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ASSOCIATION OF CEREBRAL ATROPHY WITH WHITE MATTER DISEASE BURDEN IN CEREBRAL SMALL VESSEL DISEASE (CSVD)

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Keywords

Cerebral small vessel disease, white matter hyperintensities, Fazekas score, cerebral atrophy, MRI brain, vascular cognitive impairment.

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Abstract

Background: *Cerebral small vessel disease (CSVD) is a leading cause of stroke, cognitive decline, and functional impairment in older adults. White matter hyperintensities (WMH) and cerebral atrophy are key MRI markers of small vessel injury, yet their interrelationship remains incompletely understood, especially in South Asian populations.*

Objective: *To evaluate the association between cerebral atrophy and white matter disease burden in patients with MRI evidence of CSVD.*

Methods: *This retrospective cross-sectional study included 208 consecutive patients with CSVD on brain MRI at Lady Reading Hospital, Peshawar (Sep 2022–Dec 2023). Exclusion criteria included large territorial infarcts, mass lesions, or demyelinating disease. WMH were graded using the Fazekas scale (1–3), and cerebral atrophy was categorized as mild, moderate, or severe. Demographic and clinical data, including age, sex, hypertension, and diabetes mellitus, were recorded. Associations between atrophy grade and Fazekas score were assessed using chi-square and Spearman correlation. Ordinal logistic regression adjusted for age and vascular risk factors.*

Results: *Among 208 patients (mean age 64.3 ± 11.8 years; 53.8% males), cerebral atrophy was present in 124 (59.6%) and moderate-to-severe WMH (Fazekas 2–3) in 130 (62.5%). Fazekas score was significantly associated with atrophy grade (χ^2 = 20.23, df = 6, p = 0.003) and showed a weak but positive monotonic correlation (Spearman's rs = 0.195, p = 0.005). On multivariable ordinal logistic regression, higher Fazekas scores and increasing age independently predicted more severe atrophy (adjusted OR for Fazekas 1 vs 3 = 0.36, 95% CI: 0.18–0.74; Fazekas 2 vs 3 = 0.44, 95% CI: 0.23–0.88; age OR per year = 1.06, p < 0.001), whereas hypertension and diabetes were not independently associated.*

Conclusion: *Cerebral atrophy is significantly associated with WMH burden in CSVD, supporting a shared microvascular pathophysiology. Assessment of both markers on MRI may facilitate early identification of patients at risk for vascular cognitive decline.*

INTRODUCTION

Cerebral small vessel disease (CSVD) represents a group of pathological processes affecting the small perforating arterioles, capillaries, and venules of the brain, and is recognized as a major contributor to

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stroke, gait impairment, cognitive decline, and dementia worldwide.[1,2] Magnetic resonance imaging (MRI) is central to its evaluation and typically demonstrates characteristic markers such as white matter hyperintensities (WMH), lacunar infarcts, cerebral microbleeds, and cortical or subcortical atrophy.[3] Among these markers, WMH are considered the hallmark of chronic ischemic injury, reflecting long-standing hypoperfusion and blood–brain barrier dysfunction.[4] Cerebral atrophy, meanwhile, represents irreversible neuronal and axonal loss, but whether it develops as a downstream consequence of progressive ischemic damage or through independent neurodegenerative pathways remains debated. [5,6]

Magnetic resonance imaging (MRI) is the key diagnostic tool for CSVD (7), offering higher sensitivity and specificity than CT. Reliable assessment requires at least 1.5 T MRI with sequences including: FLAIR (fluid-attenuated inversion recovery), T2* (gradient recalled echo T2*-weighted images) or SWI (susceptibility-weighted imaging), T1, and DWI (diffusion-weighted imaging). Emerging evidence suggests that greater WMH burden is associated with accelerated global and regional brain volume loss, supporting the concept of a continuum of chronic ischemic injury. [8,9] However, most of these data originate from Western populations. Limited evidence is available from South Asian cohorts, where vascular risk factors—particularly hypertension and diabetes mellitus—are highly prevalent and may contribute to both WMH progression and cerebral atrophy at an accelerated rate.[10,11]

Therefore, this study aimed to examine the association between cerebral atrophy and WMH burden in patients with MRI-defined CSVD, and to determine the modifying role of common vascular risk factors within this population.

MATERIAL AND METHODS

This cross-sectional study was conducted in the Department of Radiology, Lady Reading Hospital, Peshawar in Nov,25 retrospectively collecting data from Sep, 2022 to Dec, 2023. Institutional approval was obtained, and patient confidentiality was maintained. All adult patients who underwent brain MRI during this period, showing imaging features of CSVD were included. Exclusion criteria were:

- Large territorial infarcts
- Intracranial mass lesions
- Demyelinating diseases
- Significant motion artifacts

All scans were performed using a Toshiba 1.5-Tesla MRI machine using T1-weighted, T2-weighted, FLAIR, and diffusion-weighted images. Images were independently reviewed by two consultant radiologists with >5 years' experience. White Matter Hyperintensities (WMH) were graded using the Fazekas scale:

- Grade 0: No WMH
- Grade 1: Punctate foci
- Grade 2: Early confluent lesions
- Grade 3: Large confluent areas

Cerebral Atrophy was visually graded as:

- Mild: Minimal sulcal and ventricular enlargement
- Moderate: Obvious enlargement
- Severe: Marked widening and volume loss

Demographic data (age, sex) and clinical variables (hypertension, diabetes mellitus) were recorded from HMIS (Hospital Management Information System). Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD; categorical variables as frequency and percentage. Association between atrophy grade and Fazekas score was assessed using the chi-square test. Correlation was tested using Spearman's rho. Multivariate regression controlled for age, sex, hypertension, and diabetes. A p-value <0.05 was considered statistically

RESULTS

A total of 208 patients met the inclusion criteria. Mean age was 64.26 ± 11.8 years, with 53.8% males (n=112) and 46.2% females (n=96). Hypertension was present in 65.9% (n=137) and diabetes mellitus in 34.1% (n=71). Cerebral atrophy was found in 124 patients (59.6%). It was characterized as Mild in 48(23.1%), Moderate in 72 (34.6%) and Severe in 4 (1.9%). There was no atrophy in 84 (40.4%) as shown in figure 1. Fazekas Grades were Grade 1 in 78 (37.5%), Grade 2 in 81 (38.9%) and Grade 3 in 49 (23.6%) as shown in figure 2.

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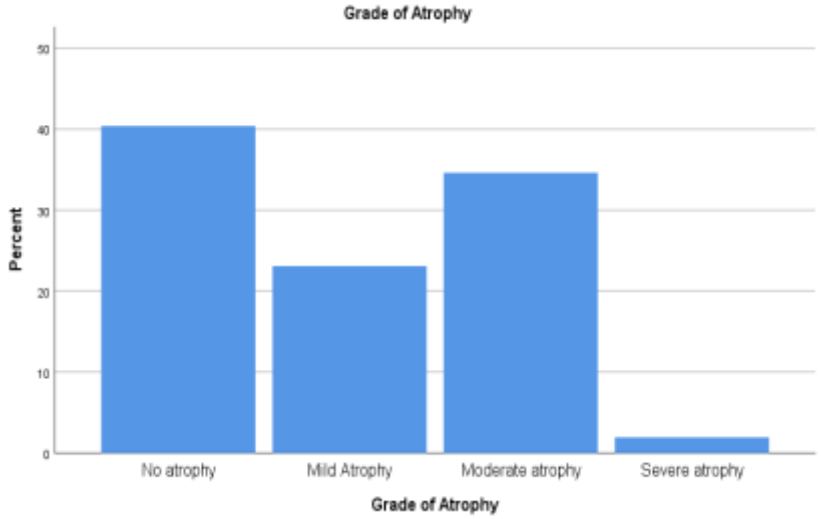

Figure 1. Distribution of cerebral atrophy severity in patients with cerebral small vessel disease, showing predominance of no to moderate atrophy and a low frequency of severe atrophy.

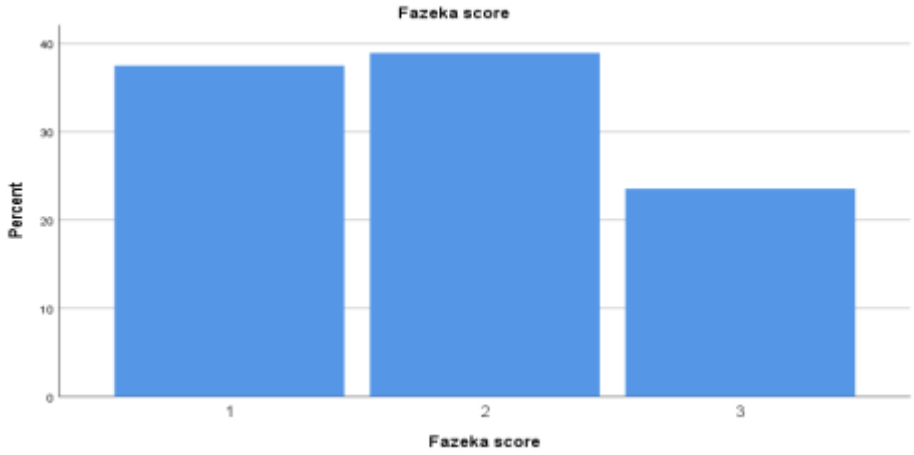

Figure2. Percentage distribution of Fazekas scores indicating white matter hyperintensity burden in the study population.

A statistically significant association was observed between **Fazekas score** and **grade of cerebral atrophy** (Pearson χ^2 = 20.23, df = 6, p = 0.003). This was supported by a significant linear-by-linear trend (p = 0.004), indicating increasing atrophy with higher Fazekas grades as shown in table 1. Patients with **lower Fazekas scores** predominantly showed **no or mild atrophy**, whereas **moderate to severe atrophy** was more frequently observed in those with **Fazekas scores 2 and 3**. The strength of association was **small to moderate** (Cramer's V = 0.221, p = 0.003) as shown in figure 3.

Table 1. Association Between Fazekas Score and Grade of Cerebral Atrophy

Pearson χ^2 (df = 6)	p-value (association)	Linear-by-linear trend (p-value)	Cramer's V	p-value (effect size)

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20.23	0.003	0.004	0.221	0.003

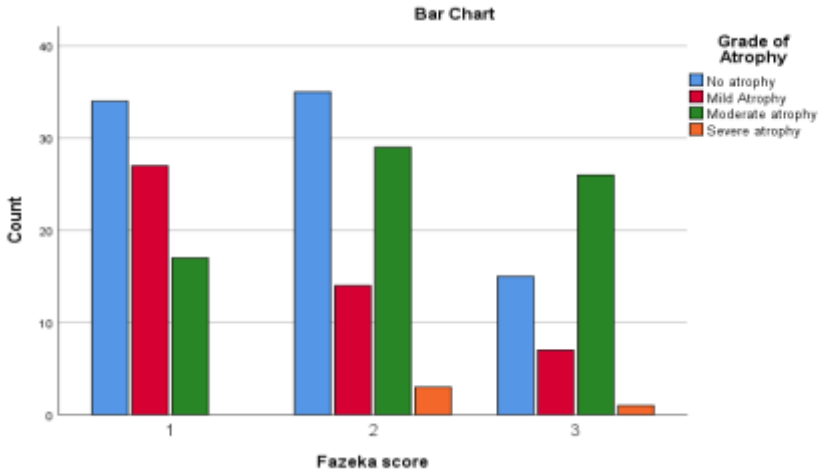

Figure 3. Distribution of cerebral atrophy grades across Fazekas scores, demonstrating increasing prevalence of moderate and severe atrophy with higher white matter hyper intensity burden.

Spearman's rank correlation further demonstrated a **weak but significant positive correlation** between Fazekas score and cerebral atrophy (r_s = 0.195, p = 0.005), suggesting a monotonic increase in atrophy severity with increasing white matter hyperintensity burden as shown in table 2.

Table 2. Correlation Between Fazekas Score and Cerebral Atrophy Severity

Correlation coefficient (r_s)	p-value	Direction	Strength
0.195	0.005	Positive	Weak

On ordinal logistic regression analysis, the model was statistically significant (likelihood ratio χ^2 = 34.26, p < 0.001). Increasing age was independently associated with higher grades of cerebral atrophy (adjusted OR = 1.06 per year, p < 0.001). After adjustment for age, hypertension, and diabetes mellitus, higher Fazekas scores remained significantly associated with increasing atrophy severity. Compared with Fazekas score 3, patients with Fazekas scores 1 and 2 had significantly lower odds of higher atrophy grades (adjusted OR = 0.36 and 0.44, respectively). Hypertension and diabetes mellitus were not independently associated with cerebral atrophy as shown in table 3.

Table 3. Ordinal Logistic Regression Analysis for Predictors of Cerebral Atrophy Severity

Variable	Adjusted Odds Ratio (OR)	p-value
Age (per year increase)	1.06	<0.001
Fazekas score 1 vs 3	0.36	<0.05
Fazekas score 2 vs 3	0.44	<0.05
Hypertension	Not significant	>0.05
Diabetes mellitus	Not significant	>0.05

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DISCUSSION:

The current research depicts a considerable relationship between the burden of white matter hyperintensities (WMH) and the atrophy of the brain among individuals suffering from MRI-diagnosed CSVD (Cerebral Small Vessel Disease). Fazekas scores revealed a direct correlation between the grade of atrophy in the brain, which remained significant even after adjusting for age and typical vascular risk parameters. This evidences the theory proposing that both WMH and brain atrophy are correlated structural manifestations of CSVD and not merely separate imaging abnormalities.[12,13]

The correlation between the burden of white matter hyperintensities (WMH) and cerebral atrophy makes is biologically plausible. Chronic ischemic injury, microstructural white matter damage, and blood-brain barrier dysfunction are all regarded as markers of WMH. In contrast, cerebral atrophy is the loss and damage of neuronal and axonal tissues. There correlation suggests that more advanced hyperintensities and greater loss of parenchymal tissue damage exist simultaneously therefore may have a similar microvascular pathophysiological mechanism.[14] The weak correlation may also indicates that cerebral brain atrophy burden may exist even in the absence of WMH, suggesting multifactorial nature of brain volume loss in CSVD.[15,16]

While previous research indicating age-related decreases in global and sectional volumes of the brain identified age as one of the most crucial predictors of cerebral atrophy. However, the relationship between cerebral atrophy and the burden of WMH remained even when adjusting for age, indicating that WMH are contributory beyond aging. Therefore, WMH become best as an indicator of some pathological changes in the brain as opposed to changes incited simply due to aging.[17]An interesting finding in the multivariable analysis was the lack of any independent association of hypertension, as well as diabetes, with cerebral atrophy. Though diabetes mellitus and hypertension were common in the participants and were shown to increase the risk of WMH in the univariate analysis, their association with cerebral atrophy seems to have been with white matter disease, but probably it does not act as a predictor. This finding underlines the importance of MRI-based measures, particularly with WMH, as a less reliable indicator of cumulative vascular damage, and as a better measure of other vascular risk factors alone.[18,19]

The current study sheds light on a South Asian group, a population that is often overlooked in CSVD research even though they carry a considerable load of vascular risk factors and demonstrating that **higher Fazekas grades correlate with reduced brain volume**. The data is in line with the findings from Western countries that show a relation between the severity of WMH and the loss of brain volume. Hence, it supports the cross-ethnic and cross-geographical generalizability of the relationship between WMH and atrophy. Clinically, the importance of **quantitative assessment of WMH and cerebral atrophy on MRI** may assist in the identification of patients who are likely to suffer from vascular cognitive impairment and loss of function. The **coexistence of WMH and atrophy** could serve as a surrogate marker for monitoring disease progression and guiding early interventions.[20,21]

CONCLUSIONS

Cerebral atrophy demonstrates a **significant association with white matter hyperintensity burden** in patients with CSVD. Increased age independently correlated with greater degrees of atrophy along with higher Fazekas scores; however, diabetics and hypertensive patients alone with these chronic conditions have no independent effect after adjustments. The results of the study support the idea that the WMH and atrophy of the brain shares a microvascular pathophysiology. More patients who may have the potential to develop cognitive impairment from vascular conditions can be identified using quantitative MRIs assessing these conditions to refine and develop preventive programmes tailored to the 'at-risk' patients.

STRENGTHS OF THE STUDY

- **Comprehensive imaging evaluation:** All patients underwent standardized 1.5-T MRI with multiple sequences (T1, T2, FLAIR, DWI).

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- **Use of validated scales:** WMH was assessed using the Fazekas scale; cerebral atrophy was graded based on sulcal and ventricular prominence.
- **Adjustment for confounders:** Age, hypertension, and diabetes mellitus were included in multivariable analysis to identify independent predictors.
- **South Asian cohort:** Provides valuable region-specific data where vascular risk factor prevalence is high, addressing a gap in the literature.
- **Large sample size:** Inclusion of 208 patients increases statistical power and reliability of the findings.

LIMITATIONS

- **Cross-sectional design:** Limits causal inference; temporal relationships between WMH progression and atrophy cannot be established.
- **Visual grading:** Atrophy assessment was based on visual inspection rather than volumetric analysis, which may reduce precision.
- **Single-center study:** Findings may not be fully generalizable to other populations or settings.
- **Limited severe atrophy cases:** Only 1.9% of patients had severe atrophy, potentially limiting the ability to detect associations in this subgroup.
- **Other confounders not included:** Lifestyle factors, cholesterol levels, and genetic predispositions were not considered and may influence WMH and atrophy.

REFERENCES

1. *Wardlaw JM, Smith EE, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18(7):684-696.*
2. *Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: A clinical review. Neurology. 2019;92(24):1146-1156.*
3. *Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology. 2010 Jul 1;9(7):689-701.*
4. *Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke and vascular neurology. 2016 Oct 25;1(3).*
5. *Markus HS, de Leeuw FE. Cerebral small vessel disease: recent advances and future directions. International Journal of Stroke. 2023 Jan;18(1):4-14.*
6. *Habes M, Erus G, Toledo JB, Zhang T, Bryan N, Launer LJ, Rosseel Y, Janowitz D, Doshi J, Van der Auwera S, Von Sarnowski B. White matter hyperintensities and imaging patterns of brain ageing in the general population. Brain. 2016 Apr 1;139(4):1164-79.*
7. *Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. Advances in Clinical and Experimental Medicine. 2021;30(3):349-56.*
8. *Chen Y, Wang X, Guan L, Wang Y. Role of white matter hyperintensities and related risk factors in vascular cognitive impairment: a review. Biomolecules. 2021 Jul 27;11(8):1102.*
9. *Oldan JD, Jewells VL, Pieper B, Wong TZ. Complete evaluation of dementia: PET and MRI correlation and diagnosis for the neuroradiologist. American journal of neuroradiology. 2021 Jun 1;42(6):998-1007.*
10. *Jiménez-Sánchez L, Hamilton OK, Clancy U, Backhouse EV, Stewart CR, Stringer MS, Doubal FN, Wardlaw JM. Sex differences in cerebral small vessel disease: a systematic review and meta-analysis. Frontiers in neurology. 2021 Oct 28;12:756887.*
11. *Kalaria RN, Akinyemi RO, Paddick SM, Ihara M. Current perspectives on prevention of vascular cognitive impairment and promotion of vascular brain health. Expert review of neurotherapeutics. 2024 Jan 2;24(1):25-44.*
12. *Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. Advances in Clinical and Experimental Medicine. 2021;30(3):349-56.*
13. *Sun W, Huang L, Cheng Y, Qin R, Xu H, Shao P, Ma J, Yao Z, Shi L, Xu Y. Medial temporal atrophy contributes to cognitive impairment in cerebral small vessel disease. Frontiers in neurology. 2022 May 18;13:858171.*

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14. *Reaume N, Reid M, Tadros GS, Chacinski D, Denroche B, Aftab A, Wu P, Gupta Sah R, Wang M, Smith EE, Frayne R. The relationship of small vessel disease burden on cerebral and regional brain atrophy rates and cognitive performance over one year of follow-up after transient ischemic attack. Frontiers in Neurology. 2023 Nov 24;14:1277765.*
15. *Heiland EG, Welmer AK, Kalpouzos G, Laveskog A, Wang R, Qiu C. Cerebral small vessel disease, cardiovascular risk factors, and future walking speed in old age: a population-based cohort study. BMC neurology. 2021 Dec 24;21(1):496.*
16. *Wang Y, Liu X, Hu Y, Yu Z, Wu T, Wang J, Liu J, Liu J. Impaired functional network properties contribute to white matter hyperintensity related cognitive decline in patients with cerebral small vessel disease. BMC Medical Imaging. 2022 Mar 9;22(1):40.*
17. *Lingyun H, Xiaomei B, Xianglina C. Research Progress on the Correlation between the Total Imaging Load and the Damage Caused by Cerebral Small Vessel Disease. biomarkers. 2025 Nov 30;7(6):15-21.*
18. *Fang Z, Chen X, Zhao Y, Zhou X, Cai X, Deng J, Cheng W, Sun W, Zhuang J, Yin Y. Quantitative assessments of white matter hyperintensities and plasma biomarkers can predict cognitive impairment and cerebral microbleeds in cerebral small vessel disease patients. Neuroscience. 2025 Jan 9;564:41-51.*
19. *Mu R, Yang P, Qin X, Zheng W, Lv J, Huang B, Li X, Feng Y, Huang D, Li P, Dai S. White matter hyperintensities drive propagating grey matter atrophy in cerebral small vessel disease. Brain Communications. 2025;7(6):fcaf429.*
20. *Huang H, Song W, Wang P, Zhu Y, Zheng L, Shen C, Xu H, Qiu J. White Matter Hyperintensities: Cerebral Small-Vessel Diseases and White Matter Microstructural Impairments. Iradiology. 2025 Feb;3(1):5-25.*
21. *Cheng Z, Zhang W, Zhan Z, Xia L, Han Z. Cerebral small vessel disease and prognosis in intracerebral haemorrhage: A systematic review and meta-analysis of cohort studies. European Journal of Neurology. 2022 Aug;29(8):2511-25.*