Post-infection Symptomatology of Human Metapneumovirus Infection

Dorothy Kenny, MD; Samuel Martin, MD; David Quimby, MD

Introduction: Though there has been much discussion about post-acute sequelae of SARS-CoV-2 infection, there has been limited study on symptoms following infection with other respiratory viruses.

Methods: In this retrospective chart review, we reviewed the medical records of 92 patients admitted to the hospital with a diagnosis of human metapneumovirus for 17 of the common symptoms associated with post-acute sequalae of SARS-CoV-2 that were either new or worse than baseline in the time frame of 90 to 270 days after diagnosis.

Results: Of those patients hospitalized with human metapneumovirus, 55.4% had at least 1 new or worsening symptom more than 3 months after diagnosis. The most common symptoms noted were shortness of breath (29.3%) followed by fatigue and cough (17.3% each).

Conclusions: Our data suggest that other respiratory viruses – not just SARS-CoV-2 – may carry a significant burden of post-infection sequelae.

INTRODUCTION

Since the discovery and spread of the SARS-CoV-2 virus, there have been reports of patients with persistent symptoms after recovering from initial infection. This condition, commonly referred to as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), can present as 1 or more symptoms, such as fatigue, post-exertional malaise, brain fog, headache, sleep issues, loss of smell/taste, shortness of breath, chest pain, or muscle/joint pain.[1,2] The reported prevalence of PASC varies widely and may be anywhere from 10% to 45%.[2-4] Symptoms can persist for months and can occur even after mild infection.[3,5] Although the ultimate mechanisms are unclear, PASC is thought to occur for a variety of reasons, including direct tissue injury from acute infection, persistence of SARS-CoV-2 in tissue reservoirs, reactivation of latent viruses, induction of autoimmunity, or impact on the host microbiome due to immune dysregulation.[1,6]

Though there has been much discussion about PASC, there has been limited study on long-term sequelae following infection with other respiratory viruses. This makes study of PASC challenging as it is not entirely clear how the prevalence of this condition compares to other viral infections.

Human metapneumovirus (HMPV), discovered in 2001, can cause mild to severe illness; groups at risk for severe illness include infants and young children, older adults, and patients who are immunocompromised. While most patients are infected by 5 years of age, reinfection frequently occurs throughout life.[7] HMPV causes significant morbidity and mortality in older patients, with 1 study reporting 60% of infected older patients requiring hospitalization.[8] Current treatment is supportive, and there are no vaccines available at this time.[7]

To determine the prevalence of post-infectious sequelae from HMPV, we performed a retrospective chart review of adult patients hospitalized with this pathogen.

METHODS

Patients with a diagnosis of HMPV based on polymerase chain reaction (PCR) testing (FilmArray Respiratory Panel, Biomerieux) from January 1, 2018, through June 24, 2022, were reviewed. The researchers manually reviewed medical records to determine baseline demographics as well as new-onset or worsening severity of 17 symptoms that have been associated with PASC during the time period of 90 to 270 days following diagnosis of

• • •

Author Affiliations: Creighton University School of Medicine, Phoenix, Arizona (Kenny); Internal Medicine, Creighton University, Omaha, Nebraska (Martin); Section of Infectious Diseases, Department of Medicine, Creighton University, Omaha, Nebraska (Quimby).

Corresponding Author: David Quimby, MD, 7710 Mercy Road, Suite 3000, Omaha, NE 68124; phone 402.717.0759; email david.quimbymd@commonspirit.org; ORCID ID 0000-0003-3976-9522

HMPV infection. (See Table 1 for list of symptoms.) Anosmia and ageusia were not evaluated as these typically were not associated with non-SARS-CoV-2 viral infections prior to the pandemic. If symptoms were present prior to the HMPV diagnosis, patients must have had documented worsening based on patient report or clinician documentation during the study period to be counted as positive. For those individuals with no records available prior to HMPV diagnosis, the medical record needed to clearly state that subsequent symptoms were new or worsening since the infection to be counted as positive.

Given the small number of patients involved, data on baseline chronic diagnoses (eg, hypertension, diabetes, chronic obstructive pulmonary disease) were not extracted as it would be unlikely to lead to statistical significance; the goal of the study was to determine overall prevalence of post-infectious symptoms not to risk-stratify the probability of developing such symptoms. Laboratory testing, radiologic or other diagnostic testing, and billing/diagnosis codes were not extracted. As this was a retrospective study, impact of symptomatology on patient quality of life could not be determined. Data on mortality during the index hospitalization, mortality in the follow-up period, and all-cause hospitalization in the follow-up period also were collected.

Patients were excluded from the analysis if no data were available, if they had a diagnosis of SARS-CoV-2 infection prior to the HMPV infection or during the follow-up period, or if they were less than 18 years of age at diagnosis.

The Creighton University Institutional Review Board approved the study and determined that patient consent was not necessary (approval number 2003266-01).

RESULTS

During the study period, 138 patients were diagnosed with HMPV. One patient was excluded due to diagnosis of SARS-CoV-2 during the period under review. No follow-up data were available for 45 patients, leaving 92 patients for analysis. Fifty-nine (64.1%) were female, 77 (84.0%) were White, 11 (12.0%) were Black, and 6 (6.5%) were Hispanic. The mean age for included patients was 64.4 years (range 20-94, SD 16.6). None of the included patients had other viruses co-detected with respiratory panel testing at the time of HMPV diagnosis. One patient (0.7%) died during the index hospitalization. Sixteen (11.7%) died prior to the end of the study period (270 days after diagnosis); 40 (29.2%) patients had at least 1 repeat hospitalization prior to the end of the study period.

Of the 17 symptoms evaluated (Table 1), the most common symptom was shortness of breath (29.3%), followed by fatigue and cough (17.3% each). At least 1 new or worsening symptom was recorded for 55.4% of patients (Table 2).

Table 1. Symptoms Following Human Metapneumovirus (HMPV) Infection in the Study Population

Symptom	No. of Patients (%)
Shortness of breath/difficulty breathing	27 (29.3)
Cough	16 (17.4)
Fatigue	16 (17.4)
Joint/muscle pain	9 (9.8)
Sleep problems	8 (8.7)
Chest pain	6 (6.5)
Abdominal pain	6 (6.5)
Depression/anxiety	4 (4.3)
Lightheadedness/dizziness	4 (4.3)
Heart palpitations	3 (3.3)
Neuropathy	3 (3.3)
Diarrhea	2 (2.2)
"Brain fog"/memory issues/concentration difficulty	1 (1.1)
Fever	1 (1.1)
Headaches	1 (1.1)
Post-exertional malaise	1 (1.1)
Rash	1 (1.1)

Table 2. Number of Different Symptoms Following Human Metapneumovirus (HMPV) Infection in the Study Population

No. of Different Symptoms	No. of Patients (%)
0	41 (44.6)
1	18 (19.6)
2	14 (15.2)
3	14 (15.2)
4	4 (4.3)
5	1 (1.1)

DISCUSSION

Though there is variation in the symptoms experienced with PASC, the most commonly reported are fatigue, shortness of breath, and loss of smell/taste.[3,9-12] In our study of HMPV, the most common symptoms were shortness of breath, fatigue, and cough. A majority of patients (55.4%) had at least 1 symptom for longer than 3 months after the diagnosis; 35.8% reported 2 or more symptoms during the follow-up period.

The mechanisms leading to symptoms of PASC are unclear. Studies have noted immune dysregulation as a potential contributor due to increased pro-inflammatory cytokines and autoantibodies seen in COVID-19 patients. Notably, similar findings have been seen in myalgic encephalitis and chronic fatigue syndrome, which have been associated with viruses such as Epstein-Barr virus, cytomegalovirus, and SARS-CoV-1.[4,6,13] Proposed causes for physical symptoms of PASC have included tissue injury from acute infection, neuroinflammation, muscle mitrochondrial dysfunction, ongoing inflammation due to dysregulated immune response, and different psychological or environmental factors.[6,14]

Direct comparison of the frequency of long-term sequelae from different viruses is somewhat lacking in the literature. In a study comparing those hospitalized with COVID-19 and influenza, Al-Aly et al found a higher burden of new diagnoses post-dismissal in those with COVID-19.[15] One study completed prior to the onset of the COVID-19 pandemic reported a higher prevalence of lower respiratory tract symptoms at 3 months post-discharge for

respiratory syncytial virus and HMPV compared to influenza.[16] Over 50% of patients in our study had at least 1 symptom still present more than 90 days after diagnosis of HMPV, suggesting that pathogens other than SARS-CoV-2 may lead to long-term issues.

Limitations

Our study has several limitations. As a retrospective chart review, we were limited to information that was documented on follow-up visits. Eligibility for inclusion was based on those who underwent viral PCR testing; this was restricted to those admitted to the hospital. Patients not ill enough to warrant hospital admission were therefore not included in the analysis. The patients under review were limited to a single academic medical center, possibly limiting generalizability. Lack of follow-up data on all patients could lead to incorrect assessment of the true prevalence of post-infection sequelae. For example, it might be assumed that patients with ongoing symptoms would be more likely to seek medical care, while those without symptoms would not seek such care; exclusion of the latter (as was done in this analysis) would lead to an overestimation of true prevalence of the frequency of post-infection symptoms. A final limitation is lack of a control group. While these data demonstrate the frequency of symptoms following hospitalization for HMPV infection, it is impossible to determine how much of the symptomatology was due to the viral infection versus hospitalization for other reasons.

CONCLUSIONS

Although relatively small, retrospective, and with limitations as outlined, this study suggests that respiratory viral pathogens other than SARS-CoV-2 in hospitalized patients can carry a significant burden of post-infection sequelae. Obtaining data on prevalence of such symptoms for patients with a variety of respiratory viral infections can help delineate how SARS-CoV-2 is similar or differs from other pathogens. By examining patterns across pathogens, we may be able to identify commonalities, which could help determine the pathophysiology and, eventually, better management strategies. With a variety of different causative factors, however, there is likely no single intervention that will be beneficial for all patients with PASC or sequelae from other infections; it is probable that individualized management will be necessary.

Further investigation into this area can include other viral pathogens. Prospective trials would provide better data on post-infectious sequelae, avoiding many of the biases inherent in a retrospective review. Outpatients can be included in such trials, which would lead to data on those not medically ill enough to warrant acute hospital admission. If studies are performed in a prospective manner, information also can be obtained on impact of quality of life from ongoing symptoms. Gathering such data would lead to a better-crystalized profile of post-infectious syndromes from respiratory viruses.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgements: The authors would like to thank Uyen-Vy (Melanie) Nguyen for assistance with the literature search.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Proal AD, VanElzakker MB. Long COVID or Post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. *Front Microbiol.* 2021;12:698169. doi:10.3389/fmicb.2021.698169

2. Yoo SM, Liu TC, Motwani Y, et al. Factors associated with post-acute sequelae of SARS-CoV-2 (PASC) after diagnosis of symptomatic COVID-19 in the inpatient and outpatient setting in a diverse cohort. *J Gen Intern Med*. 2022;37(8):1988-1995. doi:10.1007/s11606-022-07523-3

3. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. *EClinicalMedicine.* 2022;55:101762. doi:10.1016/j.eclinm.2022.101762

4. Pintos-Pascual I, Moreno-Torres V, Ibánez-Estéllez F, et al. Is SARS-CoV-2 the only cause of long-COVID?. *AIDS Rev.* 2022;24(4):183-196. doi:10.24875/AIDSRev.22000025

5. Mizrahi B, Sudry T, Flaks-Manov N, et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. *BMJ*. 2023;380:e072529. doi:10.1136/bmj-2022-072529

6. Sherif ZA, Gomez CR, Connors TJ, Henrich TJ, Reeves WB; RECOVER Mechanistic Pathway Task Force. Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *Elife.* 2023;12:e86002. doi:10.7554/eLife.86002

7. Shafagati N, Williams J. Human metapneumovirus - what we know now. *F1000Res.* 2018;7:135. doi:10.12688/f1000research.12625.1

8. Boivin G, Abed Y, Pelletier G, et al. Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. *J Infect Dis*. 2002;186(9):1330-1334. doi:10.1086/344319

9. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open.* 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830

10. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. doi:10.1001/jama.2020.12603

11. Margalit I, Yelin D, Sagi M, et al. Risk factors and multidimensional assessment of long coronavirus disease fatigue: a nested case-control study. *Clin Infect Dis.* 2022;75(10):1688-1697. doi:10.1093/cid/ciac283

12. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect.* 2020;81(6):e4-e6. doi:10.1016/j.jinf.2020.08.029

13. Sukocheva OA, Maksoud R, Beeraka NM, et al. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. *J Adv Res.* 2022;40:179-196. doi:10.1016/j.jare.2021.11.013

14. Castanares-Zapatero D, Chalon P, Kohn L, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. *Ann Med.* 2022;54(1):1473-1487. doi:10.1080/07853890.2022.2076901

15. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9

16. Falsey AR, Walsh EE, Osborne RH, et al. Comparative assessment of reported symptoms of influenza, respiratory syncytial virus, and human metapneumovirus infection during hospitalization and post-discharge assessed by Respiratory Intensity and Impact Questionnaire. *Influenza Other Respir Viruses.* 2022;16(1):79-89. doi:10.1111/irv.12903

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 2379-3961) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. 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.

Visit www.wmjonline.org to learn more.