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Overview and management of different post-COVID conditions

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Abstract:

Coronavirus disease 2019 (COVID-19) pandemic resulted in global healthcare crises and strained health resources, both in the acute and chronic phase of the disease. Similarly to post-acute viral syndromes described in survivors of other virulent coronavirus epidemics, there are increasing reports of persistent and prolonged symptoms after acute COVID-19. These reports and studies have helped contribute to the recognition of post-COVID-19, a syndrome characterized by persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. Here, we provide a comprehensive review of different manifestations of post-COVID conditions and propose a framework for the identification of patients at higher risk for post- COVID and their coordinated management through dedicated COVID-19 outpatient clinics.

Keywords:

COVID-19, post COVID conditions, coronavirus, SARS-CoV-2

Sažetak:

Pregled i upravljanje različitim post-COVID uvjetima

Pandemija bolesti koronavirusa 2019. (COVID-19) rezultirala je globalnom zdravstvenom krizom i opterećenim zdravstvenim resursima, kako u akutnoj tako i u kroničnoj fazi bolesti. Slično kao i kod postakutnih virusnih sindroma opisanih u preživjelih od drugih virulentnih epidemija koronavirusa,

sve je više izvješća o postojanim i produljenim simptomima nakon akutnog COVID-19. Ova izvješća i studije pomogle su pridonijeti prepoznavanju post-COVID-19, sindroma kojeg karakteriziraju trajni simptomi i/ili odgođene ili dugotrajne komplikacije nakon 4 tjedna od početka simptoma. Ovdje pružamo sveobuhvatan pregled različitih manifestacija stanja nakon COVID-a i predlažemo okvir za identifikaciju pacijenata s većim rizikom od post-COVID-a i njihovo koordinirano liječenje kroz namjenske ambulante za COVID-19.

Ključne riječi: COVID-19, post COVID uvjeti, koronavirus, SARS-CoV2

Introduction

Pandemic of COVID-19, disease caused by SARS-CoV-2 virus, resulted in many persons surviving the acute disease phase. According to the available literature, as well as the experience gathered in our daily work, many of these patients will experience a wide range of symptoms in the period following the acute infection (1-3). Currently, the most widely used term describing the condition is the „post-COVID conditions". The World Health Organization (WHO) defines this condition 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 that last for at least 2 months and cannot be explained by an alternative diagnosis" (4). Despite multiple definitions, there are still no widely accepted clinical diagnostic criteria for post-COVID conditions. Still, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) has assigned a code (U09.9) that encompasses all unspecified post-COVID conditions. However, it is still not clear whether the constellation of symptoms following SARS-CoV-2 infection represents a completely new syndrome, unique for COVID-19, or an overlap with the syndrome of recovery after other infectious diseases and disease caused critical conditions. However, it has been shown, in our population as well as in other published cohorts, that the presence of post-COVID symptoms is independent of the severity of acute COVID-19 (5). The distribution of humane ACE2 receptors in different tissues, especially in the circulatory system, enables the wide spread of SARS-CoV-2. Thus, both symptoms of acute COVID-19 and post-COVID conditions vary and may involve a wide range of different organic systems (6).

Pulmonary manifestations of post-COVID conditions

In general, three out of four most common physical symptoms following acute COVID-19 are related to the respiratory system: dyspnea, cough, and chest pain/tightness. These symptoms may reflect certain structural issues such as interstitial lung disease (with the tendency of developing pulmonary fibrosis) and/or thromboembolic events (with possible emergence of chronic thromboembolic pulmonary hypertension, CTEPH). For diagnostic purposes, we commonly use imaging methods (chest X-ray, high resolution CT (HRCT) of the chest, perfusion/ventilation scintigraphy), lung function tests (spirometry with reversibility testing and diffusing capacity test), and echocardiography. In case a thromboembolic event is diagnosed, treatment recommendations are clear and do not differ significantly from the treatment of embolisms not related to SARS-CoV-2 infection. If there are no other risk factors for blood clothing, aside from COVID-19, recommended treatment time is three to six months with warfarin or one of the new anticoagulants (NOACs) (7). Those who still complain of dyspnea after the treatment period, as well as those with larger embolic masses in the acute phase, should be referred for echocardiography in order to timely diagnose CTEPH. However, in the available literature we still do not have evidence of CTEPH incidence rise (8). The reason behind it may be that pulmonary embolisms connected with COVID-19 are mechanistically different and commonly smaller and peripheral. Moreover, more time is needed for the conclusion, given that CTEPH usually occurs within two years of the acute embolism event (8). Radiologically visible changes have been described in up to 70% of patients following COVID-19 pneumonia three months after the onset of the disease. Moreover, they were still present in 24% of patients even after 12 months (9-12). Organizing pneumonia is the most common manifestation of interstitial lung disease following acute COVID-19 (13). Among lung function tests, predominant are the reduction in diffusing lung capacity for carbon monoxide (DLCO) and restrictive pattern in spirometry, while obstructive pattern is less common and seen in less than 10% of patients (11,14). Typical radiological pattern of OP includes peripheral consolidations with air bronchogram and ground glass opacities (GGO), while solitary or multiple masses/

nodules, perilobar pattern, atoll sign, linear opacifications and progressive fibrosis belong to atypical findings (15). There is no clear guidance or algorithm for both the treatment of parenchymal changes and prevention of fibrosis in the subacute or chronic phase following SARS-CoV-2 infection. Still, in the case of OP, similarly to the management of other OP causes, glucocorticoids seem like a reasonable choice. Dosage and treatment duration depend on the severity of lung parenchyma affection and the level of lung function impairment and vary from 0,25–0,5 mg/kg prednisone for up to 14 days without tapering to pulse doses of prednisone or methylprednisolone with gradual tapering over the weeks/months of the recovery period. A recent prospective observational study showed first evidence of glucocorticoid effectiveness in patients with OP after acute COVID-19 pneumonia (13). Lastly, in the management of patients with impaired lung function, multidisciplinary approach and pulmonary rehabilitation represent cornerstone therapy. Pulmonary rehabilitation is mostly implemented in the outpatient setting, beginning at least four weeks after the end of acute COVID-19, but can be stationary in the most severe cases, usually immediately or shortly after the end of acute, infective COVID-19 phase. Proposed algorithm for outpatient evaluation of patients with pulmonary post-COVID conditions is shown in Figure 1.

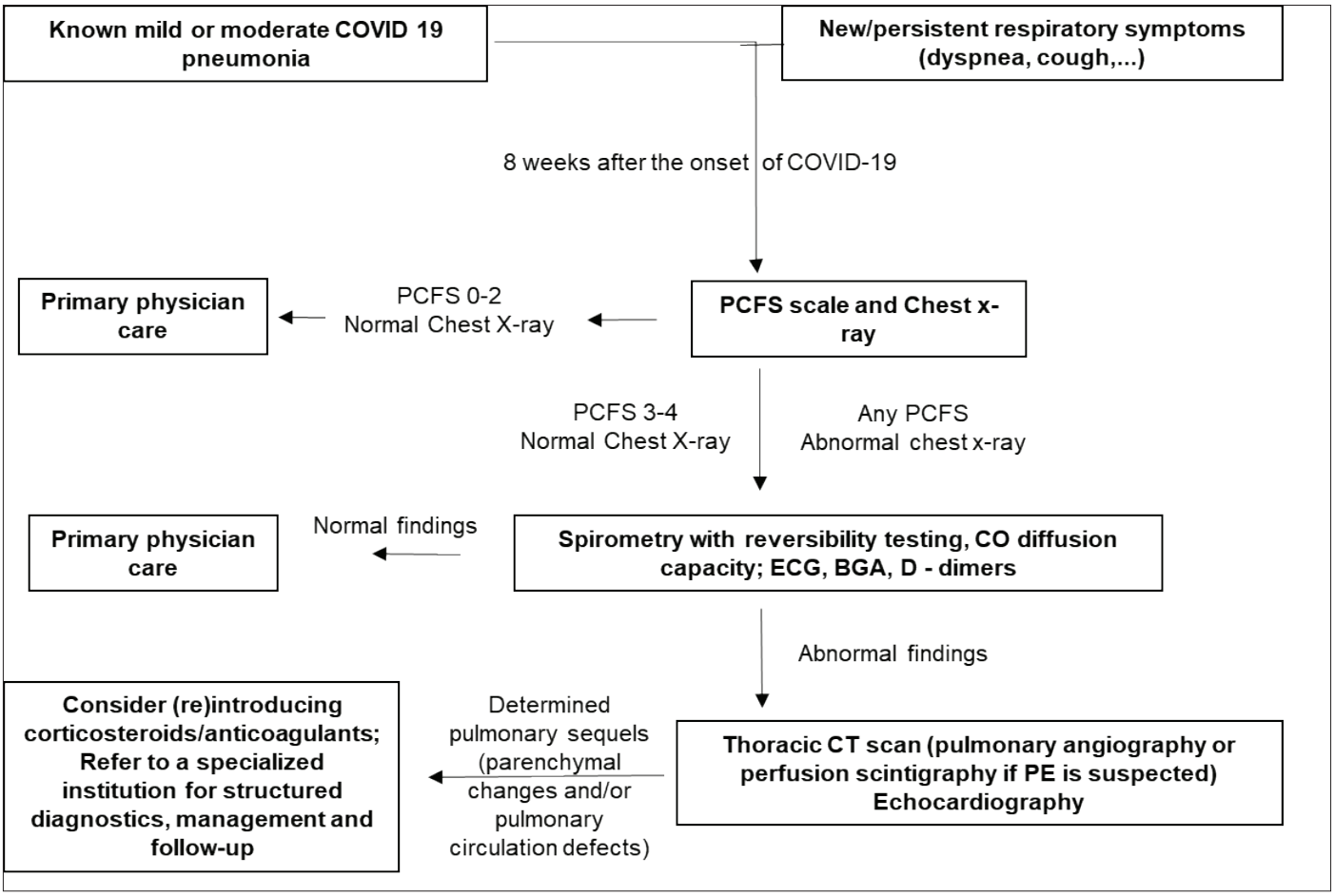

Figure 1. Proposed algorithm for out-patient evaluation of patients with pulmonary manifestation of post-COVID conditions.

ABGA – arterial blood-gas analysis; CO – carbon monoxide; ECG – electrocardiogram; PCFS – post covid functional status

Cardiac manifestations of post-COVID conditions

Cardiovascular symptoms, such as chest pain, palpitations, or higher resting heart frequencies, are among the most common in patients after acute COVID-19. Syndromes such as myocarditis, postural orthostatic tachycardia and pericarditis may also occur. Although small pericardial effusions in post-COVID are relatively common, clear symptomatic pericarditis is rare. Postural orthostatic tachycardia syndrome (POTS) is defined as an inappropriate increase in heart rate without a change in blood pressure when moving from a supine to an upright position. Treatment of POTS varies depending on the degree of symptoms and usually involves a combination of physical exercise and behavioral therapy, and sometimes drug therapy. Given the increased likelihood of a major adverse cardiac event (MACE) in the months following discharge, hospitalized patients with preexisting risk factors for cardiovascular events should be closely monitored after COVID-19. In addition, hospitalized patients with acute COVID-19 who show biomarker evidence of myocardial injury or have had a clear myocardial infarction (most commonly myocardial infarction type 2) require cardiac treatment to determine whether there is underlying coronary artery disease unmasked by increased metabolic demand conditions due to systemic inflammation and to prescribe further medical, interventional, or cardiac surgical therapy. Overcoming COVID-19 often results in chronic fatigue syndrome (CFS), which is defined as severe, disabling fatigue after exertion that affects physical and mental functioning. To diagnose CFS, symptoms must persist for at least 50% of the time for at least 6 months. Cognitive behavioral therapy with gradual exercise may be an effective treatment in CFS, while pharmacological treatment with antidepressants, steroids, and vitamin supplements has shown mixed results in small clinical trials. COVID-19 is also characterized by marked deconditioning that requires gradual exercise as the only therapy in the post-COVID period (16,17). The tendency to significantly reduce (probably due to patients' fear of hospitalization and infection) the number of patients with acute myocardial infarction and other cardiac diseases in hospitalized patients, especially during the first waves of the COVID-19 pandemic, is monitored across Europe and the United States, but also in our country (18). In addition, the pandemic is accompanied by an increased incidence of some less common complications of myocardial infarction, such as myocardial rupture or cardiogenic shock with consequent long-term decrease in the ejection fraction of the heart and symptoms of its failure. It is to be expected that this will require additional efforts by health systems in treating and monitoring these patients (Figure 2).

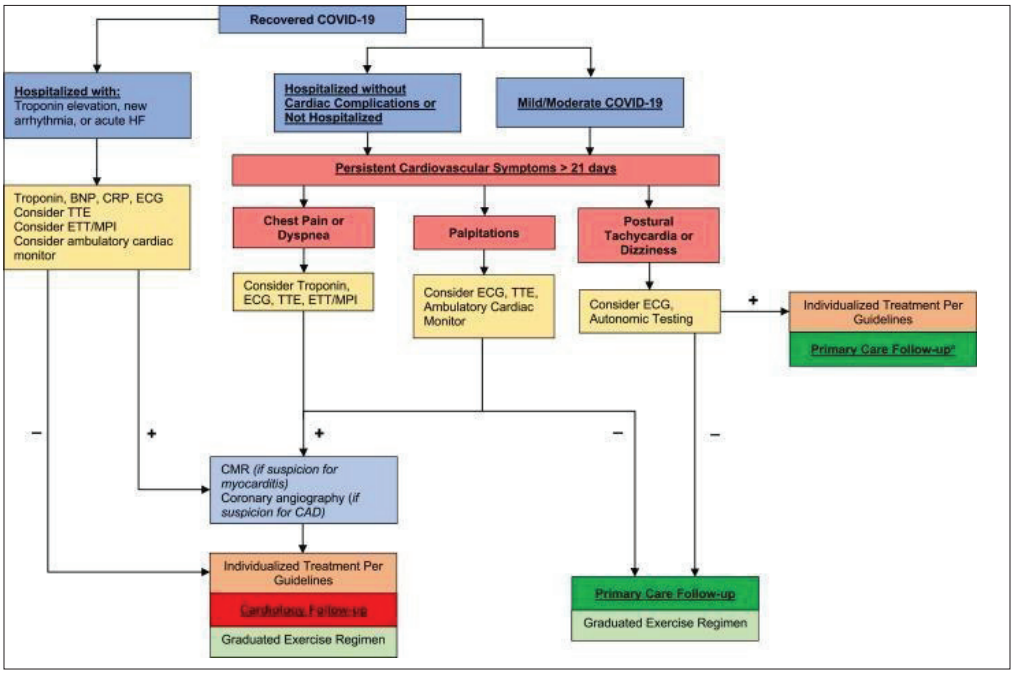

Figure 2. Proposed algorithm for the treatment of patients recovering from COVID-19 with persistent cardiovascular symptoms or previously COVID-19 hospitalized patients with cardiac complications (16)

Neurological manifestations of post-COVID conditions

Neurological manifestations of post-COVID include a broad spectrum of nonfocal symptoms and signs, such as chronic fatigue, memory disturbances, hyposmia, headache and heaviness in extremities but also include a plethora of focal and specific manifestations of central or peripheral nervous system disturbances. SARS-CoV-2 infection is associated with cognitive and neurodegenerative disorders, demyelinated disorders of the central nervous system (CNS), autoimmune encephalitis, epilepsy as well as with disorders of peripheral nervous system (PNS) (19-21). Coronavirus could be detected in the CNS of patients with Parkinson's disease (PD), Alzheimer's disease (AD) and multiple sclerosis (MS) (10-25). According to human and animal experimental models, SARS-CoV-2 could enter the brain as well as brainstem directly, probably via olfactory nerve, without prior infection of the lungs (23,24). There are several mechanisms which connect movement disorders, especially PD with COVID-19 (22). Even though etiology of PD remains unclear, neuroinflammation of dopaminergic neurons is a potential cause and the presence of the antibodies against coronaviruses in the cerebrospinal fluid (CSF) of PD patients was detected two decades ago (19,22). Also, demyelinated disorders of central nervous system (CNS) such as acute disseminated encephalomyelitis (ADEM), transverse myelitis (TM), MS and neuromyelitis optical spectrum disorder (NMOSD) are associated with SARS-CoV-2 infection (26-28). Current research data have shown that the most common pattern of demyelinated disruption is non-specific encephalitis or encephalomyelitis. The most common manifestation of isolated spinal cord involvement was longitudinal extensive transverse myelitis (LETM). Although SARS-CoV-2 is neurotrophic and passes blood-brain barrier, it is more likely that demyelinated disorders of CNS occur para- or post-infectious due to immune related mechanisms. Autoimmune response in patients with COVID-19 could lead to autoimmune encephalitis or new onset refractory status epilepticus (NORSE), especially in patients with severe manifestations of COVID-19 with respiratory insufficiency. Therapeutic approach in autoimmune encephalitis and NORSE comprises of immunomodulatory treatment (corticosteroids, intravenous immunoglobulins (IVIG) 0.4 g/kg and plasma exchange) together with clinical and electrophysiological follow up (electroencephalographic monitoring) as well as broad differential diagnostic assessment in order to exclude other potential etiologies (29-31). Epileptic seizures could be present either in the post- COVID syndrome or as a manifestation of prolonged COVID-19 (31-33). Post-COVID syndrome could also have PNS involvement: acute and chronic neuropathies, muscle disorders, autoimmune disorder of neuromuscular junction, post infectious disorders of the sensory ganglia and consecutive neuropathic pain (34). These disorders are immune mediated or could develop because of prolonged treatment of severe COVID-19. The most common disorders of PNS are autoimmune neuropathies and sometimes it is difficult to distinguish certain forms of Guillain-Barre syndrome from acute onset chronic inflammatory demyelinating polyneuropathy. In case of acute inflammatory polyneuropathy, special attention should be paid on the possible autonomic nervous system involvement. It is important to follow up the patient clinically as well as with the electroneurographic assessment and treatment should be individualized (33,34). Treatment approach according to the guidelines includes: IVIG 2 g/kg, corticosteroids, and plasma exchange. Neuropathic pain of radicular distribution could also be a part of post-COVID syndrome. Regardless of prior COVID-19, in case of suspicion on sensory ganglionopathy, diagnostic work up is mandatory including standardized protocol and treatment of consecutive neuropathic pain according to the guidelines (pregabalin, gabapentin, dual antidepressants and topic analgesia if appropriate). In persons with PNS disorders, immune mediated disorders are more prevalent after COVID-19. But one should keep in mind possible PNS complication of prolonged stay in the intensive care units such as critical illness polyneuropathies of myopathies (34,35).

Psychiatric manifestations of post-COVID conditions

Approximately 40% of people suffering from acute COVID-19 exhibit signs of a psychiatric disorder, including a vast spectrum of symptoms such as depression, anxiety, phobias, obsessive-compulsive behavior, somatizations, insomnia and lack of appetite, psychoticism, hostility and interpersonal sensitivity (36,37). Also, elevated levels of psychiatric disturbances have been detected even 3 to 7 months post-illness, with a higher risk among women, persons who underwent intensive care treatment and those with longer hospitalization stays, those with multiple comorbidities as well as patients with more intense psychological problems at the start of treatment (38,39). In addition, specific personality traits, namely depressive and cyclothymic temperaments and emotional dysregulation, are known predictors of psychological problems in the post-COVID period (40). Latest research suggests that among some individuals, psychiatric disturbances remain up to 12 months after the onset of COVID-19 (41). Because of occasional delirium and psychotic/manic symptoms in patients who were treated in intensive care units (42), the need for long-term psychiatric and psychological assessment of these individuals is more than evident. Our team has stressed out the importance of psychodynamic understanding of COVID-19 pandemic and individual reactions to this illness (43), as well as the necessity to promote global empathy in order for these patients, and the society as a whole, to achieve psychological growth (44). Evaluation and diagnostics of patients with post-COVID syndrome, particularly those with the elevated risk of developing psychiatric disorders (38-40), should include

psychiatric check-ups and pragmatic clinical assessment via psychometric scales aimed at determining the intensity of psychiatric symptoms. Although unidimensional scales are available, given the large number of different psychiatric symptoms that can emerge, multidimensional psychometric scales seem a better option (e.g., the Symptom Checklist-90-Revised - SCL-90-R). A downside of multidimensional scales is their length so the choice of psychological instruments usually depends on the broader clinical context and psychophysical state of the patient. These psychometric scales have already been used and/or validated in previous research with domestic clinical samples (45-47). For patients with post-COVID syndrome whose results suggest the presence of psychiatric symptoms or who seek out professional help, a face-to-face psychiatric appointment should be organized in the shortest possible time frame. Possible treatments include supportive psychotherapy, psychological counseling or psychoeducation by a psychiatrist or clinical psychologist. In the case of clinically significant psychiatric symptoms, medication therapy should be implemented based on the guidelines for specific psychiatric disorders. However, clinicians should always keep in mind the possibly complex and unique health status (i.e., increased risk of multiple somatic comorbidities) of each post-COVID patient (48,49).

Hematological manifestations of post-COVID conditions

The most common hematological manifestations following acute COVID-19 are laboratory abnormalities. Prothrombotic state, characterized by increased level of factor VIII and plasminogen-activator type I inhibitor (PAI-1), can persist up to four months after acute COVID-19 (50). Lymphocytopenia is commonly seen and may persist at five weeks from the disease onset, especially in patients with severe acute COVID-19 (51). In contrast, neutropenia is rare, but may present a sign of bone marrow suppression due to the inflammatory response (52). Thrombocytopenia, a well-known complication of different viral infections, is another commonly found disorder in patients following acute COVID-19, especially in elderly and patients with lymphopenia (53). Elevated level of D-dimer could be a useful parameter of prothrombotic condition, but there is no connection between D-dimer level and development of late venous thromboembolic events (VTE) (54). Most clinicians consider D-dimer levels as reliable parameter together with clinical predictors of VTE to decide the length of thromboprophylaxis. COVID-19 has been associated with hyperferritinemia which is linked to increased mortality. Levels could be increased more than 2 months after the acute disease (55). But, some patients will have iron deficiency and anemia. COVID-19 induced coagulopathy (CIC) is an immune thrombotic state that develops in acute COVID-19, but persists in chronic COVID-19 with more prothrombotic incidents, less hemorrhagic events (56). Hyperinflammatory state develops endotheliitis and activation of coagulation cascade, fibrinolysis disruption, thrombin development (57,58). Risk of thrombotic complications in post-COVID period is probably related to the duration and severity of hyperinflammatory condition, but it is unknown for how long this condition could last. Prolonged thromboprophylaxis decreases the risk of thrombotic events, but increases the risk of bleeding. Results from recent studies have shown that the incidence of thrombotic complications in post-COVID era has not been significant, but at present time we don't have a clear ratio of benefits and risks of prolonged thromboprophylaxis (59). Standardized tools for VTE risk assessment should be used in the group of patients with higher VTE risk who need prolonged thromboprophylaxis, up to 6 weeks). Standard risk factors include active malignant disease, immobility, high BMI, recent trauma, thrombophilia, surgical procedure, personal or family history of VTE. Regular monitoring of blood results and evaluation of the individualized thrombotic risk for VTE are essential for both post-acute and chronic COVID-19 (post-COVID) (60,61). Autoimmune thrombocytopenic purpura (ITP), although rarely, has been recognized as a late manifestation of COVID-19, with the highest incidence 3 to 4 weeks after the onset of COVID-19 (62).

Gastrointestinal manifestations of post-COVID conditions

The clinical picture of gastrointestinal (GI) post-COVID syndrome is heterogeneous and is similar to the symptoms of irritable bowel syndrome (IBS) which develop after resolution of COVID-19 (63, 64) Some of the symptoms that may be present in GI post-COVID syndrome are anorexia, bloating, abdominal pain, constipation, diarrhea, nausea, or heartburn. In addition to the intestinal symptoms, milder impairment has also been reported in other GI organs in patients with COVID-19, such as liver, pancreas, or spleen. The presumed mechanism of hepatobiliary organ damage is use of hepatotoxic drugs (antibiotics, glucocorticoids, non-steroidal anti-inflammatory agents etc.), systemic inflammatory response, reperfusion liver damage, with a possible direct vital effect (65). Liver damage can be of various types, hepatocellular or cholestatic with possible impairment of all liver enzymes (alkaline phosphatase, gamma-glutamyl transferase, aspartate transferase, alanine transferase). According to the studies, enzyme values returned to normal in most of the patients approximately 2 months after hospital discharge (66). It is important to point out that mortality in patients with liver cirrhosis is higher than in patients without liver cirrhosis, as shown by the study on 754 patients, which supports the fact of significant impact of SARS-CoV-2 on the liver function, especially if there is an underlying liver damage. This is very important in risk stratification and predicting the complicated course of the disease in these patients (67). In addition to the direct viral effect on the GI tract, there are possible indirect complications such as GI

bleeding due to anticoagulant therapy, for example in patients treated for pulmonary embolism after SARS-CoV-2 infection or in patients on prophylactic anticoagulant therapy. On the other hand, a case of simultaneous development of pulmonary embolism and gastrointestinal bleeding in patients without anticoagulant therapy has been described, which also supports the possible direct effect of the virus on intestinal cells and increased risk of bleeding (68). In conclusion, physicians should be aware of a wide range of post-COVID signs and symptoms, from IBS symptoms to liver damage or coagulation impairment. Also, rational drug usage could help in preventing some of the potential GI complications.

Nephrological manifestations of the post-COVID conditions

SARS-CoV-2 infection exhibits signs in all organ systems, including kidneys. Studies have revealed kidney injury in 12% of patients (1). Renal complications with the need for renal replacement therapies are present in 5% of all patients after COVID-19 (69). A study including over 4700 patients recovered from acute COVID-19 revealed a 30% decrease in renal function within one year. Additionally, the authors found that patients after COVID-19 have double the incidence of acute kidney injury and end-stage renal disease three times more often than persons who have never had COVID-19 (70).

Dialysis patients have an increased incidence of SARS-CoV-2 infection and higher mortality from acute COVID-19. During post-COVID, cachexia was described as a significant problem in 13% of dialysis patients (71). Renal transplant recipients (RTRs) are a delicate patient population due to chronic immunosuppressive therapy. Mortality rates in recent studies approached 20%, with mortality in patients requiring mechanical ventilation being around 50% (72,73). In the short-term follow-up after acute COVID-19, only 11.5% of RTRs were symptom-free. Most frequent clinical complications include shortness of breath (19.2%) and fatigue (11.5%), while 71.2% of participants had abnormal laboratory findings. Reactivations of opportunistic infections were frequent (74). A recent multicentric study revealed that 15.9% of RTRs required hospital admission after acute COVID-19. Some were readmitted, but a certain proportion represented patients who had mild acute SARS-CoV-2 infection, which did not require hospital treatment. They developed significant clinical and/or laboratory complications which required hospital admission (75). Most frequent indications were pneumonia (24-5%), graft dysfunction (22.4%), sepsis (14.3%) and thrombotic events (10.2%). The strongest indicator of admission after COVID-19 was hospital admission during acute COVID-19, while better graft function decreased the odds of admission after acute COVID-19 (75). Different post-COVID-19 histopathological changes, including the collapsing form of focal segmental glomerulosclerosis were found on indication biopsies of RTRs with post-COVID renal allograft dysfunction (76). Renal complications are frequent during the acute COVID-19 and should not be neglected during the post-COVID. A structured multidisciplinary approach is required to avoid further deterioration of kidney function in patients with acute kidney injury during the acute SARS-CoV-2 infection and to prevent post-COVID complications in patients with chronic kidney disease.

Addressing Post-COVID conditions in Primary Care and Family Medicine.

Family physicians (FP) as primary care providers are often the first point of contact for patients experiencing potential post-COVID symptoms (77). It is important to keep in mind that post-COVID syndrome has been identified not only among hospitalized patients with severe symptoms but also among those who were asymptomatic or with mild symptoms. FP should assess these symptoms systematically starting with detailed history and physical examination, followed by judicious test ordering as needed. FP should be equipped to evaluate alternative etiologies of symptoms, validate symptoms as potentially related to post-COVID when appropriate and provide support as needed. Patients with post-COVID symptoms should primarily be managed symptomatically in the primary care setting, avoiding over investigation and considering pre-existing or new comorbidities (78). There is a need for interdisciplinary guidelines for the diagnosis and management of post- COVID conditions, based on joined established criteria to support the provision of appropriate healthcare at the primary care level.

Musculoskeletal manifestations of post-COVID conditions

Studies from patients who contracted moderate and severe SARS and COVID-19 have indicated a substantial musculoskeletal burden of this diseases, including skeletal muscle, neurological, bone, and joint disorders (79). Extended ventilator times are also known to induce proinflammatory conditions that lead to muscle and bone frailty, which can reduce overall quality of life. In addition to directly infecting cells outside of the respiratory tract, the inflammatory response in the airway can also lead to systemic inflammation that can impact nearly every organ system, including the musculoskeletal system (79,80). The most common musculoskeletal symptoms are fatigue, myalgia, and arthralgia. Karaarslan and colleagues in their extension cohort study, found that at 3 months, 89% of survivors had at least one symptom, 74.6% had at least one rheumatic and musculoskeletal symptom, and 82.1% had at least one other COVID-19 symptom (81). At 6 months, 59.6% of survivors had at least one symptom, 43.2% had at least one rheumatic and musculoskeletal symptom, and 51.2% had at least one other COVID-19 symptom. Regarding the rheumatic and musculoskeletal symptoms, 31.6% had fatigue, 18.6% had joint pain, and 15.1%

had myalgia; and regarding the other-COVID-19-symptoms, 25.3% had dyspnea, 20% had hair loss, and 17.2% sweat at 6 months. In an adjusted model, female patients were more likely to have fatigue (OR: 1.99, 95% CI: 1.18–3.34), myalgia (3.00, 1.51–5.98), and joint pain (3.39, 1.78–6.50) at 6 months. Less is known about bone and joint than skeletal muscle disorders in patients with COVID-19. Arthralgias are commonly reported in patients with COVID-19, but are often combined with myalgias (81, 82), making it challenging to specifically identify arthralgia prevalence. The reduced BMD observed in patients with SARS was largely thought to be dependent on the extent and duration of treatment with glucocorticoids, which were a mainstay therapy that attempted to reduce inflammation during the initial infection and subsequent early rehabilitation and recovery period (83). However, decreased BMD has also been reported in other acute critical illnesses and may occur independently of treatment with glucocorticoids (84). Osteonecrosis has been frequently reported in patients with severe SARS, with rates from 5% to 58% (79, 85). The majority of these cases involve the femoral head, although the knee, humeral head, talus, calcaneus, and other anatomical sites were affected in lower frequencies (85). Similar to osteoporosis, patients who had higher or longer doses of glucocorticoids had an elevated risk of developing osteonecrosis (79,85). Hypercoagulability has also been noted in both patients with COVID-19 and those with SARS, leading to large-vessel stroke in some patients (79, 86). The SARS-CoV-1 infection can also induce the expression of the E3 ubiquitin ligase gene TRIM55 in vascular smooth muscle cells, which is associated with leukocyte aggregation and blood vessel inflammation (79). The combination of hypercoagulability, leukocyte aggregation, and vessel inflammation may impair bone microvascular blood flow and contribute to the development of osteonecrosis.

Conclusion

The multi-organ sequelae of COVID-19 beyond the acute phase of infection are increasingly being recognized. Continuation of research, including the identification and characterization of key clinical, serological, imaging and epidemiologic features of COVID-19 in the acute, subacute and chronic phases of disease, will help us to better understand the natural history and pathophysiology of this new disease entity. Currently, healthcare professionals caring for patients after acute COVID-19 have the key role of recognizing, documenting, investigating and managing ongoing or new symptoms, as well as following up organ-specific complications that developed during acute illness. Interdisciplinary cooperation is needed for comprehensive care of these patients in the outpatient setting. Given the global scale of this pandemic, it is apparent that the healthcare needs for patients with sequelae of COVID-19 will continue to increase for the foreseeable future, which will substantially burden the existing outpatient infrastructure. Thus, the development of scalable healthcare models and integration across disciplines for improved mental and physical health of survivors of COVID-19 in the long term is needed.

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