Am J Transl Res 2025;17(6):4306-4314
www.ajtr.org /ISSN:1943-8141/AJTR0163498

Original Article

DTI-ALPS index as a predictor of glymphatic system dysfunction in cerebral infarction

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Received January 22, 2025; Accepted May 19, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objectives: To evaluate glymphatic system (GS) dysfunction in patients with cerebral infarction using diffusion tensor imaging - along the perivascular space (DTI-ALPS), and to investigate factors associated with glymphatic function impairment following stroke. Methods: A retrospective study was conducted on 82 patients diagnosed with cerebral infarction at Zhujiang Hospital of Southern Medical University between July 2019 and June 2022. Based on 90-day modified Rankin Scale (mRS) scores, patients were categorized into a good prognosis group (n = 40) and a poor prognosis group (n = 42). Clinical data, National Institutes of Health Stroke Scale (NIHSS) scores, DTI-ALPS indices (L-ALPS, R-ALPS, mean-ALPS), 90-day mRS scores, and infarct location were compared between groups. Results: At admission, the L-ALPS, R-ALPS, and mean-ALPS values were significantly higher in the good prognosis group compared to the poor prognosis group (all $P < 0.05$). At 90 days post-onset, Hamilton Depression (HAMD) and Anxiety (HAMA) scores were significantly lower than baseline in the good prognosis group, indicating better psychological recovery compared to the poor prognosis group (both $P < 0.05$). Additionally, NIHSS scores were lower, while Glasgow Coma Scale (GCS) and activities of daily living (ADL) scores were higher in the good prognosis group (both $P < 0.05$). Logistic regression analysis identified L-ALPS, R-ALPS, mean-ALPS, 90-day mRS, ADL, and GCS scores as independent predictors of poor prognosis. Furthermore, ADL, 90-day mRS, and GCS scores were independently associated with GS dysfunction. Conclusion: Patients with poor prognosis after cerebral infarction exhibit significant GS dysfunction. This dysfunction correlates with the severity of neurological impairment, suggesting that glymphatic impairment is both a marker and a potential contributor to stroke outcomes.

Keywords: Glymphatic system function, cerebral infarction, diffusion tensor imaging analysis along the perivascular space

Introduction

Cerebral infarction is the second leading cause of death and the third leading cause of disability worldwide, imposing a significant burden on both individuals and healthcare systems [1]. Stroke encompasses both hemorrhagic and ischemic types, with ischemic stroke accounting for approximately 80% of all cases [2]. Cerebral infarction results from various etiologies that disrupt cerebral blood flow, leading to hypoxic-ischemic necrosis in affected brain regions and the rapid onset of neurological deficits [3]. With an aging global population and the accelerating pace of modern life, the incidence of cerebral infarction is steadily increasing [4, 5].

Alterations in glymphatic function may occur following cerebral infarction [6]. Lymphatic vessels are essential for the clearance of metabolic waste and inflammatory mediators. Disruption of normal lymphatic drainage after infarction may result in the accumulation of neurotoxic substances, potentially hindering recovery and negatively impacting prognosis [7]. Impaired glymphatic function may prolong inflammation, delay the clearance of necrotic tissue and cellular debris, and compromise the immune response in affected regions, increas-

https://doi.org/10.62347/ANQP2661

ing the risk of secondary complications and impairing tissue repair [8, 9].

Moreover, changes in glymphatic flow may contribute to cerebral edema and fluid accumulation in perilesional areas [10-13]. Therefore, accurately evaluating lymphatic function in patients with cerebral infarction is critical for understanding prognosis and guiding treatment strategies.

Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) is a specialized neuroimaging technique used to assess microstructural changes in perivascular spaces [14]. These spaces serve as vital conduits for interstitial fluid exchange and are closely associated with glymphatic function [15]. DTI-ALPS provides insights into the anisotropic water diffusion properties within perivascular regions, offering a noninvasive approach to evaluate the structural integrity and functional state of the brain's glymphatic drainage system [16-18]. This method has been increasingly applied in the study of neurodegenerative and cerebrovascular disorders to assess glymphatic system (GS) function and its role in disease progression [19].

Abnormalities in DTI-ALPS parameters have been linked to impaired waste clearance and fluid dysregulation in conditions such as Alzheimer's disease, multiple sclerosis, and small vessel disease [20-23]. However, no studies to date have evaluated glymphatic function using the DTI-ALPS index specifically in patients with cerebral infarction.

Therefore, the present study aimed to assess function in patients with cerebral infarction using the DTI-ALPS index and to explore factors associated with GS impairment in this population.

Methods and materials

Case selection

A retrospective analysis was conducted on 82 patients diagnosed with cerebral infarction at our hospital between July 2019 and June 2022. All patients underwent comprehensive clinical evaluations, including routine MRI and diffusion tensor imaging (DTI). This study was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University. Upon admission, modified Rankin Scale (mRS) scores were assessed by trained neurologists [24]. Follow-up evaluations were conducted at 90 days to assess neurological functional outcomes using the mRS [25].

Inclusion criteria: (1) Clinical diagnosis of cerebral infarction based on medical history, neurological examination, and imaging (e.g., MRI or CT) [26]; (2) Availability of complete imaging data, including high-quality DTI sequences suitable for DTI-ALPS assessment; (3) Age ≥ 18 years at the time of enrollment; (4) Availability of complete clinical data.

Exclusion criteria: (1) Other serious neurological disorders (e.g., neurodegenerative diseases such as Alzheimer's or Parkinson's disease, brain tumors, or prior major brain lesions); (2) Incomplete or unreliable clinical, imaging, or follow-up data, preventing accurate DTI-ALPS evaluation; (3) Contraindications to MRI (e.g., metal implants, pacemakers, cochlear implants); (4) Severe systemic illnesses (e.g., advanced cardiovascular disease, end-stage renal failure, uncontrolled diabetes, or liver failure); (5) Pregnancy or lactation, due to potential MRI-related risks; (6) Structural brain abnormalities or lesions identified on routine MRI that could interfere with glymphatic system evaluation; (7) Inability to undergo or tolerate MRI scanning due to claustrophobia, movement disorders, or implanted incompatible medical devices.

Magnetic resonance imaging (MRI) acquisition

MRI examinations were performed using a Philips Ingenia 3.0T scanner equipped with an 8-channel standard head coil. DTI data were post-processed using FSL software. The main processing steps were as follows.

DTI DICOM data were converted into. nii.gz, bvec, and bval formats using the dcm2niigui tool. A mask was applied to remove background regions and enhance reconstruction quality. DTI reconstruction was performed to extract the principal diffusion directions of white matter fibers.

Fiber tracking was performed on the diffusion color-coded fractional anisotropy image at the level of the lateral ventricle. Square regions of

interest (ROIs) were manually drawn in both the projection and association fiber areas on the left hemisphere to obtain diffusivity (D) values along the X, Y, and Z axes within each ROI.

To assess the repeatability of ALPS index measurements, ROI delineation was repeated at two time points separated by six months for each group. The D values of projection and commissural fibers along each axis (X, Y, Z) were obtained, and the ALPS index was then calculated. The intraclass correlation coefficient (ICC) was used to assess the reproducibility of the ALPS index between the two measurements.

Data collection and outcome measurement

The primary outcome was GS function, assessed by the DTI-ALPS index upon admission. The ALPS index was calculated as follows:

ALPS = (Dx_projection + Dx_association)/(Dy_projection + Dz_association) [27].

Here, Dx_projection and Dx_association represent the diffusivity of the projection and association fibers along the X-axis, Dy_projection is the diffusivity of the projection fibers along the Y-axis, and Dz_association is the diffusivity of the association fibers along the Z-axis.

Secondary indicators included demographic data, NIHSS scores at admission, cognitive function, 90-day mRS scores, infarction location, and cardiovascular risk factors such as hypertension, cardiac history (e.g., atrial fibrillation, coronary artery disease, heart failure), diabetes, hyperlipidemia, prior stroke, smoking, and alcohol use. Additional outcomes included psychological status and neurological function. The 90-day mRS scores were obtained through telephone follow-up, outpatient chronic disease management systems, or hospital readmission records. Patients with mRS scores of 0-1 were classified as having good prognosis, while those with scores of 2-6 were classified as having poor prognosis. Accordingly, 40 patients were assigned to the good prognosis group and 42 to the poor prognosis group [25].

Psychological status was assessed using the Hamilton Depression Rating Scale (HAMD) [28] and the Hamilton Anxiety Rating Scale (HAMA) [29]; HAMD was used for subjective assessment, while HAMA was used for objective evaluation. Anxiety severity based on HAMD was categorized as follows: ① < 40: no anxiety; ② 40-47: mild; ③ 48-55: moderate; ④ > 56: severe.

HAMA consists of 14 items covering symptoms such as anxious mood, tension, fears, insomnia, cognitive disturbances, depressive mood, and somatic symptoms affecting various systems (muscular, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic). Each item is rated from 0 (none) to 4 (severe), and the total score reflects the overall severity of anxiety symptoms.

Neurological function was evaluated using the National Institutes of Health Stroke Scale (NIHSS) [30], Glasgow Coma Scale (GCS) [31] and activities of daily living (ADL) [32]. GCS scores range from 3 to 15, with higher scores indicating better consciousness levels. ADL scores range from 0 to 100, with higher scores reflecting better functional independence.

Self-care ability was evaluated using the scale adapted by Kazawa et al. [33], covering four dimensions: stroke-related knowledge, self-care skills, self-care responsibility, and rehabilitation knowledge. Each domain is scored out of 100, with lower scores indicating poorer self-care capacity [34]. The NIHSS has a total score of 42 points; higher scores indicate more severe neurological deficits [35].

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality. Normally distributed data were expressed as mean ± standard deviation (SD) and analyzed using independent or paired t-tests as appropriate. Non-normally distributed data were presented as median and interquartile range and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, depending on expected counts. To assess associations between the ALPS index and clinical parameters while adjusting for age and sex, Pearson correlation analysis was applied. All tests were two-tailed,

Table 1. Comparison of clinical characteristics between the two groups

Indexes	Poor prognosis group (n = 42)	Good prognosis group (n = 40)	T/χ^2	*P*
Sex			0.391	0.532
Male	30	26		
Female	12	14		
Age (years)	51.05±2.81	50.13±4.72	1.081	0.283
Body mass index	20.62±2.60	21.10±2.21	0.902	0.370
Smoking	31	28	0.147	0.701
Drinking	17	19	0.410	0.522
Hypertension	22	19	0.195	0.659
Diabetes mellitus	13	11	0.118	0.731
Dyslipidemia	15	12	0.303	0.582
Previous stroke	13	14	0.152	0.697
Abnormal sensation	12	12	0.020	0.887
Course of stroke (Days)	18.67±2.22	19.25±1.74	1.323	0.190
Hemiplegic sites (Cases)			0.178	0.673
Left	18	19		
Right	24	21		
Baseline NIHSS score	21.88±2.16	22.30±2.73	0.774	0.441
Baseline mRS scores	2.88±1.15	2.90±1.10	0.076	0.939
mRS scores at 90 days	1.86±0.35	4.25±1.03	14.185	0.000

Note: NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale.

and a *P*-value < 0.05 was considered statistically significant.

Results

Comparison of clinical characteristics

Among the 82 patients with cerebral infarction included in this study, 40 patients with mRS scores of 0-1 were assigned to the good prognosis group, while the remaining 42 patients with mRS scores of 2-6 were assigned to the poor prognosis group. As shown in **Table 1**, the 90-day mRS scores differed significantly between the two groups (P < 0.05). However, there were no statistically significant differences in gender, age, body mass index, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, history of stroke, abnormal sensation, stroke duration, or hemiplegic side (all P > 0.05).

Comparison of GS function

At admission, L-ALPS, R-ALPS, and mean-ALPS values were significantly higher in the good prognosis group compared to the poor prognosis group (all P < 0.05) (**Figure 1**).

Comparison of negative psychological status

On day 90 after stroke onset, both HAMD and HAMA scores were significantly reduced compared to admission levels in the good prognosis group, indicating an improvement in negative psychological symptoms (both P < 0.05). The extent of improvement in the good prognosis group was significantly greater than that observed in the poor prognosis group (P < 0.001) (**Figure 2**).

Comparison of neurological function

At admission, no significant differences were observed between the two groups in terms of NIHSS, GCS, or ADL scores (all P > 0.05). However, at 90 days post-onset, the good prognosis group showed significantly lower NIHSS scores and significantly higher GCS and ADL scores compared to the poor prognosis group (all P < 0.001) (**Figure 3**).

Logistic regression analysis of factors influencing poor prognosis

As shown in **Table 2**, logistic regression analysis identified L-ALPS, R-ALPS, mean-ALPS,

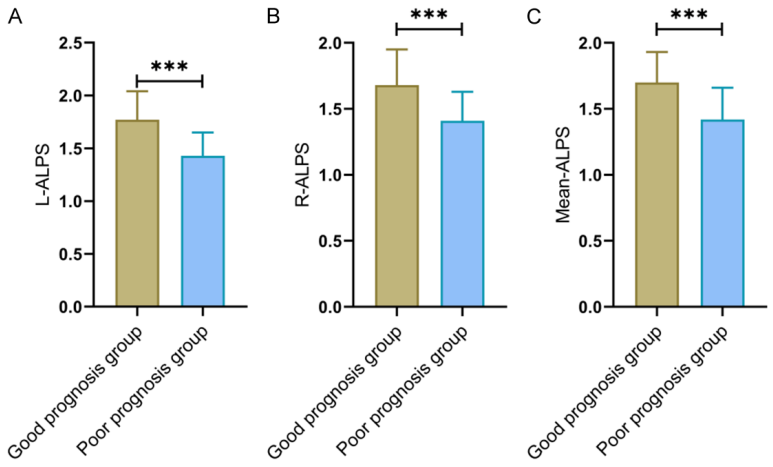

Figure 1. Comparison of glymphatic system function between the two groups. (A) L-ALPS, (B) R-ALPS, (C) Mean-ALPS. L-ALPS: left diffusion tensor imaging along the perivascular space index, R-ALPS: Right diffusion tensor imaging along the perivascular space index, Mean-ALPS: mean diffusion tensor imaging along the perivascular space index. Compared to the good prognosis group, ***P < 0.001.

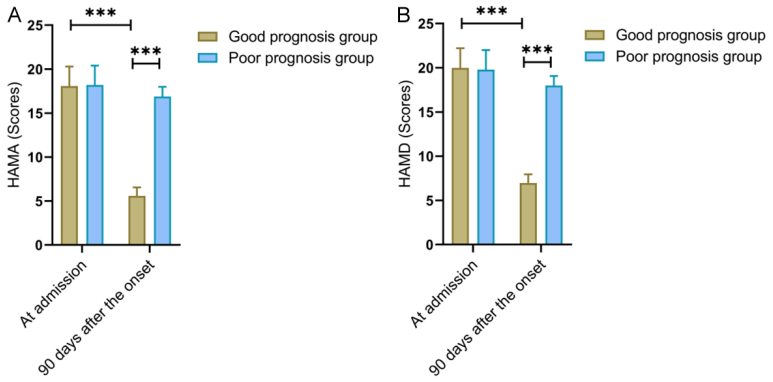

Figure 2. Comparison of negative psychological status between the two groups. (A) HAMA, (B) HAMD. Note: HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale. Compared to the good prognosis group, ***P < 0.001.

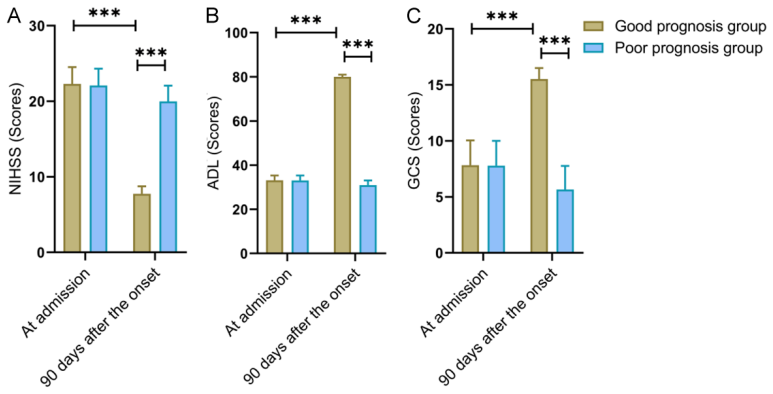

Figure 3. Comparison of neurological function between the two Groups. (A) NIHSS; (B) ADL; (C) GCS. Note: NIHSS: National Institutes of Health Stroke Scale, ADL: Activity of Daily Living Scale score, GCS: Glasgow Coma Scale. Compared to the good prognosis group, ***P < 0.001.

90-day mRS scores, ADL, and GCS scores as independent predictors of poor prognosis in patients with cerebral infarction.

Logistic regression analysis of factors influencing GS function

As presented in **Table 3**, logistic regression analysis of factors associated with GS function (mean-ALPS) revealed that ADL, 90-day mRS scores, and GCS were independent predictors of impaired glymphatic function.

Discussion

In this study, we investigated the factors influencing prognosis and glymphatic system function in patients with cerebral infarction. Our findings highlight the predictive value of early clinical indicators, neurological function, psychological status, and glymphatic system integrity in stroke outcomes. These results contribute to the growing body of literature on stroke recovery and prognosis, and are discussed in comparison with existing studies to provide context.

Our results emphasize the pivotal role of early stroke severity, as assessed by the NIHSS, in predicting long-term outcomes. This is consistent with prior studies [36-38], which have demonstrated that higher baseline NIHSS scores are associated with worse prognosis. While other studies have suggested that demographic variables and comorbidities, such as age, diabetes, or hypertension, may influence recovery [39, 40], our study did not find significant differences in these

Table 2. Logistic regression analysis of factors influencing poor prognosis

	B	P	OR	95% CI of OR	
				lower limit	upper limit
L-ALPS (< 1)	-2.720	< 0.001	0.066	0.021	0.203
R-ALPS (< 1)	-0.133	< 0.001	0.875	0.816	0.939
mRS scores at 90 days (2-6)	1.206	0.019	3.340	1.216	9.175
Mean-ALPS (< 1)	-1.442	0.003	0.236	0.091	0.617
ADL(< 50)	0.368	< 0.001	1.444	1.224	1.704
GCS (< 15)	1.068	< 0.001	2.910	1.927	4.394
Constant	-11.313	0.004	0.000		

Note: mRS: modified Rankin Scale; L-ALPS: left diffusion tensor imaging along the perivascular space index; R-ALPS: Right diffusion tensor imaging along the perivascular space index; Mean-ALPS: mean diffusion tensor imaging along the perivascular space index; NIHSS: National Institutes of Health Stroke Scale; ADL: Activity of Daily Living Scale score; GCS: Glasgow Coma Scale; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale.

Table 3. Logistic regression analysis of factors influencing glymphatic system function

	B	P	OR	95% CI of OR	
				lower limit	upper limit
ADL (< 50)	2.660	< 0.001	14.300	5.958	34.320
mRS scores at 90 days (2-6)	1.589	< 0.001	4.901	2.214	10.849
GCS (< 15)	1.000	< 0.001	2.719	2.013	3.673
Constant	-13,180	< 0.001	0.000		

Note: NIHSS: National Institutes of Health Stroke Scale; ADL: Activity of Daily Living Scale score; mRS: modified Rankin Scale; HAMA: Hamilton Anxiety Scale; GCS: Glasgow Coma Scale; HAMD: Hamilton Depression Scale.

factors between the good and poor prognosis groups. This suggests that recovery may be more strongly associated with the extent of initial neurological damage than with demographic factors. This finding contrasts with studies indicating that comorbidities significantly impact post-stroke rehabilitation outcomes [41, 42], indicating that such effects may vary depending on stroke subtype, population characteristics, or sample size.

Regarding GS function, our findings align with recent research [43, 44], indicating that ALPS scores are predictive of stroke outcomes. The significant differences in ALPS indices at admission suggest that glymphatic dysfunction may contribute to impaired recovery, potentially due to reduced clearance of interstitial waste, impaired fluid balance, and altered neuroinflammatory responses. While the mechanisms remain speculative, the GS's role in modulating brain homeostasis may be central to the repair process following stroke. These insights suggest a novel direction for future studies aimed at enhancing glymphatic function to improve recovery and long-term prognosis.

Psychological well-being, as measured by HAMD and HAMA scores, also played a significant role. Patients in the good prognosis group showed marked improvement in depressive and anxiety symptoms by day 90. This is consistent with previous studies demonstrating that psychological distress negatively affects stroke recovery [45]. Emotional health may influence neuroplasticity and patient engagement with rehabilitation, ultimately shaping functional outcomes. Our findings underscore the need for comprehensive stroke care that addresses both neurological and psychological domains to optimize recovery.

Improvements in neurological function, reflected by NIHSS, GCS, and ADL scores, further reinforce the importance of aggressive early intervention. Our results are in line with established research showing that neurological recovery is a key determinant of functional outcomes [46].

The observed improvements over 90 days support the role of neuroplasticity in post-stroke recovery and highlight the need for strategies

that support both central and peripheral nervous system rehabilitation.

These findings have important clinical implications. The identification of GS function as a potential prognostic biomarker introduces a novel target for therapeutic intervention. If validated in larger cohorts, the ALPS index could help stratify patients based on glymphatic dysfunction severity and identify those most likely to benefit from therapies that enhance waste clearance or reduce neuroinflammation. Personalized rehabilitation programs guided by ALPS scores may improve functional outcomes. Additionally, our findings support the inclusion of mental health assessment and intervention in routine stroke care, reinforcing the value of integrated rehabilitation models.

From a research perspective, this study opens several avenues for further exploration. Longitudinal studies are needed to confirm the prognostic value of ALPS scores and psychological health indicators. Clinical trials testing glymphatic-targeted therapies - such as interventions promoting interstitial fluid clearance or regulating inflammatory pathways - could yield new strategies for stroke treatment. Moreover, research into optimal timing, intensity, and modalities of psychological intervention could refine rehabilitation protocols and improve adherence and outcomes.

Despite these insights, several limitations should be acknowledged. First, the study was based on a relatively small sample from a single center, which may limit the generalizability of the findings. Larger, multi-center studies are needed to validate our results across diverse populations. Second, the retrospective design introduces inherent limitations, including potential selection bias and limited ability to infer causality. Prospective studies with standardized protocols are needed to better understand the dynamic relationships between glymphatic function, psychological status, and recovery. Finally, the absence of other potential biomarkers, including genetic or molecular indicators, may limit the comprehensiveness of our model. Future research should incorporate broader datasets to capture the multifactorial nature of stroke recovery.

In conclusion, this study highlights the multifactorial nature of stroke recovery, emphasizing the roles of early neurological assessment, GS function, and psychological well-being. By comparing our findings with prior literature, we contribute to a deeper understanding of recovery predictors in cerebral infarction. Our results suggest that early interventions targeting both neurological and psychological aspects may enhance patient outcomes. Future research should focus on validating glymphatic function as a prognostic biomarker and exploring its therapeutic modulation, alongside integrated psychological support, to improve rehabilitation strategies and long-term prognosis in stroke patients.

Disclosure of conflict of interest

None.

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