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# CLINICO-RADIOLOGIC EVALUATION OF CEREBRAL SMALL VESSEL DISEASE: EVIDENCE OF PREMATURE CEREBROVASCULAR AGING IN PAKISTANI POPULATION

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## Abstract

***Background:*** *Although Cerebral small vessel disease (CSVD) is one of the leading causes of stroke, cognitive impairment, and disability globally, there remains a dearth of information on the region-specific differences in the clinical and radiological profile as well as age of onset in South Asia.*

***Objective:*** *To describe the clinico-radiological profile of CSVD and its relationship to hypertension and diabetes mellitus in patients referred for brain MRI at a tertiary care facility in Pakistan.*

***Methods:*** *A cross-sectional study was carried out from September 2022 to December 2023 on 208 patients with MRI diagnosed cases of Chronic Small Vessel Disease (CSVD) at Lady Reading Hospital (LRH) , Peshawar. For the purpose of the study, Magnetic Resonance Imaging (MRI) sequences (T1, T2, FLAIR, Diffusion Weighted Imaging) were reviewed looking for White Matter Hyperintensities (WMH) according to the 5-point Fazekas scale, lacunar infarcts (LIs) and brain atrophy. The presence of hypertension and diabetes was statistically analyzed for using Chi Square tests, calculating odds ratios (OR) with 95% confidence intervals (CI).*

***Results:*** *The average age of the registered study patients was 64.26 ± 11.8 years and 53.8 were males. Moderate to severe WMH were noted in 62.5% of cases, lacunar infarcts were noted in 62% and brain atrophy was noted in 59.6%. Chronic WMH predominance did not change with the presence of hypertension (65.9%) and the presence of diabetes (36.5%) for the study cohort. Lacunar infarcts were noted to be more prevalent in hypertensive patients (41.6% vs. 29.6%; OR = 1.68, 95%CI = 0.92-3.08; p = 0.089). A statistically significant relationship was noted between diabetes and the presence of acute lacunar infarcts (32.9% vs. 19.7%; OR = 2.01, 95%CI = 1.06-3.80; p = 0.033).*

***Conclusion:*** *CSVD appears at a relatively younger age in the Pakistani population, pointing to an accelerated aging of the cerebrovascular system. Diabetes was significantly linked to the presence of acute ischemic lesions, whereas hypertension had a non-significant correlation with chronic lacunar infarcts. Dedicating midlife to early screening and aggressive management of risk factors may lessen the burden of CSVD-related disability in this area.*

## INTRODUCTION

Stroke is one of the world's leading causes of death and disability, and a substantial proportion of stroke burden arises from disease of the small cerebral vessels. According to the global burden of disease (GBD) data, stroke still ranks among the top causes of death and disability around the world.[1] Cerebral small vessel disease (CSVD) is the chronic, progressive disease of the arteriols, capillaries, and venules of the brain which can be diagnosed using advanced medical imaging because of the presence of recent small subcortical infarcts and lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces, microbleeds, and atrophy. It is also a leading cause of lacunar stroke and is a significant contributor to the co-morbidities of aging, including cognitive decline and gait disturbance.[2]

From an epidemiological standpoint, CSVD is highly dependent on age, with the prevalence of white matter hyperintensities (WMH) and other markers sharply increasing with age (estimates range from a few percent at age 50 to nearly universal prevalence among the very old) and CSVD involved in approximately a quarter of ischemic strokes and in a considerable portion of vascular dementia. These impacts result in CSVD being a foremost agent of late-life disability.[3] The process which leads to certain diseases is not uniform. For sporadic CSVD, the most frequent cause is the enduring vascular risk features, particularly hypertension and diabetes, and the subsequent arteriolosclerotic changes.[4] Other causes are cerebral amyloid angiopathy, various genetic arteriopathies, inflammatory small vessel diseases, and venous collagenosis. For the majority of CSVD forms, no causal therapy exists and hence, prevention and control of risk factors (has been blood-pressure, glucose control, and lifestyle modifications) continue to dominate clinical management. The standards of CSVD Neuroimaging (STRIVE) and visual rating scales, like the Fazekas scale, are commonly employed to provide uniformity in CSVD burden detection and quantification.[5,6]

However, the clinical pattern and age of presentation may vary between populations. South Asian countries, which include Pakistan, have a high and rising prevalence of vascular risk factors such as hypertension, diabetes, obesity, and smoking that often manifest at an earlier age compared with many high-income countries.[7,8] Studies from Pakistan have reported a high burden of hypertension, with a relatively greater proportion of young and early-onset stroke, suggesting that cerebrovascular ageing and CSVD-related pathology may present at younger ages in this region. If CSVD manifests earlier, the public-health and functional consequences are amplified because affected people lose years of productive life.

Considering these factors, a specialized clinico-radiologic study of CSVD on a Pakistani tertiary population can (1) stratify age and measure the burden of radiologic CSVD markers (using standardized Clinical CSVD and Fazekas/STRIVE scoring using proprietary software-defined MRI sequences), (2) correlate the imaging burden with clinical syndromes and profiles of Vascular Risk Factors, and (3) examine the hypothesis whether the CSVD ill era of this population is of comparatively lower age i.e., Premature evidence of cerebrovascular aging is a growing concern. Showing earlier manifestation CSVD would justify midlife screening and more potent and stringent risk factor modification policies in South Asia to reduce strokes, cognitive and functional decline and disability.[9,10]

The present study investigated and characterized the clinico-radiological patterns of cerebral small vessel disease (CSVD) and assessed the relationship with the main vascular risk factors of hypertension and diabetes mellitus in the CSVD population attending one of the tertiary care hospitals in the Pakistan.

## METHODOLOGY

### Study design and setting

This cross-sectional observational study was carried out in the Department of Radiology, Lady Reading Hospital, Peshawar, Pakistan, from September 2022 to Dec, 2023.

**Study population and sampling**

A total of 208 patients were included using a convenient sampling technique. All patients referred to the Radiology Department for MRI brain during the study period showing small vessel ischemic changes were included.

**Inclusion and exclusion criteria**

- **Inclusion criteria:** Patients of both gender and all age groups with MRI findings consistent with CSVD.
- **Exclusion criteria:** Patients with a known history of prior stroke, intracranial hemorrhage, space-occupying lesions, demyelinating or leukoencephalopathies or those with incomplete clinical or imaging records were excluded to avoid confounding.

**Data collection**

After obtaining informed consent, demographic data (age, gender) and relevant clinical history were recorded, with particular attention to vascular risk factors such as hypertension and diabetes mellitus. Information was documented on a structured proforma specifically designed for this study.

**Radiological assessment**

MRI was performed on Toshiba1.5 Tesla machine using T1, T2, FLAIR, DWI sequences and were reviewed independently by two consultant radiologists. Discrepancies were resolved by consensus.

Findings recorded included:

- White matter hyperintenities graded by Fazekas scale
- Presence of lacunar infarcts
- Cerebral atrophy.

**Ethical considerations**

The study was approved by the Institutional Review Board of Lady Reading Hospital, Peshawar (469/LRH/MTI) dated 22nd Aug,2022. Written informed consent was obtained from all participants prior to enrollment. No additional imaging or invasive procedure was performed for the purposes of this research. Patient confidentiality was maintained.

**Statistical analysis**

Data were analyzed using SPSS version 26. Mean age and SD were calculated. Frequency of radiologic findings and comorbidities were presented as percentages. Mean CSVD age was compared narratively to reported international averages (70–75 years). The degree of white matter changes was assessed using the Fazekas scale, categorized as mild (grade 1) and moderate–severe (grades 2–3). Association of groups (e.g., hypertensive vs. non-hypertensive, diabetic vs. non-diabetic) with CSVD were performed using the Chi-square test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of associations. A p-value <0.05 was considered statistically significant.

**RESULT**

Table 1 shows that a total of 208 patients with radiological evidence of small vessel ischemic changes were included. The age ranged from 23 to 96 years, with a mean of 64.26 ± 11.8 years. Males accounted for 53.8% (n=112) and females for 46.2% (n=96). Moderate to severe white matter hyperintensities (Fazekas 2-3) were found in 130 patients (62.5%), lacunar infarcts were found in 129 (62%) subjects (acute; 51 and chronic; 78). Brain atrophy was observed in 124 patients (59.6%). (Fig 1) Hypertension was present in 137 patients (65.9%) and diabetes mellitus in 76 (36.5%).

**Table1. Baseline characteristics of patients (n = 208)**

| Variable | Categories | n (%) / Mean ± SD |
|---|---|---|
| **Age (years)** | | 64.26 ± 11.8 (range 23–96) |
| | **Male** | 112 (53.8%) |

| | | |
|---|---|---|
| | Female | 96 (46.2%) |
| Hypertension | | 137(65.9%) |
| Diabetes mellitus | | 76(36.5%) |
| Fazeka score | Grade 1 | 78(37.5%) |
| | Grade 2 | 81(38.9%) |
| | Grade 3 | 49(23.6%) |
| | Mild (1) | 78(37.5%) |
| | Moderate-severe (2+3) | 130(62.5%) |
| Lacunar infarcts | Acute Lacunar infarcts | 51 (24.5%) |
| | Chronic Lacunar infarcts | 78 (37.5%) |
| Brain atrophy | | 124 (59.6%) |

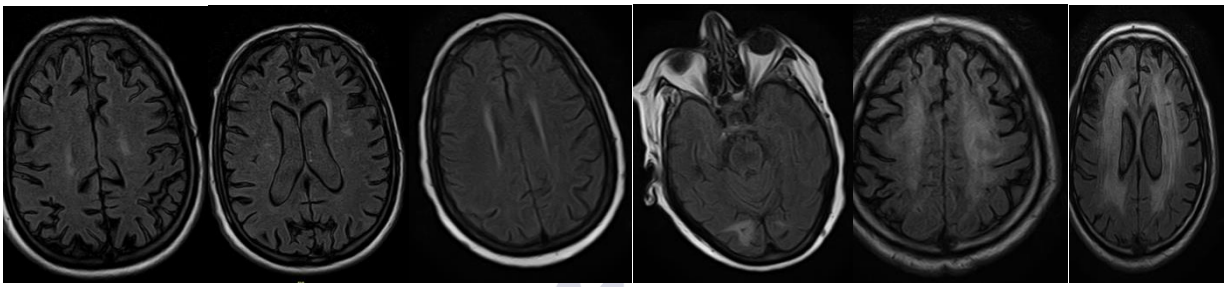


**Fig1: MRI FLAIR images showing bilateral symmetrical dicrete patches of white matter hperintensities in centrum semiovale and periventricular regions in first two images (Fazekas 1), tending to confluent hyperintensities in 3rd and 4th images (Fazekas 2) and confluent hyperintensities in last two images (Fazekas 3)**

Table 2 shows that Moderate-to-severe white matter hyperintensities (Fazekas grades 2–3) were observed more frequently in patients with hypertension (65.0%) compared to those without hypertension (57.7%), though this difference did not reach statistical significance ($\chi^2$ = 1.039, p = 0.308; OR = 1.36, 95% CI: 0.75–2.44). Similarly, diabetic individuals demonstrated a slightly lower prevalence of moderate-to-severe WMH (59.2%) compared to non-diabetic participants (64.4%), which was also statistically insignificant ($\chi^2$ = 0.553, p = 0.457; OR = 0.80, 95% CI: 0.45–1.43). These findings suggest that neither hypertension nor diabetes mellitus showed a significant independent association with WMH severity in this study cohort.

**Table 2. Association of Hypertension and Diabetes Mellitus with White Matter Hyperintensity Severity (Fazekas Scale)**

| Variable | Variable | Mild WMH (Fazekas 1) | Moderate–Severe WMH (Fazekas 2–3) | $\chi^2$(df :1) | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| Hypertension | Absent | 30 (42.3%) | 41 (57.7%) | 1.039 | 0.308 | 1.36 (0.75–2.44) |
| | Present | 48 (35.0%) | 89 (65.0%) | | | |
| Diabetes Mellitus | Absent | 47 (35.6%) | 85 (64.4%) | 0.553 | 0.457 | 0.80 (0.45–1.43) |
| | Present | 31 (40.8%) | 45 (59.2%) | | | |

**Abbreviations:** WMH – White Matter Hyperintensities; $\chi^2$ – Chi-square; OR – Odds Ratio; CI – Confidence Interval. **Note:** $p < 0.05$ considered statistically significant.

MRI results do not demonstrate any significant association between hypertension and brain atrophy, acute lacunar infarcts, or chronic lacunar infarcts as seen in Table 3. Although chronic lacunar infarcts were more common in individuals with hypertension (41.6%) than in those without (29.6%), this difference was not statistically significant ($\chi^2 = 2.887$, $p = 0.089$; OR = 1.68, 95% CI: 0.92–3.08). In contrast, the presence of diabetes mellitus was positively associated with the occurrence of acute lacunar infarcts, as these were more common in diabetic patients (32.9%) than in non-diabetics (19.7%) ($\chi^2 = 4.539$, $p = 0.033$; OR = 2.01, 95% CI: 1.06–3.80). Nonetheless, no significant relationships were found between diabetes and chronic lacunar infarcts or brain atrophy. This finding tends to suggest that in diabetics the acute small vessel ischemic injury may be more prominent, while in hypertensive patients there is a non-significant trend toward more chronic cerebrovascular changes.

**Table 3. Association of Hypertension and Diabetes Mellitus with MRI Brain Findings**

| Clinical Variable | MRI Finding | Without Lesion n (%) | With Lesion n (%) | $\chi^2$ (df = 1) | *p*-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| **Hypertension** | **Brain Atrophy** | No HTN: 26 (36.6%)<br>HTN: 58 (42.3%) | No HTN: 45 (63.4%)<br>HTN: 79 (57.7%) | 0.635 | 0.426 | 1.26 (0.70 – 2.26) |
| | **Acute Lacunar Infarct** | No HTN: 56 (78.9%)<br>HTN: 101 (73.7%) | No HTN: 15 (21.1%)<br>HTN: 36 (26.3%) | 0.670 | 0.413 | 1.32 (0.67 – 2.57) |
| | **Chronic Lacunar Infarct** | No HTN: 50 (70.4%)<br>HTN: 80 (58.4%) | No HTN: 21 (29.6%)<br>HTN: 57 (41.6%) | 2.887 | 0.089 | 1.68 (0.92 – 3.08) |
| **Diabetes Mellitus** | **Brain Atrophy** | No DM: 49 (37.1%)<br>DM: 35 (46.1%) | No DM: 83 (62.9%)<br>DM: 41 (53.9%) | 1.598 | 0.206 | 0.69 (0.38 – 1.25) |
| | **Acute Lacunar Infarct** | No DM: 106 (80.3%)<br>DM: 51 (67.1%) | No DM: 26 (19.7%)<br>DM: 25 (32.9%) | 4.539 | **0.033** | **2.01 (1.06 – 3.80)** |
| | **Chronic Lacunar Infarct** | No DM: 81 (61.4%)<br>DM: 49 (64.5%) | No DM: 51 (38.6%)<br>DM: 27 (35.5%) | 0.199 | 0.655 | 0.87 (0.48 – 1.56) |

***Abbreviations:*** *OR = Odds Ratio; CI = Confidence Interval.* ***Significance level:*** *$p < 0.05$ considered statistically significant.*

## DISCUSSION

This study examined the clinical and radiological characteristics of cerebral small vessel disease

(CSVD) and its relationship with hypertension and diabetes mellitus as vascular risk factors in a population of a tertiary hospital in Pakistan. Findings showed that almost two-thirds of the participants (62.5%) had moderate-to-severe white matter hyperintensities (WMH), and that lacunar infarcts and brain atrophy also represented frequent findings in the brain MRI. Patients with CSVD had a mean age of 64.26 ± 11.8 years, younger than what most Western studies report, which is a mean age of 70–75 years, and indicating that there may be a CSVD in Pakistan that occurs earlier in life or perhaps an advanced cerebrovascular aging process.[11,12]

In this study, hypertension was present 65.9%, and diabetes mellitus 36.5% of patients, reaffirming their status as key vascular risk factors in the development of CSVD.[13] However, hypertension and diabetes neither, individually, nor in combination, have statistically significant relationships with WMH severity on the Fazekas scale. This aligns with previous regional studies that document inconsistent relationships between WMH burden and single risk factors, likely due to the presence of overlapping vascular mechanisms along with genetic and environmental factors.[14]

Despite the fact that many international studies characterize hypertension as the most important determinant of WMH, the results of this study may reflect effective blood pressure control in the study population or that other unmeasured risk factors, possibly cholesterolemia, obesity, or smoking, may have been working to promote CSVD in this population.

Interestingly, the MRI findings showed that hypertension has a non-significant trend toward more chronic lacunar infarcts (41.6% vs. 29.6%, p = 0.089), consistent with the longstanding notion that chronic hypertension induces microangiopathic and arteriolosclerotic changes sufficient to produce lacunar infarcts.[15] Although non-significant, this trend may indicate the effect of prolonged hypertension on the integrity of small vessels over time[11].

There was a higher incidence of acute lacunar infarcts in cases when diabetes mellitus was present as compared to those cases without it (p = 0.033 and OR = 2.01). This solidifies the acute ischemic vulnerability in this population as a possible consequence of diabetes correlating to a lower degree of microvascular autoregulatory control and dysfunctions, basement membrane thickening of the microvessels, and aberrations within the microvascular permeabilities of the brain as described in the literature.[16] The absence of a significant association between diabetes and the presence of chronic lacunar infarcts and brain atrophy may suggest that diabetes predominantly precipitates acute ischemic compared to chronic degenerative sequelae.[17]

This unexplained gap in [this aspect of the literature review] has also been noted in other studies involving Asian countries as well as Europe, which pointed out different degrees of association involving diabetes as well. For instance, out of the studies conducted in Rotterdam and on the Leukoaraiosis and Disability (LADIS) cohort, hypertension was reported as the most consistent predictor of white matter hyperintensities (WMHs) on brain imaging, while diabetes demonstrated weak and inconsistent correlations.[18,19] Nevertheless, similar to what we have documented in our studies, research conducted in China and India showed earlier manifestations of cervicocephalic small vessel disease (CSVD) and greater lesion burdens at younger ages. This could relate to differences in the population average diabetes and hypertension risk factor profiles, diet, other environmentally mediated exposures, and some forms of genetic vulnerability associated with small vessel disease.[20]

The average age in this cohort reinforces the probable premature cerebrovascular aging in the Pakistani population. The early emergence of CSVD-related MRI changes could be explained by the documented high rates of uncontrolled hypertension, diabetes, and metabolic syndrome in South Asia. These results have major consequences; the midlife early identification and active management of these vascular risk factors could help in diminishing stroke, cognitive decline, and disability accumulation later in life.

## CONCLUSION

In conclusion, this study shows that a large number of younger people in Pakistan presents

with radiological CSVD. Although many people with the condition have diabetes and hypertension, in relation to acute lacunar infarcts only diabetes was significantly associated, and hypertension was non-significant with chronic ischemic lesions. The early mean age of CSVD presentation relative to global averages suggests cerebrovascular aging occurs more rapidly in this population. Implementing early vascular risk factor interventions and more aggressive control in this population may help lessen the impact of the range of disabilities associated with CSVD.

## LIMITATIONS AND RECOMMENDATIONS

This study had several limitations. First, although it is cross-sectional research, it does not measure causality between risk factors and CSVD results. In addition, the study used a convenient sampling technique which may introduce selection bias. Also, some risk factors were not analyzed such as dyslipidemia, smoking, and BMI, or the duration of hypertension or diabetes. Besides, the analysis did not study the cognitive or gait variables which are important clinical aspects associated with CSVD. Longitudinal and neuropsychological studies are needed to explain the temporal relationship between vascular risk factors and the advancement of CSVD more clearly.

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