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ORIGINAL RESEARCH

Glymphatic Function Alterations in Sleep Disorder Patients Post-COVID-19: A Longitudinal DTI-ALPS Study

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Background: Coronavirus disease-2019 (COVID-19) has led to widespread sleep disturbances, yet the link between post-COVID sleep problems and glymphatic-system function remains unclear.

Methods: Between January and March 2023, we enrolled 59 participants with newly developed sleep disorder after COVID-19 (COVID_SD; 24 males; median age 28 years) and 39 age-/sex-matched participants without such problems after COVID-19 (COVID_NSD; 15 males; median age 25 y). Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI; 0–21, higher = poorer). All volunteers underwent brain magnetic-resonance imaging (MRI), including diffusion-tensor imaging (DTI), and computation of the DTI analysis along the perivascular space (DTI-ALPS) index. At two-month follow-up, 41 COVID_SD and 25 COVID_NSD participants were rescanned.

Results: Baseline bilateral ALPS indices were lower in COVID_SD than in COVID_NSD (left 1.23 ± 0.08 vs 1.29 ± 0.11, $p = 0.033$; right 1.29 ± 0.08 vs 1.33 ± 0.11, $p = 0.013$). PSQI correlated negatively with ALPS (left $r = –0.636$, $p = 0.0002$; right $r = –0.539$, $p < 0.0001$). Over two months, ALPS increased and PSQI decreased, indicating partial recovery of glymphatic function alongside improved sleep.

Conclusion: Impaired glymphatic clearance is strongly associated with poorer sleep quality in participants with post-COVID sleep problems; improvement in sleep parallels restoration of DTI-ALPS indices.

Keywords: COVID-19, glymphatic system, diffusion-tensor imaging, DTI-ALPS, Pittsburgh sleep quality index, sleep quality

Introduction

The COVID-19 pandemic has evolved into a global public health crisis, profoundly disrupting daily life and inducing lasting changes in the sleep patterns of many individuals.[1] Estimates suggest that 40.49% of people globally experienced sleep disturbances during the COVID-19 pandemic. A considerable percentage of patients have experienced long COVID, frequently linked to neuropsychiatric symptoms, with sleep disorders representing the most commonly observed manifestation. Research indicates that about 34% of people recovering from COVID-19 face sleep issues, such as trouble falling asleep, frequent night awakenings, and excessive daytime sleepiness sleepiness.[2,3] These sleep problems diminish life quality and can worsen cognitive impairments, emotional issues, and chronic conditions of fatigue.

SARS-CoV-2, while not a typical neurotropic virus, can potentially invade the nervous system and is recognized for exhibiting neurovirulence.[4] Research indicates that the virus has the capacity to infiltrate brain tissue; however, the precise mechanisms by which it gains entry remain elusive and unclear. The glymphatic system plays a critical role in clearing interstitial waste from the brain.[5] One hypothesis posits that the glymphatic system may offer a direct pathway for SARS-CoV-2 to infiltrate the brain, potentially resulting in a range of neuropsychiatric symptoms, notably disturbances in sleep disorders.[6]

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Numerous studies reveal a significant association between the glymphatic system and various diseases, including sleep disorders disorder,[7,8] Parkinson's disease,[9] Alzheimer's disease,[10] and post-traumatic stress disorder.[11] Thus, it is proposed that new sleep disturbances arising after COVID-19 could be closely associated with changes in glymphatic system function, warranting more extensive longitudinal studies to confirm this hypothesis.

Taoka et al developed and validated a method for estimating the clearance of interstitial fluid from the brain through the measurement of fluid diffusion along the perivascular spaces (DTI-ALPS), which serves as an indirect quantification of alterations in glymphatic function function.[12,13] DTI-ALPS is a reliable, non-invasive method widely used to evaluate the activity of the glymphatic system in various conditions, such as chronic insomnia in middle-aged individuals, Alzheimer's disease,[12] restless legs syndrome,[14] chronic migraines,[15] and temporal lobe epilepsy.[16]

This study utilizes DTI-ALPS to evaluate the functionality of the glymphatic system and to explore changes in glymphatic function in individuals who have recently developed sleep disturbances after COVID-19. Furthermore, it seeks to ascertain whether symptoms of sleep disturbance and glymphatic dysfunction show improvement over a 2-month follow-up period. We hypothesize that (1) individuals experiencing sleep disturbances subsequent to COVID-19 will exhibit impaired glymphatic outflow, and (2) glymphatic dysfunction will demonstrate improvement in conjunction with the resolution of sleep disturbances symptoms.

Methods

Ethics

The prospective study protocol was approved by the Ethics Committees of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine [2023–485-01], and the First Affiliated Hospital of Hunan Normal University [(2023)-22]. All procedures were carried out at the First Affiliated Hospital of Hunan Normal University in Changsha, Hunan Province, China.

Participants and Study Design

Between January and March 2023, participants experiencing sleep disturbances were recruited through WeChat surveys. All participants presented a documented history of positive SARS-CoV-2 antigen or nucleic acid test results or a previous diagnosis of COVID-19, accompanied by recent negative testing outcomes results. A preliminary screening was conducted utilizing questionnaires to collect demographic data, which included education level, age, ethnicity, dominant hand, MRI contra-indications, psychiatric medication usage, psychiatric history, and any history of physical illness or brain injury. Additionally, self-reported information regarding emotional or sleep changes subsequent to COVID-19 has also gathered in recovery.

The inclusion criteria encompassed: a prior positive SARS-CoV-2 antigen or nucleic acid test, accompanied by a current negative antigen test; a minimum of a high school education; an age range of 18 to 60 years; right-handedness; Han ethnicity; the absence of MRI contraindications; and documented informed consent. The exclusion criteria encompassed the following: a personal or familial history of mental disorders as defined by the DSM-5; the use of psychiatric medications (such as antipsychotics and antidepressants) within the preceding three months; the presence of organic brain diseases, brain injuries, or a history of coma; clinically significant physical illnesses or endocrine disorders (including diabetes); abnormal findings on hematologic, hepatic, renal, or cardiac function tests; pregnancy or lactation; and/or sleep disturbances attributed to factors not related to COVID-19 (for instance, work-related or life-related stressors) stress). In addition, participants were asked whether they had taken any sleep medications during the study period, and all respondents reported no use of hypnotics or other sleep-related interventions. Thus, no pharmacological or behavioral interventions for sleep disturbances were administered throughout the two-month follow-up. Eligible participants were duly informed about the study and provided with written informed consent prior to being scheduled for MRI scans and clinical evaluations at our facility hospital. The experimental design is shown in Figure 1.

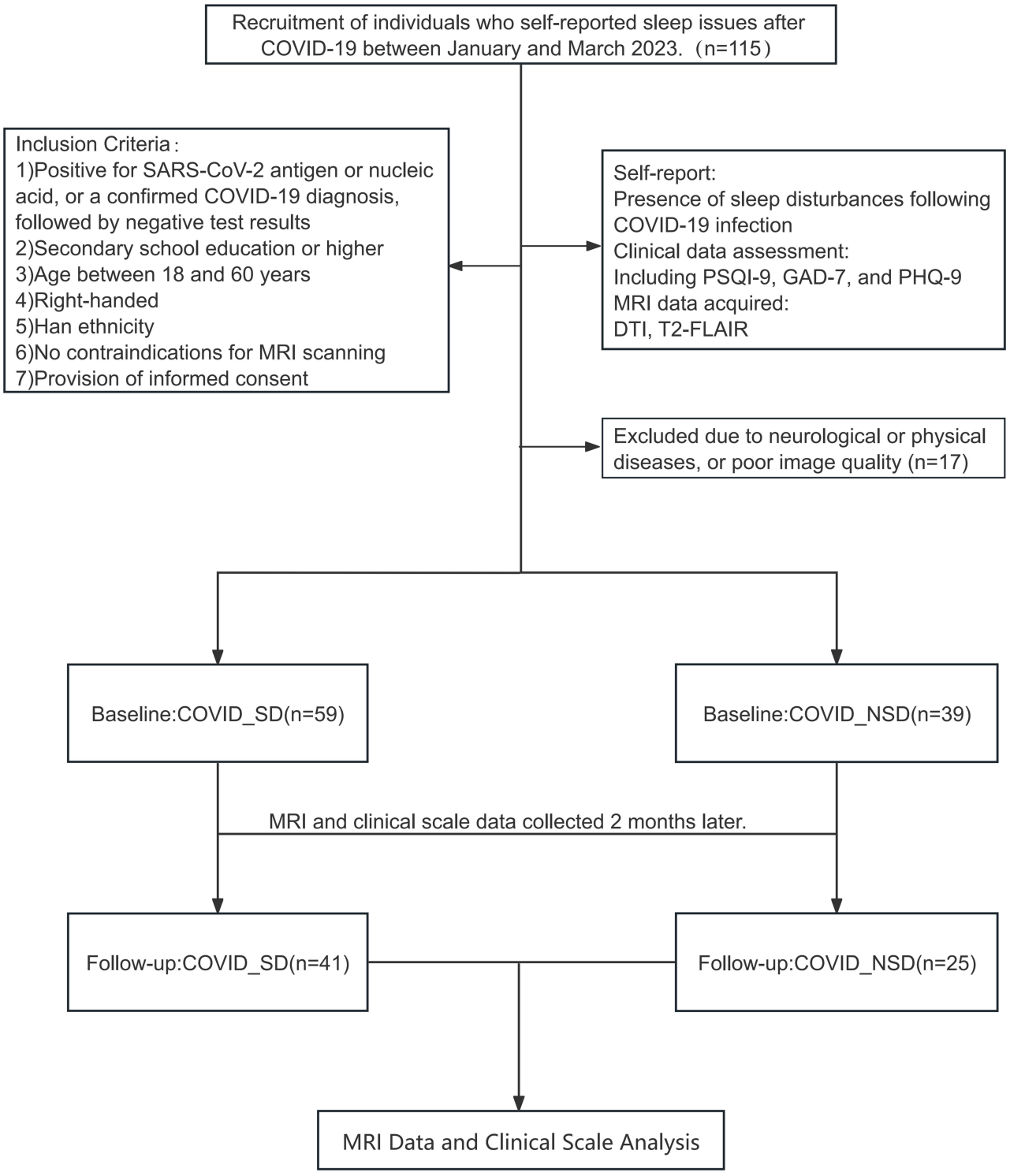

Figure 1 Flowchart of participant inclusion.

Measurements

Demographic Data and Neuropsychological Assessments

Demographic characteristics, encompassing gender, age, marital status, place of residence, and educational background, were gathered through a meticulously designed instrument questionnaire.

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All participants underwent standardized neuropsychological assessments including: 1) The Pittsburgh Sleep Quality Index (PSQI) items,[17–20] scoring from 0 to 21, with higher scores indicating worse sleep quality; 2) The Generalized Anxiety Disorder-7 (GAD-7)[21] is a tool utilized to evaluate the severity of anxiety. It has a scoring range from 0 to 21, where scores of 0 to 4 indicate minimal anxiety, scores of 5 to 9 signify mild anxiety, scores of 10 to 14 represent moderate anxiety, and scores of 15 to 21 denote severe anxiety. 3) The Patient Health Questionnaire-9 (PHQ-9)[22,23] consists of nine items used to evaluate the severity of depression, with scores ranging from 0 to 27. A score of 0–4 indicates minimal depression, 5–9 signifies mild depression, 10–14 reflects moderate depression, 15–19 suggests moderate to severe depression, and 20–27 represents severe depression. All instruments were used in compliance with the copyright holders' non-commercial research policies, as detailed on their official websites (PSQI: https://www.sleep.pitt.edu/instruments/;[18] GAD-7/PHQ-9 https://www.phqscreeners.com/).

Group Definitions

Participants were divided into two groups according to the severity of sleep disturbances seen post-COVID-19, employing a PSQI cutoff of 7, as set by Liu et al[17] for the Chinese population. Individuals were classified as follows: a) The COVID_SD (COVID-19-related sleep disturbance) group comprised participants who had a PSQI score of ≤7 before COVID-19 infection but >7 after infection, indicating newly developed or worsened sleep disturbances post-COVID-19. b) The COVID_NSD (COVID-19-related no sleep disturbance) group included participants whose PSQI scores remained ≤7 before and after infection, indicating no significant sleep disruption.

During the baseline data collection, participants retrospectively assessed their sleep and emotional states during the two weeks before (pre-COVID) and after (post-COVID) their COVID-19 diagnosis infection. MRI scans were conducted at baseline. A follow-up assessment was conducted two months later,[2] and the participants evaluated their sleep and emotional states for the two weeks preceding the follow-up while follow-up MRI scans were acquired.

DTI MRI Acquisition and Preprocessing

MRI data were collected daily from 6:00 PM to 10:00 PM for the enrolled participants. All participants underwent scanning while awake using a 3.0T MRI scanner (Siemens Prisma) equipped with a 64-channel head and neck coil. They were positioned in a supine posture with earplugs and foam padding placed around the head to minimize motion artifacts. Standard structural brain imaging modalities, which include axial T1-weighted (T1WI), T2-weighted (T2WI), and T2 Fluid Attenuated Inversion Recovery (T2FLAIR) images, were employed to eliminate any lesions delineated in the exclusion criteria. Diffusion Tensor Imaging (DTI) was acquired utilizing the following parameters: repetition time (TR) set at 3300 milliseconds, echo time (TE) at 89 milliseconds, a flip angle of 90 degrees, a field of view (FOV) of 210×210 millimeters, a matrix size of 128 × 128, a voxel size measuring 1.5 cubic millimeters, slice thickness of 1.5 millimeters, including a total of 92 slices, 30 diffusion-sensitizing gradient orientations, and a b-value of 1000 seconds per square millimetre, accompanied by an unweighted B0 image with a b-value of 0 s/mm²).

The preprocessing of Diffusion Tensor Imaging (DTI) encompassed several critical steps. Initially, the DICOM images were converted to the NIfTI format. Subsequently, preprocessing was conducted utilizing TORTOISE software (https://tortoise.nibib.nih.gov/), which entailed quality control, denoising, elimination of Gibbs ring artefacts, corrections for EPI and eddy currents, along with image registration. Thereafter, diffusion parameter maps were reconstructed using the Diffusion Toolkit software (http://trackvis.org/) to accurately characterize the principal diffusion direction of the fibers. Ultimately, Fractional Anisotropy (FA) maps and diffusion maps along the x-, y-, and z-axes were generated for each participant. The DTI-ALPS index was calculated accordingly calculation.

The calculation of the DTI-ALPS index was performed using the method described by Toshiaki Taoka et al[12,24] A radiologist manually delineated 12-voxel ROIs, which were located within the projection and association fibre regions without any overlap or intersection on the FA map at the lateral ventricles level, using FSLeyes, while blinded to clinical data and other images regions. Manual corrections were made for each subject. Diffusion rates for the x (Dx), y (Dy), and z (Dz) axes were measured at the voxel level for both projection and association fibers ROIs. The DTI-ALPS index was calculated using the following formula:

$$\text{ALPS index} = \text{mean}\,(\text{Dx\_proj},\ \text{Dx\_assoc})/\text{mean}\ (\text{Dy\_proj},\ \text{Dz\_assoc}).$$

Dx_proj: Diffusion rate along the x-axis in the projection fibres,
Dx_assoc: Diffusion rate along the x-axis in the association fibres,
Dy_proj: Diffusion rate along the y-axis in the projection fibres,
Dz_assoc: Diffusion rate along the z-axis in the association fibres.

The study exclusively included participants who were right-handed, and ROIs) were defined in both hemispheres. The workflow for the preprocessing of diffusion tensor imaging (DTI) data and the calculation of the DTI-ALPS index is summarized in Figure 1.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.0 (GraphPad Software). Data normality was assessed using the Shapiro–Wilk test. Depending on the nature of the variables, whether continuous or categorical, and their respective distributions, comparisons between the two groups were conducted utilizing the Chi-square test, the independent Student's *t*-test, or the Mann–Whitney *U*-test appropriate. A paired-sample *t*-test was used to compare changes between baseline and follow-up. Spearman's rank correlation coefficient was employed to evaluate the relationship between the DTI-ALPS index and PSQI scores. In order to investigate the effects of various factors and their interactions on the DTI-ALPS index, a mixed-design analysis of variance (ANOVA) will be conducted. A significance level of 0.05 was applied for all statistical tests.

Results

Demographic and Clinical Characteristics

A total of 59 participants were enrolled in the COVID_SD group, and 39 age-matched participants were included in the COVID_NSD group (Figure 1). No significant differences were identified between the groups concerning age, gender, educational attainment, duration from infection to scanning, or disease status duration. However, significant differences were observed between the groups in the Pittsburgh Sleep Quality Index (PSQI) total score and its sub-scores. These sub-scores evaluate various dimensions of sleep, encompassing sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, sedative use, and daytime dysfunction ($p < 0.05$). Furthermore, GAD and PHQ scores showed significant group differences ($p < 0.001$), with the COVID_SD group scoring higher than the COVID_NSD group on both GAD and PHQ (Table 1).

Table 1 Summary of Participant Characteristics at Baseline

Characteristic	COVID_SD (n = 59)	COVID_NSD (n= 39)	P-value
Age (years)	28.00 (25.00, 35.00)	25.00 (23.00, 35.00)	0.114
Sex (male/female)[a]	24/35	15/24	0.826
Education (years)	17.00 (16.00, 18.00)	17.00 (16.00, 19.00)	0.681
Infection time to scan (days)[b]	37.98±16.45	40.27±18.05	0.643
Course of disease, (days)	9.00 (7.00, 13.00)	9.00 (7.00, 11.00)	0.781
GAD (pre)	2.00 (0.00, 4.00)	2.00 (0.00, 4.00)	0.581
PHQ (pre)	2.00 (1.00, 4.00)	2.00 (0.00, 6.00)	0.538
PSQI (pre)	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	0.287
Sleep quality (pre)	1.00 (1.00, 1.00)	1.00 (0.00, 1.00)	0.293
Sleep duration (pre)	1.00 (1.00, 1.00)	1.00 (0.00, 1.00)	0.014*
Sleep latency (pre)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.339
Habitual sleep efficiency (pre)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.454
Sleep disturbances (pre)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.904
Use of sleep medication (pre)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.416

(*Continued*)

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Table 1 (Continued).

Characteristic	COVID_SD (n = 59)	COVID_NSD (n= 39)	P-value
Daytime dysfunction (pre)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.423
GAD (post)	5.00 (3.00, 8.00)	3.00 (1.00, 4.00)	<0.001*
PHQ (post)	9.00 (6.00, 12.00)	5.00 (2.00, 7.00)	<0.001*
PSQI (post)	11.00 (9.00, 13.00)	6.00 (5.00, 7.00)	<0.001*
Sleep quality (post)	2.00 (2.00, 2.00)	1.00 (1.00, 2.00)	<0.001*
Sleep duration (post)	3.00 (2.00, 3.00)	1.00 (0.00, 2.00)	<0.001*
Sleep latency (post)	1.00 (1.00, 2.00)	1.00 (0.00, 1.00)	<0.001*
Habitual sleep efficiency (post)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)	<0.001*
Sleep disturbances (post)	1.00 (1.00, 2.00)	1.00 (1.00, 1.00)	<0.001*
Use of sleep medication (post)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.002*
Daytime dysfunction (post)	3.00 (2.00, 3.00)	1.00 (1.00, 2.00)	<0.001*
L_ALPS (baseline)[b]	1.23±0.08	1.29±0.11	0.033*
R_ALPS (baseline)[b]	1.29±0.08	1.33±0.11	0.013*

Notes: *P values < 0.05 were considered statistically significant. [a]Categorical data analysed with the χ^2-test. [b]Values are mean ± SD and compared using a two-sample *t*-test. Variables without superscripts are reported as median (P25, P75) and compared with the Wilcoxon–Mann–Whitney *U*-test. "Pre" and "post" indicate participants' self-reported scale scores before and after SARS-CoV-2 infection.
Abbreviations: COVID_SD, individuals with sleep problems following COVID-19; COVID_NSD, individuals without sleep problems following COVID-19.

A follow-up assessment was conducted two months later, involving 41 participants from the COVID_SD group and 25 matched participants from the COVID_NSD group (Figure 1). Detailed participant characteristics are provided in Table 2. A repeated measures ANOVA was conducted with Time (three time points: pre, post, follow-up) as a within-subject factor and Group (COVID_SD vs COVID_NSD) as a between-subject factor for each outcome (PSQI, PHQ, and GAD) (Figure 2). For PSQI, there was a significant main effect of Time ($F(2,64) = 67.68$, $p < 0.001$) and a significant Time × Group interaction ($F(2,64) = 13.96$, $p < 0.001$), whereas the main effect of Group was not significant ($F(1,64) = 0.19$, $p = 0.661$). This indicates that PSQI scores changed significantly over time and that the pattern of change differed

Table 2 Summary of Participant Characteristics at Follow-Up

Characteristic	COVID_SD_2mon (n = 41)	COVID_NSD_2mon (n= 25)	P-value
Age (years)	27.00 (25.00, 33.00)	25.00 (23.00, 35.00)	0.036*
Sex (male /female)[a]	15/26	9/16	0.962
Education (years)	17.00 (16.00, 18.00)	17.00 (16.00, 19.00)	0.973
GAD (follow)	3.00 (2.00, 5.00)	2.00 (0.00, 4.00)	0.035*
PHQ (follow)	5.00 (2.00, 7.00)	3.00 (1.00, 5.00)	0.095
PSQI (follow)	8.00 (5.00, 10.00)	5.00 (4.00, 6.50)	<0.001*
Sleep quality (follow)	1.00 (1.00, 2.00)	1.00 (1.00, 1.00)	0.003*
Sleep duration (follow)	2.00 (1.00, 3.00)	1.00 (0.00, 1.50)	0.002*
Sleep latency (follow)	1.00 (1.00, 2.00)	1.00 (0.50, 1.00)	0.105
Habitual sleep efficiency (follow)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.038*
Sleep disturbances (follow)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.091
Use of sleep medication (follow)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.013*
Daytime dysfunction (follow)	2.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.106
L_ALPS (follow)[b]	1.31±0.09	1.31±0.09	0.76
R_ALPS (follow)[b]	1.33±0.11	1.32±0.11	0.64

Notes: *P values < 0.05 were considered statistically significant. [a]Categorical data analysed with the χ^2-test. [b]Values are mean ± SD and compared using a two-sample *t*-test. Variables without superscripts are reported as median (P25, P75) and compared with the Wilcoxon–Mann–Whitney *U*-test.
Abbreviations: COVID_SD_2mon, individuals in the COVID_SD group at the 2-month follow-up; COVID_NSD_2mon, individuals in the COVID_NSD group at the 2-month follow-up.

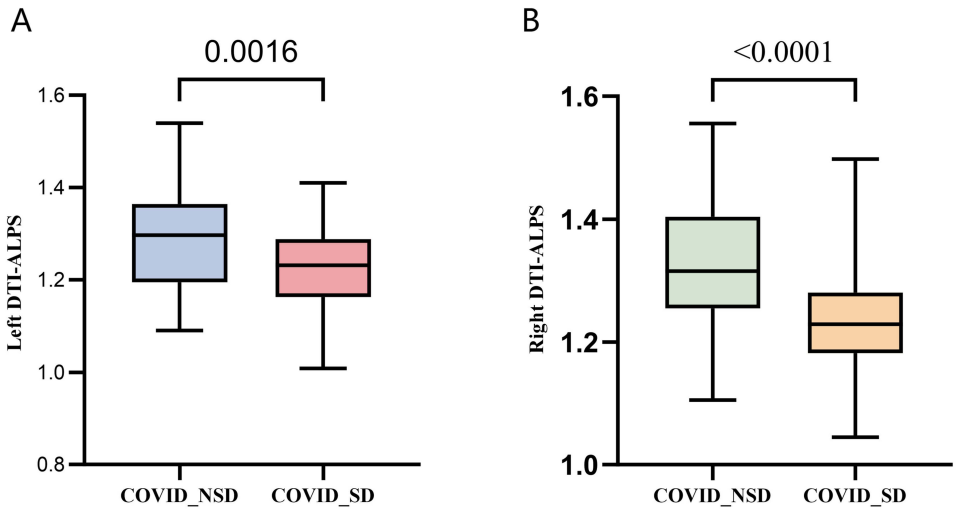

Figure 2 Comparison of Brain Lymphatic System Function Between the COVID_SD and COVID_NSD Groups. (**A**) The left hemisphere DTI-ALPS index was significantly lower in the COVID_SD group compared to the COVID_NSD group. (**B**) The right hemisphere DTI-ALPS index also showed a significant reduction in the COVID_SD group. These findings suggest dysfunction of the lymphatic system in post-COVID sleep disorder patients.

between the COVID_SD and COVID_NSD groups. For PHQ, the analysis revealed a significant effect of Time ($F(2,64) = 6.89$, $p = 0.002$), but no significant main effect of Group ($F(1,64) = 3.14$, $p = 0.081$) and no Time × Group interaction ($F(2,64) = 2.29$, $p = 0.110$), suggesting that while PHQ scores increased over time in both groups, the overall level of depressive symptoms did not differ significantly between the two groups and their trajectories over time were similar. For GAD, there was a significant main effect of Time ($F(2,64) = 8.03$, $p < 0.001$) and a significant main effect of Group ($F(1,64) = 6.53$, $p = 0.013$), indicating that the COVID_SD group had higher anxiety scores on average than the COVID_NSD group. The Time × Group interaction for GAD was not significant ($F(2,64) = 2.57$, $p = 0.084$), which suggests that both groups showed a comparable pattern of change in anxiety levels across the three time points. Post hoc pairwise comparisons were adjusted using Sidak correction to control for the family-wise error rate (Table 3, Supplementary Tables 7−9).

DTI-ALPS Index Analysis

Regions of interest (ROIs) were defined within the lateral ventricles of both hemispheres, and the DTI-ALPS indices (L_ALPS, R_ALPS) were calculated. At baseline, significant differences were observed in L_ALPS and R_ALPS between the COVID_SD and COVID_NSD groups (L_ALPS: 1.23 ± 0.08 vs 1.29 ± 0.11; P = 0.033; R_ALPS: 1.29 ± 0.08 vs 1.33 ± 0.11; P = 0.013) (Figure 3). After 2 months, a follow-up assessment of 41 participants from the COVID_SD group and 25 matched participants from the COVID_NSD group showed no significant differences in L_ALPS_follow and R_ALPS_follow between the COVID_SD_2mon and COVID_NSD_2mon groups (L_ALPS: 1.31 ±0.09 vs 1.31±0.09; P = 0.76; R_ALPS: 1.33±0.11 vs 1.32±0.11; P = 0.64).

Correlation Analysis of DTI-ALPS with Clinical Characteristics

L_ALPS and R_ALPS exhibited significant negative correlations with the PSQI score (L_ALPS: $r = -0.636$, $p = 0.0002$; R_ALPS: $r = -0.5388$, $p < 0.0001$) (Figure 4). Among the seven PSQI components, only *Sleep Quality* and *Sleep Latency*

Table 3 Summary of ANOVA Results for PSQI, PHQ, and GAD

Measure	F (Time)	P (Time)	F (Group)	P (Group)	F (Time × Group)	P (Time × Group)
PSQI	67.68	<0.001	0.19	0.661	13.96	<0.001
PHQ	6.89	0.002	3.14	0.081	2.29	0.11
GAD	8.03	<0.001	6.53	0.013	2.57	0.084

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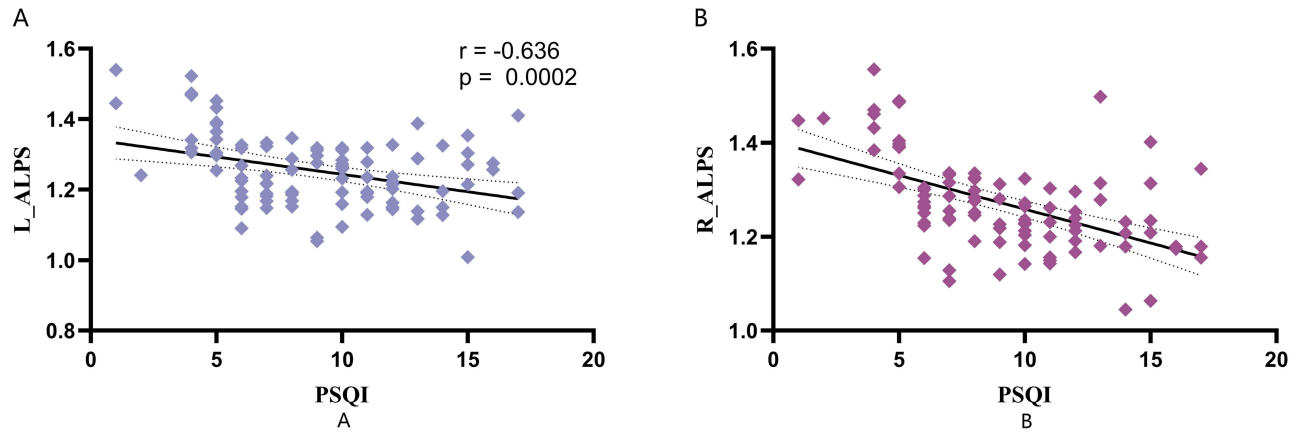

Figure 3 Scatter Plot Depicting the Relationship Between Bilateral ALPS Indices and PSQI Scores. (**A**) A significant negative correlation is observed between the left ALPS index and PSQI scores. (**B**) A significant negative correlation is observed between the right ALPS index and PSQI scores. These findings demonstrate a consistent association between impaired lymphatic function and poor sleep quality in the study participants.

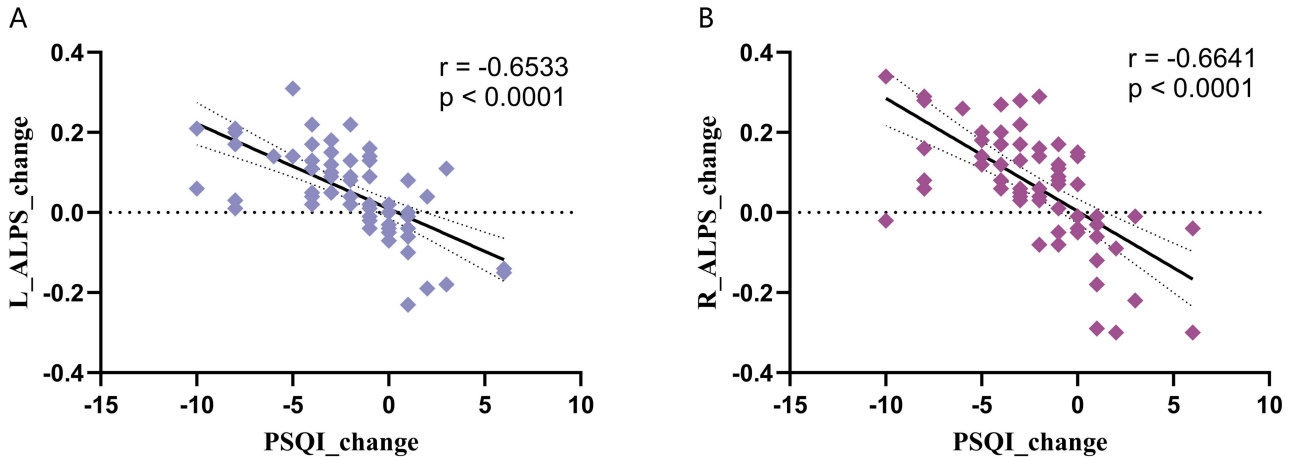

Figure 4 Scatter Plot of the Relationship Between Changes in Bilateral ALPS Indices (ALPS_change) and Changes in PSQI Scores (PSQI_change) from Baseline to Follow-Up. (**A**) Correlation between L_ALPS_change and PSQI_change. (**B**) Correlation between R_ALPS_change and PSQI_change. A significant negative correlation was found in both subplots, suggesting that improvement in lymphatic function is associated with improved sleep quality over time.

exhibited significant relationships with the ALPS indices at baseline. Higher *Sleep Quality* scores (worse perceived sleep) were inversely correlated with both L_ALPS (β = –0.37, p = 0.005) and R_ALPS (β = –0.27, p = 0.025). In addition, longer *Sleep Latency* was negatively associated with R_ALPS (β = –0.23, p = 0.033) but showed no significant correlation with L_ALPS (p = 0.85). No other subscales reached statistical significance after Sidak adjustment (Supplementary Tables S1–S4). Scatter plots for the significant pairs are provided in Supplementary Figures S1–S3. Furthermore, a comprehensive summary of the correlations between demographic/clinical variables and clinical/neuroimaging scores at both baseline and follow-up is provided in Supplementary Tables S5 and S6, respectively. L_ALPS showed no correlation with other clinical scales or demographics, such as age (r = −0.133, p = 0.192), education (r = 0.06, p = 0.559), time from infection to scan (r = 0.16, p = 0.116), disease duration (r = 0.07, p = 0.495), GAD score (r = −0.035, p = 0.732), or PHQ score (r = −0.066, p = 0.521). Similarly, R_ALPS also showed no correlation with clinical scales or demographic factors like age (r = −0.12, p = 0.239), education (r = −0.01, p = 0.923), time from infection to scan (r = −0.79, p = 0.439), disease duration (r = 0.07, p = 0.949), GAD score (r = −0.110, p = 0.283), or PHQ score (r = −0.155, p = 0.127).

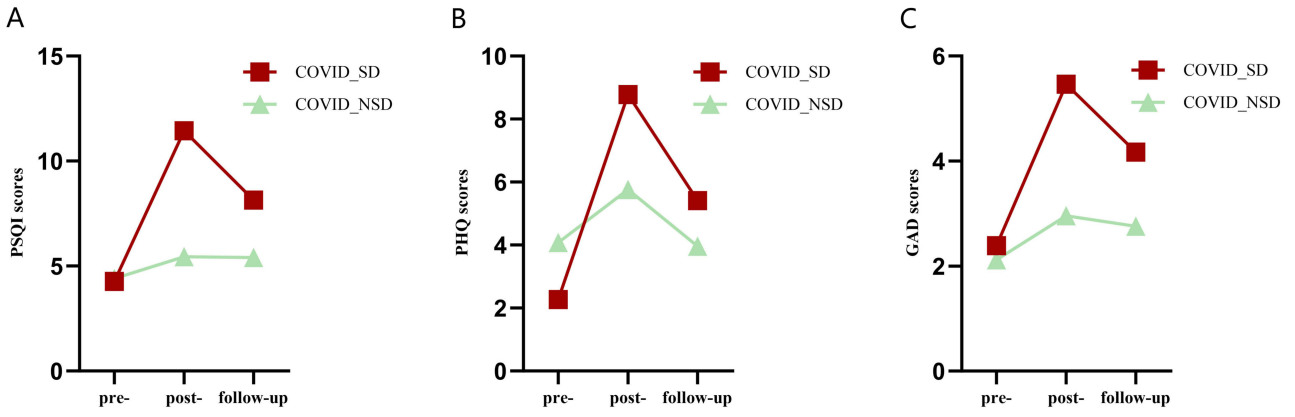

Figure 5 Changes in PSQI, PHQ-9, and GAD-7 Scores Over Time in COVID_SD and COVID_NSD Groups. (**A**) PSQI scores at pre-infection, post-infection, and 2-month follow-up. (**B**) PHQ-9 scores over the same time points. (**C**) GAD-7 scores across the three time points. Lines represent group means for the COVID_SD and COVID_NSD groups, depicting trends in sleep quality, depressive symptoms, and anxiety symptoms over time.

It is noteworthy that the alterations observed in L_ALPS and R_ALPS from baseline to follow-up (L_ALPS_change, R_ALPS_change) demonstrated a significant negative correlation with the changes in PSQI scores from baseline to follow-up (PSQI_change), with correlation coefficients of $r = -0.6533$ ($p < 0.0001$) and $r = -0.6641$ ($p < 0.0001$), respectively (Figure 5).

Analysis of the Interaction Effects of DTI-ALPS with Group, Time, and Hemisphere

A mixed-design analysis of variance (ANOVA) was conducted to evaluate alterations in DTI-ALPS indices between the COVID-19 patients with sleep disturbances (COVID_SD) and those without (COVID_NSD) across both hemispheres at baseline and follow-up (Figure 6). The analysis revealed significant main effects of group ($F(1, 64) = 5.753$, $p = 0.019$, partial $\eta^2 = 0.082$), time ($F(1, 64) = 11.353$, $p = 0.001$, partial $\eta^2 = 0.151$), and hemisphere ($F(1, 64) = 4.103$, $p = 0.047$, partial $\eta^2 = 0.060$).

The interaction effects of time × hemisphere, group × hemisphere, and time × group × hemisphere were not significant (all $p > 0.05$). However, a significant interaction between time and group was observed ($F(1, 64) = 16.519$, $p < 0.001$, partial $\eta^2 = 0.205$), indicating differing temporal trends in ALPS indices between the two groups.

Post hoc pairwise comparisons with Bonferroni correction showed that the COVID_SD group experienced a significant decline in ALPS indices from baseline to follow-up (mean difference = −0.098, SE = 0.016, adjusted $p <$

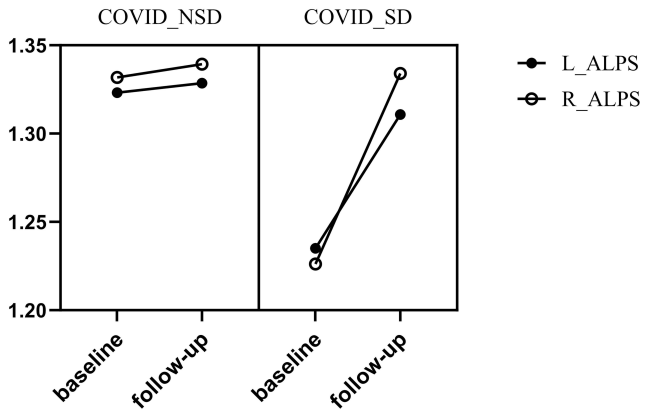

Figure 6 A mixed-design analysis of variance (ANOVA) on Sleep Quality. This figure displays the impact of various confounding factors (group, time, and hemisphere effects) on sleep quality, as measured by the Alps indices. The x-axis represents the categories of these influencing factors, and the y-axis shows the ALPS indices, reflecting the degree of their influence on the outcome variable. The results show that the main effects of time, group, and hemisphere are significant, with a significant interaction between time and group.

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0.001), whereas the COVID_NSD group showed no significant change over time (mean difference = 0.009, SE = 0.021, adjusted p = 0.661). These findings suggest a pronounced reduction in glymphatic function over time among patients with sleep disturbances compared to those without.

Discussion

This study demonstrates a substantial correlation between sleep disorders and glymphatic function in the aftermath of COVID-19 infection. The key findings of this study are as follows: 1) The ALPS index in the COVID_SD group was significantly lower than in the COVID_NSD group. 2) A significant negative correlation was found between the DTI-ALPS index and PSQI scores. 3) The ALPS index related to COVID-19-associated sleep disorders exhibited a dynamic trend over time, with asynchronous variations noted in the bilateral ALPS indices.

Taoka et al have developed and validated the DTI-ALPS index as a methodology for the indirect quantification of changes in the glymphatic system function,[12,13] a technique that has been widely utilized in evaluating the glymphatic system's role in various disease contexts.[7,15,16,25] Traditional tracer studies have revealed a substantial correlation between the ALPS index and cerebral glymphatic function clearance.[26] Several studies[7,27–31] have highlighted a close association between sleep disorders and alterations in glymphatic function. Generally, a decline in the DTI-ALPS index signifies impaired glymphatic function function. The results of this study revealed that the ALPS index in the COVID_SD group was significantly lower than in the COVID_NSD group. This finding aligns with prior literature, indicating that COVID-19 infection may contribute to sleep disturbances via the immune system modulation. The drop in the ALPS index might suggest that the immune response triggered by the SARS-CoV-2 virus has a dampening effect on glymphatic function, which could, in turn, influence how we regulate our sleep mechanisms.

Notably, our prior study demonstrated abnormal functional connectivity (FC) patterns in post-COVID-19 individuals with sleep disturbances, specifically involving the right precentral gyrus (PrG), left inferior parietal lobule (IPL), and left hippocampus.[32] These observations suggest that shared pathophysiological mechanisms may link these findings. Specifically, impaired metabolic clearance by the glymphatic system could lead to the accumulation of neurotoxic substances within these vulnerable regions, subsequently disrupting their functional coordination with other brain areas.[4]

The substantial negative correlation observed between the DTI-ALPS index and PSQI scores indicates that dysfunction in the brain's glymphatic system may be closely associated with inadequate sleep quality. As an indirect indicator of alterations in glymphatic function, the decrease in the DTI-ALPS index reflects the degree of glymphatic dysfunction in individuals suffering from sleep disorders, which may be linked to neurological impairment and the pathophysiological mechanisms of prolonged conditions COVID.[4] Previous studies have established a strong relationship between glymphatic dysfunction and sleep quality,[27] and the negative correlation observed in this study provides additional evidence supporting this hypothesis. Furthermore, these findings offer valuable insights into the potential function of the brain's glymphatic system in the pathophysiology of sleep disturbances associated with long-term COVID-19 disturbances.

Poorer Sleep Quality and longer Sleep Latency were each associated with lower ALPS indices, indicating that sleep inefficiency parallels glymphatic compromise. This pattern agrees with DTI-ALPS findings of reduced perivascular clearance in individuals experiencing sleep disruption and with a systematic review showing that diminished sleep quality and prolonged latency impair glymphatic function.[8,33] Because our data are cross-sectional and the sample is modest, causal inference is not possible; larger longitudinal studies are required. Notably, previous research has reported a negative correlation between age and the DTI-ALPS index.[33,34] However, no such correlation was observed in the current study, which is likely attributable to the predominantly young and middle-aged cohort of participants.

Previous research[35,36] has demonstrated that Patients with post-COVID insomnia show dynamic white matter changes in brain regions over time abnormalities. Our study found that the ALPS index linked to COVID-related sleep disorders showed a dynamic trend time. Compared to baseline data in the COVID_SD group, the PSQI, GAD, and PHQ scores at 2 months showed significant reductions, indicating recovery trends in sleep and anxiety depression.

Both hemispheres of the ALPS index exhibited an upward trajectory, signifying an enhancement in glymphatic dysfunction compared to the baseline measurement. In contrast, no significant changes were observed in the bilateral ALPS indices or clinical scale scores for the COVID_NSD group. This phenomenon indicates that sleep disturbances associated with COVID-19 diverge from other chronic sleep disorders, demonstrating a significant time-dependent effect.

In a study by Xu et al[16] investigating the asymmetry of glymphatic dysfunction in temporal lobe epilepsy patients, it was proposed that the brain's glymphatic system in normal adults tends to exhibit left-sided asymmetry. However, our paired sample *t*-test revealed that the left ALPS index was significantly lower than the right ($p = 0.029$) in our cohort of post-COVID-19 patients with sleep disturbances. This observation suggests an altered lateralization pattern potentially caused by COVID-19 infection, consistent with the findings of Chaganti et al, who reported significant left hemisphere ALPS reduction in long COVID patients associated with blood-brain barrier disruption.[37]

In this study, a mixed-design ANOVA reveals an asynchronous variation between the two cerebral hemispheres; however, the overall trend remains consistent and symmetrical. SARS-CoV-2 has the potential to induce neuronal damage via neuroinflammatory mechanisms, with the glymphatic system serving as a conduit for fluid transport system,[1] which permeates all regions of the brain. It facilitates cerebrospinal and interstitial fluid (ISF) circulation, contributing to the elimination of metabolic waste produced by the body's inflammation.[38] Considering that the blood flow and blood volume in the left hemisphere of right-handed individuals are generally elevated, the asynchronous variations observed in the bilateral ALPS indices may correlate with the differences in blood volume between the two hemispheres hemispheres.[25,39] Since all participants in this study were right-handed, studies have shown that handedness is often associated with structural and functional asymmetries in the brain hemispheres,[40] which may lead to differential impacts on the left and right hemispheres following infection, thus contributing to the asynchronous changes observed in the bilateral ALPS indices. Our observation of a faster recovery rate in right hemisphere ALPS indices further indicates hemispheric differences in response and recovery following COVID-19, rather than a structural disadvantage in the right hemisphere. This finding suggests complex hemispheric heterogeneity in COVID-19 neuropathology, warranting further mechanistic studies. This may elucidate the asynchronous alterations in the bilateral ALPS indices reflected in our findings, as well as the hemispheric distribution documented in preceding studies. Further exploration of the underlying mechanisms would be valuable for future research.

Limitations

While this investigation presents initial evidence associating sleep disorders with glymphatic function after COVID-19 infection, it is imperative to acknowledge several limitations that should be considered. Firstly, as a single-centre longitudinal study characterized by a relatively small sample size, the generalizability of the findings is limited. Consequently, larger studies encompassing a greater number of participants are warranted to enhance the statistical power.

The absence of a non-COVID insomnia control limits any inference regarding disease specificity. Comparable ALPS reductions have been reported in primary insomnia, REM sleep-behaviour disorder, and obstructive sleep apnoea, suggesting that impaired glymphatic clearance may represent a general consequence of poor sleep.[2,28,29,41] While insomnia-like symptoms predominated in our cohort, the lack of objective sleep assessments precludes exclusion of undiagnosed sleep apnoea. Future multicentre studies that include well-characterized cohorts of primary insomnia will be necessary to determine whether the observed association is disease-specific.

The DTI-ALPS index, a non-invasive imaging tool, correlates strongly with brain glymphatic function from intrathecal gadolinium injection, but it only reflects transient glymphatic function during awake MRI scanning. Brain glymphatic function during sleep may differ from that observed during wakefulness.[42,43] Furthermore, this study did not establish a correlation between the ALPS index and biomarkers, including inflammatory factors or positron emission tomography (PET) utilizing intrathecal methods tracers.[27,35] Future research endeavors should encompass a more extensive array of biomarkers and larger sample sizes to further explore the neurobiological mechanisms associated with sleep disorders subsequent to COVID-19 infection. This approach will enhance our comprehension of the relationship between post-COVID sleep disturbances and the glymphatic system function.

Conclusion

In conclusion, this study utilized the DTI-ALPS index to evaluate brain glymphatic function, indicating the presence of glymphatic dysfunction in individuals who have recently developed sleep disorders subsequent to COVID-19 infection. Glymphatic dysfunction exhibits a strong correlation with sleep disturbances; moreover, an improvement in sleep quality

is associated with a longitudinal recovery trend in glymphatic function. The DTI-ALPS technique could be a useful imaging tool for identifying functional changes in the glymphatic system among patients with long-term neurological sequelae from COVID-19, offering new insights into the neurobiological mechanisms that affect sleep disorders.

Abbreviations

COVID, Coronavirus Disease; SD, Sleep Disorder; NSD, No Sleep Disorder; DTI, Diffusion Tensor Imaging; ALPS, Arachnoid Lymphatic Pumping System; PSQI, Pittsburgh Sleep Quality Index; MRI, Magnetic Resonance Imaging; GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire; SPSS, Statistical Package for the Social Sciences.

Data Sharing Statement

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

Ethics and Consent

Ethics approval and consent to participate.

All methods were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. All participants provided written informed consent.

Author Contributions

All authors made significant contributions to this work, from study conception and design to data acquisition, analysis, and interpretation. Each participated in drafting and revising the manuscript, approved the final version for publication, and agreed on the submission to this journal. All authors take full responsibility for the content of this article. The individual contributions of the authors, based on the CRediT taxonomy, are as follows: Ying-Lan Tang: Conceptualization, Methodology, Funding Acquisition, Writing - Original Draft, Writing – Review & Editing. Hao-bo Chen: Methodology, Investigation, Data Collection, Visualization, Software, Validation, Writing - Review & Editing. Peng Liu: Data Curation, Resources, Investigation, Writing - Review & Editing. Yan-hui Liao: Formal Analysis, Visualization, Project Administration, Writing - Review & Editing, Supervision. An Xie: Conceptualization, Supervision, Resources, Funding Acquisition, Writing - Review & Editing.

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Disclosure

The authors declare no competing interests.

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