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Issues related to post-COVID-19 syndrome

Öner Özdemir, Zeynep Arslan

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Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019-2022 leads to a multisystem illness that results in damage to numerous organ systems. In this review, our goal was to assess current research on long-term respiratory, cardiac, neurological, digestive, rheumatological, urogenital, and dermatological system complications of coronavirus disease 2019 (COVID-19). Bibliographic searches were conducted in December 2021 using PubMed and Google Scholar, retrospectively, covering all COVID-19 literature to determine the consequences of the disease. This review may help to determine the prospects for new studies and predict the upcoming aspects requiring assessment in post-COVID-19 syndrome.

Key Words: Coronavirus; COVID-19; Post-COVID-19 syndrome; Pandemic; SARS-CoV-2

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Core Tip: Coronavirus disease 2019 causes damage to multiple organ systems. Most of the current studies are based on the acute stage of illness, treatment, and vaccination. As more than two years have passed since the start of the pandemic, we should be familiar with its long-term sequelae.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has invaded the globe. As of 8 June 2022, the cumulative number of recorded infected cases is 536.613.318, with 6.323.467 deaths[1]. Although the pathophysiologic process remains unclear, a probable hypothesis suggests that SARS-CoV-2 is an enveloped and positive-stranded RNA virus that binds to the angiotensin-converting enzyme 2 (ACE2) receptor of host cells with the structural protein spike domain S1[2]. Consequently, the novel coronavirus invades all cells that express ACE2 receptors, such as respiratory, gastrointestinal, and urinary systems[3]. Studies have indicated that the incubation period may take up to 11.2 d, and symptoms of the disease are likely to be evident on day 5.5 after infection in most cases[4]. Additionally, current studies revealed that the average incubation period in the pediatric age group is 6.5 d, which is slightly longer than that in adults[5].

SARS-CoV-2 has additional features that most other organisms may not have: (1) Ability to escape immunological response; (2) Tissue tropism which depends on ACE2 receptor consistency; and (3) Capability to reach various organs and systems[6].

Common clinical manifestations in COVID-19 patients include fever, dry cough, fatigue, dyspnea, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhea, hemoptysis, and conjunctival congestion[7]. Another study involving pediatric participants demonstrated that 61.7% had a fever, 53.2% cough, and 16.8% diarrhea or nausea[8].

The aim of this mini-review was to conduct a bibliographic search of post-COVID-19 syndrome which was carried out in December 2021 using PubMed and Google Scholar, retrospectively, and included all COVID-19 literature to determine the consequences of this disease. This review may help to determine the prospects for new studies and predict the upcoming aspects requiring assessment in post-COVID-19 syndrome.

WHAT IS POST (LONG)-COVID-19 SYNDROME?

According to the studies that were conducted to assess hospitalization and mortality data, the majority of patients have the burden of long-term morbidity complications despite 'recovery'[9,10]. A group of patients had persistent complaints, which necessitated the need to determine long-term complications of the disease. Approximately 10% of the infected patient population reported experiencing symptoms such as confusion, sleep problems, decreased exercise capacity, autonomic complaints, persistent low-grade fever, and lymphadenopathy after recovery from the acute stage[11,12]. Another large cohort study including data from patients 6 mo after recovery showed that a considerable number of patients had persistent complaints of fatigue, muscle weakness, sleep difficulties, anxiety, and depression[13]. Severely ill patients with extensive lung involvement at admission was a probable risk factor associated with pulmonary diffusion abnormality, fatigue or muscle weakness, and depression which are manifestations of a new term called 'post-COVID-19 syndrome'[14]. These manifestations are reliant on the severity of pulmonary involvement, age, muscle pain, intensive care unit (ICU) requirement, viral load, and immune response at admission[15-17]. Obesity, underlying chronic respiratory illness, abnormal radiologic findings, diminished pulmonary function on spirometry, female gender, and Black and Asian races are also reported to be potential risk factors for long-term sequelae[18].

The novel terminology of 'COVID long-haulers', 'long-COVID', or 'post-COVID-19 syndrome' covers these complaints[10]. 'Acute COVID-19' describes symptoms that extend to 4 wk after the onset of the disease. On the other hand, the definition of 'post-acute COVID-19', is symptoms present between 4 to 12 wk after onset of the disease[19,20]. Post-COVID-19 syndrome or long-COVID consists of complaints that remain beyond 12 wk and are not associated with any other disease[19,20]. A study investigating children with persistent COVID-19 symptoms found that symptoms were present for 4 to 12 wk, and could even persist for 7 to 8 mo[21]. In this review, we use the term 'post-COVID-19 syndrome'.

Studies have shown that among symptomatic patients, 21.4% had profound symptoms even 20 wk after recovery[22]. The duration of COVID-19 and comorbidities (such as unstable diabetes mellitus, and hypertension) were found to be associated with post-COVID-19 syndrome[22]. Interestingly, the age group of 1-10 years had no complaints after recovery, but patients older than 40 years had remnant findings even 20 wk after onset[22].

Although current knowledge on symptomatic patients after discharge is insufficient, in order to have a comprehensive framework, studies that investigated post-COVID-19 syndrome have been included in this review (Table 1).

Respiratory system involvement

During the course of COVID-19, an important proportion of cases suffer from severe pneumonia and tend to have long-term sequelae[23]. Ongoing fibrosis during the recovery period results in decreased diffusion capacity of the lung[24]. Studies have indicated that a large variation in respiratory morbidity may appear such as decreased exercise capacity, an increased need for continuous positive airway pressure, tracheostomy, or ventilator dependence for COVID-19 long-haulers[13,24-27].

Table 1 Involvement of organ systems in post-coronavirus disease 2019 syndrome

Systems	Findings
Respiratory system	Decreased diffusion capacity of the lung due to ongoing fibrosis Decreased exercise capacity, cough, and chest pain
Hematologic system	CD4+ T lymphocytes remained lower Mild elevation in white blood cell (WBC) count High levels of WBCs are driven by raised neutrophils Direct injury of endothelium and cytokine release causing prothrombotic tendency Elevation of Von Willebrand Factor antigen (VWF: Ag), VWF propeptide (VWFpp), and Factor VIII coagulation (FVIII: C) elements
Cardiovascular system	Vascular, pericardial, and myocardial tissue inflammation Chest pain, palpitations, dizziness, and increment in resting heart rate Postural orthostatic tachycardia syndrome (POTS)
Gastrointestinal system	Diarrhea, abdominal pain, and nausea Viral RNA could still be present in the stool after 30 d Weight loss and risk of malnutrition due to decreased appetite
Neurologic system	Mild headache, hyposmia, hypogeusia, fatigue, sleep disorders, pain, cognitive impairment, and rarely Guillain-Barré syndrome Anosmia and hypogeusia, underlying low-grade inflammation of the frontal lobe, loss of cognition, brain fog, and headache
Psychiatric issues	Social withdrawal, social isolation, economic loss due to being unable to work, increased child care and familial charges, and burden of guilt if other contacts contract the virus Psychological distress and post-traumatic stress disorder

The up-to-date pathophysiological process of lung fibrosis development in COVID-19 includes pulmonary consolidation, hyaline membrane formation, capillary damage and bleeding, diffuse alveolar epithelium destruction, and alveolar septal fibrous proliferation[28]. A cohort study reported that more than 50% of patients with SARS-CoV-2 pneumonia at 30 d post-infection had abnormal results for functional residual capacity, total lung capacity, and diffusing capacity of the lungs[29]. Although, pulmonary fibrosis occurs in most patients it was reversed in less than half of the patients 3 mo after onset[30].

Myall *et al*[31] conducted a cohort study that included 837 COVID-19 patients. The patients were screened *via* phone calls 4 wk after discharge. 325 patients had ongoing symptoms. Following assessment of this group using various tests [chest X-ray, 6-min walking, echocardiogram, and computed tomography (CT)], 35 (4.18%) patients were diagnosed with interstitial lung involvement, and were successfully treated with corticosteroids. The main characteristics of the group with lung involvement were being male, obese, in need of oxygen therapy, and mechanical ventilation during the acute phase.

In a study conducted to highlight long-term respiratory results, 244 patients required prolonged ICU and inpatient stay, and follow-up chest X-rays. Of these patients, 23 (9%) showed significant deterioration 2 mo after onset of the disease[32]. To evaluate the relationship between radiological involvement at admission and impaired lung function, a prospective cohort study was conducted. Patients who presented with acute respiratory distress syndrome (ARDS) during ICU stay resulting from COVID-19 were included in the study and examined *via* chest CT and pulmonary function tests 3 mo after discharge. Pulmonary function tests were abnormal in 55% of patients, with restricted diffusing capacity of the lungs[33]. In a large study of more than 4000 COVID-19 survivors, risk factors for 90-d mortality were reported as older age, immunosuppression, severe obesity, diabetes, higher renal and cardiovascular sequential organ failure assessment (SOFA) score components, lower PaO₂/FiO₂ ratio and a shorter time between first symptoms and ICU admission[34].

CT changes in post-COVID-19 syndrome provide information on long-term pulmonary effects. A study that included 52 subjects with COVID-19 assessed *via* CT 3 mo after diagnosis showed that 22 (42%) patients had residual findings. Problems with decreased lung capacity, cough, and chest pain were more common among patients with abnormal CT scans[35].

Cardiovascular system involvement

A history of pre-existing cardiovascular illness or hospitalization were not associated with post-acute-COVID-19 syndrome (PACS)[36]. Before the pandemic, it was hypothesized that the density of ACE2 receptors in the heart was due to myocardial injury. However, recent studies demonstrated that the

cause of type 2 myocardial infarction was increased systemic inflammation[37]. Vascular, pericardial and myocardial tissue inflammation yields typical cardiac complaints of chest pain, palpitations, dizziness, and an increment in resting heart rate[25,38].

A cohort study was performed by Puntmann *et al*[39] to determine myocardial inflammation rates in patients with a history of COVID-19 infection. The patients were analyzed 2 wk after hospital discharge by cardiac magnetic resonance (CMR) imaging to evaluate myocardial involvement. A control group was also included to investigate similar risk factors to the study group. The study group subjects were found to have significant T2 signal and late gadolinium enhancement. Another study of 148 patients with elevated troponin levels during hospitalization were followed up for 2 mo after discharge. It was reported that 26% of the patients developed a myocarditis-like pattern, while all patients had normal left ventricle function. Active myocarditis with regional elevation in T1 and T2 signals was demonstrated in 8% of patients. However, elevated troponin was not found to be predictive of myocarditis[40]. In a multicenter study, almost 20,000 athletes following recovery from COVID-19 were examined and only 3% of them were found to have possible pathology 113 d after onset of the disease [41]. It may be inferred from recent studies that myocarditis is a very rare condition, especially in asymptomatic and mild cases.

In another study, 59 patients following hospitalization due to COVID-19 were screened *via* CMR imaging. One patient's imaging data indicated pericarditis[42]. Other research demonstrated that 5% of patients were estimated to have mild pericardial effusion[43]. Although further investigations are required, it can be inferred that pericarditis after COVID-19 is rare, while effusion is a relatively more common pathology.

Postural orthostatic tachycardia syndrome (POTS) is another disorder seen in a considerable number of COVID-19 long haulers. To estimate the incidence of this condition, 28 patients with persistent cardiac complaints after COVID-19 recovery were enrolled in a study. The results of the tilt table and ten minutes-standing tests demonstrated that 20 patients (70%) had POTS[44].

Arrhythmias after COVID-19 are quite rare and investigations on this issue are scarce. An analysis of arrhythmias in 5000 patients hospitalized with COVID-19 and influenza was carried out. Similar percentages of atrial fibrillation and atrial flutter were detected in both groups[43].

Hematologic system involvement

Laboratory markers for predicting the severity of disease and mortality have been questioned. It is known that several changes occur during the course of COVID-19. A study of 1099 reverse transcriptase-polymerase chain reaction (RT-PCR) positive patients demonstrated lymphocytopenia (83.2%), thrombocytopenia (36.2%), and leukopenia (33.7%) in the initial phase of the disease[45]. A few studies have investigated hematological findings after recovery. In a study of 313 participants, 12.9% of patients had leukocytosis, which increased to 16.1% 4 wk after recovery. The percentage with neutrophilia in the initial phase was found to be 17.7%, which increased to 33.8% and lymphocytopenia decreased from 17.7% to 14.5%. Almost half of the patients had increased D-dimer levels in the acute stage, which decreased to 6.4% after 1 mo[22].

Lymphopenia is a common finding in patients with COVID-19 and represents a defective immune response to the virus[1]. Cytotoxic lymphocytes such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells have a main role in the control of infection. During the acute phase of the disease, both CTLs and NK cells decrease in number. However, after recovery, these cell numbers then increase. Hence, Zheng *et al*[46] suggested that the recovered numbers of these cells may predict convalescence.

Studies investigating the prevalence of lymphopenia in COVID-19 positive patients have provided different estimates ranging from 63% to 75%[47,48]. In patients with severe disease, a decrease in both CD4 and CD8 cells was noted. Additionally, lymphocyte count, especially CD4, may predict severity and prognosis[49]. A prospective study showed that CD8+ T lymphocytes recovered to their normal level 3 mo after onset of the disease. Another finding in this study showed that CD4+ T lymphocytes remained lower than in the healthy population even 4 wk after onset[50].

A large comprehensive meta-analysis of hematologic laboratory data demonstrated that patients with serious disease had a mild elevation in white blood cell (WBC) count. Additionally, patients who died due to COVID-19 had a significant increase in WBCs. According to this finding, WBC levels signify the severity of the disease. Despite reduced lymphocyte, monocyte, and eosinophil counts; high levels of WBCs were driven by raised neutrophils[49]. Similarly, recent research demonstrated that increased neutrophil/lymphocyte and peak thrombocyte/lymphocyte counts may help predict prognosis[51].

Thrombocytopenia in COVID-19 patients may be caused by disseminated intravascular coagulation, sepsis, or drug-induced, which was also shown to be a risk factor for increased morbidity and mortality [52]. Several studies have reported late-onset immune thrombocytopenia 4 wk after the onset of COVID-19[53].

A new description of the immune thrombotic state is termed COVID-19-induced coagulopathy[54]. A possible mechanism responsible for this prothrombotic tendency is the direct injury of endothelium and cytokine release which activates the coagulation cascade[55]. A cohort study screened 50 patients for endotheliopathy 68 d after recovering from COVID-19. This study showed that endothelial biomarkers von Willebrand Factor antigen (VWF: Ag), VWF propeptide (VWFpp), and Factor VIII coagulation (FVIII: C) elements were significantly elevated in post-acute-COVID-19 patients. Endothelial damage

may be a possible explanation for the pathogenesis of long-COVID-19 syndrome[56].

Post-discharge thromboprophylaxis has been assessed in post-COVID-19 patients. A prospective cohort study of 146 patients showed that 6 wk after discharge, while the percentage of thrombotic events was 0.7%, 30% of patients had increased D-dimer values[57]. Although there are ongoing studies to determine the rates of thrombotic events after COVID-19, routine thromboprophylaxis after discharge is not recommended. The Global COVID-19 Thrombosis Collaborative group recommends prophylaxis for selected patient groups only such as the elderly population and those with existing comorbidities [58].

Gastrointestinal system-related issues

SARS-CoV-2 mainly leads to diseases associated with the respiratory tract, but gastrointestinal disturbances can also occur. During the natural course of the disease, patients develop anorexia, nausea, vomiting, and diarrhea[47]. In contrast to early studies that suggested lower rates of diarrhea and other digestive symptoms, recent data show that almost half of patients have gastrointestinal system complaints[59,60]. A large cross-sectional study including 979 participants who recovered from COVID-19 demonstrated that almost half of the patients had diarrhea, abdominal pain, and nausea[61]. The appearance of digestive system complaints is delayed, compared to respiratory symptoms and begin at about 9.0 d[62]. Although there are numerous reports regarding gastrointestinal involvement during the acute stage, the effects of post-COVID-19 syndrome on the digestive system remain unclear.

Viral shedding from the gastrointestinal tract may be massive and continue long after the resolution of clinical signs[63]. A study on SARS-CoV-2 demonstrated that viral RNA could remain in the stool even after 30 d[64]. More than half of the patients were found to have viral RNA in their stool during the acute stage of disease, and one in five patients had positive stool samples even after viral RNA was eliminated from their airways[59]. Another investigation which assumed that SARS-CoV-2 spread *via* the stool displayed similar conclusions showing that virus shedding continued even after the convalescent phase of the disease. It was also suggested that viral RNA in feces detected by RT-PCR can be used to monitor infection[65].

Early data suggested that higher numbers of ACE2 receptors in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6% of cells) show that the virus may be directly attached to ACE2-positive cholangiocytes and damage liver function[66]. Nevertheless, autopsy studies reported no viral inclusion in the liver[67]. Correspondingly, an overactive inflammatory reaction may be responsible. The underlying mechanism can be explained as follows: Typical lymphopenia detected in SARS-CoV-2 infection causes increased serum levels of interleukin-6 (IL-6), IL-10, IL-2, and interferon (IFN)- γ which may damage liver tissue[68]. Likewise, a strong association between lymphopenia and increased serum C-reactive protein level with liver injury has been proposed[69].

Studies on COVID-19 patients after remission indicate that weight loss and risk of malnutrition were highly prevalent 3 wk after recovery. Increased inflammation leads to decreased appetite. A prospective cohort study aiming to understand the long-term results of malnutrition in post-COVID-19 syndrome was carried out, and included 288 hospitalized COVID-19 patients who were followed up for 6 mo. On day 30, 136 (47.2%) patients had persistent malnutrition or sarcopenia. Gérard *et al*[70] found that the time taken to regain weight was 6 mo, but all patients generally remained 1.4 kg lighter than their weight on admission.

Urinary system involvement

An increased numbers of urinary frequency complaints have prompted the question: "Does SARS-CoV-2 infection cause viral cystitis?"[71]. The existence of viral RNA in the urine of COVID-19 sufferers showed that the urinary tract is potentially affected throughout the disease[45,72]. Ischemic and/or toxic tubular damage was detected in more than 14% of acute kidney injury (AKI) cases with COVID-19 [73]. The greater number of AKI patients with COVID-19 was related to acute tubular injury. The probable mechanism of acute tubular damage may involve volume reduction that reduces kidney perfusion. Another possible explanation is that the immune response produces cytokines that affect renal circulation[74]. There are no available data on the long-term complications of SARS-CoV-2 infection in the urinary tract.

Neurologic system involvement

Several studies have reported a large number of neurologic disorders ranging from mild headache, hyposmia, hypogeusia, and fatigue to sleep disorders, pain, cognitive impairment, and rarely Guillain-Barré syndrome[40]. To ascertain the main cause of neurological disorders, it is necessary to define the components of neuro-COVID, which tends to cause more disabling disease[6,75]. In patients with or without neurological manifestations during the acute phase of COVID-19, the cytological and biochemical study of cerebrospinal fluid, as well as neuroimaging, revealed significant alterations that represented inflammatory activity. It was also noted that during the acute phase of the disease, a consequential number of inflammatory events were demonstrated by radiological surveys of the central nervous system and both cytological and biochemical evaluations of cerebrospinal fluid[76].

To shed light on the neurological disturbances after COVID-19, it is essential to know the tropism of the virus and how it accesses the nervous system. The nasal and oral cavities provide an area for seeding of SARS-CoV-2. From the olfactory mucosa *via* retrograde neuronal transport, the virus reaches the central nervous system[77]. The inflammatory response of nasal and oral mucosa may be the reason for anosmia and hypogeusia. Moreover, as anosmia and hypogeusia have a similar mechanism, underlying low-grade inflammation of the frontal lobe might be the cause of the loss of cognition, brain fog, and headache[77]. As silent target organ damage and underdiagnosis of post-COVID syndrome results in neurological manifestations, taking precautions with regard to initial neurorehabilitation is essential[78].

There are a considerable number of reports of patients with demyelinating pathologies such as Guillain-Barre syndrome, Miller-Fisher, and other inflammatory polyneuropathies. A review of these cases showed that symptomatic neuropathy may be diagnosed 3 to 33 d after onset. The absence of SARS-CoV-2 RNA in the cerebrospinal fluid indicates that a post-infectious process is thought to be responsible rather than a para-infectious process[79]. There is another case report of status epilepticus and hippocampal atrophy due to prolonged inflammation 6 wk after SARS-CoV-2 infection[80]. Another patient with orthostatic cerebral hypoperfusion syndrome and painful small fiber neuropathy after recovery has been reported[81].

The most commonly reported neurological disturbance in COVID-19 patients is headache (18%-38%) [82,83]. Other complaints consist of peripheral neuropathy symptoms, tinnitus, memory issues, concentration, and sleep disturbances[84].

Psychiatric issues

The psychological health outcomes during COVID-19 recovery may contribute to social withdrawal, social isolation, economic loss due to being unable to work, increased child care and familial charges, and burden of guilt if other contacts contract the virus[85]. Nonetheless, patients with SARS-CoV-2 heal physically; however, they are prone to psychological distress and post-traumatic stress disorder. A study showed that more than half of patients had these mental disorders after surviving severe disease [86]. The first study on the neuropsychological findings of post-COVID-19 patients showed that the Beck Depression Inventory scores were significantly higher in post-COVID-19 patients than in healthy controls[87].

Endocrinological involvement

The impact of post-COVID syndrome on the endocrine glands cannot be underestimated. Symptoms such as tiredness, weakness, nausea, diarrhea, dizziness, and joint pain may overlap with adrenal insufficiency symptoms. For instance, Salzano *et al* reported a patient with adrenal insufficiency following recovery from SARS-CoV-2 infection[88]. Additionally, a cohort study of 453 patients was conducted and thyroid-stimulating hormone (TSH) and thyroxine (T4) levels before, during, and after SARS-CoV-2 infection were evaluated. According to this study, while most cases were found to be euthyroid, a slight decrease was reported in both TSH and T4 levels, which normalized after infection [77].

Dermatological issues

A single-center prospective study to define the skin manifestations of long COVID syndrome in 104 patients was conducted by Diotallevi *et al*[89]. Following hospital discharge, the patients were followed up at 1, 3, and 6 mo and examined by dermatologists who reported a wide spectrum of findings such as telogen effluvium, skin xerosis, diffuse folliculitis, vesicular exanthema, relapse of seborrheic dermatitis, relapse of psoriasis and pityriasis versicolor. According to the study, telogen effluvium due to interruption of the anagen phase was the most prevalent dermatological finding in patients after SARS-CoV-2 infection.

CONCLUSION

As the new coronavirus, SARS-CoV-2, involves multiple organ systems and the number of COVID-19 survivors increases every day, there is a need to develop new strategies for the systematic assessment of these patients as well as the need for rehabilitation services. Multidisciplinary post-acute COVID-19 care services should include several specialists to evaluate the consequences of the disease, and highlight some of the unrecognized disorders of COVID-19.

FOOTNOTES

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