Review
https://doi.org/10.23934/2223-9022-2021-10-2-248-258

COVID-19 and Cardiovascular System. Part II. Post-COVID Syndrome

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ABSTRACT Long-term consequences of COVID-19 remain the subject of active research interest. In this article the Post-COVID-19 syndrome (PCS) main features and symptoms are considered, its incidence and link with comorbidity is presented and the possible mechanisms are discussed. Due to the damage COVID-19 has on lungs, heart, brain and other systems, patients with PCS require multidisciplinary management.

Keywords: COVID-19, postcovid syndrome, comorbidity

For citation Ivannikov A.A., Esaulenko A.N., Vasilchenko M.K., Alidzhanova Kh.G., Petrikov S.S. COVID-19 and Cardiovascular System. Part II. Post-COVID Syndrome. Russian Sklifosovsky Journal of Emergency Medical Care. 2021;10(2):248–258. https://doi.org/10.23934/2223-9022-2021-10-2-248-258 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study had no sponsorship

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ACE 2 — angiotensin converting enzyme 2
AH — arterial hypertension
AKI — acute kidney injury
ARDS — acute respiratory distress syndrome
ATII — angiotensin II
BBB — blood-brain barrier
BS — brain stem
CKD — chronic kidney disease
CRP — C-reactive protein
CVD — cardiovascular diseases
CVS — cardiovascular system
DM — diabetes mellitus
ED — endothelial dysfunction
HF — heart failure
IL-6 — interleukin-6
MI — myocardial infarction
NICE —UK National Institute of Health and Care Excellence
PCR — polymerase chain reaction
PCS — post-COVID syndrome
RAAS — renin-angiotensin-aldosterone system
RF — risk factor
RNA — ribonucleic acid
ROS — Reactive oxygen species

TNF-α - tumor necrosis factor-α
VTE — venous thromboembolism

INTRODUCTION

Most people with COVID-19 recover, but some have long-term multiple organ symptoms and complications, and their number increases [1]. Long-term COVID or post-covid syndrome (PCS), or post-acute COVID, is a relatively new problem that requires an interdisciplinary involvement, is recognized by the medical community and causes concern [2]. It is difficult to predicting long-term cardiac outcomes of COVID-19. The genetic similarity between SARS-CoV-1 and SARS-CoV-2, as well as the experience of previous viral outbreaks, where cardiovascular disorders were detected in 40% of patients during a 12-year follow-up, suggest long-term consequences of COVID-19 [3-4]. About 10% of patients with a positive polymerase chain reaction (PCR) test for the SARS-CoV-2 virus do not recover for more than 3 weeks, and a smaller proportion do not recover for months [5]. A hundred days after COVID-19 manifestation 41% of patients still have persistent symptoms, with the most common symptom being shortness of breath (36%). Less frequently, a decreased left ventricular function and signs of pulmonary hypertension are diagnosed [6]. The long-term effects of COVID-19 on the human body are still unknown, but the symptoms described after the SARS-CoV-2 pandemic are alarming and require a long-term follow-up of patients [7-8]. The prognosis may depend not only on the degree of lung damage during the acute phase of the disease, but also on extrapulmonary manifestations. Thus, the initial focus on the diagnosis, emergency medical care, studying the course of the disease and its complications, as well as its prevention shifted towards studying the changes occurring in the body of survivors with long-term consequences [9-10].

DEFINITION AND EPIDEMIOLOGY

Long-term COVID, or PCS, is a multisystem disease of people who have had COVID-19 and who show symptoms at 12 weeks or more after the diagnosis. PCS develops regardless of the initial disease severity and age and lasts from several weeks to months. PCS is accompanied by a wide range of recurrent symptoms, which vary in intensity and duration and do not necessarily occur in parallel or sequentially [8, 11]. National Institute of Health and Care Excellence (NICE) in the UK, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) have developed a "*COVID-19 rapid guideline: managing the long-term effects of COVID-19*" where the PCS is defined as a set of signs and symptoms that develop during or after COVID-19, and persisting for more than 12 weeks, which may not be associated with alternative diagnoses [12]. In 2020, PCS was included in the International Classification of Diseases ICD-10. It is assumed that PCS can be manifested by such syndromes as: post-intensive care syndrome, post-viral asthenia syndrome, irreversible organ damage syndrome, and long-term COVID-19 [13].

PCS includes persistent symptoms that may be associated with residual inflammation (reconvalescence phase), organ damage, non-specific effects of hospitalization or prolonged mechanical lung ventilation, and social isolation [14]. Available data on the incidence (occurs in 2% — no less than 50% of cases) and the evolution of PCS are few and heterogeneous [7-9]. In the UK, one in ten patients has symptoms lasting for 12 weeks or longer [15]. Among those infected with SARS-CoV-2, 80% have one or more long-term symptoms [7-8]. Post-acute symptoms of COVID-19 vary greatly. Even a mild course of COVID-19 can be associated with long-term symptoms (cough, low-grade fever, and fatigue) that can either recur or go away completely. In 10-14 weeks after the onset of the disease, the PCS was diagnosed in 50.9% of patients [7]. People with mild COVID-19 who had not been hospitalized had persistent or prolonged symptoms. Analysis of the spectrum and severity of these effects showed that persistent fatigue was observed in 39-73% of the patients, shortness of breath was seen in 39-74%, reduced quality of life in 44-69%, 39-83% of patients had lung function impairments, abnormal results of computed tomography, including pulmonary fibrosis, the signs of peri/myocarditis were seen in 3-26%, the changes of microstructure and functional integrity of the brain with persistent neurological symptoms were observed in 55%, 5.8% had a high occurrence of psychiatric diagnoses; persistent anosmia-dysgeusia was seen in 33%-36% [16]. The severity of neurological and respiratory symptoms generally decreased at 16-18 weeks after the onset of the disease [7].

PCS is more often observed in middle-aged people and does not depend on the severity of the COVID-19 course. There was a statistically significant association of the age and PCS with the presence of such manifestations as shortness of breath (p=0.007), persistent cough (p<0.001), pain in joints (p<0.001), and chest pain (p<0.001). Egyptians with a severe form of COVID-19 experienced more severe post-recovery symptoms than those with a milder form of the disease. The studies conducted in Italy, Great Britain, and Egypt have shown that fatigue is the most common manifestation of PCS [8, 17]. *Y.M. Zhao et al*. [18] reported that 64% of the patients who were discharged from the hospital had

persistent symptoms of PCS 3 months after their discharge from the hospital: 71% had X-ray abnormalities, and 25% had a decrease in diffuse lung capacity. The study of B. van den Borst et al. [19] showed that after 3 months, 42% of discharged patients retained reduced diffuse lung capacity in combination with other symptoms of PCS. After 6 months, the survivors of a severe form of the disease, in addition to various symptoms, also had serious impairments of the diffuse lung capacity [20]. Independent predictors of the PCS development in individuals with severe pneumonia were the expansion of lung lesion areas corresponding to the damage in the acute phase of the disease, as well as high heart rate [7]. *B. Oronsky et al*. [9] believe that in patients with acute respiratory distress syndrome (ARDS) who recovered from COVID-19, the condition progresses to the development of pulmonary fibrosis, which main symptoms are the shortness of breath, chronic dry cough; and their treatment is mainly supportive. They have reduced exercise tolerance, quality of life, and an increased risk of death.

PATHOPHYSIOLOGICAL MECHANISMS OF THE POST-COVID SYNDROME DEVELOPMENT

Several pathophysiological pathways of the PCS formation have been suggested, including viral infiltration, microthrombi formation, and suppression of angiotensin converting enzyme 2 (ACE 2) receptors [21-22]. A long-term inflammatory process and recurrent infection with SARS-CoV-2 are considered as one of the possible mechanisms of the PCS development [22]. Patients who could "endure" the initial hyperinflammatory response, including the "cytokine storm", can get into the stage of long-term immunosuppression. In addition, a persistent inflammatory response, as well as immunosuppression and post-septic catabolic process may be hypothetical causes of the PCS development. This hypothesis is supported by the fact that post-septic patients are prone to latent reactivation of the virus [23-24], and numerous scientific sources report relapses or reactivation of SARS-CoV-2 in recovered patients [25-27]. Similarly as in sepsis, the patients with COVID-19 are at a risk of developing secondary bacterial and fungal infections [28], which highlights the presence of immunosuppression and dysregulation.

A prolonged exposure to SARS-CoV-2 may be one of the main mechanisms of PCS. Persistent viremia probably contributes to the PCS development due to a weak or absent humoral response, relapse or re-infection, inflammatory and other immune responses, and psychiatric factors such as post-traumatic stress. SARS-CoV-2 has a highly structured ribonucleic acid (RNA) genome, an attribute common to other human coronaviruses. They are capable of long-term preservation, possibly due to poorly understood effects mediated by RNA structure on the innate and adaptive host immune responses. A prolonged release of SARS-CoV-2 occurs regardless of the disease severity or the level of virus neutralizing antibodies. The presence of SARS-CoV-2 RNA and expressed viral proteins in the olfactory neuroepithelium of patients was documented at 110-196 days after primary infection with COVID-19 [22].

Persistent brainstem (BS) dysfunction is considered another cause of PCS [29]. BS has a relatively high ACE2 expression compared to other brain regions, and SARS-CoV-2 has tropism to it. In addition, in COVID-19, the BS is susceptible to damage as a result of pathological activation of the immune system. There is evidence that neuropilin-1, a co-receptor of SARS-CoV-2, can be expressed in BS. At autopsy, RNA and SARS-CoV-2 proteins were detected in the stem. The BS contains many individual nuclei and parts that regulate the respiratory, cardiovascular, gastrointestinal, and neurological processes that can be associated with long-term COVID. Since neurons do not regenerate quickly, the brainstem dysfunction can be long-lasting and, therefore, the manifestations of COVID-19 can also be long-lasting. The BS dysfunction is also associated with disorders such as chronic pain and migraines, myalgic encephalomyelitis, or chronic fatigue syndrome.

Despite the fact that the above pathological conditions occur in different systems of the body, they are characterized by a number of common typical pathophysiological processes.

CHRONIC ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction (ED) is one of the central links in the pathophysiology of cardiovascular diseases (CVDs). Its role in initiating the cascade of events leading to atherosclerosis and atherothrombosis allows us to consider the endothelium as an integrator of cardiovascular risk: the mechanisms by which epidemiologically confirmed CVD risk factors (RF) lead to atherosclerosis can best be investigated at the endothelial level [30]. It has been suggested that the ED provides a link between diseases such as arterial hypertension (AH), chronic kidney disease (CKD), and diabetes mellitus (DM), as well as the high risk of cardiovascular events that occur in patients with these conditions. The CVD RFs, such as AH, can cause ED and even endothelial destruction, which eventually leads to desolation of the microcirculatory bed vessels and, as a result, to tissue ischemia with the subsequent development of dystrophic conditions in the organs. In patients with CKD, the ongoing damage to the endothelium of the capillary system of the renal medulla and concomitant

vasoconstriction are considered central processes leading to progressive kidney damage [31]. The chronic impairment of a systemic endothelial function in patients with cardiovascular and metabolic disorders, enhanced by the exposure to SARS-CoV-2, may explain the adverse outcomes of COVID-19. Chronic ED and/or direct cytotoxic effects on endothelial cells can contribute to the pathogenesis of pneumonia and ARDS, as well as cause disturbances in the myocardial microcirculation, leading to its damage. Lymphopenia and hypoalbuminemia observed in patients with severe COVID-19 can be partially explained by an impaired integrity of the endothelial barrier in vascular or lymphatic capillaries. Endothelial damage can also cause the activation of the coagulation cascade, as is indicated by the presence of high plasma levels of *D*-dimer in patients with severe COVID-19. Finally, COVID-19 can provoke vascular ED present in the lungs, heart, as well as kidneys and liver, thereby contributing to the induction of tissue damage at these levels [32].

Thus, the recognition of the ED role in the pathophysiology of COVID-19 in patients with cardiometabolic disorders is relevant and may suggest a potentially new target for therapeutic intervention aimed at minimizing the severity of infection in the population of comorbid patients [33].

INTERLEUKIN-6 (IL-6)

IL-6, as well as a number of other proinflammatory cytokines, are involved in the pathogenesis of various diseases [34]. IL-6 is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to various stimuli in systemic inflammation [35]. IL-6 levels increase with age and are associated with higher mortality both from CVD, and other causes in people over 65 years of age [36]. The classical IL-6 signaling pathway involves binding of IL-6 to its receptor on cells and subsequent cell regeneration, hematopoiesis, and the synthesis and release of C-reactive protein (CRP) and other acute phase proteins [37]. IL-6, participating in the vascular inflammatory response initiates and potentiates the process of atherosclerosis and degradation of fibrous plaque, leading to its subsequent destabilization. The studies conducted have shown that higher IL-6 concentrations are associated with vascular deterioration in individuals free from clinical manifestations of atherosclerotic lesions and with the risk of future myocardial infarction (MI) [38]. In addition, IL-6 acts as an activator of the coagulation cascade. The hypothesis that IL-6 may be one of the links in the pathophysiological intersection between inflammatory processes, endothelial dysfunction, and prothrombotic conditions has initiated a number of studies describing the relationship between high levels of circulating IL-6 and an increased risk of cardiovascular events [39]. In addition, IL-6 is an inducer of the expression of matrix metalloproteinases involved in inducing collagen synthesis, which leads to progressive fibrosis followed by myocardial remodeling, which are known to contribute to the mechanism of heart failure (HF) development [38].

In a systematic review by E. Coomes et al. the serum IL-6 levels have been shown to increase significantly in severe cases of COVID-19. A meta-analysis of available data shows that such elevated levels are significantly associated with adverse clinical outcomes, including the admission to the intensive care unit, ARDS development, and death. In patients with a complicated COVID-19 course, the level of *IL*-6 in the blood serum was almost 3 times higher than in patients with an uncomplicated course of the disease [40].

TENDENCY TO CLOT FORMATION

Concomitant comorbidity in patients with COVID-19 is characterized by an increased propensity to prothrombotic conditions as a result of dysregulation in the system of both primary and secondary chains of hemostasis. Thus, the mechanisms that regulate platelet reactivity become multifactorial with age (for example, genetics, inadequate glucose control, dyslipidemia, and oxidative stress). The exact pathways linking inflammation to platelet function have not yet been fully determined. However, inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1, IL-8, and IL-6 can alter platelet function. For example, IL-6 is involved in changing the megakaryocyte-platelet axis, potentially leading to polyploidization and subsequent thrombopoiesis with a shift towards a prothrombotic phenotype and a higher average platelet volume. In addition, gp 130 receptors expressed by platelets can bind to IL-6 and the soluble IL-6α receptor (*sIL-6R*α), activating intracellular signal transmission, resulting in an increase in their reactivity [41].

ED is associated with an increase in the prothrombotic potential of the arterial and venous systems. It was shown that DM, which is an established risk factor for the development of atherosclerotic CVD, is associated with a prothrombotic state that occurs due to dysregulation of the primary hemostasis chain caused by the ED and platelet activation. DM increases oxidative stress and reduces the expression of protective endothelial factors, especially nitric oxide. AH, which is one of the most important RFs of atherothrombotic diseases, is probably also associated with an increased risk of venous thromboembolism (VTE). In addition, the metabolic syndrome significantly increases the risk of developing these conditions. The coagulation system activation both in arterial and venous channels is

associated with increased levels of pro-inflammatory and proatherogenic mediators (leptin, TNF-α, IL-6) in patients with metabolic syndrome. Other non-classical RFs, such as hyperhomocysteinemia, which causes endothelial damage, represent a potential risk of developing both atherosclerosis and VTE [32].

ELEVATED ANGIOTENSIN II LEVELS

Over time, many data have been accumulated indicating that angiotensin II (ATII) is involved in the pathogenesis of atherosclerosis, vascular and myocardial remodeling, and congestive heart failure. One of the most important of AT1 receptor activation effects, especially in the cardiovascular system (CVS), is the production and release of reactive oxygen species (ROS). Excessive ROS production is implicated in many pathophysiological conditions of the cardiovascular system, including hypercholesterolemia, DM, AH, and HF [42]. ATII reduces the bioavailability of nitric oxide. Thus, the pharmacological action on the renin-angiotensin-aldosterone system (RAAS) may be a suitable means of managing ED [43]. ATII is involved in cell growth, apoptosis, cell migration and differentiation, extracellular matrix remodeling, regulates gene expression, and can activate multiple intracellular signaling pathways leading to tissue damage. In the kidneys, heart, and blood vessels, ATII induces an inflammatory response by stimulating the expression of proinflammatory chemokines responsible for the accumulation of immunocompetent cells in tissues [44]. The inflammatory process that occurs in the walls of blood vessels contributes to the initiation and progression of atherosclerosis, and also contributes to vascular complications of AH and/or diabetes. In addition, ATII affects an increase in IL-6 production and gene expression in smooth muscle cells, macrophages, and mesangial cells. On the other hand, IL-6 also increases the formation of angiotensinogen in the vascular wall and, thus, increases the local formation of ATII, which supports vascular inflammation. Separately, it should be noted that physiologically ATII causes platelet activation and aggregation, balancing the antithrombotic properties of the endothelium [45]. Excessive activation of the RAAS is thought to directly cause vascular damage in DM. The RAAS activation and a subsequent positive feedback regulation of ATII levels cause increased fluid and sodium retention and increase vascular tone, which predisposes the patients to endothelial, kidney, heart, and nervous system damage [46]. Plasma ATII levels in patients with COVID-19 were markedly elevated and correlated with viral load and lung damage. In particular, it is known that ATII increases the permeability of microvessels, induces the transcription of tissue factor in endothelial cells, and activates platelets. In addition, ATII can trigger the release of the complement system components from endothelial cells, which once again confirms the key role of the endothelium in the pathogenesis of venous and arterial thrombosis in patients with COVID-19 [47].

CLINICAL SYMPTOMS OF POST-COVID SYNDROME

In patients who have had COVID-19, many body systems are affected in the intermediate and long term:

- cardiovascular system: carditis;
- bronchopulmonary system: impaired lung function;
- urinary system: acute kidney injury;
- central nervous system: anosmia, dysgeusia, sleep disorders, difficulty concentrating, memory problems;
- dermatology: rash, hair loss;
- mental sphere: depression, anxiety, mood swings, panic attacks.

E. M. Amenta et al. [48] propose to divide the post-acute symptoms into three categories: (1) residual symptoms that persist after recovery from acute infection; (2) organ dysfunction that persists after the initial recovery; and (3) new symptoms or syndromes that develop after the initial asymptomatic or mild infections.

T. Greenhalgh et al. [15] divided patients with PCS into three groups: those with serious complications (arterial/venous thromboembolism), non-specific symptoms (asthenia, shortness of breath), and patients requiring intensive care.

Myocarditis, pericarditis, HF, MI, arrhythmias, and pulmonary embolism can develop several weeks after acute COVID-19 and are more common in patients with pre-existing CVD [49]. According to magnetic resonance imaging of the heart, 60% of those who recovered, regardless of COVID-19 severity, were diagnosed with a myocardial inflammation pattern [50].

Mechanisms that determine cardiovascular complications in PCS include direct viral invasion, dysregulation in the ACE/ACE2 system, and a chronic inflammatory response that affects the structural integrity of the myocardium, pericardium, and cardiac conduction system. Recovered patients may have increased cardiometabolic requirements, as observed in long-term follow-up of SARS survivors. This may be due to a decreased energy reserve of cardiomyocytes, the use of corticosteroids, and an impaired regulation of RAAS. Fibrosis or scarring of the myocardium, as well as cardiomyopathy caused by a viral

infection, can lead to recurrent arrhythmias. COVID-19 can also provoke the development of arrhythmias due to an elevated catecholaminergic state, as well as elevated blood levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α, which can alter cardiomyocyte action potentials by modulating the expression of cardiomyocyte ion channels [51]. Those who had been ill were highly likely to develop a myocardial injury associated with cardiotoxicity of the drugs used, such as azithromycin, chloroquine/hydroxychloroquine (heart conduction disorders, manifested in the QT interval prolongation); tocilizumab (increased cholesterol levels); lopinavir/ritonavir (increased PR and QT intervals, the inhibition of the CYP3A4 activity) [9].

COVID-19-related inflammation increases blood-brain barrier (BBB) permeability, aggravates thrombosis, and coagulopathy, which contribute to the further spread of neurological damage [52]. When the BBB is impaired (due to a cytokine storm or direct viral damage to the nervous tissue), the scar formation is induced. It is known that the risk factors for cognitive impairment are old age, traumatic brain injury, obesity, hypertension, smoking, and diabetes [53]. In addition, the initial decline in neurocognitive abilities may worsen both during and after inflammatory conditions [54].

Anosmia-dysgeusia was more often observed in people under 65 years of age (24.9%) compared to the older age group (13.5%) [7]. The long-term prognosis, including neurological symptoms such as headache, fatigue, dizziness, memory loss, confusion, and difficulty concentrating, is associated with the effects of COVID-19 infection [55]. More than 30% of COVID-19 survivors have complaints of memory loss [56]. The effect of SARS-CoV-2 infection on the onset and progression of neuropsychic symptoms of neuroinflammatory origin can have serious consequences in the long term. Neurological symptoms, which manifest themselves as the development of varying severity depression, sleep disorders, and anxiety, are probably associated with the neuroinflammatory effects of COVID-19 [57]. Delirium in COVID-19 is 2 times more common than in other conditions [58]. Delirium is associated with adverse outcomes, including high mortality, increased length of hospital stay, long-term cognitive and functional decline, and the risk of rehospitalization. The pathophysiology of delirium in COVID-19 and its long-term results are probably multifactorial. Neuroinflammation and vascular damage are primary in the delirium development, while hyperthermia, hypoxia, dehydration, and concomitant metabolic disorders are secondary [59-60]. According to B.C. Mcloughlin et al., 42% (mean age 61 years, 72% male) of COVID-19 patients were diagnosed with delirium 4 weeks after the onset of the disease [60]. One of the highest risk groups for severe COVID—19 includes patients over 65 years of age who often have mild cognitive impairment and are already at increased risk of delirium as a result of the underlying "neurocognitive weakness" [61-62]. Among the large number of asymptomatic patients or patients who have had mild COVID-19, there are long-lasting effects that persist for several months, such as muscle pain, dizziness, headaches, fatigue and anosmia, which emphasizes the need for their constant monitoring by neurologists and general practitioners [63]. Keep in mind that many of these symptoms may disappear over time, and therefore their prevalence depends on the time of assessment.

PROGNOSTIC SIGNIFICANCE OF COMORBIDITY IN THE DEVELOPMENT OF POST-COVID SYNDROME

Comorbidity is the major factor in the course and prognosis of COVID-19, as statistics prove: 80% of patients with comorbidity suffer from severe infection [64]. Comorbidity, which increases the susceptibility of patients to infectious diseases, including COVID-19, is a risk of developing both a severe course and PCS. In comorbid patients, persistent tissue damage, viral persistence, and chronic inflammation are considered to be the causes of PCS. It is rather difficult to establish a causal relationship between COVID-19 and symptoms that develop after the acute phase of the disease, since patients with a history of chronic diseases and PCS may have common predisposing factors, such as an old age, baseline AH and/or DM, smoking, malnutrition or obesity, baseline immunosuppression, etc. In the presence of AH, the inflammatory process is more intense, and there is an increased risk of death from COVID-19 compared to patients without hypertension [65]. A meta-analysis made by R. Pranata et al. (2020) showed that CKD increases the risk of developing severe COVID-19 and death by about 3 times. The results of this study support the theory about the co-relation between hypertension, diabetes, age, CKD and severe course of COVID-19. In people with CKD, elevated circulating ACE-2 levels are associated with unregulated increased ATII activity and multiple organ failure. This suggests that the presence of CKD at an early stage increases the risk of an adverse outcome in COVID-19; however, further studies of this co-relation are needed [66]. According to S. K. Kunutsor et al. (2020), pre-existing CKD is associated with a severe course and an increased risk of death in COVID-19, and it is also an independent risk factor for acute kidney injury (AKI). Monitoring the markers of renal function during hospitalization for COVID-19 can help identify patients at a high risk of adverse outcomes for to make an earlier and more aggressive intervention [67]. Numerous studies have shown that IL-6 secretion is moderately elevated in a chronic mild inflammatory process characteristic of CKD.

This fact was fully reflected in the study, where there was a statistically significant increase in IL-6 content in CKD. In turn, it was possible to demonstrate a significant relationship between the calculated glomerular filtration rate and the IL-6 content in blood serum [68].

DIAGNOSTIC CRITERIA FOR POST-COVID SYNDROME

Diagnosis of long-term COVID-19 is fraught with many problems [5]. For the diagnosis of PCS, in opinion of C. Fernández-de-las-Peñas et al. [69], a combination of two conditions is required: 1) there should be a temporal relationship between the symptoms and COVID-19; 2) the symptoms should appear after infection with SARS-CoV-2 (new post-COVID symptoms that previously were not present). Therefore, clinicians and investigators need to find out if the symptoms are related to a potential SARS-CoV-2 infection. The *NICE guideline* [12] suggests the following classification: acute *COVID*- 19 (symptoms up to 4 weeks), ongoing symptomatic COVID-19 (signs and symptoms of COVID-19 from 4 to 12 weeks), and post-COVID syndrome: (signs and symptoms that develop during or after an infection, continue for more than 12 weeks). At the same time, C. *Fernández-de-las-Peñas et al*. [69] proposed their own classification of PCS:

– Transition Phase: Symptoms potentially associated with acute COVID-19: symptoms up to 4–5 weeks;

– Phase 1: Acute post-COVID symptoms: symptoms from week 5 to week 12;

– Phase 2: Long post-COVID symptoms: symptoms from week 12 to week 24;

– Phase 3: Persistent post-COVID symptoms: symptoms lasting more than 24 weeks.

The presence of persistent, long-lasting symptoms in patients with a history of COVID-19 and a positive PCR result make the diagnosis of PCS obvious. However, patients with COVID-19 symptoms and negative PCR results present a real challenge in everyday clinical practice. A significant proportion of SARS-CoV-2 infected cases are asymptomatic, and the development of long-lasting symptoms of COVID-19 in people with an asymptomatic course adds to diagnostic confusion. It is difficult to distinguish between acute COVID-19 and PCS with a long duration of symptoms [5]. The most important laboratory data in the diagnosis of PCS are considered to be lymphopenia, high blood levels of ferritin, *D*-dimer, CRP and brain natriuretic peptide [7].

CONCLUSION

The long-term prognosis of patients who have had COVID-19 remains unclear. Post-covid syndrome is a multisystem condition that, according to a number of authors, develops 12 weeks after recovery. Post-kidney syndrome can manifest itself in one or more symptoms associated with damage to body organs and systems. Regardless of the severity of the lesion and age, some patients develop fibrosis of the lungs, heart, and brain. Comorbidity is a trigger for the intensification of existing pathological processes. Most likely, the treatment and rehabilitation of individuals with post-covid syndrome will focus on cardiopulmonary consequences.

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Received on 14.04.2021

Review completed on 19.05.2021

Accepted on 19.05.2021