Persistent and Emergent Clinical Sequelae of Mild COVID-19

Victoria Tucci; Joan Saary

BACKGROUND: Knowledge of the clinical course and consequences of COVID-19 initially evolved in the context of severe presentations and among those with comorbidities. However, understanding the outcomes of milder infections in healthy individuals is important for safe return-to-duty in extreme environments or to occupations requiring significant fitness. We reviewed the literature to characterize the nature and timing of persistent and emergent clinical sequelae in milder COVID-19 cases to facilitate development of post-COVID-19 screening and surveillance protocols.

METHODS: We searched databases including EMBASE, MEDLINE, Cochrane COVID-19 study register, gray literature, clinical trial registries, and relevant health and disease prevention sources for publications from 2019 to February 18th, 2021, documenting COVID-19 sequelae. Articles were included if the COVID-19 severity was mild and there were no, or only minor, pre-existing comorbidities. Persistent and emergent sequelae were then stratified based on time since diagnosis.

RESULTS: Among those with mild COVID-19, sequelae were shown to emerge or persist for months following presumed recovery. Among those with no comorbidities, cardiac, hematological, and respiratory sequelae emerged after 1-2 mo, and primarily cardiac abnormalities persisted at ≥ 3 mo. Among those with minor comorbidities, persistent respiratory abnormalities, fatigue, dyspnea, and headache were common, and mental health symptoms emerged by 1-2 mo postinfection.

DISCUSSION: After presumed recovery from mild COVID-19, a range of symptoms can persist and later emerge. Whether these are new or previously unrecognized is unclear. Under-recognized COVID-19 sequelae may increase the risk of subtle or sudden incapacitation and have implications for return-to-work (RTW) screening and surveillance for safety-critical roles.

KEYWORDS: COVID-19, SARS-CoV-2, mild COVID-19, coronavirus infections, sequelae, persistent symptoms, non-hospitalized.

Tucci V, Saary J. *Persistent and emergent clinical sequelae of mild COVID-19*. Aerosp Med Hum Perform. 2021; 92(12):962–969.

The emergence of COVID-19 caused by SARS-CoV-2 quickly evolved into a global pandemic.[63] Much has already been learned about the clinical course and health consequences of this novel disease, particularly in association with severe presentations and hospitalized patients. However, approximately 80% of individuals are managed as outpatients.[68] To date, research regarding the clinical sequelae of nonhospitalized individuals with no, or only minor, pre-existing conditions who suffered asymptomatic or mild COVID-19 is comparatively lacking.

Although limited, some evidence has suggested that among those with a milder course of COVID-19, sequelae can persist for weeks to months beyond the acute illness.[17,28,35,36,68] There are also increasing reports of emergent adverse health events post-acute infection that introduce concern about the risk for sudden or subtle incapacitation. Documented post-acute sequelae broadly include cardiac, hematological, respiratory, and neurological abnormalities, among others.[7,9,17,28,30,35,68]

Since COVID-19 is a novel disease, postrecovery follow-up durations rarely extend beyond 6 mo at the time of this review.[37] However, based on clinical knowledge about long-term outcomes from other coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), it seems reasonable to suspect that COVID-19 may have post-acute effects, and that

From the Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; Division of Occupational Medicine, Department of Medicine, University of Toronto, Toronto, ON, Canada; and Canadian Forces Environmental Medicine Establishment, Toronto, ON, Canada.

This manuscript was received for review in March 2021. It was accepted for publication in August 2021.

Address correspondence to: Victoria Tucci, BHSc (Hons) Candidate, Honours Health Sciences Program, Faculty of Health Sciences, McMaster University, 19 Esposito Drive, Bolton, ON L7E 1T3, Canada; tucciv1@mcmaster.ca.

DOI: https://doi.org/10.3357/AMHP.5892.2021

they may occur in multiple physiological systems, such as the pulmonary, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems.[4,37,74]

Occupational exposures (e.g., hypoxia, G-forces, etc.) in some high-performance operational populations are likely to affect these same systems. New or previously unrecognized sequelae of COVID-19 could thus have implications for fitness to return-to-work (RTW) for safety-sensitive trades, such as aircrew and divers.

We, therefore, performed a review of the literature to better characterize the persistent and emergent sequelae of asymptomatic and relatively mild COVID-19. We focused on relatively healthy patients with no, or only minor comorbidities because these characteristics are most representative of highly screened populations, such as aircrew, divers, military personnel, athletes, etc. Due to minimal tolerance for sudden and subtle incapacitation in these work environments, improved awareness of COVID-19 sequelae is important for post-COVID-19 RTW policy development, and to inform postrecovery surveillance for safety-sensitive trades.

METHODS

Literature Review

A comprehensive review of the literature was conducted to identify studies which describe the nature and temporality of emergent and persistent sequelae of mild COVID-19 in relatively healthy individuals (**Fig. 1**). Both peer-reviewed and preprint articles published or available between 2019 to February 18th, 2021, were eligible for inclusion. Studies of interest included those that reported persisting symptoms or emerging adverse effects postmild COVID-19. Studies were not excluded based on design.

Relevant studies were identified by searching databases including Ovid MEDLINE, Ovid EMBASE, the Cochrane COVID-19 Study Registry, the OMA Research Portal COVID-19 Clinical Trials, and Google Scholar. Health and disease prevention sites (e.g., World Health Organization (WHO), Centre for Disease Control and Prevention (CDC), Center for Infectious Disease Research and Policy (CIDRAP), etc.), gray literature sources (including the medRxiv preprint server), as well as organizational guidelines and repositories were manually searched for additional relevant information.

Search terms included ("COVID-19" OR "Novel corona virus" OR "Sars-cov-2" OR "corona virus") AND ('long term' or 'sequelae' or ' follow up' or 'discharge' or 'outcome' or 'emerg*' or 'persist*'), as well as physiological system-specific descriptors (search strategy available upon request). The search terms were used in combination with MeSH terms to extend the comprehensiveness of the literature searches. Only human studies were reviewed. Additional references were identified from the citations of relevant articles. We also searched the literature with specific interest in the sequelae of mild and asymptomatic COVID-19 in athletic populations, as these are highly screened individuals with substantial preinfection fitness. This allowed for increased applicability of the results to a screened and healthy population.

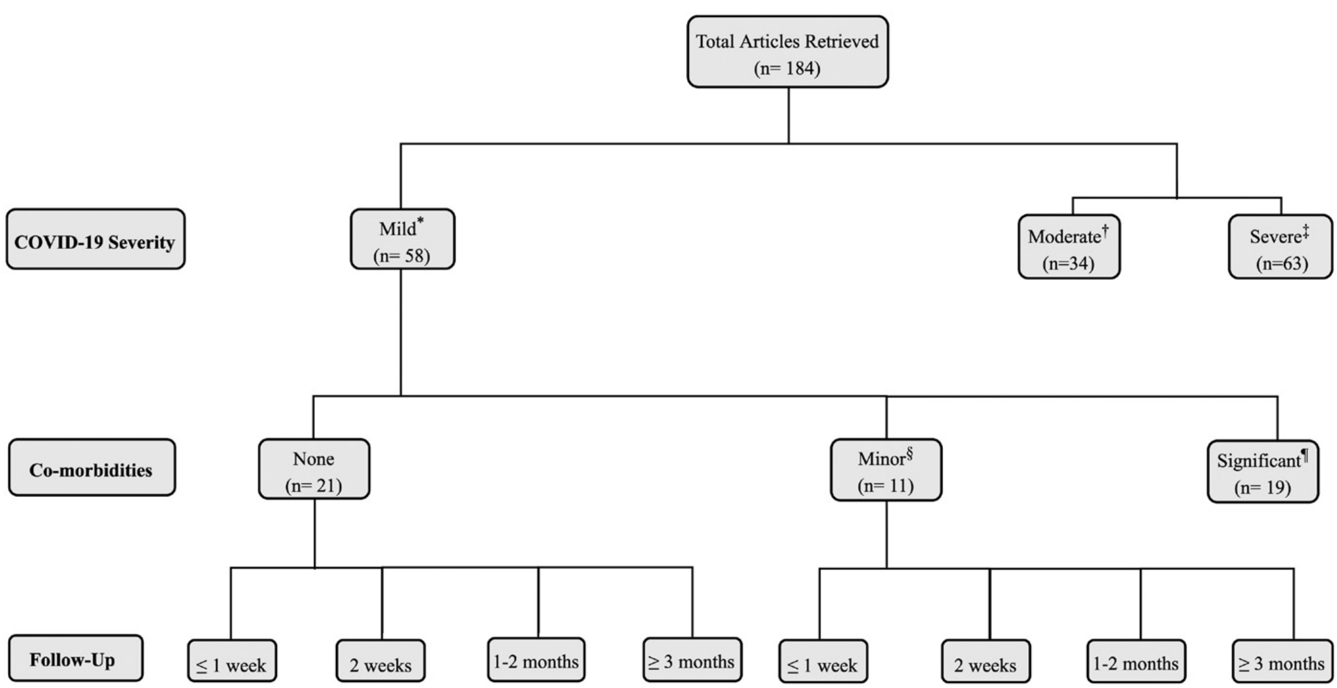

Fig. 1. Literature search and article retrieval process. *Primarily nonhospitalized individuals, but categorized based upon severity designation stated in the individual studies; †primarily non-ICU hospitalized patients; ‡primarily hospitalized patients admitted to the ICU; §comorbidities considered minor included treated hypertension, treated thyroid disorders, and treated high cholesterol; ¶any other stated comorbidity including diabetes mellitus, respiratory and heart disease.

Data extracted from primary studies included study features (location, research question/purpose, research design, principal organ system), temporality (months until follow-up, duration of COVID-19, duration of sequelae), severity of COVID-19, and the type of sequelae assessment measures. Relevant information and recommendations from medical associations ($N = 2$), international health and disease prevention organizations and societies ($N = 10$), and government agencies ($N = 3$) were also considered. A single reviewer recorded data that were then verified by an independent second reviewer.

Classification of COVID-19 Severity, Sequelae, and Duration of Follow-Up

For this review, the COVID-19 severity designations were based upon severity definitions in the individual studies. When classifying studies by COVID-19 severity, we found significant inconsistency in these definitions between studies. Nonetheless, mild COVID-19 usually entailed nonhospitalized individuals. Moderate COVID-19 primarily considered non-ICU hospitalized patients, and severe COVID-19 was primarily hospitalized patients admitted to the ICU.

Persistent sequelae were defined as those lasting from initial patient assessment and/or acute phase of COVID-19 through to the follow-up time in the study. Conversely, emergent sequelae were defined as those that were not present as part of the initial presentation and/or acute phase of COVID-19 but emerged thereafter, by the follow-up time.

We stratified both persistent and emergent sequelae by broad follow-up time intervals of ≤ 1 wk, 2 wk, 1–2 mo, and ≥ 3 mo based on recurrent trends in the literature regarding COVID-19 patient follow-up periods. Studies with similar follow-up times were then grouped together to examine and compare sequelae occurring within each of these intervals.

Analysis

The initial searches generated a total of 184 articles for retrieval. These were then reviewed in detail to identify those that contained results of clinical follow-up of individuals specifically experiencing mild or asymptomatic COVID-19. Studies discussing moderate and/or severe COVID-19, as well as those with insufficient detail about severity or duration of follow-up resulted in the exclusion of 126 articles. The study populations of the remaining 58 articles were examined in greater detail to exclude studies in which participants had significant comorbidities. The rationale for this was to ensure comparability of the final sample to a screened and healthy population. Comorbidities other than treated hypertension, treated thyroid disorders, and treated high cholesterol were considered significant; such illnesses included diabetes mellitus and pre-existing respiratory and heart diseases. This resulted in the further elimination of 26 articles: 19 articles in which study participants had significant comorbidities and 7 articles due to the lack of comorbidity delineation, or because clinical results were based on patient self-reports on social media platforms. The remaining 32 articles were retained for inclusion in the final summary in which studies presenting sequelae in those with no and minor comorbidities were stratified by follow-up period (Fig. 1).

RESULTS

Both persistent and emergent sequelae over the course of follow-up at four separate time intervals (≤ 1 wk, 2 wk, 1-2 mo, and ≥ 3 mo) are presented for those with no comorbidities (**Table I**) and with minor comorbidities (**Table II**).

Among individuals with "no known pre-existing comorbidities," the main persistent sequelae reported at 2 wk included cough, fatigue, and dyspnea.[64] At a follow-up time of 1–2 mo, common reported sequelae included chest pain, fatigue, and dyspnea,[1,14,20,67] with difficulty concentrating, memory loss, and anosmia/ageusia being among the less commonly reported persistent symptoms at this follow-up time.[20,26,41] Persistent sequelae identified at a follow-up time of ≥ 3 mo included primarily cardiac findings, such as myo- and pericarditis, pericardial effusion, and peri-, epi- and intramyocardial enhancement upon imaging.[56] Similar to persistent sequelae identified at 1–2 mo, chest pain, memory loss, and anosmia/ageusia were also reported at ≥ 3 mo postmild SARS-CoV-2 infection (Table I).[20] Interestingly, at a follow-up time of 1–2 mo after mild or asymptomatic COVID-19, no significant clinical or biomarker abnormalities were detected in elite soccer athletes.[41] Although high sensitivity cardiac troponin I (hs-cTnI) elevation was more prevalent in the infected group, it was rare and not significantly associated with previous SARS-CoV-2 infection or with cardiac pathology.[41] In another professional athletic population, a comprehensive screening protocol consisting of blood tests, spirometry, resting ECG, stress-test ECG with oxygen saturation monitoring, and echocardiogram did not reveal significant abnormalities after recovery from asymptomatic or mild COVID-19.[26]

By comparison, persistent sequelae reported in patients with "minor comorbidities" at a follow-up time of 2 wk included impaired diffusing capacity, and progressive lung fibrosis upon absorption of pulmonary lesions in older patients (Table II).[23,44] The common sequelae persisting at 1–2 mo included chest pain, anosmia/ageusia, dyspnea, and fatigue, similar to those with no comorbidities at this time period in recovery.[50,65] Headache was also reported in patients with minor comorbidities, but not in patients without comorbidities. Persistent sequelae identified at a follow-up time of 3 mo primarily included dyspnea, fatigue, and behavioral impairment, the latter occurring in patients with minor comorbidities but not in patients without (Table II).[28,71] Sequelae, such as respiratory symptoms and imaging anomalies, tended to be reported in studies where outcomes could not be stratified based on comorbidities. As a result, we labeled these as 'possibly confounded'. In these instances, it was not known whether the reported sequelae occurred in the specific portion of the population with comorbidities, or if a particular comorbidity was associated with an increased sequelae incidence.[29,31] Notable (but possibly confounded) sequelae that occurred only in patients with minor

Table I. Persistent and Emergent Sequelae Stratified by Follow-Up Time in Patients With Mild COVID-19 and No Comorbidities.

Comorbidities:	**None**			
Follow-Up Time	**≤ 1 wk**	**2 wk**	**1–2 mo**	**≥ 3 mo**
Persistent Sequelae		• Cough[64] • Fatigue[64] • Dyspnea[64]	• Chest pain[1,20] • Muscle weakness[20] • Fatigue[1,67] • Dyspnea[1,14] • Anosmia/Ageusia[20] • Difficulty concentrating[20] • Memory loss[20] • None[26,41,*]	• Myocarditis[56] • Perimyocarditis[56] • Pericardial effusion and enhancement[56] • Epicardial enhancement[56] • Intramyocardial enhancement[56] • Intracellular edema of cardiomyocytes[56] • Acute lymphocytic infiltration[56] • Bone/joint pain[20] • Chest pain[20] • Confusion[20] • Memory loss[20] • Anosmia/ Ageusia[20]
Emergent Sequelae	• Pulmonary embolism[46] • Acute myo-pericarditis[33] • Large vessel stroke[51] • Herpes zoster[25]	• Bilateral spontaneous pneumothorax[29] • Myocarditis[57] • Pericardial effusion[57] • Monoclonus cerebellar ataxia[24] • None [26,69,*] **Imaging Anomalies** • Abnormal T2 values[57] • Late gadolinium enhancement[57] *Possibly Confounded*[†] • *Liver injury*[34]	• Pulmonary embolism[5,14] • DVT[5] • Myocardial strain abnormalities[16] • Myocarditis[21,57] • Pericarditis[21] • Late gadolinium enhancement[21] • Left ventricle dysfunction[21] • Pericardial effusion[16,52,57] • Pericardial enhancement[16] • Dyspnea [1, ‡] • Fatigue[1, ‡] • Chest pain [1, ‡] • None [26, 69,*] **Imaging Anomalies** • Ground glass opacities[52] • Late gadolinium enhancement[57] • Increased T1[16] • Abnormal T2[57]	• Rise of troponin T levels[56] **Imaging Anomalies** • Raised native T1 & T2[56] • Late gadolinium enhancement[56] • None[69,*]

*No significant adverse outcomes at follow-up; these studies tended to involve athletes.
†Comorbidities not separated based on our aircrew definition and outcomes not stratified by comorbidities, therefore, classification of outcomes was conservative.
‡Sequelae re-emerged.

comorbidities included numbness in extremities, impaired mobility, and hearing loss (Table II).[39]

We also examined what we have called *emergent* sequelae, i.e., sequelae that emerged after a period of presumed complete recovery of mild or asymptomatic COVID-19 (e.g., resumption of usual function). Among those with no comorbidities, pulmonary embolism, acute myo-pericarditis, and large vessel stroke were notable emergent adverse events at a follow-up time of ≤ 1 wk (Table I).[33,46,51] Important emergent sequelae at 2 wk included pneumothorax, myocarditis, pericardial effusion, and monoclonus cerebellar ataxia.[24,29,57] Emergent cardiovascular and pulmonary imaging anomalies, as well as liver injury, were also reported sequelae at 2 wk.[34,57] The majority of the emergent sequelae occurred at a follow-up time of 1–2 mo. These consisted of adverse cardiac, hematological, and respiratory findings.[1,5,14,16,21,52,57] Emergent sequelae identified at a follow-up time of ≥ 3 mo primarily included a rise in troponin T levels and cardiovascular imaging anomalies (Table I).[56] Studies in which no significant emergent events occurred at various follow-up times tended to involve athletic populations.[26,69] A study by Vago et al., revealed that athletes who recently recovered from COVID-19 did not show signs of cardiac involvement on cardiac magnetic resonance.[69]

By comparison, emergent sequelae (after presumed recovery from mild COVID-19) reported in those with minor comorbidities at a follow-up time of ≤ 1 wk included stroke, transverse myelitis, and intracranial hypertension, the latter two of which did not occur in patients with no comorbidities (Table II).[8,61,62] The majority of emergent sequelae among those with minor comorbidities appeared to occur at 1–2 mo postinfection and included insomnia and mental health symptoms, which did not occur among those with no comorbidities.[42,65] Although possibly confounded, impaired diffusing capacity was also found to only occur in patients with minor comorbidities at this follow-up period (Table II).[31] Emergent sequelae identified at a follow-up time of ≥ 3 mo primarily also included impaired diffusing capacity, as well as brain imaging volumetric and microstructural abnormalities (Table II).[39,44]

Table II. Persistent and Emergent Sequelae Stratified by Follow-Up Time in Patients With Mild COVID-19 and Minor Comorbidities.

Comorbidities:	**Minor**			
Follow-Up Time	**≤ 1 wk**	**2 wk**	**1-2 mo**	**≥ 3 mo**
Persistent Sequelae		• **Progressive lung fibrosis as lesions absorbed (older patients)[23]** • **Impaired diffusing capacity[44]**	• **Headache[65]** • Chest pain[65] Dyspnea[50,65] • Fatigue[50,65] • Anosmia/ageusia[50] • None[58*] *Possibly Confounded*[†] • *Respiratory symptoms*[29] • *Imaging anomaly (ground glass opacities)*[31] • *Altered DLCO*[66] • *Asthenia*[29] • *Anosmia*[29] • *Dysgeusia*[29]	• Dyspnea[28,71] • Fatigue[28,71] • **Decreased HRQoL[71]** • **Behavioral impairment[71]** *Possibly Confounded*[†] • ***Numbness in extremities[39]*** • ***Impaired mobility[39]*** • ***Hearing loss[39]*** • *Headache*[39] • *Anosmia*[39]
Emergent Sequelae	• **Transverse myelitis[61]** • Stroke[8] • **Intracranial Hypertension[62, ‡]**		• Joint pain[65] • Dementia[65] • **Insomnia[42]** **Mental Health** • **Depression[42,65]** • **Anxiety[42,65]** • **PTSD[42]** • **Obsessive compulsive symptoms[42]** *Possibly Confounded*[†] • *Pulmonary embolism*[29] • *Liver function abnormalities*[6] • ***Impaired diffusing capacity[31]***	*Possibly Confounded*[†] • *Impaired diffusing- capacity*[44] • *Memory loss*[39] • ***Volumetric & microstructural abnormalities in central olfactory cortices & partial right hemisphere white matter[39]*** • *Myalgia*[39]

Note: Bolded events occurred in patients with minor comorbidities but not in patients with no comorbidities.
*Mo significant adverse outcomes at follow-up; these studies tended to involve athletes.
[†]Comorbidities not separated based on our aircrew definition and outcomes not stratified by comorbidities, therefore, classification of outcomes was conservative.
[‡]Hospitalized, but considered mild by the respective study.

DISCUSSION

With the passage of time, studies discussing post-acute effects of COVID-19 are becoming available, primarily among hospitalized populations who thus represent more severe cases.[45] The unique aspect of our study is the focus on relatively healthy, nonhospitalized individuals with mild COVID-19, as we sought to examine emergent and persistent sequelae to inform RTW considerations for high-performance, safety sensitive populations. Our findings tend to be consistent with a small emerging body of research focusing on nonhospitalized individuals.[38,40] Overall, it is apparent that COVID-19 not only poses health concerns during the infection phase, but also in the post-acute recovery period, and that the health impacts of COVID-19 do not solely affect multimorbid patients with severe infection. Our findings are relevant for RTW decisions and screening and surveillance protocol development in safety-sensitive occupations that require individuals to have high levels of fitness to withstand their working environments and maintain a predictably low risk for causes of subtle or sudden incapacitation.

As a result of our findings, we sought to examine COVID-19 sequelae identified in athletic populations, as these highly screened individuals are generally healthy and have high levels of fitness pre-COVID-19. Such population characteristics increase the relevance and applicability of results regarding persistent and emergent effects postmild or asymptomatic infection to safety-sensitive trades and high-performance operator populations that require optimal health.

In athletes, cardiac involvement appeared to be among the most common identified sequelae, which included myocardial and pericardial effusion, late gadolinium enhancement, physical function and fitness impairment, myocarditis, pericarditis, and left ventricular dysfunction (Table I).[16,21,57,59] These results introduce concern for highly active populations because cardiac pathology can be exacerbated by exercise during the acute phase of viral myocarditis.[55]

A recent study by Puntmann et al. reported cardiovascular magnetic resonance imaging consistent with signs of cardiac involvement and ongoing inflammation in over two-thirds of recovered patients two months after COVID-19.[56] These findings are relevant to highly active populations, such as athletes, in whom myocarditis is a risk factor for sudden cardiac death.[53,70] Rajpal et al. studied athletes recovering from asymptomatic or mild COVID-19.[57] Despite no control group, they reported myocardial late gadolinium enhancement in 12 participants (46%). However, these subjects did not experience elevated troponins, nor ST/T wave changes on ECG data. T2 mapping revealed signs of edema in 4 out of 12 subjects with late gadolinium enhancement, suggesting that although there is still a risk of acute inflammatory myocardial injury or myocarditis, it can be considered relatively unlikely.[57] Nonetheless, cardiac pathology in the absence of severe COVID-19 symptoms poses a concern for the RTW of high-performance occupations that need to maintain optimal health.[55]

Although some studies did not identify significant COVID-19 sequelae at follow-up, this demonstrates the variability and heterogeneity of the potential lasting health impacts and risks of mild or asymptomatic SARS-CoV-2 infection.[26,41,69] Nevertheless, significant potential consequences have prompted the development of professional consensus statements and organizational guidelines that intend to inform the evaluation of athletes upon COVID-19 recovery to ensure a safe return-to-play/work.

We examined select guidelines, consensus statements, and organizational recommendations regarding post-COVID-19 screening measures, system-specific screening measures, and follow-up guidelines for return-to-play, especially for asymptomatic or mild infection.[3,11,13,15,18,32,48,54,55,72,73] This literature, as well as current data from athletic populations, highlights the gravity of mild COVID-19 sequelae and further corroborates our recommendation to develop specific RTW screening procedures upon recovery from minor illness.

To ensure the absence of cardiac complications associated with mild COVID-19, additional cardiac investigations, such as ECG and cardiac echo, have been recommended before returning to high performance activities.[43] Based on our review of persistent and emergent cardiac sequalae, in combination with the data from athletic populations, and consideration of the environmental stressors to which safety-sensitive and high-performance operator populations are exposed, we support this recommendation to implement cardiac investigations prior to RTW. Additional assessment may be warranted following more severe cases of COVID-19.

Based on findings of notable persistent and emergent respiratory sequelae, as well as emergent liver injury and hematological events like pulmonary embolism, we agree with Wilson et al. and Phelan et al. that it would also be prudent to consider implementing additional laboratory testing when developing RTW policies.[54,55,73] Although dyspnea can be multifactorial, notable nonconfounded respiratory sequelae occurred in those with no comorbidities (ground glass opacities and bilateral spontaneous pneumothorax) and in those with minor comorbidities (progressive lung fibrosis and impaired diffusing capacity). These findings, combined with return-to-play considerations for athletes noted by Wilson et al. and Santos-Ferreira et al., lead us to recommend considering chest X-ray and pulmonary function testing.[60,73]

Gilad et al. outline the Israeli Aeromedical Center's recommendations to flight surgeons regarding the medical examinations required before military aviators return to flight post-COVID-19 recovery.[27] They are consistent with our suggested considerations for lab testing, chest radiography, electrocardiography, pulmonary function testing, and further evaluation in the event of abnormal results. Additional investigation, particularly among those with moderate or severe illness, is also justified.

We concluded that after mild COVID-19 illness, a range of symptoms can persist beyond acute infection, and new symptoms can emerge even after an individual is assumed to have recovered. This prompted us to further question when recovery can be considered complete, and, therefore, at what point enhanced post-illness surveillance can confidently cease. The ultimate duration of persistent symptoms remains unclear, and there is now suspicion that a protracted course of illness may exist.[28]

Research supports a growing concern about a syndrome of 'long COVID-19', also identified as 'chronic COVID-19 syndrome' or 'long-haul COVID-19'.[12,19,49] This condition is characterized by long-term manifestations of SARS-CoV-2 infection that persist beyond the normal convalescence phase and could be a potential explanation for persistent sequelae experienced by recovered COVID-19 patients.[47] Our review is consistent with recent studies on athletic populations, which suggest that young and healthy patients are at risk of suffering from longer COVID-19 postrecovery, even if they only experienced mild disease at the peak of their illness.[16,21,57,59] It is common for patients suffering from long-COVID-19 to report persistent multisystem involvement and substantial functional disability.[22] In a preprint study on long-COVID-19 by Davis et al., the majority of patients failed to return to previous levels of work at 6 mo postinfection, and many still experienced prolonged symptoms at 7 mo.[22] They reported that the most frequent symptoms at 6 mo included fatigue, postexertional malaise, and cognitive dysfunction.[22] There are also post-COVID-19 hubs for patients and researchers dedicated to investigating the persistent sequelae associated with this disease through patient testimonials and patient-led research.[9,10]

Limitations

Due to the novelty of COVID-19, most survivors have only had relatively short follow-up times postrecovery, and data regarding longer-term outcomes of COVID-19 patients postrecovery is limited at this time. The application of statistical analyses and utilization of larger clinical and administrative records databases may offer a more extensive evaluation of COVID-19 sequelae in various populations.[37]

This study is specifically confined to information available as of February 2021, thus we recommend on-going regular review of post-COVID-19 screening and surveillance procedures. Since we completed data gathering, we have already become aware of emerging mental health issues, and new information describing ophthalmological outcomes that may be relevant for screening prior to RTW.[2]

In summary, our findings highlight the need to remain vigilant following seemingly minor infections. Coronaviruses in general have caused repeated outbreaks in recent years and are likely to re-emerge again in the future. Awareness of the timing and spectrum of sequelae associated with seemingly mild illness can be useful not only to guide protocol development for RTW, but also to anticipate the need for increased interval surveillance. The results of this study lead us to make the following key recommendations:

1. Do not underestimate mild illness and assume no sequelae.
2. On-going monitoring even after mild infection is recommended.
3. ECG, cardiac echo, pulmonary testing, labs, and imaging may still be relevant after the point of presumed recovery.
4. As COVID-19 continues to evolve and variants emerge, new sequelae may also emerge as time progresses.

ACKNOWLEDGMENTS

We would like to thank the Royal Canadian Air Force (RCAF), Aerospace and Undersea Medical Board (AUMB) for their positive feedback on an early presentation of this review.

Financial Disclosure Statement: The authors affirm that there are no conflicts of interests.

Authors and Affiliations: Victoria Tucci, HBHSc, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; and Joan Saary, M.D., Ph.D., Division of Occupational Medicine, Department of Medicine, University of Toronto, and Canadian Forces Environmental Medicine Establishment, Toronto, ON, Canada.

REFERENCES

1. Abdallah H, Porterfield F, Fajgenbaum D. Symptomatic relapse and long-term sequelae of COVID-19 in a previously healthy 30-year-old man. BMJ Case Rep. 2020; 13(12):e239825.
2. Abrishami M, Tohidinezhad F, Daneshvar R, Omidtabrizi A, Amini M, et al. Ocular manifestations of hospitalized patients with COVID-19 in northeast of Iran. Ocul Immunol Inflamm. 2020; 28(5):739–744.
3. Aerospace and Undersea Medical Board. FSG 100-05 AIRCREW MEDICAL FITNESS POST COVID-19. Canadian Armed Forces, Aerospace Medicine Authority; 2020. [Accessed 2021 Sept 23]. Available at https://www.aerospacemedicine.ca/FSG100-05.pdf.
4. Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, 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.
5. Alharthy A, Balhamar A, Faqihi F, Alshaya R, Noor A, et al. Insidious development of pulmonary embolism in asymptomatic patients with COVID-19: Two rare case-reports. Respir Med Case Rep. 2020; 31:101186.
6. An Y-W, Song S, Li W-X, Chen Y-X, Hu X-P, et al. Liver function recovery of COVID-19 patients after discharge, a follow-up study. Int J Med Sci. 2021; 18(1):176–186.
7. Arnold DT, Hamilton FW, Milne A, Morley A, Viner J, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. medRxiv. 2020 Aug 14; 2020.08.12.20173526.
8. Ashrafi F, Zali A, Ommi D, Salari M, Fatemi A, et al. COVID-19-related strokes in adults below 55 years of age: a case series. Neurol Sci. 2020; 41(8):1985–1989.
9. Assaf G, Davis H, McCorkell L, Wel H, O'Neil B, et al. Patient led research for COVID-19 long Covid [Internet]. 2020. [Accessed 2021 Feb 22]. Available from: https://patientresearchcovid19.com/.
10. Asthma UK and British Lung Foundation. Post-COVID HUB [Internet]. 2020. [Accessed 2021 Feb 24]. Available from: https://www.post-covid.org.uk/.
11. Baggish A, Drezner JA, Kim J, Martinez M, Prutkin JM. Resurgence of sport in the wake of COVID-19: cardiac considerations in competitive athletes. Br J Sports Med. 2020; 54(19):1130–1131.
12. Baig AM. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. J Med Virol. 2021; 93(5):2555–2556.
13. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med. 2020; 54(16):949–959.
14. Beckman M, Nyrén S, Kistner A. A case-report of widespread pulmonary embolism in a middle-aged male seven weeks after asymptomatic suspected COVID 19 infection. Thromb J. 2020; 18(1):19.
15. British Thoracic Society. British Thoracic Society Guidance on Respiratory Follow Up of Patients with a Clinico-Radiological Diagnosis of COVID-19 Pneumonia V1.2 2020. [Accessed 2021 Feb 16]. Available from: https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/resp-follow-up-guidance-post-covid-pneumonia/.
16. Brito D, Meester S, Yanamala N, Patel HB, Balcik BJ, et al. High prevalence of pericardial involvement in college student athletes recovering from COVID-19. JACC Cardiovasc Imaging. 2021; 14(3):541–555.
17. 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.
18. Centers for Disease Control and Prevention. Late Sequelae of COVID-19 [Internet]. 2020. [Accessed 2021 Feb 24]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html.
19. Centers for Disease Control and Prevention. COVID-19 and Your Health [Internet]. 2020. [Accessed 2021 Feb 23]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html.
20. Cirulli E, Barrett KMS, Riffle S, Bolze A, Neveux I, et al. Long-term COVID-19 symptoms in a large unselected population. medRxiv. 2020 Dec 1; 2020.10.07.20208702.
21. Clark DE, Amar P, Dendy JM, Diamond AB, Kristen G-D, et al. COVID-19 myocardial pathology evaluation in athletes with cardiac magnetic resonance (COMPETE CMR). Circulation. 2021; 143(6):609–612.
22. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. medRxiv. 2020; Dec 27; 2020.12.24.20248802.
23. Deng L, Khan A, Zhou W, Dai Y. Follow-up study of clinical and chest CT scans in confirmed COVID-19 patients. Radiol Infect Dis. 2020; 7(3):106–113.
24. Dijkstra F, Van den Bossche T, Willekens B, Cras P, Crosiers D. Myoclonus and cerebellar ataxia following Coronavirus Disease 2019 (COVID-19). Mov Disord Clin Pract. 2020. [Accessed 2020 Nov 7].
25. Elsaie ML, Nada HA. Herpes zoster (shingles) complicating the course of COVID19 infection. J Dermatolog Treat. 2020; Oct. 12:1–3.
26. Gervasi SF, Pengue L, Damato L, Monti R, Pradella S, et al. Is extensive cardiopulmonary screening useful in athletes with previous asymptomatic or mild SARS-CoV-2 infection? Br J Sports Med. 2020. [Accessed 2020 Oct 22]; Available from: https://bjsm-bmj-com.libaccess.lib.mcmaster.ca/content/early/2020/10/04/bjsports-2020-102789.
27. Gilad D, Gabbai D, Tehori O, Nakdimon I, Bar-Shai A, et al. Return to aviation duty after recovery from COVID-19. J Mil Veteran Fam Health. 2021; 7(2):116–120.
28. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020; Oct 6(4):00542-2020.
29. González-Pacheco H, Gopar-Nieto R, Jiménez-Rodríguez G-M, Manzur-Sandoval D, Sandoval J, Arias-Mendoza A. Bilateral spontaneous pneumothorax in SARS-CoV-2 infection: A very rare, life-threatening complication. Am J Emerg Med. 2021; 39:258.e1–3.
30. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020; 370:m3026.
31. Huang Y, Tan C, Wu J, Chen M, Wang Z, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020; 21(1):163.
32. Ibarrola M, Dávolos I. Myocarditis in athletes after COVID-19 infection: The heart is not the only place to screen. Sports Medicine and Health Science. 2020. [Accessed 2021 Jan. 2].
33. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, et al. Cardiac involvement in a patient with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7):819–824.
34. Kaneko S, Kurosaki M, Nagata K, Taki R, Ueda K, et al. Liver injury with COVID-19 based on gastrointestinal symptoms and pneumonia severity. PLoS One. 2020; 15(11):e0241663.
35. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. BMC Health Serv Res. 2020; 20(1):1144.
36. Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, et al. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. Intern Emerg Med. 2020; 15(5):813–817.

37. Leung TYM, Chan AYL, Chan EW, Chan VKY, Chui CSL, et al. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. Emerg Microbes Infect. 2020; 9(1):2190–2199.
38. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Netw Open. 2021; 4(2):e210830.
39. Lu Y, Li X, Geng D, Mei N, Wu P-Y, et al. Cerebral micro-structural changes in COVID-19 patients – an MRI-based 3-month follow-up study. eclinicalmedicine. 2020; 25:100484.
40. Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, et al. Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. The Lancet Infectious Diseases. 2021. [Accessed 2021 June 6]. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00211-5/abstract.
41. Mascia G, Pescetelli F, Baldari A, Gatto P, Seitun S, et al. Interpretation of elevated high-sensitivity cardiac troponin I in elite soccer players previously infected by severe acute respiratory syndrome coronavirus 2. Int J Cardiol. 2020. [Accessed 2021 Jan. 4]. Available from: http://www.sciencedirect.com/science/article/pii/S0167527320341620.
42. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020; 89:594–600.
43. Metzl JD, McElheny K, Robinson JN, Scott DA, Sutton KM, Toresdahl BG. Considerations for return to exercise following mild-to-moderate COVID-19 in the recreational athlete. HSS J. 2020; 16(S1):102–107.
44. Mo X, Jian W, Su Z, Chen M, Peng H, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Resp J. 2020. [Accessed 2021 Jan. 2]. Available from: https://erj.ersjournals.com/content/early/2020/05/07/13993003.01217-2020.
45. Morin L, Savale L, Pham T, Colle R, Figueiredo S, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA. 2021; 325(15):1525.
46. Motwani M. Abrupt deterioration and pulmonary embolism in COVID-19: a case report. Clin Med (Lond). 2020; 20(4):e95–e96.
47. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, et al. Post-acute COVID-19 syndrome. Nat Med. 2021Apr 27(4):601–615.
48. National Health Service England, National Health Service Improvement. National Guidance for post-COVID syndrome assessment clinics. [Internet] 2020. [Accessed 2021 Feb. 24]. Available from: https://www.england.nhs.uk/coronavirus/publication/national-guidance-for-post-covid-syndrome-assessment-clinics/.
49. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. [Internet]. 2020. [Accessed 2021 Feb. 23]. Available from: https://www.nice.org.uk/guidance/NG188.
50. Nehme M, Braillard O, Alcoba G, Aebischer Perone S, Courvoisier D, et al. COVID-19 symptoms: longitudinal evolution and persistence in outpatient settings. Ann Intern Med. 2020. [Accessed 2021 Jan. 2]. Available from: https://www.acpjournals.org/doi/10.7326/M20-5926.
51. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med. 2020. [Accessed 2020 Nov. 7].
52. Patel R, Chowdhury S, Meng W, Sharma H, Bellary S, et al. An isolated pleural effusion as a sequela of COVID-19 infection. Chest. 2020; 158(4, Supplement):A366.
53. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J. 2021; 42(1):17–96.
54. Phelan D, Kim JH, Chung EH. A game plan for the resumption of sport and exercise after Coronavirus Disease 2019 (COVID-19) infection. JAMA Cardiol. 2020; 5(10):1085.
55. Phelan D, Kim JH, Elliott MD, Wasfy MM, Cremer P, et al. Screening of potential cardiac involvement in competitive athletes recovering from COVID-19. JACC Cardiovasc Imaging. 2020; 13(12):2635–2652.
56. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020. [Accessed 2020 Sept. 30].
57. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol. 2021; 6(1):116–118.
58. Rogliani P, Calzetta L, Coppola A, Puxeddu E, Sergiacomi G, et al. Are there pulmonary sequelae in patients recovering from COVID-19? Respir Res. 2020; 21(1):286.
59. Rooney S, Webster A, Paul L. Systematic review of changes and recovery in physical function and fitness after severe acute respiratory syndrome–related coronavirus infection: implications for COVID-19 rehabilitation. Phys Ther. 2020. [Cited 2021 Jan 2].
60. Santos-Ferreira D, Tomás R, Dores H. Return-to-play guidelines for athletes after COVID-19 infection. JAMA Cardiol. 2021; 6(4):478–479.
61. Sarma D, Bilello LA. A case report of acute transverse myelitis following novel coronavirus infection. Clin Pract Cases Emerg Med. 2020; (3):321–323.
62. Silva MTT, Lima MA, Torezani G, Soares CN, Dantas C, et al. Isolated intracranial hypertension associated with COVID-19. Cephalalgia. 2020; 40(13):1452–1458.
63. Singhal T. A review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020; 87(4):281–286.
64. Tenforde MW. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March–June 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(30):993–998.
65. Tolba M, Omirah MA, Hussein A, Saeed H. Assessment and characterization of post-COVID-19 manifestations. Int J Clin Pract. 2020:e13746.
66. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology. 2020. [Accessed 2021 Jan. 6].
67. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020; 15(11):e0240784.
68. Vaes AW, Machado FVC, Meys R, Delbressine JM, Goertz YMJ, et al. Care dependency in non-hospitalized patients with COVID-19. J Clin Med. 2020; 9(9):2946.
69. VagoH, Liliana Szabo MD, Zsofia Dohy MD, Bela Merkely MD. Cardiac magnetic resonance findings in patients recovered from COVID-19: initial experiences in elite athletes. Cardiovascular Imaging. 2021; 14(6):1279–1281.
70. Van De Heyning CM, Miljoen H. Cardiovascular screening of athletes during the COVID-19 pandemic: The (ir)relevance of elevated cardiac troponins. Int J Cardiol. 2021; 326:252–253.
71. Van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, et al. Comprehensive health assessment 3 months after recovery from acute Coronavirus Disease (COVID-19). Clin Infect Dis. 2021; 73(5):e1089–e1098.
72. Verwoert GC, de Vries ST, Bijsterveld N, Willems AR, Vd Borgh R, et al. Return to sports after COVID-19: a position paper from the Dutch Sports Cardiology Section of the Netherlands Society of Cardiology. Neth Heart J. 2020; 28(7–8):391–395.
73. Wilson MG, Hull JH, Rogers J, Pollock N, Dodd M, et al. Cardiorespiratory considerations for return-to-play in elite athletes after COVID-19 infection: a practical guide for sport and exercise medicine physicians. Br J Sports Med. 2020; 54(19):1157–1161.
74. World Health Organization. What we know about long-term effects of COVID-19 [Internet]. EPI WIN COVID Update; [Accessed 2020 Sept. 9]. Available from: https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-36-long-term-symptoms.pdf?sfvrsn=5d3789a6_2.