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Research article

Carotid artery stenosis is related to cerebral small vessel disease magnetic resonance imaging burden

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ABSTRACT

Background: Cerebral small vessel disease (CSVD) encompasses conditions that affect small blood vessels of the brain, the most common being atherosclerosis. Magnetic resonance imaging (MRI) CSVD markers include lacunar strokes (LS), white matter hyperintensities (WMH), microbleeds, enlarged perivascular spaces (EPVS), and brain atrophy. Large and small cerebral arteries share an anatomical and functional connection, but the role of large vessel atherosclerosis in atherosclerotic CSVD hasn't been established. The aim of this study was to evaluate the involvement of large vessel pathology in atherosclerotic CSVD.

Methods: This cross-sectional study included 98 patients treated at the Neurology Clinic of the University Clinical Center of Serbia in Belgrade, from February 2018 to December 2023, who had atherosclerotic CSVD confirmed by neuroimaging and underwent extracranial color duplex sonography. Data on patients' gender, age, cerebrovascular risk factors (dyslipidemia, hypertension, diabetes mellitus, smoking status), ultrasonography findings (intima-media thickness - IMT, carotid and vertebral artery stenosis, and hemodynamics), and CSVD imaging markers were collected, and the CSVD MRI burden score was calculated.

Results: Age correlated with LS and WMH ($p < 0.05$ for both). Hypertension correlated with WMH ($p = 0.016$), and smoking with LS ($p = 0.043$). Brain atrophy was more common in women ($p = 0.016$). The majority of patients had low-grade (<50 %) carotid stenosis. There was a strong correlation between all morphological parameters of internal carotid artery stenosis and the CSVD burden score ($p < 0.05$ for all). The hemodynamic parameters of internal carotid artery stenosis and morphological and hemodynamic parameters of vertebral artery stenosis didn't correlate with the CSVD burden score.

Conclusions: This study shows a strong correlation between cerebral large and small vessel pathology. We recommend the use of extracranial color duplex sonography in the evaluation of patients with CSVD as a supplementary method for follow-up, as this would allow the identification of patients whose condition might progress.

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1. Introduction

Cerebral small vessel disease (CSVD) includes different etiologies that affect small vessels of the brain (small arteries, arterioles, capillaries, venules) which supply the deep gray matter and the white matter [1,2]. Even though CSVD can cause both ischemic and hemorrhagic brain lesions, the mechanism is still unknown [3]. CSVD is the cause of 20 %–25 % of all ischemic strokes, as well as 45 % of vascular dementia cases [1–6]. Out of all conditions that make CSVD, atherosclerosis and amyloid-related CSVD are the most common two [2,5]. Atherosclerosis is often referred to as age-related or vascular risk factor-related CSVD [3]. It is also considered to be a systemic condition associated with systemic vascular changes, aging, and hypertension [3,7]. Recently, atherosclerotic CSVD has been linked with atherosclerosis in other small vessels (e.g. coronary circulation) [8].

Magnetic resonance imaging (MRI) or computed tomography (CT) are used to diagnose CSVD, however, only MRI can assess all imaging features and CSVD brain burden [3,9]. Markers of CSVD on imaging include lacunar strokes (LS), white matter hyperintensities (WMH), microbleeds, enlarged perivascular spaces (EPVS), and atrophy. LS appear as round infarcts less than 20 mm in diameter, typically found in the basal ganglia. Over time, they might completely disappear, transform into lacunes, or lead to WMH. Lacunes and LS result from atherosclerosis-related pathology of penetrating arterioles including loss of smooth muscle cells, fibroblast proliferation, hyalinization, and narrowing of the lumen. These changes are typically associated with aging and hypertension [3,4,9]. When multiple small arterioles in the white matter are affected, it leads to incomplete ischemia of the area, appearing as WMH. On imaging, WMH are seen as areas of hyperintensities on MRI in the periventricular white matter and deep gray matter, involving the basal ganglia. They are graded according to the Fazekas scale. Microbleeds are small lesions (2–5 mm) caused by hemosiderin deposition in the perivascular space, hypodense on MRI. They are usually found in the cortical-subcortical junction and deep white matter. Perivascular spaces are physiologic spaces around penetrating arterioles of the brain. However, they can become enlarged due to atrophy or inflammation. The final marker of CSVD, brain atrophy, is defined as lower cerebral volume not related to injury, trauma, or acute ischemia [2,3,9]. CSVD MRI burden score involves four markers of the disease (LS, WMH, microbleeds, and EPVS). It is a reliable measure of disease progression and has been correlated with symptomatic CSVD, mild cognitive impairment, symptomatic carotid stenosis, and even outcomes after endovascular thrombectomy [10–12]. Additionally, Tang et al. in their research showed that CSVD burden score is greater in patients with first-ever LS, pointing to the importance of this disease quantification, especially since CSVD is a silent disease in which measuring progression is difficult [13].

Large extracranial vessel atherosclerosis has been known for a long time as a cause of ischemic strokes and is regarded as one of the most important risk factors for brain ischemia. Extracranial vessel atherosclerosis shares similar risk factors as CSVD including aging and hypertension [14]. However, the involvement of large vessel atherosclerosis in CSVD hasn't been completely established. It makes sense that such involvement would exist as large and small vessels are morphologically, functionally, and anatomically connected. Additionally, there is a connection between them on the basis of common pathology (i.e. atherosclerosis) and shared risk factors. There is also a possibility of a causative correlation between large vessel disease and CSVD referred to as vessel-to-vessel embolization [15].

1.1. Aim

The aim of this study was to evaluate the involvement of large vessel pathology in atherosclerotic CSVD confirmed with neuroimaging by determining the frequency, type, and degree of atherosclerosis in large extracranial vessels (carotid and vertebral arteries) using extracranial color duplex sonography. We also aimed to show if there is a correlation between morphological and hemodynamic parameters of extracranial vessel stenosis and CSVD MRI imaging markers and the burden score.

2. Materials and methods

2.1. Study population

This cross-sectional study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Ethics Committee of the Neurology Clinic, University Clinical Centre of Serbia (Protocol code NE/2011/34, September 14, 2011). All patients provided written informed consent to participate in the study and for their data to be published. The study included 98 patients treated at the Neurology Clinic of the University Clinical Center of Serbia in Belgrade, from February 2018 to December 2023. All information was acquired from patients' medical histories using the hospital information system "Heliant".

Basic demographic data including age and sex and data on cerebrovascular risk factors (dyslipidemia, hypertension, diabetes mellitus, and smoking status) were noted from patients' medical histories. All patients in this cohort had a diagnosis of atherosclerotic CSVD based on neuroimaging features and have undergone color duplex sonography examination of extracranial vessels. Patients with ischemic stroke etiologically due to atherosclerosis of large cerebral blood vessels or cardio-embolism, as well as those with the presence of other non-atherosclerosis-related brain lesions (e.g. tumors) were excluded from the study. Patients with other types of CSVD (e.g. CADASIL), patients with incomplete or inaccessible data, and those with inadequate color duplex sonography examination were also excluded.

2.2. Neuroimaging interpretation: computerized tomography (CT) and magnetic resonance imaging (MRI)

All patients were diagnosed with CSVD using MRI and/or CT. All patients underwent CT imaging, while the majority had MRI performed as well. Standardized MRI sequences were used (i.e. T1-weighted, T2-weighted, and fluid-attenuated inversion recovery or

FLAIR). LS were defined as hyperintense lesions on T2-weighted and FLAIR MRI, 3–15 mm in size. LS localization was defined as in the right, left, or both cerebral hemispheres. WMH were defined as bilateral, symmetrical, confluent hyperintense areas on T2-weighted and FLAIR MRI or bilateral, symmetrical, confluent hypointense areas on T1-weighted MRI. WMH were graded based on the Fazekas scale. Grade 0 meant that there were no WMH. If WMH appeared as a thin lining around ventricles, it was graded as Fazekas 1. The presence of periventricular "halo" was graded as Fazekas 2, and periventricular hyperintensity extending into the white matter was noted as Fazekas 3. Microbleeds were defined as hypointense lesions less than 10 mm in size on T2-or susceptibility-weighted imaging. EPVS were defined as round, ovoid, or linear lesions less than 3 mm in size with signal intensity of cerebrospinal fluid. Atrophy was defined as decreased brain volume not related to injury, trauma, or acute ischemia, marked by widening of the ventricular system and sulcal widening [16,17].

CSVD MRI burden score was calculated based on previous publications. One point was awarded for asymptomatic LS; 1 for WMH of Fazekas 2 or 3; 1 point for microbleeds; and 1 point was awarded in the case when there are more than 10 EPVS in the basal ganglia [17]. To avoid bias, CSVD MRI burden measurement and statistical analysis were performed by different investigators.

2.3. Extracranial color duplex sonography findings collection and interpretation

Specially trained neurologists performed color duplex sonography on all patients in this cohort. We used the Aloka Prosound Alpha 10 (Aloka, Japan) ultrasound machine. The examination was performed with a linear ultrasound probe 5–13 MHz in the standardized protocol. We recorded morphological and hemodynamic parameters of internal carotid arteries (ICA) and vertebral arteries (VA), including intima-media thickness (IMT) of the carotid arteries in millimeters, measured in the common carotid artery, 2 cm from the carotid bifurcation [18]; the sum of IMT in both carotid arteries; the presence of plaques and its characteristics (echogenicity, morphology, stability); the degree of carotid diameter stenosis in percentage using the combined criteria [14]; the sum of stenosis in both ICA; maximal stenosis of both ICA; ICA anatomic variations (kinking, coiling); hemodynamic parameters of ICA: peak systolic velocity (PSV) and end-diastolic velocity (EDV); the presence of plaque and hypoplasia of VA; and hemodynamic parameters of VA (PSV and EDV). Low-grade carotid artery stenosis was defined as diameter stenosis ranging from 1 to 49 %. Values above this were considered high-grade hemodynamically significant stenosis, while ICA with a stenosis degree of less than 1 % was considered as not having stenosis.

2.4. Statistical analysis

Tables and figures were used to present the data. Numeric variables are presented as median with interquartile range (IQR). Nominal and ordinal variables are presented as counts and percentages. Numeric variables were first analyzed for normality of distribution using descriptive statistics and the Kolmogorov-Smirnov test. Due to the irregular distribution, the Kruskal-Wallis and Fisher exact tests were used to test for differences between the groups, depending on whether the grouping variable was ordinal or nominal. Cases with missing data were excluded from the analysis for that variable. P values of <0.05 were considered statistically significant. R studio (version 4.3.2) [19] was used to perform all statistical analyses. Packages gtsummary and datawizard were used for statistical analysis and to create tables and package ggplot2 was used to create figures [20–22].

3. Results

Our cohort included 98 patients with isolated atherosclerotic CSVD. Out of them, 58 (59 %) were women and 40 (41 %) were men,

Table 1
Patient demographic characteristics and risk factors.

	N = 98[a]
Sex	
Female	58 (59 %)
Male	40 (41 %)
Age	65 (56, 71)
Hypertension	
Hypertension	85 (87 %)
no hypertension	13 (13 %)
Dyslipidemia	
Dyslipidemia	45 (46 %)
no dyslipidemia	53 (54 %)
Cholesterol	4.85 (4.18, 5.79)
Triglycerides	1.28 (0.99, 1.65)
Diabetes mellitus	
diabetes	27 (28 %)
no diabetes	71 (72 %)
Smoking	
non-smoker	52 (53 %)
Smoker	46 (47 %)

[a] n (%); Median (IQR).

ages ranging from 38 to 87 years (median 65, IQR 56–71 years). The basic demographic data and cerebrovascular risk factors characteristics are shown in Table 1. Hypertension was found in 85 (87 %) patients, while 45 (46 %) had dyslipidemia. The median cholesterol value was 4.85 (IQR 4.18–5.79) and for triglycerides, the median was 1.28 (IQR 0.99–1.65). Diabetes mellitus was found in 27 (28 %) patients, and 46 (47 %) were smokers.

As for the neuroimaging findings, 87 (89 %) patients had LS, out of which 7 (8 %) had lesions in the right brain hemisphere, 6 (6.9 %) in the left, and 74 (85 %) had bilateral lesions. WMH were present in 37 (38 %) patients. Among patients with MRI findings only (n = 75), LS were found in 69 (92 %), while WMH were present in 24 (32 %) patients. Fazekas score of 1 was found in 5 (21 %) patients, while 14 (58 %) had Fazekas 2, and 5 (21 %) had a Fazekas score of 3. Next MRI marker of CSVD, microbleeds were present in 4 (17 %) patients, while EPVS were found in 17 (23 %). When quantified, 5 (29 %) patients had less than 10 EPVS, 10 (59 %) patients had between 11 and 25 EPVS, and only 2 (12 %) had more than 25 EPVS in the basal ganglia. Brain atrophy was found in 30 (31 %) patients. Lastly, among the 75 patients with MRI, the CSVD burden score ranged from 0 to 3. Seven (9 %) patients had a score of 0, while 48 (64 %) had a score of 1. A score of 2 was found in 18 (24 %) patients, while only 2 (2.7 %) patients had a score of 3 (Fig. 1).

In terms of extracranial color duplex sonography findings, the median IMT of the right and left ICA and IMT sum were 1.10 (IQR 0.90–1.20), 1.10 (IQR 1.00–1,20), and 2.20 (IQR 2.00–2.40), respectively. Carotid stenosis was detected in 67 (68 %) patients. In the right ICA, low-grade stenosis up to 49 % was present in 51 (52 %) patients. Twelve (12 %) had hemodynamically significant stenosis equal to or more than 50 %, while 35 (36 %) didn't have stenosis. In the left ICA, 49 (50 %) patients had low-grade stenosis, 10 (10 %) had hemodynamically significant stenosis, and 39 (40 %) patients had no stenosis. The median carotid stenosis value for the entire cohort was 30 % (IQR 0–34) in the right ICA and 23 % (IQR 0–30) in the left ICA. Stenosis values in right and left ICA ranged from 0 to 100 %. Stenosis sum ranged from 0 to 170 %, with a median of 50 % (IQR 0–69). The maximal stenosis median was 30 % (IQR 0–40). When it comes to hemodynamic parameters, median PSV in right and left ICA were 76 (IQR 62–87) and 80 (IQR 68–90), respectively. The median EDV in the right ICA was 29 (IQR 24–35), while in the left ICA, it was 30 (IQR 25–38). Morphological and hemodynamic parameters of carotid arteries are shown in Table 2.

VA stenosis was not common in our population. Only 9 (9 %) patients had right VA stenosis, while 5 (5 %) had stenotic plaques in the left VA. The median PSV of the right and left VA were 39 (IQR 31–43) and 40 (IQR 35–45), respectively. The median EDV in the right VA was 15 (IQR 12.3–19), while in the left VA, it was 16 (IQR 14–20).

There was a statistically significant correlation between the female gender and brain atrophy. Atrophy was present in 23 (77 %) females and 7 (23 %) males ($p = 0.016$). Age correlated with the presence of LS and WMH. While LS were more common in younger patients (median age 63 vs. 70; $p = 0.009$), WMH were usually detected in older patients (median age 70 vs. 63, $p < 0.001$). Hypertension also correlated with the presence of WMH ($p = 0.016$). Out of 37 patients with WMH, 36 (97 %) had hypertension while out of 61 patients without WMH, 49 (80 %) had hypertension. There was a correlation between smoking and LS ($p = 0.043$). Among 87 patients with LS, 44 (51 %) were smokers, while out of 11 patients without LS, only 2 (11 %) were smokers. There was no correlation between other demographic parameters and risk factors and CSVD burden score, nor separate CSVD neuroimaging markers.

The statistical analysis showed a significant difference in all morphological parameters of carotid artery atherosclerosis based on the CSVD burden score (Table 3, Fig. 2). IMT values showed a difference between groups ($p = 0.003$ for right ICA, $p = 0.022$ for left ICA, $p = 0.006$ for IMT sum). The presence of carotid stenosis correlated with the CSVD burden score ($p = 0.003$), while the presence of carotid stenosis in the right and left ICA separately had a very strong correlation with the CSVD burden score ($p < 0.001$ and $p = 0.002$, respectively). There was a difference among CSVD burden score groups in diameter stenosis measured in percentages in the right and left ICA, stenosis sum, and maximal stenosis. ($p < 0.001$ for all). Since atherosclerosis is an age-related disease, there was a concern that these results might be influenced by the age of our patients. Because of that, we performed the same analysis with morphological parameters adjusted for age. All tests remained statistically significant even after adjustment.

When looking at each marker separately, morphological parameters of ICA stenosis correlated with the localization of LS. Left ICA stenosis was most severe when LS were localized in the left hemisphere ($p = 0.035$). In patients with WMH, right ICA stenosis was more commonly found ($p = 0.023$). They also had greater stenosis degree in the right and left ICA ($p = 0.005$ and $p = 0.022$, respectively), greater stenosis sum and maximal stenosis degree ($p = 0.006$ and $p = 0.015$, respectively), and greater left ICA IMT values ($p = 0.015$).

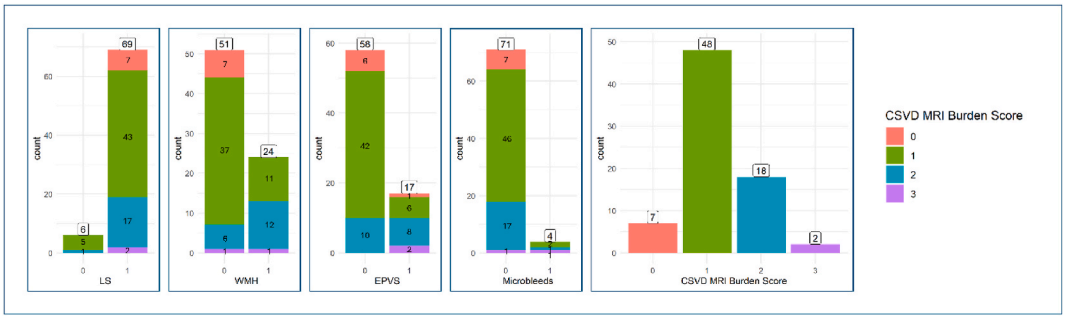

Fig. 1. Magnetic resonance imaging findings in patients with cerebral small vessel disease
Abbreviations: LS – lacunar stroke; WMH – white matter hyperintensities; EPVS – enlarged perivascular spaces; CSVD – cerebral small vessel disease; MRI – magnetic resonance imaging.

Table 2
Carotid artery ultrasonography findings.

Characteristic	N = 98[a]
ICA Stenosis	
no stenosis	31 (32 %)
stenosis	67 (68 %)
RICA Stenosis severity	
no stenosis	35 (36 %)
1–49 % stenosis	51 (52 %)
≥50 % stenosis	12 (12 %)
LICA Stenosis severity	
no stenosis	39 (40 %)
1–49 % stenosis	49 (50 %)
≥50 % stenosis	10 (10 %)
RICA Stenosis %	30 (0, 34)
LICA Stenosis %	23 (0, 30)
ICA Stenosis sum	50 (0, 69)
ICA max stenosis %	30 (0, 40)
RCA IMT	1.10 (0.90, 1.20)
LCA IMT	1.10 (1.00, 1.20)
IMT sum	2.20 (2.00, 2.40)
RICA PSV	76 (62, 87)
LICA PSV	80 (68, 90)
RICA EDV	29 (24, 35)
LICA EDV	30 (25, 38)

Abbreviations: ICA – internal carotid artery; RICA – right internal carotid artery; LICA – left internal carotid artery; RCA – right carotid artery; LCA – left carotid artery; IMT – intima-media thickness; PSV – peak systolic velocity; EDV – end-diastolic velocity.
[a] n (%); Median (IQR).

Table 3
Correlation between morphological markers of carotid artery atherosclerosis and cerebral small vessel disease burden score.

CSVD Burden Score	0, N = 7[a]	1, N = 48[a]	2, N = 18[a]	3, N = 2[a]	p-value[b]	p-value[b] (age-adjusted)
ICA Stenosis					**0.003**	**0.015**
no stenosis	4 (57 %)	22 (46 %)	1 (5.6 %)	0 (0 %)		
stenosis	3 (43 %)	26 (54 %)	17 (94 %)	2 (100 %)		
RICA Stenosis					**<0.001**	**<0.001**
no stenosis	7 (100 %)	23 (48 %)	1 (5.6 %)	0 (0 %)		
stenosis	0 (0 %)	25 (52 %)	17 (94 %)	2 (100 %)		
LICA Stenosis					**0.002**	**0.008**
no stenosis	4 (57 %)	27 (56 %)	2 (11 %)	0 (0 %)		
stenosis	3 (43 %)	21 (44 %)	16 (89 %)	2 (100 %)		
RICA Stenosis %	0 (0, 0)	15 (0, 30)	30 (30, 44)	85 (78, 93)	**<0.001**	**<0.001**
LICA Stenosis %	0 (0, 25)	0 (0, 30)	30 (26, 30)	75 (63, 88)	**<0.001**	**0.003**
ICA Stenosis sum	0 (0, 25)	20 (0, 60)	60 (60, 78)	160 (155, 165)	**<0.001**	**<0.001**
ICA max stenosis %	0 (0, 25)	20 (0, 30)	33 (30, 50)	100 (100, 100)	**<0.001**	**<0.001**
RCA IMT	0.90 (0.85, 1.00)	1.00 (0.90, 1.20)	1.20 (1.10, 1.30)	1.15 (1.08, 1.23)	**0.003**	**0.007**
LCA IMT	1.00 (0.85, 1.15)	1.10 (0.90, 1.20)	1.25 (1.03, 1.38)	1.20 (1.15, 1.25)	**0.022**	**0.040**
IMT sum	1.90 (1.75, 2.10)	2.05 (1.80, 2.40)	2.35 (2.20, 2.68)	2.35 (2.23, 2.48)	**0.006**	**0.016**

Abbreviations: CSVD – cerebral small vessel disease; ICA – internal carotid artery; RICA – right internal carotid artery; LICA – left internal carotid artery; RCA – right carotid artery; LCA – left carotid artery; IMT – intima-media thickness.
[a] n (%); Median (IQR).
[b] Fisher's exact test; Kruskal-Wallis rank sum test.

However, there was no correlation with WMH Fazekas score. We didn't *t*-test if EPVS and microbleeds correlated with any markers of ICA atherosclerosis as the groups were too small to make reliable conclusions (EPVS n = 17, microbleeds n = 4). Lastly, right ICA stenosis was more prevalent in patients with brain atrophy (p = 0.035). Stenosis degree (p = 0.009), stenosis sum (p = 0.018), and maximal degree of stenosis (p = 0.034) were also greater in these patients. There was no correlation between hemodynamic parameters of ICA stenosis or any markers of VA stenosis and the CSVD burden score, nor with any CSVD neuroimaging markers separately.

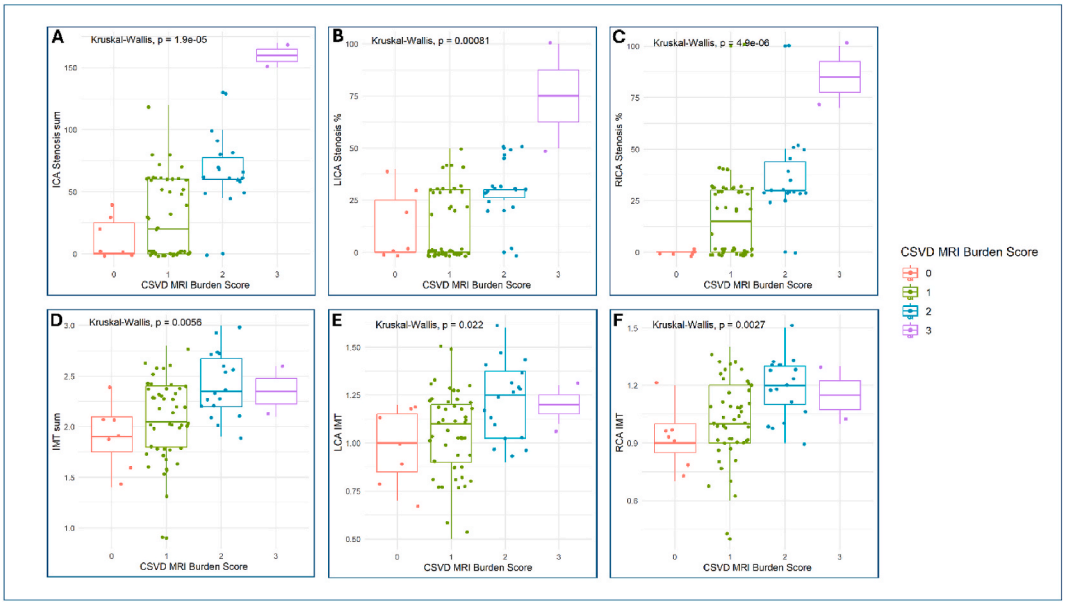

Fig. 2. Difference in carotid artery atherosclerosis morphological parameters based on cerebral small vessel disease burden score, showing p values for each test

A – stenosis sum; B – left ICA stenosis degree; C – right ICA stenosis degree; D – IMT sum; E – left carotid artery IMT; F – right carotid artery IMT. Abbreviations: ICA – internal carotid artery; CSVD – cerebral small vessel disease; MRI – magnetic resonance imaging; RICA – right internal carotid artery; LICA – left internal carotid artery; IMT – intima-media thickness; LCA – left carotid artery; RCA – right carotid artery.

4. Discussion

In our study, the CSVD burden score ranged from 0 to 3, with only 2 (2.7 %) patients having a score of 3. No patient had a maximal possible score of 4. These findings are similar to other studies on the subject, as a severe CSVD burden is not commonly found [17,23].

The main finding in our study is the correlation between carotid artery stenosis and CSVD MRI burden score. In fact, all morphological parameters of carotid stenosis (presence of stenosis, degree of stenosis, IMT) showed a strong statistical correlation with the CSVD burden. Most of our patients had low-grade asymptomatic carotid stenosis. This type of carotid atherosclerosis is often clinically overlooked as the focus is on the high-grade carotid stenosis due to the high possibility of stroke [24]. A recent SMART-MR study by Ghaznawi et al. showed that over a longer period of time (follow-up of 12 years), low-grade carotid stenosis was associated with brain atrophy and cognitive decline, both of which are features of CSVD. The authors focused only on low-grade asymptomatic carotid stenosis, which was prevalent in our cohort. However, in our study symptoms and degree of carotid stenosis weren't among the exclusion criteria. This way, we were able to assess the association between any grade of carotid artery stenosis and CSVD burden score in all atherosclerotic CSVD patients, showing that a higher degree of stenosis is associated with increasing CSVD burden score. This is especially interesting as symptomatic patients should have a lower burden score because only asymptomatic LS are calculated in the overall score [25].

Other authors that looked at imaging features of CSVD and carotid stenosis had similar results to our own. Del Brutto et al. included Atahualpa individuals ≥60 years old in their study due to their homogeneity in lifestyle. As most of these individuals didn't have a diagnosis of CSVD, their burden score was significantly lower than in our own cohort. However, authors found that carotid artery stenosis was strongly associated with CSVD burden score, especially in individuals with higher scores, meaning 3–4. The major difference here is that our cohort is made up of patients with atherosclerotic CSVD alone. Additionally, our cohort isn't as homogenous because it consists of CSVD patients exposed to different cerebrovascular risk factors (i.e. smoking, hypertension, dyslipidemia, and diabetes). Even though some risk factors were associated with certain features of CSVD (e.g. hypertension and WMH), no risk factor affected the overall CSVD burden score, further highlighting the association between carotid artery stenosis morphological parameters and the CSVD MRI burden score. Finally, it is important to mention that Del Brutto et al. didn't consider hemodynamic parameters of carotid artery stenosis, while we did, showing that hemodynamics did not influence the CSVD burden score [23]. Lu et al. also evaluated the relationship between the CSVD burden score and ultrasound-detected carotid stenosis. Even though their study included more male patients (74 % vs 41 % in our cohort), they had similar findings, concluding that carotid artery stenosis is associated with higher CSVD burden. There are some differences between this study and our own that should be pointed out. Lu et al. included patients presenting with ischemic stroke either originating from large or small vessel disease, as the authors believed this presentation is most likely to be associated with intracranial or extracranial large artery atherosclerosis. Our cohort included all patients with a diagnosis of atherosclerotic CSVD regardless of their presentation, meaning patients with gait dysfunction, cognitive decline, acute ischemic stroke, headaches, and incidentally found CSVD. We believe that this makes our findings more interesting, as they show an association

between carotid artery atherosclerosis and CSVD even in patients who do not present with ischemic disease. Additionally, the authors didn't specify the type of CSVD included in their study, while our research focused on atherosclerotic CSVD. Even though this reduced the number of patients eligible for the study, it created a cohort of pure atherosclerotic disease, reducing the influence of genetics and other factors like inflammatory disease. This is especially important to consider as CSVD is an umbrella term including multiple etiologies affecting the same blood vessels [17]. Interestingly, the CSVD burden score was associated with atherosclerosis in other vessels, not just cerebral ones. Song et al. looked at aortic atheroma identified by transesophageal echosonography and found that patients with aortic atheromas had higher CSVD burden scores [26]. Johansen et al. evaluated the association between coronary artery plaques and WMH, concluding that the presence and volume of plaques in coronary arteries are associated with larger WMH [8].

The exact mechanism of carotid artery stenosis on the brain is not fully understood. One proposed explanation is that stenosis in extracranial cerebral vessels causes global hypoperfusion of the brain leading to the development of brain atrophy and cognitive decline [25]. However, in some of these studies [25] and our own, most patients had hemodynamically non-significant stenosis, which is further confirmed by the fact that we found no correlation between hemodynamic parameters of carotid artery stenosis and CSVD burden score, leading us to believe that hemodynamics and brain perfusion are maintained in our patients. This makes the mechanism of hypoperfusion highly unlikely in our cohort. This fact, combined with other authors showing the correlation between CSVD and atherosclerosis found in different vascular beds (aorta and coronary circulation), and our previous finding that low-grade carotid artery stenosis is correlated with the function of cerebral small vessels, lead us to believe that carotid artery stenosis might not be directly related to CSVD, but could serve as a good marker for CSVD disease burden and progression [8,26,27]. Recent studies have found an association between carotid artery stenosis, impaired cognition, WMH, and altered brain network connectivity, which could provide more insight into this mechanism. These studies focused on high-grade hemodynamically significant carotid artery stenosis, which wasn't prevalent in our cohort. Since our study didn't include any measurement of cognitive function or brain network connectivity, we wouldn't be able to speculate if brain connectivity is affected in our cohort nor if it's influenced by carotid artery stenosis, which could be addressed by future research [28–31].

When looking at separate imaging markers of CSVD, we found a correlation between carotid artery stenosis and LS localization, WMH, and brain atrophy separately. This is not a novel finding as other authors showed this type of correlation previously. The correlation between LS and carotid stenosis has been investigated before, with inconsistent results. Some authors point to the importance of this correlation and the need for evaluation of carotid stenosis in patients with LS, while others believe that these findings are incidental [32–34]. All these studies focus on hemodynamically significant carotid stenosis, which was not prevalent in our cohort, thus making it difficult to compare results. We found only an association between the degree of left carotid artery stenosis and LS in the left cerebral hemisphere, showing that these patients had a higher degree of stenosis (35 % vs 20 % in right-sided or bilateral LS). As the number of patients who had unilateral LS was small ($n = 6$ for the left side, and $n = 7$ for the right side) we wouldn't be able to make conclusions based on these findings. WMH have been associated with both low- and high-grade carotid stenosis [25,35,36]. However, the correlation between the grade of WMH and carotid stenosis remains to be elucidated. Kandiah et al. noted an association between WMH grade and carotid artery stenosis degree, with modified Fazekas score being highest among patients in the highest quartile of carotid stenosis. The authors point out that these patients had carotid stenosis of over 50 %. As this grade of stenosis was not prevalent in our population, it is reasonable that we couldn't make this correlation [37]. When it comes to atrophy, it too has been previously correlated with carotid stenosis. However, to our knowledge, there isn't much research dealing with the correlation between atrophy and low-grade carotid stenosis. The aforementioned SMART-MR study showed this correlation after 12 years of follow-up. The same authors found that severe carotid stenosis over 70 % is associated with the progression of brain atrophy after 4 years of follow-up [25,38,39].

In our study, there was no correlation between hemodynamic parameters of ICA stenosis and any parameters of VA stenosis with the CSVD burden score. VA stenosis was not prevalent in our population, so we wouldn't expect to be able to show any statistically significant findings here.

When analyzing demographic data, we showed that brain atrophy is more common in women. This finding could be correlated with the incidence of dementia being more common in women. In addition, physiologically, women exhibit greater loss of brain volume over midlife which could be a confounding factor in our cohort [40–43]. Our analysis also showed a correlation between age and the presence of LS and WMH. In fact, LS were more common in younger patients, while WMH were more common in older ones. Previous studies have shown that WMH are more typically found in older adults. If we look at the natural progression of these lesions, LS are the ones that appear earlier and over time might cause hypoperfusion of the white matter leading to WMH. With this in mind, it is reasonable that LS would show up more commonly in younger patients and WMH in older ones [4,10,44–46]. Lastly, there was a correlation between hypertension and WMH, and smoking status and LS. These findings are not surprising as both hypertension and smoking are well-established risk factors for ischemic brain lesions [1,2,47,48].

4.1. Limitations

The main limitation of this study is its cross-sectional design, which doesn't allow for follow-up or estimation of the long-term effect of studied variables. As we aimed to evaluate only isolated atherosclerotic CSVD, the number of patients in this cohort was limited. Only a part of the cohort had undergone MRI which reduced the number of patients with CSVD MRI burden score. Additionally, our cohort included only patients with a diagnosis of CSVD, which was commonly due to their symptoms (e.g. cognitive impairment, lacunar stroke). Therefore, most patients had symptomatic disease, which didn't allow us to estimate the effect of carotid stenosis in those with asymptomatic CSVD and CSVD of earlier stage. Future research aims to evaluate intracranial atherosclerosis in these patients as well as cognitive function, allowing us to assess if carotid artery atherosclerosis is associated with these elements of CSVD

individually.

5. Conclusion

This study highlights the strong correlation between carotid artery stenosis morphological parameters and CSVD MRI burden. We believe the connection between the two comes from shared etiology, and not from the cause-effect mechanism. However, more research is needed with longitudinal follow-up of patients to make this conclusion. We suggest the use of carotid ultrasound as a supplementary method in the evaluation of patients with CSVD and their follow-up. This would allow the identification of patients whose condition might progress and allow for timely intervention.

Ethical approval statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Ethics Committee of the Neurology Clinic, University Clinical Centre of Serbia. (Protocol code NE/2011/34, September 14, 2011).

All patients provided written informed consent to participate in the study and for their data to be published.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy concerns. The data are available on request from the corresponding author.

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CRediT authorship contribution statement

Stefan Stoisavljevic: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Mirjana Zdraljevic:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation. **Aleksandra Radojicica:** Writing – review & editing, Project administration, Investigation, Data curation. **Aleksandra Pavlovic:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Formal analysis. **Milija Mijajlovic:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Milija Mijajlovic reports a relationship with Heliyon that includes: board membership.

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