Original Article

DOI: 10.5582/ddt.2021.01093

Post COVID-19 sequelae: A prospective observational study from Northern India

Shivdas Naik, Soumendra Nath Haldar, Manish Soneja, Netto George Mundadan, Prerna Garg, Ankit Mittal, Devashish Desai, Praveen Kumar Trilangi, Sayan Chakraborty, Nazneen Nahar Begam, Bisakh Bhattacharya, Ganesh Maher, Niranjan Mahishi, Chaithra Rajanna, Swasthi S Kumar, Bharathi Arunan, J Kirtana, Ankesh Gupta, Diksha Patidar, Parul Kodan, Prayas Sethi, Animesh Ray, Pankaj Jorwal, Arvind Kumar, Neeraj Nischal, Sanjeev Sinha, Ashutosh Biswas, Naveet Wig*

Department of Medicine, All India Institute of Medical Sciences, New Delhi, India.

SUMMARY Post COVID-19 sequelae are a constellation of symptoms often reported after recovering from COVID-19. There is a need to better understand the clinical spectrum and long-term course of this clinical entity. The aim of this study is to describe the clinical features and risk factors of post COVID-19 sequelae in the North Indian population. This prospective observational study was conducted at a tertiary healthcare centre in Northern India between October 2020 and February 2021. Patients aged >18 years with laboratory-confirmed COVID-19 were recruited after at least two weeks of diagnosis, and details were captured. A total of 1234 patients were recruited and followed up for a median duration of 91 days (IQR: 45-181 days). Among them, 495 (40.1%) had persistent symptoms post-discharge or recovery. In 223 (18.1%) patients, the symptoms resolved within four weeks; 150 (12.1%) patients had symptoms till 12 weeks, and 122 (9.9%) patients had symptoms beyond 12 weeks of diagnosis/symptom-onset of COVID-19. Most common symptoms included myalgia (10.9%), fatigue (5.5%), shortness of breath (6.1%), cough (2.1%), insomnia (1.4%), mood disturbances (0.48%) and anxiety (0.6%). Patients who were hospitalized were more likely to report fatigue as a feature of long COVID. Hypothyroidism (OR: 4.13, 95% CI: 2.2-7.6, *p*-value < 0.001) and hypoxia ($SpO_2 \leq 93\%$) (OR: 1.7, 95% CI: 1.1-2.4, *p*-value 0.012) were identified as risk factors for long COVID sequelae. In conclusion, long COVID symptoms were common (22%), and 9.9% had the post COVID-19 syndrome. Myalgias, fatigue and dyspnoea were common symptoms. Patients with hypothyroidism and hypoxia during acute illness were at higher risk of long COVID.

Keywords COVID-19, post COVID-19 sequelae, long COVID, post COVID-19 syndrome

1. Introduction

Coronavirus disease 2019 (COVID-19) is a multisystem disease caused by the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2). While the respiratory system bears the maximal brunt of the disease, the virus may affect all major systems in the body. Even after recovery from the disease, widespread respiratory, circulatory, neurological, and musculoskeletal complaints may persist. The epidemio-pathological basis of these 'Post COVID-19' complaints is not completely understood. Apart from direct viral damage, these post COVID-19 sequelae may also be attributed to the immune response, cytokine storm, as a side effect of the therapy, underlying comorbidities or due to a combination of any of these. Additionally, the role of psychosocial factors like prolonged isolation, fear of infecting family members, socio-economic disturbances, and the stigma associated with the infection may have far-reaching consequences on mental health and well-being (*1*).

As per NICE (National Institute for Health and Care Excellence) guidelines, post COVID-19 sequelae have been divided into acute COVID-19, ongoing symptomatic COVID-19 and post COVID-19 syndrome (*2*). The term 'long COVID' is commonly being used to describe signs and symptoms that continue or develop after acute COVID 19. It includes both ongoing

symptomatic COVID 19 and post COVID 19 syndrome.

The epidemiology of post COVID-19 sequelae is not well described (*3*). We conducted this prospective observational study to describe the incidence and risk factors of post COVID-19 sequelae among the Northern Indian population.

2. Materials and Methods

2.1. Study design and settings

This prospective observational study was conducted in a tertiary care centre in Delhi, India, between October 2020 and February 2021.

2.2. Participants

The study included patients of age more than 18 years who had a confirmed COVID-19 infection (as per WHO definition) at least two weeks prior to the enrolment, had been discharged from the institute after treatment for COVID-19 and were willing to participate (*4*).

2.3. Data collection

Participants were followed-up either at the institute's post COVID-19 clinic or telephonically. Interviews were conducted by residents trained in administering the questionnaire and able to communicate with the patients in their local languages. Verbal consent was taken before the enrolment. Confidentiality of subjects was ensured throughout the study. The study protocol was approved by the Institute Ethics Committee (IECPG/162/4/2020).

The questionnaire included details related to demographics, symptomatology, hospitalization, and oxygen use during the acute disease as well as any symptoms after recovery from acute COVID-19. Patients were systematically asked about a list of post COVID-19 symptoms (dyspnea, myalgia, fatigue, anosmia, ageusia, chest pain, cough, mood disturbances *etc*.), but they were also free to report any other symptoms that they considered relevant. A follow-up interview was conducted after one month and three months to look for the resolution of symptoms or any new symptoms. Patients could visit the clinic at any time if they desired.

The severity of acute COVID-19 was defined as mild, moderate or severe with reference to national guidelines for COVID-19 (*5*). The patients with COVID-19 without evidence of breathlessness or hypoxia (defined as room air oxygen saturation ≤ 94%) during the course of acute illness were categorized as mild COVID-19 disease. Those who had breathlessness and a room air oxygen saturation (SpO_2) of ≥ 90% and ≤ 93% were catagorised as moderate disease and those with room air SpO_2 of < 90% were categorized as severe COVID-19 disease. The post COVID-19 symptoms of the patients were classified as per NICE guidelines (*2*). Acute COVID-19 has been defined as patients with symptoms and signs of COVID-19 for up to 4 weeks. Ongoing symptomatic COVID-19 includes patients with symptoms and signs from 4 to 12 weeks. Patients with symptoms and signs that develop during or after an infection consistent with COVID-19, which continued for more than 12 weeks and are not explained by an alternative diagnosis, are said to have Post COVID-19 syndrome. Long COVID is defined as signs and symptoms that persist or develop after acute COVID-19 and included both "ongoing symptomatic COVID-19" and "post COVID-19 syndrome" (*2*).

2.4. Statistical analysis

The data were analyzed using STATA 16.0 (StataCorp, College Station, TX) software. Categorical variables are presented as *n* (%), continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) as applicable. For the comparison of variables, two groups were considered. Group 1 included patients who developed the long COVID, and Group 2 included patients who did not develop long COVID. Categorical variables were compared using the Fisher exact test or chi-square test, wherever applicable, and continuous variables were compared using an independent sample Student's *t*-test. In addition, a binary logistic regression model was developed to assess the impact of different variables on the likelihood of developing post COVID-19 syndrome with the forward conditional method. Independent variables which had a *p*-value of < 0.2 were included for binary logistic regression. Statistical significance was set at a *p*-value of < 0.05.

3. Results

3.1. Clinical characteristics of the patients in our study

A total of 2,243 patients were contacted, of whom 1,645 patients responded. Of these, 147 were excluded as they were less than 18 years old, and 264 patients did not consent to the study. Thus, a total of 1,234 patients were recruited for the study. We followed up 276 patients (26%) for more than six months, 264 (24%) for 3-6 months, 398 (37%) for up to three months, and 140 (13%) for less than 1-month post-discharge/post-end of isolation. The median duration of follow-up was 91 days (IQR: 45-181 days).

Our cohort had a mean age of 41.4 ± 14.2 years and included 856 (69.4%) males. Of these 1,234 patients, 1,059 (85.8%) patients had mild COVID-19 disease, 135 (10.9%) had moderate, and 40 (3.3%) patients had severe COVID-19 disease. In addition, there were 352 (28.5%) patients who had at least one comorbidity. The most common comorbidities were diabetes mellitus (13.4%), hypertension (8.1%) and hypothyroidism

Table 1. Demographic profile of the patients recruited for the study (*n* = 1,234)

Variables	Observations *n* (%)
Age in years (mean ± SD)	41.6 ± 14.2
Range	18-97 years
Gender	
Males	856 (69.4)
Females	378 (30.6)
Disease severity	
Mild ($SpO_2 \geq 94\%$ on room air)	1,059 (85.8)
Moderate ($SpO_2 \geq 90\%$ & $\leq 93\%$ on room air)	135 (10.9)
Severe ($SpO_2 < 90\%$ on room air)	40 (3.3)
Comorbidities	352 (28.5)
Diabetes mellitus	165 (13.4)
Hypertension	100 (8.1)
Hypothyroidism	71 (5.8)
Chronic lung disease	24 (1.9)
Connective tissue diseases	20 (1.6)
Tuberculosis	28 (2.3)
Coronary artery disease	30 (2.4)
Chronic kidney disease	27 (2.2)
Chronic liver disease	8 (0.6)
HIV	5 (0.4)
Malignancy	21 (1.7)
Post-transplant	3 (0.2)
Patients requiring admission	711 (56.6)
Admission details	
Duration of hospital stay (*n* = 711)	
Mean ± SD	11.4 ± 5.6 days
Median (IQR)	10 (7-14) days
Oxygen requirement	175 (14.2)
Ventilator requirement	15 (1.2)

(5.8%) (Table 1).

A total of 711 (56.6%) patients were hospitalized for COVID-19, for a mean duration of 11.4 ± 5.6 days, with a range of 1-36 days. Oxygen support was required by 175 patients (14.2%), of whom 15 patients (1.2%) required ventilatory support (Table 1).

3.2. The post COVID-19 symptomatology in the patients

Of these 1234 patients, 495 (40.11%) patients had symptoms after their discharge or end of quarantine (Figure 1). In 223 (18.1%) patients, the symptoms resolved within four weeks. The remaining 272 (22.0%) patients had long COVID. Of all patients with long COVID, 150 (12.1%) patients had symptoms till twelve weeks, and 122 (9.9%) patients had symptoms beyond twelve weeks. The most common long COVID symptoms included myalgia (10.9%), fatigue (5.5%), shortness of breath (6.1%), dry cough (2.1%) and chest pain (1.2%). Other symptoms included insomnia (1.4%), mood disturbances (0.48%) and anxiety (0.6%) (Table 2; Figure 2). The proportion of patients reporting persistent symptoms diminished with a longer time to follow-up (Table 2).

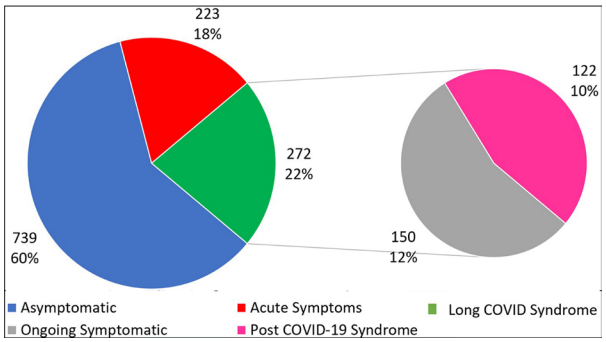

Figure 1. Post COVID-19 symptoms in the study group (*n* = 1,234). The blue portion represents patients who did not have any symptoms. The red portion represents the patients with acute COVID-19. The green portion represents patients with long COVID symptoms, which included patients with ongoing symptoms, represented as the grey portion, and post COVID-19 syndrome, represented as the pink portion.

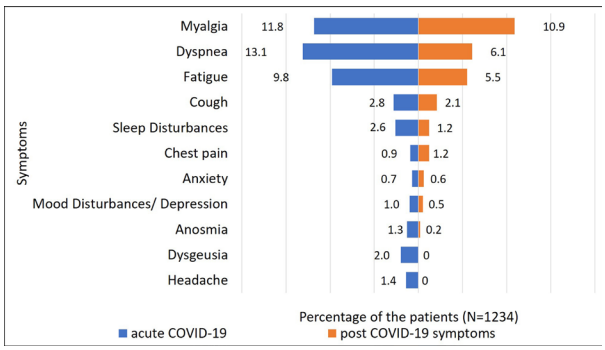

Figure 2. Spectrum of post COVID-19 symptoms (*n* = 1,234). The blue graph represents the patients (in percentage) with symptoms less than four weeks from diagnosis, and the orange graph represents the patients (in percentage) with symptoms beyond four weeks from diagnosis.

Table 2. Post COVID-19 symptomatology among the recruited patients (*n* = 1234)

Symptoms	Long COVID Symptoms		Duration of symptoms in days Median (IQR)
	Ongoing symptoms *n* (%)	Post COVID-19 syndrome *n* (%)	
Loss of taste	0	0	-
Loss of smell	2 (0.16)	0	-
Anxiety	4 (0.3)	4 (0.3)	
Low mood/depression	4 (0.32)	2 (0.16)	67 (40-177)
Chest pain	8 (0.7)	6 (0.5)	60 (41-112)
Insomnia	13 (1.1)	4 (0.3)	45 (40-70)
Cough	14 (1.1)	12 (1)	60 (45-118)
Dyspnea	33 (2.7)	42 (3.4)	90 (45-124)
Fatigue	45 (3.7)	22 (1.8)	60 (45-135)
Myalgia	80 (6.5)	54 (4.4)	60 (45-150)
Total*	150 (12.1)	122 (9.9)	

*The total numbers do not add up as many patients had more than 1 symptom.

3.3. Clinical characteristics of the patients hospitalized

The characteristics of patients who were admitted are compared with patients who were not hospitalized for the management of COVID-19 in Table 3. Patients with increasing age, comorbidities like diabetes mellitus, hypertension, coronary artery disease and hypothyroidism were more likely to be hospitalized. Patients who were hospitalized were also more likely to report fatigue as a feature of long COVID.

3.4. Risk factors for developing long COVID symptoms

The risk of developing long COVID symptoms was higher in patients with hypothyroidism (OR: 4.13, 95% CI: 2.2-7.6, *p*-value < 0.001) and disease severity. Compared to mild disease, the patients who had either moderate or severe COVID-19 disease, *i.e.* the patients having hypoxia or SpO_2 on room air of ≤ 93%, was associated with a higher chance of developing long COVID symptoms (OR: 1.7, 95% CI: 1.1-2.4, *p*-value 0.012) (Table 4).

4. Discussion

The COVID-19 pandemic has affected hundreds of millions of people. Even after recovery, prolonged symptoms have been noted. These post COVID-19

Table 3. Comparison of characteristics between hospitalized and non-hospitalized patients

Variable	Non- Hospitalised, *n* = 523	Hospitalised, *n* = 711	*p* value	OR (95% CI)	*p* value
Age in years (Mean + SD)	38.1 ± 11.9	44.2 ± 15.3	< 0.001	1.01-1.03	< 0.001
Comorbidity	61 (11.7)	291 (40.9)	< 0.001		
Diabetes Mellitus	42 (8)	123 (17.3)	< 0.001	1.5 (1-2.2)	0.05
Hypertension	14 (2.7)	86 (12.1)	< 0.001	3.1 (1.7-5.7)	< 0.001
Coronary Artery Disease	2 (0.4)	28 (41.9)	< 0.001	4.6 (1.1-20.1)	0.04
Chronic Kidney Disease	4 (0.7)	23 (3.2)	0.003		0.07
Chronic Lung disease	4 (0.8)	20 (4.9)	0.01		0.15
Chronic Liver Disease	0	8 (1.1)	< 0.001	1	
Malignancy	0	21 (3)	< 0.001	1	
Hypothyroidism	3 (0.6)	68 (9.6)	< 0.001	15.8 (4.9-51)	< 0.001
Long COVID	103 (19.7)	169 (23.8)	0.09		0.15
1.Cough	9 (1.7)	17 (2.4)	0.6		
2.Dyspnea	18 (3.4)	57 (8)	0.001	2.9 (1.4-6.3)	0.006
3.Fatigue	17 (3.3)	58 (8.2)	< 0.001		
4.Myalgia	64 (12.2)	70 (9.8)	0.2		
Post COVID-19 syndrome	50 (9.6)	72 (10.1)	0.8		
1.Cough	8 (1.5)	4 (0.6)	0.14		0.8
2.Dyspnea	15 (2.9)	27 (3.8)	0.4		
3.Fatigue	5 (1)	17 (2.4)	0.08		
4.Myalgia	19 (3.6)	35 (4.9)	0.3		

Table 4. Multi-variate analysis for risk factors of developing Long COVID symptoms

Variable	No long COVID *n* = 962	long COVID *n* = 272	*p*-value (univariate)	Multi-variate analysis	
				OR (95% CI)	*p* value
Age	40.8 ± 14.6	44.3 ± 13	< 0.001	1.01 (0.99-1.02)	0.056
Gender					
Males	665 (69.1)	191 (70.2)	0.8		
Females	297 (30.9)	81 (29.8)			
Comorbidities	256 (26.6)	96 (35.3)	0.006		0.24
Diabetes Mellitus	120 (12.5)	45 (16.5)	0.09		0.18
Hypertension	75 (7.8)	25 (9.2)	0.45		
Hypothyroidism	38 (4)	33 (12.1)	< 0.001	4.13 (2.2-7.6)	< 0.001
Chronic Lung disease	16 (1.7)	8 (2.9)	0.21		
Connective Tissue Disorder	14 (1.5)	6 (2.2)	0.4		
Coronary Artery Disease	26 (2.7)	4 (1.5)	0.4		
Chronic Kidney Disease	23 (2.4)	4 (1.5)	0.5		
Need of ventilator	10 (1)	5 (1.8)	0.34		
Mild disease	839 (87.2)	220 (80.9)	0.01	Taken as 1	
Moderate disease/Severe disease*	123 (12.8)	52 (19.1)	0.01	1.7 (1.1-2.4)	0.012
Admission	542 (56.3)	169 (62.1)	0.09		0.7

*Moderate disease are patients with COVID-19 disease who had a room air saturation of ≥ 90% & ≤ 93% and Severe disease are the patients with COVID-19 disease who had a room air saturation of ≤ 90%.

symptoms significantly affect the quality of life in patients (*6*). Long COVID, or post COVID-19 sequelae, is being seen in a growing number of patients reporting a constellation of symptoms, both pulmonary and extrapulmonary, with known or undeciphered mechanisms.

In our cohort of 1,234 patients, 272 (22%) patients had symptoms that persisted beyond four weeks or 'long COVID' (*2*). This is lower than previous estimates of prevalence which range from 50-80% (*3,7-13*). Multiple reasons may have caused this; the proportions of mild and asymptomatic patients recruited in previous studies were lower; many of the studies included had a risk of selection bias, with symptomatic patients more likely to seek medical attention.

Persistent musculoskeletal complaints, including fatigue and myalgias, have been reported in 37-62% of patients who recovered from COVID-19 (*3,7-9,11,13,14*). The most common post COVID-19 symptoms in our cohort were myalgia (134, 10.9%) and fatigue (67, 5.5%). Studies have demonstrated frontal and cerebellar hypometabolism in patients with post COVID-19 fatigue (*15*). Decreased levels of neurotransmitters, reduced neuronal excitability, inflammation, and inhibition in the firing of motor neuron units have all been hypothesized as central factors contributing to post COVID-19 fatigue and myalgias (*16*). Metabolic factors like vitamin D deficiency, anaemia, hypothyroidism, and underlying chronic diseases also contribute to prolonged fatigue (*17*). Importantly, the role of psychological influences cannot be ruled out.

The massive socio-economic upheaval caused by the pandemic has had a significant impact on the psyche of the population. Isolation, mobility restrictions, fear of infection, financial losses, and stigma have led to mood disorders (*18,19*). In our study, 49 (4%) patients reported difficulty sleeping while 17 (1.4%) patients each had depression and anxiety that occurred after recovery from the infection. However, these complaints were resolved within three weeks in most patients.

Apart from psychosomatic complaints, many patients suffered from prolonged respiratory complaints, including shortness of breath (75, 6.1%) and dry cough (26, 2.1%). This is lesser than the previously estimated prevalence of 24-40% and 11-14% of dyspnoea and cough, respectively (*3,8,10,14*). In addition to the causes discussed above, a higher proportion of patients with underlying respiratory conditions may have contributed to the higher prevalence in previous studies. Dyspnea was also the most persistent complaint, with a median duration of 90 days in our cohort.

Pulmonary parenchymal injury and acute respiratory distress syndrome (ARDS) are hallmarks of acute COVID-19. Direct viral injury, cell and cytokine and cell-mediated injury, activation of profibrotic pathways, and trauma due to positive pressure ventilation can cause permanent scarring of lung parenchyma (*20*). Follow-up studies have shown that in up to 98% of patients, abnormalities like ground-glass opacities, crazy paving patterns and bands of fibrosis persist in chest imaging even after 28 days from symptom onset (*21*). Additionally, COVID-19 induced thromboembolic microangiopathy, and the resulting immune-inflammatory cascade causes sizable damage to the pulmonary vasculature (*22*). This may explain the high prevalence of chest pain in patients with dyspnea post COVID-19.

Neurotropism by the SARS-CoV-2 virus, neuronal inflammation mediated by direct invasion and bystander injury by the immune response to the virus, and neuroimmunomodulation through the vagus nerve has been implicated in cough hypersensitivity causing persistent cough in post COVID-19 (*23*). This is like the neurogenic sensitization that has been proposed for chronic fatigue syndrome. Thus, this may explain the co-existence of other symptoms like fatigue, myalgia and neurocognitive symptoms in post COVID-19 patients (*24*).

The factors associated with long COVID symptoms in our study were the severity of the COVID-19 infection (mild *vs*. severe/moderate) and hypothyroidism. More severe illness is associated with a prolonged course of the disease and more significant damage. In patients with comorbidities like hypothyroidism, musculoskeletal and respiratory complaints are common. Additionally, non-mild COVID-19 may induce a sick euthyroid state, recovery from which may be delayed in patients with hypothyroidism (*25*). Thyroid disorder may adversely affect the disease outcome in several ways like the effect of the virus on the tissue distribution of ACE2 receptor, increased burden of cardiovascular and psychiatric comorbidities in turn affecting the metabolic stress (*26*). Hypothyroidism (with or without levothyroxine supplementation) has shown to negatively affect the long-term outcomes in COVID-19 survivors in our study, and more prospective studies can throw more light on this association.

Our study is a large prospective study recruiting 1,234 patients of all severity of COVID-19. It is also the first study to recruit many patients with an asymptomatic and mild infection and thus may provide a more accurate estimate of the prevalence of post COVID-19 symptoms in a real-life scenario. Furthermore, since patients were actively asked about various symptoms at pre-defined intervals, recall bias was reduced. To our knowledge, our study is the first to show that hypothyroid patients are at higher risk of developing long COVID symptoms. However, more robust studies are required to draw further conclusions.

The study has a few limitations. There is an inherent selection bias since the centre is a tertiary care hospital, and more patients requiring admission were tested in the facility. However, the admission policy had varied over the period, which was based on the caseload in the community and the availability of beds. Many patients

with mild disease were admitted for management of co-existing systemic illness. Loss to follow-up is inherent in all cohort studies, and this was exacerbated in our study due to significant social upheaval and mobility restrictions during the pandemic. Due to mobility restrictions and limited services during the pandemic surge, data on laboratory workup and imaging of patients could not be collected systematically.

In conclusion, long COVID symptoms were common and seen in 22% of the recovered patients whereas 9.9% had symptoms that persisted beyond three months from symptom onset/diagnosis of COVID-19. The most common among the spectrum of symptoms include myalgias, fatigue and dyspnoea. In addition, patients with hypothyroidism and hypoxia (room air $SpO_2 \leq 93\%$) during acute illness were at higher risk for developing long COVID.

Acknowledgements

We thank the members of the POSTCOV [post COVID-19 investigator group] team: Nikhil Kumar, Prateek Prasoon, Sayan Maharatna, Akashneel Bhattacharya, Vishakh C Keri, Sameer A Samed, Adarsh AK, Imtiyaz Shareef, Neeren Ravela, Satish Swain, Radhika Sarda, Harshith B Kadnur, Ashok Dudhwal, Ayush Agarwal, Kartik Vedula, Ashish Gupta, Shubham Agarwal, Anand R, Pratima Lalikar, Pallavi Jagtap, Premjeet B; for their efforts in interviewing the patients and data collection. We also thank all the Nursing Staff at the Post COVID-19 clinic, AIIMS New Delhi, for their help and support in the study.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. Nat Med. 2021; 27:601-615.
2. National Institute for Health and Care Excellence. COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19).(NG188). Evidence reviews 2 and 3: prevalence. 2020. *https://www.nice.org.uk/guidance/ng188* (accessed June 8, 2021).
3. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, Vasconcello-Castillo L, Valiro J. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Chron Respir Dis. 2021; 18:147997312110022.
4. World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance. *https://apps.who.int/iris/handle/10665/331501*(19 March 2020) (accessed Jun 25, 2021).
5. Government of India; Ministry of Health and Family Welfare; Directorate General of Health Services (EMR Division). Clinical Management Protocol for COVID19 dated 27/06/2020. *https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf* (accessed Jul 19, 2021).
6. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining post COVID symptoms (post-acute COVID, long COVID, persistent post COVID): An integrative classification. Int J Environ Res Public Health. 2021; 18:2621.
7. Chakraborty T, Jamal RF, Battineni G, Teja KV, Marto CM, Spagnuolo G. A review of prolonged post COVID-19 symptoms and their implications on dental management. Int J Environ Res Public Health. 2021; 18:5131.
8. Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine. 2021; 36:100899.
9. Iwu CJ, Iwu CD, Wiysonge CS. The occurrence of long COVID: a rapid review. Pan Afr Med J. 2021; 38:65.
10. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo P, Cuapio A, Villapol S. More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. Res Sq. 2021; rs.3.rs-266574.
11. Mandal S, Barnett J, Brill SE, *et al*. 'Long COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2020; thoraxjnl-2020-215818.
12. Moreno-Pérez O, Merino E, Leon-Ramirez J-M, *et al*. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. J Infect. 2021; 82:378-383.
13. Yelin D, Margalit I, Yahav D, Runold M, Bruchfeld J. Long COVID-19-it's not over until? Clin Microbiol Infect. 2021; 27:506-508.
14. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: A systematic review. JAMA Netw Open. 2021; 4:e2111417.
15. Delorme C, Paccoud O, Kas A, *et al*. COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. Eur J Neurol. 2020; 27:2651-2657.
16. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post COVID-19 fatigue: potential contributing factors. Brain Sci. 2020; 10:E1012.
17. Garg P, Arora U, Kumar A, Malhotra A, Kumar S, Garg S, Arora M, Sarda R, Wig N. Risk factors for prolonged fatigue after recovery from COVID-19. J Med Virol. 2021; 93:1926-1928.
18. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020; 7:611-627.
19. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet. 2020; 395:912-920.
20. McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol. 2021; 320:L257-265.
21. Shaw B, Daskareh M, Gholamrezanezhad A. The

lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). Radiol Med (Torino). 2021; 126:40-46.
22. Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, Wallner I, Marsden P, Dave S, Barnley H, Russel G, Dharmarajah N, Kon OM. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med. 2021; 9:107-116.
23. Song WJ, Hui CKM, Hull JH, *et al*. Confronting COVID-19-associated cough and the post COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med. 2021; 9:533-544.
24. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994; 121:953-959.
25. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2020; doi: 10.1007/s11154-020-09615-z.
26. Gosain A, DiPietro LA. Aging and wound healing. World J Surg. 2004; 28:321-326.

Received October 11, 2021; Revised October 26, 2021; Accepted October 27, 2021.

**Address correspondence to:*
Naveet Wig, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India 110029.
E-mail: naveetwig@gmail.com

Released online in J-STAGE as advance publication October 30, 2021.