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Post-COVID-19 Condition

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Abstract

An estimated 10–15% of those infected with SARS-CoV-2 may have post-COVID-19 condition. Common lingering signs and symptoms include shortness of breath, fatigue, high heart rate, and memory and cognitive dysfunction even several months after infection, often impacting survivors' quality of life. The prevalence and duration of individual symptoms remain difficult to ascertain due to the lack of standardized research methods across various studies and limited patient follow-up in clinical studies. Nonetheless, data indicate post-COVID-19 condition may occur independent of acuity of initial infection, hospitalization status, age, or pre-existing comorbidities. Risk factors may include female sex and underlying respiratory or psychiatric disease. Supportive therapies to mitigate symptoms remain the mainstay of treatment. Reassuringly, most patients experience a reduction in symptoms by 1 year. The use of a universal case definition and shared research methods will allow for further clarity regarding the pervasiveness of this entity and its long-term health consequences.

INTRODUCTION

A growing body of clinical data, reports, and testimony from recovered COVID-19 (coronavirus disease 2019) patient advocacy groups has helped increase recognition of the postinfectious sequelae of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection since the initial waves of the pandemic (1). With over 480 million confirmed cases of COVID-19 globally to date (2), and an estimated prevalence of post-COVID-19 condition of 10–15%, a cohesive effort for the systematic study of the syndrome is necessary to ascertain its pervasiveness. The US National Institutes of Health has designated $1.15 billion in grant funding to study the long-lasting health effects of COVID-19 (3), with other governmental and research institutions worldwide following suit.

A comprehensive, standardized assessment of the epidemiology of post-COVID-19 condition, characterization of the nature and duration of its clinical manifestations, and elucidation of its pathophysiologic mechanisms are gargantuan works in progress, which, in addition to investment of resources and personnel, will require the passage of time. In this article, we present a narrative review of the current understanding and general trends in postinfectious sequelae of COVID-19, highlighting relevant findings while acknowledging limitations in available data thus far.

A WORKING CASE DEFINITION

Postinfectious sequelae of COVID-19 have variably been termed postacute COVID-19 syndrome, long-haul COVID, or long COVID, among other names. While a unifying name and definition are lacking, there is general consensus among the medical literature and healthcare organizations that symptoms occur $\geq$4 weeks from initial infection (1), with the period between 4 and 12 weeks further being classified as subacute or ongoing symptomatic infection (4). Recognizing the need for standardization of the nomenclature and description of this entity, the World Health Organization (WHO) engaged a global panel of 265 patients, clinicians, researchers, and WHO staff in a systematic, iterative-survey Delphi process, which involves several rounds of surveys to obtain group opinion from a panel of experts. This panel coined the term post-COVID-19 condition, defined as occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms lasting for at least 2 months and not explained by an alternative diagnosis (5).

While the WHO case definition of post-COVID-19 condition provides a helpful framework for consolidation of clinical and research efforts, many of the existing data were collected prior to the formalization of this case definition and reflect heterogeneous study designs, survey methods, and variable patient follow-up, thus limiting their generalizability. However, these studies nonetheless highlight emerging clinical trends and research voids that can inform the global community's efforts in addressing this pandemic's anticipated long-lasting health effects.

EPIDEMIOLOGIC AND CLINICAL TRENDS

Currently, multinational data in the form of prospective clinical studies, retrospective mining of electronic health records, case reports, and online and telephone surveys demonstrate discernible trends which help to refine our understanding of post-COVID-19 condition. Common manifestations include fatigue, shortness of breath, neurocognitive impairment, autonomic dysfunction, and psychiatric ailments such as anxiety and depression (1) (**Figure 1**). Estimates of prevalence and burden of post-COVID-19 condition and individual symptoms are difficult to ascertain, given the varied research protocols and patient populations studied. While age, comorbidities such as obesity and preexisting psychiatric illness, and severity of acute COVID-19 appear to be risk factors, young and previously healthy individuals with mild COVID-19 are also subject to long-lasting

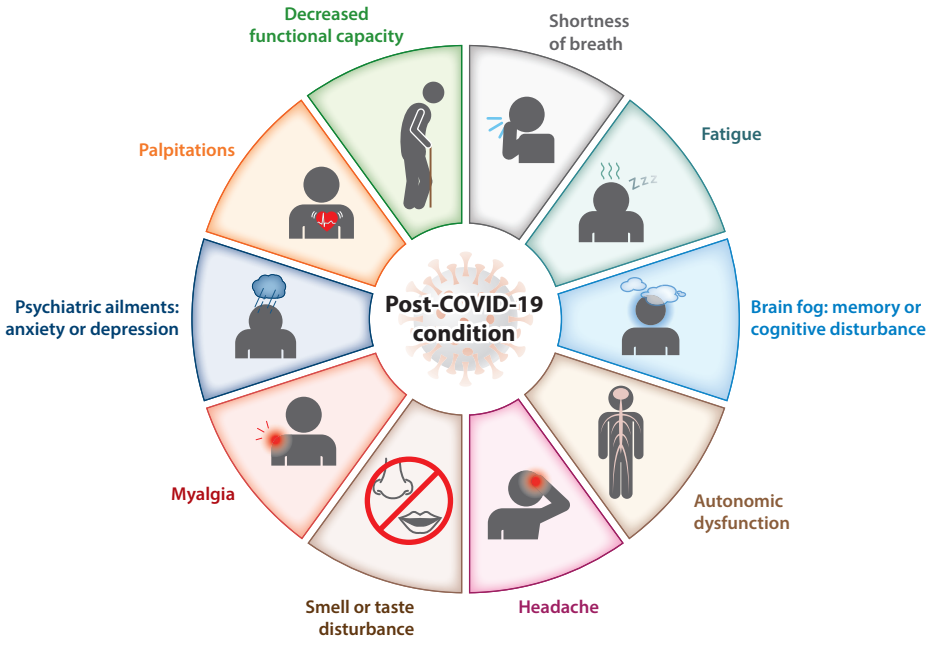

Figure 1

Common signs and symptoms of post-COVID-19 condition include pulmonary, cardiovascular, and neuropsychiatric manifestations. Symptoms may include shortness of breath, fatigue, cognitive disturbances, autonomic dysfunction, headache, smell or taste disturbance, myalgia, anxiety or depression, palpitations, and decreased functional capacity.

effects of COVID-19 (6). Symptoms may be new onset, persist after initial COVID-19 infection, or occur in a relapsing-remitting fashion (5).

Duration of symptoms is variable, but by 1 year postdiagnosis, most patients have a significant reduction in symptoms. In a cohort study of COVID-19 survivors in China assessed via interview, exam, and functional testing at 6 and 12 months postdischarge, the proportion of patients with at least one symptom decreased from 68% at 6 months to 49% at 12 months, with the proportion reporting fatigue or muscle weakness falling from 52% at 6 months to 20% at 12 months (7). Additionally, 88% of subjects had returned to their original work status by 12 months (7). Similar trends were observed in a study of hospitalized patients in Italy, of whom 40.5% reported at least one symptom at 12 months during telephone follow-up; the most common symptoms were fatigue, exertional dyspnea, cough, insomnia, fear, and depression (8). In this study, age, female gender, chronic obstructive pulmonary disease, >2 symptoms at initial interview at 1 month, and frailty were associated with a higher probability of symptoms at 1 year (8). These findings were reiterated by a large retrospective cohort study based on electronic health record data of over 270,000 COVID-19 survivors primarily in the United States, of whom 57% had one or more long-COVID features—including breathing difficulties, fatigue, malaise, chest pain, throat pain, headache, abdominal symptoms, other pain, myalgia, cognitive symptoms, anxiety, or depression (9)—in the 6 months after a COVID-19 diagnosis.

Rehabilitation Post-COVID

While the initial focus was largely geared toward understanding the aftermath of COVID-19 in hospitalized patients, subsequent studies have shifted toward nonhospitalized patients. Among

a cohort of 100 patients evaluated at a multidisciplinary COVID-19 rehabilitation program at Mayo Clinic, 75% were nonhospitalized, self-referred patients presenting a mean of 93 days after infection. Common symptoms were fatigue (80%), respiratory complaints (59%), and neurologic complaints (59%), with 34% reporting difficulty with activities of daily living, and only 33% having returned to unrestricted work duty at the time of analysis. Notably, 23% and 34% of those in this population had preexisting respiratory and mental health conditions, respectively (10).

A Danish nationwide cohort study of nonhospitalized SARS-CoV-2-positive and matched SARS-CoV-2-negative individuals assessed 2 weeks to 6 months after a SARS-CoV-2 test did not demonstrate an increased risk of new-onset chronic disease, apart from a slightly increased absolute risk of venous thromboembolism. However, it did reveal that SARS-CoV-2-positive individuals visited their general practitioner more often after infection than controls did and were also more likely to initiate treatment with short-acting β-2 agonists and triptans in this timeframe (11).

While persistent significant laboratory abnormalities have not been identified among individuals with post-COVID-19 condition overall, initial research has demonstrated an elevated antinuclear antibody (ANA) titer (≥1:160) among those with neurocognitive symptoms (12), offering some support to the hypothesis that the syndrome may have an autoimmune component. However, the significance of raised ANA titers remains unclear and far from generalizable (13).

Children and Adolescents

Studies investigating the longer-term consequences of COVID-19 infection in children are few and limited in their scope for similar reasons as those in adults, including the lack of a clear case definition, variable follow-up times, inclusion of individuals with unconfirmed infection, the absence of a control group, and reliance on self- or parent-reported symptoms. Not surprisingly, the prevalence of long COVID symptoms in the pediatric population varies considerably, from 4% to 66%, with similarly large variation in the reported frequency of individual symptoms, including headache (3–80%), fatigue (3–87%), sleep disturbance (2–63%), concentration difficulties (2–81%), loss of appetite or weight (2–50%), and rash (2–52%) (14).

While there is uncertainty around the true prevalence of long COVID in children, emerging data suggest that there was an increase in healthcare utilization during the COVID-19 pandemic. A nationwide registry of 1.3 million children and adolescents in Norway demonstrated an increase in primary care use after COVID-19 infection secondary to respiratory and general complaints, occurring most frequently 4 weeks after infection, but persisting up to 6 months among children ages 1–5 years (15). More broadly, however, reports suggest that more than half of children have experienced symptoms of headache, fatigue, sleep disturbance, and concentration difficulties during the pandemic, independent of infection status (16).

PREDOMINANT CLINICAL MANIFESTATIONS

Pulmonary

Pulmonary complications post-COVID-19 include persistent shortness of breath, supplemental oxygen dependence, fibrotic lung disease, and pulmonary function test abnormalities (17) in both hospitalized and nonhospitalized SARS-CoV-2-infected patients.

In a study of 120 critically ill patients with COVID-19 acute respiratory distress syndrome in Spain, 57% of patients reported dyspnea on exertion at 6 months (18), compared to 8.6% of nonhospitalized patients with mild or asymptomatic infection assessed prospectively at 4 months in a study in Germany (19). Mechanisms of dyspnea appear to be multifactorial, extending beyond lung parenchymal changes to include deconditioning, cardiovascular dysfunction, and dysfunctional breathing (20).

In a systematic review of studies assessing lung function testing post-COVID-19, the most consistent abnormality was in carbon monoxide diffusion capacity (21). Radiographic analysis of pulmonary fibrosis may demonstrate a variety of lesions, such as interstitial abnormalities including reticulation, traction bronchiectasis, and honeycombing (20). Among the risk factors identified for pulmonary fibrosis diagnosed from 90 to 150 days after COVID-19 diagnosis are age, body mass index, and inflammatory markers such as procalcitonin (22). Other lesions such as ground-glass opacities are generally considered reversible signs of parenchymal inflammation; however, they have been noted to persist up to 12 months post-COVID-19 diagnosis (23), with an incidence widely ranging from 7% to 92% (20). The consequence of these radiographic abnormalities is not always directly clinically correlated, as evidenced by findings from a prospective cohort study of hospitalized patients, which demonstrated overall mild impairment in pulmonary function tests of patients with fibrotic lesions at 4 months post-COVID-19 infection (24).

Cardiovascular

Data from retrospective studies indicate that both hospitalized and nonhospitalized patients bear a higher incidence of major adverse cardiovascular events between 30 days and 4 months post-COVID-19 diagnosis (25, 26). Prospective studies have utilized several diagnostic testing modalities, including electrocardiography, echocardiography, cardiac magnetic resonance (CMR), and cardiopulmonary testing, to evaluate cardiac abnormalities post-COVID-19 diagnosis. These studies have yielded variable results, likely due to differences in patient population. Review of electrocardiographic data indicates that dynamic changes (e.g., depolarization and repolarization abnormalities and incidence of arrhythmias) during acute illness tend to resolve in the majority of hospitalized patients by 6 months. In addition to inappropriate sinus tachycardia, increasingly noted is autonomic dysfunction—namely, postural orthostatic tachycardia syndrome, neurocardiogenic syncope, and orthostatic hypotension (27, 28)—for which referral for further autonomic cardiovascular reflex testing may be warranted.

Findings from CMR studies have garnered much attention in both the medical and lay communities. While initial studies reported alarmingly high rates (60%) of persistent myocardial inflammation 2–3 months postinfection (29), further scrutiny and discussion acknowledged inherent limitations to these studies, including subjects' comorbidities and lack of a comparator group (30). Other studies have since reported lower prevalence of CMR abnormalities, including one in healthcare workers, which found no significant difference in 6-month CMR findings between seropositive and seronegative individuals (31). Studies in athletes have demonstrated a low (0–3%) prevalence of myocarditis, with the majority of studies being conducted within 1–2 months of infection (32–34).

Echocardiographic abnormalities, such as right ventricular dilatation and dysfunction in the acute setting, have been noted to improve in most patients after acute infection (35). However, as with many of the analyses regarding COVID-19, interpretation of study findings is often limited by the lack of pre-COVID-19 baseline assessments.

The application of cardiopulmonary exercise testing has proven informative with regard to understanding pathophysiologic changes in the wake of COVID-19. Predominant patterns include a reduction in peak oxygen consumption, thought to be due to impaired oxygen extraction and hyperventilation or dysfunctional breathing (36–38). A myriad of factors may influence these results, including deconditioning, drugs (e.g., dexamethasone), poor nutrition, and mechanical ventilation (30).

Cardiovascular complications of COVID-19 also include thrombotic complications such as pulmonary embolism and venous thromboembolism. Thrombotic risk following COVID-19 is hypothesized to be linked to endothelial cell activation and a hyperinflammatory state with

unclear duration. Data from studies with heterogeneous outcomes suggest that the rate of venous thromboembolism is below 5% (39). Given the overall ambiguity in the rate and duration of increased risk of thrombotic complications postacute COVID-19, standard tools for risk assessment apply.

Neuropsychiatric

Neuropsychiatric problems may have a significant impact on quality of life and persist more than 3 months after diagnosis, including among nonhospitalized individuals (40). Commonly reported symptoms are cognitive or memory disturbances, colloquially known as brain fog; vertigo; postexertional malaise, as invoked in patients with chronic fatigue syndrome; insomnia or other sleep disturbances; headache; and taste or smell disturbance. Data on each of these manifestations remain imprecise due to the varied questionnaires and surveys used in these studies. However, general trends suggest a higher preponderance of sequelae among women than men, such as in a prospective study of nonhospitalized patients presenting to a neuro-COVID-19 clinic, where 70% of patients with neurologic symptoms lasting over 6 weeks were women (41).

The impact of these neurologic sequalae is highlighted by results such as those in an international online survey, in which approximately 30% of those aged 30–59 who reported cognitive disturbance felt diminished ability to function at work (40). This figure is thought to be underestimated in Black, Latino, Indigenous, and other minority communities, who remain two to three times more likely to be infected with SARS-CoV-2 but are underrepresented in research, and post-COVID-19 hospitalization care (42, 43). Other neurologic sequelae include hyposmia or anosmia, which may result from damage to olfactory sensory neurons. A recent study suggested however an excellent prognosis, with nearly complete recovery in 1 year (44).

Multiple initiatives have been born out of the imperative for further research in this realm, including the European Academy of Neurology core NeuroCOVID-19 task force, and the United States–based National Institute of Neurological Disorders and Stroke NeuroCOVID Project (45), which are working to consolidate and concentrate efforts to understand the long-term effects of COVID-19.

Anxiety, depression, posttraumatic stress symptoms, and sleep disorders have been reported following acute COVID-19 infection. However, ascertainment of viral-related versus pandemic-related psychiatric sequelae poses a significant challenge. Data from a systematic review found that the frequency of depressive symptoms ranges from 11% to 28% at 3 months after acute infection, with the frequency of clinically significant or severe depression ranging from 3% to 12% at 3 months (46). However, studies to date remain hindered in their conclusiveness by their lack of control groups, differences in modes of symptom assessment, and differences in questionnaires and surveys used to assess mood and quality of life.

Renal

Renal complications noted post-COVID-19 include increased risk of acute kidney injury and major adverse kidney effects, which encompass a decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, or all-cause mortality. In a cohort analysis of close to 90,000 veterans with COVID-19, 30-day survivors exhibited excess decline in eGFR (ranging from −3.26 to −7.69 mL/min/1.73 m^2) compared with controls (47). While exact diagnoses and rates of renal complications post-COVID-19 are difficult to ascertain, initial data suggest that approximately one-third of hospitalized COVID-19 survivors have persistent renal dysfunction at 6 months post-discharge, with a subgroup of these continuing to require dialysis (48, 49).

Dermatologic

Dermatologic manifestations of acute COVID-19 have most commonly consisted of acral chilblain-like or pernio-like lesions (often referred to as COVID toes). While most such lesions resolve spontaneously 2 weeks from onset, a subset of patients in multidisciplinary or specialty clinics have been noted to have persistent chilblain lesions. In such cases, screening for underlying causes is prudent, and the use of nailfold capillaroscopy has been suggested for identification of potential microcirculatory morphological alterations, as is used in rheumatologic practice (50–52). Early reports also indicate rheumatologic illnesses, such as inflammatory arthritis and large-vessel vasculitis, following the resolution of acute infection (50, 53). However, such research remains in nascent phases, and it is too early to draw meaningful conclusions about the causality versus the coincidence of COVID-19 in these instances.

Although initial studies indicated that approximately 20–22% of patients reported hair loss in the period of 3–6 months after recovery (49, 54), this remains open to further investigation. Subsequent analyses, including a Korean national cohort study of 226,737 SARS-CoV-2-positive individuals, found that the diagnosis of COVID-19 was not significantly associated with development of alopecia areata compared to controls (incidence rate ratio of 0.6) (55).

CONCLUSIONS

With the exponential increase of COVID-19 cases and high prevalence of post-COVID-19 condition, it is incumbent on medical professionals to gain familiarity with this disease to mitigate the burden on individual patients and the collective healthcare system. While exact characterization of post-COVID-19 epidemiology and demographics of affected populations remain elusive, definite trends have been observed in reported data, which provide a shape and outline to this entity. "Post-COVID-19 condition" describes a constellation of symptoms ranging across all organ systems, but primarily manifesting with respiratory, neuropsychiatric, and cardiac symptoms. Accurate assessment of the clinical causality or correlation of COVID-19 to the described clinical phenomena requires rigorous, comprehensive and long-standing analysis of the kind only time and systematic standardization of research will afford. Moving forward, the use of a universal case definition of post-COVID-19 condition, consolidation of registry data and prospective clinical trial efforts, and re-evaluation of existent data with the application of standardized analytic methods are ways to improve our understanding of this entity. Management of post-COVID-19 condition largely consists of supportive care, but timely identification of affected individuals and implementation of therapies such as physical rehabilitation and mental health support services may ultimately yield the most significant and sustained impact on patients' overall well-being.

DISCLOSURE STATEMENT

E.Y.W. has been a consultant for Medtronic, Boston Scientific, Sanofi, Abbott, and Cardiologs, not related to this review. A.N. has been a consultant for Knowledge to Practice (K2P), not related to this review.

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