The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 3, 2025

ASSESSMENT OF ENLARGED PERIVASCULAR SPACES AND INDEX FOR DIFFUSIVITY ALONG THE PERIVASCULAR SPACES AS EMERGING NEUROIMAGING BIOMARKER OF NEUROLOGICAL DISEASE

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DOI: https://doi.org/10.5281/zenodo.14974244

Keywords
Acyl CoA-Carboxylase, Perivascular Space, Cerebrospinal Fluid, Intramural Periarterial Drainage, Intracranial Dural Parasagittal spaces.

Article History
Received on 18 January 2025
Accepted on 18 February 2025
Published on 05 March 2025

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Abstract

Background: The assessment of enlarged perivascular spaces (ePVS) and diffusivity along the perivascular spaces (DTI-ALPS) has gained significant attention as emerging biomarkers in neurological disease. These imaging markers provide insights into the glymphatic system, which plays a critical role in brain waste clearance and neurovascular health. Alterations in ePVS and DTI-ALPS have been linked to various conditions such as Alzheimer's disease, stroke, and hypertension, highlighting their potential for early diagnosis and monitoring of disease progression.

Objective: To Assess Enlarged Perivascular Spaces and Index for Diffusivity along the Perivascular Spaces as Emerging Neuroimaging Biomarker of Neurological Disease.

Methodology: This cross-sectional study was conducted at National Hospital, Lahore from July 2024 to December 2024. A sample size of 60 patients, aged between 18-65 years, with suspected neurological disorders was selected, excluding those with a history of brain trauma or prior treatment for malignancy. All patients underwent MRI using a 1.5T MRI machine, including T1, T2, and diffusion tensor imaging (DTI). Statistical analysis was performed using SPSS version 25, with cross-tabulation and T-test applied to compare the findings of DTI and conventional MRI sequences.

Results: The study included 56 patients, with 38 (67.9%) males and 18 (32.1%) females. Enlarged perivascular spaces (EPVS) were most commonly found in the basal ganglia (26.8%) and centrum semi ovale (25.0%), with severity increasing across grades 1–4. Greater EPVS burden correlated significantly ($p < 0.001$) with higher apparent diffusion coefficient (ADC) values, indicating microstructural brain changes. Patients with severe EPVS showed higher rates of motor (39.3%) and cognitive impairment (60.7%), with MMSE scores declining as EPVS severity increased. The strong association between EPVS, ADC values, and neurological dysfunction supports diffusion indices as a reliable tool for assessing neurodegenerative changes.

Conclusion: The study concluded that enlarged perivascular spaces (ePVS) and diffusion indices were valuable neuroimaging biomarkers for assessing neurological disease severity. Significant correlations between neurological disorder type,

MMSE scores, disease severity, and ADC values supported the role of glymphatic dysfunction in neurodegeneration. The findings highlighted the potential of diffusion-based imaging for early disease detection and monitoring cognitive decline, emphasizing its clinical relevance in neurological assessment.

INTRODUCTION

Virchow-Robin spaces or brain perivascular spaces are virtual spaces between the neurovascular system and the cranial meninges and were first explained by pathologists Rudolf Virchow and Charles Robin individually in the 19th century. They form routes within the subarachnoid spaces around the arterioles and venules, helping in the movement of cerebrospinal fluid and the exchange of intracellular substances, which supports the efficient removal of metabolic waste products from the brain. Although it was previously believed that the human brain lacked a lymphatic drainage system, recent findings suggest that the brain-wide perivascular space pathway may act as a "glymphatic" system.[1] The central nervous system (CNS) has traditionally been viewed as lacking lymphatic vasculature. However, some cerebrospinal fluid (CSF) drains into the cervical lymph nodes (LNs), though the mechanism of this process remained unclear.[2]

Perivascular Spaces (PVS) are a hallmark of Small Vessel Disease (SVD) and play a critical role in the brain's circulation and glymphatic drainage system. Conducting quantitative analyses of PVS on Magnetic Resonance Imaging (MRI) is essential for elucidating their connection to neurological diseases.[3] Subsequent studies used dynamic contrast-enhanced magnetic resonance imaging (MRI) to visualize the exchange of CSF and interstitial fluid (ISF) in the rat brain after intrathecal paramagnetic contrast administration. This led to the preliminary identification of the main anatomical structures and functions of the glymphatic system. The glymphatic system is a recently characterized brain-wide paravascular pathway that facilitates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF), enabling efficient clearance of solutes and waste from the brain. CSF flows into the brain along para-arterial channels, where it exchanges with ISF, which is subsequently cleared via para-venous pathways.[4]

Recent studies have revealed that meningeal lymphatic vessels (MLVs) play a role in regulating brain tumor drainage and influencing the efficacy of radiotherapy by modulating anti-tumor immunity. Central to glymphatic system research are advancements in imaging technologies, which have enabled the visualization of solute exchange and clearance within brain fluids. These innovations also facilitate the study of pathological changes associated with neurological disorders, deepening our understanding of their mechanisms.[5] Current advanced imaging methods focus on contrast agents or diffusion-weighted imaging techniques to evaluate the glymphatic system. The glymphatic system hypothesis describes a mechanism for clearing waste products from the brain. The term "glymphatic system" combines elements of the glial and lymphatic systems, reflecting its unique function. In this system, the perivascular space acts as a conduit, facilitating the flow of cerebrospinal fluid (CSF) into the brain parenchyma.[6] MRI using an intrathecal injection of the contrast agent as a CSF tracer for glymphatic function assessment has been reported in humans. Before those clinical studies, the key features of the glymphatic pathway were confirmed when contrast was used in rodents to observe the characteristics of cerebrospinal fluid flow.[7] An accurate, simple, and precise PVS rating scale is necessary to effectively investigate the diagnostic and prognostic significance of EPVS. Some investigators developed a visual PVS rating scale that allowed the rating of all grades of PVS severity on structural brain imaging.[8] In that scale, Basal ganglia and centrum semi vale PVS were rated as 0 (absent), 1 (1–10), 2 (11–20), 3 (21–40), and 4 (> 40), and midbrain PVS was rated as 0 (not visible) or 1 (visible). However, visual rating scales rely on subjective choices in the rating section and do not provide information on the morphology of the EPVS, which is less reliable and less efficient in large cross-sectional studies. Recent studies have focused on implementing automated methods to assess the number of EPVS and morphology including linearity, width.[9]

Material and Methods:
This cross-sectional study was conducted at National Hospital, Lahore, from July to December 2024, with a sample size of 56 patients aged 11-85 years. Participants were selected based on a history of neurological events and elevated intracranial pressure, and all provided informed consent. Exclusion criteria included a history of brain trauma, prior treatment for malignancy, and pregnancy. MRI scans were performed using a 1.5T MRI machine, including T1, T2, and diffusion tensor imaging (DTI). Convenient sampling was used, and data were analyzed using SPSS version 25, with cross-tabulation and T-tests to compare DTI findings with conventional MRI sequences.

Results:
Enlarged perivascular spaces (EPVS) and diffusivity indices have emerged as potential neuroimaging biomarkers for assessing neurological diseases. Understanding their correlation with cognitive function and disease severity could enhance early diagnosis and monitoring of disease progression. For this purpose, this study was conducted which included a total of 56 patients, of whom 18 (32.1%) were female and 38 (67.9%) were male. Enlarged perivascular spaces (EPVS) were most commonly found in the basal ganglia (26.8%) and centrum semi ovale (25.0%), with severity increasing across grades 1–4. Greater EPVS burden correlated significantly ($p < 0.001$) with higher apparent diffusion coefficient (ADC) values, indicating microstructural brain changes. Patients with severe EPVS showed higher rates of motor (39.3%) and cognitive impairment (60.7%), with MMSE scores declining as EPVS severity increased. The strong association between EPVS, ADC values, and neurological dysfunction supports diffusion indices as a reliable tool for assessing neurodegenerative changes. The correlation analysis demonstrated statistically significant relationships ($p < 0.001$) among the type of neurological disorder, MMSE scores, disease severity grades, and ADC values. The type of neurological disorder was positively correlated with MMSE ($\tau = 0.426$, $\rho = 0.623$) and negatively correlated with grades ($\tau = -0.464$, $\rho = -0.639$) and ADC values ($\tau = -0.390$, $\rho = -0.603$), indicating that more severe disorders were associated with cognitive decline and increased diffusion abnormalities. MMSE scores showed a strong inverse correlation with both grades ($\tau = -0.781$, $\rho = -0.898$) and ADC values ($\tau = -0.676$, $\rho = -0.860$), reinforcing the link between worsening cognitive function and disease progression. Additionally, grades and ADC values demonstrated a strong positive correlation ($\tau = 0.780$, $\rho = 0.909$), suggesting that increasing disease severity was associated with higher diffusivity.

Variable	Category	Frequency
Age Group	11-20	5
	21-30	7
	31-40	9
	41-50	8
	51-60	10
	61-70	7
	71-80	6
	81-85	4
Gender	Female	18
	Male	38
Type of Neurological Disorder	Motor	22
	Mild Cognitive	22
	Moderate Cognitive	12
	4	2
	5	1
	6	4
	7	6

Mini-Mental State Examination	8	6
	9	3
	12	1
	13	2
	14	2
	15	2
	16	2
	17	1
	18	1
	21	2
	22	6
	23	11
	24	4
Hypertension	No	41
	Yes	15
Diabetes	No	51
	Yes	5
Smoking	No	54
	Yes	2
Location	Basal Ganglia	15
	Centrum Semi Ovale	14
	Cerebral Small Vessels	8
	Mid Brain	13
	Pons	6
Grades	1	10
	2	11
	3	13
	4	22
ADC Value	.10	1
	.71	1
	.76	1
	.79	2
	.84	1
	.89	2
	.90	1
	.95	1
	.98	2
	1.00	2
	1.05	1
	1.17	3
	1.20	2
	1.25	3

Table No.1: The table summarizes data from 56 participants, detailing age, gender, neurological disorders, MMSE scores, and other health factors. The majority were male (67.9%) and in the 51–60 age range. Most had motor impairments or mild cognitive issues. MMSE scores varied, with many participants scoring between 7–9, indicating varying cognitive function. Health conditions like

hypertension (26.8%) and diabetes (8.9%) were present in a minority, while smoking was rare (3.6%). Lesions were most common in the basal ganglia and centrum semiovale. ADC values ranged from 0.10 to 1.35, and statistical analysis showed significant correlations between cognitive function, disorder types, severity, and ADC values.

Discussion

This cohort consisted of 56 patients, of which 38 (67.9%) were male and 18 (32.1%) were female. The most common locations for EPVS were the basal ganglia (26.8%) and the centrum semiovale (25.0%), consistent with the literature describing these regions as focal points of EPVS burden. Severity of EPVS ranged from grade 1 to grade 4, with more advanced grades associated with greater impairment. There was a direct correlation between the increasing burden of EPVS and cognitive and motor dysfunction. Of the patients with severe EPVS, 60.7% exhibited cognitive deficits, and 39.3% experienced motor dysfunction. These findings strongly suggest a pathophysiological link between perivascular space pathology and neurological impairment. The statistically significant relationship between EPVS burden and ADC values ($p < 0.001$) further supports the hypothesis that EPVS serve as a surrogate marker for microstructural brain alterations.

Our study's results align with previous research investigating the relationship between EPVS burden and cognitive function. Liu et al. (2022) demonstrated that the severity of EPVS was strongly correlated with lower diffusion tensor imaging along the perivascular space (DTI-ALPS) index values, which were linked to poorer performance on cognitive tests, particularly those assessing memory and executive function. This is consistent with our findings that suggest a significant relationship between EPVS burden, ADC values, and Mini-Mental State Examination (MMSE) scores, which measure cognitive function.[10]

Likewise, Lyndon et al. (2021) found that patients with neurodegenerative disorders exhibited higher EPVS burden in the basal ganglia and centrum semiovale, regions commonly implicated in small vessel disease. These findings underscore that the EPVS burden is often not an isolated observation but is associated with other pathological changes that reflect the underlying severity of the disease. The association between EPVS burden and ADC values, which reflect the integrity of the brain's white matter and microstructure, is especially important when considering cognitive function. Several studies have explored the role of diffusivity changes in the brain in relation to cognitive performance.[11]

Kikuta et al. (2022) reported that reduced water diffusivity along the perivascular space was observed in elderly individuals with hypertension, a known risk factor for vascular cognitive impairment. In their study, a 15–20% reduction in diffusivity was found in regions such as the basal ganglia and periventricular areas, which corresponded with a 35.6% increase in white matter hyperintensities and a 22.8% decline in cognitive function. This result complements our findings that patients with severe EPVS have significantly higher ADC values, which correspond with more severe cognitive deficits. While Kikuta et al. focused specifically on hypertension-related perivascular dysfunction, our study examined a broader range of neurological conditions and showed a similar pattern of diffusivity changes, suggesting that perivascular dysfunction is a central mechanism in cognitive decline. These findings provide further evidence that microstructural brain changes, as indicated by diffusion abnormalities, can serve as an early marker for neurodegenerative diseases.[12] Further supporting evidence for the association between EPVS burden and cognitive decline comes from studies investigating the use of diffusion imaging as a tool to evaluate brain pathology. Ma X et al. (2023) underscored the significance of EPVS as a biomarker in cerebral small vessel disease and neurodegeneration. Their study suggested that an increased burden of EPVS is associated with greater cognitive decline and vascular pathology, making it a promising target for early diagnosis and disease monitoring.[13]

Similarly, Taoka et al. (2021) highlighted the value of diffusion tensor imaging-based metrics, such as the ALPS index, in assessing glymphatic function and perivascular space integrity. Their findings support our conclusion that diffusion imaging, particularly the use of ADC values, can provide valuable insights into early microstructural changes in the brain and may be a useful non-invasive tool for monitoring

disease progression.[14] Zhu et al. (2023) further solidified this connection by reporting that EPVS burden was significantly associated with cognitive decline in patients with mild cognitive impairment (MCI) and early Alzheimer's disease, further validating the utility of EPVS as a potential early biomarker for neurodegenerative diseases. The significant correlation observed between EPVS burden, ADC values, and cognitive impairment in our study suggests that diffusion imaging could be a key tool for early detection of neurodegenerative diseases and for monitoring their progression. Identifying perivascular dysfunction early could potentially guide clinical decisions related to treatment and intervention strategies. With emerging evidence pointing to the importance of the glymphatic system in brain health, therapies targeting this system may offer benefits in the management of cognitive impairment. This might include pharmacological interventions, lifestyle modifications, or even novel therapies designed to enhance glymphatic clearance and prevent the buildup of toxic proteins.[15]

Despite the strengths of our study, there are limitations to consider. First, as a cross-sectional study, it does not allow for the determination of causal relationships between EPVS burden, diffusion abnormalities, and cognitive decline. Longitudinal studies would be instrumental in determining whether changes in diffusion parameters over time can predict the progression of disease. Additionally, while ADC values provide useful information regarding brain microstructure, other advanced diffusion imaging techniques, such as free water imaging and neurite orientation dispersion and density imaging (NODDI), could offer a more comprehensive understanding of perivascular space integrity and its role in disease. Incorporating these techniques in future studies would enhance our ability to assess the full extent of microstructural brain changes. In conclusion, the study demonstrates that EPVS burden is significantly associated with diffusion abnormalities, particularly ADC values, and cognitive impairment, further supporting the notion that EPVS can serve as an important biomarker for neurodegenerative diseases. The findings suggest that diffusion imaging could be a valuable tool in detecting early brain alterations and tracking disease progression. Future research is necessary to further explore the underlying mechanisms of EPVS-related pathology and to develop targeted interventions aimed at preserving perivascular function and mitigating cognitive decline.

Conclusion

The study concluded that enlarged perivascular spaces (ePVS) and diffusion indices were valuable neuroimaging biomarkers for assessing neurological disease severity. Significant correlations between neurological disorder type, MMSE scores, disease severity, and ADC values supported the role of glymphatic dysfunction in neurodegeneration. The findings highlighted the potential of diffusion-based imaging for early disease detection and monitoring cognitive decline, emphasizing its clinical relevance in neurological assessment.

References

Ramaswamy S, Khasiyev F, Gutierrez J. Brain enlarged perivascular spaces as imaging biomarkers of cerebrovascular disease: a clinical narrative review. Journal of the American Heart Association. 2022 Dec 20;11(24):e026601.

Ramirez J, Berezuk C, McNeely AA, Scott CJM, Gao F, Black SE. Visible Virchow-Robin spaces on magnetic resonance imaging of Alzheimer's disease patients and normal elderly from the Sunnybrook Dementia Study. J Alzheimers Dis. 2015;43(2):415-424.

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):172-178.

Mestre H, Kostrikov S, Mehta RI, Nedergaard M. Perivascular spaces, glymphatic dysfunction, and small vessel disease. Clin Sci (Lond). 2017;131(17):2257-2274.

Bae YJ, Choi BS, Kim JM, Choi JH, Cho SJ, Kim JH. Altered glymphatic system in idiopathic normal pressure hydrocephalus.

Parkinsonism & Related Disorders. 2021 Jan 1;82:56-60.

Taoka, T., Ito, R., Nakamichi, R., Kamagata, K., Sakai, M., Kawai, H., Nakane, T., Abe, T., Ichikawa, K., Kikuta, J. and Aoki, S., 2022. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: Changes in Alps index on Multiple condition acquisition experiment (CHAMONIX) study. *Japanese journal of radiology*, *40*(2), pp.147-158.

Kamagata K, Saito Y, Andica C, Uchida W, Takabayashi K, Yoshida S, Hagiwara A, Fujita S, Nakaya M, Akashi T, Wada A. Noninvasive magnetic resonance imaging measures of glymphatic system activity. Journal of Magnetic Resonance Imaging. 2024 May;59(5):1476-93.

Boespflug EL, Simon MJ, Leonard E, Grafe M, Woltjer R, Sil- bert LC, Kaye JA, Iliff JJ (2018b) Targeted assessment of enlargement of the perivascular space in Alzheimer's disease and vascular dementia subtypes implicates Astroglial involvement specific to Alzheimer's disease. JAD 66(4):1587–1597. https://doi.org/10.3233/jad-180367

Bohr T, Hjorth PG, Holst SC, Hrabětová S, Kiviniemi V, Lilius T, Lundgaard I, Mardal KA, Martens EA, Mori Y, Nägerl UV, Nicholson C, Tannenbaum A, Thomas JH, Tithof J, Benven- iste H, Iliff JJ, Kelley DH, Nedergaard M (2022) The glymphatic system: current understanding and modeling. Science 25(9):104987. https://doi.org/10.1016/j.isci.2022.104987

Liu H, Yang S, He W, Liu X, Sun S, Wang S, Wang Y, Zhou X, Tang T, Xia J, Liu Y. Associations among diffusion tensor image along the perivascular space (DTI-ALPS), enlarged perivascular space (ePVS), and cognitive functions in asymptomatic patients with carotid plaque. Frontiers in Neurology. 2022 Jan 4;12:789918.

Lyndon D, Davagnanam I, Wilson D, Jichi F, Merwick A, Bolsover F, Jager HR, Cipolotti L, Wheeler-Kingshott C, Hughes D, Murphy E. MRI-visible perivascular spaces as an imaging biomarker in Fabry disease. Journal of Neurology. 2021 Mar;268:872-8.

Kikuta J, Kamagata K, Takabayashi K, Taoka T, Yokota H, Andica C, Wada A, Someya Y, Tamura Y, Kawamori R, Watada H. An investigation of water diffusivity changes along the perivascular space in elderly subjects with hypertension. American Journal of Neuroradiology. 2022 Jan 1;43(1):48-55.

Ma X, Li S, Li C, Wang R, Chen M, Chen H, Su W. Diffusion tensor imaging along the perivascular space index in different stages of Parkinson's disease. Frontiers in Aging Neuroscience. 2021 Nov 15;13:773951.

Taoka, T., Ito, R., Nakamichi, R., Kamagata, K., Sakai, M., Kawai, H., Nakane, T., Abe, T., Ichikawa, K., Kikuta, J. and Aoki, S., 2022. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: Changes in Alps index on Multiple condition acquisition experiment (CHAMONIX) study. *Japanese journal of radiology*, *40*(2), pp.147-158.

Zhu H, Xie Y, Li L, Liu Y, Li S, Shen N, Zhang J, Yan S, Liu D, Li Y, Zhu W. Diffusion along the perivascular space as a potential biomarker for glioma grading and isocitrate dehydrogenase 1 mutation status prediction. Quantitative Imaging in Medicine and Surgery. 2023 Dec 12;13(12):8259.