BMC Medical Imaging

RESEARCH

Open Access

Assessing neonatal brain glymphatic system development using diffusion tensor imaging along the perivascular space and choroid plexus volume

Ting Peng[1,2†], Ying Lin[2†], Xin Xu[3], Jiaqi Li[1], Miaoshuang Liu[3], Chaowei Zhang[4], Xiaohui Liao[1], Xiaoshan Ji[1], Zhongmeng Xiong[1], Zhuoyang Gu[5], Xinyi Cai[5], Tianli Tao[5], Yajuan Zhang[5], Lixuan Zhu[5], Deyi Zhuang[2], Xianghui Huang[2], Man Xiong[6], Peng Zhang[1*], Jungang Liu[7*] and Guoqiang Cheng[1,2*]

Abstract

Purpose Neonatal brain development constitutes a critical period of structural and functional maturation underpinning sensory, motor, and cognitive capacities. The glymphatic system—a cerebral waste clearance network—remains poorly understood in neonates. We investigated non-invasive magnetic resonance imaging (MRI) biomarkers of glymphatic system and their developmental correlates in neonates.

Methods In 117 neonates undergoing high-resolution T1-weighted and diffusion MRI, we quantified two glymphatic metrics: (1) diffusion tensor imaging along the perivascular space (DTI-ALPS) index, reflecting perivascular fluid dynamics; (2) choroid plexus (CP) volume, a cerebrospinal fluid (CSF) production marker. Associations with postmenstrual age (PMA) at MRI scan, gestational age (GA), birth weight (BW), and sex were analyzed using covariate-adjusted models.

Results Preterm neonates displayed significantly reduced DTI-ALPS indices versus term neonates (total index: 1.01 vs. 1.05, $P=0.002$), with reductions persisting after adjustment ($P<0.05$). CP volumes showed right-dominant pre-adjustment differences (preterm: 0.33 vs. term: 0.39, $P=0.039$) that attenuated post-adjustment ($P=0.348$). DTI-ALPS indices demonstrated transient correlations with PMA/GA/BW in unadjusted analyses ($P<0.05$), whereas CP volumes maintained robust PMA associations post-adjustment in all neonates ($P=0.037$) and term subgroup ($P=0.013$). No significant effects of sex on both metrics were observed.

†Ting Peng, Ying Lin and Xin Xu contributed equally to this work.

*Correspondence:
Peng Zhang
pzhang_zp@fudan.edu.cn
Jungang Liu
jgliu_XMChospital@hotmail.com
Guoqiang Cheng
gqcheng_cm@fudan.edu.cn

Full list of author information is available at the end of the article

Conclusion Our findings reveal prematurity-associated delays in glymphatic maturation, rather than biological sex. The persistent PMA-CP volume relationship suggests developmental regulation of CSF production, while attenuated DTI-ALPS correlations highlight covariate-mediated effects. These glymphatic metrics show potential for monitoring neurodevelopmental trajectories, though longitudinal validation is required to establish their clinical utility in neonatal care.

Clinical trial number Not applicable.

Keywords Neonate, Diffusion tensor imaging along the perivascular space, Choroid plexus, Glymphatic system

Introduction

Neonatal brain development represents a critical period characterized by profound structural and functional maturation. During this phase, the brain undergoes near-completion of neuronal migration, rapid synaptogenesis, and accelerated axonal myelination at the microscopic level [1–3]. Macroscopically, cortical expansion through increased surface area and significant thickening establishes the foundation for sensory, motor, and cognitive functions [4–7]. These processes exhibit heightened vulnerability in preterm neonates, whose incomplete brain maturation at birth elevates risks for neurodevelopmental impairments [8–11]. Understanding brain developmental trajectories during this period, especially in preterm populations, is vital for deciphering key mechanisms and guiding early interventions.

The glymphatic system, a recently discovered brain clearance pathway, plays a crucial role in maintaining cerebral homeostasis by facilitating metabolic waste removal, preventing neurotoxic accumulation, and mitigating neuroinflammation [12, 13]. Central to this system is cerebrospinal fluid (CSF), predominantly produced by the choroid plexus (CP), which enters brain tissue via astrocytic aquaporin-4 (AQP4) water channels. Through dynamic exchange with interstitial fluid (ISF), CSF enables waste clearance along perivascular spaces (PVS), thereby supporting neural health [14, 15]. While glymphatic dysfunction has been extensively studied in neurodegenerative and neurodevelopmental disorders, its developmental trajectory and functionality during the neonatal period remain poorly understood [16–19].

Emerging evidence suggests that the glymphatic system undergoes critical maturation in early life. Kim et al. observed an inverse relationship between basal ganglia PVS fraction (a glymphatic biomarker) and postmenstrual age (PMA) at MRI scan (hereafter referred to as PMA), with preterm birth altering PVS volume [20]. Similarly, Lin et al. reported a positive correlation between the diffusion tensor imaging along the perivascular space (DTI-ALPS) index (another glymphatic biomarker) and PMA, alongside reduced ALPS indices in preterm neonates [21]. Complementary work by El-Khoury et al. demonstrated gestational age (GA)-dependent increases in perivascular astrocytic endfoot coverage, a structural prerequisite for glymphatic function [22]. Collectively, these findings highlight progressive glymphatic development during the perinatal period and its vulnerability in preterm birth. However, the mechanisms underlying disrupted maturation—such as astrocyte immaturity or altered CSF dynamics—require further investigation.

Historically, glymphatic function has been evaluated through invasive intrathecal gadolinium injections to visualize CSF-ISF exchange [23]. However, this approach is impractical for neonates due to procedural risks [24, 25]. Recent advances in non-invasive MRI biomarkers, including the DTI-ALPS index (quantifying water diffusivity along PVS) and CP volume (reflecting CSF production and clearance capacity), provide a comprehensive framework for studying neonatal glymphatic development [26–29].

Critical knowledge gaps persist in this field. First, systematic investigations into preterm birth's impact on glymphatic development are still lacking. Second, the interplay between glymphatic function, PMA, GA, birth weight (BW), and sex differences remains underexplored. This study investigates neonatal glymphatic development by integrating DTI-ALPS indices and CP volume, addressing three objectives: (1) comparing glymphatic metrics between preterm and term neonates; (2) examining relationships with PMA, GA, and BW; (3) exploring potential sex-specific patterns. We hypothesize that preterm birth, but not biological sex, significantly impacts glymphatic maturation. Clarifying these dynamics may advance neonatal brain health assessment and inform early interventions for high-risk populations.

Methods

Participants

This study was approved by the Ethics Committee of Children's Hospital in accordance with the Declaration of Helsinki (2013). Written informed consent was obtained from all parents or guardians. Between January 2023 and April 2024, 268 neonates (GA range: 23–42 weeks) were recruited. Exclusion criteria included: (1) PMA outside 35–45 weeks; (2) congenital malformations, chromosomal abnormalities, infections, or genetic metabolic disorders; (3) severe birth asphyxia or respiratory failure; and (4) cranial abnormalities including brain injury,

intracranial hemorrhage, or seizures. Clinically diagnosed infections (e.g., meningitis) were excluded through rigorous screening to enhance sample homogeneity and internal validity. The final cohort included 117 neonates. Notably, systemic inflammatory biomarkers (e.g., CRP, IL-6) and maternal infection histories were not routinely collected, potentially limiting adjustment for inflammatory confounders. Study population 1 (DTI-ALPS analysis, $n = 100$) excluded cases with missing/poor-quality diffusion MRI (dMRI) data and one twin from each pair, while Study population 2 (CP volume analysis, $n = 90$) followed analogous exclusion criteria for structural MRI (sMRI) data (Fig. 1).

MRI acquisition

All scans were conducted on a 3-Tesla MRI system (uMR890, United Imaging, Shanghai, China) with a 64-channel head coil. Foam cushions and noise-canceling headphones minimized motion artifacts and noise interference. High-resolution 3D T1-weighted sMRI data (0.8 mm isotropic resolution) were obtained sagittally using parameters optimized for neonatal imaging: repetition time (TR) = 6.7 ms, echo time (TE) = 2.3 ms, flip angle = 8°, acceleration via AI-assisted compressed sensing (ACS, United Imaging), matrix = 320 × 300, FOV = 256 × 240 mm. This protocol balanced scan duration (< 4 min) and spatial resolution to mitigate partial volume effects (PVEs)—critical for small neonatal brain structures. Preterm neonates were scanned at near-term equivalent age (≥ 36 weeks) to minimize brain size differences on segmentation accuracy. The dMRI data employed 72 directions with three b-values (500, 1,000, 3,000 s/mm^2) and dual phase-encoding directions, using axial acquisition: TR = 3,016 ms, TE = 77.1 ms, flip angle = 90°, multi-band acceleration factor = 4, matrix = 140 × 140, FOV = 210 × 210 mm, slice thickness = 1.5 mm [30].

Image preprocessing

sMRI data preprocessing involved: (1) quality control for motion artifacts or missing slices; (2) automated brain segmentation (United Imaging Intelligence uAI Discover Brain System); (3) cortical reconstruction via Infant FreeSurfer (v7.1.1; https://surfer.nmr.mgh.harvard.edu/fswiki/infantFS) [31]; and (4) neuroradiologist verification of segmentation and reconstruction accuracy.

For dMRI data, preprocessing utilized MRtrix3 (v3.0.4; https://www.mrtrix.org/) and DSI Studio (v2022; https://dsi-studio.labsolver.org/), including: (1) data qualit y assessment; (2) denoising via random matrix theory; (3) Gibbs ringing artifacts removal; (4) motion/distortion correction; (5) bias field correction; (6) background masking in DSI Studio; (7) DTI reconstruction; and (8) fiber tracking [32, 33].

DTI-ALPS index calculation

Following established methods, bilateral 3-mm regions of interest (ROIs) were placed at the lateral ventricle body level on projection and association fibers [34, 35]. Fiber orientation and diffusivities along x- (right-left; Dxx), y- (antero-posterior; Dyy), and z-axes (infero-superior; Dzz) within ROIs were obtained. The DTI-ALPS index was computed as: DTI-ALPS index = mean (Dxxproj, Dxxassoc)/ mean (Dyyproj, Dzzassoc) [36]. Separate indices were calculated for each hemisphere, and the total DTI-ALPS index was determined by averaging these values.

CP volume estimation

CP volumes were automatically segmented and reconstructed from 3D T1-weighted images using the United

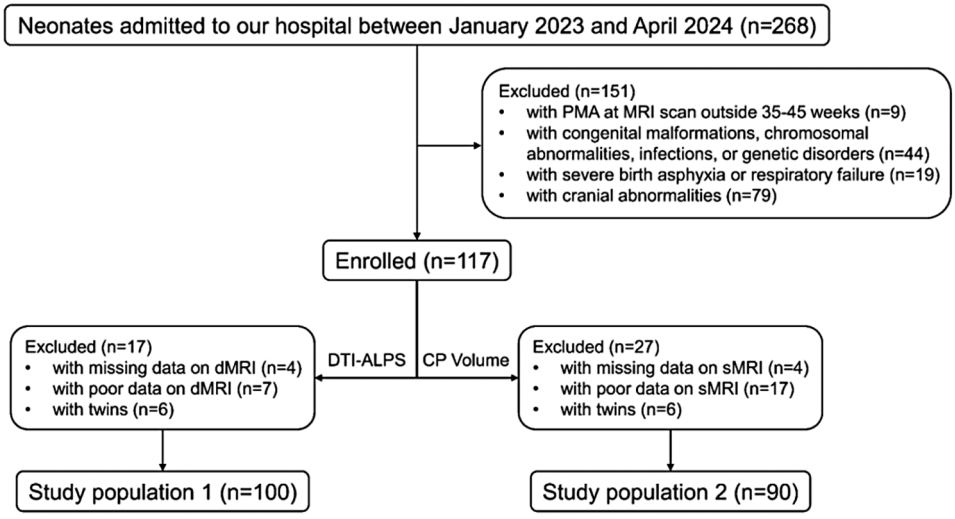

Fig. 1 The flow chart of study population selection

Table 1 Comparison of DTI-ALPS index between term and preterm neonates

Variables	Term neonates (*n* = 42)	Preterm neonates (*n* = 58)	*P*-value
Total DTI-ALPS index	1.05(1.01,1.11)	1.01(0.96,1.08)	0.002
Left DTI-ALPS index	1.04(0.99,1.11)	1.01(0.95,1.08)	0.022
Right DTI-ALPS index	1.04(1.00,1.11)	1.01(0.96,1.09)	0.023

Abbreviations: DTI-ALPS, diffusion tensor imaging along the perivascular space

Imaging Intelligence uAI Discover Brain System and Infant FreeSurfer, referenced to the Desikan-Killiany Atlas. Volumes were expressed as a ratio to the estimated total intracranial volume (eTIV) and multiplied by 1,000, in accordance with previous recommendations [37]. The total volume was represented as the average of the left and right hemisphere volumes.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (normal distribution) or median (interquartile range) (non-normal), and categorical variables as frequencies. Group comparisons utilized Mann-Whitney U tests (non-parametric), independent samples t-tests (parametric), or chi-square tests (categorical). Generalized linear models (GLMs) evaluated preterm-term differences in DTI-ALPS index and CP volume, adjusting for PMA and sex, as PMA reflects neurodevelopmental maturity at the time of imaging and sex differences in brain anatomy are widely reported [38, 39]. Sex effects were assessed by adjusting for PMA to account for total developmental stage confounds. Spearman's correlations examined unadjusted associations, while partial correlations controlled for covariates selected based on known biological plausibility, potential confounding pathways, and previous literature [21, 40]. Specifically, PMA analyses adjusted for GA and sex to isolate PMA effects from prenatal maturity and sex-related variability, GA analyses adjusted for PMA and sex to evaluate prenatal maturity independent, and BW analyses adjusted for PMA and sex to disentangle BW effects from developmental stage and sex differences. All analyses used R software (v4.2.3), with two-tailed $P < 0.05$ considered significant.

Results

Demographic characteristics

Demographic features of the study populations are detailed in Supplementary Tables S1-S2. While sex distributions were comparable between term and preterm groups (all $P > 0.10$), preterm neonates underwent MRI scans at earlier PMA, consistent with their clinical timelines.

Between-group comparisons of DTI-ALPS index and CP volume

Preterm neonates demonstrated significantly lower DTI-ALPS indices compared to term neonates across all measurements (Total index: 1.01 vs. 1.05, $P = 0.002$; Left: 1.01 vs. 1.04, $P = 0.022$; Right: 1.01 vs. 1.04, $P = 0.023$) (Table 1; Fig. 2a, Supplementary Fig. S1). The total index difference remained significant after adjusting for covariates ($P < 0.05$). No sex-specific effects were observed on indices (Fig. 2b).

While preterm neonates initially exhibited smaller right CP volumes than term neonates (0.33 vs. 0.39, $P = 0.039$) (Table 2; Fig. 3a), this difference lost statistical significance after covariates adjustment ($P = 0.348$).

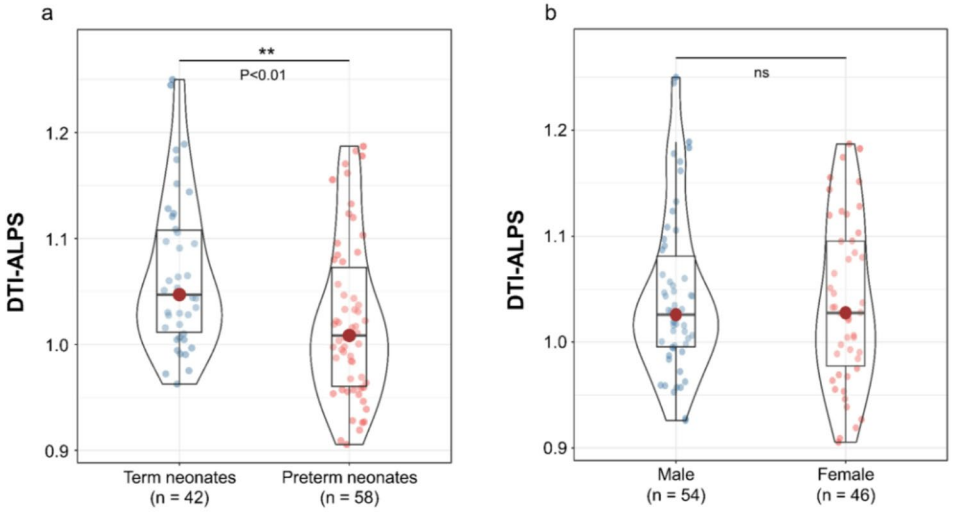

Fig. 2 Comparative analysis of the diffusion tensor imaging along the perivascular space (DTI-ALPS) index by gestational age and sex (**a**) Preterm neonates exhibited lower DTI-ALPS indices compared to term neonates, even after adjusting for postmenstrual age (PMA) at MRI scan and sex. (**b**) No significant sex-based differences in the DTI-ALPS indices among neonates. The double asterisks (**) indicated a statistically significant difference ($P < 0.01$) between the two groups

Table 2 Comparison of choroid plexus volume between term and preterm neonates

Variables	Term neonates (*n* = 35)	Preterm neonates (*n* = 55)	*P*-value
Total CP volume	0.37(0.29,0.48)	0.30(0.23,0.43)	0.061
Left CP volume	0.35(0.24,0.52)	0.29(0.19,0.46)	0.153
Right CP volume	0.39 ± 0.15	0.33 ± 0.12	0.039

Abbreviations: CP, choroid plexus

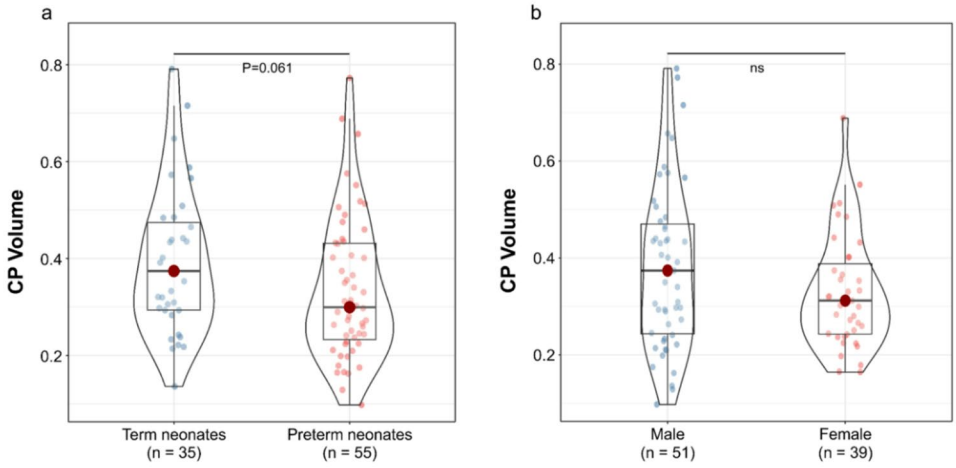

Fig. 3 Comparative analysis of choroid plexus (CP) volume by gestational age and sex (**a**) Preterm neonates tended to have lower CP volumes compared to term neonates; however, these differences did not reach statistical significance. (**b**) No significant differences in CP volumes based on sex among neonates

The marginal pre-adjustment difference suggests potential developmental variations that may be confounded by maturation-related factors. Sex did not significantly impact neonatal CP volume (Fig. 3b).

Associations of DTI-ALPS index with PMA, GA and BW

DTI-ALPS indices showed positive correlations with PMA across all neonates ($P = 0.008$), but not within term/preterm subgroups (Fig. 4). These relationships diminished after adjusting for GA and sex (Supplementary Tables S3). While initial correlations with GA ($P = 0.009$) and BW ($P = 0.022$) were observed among all neonates, these did not persist following adjustment (Supplementary Fig. S2).

Associations of CP volume with PMA, GA and BW

CP volumes exhibited stronger positive correlations with PMA in all neonates and term subgroup, maintaining significant even after adjustment (All neonates: $P = 0.037$; Term subgroup: $P = 0.013$; see Fig. 5 and Supplementary Tables S4). No significant correlations emerged with GA or BW in all neonates (Supplementary Fig. S3).

Discussion

Our multiparametric MRI study reveals three key findings regarding neonatal glymphatic development: (1) Preterm neonates demonstrated bilaterally reduced DTI-ALPS indices and right-dominant CP volume reductions compared to term neonates; (2) Neither glymphatic metric exhibited sex-based differences; (3) While PMA, GA, and BW showed transient correlations with DTI-ALPS indices in all neonates, CP volumes maintained robust PMA associations even after adjustment in all neonates and term subgroup.

Before elaborating on biological implications, critical methodological constraints must be foregrounded. The cross-sectional design precludes causal inferences between developmental parameters (PMA/GA/BW) and glymphatic metrics. Specifically, concurrent assessment of exposures and outcomes introduces temporal ambiguity—we cannot determine whether observed brain differences drive developmental outcomes or vice versa. This fundamental limitation necessitates interpreting all correlations as hypothesis-generating associations requiring longitudinal confirmation.

The findings suggest that prematurity may delay the maturation of the brain's glymphatic system, supporting hypotheses by Lin et al. that prematurity could impair astrocyte functionality during embryonic development, thus hindering glymphatic maturation [21, 41, 42]. Notably, Lin et al. further identified birth asphyxia—rather than germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH)—as a critical modulator of preterm glymphatic dysfunction [43]. Furthermore, our observed

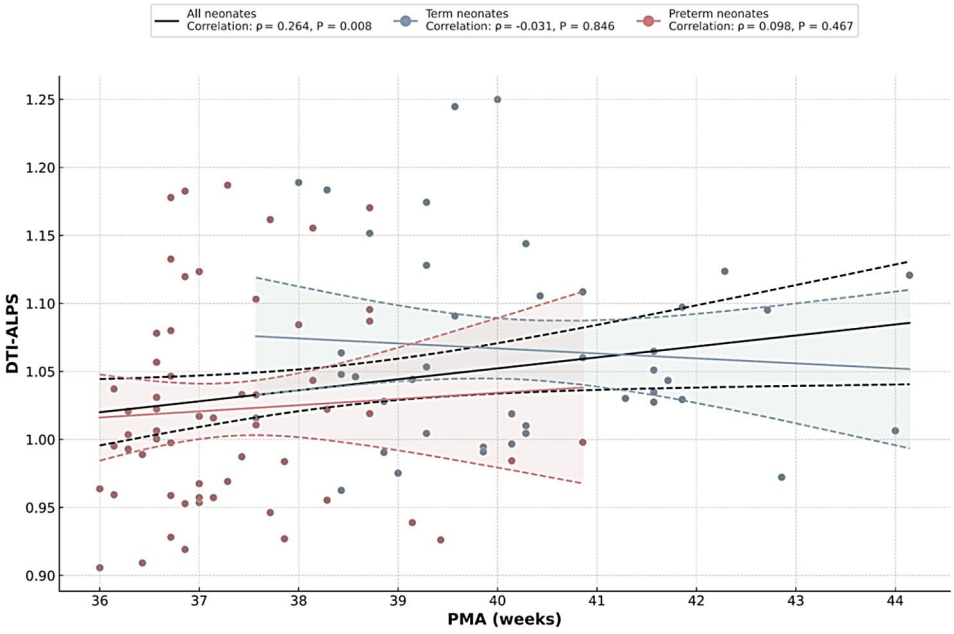

Fig. 4 Correlation between postmenstrual age (PMA) at MRI scan and the diffusion tensor imaging along the perivascular space (DTI-ALPS) index This figure illustrated the correlation between PMA at MRI scan and the DTI-ALPS index in all neonates, showing a significant relationship initially. However, this correlation was not observed when data were analyzed separately for term and preterm neonates. Furthermore, after adjustments were made for gestational age and sex, the correlation between PMA and DTI-ALPS index disappeared in all neonates

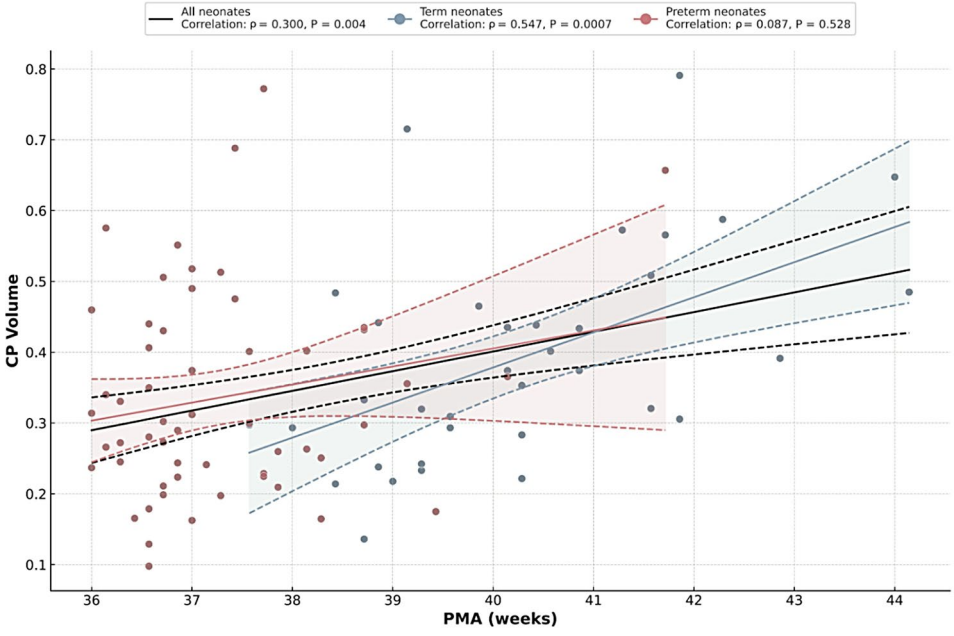

Fig. 5 Correlation between postmenstrual age (PMA) at MRI scan and choroid plexus (CP) volume This figure showed that PMA at MRI scan was significantly correlated with CP volume in both all neonates and specifically in term neonates. However, this correlation was not observed in preterm neonates. Notably, after adjustments were made for gestational age and sex, these relationships persisted

hemisphere-specific disparities in DTI-ALPS indices extends prior work, highlighting potential lateralization in glymphatic maturation that merits targeted investigation [44]. Research by Kim et al. on glymphatic function, assessed through PVS analysis, also suggests that prematurity might impact these spaces within the basal ganglia due to elevated AQP4 levels in preterm neonates [20, 45]. Although CP volume serves as a CSF production proxy in studies of conditions like Alzheimer's disease and fibromyalgia, its use in neonatal populations

remains underexplored [27, 46]. Our exploratory analysis tentatively suggests that preterm birth may associate with altered CP volumetric trajectories, as evidenced by pre-adjustment right-dominant reductions. However, the attenuation of this effect after covariate control highlights the complex interplay between prematurity, maturation-related factors, and CP development. The increase of CP volume in adults often indicates pathological states, while in neonates, it appears to reflect their developmental immaturity [47, 48]. This can be a reason for future mechanistic studies that combine CSF dynamics with neuroimaging biomarkers.

The absence of sex effects on glymphatic metrics contrasts with reported sex differences in neonatal brain injury, related inflammation, and cortical morphometric similarity [49, 50]. This discrepancy may be attributed to comparable numbers of astrocytes and sex hormone levels during this developmental stage [51, 52]. Nevertheless, our cross-sectional design cannot exclude potential sex-dependent effects manifesting at later developmental stages.

Moreover, the PMA-DTI-ALPS association of all neonates in unadjusted analyses corroborates prior work, yet its attenuation after GA/sex adjustment suggests covariate-mediated effects rather than direct biological relationships [21]. Similarly, the null GA/BW-DTI-ALPS associations post-adjustment highlight the challenge of disentangling intertwined developmental factors in observational studies.

The sustained PMA-CP volume correlations were observed in both all neonates and term neonates, potentially indicative of enhanced CSF production and advancing physiological maturation. This is consistent with literature that reports an increase in CP thickness and volume during the early stages of life [53, 54]. Notably, the non-significant PMA-CP volume relationship of preterm infants warrants cautious interpretation. While we propose three speculative explanations for this observation—(1) non-linear CP growth trajectories; (2) prematurity-induced disruption of CP maturation [55]; (3) limited statistical power from sample heterogeneity—these hypotheses remain provisional and require rigorous validation in longitudinal cohorts.

In summary, the glymphatic metrics hold significant clinical value as potential biomarkers for early detection and precision interventions in neurodevelopmental disorders. In neonatal intensive care units (NICUs) settings, longitudinal tracking of these metrics in high-risk preterm neonates could enable risk stratification, identifying individuals at increased neurodevelopmental risk and facilitating early screening [56]. To translate this potential into clinical practice, practical challenges in MRI integration must be addressed. These include motion artifact minimization, scan duration reduction, and compatibility with life-support equipment [57]. Emerging technologies such as accelerated MRI sequences, motion-tolerant protocols, and compact neonatal-specific MRI coils could enhance feasibility [58, 59]. Additionally, combining brief, targeted MRI assessments with routine clinical care windows and leveraging automated AI-driven analysis pipelines may streamline workflow integration [60]. Furthermore, these glymphatic metrics may serve as a robust supplement to electrophysiological measurements (e.g., aEEG), aiding in the detection of subclinical cases with mild perinatal injuries that remain undetected by conventional neuroimaging examinations [61, 62]. For neonates exhibiting persistently low DTI-ALPS indices or aberrant CP growth patterns, early targeted interventions such as nutritional optimization and neurodevelopmental therapies may help promote neural circuit maturation [63]. Concurrently, integrating these metrics with established neurobehavioral assessment tools (e.g., Hammersmith Infant Neurological Examination) could optimize predictive models for cognitive and motor developmental delays, enhance early identification of high-risk children, and ultimately strengthen the evidence base for personalized intervention strategies [64].

We acknowledge several limitations in our study. Firstly, the cross-sectional nature of our study restricts causal inference between developmental parameters and glymphatic metrics, as it only captures a single time point and cannot track developmental trajectories. Longitudinal studies with larger sample size and serial MRI acquisitions are essential to establish temporal sequences of glymphatic maturation [65]. Second, while we excluded neonates with overt pathological conditions, some potential confounders remain. In particular, subclinical maternal or neonatal inflammation—a known contributor to preterm birth—may affect glymphatic function by altering perivascular fluid dynamics and CP function, potentially confounding the observed associations between prematurity and DTI-ALPS index/CP volume [66]. However, our dataset lacked biomarkers of inflammation (e.g., maternal CRP levels, neonatal cytokine profiles) and detailed maternal infection histories, precluding direct adjustment for this confounder. Future longitudinal studies incorporating inflammatory markers are needed to disentangle the interplay between prematurity, inflammation, and glymphatic function. Third, while our high-resolution protocol and AI segmentation substantially reduce PVEs, residual uncertainties persist particularly for small structures like the CP. Preterm neonates' smaller absolute brain dimensions combined with intrinsically irregular CSF-brain interfaces may introduce systematic measurement biases. Future ultra-high-field 7T studies or advanced PVEs correction algorithms could further resolve these challenges. Fourth, caution is warranted regarding the relationship between the DTI-ALPS

index and glymphatic clearance function, as the direct linkage of this index to human glymphatic function has not been rigorously validated through pathophysiological research [67]. Although our study attempted to assess glymphatic functionality by incorporating CP volume, future research should employ additional corroborative metrics to enhance the credibility and interpretability of the findings [68].

In conclusion, this study establishes prematurity—rather than sex—as a key modulator of neonatal glymphatic maturation. By employing non-invasive multiparametric MRI, we present the translational potential of DTI-ALPS indies and CP volume for understanding preterm brain development. Future longitudinal investigations should elucidate how these biomarkers interact with neurodevelopmental outcomes, advancing personalized intervention strategies for at-risk neonates.

Abbreviations

AQP4	Astrocytic aquaporin-4
BW	Birth weight
CP	Choroid plexus
CSF	Cerebrospinal fluid
DTI-ALPS	Diffusion tensor imaging along the perivascular space
GA	Gestational age
ISF	Interstitial fluid
MRI	Magnetic resonance imaging
PVS	Perivascular spaces
PMA	Postmenstrual age
PVEs	Partial volume effects
ROIs	Regions of interest
TE	Echo time
TR	Repetition time

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12880-025-01673-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
TP, YL, and XX contributed to data processing, analysis, and the writing of the original manuscript. JL, ML, CZ, XL, XJ, and ZX were responsible for participant recruitment and data collection. ZG, XC, TT, YZ, and LZ were responsible for image preprocessing and quality control. DZ, XH, and MX coordinated the project development. PZ, JLiu, and GC oversaw the study design and project coordination. All authors reviewed and approved the final manuscript, providing input on the interpretation of the results and contributing to revisions.

Funding
This study was supported by the Fujian Provincial Health Commission Science and Technology Plan Project (Grant No. 2021ZQNZD017) and Key Program of the Xiamen Medical and Health (Grant No. 3502Z20234013).

Data availability
All data generated or analyzed during this study are included in this published article. The raw data are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Xiamen Children's Hospital (approval no.2022-026). Informed consent was obtained from all participants' legal guardians prior to their inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neonatology, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai 201102, China
[2]Fujian Key Laboratory of Neonatal Diseases, Children's Hospital of Fudan University (Xiamen Branch), Xiamen Children's Hospital, Xiamen 361006, China
[3]Department of Neonatology, Children's Hospital of Fudan University (Xiamen Branch), Xiamen Children's Hospital, Xiamen 361006, China
[4]Department of Neonatology, People's Hospital of Longhua, Shenzhen 518000, China
[5]School of Biomedical Engineering, ShanghaiTech University, Shanghai 201102, China
[6]State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Fudan University, Shanghai 200032, China
[7]Department of Radiology, Children's Hospital of Fudan University (Xiamen Branch), Xiamen Children's Hospital, Xiamen 361006, China

Received: 24 November 2024 / Accepted: 11 April 2025
Published online: 17 April 2025

References

1. Sidman RL, Rakic P. Neuronal migration, with special reference to developing human brain: a review. Brain Res. 1973;62(1):1–35.
2. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997;387(2):167–78.
3. Ortinau C, Neil J. The neuroanatomy of prematurity: normal brain development and the impact of preterm birth. Clin Anat. 2015;28(2):168–83.
4. Meredith Weiss S, Aydin E, Lloyd-Fox S, Johnson MH. Trajectories of brain and behaviour development in the womb, at birth and through infancy. Nat Hum Behav. 2024;8(7):1251–62.
5. Pagnozzi AM, van Eijk L, Pannek K, Boyd RN, Saha S, George J, et al. Early brain morphometrics from neonatal MRI predict motor and cognitive outcomes at 2-years corrected age in very preterm infants. NeuroImage. 2023;267:119815.
6. Fenchel D, Dimitrova R, Seidlitz J, Robinson EC, Batalle D, Hutter J, et al. Development of microstructural and morphological cortical profiles in the neonatal brain. Cereb Cortex. 2020;30(11):5767–79.
7. Fukami-Gartner A, Baburamani AA, Dimitrova R, Patkee PA, Ojinaga-Alfageme O, Bonthrone AF, et al. Comprehensive volumetric phenotyping of the neonatal brain in Down syndrome. Cereb Cortex. 2023;33(14):8921–41.
8. Pickier RH, McGrath JM, Reyna BA, McCain N, Lewis M, Cone S, et al. A model of neurodevelopmental risk and protection for preterm infants. Adv Neonatal Care. 2013;13(Suppl 5):S11–20.
9. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110–24.
10. Kelly C, Dhollander T, Harding IH, Khan W, Beare R, Cheong JL, et al. Brain tissue microstructural and free-water composition 13 years after very preterm birth. NeuroImage. 2022;254:119168.
11. Christensen R, Chau V, Synnes A, Guo T, Ufkes S, Grunau RE et al. Preterm sex differences in neurodevelopment and brain development from early life to 8 years. J Pediatr. 2024;114271.
12. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The glymphatic system: A beginner's guide. Neurochem Res. 2015;40(12):2583–99.
13. Yankova G, Bogomyakova O, Tulupov A. The glymphatic system and meningeal lymphatics of the brain: new Understanding of brain clearance. Rev Neurosci. 2021;32(7):693–705.

14. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol. 2018;17(11):1016–24.
15. Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis J. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. J Clin Invest. 2017;127(9):3210–9.
16. Li X, Ruan C, Zibrila AI, Musa M, Wu Y, Zhang Z, et al. Children with autism spectrum disorder present glymphatic system dysfunction evidenced by diffusion tensor imaging along the perivascular space. Med (Baltim). 2022;101(48):e32061.
17. Cai X, Chen Z, He C, Zhang P, Nie K, Qiu Y, et al. Diffusion along perivascular spaces provides evidence interlinking compromised glymphatic function with aging in Parkinson's disease. CNS Neurosci Ther. 2023;29(1):111–21.
18. Zhang C, Xu K, Zhang H, Sha J, Yang H, Zhao H, et al. Recovery of glymphatic system function in patients with Temporal lobe epilepsy after surgery. Eur Radiol. 2023;33(9):6116–23.
19. Chen Y, Wang M, Su S, Dai Y, Zou M, Lin L, et al. Assessment of the glymphatic function in children with attention-deficit/hyperactivity disorder. Eur Radiol. 2024;34(3):1444–52.
20. Kim JY, Nam Y, Kim S, Shin NY, Kim HG. MRI-visible perivascular spaces in the neonatal brain. Radiology. 2023;307(2):e221314.
21. Lin S, Guo M, Liang Q, Lin X, Chen S, Li Y, et al. Evaluation of glymphatic system development in neonatal brain via diffusion analysis along the perivascular space index. Ann Neurol. 2024;96(5):970–80.
22. El-Khoury N, Braun A, Hu F, Pandey M, Nedergaard M, Lagamma EF, et al. Astrocyte end-feet in germinal matrix, cerebral cortex, and white matter in developing infants. Pediatr Res. 2006;59(5):673–9.
23. Lee H, Choi SH, Anzai Y. Glymphatic MRI techniques in sleep and neurodegenerative diseases. Curr Opin Pulm Med. 2022;28(6):499–510.
24. Taoka T, Naganawa S. Gadolinium-based contrast media, cerebrospinal fluid and the glymphatic system: possible mechanisms for the deposition of gadolinium in the brain. Magn Reson Med Sciences: MRMS: Official J Japan Soc Magn Reson Med. 2018;17(2):111–9.
25. Patel M, Atyani A, Salameh JP, McInnes M, Chakraborty S. Safety of intrathecal administration of Gadolinium-based contrast agents: A systematic review and Meta-Analysis. Radiology. 2020;297(1):75–83.
26. Naganawa S, Taoka T. The glymphatic system: A review of the challenges in visualizing its structure and function with MR imaging. Magn Reson Med Sci. 2020;21(1):182–94.
27. Tu Y, Li Z, Xiong F, Gao F. Decreased DTI-ALPS and choroid plexus enlargement in fibromyalgia: a preliminary multimodal MRI study. Neuroradiology. 2023;65(12):1749–55.
28. Andica C, Kamagata K, Takabayashi K, Kikuta J, Kaga H, Someya Y, et al. Neuroimaging findings related to glymphatic system alterations in older adults with metabolic syndrome. Neurobiol Dis. 2023;177:105990.
29. Tadayon E, Pascual-Leone A, Press D, Santarnecchi E. Choroid plexus volume is associated with levels of CSF proteins: relevance for Alzheimer's and Parkinson's disease. Neurobiol Aging. 2020;89:108–17.
30. Howell BR, Styner MA, Gao W, Yap PT, Wang L, Baluyot K, et al. The UNC/UMN baby connectome project (BCP): an overview of the study design and protocol development. NeuroImage. 2019;185:891–905.
31. Zöllei L, Iglesias JE, Ou Y, Grant PE, Fischl B. Infant freesurfer: an automated segmentation and surface extraction pipeline for T1-weighted neuroimaging data of infants 0–2 years. NeuroImage. 2020;218:116946.
32. Yeh FC. Shape analysis of the human association pathways. NeuroImage. 2020;223:117329.
33. Tournier JD, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. NeuroImage. 2019;202:116137.
34. Xu K, Zhang J, Xing C, Xu X, Yin X, Wu Y, et al. Evaluation of glymphatic system activity by diffusion tensor image analysis along the perivascular space in presbycusis. Cns Neurosci Ther. 2023;30(3):e14458.
35. Pu W, Wei S, Qiu M, Chen X, Zou W, Ge Y, et al. Dysfunction of the glymphatic system in childhood absence epilepsy. Front Neurosci. 2023;17:1312676.
36. Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn J Radiol. 2017;35(4):172–8.
37. Xie Y, Zhu H, Yao Y, Liu C, Wu S, Zhang Y, et al. Enlarged choroid plexus in relapsing-remitting multiple sclerosis may lead to brain structural changes through the glymphatic impairment. Mult Scler Relat Disord. 2024;85:105550.
38. Tomasi D, Volkow ND. Measures of brain connectivity and cognition by sex in US children. JAMA Netw Open. 2023;6(2):e230157.
39. Gennatas ED, Avants BB, Wolf DH, Satterthwaite TD, Ruparel K, Ciric R, et al. Age-Related effects and sex differences in Gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. J Neurosci. 2017;37(20):5065–73.
40. López-Guerrero N, Alcauter S. Developmental trajectories and differences in functional brain network properties of preterm and At-Term neonates. Hum Brain Mapp. 2025;46(1):e70126.
41. Volpe JJ. Dysmaturation of premature brain: importance, cellular mechanisms, and potential interventions. Pediatr Neurol. 2019;95:42–66.
42. Disdier C, Awa F, Chen X, Dhillon SK, Galinsky R, Davidson JO, et al. Lipopolysaccharide-induced changes in the neurovascular unit in the preterm fetal sheep brain. J Neuroinflamm. 2020;17(1):167.
43. Lin S, Lin X, Liang Q, Chen S, Zhang Y, Li Y, et al. Glymphatic system in preterm neonates: developmental insights following birth asphyxia. J Magn Reson Imaging. 2025;61(4):1761–9.
44. Wu L, Zhang Z, Liang X, Wang Y, Cao Y, Li M, et al. Glymphatic system dysfunction in recovered patients with mild COVID-19: a DTI-ALPS study. iScience. 2024;27(1):108647.
45. Eidahl JML, Stray-Pedersen A, Rognum TO, Opdal SH. Aquaporin 4 expression in the hippocampus in sudden infant death syndrome and sudden unexplained death in childhood. J Chem Neuroanat. 2021;115:101962.
46. Choi JD, Moon Y, Kim HJ, Yim Y, Lee S, Moon WJ. Choroid plexus volume and permeability at brain MRI within the alzheimer disease clinical spectrum. Radiology. 2022;304(3):635–45.
47. Bravi B, Melloni EMT, Paolini M, Palladini M, Calesella F, Servidio L, et al. Choroid plexus volume is increased in mood disorders and associates with Circulating inflammatory cytokines. Brain Behav Immun. 2024;116:52–61.
48. Tadayon E, Pascual-Leone A, Press D, Santarnecchi E, Alzheimer's Disease Neuroimaging Initiative. Choroid plexus volume is associated with levels of CSF proteins: relevance for Alzheimer's and Parkinson's disease. Neurobiol Aging. 2020;89:108–17.
49. Wang Y, Zhu D, Zhao L, Wang X, Zhang Z, Hu B, et al. Profiling cortical morphometric similarity in perinatal brains: insights from development, sex difference, and inter-individual variation. NeuroImage. 2024;295:120660.
50. Kelly LA, Branagan A, Semova G, Molloy EJ. Sex differences in neonatal brain injury and inflammation. Front Immunol. 2023;14:1243364.
51. Marques F, Sousa JC, Brito MA, Pahnke J, Santos C, Correia-Neves M, et al. The choroid plexus in health and in disease: dialogues into and out of the brain. Neurobiol Dis. 2017;107:32–40.
52. Rurak GM, Simard S, Freitas-Andrade M, Lacoste B, Charih F, Van Geel A, et al. Sex differences in developmental patterns of neocortical astroglia: A mouse translatome database. Cell Rep. 2022;38(5):110310.
53. Madhukar M, Choudhary AK, Boal DK, Dias MS, Iantosca MR. Choroid plexus: normal size criteria on neuroimaging. Surg Radiol Anat. 2012;34(10):887–95.
54. Hashimoto H, Takemoto O, Nishimoto K, Moriguchi G, Nakamura M, Chiba Y. Normal growth curve of choroid plexus in children: implications for assessing hydrocephalus due to choroid plexus hyperplasia. J Neurosurg Pediatr. 2023;32(6):627–37.
55. Liu J, Feng ZC, Yin XJ, Chen H, Lu J, Qiao X. The role of antenatal corticosteroids for improving the maturation of choroid plexus capillaries in fetal mice. Eur J Pediatr. 2008;167(10):1209–12.
56. Spittle AJ, Anderson PJ, Tapawan SJ, Doyle LW, Cheong JLY. Early developmental screening and intervention for high-risk neonates - From research to clinical benefits. Semin Fetal Neonatal Med. 2021;26(3):101203.
57. Barkovich MJ, Li Y, Desikan RS, Barkovich AJ, Xu D. Challenges in pediatric neuroimaging. NeuroImage. 2019;185:793–801.
58. Dubois J, Alison M, Counsell SJ, Hertz-Pannier L, Hüppi PS, Benders MJNL. MRI of the neonatal brain: A review of methodological challenges and neuroscientific advances. J Magn Reson Imaging. 2021;53(5):1318–43.
59. Hughes EJ, Winchman T, Padormo F, Teixeira R, Wurie J, Sharma M, et al. A dedicated neonatal brain imaging system. Magn Reson Med. 2017;78(2):794–804.
60. Delannoy Q, Pham CH, Cazorla C, Tor-Díez C, Dollé G, Meunier H, et al. SegSRGAN: super-resolution and segmentation using generative adversarial networks - Application to neonatal brain MRI. Comput Biol Med. 2020;120:103755.
61. El-Dib M, Abend NS, Austin T, Boylan G, Chock V, Cilio MR, et al. Neuromonitoring in neonatal critical care part I: neonatal encephalopathy and neonates with possible seizures. Pediatr Res. 2023;94(1):64–73.
62. Santos MMD, Eilers IS, Werle TM, Trein GL, da Silva LM, Canton LEL, et al. Which aEEG patterns could predict neurodevelopmental outcome in preterm neonates? - A systematic review. Brain Dev. 2025;47(1):104315.

63. Spittle A, Treyvaud K. The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. Semin Perinatol. 2016;40(8):542–8.
64. Caesar R, Colditz PB, Cioni G, Boyd RN. Clinical tools used in young infants born very preterm to predict motor and cognitive delay (not cerebral palsy): a systematic review. Dev Med Child Neurol. 2021;63(4):387–95.
65. Cao Y, Chen RC, Katz AJ. Why is a small sample size not enough? Oncologist. 2024;29(9):761–3.
66. Mogensen FLH, Delle C, Nedergaard M. The glymphatic system (En)during inflammation. Int J Mol Sci. 2021;22(14):7491.
67. Taoka T, Ito R, Nakamichi R, Nakane T, Kawai H, Naganawa S. Diffusion tensor image analysis along the perivascular space (DTI-ALPS): revisiting the meaning and significance of the method. Magn Reson Med Sci. 2024;23(3):268–90.
68. Li H, Jacob MA, Cai M, Kessels RPC, Norris DG, Duering M, et al. Perivascular spaces, diffusivity along perivascular spaces, and free water in cerebral small vessel disease. Neurology. 2024;102(9):e209306.

Publisher's note