Original Article

Relationship between glymphatic system dysfunction and cognitive impairment in patients with mild-to-moderate chronic traumatic brain injury: an analysis of the analysis along the perivascular space (ALPS) index

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Background: Cognitive impairment associated with mild-to-moderate chronic traumatic brain injury (TBI) presents substantial challenges for which the functionality of the brain glymphatic system is a key area of interest. This study aimed to explore the functionality of the brain glymphatic system in patients with chronic cognitive impairment following mild-to-moderate TBI using diffusion tensor image analysis along the perivascular space (DTI-ALPS).

Methods: This was a prospective cross-sectional study. A total of 56 patients with mild-to-moderate chronic TBI at the Radiology Outpatient Clinic of the First Affiliated Hospital of Hainan Medical University were enrolled in the study between January 2021 and July 2022. Additionally, 20 healthy control (HC) subjects were recruited from the Health Screening Center during the same period as the HC group. Relevant clinical data for all the participants were collected, and cognitive assessments were conducted using cognitive scales. The TBI patients were categorized into the traumatic brain injury cognitive impairment (TBI-CI) and traumatic brain injury cognitively normal (TBI-CN) groups based on their of the Chinese Version of the Montreal Cognitive Assessment-Basic (MoCA-BC) scores. Each group comprised 20 subjects. All three groups of participants underwent diffusion tensor imaging (DTI). The DTI data were processed and analyzed using the MRIcron and FMRIB Software Library (FSL) toolboxes, and the analysis along the perivascular space (ALPS) index was calculated. Differences in the ALPS index among the three groups were examined by an analysis of covariance, adjusted for age and gender. A corrected receiver operating characteristic (ROC) curve analysis was employed to evaluate the diagnostic performance of the ALPS index in identifying patients with traumatic chronic cognitive impairment.

Results: Compared with the HC group, both the mild-to-moderate TBI patients with and without cognitive impairment had a decreased ALPS index (HC *vs.* TBI-CI: 1.629 *vs.* 1.302, P<0.001; HC *vs.* TBI-CN: 1.629 *vs.* 1.523, P=0.003). Moreover, the decrease in the ALPS index was more significant in the mild-to-moderate TBI patients with cognitive impairment (TBI-CN *vs.* TBI-CI: 1.523 *vs.* 1.302, P<0.001). The adjusted ROC curve analysis revealed that the area under the curve (AUC) of the ALPS index for diagnosing traumatic chronic cognitive impairment was 0.983 [95% confidence interval (CI): 0.953–1, P<0.001], with a

sensitivity of 90% and specificity of 95%.

Conclusions: Cognitive impairment in patients with mild-to-moderate chronic TBI may be associated with impairment of the glymphatic system. Additionally, the ALPS index may serve as a potential predictor of the disease. Our findings provide some novel insights into the pathophysiological mechanisms underlying cognitive impairment in mild-to-moderate chronic TBI.

Keywords: Mild-to-moderate traumatic brain injury (mild-to-moderate TBI); glymphatic system; diffusion tensor image analysis along the perivascular space index (DTI-ALPS index); cognitive impairment

Submitted May 04, 2024. Accepted for publication Sep 12, 2024. Published online Nov 07, 2024.
doi: 10.21037/qims-24-895
View this article at: https://dx.doi.org/10.21037/qims-24-895

Introduction

Traumatic brain injury (TBI) is defined as a dysfunction or evidence of pathology in the brain caused by an external force, such as a blow or jolt to the head. About 90% of TBI patients have mild-to-moderate injuries and few die (1,2). Around one-third of mild-to-moderate TBI patients experience cognitive impairment symptoms that persist for over 3 months (3,4). Studies have indicated that the neuro-psychological symptoms of the majority of mild-to-moderate TBI patients show significant improvements within 6–12 months (5). If no improvement occurs beyond this period, symptoms may persist or result in permanent sequelae. Chronic cognitive impairment resulting from TBI is one of the most common long-term effects (6), and places substantial psychological and economic burdens on patients and their families.

The mechanisms underlying chronic cognitive impairment caused by TBI have not been fully elucidated. Currently, no single mechanism has been identified that can comprehensively explain this process. The primary mechanisms under investigation include metabolic disruptions (7), abnormal protein accumulation (8,9), neuroinflammation (10,11), mitochondrial dysfunction (12,13), and diffuse axonal injury (DAI) (14,15). Recent research suggests that the glymphatic system may be involved in the pathophysiology of TBI (16). Impaired glymphatic system function has been found in animal models of TBI, promoting post-traumatic neuroinflammation and exacerbating cognitive impairment (17). Further, a correlation between the severity of TBI and the extent of glymphatic system damage has been observed (18).

The glymphatic system, which serves as a brain-wide clearance pathway, plays a crucial role in clearing soluble amyloid-beta (Aβ) proteins (19), tau proteins (17), lipids (20), and other metabolites. Several studies have linked glymphatic system dysfunction to cognitive impairment resulting from various diseases such as diabetes (21), Alzheimer's disease (22), cerebral small vessel disease (23,24), and depression-related cognitive impairment (25). Additionally, research has reported an association between acute cognitive impairment following mild TBI and damage to the glymphatic system (26). However, for acute cognitive impairment after TBI, the main pathological mechanisms include excitotoxicity, cell apoptosis, inflammation, and axonal injury (27), and glymphatic system dysfunction is not the primary mechanism. Nevertheless, in the context of chronic cognitive impairment following TBI, impaired glymphatic system function and the resulting hindrance in clearing brain metabolic waste, such as Aβ proteins, could potentially be one of the key contributing factors. Currently, there are no reports on the relationship between mild-to-moderate TBI-induced chronic cognitive impairment and the glymphatic system; thus, further research in this area is needed.

Currently, magnetic resonance imaging (MRI), including both non-contrast-enhanced imaging and contrast-enhanced imaging using gadolinium-based agents, is the most commonly used technique for evaluating the human glymphatic system (28). Intrathecal contrast agent injection can confirm the delayed clearance of the contrast agent, providing evidence of glymphatic system dysfunction. However, this invasive procedure is restricted in some countries (29), and it carries the risk of gadolinium deposition in the brain (30). Considering these factors, our preferred approach for assessing glymphatic system function was the use of non-contrast-enhanced imaging methods, specifically diffusion tensor image analysis along the perivascular space (DTI-ALPS) to derive the analysis along the perivascular space (ALPS) index (31).

The ALPS index has been shown to effectively reflect brain glymphatic system functionality (32,33). Further, we evaluated DAI through the use of global fractional anisotropy (FA) and global mean diffusivity (MD) (14). Some studies have shown that, compared with the Montreal Cognitive Assessment (MoCA), the Chinese Version of the Montreal Cognitive Assessment-Basic (MoCA-BC) is a reliable cognitive screening test for people of all educational levels, has high acceptability and reliability, and is more appropriate for TBI subjects with lower levels of education (34,35).

This study aimed to investigate the relationship between cognitive impairment and the glymphatic system, as assessed by the ALPS index, in patients with mild-to-moderate chronic TBI. Additionally, it sought to explore whether the ALPS index can serve as a potential predictor of cognitive impairment in patients with mild-to-moderate chronic TBI. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-895/rc).

Methods

Participants

This prospective cross-sectional study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Biomedical Ethics Committee of Hainan Medical University (No. 2023-KYL-084). All methods in this study were carried out in accordance with the relevant guidelines and regulations, and all participants and/or their families were informed about the study and provided informed consent by signing the informed consent form.

This study included 56 TBI patients undergoing MRI at the First Affiliated Hospital of Hainan Medical University between January 2021 and July 2022. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) be aged between 18 and 60 years; (II) have been diagnosed with TBI based on a trauma that occurred only once and not multiple times, have suffered from TBI for over a year, and have a Glasgow Coma Scale (GCS) score >8 (36); (III) have no history of cognitive impairment prior to the injury; (IV) have undergone diffusion tensor imaging (DTI); and (V) be right-handed (to minimize variability due to brain lateralization differences and ensure the stability and consistency of the study results). Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a history of acute cerebral infarction or hypoxic-ischemic encephalopathy; (II) had a history of periventricular or deep white matter hemorrhage [with regions of interest (ROI) located in these areas]; (III) had a history of mental illness, tumors, Alzheimer's disease, diabetes, neurodegenerative diseases, hydrocephalus, alcohol intoxication, cerebral small vessel disease, or other diseases causing cognitive impairment; and/or (IV) had contraindications to MRI.

The cut-off scores of the MoCA-BC for mild cognitive impairment (MCI) detection were 19 in the low-level education group (≤6 years), 22 in the mid-level education group (7–12 years), and 24 in the high-level education group (>12 years) (35). Based on the MoCA-BC scale, the TBI patients were divided into the traumatic brain injury cognitively normal (TBI-CN) (TBI-CN) group and the traumatic brain injury cognitive impairment (TBI-CI) group.

During the study period, 20 additional healthy control (HC) subjects were also included in the study based on the following inclusion criteria: (I) they had undergone a neurological examination and DTI); (II) they had no history of neurological disorders; and (III) they had no history of taking any medication affecting the central nervous system.

In summary, a total of 56 patients with mild-to-moderate TBI were included in the study, while 16 patients were excluded. Additionally, 20 HC subjects were included, resulting in a total of 60 subjects (*Figure 1*).

Sample-size calculation

The PASS 25.0 software (NCSS, Kaysville, Utah, USA) was used for the sample-size estimation. This study was a cross-sectional study in which the ALPS index of the study population was the primary observation. The preliminary trial results showed that the ALPS index values [expressed as mean ± standard deviation (SD)] for the HC, TBI-CN, and TBI-CI groups were 1.664±0.049, 1.561±0.109, and 1.294±0.015, respectively. With a significance level set at α=0.05 and a statistical power (1-β) of 0.9, the estimated sample size for each group was N1=N2=N3=8. Considering an anticipated dropout rate of 20%, the final required sample size for each group was at least 10.

MRI scanning

All the subjects underwent 3.0 Tesla MRI scanning (GE Medical Systems, Signa HD, Waukesha, WI, USA) with an eight-channel head coil. Each subject was stabilized

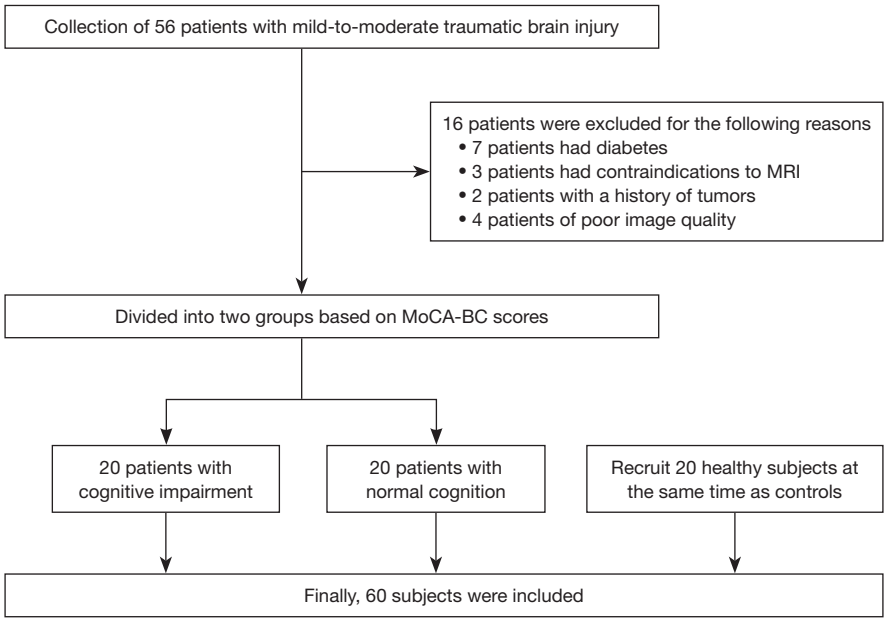

Figure 1 Subject inclusion flowchart. MRI, magnetic resonance imaging; MoCA-BC, Chinese Version of the Montreal Cognitive Assessment-Basic.

with comfortable foam pads to minimize head movement and wore earplugs to reduce the influence of noise during scanning. DTI scans were obtained using a single shot echo planar imaging sequence. The parameters were as follows: repetition time =8,000 ms; echo time =95 ms; field of view =240×240 mm^2; flip angle =90°; matrix size =256×256; slice thickness =3.6 mm; and diffusion directions =30 with a b-value of 1,000 s/mm^2.

MRI image analysis

All the MRI images were independently evaluated by two radiologists with extensive experience in neuroimaging diagnosis (6 years of experience each). The radiologists were blinded to the clinical information of each patient. If any discrepancies arose in relation to their assessments, a third radiology chief physician (with more than 20 years of experience) was consulted.

Based on the DTI data, diffusion tensor images were generated using the FMRIB Software Library (FSL) (version 6.0; Analysis Group, FMRIB, University of Oxford, Oxford, UK; http://fsl.fmrib.ox.ac.uk/fsl), including color-encoded FA maps, MD maps, and diffusivity maps. To accurately assess glymphatic system activity, an analysis was performed in the individual space of two adjacent axial slices at the lateral ventricle body level. Next, using the FSLstats tool with the pre-existing brain mask, the mean whole-brain FA and MD values were calculated. From each frame of diffusivity images (automatically generated by the FSL software), diffusivity values along the X-, Y-, and Z-axes were obtained separately. As the direction of the perivascular space (PVS) around blood vessels on the level of the lateral ventricle body is perpendicular to the ventricular wall (mostly in the left-right direction/X-axis direction), it is also perpendicular to the direction of projection fibers (primarily along the Z-axis) and association fibers (mainly along the Y-axis). Thus, the diffusivity along the X-axis of the projection and association fibers partly represents the diffusivity along the PVS direction, thus reflecting the glymphatic activity. Conversely, the diffusivity of subcortical fibers along the X-axis does not reflect pure perivascular water diffusion, as subcortical fibers flow parallel to the perivascular flow, masking glymphatic diffusion. In the left hemisphere (all the participants were right-handed), on two adjacent axial slices at the level of the lateral ventricle body, square ROIs measuring 3 mm per side were independently outlined around the projection, association, and subcortical fiber areas by two experienced neuroradiologists (*Figure 2*). diffusivity values were obtained for each type of fibers in the X, Y, and Z directions.

A recent report stated that the shape and size of the ROI do not affect the calculation of the ALPS index (37).

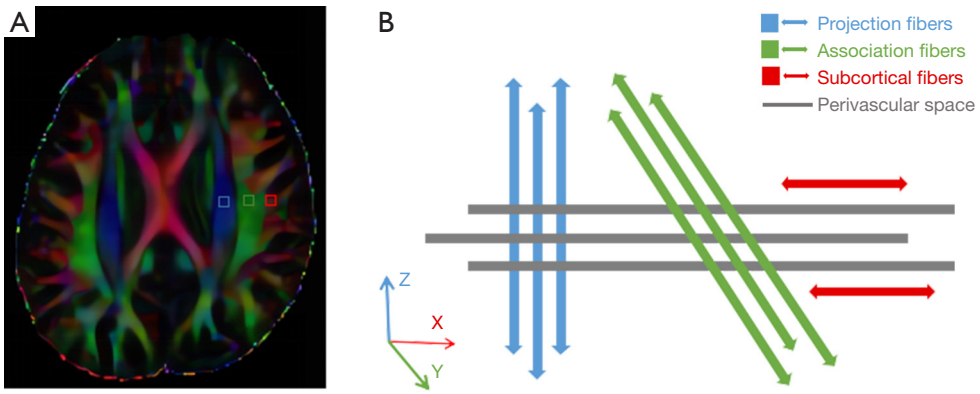

Figure 2 The concept of the DTI-ALPS method for perivascular diffusion. (A) DTI color map showing the direction of the projection fibers (blue; Z-axis), association fibers (green; Y-axis) and subcortical fibers (red; X-axis), and the ROIs placed to measure the DTI parameters of the projection and association fibers. (B) Schematic showing the relation and directions of the PVS. and three fiber types (i.e., the projection, association, and subcortical fibers). DTI-ALPS, diffusion tensor image analysis along the perivascular space; ROI, region of interest; DTI, diffusion tensor imaging; PVS, perivascular space.

As in Taoka *et al.*'s study (31), this index is determined by the ratio of two diffusivity value sets, i.e., the ratio of the average values of the X-axis diffusivity in the area of the projection fibres (Dxxproj) and the X-axis diffusivity in the area of the association fibres (Dxxassoc) to the average value of the Y-axis diffusivity in the area of the projection fibres (Dyyproj) and the Z-axis diffusivity (Dzzassoc) of the association fibres area. More specifically, this relationship is defined as follows: ALPS index = mean (Dxxproj, Dxxassoc)/ mean (Dyyproj, Dzzassoc). In the area of the projection fibers, the dominant fibers run along the direction of the Z-axis, and the X- and Y-axes are perpendicular to the dominant fibers. Similarly, in the area of the association fibers, the dominant fibers run along the direction of the Y-axis, and both the X- and Z-axes are perpendicular to the dominant fibers. The major difference in the behavior of water molecules between the X-axis diffusivity in these areas (Dxxproj and Dxxassoc) and the diffusivity perpendicular to them (Dyyproj and Dzzassoc) is the existence of the PVS. Therefore, the ALPS index was calculated by measuring the diffusivity from the composite along the direction of the PVSs in perpendicular association fibers and projection fibers to reflect the function of the glymphatic system.

Statistical analysis

The statistical analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). The chi-square test was used to compare the categorical variables related to the participant characteristics. The Shapiro-Wilk test was used to assess whether the continuous variables adhered to a normal distribution. Variables with a normal distribution are presented as the mean ± SD and were compared by a one-way analysis of variance and *t*-test. Variables with a non-normal distribution are presented as the median (interquartile range), and were compared using the Kruskal-Wallis H and Mann-Whitney U tests. Inter-observer agreement on the ALPS measurements between the two readers was evaluated using the interclass correlation coefficient (ICC) (38,39). An analysis of covariance was used to compare the FA, MD, ALPS index, and diffusivities among the HC, TBI-CN, and TBI-CI groups, adjusted for age and gender. In relation to the indexes that differed significantly among the three groups, multiple comparisons between groups were performed using the Bonferroni method. The diagnostic performance of the ALPS index for chronic cognitive impairment in cases of TBI was quantified by calculating the area under the curve (AUC), specificity, and sensitivity from a covariate-adjusted receiver operating characteristic (ROC) curve, accounting for age and gender. The assessment focused solely on comparing the TBI-CN and TBI-CI groups. A two-sided P value <0.05 was considered significant for all statistical analyses.

Results

Participant characteristics

The study included 60 subjects, and the baseline demographic and clinical features of the subjects are

Table 1 Baseline demographic and clinical features of the study sample

Variables	HC (N=20)	TBI-CN (N=20)	TBI-CI (N=20)	P value
Age (years)	34.90±7.72	40.20±11.00	42.45±12.19	0.078†
Gender (n)				0.153‡
Male	10	15	15	
Female	10	5	5	
Initial GCS upon injury	N/A	15 [1]	14 [1]	0.096§
Course of disease (month)	N/A	20 [1]	18 [1]	0.321§
Education years (n)				0.607‡
≤6	4	4	7	
7–12	11	13	10	
>12	5	3	3	
MoCA-BC scores	25 [4]	25 [2]	18 [10]	N/A
TBI severity (n)				0.405‡
Mild TBI	N/A	18	15	
Moderate TBI	N/A	2	5	
Type of injury (n)				0.888‡
Motor vehicle accident	N/A	14	13	
Fall	N/A	4	4	
Violent injury	N/A	2	3	

Age is expressed as the mean ± SD; initial GCS upon injury, disease course, and MoCA-BC scores are expressed as the median [interquartile range]. †, indicates the use of a one-way analysis of variance; ‡, indicates the use of the Chi-squared test; §, indicates the use of the Mann-Whitney U test. HC, healthy control; TBI-CN, traumatic brain injury cognitively normal; TBI-CI, traumatic brain injury cognitive impairment; GCS, Glasgow coma scale; N/A, not applicable; MoCA-BC, Chinese Version of the Montreal Cognitive Assessment-Basic; TBI, traumatic brain injury; SD, standard deviation.

presented in *Table 1*. There were no statistically significant differences among the three groups of subjects in terms of age (P=0.078), gender (P=0.153), and years of education (P=0.607). Additionally, there were no statistically significant differences between the TBI-CN and TBI-CI groups in terms of GCS (P=0.096), disease course (P=0.321), severity of TBI (P=0.405), and type of injury (P=0.888).

Group analysis of the diffusivities, ALPS index, FA, and MD

As Supplementary Table S1 shows, inter-observer agreement was good for the ALPS index {ICC: 0.823 [95% confidence interval (CI): 0.716–0.892], P<0.001}. *Tables 2*,*3* and *Figure 3* illustrate the diffusivity, ALPS index, FA and MD between the three groups, adjusted for age and gender. Compared to the HC group (1.629), both the TBI-CN group (1.523) and TBI-CI group (1.302) exhibited a decrease in the mean ALPS index (P=0.003 and P<0.001, respectively). The reduction was more pronounced in the TBI-CI group. Further, the mean ALPS index of the TBI-CI group was significantly lower than that of the TBI-CN group (P<0.001). There were also inter-group differences in the diffusion rates of the projection fibers along the Y- (Dyyproj) and Z-axes (Dzzproj), and in the diffusion rate of the fibers along the Z-axis (Dzzassoc) (P<0.001, P=0.033, P<0.001, respectively) across the three groups.

ROC curve for the prediction of chronic cognitive impairment following mild-to-moderate TBI using the ALPS index

After adjusting for covariates (age and gender), the ROC curve indicated that the ALPS index had an AUC of 0.983 (95% CI: 0.953–1; P<0.001) for diagnosing chronic

Table 2 Comparison of the diffusivities, ALPS indexes, FA, and MD among the study groups

Variable	HC	TBI-CN	TBI-CI	F value	P value
Dxxproj (ADC, $\times10^{-3}$ mm^2/s)	0.660±0.051	0.655±0.065	0.653±0.056	0.008	0.992
Dyyproj (ADC, $\times10^{-3}$ mm^2/s)	0.441±0.038	0.478±0.057	0.527±0.064	13.098	<0.001**
Dzzproj (ADC, $\times10^{-3}$ mm^2/s)	1.110±0.094	1.152±0.108	1.206±0.137	3.643	0.033*
Dxxassoc (ADC, $\times10^{-3}$ mm^2/s)	0.675±0.064	0.638±0.062	0.643±0.065	1.231	0.299
Dyyassoc (ADC, $\times10^{-3}$ mm^2/s)	1.141±0.116	1.178±0.142	1.136±0.271	0.339	0.713
Dzzassoc (ADC, $\times10^{-3}$ mm^2/s)	0.380±0.047	0.374±0.043	0.471±0.058	22.776	<0.001**
Dxxsubc (ADC, $\times10^{-3}$ mm^2/s)	1.121±0.115	1.062±0.108	1.163±0.159	2.939	0.061
Dyysubc (ADC, $\times10^{-3}$ mm^2/s)	0.653±0.099	0.656±0.082	0.714±0.137	1.686	0.194
Dzzsubc (ADC, $\times10^{-3}$ mm^2/s)	0.590±0.104	0.610±0.125	0.612±0.131	0.151	0.860
ALPS index	1.629±0.104	1.523±0.083	1.302±0.072	66.175	<0.001**
FA	0.393±0.005	0.392±0.007	0.387±0.009	2.670	0.078
MD (10^{-3} mm^2/s)	0.749±0.210	0.763±0.027	0.772±0.038	2.211	0.119

Values are presented as the mean ± SD. An analysis of covariance was used to compare the FA, MD, ALPS index, and diffusivities among the three groups, with age and gender as covariates. Diffusivities are presented as the apparent diffusion coefficients ($\times10^{-3}$ mm^2/s). MD is expressed in units of 10^{-3} mm^2/s, FA is a dimensionless quantity. *, P<0.05; **, P<0.001. ALPS, analysis along the perivascular space; FA, fractional anisotropy; MD, mean diffusivity; HC, healthy control; TBI-CN, traumatic brain injury cognitively normal; TBI-CI, traumatic brain injury cognitive impairment; Dxxproj, diffusivity along the X-axis measured at the projection area; ADC, apparent diffusion coefficient; Dyyproj, diffusivity along the Y-axis measured at the projection area; Dzzproj, diffusivity along the Z-axis measured at the projection area; Dxxassoc, diffusivity along the X-axis measured at the association area; Dyyassoc, diffusivity along the Y-axis measured at the association area; Dzzassoc, diffusivity along the Z-axis measured at the association area; Dxxsubc, diffusivity along the X-axis measured at the subcortical area; Dyysubc, diffusivity along the Y-axis measured at the subcortical area; Dzzsubc, diffusivity along the Z-axis measured at the subcortical area; SD, standard deviation.

Table 3 Subgroup comparison of the diffusivities and ALPS indexes among the study groups

Variable	HC *vs.* TBI-CN	HC *vs.* TBI-CI	TBI-CN *vs.* TBI-CI
Dyyproj (ADC, $\times10^{-3}$mm^2/s)	0.056	<0.001***	0.045*
Dzzproj (ADC, $\times10^{-3}$mm^2/s)	0.598	0.041*	0.523
Dzzassoc (ADC, $\times10^{-3}$mm^2/s)	0.999	<0.001***	<0.001***
ALPS index	0.003**	<0.001***	<0.001***

Diffusivities are presented as the apparent diffusion coefficients ($\times10^{-3}$ mm^2/s). *, P<0.05; **, P<0.01; ***, P<0.001. ALPS, analysis along the perivascular space; HC, healthy control; TBI-CN, traumatic brain injury cognitively normal; TBI-CI, traumatic brain injury cognitive impairment; Dyyproj, diffusivity along the Y-axis measured at the projection area; ADC, apparent diffusion coefficient; Dzzproj, diffusivity along the Z-axis measured at the projection area; Dzzassoc, diffusivity along the Z-axis measured at the association area.

cognitive impairment following mild-to-moderate trauma with a sensitivity of 90% and a specificity of 95% (*Figure 4*).

Discussion

This study showed that the ALPS index reflects impairment in glymphatic system function among patients with mild-to-moderate chronic TBI, and dysfunction in the glymphatic system may be associated with the onset of cognitive deficits. Further, the ALPS index showed promising predictive value for diagnosing cognitive impairments in patients with mild-to-moderate chronic TBI, indicating its potential as a predictive biomarker for the condition. Our findings provided novel insights into the pathophysiological

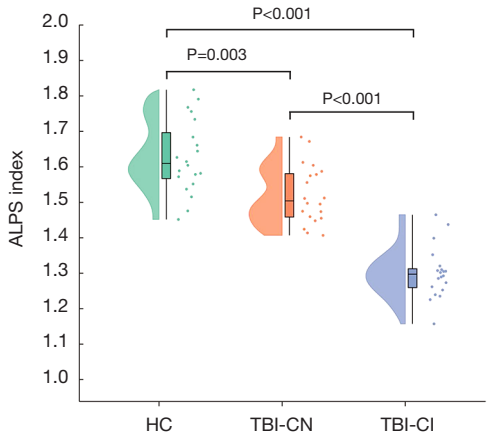

Figure 3 Raincloud plot depicting the ALPS index of each individual. After correcting for age and gender, the ALPS index was lower in the TBI-CN and TBI-CI patients than the HC patients (P=0.003, P<0.001). The ALPS index was also lower in the TBI-CI patients than the TBI-CN patients (P<0.001). ALPS, analysis along the perivascular space; HC, healthy control; TBI-CN, traumatic brain injury cognitively normal; TBI-CI, traumatic brain injury cognitive impairment.

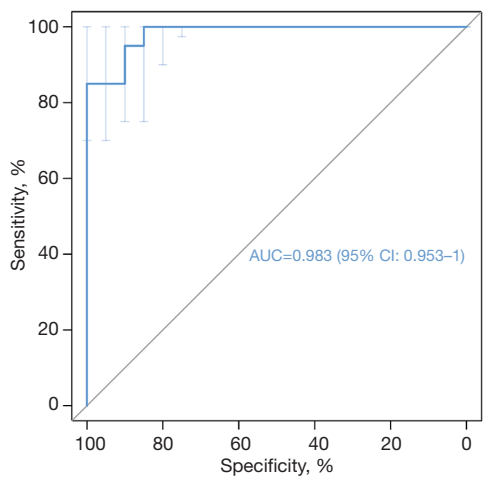

Figure 4 Corrected ROC curves of the ALPS index for diagnosing chronic cognitive dysfunction after mild-to-moderate TBI. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; ALPS, analysis along the perivascular space; TBI, traumatic brain injury.

mechanisms underlying cognitive impairment in mild-to-moderate chronic TBI.

As mentioned above, the ALPS index is a method used to assess PVS diffusivity, where higher values indicate better glymphatic system activity (31). In this study, we observed elevated diffusivity along the Y-axis (Dyyproj) of the projection fibers and along the Z-axis (Dzzassoc) of the association fibers in mild-to-moderate TBI patients compared to the control group. This could be due to the increased water diffusivity around the periventricular white-matter hyperintensities (40,41). Correspondingly, the ALPS index was decreased, which may suggest that these patients have impaired glymphatic systems. Since the ALPS index can minimize the influence of white-matter changes and neural tract degeneration, it may be more suitable for the individual assessment of the glymphatic function than the Dyyproj and Dzzassoc. This finding is consistent with previous research (17,18,26,42).

Previous animal studies have shown that the intrathecal injection of cerebrospinal fluid tracers in a model of TBI results in a significant decrease in clearance, indicating impaired glymphatic system function (17,42). Research has reported that aquaporin-4 show abnormal regulation and depolarization in astrocytes after TBI (43), which may be an important reason for the dysfunction of the glymphatic system after TBI. Further, the dysfunction of the glymphatic system may be exacerbated by the buildup of catabolic products from the injured brain or blood, which can impede glymphatic flow. Additionally, we also identified differences in the diffusivity along the Z-axis (Dzzproj) of the projection fibers in the mild-to-moderate TBI patients compared to the control group. However, this does not align with diffusion parallel to perivascular water flow; thus, this difference likely arises not from glymphatic system functionality but from individual variations in white-matter degeneration or integrity (31,40,44).

MCI is considered a precursor of elderly dementia, and glymphatic dysfunction, which is a crucial clearance pathway for brain metabolic waste, is believed to be a common final pathway in dementia (45). Our study found that patients with mild-to-moderate chronic TBI cognitive impairment had lower ALPS index values than those with normal cognitive function. The decline in the ALPS index in patients with cognitive impairment is related to dysfunction in the glymphatic system, as the ALPS index serves as a marker of glymphatic function. Further, lower ALPS index values have been observed in neurological disorders characterized by cognitive decline, including Alzheimer's disease (31), cerebral small vessel disease (23,24), and idiopathic normal pressure hydrocephalus (44). In cerebral small vessel disease, the ALPS index was lower in the cognitively dysfunctional group than the cognitively

normal group (1.054 *vs.* 0.958, P<0.001), which suggests that the onset of cognitive dysfunction is associated with the dysfunction of the glymphatic system. This finding is consistent with our research. Further, there were no statistically significant differences in the global FA and global MD values across the three groups, which provides further support for our conclusion that the observed decrease in the ALPS index among TBI patients is not influenced by structural axonal injuries but rather reflects an impairment in perivascular water diffusion capacity.

Based on the evidence gathered, we hypothesize that there is a nexus between cognitive impairment and glymphatic system dysfunction in mild-to-moderate chronic TBI. Specifically, we suggest that post-injury, there may be a disruption in the functionality of the glymphatic system, culminating in the substantial buildup of Aβ and Tau proteins (46). These proteins are pivotal in the mediation of neurodegeneration and cognitive deficits (47). In addition, the glymphatic system can carry immune cells (48) and inflammatory factors (49). As a result, the dysfunction of the glymphatic system may result in neuroinflammation and neuronal damage. The ultimate outcome results in cognitive impairment. Our study found that the ALPS index has good predictive value for diagnosing cognitive impairment in patients with mild-to-moderate chronic TBI, using corrected ROC curves. This suggests that it has the potential to serve as a predictive biomarker for the disease.

This study had several limitations. First, the ALPS index is not a direct method for evaluating the function of the glymphatic system, and it can only be assessed at the level of the lateral ventricle body. Although glymphatic function assessed using the ALPS index has been shown to correlate with results obtained through the direct intrathecal tracer-based (gold standard method) measurement in humans (32), it still needs to be validated in more studies in the future. Second, this study was a cross-sectional study conducted at a single center with a small sample size. To confirm our findings, larger sample-sized and longitudinal studies need to be conducted in the future. Third, the ROIs were drawn manually by two readers, which could have induced observer bias. However, the inter-observer agreement values for the ALPS index were good between the two readers. Therefore, the results appear not to have been considerably affected by observer bias and measurement variances between the two readers.

Conclusions

This study found that the occurrence of cognitive impairment in patients with mild-to-moderate chronic TBI was associated with impaired glymphatic system function. In addition, the ALPS index could serve as a potential predictor of the disease.

Acknowledgments

We would like to thank Dr. Haixia Li for her contributions, including the statistical analysis.
Funding: This work was supported by funding from the National Natural Science Foundation of China (Nos. 81960237 and 82260343) and the Natural Science Foundation of Hainan Province (Nos. 2019RC388 and 821RC692).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-895/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-895/coif). J.C. was supported by the National Natural Science Foundation of China (Nos. 81960237 and 82260343) and the Natural Science Foundation of Hainan Province (Nos. 2019RC388 and 821RC692). The other authors have no conflicts of interest to declare.

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 (as revised in 2013) and was approved by the Biomedical Ethics Committee of Hainan Medical University (No. 2023-KYL-084). All participants and/or their families were informed about the study and provided informed consent by signing the informed consent form.

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Cite this article as: Wang X, Deng L, Liu X, Cheng S, Zhan Y, Chen J. Relationship between glymphatic system dysfunction and cognitive impairment in patients with mild-to-moderate chronic traumatic brain injury: an analysis of the analysis along the perivascular space (ALPS) index. Quant Imaging Med Surg 2024;14(12):9246-9257. doi: 10.21037/qims-24-895

