

Post COVID-19 Syndrome: Biomarkers and Laboratory Evaluation

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Dear Sir

COVID-19 is a highly contagious acute respiratory disease caused by an RNA virus called SARSCoV-2 (severe acute respiratory syndrome corona virus-2). Two-year experience with COVID-19 demonstrates that the infection is not localized to respiratory system but is a multi-system or multi-organ disease and may become chronic. The persistence of symptoms was observed for weeks, or months following recovery from COVID-19 and was identified as a distinct entity called post-COVID-19 syndrome (PCS), long COVID-19, Chronic COVID-19, or post-acute sequelae of COVID-19 (PASC). Though there is no general agreement on the duration, continuity of symptoms for at least three months from the onset of disease or two months following the hospital discharge was usually considered as PCS¹.

As is true for any new disease, PCS is an underrecognized and underreported condition. A recent systematic review of 57 studies with 250351 COVID-19 survivors showed that 54% (31-67%) of such patients had post-covid symptoms after 6 months of infection². Most frequent complaints were fatigue and dyspnoea, but patients with PCS might suffer from mental, cognitive, cardiac, rheumatological and gastrointestinal issues¹. Many patients with PCS had shown changes in their chest x-rays and in pulmonary or cardiac function tests. Most surprisingly, PCS was observed in all types of patients irrespective of their age, gender, and the severity of acute symptoms³ while prolonged hospital-stay, ICU admissions and mechanical ventilation were identified as the risk factors for

PCS in a few reports. In a survey at local setting, 83% of 158 post-COVID-19 patients reported fatigue and significant correlation was observed with age, female gender, and time since recovery⁴.

Another survey of 257 COVID-19 survivors showed residual symptoms in 84% population with body aches, low mood and cough as the commonest symptoms following 1-3 months after infection⁵.

The underlying pathophysiology of PCS remained obscured. It is postulated that hyperinflammation secondary to lymphocytopenia and neutrophilia with subsequent tissue damage and immune dysregulation may result in the multiorgan disease⁶. This unresolved inflammation in PCS is closely intertwined with the increase in proinflammatory markers like C-reactive protein (CRP), d-dimers, interleukin-6 (IL-6) and lymphocytopenia⁷. Colarusso et al in 2021 studied 52 patients with PCS and observed high CRP, complement complex C5b-9, lactate dehydrogenase (LDH), (but not IL-6) in patients irrespective of the disease severity or lung fibrosis⁸. This study also reported a higher relative risk (of 2.8) for developing lung fibrosis-like changes with various cytokines (high IL-1 α /TGF- β and lower plasma levels of IFN- α)⁸. Similarly, Saricam E et al (in 2021) studied biomarkers in patients having cardiac symptoms following COVID-19 infection and observed higher NT-pro B-type natriuretic peptide (BNP) (132.30 \pm 35.15; 76.86 \pm 16.79, respectively; p < 0.001) and lower nitrous oxide (NO) levels (9.20 \pm 3.08; 16.15 \pm 6.02, respectively; p<0.001) in those having cardiac issues compared to the asymptomatic patients⁹. These studies underscore the significance of various biomarkers in PCS. However, a few reports have denied the association of biomarkers with PCS. For example, low platelet count and low LDH levels were observed as the independent risk factors for fatigue and dyspnoea

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but the variance in these biomarkers failed to explain the observed symptoms of PCS¹⁰.

Diagnosing PCS will require a set of laboratory tests following detailed clinical history and complete examination of the patients. Co-morbidities like diabetes, hypertension, renal disease, and ischemic heart disease may require appropriate testing for the concomitant management of these disorders¹¹.

PCS is a multisystem disease, and no laboratory test can truly distinguish PCS from other diseases having similar manifestations¹². Therefore, patients having fatigue and dyspnoea may need several laboratory routine tests like complete blood count, urine analysis, serum electrolytes, blood urea nitrogen, serum creatinine and liver function test, CRP, thyroid stimulating hormone, vitamin B12 and vitamin D. Serum ferritin and D-dimer will be high because of inflammatory and prothrombotic state and can help to evaluate the ongoing inflammation^{11,12}. More specialized tests can be requested from the laboratory depending on the underlying condition of the patient. Patients having cardiac problems may need troponin and BNP to rule out cardiac injury. Those presenting with joint pain will require tests (anti-nuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide, creatine phosphokinase, anticardiolipin antibodies-IgG/IgM) to diagnose inflammatory arthritis^{11,12}. D-dimer and fibrinogen assays are required for evaluating persistent coagulopathy^{11,12}.

In summary, PCS is a newly recognized condition and our understanding for the disease is evolving but still far from perfect. With 1.53 million confirmed cases of COVID-19 and a high reported frequency for PCS^{4,5}, one can estimate that millions would be suffering from PCS in the country. This quantum seems to be disproportionality large when compared to the availability of the locally published literature. We need well-design large scale studies to evaluate the true magnitude of this burden and to determine the role of biomarkers in the diagnosis and management of PCS.

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