The Emerging Chronic Sequelae of COVID-19 and Implications for North Carolina

Robert J. Rolfe, Colin M. Smith, Cameron R. Wolfe

The acute morbidity and mortality of COVID-19 have been well described. Evidence is emerging that COVID-19 may also result in negative long-term medical and psychiatric outcomes. A broad response from the public health community in North Carolina that includes robust surveillance and catch-up care is needed to reduce the long-term sequelae of COVID-19.

Introduction

The novel coronavirus (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), first emerged in North Carolina on March 3, 2020, and, as of October 1, 2020, had led to over 200,000 infections and 3,000 deaths in the state and remains a major public health threat [1]. In the first four months of the pandemic, North Carolina incurred over $300 million in COVID-19-related costs [2]. As in other parts of the country, COVID-19 has disproportionately affected racial and ethnic minorities in North Carolina, and disproportionately impacted rural communities [3].

As an emerging infectious disease, there have been many descriptions of acute COVID-19-related illness, but long-term effects remain uncertain. The most commonly recognized symptoms of COVID-19 are fever, cough, myalgia, expectoration, and dyspnea [4], though it is now apparent that COVID-19 has significant extrapulmonary manifestations [5]. Although acute COVID-19-related morbidity and mortality are well documented, emerging evidence suggests that SARS-CoV-2 may also lead to long-term medical and neuropsychiatric sequelae. Indeed, the United Kingdom COVID Symptom Study found that about 10% of infected persons have illness that lasts longer than three weeks [6].

Here, we discuss potential long-term complications of COVID-19 in light of known sequelae of the previous widespread coronavirus infections Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). We suggest that a potential wave of chronic complications associated with COVID-19 requires a broad response from the public health sector in North Carolina. The following is a survey of select potential COVID-19 long-term sequelae and is not intended to be an exhaustive review.

History of Widespread Coronavirus Infections

SARS-CoV-2 is the third coronavirus to cause widespread infection in the 21st century. From 2002 to 2003, the SARS-associated coronavirus (SARS-CoV), the virus causing SARS, spread from China to 28 other countries and infected over 8,000 people, killing 774 [7]. MERS, caused by MERS coronavirus (MERS-CoV), emerged in 2012 in Saudi Arabia. By May 31, 2015, there had been 1,180 laboratory-confirmed infections caused by MERS-CoV with 483 deaths, approximately a 40% mortality rate [8].

Sequelae of SARS-CoV-2 Infection

Pulmonary Sequelae

Similar to both SARS and MERS, the most apparent acute complication described early in the COVID-19 pandemic was severe pulmonary disease requiring high rates of mechanical ventilation [9]. Pulmonary embolisms triggered by SARS-CoV-2 have an additive burden to respiratory compromise in many with COVID-19 [10]. In the case of SARS, cohort studies have evaluated the long-term pulmonary sequelae of SARS-CoV infection. In Hong Kong, a prospective cohort of 123 participants previously hospitalized with SARS-CoV were followed for two years after infection. For those who completed all follow-up visits over the two-year period, 52% had persistent impairment in their pulmonary diffusion capacity [11]. Another prospective cohort of 71 SARS-infected health care workers in Beijing found that, at 15-year follow-up, participants had persistent mildly impaired lung function, although most of the decline occurred in the first year post-infection. Notably, despite no marked improvement in diffusion capacity, pulmonary function did not decline significantly over the duration of the study [12].

Studies of SARS-CoV-2 are still emerging, but persistent decreases in diffusion capacity in recovered patients have

Electronically published January 4, 2021.

Address correspondence to Robert Rolfe, Duke University Medical Center, 315 Trent Dr, Hanes House, Durham, NC 27710 (Robert.Rolfe@duke.edu).

N C Med J. 2021;82(1):75-78.
0029-2559/2021/82117

been reported three months after discharge [13]. A single center retrospective study of 143 patients in Italy found that 87.4% of patients continued to have at least one symptom, namely dyspnea or fatigue, two months after recovering from acute SARS-CoV-2 infection [14].

Cardiovascular Sequelae

Little is known about the acute and long-term cardiovascular impacts of SARS, though MERS-associated myocarditis leading to persistent systolic dysfunction has been reported [15]. Acute cardiovascular complications, such as acute coronary syndrome, myocarditis, arrhythmias, and heart failure, have been widely reported in patients with COVID-19 [16]. In one meta-analysis, the prevalence of myocardial injury in patients with COVID-19 was 5%-38% [17]. The long-term implications of increased acute cardiovascular complications in COVID-19 are less clear. However, in one observational cohort of 100 patients recovered from COVID-19, 78% had abnormal findings on cardiovascular MRI at a median of 71 days after diagnosis, independent of preexisting comorbidities, most pointing toward ongoing perimyocarditis [18]. In this same report, 36% of patients reported persistent dyspnea and exhaustion [18]. Patients with ventricular dysfunction, myocarditis, or pericarditis may require at least 3-6 months abstention from intense exercise to avoid worsening cardiovascular compromise or death [6].

Neuropsychiatric and Cerebrovascular Sequelae

SARS has been associated with long-term neuropsychiatric morbidity. In one cohort study of 99 SARS survivors, 33.5% of patients were diagnosed with a psychiatric disorder 30 months post-SARS infection, while only 6% of patients had a documented mental illness prior to SARS infection [19]. Furthermore, a meta-analysis of patients who were infected with either SARS or MERS reported 39% of patients had posttraumatic stress disorder (PTSD), and 30%-33% had anxiety and depression, respectively [20]. In a larger cohort study of 233 SARS survivors at 4 years post-SARS infection, over 40% of patients had active psychiatric illness [21]. The most commonly reported diagnoses in both reports were depression and PTSD [21]. A meta-analysis of psychiatric and neuropsychiatric presentations for severe coronavirus infections found that nearly 19% of patients with SARS or MERS had impaired memory between 6 weeks and 39 months post-infection [22].

Although long-term neuropsychiatric outcomes of COVID-19 are yet to be determined, acute neuropsychiatric symptoms have been reported in 40%-88% of patients with severe acute COVID-19 [23]. In a United Kingdom surveillance study of 125 unique cases of SARS-CoV-2 infection, 77 patients presented with a cerebrovascular event and 39 presented with altered mental status. Mania, depression, and catatonia have also been reported [24].

Cerebrovascular events like acute strokes have also been associated with COVID-19. These are thought to be related to abnormal blood clotting in the brain, and likely share a similar cause or set of causes as pulmonary emboli, or blood clots in the lungs, as blood vessels in the lungs and brain both have the receptor angiotensin converting enzyme-2 that is targeted by SARS-CoV-2 [25].

Consequences of COVID-19 Therapies

A number of therapeutics, such as anti-inflammatories, antivirals, or immunomodulators, have been repurposed for treatment of COVID-19. The use of corticosteroids in critically ill patients does appear to reduce 28-day all-cause mortality and should be used when needed [26]. However, high-dose corticosteroid use could cause long-term issues for recipients. In a study of 71 survivors of SARS who received short-term high-dose steroids who were followed for 15 years, 15 had femoral head necrosis thought to be related to their steroid use, with four cases of poor mobility due to resulting arthritis [12].

Indirect Consequences of COVID-19

In the 10 weeks after a national emergency was declared in the United States due to COVID-19, the rates of emergency department visits for heart attacks and strokes decreased by 23% and 20%, respectively [27]. The long-term morbidity from these untreated or unrecognized acute neurovascular or cardiovascular events poses a large indirect burden associated with the pandemic. A study in Italy showed a decrease of 55% in the number of emergency department visits between February and April 2020 compared to the same period in 2019 [28]. With this decrease in presentations, there was a concomitant increase in patients presenting with acute or chronic heart failure, an increase in those requiring intensive care, and higher rates of atrial fibrillation, ischemic heart disease, and severe renal dysfunction, all suggesting that delayed presentation to health care led to decompensation of chronic comorbidities [28].

Many medical clinics across the world were temporarily closed, while others still remain closed to in-person visits. This has led to delayed (or missed) primary care, including vaccinations for both adults and children, delays in cancer screening, and delays in other age-specific health screening. In the United States, 33% of those living in rural areas do not have high-speed internet access that would be able to support a video telehealth visit [29]. This has the potential to perpetuate or increase barriers to care for underserved or rural populations.

An additional unintended side effect of the pandemic is the rising rate of unemployment, which may directly or indirectly compound the burden of COVID-19-related medical and psychiatric sequelae. As many individuals receive employer-related health and dental insurance, rising rates of unemployment have the potential to further impact access to care [30].

Preparing for Long-term Sequelae

Management of the persistent symptoms or the potential long-term sequelae related to the COVID-19 pandemic will require thoughtful and concerted efforts to first identify and then to treat. There need to be well-designed prospective cohort studies for structured surveillance for long-term effects. It will be imperative that these studies work to have appropriate representation from the populations that have been disproportionately affected by COVID-19, including geriatric populations and Latinx and African American communities. Some hospitals have begun to create COVID-19 follow-up clinics for those suffering from persistent disease related to COVID-19. The North Carolina Department of Health and Human Services has also supported projects looking into the impact of COVID-19 in marginalized communities [31].

Policy Efforts

In North Carolina, we would encourage developing common standards for the surveillance of symptoms or sequelae related to COVID-19. Improved surveillance for acute disease should be mirrored by improving surveillance methods for long-term complications.

Resources should be dedicated to providing care to those who have been affected and continue to have symptoms. This could include the creation of educational material that can be shared with the community at large or targeted toward those primarily affected. Creation of COVID-19 follow-up clinics could be incentivized or subsidized, particularly if care is provided for populations who typically face disparities in health care. It is likely that the number of individuals requiring rehabilitation services will increase both from ongoing complications of COVID-19 and from morbidity suffered from deferred care during the pandemic. There should be efforts made to strengthen or expand these services to meet these needs. Post-COVID-19 clinics that combine specialist care and rehabilitation for people who had COVID-19 have started to be established around the United States [32]. Some of the provisions described may be well suited to telemedicine, which has flourished during the pandemic as social and medical distancing has become a necessity.

Campaigns to encourage catch-up vaccine schedules in pediatric populations will be crucial in ensuring vaccine-preventable diseases do not reemerge in the United States as a result of the pandemic. The Centers for Disease Control and Prevention has detailed guidelines for how best to perform catch-up vaccines for children and adolescents, and they recommend implementing reminder and recall systems to identify patients who have missed vaccine doses [33]. It will be important for these reminder systems to be implemented across the state.

Decreasing rates of concomitant risk factors for the general population could help decrease long-term sequelae from the COVID-19 pandemic. Modifiable risk factors for organ dysfunction like tobacco abuse, poor physical activity, poor diets, or poor glucose control in diabetic patients are potential targets. Stricter regulations on smoking and vaping accompanied by incentives or support for those trying to quit could help assuage the compound risks of smoking and prior COVID-19 on the development of progressive declines in lung function.

The many potential mental health repercussions from the COVID-19 pandemic warrant increased funding for psychiatric services, collaboration between primary care providers and psychiatrists in mental health care, and internet-based mental health resources [34].

Conclusion

Despite growing knowledge of acute COVID-19-related disease, evidence of potential long-term consequences remains scant and research in this field is in its infancy. Continuing support for public health and surveillance is critical to identifying emerging direct and indirect negative consequences of COVID-19. Collaboration from researchers, clinicians, and policymakers is also needed to ameliorate disease-related sequelae. NCMJ

Robert J. Rolfe, MD fellow, Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, North Carolina.
Colin M. Smith, MD resident, Department of Medicine and resident, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina.
Cameron R. Wolfe, MBBS(Hons), MPH associate professor of medicine, Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, North Carolina.

Acknowledgments

The opinions expressed in this article represent those of the authors and do not represent official policy of Duke University Medical Center, the US Government, or any of its agencies.

Potential conflicts of interests. The authors report no conflicts of interest.

References

1. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. CSSE website. https://coronavirus.jhu.edu/map.html. Updated daily. Accessed October 5, 2020.
2. U.S. Treasury Department. Interim Report of Costs Incurred by State and Local Recipients through June 30. Washington, DC: U.S. Treasury Department; 2020. https://home.treasury.gov/system/files/136/Interim-Report-of-Costs-by-Category-Incurred-by-State-and-Local-Recipients-through-June-30.pdf. Revised August 24, 2020. Accessed October 5, 2020.
3. Turner NA, Pan W, Martinez-Bianchi VS, et al. Racial, ethnic, and geographic disparities in novel coronavirus (SARS-CoV-2) test positivity in North Carolina. Open Forum Infect Dis. 2020. https://doi-org.proxy.lib.duke.edu/10.1093/ofid/ofaa413
4. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92(6):577-583. doi: 10.1002/jmv.25757
5. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-1032. doi: 10.1038/s41591-020-0968-3
6. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026. doi: 10.1136/bmj.m3026
7. Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome.

Nat Med. 2004;10(12 suppl):S88-S97. doi:10.1038/nm1143
8. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015;386(9997):995-1007. doi: 10.1016/S0140-6736(15)60454-8
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. doi: 10.1001/jama.2020.1585
10. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-147. doi: 10.1016/j.thromres.2020.04.013
11. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010;15(3):543-550. doi: 10.1111/j.1440-1843.2010.01720.x
12. Zhang P, Li J, Liu H, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res. 2020;8:8. doi: 10.1038/s41413-020-0084-5
13. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. doi: 10.1016/j.eclinm.2020.100463
14. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-605. doi: 10.1001/jama.2020.12603
15. Alhogbani T. Acute myocarditis associated with novel middle east respiratory syndrome coronavirus. Ann Saudi Med. 2016;36(1):78-80. doi: 10.5144/0256-4947.2016.78
16. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol. 2020;5(7):831-840. doi: 10.1001/jamacardio.2020.1286
17. Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Acute myocardial injury in patients hospitalized with COVID-19 infection: A review. Prog Cardiovasc Dis. 2020;S0033-0620(20)30123-30127. doi: 10.1016/j.pcad.2020.05.013
18. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;e203557. doi: 10.1001/jamacardio.2020.3557
19. Mak IWC, Chu CM, Pan PC, Yiu MGC, Chan VL. Long-term psychiatric morbidities among SARS survivors. Gen Hosp Psychiatry. 2009;31(4):318-326. doi: 10.1016/j.genhosppsych.2009.03.001
20. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. J Rehabil Med. 2020;52(5):jrm00063. doi: 10.2340/16501977-2694
21. Lam MHB, Wing YK, Yu MWM, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Arch Intern Med. 2009;169(22):2142-2147. doi: 10.1001/archinternmed.2009.384
22. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611-627. doi: 10.1016/S2215-0366(20)30203-0
23. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690. doi: 10.1001/jamaneurol.2020.1127
24. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 2020;7(10):875-882. doi: 10.1016/S2215-0366(20)30287-X
25. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. Cell. 2020;183(1):16-27.e1. doi: 10.1016/j.cell.2020.08.028
26. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020;324(13):1-13. doi: 10.1001/jama.2020.17023
27. Lange SJ, Ritchey MD, Goodman AB, et al. Potential indirect effects of the COVID-19 pandemic on use of emergency departments for acute life-threatening conditions - United States, January-May 2020. MMWR Morb Mortal Wkly Rep. 2020;69(25):795-800. doi: 10.15585/mmwr.mm6925e2
28. Colivicchi F, Di Fusco SA, Magnanti M, Cipriani M, Imperoli G. The impact of the coronavirus disease-2019 pandemic and Italian lockdown measures on clinical presentation and management of acute heart failure. J Card Fail. 2020;26(6):464-465. doi: 10.1016/j.cardfail.2020.05.007
29. Hirko KA, Kerver JM, Ford S, et al. Telehealth in response to the Covid-19 pandemic: implications for rural health disparities. J Am Med Inform Assoc. 2020;ocaa156. doi: 10.1093/jamia/ocaa156
30. Choi SE, Simon L, Riedy CA, Barrow JR. Modeling the impact of COVID-19 on dental insurance coverage and utilization. J Dent Res. 2020:22034520954126. doi: 10.1177/0022034520954126
31. NCDHHS Identifica a Organizaciones para Enfocarse en el Impacto de COVID-19 en la Comunidad LatinX [press release]. Raleigh, NC: NC Department of Health and Human Services; 2020. https://files.nc.gov/ncdhhs/press-release/files/NCDHHS%20Selects%20Organizations%20to%20Address%20Impact%20of%20COVID-19%20on%20LatinX%20Community-Spanish.pdf. Published 2020. Accessed 26 October 2020.
32. Weiner S. Post-COVID-19 clinics help survivors recover. AAMC.org. https://www.aamc.org/news-insights/post-covid-19-clinics-help-survivors-recover. Published August 25, 2020. Accessed October 5, 2020.
33. Centers for Disease Control & Prevention. Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic. CDC website. https://www.cdc.gov/vaccines/pandemic-guidance/index.html. Published 2020. Accessed 20 October 2020.
34. Öngür D, Perlis R, Goff D. Psychiatry and COVID-19. JAMA. 2020;324(12):1149-1150. doi: 10.1001/jama.2020.14294