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The Issues of Post-COVID-19 Syndrome

Öner Özdemir, Zeynep Arslan

Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019-2022 Led to a multisystem illness that ended up with numerous damages to organ systems. In this narrative review, our aspect is to assess current research on respiratory, cardiological, neurological, digestive, rheumatological, urogenital, and dermatological system complications of COVID-19 disease in long term. Bibliographic searches were conducted in December 2021 using PubMed and Google Scholar, covering retrospectively all COVID-19 Literature. To view through consequences of the disease, a delicate search of the literature is made. This review may help to determine the prospects of new studies and foresee the upcoming aspects of necessary assessments of reports with post-COVID-19 syndrome.

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19), caused by violent acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has briskly invaded the globe. As of 31 January 2022, the cumulative number of recorded infected cases is 375,241,633, with 5,681,747deaths [1]. Even though the pathophysiologic process is still unclear, a probable hypothesis suggests that the virus 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 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]. While there are studies indicating that the incubation period may take up to 11.2 days, the symptoms of the disease likely to become evident on day 5.5 after being infected for most cases [4]. Additionally, current studies revealed that the average incubation period in the pediatric age group is 6.5 days, which is a bit longer than adults [5].

SARS-CoV-2 comes out with a couple of additional features that most the other organisms may not have:

(a) Ability to escape immunological response,

(b) Tissue tropism which depends on ACE2 receptor consistency,

(c) 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% of them had a fever, 53.2% cough, and 16.8% diarrhea or nausea [8].

The aim of this mini-review was bibliographic searches on the post-COVID-19 syndrome that were conducted in December 2021 using PubMed and Google Scholar, covering retrospectively all COVID-19 Literature. To view through consequences of the disease, a delicate search of the literature is made. This review may help to determine the prospects of new studies and foresee the upcoming aspects of necessary assessments of reports with post-COVID-19 syndrome.

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

According to the studies that are conducted to overview the hospitalization and mortality data, the majority of patients are going through the obvious burden of long-term morbidity complications despite 'recovery' [9,10]. A group of patients had persistent complaints, which emerged the need to determine long-term complications of the disease. Overall the infected population, 10% of patients reported after being recovered

from the acute stage, have had symptoms such as confusion, sleep problems, decreased exercise capacity, autonomic complaints, persistent low-grade fever, and lymphadenopathy [11,12]. Another large cohort study including the patients six months after recovery showed that a considerable number of patients had persistent complaints of fatigue, muscle weakness, sleep difficulties, anxiety, and depression [13]. More severely ill patients with intense lung involvement at admission is a probable risk factor that is 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 the pulmonary involvement, age, muscle pain in admission, intensive care unit (ICU) requirement, viral load, and immune response [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 sequela [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', symptoms presents between 4 to 12 weeks after the onset of the disease [19,20]. Post-COVID-19 syndrome or long-COVID consists of complaints that remain beyond 12 weeks and are not associated with any other disease [19,20]. A study that investigates children with persistent COVID-19 symptoms is found to extend 4 to 12 wk, even if they may persist for 7 to 8 mo [21]. In this narrative review, we always use the terminology of 'post-COVID-19 syndrome'.

Studies showed that among symptomatic patients, 21.4% of them had profound symptoms even after 20 wk after recovery [22]. Duration of COVID-19 illness and comorbidities (such as unstable diabetes mellitus, and hypertension) are 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 after 20 wk from onset [22].

Even though current knowledge about symptomatic patients after discharge is insufficient, to have a comprehensive framework, studies that investigate post-COVID-19 syndrome have been overviewed in this manuscript.

1. Respiratory System Involvement

In the course of COVID-19 disease, important proportions 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 indicate that a large variety of respiratory morbidity may appear such as decreased exercise capacity, the increased need for continuous positive airway pressure (CPAP), tracheostomy, or ventilator dependence for COVID-19 Long-haulers [13,24-27].

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 more than 50% of the patients with SARS-CoV-2 pneumonia at 30 days post-infection had abnormal results of functional residual capacity (FRC), total lung capacity (TLC), and diffusing capacity of the lungs (DLCO) measurements [29]. Even though, pulmonary fibrosis occurs in most of the patients it could be reversed in less than a half of the patients after 3 mo from onset [30].

Myall *et al* conducted a cohort study that includes 837 COVID-19 patients. Patients are screened *via* phone calls four weeks after discharge. 325 patients had ongoing symptoms. After assessment of this group with various tests (chest X-ray, 6-minutes walking, echocardiogram, and computerized tomography (CT)), 35 (%4.8) patients were diagnosed to have interstitial lung involvement, and they were treated successfully with corticosteroids. The main characteristics of the group with lung involvement were being male gender, obese, in need of oxygen therapy, and mechanical ventilation during the acute phase [31].

In a study to highlight the long-term respiratory results, the number of 244 patients required prolonged ICU and inpatient stay followed up *via* chest X-rays.

Among these patients, 23 (9%) of them had significant deterioration after the two months from the onset of the disease [32]. To show the relationship between radiological involvement at admission and impaired lung function, a prospective cohort study was conducted. Patients presented with acute respiratory distress syndrome (ARDS) during ICU because of COVID-19 were included in the study and examined *via* chest CT and pulmonary function test (PFT) 3 mo after discharge. Pulmonary function tests remained abnormal in 55% of patients, with a restricted diffusing capacity of the lungs [33]. In a large study among more than 4.000 COVID survivors, risk factors for 90-day mortality were reported as older age, immunosuppression, severe obesity, diabetes, higher renal and cardiovascular SOFA score components, lower PaO2/FiO2 ratio, and a shorter time between first symptoms and ICU admission [34].

Computerized tomography changes in post-COVID-19 syndrome give information for long-term pulmonary effects. A study that includes 52 subjects with COVID-19 assessed *via* CT three months 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].

2. *Cardiovascular System Involvement*

History of pre-existing cardiovascular illness or hospitalization is not associated with the post-acute-COVID-19 syndrome (PACS) [36]. Beforehand of the pandemic, it has been hypothesized that the density of ACE2 receptors in the heart is obligated to myocardial injury. However, recent studies demonstrated the cause of type 2 myocardial infarction as increased systemic inflammation [37]. Vascular, pericardial and myocardial tissue inflammation yields typical cardiac complaints of chest pain, palpitations, dizziness, and increment in resting heart rate [25,38].

A cohort study was organized by Puntmann *et al* to find out the myocardial inflammation rates, in patients with a history of COVID-19 infection. Patients have been analyzed two weeks after hospital discharge with cardiac magnetic resonance (CMR) to evaluate myocardial involvement. A control group was also included to investigate

similar risk factors with the study group. It has been recorded that study group subjects were found to have significant T2 signal and late gadolinium enhancement [39]. Another research was performed on 148 patients with elevated troponin levels during hospitalization who have been followed up for 2 mo after discharge. This study reported that 26% of patients developed a myocarditis-like pattern, while all patients had normal left ventricle functions. Active myocarditis with regional elevation in T1 and T2 signals was demonstrated in 8% of patients. However, elevated troponin has not been found as predictive for myocarditis [40]. In a multicenter study, almost 20.000 athletes after recovering from COVID-19 infection were examined and only 3% of them were detected to have possible pathology after 113 days from the 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 after hospitalization due to COVID-19 were screened *via* CMR. One patient's imaging data was indicating pericarditis [42]. Other research demonstrated that 5% of patients were estimated to have mild pericardial effusion [43]. In need of more investigations, it can be inferred that pericarditis after COVID-19 infection is rare, while effusion is a relatively more common pathology.

Postural orthostatic tachycardia syndrome (POTS) is another disturbance that a considerable number of COVID-19 Long haulers suffer. To estimate the incidence of this condition, there is a demand for more data. Twenty-eight patients with persistent cardiac complaints after healing from COVID-19 enrolled in a study. Results demonstrated that 20 patients (70%) have had POTS *via* tilt table and ten minutes-standing test [44].

Arrhythmias after COVID-19 infection are quite rare and investigations about this issue are also infrequent. An analysis of arrhythmias in 5.000 hospitalized patients for COVID-19 and influenza infection has been made. Similar percentages both for atrial fibrillation and atrial flutter have been detected in both groups [43].

3. Hematologic System Involvement

Laboratory markers in favor of predicting the severity of disease and mortality have been questioned. It has been known that several changes occur in the course of the disease. A research 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]. There are a few studies that investigated hematological findings after recovery. A study among 313 participants showed that 12.9% of patients had leukocytosis, which increased to 16.1% four weeks after recovery. The percentage of neutrophilia in the initial phase was found at 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 is decreased to 6.4% after a month [22].

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

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

A large comprehensive metaanalysis of hematologic laboratory data demonstrated that patients with serious diseases have had a mild elevation in white blood cell (WBC) count. Additionally, patients who died from COVID-19 infection had a significant increase in WBC. According to this finding, WBC levels signify the severity

of the disease. Despite reduced counts of lymphocytes, monocytes, and eosinophils; high values in WBC were driven by raised neutrophils [49]. Similarly, recent research demonstrated that increased neutrophil/Lymphocyte and peak thrombocyte/Lymphocyte counts may help predict the prognosis [51].

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

A new description of the immune thrombotic state is called COVID-19-induced coagulopathy [54]. A possible mechanism responsible for this prothrombotic tendency is a direct injury of endothelium and cytokine release which activates the coagulation cascade [55]. A cohort study screened 50 patients for endotheliopathy 68 days 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 the possible explanation for the pathogenesis of long-COVID-19 syndrome [56].

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

4. Gastrointestinal System-related Issues

The disease that SARS-CoV-2 Leads to is mainly associated with the respiratory tract, but gastrointestinal disturbances also occur. During the natural course of the disease, patients develop anorexia, nausea, vomiting, and diarrhea [47]. In contrast to early

studies that suggest lower rates of diarrhea and other digestive symptoms, recent data shows that almost half of patients have had complaints of the gastrointestinal system [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 findings relatively is postponed, compared to respiratory symptoms beginning about 9.0 days [62]. Though there are a lot of reports about 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 may continue long after the resolution of clinical signs [63]. Even a study of SARS-CoV2 pointed out that viral RNA could still be remaining after 30 days in stool [64]. More than half of the patients were attained to have viral RNA existing in their stool at the acute stage of disease, besides one in five patients had positive stool samples even after the viral RNA was removed from their airways [59]. Another investigation assuming SARS-CoV-2 spread *via* stool displayed similar conclusions showing that even after the convalescent phase of the disease virus shedding continued. It is also suggested that viral RNA in feces by RT-PCR can be taken to monitor infection [65].

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

Studies of 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 to understand long-term results of malnutrition in post-COVID-19 disease with 6 mo follow-up of 288 hospitalized COVID-19 sufferers presented tremendous results. On day 30, 136 (47.2%) patients had persistent malnutrition or sarcopenia. Healer *et al* found the time to regain the weight as 6 mo, but all patients generally remained 1.4 kg lighter than their weight on admission [70].

5. Urinary System Involvement

Increased numbers of urinary frequency complaints' have proposed the question: "Does SARS-CoV-2 infection cause viral cystitis?" [71]. The existence of viral RNA in the urine of COVID-19 sufferers showed the urinary tract has been potentially affected throughout the disease [45,72]. The ischemic and/or toxic tubular damage was detected in greater than 14% of acute kidney injury (AKI) cases of COVID-19 [73]. The greater part of AKI subjects in patients with COVID-19 wasrelated to an acute tubular injury. The probable mechanism of acute tubular damage may be the basis of volume reduction that cuts down kidney perfusion. Another possible explanation is the immune response producing plenty of cytokines that fail the renal circulation [74]. There are no available data showing long-term complications of SARS-CoV-2 infection in the urinary tract.

6. Neurologic System Involvement

There are several cases are reporting a large spectrum of ailments, from mild headache, hyposmia, hypogeusia, and fatigue to sleep disorders, pain, cognitive impairment, and rarely Guillain-Barré syndrome [40]. To ascertain clearly the concept that implies the main cause of the neurological disorder, it is required to define the components of neuro-COVID, which tends to cause a less mortal 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, reveal significant alterations that represent inflammatory activity. It is also noticed that during the acute phase of the disease, a consequential number of

inflammatory events have been demonstrated by radiological surveys of the central nervous system and also with cytological and biochemical evaluations of cerebrospinal fluid [76].

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

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

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

7. Psychiatric Issues

The psychological health outcomes of getting through COVID- 19 may be contributed to social withdrawal to 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; they are prone to have psychological distress and post-traumatic stress disorder. A study showed that more than half of patients showed these mental problems after surviving severe disease [86]. The first study associated with neuropsychological findings of post-COVID-19 patients has shown that Beck Depression Inventory scores were significantly higher in post-COVID-19 patients than in healthy controls [87].

8. 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 after being recovered from COVID-19 infection [88]. Additionally, a cohort study was conducted in among 453 patients by evaluating TSH and T4 Levels before, during, and after SARS-CoV-2 infection. According to this study, while most of the cases were found to be euthyroid, a slight decrease was reported both for TSH and T4 Levels, which normalized after infection [77].

9. Dermatological Issues

A single-center attempt to define the skin manifestations of long COVID syndrome by Diovalletti *et al* composed a prospective study that covers 104 patients. After the day of hospital discharge, patients followed up in 1, 3, and 6 mo and examined by dermatologists 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

the interruption of the anagen phase was the most prevalent dermatological finding in patients after SARS-CoV2 infection [89].

CONCLUSION

Since the new coronavirus involves multiple organ systems and the numbers of COVID-19 survivors increase every day, there is an upcoming need for developing new strategies for the assessment of these patients systematically as well as the need for rehabilitation services. Multidisciplinary post-acute COVID-19 care services should include several specialists to be able to evaluate the consequences of the disease, which it can promise to highlight most of the unknown points of COVID-19 disease.

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