

## LETTER TO THE EDITOR

# Post-COVID-19 complications: Multisystemic approach

To The Editor,

Coronavirus disease 2019 (COVID-19) is a communicable disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Following a reported incubation period of 1–14 days, the disease commonly presents through symptoms of fever, cough, fatigue, breathing difficulties, and loss of taste and smell.<sup>1</sup> The majority of COVID-19 patients are, however, either asymptomatic or only have mild symptoms; while a few may develop acute respiratory distress syndrome (ARDS), which can be life-threatening or fatal.<sup>1</sup>

Although many COVID-19 patients eventually recover, some do not cease experiencing symptoms long after their COVID-19 polymerase chain reaction test turns negative; this is commonly referred to as “post-COVID-19 syndrome” or “long COVID.” As per guidelines by the National Institute for Health and Care Excellence (NICE), Post COVID-19 syndrome is defined as, “signs and symptoms that develop during or after an infection consistent with COVID-19, continuing for more than 12 weeks (3 months), and not explained by an alternative diagnosis.”<sup>2</sup> NICE has also recommended research on the following topics regarding the post-COVID-19 syndrome:

- Risk factors for the post-COVID-19 syndrome,
- Prevalence of the post-COVID-19 syndrome,
- Interventions in patients with the post-COVID-19 syndrome,
- Natural history, clinical presentation, and prognostic markers for the post-COVID-19 syndrome, and
- Validated tools for post-COVID-19 syndrome screening.

Based on available evidence to date, the bulk of post-COVID-19 complications seem to be associated with the cardiopulmonary systems. The cardiac post-COVID-19 manifestations include myocarditis, arrhythmia, and ischemia; while the most common pulmonary complications reported are bacterial pneumonia, pneumothorax, and pleural effusion. Other systemic post-COVID-19 symptoms often noted include fatigue, headache, body pains, dyspnea, and anxiety/depression.<sup>3</sup> Guillain-Barré syndrome, encephalitis, polyneuropathy, depressive syndrome, delirium, and psychosis were also frequently reported as neuropsychiatric manifestations, and tinnitus, possibly associated with vestibular neuritis, has also been reported significantly. Thrombotic complications like deep-vein thrombosis and pulmonary embolism have also been described as possible consequences, along with acute kidney injury and renal failure.<sup>3–5</sup> A detailed description outlining the reported and published complications<sup>6–21</sup> has been given in (Table 1).

Having understood the possible long-term consequences of COVID-19, it is recommended to study a number of patients through long prospective cohort studies with common methodology and

standards. This practice has been previously employed in observing the consequences of outbreaks of other major infectious diseases such as SARS in 2003 and Ebola in 2004. If we look at the literature regarding SARS, it was found that 52% of the survivors suffered long-term respiratory impairment and reduced exercise endurance; considering that similar manifestations have been reported in patients recovering from COVID, it would bode well to investigate the epidemiology, clinical features and burden of possible post-COVID symptoms now more than ever, as the acute phase of the COVID pandemic appears to be approaching its end. The assessment of not only respiratory insufficiency, but also of symptoms such as anxiety and depression, joint and chest pain, headache, and dementia should be taken into consideration, considering their debilitating effect and their increased prevalence in the general population.<sup>22</sup>

In a study by Ferraro et al.,<sup>23</sup> it was reported that seven patients underwent personalized rehabilitation intervention (30–60 min per day for 6 days per week) to support their recovery from COVID-19 infection. The patients were involved in physical exercise such as postural changes, breathing exercises, passive movement of upper and lower limbs, passive muscle stretching, exercises for balance and coordination. Patients were clinically evaluated during discharge from the rehabilitation unit, as well as being assessed for COVID-19-related fatigue, muscle strength, physical performance, 10-m walking test, dyspnea, and disability status using standard scales and tests. Initially, 85.7% of the patients were found to have COVID-19-related fatigue and after the rehabilitation, 71.4% reported no fatigue, with the remaining patients reporting low levels of fatigue.<sup>23</sup> This can demonstrate that an evaluation of fatigue and functional status post-COVID-19 recovery is needed, alongside the development of guidelines to ensure equitable rehabilitation access worldwide.

Demeco et al.,<sup>24</sup> detected more than 100 studies related to post-COVID rehabilitation, highlighting the relevance of the field. Nearly one-fifth of these studies qualified for further analysis, indicating physical and respiratory rehabilitation as a dire need for patients with comorbidities and individuals residing in remote areas. A higher level of functionality reduced anxiety and depression symptoms contributing to both physical and mental wellbeing during the recovery period.<sup>24</sup> So, patients severely affected by COVID-19 are in need of rehabilitation to achieve better functional outcomes postrecovery. Physical and pulmonary rehabilitation needs to be encouraged and organized at the correct time to observe overall better functional outcomes.

A clear understanding of the long-term sequelae of the disease will allow physicians and governments to draw guidelines to support patients who survived COVID-19 comprehensively, considering that the long-term sequelae of COVID-19 are expected to have a physical,

**TABLE 1** A detailed description of the reported and published systemic complications of COVID-19

Authors	Study type	Systems involved	Sample	Complications found	Country
Sonnweber et al. <sup>6</sup>	Observational prospective multicenter trial	Cardiopulmonary	145	36% - dyspnea (common), 41% - persistent symptoms (after 100 days), 21% - reduced diffusing capacity, 63% - persisting lung pathologies	Austria
Huang et al. <sup>7</sup>	Single-center, retrospective, observational study	Cardiac system	26	58% - abnormal cardiac magnetic resonance (CMR), 54% - myocardial edema, impaired right ventricle function	China
Ng et al. <sup>8</sup>	Case series	Cardiac system	16	CME was performed 56 days postrecovery and myocardial inflammation (myocarditis) was seen	China
Blanco et al. <sup>9</sup>	Prospective study after 104 days (median)	Pulmonary system	100	47% - showed diffusing capacity for carbon monoxide (DLCO) <80% Lower serum lactate dehydrogenase levels were associated with severe COVID-19	Spain
Zhao et al. <sup>10</sup>	Retrospective multicenter cohort study, after 3 months of discharge	Pulmonary system	55	35 patients had persistent SARS-CoV-2 symptoms 39 patients had radiological abnormalities 14 patients had lung function abnormalities 47 patients showed SARS-CoV-2 IgG in their serum	China
Mandal et al. <sup>11</sup>	Multicentric study, after 4–6 weeks of discharge	Overall persistent symptoms from all body systems	384	53% - breathlessness 34% - persistent cough 69% - persistent fatigue 15% - depression 30.1% - elevated D-dimer levels 9.5% - elevated CRP	UK
Kumar et al. <sup>12</sup>	Case report	Cardiac and gastrointestinal	1 (71-year-old man)	Venous thromboembolism complicated by lower GI bleed	India
Lim et al. <sup>13</sup>	Case report	Neuropsychiatric	1 (55-year-old woman)	Psychotic symptoms persisted for 40 days, which included delirium, persecutory delusion, complex visual and auditory hallucinations	UK
Venturelli et al. <sup>14</sup>	Postdischarge multidisciplinary assessment (median time of 81 days after discharge)	Overall persistent symptoms from all body systems	767 patients	1.4% have persistent symptoms of which fatigue and dyspnea were most common 30.5% - posttraumatic psychological problems 19% - impaired lung diffusion 17% - higher D-dimer values	Italy

TABLE 1 (Continued)

Authors	Study type	Systems involved	Sample	Complications found	Country
Ayoubkhani et al. <sup>15</sup>	Observational, retrospective, matched cohort study (mean follow-up time was 140 days)	Epidemiology of post-COVID syndrome	47,780 individuals	1/3rd of the patients were re-admitted post-COVID-19 hospital discharge. Higher incidence of multiorgan dysfunction and organ impairment (33% - lungs, 32% - heart, 12% - kidney and 10% - liver) were detected in patients post-COVID-19	UK
Parpas et al. <sup>16</sup>	Case report	Post-COVID multisystem inflammatory syndrome	1 (67-year-old male)	Acute Kidney Injury (AKI) and diastolic dysfunction along with Leukocytosis, and Severe Hyponatremia	US
Nugent et al. <sup>17</sup>	Retrospective cohort study	Renal functions	1612 patients (only 182 have COVID-19-associated AKI)	In patients with COVID-19-associated AKI, decline in glomerular filtration and increased severity of AKI leading to renal failure were observed	US
Taquet et al. <sup>18</sup>	Retrospective cohort study (6 months post-COVID)	Neurology and psychiatry	2.36 379 patients	33.62% have neurological or psychiatric disorders. 17.39% - anxiety disorders 0.11% - parkinsonism 0.56% - intracranial hemorrhage (above values are for normal COVID-19 patients, percentages were higher in severe COVID-19 patients)	UK
Weng et al. <sup>19</sup>	Follow-up study	Gastrointestinal system	117 patients	44% reported GI symptoms after 90 days of discharge: 24% - loss of appetite 18% - nausea and acid reflux Less reported symptoms were, 9% - vomiting, 7% - abdominal pain	China
Roth et al. <sup>20</sup>	Follow-up cases	Liver (GI), post-COVID-19 cholangiopathy	3 patients	Secondary sclerosing cholangitis with unique histologic features and intrahepatic microangiopathy	US
Durazo et al. <sup>21</sup>	Case report	Liver (GI)	1 patient (47-year-old man)	End-stage liver disease due to post-COVID-19 cholangiopathy, and underwent liver transplantation	US

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

mental, and financial burden on the patients, carers, and healthcare systems.<sup>25</sup> Hence, there must be a comprehensive plan laid out to prevent and manage post-COVID-19 complications, and support the patients who are experiencing delayed morbidity and disability resulting from those complications. More research, time, and health education are required to better understand and recognize the post-COVID complications in diverse populations and settings; and hopefully, will eventually allow us to understand the long-term effects of the infection.

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*Conceptualized the idea and designed the manuscript:* Tarun, Simhachalam. *Overall manuscript supervision:* Dr. Ramana. *Drafting of the manuscript:* Tarun, Simhachalam, Christos, and Anna. *Editing and reviewing of the manuscript:* Dr. Ramana, Christos, Anna, and Tarun. *Additional changes to the manuscript:* Christos and Anna. All authors revised and approved the final draft.

## CONFLICTS OF INTEREST

All the authors declare that there are no conflict of interests.

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