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Post–COVID-19 syndrome in everyday clinical practice: interdisciplinary expert position statement endorsed by the Polish Society of Civilization Diseases

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Abstract

Post-COVID-19 syndrome, also known as long-COVID-19 syndrome, is a complex set of symptoms that persist for weeks or months after recovery from the acute phase of COVID-19. These symptoms can affect various body systems, including the respiratory, nervous, cardiovascular, and digestive systems. The most common complaints are fatigue, shortness of breath, joint pain, taste and smell disorders, as well as problems with memory and concentration. The pathogenesis of the post-COVID-19 syndrome is complicated and not fully understood, but it is likely related to an overactive immune system, disturbances in the intestinal microbiome, and cell and tissue damage caused by the virus. Incorporating a multidisciplinary approach to treating and rehabilitating patients and further research into this syndrome's underlying mechanisms and therapy is crucial for understanding and effectively treating this complex and multi-faced condition.

Key words

long-term symptoms of COVID-19, over-reactivity of the immune system, post-COVID-19 syndrome

Introduction Over the last few years, many people have been infected with the SARS-CoV-2 virus and consequently suffered COVID-19. In many cases, the symptoms of the disease or its long-term sequelae lasted much longer than the initial phase of the acute infection. For this reason, the terms long-COVID-19 and post-COVID-19 have come to be used in the literature. It is widespread to use both terms interchangeably to describe the same group of symptoms, for example, ”long-haul COVID-19”, “post-acute COVID-19”, “long-term effects of COVID-

19" or "chronic COVID-19". One of the Polish documents also adopted a time census defining long-COVID-19 as symptoms of COVID-19 lasting for 4 to 12 weeks and post-COVID-19 as the same symptoms lasting longer than 12 weeks [1]. However, this division is not commonly accepted in international literature. In this paper, we will use the term post-COVID-19.

The official definition of post-COVID-19 syndrome, according to the Delphi Consensus, is as follows: "Post-COVID-19 syndrome occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually three months after the onset of COVID-19 with symptoms persisting for at least two months and not explained by an alternative diagnosis. Typical symptoms include fatigue, shortness of breath, and cognitive impairment, affecting daily functioning. Symptoms may appear *de novo* after initial recovery from an acute episode of COVID-19 or persist after illness. Symptoms may also change in intensity or recur over time" [2].

The number of people with post-COVID-19 globally is estimated at at least 65 million [3]. The actual number is likely much higher due to the many undocumented cases. The prevalence of COVID-19 is estimated at 10–30% of non-hospitalized cases and 50-70% of hospitalized cases. About vaccination against COVID-19, recent observations indicate that the disease affects 10–12% of those vaccinated. Post-COVID-19 syndrome occurs across all age groups, with the highest diagnosis rates between 36 and 50. Most post-COVID-19 cases are in non-hospitalized patients with mild acute illness, as this population represents most COVID-19 cases.

Diagnosis of post-COVID-19 syndrome is challenging, and specific diagnostic tests are still lacking. However, recently a study by Klein et al. has been published showing that levels of circulating immune cell populations, soluble immune mediators, and hormones differ in patients with post-COVID-19 syndrome compared to the general population. [4] This

approach still waits to be incorporated into general practice. It is still too early to establish a single biomarker, or a diagnostic test capable of properly identifying all post-COVID-19 patients.

The differential diagnosis of complications associated with post-COVID-19 syndrome entails a comprehensive evaluation to discern between sequelae directly stemming from the viral infection and those arising from secondary physiological, psychological, or iatrogenic factors. Clinical manifestations such as persistent fatigue, dyspnea, cognitive impairment, and musculoskeletal pain present diagnostic challenges, necessitating a thorough exploration of potential etiologies, including but not limited to post-viral inflammatory processes, deconditioning, psychological distress, and medication-related side effects. Differential diagnoses further encompass cardiopulmonary complications, including myocardial injury, pulmonary fibrosis, and thromboembolic events, alongside neurological sequelae such as peripheral neuropathy, encephalopathy, and neuropsychiatric disorders. Moreover, consideration must be given to cognitive disorders including dementia, cerebrovascular diseases such as stroke, psychiatric disturbances, and structural brain disorders, underscoring the need for a multidisciplinary approach to diagnosis and management to address the multifaceted nature of post-COVID-19 complications. In all cases, post-COVID-19 syndrome should be a diagnosis of exclusion.

The pathology spectrum of the post-COVID-19 syndrome is vast and includes the involvement of various systems and organs [5,6]. The most common are cardiovascular symptoms, thrombotic complications, involvement of the nervous system, especially in the cerebral circulation, as well as chronic fatigue syndrome / myalgic encephalomyelitis (CFS / ME), dysautonomia, postural orthostatic tachycardia syndrome (postural orthostatic tachycardia syndrome, POTS), enteritis, and type 2 diabetes [7,8]. Symptoms can persist for years, and in the case of newly diagnosed ME / CFS and dysautonomia, there is concern that

they will persist throughout life. Persistence of the post-COVID-19 syndrome may result in long-term incapacity for work and socio-economic consequences. Currently, there are no known effective treatments for post-COVID-19 syndrome. A proposed, systematic approach to conducting research and understanding the pathogenesis and management of post-COVID-19 is presented in Figure 1. [8]

Reasons for the development of post-COVID-19 syndrome The pathogenesis of the syndrome is believed to be complex. There are likely to be many potentially overlapping reasons for the development of post-COVID-19 syndrome, most of which are not scientifically confirmed. These include survival of SARS-CoV-2 reservoirs in tissues, dysregulation of the immune system, reactivation of latent viruses such as Epstein-Barr virus and human herpes virus type 6, autoimmune mechanisms, mechanisms of molecular mimicry, intestinal microbiome dysregulation and excessive coagulation processes in microvessels with endothelial dysfunction. Attention is also drawn to the possible signaling dysfunction in the brainstem and / or vagus nerve.

More and more data are available in the literature analyzing the possible contribution of individual mechanisms to developing the post-COVID-19 syndrome [9, 10]. The presence of viral proteins and / or RNA has been demonstrated in the cardiovascular system, brain, muscles, lymph nodes, appendix, liver tissue, lung tissue, as well as plasma, feces, and urine of patients with symptoms of post-COVID-19 syndrome. Similarly, antibodies against the SARS-CoV-2 receptor, β2-adrenoreceptor, muscarinic receptor, angiotensin II receptor, and several others, as well as autoantibodies against many tissues, such as endothelium, lung tissue, or connective tissue, have been found. Numerous studies document the increased or decreased activation of individual immune system elements. At this stage, it is difficult to interpret the meaning of individual results unambiguously.

Respiratory system in patients with post-COVID syndrome Respiratory symptoms occur after COVID-19 at least twice as often as in the general population. Shortness of breath and cough are the most common respiratory symptoms. Studies show that they persisted for at least seven months in 40% (shortness of breath) and 20% (cough) of post-COVID-19 patients, respectively. [6-8] Several imaging studies that included post-COVID-19 patients showed lung abnormalities, including air traps and perfusion abnormalities. The presence of a general inflammatory reaction during the post-COVID-19 syndrome correlated negatively with the efficiency of the respiratory system. [6-8] The most common respiratory symptoms are shown in Table 1.

Neurological and psychiatric aspects of long-COVID-19 and post-COVID-19

COVID-19 is an infectious disease that also damages the nervous system. At least several mechanisms are affecting not only the cells of the nervous system but also the endothelium; modification of the immune system through the inflammatory reaction and hypoxia have been observed. Therefore, the impact of SARS-CoV-2 infection on the nervous system is multidirectional and can cause or exacerbate a whole spectrum of neurological and mental diseases.

The basic mechanisms of action of the virus on the nervous system include:

- damage to nerve cells by the direct action of the virus,
- result of the inflammatory reaction by stimulating the immune system, secondary damage to the cells of the nervous system occurs through antibodies and / or activated lymphocytes,
- decreased expression of angiotensin-converting enzyme 2,
- damage to the endothelium of endothelial vessels, leading to the formation of local thrombi or damage to the vascular wall, resulting in ischemic or hemorrhagic stroke,

- acute or chronic decrease in hemoglobin oxygen saturation resulting from lung damage and impaired gas exchange, leading to neuron hypoxia [11-13].

Previous studies have found that within six months of acute COVID-19, one-third of patients will have damage to the nervous system manifested in the form of neurological and mental disorders [14]. An increased risk of these diseases is observed even up to 2 years after infection with the SARS-CoV-2 [15].

Several neurological disorders are common in people with COVID-19 or are directly related to the infection. [16,17] These include symptoms shown in Table 2.

For most of the above complaints, no specific therapy has been established in post-COVID-19 patients. They should be treated following the standards of treatment of individual neurological and mental diseases. Among the specific therapies in patients with post-COVID-19 in the case of vascular diseases, including stroke, additional treatment stabilizing the endothelium, e.g. sulodexide, may be beneficial [18,19].

Post-COVID-19 peripheral neuropathies and myopathies are mainly related to inflammation and oxidative stress. Therefore, it is postulated to use substances with antioxidant properties. α-lipoic acid is effective in treating diabetic neuropathy, which is also associated with oxidative stress [20]. Other substances with potential beneficial effects in post-COVID-19 neuropathy include vitamin D, B vitamins, and acetyl-L-carnitine. For all of the above, further research is needed.

Newly diagnosed mental disorders associated with COVID-19 are diagnosed within 30-120 days of infection. Later, the risk was not shown to be higher than in the general population [21]. The most common mental disorders are mood disorders, especially depression and anxiety disorders. In their case, treatment should also be in line with the standards of therapy for the general population.

In the described cases research focuses on the use of pharmaceuticals such as coenzyme Q10, D-ribose, tramadol, naltrexone, cannabinoids, alpha-lipoic acid, low dose aripiprazole, and honokinol. Specific recommendations are shown in the chapter considering treatment.

Chronic fatigue syndrome and autonomic dysregulation ME/CFS is a multisystem neuroimmune disease that often begins immediately following a viral infection. The criteria include "a significant reduction or impairment in the ability to engage in occupational, educational, social or personal activities at a pre-disease level" for at least six months, accompanied by profound fatigue not relieved by rest. In addition, post-workout fatigue, malaise, non-recovery sleep, and cognitive impairment or orthostatic intolerance may occur. As many as 75% of people with ME / CFS cannot work full-time, and 25% have severe ME / CFS, which often means they are bedridden, have extreme sensory sensitivity, and depend on others for care. Approximately half of people with post-COVID-19 syndrome are estimated to meet the ME / CFS criteria. An even higher percentage reports post-exercise malaise [7,8].

Dysautonomia, especially POTS, often coexists with ME / CFS. POTS results from autoantibodies against the G protein-coupled adrenergic receptor, muscarinic acetylcholine receptors, and small fiber neuropathy. One study found that up to 67% of patients with post-COVID-19 syndrome may be affected by POTS. Moreover, sensitization of the carotid chemoreflex occurs, which may explain dysregulated breathing and exercise intolerance in these patients, also contributing to inappropriate sinus tachycardia and blood pressure dysregulation. [22]

In a recent study of 200 consecutive patients with an increased heart rate, a history of mild COVID-19 infection was confirmed in 83% of cases with no coexisting structural heart disease. [23] Inappropriate sinus tachycardia was accompanied by a decrease in most heart rate variability parameters, especially those related to cardiovagal tone. The etiology of

inappropriate sinus tachycardia in post-COVID-19 syndrome patients is unknown; however, the proposed mechanisms overlap with those of POTS, including increased sympathetic and / or reduced cardiovagal activity. Even in patients not meeting inappropriate sinus tachycardia diagnostic criteria, an increased resting heart rate is so common that the term "post-COVID-19 tachycardia syndrome" has been recently proposed. [24]

Autonomic dysregulation is one of the mechanisms of frequent blood pressure abnormalities in post-COVID-19 syndrome patients. Other include disturbances of the renin-angiotensin-aldosterone system with autoantibodies against angiotensin II being present during COVID-19 infection. [25] The presence of these antibodies correlates with lower blood oxygenation, poorer blood pressure control, and overall higher disease severity. Transiently altered blood pressure values are observed in some COVID-19 cases.

Metabolic disturbances are one of the less discussed, but potentially long-lasting features of post-COVID-19 syndrome. It is observed that systemic COVID-19 infection in some cases triggers new-onset diabetes mellitus type 1 or 2, dyslipidemia, hypertension, and dyslipidemia. [26-28] The exact epidemiology of this phenomenon is not known, and it is hard to establish which new-onset cases are attributable to the infection. Nevertheless, after the pandemic, an increase in the total number of the aforementioned conditions was noted. Moreover, there are pathophysiological premises indicating that SARS-CoV poses a direct and indirect effect on the β-cells, glucose, and lipid metabolism as well as the renin-angiotensin-aldosterone system.

Another metabolic consideration in post-COVID-19 syndrome is associated with thyroid gland pathologies. New-onset and relapsed Graves' disease has been reported in several patients with acute COVID-19, post-COVID-19 syndrome as well as rarely after COVID-19 vaccination. [29, 30] It was reported to be associated with autoimmunization and in most cases resolved after several weeks.

Abdominal symptoms after SARS-CoV-2 infection and post-COVID irritable bowel syndrome SARC-CoV-2 infection may also affect the gastrointestinal tract. Abdominal symptoms, after pulmonary symptoms, are the most common symptoms of infection; according to many publications, they occur in more than half of patients. The most common abdominal symptoms are shown in Table 3. The virus exerts its pathogenic effect by binding to the angiotensin-2 receptor; significant amounts of these receptors are found in the lung tissue and the gastrointestinal tract, including the intestines. In the pathogenesis of abdominal symptoms, the so-called cytokine storm, i.e., a significant increase in the secretion of proinflammatory cytokines and, above all, disturbance of the intestinal microbiome [31-33]. Because of dysbiosis during the hospitalization of patients with SARS-CoV-2 infection, a significantly higher infection rate of *Clostridioides difficile* was observed compared to a similar population hospitalized for other reasons [34].

Another problem considered in the aspect of persistent abdominal symptoms after SARS-CoV-2 infection is post-infectious irritable bowel syndrome (IBS). IBS is a functional disease of the gastrointestinal tract characterized by recurrent pain in the abdominal cavity with accompanying bowel movements in the absence of an organic etiology. It is understood mainly as a disorder of the functioning of the gut-brain axis, most often resulting from a disorder of the intestinal microbiome. Among the many potential causes of intestinal function disorders in irritable bowel syndrome mentioned in the literature, post-infectious disturbances in the composition of the intestinal microbiome (dysbiosis), leading to post-infectious IBS, seem very important. A significant increase in the number of patients after various types of food poisoning or even in the number of cases of travelers' diarrhea has been known for a long time and described in the literature [35-37]. Risk factors for post-infectious IBS include genetic factors, intestinal microinflammation, earlier change in intestinal barrier permeability,

motility disorders, the severity of infection, psychological / psychiatric disorders, infectious factors (more often after bacterial infection), younger age, and female sex.

Infection with the SARS-CoV-2 virus, including this affecting the gastrointestinal tract, is also a risk factor for post-infectious IBS. Abdominal symptoms, such as abdominal pain and bowel rhythm disorders (following the Rome IV diagnostic criteria), occur 3 and 6 months after the infection, also in people who have not previously reported such symptoms. The frequency of IBS symptoms varies, according to various studies, depending on the examined population, from several to even several dozen percent of patients, which, considering the prevalence of COVID-19, constitutes a significant group of patients with new symptoms, such as pain abdominal pain, diarrhea, flatulence significantly impairing the quality of life [38]. A recently published meta-analysis of 50 studies shows that IBS symptoms were observed in about 12% of patients immediately after infection and up to 22% as persistent “long COVID-19”symptoms. The incidence of diarrhea in this group is approximately 10% of patients. One of the studies considered in the presented meta-analysis reported as many as 39% of patients showing symptoms of IBS after SARS-CoV-2 infection [39, 40]. Thus, abdominal symptoms meeting the post-COVID-19 criteria are described in almost 1/3 of patients after six months of observation, and post-infectious IBS has become one of the components of post-COVID-19 syndrome.

Following the current recommendations, post-infectious IBS, including post-COVID-19 IBS, is treated according to the same schemes as the general population. Polish guidelines for the management of this group of patients were published in 2018 [41] and included step-up treatment based on dietary modifications, antispasmodics, probiotics, and in subsequent stages, rifaximin-α or psychotropic drugs. In the case of post-infectious IBS, due to the known mechanism of symptoms, a rapid response strategy should be implemented, and therapies targeted at the intestinal microbiota should be used, i.e., the gold standard of treatment -

rifaximin-α, soluble fiber, microencapsulated butyric acid preparations, probiotics. It should be remembered that the effect of probiotics is strain-dependent, so the recommended strains in this case are primarily *Lactiplantibacillus plantarum 299v, Bacillus coagulans, Saccharomyces boulardi and Saccharomyces cerevisiae* [42]. *Lactobacillus paracasei DG* also has good recommendations, especially in post-infectious IBS [43]. Rifaximin-α should be used, according to well-documented clinical trials, at a dose of 1600 mg daily (in 4 divided doses) for 14 days [44]. In case of relapse in patients responding to rifaximin-α treatment, treatment may be repeated after a period of 4 weeks.

It seems that due to the high frequency of symptoms and the significant number of patients who have experienced SARS-CoV-2 infections, the issue of post-infectious irritable bowel syndrome is a new challenge for modern gastroenterology and primary care physicians, so it is worth remembering how to proceed in this group.

In the described cases research focuses on the use of pharmaceuticals such as coenzyme probiotics, rifaximin-α and metformin. Specific recommendations are shown in the chapter considering treatment.

Cardiovascular symptoms in patients with post-COVID-19 syndrome

Cardiovascular complications are an essential aspect of the post-COVID-19 syndrome, affecting a significant percentage of people who have recovered from the acute phase of the disease. These symptoms can be associated with direct cell damage by viruses, hypercoagulable state caused by systemic inflammation, or myocardial damage due to excessive immune response to the virus [45]. The most common cardiovascular symptoms are shown in Table 4.

The mechanisms underlying these symptoms are multifaceted, with some reports linking them to endothelial dysfunction that triggers thrombosis and leads to myocardial

damage. The most common cardiovascular sequelae include myocarditis, heart failure, arrhythmias, and coagulopathy, including deep vein thrombosis and pulmonary embolism [45].

Myocarditis has been observed even in mild cases of acute COVID-19 disease, suggesting that myocardial damage can occur regardless of the severity of the infection [46]. Myocarditis is not only a disease that occurs in the acute phase of COVID-19. Due to its often long-term nature, it also affects patients diagnosed with post-COVID-19 syndrome. It can be manifested by reduced exercise tolerance, chest pain, or cardiac arrhythmias. Markers of myocardial necrosis, such as elevated troponin levels and the results of imaging tests, point to changes in the structures of the heart that persist even for a long time after recovering from COVID-19. [47]. Moreover, the impact of COVID-19 on the cardiovascular system seems to be long-lasting in some cases and may be observed for up to several months after the acute infection has resolved.

It is worth noting that in the context of the post-COVID-19 syndrome, heart failure has been reported to occur *de novo* or due to deterioration of a previous health condition [48]. Symptoms of post-COVIDO heart failure, such as shortness of breath, fatigue, and fluid retention, can significantly impact patients' quality of life, potentially hindering their full recovery. There are currently no dedicated treatment regimens for post-COVID-19 heart failure, which should be treated like any other case.

Cardiac arrhythmias, including atrial fibrillation, are other significant cardiovascular pathologies and may result from myocarditis, ischemia, or neurohormonal stress associated with severe disease [49]. Arrhythmias in COVID-19 patients are associated with hypoxia, myocardial ischemia, the presence of proinflammatory cytokines, inflammation, electrolyte disturbances, proarrhythmic or QT-prolonging drugs, and cardiovascular diseases such as severe congestive heart failure. Arrhythmias and episodes of cardiac arrest are the most

common in the population of COVID-19 patients in intensive care units [49]. Nevertheless, some cardiac arrhythmias, especially in patients with a history of myocarditis, may persist for a long time and be part of the post-COVID-19 syndrome. In patients with post-COVID-19, the most common abnormality is resting tachycardia, but all kinds of ventricular and supraventricular arrhythmias may occur.

Thromboembolic events have proven to be a severe problem in both the acute phase of COVID-19 and the post-COVID-19 syndrome. The underlying pathophysiology appears to be multifactorial, involving a combination of endothelial dysfunction, systemic inflammation, and hypercoagulable conditions [50]. Studies have shown an increased incidence of deep vein thrombosis and pulmonary embolism in patients recovering from COVID-19, highlighting the need for vigilant monitoring and prophylaxis, especially among high-risk patients [51]. Management of thromboembolic events may include the use of anticoagulants, close observation, and personalized therapeutic strategies, depending on individual risk factors [52]. Long-term studies are needed to evaluate further the impact, optimal prevention strategies, and therapeutic interventions for thromboembolic complications in COVID-19 patients [53]. There are no established principles of thromboprophylaxis in high-risk patients with post-COVID-19 syndrome; however, for some drugs, such as sulodexide, research is currently being conducted on their usefulness in this group of patients. Sulodexide is recommended following the International Society on Thrombosis and Haemostasis recommendations, in non-hospitalized COVID-19 patients at a higher risk of disease progression, within 3 days of the onset of symptoms, due to the reduction of the risk of hospitalization and the need for oxygen therapy. [54] In long-COVID-19 patients, it has been shown that the use of sulodexide is associated with the abolition of endothelial dysfunction and relieves chest pain and palpitations, which, together with the anticoagulant effect of the drug, may indicate its significant usefulness in patients with post-COVID-19 [55]. It should be noted that sulodexide

has an established position in prolonged, secondary antithrombotic prophylaxis and is recommended in this indication by many scientific societies. [56-57]

Managing these complications requires a patient-centered approach, including pharmacotherapy, lifestyle modification, and rehabilitation. A multidisciplinary team of cardiologists, physiotherapists, dietitians, and primary care physicians is often required to provide comprehensive care. Despite the growing knowledge about the symptoms mentioned above, many issues regarding their long-term impact on prognosis and optimal treatment strategies remain unresolved.

In the described cases research focuses on the use of pharmaceuticals such as angiotensin-converting enzyme inhibitors, statins, beta-blockers, ezetimibe, fibrates, omega-3 fatty acids, ranolazine, magnesium salts, potassium, sulodexide and anticoagulants. Specific recommendations are shown in the chapter considering treatment.

The impact of vaccination and reinfection on the incidence of post-COVID-19 syndrome

The results of studies on the effect of vaccination on post-COVID-19 syndrome vary between publications, partly due to different research methods, time since vaccination, and definition of post-COVID-19. Most studies indicate that vaccines provide partial protection and reduce the risk of long-term consequences of COVID-19 in the range of 15% to 41% [58]. There are also consistent observations regarding the increasing risk of long-term consequences of COVID-19 after the second and third infection. Existing literature suggests multiple infections may cause additional medical problems or susceptibility to CFS symptoms.

Education about the long-term consequences of COVID-19 is essential. There is a widespread belief that COVID-19 causes only respiratory sequelae, making it difficult to properly diagnose the neurological, cardiovascular, and other multisystem effects of COVID-

19. There is still a disproportionate dominance of pulmonary rehabilitation activities. For obvious reasons, it is more accessible and better documented to monitor people hospitalized for COVID-19 than those not hospitalized. Proper diagnosis and linking, for example, neurological or ME / CFS symptoms with a history of COVID-19 causes problems.

These so-called mild cases that develop post-COVID-19 syndrome often have a different biological basis than acute severe cases and require appropriate diagnostic tools. Commonly used basic tests such as d-dimer, C-reactive protein, and complete blood count are normal. For example, in patients with ME / CFS and dysautonomia, it is necessary to use total immunoglobulin tests, measure cortisol in saliva, or study brain perfusion. Symptoms such as post-exercise malaise are not widely known and are rarely included in research panels [59,60].

Treatment in patients with post-COVID-19 syndrome The management of post-COVID-19 syndrome poses unique challenges due to the lack of official guidelines and the complex nature of the illness. Unfortunately, in many cases, the management of the disease is focused solely on relieving the symptoms and waiting for the spontaneous resolution of the disease. It should be stressed that the treatment of post-COVID-19 patients should focus on patient education, providing support, and reassurance, and offering holistic support. Patients with post-COVID-19 syndrome most of all need rehabilitative care, including well-established symptom management techniques, physical rehabilitation programs, and addressing mental health and well-being. However, in many cases, pharmacotherapy is crucial in symptom relief. A step-by-step approach is summarized in Figure 2.

Pharmacotherapy of the long-COVID-19 syndrome must assume individualization in terms of the patient's specificity and the specificity of the symptoms. The most important factors regarding the assumptions of appropriate pharmacotherapy in this group of patients are

summarized in Table 5. [61-63] In all cases the pharmacotherapy must follow the current guidelines for specific chronic diseases.

Moreover, a summary of the current knowledge on drugs used to treat individual symptoms of the post-COVID-19 syndrome is presented in Table 6. [64-67] It should be noted that the knowledge regarding the COVID-19 disease itself and its long-term consequences is constantly expanding, and the presented indications may be updated soon. None of the presented substances are currently registered for post-COVID-19 syndrome treatment and this summary should be considered as promising not recommended.

Summary It should be emphasized that the post-COVID-19 syndrome, which refers to several symptoms that may persist after coronavirus infection, is a complex, interdisciplinary clinical problem. Studies show that a significant percentage of COVID-19 survivors experience long-term effects, such as fatigue, shortness of breath, arthralgia, and neurological problems, but the clinical presentation can be very variable and significantly affect patients' quality of life. Extensive and long-term research is paramount in understanding the full range of long-term effects that COVID-19 may have on human health. It should also be emphasized that a coordinated, multidisciplinary approach to treatment and rehabilitation is essential to help patients suffering from post-COVID-19 syndrome effectively. To this end, it is also essential to popularize knowledge about this disease among the general public and doctors, which will allow for more effective diagnosis and treatment of the post-COVID-19 syndrome.

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AK analyzed the data. GR coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Table 1 Respiratory symptoms of post-COVID-19 syndrome

Respiratory symptoms of post-COVID-19 syndrome
• dyspnea • persistent cough • chest pain • decreased exercise tolerance • wheezing or other abnormal auscultation sounds • pulmonary fibrosis

Table 2 Neurological symptoms of post-COVID-19 syndrome

Central nervous system symptoms of post-COVID-19 syndrome
• chronic fatigue syndrome • "brain fog” • cognitive impairment • headaches • sleep disorders • mood/emotional disorders

• dizziness/balance disorders • extrapyramidal syndromes • stroke • epilepsy
Peripheral nervous system symptoms of post-COVID-19 syndrome
• myopathies: including muscle weakness or myalgia • smell disorder • taste disturbances • peripheral nerve damage: including Guillain-Barre syndrome or Bell's palsy • muscle tremors
Autonomic system disorders
• chronic fatigue syndrome • postural orthostatic tachycardia syndrome • hypertension • inappropriate sinus tachycardia

Table 3 Abdominal symptoms of post-COVID-19 syndrome
Abdominal symptoms of post-COVID-19 syndrome
• abdominal pain • nausea • diarrhea • loss of appetite • impaired smell and taste

Table 4 Cardiovascular symptoms of post-COVID-19 syndrome
Cardiovascular symptoms of post-COVID-19 syndrome
• chest pain • reduced exercise tolerance • dyspnea • increased resting heart rate • arrhythmias • myocarditis • thromboembolism • hypertension

Table 5 Factors to be considered when using pharmacotherapy in a patient with post-COVID-19 syndrome	
Factors affecting the course of the post-COVID-19 syndrome	**Practical conclusions**
Patient characteristics	Both residual characteristics of the patient and the most optimal therapeutic management concerning post-COVID-19 symptoms should be considered.
Multimorbidity	Multimorbidity may modify the course of the post-COVID-19 syndrome due to common determinants with comorbidities
Effectiveness of post-COVID-19 symptom control	It depends on the course of infection with the SARS-CoV-2 virus and the severity of post-COVID-19 symptoms

Optimal drug combinations	The therapy should use optimal polypharmacotherapy based both on the clinical picture of the occurring symptoms and the specificity of the mechanism of action of the drugs used
Stable effect of pharmacotherapy	The optimal choice of drug, as well as their combinations, are one of the most critical elements of rationalizing pharmacotherapy in patients with post-COVID-19
The benefit-to-risk ratio of the pharmacotherapy used	It should be remembered that the drugs used may cause side effects, the clinical picture of which may be consistent with disorders that are part of the post-COVID-19 clinical picture
Contextuality of pharmacotherapy	The effectiveness and safety of pharmacotherapy are not an absolute concept. The choice of the drug and its dosage must always be contextual, which in practice means that it must take into account the essential characteristics of the patient, which are unmodifiable and significantly affect the choice of the drug and the way it is used. Before choosing a pharmacotherapy to be used in a particular patient, both residual factors and the impact of comorbidity and other concomitant medications on the efficacy and safety of pharmacotherapy should be considered.
Changes in the pharmacokinetic profile of the drugs used	Inflammation is the most critical element modifying the pharmacokinetics of drugs, which should be taken into account when choosing pharmacotherapy

Table 6 Post-COVID-19 symptoms and current pharmacotherapy and supplementation options that are being investigated	
	Options of pharmacotherapy/supplementation
Cardiovascular disorders	angiotensin-converting enzyme inhibitors, statins, beta-blockers, ezetimibe, fibrates, omega-3 fatty acids, ranolazine, magnesium salts, potassium
Feeling tired, exhausted	coenzyme Q10, D-ribose, metformin
Nocplastic pain	tramadol, naltrexone, cannabinoids, alpha-lipoic acid
Coagulation disorders	anticoagulants
Vascular endothelial dysfunction	sulodexide
Gastroenterological disorders	probiotics, rifaximin-α, metformin
Microcirculation disorders	pycnogenol, sulodexide
Mast cell activation syndrome	bilastine, famotidine
Brain fog	low dose aripiprazole, coenzyme Q10, honokinol
New-onset type 2 diabetes	metformin

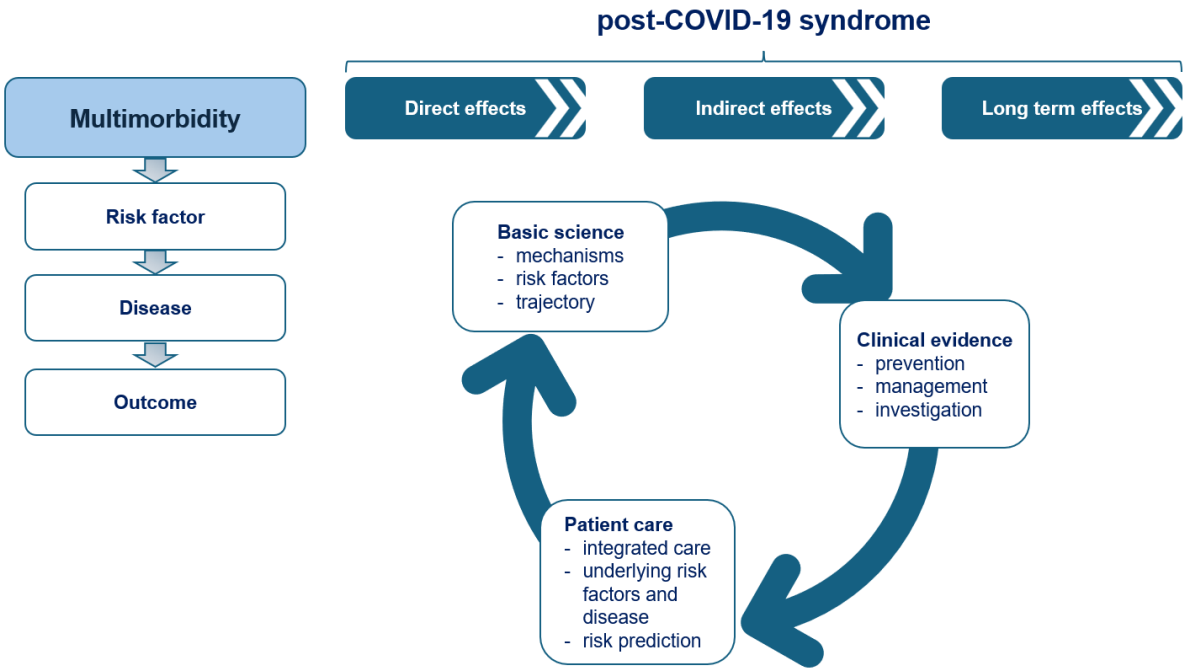

Figure 1 A multiway approach to COVID-19 and the post-COVID-19 syndrome. Modified from [8]

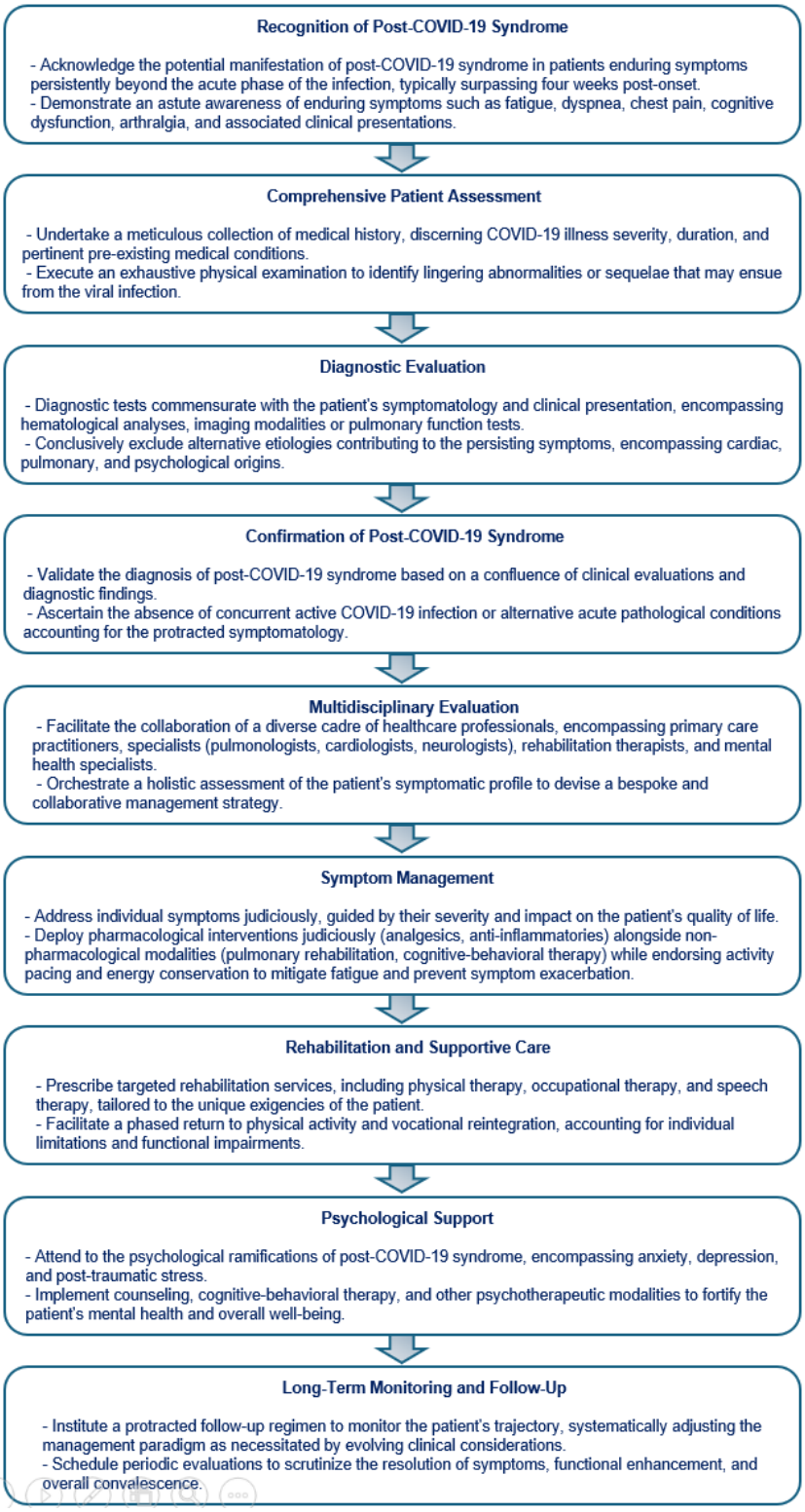

Figure 2 A step-by-step approach to diagnosis, management and treatment of post-COVID-19 syndrome