

Research Report

Self-Reported Neurological Symptoms Two Years After Hospital Discharge Among COVID-19 Survivors

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Abstract.

Background: The acute stage of COVID-19 often presents with neurological manifestations.

Objective: This study aims to investigate the long-term neurological effects on survivors.

Methods: This study recruited 1,546 COVID-19 survivors from Wuhan, including 1,119 nonsevere cases and 427 severe survivors. Participants were interviewed two years after discharge to report their neurological symptoms. The neurological symptoms of COVID-19 were compared between survivors of severe and nonsevere COVID-19.

Results: Among the 1,546 COVID-19 survivors, 44.24% discovered at least one neurological symptom. The most prevalent self-reported symptom was fatigue (28.33%), memory deficit (13.26%), attention deficit (9.96%), myalgia (8.34%), dizziness (3.82%), and headache (2.52%). Severe cases had higher incidences of fatigue, myalgia, memory deficit, attention deficit than nonsevere cases. Older age, severe COVID-19, and comorbidity burden were associated with long-term neurological symptoms.

Conclusions: Neurological symptoms are common among COVID-19 survivors, especially in severe cases.

Keywords: COVID-19, long-COVID, neurological symptoms, sequelae

INTRODUCTION

More than 6 million people have been infected with coronavirus disease-2019 (COVID-19), and it continues to spread globally [1]. The infection of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to detrimental effects on various systems

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and organs, such as the respiratory, cardiovascular, digestive, renal, immune, and nervous systems [2]. Although some survivors of COVID-19 have persistent symptoms or even develop new-onset symptoms, the neurological aspects of long-COVID are largely unknown [3, 4]. Our previously reported neurological sequelae of the nervous system include fatigue, cognitive impairment, dizziness, and headache one year after COVID-19 infection [5]. Although the omicron variant has become more contagious, it is less pathogenic than the primary Wuhan SARS-CoV-2 strains [6]. The first batch of patients during the pandemic in Wuhan have been discharged for over two years and the persistent neurological sequelae of this population has rarely been investigated. We conducted a study to investigate the self-reported neurological symptoms of these survivors, specifically focusing on the time period of two years after they were discharged.

MATERIALS AND METHODS

Participants

This study recruited 1,546 subjects who were discharged from three COVID-19 designated hospitals in Wuhan, including Huoshenshan Hospital, Taikang Tongji Hospital, the General Hospital of the Central Theatre Command of PLA. All adult patients with laboratory-confirmed COVID-19 were screened for eligibility. The inclusion criteria included: 1) willing to participate; 2) had the ability to complete the interview. The exclusion criteria included: 1) not willing to participate; 2) could not be connected; 3) had severe hearing or language impairments that hinder the ability to complete the interview. The participants were contacted via telephone and asked to report any current neurological symptoms they were experiencing, such as headache, dizziness, fatigue, myalgia, memory deficit, seizure, attention deficit, anosmia, dysgeusia, visual deterioration, and nerve pain, among others. Since the interviews were conducted over the phone, the need for written informed consent was waived, and all participants provided verbal consent instead. The study adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology Checklist (STROBE) for cohort studies, and the research protocols were reviewed and approved by the Ethics Committee of Daping Hospital, Third Military Medical University (approval No. YYL20210310).

Clinical examinations

From the medical records, we gathered demographic information (such as age, sex, and clinical characteristics) and details about the treatment received during hospitalization (including intensive care unit (ICU) admission, mechanical ventilation, high flow oxygen therapy, and length of stay). The diagnosis of COVID-19 was determined based on the guidance provided by the World Health Organization [7]. The severity of COVID-19 was categorized as either severe or nonsevere using the guidelines established by the American Thoracic Society for community-acquired pneumonia [8]. Accordingly, severe cases of COVID-19 were identified as confirmed SARS-CoV-2 infection accompanied by at least one of the following conditions: a respiratory rate exceeding 30 breaths per minute, severe respiratory distress, or SpO₂ levels below 90% on room air. Confirmation of SARS-CoV-2 infection was done through high-throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction tests conducted on nasal and pharyngeal swab samples.

Statistical analysis

The demographic and clinical characteristics of participants were provided as mean (SD) or medians (IQRs) for continuous variables and absolute values along with percentages for categorical variables. The χ^2 test, independent *t*-test, or Mann-Whitney U test was used, as appropriate, to compare the demographic and clinical characteristics between groups. Logistic regression models were utilized to examine factors associated with neurological symptoms two years after discharge. The models were adjusted for age, sex, number of symptoms during hospitalization, and coexisting disorders. The statistical analyses were performed using SPSS statistical package version 25 (IBM SPSS Statistics for Windows, Armonk, NY, USA) and R software version 3.6.2 (R Foundation for Statistical Computing).

RESULTS

Characteristics of participants

Among the 1,546 participants, 1,119 were survivors of nonsevere cases and 427 were survivors of severe cases. Comparatively, severe cases were characterized by being older and having a higher

Table 1
Demographic and clinical characteristics of participants

Variables	Total (n = 1,546)	Nonsevere (n = 1,119)	Severe (n = 427)	p
Age – mean (SD)	57.93 (13.55)	56.19 (13.62)	62.48 (12.27)	<0.001 ^a
Male – number (%)	773 (50.00)	546 (48.79)	227 (53.16)	0.07 ^b
Smoking – number (%)	129 (8.34)	97 (8.67)	32 (7.49)	0.26 ^b
Co-existing disorders – number (%)				
Hypertension – number (%)	459 (29.69)	292 (26.09)	167 (39.11)	<0.001 ^b
Diabetes mellitus – number (%)	219 (14.17)	139 (12.42)	80 (18.74)	0.001 ^b
CAD – number (%)	99 (6.40)	57 (5.09)	42 (9.84)	0.001 ^b
Stroke – number (%)	35 (2.26)	23 (2.06)	12 (2.81)	0.24 ^b
Tumor – number (%)	25 (1.62)	15 (1.34)	10 (2.34)	0.12 ^b
CKD – number (%)	33 (2.13)	25 (2.23)	8 (1.87)	0.42 ^b
CHD – number (%)	85 (5.50)	64 (5.72)	21 (4.92)	0.32 ^b
COPD – number (%)	14 (0.91)	7 (0.64)	7 (1.64)	0.06 ^b
Characteristics during hospitalization				
LFOT – number (%)	775 (50.13)	543 (48.52)	232 (54.33)	0.02 ^b
HFOT – number (%)	354 (22.90)	205 (18.32)	149 (34.89)	<0.001 ^b
NIMV – number (%)	83 (5.37)	1 (0.09)	82 (19.20)	<0.001 ^b
IMV – number (%)	30 (1.94)	0	30 (7.03)	<0.001 ^b
ICU admission – number (%)	86 (5.56)	0	86 (20.14)	<0.001 ^b
Days of hospitalization – median (IQR)	14 (9, 21)	13 (9, 20)	15 (10, 23)	<0.001 ^c
Symptoms at disease onset				
Fever – number (%)	859 (55.56)	589 (52.64)	270 (63.23)	<0.001 ^b
Myalgia – number (%)	412 (26.65)	300 (26.81)	112 (26.23)	0.44 ^b
Chill – number (%)	35 (2.26)	17 (1.52)	18 (4.22)	0.002 ^b
Fatigue – number (%)	861 (55.69)	605 (54.07)	256 (59.95)	0.02 ^b
Cough – number (%)	1,079 (69.79)	765 (68.36)	314 (73.54)	0.03 ^b
Sore throat – number (%)	95 (6.14)	74 (6.61)	21 (4.92)	0.13 ^b
Hemoptysis – number (%)	12 (0.78)	9 (0.80)	3 (0.70)	0.57 ^b
Expectoration – number (%)	261 (16.88)	179 (16.00)	82 (19.20)	0.08 ^b
Rhinoboyon – number (%)	11 (0.71)	5 (0.45)	6 (1.41)	0.054 ^b
Anorexia – number (%)	793 (51.29)	566 (50.58)	227 (53.16)	0.20 ^b
Diarrhea – number (%)	103 (6.66)	76 (6.79)	27 (6.32)	0.42 ^b
Nausea – number (%)	45 (2.91)	33 (2.95)	12 (2.81)	0.52 ^b
Vomiting – number (%)	40 (2.59)	27 (2.41)	13 (3.04)	0.30 ^b
Dizziness – number (%)	41 (2.65)	28 (2.50)	13 (3.04)	0.33 ^b
Headache – number (%)	36 (2.33)	30 (2.68)	6 (1.405)	0.09 ^b
Chest tightness – number (%)	445 (28.78)	288 (25.74)	157 (36.77)	<0.001 ^b
Short of breath – number (%)	648 (41.91)	416 (37.18)	232 (54.33)	<0.001 ^b
Dyspnea – number (%)	124 (8.02)	49 (4.38)	75 (17.56)	<0.001 ^c

^aIndependent *t*-test. ^bPearson χ^2 test. ^cMann-Whitney U test. CAD, Coronary artery disease; CKD, Chronic kidney disease; CHD, Chronic hepatic disease; COPD, Chronic obstructive pulmonary disease; LFOT, Low-flow oxygen therapy; HFOT, High-flow oxygen therapy; NIMV, Noninvasive mechanical ventilation; IMV, Mechanical Ventilation; ICU, Intensive care unit.

proportion of individuals with hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary disease compared to nonsevere cases. Additionally, severe cases had a higher number of individuals who received low-flow oxygen therapy, high-flow oxygen therapy, noninvasive mechanical ventilation, mechanical ventilation, and admission to the ICU than nonsevere cases. In terms of symptoms experienced during hospitalization, severe cases were more likely to have fever, chills, fatigue, shortness of breath, and dyspnea compared to nonsevere cases (Table 1).

Neurological symptoms among COVID-19 survivors 2 years after discharge

Two years after hospital discharge, 44.24% survivors had at least one neurological symptom. In comparison with nonsevere cases, more subjects with severe cases had least one neurological symptom. Among the self-reported symptoms, fatigue (28.33%) is the most prevalent symptom, followed by memory deficit (13.26%), attention deficit (9.96%), myalgia (8.34%), dizziness (3.82%), headache (2.52%), dysgeusia (1.68%), and anosmia (1.55%). The

Table 2
Self-reported neurological symptoms two years after discharge in COVID-19 survivors

Variables	Total (n = 1,546)	Nonsevere (n = 1,119)	Severe (n = 427)	p
At least one symptom (%)	684 (44.24%)	437 (39.05)	247 (57.84)	<0.001
Dizziness – number (%)	59 (3.82)	40 (3.57)	19 (4.45)	0.25
Headache – number (%)	39 (2.52)	25 (2.23)	14 (3.28)	0.16
Fatigue – number (%)	438 (28.33)	287 (25.65)	151 (35.36)	<0.001
Myalgia – number (%)	129 (8.34)	79 (7.06)	50 (11.71)	0.003
Memory deficit – number (%)	205 (13.26)	102 (9.12)	103 (24.12)	<0.001
Attention deficit – number (%)	154 (9.96)	77 (6.88)	77 (18.03)	<0.001
Seizure – number (%)	2 (0.13)	1 (0.09)	1 (0.23)	0.48
Anosmia – number (%)	24 (1.55)	13 (1.16)	11 (2.58)	0.04
Dysgeusia – number (%)	26 (1.68)	16 (1.43)	10 (2.34)	0.15
Visual deterioration – number (%)	14 (0.91)	5 (0.45)	9 (2.11)	0.004
Nerve pain – number (%)	7 (0.45)	3 (0.27)	4 (0.94)	0.10

Pearson χ^2 test.

prevalence rate of seizure, visual deterioration, and nerve pain was below 1%. In comparison with non-severe cases, severe COVID-19 survivors were more prevalent in fatigue, memory deficit, attention deficit, myalgia, anosmia, and visual deterioration (Table 2).

Factors associated with neurological symptoms among COVID-19 survivors 2 years after discharge

Using multivariate logistical regression models, we investigated factors associated with the neurological symptoms two years after discharge among these participants. Older age, symptom burden (number of symptoms) during hospitalization, coronary artery disease, and stroke history were associated with dizziness. Male sex was associated with headache. Older age, male sex, symptom burden during hospitalization, and severe COVID-19 were associated with fatigue. Male sex, symptom burden during hospitalization, diabetes, chronic hepatic disease, and chronic obstructive pulmonary disease were associated with myalgia. Older age and severe COVID-19 were associated with memory and attention deficits. Older age was associated with dysgeusia. No risk factor for seizure, anosmia, visual deterioration, or nerve pain was identified (Table 3).

DISCUSSION

In the present study, we found a panel of self-reported neurological symptoms two years after hospital discharge among COVID-19 survivors from Wuhan. The most prevalent symptoms include fatigue, memory deficit, attention deficit, and myalgia. Older age, comorbidities, and disease severity

were associated with long-term neurological symptoms.

In the acute phase of COVID-19, about 36% of patients from Wuhan had at least one neurological symptom, and this rate was 45.5% in severe cases [2]. It is not fully clear whether these symptoms would be consistent. In this study, we found that 44.24% of COVID-19 survivors had at least one symptom of the nervous system, suggesting a high burden of neurological sequelae after COVID-19 infection, especially in severe cases. Specifically, fatigue, memory and attention deficits, myalgia, and dizziness were frequently reported. Fatigue, with a prevalence rate of 28.33%, is the most commonly self-reported neurological symptom. The proportion of subjects with fatigue two years after discharge was significantly lower than the that at disease onset and may gradually decrease as heart and lung functions recover. Self-reported memory deficits were observed in 13.25% of all participants and 24.12% in severe cases. Additionally, 9.96% of all participants and 18.03% of severe cases experienced attention deficits. These findings align with a previous report which revealed that a significant number of COVID-19 survivors suffered from cognitive impairment one year after infection [9]. This suggests that the ongoing global spread of COVID-19 could contribute to an increased burden of cognitive impairment. Myalgia is also a common manifestation in the acute phase of COVID-19. We found the prevalence rate of myalgia was 8.34% in all cases and was 11.71% in severe cases. A recent meta-analysis indicates that 23.14% of COVID-19 survivors had persistent myalgia between 30- and 60-days post infection [10]. In this study, dizziness and headache were also frequently reported neurological symptoms post

Table 3
Risk factors for neurological symptoms two years after discharge in COVID-19 survivors

Variables	Risk factors	RR (95% CI)
Dizziness	Age	1.027 (1.003, 0.026)
	Symptom burden during hospitalization	1.155 (1.012, 1.320)
	CAD	2.250 (1.012, 5.006)
	Stroke	3.713 (1.270, 10.852)
Headache	Male	2.824 (1.322, 6.034)
Fatigue	Age	1.014 (1.004, 1.024)
	Male	1.304 (1.025, 1.659)
	Symptom burden during hospitalization	1.124 (1.060, 1.191)
	Severe disease	1.354 (1.050, 1.746)
Myalgia	Male	1.908 (1.266, 2.875)
	Symptom burden during hospitalization	1.106 (1.006, 1.216)
	Diabetes	1.635 (1.004, 2.663)
	CHD	2.563 (1.312, 5.008)
	COPD	4.699 (1.204, 18.343)
Memory deficit	Age	1.020 (1.006, 1.033)
	Severe disease	2.709 (1.969, 3.728)
Attention deficit	Age	1.039 (1.023, 1.056)
	Severe disease	2.268 (1.577, 3.261)
Seizure	None	NA
Anosmia	None	NA
Dysgeusia	Age	1.057 (1.018, 1.098)
Visual deterioration	None	NA
Nerve pain	None	NA

Multivariate logistical regression models. Included variables: Age, Sex, length of hospital stay, smoking, symptom burden during hospitalization (number of symptoms), hypertension, diabetes, coronary artery disease (CAD), stroke, tumor, chronic kidney disease, chronic hepatic disease (CHD), chronic obstructive pulmonary disease (COPD), severity.

COVID-19 infection [11]. In our cohort, the prevalence rate of dizziness and headache was 3.82% and 2.52%, which was much lower than previous reports. This might suggest that these symptoms may remit with time according to previous reports [12, 13]. Notably, taste and smell impairments, which are the most common manifestations of COVID-19 [14], are rarely reported in COVID-19 survivors. In a recent report, the rate of altered taste or smell reduced from 64.3% at disease onset to 8.3% at two years post infection [12, 13], suggesting that these symptoms may be reversible.

Risk factors for long-COVID symptoms include older age, severe COVID-19, and comorbidities according to previous reports [15, 16]. In this study, we found that older age, disease severity, comorbidities were associated with long-term neurological sequelae of COVID-19 survivors. For example, older age was a risk factor for dizziness, fatigue, memory and attention deficits, and severe COVID-19 was a risk factor for fatigue and memory and attention deficit. These long-term neurological symptoms significantly affect the quality of life of COVID-19 survivors [17]. In this regard, patients with these risk factors should be paid more attention for future

long-term health consequences following COVID-19 infection. However, we found in this study that male sex was associated long-term fatigue and myalgia, which is not consistent with previous studies [18]. This might be due to the difference in study populations and study design.

Limitations and conclusions

There are several limitations to the study design of this research. Firstly, the symptoms reported in this study are based on self-reporting by survivors, without the use of objective measures. Secondly, a control group consisting of individuals with other viral infectious diseases was not included, making it impossible to determine whether COVID-19 has a greater long-term impact on the neurological system compared to other infectious diseases. Additionally, this study is limited by its cross-sectional nature and the absence of longitudinal cohort investigations, which prevents the determination of the dynamic changes in neurological symptoms. Nevertheless, this study provides new information regarding the long-COVID syndrome among survivors of the Wuhan COVID-19 pandemic.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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