

POST-COVID SYNDROME: PREVALENCE, COURSE FORMS, DIAGNOSTIC ASPECTS

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ABSTRACT

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.

Keywords: *COVID-19, SARS-CoV-2, Post-infectious, Complications, Long term, Fatigue syndrome, Management, 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 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

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).

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) (19,21.). 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).

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 (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 (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 (23).

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.

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 (11). It is being recognized by healthcare professionals internationally, that the mental health impact could be as significant as SARS-CoV-2 itself (22). 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 (13).

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.

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.

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