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REVIEW ARTICLE

# Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals

Androula Pavli,<sup>a</sup> Maria Theodoridou,<sup>b</sup> and Helena C. Maltezo<sup>c</sup>

<sup>a</sup>Department of Travel Medicine, National Public Health Organization, Athens, Greece

<sup>b</sup>First Department of Pediatrics, University of Athens, Athens, Greece

<sup>c</sup>Directorate of Research, Studies and Documentation, National Public Health Organization, Athens, Greece

Received for publication March 22, 2021; accepted March 31, 2021 (ARCMED-D-21-00330).

Post-COVID syndrome also known as long COVID refers to symptoms persisting for more than three weeks after the diagnosis of COVID-19. We reviewed the current evidence on post-COVID syndrome, focusing on its clinical manifestations and addressing the challenges for its management in primary healthcare. The incidence of post-COVID syndrome is estimated at 10–35%, while for hospitalized patients it may reach 85%. Fatigue is the most common symptom reported in 17.5–72% of post-COVID cases, followed by residual dyspnea with an incidence ranging from 10–40%. Mental problems, chest pain, and olfactory and gustatory dysfunction may affect up to 26, 22 and 11% of patients, respectively. More than one third of patients with post-COVID syndrome have pre-existing comorbidities, hypertension and diabetes mellitus being the most common. Beyond the prolonged duration of symptoms, the scarce published data indicate that most patients with post-COVID syndrome have a good prognosis with no further complications or fatal outcomes reported. Given the clinical spectrum of patients with post-COVID syndrome, most of them will be managed by primary healthcare professionals, in conjunction with pre-existing or new co-morbidities, which, in turn, may increase the burden of COVID-19 on primary healthcare. In conclusion approximately 10% of patients with COVID-19 may have symptoms persisting beyond three weeks, fulfilling the criteria of post-COVID syndrome. Primary healthcare professionals have a key role in the management of patients with post-COVID syndrome. Research is needed to elucidate the pathogenesis, clinical spectrum, and prognosis of post-COVID syndrome. © 2021 Instituto Mexicano del Seguro Social (IMSS). Published by Elsevier Inc. All rights reserved.

**Key Words:** COVID-19, SARS-CoV-2, Post-infectious, Complications, Long term, Fatigue syndrome, Management, Primary healthcare, Prevention.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic has induced a substantial burden worldwide. The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections may vary from asymptomatic infection to respiratory illness, multi-organ failure, and fatal outcome (1). The epidemiological and clinical manifestations, pathogenesis, and complications of patients with COVID-19 during the acute phase have been explicitly

described; however, the long-term sequelae of COVID-19 remain largely unclear (2).

Post-COVID syndrome, also known as long-COVID, was described as a clinical entity for the first time in spring 2020, when COVID-19 patients still had symptoms several weeks after their acute infection and soon after the first cases evolved; in particular, relevant information emerged from the first detailed patient survey of post-COVID syndrome (3). Post-COVID syndrome appears to be a multisystem disease, occurring even after a relatively mild acute illness (3,4). Although there are indications that the evolution of post-COVID syndrome is driven by cytokines, research is needed to elucidate its pathogenesis (5,6). Evidence regarding the spectrum of post-COVID syndrome

Address reprint requests to: Helena C. Maltezo, Dr. Directorate of Research, Studies and Documentation, National Public Health Organization, 3-5 Agrafon Street, Athens 15123 Greece; Phone: (+0030) (210) 5212175; E-mail: [helen-maltezo@ath.forthnet.gr](mailto:helen-maltezo@ath.forthnet.gr)

and its management is evolving and will continue so in the next few years. The incidence of post-COVID sequelae is estimated between 10 and 35% (4,7,8). Fatigue, shortness of breath, chest pain, mental disorders and olfactory and gustatory dysfunction are amongst the most common symptoms (9–13). Post-infectious olfactory dysfunction which may affect over 60% of those with SARS-CoV-2 infection (12) including asymptomatic infections, represents also an important frequent symptom of post-COVID syndrome (12,13). Although the current evidence is limited, it is anticipated that most patients with post-COVID syndrome will recover through a primary healthcare-based holistic approach (4). Our aim is to review the published evidence on post-COVID syndrome, and describe its incidence and clinical spectrum, with a special emphasis on the challenges of its management in primary healthcare.

## Methods

The PubMed was searched for articles published as of March 15, 2021 using combinations of the following words: COVID-19, SARS-CoV-2, long-term, complications, post-COVID syndrome, chronic fatigue syndrome, chest pain, dyspnea, and psychological problems. We read the abstracts of a total of 125 articles and selected 60 articles based on their relevance. Of them, 45 articles were used in the current review, including five review articles referring to COVID-19, its complications and primary healthcare services, and one scientific book. Articles focusing on the most common symptoms of post-COVID syndrome were selected. Evaluation of the quality of the included studies was based on the fact that only peer-reviewed studies published in core medical journals pertaining to post-COVID syndrome were selected. We also included information from seven official public health and scientific websites.

COVID-19 was defined as a case with laboratory-confirmed SARS-CoV-2 infection through real-time reverse-transcriptase polymerase chain reaction (RT-PCR) in a patient with compatible symptoms. SARS-CoV-2 infection was defined as a positive RT-PCR in a patient with or without symptoms. Post-COVID syndrome or long-COVID was defined as COVID-19 associated illness extending for more than three weeks from the onset of symptoms and chronic COVID-19 as illness extending beyond 12 weeks from the onset of symptoms (4).

### *Epidemiology and Clinical Spectrum of Post-COVID Syndrome*

The incidence of post-COVID sequelae in those who have tested positive for SARS-CoV-2 infection and who have been managed in an outpatient setting or in the home is estimated between 10 and 35% (4,7), however for those hospitalized, the incidence of post-COVID syndrome may

be nearly 80% (8). Symptoms for those who were not hospitalized may last for more than four weeks and for hospitalized cases for eight or more weeks following discharge (8). Post-COVID syndrome is not limited to severe acute COVID-19 patients. Symptoms during the acute COVID-19 illness in patients who subsequently develop post-COVID syndrome are mostly mild, showing improvement with time, and with no identified predictors (14). Cases of olfactory and gustatory dysfunction have been documented following an asymptomatic SARS-CoV-2 infection (12,13).

Persistent medical problems reported following acute COVID-19 may include a wide spectrum of symptoms and conditions (8). Persistent medical problems may be related to residual inflammation during the convalescent phase, organ damage, non-specific effects from prolonged ventilation such as post-intensive care syndrome, prolonged hospitalization, social isolation, or impact on underlying medical conditions (15,16). Supplementary Table 1 shows the characteristics and symptoms of patients with post-COVID syndrome per published study as of March 15, 2021. Published data on the epidemiology and clinical spectrum of post-COVID cases are presented per symptom below:

### *Fatigue*

Patients with COVID-19 may develop chronic fatigue syndrome/myalgic encephalomyelitis, which presents with prolonged relapse of exhaustion, cognitive dysfunction, depression, and other symptoms after a minimal amount of activity (17). Fatigue is the most common symptom of post-COVID syndrome (Supplementary Table 1), with an incidence ranging from 17.5% to much higher rates for hospitalized COVID-19 patients either in wards or in intensive care units (up to 60.3 and 72.0%, respectively) (9–11,14,16,18–21). Fatigue has been reported up to seven months by patients after the onset of COVID-19 causing significant disability, while many patients continue to experience fatigue beyond seven months requiring thorough investigation (14,21). Male gender and comorbidities e.g., hypertension and diabetes mellitus have been significantly associated with fatigue (10). Since there is currently no generally accepted diagnostic method for, it is first necessary to exclude any disorders with similar symptoms. Potential causes in the pathophysiology of the disorder may include hormonal disturbances, immune system dysfunction, infection, and nervous system abnormalities (10).

### *Dyspnea and Chest Pain*

Respiratory and physical sequelae may be more common among patients who had been hospitalized for COVID-19 (21,22). Symptoms such as dyspnea and decreased exercise tolerance associated with COVID-19 may be still reported in a significant proportion of patients hospitalized

for COVID-19 up to four months after hospital discharge, with reduced exercise tolerance being the most common (21,22). Residual dyspnea persisted in approximately 10% and 40% of survivors of COVID-19 who reported experiencing it during the acute phase of COVID-19 two and four months, respectively (21,22). New or worsened breathlessness was a significant symptom in hospitalized patients (14) even several weeks post-discharge, affecting up to 42.6% and 65.6% of ward patients and of intensive care unit patients, respectively (18). Chest pain affected up to 22% of survivors after two months (9,11,19,20). COVID-19 sequelae, such as respiratory and physical functional impairment are associated with residual lung injury and may impact psychological health due to reduced quality of life in survivors of COVID-19 (22). Chronic obstructive pulmonary disease emerged as a risk-factor contributing to severe lung function impairment in patients with post-COVID syndrome; whether these patients are at increased risk for progressive lung fibrosis will require a longer follow-up (22).

#### *Psychiatric Symptoms and Post-traumatic Stress Disorder*

The underlying mechanism of persistent psychiatric symptoms among COVID-19 patients, including post-traumatic symptoms, depression, anxiety, and cognitive impairment, is likely to be multifactorial and might include the direct effects of viral infection, the immunological response, corticosteroid therapy, intensive care unit stay, social isolation, and stigma (9). Sleeping disorders, anxiety and depression may affect up to 26 and 23% of patients, respectively, even up to six months following COVID-19 (9). Clinical signs of stress disorders include a variety of manifestations such as development of obsessions and compulsions, distrust of other people, reduced of social activity, difficulty in concentration, aggression, irritability, substance use, and cognitive deficit (22). Post-traumatic stress disorder which refers to a category of psychiatric conditions triggered by trauma or other life-stressing factors could occur after recovery from a life-threatening illness including COVID-19; as shown by recent studies the prevalence rate may range from 5.8–20% (10,23,24).

There is a high probability that symptoms of psychiatric, neurological, and physical illnesses as well as inflammatory complications on the brain in patients with post-COVID syndrome increase suicidal ideation and behavior in this group of patients but also in COVID-19 survivors without post-COVID syndrome (25). Neurological symptoms and sub-clinical cognitive dysfunction following COVID-19 infection are likely to result from multiple and interacting causes, notably direct damage by the virus to the cortex and adjacent sub-cortical structures, indirect effects due to non-central nervous system systemic impairment and psychological trauma (26). Risk factors for persisting psychological symptoms such as anxiety

and depression include female gender (9). However, there has been no supporting evidence about the association of persisting psychological symptoms with underlying psychiatric or psychological illness. In terms of neurological sequelae, there has been a male predominance in neurological complications of post-COVID syndrome including Guillain-Barré syndrome, a gender difference not seen in the classical form (27).

#### *Rare Neurologic Clinical Syndromes*

Neurological post-COVID complications have been rarely reported and the various aspects of neurological involvement are increasingly uncovered (27–29). As a neuro-inflammatory disorder, novel neurological symptoms are being reported; cerebrovascular disorders (e.g., ischemic stroke, cerebral vasculitis and hemorrhage), altered mental status (e.g. encephalitis, encephalopathy, seizure, myoclonus), peripheral nervous system involvement (e.g. Guillain-Barré syndrome, myositis), and neuropsychiatric involvement (e.g. depression, personality change) have been the major COVID-19-associated neurological manifestations reported (27–29), however severe neurological conditions are rare and usually are attributed to indirect pathogenic mechanisms like systemic inflammation and post-infectious autoimmune mechanism (30).

Late onset Guillain-Barré syndrome is a rare but recognized complication of acute SARS-CoV-2 infection. The etiology of Guillain-Barré syndrome is complex and most likely caused by an immune-mediated reaction secondary to preceding infection (27). This would probably result in larger series and would help clarify the spectrum of this neurological condition (28).

Cases of opsoclonus-myoclonus syndrome, a post-infectious neurologic complication of COVID-19, which may be related to an immune-mediated mechanism, have also been reported (29). Awareness of the possibility of such disorder and becoming familiar with its clinical picture might assist in better diagnosis and appropriately choosing relevant immunotherapy (29).

Acute transverse myelitis has also been reported as a post-COVID complication. It is characterized by an acute inflammatory process of the spinal cord that can be classified into various etiologically distinct groups. Myelitis with a suspected autoimmune basis is the most common form. Myelitis usually occurs as a post- or para-infectious condition through an immunologic process that targets the peripheral nervous system and a subsequent viral inflammatory process could result in neuronal death or spinal tract lesions (30–32).

#### *Olfactory and Gustatory Dysfunction*

Recovery of olfactory and gustatory dysfunction may last more than one month after the onset of smell and taste loss

**Table 1.** COVID-19 sequelae subtype criteria\*, COVID-19 Clinic of the University of Cincinnati Medical Center.

	Type 1	Type 2	Type 3		Type 4		Type 5
Initial symptoms	Variable <sup>a</sup>	Mild	A Mild	B Mild	A None	B None	None
Duration of symptoms	Variable <sup>a</sup>	>6weeks	3-6 months	>6 months	Variable	Variable	N/A
Period of quiescence	No	No	Yes	Yes	No	No	N/A
Delayed onset of symptoms	No	No	No		Yes ≥3 months	Yes ≥6 months	Yes

<sup>a</sup>Correlate with the severity of initial infection, number of organ system injured and pre-existing medical conditions.

\*Modified from reference (34).

(12,13,33) and may affect up to 11% and 9% of patients after six months post-hospital discharge, respectively (11). Neither gender nor age has been a predictor for olfactory outcome (13). The mechanism that SARS-CoV-2 induces olfactory dysfunction may be related to the partial loss of olfactory receptor neurons in the olfactory epithelium and the cells which express two known proteins used by SARS-CoV-2 to infect human cells (ACE2 and TMPRSS2) at the peripheral level. The mechanism by which SARS-CoV-2 leads to taste impairment is still unclear. It may be via direct damage of the gustatory organ, as ACE2 receptors have been identified in the mouth and on the tongue (11).

Other common persisting symptoms of post-COVID syndrome include also gastrointestinal symptoms, in particular diarrhea and vomiting, which may persist up to one third of patients two months after discharge (9,16,19).

#### Characteristics of Patients with Post-COVID Syndrome

More than one third of patients with persisting symptoms have pre-existing co-morbidities (16). The most common comorbidities in a large proportion of patients with post-COVID syndrome include hypertension, diabetes mellitus, cardiovascular disease, pulmonary disease, and obesity (9,11,16,18). Hypertension and diabetes mellitus were reported in up to 35 and 26% of patients with persisting post-COVID symptoms, whereas cardiovascular and pulmonary disease in up to 16 and 9% of them, respectively (9–11).

Prolonged post-COVID symptoms may be associated with age 40–60 years old, hospital admission at symptom onset, severe COVID-19 and shortness of breath or abnormal auscultation (19). Although age is a major factor associated with COVID-19-related mortality, persistence of post-COVID symptoms is not higher in older patients (22). Current evidence shows that up to 70% of low-risk patients with COVID-19, such as people 40–50 years of age without pre-existing medical conditions, have symptoms, including fatigue, breathlessness, chest pain, and olfactory and gustatory dysfunction up to six months following the initial infection (34).

#### COVID-19 Sequelae Subtypes

The multi-disciplinary COVID-19 Clinic of the United States University of Cincinnati Medical Center proposed criteria for COVID-19 sequelae subtypes, based on initial symptoms, duration of symptoms, period of quiescence, and time of onset of symptoms (34). There are five categories of long COVID-19 syndrome: Type 1 includes patients with varying duration of recovery that directly relates to the severity of infection, organ damage, and underlying medical conditions; Type 2 is characterized by symptoms persisting six weeks from the onset of illness; Type 3 shows a period of quiescence or nearly full recovery after initial infection, followed by a recurrence of symptoms that persist for at least three months (Type 3A) or at least six months (Type 3B); Type 4 includes patients who are initially asymptomatic at the time of a positive SARS-CoV-2 test but develop symptoms one to three months (Type 4A) or at least three months later (Type 4B), that persist for varying lengths of period; and Type 5 includes patients who have no or few symptoms at the time of a positive SARS-CoV-2 test and experience sudden death within the next 12 months (Table 1) (34).

#### Prognosis of Patients with Post-COVID

In terms of prognosis of post-COVID syndrome, beyond the prolonged symptoms, scarce published data indicate that most patients with post-COVID syndrome have a good prognosis with no further complications or fatal outcomes reported.

#### Implications for Primary Healthcare Professionals

Current evidence indicates that approximately 10% of patients with COVID-19 may have persisting symptoms beyond three weeks, which is rather underestimated given that half of COVID-19 cases are not formally diagnosed (4). Moreover, surveillance systems have not been monitoring long-term complications of COVID-19 on a routine basis and only late or long-term deaths are reported. It is important that patients with post-COVID syndrome are

prospectively and systematically monitored, to estimate its incidence, clinical spectrum, and prognosis in the long-term (1).

The management of post-COVID syndrome as a novel clinical syndrome includes clinicians and other healthcare professionals of various backgrounds. Clinical and experiential knowledge of healthcare professionals is an important resource for both provision of healthcare services and research (35,36).

Based on the limited current evidence and on the patients' prevalent clinical findings, it is anticipated that many patients with persisting post-COVID symptoms will be managed by primary healthcare professionals, in conjunction with the management of pre-existing or new comorbidities (4). However, in the context of the COVID-19 pandemic, primary healthcare will be put under additional strain by poorly controlled long-term conditions, the need to manage COVID-19 cases, the widened socioeconomic inequalities due to COVID-19 and the associated response, the effects of post-COVID, and delivery of COVID-19 vaccines (4,37).

Current scientific evidence on COVID-19 has focused mainly on acute and institutional medical care overlooking the fundamental and key role of primary healthcare, in the health system in particular the importance of team-based primary care (e.g., family physicians, psychologists, physiotherapists, dietitians, and other specialist doctors) (38). As a result of the rapidly shifting inter-professional roles of primary healthcare professionals, there is an urgent need for guidelines for clinical, behavioral, and mental health needs associated with post-COVID syndrome (39,40).

Management of patients with post-COVID syndrome should be pragmatic and symptomatic, avoiding over-investigation. Serious complications and alternative causes of ongoing symptoms should be excluded. New or deteriorating symptoms must be investigated; these could indicate delayed sequelae such as cardiac complications or pneumonia. For those who have had significant respiratory illness a chest radiograph at 12 weeks should be considered. Investigations, although not always necessary, can assist in determining causes of persisting symptoms, and to exclude serious problems such as pulmonary embolism and myocarditis; these include blood tests e.g. full blood count, electrolytes, liver and renal function, troponin, C reactive protein, creatinine kinase, D-dimer, brain natriuretic peptides and ferritin, in order to assess inflammatory and prothrombotic states, and other tests including 12 lead electrocardiogram, chest radiograph and urine tests (4).

COVID-19-associated mental health conditions are also prevalent problems in primary healthcare. A surge in mental health issues has been seen and is expected to continue to increase in response to COVID-19. Current evidence suggests that the COVID-19 pandemic will increase the need for acute and long-term mental health management for COVID-19 patients within primary healthcare (41). It

is being recognized by healthcare professionals internationally, that the mental health impact could be as significant as SARS-CoV-2 itself (42). Patients with post-COVID symptoms may be unable to engage in work and family activities or may have experienced family bereavements as well as job losses and financial difficulties and therefore they may need social and financial support too (4). Attention should be paid to the fact that young patients, who were healthy prior to their illness, may be treated as hypochondriacs (43).

The burden of other health conditions not related to COVID-19 has grown as routine services were suspended at the peak of the pandemic and patients have avoided general practices, hospital outpatients, and emergency departments (44). Primary care consultations per person according to United Kingdom National Health System Data were reduced by approximately 30% after lockdown (45). Therefore, in addition to post-COVID syndrome, it is important to optimize the management of chronic conditions. Collaboration with the patient to develop an individualized management plan to support recovery is crucial through a multidisciplinary team, including physiotherapists, exercise physiologists and dietitians, social workers, along with outpatient rehabilitation physicians and other healthcare professionals, to support individual management planning (40).

Future research is needed to elucidate the pathogenesis, clinical spectrum, and prognosis of post-COVID syndrome. Markers to enable the prompt diagnosis of post-COVID syndrome, and monitor the associated morbidity and prognosis are also needed.

### *Limitations*

Limitations of this review include the fact that most available published evidence concerns hospitalized COVID-19 cases. A high rate of unreachable non-hospitalized or undiagnosed missed patients, could lead to bias. In addition, information provided here in terms of the clinical spectrum of post-COVID syndrome is based on current evidence but may be modified as more information becomes available in the future.

### **Conclusion**

Post-COVID syndrome, which affects approximately 10% of COVID-19 patients, is not limited to patients with severe acute COVID-19. Symptoms of post-COVID syndrome are usually mild, showing improvement with time, and with no identified predictors. Fatigue, dyspnea, chest pain, mental health problems, and protracted olfactory and gustatory dysfunction are the most common symptoms of post-COVID syndrome. It is expected that primary healthcare will play a vital role in the management of patients with post-COVID syndrome. This review describes the impact

of these complex problems of patients with post-COVID syndrome, as well as the importance of prompt diagnosis based on well-described criteria. Patients with post-COVID syndrome should be managed symptomatically avoiding over investigation and considering pre-existing or new comorbidities. There is a need for guidelines for the diagnosis and management of post-COVID syndrome based on established criteria to support the provision of appropriate healthcare services. In addition, registries to actively and systemically follow-up COVID-19 patients are imperative, to estimate the incidence, clinical spectrum, and outcome of patients with post-COVID syndrome.

### Funding

No funding was received for this work.

### Conflict of Interest

There is no conflict of interest to declare.

### Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.03.010.

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