Original Article

Correlation between glymphatic dysfunction and cranial defect in severe traumatic brain injury: a retrospective case-control study based on a diffusion tensor image analysis along the perivascular space (DTI-ALPS) investigation

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Background: To date, limited research has been conducted on the functionality of the glymphatic system during the recovery phase of severe traumatic brain injury (sTBI). This study aimed to use a diffusion tensor image analysis along the perivascular space (DTI-ALPS) to evaluate glymphatic system function in patients recovering from sTBI who underwent unilateral decompressive craniectomy, and to examine the correlation between the ALPS index and the size of the cranial defect. We hypothesized that assessments would reveal ongoing impairments in glymphatic system function among sTBI patients during the recovery phase.

Methods: A total of 23 patients with a history of sTBI who had previously undergone unilateral decompressive craniectomy at Xiangya Hospital of Central South University from January 2020 to December 2020 were enrolled in the study, along with 33 healthy control (HC) subjects. All the subjects underwent magnetic resonance imaging (MRI) with DTI scans, and the ALPS index was subsequently calculated to assess glymphatic system functionality. Additionally, the circumference and sectional area of the cranial defect were measured for each patient. An analysis of variance (ANOVA) was used to compare the ALPS index values between the sTBI patients and HC subjects, while a Pearson correlation analysis was used to examine the correlation between the ALPS index and cranial defect characteristics.

Results: The ALPS index values of both the craniectomy side ($t=-9.08$, $P<0.001$) and non-craniectomy side ($t=-5.06$, $P<0.001$) of the sTBI group were significantly lower than those of the HC group. However, no statistically significant differences were observed between the ALPS index values of the craniectomy and non-craniectomy sides. Additionally, no significant differences were observed in the ALPS index values of both the craniectomy and non-craniectomy sides among the early, intermediate, and late recovery phases. In the sTBI patients, a moderately strong negative correlation was found between the circumference of the cranial defect and the ALPS index of the craniectomy side ($r=-0.62$, $P=0.002$), and a moderately negative correlation was found between the sectional area of the cranial defect and the ALPS index of the craniectomy side ($r=-0.56$, $P=0.005$).

Conclusions: The non-invasive DTI-ALPS technique revealed significantly reduced ALPS index values during the recovery phase of sTBI, indicating persistent impairment in glymphatic system function. A significant negative correlation was found between the ALPS index value of the craniectomy side and the size of the cranial defect. These findings suggest that the ALPS index may serve as a valuable prognostic factor in

the recovery phase of sTBI.

Keywords: Glymphatic system; severe traumatic brain injury (sTBI); diffusion tensor imaging; cranial defect

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Introduction

The glymphatic system, a recently identified waste clearance pathway in the brain (1-3), facilitates the flow of cerebrospinal fluid (CSF) into the brain's interstitial space along the perivascular space of the leptomeningeal and penetrating arteries. After exchanging with interstitial fluid (ISF), solutes and waste are transported into the venous perivascular space and perineuronal space, eventually reaching the meningeal and cervical lymphatic drainage vessels. Dysfunction of the glymphatic system may lead to the accumulation of waste products, including amyloid-beta and tau proteins, which could contribute to various neurological disorders (4-6). Recent research has shown that these dysfunctions are associated with conditions such as Alzheimer's disease, Parkinson's disease, ischemic stroke, and traumatic brain injury (TBI) (7).

Severe TBI (sTBI) is a critical and extensive manifestation of TBI, characterized by profound neurological dysfunction and structural brain damage. Individuals who survive sTBI often undergo surgical interventions, such as craniectomy (8-10). The primary phase of recovery, which spans the initial months to one-year post-injury, plays a crucial role in the overall rehabilitation process (11). Preclinical evidence has shown the importance of the functional glymphatic system in facilitating debris and toxic protein clearance from the brain during this period (12,13). Early studies of diverse patient populations have indirectly suggested that glymphatic function is impaired in the acute and subacute phases of TBI (14-18); however, investigations into the functionality of glymphatic system during the recovery phase remain limited. Notably, to date, no subgroup analyses based on TBI severity have been conducted due to sample-size constraints.

The clinical imaging of the glymphatic system in humans is an evolving area of research that has been explored using various imaging approaches (7). Diffusion tensor image analysis along the perivascular spaces (DTI-ALPS) is a recent non-invasive method that has shown promising results, particularly in measuring disease-specific glymphatic system function (19,20). This method is based on the hypothesis that glymphatic system activity is correlated with water diffusivity in the perivascular space direction. In instances of glymphatic system dysfunction, histological changes in the perivascular space may affect water diffusivity in both projection and association fibers at the level of the lateral ventricles. This phenomenon can be assessed through DTI measurements, allowing for the indirect appraisal of glymphatic system dysfunction.

During the recovery phase of sTBI, certain survivors undergo skull reconstruction to facilitate additional recovery (21,22). This stable subset of patients is capable of tolerating magnetic resonance imaging (MRI) scans and thus offers a unique opportunity to investigate whether the function of the glymphatic system returns to normal levels during sTBI recovery. The brains of individuals with cranial defects are exposed to constant atmospheric pressure in this period (23); however, the effect of this exposure on the recovery of glymphatic function remains unknown. This study employed DTI-ALPS to assess glymphatic system function in this specific population and explored the correlation between the ALPS index and the size of the cranial defect. We hypothesized that assessments would reveal ongoing impairments in glymphatic system function among sTBI patients during the recovery phase. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-348/rc).

Methods

Participants

The present study was conducted at Xiangya Hospital, Central South University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Xiangya Hospital, Central South University (No. 2022111433). The requirement of informed consent was waived for the trauma patients due to the retrospective

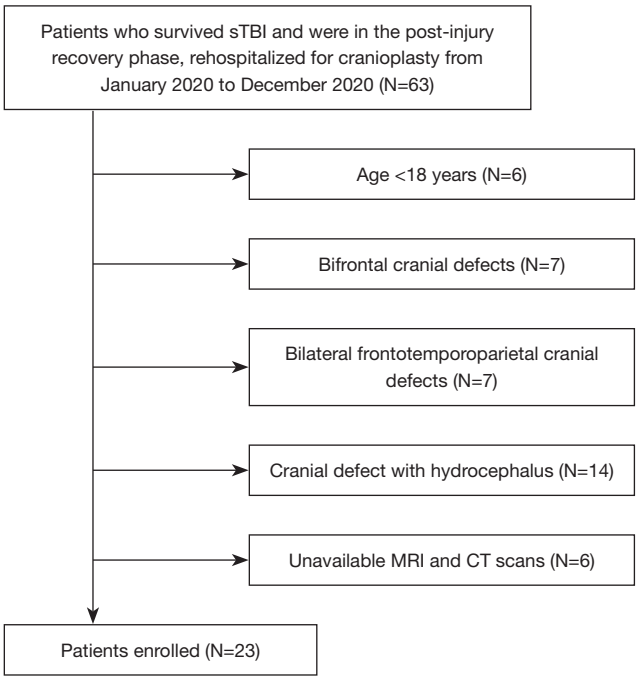

Figure 1 Patient enrollment flow diagram. sTBI, severe traumatic brain injury; MRI, magnetic resonance imaging; CT, computed tomography.

nature of the investigation.

A total of 23 patients with a history of sTBI who had previously undergone unilateral decompressive craniectomy and later returned for skull reconstruction at Xiangya Hospital between January 2020 and December 2020 were enrolled in this single-center retrospective study. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) be aged 18 years and older; (II) have a documented history of sTBI; (III) have undergone unilateral frontotemporoparietal decompressive craniectomy during the acute phase; (IV) have been re-hospitalized specifically for cranioplasty; and (V) have computed tomography (CT) and MRI data preceding cranioplasty, including DTI scan data, available. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a history of substance or alcohol misuse; (II) were pregnant; and/or (III) had any contraindications to MRI. The patient enrollment process is illustrated in *Figure 1*. Additionally, 33 healthy age and sex-matched volunteers were prospectively enrolled in this study as the healthy control (HC) group. Patients were excluded from the HC group if they met any of the following exclusion criteria: (I) had pre-diagnosed neurological conditions (e.g., an intracranial infection, tumor, stroke, or neurodegenerative disorder); and/or (II) had a history of head trauma or surgery.

MR image acquisition

All the MRI scans were conducted using a Siemens 3T Prisma scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel head coil. The imaging protocol comprised a standard T1-weighted magnetization-prepared rapid gradient echo, T2-weighted turbo spin-echo sequence, diffusion-weighted imaging, and DTI. This study primarily focused on the analysis of the DTI-MRI datasets. The DTI scans were executed using spin-echo single-shot echo-planar pulse sequences, including a total of 32 distinct diffusion directions. The parameters were as follows: repetition time (TR)/echo time (TE): 8,620/85 ms; flip angle: 90°; slice thickness: 2.25 mm, acquisition matrix: 120×120; field of view: 240×240; and b-value: 1,000 s/mm^2.

DTI-ALPS processing

The DTI dataset underwent processing using DSI-Studio (version 2023.07.08, https://dsi-studio.labsolver.org) to execute a series of procedural steps. Color-coded fractional anisotropy (FA) maps and diffusivity maps along the x-, y-, and z-axes were generated. Deterministic tractography was performed to visualize the projection and association fibers, which run perpendicular to one another (*Figure 2*). The DTI-ALPS method, as previously described by Taoka *et al.* (20), was employed to assess glymphatic system activity. At the lateral ventricle body level, the projection fibers adjacent to the lateral ventricle ran in the z-axis direction, while the association fibers ran in the y-axis direction, and the subcortical fibers followed the perivascular spaces in the x-axis direction. Spherical regions of interest (ROIs) were placed within the projection fibers and association fibers on color-coded FA maps in the bilateral hemispheres. Subsequently, the FA values and diffusivities along the different directions in these ROIs were extracted.

The movement of water molecules along the x-axis in projection fibers (Dxxproj) and association fibers (Dxxassoc) is distinct from their movement along the y-axis in projection fibers (Dyyproj) and along the z-axis in association fibers (Dzzassoc). This behavioral difference is likely influenced by the presence of perivascular spaces. The ALPS index was computed as follows: ALPS index = mean (Dxxproj, Dxxassoc)/mean (Dyyproj, Dzzassoc).

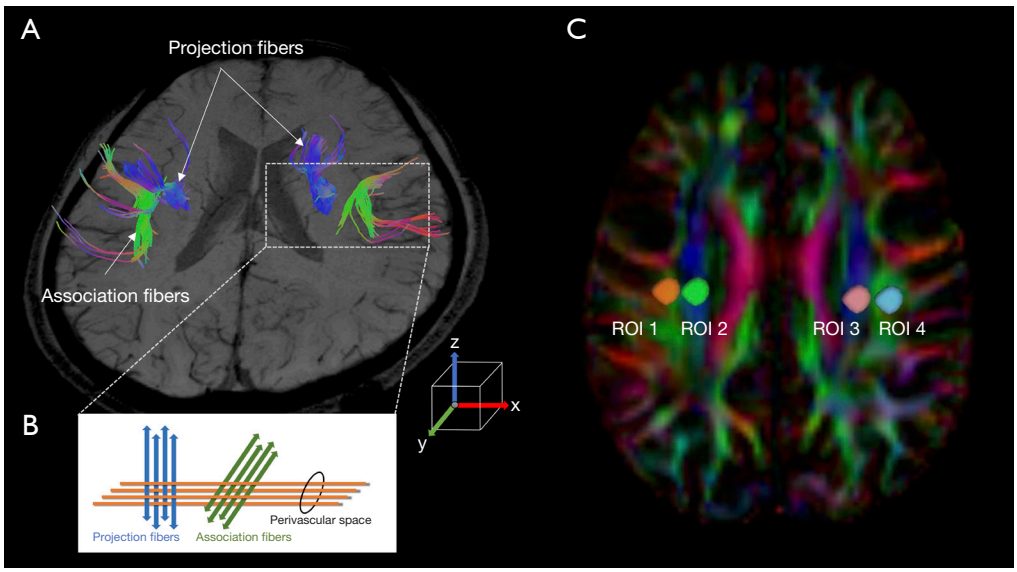

Figure 2 DTI-ALPS methodology. (A) Axial SWI at the level of the lateral ventricle body showing the lateral orientation of medullary veins along the x-axis. Overlaying fiber tracking showing the distribution of projection fibers (blue) along the z-axis and association fibers (green) along the y-axis. (B) Schematic diagram showing the relationship between the direction of the perivascular space (orange color) and the orientation of the fibers. The ALPS index was computed based on the difference in water molecule movement along the x-axis in the projection and association fibers, and their movement along the y-axis in the projection fibers and along the z-axis in the association fibers. (C) Four spherical ROIs were placed within the projection fibers and association fibers on a color-coded FA map in bilateral hemispheres. DTI-ALPS, diffusion tensor image analysis along the perivascular space; SWI, susceptibility-weighted imaging; ROIs, regions of interest; FA, fractional anisotropy.

Measurements of cranial defect size

CT scans conducted prior to cranioplasty were accessed and thoroughly examined. A three-dimensional (3D) virtual skull model based on the CT scan was generated using the open-source software 3D-Slicer (version 5.4.0). Using the curve tool, landmarks were manually positioned along the periphery of the cranial defect, enabling simultaneous acquisition of both the circumference and the sectional area of the defect (24).

Statistical analysis

The statistical analysis was executed using GraphPad Prism (version 9, GraphPad Inc., USA). The Shapiro-Wilk normality test was employed to assess the normality of variable distribution. The comparative analysis of the continuous variables with a normal distribution was conducted using the two-sample *t*-test or an analysis of variance (ANOVA), while the Mann-Whitney test or Kruskal-Wallis test was applied to continuous variables with a non-normal distribution. The categorical variables were compared using the Chi-squared test. A subgroup analysis based on the timing of cranioplasty was conducted to explore whether the ALPS index varied across the different subgroups. A Pearson correlation analysis was employed for the normally distributed data, and a Spearman correlation analysis was employed for the non-normally distributed data to assess the correlations between the ALPS index and cranial defect characteristics. All the tests were two-sided, and the threshold for statistical significance was set at $P<0.05$. The sample-size calculation was conducted using an expected effect size (d) of 0.8, a significance level (α) of 0.05, and a power ($1-\beta$) of 0.80. The analysis indicated that a minimum of 21 subjects per group would be necessary to detect a statistically significant difference. Our sample of 23 sTBI patients and 33 HC subjects exceeded this minimum requirement, ensuring the adequate statistical power for our analyses.

Results

Participant characteristics

The detailed demographic and clinical characteristics of

both the sTBI patients and HC subjects are presented in *Table 1*. No statistically significant differences were observed between the sTBI and HC groups in terms of age, gender, and education. The post-injury duration among the sTBI patients varied from 30 to 353 days (mean duration: 131.74±95.74 days). Notably, all the sTBI patients included in the study were in the post-injury recovery phase and were re-hospitalized specifically for cranioplasty. The patients were assigned to the following three categories based on the timing of the cranioplasty: the early category (i.e., patients re-hospitalized within 90 days of craniectomy), which comprised 10 patients; the intermediate category (i.e., patients re-hospitalized 91–180 days of craniectomy), which comprised 6 patients; and the late category (i.e., patients re-hospitalized more than 180 days after craniectomy), which comprised 7 cases (25). The ANOVA results revealed no significant differences among these three categories in the ALPS index values of the craniectomy side (P=0.94) and non-craniectomy side (P=0.74), and of the mean value of both sides (P=0.84) (*Figure 3*). The Glasgow Coma Scale (GCS) scores were assessed at the time of re-hospitalization (mean score: 9.13±3.70; range, 3–15). All the selected patients underwent unilateral frontotemporoparietal decompressive craniectomy during the acute phase of sTBI. Among the 23 patients, 14 underwent craniectomy on the left side, while 9 underwent it on the right side.

Table 1 Demographic and clinical characteristics of the subjects

Characteristics	sTBI group	HC group	P value
Number of participants	23	33	N/A
Age (years)	46.35±16.82	42.84±11.24	0.35
Gender, n			0.88
Female	6	8	
Male	17	25	
Education (years)	9.78±3.29	10.88±3.63	0.25
Mechanism of injury, n			N/A
Traffic accident	13	N/A	
Falling	8	N/A	
Assault	2	N/A	
Post-injury duration (days)	131.74±95.74	N/A	N/A
GCS at re-hospitalization	9.13±3.70	N/A	N/A
Craniectomy side, n			N/A
Left side	14	N/A	
Right side	9	N/A	

Data are presented as the mean ± standard deviation for the continuous variables and as the frequency for the categorical variables. Group comparisons were assessed using the Mann-Whitney test, *t*-test or Chi-squared test. Significant differences are indicated in bold font. sTBI, severe traumatic brain injury; HC, healthy controls; N/A, not applicable; GCS, Glasgow Coma Scale.

Comparisons of the ALPS index within and between the two groups

In the HC group, the ALPS index measured 1.386±0.101 on the left side and 1.394±0.083 on the right side, resulting in a mean value for both sides of 1.390±0.087. Notably, no significant differences were observed between the left and right sides of the ALPS index within the HC group (P=0.72).

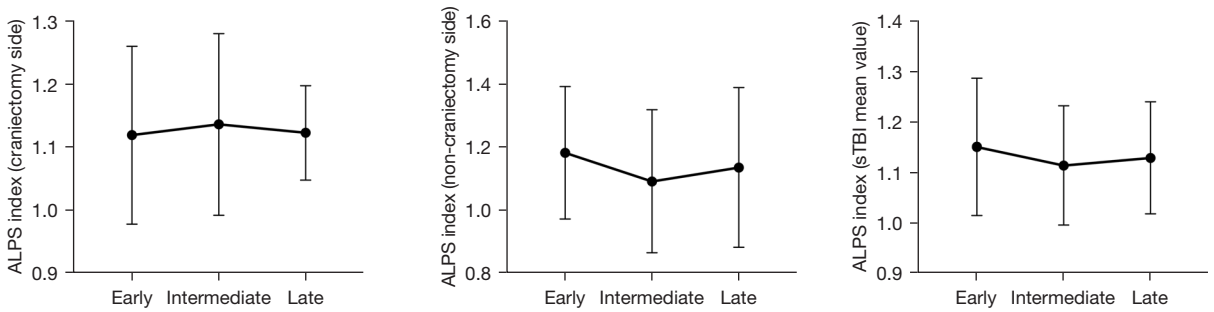

Figure 3 ALPS index across recovery phases. Patients were classified into the following three categories: early (within 90 days of craniectomy), intermediate (within 91–180 days of craniectomy), and late (more than 180 days after craniectomy). The ANOVA results revealed no significant differences in the ALPS index values of the craniectomy side (P=0.94) and non-craniectomy side (P=0.74), and the mean values of both sides (P=0.84) among these three categories. ALPS, analysis along the perivascular space; sTBI, severe traumatic brain injury; ANOVA, analysis of variance.

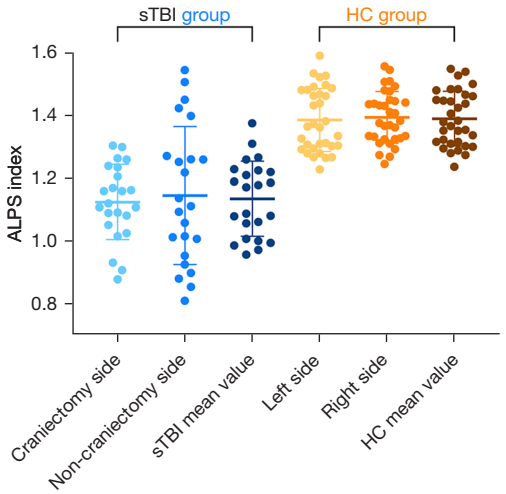

Figure 4 Comparisons of the ALPS index within and between sTBI and HC groups. Within the sTBI group, no significant differences were observed between the craniectomy and non-craniectomy sides (P=0.69); both sides had significantly lower values than the mean value observed in the HC group (P<0.001 and P<0.001). Additionally, within the HC group, no significant differences were observed between the left and right sides of the ALPS index (P=0.72). ALPS, analysis along the perivascular space; sTBI, severe traumatic brain injury; HC, healthy control.

In the sTBI group, the ALPS index measured 1.125±0.119 on the craniectomy side, and 1.145±0.219 on the non-craniectomy side, resulting in a mean value for both sides of 1.127±0.121. No significant differences were observed between the craniectomy and non-craniectomy sides (P=0.69). Both the craniectomy side (t=–9.08, P<0.001) and non-craniectomy side (t=–5.06, P<0.001) had significantly lower values than the mean value observed in the HC group (*Figure 4*).

Analysis of FA values between groups

The FA values in the same ROIs used in ALPS index calculation were measured. The statistical analysis revealed no significant differences in either the projection fiber area (F=2.39, P=0.09) or association fiber area (F=2.25, P=0.12) between the TBI patients and HC (Table S1).

Cranial defect characteristics

The circumference of the cranial defect ranged from 255.6 to 446 mm (mean value: 361.2±49.8 mm). The sectional area of the defect varied from 45.3 to 134.2 cm^2 (mean value: 87.1±23.6 cm^2). A statistically significant positive correlation was observed between the circumference of the cranial defect and its sectional area (Pearson r=0.91, P<0.001) (*Figure 5A*).

Correlations between the ALPS index and cranial defect characteristics

The circumference of the cranial defect exhibited a moderately strong negative correlation with the ALPS index value of the craniectomy side of the sTBI patients as indicated by a Pearson correlation coefficient (r) of –0.62 and a statistically significant P value of 0.002 (see *Figure 5B*). Similarly, the sectional area of the cranial defect demonstrated a moderate negative correlation with the ALPS index value of the craniectomy side of the sTBI patients with a Pearson correlation coefficient of –0.56 and a statistically significant P value of 0.005 (*Figure 5C*). However, neither the circumference nor the sectional area exhibited a correlation with the ALPS index value of the non-craniectomy side or the mean value of both sides (Figure S1).

Discussion

This study employed non-invasive DTI images to explore glymphatic system functionality during the recovery phase of sTBI. Patients who underwent decompressive craniectomy for sTBI exhibited reduced glymphatic function as evidenced by lower ALPS index values of both the craniectomy and non-craniectomy sides compared to those of the HC subjects. Notably, the ALPS index value of the craniectomy side was negatively correlated with both the circumference and sectional area of the cranial defect. A lower ALPS index indicates compromised perivascular water flow and impaired glymphatic system. This was the first human study to show impaired glymphatic system during the recovery phase of sTBI and its correlation with cranial defect characteristics in sTBI patients.

Our study revealed diminished ALPS index values on both sides of the brain during the recovery phase of sTBI, indicating the persistent impairment of glymphatic function in this stage. However, it is difficult to make any comprehensive comparisons with previous results, as research specifically focusing on sTBI in the recovery phase is limited. In a mouse model of TBI, Iliff *et al.* showed impaired paravascular clearance of interstitial solutes,

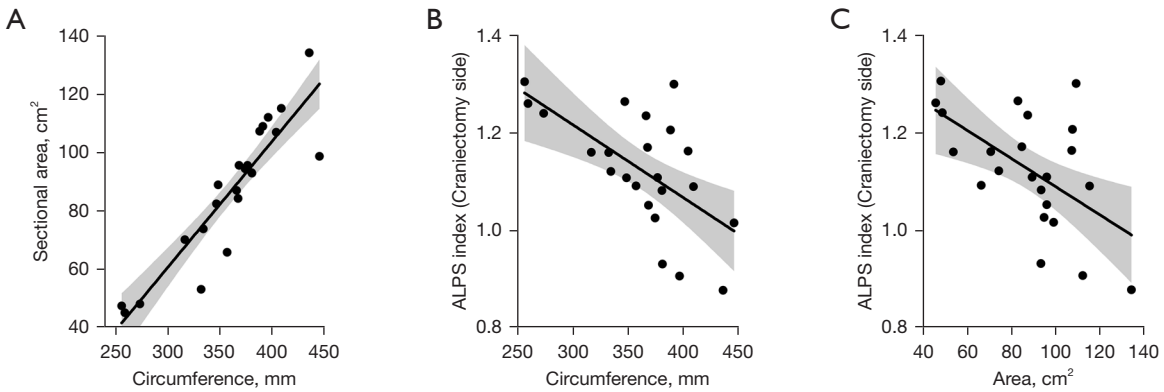

Figure 5 Correlation analysis. (A) A very strong positive correlation was observed between the circumference of the cranial defect and its sectional area (r=0.91, P<0.001). (B) The circumference of the cranial defect exhibited a moderately strong negative correlation with the ALPS index value of the craniectomy side of sTBI patients (r=–0.62, P=0.002). (C) The sectional area of the cranial defect demonstrated a moderate negative correlation with the ALPS index value of the craniectomy side of sTBI patients (r=–0.56, P=0.005). ALPS, analysis along the perivascular space; sTBI, severe traumatic brain injury.

resulting in a 60% reduction in glymphatic function lasting up to 28 days after injury (13). CSF flow patterns in the human brain resemble those in rodents (3,7,26); however, the extent to which impairment (and the duration of that impairment) in humans mirrors that observed in rodents remains uncertain.

In a study by Park *et al.* on human subjects, TBI patients exhibited significantly lower ALPS index values (1.317) within 28 days post-injury than HC subjects (1.456), indicating a notable 9.3% reduction in glymphatic function (14). Another human study by Butler *et al.*, conducted during the subacute phase, reported ALPS index values of 1.336 for TBI patients and 1.389 for controls, suggesting a 3.6% reduction in glymphatic function (15). However, while these human studies examined a diverse spectrum of TBI severities, they lacked subgroup analyses, and thus did not examine the effects of specific levels of TBI severity.

Variations in glymphatic system impairment between rodents and humans persist (27), and the precise reasons for these differences remain unknown, but could be related to methodological disparities or species-specific mechanisms. Our results in the recovery phase revealed no significant differences between the craniectomy and non-craniectomy sides, with mean ALPS index values of 1.127 in sTBI patients compared to 1.390 in HC subjects, indicating an 18.8% reduction in glymphatic function. Our analysis provides a snapshot rather than evidence of a dynamic trend; however, it is the first report to show that in the recovery phase of sTBI, glymphatic system function remains impaired.

Our observations on the discernible impairment of the glymphatic system across both brain hemispheres, even in cases in which one hemisphere underwent craniectomy but the other did not, aligns with similar observations in various animal studies. Iliff *et al.* identified compromised glymphatic influx in both cerebral hemispheres, despite the experimental model designed for injury induction on one side (1). Ishida *et al.* observed that clearance of interstitial solutes from the brain parenchyma on the contralateral hemisphere was compromised (28), while Li *et al.*'s research suggested a widespread decline in glymphatic system functionality, affecting both brain hemispheres (29). However, it is crucial to note that these investigations were not explicitly designed to examine the glymphatic system on the contralateral side of the brain. The precise reasons for this phenomenon-characterized by reduced glymphatic function across both brain hemispheres remain unclear. Thus, further in-depth studies need to be conducted to ensure a comprehensive understanding.

We posit that this observed phenomenon may be attributed to the fact that unilateral decompressive craniectomy in patients does not necessarily imply the absence of lesions on the contralateral side. In reality, in traumatic injury, forces propagate bilaterally, affecting both left and right hemispheres, even if the direct impact occurred on one side (30). The contralateral hemisphere may incur injury that either does not necessitate surgical intervention or manifests as a subtle injury undetectable

by conventional CT or MRI scans. Our findings indicate that the non-craniectomy side exhibited a slightly wider range of fluctuations in the ALPS index, but the values consistently remained lower than those of the HC group. This suggests a decline in glymphatic system functionality on the contralateral side. To address the potential effect of contralateral lesions and comprehensively explore glymphatic system impairment on both sides, future research may seek to exclude significant lesions identified through CT or MRI scans.

The ALPS index value of the craniectomy side was found to be negatively correlated with both the circumference and sectional area of the cranial defect. A larger cranial defect suggests diminished glymphatic system function. The glymphatic circulation relies on the integrity of a closed cranial compartment (31,32), where arterial pulsations generate motile forces for CSF and ISF flow (33). A larger cranial defect disrupts this equilibrium by exposing a greater area to atmospheric pressure (34,35). A previous animal model study showed the persistent impairment of glymphatic flow after craniectomy, lasting up to day 28, followed by recovery (36). Speculatively, during the recovery phase of TBI in humans, the effect of a cranial defect on the glymphatic system may be alleviated. However, it is crucial to note that this proposition remains speculative and awaits substantiation in human studies.

In animal studies, research protocols can be tailored to specifically investigate the effects of cranial opening on healthy animals (36) or to solely explore the effects of TBI without cranial opening (29,37). Conversely, human subjects undergoing decompressive craniectomy are generally those with a sTBI (38). The intertwined effects of both the brain injury and cranial opening make it challenging to investigate their individual effects separately. Consequently, the observed reduction in the glymphatic system in our study likely resulted from their combined influence. This study represents an inaugural report shedding light on the correlation between cranial defects and the glymphatic system.

We recognize several limitations inherent in this study. First, the study included a specific subset of stable patients with sTBI who returned to the hospital for skull reconstruction, which typically indicates positive outcomes. However, this selection criterion might have led to the exclusion of other patients who were unable to undergo skull reconstruction due to TBI deterioration or other complications such as hydrocephalus or infection. Consequently, our results may not fully represent all individuals with sTBI in the recovery phase. Second, it was a retrospective study conducted at a single center, and the sample size was relatively small. In the future, we intend to conduct a prospective study, encompassing a larger cohort, to compare the ALPS index before and after cranioplasty. This will allow for a comprehensive exploration of the effectiveness of cranioplasty in ameliorating impaired glymphatic activity and provide validation for the observations made in this study. Third, our study focused exclusively on patients in the recovery phase of sTBI. The retrospective design prevented the acquisition of MRI during the acute phase, as MRI examinations were not part of the routine examinations for a significant portion of these patients. We acknowledge the importance of obtaining initial DTI scans to establish the baseline for the ALPS index and to dynamically understand chronological changes over time. This constitutes a key objective of our ongoing and future research endeavors.

Conclusions

In summary, the application of the non-invasive DTI-ALPS technique revealed markedly reduced ALPS index values during the recovery phase of sTBI, indicative of diminished glymphatic system function in affected patients. Notably, this impairment in the glymphatic system was evident on both the craniectomy and non-craniectomy sides of the brain. Further, a significant negative correlation was observed between the ALPS index value of the craniectomy side and the size of the cranial defect. This correlation finding has the potential to serve as a foundation for in-depth investigations into the pathophysiology of glymphatic system function and the ALPS index may serve as a valuable prognostic factor in the recovery phase of sTBI.

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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-24-348/rc

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-348/coif). The 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). The study was approved by the Institutional Review Board of Xiangya Hospital, Central South University (No. 2022111433). The requirement of informed consent was waived for the trauma patients due to the retrospective nature of the investigation.

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