Am J Transl Res 2025;17(12):9705-9714
www.ajtr.org /ISSN:1943-8141/AJTR0169007

Original Article

Association between diffusion tensor imaging analysis along the perivascular space (DTI-ALPS)-based glial-lymphatic dysfunction and cognitive impairment in non-small cell lung cancer

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Received September 25, 2025; Accepted November 24, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Objective: To investigate the correlation of glial-lymphatic (glymphatic) system function with cognitive deficits in non-small cell lung cancer (NSCLC). Methods: Data (demographic, clinical, and magnetic resonance imaging [MRI] information) from 83 NSCLC cases and 96 healthy controls were retrospectively analyzed. We evaluated glymphatic activity by using the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index and cognitive function with the Montreal Cognitive Assessment (MoCA). Medial Temporal Atrophy (MTA) and Fazekas scores were also rated. Statistical analyses included inter-group comparisons, partial correlation assessments, mediation modeling, and regression to identify predictors of cognitive impairment. Results: NSCLC patients had higher MTA and Fazekas scores but lower MoCA and ALPS index scores than controls (all $P < 0.05$). The ALPS index was symmetrically reduced in both hemispheres, correlating positively with MoCA ($r = 0.276$, $P = 0.012$). In the mediation model, the ALPS index exhibited a partial mediating role (4.6%) in the NSCLC-MoCA association. Older age was an independent predictor of cognitive impairment (odds ratio [OR]: 1.229; 95% confidence interval [CI]: 1.111-1.360). Conclusion: In NSCLC patients, glymphatic dysfunction was associated with cognitive impairment, and the DTI-ALPS index may facilitate early detection of these deficits. Advanced age remains a major contributing risk factor.

Keywords: Glymphatic system, non-small cell lung cancer, cognitive impairment, DTI-ALPS index

Introduction

Non-small cell lung cancer (NSCLC) is a malignant tumor with high incidence and mortality rates worldwide, accounting for approximately 85% of all lung cancer cases [1]. Notably, despite the presence of distant metastases, both the disease itself and its treatment can have adverse effects on the central nervous system (CNS) [2]. The brain's unique anatomic complexity, cellular heterogeneity, and functional specificity make it vulnerable to microenvironmental disruptions under the influence of multiple factors such as systemic inflammatory responses, immune abnormalities, and metabolic alterations [2]. These disturbances can impair neural function, thereby triggering a series of neurocognitive disorders. Cognitive dysfunction is a frequent and severe complication in NSCLC patients, considerably reducing patients' quality of life while possibly affecting treatment compliance and disease outcomes [3]. Previous research suggests that this cognitive decline is multifactorial in mechanism and may be related to systemic inflammation, hypoxia, cancer-related fatigue, anemia, and treatment-related toxicities (e.g., radiotherapy and chemotherapy) [4, 5].

Historically, the CNS was considered as an immunologically privileged site. However, recent studies have shown that it has a complex immune regulatory network, with the glymphatic system playing a crucial role. This three-dimensional network, comprising the glymphatic network and meningeal lymphatic vessels

https://doi.org/10.62347/QFOR5108

(MLVs), not only performs important functions like cerebrospinal fluid circulation, immune surveillance, and metabolic waste clearance [6, 7], but also functions as a precise biological communication hub, facilitating two-way communication between the central and peripheral immune organs. Glymphatic dysfunction is a well-established contributor to cognitive impairment in neurodegenerative disorders [8, 9]. However, its role in cognitive decline caused by cancer remains an unsolved issue.

As the primary regulator of brain metabolic homeostasis, the glymphatic system establishes a conductive pathway for the migration of tumor-associated antigens and immune cells through MLVs [6]. In NSCLC, systemic inflammatory response, tumor metabolites, treatment-related toxicity, and cancer-related fatigue (CRF) may all impair glymphatic function, reducing the efficiency of cerebrospinal fluid (CSF) circulation and metabolic waste clearance. This disruption compromises CNS immune homeostasis and triggers cognitive dysfunction [5, 10-12]. According to preclinical research, MLVs play a key role in regulating antigen presentation and immune cell infiltration, thereby influencing the state of the central immune environment [13]. This discovery provides new avenues for investigating the mechanisms underlying cognitive dysfunction in NSCLC.

With the advancement in neuroimaging techniques, especially the revolutionary integration of magnetic resonance imaging (MRI), non-invasive functional analysis of the glymphatic system has become feasible. Among these methods, the analysis along the perivascular space (ALPS) index based on diffusion tensor imaging (DTI; DTI-ALPS) has become a powerful tool for visualizing glymphatic system activity. By quantifying water molecule diffusion anisotropy along perivascular channels, it this index can quantitatively reflect the functional state of the glymphatic system [14]. An elevation in this index corresponds to perivascular fluid flow enhancement, suggesting an increased glymphatic activity [15]. This biomarker not only enables real-time monitoring of fluid dynamics in the brain's microenvironment, but also reveals the potential association between glial lymph dysfunction and cognitive impairment in NSCLC.

Therefore, this study aimed to investigate potential damage to the glial-lymphatic system in NSCLC patients using DTI-ALPS, and to assess its relationship with cognitive function using the Montreal Cognitive Assessment (MoCA) scale. We hypothesize that glymphatic dysfunction plays a critical mechanistic role in the association between NSCLC and cognitive impairment. The innovation of this study lies in the application of the DTI-ALPS index to assess the glymphatic system function in the NSCLC population, offering the first empirical evidence of its partial mediating role in NSCLC-associated cognitive impairment. This approach provides new imaging evidence for understanding the mechanism of tumor-induced neurological complications and offers a potential tool for early identification of high-risk patients.

Materials and methods

General information

This retrospective study was approved by the Ethics Committee of The Affiliated Hospital of Jiangnan University (Approval No. LS2024589) and adhered to the Declaration of Helsinki. A total of 83 NSCLC patients were enrolled between January and November 2024.

Eligibility criteria: ① Histologically confirmed NSCLC following surgical resection or biopsy; ② Adults (≥ 18 years old); ③ Examination with DTI-ALPS. Exclusion criteria: ① Significant motion artifacts on imaging; ② History of intracranial surgery; ③ Presence of brain metastases; ④ Dural arteriovenous fistula. Additionally, matched healthy controls who underwent MRI without a lung cancer diagnosis were included as controls. Group discrepancies were minimized by selecting controls by matching to NSCLC cases by sex, age (±5 years), scan date, and scanner model. The healthy control group consisted of patients who underwent routine examinations, rather than randomly selecting all patients who received the scans.

Imaging methods

A 3.0-T scanner (AchievaTx, Philips Medical Systems, Best, the Netherlands) equipped with a 32-channel head receiver coil was used for MRI scanning. Each participant underwent a standardized brain MRI protocol, including T1-weighted (T1WI), T2-weighted (T2WI), T2-fluid-attenuated inversion recovery (T2-FLAIR), and DTI sequences. Scanning parameters: T1WI:

repetition time (TR)/echo time (TE) = 2000/20 ms, field of view (FOV) = 230 × 190 mm, slice thickness = 5 mm, flip angle = 90°; T2WI: TR/TE = 3500/120 ms, FOV = 230 × 230 mm, slice thickness = 5 mm, flip angle = 90°; T2-FLAIR: TR/TE = 8500/130 ms, FOV = 230 × 200 mm, slice thickness = 5 mm, flip angle = 90°; DTI: TR/TE = 5100/75 ms, FOV = 230 × 230 mm, slice thickness = 5 mm, flip angle = 90°.

DTI image post-processing and ALPS index calculation

In this study, the DTI-ALPS index was used to assess the water diffusion rate in the perivascular spaces surrounding the medullary veins at the lateral ventricle level. It primarily reflects the brain's ability to transport fluid from the subcortical areas to the lateral ventricles, serving as an indirect indicator of the overall glial lymphatic function of the entire brain. The analysis steps are detailed below: ① DTI data were preprocessed on the Linux workstation Using FSL software (RRID number: SCR_002823) to correct signal distortions caused by eddy currents, subject motion, magnetic susceptibility artifacts, and bias fields. ② Diffusion tensors were derived via Diffusion Toolkit (RRID number: SCR_017345), producing color-encoded fractional anisotropy (FA) maps and diffusion coefficients corresponding to the x-, y-, and z-axes. ③ At the lateral ventricle level of the cerebral hemisphere contralateral to the tumor, two neuroradiologists manually defined two 3 mm3 volumes of interest (VOIs), selecting regions within projection and association fibers. ④ Voxel-wise diffusion coefficients (D) within the VOIs were analyzed. The diffusion rate of the projection fibers along the X-axis was recorded as Dx_proj, and along the Y-axis as Dy_proj; the diffusion rate of the association fibers along the X-axis was recorded as Dx_assoc, and along the Z-axis as Dz_assoc. Subsequently, the average values were then calculated.

Cognitive function assessment

Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) [16]. MoCA is an efficient and systematic cognitive screening tool, with scores ranging from 0 to 30. A score below 26 is indicative of cognitive impairment. This tool is widely used in clinical and research fields, not only enabling the early identification of mild cognitive impairment, but also having high sensitivity and tracking ability for diseases such as Alzheimer's disease. Through structured assessment of multiple cognitive fields, MoCA provides a more comprehensive and accurate evaluation of cognitive deficits, providing an accurate assessment of an individual's cognitive health status.

Measurement of clinical characteristics

The research data included age, sex, hypertension, diabetes, and smoking status, all of which were retrieved from digitized medical records. The Medial Temporal Atrophy (MTA) score was derived from visual ratings (on a 0-4 scale) provided by two neuroradiologists, automated hippocampal volume measurement (standardized for intracranial volume, with Z values compared to age/gender standards), and Fazekas scores, which derived from semi-automated FLAIR image analysis (with pixel intensity threshold set at over 120% of the contralateral white matter, using a region-growing algorithm) [17].

Statistical methods

Statistical analyses were conducted using SPSS 25.0 (IBM SPSS Statistics, Chicago, USA), and figures were prepared using GraphPad Prism 9.0 (GraphPad Software, San Diego, USA). Following normality examination with Shapiro-Wilk testing, normally distributed continuous data were summarized as mean ± standard deviation; otherwise, the median was reported. The comparisons of normally and non-normally distributed continuous data were performed using independent samples t-tests and Mann-Whitney U tests, respectively. Categorical variables were expressed as counts (percentages) and compared using chi-square/Fisher's exact tests.

Inter-observer agreement was evaluated using the intraclass correlation coefficient (ICC). The correlation between the ALPS index in brain metastasis patients and clinical datan was evaluated using partial correlation analysis adjusted for age, sex, hypertension, and diabetes. Meanwhile, the mediating role of ALPS in the brain metastasis-MoCA relationship were evaluated through a bias-corrected bootstrap mediation analysis (10,000 iterations) on

Table 1. Comparison of baseline characteristics between the control and NSCLC groups

Variable	Healthy control group (n = 96)	NSCLC group (n = 83)	t/χ^2 value	*p* value	d/ϕ
Age/years	62.09±12.13	61.93±10.57	t = 0.093	0.926	0.01
Sex			χ^2 = 0.558	0.455	0.06
Female/n (%)	47 (49)	36 (43.4)			
Male/n (%)	49 (51)	47 (56.6)			
Hypertension/n (%)	24 (25.00)	19 (22.89)	χ^2 = 0.108	0.742	0.03
Hyperglycemia/n (%)	7 (7.29)	10 (12.05)	χ^2 = 1.172	0.279	0.08
Smoking history/n (%)	18 (18.75)	16 (19.28)	χ^2 = 0.008	0.929	< 0.01
MTA score	1.07±1.04	1.73±1.62	t = 3.285	0.001	0.49
Fazekas score	2.58±1.06	3.19±1.42	t = 3.283	0.001	0.49
MoCA score	27.88±1.61	25.81±1.71	t = 8.334	< 0.001	1.26

Note: NSCLC, non-small cell lung cancer; MTA, Medial Temporal Atrophy; MoCA, Montreal Cognitive Assessment.

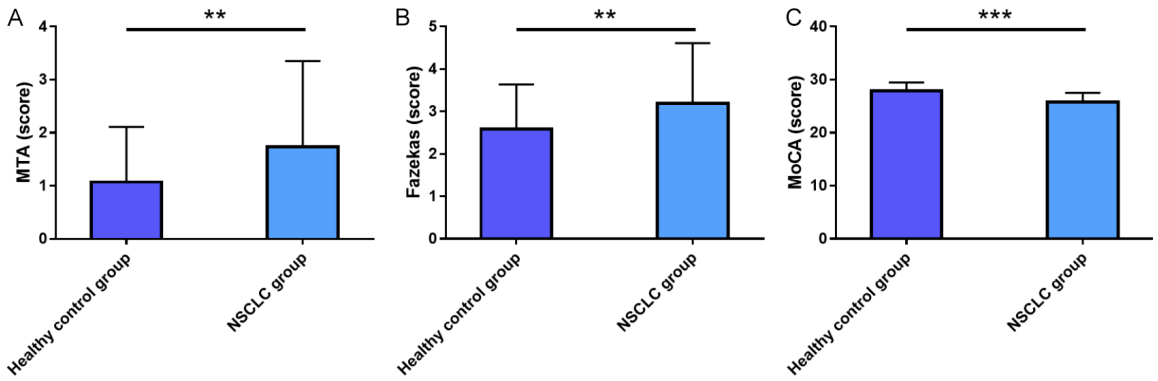

Figure 1. Pairwise analysis of MTA score (A), Fazekas score (B), and MoCA score (C) between healthy controls versus NSCLC patients. Note: NSCLC, non-small cell lung cancer; MTA, Medial Temporal Atrophy; MoCA, Montreal Cognitive Assessment; **P < 0.01, ***P < 0.001.

the SPSSAU platform (https://spssau.com/). Additionally, univariate and multivariate binary logistic regression analyses were performed to identify determinants of NSCLC-associated cognitive impairment. Effect sizes were calculated to quantify the magnitude of differences between groups, using Cohen's d for continuous variables and the Phi (ϕ) coefficient for categorical variables. Cohen's d values were interpreted as follows [18]: |d| ≈ 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively. The interpretation of the ϕ coefficient follows similar criteria.

Results

Clinical characteristics of participants

A total of 179 participants (83 NSCLC cases and 96 non-NSCLC controls) were enrolled in this study. The demographic, clinical, and laboratory characteristics of the two groups are summarized in **Table 1**. The two groups were comparable in age (P = 0.923), gender distribution (P = 0.455), hypertension (P = 0.742) and diabetes (P = 0.279) prevalence, and smoking status (P = 0.929). MTA (P = 0.002), Fazekas (P = 0.002), and MoCA (P < 0.001) scores; however, significant inter-group disparities were observed in MTA, Fazekas and MoCA scores (P < 0.001), with NSCLC patients showing significantly higher MTA and Fazekas scores and lower MoCA scores (**Figure 1**).

Group differences in the DTI-ALPS index

The ALPS index was significantly lower in NSCLC patients than in non-NSCLC patients (1.3185±0.1751 vs. 1.3862±0.1917, P = 0.0152; **Figure 2**). This reduction was consistent in both cerebral hemispheres: the left (1.3196±0.2096 vs. 1.3881±0.2052; P =

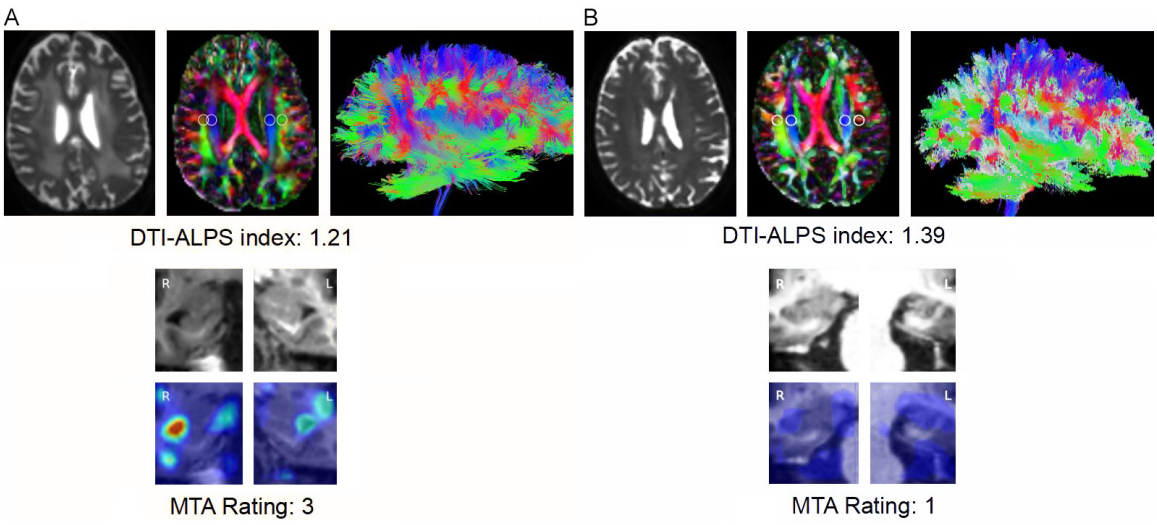

Figure 2. Representative images of the DTI-ALPS in an NSCLC patient (A) and a healthy control (B). Note: NSCLC, non-small cell lung cancer; DTI-ALPS, diffusion tensor imaging analysis along the perivascular space.

Table 2. Comparison of the DTI-ALPS index between the control and NSCLC groups

Variable	Healthy control group	NSCLC group	t value	*p* value	d/ϕ
ALPS left	1.3881±0.2052	1.3196±0.2096	t = 2.2052	0.0287	0.348
Diffusivity x left proj	0.0006±0.0001	0.0006±0.0002	t = 0	> 0.99	0.000
Diffusivity x left assoc	0.0007±0.0001	0.0007±0.0002	t = 0	> 0.99	0.000
Diffusivity y left proj	0.0005±0.0002	0.0005±0.0002	t = 0	> 0.99	0.000
Diffusivity y left assoc	0.0009±0.0001	0.0009±0.0001	t = 0	> 0.99	0.000
Diffusivity z left proj	0.0010±0.0001	0.0011±0.0001	t = 6.672	< 0.0001	1.054
Diffusivity z left assoc	0.0006±0.0003	0.0005±0.0002	t = 2.5807	0.0107	0.407
ALPS right	1.3843±0.2325	1.3174±0.2098	t = 2.0081	0.0460	0.317
Diffusivity x right proj	0.0006±0.0001	0.0006±0.0001	t = 0	> 0.99	0.000
Diffusivity x right assoc	0.0007±0.0001	0.0007±0.0002	t = 0	> 0.99	0.000
Diffusivity y right proj	0.0005±0.0001	0.0005±0.0002	t = 0	> 0.99	0.000
Diffusivity y right assoc	0.0009±0.0001	0.0009±0.0001	t = 0	> 0.99	0.000
Diffusivity z right proj	0.0010±0.0001	0.0011±0.0001	t = 6.672	< 0.0001	1.054
Diffusivity z right assoc	0.0006±0.0003	0.0005±0.0002	t = 2.5807	0.0107	0.407
ALPS	1.3862±0.1917	1.3185±0.1751	t = 2.4522	0.0152	0.387

Note: DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; NSCLC, non-small cell lung cancer.

0.0287) and the right (1.3174±0.2098 vs. 1.3843±0.2325; P = 0.0460). Notably, although most diffusion indices showed no significant differences, z-axis diffusivity varied markedly between groups (left projection area: 0.0011±0.0001 vs. 0.0010±0.0001, P < 0.0001; right projection area: 0.0011±0.0001 vs. 0.0010±0.0001, P < 0.001; left association area: 0.0005±0.0002 vs. 0.0006±0.0003, P = 0.0107; right association area: 0.0005±0.0002 vs. 0.0006±0.0003, P = 0.0107), as shown in **Table 2**.

Correlation analysis

To evaluate the relationship between MoCA scores and other variables, a correlation analysis was conducted in cases with brain metastases. The DTI-ALPS index was positively correlated with the MoCA score (r = 0.276, P = 0.012) but inversely with the MTA score (r = -0.288, P = 0.008). However, no significant correlation was found that could link MTA scores to MoCA scores (P = 0.150; **Figure 3**).

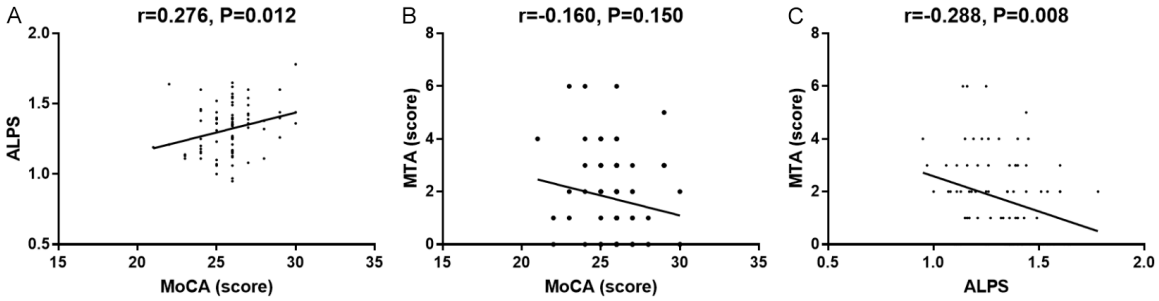

Figure 3. Scatter plots of Spearman correlation analysis. A. Association between the mean bilateral ALPS index and MoCA scores. B. Association between MoCA scores and MTA scores. C. Association between the mean bilateral ALPS index and MTA scores. Note: ALPS, analysis along the perivascular space; MoCA, Montreal Cognitive Assessment; MTA, Medial Temporal Atrophy.

Table 3. Mediating effects of the DTI-ALPS index on the relationship between NSCLC and MoCA scores

Path/variable	B value	SE value	*p* value	95% CI
Total effect (NSCLC→MoCA)	-2.065	0.245	< 0.001	-2.549 - -1.581
Path a (NSCLC→ALPS)	-0.067	0.025	0.009	-0.117 - -0.017
Path b (ALPS→MoCA)	1.411	0.735	0.056	-0.039 - 2.862

Note: DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; NSCLC, non-small cell lung cancer; MoCA, Montreal Cognitive Assessment.

Mediation analysis

This study conducted a mediation analysis to investigate whether the DTI-ALPS index mediated the brain metastasis-MoCA association. The indirect effect of lung cancer on MoCA through DTI-ALPS index was statistically significant (a*b = -0.095, 95% confidence interval: -0.270 to -0.004, excluding zero). These findings indicate that the ALPS index plays a significant partial mediating role between brain metastases and cognitive function, accounting for 4.6% of the total effect (**Table 3**).

Analysis of contributors to cognitive dysfunction in NSCLC patients

Cognitive impairment was defined as a MoCA score < 26, with 29 out of 83 NSCLC patients meeting this criterion. According to univariate analysis results, age, smoking history, MTA score, and Fazekas score were significant contributors (all P < 0.05). However, sex, hypertension, hyperglycemia, and ALPS did not show a significant association with cognitive dysfunction (P > 0.05; **Table 4**).

In the multivariate analysis, only age remained as an independent predictor of cognitive impairment (OR: 1.229, 95% CI: 1.111-1.360; P < 0.001), while smoking history, MTA score, and Fazekas score, lost significance (P > 0.05; **Table 5**).

Discussion

This study found marked differences in several cognitive and neuroimaging metrics when comparing NSCLC cases to a healthy control group. Specifically, NSCLC cases had increased MTA and Fazekas scores, coupled with reduced MoCA scores, suggesting greater severity of hippocampal atrophy, white matter pathology, and cognitive deterioration. This is consistent with the conclusion of previous studies, which documented that structural brain alterations and cognitive deficits can occur even in lung cancer patients without brain metastases [18, 19].

More notably, this study was the first to report a significant decrease in the DTI-ALPS index among NSCLC patients and a positive correlation between DTI-ALPS index and MoCA scores, suggesting that impaired glymphatic system function could be a key underlying mechanism contributing to lung cancer-related cognitive impairment. Functioning through MLVs, the

Table 4. Univariate analysis of factors associated with cognitive impairment in NSCLC patients

Variable	Cognitive impairment (n = 29)	Non-cognitive impairment (n = 54)	t/χ^2 value	*p* value	d/ϕ
Age/years	70.55±6.36	57.30±9.43	6.775	< 0.001	1.63
Sex			2.763	0.097	0.18
Female/n (%)	9 (31.03)	27 (50.00)			
Male/n (%)	20 (68.97)	27 (50.00)			
Hypertension/n (%)	8 (27.59)	11 (20.37)	0.557	0.456	0.08
Hyperglycemia/n (%)	6 (20.69)	4 (7.41)	3.141	0.076	0.19
Smoking history/n (%)	10 (34.48)	6 (11.11)	6.623	0.010	0.28
MTA score	2.24±1.70	1.46±1.53	2.130	0.036	0.48
Fazekas score	3.72±1.51	2.91±1.29	2.568	0.012	0.58
ALPS	1.28±0.17	1.34±0.18	1.476	0.144	0.34

Note: NSCLC, non-small cell lung cancer; MTA, Medial Temporal Atrophy; ALPS, analysis along the perivascular space.

Table 5. Multivariate analysis of independent predictors for cognitive impairment in NSCLC patients

Variable	B	SE	WALD	P	OR	95% CI
Age/years	0.207	0.052	16.080	< 0.001	1.229	1.111-1.360
Smoking history/n (%)	-0.152	0.745	0.042	0.838	0.859	0.200-3.697
MTA score	0.102	0.200	0.260	0.610	1.108	0.748-1.640
Fazekas score	0.318	0.238	1.784	0.182	1.375	0.862-2.192

Note: NSCLC, non-small cell lung cancer; MTA, Medial Temporal Atrophy.

glymphatic system facilitates the exchange and drainage of CSF and interstitial fluid (ISF), playing a crucial role in metabolic waste clearance, immune monitoring, and maintaining CNS homeostasis [20, 21]. A reduced ALPS index may indicate a reduced efficiency of the CSF-ISF pathway flow, possibly hindering the clearance of neurotoxic metabolites and subsequently reducing cognitive performance [22].

The mediation analysis further supported the index's partial mediating role (4.6% of the total effect) in the association between NSCLC-cognitive function. This implies that lung cancer influences cognitive function not only through pathways such as systemic inflammation, oxidative stress, and vascular risk factors [23, 24], but may also exert an indirect effect by impairing glymphatic system function. Lin et al. [25] reported that DTI-ALPS mediates the relationship between peripheral inflammation (the neutrophil-to-lymphocyte ratio and neutrophils) and motor symptom severity in Parkinson's disease, suggesting an association between DTI-ALPS and systemic inflammation. Additionally, Gong et al. [26] suggested that DTI-ALPS was significantly associated with the inflammation-oxidative stress panel (lymphocyte-to-high-density lipoprotein ratio, monocyte-to-high-density lipoprotein ratio).

Highly prevalent among NSCLC patients, CRF exhibits a significant inverse correlation with cognitive performance [11, 27, 28]. Potential mechanisms may involve damage to the glymphatic system, which induces proinflammatory mediator accumulation within the CNS, thus initiating or intensifying neuroinflammation, and ultimately promoting fatigue and cognitive deficits [29, 30]. Additionally, the glymphatic system is active during deep sleep, while CRF-affected patients often suffer from sleep disorders. This decline in sleep quality may lead to a reduced efficiency in clearing metabolic waste, thereby triggering or exacerbating inflammatory responses in the CNS, and further promoting fatigue and cognitive decline [31-33]. Moreover, oncological treatments, radiotherapy and chemotherapy in particular, can compromise blood-brain barrier (BBB) integrity and alter CSF dynamics, thus indirectly weakening glymphatic function [34, 35]. These factors may interact with each other, further reducing glymphatic efficiency, and intensifying the correlation between the decline in the ALPS index and the deterioration of cognitive function.

In addition, we observed a bilateral reduction in the ALPS index among patients and detected differences in z-axis diffusion rates within certain white matter areas, suggesting that glymphatic dysfunction may be bilateral and regional-specific. This is consistent with the results observed in animal experiments, which showed uneven MLV distribution and a different susceptibility of different brain regions to fluid dynamic changes [36]. Finally, age was confirmed to independently influence cognitive impairment among NSCLC patients, with advanced age elevating this risk. A proposed mechanism for this outcome is immunosenescence. This age-driven immune function decline not only weakens antigen responses but also promotes senescence-associated cell accumulation, fostering chronic inflammation. A key consequence is BBB integrity disruption, ultimately promoting cognitive deficits [37]. Zeng et al. [38] similarly documented a temporal decline in cognitive function in radically treated stage III NSCLC patients. Although the ALPS index plays a mediating role between brain metastases and cognitive function, its direct association with cognitive impairment did not reach statistical significance in the multivariate analysis after controlling for multiple confounding factors. This suggests that while brain metastasis may affect cognitive function through the ALPS index, its effect size seems modest. Besides, the ALPS index-cognitive impairment association is likely confounded by age and cerebrovascular risks. Although the ALPS index (an indicator of glymphatic activity) has statistical significance in mediating the pathway of cognitive impairment, its clinical effect may be limited when used alone. Thus, the cognitive impairment observed in patients with brain metastasis requires explanation through the integration of this pathway with other pathologic mechanisms.

From a clinical perspective, the non-invasive DTI-ALPS holds potential for evaluating risk of early cognitive impairment in NSCLC patients. By regularly monitoring changes in the ALPS index, clinicians can identify high-risk patients before cognitive symptoms occur, thereby providing a basis for early intervention. Future studies should investigate whether enhancing glymphatic function, using methods such as sleep optimization, respiratory training, or pharmacologic approaches, can effectively delay or reverse lung cancer-associated cognitive decline.

Still, several limitations of this study should be noted. First of all, due to the cross-sectional design, the study could not establish a causal relationship. Second, the study had a relatively small sample size, which can reduce the statistical power and make it difficult to detect the effects and increase the probability of Type II errors. Future studies should increase the sample size to enhance statistical power, ensuring the reliability of the results and the detectability of the effects. Third, given the absence of subgroup analysis by treatment methods (chemotherapy vs. immunotherapy), future studies should consider treatment methods as a stratification variable to reveal the differences in the effect of different treatment methods on the glymphatic system. Furthermore, variables like inflammatory markers and sleep quality, which may affect glymphatic function, were not accounted for. Subsequent studies should conduct multi-center, large-sample longitudinal follow-ups, and combine multimodal imaging and biomarkers to further clarify the causal influences between NSCLC, glymphatic function, and cognitive impairment.

Conclusion

Glymphatic dysfunction, indicated by a decreased ALPS index, may contribute to cognitive dysfunction in NSCLC patients. Besides, impaired glymphatic function partially mediates the association between lung cancer and cognitive decline, and advanced age further exacerbates this risk. This discovery not only offers a new perspective for understanding the pathologic mechanism of cognitive impairments associated with lung cancer, but also lays a foundation for early identification and intervention strategies.

Disclosure of conflict of interest

None.

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