The Open COVID Journal

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OPINION ARTICLE

It is Time to Recognize the Severity of Post-Acute Sequelae of COVID-19 (PASC)

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Abstract:

Introduction:

Post-acute sequelae of COVID-19 (PASC), often referred to as "long COVID" or "COVID long hauler" syndrome, is an increasingly recognized subacute to chronic manifestation of COVID-19. The incidence of PASC has been estimated to be 10-30% of all infections.

Methods:

We reviewed the literature on PASC to determine the frequency of the most severe forms of PASC based on medical complications, degree of disability, and ability to return to work following COVID-19.

Results:

We found that the reported frequency of the most severe forms of PASC ranges from 6-18%, and is higher among hospitalized patients and among older patients. Given the degree of morbidity, mortality, and strain to health systems, increasingly attributed to PASC, we advocate that PASC be recognized as a severe manifestation of COVID-19.

Conclusion:

Recognizing PASC as a severe manifestation of COVID-19 could help mobilize attention and resources to this important diagnosis.

Keywords: COVID-19, Long COVID, Post-acute sequelae of COVID-19, PASC, Long hauler, Manifestation.

Article History	Received: May 23, 2022	Revised: June 29, 2022	Accepted: August 5, 2022

1. INTRODUCTION

Early in the pandemic, SARS-CoV-2 infection was recognized as causing a range of illness severity, from asymptomatic to profound critical illness and death. Given the prominence of respiratory disease, efforts to stratify disease severity focused on oxygenation, lung injury, and hospitalization. Additionally, severe end organ injury was occurring outside of the pulmonary system. Non-pulmonary manifestations, such as acute kidney injury, myocardial infarction, arrhythmia, thromboembolism, diabetic keto-acidosis, and stroke also occurred at alarming numbers [1 - 8]. Many patients suffering from these non-pulmonary manifestations of COVID-19, were not classified as having "severe" disease by respiratory support definitions. We reported that up to 60% of patients hospitalized with "moderate" COVID-19 suffered from at least one of these complications while hospitalized [8, 9]. These findings have been mirrored by many other groups and COVID-19 is now recognized as more than pure respiratory infection [10]. Over time, another group of patients has been overlooked by attempts to categorize "severe" COVID-19, those with Post-Acute Sequelae of COVID-19 (PASC). Here, we intend to present an overview of the frequency and severity of PASC that we believe justifies recognition as a severe manifestation of COVID-19.

A major limiting factor in characterizing the frequency and severity of PASC is the lack of a clear unifying clinical definition. The World Health Organization (WHO) has put forth a case definition that includes a number of signs or symptoms occurring for more than 2 months following

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COVID-19 infection, but this definition is quite general and yet to be agreed upon by other organizations [11]. Our understanding of PASC is limited by uncertainty regarding the underlying pathogenesis of its manifestations, likely heterogeneity of its pathogenesis, and a lack of an agreed definition of the syndrome [12]. PASC pathogenesis is complex and likely multifactorial, involving multiple mechanisms and organ systems, and possibly linked to the multi-organ system involvement of acute COVID-19. Proposed mechanisms include direct neuro-invasion, autonomic dysregulation, immune dysregulation, endothelial injury, clotting dysregulation, and autoimmune phenomena [13 - 15]. These divergent mechanisms may explain the heterogeneous phenotype of PASC. Other evolving variables add complexity to this analysis, including variations in the clinical manifestations of SARS-CoV-2 variants, the uncertain impact on PASC by vaccinations and the rapid rise in short-term natural immunity during each wave of infection. Nonetheless, due to the enormity of the potential burden on health systems and individuals at risk, there is value in providing informed estimates of the incidence and severity of PASC as more evidence accumulates.

2. METHODS

To better understand and describe the incidence and the severity of COVID-19, we performed a review of the literature focused on the impact of PASC over three domains, individual patients, larger populations, and economic impacts. After reviewing the severity of PASC in these domains, we briefly review the available literature on the treatment and prevention of PASC. This review is not a systematic analysis but a review of a large and diverse sample of multi-centered cohort studies with 6 months or more of follow up, which report PASC as a severe manifestation of COVID-19. To estimate the prevalence of "severe PASC" we first defined severe PASC as any new diagnosis of a chronic medical condition, cognitive dysfunction, hospitalization, or death. To capture the severe economic impacts of PASC, we also included PASC that prevented return to work. We then performed a focused review of representative studies describing PASC that included details on the above definition of severe PASC and estimated incidence of severe PASC in each study.

3. RESULTS AND DISCUSSION

3.1. PASC Severity at the Individual Level

The estimated incidence of PASC among previously hospitalized patients is alarmingly high, potentially greater than 50% and highest in older patients and those with co-morbidities [1 - 3]. Despite the growing body of observational literature, estimating a precise incidence is limited by lack of a unified definition as well as limitations identifying PASC in patients who were never hospitalized. One group surveyed a cohort of patients in Southern California and found as many as one-third of patients reporting symptoms of PASC following COVID-19 diagnosis [16]. In this group, a wide array of symptoms were present in several organ systems including constitutional, neurological, sensory, respiratory, gastrointestinal, musculoskeletal, and dermatological. The most common symptoms at the two-month mark were fatigue, dyspnea, ageusia, anosmia, and myalgia/arthralgia. Another study of non-hospitalized patients aged 16-30 years with mild to moderate COVID-19, 52% had persistent symptoms after 6 months of illness, underscoring the high prevalence of PASC in both hospitalized patients at higher risk of severe illness and in younger, non-hospitalized patients [15].

Large studies describing the morbidity and mortality associated with PASC are accumulating. One such study, including 267,000 patients, found 57% of patients with SARS-CoV-2 had one or more symptoms after 6 months. Cognitive dysfunction occurred in 7.8% overall, with a higher incidence and severity in the elderly [2]. Two large studies evaluating PASC among patients in the US Department of Veterans Affairs medical system analyzed over 70,000 US veterans who survived acute COVID-19 and assessed for excess morbidity and mortality in a variety of organ systems [17, 18]. They found COVID-19 survivors had a 46-73% increased hazard for death as well as excess burden of disease in respiratory, cardiovascular, gastrointestinal, nervous, metabolic and mental health outcomes. They also demonstrated objective laboratory evidence of persistent disease and excess use of opioid analgesia, benzodiazepines, antidepressants, and antihypertensive medications in COVID-19 survivors. These findings remained significant when comparing COVID-19 survivors to influenza survivors. A subsequent study looked at cardiovascular outcomes following COVID-19 [18]. They found significant excess morbidity among survivors of COVID-19 in all measured categories of cardiovascular disease, including ischemic heart disease, inflammatory heart disease, arrhythmia, heart failure, venous thromboembolism, and cerebrovascular disease. Despite the heterogeneity in these studies, the trend is clear. On review of studies for the most severe manifestations of PASC we found an estimated incidence of severe PASC among previously hospitalized patients ranged from 5-18% [1 - 7] (Table **1**).

Table 1. Study related to the outcomes and estimated rate of severe PASC.

Author	Cohort Size & Characteristics	Time Period	Overall PASC Incidence	Estimated Severe PASC
Zhang [1]	2,433	12 mos	50%	12%
Taquet [2]	273,618	6 mos	57%	7-11%
Groff [3]	250,000	6 mos	55%	15-18%
Ziauddeen [4]	3,000	6 mos	64-80%	17%
Logue [5]	237	6 mos	30%	6%
Bull-Otterson [6]	353,164	30 mos	21-27%	8-11%
Wulf Hanson [7]	1.3M	12 mos	3.7%	15%

3.2. PASC Severity at the Population Level

PASC poses a significant threat to entire healthcare systems and populations recovering from spikes in acute COVID-19. A systematic review including 57 studies and more than 250,000 patients on 3 continents demonstrated the massive burden of disease caused by PASC [3]. They found at least one symptom was present in more than half of patients at

all time points studied, 1 month, 2-5 months, and >6 months post SARS-CoV-2 infection. Symptoms were experienced in all organ systems studied, the most common in each group were oxygen requirement, functional impairment, fatigue, difficulty concentrating, and anxiety. Mitigating these widespread impacts of PASC requires increased recognition, allocation of resources, and support for patients, clinicians, and health professionals taking care or PASC patients.

3.3. PASC Severity at the Economic Level

PASC related debility also likely has significant and severe economic impacts. In one study from China with one year of follow-up, 12% of previously hospitalized patients with SARS-CoV-2 had not returned to work after 12 months [1]. More worrisome is a UK survey of over 3,000 patients with PASC that revealed that 64-80% of patients had decreased ability to work or perform usual duties, 37% lost income, and 17% reported complete inability to work due to lingering symptoms following COVID-19 infection [2, 4]. These serious consequences extend beyond medicine and could impact entire global economies.

3.4. Opportunity for Intervention

Despite the striking morbidity and mortality associated with PASC, the underlying pathogenesis and pathophysiology of PASC remain elusive. Given the multisystem manifestations of acute COVID-19, PASC may also be a collection of pathophysiologically distinct syndromes that have yet to be distinguished. The complex nature of PASC has also made treatment strategies difficult to establish. Current treatment modalities are focused on evaluation for medical conditions with symptomatic overlap, supportive care, symptomatic management, and return to functional status [19]. COVID-19 vaccination appears to offer protection against PASC and may even be a treatment strategy for those suffering from PASC, underlying the urgent need to make vaccination available to all populations [20 - 22]. In addition to vaccination, other treatments for acute COVID-19 have been extensively studied, such as passive immunity, immunomodulation, and direct antivirals [23]. Despite this extensive study, PASC is rarely if ever, considered a study endpoint for the efficacy of these treatments. Significant research is still needed to identify the impact of established COVID-19 treatments on PASC as well as novel treatment strategies directed at PASC. Recognizing PASC as a severe manifestation of COVID-19 is central to understanding the underlying pathophysiology, identifying optimal treatments, supporting PASC patients, and allocating appropriate resources to this morbid diagnosis.

CONCLUSION

In summary, PASC is a poorly understood disease process that is a significant cause of morbidity and mortality across all survivors of acute COVID-19. Its impacts extend from individual patients to communities, health care settings, and whole economies. Despite these impacts, PASC is not generally recognized as a "severe" manifestation of COVID-19. The current literature supports an estimate of overall incidence of severe PASC in 6-18% of all patients with COVID-19 infection, with higher frequencies in post-hospitalized patients and elderly patients. In order to give PASC the recognition necessary to be understood, prevented, controlled, and treated, it must be recognized as a severe manifestation of COVID-19.

LIST OF ABBREVIATION

PASC = Post-Acute Sequelae of COVID-19

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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