Review

SAGE Open Medicine

SAGE Open Medicine
Volume 9: 1–5

DOI: 10.1177/20503121211023631
journals.sagepub.com/home/smo
SAGE

An emerging entity after pandemic: Post-coronavirus disease 2019 syndrome and associated medical complications

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Abstract

The coronavirus disease 2019 is a devastating illness that has infected millions of people since the beginning of year 2020, through its multi-systemic manifestations that range widely in severity. Because current knowledge on the types and severities of medical illnesses encountered by patients who recovered from coronavirus disease 2019 is limited, it remains unknown whether these illnesses are direct sequelae of coronavirus disease 2019 infection or unrelated coincidences. In this article, we summarize the evidence currently available on post-coronavirus disease 2019 medical complications and propose directions for studying the long-term complications of coronavirus disease 2019 in the future.

Keywords

Post-coronavirus disease 2019 syndrome, coronavirus disease 2019, coronavirus disease 2019 sequelae

Date received: 6 December 2020; accepted: 8 March 2021

Background

Patients suffering from coronavirus disease 2019 (COVID-19) have presented with a wide variety of clinical manifestations ranging from mild upper respiratory tract infection symptoms such as fever, dry cough, and dyspnea to acute respiratory failure from interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), which may lead to mechanical ventilation requirement and death.[1,2] Currently, much of the focus on COVID-19 pandemic is related to the prevention, isolation, and supportive treatment strategies for the acute infection. However, while COVID-19 primarily affects the lungs, it is also known for its multi-organ manifestations which may plausibly render patients with long-term complications after the acute infection subsides, depending on the extent and severity of illness affecting different cell types and organs.[3] Such data would be essential to formulate management approaches to patients who require medical care after surviving the COVID-19 infection.

In recent months, reports of unplanned patient re-attendance at medical facilities after recovery from COVID-19 infection have increased dramatically throughout the world.[4,5] Despite the abundance of journal articles published on acute COVID-19 infection, the clinical picture of post-COVID-19 recovery and its sequelae are still under investigation. Currently, clinicians can only deduce from case reports and/or observational studies, while larger prospective studies are only now starting.[6] In addition, extrapolating from the clinical observational studies on sequelae of severe acute respiratory syndrome (SARS), which is also a coronavirus, may provide insight to understand and manage post-COVID-19 sequelae. Patients who recovered from SARS had radiologic, functional, and psychological abnormalities of varying degrees, as well as end-organ damage dysfunction, including cardiopulmonary and hepatobiliary systems.[7–11] In light of the medical complication observed among SARS survivors, Perrin et al.[12] have proposed the possibility of a post-viral syndrome to manifest following COVID-19 infection, similar to the chronic fatigue syndrome/myalgic encephalomyelitis-like illness that developed in some patients after recovery from the acute SARS episode. Here, we aim to review current literature systemically on the clinical sequelae in the recovery of COVID-19 survivors, as well as the dynamic changes and severity of these sequelae.

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Methods

A literature search was performed in PubMed, MEDLINE, and Google Scholar databases using the following search strategy: "post-COVID-19 OR COVID-19 sequelae OR COVID-19 complications." Articles were identified for potential inclusion during three stages of assessment by two members of the research team: title, abstract, and full text. In addition to the database search strategy, relevant articles previously known by the authors were added, and the reference lists of identified articles were screened to find additional articles that also satisfied the search criteria. Articles included are original research articles encompassing cross-sectional, cohort, case-control, interventional, and randomized-control studies. Case reports and expert opinions were excluded. Only English language peer-reviewed journal papers were considered. There was no limitation for publication year.

Symptoms and complications arising after COVID-19 infection

From our literature review, only a few studies with mostly limited sample size have been published on COVID-19 sequelae, with the longest follow-up duration of 6 months after discharge from hospital (Table 1). Persisting symptoms such as fatigue and dyspnea were commonly reported in patients following hospital discharge, as well as impaired pulmonary function and chest image abnormalities.

A study in Italy had monitored 143 individuals at routine visits 7 weeks after recovering from COVID-19 and found that 53% of the patients reported fatigue, 43% reported breathlessness, and 27% reported joint pain at the visit. Furthermore, up to 32.2% of patients reported having one to two persistent symptoms, while 55.2% reported at least three symptoms persisting up to an average of 36.1 days after discharge.[13] Another series of 100 patients in the United Kingdom reported fatigue in 64% of patients, breathlessness in 50% of patients, neuropsychological symptoms in 31% of patients, and new urinary incontinence in 13% of patients, persistent up to 48 days after discharge.[14] In addition to monitoring post-COVID-19 symptoms, an Italian group evaluated the laboratory parameters of 453 COVID-19 survivors in a tertiary medical center and found these patients' PaO2/FiO2 ratio, lymphocyte count, C-reactive protein, and lactate dehydrogenase levels did not differ significantly between the levels obtained during hospitalization compared to the levels at 4 weeks after discharge. The authors proposed that a long-term evaluation post-discharge is necessary to monitor for normalization of the blood tests and evaluate for the sequelae of COVID-19 which may not be clinically apparent in the acute post-recovery period.[15]

A larger ambidirectional cohort study in China by Huang et al. had followed up COVID-19 patients 6 months after their discharge from acute infection. Out of 1733 patients, 1265 patients (76%) have reported symptoms at follow-up, and the most commonly reported symptoms were fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety/depression (23%). The authors also reported significantly decreased pulmonary function in COVID-19 survivors, especially among those who were more severely ill during the acute COVID-19 infection.[16] Similar post-COVID-19 symptoms have been observed in other observational studies with shorter follow-up period.[4,17] Consistent with the commonly reported post-COVID-19 symptoms of fatigue and myalgia, Davido et al.[18] have described an increase in cases presenting with chronic fatigue symptoms post-COVID-19 infection similar to the post-viral syndrome following Epstein-Barr virus infection. These studies and our experience from SARS sequelae suggest that a proportion of COVID-19 affected patients may go on to develop a post-viral syndrome—possibly a "post-COVID-19 syndrome"—a long-term state of chronic fatigue and multi-systemic inflammatory responses, with potential long-term end-organ damages (Table 2).[19–21]

Discussion

To date, we have yet to obtain a clear clinical picture on the long-term medical problems which survivors of COVID-19 encounter after discharge from hospital. The possibility of post-COVID-19 syndrome is particularly interesting because we are facing an unprecedented pandemic. British Thoracic Society guidelines recommend that all patients who were admitted to the hospital with COVID-19 pneumonia receive clinical follow-up regardless of severity.[22] Raising awareness on post-COVID-19 sequelae is crucial to deliver prompt and informed medical care. The complexity of managing post-COVID-19 syndrome, including the affected patients' diverse pre-morbidities and multi-systemic manifestations of COVID-19 infection, calls for a multi-disciplinary team to adequately respond to the medical needs of COVID-19 survivors.

In such a scenario, we believe the internists' involvement is crucial to the evaluation and management of medical illness that these patients encounter post-COVID-19 infection. These survivors may experience a worsening of preexisting medical conditions, in addition to the COVID-19-associated physical strain and mental stress. While COVID-19 is an infectious disease primarily affecting the lungs, its survivors have reported multi-systemic complications, which encompasses virtually all branches of medicine. For patients requiring admission after recovery from COVID-19, an internist-led medical service is an efficient way to deliver multi-disciplinary care with comprehensive patient management. These patients need to be attended by physicians who are capable of managing multi-dimensional health problems and cared for by a multi-disciplinary team

Table 1. Clinical characteristics of patients with persistent symptoms after COVID-19 infection..

Study	Sample size (n)	Gender (female: male ratio)	Age, mean, or median (SD or range or IQR), y	Ethnicity (%)	Smoking status (%)	Acute COVID-19 characteristics (%)		Length of hospital stay, mean or median (SD or range), days	Post-COVID-19 follow-up time, mean or median (SD or range or IQR), days		Persistent symptoms or complications (%)	
Carfi et al.[13]	143	37.1%:62.9%	Mean: 56.5 (SD: 14.6)	Not available	None 44.1%	ICU	12.6%	Mean: 13.5 (SD: 9.7)	Days since symptom onset	Mean: 60.3 (SD: 13.6)	Fatigue	53%
					Active 10.5%	Oxygen therapy	53.8%		Days since discharge	Mean: 36.1 (SD: 12.9)	Breathlessness	43%
					Former 45.5%	Noninvasive ventilation	14.7%				Joint pain	27%
						Mechanical ventilation	4.9%					
Halpin et al.[14]	100	46%:54%	Median in ICU patients: 70.5 (range: 20–93)	White 73%, Mixed 1%, Asian 10%, Black 8%, Unknown 8%	Not available	ICU	32%	Median in ICU patients: 12	Days since discharge	Mean: 48 (SD: 10.3)	Fatigue	64%
			Median in ward patients: 58.5 (range: 34–84)			Oxygen therapy	78%	Median in ward patients: 6.5			Breathlessness	50%
						Noninvasive ventilation	30%				Neuropsychological Symptoms	31%
						Mechanical ventilation	1%				New continence problem (bowel and bladder)	13%
Rovere-Querini et al.[15]	453	68%:32%	Mean: 59 (range: 49–68)	Not available	Not available	Requiring hospitalization	80%	Not available	Days since discharge (hospitalized cohort)	Median: 28 (range: 24–38)	No significant abnormalities found in PaO2/FiO2, lymphocyte counts, LDH, and CRP	Not available
						Discharged from ED	20%		Days since discharge (ED discharge cohort)	Median: 27 (range: 21–41)		
Huang et al.[16]	1733	52%:48%	Median: 57.0 (range: 46.0–65.0)	Not available	None 93%	ICU	4%	Median: 14 (range: 10–19)	Days since discharge	Median: 153 (range: 146–160)	At least one post-COVID symptom	76%
					Active 4%	Oxygen therapy	68%				Fatigue or muscle weakness	63%
					Former 3%	Noninvasive ventilation	6%				Sleep difficulties	26%
						Mechanical ventilation	1%				Anxiety/depression	23%
Xiong et al.[17]	538	45.5%:54.5%	Median: 52 (IQR: 41–62)	Not available	Not available	General	61.5%	Not available	Days since discharge	Median: 97 (IQR: 95–102)	At least one post-COVID symptom	49.6%
						Severe	33.5%				Fatigue	28.3%
						Critical	5%				Myalgia	4.5%
Rokadiya et al.[4]	25	60%:40%	Median: 73 (range: 58–82)	White 42%	Not available	Not available		Median: 6 (range: 1–9)	Days since discharge	Median: 10 (range: 6–15)	Breathlessness	52%

COVID-19: coronavirus disease 2019; SD: standard deviation; IQR: interquartile range; ICU: intensive care unit; LDH: lactate dehydrogenase; CRP: C-reactive protein; ED: emergency department; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen.

Table 2. Summary of reported post-COVID-19 symptoms and complications by organ systems.

Organ system	Post-COVID-19 symptoms	Post-COVID-19 complications
Pulmonary	Chronic cough, breathlessness	Impaired pulmonary function, hypoxia
Cardiac	Reduced effort tolerance, chest pain, palpitation	Myocardial inflammation, ventricular dysfunction, tachyarrhythmias
Neurological	Olfactory and gustatory dysfunction, sleep dysregulation, altered cognition, memory impairment	Cognitive decline, peripheral neuropathy
Musculoskeletal	Myalgia, joint pain	Post-viral chronic fatigue syndrome, corticosteroid-induced myopathy, worsening of existing condition
Gastrointestinal and hepatobiliary	Diarrhea, vomiting, difficulty swallowing, abdominal discomfort	Gastroesophageal reflux, irritable bowel syndrome, hepatic injury with raised liver enzyme
Renal and urological	Low urine output, fluid retention, incontinence, urinary frequency	Acute kidney injury
Endocrinological and metabolic	Orthostatic hypotension, malaise	Subacute thyroiditis, adrenal insufficiency
Hematological	Easy bruising, lower limb swelling	Immune thrombocytopenic purpura, antiphospholipid syndrome, venous thromboembolism
Dermatological	Alopecia, skin rash	Contact dermatitis
Mental health	Sleep difficulties, decreased appetite, low mood	Anxiety disorder, major depression disorder, post-traumatic stress disorder

COVID-19: coronavirus disease 2019.

including nurses, physiotherapists, occupational therapists, and medical social workers who are trained to provide psychosocial support for patients and families. Similar approach had been recommended in managing critically ill COVID-19 patients with delirium.[23] In our institution's multi-disciplinary approach, internists perform the initial clinical and functional assessment of the patients, manage health problems that arise from the specific evaluations, and provide additional diagnostic services whenever indicated. The multi-disciplinary team designs and implements the individualized management plan emphasizing on the psychosocial well-being of the patients and family members. The forging of close interdisciplinary ties enhances workflow and care delivery processes, as well as strengthening crucial collegial support.

To this aim, an internist-led, multi-disciplinary care service at Singapore General Hospital, one of the largest tertiary centers in Southeast Asia, has initiated a prospective cohort study to specifically evaluate the medical illnesses and psychosocial impacts faced by COVID-19 survivors. The study population will include all patients admitted to Singapore General Hospital, Department of Internal Medicine, from 1 August 2020 to 31 July 2021 for acute medical illnesses. We aim to evaluate the demographics, clinical characteristics, hospitalization course, and psychosocial concerns between admitted patients who had recovered from COVID-19 within 6 months and admitted patients without previous COVID-19 infection. We believe this study will enhance our understanding of post-COVID-19 syndrome and its associated medical complications, which is vital in minimizing long-term morbidity and mortality.

This current review has its limitations. First, the number of clinical studies on patients who recovered from COVID-19 is limited. Second, the available studies are heterogeneous in setup protocols, study designs, patient selections, and outcomes measured, prohibiting firm conclusions to be drawn based on these studies. Larger, prospective studies are necessary to further evaluate the clinical course and develop tailored management strategies for the COVID-19 sequelae.

Conclusion

Few studies have described the long-term consequences of COVID-19 in patients after hospital discharge or identified the potential risk factors associated with these consequences, but emerging evidence has suggested the possible existence of a "post-COVID-19 syndrome"—a multi-systemic, post-infection, inflammatory condition after COVID-19 infection. To optimize their care, it is important to attend to these post-COVID-19 patients with multi-disciplinary, team-based approach. Further long-term follow-up studies on the persistent symptoms, organ dysfunction, and psychosocial problems of re-admitted COVID-19 patients are urgently required to better understand, recognize, and assess the post-COVID-19 syndrome and to ensure that the morbidity and mortality of post-COVID-19 infection remain as low as possible.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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