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One-year self-reported neurological sequelae in older COVID-19 survivors

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Abstract

Aim: With the increasing number of patients recovered from COVID-19, the long-term health consequences of this disease have attracted much attention. Neurological complications are commonly seen in the acute phase of COVID-19, especially in older adults. This study aimed to investigate the long-term neurological sequelae in older COVID-19 survivors.

Methods: A total of 1438 COVID-19 survivors were recruited in this study. One year after hospital discharge, information about self-reported symptoms of the central and peripheral nervous system was collected. Comparisons of these neurological symptoms between COVID-19 survivors with severe and nonsevere cases were performed.

Results: A total of 139 (53.46%) COVID-19 survivors with severe cases and 328 (27.84%) survivors with nonsevere cases reported at least one neurological symptom one year after discharge. Most of these neurological symptoms were symptoms of the central nervous system. Specifically, 126 (48.46%) survivors with severe cases and 306 (25.98%) survivors with nonsevere cases reported at least one CNS symptom. The most frequently reported symptoms were memory deficit [234 (16.27%)] and attention deficit [80 (5.56%)]. Disease severity was



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associated with increased risks of long-term neurological sequelae of COVID-19.

Conclusion: This study demonstrated that neurological sequelae of COVID-19 are common one year after patient discharge, suggesting that the effects of COVID-19 on the neurological system are prolonged.

Keywords: COVID-19, neurological sequelae, survivors

INTRODUCTION

COVID-19 has infected over 4 billion people worldwide and the number is increasing. With the increasing number of patients who recovered from COVID-19, the long-term health consequences of COVID-19 have attracted much attention^[1]. Neurological manifestations of COVID-19 are commonly observed in the acute phase of the disease, including symptoms of the central and/or peripheral nervous system^[2]. Neurological sequelae such as headache, dizziness, movement disorders, and attention deficits were observed, and these symptoms are more prevalent in survivors with severe cases^[3,4]. We have previously demonstrated that COVID-19 had long-term effects on the cognitive performances of older survivors, especially those who survived severe cases^[1,5]. Therefore, it is more urgent to demonstrate the neurological sequelae of COVID-19 in older adults, especially survivors of severe cases. This study aims to investigate the self-reported neurological sequelae of COVID-19 one year after patient discharge.

METHODS

Subjects

This cross-sectional study was conducted one year after patient discharge, which included 1438 COVID-19 survivors aged 60 years or above. These subjects were discharged from three COVID-19 designated hospitals in Wuhan, China, from February 10 to April 10, 2020. Among these subjects, 260 were severe cases and 1178 were nonsevere cases. This study was conducted simultaneously with our previous reports, which aimed to determine the long-term effects of COVID-19 on cognition in older hospital survivors^[1,5]. Therefore, the inclusion and exclusion criteria were consistent with these two publications.

The research protocols were approved by the institutional review boards of Daping Hospital, as the medical staff of this hospital worked in the COVID-19-designated Huoshenshan Hospital and Tongji Taikang Hospital, which were dismissed after the pandemic. Since this study was conducted based on telephone interviews, the requirement for written informed consent was waived, but verbal informed consent was obtained from all participants or their legal guardians. The findings of this study were reported following the Strengthening the Reporting of Observational Studies in Epidemiology Checklist (STROBE) for cohort studies.

Clinical examinations

The demographic information, including age and sex, and clinical characteristics, including body mass index (BMI) and coexisting disorders, including hypertension, diabetes, hyperlipidemia, stroke history, coronary heart disease, and chronic obstructive pulmonary disease (COPD), the treatment during hospitalization, such as intensive care unit (ICU) admission, mechanical ventilation, high flow oxygen therapy, length of hospital stay, antiviral therapy, antibacterial therapy, intravenous globulin (IVIg) use, and glucocorticoid use, were collected from the medical records.

The diagnosis of COVID-19 was made based on the World Health Organization interim guidance^[6]. The severity of COVID-19 was defined as severe or nonsevere following the American Thoracic Society (ATS) guidelines for community-acquired pneumonia^[7]. Accordingly, severe cases with COVID-19 were defined

as confirmed SARS-CoV-2 infection plus one of the following conditions: respiratory rate > 30 breaths/min, severe respiratory distress, or SpO₂ < 90% on room air. SARS-CoV-2 infection was confirmed by high-throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction assays of nasal and pharyngeal swab specimens.

Participants were interviewed by telephone and were asked to report their neurological manifestations one year after hospital discharge. These symptoms were classified into sequelae of the central nervous system, including dizziness, headache, memory deficit, attention deficit, ataxia, and seizure, and those of the peripheral nervous system, including taste problem, smell problem, vision problem, nerve pain, and myalgia [Supplementary Table 1].

Statistical analysis

The demographic and clinical characteristics of participants were presented as medians (IQRs) for continuous variables and absolute values along with percentages for categorical variables. For the comparison of demographic and clinical characteristics among groups, the Kruskal-Wallis test, χ^2 test, Fisher's exact test, or Mann-Whitney *U* test was used where appropriate.

Logistic regression models were used to explore risk factors associated with neurological symptoms one year after discharge, adjusting for age, sex, BMI, and coexisting disorders. Statistical analyses were conducted 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

Demographic characteristics of participants

This study included 1178 COVID-19 survivors with nonsevere cases and 260 survivors with severe cases. Severe cases were older than nonsevere cases [median (IQR): 71 (67, 79) vs. 68 (66, 73), $P < 0.001$]. Severe cases had lower education levels [median (IQR): 12 (6, 12) vs. 12 (9, 12), $P = 0.05$] and higher BMI [median (IQR): 24.38 (22.90, 25.64) vs. 23.93 (22.44, 25.33), $P = 0.009$] than nonsevere cases. Severe cases had higher proportion of subjects with hypertension [number (%): 133 (51.15) vs. 426 (36.16), $P < 0.001$], diabetes [number (%): 65 (25.00) vs. 208 (17.66), $P = 0.01$], stroke history [number (%): 42 (16.15) vs. 37 (3.14), $P < 0.001$], coronary heart disease [number (%): 71 (27.31) vs. 121 (10.27), $P < 0.001$] and COPD [number (%): 43 (16.38) vs. 99 (8.40), $P < 0.001$]. As expected, severe cases had higher proportion of subjects received ICU treatment [number (%): 72 (27.69) vs. 0, $P < 0.001$], mechanical ventilation [number (%): 83 (31.92) vs. 0, $P < 0.001$], high flow oxygen therapy [number (%): 106 (40.77) vs. 184 (15.62), $P < 0.001$], delirium [number (%): 82 (31.54) vs. 10 (0.85), $P < 0.001$], and had longer length of hospital stay [median (IQR): 28 (22, 34) vs. 19 (14, 23), $P < 0.001$]. Furthermore, severe cases had higher proportion of subjects who received antibacterial therapy [number (%): 143 (55.00) vs. 131 (11.12), $P < 0.001$], IVIg treatment [number (%): 143 (55.00) vs. 22 (1.87), $P < 0.001$] and glucocorticoid treatment [number (%): 144 (55.38 vs. 152 (12.90), $P < 0.001$] than nonsevere cases [Table 1].

Neurological sequelae of COVID-19 survivors

One year after patient discharge, 467 (32.48%) survivors reported at least one neurological symptom. Specifically, 432 (30.04%) survivors reported at least one symptom of the central nervous system, and 45 (3.13%) survivors reported at least one symptom of the peripheral nervous system. The most-reported symptom was memory loss [234 (16.27%)], followed by dizziness [96 (6.68%)], headache [80 (5.56%)], attention deficit [80 (5.56%)], smell loss [16 (1.11%)], and taste loss [15 (1.04%)].

Table 1. Demographic and baseline information of participants

	Total group (n = 1438)	Severe cases (n = 260)	Nonsevere cases (n = 1178)	P value
Age - Median (IQR), year	69 (66, 74)	71 (67, 79)	68 (66, 73)	< 0.001 ^a
Male - No. (%)	691 (48.05)	133 (51.15)	557 (47.28)	0.27 ^b
Education - Median (IQR), year	12 (9, 12)	12 (6, 12)	12 (9, 12)	0.05 ^a
BMI - Median (IQR), kg/m ²	23.99 (22.54, 25.38)	24.38 (22.90, 25.64)	23.93 (22.44, 25.33)	0.009 ^a
Coexisting disorders - No. (%)				
Hypertension	561 (39.01)	133 (51.15)	426 (36.16)	< 0.001 ^b
Diabetes mellitus	274 (19.05)	65 (25.00)	208 (17.66)	0.01 ^b
Hyperlipidaemia	142 (9.87)	31 (11.92)	111 (9.42)	0.25 ^b
Stroke history	79 (5.49)	42 (16.15)	37 (3.14)	< 0.001 ^b
Coronary heart disease	193 (13.42)	71 (27.31)	121 (10.27)	< 0.001 ^b
COPD	142 (9.87)	43 (16.38)	99 (8.40)	< 0.001 ^b
ICU admission - No. (%)	72 (5.01)	72 (27.69)	0 (0)	< 0.001 ^b
Mechanical ventilation, No. (%)	83 (5.77)	83 (31.92)	0 (0)	< 0.001 ^b
High flow oxygen therapy, No. (%)	290 (20.17)	106 (40.77)	184 (15.62)	< 0.001 ^b
Delirium, No. (%)	92 (6.40)	82 (31.54)	10 (0.85)	< 0.001 ^b
Length of hospital stay (IQR), day	20 (15, 25)	28 (22, 34)	19 (14, 23)	< 0.001 ^a
Antiviral therapy - No. (%)	1107 (76.98)	209 (80.38)	898 (76.23)	0.17 ^b
Lianhua Qingwen	703 (48.89)	136 (52.31)	567 (48.13)	0.24 ^b
Arbidol	530 (36.86)	106 (40.77)	424 (35.99)	0.16 ^b
Kaletra	125 (8.69)	28 (10.77)	97 (8.23)	0.18 ^b
Oseltamivir	52 (3.62)	10 (3.85)	42 (3.57)	0.85 ^b
Ribavirin	9 (0.63)	2 (0.77)	7 (0.59)	0.67 ^b
Other antiviral drugs	20 (1.39)	3 (1.15)	17 (1.44)	1.00 ^b
Antibacterial therapy - No. (%)	274 (19.05)	143 (55.00)	131 (11.12)	< 0.001 ^b
IVIg treatment - No. (%)	165 (11.47)	143 (55.00)	22 (1.87)	< 0.001 ^b
Glucocorticoid - No. (%)	296 (20.58)	144 (55.38)	152 (12.90)	< 0.001 ^b

Other antiviral drugs included chloroquine phosphate, hydroxychloroquine, and ritonavir. ^aMann-Whitney *U* test. ^bPearson χ^2 test. IQR: Interquartile range; BMI: body mass index; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; IVIg: intravenous immunoglobulin.

Severe and nonsevere cases had similar frequencies in dizziness [number (%): 20 (7.69) *vs.* 76 (6.45), *P* = 0.49], ataxia [number (%): 2 (0.77) *vs.* 1 (0.08), *P* = 0.09], taste problem [number (%): 5 (1.92) *vs.* 10 (0.85), *P* = 0.17], nerve pain [number (%): 2 (0.77) *vs.* 1 (0.08), *P* = 0.09] and myalgia [number (%): 4 (1.54) *vs.* 5 (0.42), *P* = 0.06]. Severe cases had higher proportion of subjects with headache [number (%): 27 (10.38) *vs.* 53 (4.50), *P* < 0.001], memory problem [number (%): 72 (27.69) *vs.* 162 (13.75), *P* < 0.001], attention deficit [number (%): 28 (10.77) *vs.* 52 (4.41), *P* < 0.001], seizure [number (%): 2 (0.77) *vs.* 0, *P* = 0.03], smell loss [number (%): 8 (3.08) *vs.* 8 (0.68), *P* = 0.003] and vision problem [number (%): 2 (0.77) *vs.* 0, *P* = 0.03] [Table 2].

Associations between disease severity and neurological sequelae of COVID-19

In this study, we investigated the associations between disease severity and neurological sequelae of COVID-19. We found that severe disease was associated with a higher risk of any neurological symptom [OR (95%CI): 2.908 (2.809, 3.011)], any CNS symptom [OR (95%CI): 2.623 (2.533, 2.716)] and PNS symptom [OR (95%CI): 4.486 (4.153, 4.846)]. Furthermore, severe disease was associated with a higher risk of almost all the symptoms, including dizziness [OR (95%CI): 1.259 (1.182, 1.342)], headache [OR (95%CI): 2.198 (2.066, 2.337)], memory loss [OR (95%CI): 2.157 (2.072, 2.246)], attention deficit [OR (95%CI): 1.142

Table 2. Neurological sequelae one year after discharge in COVID-19 survivors

	Total group (n = 1438)	Severe cases (n = 260)	Nonsevere cases (n = 1178)	P value
Any - No. (%)	467 (32.48)	139 (53.46)	328 (27.84)	< 0.001
CNS sequelae				
Any - No. (%)	432 (30.04)	126 (48.46)	306 (25.98)	< 0.001
Dizziness - No. (%)	96 (6.68)	20 (7.69)	76 (6.45)	0.49
Headache - No. (%)	80 (5.56)	27 (10.38)	53 (4.50)	< 0.001
Memory deficit - No. (%)	234 (16.27)	72 (27.69)	162 (13.75)	< 0.001
Attention deficit - No. (%)	80 (5.56)	28 (10.77)	52 (4.41)	< 0.001
Ataxia - No. (%)	3 (0.21)	2 (0.77)	1 (0.08)	0.09
Seizure - No. (%)	2 (0.14)	2 (0.77)	0 (0)	0.03
PNS sequelae				
Any - No. (%)	45 (3.13)	21 (8.08)	24 (2.04)	< 0.001
Taste problem - No. (%)	15 (1.04)	5 (1.92)	10 (0.85)	0.17
Smell disorder - No. (%)	16 (1.11)	8 (3.08)	8 (0.68)	0.003
Vision problem - No. (%)	2 (0.14)	2 (0.77)	0 (0)	0.03
Nerve pain - No. (%)	3 (0.21)	2 (0.77)	1 (0.08)	0.09
Myalgia - No. (%)	9 (0.63)	4 (1.54)	5 (0.42)	0.06

All comparisons were conducted using Pearson χ^2 test.

(1.078, 1.210)], taste loss [OR (95%CI): 2.054 (1.780, 2.370)] and smell loss [OR (95%CI): 4.577 (4.042, 5.182)] [Figure 1]. Notably, these associations remained significant after adjusting for age, sex, BMI, and coexisting disorders, including hypertension, diabetes, hyperlipidemia, stroke, coronary heart disease, and COPD, suggesting that severe disease had a significant impact on postinfection neurological sequelae beyond these factors.

DISCUSSION

In this study, we investigated the self-reported neurological symptoms of COVID-19 in a cohort of older survivors one year after discharge. Overall, older COVID-19 survivors, especially those who survived severe cases, had a high burden of neurological sequelae. Symptoms of the central nervous system were more common than those of the peripheral nervous system. The most-reported symptom was memory loss, followed by attention deficit and dizziness.

Neurological symptoms are common in both the acute phase and post-acute phase of COVID-19^[8]. The neurological sequelae of COVID-19 include a variety of symptoms, such as smell problems, taste problems, and memory deficit^[9,10]. COVID-19 also increases the risk of a panel of neurological diseases, such as stroke^[11] and autoimmune diseases^[12]. We have recently reported that older COVID-19 survivors had an increased risk of longitudinal cognitive decline and that severe cases had a higher speed of cognitive decline than nonsevere survivors and uninfected subjects^[1], which is consistent with the present findings that memory deficit was reported by 16.27% of older COVID-19 survivors. The postinfection memory deficit might be attributed to the fact that older adults are at a higher risk of cognitive impairment and that the postinfection low-grade inflammation or hypoxia status would further exacerbate long-term cognitive impairment.

Other symptoms, such as attention deficit, dizziness, and headache, have also been reported months after COVID-19 infection. It is suggested that attention deficits are very commonly seen in COVID-19

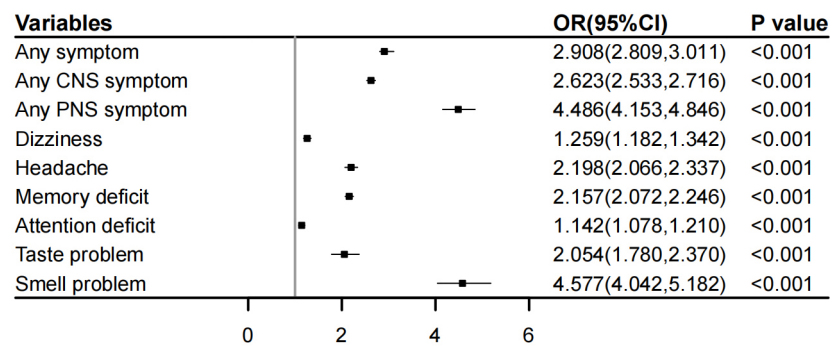


Figure 1. Associations between disease severity and neurological symptoms one year after discharge. Logistic regression models with adjustment for age, sex, body mass index, and coexisting disorders.

survivors^[13]. This sequela of COVID-19 would dramatically impact the living quality and work efficiency of survivors. The possible association between COVID-19 and attention deficit might be attributed to the altered neurotransmitter secretion profile after SARS-CoV-2 infection^[14]. Headache and dizziness after COVID-19 have also been reported by other studies^[9]. However, we found in this study that symptoms of the periphery nervous system were rarely reported in COVID-19 survivors, suggesting that symptoms such as smell and taste problems could be reversible and more attention should be focused on the long-term impact of COVID-19 on the central nervous system. This might also be because our study did not utilize objective measures to determine the smell and taste of participants.

The common mechanism of postinfection neurological symptoms might be multifactorial. Evidence regarding the direct invasion of the virus into the brain was limited. The most possible contributions of COVID-19 to postinfection neurological sequelae might be associated with chronic inflammatory^[15,16] and long-term hypoxia status after COVID-19^[17]. Other pathways by which COVID-19 insults the brain also exist. For example, recent studies have found that postinfection autoimmunity may damage neurons^[18]. Neuronal reactive autoantibodies were found in COVID-19 survivors, and these autoantibodies were associated with the neurological symptoms and neuronal damage biomarkers of patients^[19], suggesting an autoimmune element of neurological insult of COVID-19. Studies found that the incidence of autoimmune diseases such as Guillain-Barré syndrome^[20] and multiple sclerosis^[21] is increased after SARS-CoV-2 infection, further supporting this notion. Furthermore, SARS-CoV-2 is suggested to induce a wide variety of transcriptome changes in the brain regions that were associated with cognition and memory^[22,23]. Neurodegenerative biomarkers are altered in biofluid of COVID-19 survivors^[24]. Besides, COVID-19 is associated with mental health outcomes such as depression and anxiety, which could contribute to increased self-reported symptoms^[25].

This study has several limitations. First, the symptoms were self-reported by survivors, and no objective measures were used. Second, this study only included older adults; thus, it is not clear whether younger survivors had similar sequelae. Third, this study did not include a control group with other viral infectious diseases; thus, it could not be determined whether COVID-19 had a greater long-term impact on the neurological system than other infectious diseases. This study is limited by its cross-sectional nature and no longitudinal cohort investigations were involved; therefore, it cannot be known whether these symptoms were reversible. However, this study added novel information about the long-COVID syndrome.

DECLARATIONS

Authors' contributions

Designed this study and drafted the manuscript: Wang LR, Yang Y

Conducted the interviews: Jiang L, Liu XY, Yan XQ

Had critical reading of the manuscript: Liu YH, Wang YJ

Availability of data and materials

The data that support the findings of this study are available from authors.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The research protocols were approved by the institutional review boards of Daping Hospital. Since this study was conducted based on telephone interviews, the requirement for written informed consent was waived, but verbal informed consent was obtained from all participants or their legal guardians. The research protocols were approved by the institutional review boards of Daping Hospital (2023-175).

Consent for publication

All participants agree to publication.

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