

PREVALENCE AND CHARACTERISTICS ASSOCIATED WITH POST-COVID-19 CONDITION AMONG NONHOSPITALIZED ADOLESCENTS AND ADULTS

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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 comorbidities, 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.

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

Introduction.

Post-COVID-19 condition (PCC) is characterized by the persistence of symptoms such as fatigue, dyspnea, and what is commonly referred to as “brain fog” occurring 3 months or longer after infection with SARS-CoV-2.¹ The prevalence remains uncertain, with a review of PCC symptoms in children and adolescents

reporting fatigue rates between 3% and 87%, whereas a meta-analysis reported the confidence interval of fatigue prevalence to be 32% to 62%.^{2,3}

When sequelae arise after mild acute infection, a subset of cases might fit the label of postinfective fatigue syndrome (PIFS), in which persistent symptoms and disability accompany scarce findings on standard clinical examination.⁴⁻⁷ In the aftermath of a wide array of infectious diseases, such as mononucleosis, Q fever, and giardiasis, multiple prospective cohort studies report that 10% to 15% of patients experience moderate to severe disability meeting the diagnostic criteria for PIFS, in line with current studies of PCC.⁶⁻¹²

The underlying disease mechanisms of PCC, as well as PIFS, remain elusive. For PIFS, suggested explanations range from low-grade inflammation to functional alterations of the brain's perception of bodily states partly caused by psychosocial factors.^{13,14} Most studies of PCC have focused on infection-specific factors (what may be considered as direct factors), such as immunological aberrations, and other possible mechanisms—organ damage, endotheliopathy, persisting viral reservoirs, and autoimmune inflammation have been proposed.^{6,15-19} However, indirect, nonspecific stressors during the pandemic, such as fear of viral transmission, societal lockdown, and parents experiencing PCC, have also been suggested.^{6,20}

Studies of PIFS have benefitted from an international case definition that is centered around the symptom of fatigue, which should be persistent from onset of the acute infectious event, severely affect daily activities, and not be caused by any other condition; diagnosed individuals must experience at least 4 of 8 additional symptoms (such as headache and concentration or memory problems). In contrast, the broad case definition of PCC established by the World Health Organization (WHO) encompasses any symptom occurring in the aftermath of acute COVID-19, does not require symptom persistence since the infectious event, and does not stipulate significant disability.¹

Prospective studies of nonhospitalized patients with COVID-19 with contemporaneous, SARS-CoV-2-antibody-negative control participants are scarce in younger age groups.^{4,6} To the best of our knowledge, no previous reports have provided prevalence estimates for PCC based upon a rigorous evaluation of caseness, including the assessment of alternative medical and psychiatric diagnoses. Furthermore, few studies have investigated both direct disease-specific factors, such as immunological activation markers, and indirect general stressors.^{11,19} Hence, the aims of this prospective controlled cohort study of nonhospitalized adolescents and young adults were 3-fold: (1) to determine the point prevalence of PCC in the SARS-CoV-2-positive group according to the WHO and PIFS definitions 6 months after acute COVID-19, while as a control measure applying the case definitions to the SARS-CoV-2-negative group as well; (2) to determine the risk of development of PCC 6 months after acute

COVID-19, adjusted for possible confounders; and (3) to explore a broad range of potential risk factors for PCC.

Methods

The current paper follows the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology ([STROBE](#)). The project was approved by the Regional Committee for Ethics in Medical Research and given a limited confidentiality waiver allowing us to approach individuals eligible for recruitment by text message. Written informed consent was obtained as required by the Health Research Act.

Study Design

This was a prospective cohort study of adolescents and young adults testing positive and negative for SARS-CoV-2 who were not hospitalized, with follow-up 6 and 12 months after inclusion. Selected baseline data have been reported elsewhere.²⁸ Data from 12-month follow-up are not presented in the present report.

Statistical Analyses

PCC and PIFS at 6 months were defined as primary and secondary outcomes, respectively. The study had a power of approximately 80% to detect a relative risk (RR) of 1.5.

Prevalence data are reported separately in the SARS-CoV-2–positive and SARS-CoV-2–negative groups, and the risk difference calculated. For analyses of risk factors, bivariate analyses between the 2 outcome variables and each hypothesized risk factor were performed by generalized linear modeling using a modified Poisson approach (log-link and robust error variances). Dimensionality reduction was performed by principal component analyses (PCA). SARS-CoV-2 status, background and constitutional factors, observational period characteristics and all remaining variables with an unadjusted $P < .25$ were included in a multivariable model; variables were then removed and eventually reinserted 1 by 1 dependent on their influence on overall goodness-of-fit in order to find the most parsimonious model.

As sensitivity analyses, identical analytical procedures were performed on 2 different data sets: 1 with imputation of missing data points with mean or median values, and 1 with exclusion of participants with uncertain caseness classification, vaccination prior to enrolment or less than 5 days prior to follow-up appointment, or evidence of recent EBV infection at enrollment or during the observational period. An additional sensitivity analysis of the final multivariable model was performed where individuals in the SARS-CoV-2–negative group with baseline symptoms suggesting an acute infection were removed alongside the exclusions listed above. $P < .05$ was considered statistically significant in 2-sided tests. All statistical analyses were carried out in SPSS version 28.0 (SPSS Inc).

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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