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

Yilu Dong, PhD; Ryan Hanson, MS; Annie C. Penlesky, MPH; Ann B. Nattinger, MD, MPH; Thomas W. Heinrich, MD; Liliana E. Pezzin, PhD, JD

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.

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

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Author Affiliations: Collaborative for Healthcare Delivery Science, Medical College of Wisconsin, Milwaukee, Wisconsin (Dong, Hanson, Penlesky, Nattinger, Heinrich, Pezzin).

Corresponding Author: Yilu Dong, PhD, Collaborative for Healthcare Delivery Science, Medical College of Wisconsin, 999 N 92nd St, Milwaukee, WI 53226; phone 414.337.7706; email ydong@mcw.edu; ORCID ID 0000-0001-6859-9759

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.

Funding/Support: None declared.

Financial Disclosures: None declared.

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