Chest Heart Journal
Vol. 46, No. 2, July 2022

ORIGINAL ARTICLE

Persistence of Fatigue and its Covariates after COVID-19 Infection: A Hospital-Based Study

Md. Helaluzzaman Raqib[1], Atwar Rahman[2], Afsana Chowdhury[2], Goutam Sen[2], Dr. Rustom Ali[3], Md. Khairul Anam[4], SM Abdur Razzaque[5], Sk. Shahinur Hossain[5], Mohammed Shahedur Rahman Khan[6]

Abstract:

Background: *COVID-19 can cause symptoms that last for weeks or even months after recovery from acute illness. Persistent fatigue has been reported as a prominent symptom in recovering COVID-19 patients. The level of fatigue varies by country. In this study, we tried to evaluate the persistence of fatigue in patients after COVID-19 infection in our country and possible covariates of fatigue.*

Objective: *To find out the persistence of fatigue and its covariates after COVID-19 infection.*

Materials and Methods: *This cross-sectional observational study was conducted on 117 RT-PCR positive COVID-19 patients at National Institute of Diseases of the Chest and Hospital from July 2020 to June 2021. Patients were evaluated on an average of 105.4 (SD, 28.7) days after acute COVID-19 infection. Chalder Fatigue Scale (CFQ-11) was used to assess fatigue. Moreover, participants' dyspnoea was assessed by mMRC scale and other clinical parameters were also recorded. All data collected were analyzed using appropriate statistical formula and SPSS programme.*

Results: *Out of 117 patients (mean age 52.7 years [SD, 13.6]), fatigue was found in 64(54.7%) patients and dyspnoea in 49 (41.9%) patients. Diabetes mellitus 44(37.6%) and cardiovascular disease 38(32.5%) were commonly reported co-morbidities and were significantly higher in fatigued patients (51.6% and 48.4%, respectively). Seventy eight (66.7%) patients had severe COVID-19 and they were more fatigued (92.2% vs 35.8%). In multivariate analysis, diabetes mellitus (adjusted OR 7.6, 95% CI 1.8-32.4), cardiovascular disease (adjusted OR 23.0, 95% CI 4.1-96.2) and severe COVID-19 (adjusted OR 17.2, 95% CI 2.9-92.6) were found to be independent predictors for fatigue.*

Conclusion: *More than half of the patients suffer from persistent fatigue after COVID-19 infection. Diabetes mellitus, cardiovascular disease and severe COVID-19 are independent predictors for fatigue.*

Keywords: *COVID-19, Fatigue, Dyspnoea.*

[Chest Heart J. 2022; 46(2) : 73-80]

DOI: http://dx.doi.org/10.33316/chab.j.v46i2.2019656

Introduction:

In December 2019, the novel coronavirus disease 2019 (COVID-19) outbreak occurred in Wuhan, Hubei Province, China[1]. It has spread quickly across China and beyond, resulting in total confirmed cases 181,665,251 and 3,941,411

1. Assistant Registrar, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
2. Medical Officer, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
3. Assistant Professor, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
4. Director (Acting) & Associate Professor, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
5. Associate Professor, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka.
6. Professor of Respiratory Medicine (Rtd.), NIDCH, Mohakhali, Dhaka.

Correspondence to: Dr. Md. Helaluzzaman Raqib, Assistant Registrar, Department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka. Mobile: 01711903979, E-mail: raqibndc@yahoo.com

Submission on: 2 June, 2022 **Accepted for Publication:** 16 June, 2022
Available at http.//www.chabjournal.org

confirmed deaths across the world, as of June 30, 2021, according to World Health Organization. Until June 30, 2021, the number of confirmed cases in Bangladesh has risen to 9, 13,258, of which 14,503 have died[2].

81% of people with COVID-19 in China presented with mild symptoms; 14% presented with symptoms of severe respiratory dysfunction; and 5% developed a critical illness[3]. The medium and long-term problems faced by COVID-19 survivors after discharge from the hospital are currently unknown, but there's some emerging evidence.

A recent study- conducted in Italy shows that an overwhelming 87.4% of patients recovered from COVID-19 reported persistence of at least one symptom, particularly fatigue and dyspnoea, even two months after hospital discharge[4]. Another study in UK shows that new illness-related fatigue was the most commonly reported symptom by 72% participants in ICU group and 60.3% in ward group after an average 48 days discharge from hospital[5]. In early reports on the clinical features of infected patients, 44-69.6% listed fatigue as a presenting complaint[6].

A meta-analysis found that one fourth of the hospitalized survivors of SARS and MERS had decreased lung function and exercise capacity at 6 months after discharge[7]. It suggested that the impact of COVID-19 is probably going to be similar.

Fatigue is common in patients with symptomatic COVID-19 infection. Fatigue is measured in different ways, and its level varies by country. However, it is not known whether COVID-19 results in persistent fatigue in individuals recovered from an acute infection.

There are very limited studies in our country concerning the long-term health effects of COVID-19 and the on-going medical, psychological, and rehabilitation needs of these patients. That's why this study aims to evaluate the persistence of fatigue in patients after COVID-19 infection and possible covariates of fatigue.

This study will try to find out whether patients recovering from COVID-19 have persistent fatigue after their physical recovery, and to investigate whether there is a relationship between persistent fatigue and a variety of clinicopathological parameters.

It also emphasizes the importance of assessment of post-COVID symptoms that may identify a group worthy of further study and early intervention. This will help trials of clinical care strategies including personalised treatments to enhance long-term outcomes for current and future COVID-19 survivors.

Materials and methods:

This cross-sectional observational study was conducted in the department of respiratory medicine of National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka during the period from July 2020 to June 2021.

Inclusion criteria were:

1. Age ≥18 years
2. All symptomatic patients diagnosed as COVID-19 by reverse transcriptase-polymerase chain reaction (PCR) test
3. After 6 weeks of symptom onset

Exclusion criteria were:

1. Asymptomatic individuals with COVID-19 positive
2. Patients with Thyroid disorders
3. Patients with active Tuberculosis
4. Patients undergoing Chemotherapy or Radiotherapy
5. Dementia, Psychiatric disorders, or unable to attend hospital visits due to frailty or severe disease.

Hundred and seventeen (117) patients were included in the study using purposive sampling method. After informing full information regarding the nature of the study, possible outcome, and importance of follow-up, written consent was obtained. In order to be considered for inclusion in the current study, patient was evaluated at least 6 weeks after the date of last acute COVID-19 symptoms. Enrolled patients were given a pre-designed questionnaire. Information was collected from the patient after exploration of different complaints. Fatigue was assessed by using Chalder Fatigue Scale (CFQ-11). Briefly, participants were asked to answer these questions with particular reference to the past month in comparison to their pre-COVID-19 baseline, with responses measured

on a Likert scale (0-3). Dyspnoea was assessed by modified Medical Research Council (mMRC) scale. Besides, routine socio-demographic information, the time intervals between initial symptom onset, oxygen saturation (SpO2) at rest by pulse oximetry and investigation reports were recorded with a structured questionnaire. All information regarding the clinical features and investigations was recorded in a data collection sheet.

Results:

Out of 117 patients majority 31(26.5%) belonged to the age group 61 to 70 years with mean age was 52.7±13.6 years. Male was 90(76.9%) and female was 27(23.1%) with male-female ratio was 3.9:1. Most of the patients had diabetes mellitus 44(37.6%) and cardiovascular disease 38(32.5%). Rest had hypertension 26(22.2%), chronic lung disease 21(17.9%), chronic kidney disease 8(6.8%), and cancer 6(5.1%). The patients were followed up for a mean duration of 105.4±28.7 days from the onset of acute COVID-19 symptoms.

Fatigue was found in more than half 64(54.7%) of the patients. Among the patients, the mean Chalder fatigue score was 4.12±2.44, total score was 15.0±6.6, mean physical fatigue score was 10.8±4.7 and mental fatigue score was 4.2±2.1.

Forty Nine (41.9%) patients were found to be dyspnoeic. Among them, mMRC score was 0 in 32.5%, 1 in 25.6% and e"2 in 41.9% patients. Majority 75(64.1%) of the patients had a SpO2 >94%.

Age, sex, BMI, and smoking status were not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients.

Diabetes mellitus and cardiovascular disease were significantly higher in fatigued patients than non-fatigued patients (p<0.05). Dyspnoeic patients were more fatigued when compared with non-fatigued patients (p<0.05). Severe COVID-19 patients were more fatigued (92.2% vs 35.8%, p<0.05) than non-severe patients.

In multivariate analysis diabetes mellitus, cardiovascular disease and severe COVID-19 were found to be independent predictors for fatigue as here p value was low (p <0.05). However, dyspnoea was not found to be independent predictor for fatigue as p value was high (p >0.05).

Table-I

Demographic characteristics of the study population (n=117)

Demographic characteristics	*f*	%
Age (years)		
≤30	2	1.7
31-40	29	24.8
41-50	23	19.7
51-60	21	17.9
61-70	31	26.5
>70	11	9.4
Mean ±SD	52.7±13.6	
Range (min-max)	28.0-75.0	
Sex		
Male	90	76.9
Female	27	23.1

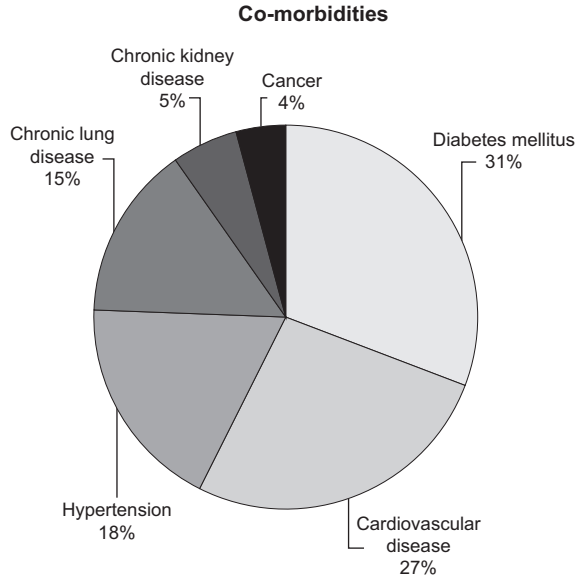

Fig.-1: *Pie chart showing co-morbidities of the study patients (n=117)*

Table-II

Distribution of the study population according to duration of follow up from the onset of acute COVID-19 symptoms (n=117)

Onset of acute COVID-19 symptoms to follow-up (days)	*f*	%
≤60	3	2.6
61-90	36	30.8
91-120	47	40.2
120-150	26	22.2
>150	5	4.3
Mean ±SD	105.4±28.7	
Range (min-max)	54.0-199.0	

Table- III

Distribution of the study population according to fatigue (n=117)

	f	%
Fatigue		
Yes	64	54.7
No	53	45.3
Chalder fatigue score (Bimodal Scoring)	4.12	±2.44
Range (min-max)	0.0	-9.0
Total score (Likert Scoring)	15.0	±6.6
Range (min-max)	4.0	-29.0
Physical fatigue score (CFQ-11 items 1-7)	10.8	±4.7
Range (min-max)	3.0	-20.0
Mental fatigue score (CFQ-11 items 8-11)	4.2	±2.1
Range (min-max)	1.0	-9.0

Table-IV

Distribution of the study population according to dyspnoea (n=117)

		f	%
Dyspnoea at rest	Yes	49	41.9
	No	68	58.1
mMRC scale	0	38	32.5
	1	30	25.6
	≥2	49	41.9

Table-V

Distribution of the study population according to SpO2 (n=117)

SpO2 (%)	*f*	%
<94	42	35.9
>94	75	64.1

Table-VI

Association between socio-demographic characteristics with fatigue (n=117)

Socio-demographic characteristics	Fatigue (n=64)		Non- fatigue(n=53)		χ^2 value	P value
	f	%	*f*	%		
Age (years)						
d 30	2	3.1	0	0.0		
31-40	12	18.8	17	32.1		
41-50	15	23.4	8	15.1	5.33	0.378^{ns}
51-60	12	18.8	9	17.0		
61-70	18	28.1	13	24.5		
>70	5	7.8	6	11.3		
Sex						
Male	53	82.8	37	69.8	2.76	0.097^{ns}
Female	11	17.2	16	30.2		
BMI (kg/m^2)						
<25.0	38	59.4	34	64.2	0.28	0.597^{ns}
≥25.0		26	40.6	19	35.8	
Smoking status						
Smoker	7	10.9	11	20.8	2.15	0.143^{ns}
Non-smoker	57	89.1	42	79.2		

ns= not significant

P value reached from chi square test

Table-VII

Association between co-morbidities with fatigue (n=117)

Co-morbidities	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Diabetes mellitus	33	51.6	11	20.8	11.73	[a]0.001[s]
Cardiovascular disease	31	48.4	7	13.2	16.41	[a]0.001[s]
Hypertension	18	28.1	8	15.1	2.85	[a]0.091[ns]
Chronic lung disease	9	14.1	12	22.6	1.45	[a]0.229[ns]
Chronic kidney disease	6	9.4	2	3.8	1.43	[b]0.206[ns]
Cancer	5	7.8	1	1.9	2.09	[b]0.153[ns]

s= significant, ns= not significant

[a]P value reached from chi-square test

[b]P value reached from Fisher exact test

Table-VIII

Association between dyspnoea with fatigue (n=117)

	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Dyspnoea at rest						
Yes	39	60.9	10	18.9	21.08	0.001[s]
No	25	39.1	43	81.1		
mMRC scale						
0	8	12.5	30	56.6		
1	17	26.6	13	24.5	29.66	0.001[s]
≥2	39	60.9	10	18.9		

s= significant

P value reached from chi-square test

Table-IX

Association between severity of COVID-19 with fatigue (n=117)

Severity of COVID-19	Fatigue (n=64)		Non- fatigue (n=53)		χ^2 value	P value
	f	%	*f*	%		
Non-severe	5	7.8	34	64.2	41.41	0.001[s]
Severe	59	92.2	19	35.8		

s= significant

P value reached from chi-square test

Table-X

Multivariate logistic regression analysis prediction for fatigue after COVID-19 infection

Parameters	Adjusted OR	95% CI for OR		P value
		Lower	Upper	
Diabetes mellitus	7.661	1.809	32.440	0.006[s]
Cardiovascular disease	23.070	4.150	96.253	0.001[s]
Dyspnoea	3.381	0.960	11.912	0.058[ns]
Severe COVID-19	17.259	2.988	92.672	0.001[s]

s= significant, ns= not significant

P value reached from multivariate analysis by binary logistic regression analysis

OR=Odd's Ratio

Discussion:

This cross-sectional observational study was carried out with an aim to assess the persistence of fatigue and its covariates after COVID-19 infection. One hundred and seventeen (117) symptomatic patients diagnosed as COVID-19 by polymerase chain reaction (PCR) test during the period from July 2020 to June 2021 were included in this study. The present study findings were discussed and compared with previously published relevant studies.

In this study, it was observed that most 31(26.5%) of the patients belonged to the age group 61 to 70 years with mean age was 52.7±13.6 years. Age was not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients. An almost similar study was done by Carfi et al.[4] and Townsend et al.[9] that found mean age was 56.5±14.6 years and 49.5±15 years and age was not statistically significant when compared between fatigued and not-fatigued patients. Their study findings were also consistent with this study.

In this present study, it was observed that the majority 90(76.9%) patients were male with male-female ratio was 3.9:1. Sex difference was not statistically significant (p>0.05) when compared between fatigued and non-fatigued patients. Townsend et al.[9] reported that female patients were significantly higher in fatigued patients than non-fatigued patients (67.2% vs 39.3%). Their results also show a distinct female preponderance in the development of fatigue. This was in keeping with previous CFS findings done by Faro et al.[10]. We did not find any significant difference in fatigue between male and female patients. The possible reason might be female patients were less in number in our study.

Regarding co-morbidities, in this study it was observed that most of the patients had diabetes mellitus 44(37.6%) followed by cardiovascular disease 38(32.5%), hypertension 26(22.2%), chronic lung disease 21(17.9%), chronic kidney disease 8(6.8%), and cancer 6(5.1%). Diabetes mellitus and cardiovascular disease were significantly higher in fatigued patients than non-fatigued patients. Our findings suggested that patients with multiple co-morbidities had suffered from more fatigue.

In this present study we observed that fatigue was found in 64(54.7%) patients. Mean Chalder fatigue score was found 6.0±1.5 in fatigue group and 1.8±1.0 in non-fatigue group. The mean total score was found 20.0±4.1. The mean physical and mental fatigue score was found 14.4±2.9 and 5.6±1.8. The difference was statistically significant ($p<0.05$) between the two groups. Townsend et al.[9] reported that more than half reported persistent fatigue (52.3%), at 10 weeks (median) after initial COVID-19 symptoms. Fatigue was assessed using the CFQ-11 in all participants and the mean (±SD) score was 15.8±5.9 across the study population. The mean physical and psychological fatigue score (±SD) was 11.38±4.22 and 4.72±1.99. Qi et al.[11] and Carfi et al.[4] also found fatigue was 53.6% and 53.1%, respectively. Another study in UK done by Halpin et al.[5] where they reported new illness-related fatigue was the most common reported symptom by 72% participants in ICU group and 60.3% in ward group after a mean 48 days discharge from the hospital. However, post-SARS fatigue has been reported in 40% of individuals one year after initial infection, with 1 in 4 meeting CFS diagnostic criteria at that time point[12]. The levels of both physical and psychological fatigue seen in post-COVID are higher than those of the general population, but do not reach the levels of those seen in chronic fatigue syndrome[13,14]. Rates of fatigue seen in our cohort are roughly equivalent to those reported in chronic disease states by Coetzee et al.[15] and Jeon et al.[16]. Findings of the current study supported that the burden of post-COVID fatigue in our country might be higher than other chronic disease states.

In this current study dyspnoea at rest was found in 49(41.9%) patients. Among the dyspnoeic patients, more than sixty percent (60.9%) patients were found in fatigue group and 18.9% in non-fatigue group. The difference was statistically significant ($p<0.05$) between the two groups. Mandal et al.[8] found that 53% patients reported persistent dyspnea after a median 54 days post-discharge. These findings matched with our study.

Regarding severity of COVID-19, it was observed that the majority of the patients 78(66.7%) had suffered from severe COVID-19. Among patients diagnosed with severe COVID-19, 92.2% had fatigue and 35.8% were not fatigued. The difference was statistically significant ($p<0.05$) between the two groups. Townsend et al.[9]

demonstrated that there was no association between COVID-19 severity (need for inpatient admission, supplemental oxygen, or critical care) and fatigue following COVID-19. Their study findings do not match with our study. The possible explanation may be levels of fatigue may vary in populations as our study demonstrated that patients with co-morbidities were more fatigued.

In multivariate analysis, diabetes mellitus, cardiovascular disease and severe COVID-19 were found to be independent predictors for fatigue as here p value was low (p <0.05). In a study done by Townsend et al.[9] showed that overall, there was no association, either using unadjusted models, or models adjusted for age and sex, between COVID-19 disease-related characteristics (days since symptom onset, need for inpatient admission/ supplemental oxygen/critical care, length of hospital stay), routine laboratory markers of inflammation, cell turnover and fatigue post COVID-19. These results suggested that fatigue post-COVID-19 might be influenced by several factors.

This study highlighted the burden of fatigue, the impact on return to work, and the importance of follow-up of all patients diagnosed with COVID, not merely those who required hospitalization. A lengthy post-infection fatigue burden will impair quality of life and will have a significant impact on individuals, employers, and healthcare systems. These findings should be used to form management strategies for convalescent patients and allow intervention to occur in a timely manner.

Conclusion:

More than half of the patients suffer from persistent fatigue after COVID-19 infection. Diabetes mellitus, cardiovascular disease and severe COVID-19 are independent predictors for fatigue. Longer follow-up studies in a larger population are required to understand the full spectrum of health consequences after COVID-19 disease. A multidisciplinary post-COVID rehabilitation program should be established with special attention to people who had diabetes, cardiovascular disease and severe COVID-19.

References:

1. Zhu, H., Wei, L. and Niu, P., 2020. The novel coronavirus outbreak in Wuhan, China, *Global health research and policy*, *5*(1), pp.1-3.
2. World Health Organization 2021, Weekly epidemiological update on COVID-19-29 June 2021, viewed 12 July 2021, https://www.who.int/publications/m/item/weekly-epidemiological-upate-on-covid-19-29-june-2021.
3. Wu, Z. and McGoogan, J.M., 2020. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, *JAMA*, *323*(13), pp.1239-1242.
4. Carfì, A., Bernabei, R. and Landi, F., 2020. Gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19, *JAMA*, *324*(6), pp.603-605.
5. Halpin, S.J., McIvor, C., Whyatt, G. et al., 2021. Postdischarge symptoms and rehabilitation needs in survivors of COVID 19 infection: A cross sectional evaluation, *Journal of medical virology*, *93*(2), pp.1013-1022.
6. Huang, C., Wang, Y., Li, X. et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *The lancet*, *395*(10223), pp.497-506.
7. Ahmed, M.Z., Ahmed, O., Aibao, Z., Hanbin, S., Siyu, L. and Ahmad, A., 2020. Epidemic of COVID-19 in China and associated psychological problems, *Asian journal of psychiatry*, *51*, pp.102092.
8. Mandal, S., Barnett, J., Brill, S.E. et al., 2021. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19, *Thorax*, *76*(4), pp.396-398.
9. Townsend, L., Dyer, A.H., Jones, K. et al., 2020. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection, *Plos one*, *15*(11), p.e0240784.
10. Faro, M., Sàez-Francás, N., Castro-Marrero, J., Aliste, L., de Sevilla, T.F. and Alegre, J., 2016. Gender differences in chronic fatigue

syndrome, *Reumatología clínica (English edition)*, *12*(2), pp.72-77.

11. Qi, R., Chen, W., Liu, S. et al., 2020. Psychological morbidities and fatigue in patients with confirmed COVID-19 during disease outbreak: prevalence and associated biopsychosocial risk factors, medRxiv..
12. Lam, M.H.B., Wing, Y.K., Yu, M.W.M. et al., 2009. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up, *Archives of internal medicine*, *169*(22), pp.2142-2147.
13. Kokubun, K., Nemoto, K., Oka, H., Fukuda, H., Yamakawa, Y. and Watanabe, Y., 2018. Association of fatigue and stress with gray matter volume, *Frontiers in behavioral neuroscience*. *12*, p.154.
14. Kim, B.H., Namkoong, K., Kim, J.J. et al., 2015. Altered resting-state functional connectivity in women with chronic fatigue syndrome, *Psychiatry Research: Neuroimaging*, *234*(3), pp.292-297.
15. Coetzee, B., Loades, M.E., Du Toit, S., Read, R. and Kagee, A., 2018. Fatigue among South African adolescents living with HIV: Is the Chalder Fatigue Questionnaire a suitable measure and how common is fatigue?, *Vulnerable children and youth studies*, *13*(4), pp.305-316.
16. Jeon, H.O., Kim, J. and Kim, O., 2020. Factors affecting depressive symptoms in employed hemodialysis patients with chronic renal failure, *Psychology, health & medicine*, *25*(8), pp.940-949.