

Neuropsychiatric Manifestations and Their Impact in Post-COVID-19 Condition: A Study in A Tertiary Care Center in Bangladesh

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Abstract:

Background: Post-COVID conditions are a wide range of new, returning, or ongoing symptoms a person can experience four or more weeks after first suffering from COVID-19. Quantification of these conditions and their impact on the patient's daily living was scarce in the current literature. This study aimed to observe the different neuropsychiatric conditions in the post-COVID conditions with their severity. Additionally, we evaluated their impact on the patient's life.

Methods: This was a cross-sectional study. We followed up with the patients attending the COVID-19 post-COVID clinic of Dhaka Medical College. The study was conducted at the COVID-19 post-acute care and follow-up clinic unit of Dhaka Medical College Hospital from January 01, 2021 to June 15, 2022.

Results: In this cross-sectional study, we included 400 patients with post-COVID conditions. The mean age (SD) of the study population was 44.8 (15.5); most were male (51%), and most patients (203, 50.8%) had mild illness. The most prominent post-COVID-19 Neuropsychiatric features were fatigue (283, 70.8%), Headache (104, 26%), memory disturbances (107, 26.8%), and depression (109, 27.8%). Most patients did not fully recover; the functional scores with Karnofsky's rating were 89.8 (7.2). Most patients reported more than usual tiredness (127, 41.1%), needed to rest more (116, 37.5%), and felt weak (183, 59.2%). About 30% of patients had Headache, mostly throbbing (69, 56.5%), bilateral, and mild in severity. Increasing age (OR, 95%CI, p-value, 1.03, 1.01-1.05, 0.002) and moderate severity COVID-19 (OR, 95%CI, p-value, 7.3, 2.3-39.05, 0.02) were the risk factors for fatigue. Increasing age was the risk factor for Headaches.

Conclusions: In the post-COVID conditions, a significant number of patient had been suffering from various neuropsychiatric conditions and were not able to return to their previous functional status.

Keywords: COVID-19, post-COVID conditions, fatigue, Headache

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Introduction:

Coronavirus disease -19 (COVID-19) can present with a wide variety of symptoms, and its presentation ranges from asymptomatic to fatal.¹ COVID-19 is a disease of the respiratory system. Several kinds of literature reported on its neuropsychiatric presentations.²⁻⁷ After the apparent recovery from COVID-19, many patients remain unwell in the post-COVID state.^{8,9} Researchers all over the world quest

for a suitable term to define such conditions. At last, the centers for disease control (CDC, USA) termed the conditions post-COVID-19 conditions. The definition they gave is “*post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19*”.¹⁰ The estimated prevalence of post-covid conditions ranges from 10-50% in various

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literature.^{8,11,12} In our recently published research on post-COVID-19 syndrome, we found neurologic manifestation, fatigue, is the most prevalent symptom in post-COVID conditions. Other neuropsychiatric manifestations included sleep disturbances, headache, smell disturbances, depressive illness, memory disturbance, and burning feet.¹¹

The most common persistent symptoms is fatigue.^{8,11,13} The estimated prevalence ranges from 10-50% in different literature.^{8,11,13} Post viral fatigue was reported during previous infection with SARS CoV and MERS CoV.^{14,15,16} The etiology of this condition is still undetermined. Spread of the virus to hypothalamus and resulting formation of pro-inflammatory cytokines, interleukins, and interferon gamma is one of the suggested mechanisms.¹⁷ Immunologic alteration.^{18, 19,20} due to SARS CoV-2 might also play a role in the development of post viral fatigue. Due to this fatigue about one third of the patient did not return to normal life¹³ and similar number of patient did not return to their job.¹³

Quantification of these conditions and their impact on the patients' daily livings were scarce in the current literature. This study aimed to observe the different neuropsychiatric conditions in the post-COVID conditions with their severity. Additionally, we also evaluated their impact on the lives of the patient.

Methods

This study aimed to observe the different spectrum of neuropsychiatric conditions in post-COVID-19 conditions with their functional impact on the lives of the patient. In this study, we, observed different post-COVID conditions. It was conducted at the COVID-19 post-acute care and follow-up clinic unit of Dhaka Medical College Hospital from January 01, 2021 to June 15, 2022.

Study design

This was a cross-sectional study. We followed up with the patients who attended the COVID-19 post-acute care and follow-up clinic of Dhaka Medical College. The objective was to observe the prevalence of different post-COVID-19

neuropsychiatric symptoms, with their severity, functional impact, and risk factors.

Study population and Eligibility criteria

The patients attended the COVID-19 post-acute care and follow-up clinic of Dhaka Medical College. Patients with more than 18 years of age, who had confirmed COVID-19 as evident by positive polymerase chain reaction (PCR) test and presented four or more weeks after first being infected with the virus were recruited for the study. Non-consenting and critical post-COVID conditions were excluded from the study.

Sample size determination

The sample size was calculated with Cochran's formula, $n = \frac{z^2 p q}{d^2}$ where n = the desired sample size, $p = 50\%$ as we didn't have much information about neuropsychiatric manifestations of post-COVID-19 in Bangladesh, $q = (1-p) = (1-0.5) = 0.5$, $Z = 1.96$ at 5% level of significance. Estimated sample size was 384. For convenience we included 400 patients with at least one post-COVID -19 condition.

Sampling technique and procedure

We used purposive sampling; we included every consecutive patient who attended the clinic from January 2022 to June 2020 with at least one post-covid-19 condition after first being infected with the virus. After taking the informed consent we recorded the data in the case record form. We evaluated all the information during affection in the COVID-19 period. The neuropsychiatric post-COVID manifestations were diagnosed and evaluated by a competent neurologist

Study variables

The variables included in the study were:

Demographic variable: Age of the respondents in years and sex.

Presenting features of COVID-19: It included fever, cough, respiratory distress, sore throat, nausea, vomiting, diarrhea, body ache etc.

Investigations in COVID-19 state: Total blood count, CRP, D-dimer, creatinine, ferritin.

COVID-19-severity: COVID-19 positivity, symptoms in case of COVID-19 positivity (asymptomatic, mild, moderate, severe, critical).

Duration: Duration between symptom onset and hospital admission, duration of hospital stays.

Post-COVID-19 conditions: Fatigue, cough, respiratory distress, sleep disturbances, etc.

Functional impact: We assessed functional impact in the post covid state at presentation for overall functional status, fatigue and depression score.

Operational definition: According to WHO and National guidelines.^{21,22}

Confirmed Covid-19: Cases with positive RT-PCR for COVID- 19 irrespective of symptoms.

Post-COVID fatigue:

The diagnostic criteria for post-COVID-19 fatigue are proposed according to symptom criteria by the United states institute of medicine²³ for diagnosis of chronic fatigue syndrome is given below-

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 1 month and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest,
2. post-exertional malaise and
3. Unrefreshing sleep.

At least one of the two following manifestations is also required:

1. Cognitive impairment or
2. Orthostatic intolerance.

Symptoms must be present at least half of the time and have moderate, substantial, or severe intensity.

Assessment:

Fatigue severity was with the Chalder Fatigue Scale.²⁴ Overall functional status was assessed with the Karnofsky performance status scale.²⁵ New onset headache after the COVID-19 was labelled as headache attributed to systemic viral infection.²⁶ Headache severity was assessed

with Numerical Rating Scale (NRS) for pain.²⁷ Depression was assessed with a depression scale.²⁸ Sleep was asses with Self-Report and Actigraphy.²⁹ And cognition was assed with the cognitive failures questionnaire (CFQ).³⁰

Data collection instrument

The data was collected in a data collection sheet for the patients who attended in the clinic.

Data collection technique:

Data was collected by assigned trained data collectors (physicians). The Patient was enrolled according to defined inclusion and exclusion criteria in the current research. Informed written consent was obtained from the participants who presented in the clinic.

Data Quality Control

Every data sheet was reviewed by two researchers; in case of any differences, it was solved with discussion. No specific management was performed for missing data. In case of conflicting answers from the respondents, we excluded the response. There was no scope for double responses as each patient was coded and had a specified hospital record number.

Data Processing and Analysis

Data were analyzed using the Statistical Package for Social Sciences version 20 (IBM Corp. Armonk, NY, USA). We expressed the qualitative data as numbers and percentages, quantitative data with normal distribution as means (SD), and non-normal data as medians (IQR). Risk factors were assessed with logistic regression, an odd ratio with 95%CI was calculated and a significant p-value was set <0.05.

Ethical consideration

The Institutional Ethical Committee of Dhaka Medical College approved the study.

Results:

In this cross-sectional study, we included 400 patients with post-covid conditions, we scrutinized about 900 patients for this study. The mean age of the study population was 44.8 (15.5), most were male (51%) and most of the patients (203, 50.8%) had mild Illness (Table 1).

Table I*General characteristics and overall Post covid features of the study population*

Traits	Results
Age, Mean (SD)	44.8(15.5)
Male, n (%)	204(51)
Hospital stays, Median (IQR)	11(8-17)
Severity of COVID-19	
Mild, n(%)	203(50.8)
Moderate, n (%)	106(26.5)
Severe, n (%)	84(21)
Critical, n (%)	7(1.8)
Post-Covid features	
Feverish feeling	13(3.3)
Fatigue	283(70.8)
Cough	103(25.8)
Respiratory distress	27(6.8)
sore throat	5(1.3)
Hoarseness of voice	6(1.5)
Chest pain	95(23.8)
Diarrhea	4(1)
Anosmia	8(2)
Anorexia	90(22.5)
Headache	104(26)
Memory disturbance	107(26.8)
Insomnia	62(15.5)
Hypersomnia	3(0.8)
Alteration of sleep pattern	5(1.3)
Depression	109(27.8%)
Confusion	27(6.8)
Arthralgia	41(10.3)
New onset diabetes	16(4)
New onset hypertension	12(3)

The most prominent post covid Neuro-psychiatric features was fatigue 283(70.8%), Headache 104(26%), memory disturbances 107(26.8%), Depression 109(27.8%) (Table 1).

Most of the patients did not recover fully, the overall functional score with Karnofsky rating was 89.8(7.2). Most of patient had more than usual tiredness 127(41.1%), need to rest more 116 (37.5%) and feel week 183(59.2%) (Table II).

About 30% patient had head ache mostly throbbing 69 (56.5%), bilateral 30(24%), mild in severity in 83(68%) (Table III).

A total of in 59(14.8%) of the study population sometimes feel severe pain and the headache rarely hamper the daily activities in 41(10%), need to lie down in 40(10%) and limited the ability to concentrate in 40(10%) (Table IV).

For depression in 44(11%) feel tired, have little interest in 34 (8.5%), and feel an urge to lie down (34, 8.5%) for several days (Table V).

Increasing age (OR, 95%CI, p-value, 1.03, 1.01-1.05, 0.002) and moderate severity COVID-19 (OR, 95%CI, p-value, 7.3, 2.3-39.05, 0.02) was the risk factors for fatigue. Increasing age was the risk factor for headache. No specific risk factors for depression were found (table VI).

Table II*Fatigue assessment*

Fatigue assessment	0 None, n (%)	1 No more than usual, n (%)	2 More than usual, n (%)	3 Much more than usual, n (%)
Tiredness	145(46.9)	37(12)	127(41.1)	—
Rest more	162(52.4)	24(7.8)	116(37.5)	7(2.3)
Feel Sleepy	268(86.7)	18(5.8)	22(7.1)	3(1.3)
Problems starting thing	295(95.5)	9(2.9)	5(1.6)	
Lack energy	205(66.3)	27(8.7)	76(24.6)	1(0.3)
Less strength in muscles	295(95.5)	9(2.9)	5(1.6)	
Feel weak	50(16.2)	34(11)	183(59.2)	42(13.6)
Difficulties concentrating	275(89)	10(3.2)	24(7.8)	
Slips of the tongue	301(99.7)	1(0.3)		
Find right word	301(97.4)	1(0.3)	7(2.3)	
Memory	212(68.6)	10(3.2)	66(21.4)	21(6.8)
Fatigue score- Overall score, median (IQR) 5(4-7)				
Overall functional status: score 89.8 (7.2)				

Table III
Headache characteristics of the study population.

Traits	Results, n (%) 122(30.5%)
Compressive	3(2%)
Throbbing	69(56.5%)
Unilateral	10(8%)
Bilateral	30(24%)
Severity, VAS	
Mild	83(68%)
Moderate	32(26%)
Severe	4(3%)

Table IV
Headache assessment with HIT-6 score

Trait	Never, n (%)	Rarely, n (%)	Sometimes, n (%)	Very often, n (%)	Always, n (%)
Severe pain	288(72.2)	41(10.3)	59(14.8)	9(2.3)	—
Hamper daily activities	318(82)	41(10.3)	24(6)	5(1.3)	—
Need to lie down	331(82.8)	40(10)	19(4.8)	8(2)	1(0.3)
Feel too tired	346(86.5)	34(8.5)	17(4.3)	2(0.5)	—
Feel irritated	351(87.8)	35(8.8)	10(2.5)	3(0.8)	—
Limit the ability to concentrate	346(86.5)	40(10)	10(2.5)	3(0.8)	—

Table V
Depression assessment

Traits	Not at all, n (%)	Several days, n (%)	More than half days, n (%)	Nearly every day, n (%)
Little interest	360(90)	34(8.5)	4(1)	
Feeling down	360(90)	34(8.5)	3(0.8)	1(0.3)
Sleeping too much	338(84.5)	28(7)	28(7)	4(1)
Feeling tired	331(82.8)	44(11)	22(5.5)	1(0.3)
Poor appetite	386(96.5)	7(1.8)	4(1)	1(0.3)
Feeling bad	397(99.3)	1(0.3)		
Trouble in concentrating	391(97.8)	5(1.3)	2(0.5)	
Moving slowly	397(99.3)	1(0.3)		
Thoughts hurting	397(99.3)	2(0.5)		

Table VI
Risk factors for Fatigue, Headache and depression

Variable	B	S.E.	Sig.	OR	95% C.I. Lower	95% C.I. Upper
Fatigue						
Age	0.030	0.010	0.002	1.030	1.011	1.050
Sex(1)	0.250	0.251	0.319	1.283	0.785	2.097
Hospital stay	0.038	0.023	0.095	1.039	0.993	1.087
Severity_Covid19			0.17			
Severity_Covid19(1)	1.610	0.842	0.056	5.005	0.960	26.076
Severity_Covid19(2)	1.997	0.851	0.019	7.366	1.389	39.057
Severity_Covid19(3)	0.907	0.834	0.277	2.476	0.483	12.696
Constant	-1.020		0.033	0.114		
Headache						
Age	0.019	5.830	0.016	1.019	1.004	1.035
Sex(1)	-0.256	1.267	0.260	0.774	0.495	1.209
Hospital stay	0.009	.295	0.587	1.009	0.976	1.044
Severity covid 19		8.641	0.034			
Severity_Covid19 (1)	1.443	1.691	1.193	4.233	0.481	37.247
Severity_Covid19 (2)	0.775	0.486	0.486	2.171	0.246	19.166
Severity_Covid19 (3)	1.580	2.026	0.155	4.853	0.551	42.733
Constant	2.890	5.717	0.017	0.056		
Depression						
age	0.011	1.802	0.180	1.011	0.995	1.027
sex	0.147	0.396	0.529	1.159	0.733	1.832
Hospital stay	0.005	0.081	0.776	1.005	0.970	1.041
Severity Covid 9		9.987	0.019			
Severity Covid19 (1)	0.458	0.276	0.600	1.581	0.286	8.732
Severity Covid19 (2)	0.540	0.375	0.540	0.583	0.104	3.282
Severity Covid19 (3)	-0.108	0.015	0.902	0.898	0.160	5.022
Constant	1.709	2.894	0.089	0.181		

Discussion:

In this cross-sectional study, we elicited several neuropsychiatric features among the patients with post-COVID-19 conditions. The most prominent post-COVID Neuropsychiatric features were fatigue, Headache memory disturbances and Depression. Most of the patient did not recover fully the, overall functional score with Karnofsky rating was 89.8(7.2). Most of the patient had more than usual tiredness need to rest more and feel week. The head ache mostly throbbing, and bilateral, mild in severity. It rarely hampers the daily

activities. Increasing age and moderate or severe COVID-19 was the risk factors for fatigue. Increasing age risk factor for Headache. No specific risk factors were found for depression.

The incidence of post-COVID conditions is very high, may reach to 85% in hospitalized patient.³¹ Neuropsychiatric conditions are the most prevalent among all symptoms in the post-COVID conditions.³³ In this study most of affected patients were middle aged and male. The findings are similar to our previous study on post-COVID syndrome and other

metanalysis.^{11,31} In this study fatigue was the most prevalent symptoms. The symptoms vary between hospitalized and non-hospitalized patients. In non-hospitalized patients' anxiety disorders were the most prevalent.³² In our study most of the study population were hospitalized about 80% and median duration of hospital stay was two weeks. In this study we did not find any relation of severity of the COVID-19 with the occurrence of the post-COVID feature. Some study found weak relationship of the severity of the COVID with the development of the post-COVID condition³³ but probably that was due to stress related to stay in the critical care setting.

In this study the median fatigue score was 5 in Chaldal scoring system (bimodal).²⁵ In another study they found similar score 4.7. The cause of the fatigue in the post-COVID state is largely unknown. The persistence of the organism or the inflammatory cytokines in the hypothalamus is the postulated mechanism.¹³

Headache in the post COVID state is mostly bilateral and throbbing in quality, but intensity is mostly mild and functional impairment due to headache is very little. The mechanism of the headache is largely unknown, inflammation in the trigemino-vascular system is one of the hypotheses.³⁴ Head intensity reduces with the time in and headache quality is predominantly throbbing found in some studies.³⁵

In this study we identified some patients with depression as well, but they suffered mostly milder form of depression.

A significant number of the population suffered in the post-COVID state. In this study according to performance status most of the patient was able to carry out normal activity with minor signs or symptoms of disease.

In this study follow-up was mixed, both in the clinic and telephonic interview, so follow up seemed not to be uniform. Again, the study population belongs to different socioeconomic and cultural condition. So perceiving and reporting of different condition might be different. We did not stratify the patient according to disease severity and hospital admission.

We recommend the establishment of a post-COVID-19 clinic in every healthcare setting. An awareness program focused on post-COVID-19 conditions should be initiated. Integrated guidelines for the management of these conditions should be developed. Treatment should involve multiple disciplines, particularly neurologists, pulmonologists, and psychiatrists. Additionally, further research into the pathophysiology and treatment of post-COVID-19 conditions should be pursued.

Conclusion:

In the post-covid conditions, significant number of the patient had been suffering from various neuropsychiatric conditions and was not able to return to their previous functional status.

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