



Long-term white matter changes in patients who develop severe depression after multiple COVID-19 infections: a 3–6-month study

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Background: The white matter (WM) of patients who suffer from depression after long-term coronavirus disease 2019 (COVID-19) showed a dynamic change. However, to date, no research on the dynamic change in the WM of patients who develop severe depression after multiple COVID-19 infections has been conducted. This study aimed to evaluate long-term WM changes in patients who experience mild or moderate depression after their first COVID-19 infection followed by severe depression after their second infection.

Methods: In total, 27 outpatients who developed severe depression after two COVID-19 infections (the patient group) and 28 outpatients who developed mild or moderate depression after one COVID-19 infection (the control group) were included in this prospective study. Psychological assessments for depression, anxiety, and insomnia were conducted 3–6 months after infection. Diffusion tensor imaging was performed. The fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity were calculated and compared between the groups. The correlations between the psychological scores and image parameters were analyzed.

Results: There was no difference between the two groups in terms of age (51.857 ± 2.770 vs. 48.148 ± 2.0678 years, $P=0.222$), gender (female: 75.0% vs. 55.6%, $P=0.130$), and education ($P=0.317$). The psychological scores were higher in the patient group than the control group (Patient Health Questionnaire-9: 17.290 ± 2.600 vs. 8.640 ± 2.599 , Generalized Anxiety Disorder-7: 15.440 ± 3.490 vs. 7.640 ± 2.376 , Athens Insomnia Scale: 15.852 ± 3.219 vs. 10.179 ± 2.763 ; all $P<0.001$). The patient group showed decreased FA values in the bilateral corticospinal tracts, anterior thalamic radiations, and right superior longitudinal fasciculus ($P_{\text{family-wise error}} < 0.05$). All the psychological scores were negatively mildly to moderately correlated with the FA values of the above-mentioned WM tracts ($r=-0.491$, $r=-0.570$, and $r=-0.355$, $P<0.001$, $P<0.001$, and $P=0.008$).

Conclusions: The present study revealed impairments in the WM integrity of patients who developed severe depression within 3–6 months of repeated COVID-19 infections. The findings revealed the mechanism of COVID-19-related depression and underscored the importance of psychological intervention after COVID-19 infection.

Keywords: Coronavirus disease 2019 (COVID-19); depression; diffusion tensor imaging (DTI); white matter (WM); magnetic resonance imaging (MRI)

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Introduction

Long coronavirus disease 2019 (COVID-19) refers to the long-term symptoms that last for 2 to 3 months after recovery from COVID-19. It poses a new clinical challenge in the management of COVID-19 infection. Psychological issues like depression, anxiety, sleep disorders, and cognitive impairment are common symptoms in long COVID-19 (1). Of these symptoms, depression is the most common psychological issue worldwide. In the COVID-19 pandemic, psychological issues have been a heavy burden, and an additional 53.2 million cases of major depressive disorder have been reported globally (2). Psychological symptoms can occur 4 weeks after other symptoms (3) and can persist up to 20 months after COVID-19 infection (4,5).

A dynamic change has been observed in the white matter (WM) of patients who recover from COVID-19. Huang *et al.* showed that compared to healthy controls, COVID-19 patients had a lower volume fraction of intracellular water in the corona radiata, corpus callosum, and superior longitudinal fasciculus (SLF) (6). After 2 years, recovered COVID-19 patients showed longitudinal recovery trends for WM, but some showed persistent WM abnormalities at 2 years after discharge (7). Benedetti *et al.* showed that the severity of psychopathology is closely associated with WM microstructure change. The Beck Depression Inventory was found to be negatively associated with axial diffusivity (AD) in a small cluster, including the left superior corona radiata, SLF, and posterior corona radiata (8). Impact of Event Scale-Revised scores are negatively associated with AD in several WM tracts in bilateral superior and posterior corona radiata and SLF, and also involve the inferior longitudinal fasciculus, external capsule, and anterior thalamic radiations (ATRs) (8). These studies revealed that COVID-19 is closely related to the severity of depression and WM damage. Previous studies have primarily focused on WM changes following initial COVID-19 infection. However, multiple COVID-19 infections are common, and can lead to prolonged periods of low-grade inflammation. Despite this, alterations in cerebral function and structure in individuals experiencing multiple COVID-19 infections

remain unclear, and their correlation with the psychological burden has not been thoroughly investigated. Therefore, this study aimed to evaluate long-term changes in WM among patients who experienced mild to moderate depression following their initial COVID-19 infection and then developed severe depression after a subsequent infection. By doing so, we sought to identify the potential structural changes associated with psychological issues arising from multiple COVID-19 infections and gather objective evidence for the early prevention and treatment of these patients. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-2168/rc>).

Methods

Patients

The study design is illustrated in *Figure 1*. In total, 1,453 COVID-19 patients at the Shanghai Mobile Field Hospital from April to June 2022 who underwent psychological assessment for depression, and evaluation of the degree of anxiety and insomnia on the day of out-hospitalization were identified. In total, 103 patients had mild to moderate depression. Subsequently, these patients were followed-up for 3–6 months via cell phone. During the follow-up period, 13 patients were lost to follow up, 21 were not reinfected with COVID-19, and 17 did not have their infection confirmed by nucleic acid testing at tertiary hospitals, while 52 were reinfected with COVID-19 from December 2022 to January 2023. These 52 patients underwent comprehensive face-to-face psychological assessments for depression, anxiety, and insomnia within 3–6 months of their second infection. Among them, 32 patients with severe depression were allocated to the patient group and subsequently underwent magnetic resonance (MR) scans 1 week after the final psychological assessment. Consecutive psychological outpatients at our hospital who were infected with COVID-19 between December 2022 and January 2023 were prospectively recruited for this study. These patients underwent psychological assessment for depression, anxiety,

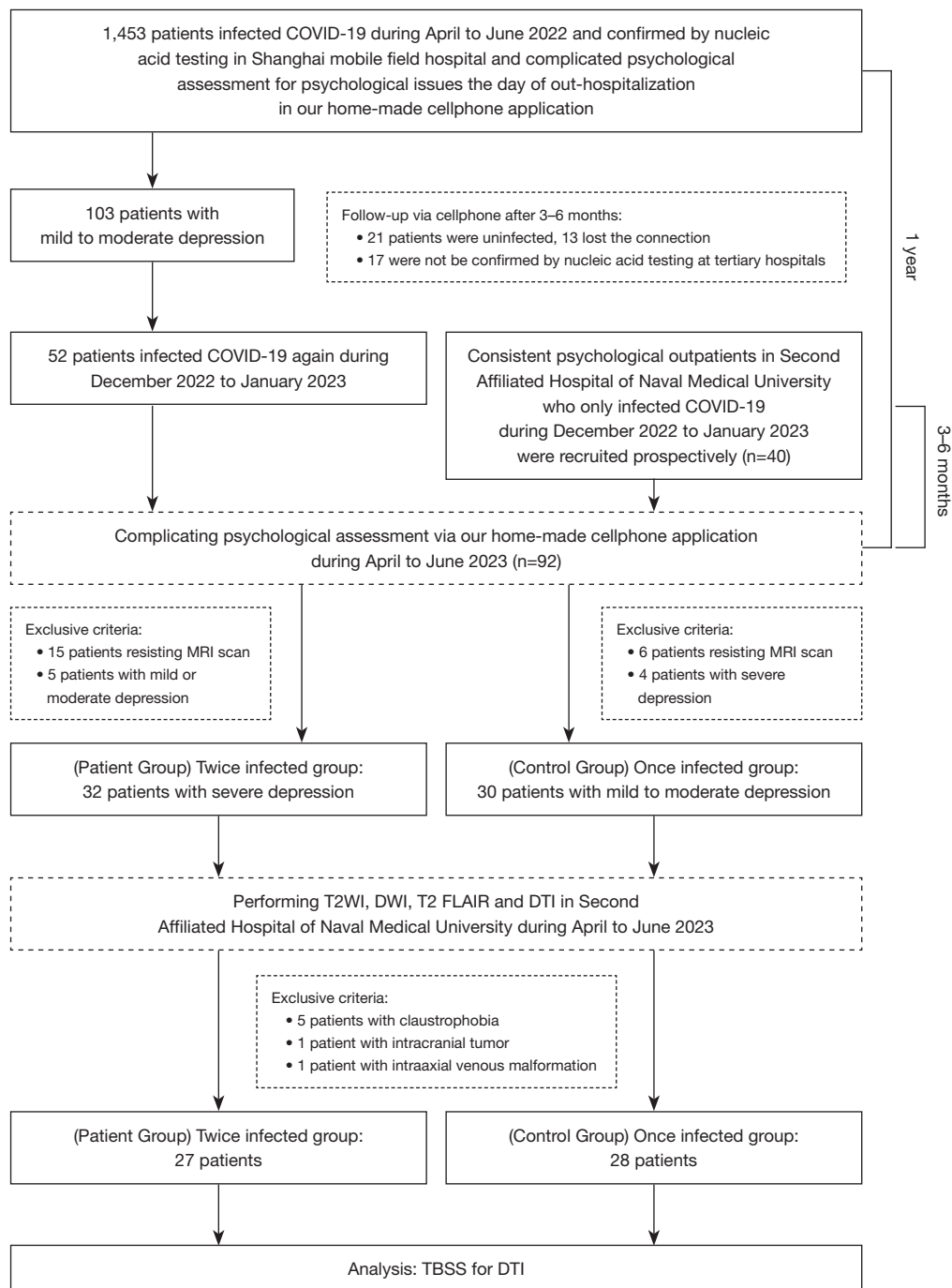


Figure 1 Study workflow. COVID-19, coronavirus disease 2019; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; T2WI, T2-weighted imaging; T2-FLAIR, T2-fluid attenuated inversion recovery; TBSS, Tract-Based Spatial Statistics.

and insomnia within 3–6 months of the infection. The patients with mild to moderate depression were allocated to the control group and underwent MR scans the next day. Age-, sex-, and education-matched patients were recruited for the final analysis.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) aged under 18 years old or were left handed; (II) had a previous history of neoplasm or other intracranial diseases; (III) had psychiatric complaints before the COVID-19 infection; (IV) had an organic disease or other serious substance addiction (e.g., tobacco, alcohol, or drug addiction); and/or (V) had contraindications to magnetic resonance imaging (MRI) (e.g., claustrophobia or metal implants).

Data on the age, gender, and educational background of the patients were collected. Educational background was classified as follows: below senior high school, senior high school, graduate, or post graduate. All the COVID-19 infections were confirmed by nucleic acid testing at tertiary hospitals. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of the Second Affiliated Hospital of Naval Medical University (No. 2023-L032). Verbal and written informed consent were obtained from all the patients.

Psychological assessment

The psychological assessment was conducted using Wen Juan Xing (Ranxing Information Technology Co., Ltd., Changsha, China), an online research tool that converts traditional paper scales into electronic formats. The assessments were carried out under the supervision of a psychiatrist with more than 5 years of experience to ensure the reliability and consistency of the evaluation process.

Depression symptoms were measured using the 9-item Patient Health Questionnaire (PHQ-9) from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The PHQ-9 evaluates the severity of depression symptoms over the past 2 weeks. Each item is rated from 0 (never) to 3 (nearly every day). The total score of the PHQ-9 ranges from 0 to 27, with higher scores indicating more severe depression symptoms. Total scores of 5, 10, 15, and 20 represent the cut-off values for mild, moderate, moderate-severe, and severe depression, respectively. The PHQ-9 has excellent internal reliability, as evidenced by a Cronbach's alpha of 0.89 in the PHQ-9 Primary Care Study and 0.86 in the PHQ-9 Ob-Gyn Study (9). Further, the

test-retest reliability of the PHQ-9 is also excellent (9).

The Generalized Anxiety Disorder-7 (GAD-7) scale from the DSM-5 was used to measure anxiety symptoms. The GAD-7 scale uses 7 items to assess the frequency of anxiety symptoms over the past 2 weeks based on a 4-point Likert scale, on which 0 represents “never” and 3 represents “nearly every day”. Higher scores indicate more severe functional impairment due to anxiety. Total scores of 5, 10, and 15 represent cut-off values for mild, moderate, and severe anxiety, respectively. The internal consistency of the GAD-7 is excellent (Cronbach's alpha: 0.92), and its test-retest reliability is good (10).

The Athens Insomnia Scale (AIS) was used to measure insomnia symptoms. This 8-item scale assesses the frequency of insomnia symptoms over the past month based on a 4-point Likert scale, on which 0 represents “never” and 3 represents “severe”. Higher scores indicate more severe functional impairment as a result of insomnia. Total scores of 4 and 6 represent cut-off values for mild and obvious insomnia, respectively. The internal consistency of the AIS is excellent (Cronbach's alpha: 0.90), and its test-retest reliability is good (11).

MRI acquisition

Axial T2-weighted imaging (T2WI), T2-fluid attenuated inversion recovery (T2-FLAIR) imaging, and axial diffusion weighted imaging (DWI) were performed to exclude patients with tumors or other intracranial diseases. The T2WI parameters were as follows: repetition time (TR) =6505 ms, echo time (TE) =103.4 ms, slice thickness =5.0 mm, slice gap =0 mm, number of slices =30, field of view (FOV) =24×24 cm², matrix =512×512, and number of excitation (NEX) =1. The T2-FLAIR parameters were as follows: TR =9,000 ms, TE =122.4 ms, slice thickness =5.0 mm, slice gap =0 mm, number of slices =30, FOV =24×24 cm², matrix =512×512, and NEX =1. The DWI parameters were as follows: TR =3,200 ms, TE =58.2 ms, slice thickness =5.0 mm, slice gap =0 mm, number of slices =30, matrix =256×256, and NEX =1. The diffusion tensor imaging (DTI) parameters were as follows: TR =5,500 ms, TE =57.5 ms, FOV =240×240 mm², matrix =160×160, slice thickness =3.0 mm, number of slices =50, b value =1,000, NEX =2, and number of diffusion weighting directions =30. The DTI was performed using the multiplexed sensitivity encoding technique, which applies multi-shot along the phase encoding direction to achieve a high signal-to-noise ratio, and which is less susceptible to distorted images.

Image and statistical analyses

TBSS

Before the data analysis, two experienced neuroradiologists visually inspected the DTI images to screen for noise artifacts. The raw digital imaging and communications in medicine images were converted to neuroimaging informatics technology initiative images using dcm2niix (<https://github.com/rordenlab/dcm2niix>). The image data were analyzed using Tract-Based Spatial Statistics (TBSS) (12) and the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL, version 4.1.8; <http://www.fmrib.ox.ac.uk/fsl>). First, susceptibility distortions were corrected using the top-up tool. Second, motion and eddy current distortions were corrected using the eddy_correct tool. Third, brain masks from the b0 image of each patient were created using the FSL brain extraction tool. Fourth, the DTIFIT was used to generate the fractional anisotropy (FA), mean diffusivity (MD), AD, and radial diffusivity (RD) maps. Next, FMRIB's nonlinear registration tool was used to align the FA, MD, AD, and RD maps of each patient to the FMRIB58_FA template in the Montreal Neurological Institute space. Using a FA threshold value of 0.2, a mean FA image was calculated from all the patients' maps and a mean FA skeleton was subsequently generated. Next, each patient's FA map was projected onto the skeleton. The script "tbss_non_FA" was used to obtain individual skeletonized MD, AD, and RD values. The voxel-wise differences in the skeletonized DTI metrics between the two groups were compared by two-sample *t*-tests. Threshold-free cluster enhancement analysis with 5,000 permutations via FSL randomize tool (version 2.1) was performed. Age and gender were added as covariates to minimize their potential effects. Statistical maps were set at $P < 0.05$ [two-sided, family-wise error (FEW) corrected]. The brain regions showing significant differences in the DTI metrics were overlaid onto the Johns Hopkins University WM Tractography Atlas.

Statistical analysis

A chi-square test was performed for sex and education. Unpaired two-sample *t*-tests and Kruskal-Wallis tests (of the non-normally distributed samples) were carried out to evaluate age differences. Similarly, unpaired two-sample *t*-tests and Kruskal-Wallis tests (of the non-normally distributed samples) were conducted to compare the neuropsychological tests. To produce aggregate results at the subject level, post-hoc analyses were performed.

For each patient, the mean levels of each diffusion metric were computed in regions that were tested for significance with TBSS. Bivariate correlation analyses, using Pearson correlation for normally distributed samples and Spearman correlation for non-normally distributed samples, were performed to assess the relationships between the DTI parameters and neuropsychological test scores among all the COVID-19 patients. Correlation coefficients of 0.2–0.4 indicated a mild relationship, 0.4–0.7 indicated a moderate relationship, and >0.7 indicated a strong relationship. All analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). A *P* value < 0.05 was considered statistically significant.

Results

Demographic and psychological characteristics

Of the initial 62 patients in both groups, 7 were excluded due to claustrophobia ($n=5$), intracranial tumor ($n=1$), and intra-axial venous malformations ($n=1$). Thus, 27 patients were included in the twice-infected (patient) group, and an additional 28 patients were included in the once-infected (control) group. No significant difference was observed between the two groups in terms of age (51.857 ± 2.770 vs. 48.148 ± 2.0678 years, $P=0.222$), gender (female: 75.0% vs. 55.6%, $P=0.130$), and educational background ($P=0.317$) (Table 1). No significant difference was found in the baseline PHQ-9 scores assessed after the first COVID-19 infection between the two groups (8.643 ± 2.599 vs. 8.667 ± 2.842 , $P=0.974$). However, the twice-infected group had significantly higher PHQ-9, GAD-7, and AIS scores than the once-infected group (all $P < 0.001$) (Table 1).

WM

Compared to the once-infected group, the twice-infected group had decreased FA values in several white matter tracts (WMTs) ($P_{\text{FEW}} < 0.05$), including the bilateral corticospinal tracts (CSTs), ATRs, and right SLF (Figure 2) (Table 2) ($P_{\text{FEW}} < 0.05$). However, no significant differences were observed between the two groups in terms of MD, RD, and AD.

Correlation between FA and psychological scores

The twice-infected group had significantly lower FA values than the once-infected group in the whole region (0.534 ± 0.015 vs. 0.561 ± 0.015 , $P < 0.001$). All the psychological

Table 1 The clinical characteristics of the patients in two groups

Clinical characteristics	Twice-infected group (n=27)	Once-infected group (n=28)	P value
Age (years)	51.857±2.770	48.148±2.0678	0.222
Gender			0.130
Female	15	21	
Male	12	7	
Educational background			0.317
Below senior high school	1	1	
Senior high school	19	16	
Graduate	6	9	
Above graduate	1	2	
PHQ	17.29±2.600	8.64±2.599	<0.001
GAD	15.44±3.490	7.64±2.376	<0.001
AIS	15.852±3.219	10.179±2.763	<0.001

Data are presented as mean ± SD or number. AIS, Athens Insomnia Scale; GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire; SD, standard deviation.

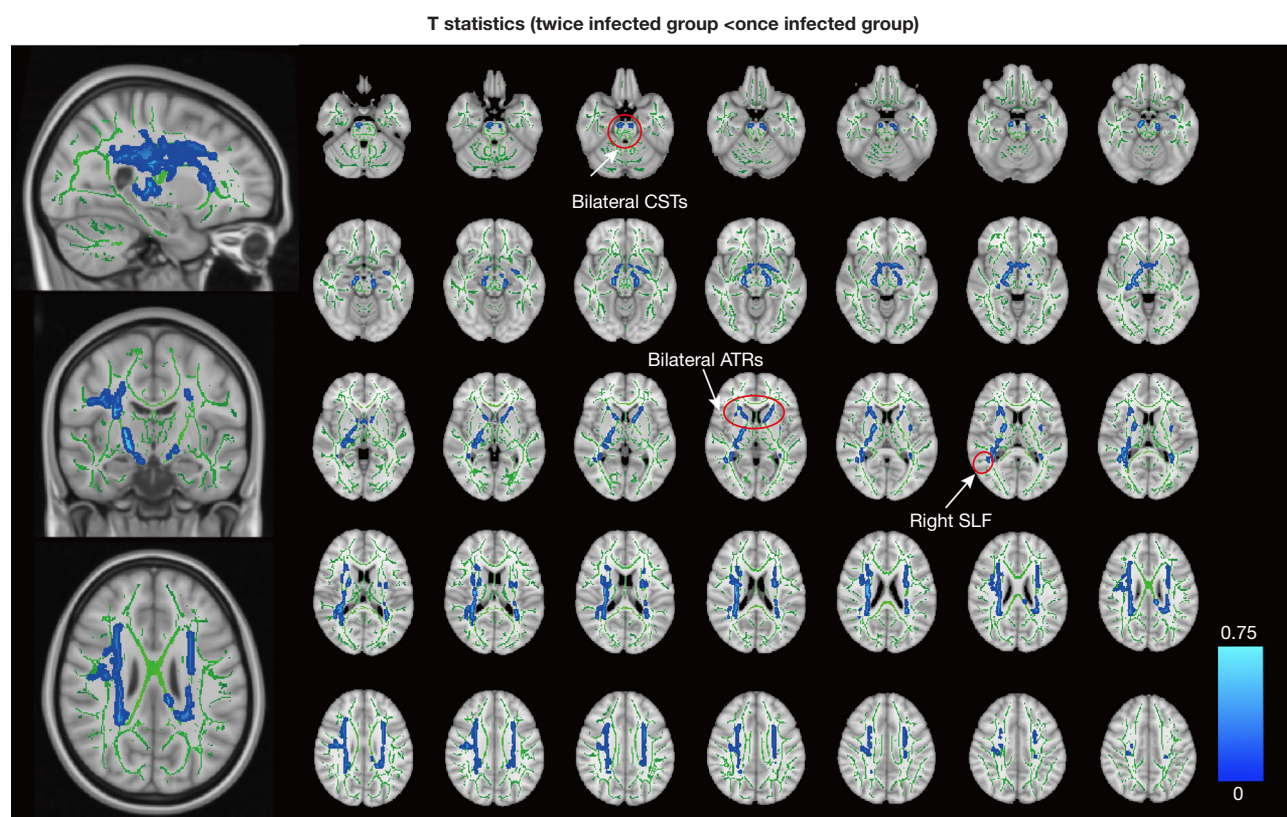


Figure 2 Different regions of FA between two groups (twice-infected group < once-infected group). The bilateral CSTs, ATRs, and right SLF based on the Johns Hopkins University White-Matter Tractography Atlas of the twice-infected group showed decreased FA compared with the once-infected group. ATRs, anterior thalamic radiations; CSTs, corticospinal tracts; FA, fractional anisotropy; SLF, superior longitudinal fasciculus.

Table 2 White matter regions with different FA values between two groups (twice-infected group < once-infected group)

Cluster index	Side	Brain regions (JHU)	Voxel size	MNI coordinate			P value
				X	Y	Z	
1	R	Corticospinal tract	2,454	35	-47	10	0.023
2	L	Corticospinal tract	1,300	-26	14	28	0.025
3	R	Anterior thalamic radiation	1,264	18	-11	-6	0.038
4	R	Anterior thalamic radiation	225	21	17	7	0.048
5	L	Corticospinal tract	221	-6	-19	-24	0.048
6	L	Anterior thalamic radiation	172	-12	9	2	0.046
7	R	Superior longitudinal fasciculus	129	36	-11	27	0.049
8	R	Anterior thalamic radiation	21	10	20	22	0.050
9	R	Anterior thalamic radiation	11	22	16	16	0.050
10	R	Corticospinal tract	6	13	-11	-13	0.050

FA, fractional anisotropy; JHU, Johns Hopkins University White-Matter Tractography Atlas; L, left; MNI, Montreal Neurological Institute space; R, right.

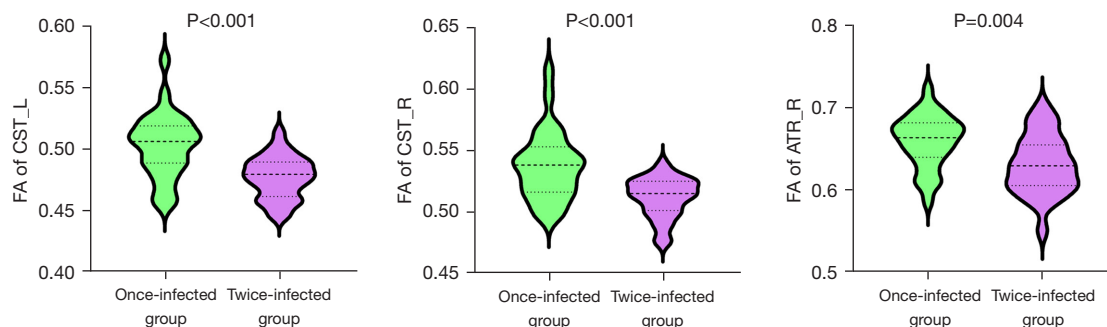


Figure 3 The comparison of FA in the regions with significant differences between the two groups. There were significant differences in the FA values of the CST_L, CST_R, and ATR_R between the groups. ATR_R, right anterior thalamic radiation; CST_L, left corticospinal tract; CST_R, right corticospinal tract; FA, fractional anisotropy.

scores were mildly to moderately negatively correlated with FA ($r=-0.491$, $r=-0.570$, and $r=-0.355$, respectively, with $P<0.001$, $P<0.001$, and $P=0.008$, respectively). Further, the FA values of the CST_L, CST_R, and ATR_R were notably lower in the twice-infected group than the once-infected group (Figure 3). Additionally, the psychological scores were mildly to moderately negatively correlated with FA in CST_L, CST_R, and ATR_R (Figure 4). However, no significant correlations were found when the analysis was conducted separately within each group.

Discussion

The present study found a discernible impairment in the

integrity of WM 3–6 months after the mild depression patients developed severe depression following another COVID-19 infection. Specifically, decreased FA was evident in the bilateral CSTs, ATRs, and right SLE. The identified abnormalities in these brain regions may provide valuable insights into potential mechanisms underlying the progression from mild or moderate to severe depression after a second COVID-19 infection. Given these findings, depression complaints from individuals recovering from COVID-19 should be taken seriously, as such patients show long-term WM changes. Timely psychological intervention is necessary to address and mitigate potential psychological sequelae in this patient population.

The patients who developed severe depression in the

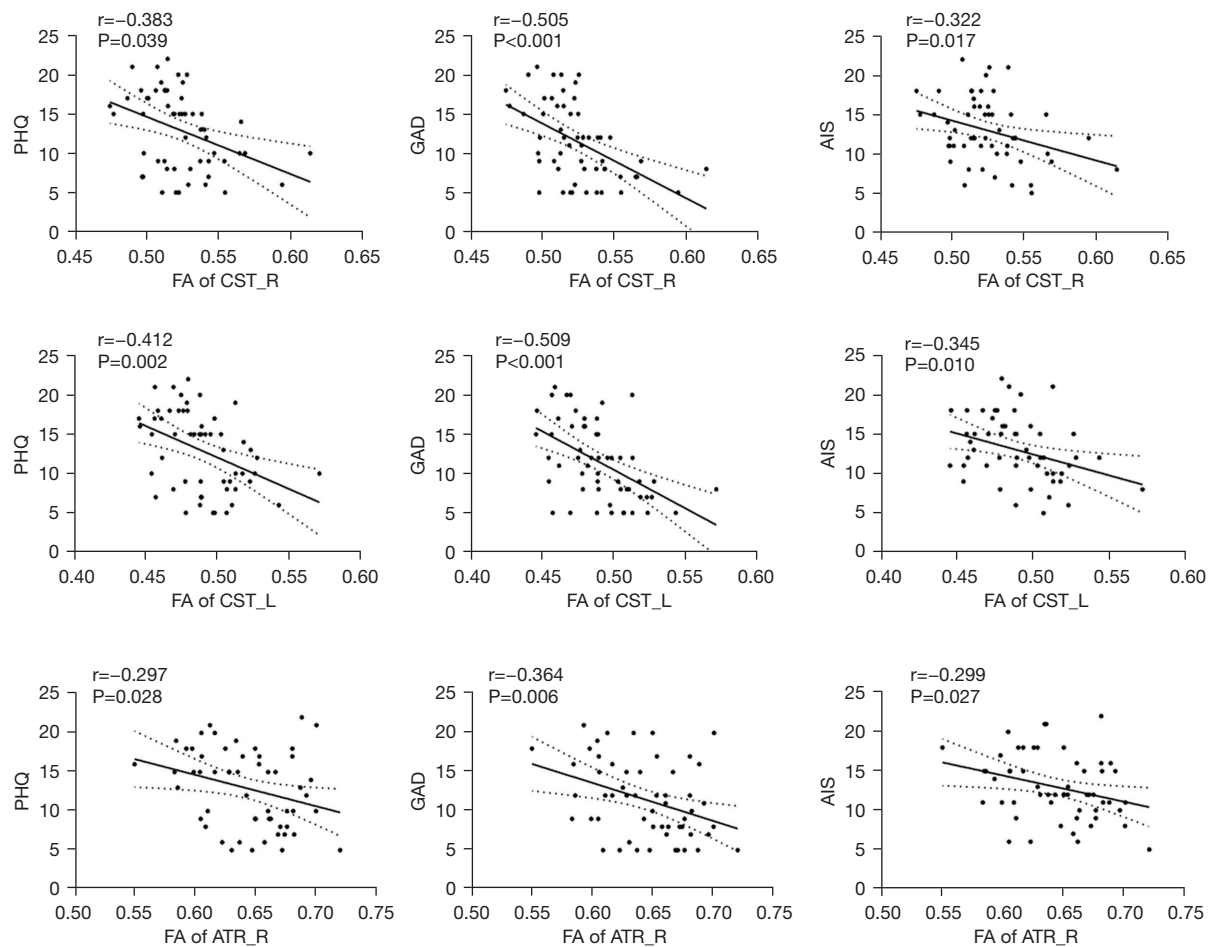


Figure 4 The significant correlations between psychological scores and FA. All the psychological scores were mildly to moderately negatively correlated with FA in CST_R, CST_L and ATR_R, respectively. The solid line represents the fitting curve, and the dashed line represents the confidence interval. AIS, Athens Insomnia Scale; ATR_R, right anterior thalamic radiation; CST_L, left corticospinal tract; CST_R, right corticospinal tract; FA, fractional anisotropy; GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire.

present study had decreased FA values for the bilateral CSTs, ATRs, and right SLF. A decreased FA indicates the deterioration of axonal myelin sheaths, which impairs the integrity of WM. Previous research has shown WM involvement in COVID-19 infection (13), with new lesions detected by follow-up MRI in recovered patients (14). Huang *et al.* reported a lower intracellular volume fraction in specific WM regions, including the bilateral corona radiata (anterior and superior parts), genu of the corpus callosum, and SLF, even one year after recovery. Interestingly, WM tends to display fewer abnormalities in cases with shorter hospital stays and longer follow-up times. Huang *et al.* reported a correlation between the severity of the condition and greater microstructural changes in WM (6), which is consistent with the findings

of our study. Our results also highlighted the enduring effect of COVID-19 on WM integrity. After the second infection, the patients who developed depression had more pronounced impairment in WM integrity. Previous findings on individuals with major depressive disorder have reported damage in the left SLF and right ATR (15). The effect of COVID-19-related depression on these specific brain regions suggests a potential structural basis for the occurrence and progression of COVID-19-related depression. Notably, the bilateral CSTs had decreased FA in the patient group, which is not common in patients solely experiencing depression or anxiety. A study on COVID-19 also reported the involvement of the CST, and documented a decrease in the CST 10 months post-recovery (16). CST is the major neural tract in the human brain for motor

function, and notably facilitates the movement of the distal extremities such as the hands (17). Our results showed that multiple COVID-19 infections may induce damage in the CST. However, we did not analyze motor function deficits; thus, further research needs to be conducted.

Unlike the localized impairment of GM typically observed near the frontal lobe or the limb system, such as in the insular, olfactory cortices, hippocampi, Heschl's gyrus, and cingulate (18), the range of impaired WM appears to be more extensive. The exact mechanism underlying WM damage following COVID-19 infection remains unclear. Huang *et al.* proposed hypoxic-ischemic changes as the potential mechanism for WM damage, rather than inflammatory storms, based on the lesion locations (7). However, according to previous studies, systemic immune dysregulation contributes to DTI signs of widespread WM microstructure abnormalities in major depressive disorder (19,20). The interaction between innate and adaptive immune systems, as well as neurotransmitters, has emerged as a mechanism underlying mood disorders, psychosis, and anxiety disorders. Interleukin-1 β , a potent pro-inflammatory cytokine crucial for host defense against infections and injuries, has been found to have a negative relationship with FA in major depressive disorder (21,22). Additionally, chronic and low-grade inflammation has been linked to a decrease in WM integrity in depressed patients (20). The persistent and chronic inflammation of the physical condition of patients with multiple COVID-19 infections over several months may cause severe and broader damage of WMTs in certain individuals.

To the best of our knowledge, this research represents the first attempt to explore the relationship between the frequency of COVID-19 infection and WM change. The study found long-term objective alterations or damage in cerebral function and microstructure in patients with severe depression following multiple COVID-19 infections. These findings emphasize the need for timely psychological intervention for individuals reporting depression after a COVID-19 infection and those at risk of multiple infections. Multiple infections accompanied by depression should be treated with the utmost seriousness. However, the study had some limitations. First, it was not a longitudinal study, and another group was used to reveal the baseline cerebral function and structure change in patients with severe depression following additional COVID-19 infection. Second, the sample size was small, emphasizing the need for investigation in a larger clinical cohort with a longitudinal approach. Third, due to the widespread

nature of COVID-19 infections in the general population, it was challenging to prospectively recruit patients without COVID-19 infection as a "true" control group. However, as mentioned above, previous studies had revealed that compared to healthy control patients, COVID-19 patients show WM damage in several regions, such as the corona radiata, corpus callosum, SLF (6), and ATR (8). This damage persists 1 to 2 years after discharge from hospital (7,12,13). Our results showed that the bilateral CSTs, ATRs, and right SLF were more severely impaired 3 to 6 months after patients progressed from mild to severe depression following another COVID-19 infection. However, if retrospective patient datasets collected before the COVID-19 infection are available, further investigation is encouraged to provide a more comprehensive understanding of the observed changes.

Conclusions

The present study showed that individuals with severe depression following multiple COVID-19 infections show widespread and profound WM damage, and this damage is negatively correlated with the severity of depression. The findings provide evidence of objective damage in cerebral microstructure, highlighting the necessity of timely psychological intervention for individuals at risk of multiple COVID-19 infections to prevent worsening psychological issues and cerebral microstructure changes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-24-2168/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of the Second Affiliated Hospital of Naval Medical University (No. 2023-L032). Verbal and written informed consent were obtained from all patients.

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