Persistence of Fatigue among COVID-19 Survivors in Bangladesh: A Prospective Cohort Study

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Abstract

Background: A limited number of studies have exclusively assessed fatigue among post-COVID patients. Our study aimed to assess the persistence and associations of fatigue among COVID-19 survivors after two months of recovery from their primary illness. **Method:** During hospital admission from August to September, 2020, a total of 373 patients were diagnosed to be suffering from fatigue using Chalder fatigue scale. After obtaining informed written consent, patients were followed up two months later over telephone. A total of 332 participants participated in the interview (36 patients could not be traced and another 5 patient died within two months). Patients were asked to categorize their present fatigue condition based on a simplified questionnaire developed for telephone interview. **Result:** Among study participants, 62.9% (n=207) were found to be still suffering from fatigue two months after their hospital discharge. A significant association of fatigue was found with age (p=0.000), hypertension (RR: 1.51; CI: 1.15-1.99; p=0.002), diabetes mellitus (RR: 1.45; CI: 1.08-1.95; p=0.010), ischemic heart disease (RR: 2.04; CI: 1.15-3.64; p=0.011), on admission SpO2 (p=0.000), on admission serum ferritin (p=0.000), d-dimer (p=0.000), CRP (p=0.000), and Hb% (p=0.019). Binary logistic regression model revealed significant association of age and on-admission SpO2 with persistence of fatigue. **Conclusion:** Fatigue is a highly prevalent symptom among the COVID-19 survivors with significant association between fatigue and patients clinical and laboratory markers.

Introduction:

As documented in cases with other viral infections, it is expected that a good portion of COVID-19 survivors will suffer from some form of post-COVID fatigue. However, the researchers and the community are still in the dark about the prevalence of post-COVID-19 fatigue and associated factors for the persistent symptoms. Chronic tiredness is the most common manifestation of fatigue. The fatigue may be reported as muscle weakness, slowed reflexes and responses, impaired decision-making and judgment, dizziness, sleep disturbance, and a majority of these remain undiagnosed (Perin et al., 2020; Griffith & Zarrouf, 2008). It usually settles after 2 or 3 weeks of viral illness; however, it can linger for weeks or months in some people. The exact mechanism of fatigue is unknown and multifactorial theories are well accepted (Cho et al., 2006; Tanriverdi et al., 2007).

The long term consequence of Severe Acute Respiratory Syndrome (SARS caused by the novel coronavirus SARS-CoV) that emerged from South East Asia in early 2003 was assessed in a Toronto study. It showed a good percentage of survivors experienced fatigue even after one year of the initial infection (Moldofsky &

Patcai, 20211). In a similar follow-up study in Hong Kong, over 40% of respondents from 233 SARS survivors reported a chronic fatigue problem 40 months after infection (Lam et al., 2009). During the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak, a longitudinal study revealed that many MERS survivors suffered from chronic fatigue even more than one year after the outbreak in South Korea. The prevalence rate of CFS was about 32.7% at 18 months after the MERS outbreak (Lee et al., 2019).

The study on fatigue syndrome among COVID-19 survivors is limited. A recent study in Ireland assessed the prevalence of fatigue in patients recovered from the acute phase of COVID-19 illness using the Chalder Fatigue Score (CFQ-11); more than half of affected people were reported to have persistent fatigue (67/128; 52.3%) at the median of 10 weeks after initial COVID-19 symptoms (Townsend et al., 2020). This was a small study and involved both admitted and non-admitted COVID patients. We wanted to assess if the Irish study's result is replicated in more extensive research in Bangladesh. Moreover, our study also aimed to look into other associations and predictors of post-COVID 19 fatigues, which were not evaluated in most other studies.

Methodology:

This prospective cohort study was conducted among patients admitted at COVID-19 wards at Dhaka Medical College Hospital between July and August, 2020. During their hospital stay patients were evaluated for complications such as fatigue, sleep disturbances, dyspnea etc. A total of 373 patients were diagnosed to be suffering from some form of fatigue using the validated bi-modal Chalder Fatigue Score, as described previously (Townsend et al., 2020). We then approached patients diagnosed as "fatigued" during hospital stay and asked them to participate in a follow-up telephone interview regarding their disease condition after two-months of their hospital discharge. All patients agreed to participate in the interview and gave informed written consent. Ethical permission was obtained from institutional review board at Dhaka Medical College. After two months, patients were contacted over phone. A total of 36 patients could not be reached even after repeated attempts and five patients died during these two months. Hence, a total of 332 patients participated in our study. Due to complexity associated with conducting telephone interview and considering the socio-economic background of most participants, they were asked to categorize their fatigue symptoms into one of the following groups – "deteriorated," "same as acute phase infection," "improved but persistent," and "completely recovered." This approach of data collection and follow-up of a heterogeneous group of COVID-19 patients through telephone conversation was recorded in previous studies (Tenforde et al., 2020).

In addition to their responses, patient demographic data, epidemiological, clinical and on- admission laboratory data (e.g. Hb%, neutrophil, lymphocyte, C-reactive protein, d-dimer, and serum ferritin) were obtained from hospital records. All the statistical analyses were conducted using software package SPSS version 25. Categorical values were presented as frequency and percentage. Continuous values were presented as median and inter-quartile range (IQR). For the purpose of statistical analysis, patients were either grouped as "fatigued" or "not-fatigued" based on their responses. Wilcoxon Rank Sum Test and Chi-square test were primarily used to test association between variables. P-values less than 0.05 were considered significant for all statistical testing.

Results:

Data from a total of 332 participants were analyzed. Male patients were overly represented with a total of 65.7% (n=218) participants and remaining 34.3% (n=114) were female. Results reveal, most patients were hypoxic during admission at the hospital for COVID-19, with a median SPO2 of 88.0 % (85.0, 91.0). Diabetes mellitus (41%, n=136) and hypertension (45.4%, n=151) were two of the most prevalent comorbidities found among participants. On interview, 62.9% (n=207) had been suffering from some form of fatigue, and only 37% (n=125) of participants were free from initial fatigue and were back to their pre-hospital admission level activities **(Table-1)** . Among the fatigued patients, 79.71% (n=165) reported improvement in their perceived fatigue level. Another 15.46% (n=32) were experiencing similar fatigue level as reported during their initial diagnosis at hospital. Finally, 4.83% (n=10) reported that their fatigue level has deteriorated since leaving the hospital. On testing, statistically significant association was observed between fatigue and

age (p=0.000), hypertension (RR: 1.51; CI: 1.15-1.99; p=0.002), diabetes mellitus (RR: 1.45; CI: 1.08-1.95; p=0.010), ischemic heart disease (RR: 2.04; CI: 1.15-3.64; p=0.011), on admission SpO2 (p=0.000), on admission serum ferritin (p=0.000), d-dimer (p=0.000), CRP (p=0.000), and Hb% (p=0.019)**(Table-1)** .

Table-1: Association between fatigue and demographic, clinical and laboratory variables

Variables	Fatigue Present (n=207)	Fatigue Absent (n=125)	p-value	Reference Value	RR
Age (Years), median (IQR)	**53 (41, 61)**	**43 (32, 53)**	**0.000**		
Gender					
Male, n (%)	143 (69.1%)	75 (60%)	0.091	Male	1.15
Female, n (%)	64 (30.9%)	50 (40%)			
Smoker, n (%)	44 (21.3%)	19 (15.2%)	0.173	Yes	1.39
HTN, n (%)	**108 (52.2%)**	**43 (34.4%)**	**0.002**	**Yes**	**1.5**
DM, n (%)	**96 (46.4%)**	**40 (32%)**	**0.010**	**Yes**	**1.4**
Asthma, n (%)	25 (12.1%)	19 (15.2%)	0.416	Yes	0.79
IHD, n (%)	**44 (21.3%)**	**13 (10.4%)**	**0.011**	**Yes**	**2.0**
COPD, n (%)	17 (8.2%)	6 (4.8%)	0.235	Yes	1.71
CKD, n (%)	14 (6.8%)	6 (4.8%)	0.466	Yes	1.40
SpO_2 (%), median (IQR)	**87 (85, 90)**	**90 (86, 92)**	**0.000**		
Serum Ferritin, median (IQR)	**423 (256,799)**	**301 (132, 539)**	**0.000**		
D-dimer, median (IQR)	**1 (0.5, 1.5)**	**0.61 (0.43, 1.02)**	**0.000**		
CRP, median (IQR)	**19 (10, 29)**	**12 (6, 20)**	**0.000**		
Hb%, median (IQR)	**11.5 (10.6, 13)**	**12.1 (11.1, 13.1)**	**0.019**		
Neutrophils (%), median (IQR)	81.6 (72.6, 85)	79 (72, 84)	0.050		
Lymphocyte (%), median (IQR)	15 (10, 23)	17 (11.5, 24.5)	0.138		

Abbreviation : DM = diabetes mellitus, IHD = ischemic heart disease, HTN= Hypertension, COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease. SpO2 (O2 saturation), d-dimer, ferritin, CRP, Hb%, lymphocyte and neutrophils were measured on admission day. All p-values were derived by Pearson's chi-square test

Note: RR: Relative Risk; CI: Confidence Interval; IQR: Interquartile Range

Normal range: Hb% (men: 13.5-17.5 gm/dl; female: 12-15.4 gm/dl); CRP (0-5 mg/L); serum ferritin (male: 20-250 ngm/ml; female: 10-120 ngm/ml); d-dimer: ([?] 0.5 µgm/ml)

Variables were then tested on a binary logistic regression model and only age (OR: 0.964; 95%CI: 0.94-0.98; p= 0.001) and on-admission SpO2 (OR: 1.064; 95% CI: 1.01-1.12; p=0.026) had statistically significant contribution to the model **(Table-2)** .

Table-2: Statistically significant variables on binary logistic regression model

Variables	B.	S.E.	Wald	p-value	OR	95% CI Lower	95% CI Upper
Age (Years)	-.036	.011	10.558	.001	0.964	0.943	0.986
SPO2 (%)	.062	.028	4.924	.026	1.064	1.007	1.124

Discussion

In our study, the overall prevalence of fatigue persistence among the COVID survivors was 62.9%. Townsend et al. reported that more than half of COVID-19 survivors reported fatigue, even after ten weeks later, regardless of their initial infection's seriousness (Townsend et al., 2020). In another study, fatigue (55%) was the most common reported symptom among post-COVID patients who recovered from acute illness

(Garrigues et al., 2020). The Italian study by Carfi et al. (2020) also had a similar result, with 53% (143 COVID-19 patients) reporting fatigue after a mean of 60 days of the first COVID-19 symptom. Locally, in a study conducted among physicians at Dhaka Medical College Hospital, fatigue level was found to be higher among SARS-CoV-2 infected individuals compared to control group. But, interestingly, no association could be established between fatigue and pre-existing co-morbidities, which are in stark contrast to our findings (Hasan et al., 2020). Another study conducted at same institution among post-COVID patients after one month, found 70% of study participants to be suffering from some form of fatigue (Mahmud et al., 2021).

On binary logistic regression, negative association was found between age and fatigue level. While the older age group is vulnerable to post-COVID complications, younger age groups are not immune to after effects of COVID-19. In a prospective Norwegian study, 21% of young people aged 16-30, isolating at home were still suffering from fatigue 6-months after their initial infection (Blomberg et al., 2021). Hence, while the association between age and fatigue level needs to be further evaluated, young people, contrary to popular belief, are highly susceptible to post-COVID complications like fatigue.

Statistically significant association was found between fatigue level and diabetes mellitus, on admission SpO2, hypertension, and ischemic heart disease. Previous studies indicate, diabetes mellitus and cardiac functioning status are common and independent predictors of fatigue among affected individuals (Kalra & Sahay, 2018; Fritschi & Quinn, 2010; Nelesen et al., 2008). Hence, our study findings perfectly complement previous researches on fatigue and its associated variables.

Among clinical and laboratory markers, fatigue was statistically associated with on admission SpO2, Hb%, serum ferritin, d-dimer, and CRP level. The relationship between Hb% and fatigue is previously documented in numerous studies where patients with lower Hb% tend to suffer from higher fatigue level (Holzner et al., 2002; Jacobsen et al., 2004). CRP, d-dimer, and serum ferritin are markers of acute infection in COVID-19 and previous studies indicate towards a strong association among these biomarkers and prevalence of fatigue (Vaucher et al., 2012; Cho et al., 2009; Townsend et al., 2021).

Limitations

Our single-Centre study has several limitations. Our study is longitudinal and assessed participants over the telephone, which the patients' judgment could have influenced. This limitation can be overcome by using the widely applied Chalder Fatigue Scale at a post-COVID clinic setting and describing fatigue's persistence at six months and beyond. Finally, this study was not free from the probability of bias, as the subjects had been familiar with the idea of post-COVID fatigue and other symptoms.

Recommendations

Further studies in large cohorts will be required to assess fatigue subgroups and the potential complex factors at play. We also suggest that it is now time to consider managing this post-COVID syndrome and advocate early analysis of multi-disciplinary fatigue management strategies.

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Data analysis: MMAM

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