Original Article

Evaluation of glymphatic system dysfunction in patients with insomnia via diffusion tensor image analysis along the perivascular space

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Background: The glymphatic system is a crucial pathway for the clearance of metabolic waste from the brain, and its dysfunction has been linked to various neurodegenerative disorders. This study examined the connection between insomnia and glymphatic system dysfunction, offering a novel perspective on the pathophysiological mechanisms underlying insomnia.

Methods: We prospectively recruited 25 patients with insomnia and 37 healthy controls for a case-control study. All participants underwent routine magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) scans. Glymphatic activity was measured via diffusion tensor image analysis along the perivascular space (DTI-ALPS). All patients with insomnia underwent a polysomnogram (PSG) examination and were evaluated using the Pittsburgh Sleep Quality Index (PSQI). We used United Imaging Healthcare artificial intelligence to count the number of enlarged perivascular spaces (ePVSs) in the centrum semiovale, corona radiata, basal ganglia, and hippocampal regions.

Results: The left ALPS index, right ALPS index, and average ALPS index were found to be lower in the insomnia group than in the control group [P false discovery rate (P_{FDR})=0.002, 0.002, and 0.002]. There was no difference in the ALPS index between the left and right sides (P>0.05) in healthy control group, insomniac group, or the entire cohort. The average ALPS index was correlated with the proportion of rapid eye movement and N1 stage sleep (r=0.478 and –0.541; P_{FDR}=0.05 and 0.03). The number of ePVSs was not statistically different between groups in the centrum semiovale, the basal ganglia region, the corona radiata region, the hippocampus region, or other regions (P_{FDR}>0.05).

Conclusions: Insomnia is associated with impairments in glymphatic circulation, and the average ALPS index can serve as an imaging biomarker for glymphatic dysfunction in insomnia, aiding in the prevention of further progression to dementia.

Keywords: Insomnia; glymphatic system; diffusion tensor imaging (DTI); enlarged perivascular spaces (ePVSs)

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Introduction

Insomnia disorder (ID) is defined as difficulty falling asleep or waking up early and falling back to sleep when there is sufficient opportunity for sleep and a suitable environment (1). Insomnia is the most prevalent sleep disorder and the second most prevalent neuropsychiatric illness (2). The prevalence of ID in the adult population exceeds 10% (3). Xie *et al.* (4) found that the restorative function of sleep results in a significant increase in the convective exchange of cerebrospinal and interstitial fluids (ISFs), enhancing the removal of potentially neurotoxic waste products that accumulate in the central nervous system during wakefulness. The glymphatic system lacks real lymphatic channels and includes the input of perivascular interstitial cerebrospinal fluid (CSF) that is driven by pulsations in the arterial walls, flowing in the same direction as blood flow (5). Using animal experiments, Taoka *et al.* (6) found that gadolinium diamine (a contrast agent) could quickly transferred from the bloodstream to the CSF via the rat's cerebral plexus through dynamic magnetic resonance imaging (MRI). They also found that the soluble form of the gadolinium contrast agent may be transferred through the glymphatic system and other mechanisms via the CSF or ISF translocation, suggesting that the glymphatic system may be involved in the effects of sleep and anesthesia in mice. Through use of intravenous contrast agent injections, Lee *et al.* (7) observed how sleep affects the glymphatic system's ability to remove gadolinium contrast agent from human bodies. They discovered that the glymphatic system was able to remove more gadolinium contrast agent after sleep than during waking hours. Another study on mice reported that chronic sleep fragmentation impaired cognition and prevented metabolites from being removed from the brains of young wild-type mice (8). In other research, MRI-informed biophysics was used to measure the solute transport in the human brain during sleep and sleep deprivation, and it was found that tracer clearance decreased during sleep deprivation (9). Sleep plays an important role in the clearance function of the glymphatic system. When the glymphatic system is blocked, this leads to impaired waste elimination, and the accumulation of some wastes can result in the emergence of diseases such as Alzheimer's disease (10-12). This system is also associated with pediatric idiopathic intracranial hypertension (13) and major depression (14).

The diffusion tensor image analysis along the perivascular space (DTI-ALPS) is an emerging noninvasive method for assessing glymphatic system function. It is a DTI-based technique that measures diffusion coefficients to assess the flow of water molecules in the perivascular space. The ALPS index is an important parameter derived based on this technique. The ALPS index has shown good interscanner, interevaluator, and retest reproducibility, making it a reliable candidate biomarker for assessing the glymphatic system's clearance function in neurological disorders.

Previous studies (15-18) have examined the relationship between insomnia and the glymphatic system, but no in-depth investigations into the sleep parameters associated with this system have been conducted. This study aimed to clarify the association between insomnia and glymphatic system dysfunction as well as the relationship between sleep quality indicators and glymphatic system function. The goal was to identify a validated assessment index for assessing glymphatic system status in insomnia, characterize the effects of insomnia on the glymphatic system, and further inform diagnostic and therapeutic approaches. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1447/rc).

Methods

Participants

This prospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of The Second Affiliated Hospital of Nanchang University {approval No. I-Medical Research and Ethical Review [2023] No. (67)}. Informed consent was provided by all individual participants. A prospective sample of 25 patients with insomnia and 37 healthy volunteers was collected between September 2022 and January 2024 (*Figure 1*). Each participant underwent MRI, keeping their heads still during the scans. All patients with insomnia were subjected to a polysomnogram (PSG) examination and tested on the Pittsburgh Sleep Quality Index (PSQI) Rating Scale in a quiet and comfortable environment. The inclusion criteria for patients with insomnia were as follows: (I) satisfying the International Classification of Sleep Disorders, Third Edition (ICSD-3) diagnostic criteria (1); (II) a PSQI score ≥8; and (III) absence of other sleep disorders, multiple sclerosis, Alzheimer's disease, Parkinson's disease, history of craniocerebral trauma, immune demyelinating lesions, metabolic disorder,

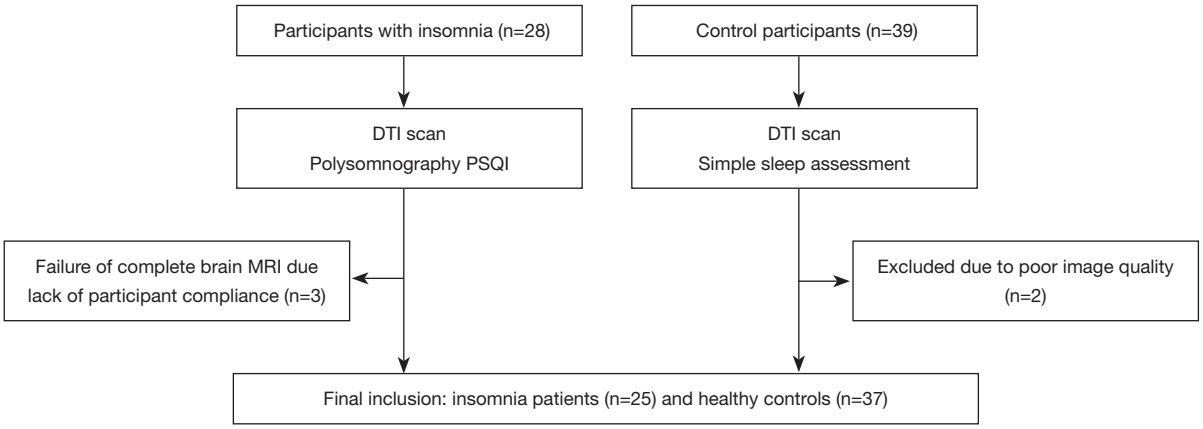

Figure 1 Flow diagram of the study sample. DTI, diffusion tensor imaging; PSQI, Pittsburgh Sleep Quality Index; MRI, magnetic resonance imaging.

Table 1 Demographic information of the participants

Group	Insomnia	Healthy control	P value
Number	25	37	
Age (years)	52.92±1.92	32.46±2.70	0.001
Sex			0.495
Male	8	15	
Female	17	22	

Data are presented as number or mean ± standard deviation.

toxicity, infections, etc. Meanwhile, the inclusion criteria for healthy controls were as follows: (I) no illnesses linked to sleep problems and (II) no organic lesions in the cranium. The exclusion criteria for the insomnia and control groups were as follows: (I) motion artifacts interfering with viewing and (II) claustrophobia or other contraindications to MRI. The basic clinical information of all participants is shown in *Table 1*.

Scanning procedures and image analysis

All scans were performed on a 3.0-T MRI scanner (SIGNA Architect; GE Healthcare, Chicago, IL, USA) with a 48-channel head coil. All participants underwent routine MRI [T1-weighted imaging, T2-weighted imaging, T2 fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging] and DTI scans at night. The DTI parameters were as follows: direction of diffusions =64, repetition time/echo time (TR/TE) =8,441/95.5 ms, field of view (FOV) =240×240 mm^2, slice thickness =3 mm, reconstruction matrix size =256×256, b value =0 and 1,000 s/mm^2, and number of excitations =1.

All images were processed by two radiologists (one junior with 3 years' experience and one senior with 15 years' experience) in a double-blind method of coprocessing according to uniform criteria, with and the average of the two measurements being recorded. Enlarged perivascular spaces (ePVSs) are perivascular spaces with a diameter greater than 2 mm (19). The ePVSs in the centrum semiovale, basal ganglia, corona radiata, and hippocampus were counted using T2-weighted imaging sequences as the primary sequences. The artificial intelligence engines developed by United Imaging Healthcare (Shanghai, China) have excellent performance in image segmentation (20-22). In our study, the number of ePVSs was first obtained with this artificial intelligence and then further corrected manually with T2 FLAIR sequences. DTI was postprocessed using DSI Studio postprocessing software (May 2021 version; http://dsi-studio.labsolver.org). The software was first used to correct the DTI images

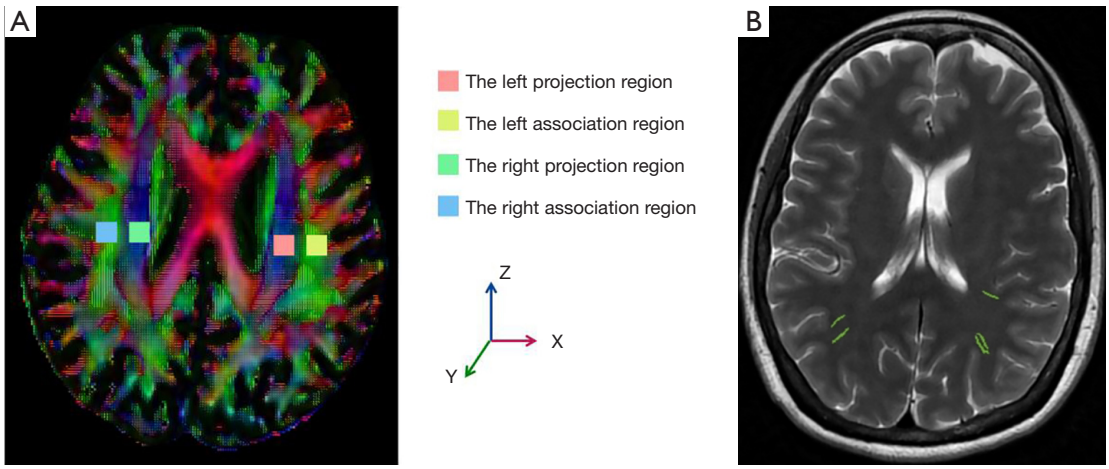

Figure 2 Postprocessed images. (A) DTI-ALPS post-processing schematics. (B) The recognition of ePVSs by the united imaging artificial intelligence. DTI-ALPS, diffusion tensor image analysis along the perivascular space; ePVS, enlarged perivascular space.

for head movement, and then regions of interest (ROIs) around 5 mm^2 in size were outlined in the original diffusion color-coded anisotropy score image at the level where the lateral ventricle was located. Four ROIs were outlined in the bilateral projection fibers and in the bilateral association fibers to measure the projection fiber X and Y directions and the association fiber X and Z directions (*Figure 2*). These were used to calculate the ALPS index. Finally, the ALPS index was calculated using the following formula (23):

$$ALPS\ index = mean\ (Dxproj, Dxassoc) / mean\ (Dyproj, Dzassoc) \quad [1]$$

The ALPS index is the ratio of the average of the x-axis diffusivity in the projection region (Dxproj) and the x-axis diffusivity in the association region (Dxassoc) to the average of the y-axis diffusivity in the projection region (Dyproj) and the z-axis diffusivity in the association region (Dzassoc).

Statistical analysis

SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA) was used for analysis. Count data are expressed as frequencies, and comparisons were made using the χ^2 test; measurement data were tested for normality via the Shapiro-Wilk test. The normally distributed variables are expressed as the mean ± standard deviation and analyzed via the *t*-test. Analysis of covariance (ANCOVA) was applied to the dependent variable with a confounding factor, which was age. Data that did not conform to a normal distribution are expressed the median and the first and third quartile (P_{25}, P_{75}) and were analyzed via nonparametric tests. Pearson or Spearman correlation analysis was conducted to examine the relationship between sleep indicators and ALPS index. The P values for intergroup comparisons of the ALPS index were corrected using the false discovery rate (FDR) test. $P<0.05$ (two-sided) was considered statistically significant.

Results

Comparison of the number of ePVSs between the insomnia group and the control group

The number of ePVSs in the four regions and in the brain regions was not statistically different between the groups (*Table 2*).

Comparison of DTI-related indicators in the insomnia and control groups

The left and right ALPS indexes were not statistically different in any of groups (*Table 3*). The left ALPS index, the right ALPS index, and the average of ALPS-index significantly differed between the insomnia group and the healthy controls (*Table 4* and *Figure 3*).

Correlation between DTI-related indicators and PSG-related indicators

The average ALPS index was positively correlated with the proportion of rapid-eye-movement (REM) (r=0.478; P_{FDR}=0.05) and negatively correlated with the proportion of N1 stage (r=–0.541; P_{FDR}=0.03). The other PSG-related

Table 2 Comparison of the number of ePVSs between the different regions

The region of ePVSs	Insomnia	Healthy control	Z value	P_B value	P_A value	P_{FDR} value
Centrum semiovale	4 (3, 6.5)	0 (0, 1)	1.534	<0.001	0.220	0.22
Basal ganglia	9 (7, 12)	4 (3, 6.5)	2.099	<0.001	0.152	0.21
Corona radiata	3 (1, 4)	0 (0, 0)	5.412	<0.001	0.023	0.12
hippocampus	1 (0, 2)	0 (0, 0)	1.967	<0.001	0.166	0.21
All	18 (14, 24)	6 (3.5, 8)	3.800	<0.001	0.056	0.14

Data are presented as median (P_{25}, P_{75}). P_B value was obtained before ANCOVA; P_A value was obtained after ANCOVA; P_{FDR} value was obtained after ANCOVA and FDR test. ePVS, enlarged perivascular space; ANCOVA, analysis of covariance; FDR, false discovery rate.

Table 3 Comparison of the ALPS indices between the two groups

Participant	ALPS index		*t* value	P value
	Left	Right		
Insomnia	1.41±0.34	1.35±0.03	1.25	0.221
Healthy controls	1.57±0.02	1.65±0.03	−1.42	0.156
All participants	1.53±0.25	1.53±0.28	−0.39	0.700

Data are presented as the mean ± standard deviation. ALPS, analysis along the perivascular space.

Table 4 Comparison of the ALPS index and the related parameters between the insomnia group and the control group

Parameter	Insomnia	Healthy control	F value/Z value	P_B value	P_A value	P_{FDR} value
Left						
Dxproj ($\times10^{-4}$)	5.70 (5.23, 5.97)	6.26 (5.54, 6.68)	9.62	<0.001	0.003	0.005
Dyproj ($\times10^{-4}$)	4.64 (4.41, 5.23)	4.44 (3.72, 4.92)	0.73	0.505	0.398	0.486
Dxassoc ($\times10^{-4}$)	5.30 (4.99, 5.88)	6.13 (4.95, 6.86)	4.70	<0.001	0.034	0.053
Dzassoc ($\times10^{-4}$)	3.26±0.27	3.17±0.14	0.17	0.756	0.682	0.682
ALPS index	1.40±0.03	1.61±0.03	15.43	<0.001	0.001	0.002
Right						
Dxproj ($\times10^{-4}$)	5.80 (5.57, 5.92)	5.54 (5.24, 6.22)	1.207	0.631	0.277	0.381
Dyproj ($\times10^{-4}$)	5.19±0.16	3.87±0.18	12.05	<0.001	0.001	0.002
Dxassoc ($\times10^{-4}$)	5.74 (5.16, 6.36)	6.29 (5.35, 6.82)	13.54	0.002	0.001	0.002
Dzassoc ($\times10^{-4}$)	3.49 (3.15, 3.75)	2.98 (2.41, 3.26)	0.20	0.047	0.657	0.682
ALPS index	1.35±0.32	1.65±0.30	30.78	<0.001	0.001	0.002
Average ALPS index	1.38±0.03	1.62±0.02	32.81	<0.001	0.004	0.002

The mean ± standard deviation is used for normal distribution, and the median (P_{25}, P_{75}) is used for non-normal distribution. P_B value was obtained before ANCOVA; P_A value was obtained after ANCOVA; P_{FDR} value was obtained after ANCOVA and FDR test. ALPS, analysis along the perivascular space; ANCOVA, analysis of covariance; FDR, false discovery rate.

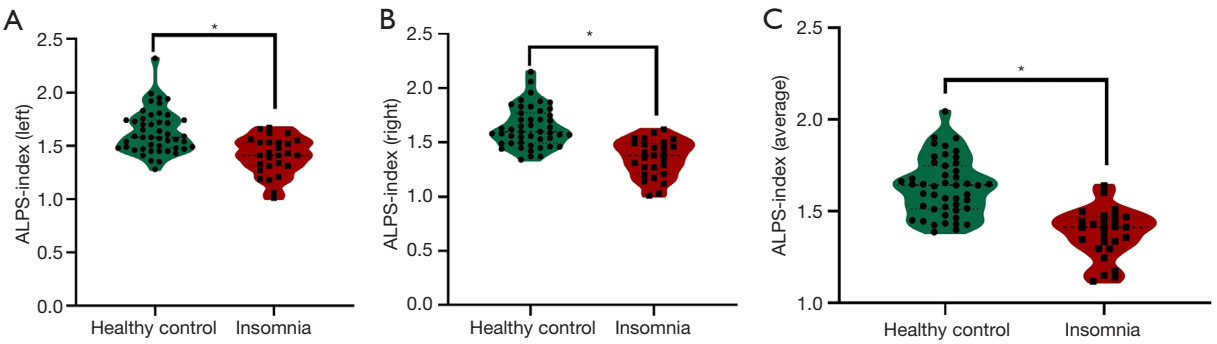

Figure 3 Comparison of the ALPS index between the insomnia and control groups. (A) Comparison of left ALPS index between the insomnia and healthy control groups. (B) Comparison of the right ALPS index between the insomnia and healthy control groups. (C) Comparison of average ALPS index between the insomnia and healthy control groups. *, P<0.05. ALPS, analysis along the perivascular space.

Table 5 Correlation analysis of the DTI-ALPS index with PSG-related parameters

Sleep indicator, ALPS index (average)	r value	P value	P_{FDR} value
Sleep latency	0.228	0.243	0.46
Wakefulness time after sleep	−0.196	0.317	0.46
Number of awakenings	−0.211	0.281	0.46
Percentage of N1 period	−0.541	0.003	0.03
Percentage of N2 period	−0.083	0.676	0.75
Percentage of N3 period	0.315	0.103	0.34
Percentage of R period	0.478	0.010	0.05
Total sleep time	0.103	0.600	0.75
Sleep efficiency	0.195	0.320	0.46
PSQI	0.012	0.952	0.95

DTI-ALPS, diffusion tensor image analysis along the perivascular space; PSG, polysomnography; FDR, false discovery rate; PSQI, Pittsburgh Sleep Quality Index.

indices were not significantly correlated with the DTI-ALPS indices (*Table 5*, *Figure 4*).

Discussion

In this study, the association between insomnia and glymphatic system dysfunction was explored using the DTI-ALPS technique and an artificial intelligence tool. The principal findings were as follows: (I) the mean values of left ALPS index, right ALPS index, and ALPS-index were significantly lower in the insomnia group than in the control group. (II) The left ALPS index correlated with the proportion of R phase. The right ALPS index correlated with the number of awakening transitions and the proportion of the N1 phase.

Change in ePVS in ID

Perivascular spaces (24) are spaces or potential spaces around small arteries, capillaries, and small veins in the brain, which constitute an important part of the glymphatic system. The enlargement of perivascular spaces reflects impaired waste clearance, resulting from a pathological cascade reaction involving perivascular inflammation and vascular reactive damage, leading to reduced clearance of ISF waste solutes (25).

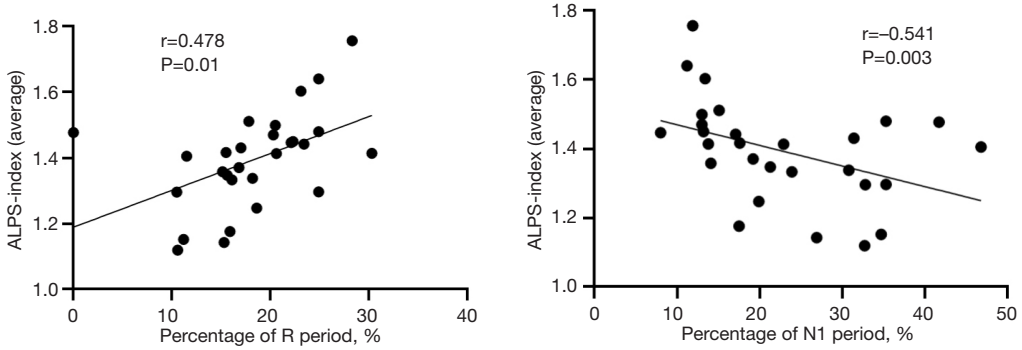

Figure 4 Scatterplot of correlation between PSG-related indicators and the ALPS index. ALPS, analysis along the perivascular space; PSG, polysomnography.

This study was able to observe a higher number of ePVSs among individuals in the insomnia group compared to those in the healthy control group. However, there was no statistical difference, possibly due to the small sample size. Further exploration with a larger sample size is needed. It is possible that the insomnia group's disruption of glymphatic circulation hinders the clearance of brain waste, leading to its accumulation. This accumulation may stimulate vascular inflammation and damage, exacerbating the burden of perivascular spaces, resulting in compensatory expansion and progressive fluid dynamic damage. This study only analyzed the quantity of ePVSs and did not conduct further analysis on related parameters of ePVS burden. However, previous studies have examined this. A study in preschool children (26) indicated a unique association between ePVSs and nocturnal awakenings. Other research (27) suggests that the load of perivascular spaces in the centrum semiovale mediates a 5% association between sleep parameters and brain changes, with sleep disorders correlating with increased perivascular space burden. Furthermore, poor sleep efficiency is independently associated with increased perivascular spaces in the basal ganglia region (28). In a study on older adults (29), it was found that older adults with better sleep quality and efficiency had larger volumes of perivascular spaces in the basal ganglia; however, sleep metrics were not correlated with perivascular space volume in the semioval center. Additionally, body mass index was found to affect perivascular space volume in middle-aged and older adult participants, with the impact of sleep on perivascular space volume varying across different age groups and ethnicities. Wang *et al.* (16) reported that patients with chronic insomnia and cognitive dysfunction had significantly increased ePVSs in the frontal cortex, centrum semiovale, and basal ganglia regions compared to cognitively normal patients with insomnia and healthy volunteers. Moreover, levels of Aβ, t-tau, and p-tau proteins in the CSF were elevated in patients with chronic insomnia and cognitive dysfunction, indicating a link between abnormal protein deposition caused by glymphatic dysfunction and cognitive impairment, which may pose a risk for further progression to dementia. Other literature (15) suggests that shallow sleep, such as longer N1 sleep and shorter slow-wave sleep, is associated with a higher burden of ePVSs, indicating a relationship between sleep structure and glymphatic system clearance function. These studies demonstrate that insomnia disrupts the brain clearance and increases the accumulation of waste products in the brain.

DTI-ALPS scores in patients with insomnia for assessing glymphatic dysfunction of ID

With the development of MRI technology, an increasing number of imaging studies are using new techniques to broaden our understanding of glymphatic circulation system. DTI-ALPS (30) is a method based on DTI measurements of diffusion rates to evaluate the movement of water molecules in the space around blood vessels. It is based on the assumption that the direction of the perivascular space around blood vessels is the same as that of the medullary veins at the level of the lateral ventricle, with the medullary veins perpendicular to the ventricular wall, defining this left-right direction as the x-axis. In the plane of this area, adjacent projection fibers run in the head-to-foot direction, while association fibers run in the anterior-posterior direction; these directions are orthogonal to the direction of the perivascular space, defined as the y-axis and z-axis, respectively. When histological changes

occur along the perivascular space, both the diffusion rates of projection fibers and association fibers are affected. A low ALPS index indicates a decrease in the water diffusion rate in the perivascular space, suggesting dysfunction in the glymphatic system (31). Therefore, DTI-ALPS can achieve noninvasive indirect evaluation of glymphatic circulation function that is consistent with the assessment of glymphatic circulation function accomplished via direct intrathecal tracing methods (32,33).

In this study, there was no difference in the ALPS index between the left and right sides in the insomnia group, control group, or the entire cohort, indicating that there is no difference in the glymphatic circulation function of the bilateral cerebral hemispheres. The left ALPS index, right ALPS index, and their average showed differences between the insomnia group and the control group, with all values being higher in the control group than in the insomnia group ($P<0.001$). This indicates that water diffusion in the perivascular spaces was restricted in those with insomnia and that the bilateral glymphatic circulation function was impaired, which is consistent with previous research (17,18). It has been reported that the left ALPS index of patients with chronic insomnia is lower than that of good sleepers, suggesting the glymphatic circulation dysfunction, which is in line with our study. A study on sleep interruption demonstrated a significant decrease in ALPS index in young people with sleep interruption, possibly due to glymphatic system dysfunction, and further reported a significant association between ALPS index and sleep quality, sleep latency, and the use of sleep medication (34). Many studies have indicated that glymphatic circulation disorders may lead to abnormal protein aggregation and cognitive dysfunction, and thus it can be surmised that patients with insomnia are at greater risk of disease progression that leads to cognitive impairment and dementia (35-37). Therefore, early detection of glymphatic circulation abnormalities in insomnia and early intervention can reduce the risk of further disease progression. The ALPS index can serve as a rapid and convenient tool for the clinical assessment of glymphatic circulation in insomnia. This can guide early targeted treatment in clinical practice and reduce the risk of disease progression to dementia.

Glymphatic circulation disorders and sleep quality

Sleep can be defined and classified based on physiological and behavioral criteria into non-REM (NREM) sleep stages (N1, N2, and N3) and REM sleep (38). Patients with insomnia exhibit disrupted sleep architecture, decreased sleep efficiency, reduced proportion of REM sleep within the sleep cycle, and an increased proportion of N1 stage sleep within the sleep cycle (39). In our study, the ALPS index was not significantly different the right and left hemispheres of the brain, so we directly correlated the mean ALPS index with PSG parameters to investigate the relationship between whole-brain glymphatic circulation and clinical sleep evaluation parameters. We found that the ALPS index was positively correlated with the percentage of the R phase in the sleep cycle. The smaller the percentage of R phase was in patients with insomnia, the lower the average value of the ALPS index and the more severely impaired the function of the whole brain glymphatic circulation. Meanwhile, our results indicated that the mean value of ALPS index was negatively correlated with the percentage of N1 period in the sleep cycle, while the patients with insomnia had difficulty in falling asleep and waking early. The larger the percentage of N1 was in the sleep cycle, the lower the ALPS index and the worse the function of the whole-brain glymphatic circulation. All these findings suggest that poor sleep quality has a negative impact on whole-brain glymphatic circulatory activity.

Evidence from previous human and animal studies suggests that CSF transport is most active during slow-wave sleep and inhibited during wakefulness (40,41). These findings suggest that poor sleep quality and disrupted sleep architecture in those with insomnia hinder glymphatic circulation activity. Additionally, a higher PSQI score indicates a greater severity of insomnia, but we found no correlation between PSQI score and ALPS index, which is consistent with previous research (18,35), suggesting there is connection between ALPS index and the severity of insomnia.

This study involved certain limitations that should be acknowledged. First, we employed a small sample size, groups were not age-matched, and no additional subgroups of patients with insomniac were defined, which precluded the examination of glymphatic circulation status in individuals with different types of insomnia. Follow-up studies will include an expanded sample size, sample matching, control for additional confounders, and subgroup analyses. Second, our study focused mainly on the quantitative changes of ePVSs and did not analyze other parameters related to ePVS load, such as the volume of the ePVSs, which limited the interpretation of the mechanism of ePVS in the glymphatic system activity of insomnia. In future studies, consideration should be

given to evaluating other parameters of the ePVS, such as volume, morphology, and distribution, in order to more fully characterize the relationship between insomnia and glymphatic system dysfunction. Third, this study failed to provide measurements of molecular biomarkers (e.g., tau protein and Aβ levels) associated with glymphatic system dysfunction, which limits the understanding of the molecular mechanisms underlying the relationship between insomnia and glymphatic system dysfunction. Future studies should include measurements of molecular biomarkers, such as tau protein and Aβ levels in the CSF, to examine the molecular mechanisms underlying the relationship between insomnia and glymphatic system dysfunction in greater depth and to validate the correlation between the ALPS index and these biomarkers. Finally, the DTI-ALPS method can only evaluate the white matter outside the lateral ventricles in an image section that includes the body of the lateral ventricles (42). Future research is anticipated to introduce new noninvasive methods for assessing glymphatic circulation, enabling qualitative and quantitative analyses of this circulatory dysfunction.

Conclusions

The quality of sleep is directly correlated with glymphatic circulation in cases of insomnia. Our findings show that a reduced ALPS index and increased number of ePVSs in the corona radiata in patients with insomnia indicate dysfunction in glymphatic circulation. The mean value of the ALPS index can serve as an imaging marker for assessing glymphatic circulation disorder in patients with insomnia, which may assist in evaluating their condition and selecting therapeutic targets to prevent the progression of the disease.

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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-24-1447/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. This prospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of The Second Affiliated Hospital of Nanchang University {approval No. I-Medical Research and Ethical Review [2023] No. (67)}. Informed consent was provided by all individual participants.

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