Original Research Article

Causatum in Adults up till 6 months after COVID-19 Infection: A longitudinal study

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Abstract

Background: According to Centers for Disease Control and Prevention (CDC), almost 10% of patients with COVID-19 infection experience symptoms beyond 3 to 4 weeks. This has been termed as "Long Covid". Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience more than four weeks after first being infected with the virus that causes COVID-19. Even people who did not have symptoms when they were infected can have post-COVID conditions. These conditions can have different types and combinations of health problems for different lengths of time. **Material and Methods:** A longitudinal prospective cohort study was conducted in adults between 18-70 years of age with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who presented at the dedicated COVID hospital associated with RajarshiDashrath Autonomous State Medical College, Ayodhya, Uttar Pradesh. COVID-19 symptom data were obtained at the time the patients presented at the hospital with symptoms or contact history. A total of 400 participants with experience of COVID-19 infection were contacted between August and November 2020 to complete a single follow-up questionnaire. **Results:** A total of 400 participants between 18- 70 years of age (mean age 46.0 years) with COVID-19 infection completed the survey. Out of these, 120 were females (30%) and remaining 280 (70%) were males. Overall, 43 (10.75%) were asymptomatic, 291 (72.75%) had mild and 66 (16.5%) had moderate or severe symptoms requiring hospitalization. The most common comorbidities (n=180) observed were Diabetes (n= 120, 66.67%), Hypertension (n=60, 33%), Chronic Obstructive Pulmonary Disease (COPD) (n=23, 13.0%), Asthma (n= 13, 7.0%), and Chronic Kidney Disease (n= 4, 2.0%). The follow up survey was completed at a median range of 169 (31-300) days after onset of symptoms in participants with COVID-19. The most common persistent symptoms reported were Fatigue (n=178, 44.5%), Dizziness on standing (n=22, 5.5%), Headache (n= 46, 11.5%), palpitations (n=49, 12.25%), cough (n=112, 28%), chest tightness (n= 59, 14.75%), difficulty in breathing (n= 77, 19.25%), myalgia (n=125, 31.25%), low grade fever (n= 100, 25.0%), loss of smell or taste (68, 17%) and diarrhoea (n=42,10.5%).**Conclusion:** This study aims at illustrating varied, unmanageable and unsure nature of long Covid shared by the recovered COVID-19 patients so that further work can be done to develop services to address these problems.

Keywords: Covid 19, Long covid ,Sequelae.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in China in December 2019. Since then, more than 90 million people have been infected after a year and over 2 million people have died with COVID-19 disease[1] . Although, innumerable efforts have been made by the scientific and medical fraternity worldwide to investigate, treat and prevent COVID-19 , the sequelae experienced by the individuals infected and recovered have yet to be ascertained in detail. A lot of authors have used different terminologies to describe the persistent effects of COVID-19 after recovery like "Persistent COVID-19 symptoms", "Post-COVID-19 manifestations", "Post COVID-19 Syndrome", "Long COVID" and "Long Haulers" etc. which is mainly used to describe Post-COVID conditions which according to Centers for Disease Control and Prevention (CDC) are a wide range of new, returning, or ongoing health problems people can experience more than four weeks after first being infected with the virus that causes COVID-19[2]. Further, CDC describes "Long COVID" as a series of symptoms that can last for weeks or months after being infected with the virus. It may singly or in combination include fatigue, brain fog, loss of smell or taste, dizziness on standing, chest pain, cough, muscle or joint pain, palpitations, headache, fever etc. The prevalence and patterning of persistent symptoms after Covid-19 is contested[3]. It has been widely accepted to be common in people with comorbidities like asthma, diabetes and autoimmune disorders[4-7] as well as in those who were hospitalized[7-9]. The exact cause of these persisting symptoms has been unknown but in most probability involve several different disease mechanisms including an inflammatory reaction with a vasculitiscomponent[10-12]. Inspite of initial guidance from numerous sources[13-17] there hasn't seems to been a congruous approach for the diagnosis, management and follow-up of patients

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with Long Covid. In this study, we aim to find answers to four key questions. Firstly, what are the most common post covid lived experiences by the patients who were infected and recovered from COVID-19 (including those who were home isolated). Secondly, how does, if at all, demographic variations like age, sex, occupation etc. affect prevalence of these long covid symptoms. Thirdly, which category of patients, either, asymptomatic, mild or moderate to severe were more affected and last but not least, what are the common comorbidities that tend to exacerbate these long covid symptoms.

Material and Methods:

Thislongitudinal cohort study was done at the dedicated COVID hospital associated with RajarshiDashrath Autonomous State Medical College, Ayodhya. The study was conducted after taking ethical clearance from the institutional ethical committee.A total of 400 adult participants aged between 18-70 years with experience of COVID-19 infection were contacted between August and November 2020 to complete a single follow-up questionnaire between 3 and 6 months after illness onset. An electronic informed consent was taken and the participants were explained about the survey and it's importance in detail. Those whose symptoms developed between May and July 2020 following an acute illness congruous with COVID-19 and those whose symptoms persisted beyond 3 weeks uptill 12 weeks were included in the study. Subjects with commonly associated comorbidities like diabetes, hypertension, chronic kidney disease (CKD), asthma and chronic obstructive pulmonary disease (COPD) were also taken into account. Phone interviews which lasted approximately 20 minutes with the consent from the participants and simultaneous notes were also jotted down.

All the participants were broadly divided into three categories according to Centers for Disease Control and Prevention (CDC)[18] viz. mild, moderate and severe. Apart from these, a fourth group i.e. those who were asymptomatic were also involved in the study. The telephonic and electronic survey involved finding and documenting details like age, sex, occupation, date of appearance of symptoms or a positive RTPCR report (in case of asymptomatic subjects with a contact history) and date of hospitalization in case of moderate to severe disease. They were also enquired about any history of common comorbidities like diabetes, hypertension, CKD, COPD and asthma. We also questioned them about the common problems they were facing after infection and recovery from COVID-19 and how it was affecting their quality of life. We made use of established techniques to strengthen the authenticity of our qualitative research[19] which included close and repeated reading of transcripts and regular discussion of emerging findings amongst team members.

Results

Table 1: shows demographic variations in the cohort study

Characteristics	N (%)			
	Total recovered (n=400)	Asymptomatic (n=43)	Mild (n=291)	Moderate to severe, req. hospitalization (n=66)
Age, mean (SD)	46.0(14.2)	48.3(18.9)	52.0(15.3)	63.8(14.6)
Male	280(70)	26(60.5)	213(73.2)	41(62.12)
Female	120(30)	17(39.5)	78(26.8)	25(37.8)
BMI, mean (SD)	27.4(5.9)	25.1(5.3)	27.8(9.7)	26.6(6.8)
Active Smoking	50(25.4)	23(16.7)	27(14.3)	0

BMI: Body Mass Index (calculated as weight in kilograms divided by height in meters squared)

Table 1 shows that out of 400 patients who recovered, 120 were females (30%) and remaining 280 (70%) were males. Out of the above, 43 (10.75%) were asymptomatic, 291 (72.75%) had mild and 66(16.5%) had moderate or severe symptoms requiring hospitalization. The mean BMI for the totally recovered was 27.4(5.9, SD), for asymptomatic cases was 25.1(5.3, SD), for mild cases was 27.8(9.7, SD) while for moderate and severe cases was 26.6(6.8, SD). The completely recovered patients showed 25.4% (n=50) active smoking, while this ratio was 16.7%(n=23) in asymptomatic, 14.3%(n=27) in mild and 0% in hospitalized patients.

Table 2: shows variations in clinical characteristics in the cohort study

Characteristics	N (%)			
Comorbidities	N=180	Asymptomatic(n=43)	Mild(n=291)	Hospitalized(n=66)
Diabetes	120(66.67)	10	30	80
HTN	60(33)	8	17	35
COPD	23(13.0)	2	9	12
Asthma	13(7.0)	2	7	4
CKD	4(2.0)	0	1	3

HTN: Hypertension, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease

Table 2 shows the percentage distribution of common comorbidities amongst the COVID-19 recovered patients. Out of the totally recovered 400 participants, 45% (n=180) presented with one or more comorbidities. Almost 66.67%(n=120) had diabetes, with 5.5%(n=10) in asymptomatic, 16.67%(n=30) in mild and almost 44.44%(n=80) in hospitalized patients. Similarly, 33%(n=60) had hypertension, 13%(n=23) had COPD, 7.0%(n=13) had asthma and 2.0%(n=4) had CKD.

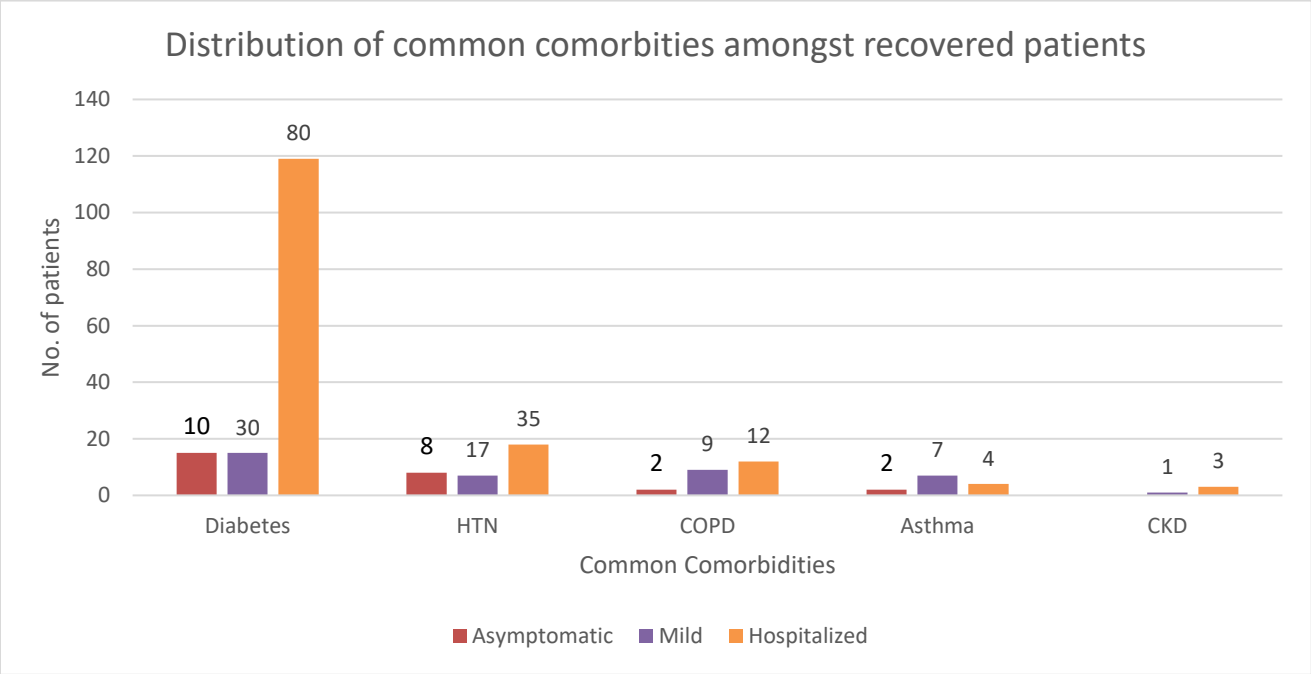

Fig 1: Distribution of common comorbidities amongst recovered patients

Table 3:shows post-COVID-19 follow-up characteristics

Characteristics	N (%)			
	Total recovered (n=400)	Asymptomatic(n=43)	Mild(n=291)	Hospitalized(n=66)
Post-COVID-19 follow-up characteristics				
Time after illness onset, median(SD)*	167(37.5)	137(45.1)	167(35.1)	177(44.7)
Symptoms**				
<=4 weeks	120(67.3)	5(11.6)	189(55.3)	48(26.6)
4-12 weeks	30(16.6)	0	57(17.7)	10(42.5)
>12 weeks	26(4.5)	0	45(13.4)	8(18.8)

*time since onset of symptoms in mild and hospitalized patients (moderate or severe), time since first positive test report in asymptomatic individuals

**participants who suffered from COVID-19 were asked whether they experienced the continuity of symptoms from their illness.

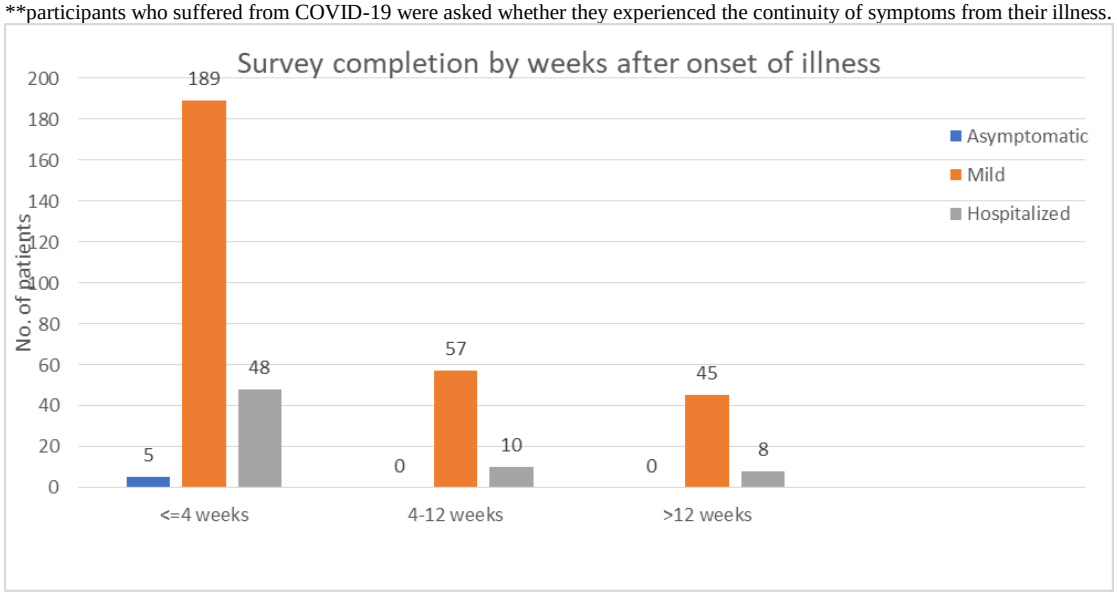

Fig 2: Survey completion by weeks after onset of illness

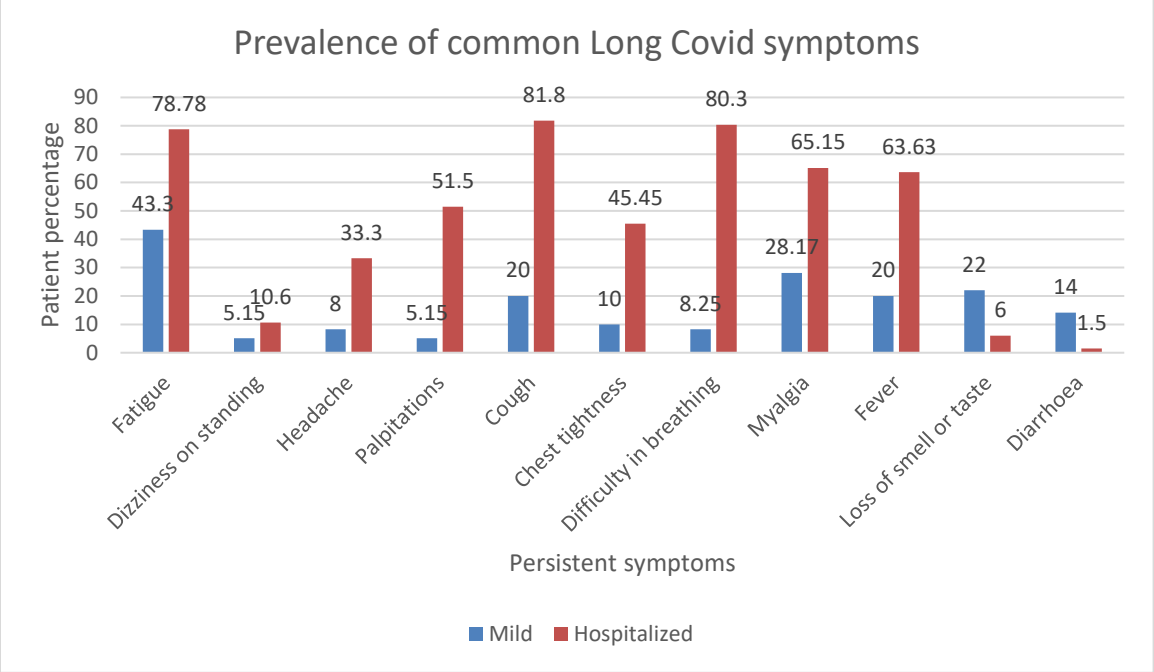

Fig 3: Prevalence of common Long Covid symptoms

Fig.3 shows the percentage distribution of various persistent post-Covid-19 symptoms in the overall recovered patients. Most common persistent symptom reported by subjects who underwent hospitalization were cough (81.8%), difficulty in breathing (80.3%) and fatigue (78.78%) while the mild cases most commonly reported cough (20%), myalgia (28.17%) and fatigue (43.3%). In general, the hospitalized patients (moderate or severe cases) were more affected by persistent long Covid symptoms rather than the mild cases.

Discussion

This qualitative cohort study involving 400 participants with Long Covid in Ayodhya, Uttar Pradesh, has been able to establish a number of essential findings[18,19]. This study has revealed that people consider Long Covid as a deterrent in daily routine chores and is seen as a big loss to stamina and confidence. These persistent symptoms have only caused more anxiety and a somewhat loss in trust factor in the medical health care system probably because of uncertain and confusing prognosis or with no clear direction or purpose as explained by Frank's "chaos narrative"[20].

In this study, the most commonly encountered persistent symptoms included fatigue, dizziness on standing, headache, palpitations, cough, chest tightness, difficulty in breathing, myalgia, low grade fever, loss of smell or taste and diarrhoea.

Pulmonary sequelae

A range of pulmonary post-Covid-19 manifestations like dyspnea, desaturation on exertion and dry cough were reported in almost 16.5% overall Covid-19 survivors. Viral-dependent mechanisms (including invasion of alveolar epithelial and endothelial cells bySARS-CoV-2) and viral-independent mechanisms (such as immunological damage, including perivascular inflammation) contribute to the breakdown of the endothelial–epithelial barrier with invasion of monocytes and neutrophils and extravasation of a protein-rich exudate into the alveolar space, consistent with other forms of ARDS[21] has been described as one of the probable cause. SARS-CoV-2 infects the sensory nerves mediating cough which leads to neuroinflammation and neuroimmune interactions leading to cough hypersensitivity[22].

Cardiovascular sequelae

Chest tightness (44.75%), dizziness on standing (15.5%) and palpitations (60.75%) were the most common cardiovascular manifestations reported. All the above symptoms correspond with a special medical condition called PoTS (Postural Tachycardia Syndrome) which is thought to be triggered by the presence of antibodies in the COVID-19 recovered patients that tend to bind to the receptors on cells regulating the vascular tone and to other receptors on the cells that are involved in the regulation of heart rate as a result of which above cardiovascular symptoms may be observed[23]. In short, the most probable mechanisms extending cardiovascular sequelae in post-COVID-19 include direct viral invasion, downregulation of ACE2 receptors, inflammation and immunologic response affecting the structural integrity of the myocardium, pericardium and conduction system[24,25].

Neurological Sequelae

A lot of COVID-19 survivors reported chronic malaise (60%), loss of taste and smell (30%), migrain like splitting headache (45%) and diffused myalgia (50%). Shabir describes the probable cause of headache to the binding of SARS-CoV-2 virus to the ACE2 receptors on the trigeminal nerve endings within the nasal cavity causing trigeminovascular activation along with an increase in cytokine levels[26]. Shabir also describes the cause of anosmia to the binding of viral particles to the ACE2 receptors present in the olfactory epithelium that in turn leads to a temporary loss of function of supporting cells causing changes in olfactory sensory neurons[27]. However, loss of taste is not as common as anosmia because the ACE2 receptors to which the viral particles bind and cause destruction of sensory receptors are more numerous in olfactory epithelium as compared to the taste buds. In some critically ill cases, Post-COVID brain fog was observed which may evolve from mechanisms such as deconditioning or

PTSD[28]. However, reports of COVID-19 brain fog after mild COVID-19 suggest that dysautonomia may contribute as well[29-30].

Neuromuscular Sequelae

We found atleast 90.25% post-covid-19 survivors complaining of muscle fatigue. Paliwal et al[31] in his study suggested that the skeletal muscle cells as well as other cells in muscles like satellite cells, leukocytes, fibroblasts and endothelial cells exhibit ACE2 receptors which makes these cells directly sensitive to SARS-CoV-2 viral invasion. Immune complex deposition in muscle cells, release of mytoxic cytokines, damage due to similarity between muscle cells and viral antigens and adsorption of viral proteins on muscle membrane may also be the possible mechanisms for muscle fatigue.

Gastrointestinal Sequelae

Almost 21% participants reported diarrhoea as a persistent Long Covid symptom. This can again be attributed to the binding of viral particles to the Angiotensin Converting Enzyme2 receptors which are 100 times more prevalent in the gastrointestinal tract than the respiratory tract[32].

Overall, most of the post-COVID-19 follow up studies have reported a significant deficit in the health related quality of life and functional incapacity in the COVID-19 survivors specially at the end of 6 months. Such surveys, however, have played an important role in identifying the common post-COVID symptoms like brain fog, fatigue and body ache and their extent of persistence even in cases that do not require hospitalization[33]. Given the severity and debility involved with the systemic inflammatory response seen in COVID-19 survivors, it has become the need of the hour to identify, diagnose and treat such persistent symptoms so that early rehabilitation programs can be incorporated which in turn will help in improving the quality of life healthwise.

Conclusion

Multi-organ sequelae of Long Covid has become a major cause of concern in the present era. It has not only hampered routine life but is also bringing about psychological distress in COVID-19 survivors. Hence, necessary and confirmatory identification of various clinical features of Long Covid in its acute, subacute and chronic phases is extremely important for planning early rehabilitation and treatment. The immediate concern should be to correctly identify, document, investigate and manage common as well as any new Long Covid symptoms. Furthermore, necessary active and future research studies should be undertaken to better understand the pathophysiology and natural history of this novel viral entity.

References

1. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo P, Cuapio A et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis, 2021.
2. COVID-19 and Your Health [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2 June 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html.
3. Alwan NA. Surveillance in underestimating the burden of the COVID-19 pandemic. Lancet.2020;396(10252):e24.
4. Assaf G, Davis H, McCorkell L, Wel H, O'Neil B et al. An Analysis of the Prolonged COVID-19 Symptoms Survey by Patient-Led Research Team. Patient Led Res.2020. https//patientresearchcovid19.com/.
5. Cafi A, Bernabei R, Landi F, GemelliAgainst C-P-ACSG. Persistent symptoms in patients after acute COVID-19.JAMA. 2020; 324(6):603-5.
6. Halpin SJ, Mclvor C, Whyatt G, Adams A, Harvey O et al. Post discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol. 2020, 30.
7. Tenforde M, Kim S, Lindsell C 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; ePub:24 July 2020. https://doi.org/10.15585/mmwr.mm6930e1external.
8. Cafi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA.2020;324:603-5.
9. Arnold DT, Hamilton FW, Milne A, Morley A, Viner J et al. Patient outcomes after hospitalization with COVID-19 and implications for follow-up; results from a prospective UK cohort.MedRxiv.2020.
10. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol.2020;20:363-74.
11. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J.2020;41(32):3038-44.
12. British Society for Immunology. Long-term immunological health consequences of COVID-19. London: BSI, 2020.https://www.immunology.org/sites/defaylt/files/BSI_Briefing_Note_August_2020_FINAL.pdf;Accessed 2 June 2021.
13. NHS England. After-care needs of inpatients recovering from COVID-19(CO388).London:NHS England, 2020.https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/06/CO388-after-care-needs-of-inpatients-recovering-from-covid-19-5-june-2020-1.pdf;Accessed 2 June 2021.
14. Rajan S, Khunti K, Alwan N, Steves C, MacDermott N, Morsella A et al. References [Internet]. Ncbi.nlm.nih.gov. 2021 [cited 8 June 2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK569602/.
15. Phillips M, Turner-Stokes L, Wade D, Walton K. Rehabilitation in the wake of Covid-19-A phoenix from the ashes: British Society of Rehabilitation Medicine, 2020.https://www.bsrm.org.uk/downloads/covid-19bsrmissue1-published-27-4-2020.pdf;Accessed 3 June 2021.
16. [Internet]. 2021 [cited 8 June 2021]. Available from: https://www.researchgate.net/publication/347516294_Persistent_symptoms_after_Covid-19_qualitative_study_of_114_long_Covid_patients_and_draft_quality_principles_for_services.
17. Barker-Davies R, O'Sullivan O, Senaratne K, Baker P, Cranley M, Dharm-Datta S et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation, 2021.
18. Healthcare Workers [Internet]. Centers for Disease Control and Prevention. 2021 [cited 3 April 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
19. Korstjens I, Moser A. Series: practical guidance to qualitative research. Part 4: trustworthiness and publishing. Eur J Gen Pract.2018;24(1):120-4.
20. Robillard B. The Wounded Storyteller: Body, Illness, and Ethics by Arthur W. Frank. Body & Society. 1997;3(2):115-116.
21. Huppert L, Matthay M, Ware L. Pathogenesis of Acute Respiratory Distress Syndrome. Seminars in Respiratory and Critical Care Medicine. 2019;40(01):031-039.
22. Song W, Hui C, Hull J, Birring S, McGarvey L, Mazzone S et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. The Lancet Respiratory Medicine. 2021;9(5):533-544.
23. Snyder B. Viral illness may spur 'standing up' disorder [Internet]. Vanderbilt University. 2021 [cited 8 June 2021]. Available from: https://news.vumc.org/2014/03/13/viral-illness-may-spur-standing-up-disorder/.
24. Gemayel C, Pelliccia A, Thompson P. Arrhythmogenic right ventricular cardiomyopathy. Journal of the American College of Cardiology. 2001;38(7):1773-1781.

25. Siripanthong B. Recognizing COVID-19 related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm.2020;17:1463-1471.
26. Dr. Osman Shabir P. COVID-19 and Headaches [Internet]. News-Medical.net. 2021 [cited 8 June 2021]. Available from: https://www.news-medical.net/health/COVID-19-and-Headache.aspx [Internet].
27. Dr. Osman Shabir P. COVID-19 and Smell Loss (Anosmia) [Internet]. News-Medical.net. 2021 [cited 8 June 2021]. Available from: https://www.news-medical.net/health/COVID-19-and-Smell-Loss-(Anosmia).aspx.
28. Kaseda ET, Levine AJ. Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors.Clin.Neurophysiol.2020;34:1498-1514.
29. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. ENeurologicalSci.2020;21:100276.
30. Miglis M, Goodman B, Chémali K, Stiles L. Re: 'Post-COVID-19 chronic symptoms' by Davido et al. Clinical Microbiology and Infection. 2021;27(3):494.
31. Paliwal V, Garg R, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurological Sciences.2020;41(11):3039-3056.
32. Coronavirus: Diarrhea and Other Confirmed Gastrointestinal Symptoms [Internet]. Healthline. 2021 [cited 8 June 2021]. Available from: https://www.healthline.com/health/coronavirus-diarrhea.
33. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C et al. Post-acute COVID-19 Syndrome. Nature Med.2021;27:601-15.

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