0.03$), EMS runs (20.21 to 26.5 opioid-related EMS runs per 1000 EMS runs in females 15-44 years, $P<0.001$), and ED visits (1.55 to 2.02 opioid-related ED visits per 1000 ED visits in females 15-44 years, $P=0.02$), while there was a significant decrease in PDMP per-person rates (27.02 to 24.03 opioid-related prescriptions per 1000 persons, $P<0.001$).

Monthly NAS rates in Wisconsin are shown in Figure 1. The statewide monthly NAS incidence rate did not change significantly during the study period, although it decreased (6.68 to 6.1 NAS births per 1000 births, $P=0.16$). Regional NAS incidence and all-cause mortality rates in childbearing-age females are shown in Figures 2A and 2B, respectively. The Southeastern Region experienced a significant decrease in NAS presentations (8.13 to 6.37

Figure 3. Deaths in Females Ages 15 – 45 years in Wisconsin, January 2019 – December 2021



Statewide rates of death in females ages 15 – 45 years with opioid-related or COVID-19-related primary or underlying cause of death. The number of deaths in this population associated with both opioid use and COVID-19 were suppressed due to low case count.

NAS births per 1000 births, $P = 0.02$), while the other regions experienced no significant change. The Southeastern, Southern, and Northeastern Regions experienced a significant increase in all-cause mortality among childbearing-age females – Southeastern: 0.77 to 0.95 deaths per 10 000 childbearing-age females, $P = 0.01$; Southern: 0.57 to 0.75 deaths per 10 000 childbearing-age females, $P < 0.001$; Northern: 0.62 to 0.78 deaths per 10 000 childbearing-age females, $P = 0.02$. Statewide opioid-associated and COVID-19 deaths over time in females of childbearing-age are shown in Figure 3. Deaths of childbearing-age females with both opioids and COVID-19 listed as underlying or contributing cause had a case count of less than 5 and were the only data suppressed in compliance with DHS policy.

DISCUSSION

This is the first study in Wisconsin to describe the overlapping effects of the COVID-19 pandemic and opioid epidemic on population rates and NAS diagnoses. These results suggest that although the burden of the opioid epidemic increased after the onset of the COVID-19 pandemic in both the statewide population and in childbearing-age females, statewide NAS rates did not significantly increase (Table 2). Furthermore, the NAS rate unexpectedly decreased in the populous Southeastern Region of the state.

Prior studies have identified an increased opioid burden in response to the COVID-19 pandemic within Wisconsin.[22] Our analysis also demonstrates a statistically significant increase in multiple markers of opioid-related burden, such as an increased proportion of opioid-associated deaths, EMS visits, and ED visits across Wisconsin after the onset of the COVID-19 pandemic. We further report that increased opioid-associated deaths, EMS runs, and ED visits were observed in childbearing-age females. Identifying these trends for childbearing-age females is paramount to understanding the circumstances of the population that most directly impacts NAS diagnosis rates. Interestingly, these patterns occurred in the setting of decreased per-person PDMP opioid prescription counts in both the overall population and in childbearing-age females.

NAS is a lagging indicator of the burden of the opioid epidemic, as it requires a pregnancy to result in delivery before the diagnosis can be made. NAS statewide incidence rates did not significantly change after the onset of the COVID-19 pandemic. However, a statistically significant decrease in NAS occurred in the Southeastern Region (Figure 2A). This is particularly notable as this region contains more than one-third of the state's population and the highest proportion of childbearing-age females (Table 1). The change in NAS rates in the Southeastern Region deserves more detailed contextualization in future studies, including recognition of the differential impact of COVID-19 and opioid-related disease burden across this racially, ethnically and economically diverse regional population.

The juxtaposition of trends in childbearing-age females and infants reveals multiple factors that deserve consideration. An increased proportion of births occurred outside of a health care

facility after March 2020, which may falsely depress NAS rates, as newborn infants born outside of a health care facility may not undergo screening and diagnosis as they would during a birth hospitalization. Also, those pregnant people who received inpatient delivery and postnatal care did so in a transformed health care system after onset of the COVID-19 pandemic.[17-21] Whether statistically significant changes in disease detection rates reflect changes in the disease or the health care system will require longer-term and more nuanced study.

Separately, mortality increased in childbearing-age females, with an increased proportion of deaths associated with opioid use. Though much attention during this period focused on the potential increased risk of death caused by COVID-19 infection, COVID-19 deaths in childbearing-age females only approached levels of opioid-associated deaths in the last months of the study period (Figure 3). This finding demonstrates the opioid epidemic's burden across Wisconsin even before the COVID-19 pandemic. Increased rates of death associated with opioid use in childbearing-age females may reduce NAS rates by interrupting current or preventing future pregnancies that could result in infants at risk of NAS. This potential impact across Wisconsin, and specifically in the Southeastern Region, deserves dedicated examination.

While this analysis provides insight into opioid burden, birth rates, death rates, and NAS rates before and after the COVID-19 pandemic, the implications are limited by the observational nature of this study. Although we speculate an interplay between these population trends, we cannot demonstrate causality. Additionally, this study aggregates time frames before and after the onset of the COVID-19 pandemic, which may obscure distinct and rapidly changing circumstances. Further study is needed to interrogate potential links between childbearing and pediatric NAS populations and requires an analysis of outcomes over time to examine possible longer-term effects. Expanding the inclusion time frame of analysis would allow for examination of subsequent evolutions or "waves" in the COVID-19 pandemic that occurred after December 2021 and may also better capture longer-term effects, such as changes in pregnancy-associated overdose deaths and NAS diagnoses.[4] Analysis of maternal mortality and NAS risk per pregnancy over a longer study period and stratified for other potential confounders of geographic distribution, such as socioeconomic status, race, and ethnicity, is necessary to interpret the changes in maternal and neonatal outcomes described in this work.

CONCLUSIONS

Multiple markers of the burden of the opioid epidemic increased after onset of the COVID-19 pandemic in Wisconsin, including in childbearing-age females. Statewide NAS rates, however, did not increase. Instead, the most populous Southeastern Region of Wisconsin experienced a significant decrease in NAS incidence after the onset of COVID-19. This pattern coincides with a significant increase in deaths of childbearing-age females and a significant increase in births occurring outside of health care facilities in this region. Contextualizing NAS incidence within regional trends may help inform more effective statewide responses to the overlapping epidemics of opioid use and COVID-19.

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Availability of Data and Material: Study materials available upon request.

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Effects of COVID-19 on Overdose Risk Behaviors Among People Who Inject Drugs in Wisconsin

Erika J. Bailey, BS; Ryan P. Westergaard, MD, PhD; Cahit Kaya, PhD; Mikaela Becker, MPH; Katy Mijal, BS; David Seal, PhD; Rachel E. Gicquelais, PhD

ABSTRACT

Background: The United States is currently experiencing the worst epidemic of drug overdose in the country's history. We sought to understand whether changes in drug use behavior and access to prevention services during the COVID-19 pandemic may have contributed to increased drug overdose.

Methods: We recruited adults with a history of injection drug use to complete an online survey during March through June 2021 to assess whether overdose experiences, drug use behaviors, and access to prevention services changed due to the pandemic.

Results: Diminished social support during the pandemic was correlated with reporting disrupted access to harm reduction services ($P=0.006$) and experiencing an overdose ($P=0.005$). Disrupted access to harm reduction services also was correlated with being female ($P=0.03$) and reporting feeling pressure to share drugs or equipment ($P=0.01$), worrying about withdrawal ($P=0.03$), and changes to how and where individuals got their drugs, drug price and availability, with whom and where drugs were used, and the quantity or properties of drugs purchased (all $P<0.01$).

Discussion: The cumulative impact of COVID-19–related disruptions may have resulted in heightened risk for overdose, as these findings suggest that, in many cases, experiencing one risk factor was suggestive of experiencing several risk factors.

BACKGROUND

The United States is currently experiencing the worst epidemic of drug overdose in the country's history. Over 106 000 Americans died from drug overdose in 2021,[1] an all-time record. Overdose deaths increased annually from 1990 to 2016.[2] Subsequently, the US experienced a stabilization or decline in deaths from 2017 to 2019, a promising trend believed to reflect drug policy reform and historic investments in addiction treatment.[2] Unfortunately, in the first 2 years of the COVID-19 pandemic, deaths from drug overdose sharply rose again, driven by a combination of numerous concurrent forces, including disruptions in medical and behavioral health services, increased contamination of the drug supply with illicit fentanyl analogues, and myriad other potential factors, such as increased prevalence of anxiety, depression, and isolation among people who use drugs.[3]

In Wisconsin, the Department of Health Services reported 1201 overdose deaths in 2019, increasing to 1531 deaths in 2020 and to 1765 deaths in 2021.[4] In addition to drug-related deaths, evidence suggests nonfatal overdoses also increased during the COVID-19 pandemic; for example, emergency department visits for nonfatal drug overdose increased 38% from January 2020 to January 2021 in Wisconsin—even greater than the national average increase of 31%.[5] To explore potential mechanisms through which COVID-19 may have contributed to the overall rise in overdose morbidity and mortality, this study sought to describe changes to the experiences and behaviors of people who inject drugs during the first year of the pandemic.

METHODS

The Rural Opioid Initiative Research Consortium (ROI) is an active network of federally funded, community-based research projects aiming to reduce the risks of drug use, including overdose, HIV, and hepatitis C in rural areas.[6] The Wisconsin-based

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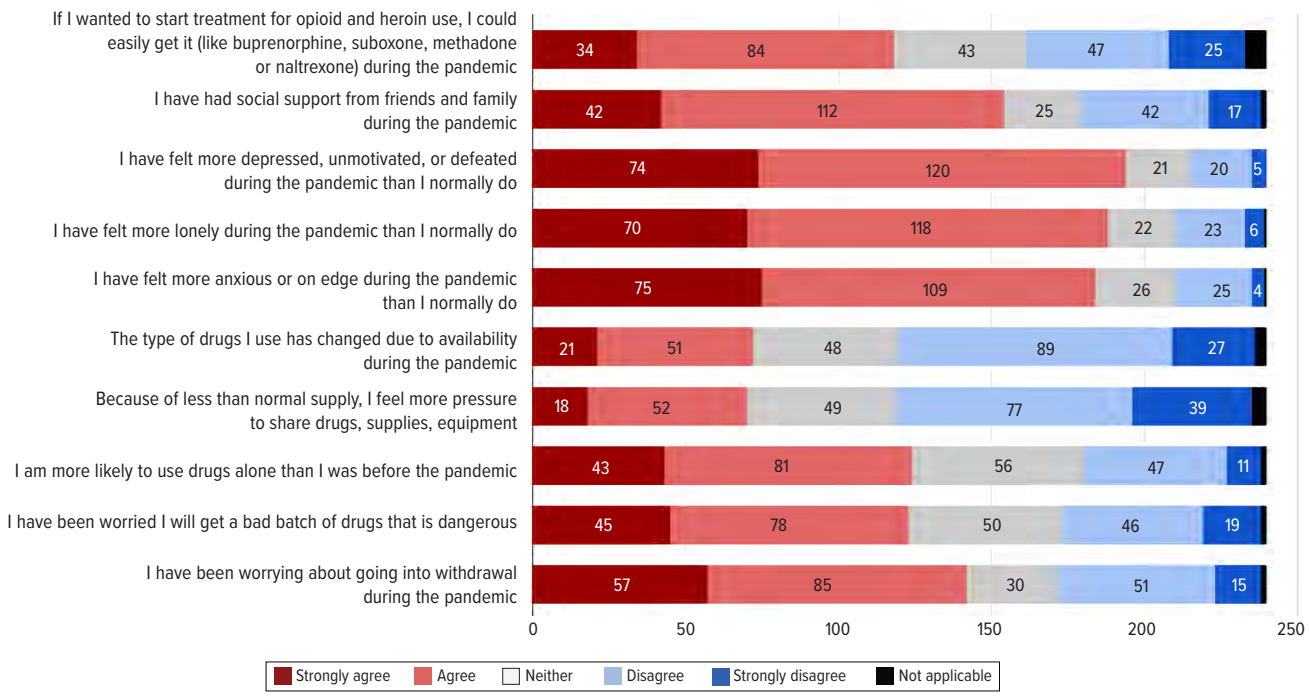
Figure 1. Summary of COVID-19–Related Impacts on Sample of 240 People Who Inject Drugs



ROI project, a partnership between the University of Wisconsin-Madison (UW-Madison) and Vivent Health, conducted a survey of people who inject drugs in Wisconsin communities during the pandemic.

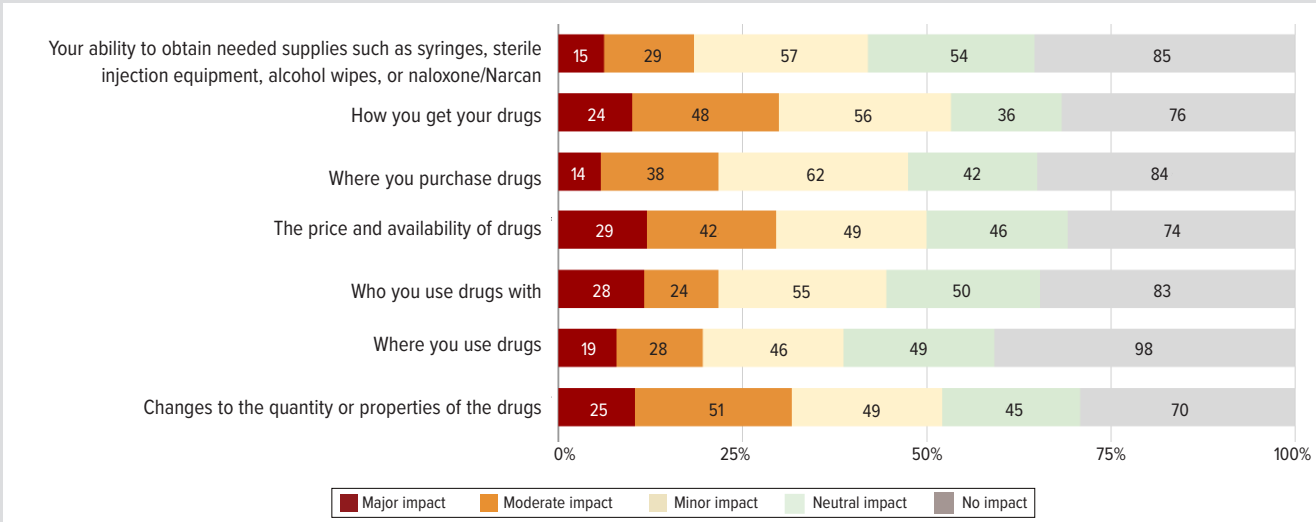
From March 8 through May 5, 2021, Vivent Health staff recruited clients from each of their 10 Wisconsin syringe service programs (SSP). The study team at the UW-Madison provided Vivent Health staff with flyers that invited clients to complete an online survey. Vivent Health staff gave the flyer to clients when they visited the SSPs to obtain supplies. The flyer contained a quick response (QR) code to gain access to the survey from a smartphone or iPad available in the SSP office. Clients also could call the number on the flyer to reach a study staff member and take the survey over the phone. The QR code opened a Qualtrics survey link that began with a brief eligibility assessment. SSP clients were eligible to participate if they were 18 years or older and reported injecting drugs to get high at least once in the past 12 months. Eligible clients advanced to an electronic informed consent page in Qualtrics. If they affirmed consent to participate, they began the 15- to 20-minute questionnaire and were compensated for completing the survey. The UW-Madison Health Sciences Institutional Review Board approved this study protocol.

A total of 393 clients responded to the online survey. For this analysis, the study team removed respondents who were ineligible based on their responses to screening questions (n = 82) and respondents who were eligible but selected "no" or did not respond to the informed consent question (n = 34). A total of 277 participants consented to participate and initiated the study survey. The study team tracked survey data to identify and remove duplicate responses completed by the same person (n=10) and incomplete surveys (n = 27), leaving 240 responses valid for analysis.

The survey assessed several sociodemographic characteristics (age, race, ethnicity, gender, employment, and education) and assessed changes in substance use and mental health due to the COVID-19 pandemic. The analysis consists of 3 primary outcomes: personally experiencing at least 1 nonfatal overdose since the start of the COVID-19 pandemic ("yes" or "no"); agreement level regarding ability to access substance use treatment during the pandemic ("strongly agree," "agree, "neither agree nor disagree," "disagree," or "strongly disagree"); and reported impact of the pandemic on ability to access harm reduction supplies ("major impact," "moderate impact," "minor impact," "neutral impact," or "no impact"). The analysis explores sociodemographic characteristics, self-reported mental health (depression, anxiety, loneliness, and social support), and drug use practices (using drugs while alone, whether they believed the composition or availability of the drugs they used had changed, drug purchasing behaviors, who drugs were used with, whether they were more likely to share drugs or injection equipment) as potential correlates of the 3 primary outcomes.

Non-sociodemographic survey questions utilized likert-scale response options ("strongly agree," "agree," "neither agree nor disagree," "disagree," or "strongly disagree") or asked participants to

Figure 2. Self-Reported Impact Rating of COVID-19 on Drug Behaviors Among 240 WIsconsin Participants



rate the degree of impact ("major impact," "moderate impact," "minor impact," "neutral impact," or "no impact") COVID-19 had on several factors. The prevalence of each response option is reported in Figures 1 and 2. For analyses of correlates, we compared affirmative responses ("strongly agree" and "agree," or "major impact" and "moderate impact") to nonaffirmative responses (all else). Two variables–"I have been able to maintain access to harm reduction services/supplies" and "I have had social support from friends and family"–were coded backwards so that "strongly disagree" and "disagree" responses reflecting a negative impact of COVID-19 were compared to other responses. We used chi-square tests ($\alpha = 0.05$) to detect statistically significant associations between correlates and outcomes.

RESULTS

The mean age of participants was 35 years (SD 8.8; minimum 19; maximum 64). Approximately half of the participants identified as female (49%), and most were White (79%) and non-Hispanic (93%). Most respondents had at least a high school diploma or GED (General Education Development) certificate (85%), with about half of those also reporting some college-level education. About one quarter (26%) were employed for wages. Participants resided in 31 different Wisconsin counties in all regions of the state. Milwaukee County (30%), Brown County (18%), and Douglas County (15%) accounted for more than half of the sample. Over one-quarter (27%) reported experiencing a nonfatal overdose since the onset of the COVID-19 pandemic (ie, during the preceding 12-14 months). Approximately half (49%) of participants responded affirmatively ("strongly agree" or "agree") that they felt they could start treatment for opioid and/or heroin use during the pandemic if they wanted to (Figure 1). Less than one fifth (18%) affirmed ("major impact" or "moderate impact") that COVID-19 affected their ability to obtain harm reduction supplies (such as sterile syringes, alcohol wipes, and naloxone), despite COVID-related limited-service hours of the partner SSP sites throughout 2020 (Figure 2). Overall, mental health symptoms appeared to worsen during the pandemic for most respondents: 81% responded affirmatively ("strongly agree" or "agree") that they felt more depressed; 77% affirmed that they felt more anxious; and 78% affirmed feeling lonelier in comparison to the year prior to the pandemic. When questioned about specific issues contributing to anxiety, 51% reported they worried about a "bad batch of drugs that is dangerous," and 59% reported worrying about going into withdrawal (Figure 1).

Reporting a lack of social support during the pandemic was correlated with reporting disrupted access to harm reduction services ($P = 0.006$) and experiencing an overdose ($P = 0.005$), (Table). Though increased feelings of depression or defeat during COVID-19 were common across the whole sample (Figure 1), those who reported these feelings also more often felt treatment was less accessible during the pandemic ($P = 0.03$, Table). Those who felt treatment was less accessible were more frequently female ($P = 0.004$) and more often reported worrying about withdrawal (P=0.03) and changes in how drugs were acquired ($P = 0.02$) (Table 1). Participants who reported disrupted access to drug use supplies, such as syringes or naloxone, also were more often female ($P = 0.03$) and more frequently reported feeling pressure to share drugs or equipment ($P = 0.01$), worrying about withdrawal ($P = 0.03$), and that COVID-19 caused changes to how and where they got drugs, drug price and availability, with whom and where drugs were used, and the quantity or properties of drugs purchased (all $P < 0.01$, Table). Results indicated worrying about a bad batch of drugs during the pandemic was correlated with not experiencing overdose ($P = 0.045$, Table). However, those who personally

Table. Correlates of COVID-19–Related Disruptions in Overdose Experiences and Access to Harm Reduction Supplies and Treatment

		Disrupted Ability to Obtain Supplies (ie, syringes, naloxone)[b]			Did Not Feel Like They Could Easily Get Treatment (ie, buprenorphine, methadone)[c]			Experienced an Overdose During Pandemic[d]		
	Total N (%) 240 (100.0)	Yes, n (%) 44 (100.0)	No, n (%) 196 (100.0)	*P* value n/a	Yes, n (%) 72 (100.0)	No, n (%) 161 (100.0)	*P* value n/a	Yes, n (%) 66 (100.0)	No, n (%) 166 (100.0)	*P* value n/a
COVID-19-related disruptions[d]										
Did not have social support[c]	59 (24.6)	18 (40.9)	41 (21.1)[f]	**0.006**	24 (33.3)	35 (22.0)[f]	0.07	25 (37.9)	33 (20.1)[f]	**0.005**
Felt more depressed/defeated[a]	194 (80.8)	36 (81.8)	158 (80.6)	0.85	65 (90.3)	126 (78.3)	**0.03**	53 (80.3)	135 (81.3)	0.86
Felt lonelier[a]	188 (78.3)	36 (81.8)	152 (78.9)[f]	0.57	62 (86.1)	123 (76.4)	0.09	50 (75.8)	132 (80)[f]	0.48
Felt more anxious or on edge[a]	184 (76.7)	36 (81.8)	148 (75.9)[f]	0.39	56 (77.8)	125 (77.6)	0.98	54 (81.8)	125 (75.8)[f]	0.32
Type of drugs used changed[a]	72 (30.0)	16 (36.4)	56 (29.2)[f]	0.35	22 (30.6)	49 (30.8)[f]	0.97	17 (25.1)[f]	50 (30.7)[f]	0.49
Felt pressure to share drugs or equipment[a]	71 (29.2[f])	20 (45.5)	50 (26.2)[f]	**0.01**	20 (28.6)[f]	49 (30.8)	0.73	23 (34.8)	45 (27.8)[f]	0.29
More likely to use alone[a]	124 (51.7)	25 (58.1)	99 (50.8)[f]	**0.38**	37 (51.4)	84 (52.5)[f]	0.88	37 (56.9)[f]	82 (49.7)[f]	0.32
Worried about a bad batch of drugs[a]	123 (51.2)	26 (59.1)	97 (50.0)[f]	**0.28**	41 (57.7)[f]	78 (48.4)	0.19	27 (40.9)	91 (55.5)[f]	**0.045**
Worried about withdrawal[a]	142 (59.2)	32 (74.4)	110 (56.4)[f]	**0.03**	51 (70.8)	89 (55.9)[f]	**0.03**	40 (61.5)[f]	95 (57.6)[f]	0.58
How you get drugs[b]	72 (30.0)	21 (47.7)	51 (26.0)	**0.004**	30 (41.7)	42 (26.1)	**0.02**	19 (28.8)	49 (29.5)	0.91
Where you purchased drugs[b]	52 (21.7)	18 (40.9)	34 (17.4)	**<0.001**	20 (27.8)	31 (19.2)	0.15	14 (21.2)	34 (20.5)	0.9
Price/availability of drugs[b]	71 (29.2)[f]	25 (56.8)	46 (23.5)	**<0.001**	27 (37.5)	43 (26.7)	0.1	28 (42.4)	42 (25.3)	0.01
Who you use drugs with[b]	52 (21.7)	19 (43.2)	33 (16.8)	**<0.001**	19 (26.4)	31 (19.2)	0.22	17 (25.8)	32 (19.3)	0.28
Where you use drugs[b]	47 (19.6)	16 (36.6[f])	31 (15.8)	**0.002**	17 (23.6)	28 (17.4)	0.27	15 (22.7)	30 (18.1)	0.42
Quantity or property of drugs purchased[b]	76 (31.7)	29 (65.9)	47 (23.9)[f]	**<0.001**	29 (40.3)	45 (27.9)	0.06	27 (40.9)	46 (27.7)	0.0508
Sociodemographic characteristics[d]										
Non-White race	47 (19.6)	13 (29.5)	34 (17.62)[f]	0.07	19 (26.4)	27 (16.9)[f]	0.1	11 (16.7)	35 (21.5)[f]	0.41
Female[e]	118 (49.2)	28 (65.1)[f]	90 (46.9)[f]	**0.03**	45 (63.4)[f]	68 (43.0)[f]	**0.004**	35 (55.6)[f]	78 (47.3)[f]	0.26
Not working for wages[f]	163 (74.0)[f]	33 (80.5)[f]	130 (73.0)[f]	0.32	53 (77.9)[f]	106 (73.6)[f]	0.49	46 (77.9)[f]	111 (72.1)[f]	0.38
Less than high school diploma	32 (13.3)	8 (18.6)[f]	24 (12.5)[f]	0.29	11 (15.5)[f]	19 (12.1)[f]	0.48	8 (12.5)[f]	23 (13.9)	0.79

[a]Strongly agree or agree (yes) vs neutral, disagree, or strongly disagree (no).

[b]Major or moderate impact (yes) response vs minor impact, neutral impact, and no impact (no).

[c]Strongly disagree and disagree (yes) vs strongly agree, agree, or neither (no).

[d]"I don't know," "I prefer not to answer," and "not applicable" responses are omitted from the "yes," "no" summary.

[e]Two participants self-reported identifying as transgender or genderqueer, which were omitted from the bivariate analysis (treated as missing).

[f]"I don't know" and "I prefer not to answer" responses were treated as missing data in all chi square tests, percentage calculations are "yes" out of data available, not column N total.

experienced an overdose after the start of COVID-19 were more likely to report diminished social support ($P = 0.005$) and that the price and availability of drugs had changed ($P = 0.01$) (Table 1).

DISCUSSION

People who inject drugs are a population with extraordinary health needs and high risk of early mortality due to overdose. According to data from the Centers for Disease Control and Prevention, 58 404 overdose deaths occurred in 2021 among Americans aged 15-44 years,[1] which is more than twice the number of deaths from COVID-19 in that age group during the same year.[7] There is a critical need to scale up evidence-based treatments and harm reduction strategies to lower the risk of overdose for people who use drugs. Understanding the factors contributing to high overdose risk in marginalized communities is important for developing strategies to implement client-centered treatment and prevention services.

The results of our study align with factors identified by Chang et al as contributors to overdose experiences: social dynamics; uncertain supply, composition, and source of drugs used; opioid-expertise, meaning their experience, tolerance, self-control, and responsibility with opioid use; and emotional pain.[8] In this study, COVID-19 reportedly exacerbated or disrupted social dynamics, such as using alone, pressure to share drugs or equipment, and with whom individuals were using drugs, along with supply and composition of drugs. These findings—that diminished social support and changes in the price and availability of drugs were associated with experiencing an overdose—corroborate prior findings about heightened vulnerability related to interruptions to social dynamics and supply. These disruptions may have left people who use drugs vulnerable to new and unknown circumstances, subsequently reducing their "opioid expertise." Surprisingly, those who experienced an overdose indicated less worry about a bad batch of drugs. The cross-sectional nature of the data makes this finding

difficult to interpret, but these data could indicate a diminished "opioid expertise" among participants who experienced an overdose; and/or, these could relate to previous reports about feeling apathetic about overdose risk in the context of passive suicidality, mental health challenges, or other vulnerability or life challenges that can accompany substance use disorder. Emotional pain also worsened, as evidenced by the large majority of participants reporting increased anxious, lonely, and depressed feelings during the pandemic, regardless of whether they experienced an overdose. There is a lack of consensus about the directional causality between mental disorders and substance use, but a large body of evidence suggests significant associations between mental disorders and overdose risk.[9] While it may not be possible to discern the true cause of increased overdose risk, it is evident that the COVID-19 pandemic intensified many compounding risk factors.

This study underscores the need to enhance implementation of evidence-based interventions to reduce risk within health care, public health, and harm reduction sectors. Some novel strategies already have been developed; for example, a shift to telehealth-provided medications for opioid use disorder during the pandemic was found to be associated with reduced overdose risk.[10] This study's findings indicate that a substantial proportion of people who use drugs—who were generally more likely to be women and worried about withdrawal—may have perceived less access to treatment and, thus, benefited from flexible treatment modalities. Brick-and-mortar syringe services programs rapidly pivoted to continue providing services during COVID-19. Further, services like Next Distro[11] and the Never Use Alone[12] hotline provide harm reduction services available anytime, anywhere. These services may be particularly important given the finding that individuals experiencing disruptions in drug supply, acquisition, and their usual drug use practices also were experiencing disrupted access to harm reduction services/supplies.

Findings from this cross-sectional survey are subject to several methodological limitations. This study surveyed clients of local SSPs, therefore sampling individuals who are likely more aware of ways to access naloxone and harm reduction services, which limits generalizability. Additionally, self-reported changes in drug use and access to services are subject to imperfect recall and subjectivity in rating of impact and agreement. We collapsed similar responses (eg, "major impact" and "moderate impact") to enhance the interpretability of the analysis of correlates of disruptions to access to harm reduction supplies and substance use treatment but show the full breadth of responses in descriptive analyses. Further, this study was only able to capture nonfatal overdose events and excludes those who died from overdose or COVID-19 before the study was conducted. Despite these limitations, this study adds to our understanding of the local effects of the COVID-19 pandemic on mental well-being, access to essential harm reduction and health services, and drug-related risks behaviors among people who use drugs at a time when overdose mortality continues to rise.

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Breastfeeding During the COVID-19 Pandemic: Personal and Professional Reflections

Caitlin Regner, MD

I was 7 months pregnant with our fourth child when the Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease Outbreak[1] was issued. Despite uncertainty, I continued seeing patients up to the day I delivered. I labored mostly at home to avoid unnecessary exposures and arrived at the hospital only minutes prior to delivering. I was discharged as quickly as possible, even before my daughter was 1 day old. Thankfully – as had been the case with my older children – she had no trouble breastfeeding.

As the pandemic continued, I considered breastfeeding to be one of the best gifts I could give my baby, so I pumped and stored up gallons of excess milk for her. Recognizing her dependence upon my own immune system, I signed up to receive the vaccine as soon as it was available, grateful for my physician status. Before vaccines had been approved for children, I gave samples of immune-laden breastmilk to my older children, assuming – as we now know – that it could afford some immune protection. Although there were other factors at play, the early pandemic clearly affected my decisions about breastfeeding.

PATIENT BREASTFEEDING EXPERIENCES

I work as a family physician with an emphasis on obstetric and newborn care in an urban Federally Qualified Health Center. Several research partners and I evaluated the impact of the COVID-19 pandemic on patient breastfeeding experience. Perhaps more importantly, however, I lived through these experiences with my patients.

> Although there were other factors at play, the early pandemic clearly affected my decisions about breastfeeding.

Some parents, already home with their children, found that the pandemic neither affected their daily routine nor their breastfeeding, though perhaps they felt lonelier. Some parents expressed gratitude for flexible parental leave, the ability to breastfeed or pump in the workplace, and greater freedom to work from home. I spoke with several who invited grandparents to come to stay or hired in-home childcare to avoid risks associated with attending daycare centers and to provide more flexibility for breastfeeding during the workday.

Yet, many faced significant challenges during the pandemic due to limited family, employer, and social support. One mother chose to breastfeed her daughter during the pandemic but later had to resign from her work due both to pumping restrictions and challenges with her childcare provider. There was a new immigrant couple who so strongly desired to breastfeed but who ultimately had to stop due to the lack of family support and insufficient time off. Many mothers who started breastfeeding, but soon added formula into their feeding plan or transitioned entirely to formula because pumping did not fit the demands of their work.

WHAT WE LEARNED AND THE PATH FORWARD

Social and health care changes during the pandemic only highlighted longstanding issues with lactation support. Even those clinicians who do not work directly in prenatal, postpartum, pediatric, or lactation care interact with breastfeeding patients or colleagues. Although the recently passed PUMP Act[2]—which protects time and space for lactation in the workplace—is a step forward, there is still work to do. As such, we physicians should advocate for greater lactation support through health and social policies. To that end, we ought to con-

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sider health care systems-based and community-based strategies.

For instance, the Academy of Breastfeeding Medicine has proposed several recommendations for a breastfeeding-friendly health care office.[3] A first step can be as simple as writing an organization-specific office policy and periodically communicating with staff about it. Additional steps could be to include signage in support of breastfeeding throughout the office or to avoid marketing material for breast milk substitutes. This short but effective protocol proposes many ideas that offices could reasonably implement.

For those who provide prenatal, postpartum, and pediatric care, there are other strategies to consider. First, infant feeding should be discussed early in prenatal care visits – ideally at the first visit or within the first trimester–to understand feeding goals and how other medical, social, and cultural factors affect feeding choices. This approach also would allow clinicians to tailor their counseling throughout the pregnancy as needed. Second, prenatal lactation visits with trained personnel should be offered as a standard of care, particularly given the growing evidence that more education prenatally about breastfeeding improves breastfeeding uptake, knowledge, and self-efficacy.[4] Third, it should be a priority to fund staff members trained in lactation to provide early and frequent lactation phone calls and in-person visits, which would allow them time to address challenges, such as pain, difficulty with latch, engorgement, and anything else that could lead to early weaning. Similarly, clinicians should be given time and support to complete evidence-based lactation training. Those who do not work directly in lactation should be able to direct patients to quality lactation support as needed.

Finally, it is worth mentioning that, in addition to anatomical challenges, many stop breastfeeding due to depression, anxiety, and insufficient social support. A key component of breastfeeding aid involves supporting the transition to parenthood and addressing postpartum mood and changes. Routine evaluation and management of parents' well-being—including mood disorders—is vital for better lactation support and infant care.

Although the official COVID-19 Public Health Emergency has ended, other public health priorities will continue to emerge. As we face each of these, I strongly urge all clinicians to consider how they are supporting infants and their families by building a healthy foundation for life through breastfeeding.

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COVID-19: What's Your Pandemic Nightmare?

Claudia Krogmeier

Film

Artist Statement:

This work amplifies the unusual feeling mask-wearing could bring o daily life during the COVID-19 pandemic. Shot with a drone in the heat of an Indiana summer, "Ravenous Shut-Eye" is a short art film that plays with the space between surreality and the new everyday during 2020. This image is a screenshot from the film.

The Protective Umbrella of COVID-19

Diane Yao

Painting

Artist Statement:

The COVID-19 pandemic has been ongoing for three years, which makes me understand the importance of taking medical protection measures to safeguard myself and others. Habits such as wearing a mask when sick, frequent handwashing, and covering sneezes can help create a cleaner living environment down the line.

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to our Reviewers

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