

POST-COVID SEQUELAE: THE BUMMOCK OF COVID ICEBERG

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Received: 24 February 2022, Revised and Accepted: 13 September 2022

ABSTRACT

Objective: Coronavirus disease of 2019 (COVID-19) is a highly transmissible and pathogenic infection caused by severe acute respiratory syndrome, which resulted in a global pandemic and a significant loss of human life. The newer variants of concern are evolving even with the broadening vaccine immunity. Much of the clinical course remains uncertain especially the possible long-term health consequences. It is observed that there is an inter-individual variability in the occurrence of these post-COVID symptoms.

Methods: A prospective observational survey was conducted to demonstrate the post-COVID-19 manifestations and to identify if there is any association of these manifestations with the disease severity and presence of comorbidities.

Results: About 85% of our study subjects reported post-COVID manifestations of varying degrees. Fatigue was the most common post-COVID manifestation reporting to 56.36%. This was followed by body ache (43.3%) and myalgia (36.81%). The least observed manifestations were myocarditis (1.81%), heart attack (1.36%), and vomiting (1.36%).

Conclusion: An association between the severity of COVID disease and comorbidities was identified. The surface plot graph signified the existence of a positive association between the post-COVID manifestations with the severity of disease and the presence of comorbidities. The functional outcomes of the subjects after recovery were assessed using a post-COVID functional status scale.

Keywords: Coronavirus, Polymerase chain reaction, COVID-19, Functional status, Comorbidity, Fatigue.

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INTRODUCTION

Latest threat to the global healthcare setting – the highly contagious coronavirus disease 2019 (COVID-19) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has spread throughout the world affecting more than 200 countries and millions of people, with a discouraging mortality and morbidity rates [1]. The World Health Organization officially declared COVID-19 as a pandemic on March 11, 2020, and as of now 248 million COVID-19 cases have been reported worldwide and the total number of deaths ranging at about 5 million since the pandemic [2]. A considerable percent of affected subjects are asymptomatic; however, a wide range of symptoms occur, ranging from fever, cough, and body ache to critical conditions such as pneumonia and respiratory distress [3,4]. The transmission of SARS-CoV-2 is through infected respiratory droplets through direct or indirect contact [5]. At present, nucleic acid amplification methods represent the gold standard for the diagnosis of COVID-19 with several RT-PCR-based tests approved by different regulatory agencies. These, together with clinical and radiological investigations have significantly enhanced the diagnosis of COVID-19 [6,7]. Management of COVID-19 includes antiviral agents, antibiotics, corticosteroids, antibodies, and convalescent plasma transfusion [8]. Several COVID-19 vaccines, including the Pfizer-BioNTech and Moderna vaccines, have been concocted to stimulate an immune response. Since January 2020, vaccine development has been accelerated through unparalleled collaboration by multinational pharmaceutical industry and governments [9].

The presumption that COVID-19 ends with the resolution of symptoms and a negative test report is not always true. The symptomatic patients are like the hummock of an iceberg, whereas the lingering aftermaths of the disease can be compared to the bummock. The post-COVID syndrome, also called long COVID, is continuance of symptoms beyond viral clearance and newer development of symptoms or exaggeration of

chronic diseases within a month after initial clinical and virological cure of the disease with a viral etiology. The most common symptoms include fatigue, myalgia, dyspnea, cognitive dysfunction, and other conditions, which have an impact on everyday functioning. These symptoms may persist from the initial infection, following initial recovery from an acute COVID-19 episode, or new onset [10]. Kamal *et al.* [11] have described in a study at Egypt that these post-COVID manifestations occur in individuals with certain risk factors. In this study, we aim to elucidate the post-COVID symptoms in our subjects in the southern parts of India and to determine if there is any association of the same with the individual risk factors such as age, disease severity, and presence of other comorbidities. Furthermore, the study also prevails to address the spectrum of the functional outcomes of the subjects using an ordinal scale coined by Klok *et al.*, [12] called the post-COVID functional status (PCFS) scale.

METHODS

A prospective cross-sectional study was done in 220 subjects who had COVID-19 infection. Subjects received a well-structured e-survey form using forms app and required data were collected. The survey questionnaire was peer reviewed and validated by experts. The subjects who tested negative after COVID-19 and who satisfied inclusion criteria were only included in the study. The data collected includes patient's demographics, COVID severity, and post-COVID manifestations. At the beginning of the questionnaire, the respondents were asked if they would accept to participate in the study and at the end, a patient consent was also attached so as to obtain their permission for using these data generated in our survey. Through our study, the post-COVID manifestations were analyzed and it has been linked with severity of COVID and with other comorbidities of the patient. COVID-19 disease severity of subjects were denoted as mild, moderate, severe, and critical illness based on the WHO COVID-19 technical guidelines [13]. Statistical

analysis was carried out using linear model and the data produced was plotted in a response surface plot with the help of Design Expert version 10 (Stat-Ease Inc. Minneapolis, MN, USA). A response surface plot was used to grade the severity of post-COVID-19 manifestations in patients with respect to their comorbidities and COVID severity. The independent variables of the response surface plot have been coded with following: Comorbidity (1=no comorbidity and 2=presence of any other disease), severity of COVID-19 (0.1=mild, 0.2=moderate, 0.3=severe), and severity of post-COVID-19 manifestations (1=mild and 2=severe). The functional status outcomes were accessed using PCFS ordinal scale.

RESULTS

Two hundred and twenty COVID-19 recovered subjects were involved in the study. Out of them, 113 were male and 107 were female. The average age of the subjects was 42.17 years ranging from 19 to 80 years. The report suggests that only 44.09% (97) of the subjects were healthy without any comorbidities and 55.90% (123) of the subjects had more than one comorbidity. The most prevalent comorbidity was hypertension, followed by type II diabetes mellitus, hyperlipidemia, heart disease, respiratory disorders, kidney disease, and dermatologic problems. Beside these, there was a case of Parkinsonism, hypothyroidism, and stroke each (Table 1).

The analysis of COVID-19 disease severity was done by broadly classifying them into mild, moderate, and severe category based on the WHO technical guidelines. The mild category included 56.3% (124), who had mild symptoms or were asymptomatic with home quarantine. Moderate category included 24.09% (53) of the subjects who had dyspnea with or without oxygen therapy. The third severe category had the lesser percentage of subjects, 19.54% (43) that had severe COVID-19 infection requiring ventilator or intensive care support.

The study set out with the aim of assessing the post-COVID manifestations, we observed that 85% had post-COVID manifestations, of which 62.27% (137) had mild manifestations, which resolved eventually, or on treatment with NSAIDs, 22.72% (50) had severe manifestations that affected organ systems and required hospitalization.

Table 1: Demographics of the subjects

Age group (years)	Number of cases (n)	Percentage
19-35	98	44.54
36-50	72	32.72
51-65	27	12.27
Gender		
Female	107	48.63
Male	113	51.36
Comorbidity		
No comorbidity	97	44.09
≥1 Comorbidity	123	55.90
Comorbidities		
Hypertension	84	38.18
Diabetes	61	27.72
Hyperlipidemia	59	26.81
Heart disease	45	20.45
Respiratory disease	33	15
Kidney diseases	9	4.09
Dermatologic diseases	2	0.90
Parkinsonism	1	0.45
Hypothyroidism	1	0.45
Stroke	1	0.45
Severity of COVID-19		
Mild	124	56.36
Moderate	53	24.09
Severe	43	19.54
Severity of post-COVID manifestations		
No manifestations	33	15.01
Mild	137	62.27
Severe	50	22.72

It is also noteworthy that only 15.01% (33) of the total subjects were emancipated from post-COVID manifestations. Among all the post-COVID manifestations reported fatigue was the most commonly observed on prevailing 56.36% (124).

The other mild manifestations observed were body ache 43.3% (96), myalgia 36.81% (81), anosmia 28.18%(62), chest pain 26.81%(59), arthralgia 25.45% (56), ageusia 24.54% (54), cough 23.63% (52), increased post activity rapid breathing 22.27% (49), dyspnea 17.72% (39), stress 15.9% (35), impaired memory 11.81% (26), sleep disturbances 9.55% (21), vertigo 7.72% (17), throat pain 7.72% (17), headache 15.45% (34), diarrhea 5% (11), sweating 2.72% (6), vomiting 1.36% (3), and newly diagnosed hypertension 3.63% (8). Psychiatric symptoms such as feeling of low 34.54% (76), anxiety 25.54% (56), unhappiness 22.27% (49), and stress 15.90% (35) were also present in modest number of subjects. However, 22.72% (50) subjects had severe manifestations, which affected organ functions such as pulmonary fibrosis 6.81% (15), pneumonia 7.72% (17), acute respiratory distress syndrome (ARDS) 1.81% (4), myocarditis (1.81%) (4), and heart attack 1.36% (3) (Fig. 1).

The PCFS tool demonstrated that 45.45% (100) of the survey population were found to be categorized as grade 0, with no functional limitations, and 0.50% (1) had grade 4 with severe functional limitations (Fig. 2).

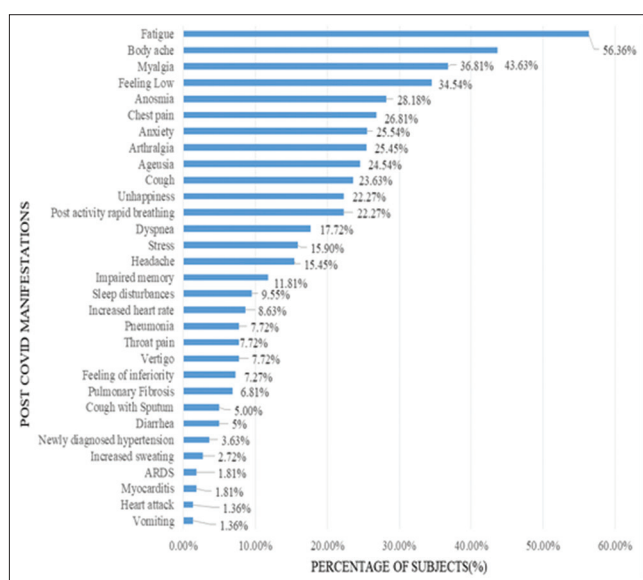


Fig. 1: Post-COVID manifestations

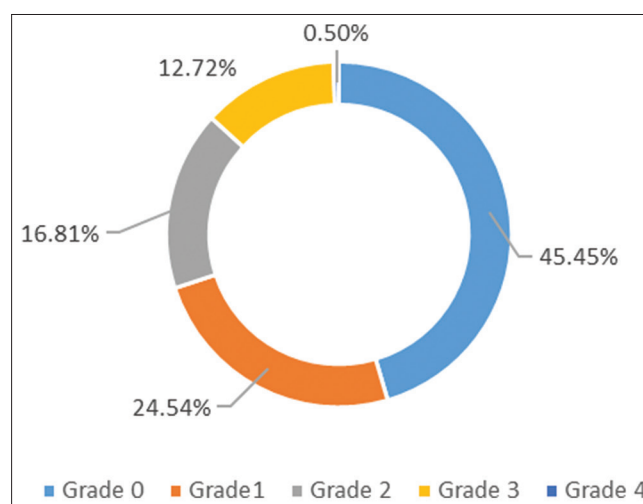


Fig. 2: Distribution of subjects based on PCFS scale

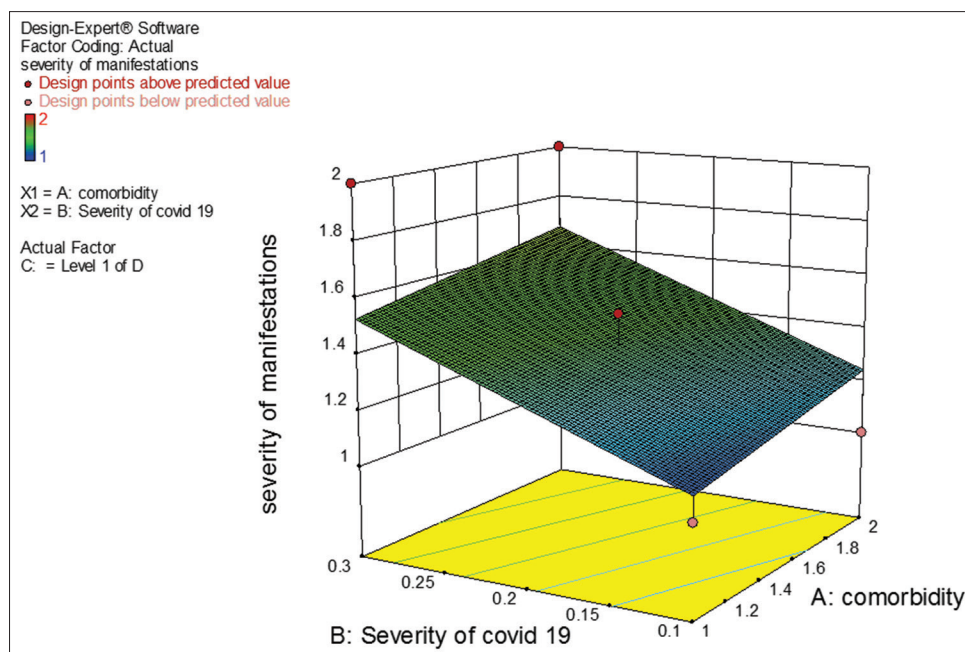


Fig. 3: Response surface plot showing the relation between comorbidities, the severity of COVID-19, and severity of manifestations post-COVID-19

There exists a possible relationship between the presence of comorbidities and the severity of COVID-19 infection with the post-COVID manifestations. The severity post-COVID manifestations were more inclined to the severity of COVID infection than the presence of comorbidities (Fig. 3).

DISCUSSION

This prospective study findings suggest that post-COVID-19 manifestations were observed in about 85% of the all the COVID-19 recovered subjects. A wide range of symptoms and conditions were recorded in the subjects that varied from a low-critical symptom like headache or fatigue to more critical conditions such as ARDS, renal failure, and pulmonary fibrosis. Most post-COVID-19 manifestations reported were mild, which did not need hospitalization. Fatigue was most commonly observed followed by myalgia and anosmia. There are several previous conclusive reports that fatigue and other physical illness were the most prominently reported symptoms in convalescent COVID-19 [14-16].

Several psychiatric symptoms such as feeling of low, unhappiness, anxiety, and loss of sleep were also prominent which might be due to psychosocial stress or central nervous system effects of cytokines [17]. There are multiple lines of evidence that suggests that COVID-19 has a serious risk of psychiatric sequelae [18,19]. Taquet *et al.* [20] have implicated in their retrospective study that the initial 6 months of COVID-19 diagnosis is the perilous time of developing neurological and psychiatric disorders. About 22% percentage of the subjects had severe post-COVID manifestations such as ARDS, pneumonia, pulmonary fibrosis, and myocarditis which had organ system involvement and required subsequent hospitalization. These severe complications can be attributed to the over expression of human ACE2 receptor in various tissues especially in the vessels giving the virus access to the hematologic system. The cytokine storm in the systemic hyper inflammatory pathway also culminates in micro vascular thrombosis, endothelial inflammation, and multiple organ failures [21].

Klok *et al.* [12] had proposed an ordinal tool to measure the functional status over time post-COVID-19 and have termed it PCFS scale. Using the PCFS scale, the functional limitations of subjects are graded from 0 to 4. Grade 0 indicated no functional limitations. Grades 1, 2, 3, and

4 indicated subjects with negligible, slight, moderate, and severe functional limitations respectively. We observed that 45.45% of our subjects were graded 0, which is that they were physically fit. This could have been partly due to the use of electronic survey forms, which is accessed and used majorly by the younger population. It is significant that 0.50% of the subjects had severe post-COVID functional limitations (grade 4) that made them dependent on assistance in everyday life due to certain symptoms of pain, anxiety, or depression. This might be due to the severe post-COVID manifestations that the subjects suffer which resulted in his/her immobility.

The severity of COVID-19 disease was classified into three categories based on the WHO Technical guidelines [13] as follows: mild cases that had symptoms and have been treated at home without the need for oxygen therapy, moderate cases which suffered from difficult breathing and needed oxygen therapy at hospitals, and severe cases that had been hospitalized with ICU or ventilator support.

The post-COVID manifestations were also grouped into three categories based on severity. The highest was the category with mild symptoms, which got better with over the counter medications or other non-pharmacological interventions. Few critical post-COVID manifestations were also recorded which had organ system involvement and required hospitalization with medical interventions. The severity of COVID-19 disease was found to be associated with the severity of post-COVID manifestations. This is consistent with the findings of Huang *et al.* [22] and Taquet *et al.* [23] which conclude that the patients who were more severely ill during their COVID-19 disease period had more severe complications following disease; however, these findings are conflicting with Sykes *et al.* [24]. The presence of comorbidities also had positive association with the severity of post-COVID manifestations in our study results. These findings corroborates with the earlier findings of Tenforde *et al.* [25] that having chronic medical conditions are a risk factor for convalescent symptoms of COVID-19. It is therefore likely that there exists a relationship between the severity of post-COVID manifestations with the severity of COVID-19 disease and the presence of comorbidities. The findings also reveal that severity of post-COVID manifestations was more dependent and inclined to the severity of the disease than the presence of comorbidities. Certain limitations encountered were that the study involved self-reported data rather than qualitative research; therefore, the data had a limitation to be

independently verified. Furthermore, a longer duration of study could elucidate the full-term lingering effects of COVID-19.

CONCLUSION

The myriad of long-term implications of COVID-19 is a rising concern with the recurrent variants and high spread rate of this novel disease. In this study, most of the subjects recovered from COVID-19 experienced several lingering manifestations which ranged from mild symptoms such as fatigue, body ache and myalgia to more critical manifestations such as pulmonary fibrosis, ARDS, pneumonia, and myocarditis. The most reported symptoms were mild such as fatigue, body ache, and myalgia. Several neuropsychiatric symptoms such as depression, anxiety, and memory loss were also reported at a higher percentage. Most of the reported manifestations were mild reversible symptoms that could be relieved without medical interventions such as fatigue and headache, which could be related to COVID-19 symptoms. The severity of manifestations was correlated to the severity of the infection, which also was related to the presence of multiple comorbidities. At present, convalescent COVID remains enigmatic, it is vital that clinical research continues to explore the conditions that might be precipitated after recovery from coronavirus infection. In addition, the need for continuous counseling of patients is important not only for maintaining good adherence to the medications but also for spotting early warning signs of the bummock.

CONFLICTS OF INTEREST

No potential conflicts of interest.

REFERENCE

- Fauci AS, Lane HC, Redfield RR. Covid-19-navigating the uncharted. *N Engl J Med* 2020;382:1268-9. doi: 10.1056/NEJMe2002387, PMID 32109011
- Uvais NA, Moideen S, Hafi B, Rajagopal S, Maheshwari V, Gafoor TA. Insomnia among active patients with COVID-19: A cross-sectional study. *Chronobiol Med* 2021;3:31-4. doi: 10.33069/cim.2021.0002
- Lovato A, De Filippis C. Clinical presentation of COVID-19: A systematic review focusing on upper airway symptoms. *Ear Nose Throat J* 2020;99:569-76. doi: 10.1177/0145561320920762, PMID 32283980
- Hui KP, Cheung MC, Perera RA, Ng KC, Bui CH, Ho JC, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: An analysis in *ex-vivo* and *in-vitro* cultures. *Lancet Respir Med* 2020;8:687-95. doi: 10.1016/S2213-2600(20)30193-4, PMID 32386571
- Leap J, Villgran V, Cheema T. COVID-19: Epidemiology, pathophysiology, transmission, symptoms. *Crit Care Nurs Q* 2020;43:338-42. doi: 10.1097/CNQ.0000000000000319
- Falzone L, Gattuso G, Tsatsakis A, Spandidos DA, Libra M. Current and innovative methods for the diagnosis of COVID-19 infection (Review). *Int J Mol Med* 2021;47:100. doi: 10.3892/ijmm.2021.4933, PMID 33846767
- Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents* 2020;55:105955. doi: 10.1016/j.ijantimicag.2020.105955, PMID 32234468
- Krammer F. SARS-CoV-2 vaccines in development. *Nature* 2020;586:516-27. doi: 10.1038/s41586-020-2798-3, PMID 32967006
- Park KS, Sun X, Aikins ME, Moon JJ. Non-viral COVID-19 vaccine delivery systems. *Adv Drug Deliv Rev* 2021;169:137-51. doi: 10.1016/j.addr.2020.12.008, PMID 33340620
- Mahmud R, Rahman MM, Rassel MA, Monayem FB, Sayeed SK, Islam MS, et al. Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLOS One* 2021;16:e0249644. doi: 10.1371/journal.pone.0249644, PMID 33831043
- Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. *Int J Clin Pract* 2021;75:e13746. doi: 10.1111/ijcp.13746, PMID 32991035
- Klok FA, Boon GJ, Barco S, Endres M, Geelhoed JJ, Knauss S, et al. The post-COVID-19 functional status scale: A tool to measure functional status over time after COVID-19. *Eur Respir J* 2020;56:2001494. doi: 10.1183/13993003.01494-2020, PMID 32398306
- World Health Organization. Clinical management of COVID-19 (Interim Guidance); Published May 27, 2020. Geneva: World Health Organization; 2020. Available from: <https://www.who.int/publications-detail/clinicalmanagement-of-covid-19> [Last accessed on 2021 Nov 23].
- Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603-5. doi: 10.1001/jama.2020.12603
- Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: A single-centre longitudinal study. *Clin Microbiol Infect* 2021;27:89-95. doi: 10.1016/j.cmi.2020.09.023, PMID 32979574
- Goërtz YM, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FV, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: The post-COVID-19 syndrome? *ERJ Open Res* 2020;6:00542-2020. doi: 10.1183/23120541.00542-2020, PMID 33257910
- Steardo L Jr., Steardo L, Verkhatsky A. Psychiatric face of COVID-19. *Transl Psychiatry* 2020;10:261.
- Sher L. Are COVID-19 survivors at increased risk for suicide? *Acta Neuropsychiatr* 2020;32:270. doi: 10.1017/neu.2020.21, PMID 32364491
- Cénat JM, Blais-Rochette C, Kokou-Kpolou CK, Noorishad PG, Mukunzi JN, McIntee SE, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis. *Psychiatry Res* 2021;295:113599. doi: 10.1016/j.psychres.2020.113599, PMID 33285346
- Taqet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021;8:416-27. doi: 10.1016/S2215-0366(21)00084-5, PMID 33836148
- Silva Andrade B, Siqueira S, Soares WR, Rangel FD, Santos NO, Freitas AD, et al. Long-COVID and post-COVID health complications: An up-to-date review on clinical conditions and their possible molecular mechanisms. *Viruses* 2021;13:700. doi: 10.3390/v13040700, PMID 33919537
- Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet* 2021;397:220-32. doi: 10.1016/S0140-6736(20)32656-8, PMID 33428867
- Taqet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;18:e1003773. doi: 10.1371/journal.pmed.1003773, PMID 34582441
- Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: What is long-COVID and how should we manage it? *Lung* 2021;199:113-9. doi: 10.1007/s00408-021-00423-z, PMID 33569660
- Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network-United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:993-8. doi: 10.15585/mmwr.mm6930e1, PMID 32730238