Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Intracranial Dolichoectasia and Cerebral Small Vessel Disease in Patients With Intracerebral Hemorrhage

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BACKGROUND: Intracranial arterial dolichoectasia (IADE) is associated with cerebral small vessel disease (CSVD) in populations with ischemic stroke. Whether IADE is related to CSVD markers in patients with intracerebral hemorrhage (ICH) is unclear but might be relevant for CSVD diagnosis and prognosis. We aimed to investigate the prevalence and associations of IADE in patients with ICH.

METHODS: We included consecutive patients with ICH between February 2016 and September 2023. IADE was determined using magnetic resonance angiography based on validated scales assessing vessel diameter, length, and tortuosity. Neuroimaging markers of CSVD were investigated using validated magnetic resonance imaging rating scales. Left ventricular mass (LVM) was determined from transthoracic echocardiography. Multivariable binary logistic regression analyses were used to evaluate associations between IADE and CSVD.

RESULTS: We included 138 patients with a mean age of 66.7±11.8 years, 58.0% men. IADE was present in 16 patients (11.6%). LVM was greater in patients with IADE (183.0±61.3 g versus 155.3±51.2 g, *P*=0.04). Patients with ICH and IADE had significantly higher proportions of deep lacunes (43.8% versus 18.0%, *P*=0.02) and deep cerebral microbleeds (56.3% versus 27.1%, *P*=0.02) compared with individuals without IADE. IADE was independently associated with deep lacunes (adjusted odds ratio [OR], 3.10 [95% CI, 1.02–9.55], *P*=0.04), severe periventricular white matter hyperintensities (adjusted OR, 3.29 [95% CI, 1.00–10.94], *P*=0.04), and deep cerebral microbleeds (adjusted OR, 2.80 [95% CI, 1.04–8.65], *P*=0.04). Among these CSVD markers, IADE had a high predictive value for deep cerebral microbleeds with a receiver operating characteristic curve of 0.75 (95% CI, 0.66–0.85). There was no statistically significant association between IADE and lobar ICH (adjusted OR, 1.29 [95% CI, 0.36–4.64], *P*=0.70) or cerebral amyloid angiopathy (adjusted OR, 0.46 [95% CI, 0.13–1.67], *P*=0.24).

CONCLUSIONS: IADE is found in approximately 12% of patients with ICH and is independently associated with neuroimaging markers of arteriolosclerosis but not cerebral amyloid angiopathy.

Key Words: cerebral microbleed ■ dolichoectasia ■ intracerebral hemorrhage ■ lacune ■ small vessel disease ■ white matter hyperintensity

Intracranial arterial dolichoectasia (IADE) is characterized by brain arterial dilatation and elongation or tortuosity of the large intracranial vessels.[1,2] It can affect both anterior and posterior circulation, but basilar artery (BA) dolichoectasia accounts for 80% of all cases.[2,3] The prevalence of IADE in patients with ischemic stroke is higher than in the general population (10% to 12% versus 1% to 6%, respectively).[4,5]

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This article was sent to Jose Rafael Romero, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.039039

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The prevalence of intracranial arterial dolichoectasia (IADE) in patients with intracerebral hemorrhage is comparable to that in patients with ischemic stroke, at ≈12%, and is independently associated with neuroimaging markers of arteriolosclerosis but not with markers of cerebral amyloid angiopathy.

What Are the Clinical Implications?

- The study provides data on an association between large-artery pathology (IADE) and cerebral small vessel disease in patients with intracerebral hemorrhage, which could be relevant for understanding disease mechanisms and prevention, as we found an association between IADE and cerebral small vessel disease neuroimaging markers of arteriolosclerosis.
- Additionally, left ventricular mass is increased considerably in patients with intracerebral hemorrhage and IADE, supporting the concept that hypertension and hemodynamic alterations might underlie the pathological mechanisms of the association between IADE and cerebral small vessel disease.

Nonstandard Abbreviations and Acronyms

CMB	cerebral microbleed
cSS	cortical superficial siderosis
CSVD	cerebral small vessel disease
IADE	intracranial arterial dolichoectasia
ICH	intracerebral hemorrhage
LVM	left ventricular mass
PVS	perivascular space
WMH	white matter hyperintensity

Although most patients with IADE remain asymptomatic, a small proportion may experience intracranial bleeding, thromboembolic-related ischemic events, or cranial nerve or brainstem dysfunction, which is determined mainly by the severity of the disease at the time of diagnosis and its evolution.[6,7] In addition, evidence suggests that symptomatic patients have an unfavorable prognosis even following antiplatelet or anticoagulant therapy for the prevention of recurrent ischemic events.[8,9]

Several studies on populations with ischemic stroke have reported the association between IADE and markers of cerebral small vessel disease (CSVD) from both neuroradiological and neuropathological evidence.[10,11] IADE is associated with an increased risk of lacunar stroke, typically defined by clinical lacunar syndrome associated with a recent small subcortical infarct <1.5 cm in diameter, white matter disease, and various hemorrhagic CSVD markers (ie, cerebral microbleeds [CMBs]) and nonhemorrhagic (ie, lacunes, white matter hyperintensities [WMHs]).[12,13] Our recent systematic review and meta-analysis confirmed the association between IADE and small vessel disease in ischemic stroke.[14] However, these data are not necessarily generalizable to patients with intracerebral hemorrhage (ICH), in whom few data are available regarding the relationship between IADE and CSVD. Such data might be relevant for diagnosing the underlying small vessel arteriopathy or understanding disease mechanisms, which could provide guidance for the prevention of vascular events after ICH. Additionally, a study on the complete range of CSVD markers, such as perivascular spaces (PVSs) and cortical superficial siderosis (cSS), is necessary to understand associations with specific small vessel arteriopathies that can cause ICH (eg, arteriolosclerosis or cerebral amyloid angiopathy [CAA]). Arteriolosclerosis, or sporadic nonamyloid microangiopathy, typically has hypertension as a risk factor and affects deep perforating arteries, whereas CAA is characterized by amyloid-β deposition in cortical and leptomeningeal vessels. Therefore, distinguishing between the 2 main types of CSVD is important to develop rational therapeutic approaches.

In this study, we aimed to investigate the prevalence of IADE in patients with SVD-related ICH and evaluate whether IADE is related to neuroimaging markers of CSVD, including lacunes, WMHs, PVSs, as well as hemorrhagic markers including CMBs, and cSS. We also studied the diagnostic value of IADE for the classification of ICH based on the association with particular patterns of CSVD markers suggesting CAA or non-CAA (ie, arteriolosclerosis) as the underlying arteriopathy. We hypothesized that IADE could be relevant to understanding disease mechanisms and, thus, potentially the prevention of CSVD and future vascular events.

METHODS

Data Availability

Requests for anonymized data should be made in writing to the corresponding author; the appropriateness of reuse will be considered by the ULYSSES collaborators. A data sharing agreement will be required before any data can be shared.

Study Design and Patient Selection

This retrospective, cross-sectional study was conducted at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Patients with

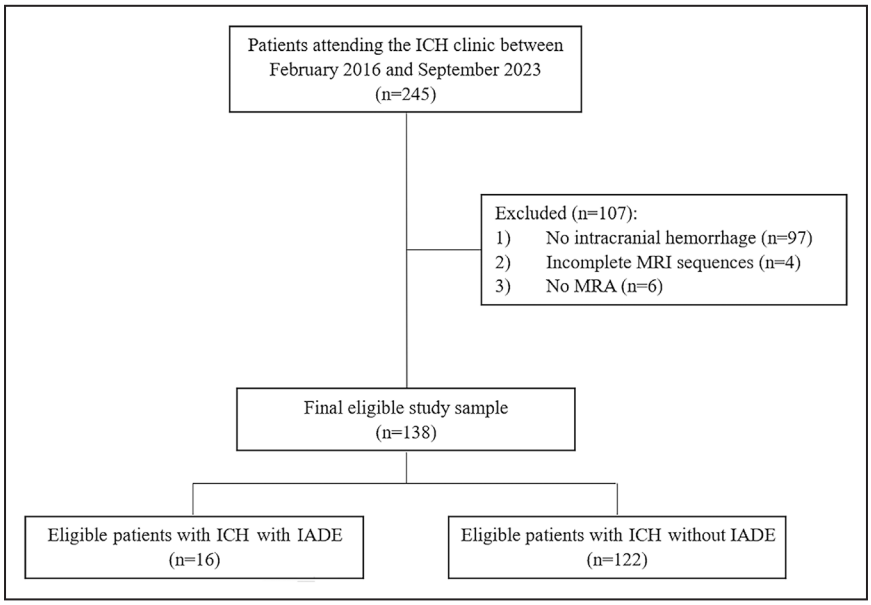

Figure 1. Flow chart of included participants.
IADE indicates intracranial arterial dolichoectasia; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiography; and MRI, magnetic resonance imaging.

symptomatic intracranial hemorrhage (ICH or nonaneurysmal subarachnoid hemorrhage) attributed to underlying SVD, including arteriolosclerosis, CAA, or mixed CSVD treated at a specialist clinic were initially enrolled between February 2016 and September 2023. Investigations for diagnosis and evaluation at the clinic were standardized and included magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), laboratory testing, transthoracic echocardiography, and neuropsychological tests. We excluded all patients diagnosed with macrovascular (ie, arteriovenous malformation, cavernoma, or aneurysm), traumatic, or other secondary causes of ICH. Patients with insufficient or incomplete MRI or MRA were also excluded. The flow chart of the included participants is illustrated in Figure 1.

Clinical Data

Demographic and clinical characteristics of the study population were collected from the electronic medical record. Demographic information included age, sex, comorbidities, and estimated glomerular filtration rate. Left ventricular mass (LVM) was calculated from 3 parameters from transthoracic echocardiography, including LV internal diameter in diastole, posterior wall thickness in diastole, and interventricular septum thickness in diastole using the standard equation for calculating LVM.[15] ICH volumes were measured using the ABC/2 formula.[16] The Cerebral Haemorrhage Anatomical Rating Instrument was used to map the anatomical location of spontaneous ICH and categorized into 3 locations: lobar, deep and infratentorial, and uncertain ICH.[17] Classification for ICH subtypes was categorized into 4 groups using an updated classification system for ICH subtypes.[18] Probable or possible CAA was defined according to the Boston criteria version 2.0 (v2.0).[19] Patients with multiple deep hemorrhages or single deep hemorrhage with severe or confluent WMH or deep lacunes were classified as arteriolosclerosis, and patients with mixed deep and lobar hemorrhages were categorized as mixed pattern CSVD.[18] Patients with ICH who had no MRI markers of CSVD were diagnosed with cryptogenic ICH.

Assessment of IADE

As a noncontrast MRI protocol was routinely used in our outpatient ICH clinic, the diameters of intracranial vessels were assessed on 3-dimensional time-of-flight MRA (Matrix 512x307x216, echo time [TE] 3.8, repetition time [TR] 23) to evaluate abnormal dilatation or ectasia. The BA was assessed at mid-pons, bilateral intracranial vertebral arteries at the V4 segment, and bilateral internal carotid arteries at the vertical portion of the cavernous segment. Ectasia was diagnosed when BA diameter >4.5 mm, vertebral artery diameter >4 mm, or internal carotid artery diameter >7.0 mm.[6,20] Abnormal elongations or tortuosity of intracranial vessels, known as dolichosis, was defined based on previously proposed criteria.[6,20–22] In the BA, a 4-point scale for laterality and height of bifurcation was applied to determine BA dolichosis.[20] The laterality of BA was scored as 0 (midline throughout), 1 (medial-to-lateral margin of clivus or dorsum sellae), 2 (lateral-to-lateral margin of clivus or dorsum sellae), and 3 (at

the cerebellopontine angle). The height of bifurcation was scored as 0 (at or below dorsum sellae), 1 (in the suprasellar cistern), 2 (at the third ventricle floor), and 3 (indentation and elevation of the third ventricular floor). BA dolichoectasia was defined when BA diameter >4.5 mm and laterality score ≥2 or height of bifurcation score ≥2. Abnormal elongation of vertebral arteries was established when the length of an intracranial part was >23.5 cm.[23] Internal carotid artery dolichosis was evaluated using a 6-point visual rating scale according to the modified criteria of Weibel-Fields and Metz, which range from 0 (normal), 1 (tortuosity), 2 (mild kinking), 3 (moderate kinking), 4 (severe kinking), and 5 (coiling).[21,24]

IADE was confirmed if the affected vessel met the criteria for abnormal elongation or tortuosity (dolichosis) and dilatation (ectasia). All MRA were rated by a trained vascular neurologist (K.T.) with random samples of 20 cases for additional review with another experienced vascular neurologist (L.P.) and senior neuroradiologist (D.M.) to determine interrater reliability. The Fleiss' kappa statistic for 2 outcomes and multiple raters revealed κ of 0.8665 for the presence of IADE, which was interpreted as substantial agreement among the authors.[25] Figure 2 demonstrates the IADE assessment in this study.

Assessment of MRI Markers of CSVD

All patients attending the clinic have a standardized whole-brain time-of-flight MRA as part of clinical care. The MRI protocol on a 3 Tesla Siemens Vida scanner for patients who attended the ICH clinic included T1-weighted, T2-weighted (matrix size 512×288, slice thickness 5 mm, TE 88, TR 4500), coronal fluid-attenuated inversion recovery (matrix 256×219, slice thickness 5 mm, TE 116, TR 8000, inversion time 2370), diffusion-weighted imaging (matrix 192×192, slice thickness 5 mm, TE 98, TR 6000, B values 0 and 1000), and susceptibility-weighted imaging (matrix 256×220, slice thickness 2.3 mm, TE 20, TR 27). Assessment of neuroimaging markers of lesions related to CSVD was defined according to proposed terms and definitions in the Standards for Reporting Vascular Changes on Neuroimaging 2.[26] Validated tools and scales for defining or mapping CSVD features on MRI were used, including the Microbleed Anatomical Rating Scale for CMBs burden and distribution,[27] the Fazekas scale for deep and periventricular WMHs,[28] and a validated 4-point scale for enlarged PVSs in basal ganglia and centrum semiovale.[29,30] The severity of the CSVD burden of each marker was dichotomized or trichotomized based on previously proposed total SVD scores.[31,32] Briefly, confluent deep WMH

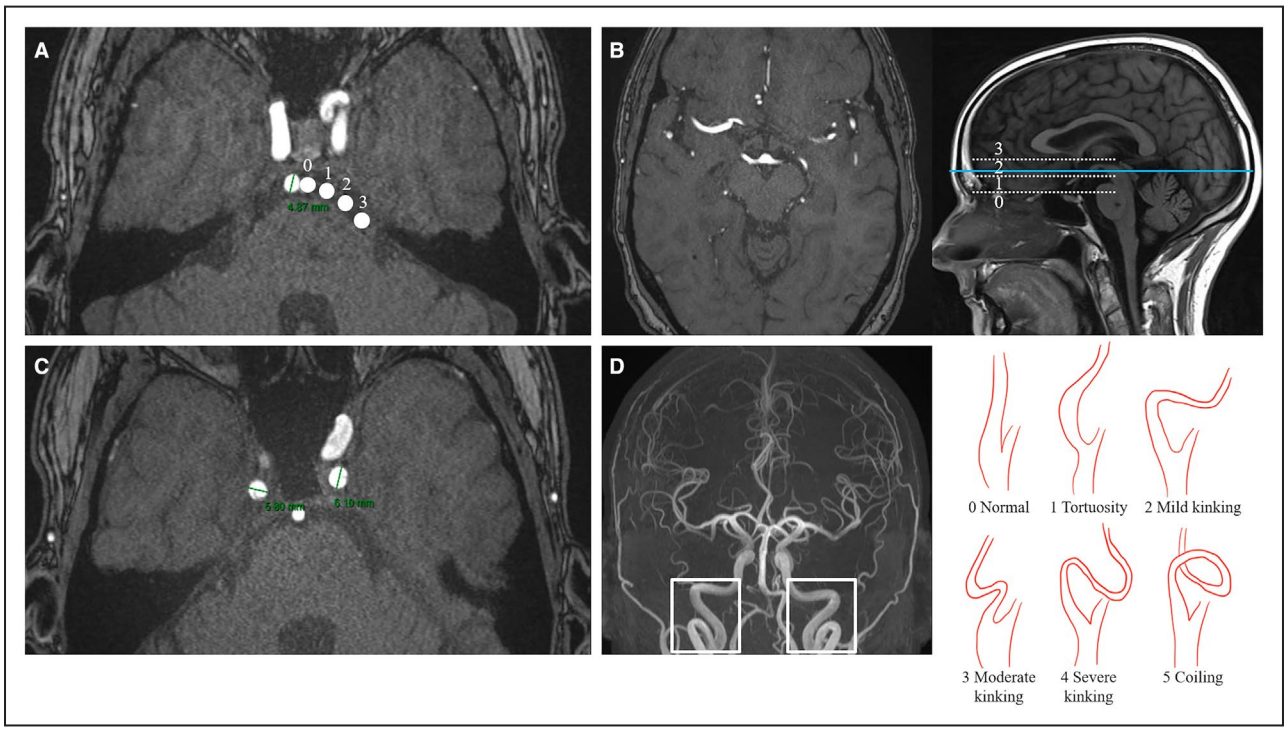

Figure 2. Demonstration of intracranial arterial dolichoectasia assessment.
A, Measurement of the maximum diameter of the basilar artery (4.87 mm) and its laterality (point 1: medial-to-lateral margin of clivus or dorsum sellae) in axial view. **B**, The same patient in Figure 2A demonstrates the height of the basilar artery bifurcation (point 2; at the floor of the third ventricle, indicated by the blue line) in a sagittal view. **C**, Another patient demonstrates the measurement of diameters of the bilateral internal carotid arteries at the vertical portion of the cavernous segment (right: 5.8 mm, left: 6.1 mm) (segmentation C4, Bouthillier classification). **D**, Angiography of carotid artery dolichoectasia (point 4: severe kinking according to the modified criteria of Weibel-Fields and Metz).

Table 1. Demographic and Clinical Characteristics of the Study Population

	Total (n=138)	IADE (+) (n=16)	IADE (–) (n=122)	*P* value
Demographics, no. (%)				
Age, y, mean±SD	66.7±11.8	63.4±3.7	67.2±1.0	0.12
Male sex	80 (58.0)	9 (56.3)	71 (58.2)	0.88
Hypertension	89 (64.5)	13 (81.3)	76 (62.3)	0.14
Diabetes	15 (10.9)	1 (6.3)	14 (11.5)	1.00
Dyslipidemia	39 (28.3)	2 (12.5)	37 (30.3)	0.24
Atrial fibrillation	12 (8.7)	3 (18.8)	9 (7.4)	0.15
Coronary artery disease	31 (22.5)	6 (37.5)	25 (20.5)	0.13
Chronic kidney disease	20 (14.5)	3 (18.8)	17 (13.9)	0.71
Smoking	23 (16.7)	4 (25.0)	19 (15.6)	0.31
Alcohol drinking	33 (23.9)	2 (12.5)	31 (25.4)	0.36
Left ventricular mass, g, mean±SD	158.6±53.0	183.0±61.3	155.3±51.2	0.04
Estimated glomerular filtration rate, mL/min per 1.73 m^2, mean±SD	75.9±13.9	74.9±18.7	76.0±13.2	0.77
ICH parameters, no. (%)				
ICH volume, cm^3—median (interquartile range)	6.2 (2.4–12.2)	6.1 (3.1–10.1)	6.4 (2.4–13.5)	0.75
ICH location (Cerebral Haemorrhage Anatomical Rating Instrument)				0.64
Lobar	103 (74.6)	11 (68.8)	92 (75.4)	
Deep and infratentorial	33 (23.9)	5 (31.2)	28 (23.0)	
Uncertain	2 (1.5)	0 (0.0)	2 (1.6)	
Classification of ICH				
CAA	78 (56.5)	5 (31.2)	73 (59.8)	0.04
Non-CAA	60 (43.5)	11 (68.8)	49 (40.2)	

CAA indicates cerebral amyloid angiopathy; IADE, intracranial arterial dolichoectasia; and ICH, intracerebral hemorrhage.

(Fazekas 2 or 3) or irregular periventricular WMHs extending into the deep white matter (Fazekas 3), as well as enlarged PVSs scores 3 to 4 (>20 basal ganglia- or centrum semiovale-PVSs) on visual rating scale were defined as severe nonhemorrhagic CSVD markers. A cutoff value of ≥5 lobar CMBs was considered a severe burden based on the CAA total SVD score from a study using a neuropathologic CAA cohort.[32] cSS was categorized into 3 groups: none, focal (1–3 sulci), and disseminated (≥4) cSS.[33] The data collection proforma (patient rating sheet) is presented in detail in Table S1.

Statistical Analysis

Descriptive statistics were used to report arterial diameters and the prevalence of IADE among the studied population. Data were displayed as numbers and proportions for categorical variables and mean±SD or median with interquartile range for continuous variables depending on data distribution. Demographic data and clinical characteristics were compared between groups using the Pearson χ^2 test (or Fisher exact test) for categorical variables and the Student *t* test (or Mann–Whitney *U* test) for continuous variables as appropriate. The associations between IADE and neuroimaging markers of CSVD were investigated using univariable and multivariable logistic regression analyses after adjustment for confounders, including older age (>60 years) and hypertension, and demonstrated as crude or adjusted odds ratio (OR) with their 95% CI. After logistic regression analysis, receiver operating characteristic curves were constructed with the area under the receiver operating characteristic curve used to quantify predictive or discriminative power. Spearman rank correlation was used to study the correlations between the severity of IADE and CSVD markers. We set the statistical significance level to $\alpha<0.05$ for all analyses. All statistical analyses were performed using licensed Stata statistical software version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Standard Protocol Approvals, Registrations, and Patient Consent

The University College London Hospitals National Health Service Foundation Trust Governance Review Board approved the study as a Service Evaluation (registration reference 07-202 324-SE) for the evaluation of brain imaging findings, clinical features, causes, and outcomes of people with different forms of intracranial hemorrhage treated in the University College London Hospitals Comprehensive Stroke Service. Because it was a retrospective study and data were collected as part of routine clinical care, the requirement for individual patient informed consent was waived.

RESULTS

Participants and IADE Diagnosis

The total number of patients assessed in the clinic was 245. After considering all exclusion criteria, including patients without ICH, incomplete MRI sequences or no MRA available (Figure 1), we included 138 final eligible patients with ICH with a mean age of 66.7±11.8 years;

Table 2. Intracranial Arterial Diameters in Patients With Intracerebral Hemorrhage With and Without IADE (IADE (+) and IADE (–))

Artery	Mean±SD, mm	Min–max, mm	*P* value
Basilar artery	3.6 (0.7)	2.0–5.1	
IADE (+)	4.8 (0.2)	4.6–5.1	<0.001
IADE (–)	3.4 (0.6)	2.0–4.9	
Right intracranial vertebral artery	2.7 (0.6)	1.2–4.2	
IADE (+)	3.2 (0.8)	1.2–4.1	0.001
IADE (–)	2.6 (0.5)	1.4–4.2	
Left intracranial vertebral artery	2.9 (0.6)	1.0–4.3	
IADE (+)	3.4 (0.8)	1.0–4.3	<0.001
IADE (–)	2.8 (0.6)	1.6–4.3	
Right internal carotid artery	5.1 (0.6)	3.7–6.5	
IADE (+)	5.4 (0.7)	4.4–6.5	0.06
IADE (–)	5.1 (0.6)	3.7–6.5	
Left internal carotid artery	5.1 (0.5)	3.8–6.6	
IADE (+)	5.4 (0.6)	4.4–6.6	0.03
IADE (–)	5.1 (0.5)	3.8–6.6	

IADE indicates intracranial arterial dolichoectasia.

80 (58.0%) were men (Table 1). Of the included participants, 16 (11.6%) patients had IADE of basilar arteries, and no IADE was documented in the anterior circulation. The mean BA diameter for BA dolichoectasia was 4.8±0.2 mm, ranging from a minimum of 4.6 to a maximum of 5.1 mm. As expected, intracranial arterial diameters were significantly dilated in patients with IADE (IADE (+)) compared with those without IADE (IADE (–)), except for the right internal carotid arteries (Table 2 and Figure 3).

Risk Factors and ICH Parameters

As delineated in Table 1, there was a higher proportion of arterial hypertension (81.3% versus 62.3%) in patients with ICH and IADE, although the difference did not reach statistical significance. LVM (a cardiac structural biomarker of systemic hypertension) was significantly greater in individuals with IADE (183.0 g versus 155.3 g, *P*=0.04). Overall, 10.9% of patients had diabetes, 28.3% had dyslipidemia, and 22.5% had coronary artery disease. The prevalence of vascular risk factors was comparable across individuals with ICH with and without IADE.

According to the Cerebral Haemorrhage Anatomical Rating Instrument, approximately three-quarters (74.6%) of patients had lobar ICH, followed by deep and infratentorial in 23.9% and uncertain ICH in 1.5%. The median ICH volume was 6.2 cm^3 (interquartile range, 2.4–12.2 cm^3). Regarding the classification of ICH, probable CAA was diagnosed in 56.5% of patients with ICH. The remaining 43.5% were classified as non-CAA, comprising 23.2% arteriolosclerosis, 16.7% mixed pattern CSVD, and 3.6% cryptogenic. Patients diagnosed with IADE had a higher proportion of non-CAA ICH (68.8% versus 40.2%, *P*=0.04).

CSVD Markers and Association With IADE

Among nonhemorrhagic CSVD markers, patients diagnosed with IADE showed a greater likelihood of having any lacunes and deep lacunes in comparison to those without IADE (56.3% versus 32.0%, *P*=0.04 and 43.8% versus 18.0%, *P*=0.02, respectively). Patients with IADE had a greater number of lacunes compared with individuals without IADE (1 [0–4] versus 0 [0–1], *P*=0.02). For hemorrhagic markers, patients with ICH and IADE had a higher prevalence of deep CMBs (56.3% versus 27.1%, *P*=0.02) and had higher deep CMBs burden (2 [0–15] versus 0 [0–1], *P*=0.003) (Table 3). There were no statistical differences between groups for other CSVD markers or total SVD scores.

Because of the small number of outcomes (IADE), multivariable regression analyses were adjusted for just 2 variables, age and hypertension, to alleviate model overfitting. These 2 variables were included in the adjusted models based on findings from previous studies that age and hypertension might be independent factors associated with IADE.[34,35] We have not adjusted for multiple testing as we are explicit regarding all the tests that have been performed.[36] We found that IADE was independently associated with deep lacunes and severe periventricular WMHs (Fazekas 3) (adjusted OR, 3.10 [95% CI, 1.02–9.55], *P*=0.04 and adjusted OR, 3.29 [95% CI, 1.00–10.94], *P*=0.04, respectively). There was an association between IADE and the presence of deep CMBs (adjusted OR, 2.80 [95% CI, 1.04–8.65], *P*=0.04) (Table S2 and Table 4). We additionally delineated the distribution of BA diameter and 4 significant CSVD markers from the present study and found that patients with ICH and deep CMBs had a greater BA diameter

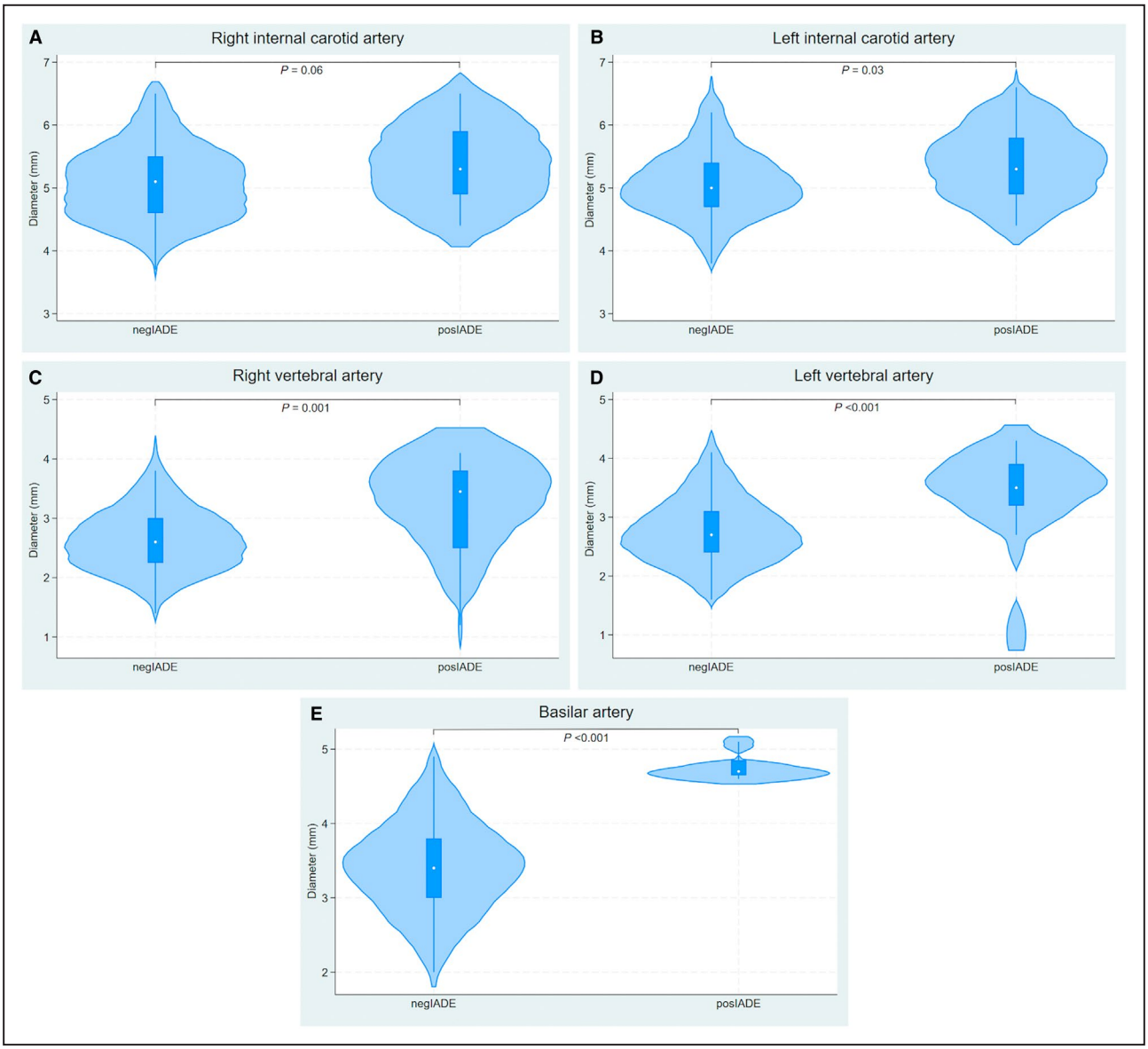

Figure 3. Arterial diameters and IADE.
Box plots and violin plots demonstrate median with interquartile range and 95% CI and distribution of diameter of right internal carotid artery (**A**), left internal carotid artery (**B**), right vertebral artery (**C**), left vertebral artery (**D**), and basilar artery (**E**) in patients with intracerebral hemorrhage with and without IADE (IADE (+) and IADE (–), respectively. IADE indicates intracranial arterial dolichoectasia.

(Figure 4). Comparing receiver operating characteristic curves among these CSVD markers, IADE showed an acceptable predictive value for the presence of deep CMBs in patients with ICH. This was determined by analyzing the receiver operating characteristic curve, which yielded a value of 0.75 (95% CI, 0.66–0.85) (Figure 5).

Correlations Between the Severity of IADE and CSVD Markers

We used Spearman rank correlation to quantify the correlation between the severity of IADE and the aforementioned CSVD markers (Table S3). BA diameter and height of bifurcation score were significantly correlated with some CSVD markers of arteriolosclerosis (eg, height of bifurcation of the BA with deep lacunes; BA diameter and abnormal elongation with the burden of basal ganglia-PVSs and deep CMBs) (Figure S1). By contrast, measures of IADE severities were negatively correlated with cSS, a hemorrhagic marker of CAA.

DISCUSSION

In this single-center retrospective, cross-sectional study examining the prevalence of IADE and its association

Table 3. Cerebral Small Vessel Disease Markers in Patients With Intracerebral Hemorrhage With and Without IADE (IADE (+) and IADE (–))

	Total (n=138)	IADE (+) (n=16)	IADE (–) (n=122)	*P* value
Lacunes, median (IQR)	0 (0–1)	1 (0–4)	0 (0–1)	0.02
Lacunes (≥1 lacunes), no. (%)	48 (34.8)	9 (56.3)	39 (32.0)	0.04
Deep lacunes (≥1 lacunes), no. (%)	29 (21.0)	7 (43.8)	22 (18.0)	0.02
Basal ganglia-PVSs, 0–4, median (IQR)	1 (0–2)	2 (1–2)	1 (0–2)	0.15
0–2, no. (%)	117 (84.8)	13 (81.2)	104 (85.3)	0.71
3–4, no. (%)	21 (15.2)	3 (18.8)	18 (14.7)	
Centrum semiovale-PVSs, 0–4, median (IQR)	3 (1–3)	2 (1–3)	3 (1–3)	0.23
0–2, no. (%)	68 (49.3)	9 (56.2)	59 (48.4)	0.55
3–4, no. (%)	70 (50.7)	7 (43.8)	63 (51.6)	
Deep WMHs, 0–3, median (IQR)	2 (1–3)	2 (1–3)	2 (1–2)	0.98
0–1, no. (%)	65 (47.1)	8 (50.0)	57 (46.7)	0.81
2–3, no. (%)	73 (52.9)	8 (50.0)	65 (53.3)	
Periventricular WMHs, 0–3, median (IQR)	2 (1–2)	2 (1–3)	2 (1–2)	0.35
0–2, no. (%)	105 (76.1)	10 (62.5)	95 (77.9)	0.18
3, no. (%)	33 (23.9)	6 (37.5)	27 (22.1)	
Deep CMBs (≥1 CMBs), no. (%)	42 (30.4)	9 (56.3)	33 (27.1)	0.02
Median (IQR)	0 (0–1)	2 (0–15)	0 (0–1)	0.003
Lobar CMBs, median (IQR)	7 (1–33)	8 (2–33)	7 (1–33)	0.78
0–1 CMB, no. (%)	35 (25.4)	4 (25.0)	31 (25.4)	0.94
2–4 CMBs, no. (%)	24 (17.4)	2 (12.5)	22 (18.0)	
≥5 CMBs, no. (%)	79 (57.2)	10 (62.5)	69 (56.6)	
Cortical superficial siderosis, no. (%)				0.06
None	72 (52.2)	13 (81.3)	59 (48.4)	
Focal (1–3 sulci)	24 (17.4)	1 (6.2)	23 (18.8)	
Disseminated (≥4 sulci)	42 (30.4)	2 (12.5)	40 (32.8)	
Total SVD score, 0–4, median (IQR)	2 (1–3)	2 (2–3)	2 (1–2)	0.27
Cerebral amyloid angiopathy total SVD score, 0–6, median (IQR)	3 (2–5)	3 (1–3)	3 (2–5)	0.05

CMBs indicate cerebral microbleeds; IADE, intracranial arterial dolichoectasia; IQR, interquartile range; PVSs, perivascular spaces; SVD, small vessel disease; and WMHs, white matter hyperintensities.

with CSVD in patients with symptomatic ICH, we found an IADE prevalence of 11.6%. IADE was strongly associated with specific neuroimaging markers of CSVD, including severe periventricular WMHs, deep lacunes, and deep CMBs, which are all considered markers of arteriolosclerosis; the observed associations remained statistically significant, even after adjusting for age and hypertension where appropriate. We also found negative correlations between IADE and cSS, a highly specific marker of CAA.

In the present study, the prevalence of IADE in patients with spontaneous ICH was comparable with a previous clinico-radiologic study of patients with ICH, which reported an IADE prevalence of 12.1%[37] using similar neuroimaging, definitions, and scoring methods for dolichoectasia.[20,22] Patients with ischemic stroke or transient ischemic attack have varied prevalences of IADE, ranging from 6.0% to 13.2%, depending on the population studied and visual assessment for defining dolichoectasia.[10,13] The prevalence of IADE was 24% in a study using semiautomatic vessel analysis.[38] Our recent systematic review and meta-analysis reported a pooled prevalence of IADE in ischemic stroke at 11.4%, with an association with markers of SVD.[14] This is a similar prevalence to the findings of the present study, suggesting that IADE may be a marker for CSVD, regardless of whether stroke is due to ischemia or hemorrhage.

Previous studies found that IADE, especially vertebrobasilar dolichoectasia (VBD), is associated with hypertension, older age, and male sex.[4,34,39] Although vascular risk factors were prevalent among individuals with IADE, the present study showed no significant differences in particular risk factors between patients with ICH with and without IADE, except for LVM. The heterogeneity of the studied population might explain this discrepancy as previous studies focused on patients with ischemic stroke, transient ischemic attack, lacunar stroke, or mixed stroke.[10,37,40] A study used data from the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial revealed that conventional risk factors, hypertension and diabetes, were significantly associated with vertebrobasilar ectasia in patients with recent lacunar stroke, a subtype of stroke that is closely correlated with hypertension.[40] We also found that individuals with ICH and IADE had considerably higher degrees of LVM detected by transthoracic echocardiography, which likely indicates longstanding systemic arterial hypertension.[15] The hemodynamic changes and subsequent vascular remodeling due to injuries of smooth muscle and endothelial cells from arterial hypertension may result in the pathogenesis of IADE-related arteriopathy and may partly explain the findings in this study that patients with IADE had more CSVD markers only in the deep brain regions, including deep lacunes and deep CMBs.[2,6]

Because CSVD accounts for ≈80% of all nontraumatic or spontaneous ICH, understanding the underlying pathophysiological associations with IADE might guide the diagnosis and prevention of CSVD progression in the population with ICH.[41] The independent

Table 4. Association Between Intracranial Arterial Dolichoectasia and Neuroimaging Markers of Cerebral Small Vessel Disease and ICH Classification

	IADE (+) (n=16)	IADE (–) (n=122)	Unadjusted		Adjusted*	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Cerebral small vessel disease markers, no. (%)						
Lacunes ≥1	9 (56.3)	39 (32.0)	2.74 (0.83–9.27)	0.05	2.41 (0.82–7.11)	0.11
Deep lacunes ≥1	7 (43.8)	22 (18.0)	3.54 (1.01–11.90)	0.02	3.10 (1.02–9.55)	0.04
Basal ganglia-PVSs 3–4	3 (18.8)	18 (14.7)	1.33 (0.22–5.56)	0.71	1.87 (0.44–7.95)	0.39
Centrum semiovale -PVSs 3–4	7 (43.8)	63 (51.6)	0.73 (0.22–2.36)	0.55	0.95 (0.31–2.88)	0.93
Deep WMHs 2–3	8 (50.0)	65 (53.3)	0.88 (0.27–2.88)	0.80	1.31 (0.41–4.17)	0.65
Periventricular WMHs 3	6 (37.5)	27 (22.1)	2.11 (0.57–7.08)	0.18	3.29 (1.00–10.94)	0.04
Deep CMBs ≥1	9 (56.3)	33 (27.1)	3.47 (1.04–11.81)	0.02	2.80 (1.04–8.65)	0.04
Lobar CMBs ≥5	10 (62.5)	69 (56.6)	1.28 (0.39–4.56)	0.65	1.94 (0.61–6.18)	0.26
ICH location, no. (%)						
Lobar	11 (68.8)	92 (75.4)	0.72 (0.21–2.86)	0.55	1.29 (0.36–4.64)	0.70
Classification of ICH, no. (%)						
Cerebral amyloid angiopathy	5 (31.2)	73 (59.8)	0.31 (0.08–1.03)	0.04	0.46 (0.13–1.67)	0.24

CMBs indicates cerebral microbleeds; IADE, intracranial dolichoectasia; ICH, intracerebral hemorrhage; OR, odds ratio; PVSs, perivascular spaces; and WMHs, white matter hyperintensities.

*Adjusted for age >60 years and hypertension with binary logistic regression analysis.

associations between IADE and neuroimaging markers of CVSD, including severe periventricular WMHs and deep lacunes and deep CMBs, were strongly confirmed in our study, which is in line with prior studies in patients with ischemic stroke or transient ischemic attack.[11,12,35] Other recent studies also found relevant

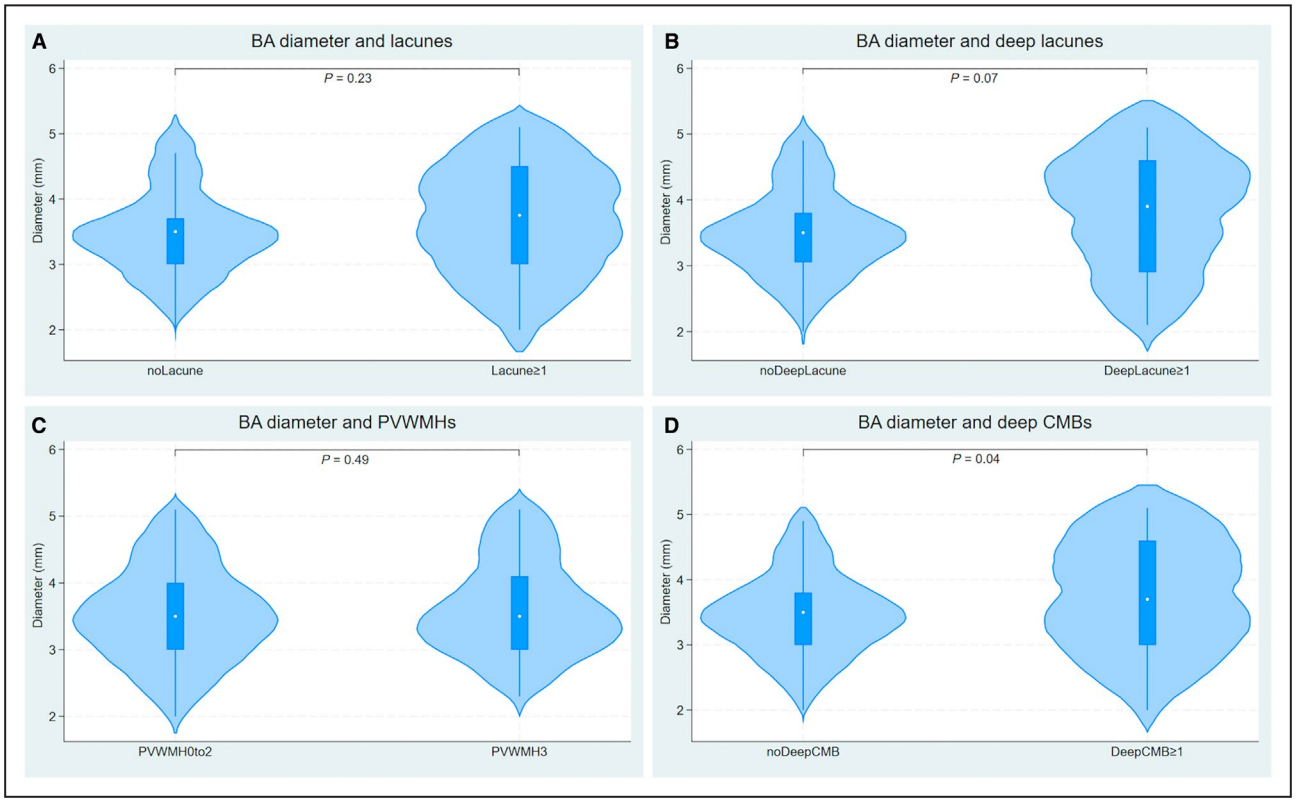

Figure 4. BA diameter and CSVD markers.
Box plots and violin plots demonstrate medians with interquartile ranges and 95% CI and distributions of BA diameter and lacunes (no vs ≥1 lacunes) (**A**), deep lacunes (no vs ≥1 deep lacunes) (**B**), PVWMHs (Fazekas scale 0–2 vs Fazekas scale 3) (**C**), and deep CMBs (no vs ≥1 CMBs) (**D**). BA indicates basilar artery; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; and PVWMHs, periventricular white matter hyperintensities.

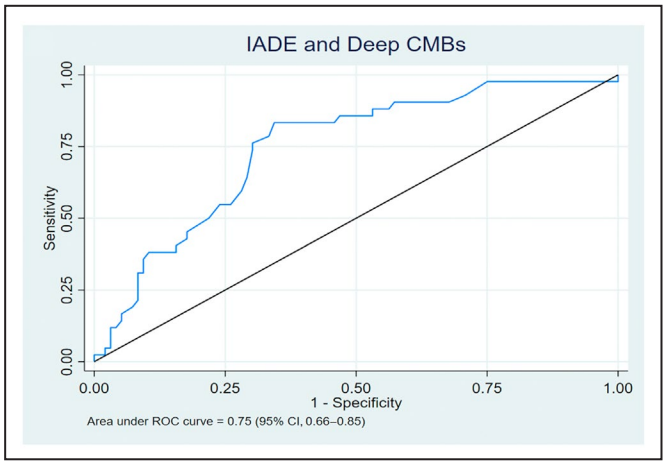

Figure 5. ROC curve analysis of IADE and CSVD markers.
AuROC curve of IADE and deep CMBs. AuROC indicates area under the receiver operating characteristic; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; IADE, intracranial arterial dolichoectasia; PVWMHs, periventricular white matter hyperintensities; and ROC, receiver operating characteristic.

relations between BA dolichoectasia and severe degrees of WM changes and lacunes.[34,42] Additionally, there is robust evidence on associations between CMBs and IADE, particularly regarding the burden or location of CMBs and the diameter or affected vascular territory. One study of hospitalized patients with ischemic stroke or transient ischemic attack found a substantial association between VBD and CMBs in the posterior circulation territory.[13] Importantly, apart from the presence of CMBs, BA diameter is associated with CMB burden.[43] It is important to note that the population in the aforementioned study is made up of outpatients with no documented cerebrovascular events. Our study also illustrated the significance of IADE on specific CSVD markers because of the substantial difference in BA diameter and the presence of deep CMBs.

Pathways associated with blood vessel structure and remodeling are postulated to account for the mechanisms underlying the association between IADE and CSVD.[2,3] Vascular aging and hypertension cause hemodynamic alterations.[44] Also, the imbalance of matrix metalloproteinase and its tissue inhibitor pathway attributed to tunica media injury and abnormal vascular remodeling might underline the association between IADE and CSVD.[1,3] Arterial wall abnormalities, characterized by internal elastic lamina defects and thinning of the media due to smooth muscle atrophy, may increase the risk of ICH in patients with IADE.[5] A prospective study of patients with VBD found that intracranial bleeding was independently associated with the diameter and laterality of BA and hypertension.[45] Data on 107 patients with brain hemorrhage further supported this hypothesis because 92.4% of ICH in patients with VBD occurred at the pons (38.5%), basal ganglia (23.1%), thalamus (15.4%), and deep cerebellum (15.4%), brain areas strongly related to arteriolosclerosis.[37] Although findings from the present study provided a nonsignificant difference regarding ICH location due to a high proportion of CAA-associated ICH in our cohort, resulting in a greater number of lobar ICH, we found that IADE was selectively associated with CSVD markers for arteriolosclerosis-related ICH, including deep lacunes and deep CMBs, and negatively associated with cortical superficial siderosis, a highly specific marker of CAA. These findings imply that maintaining optimal blood pressure levels could be especially beneficial in preventing ICH in people with IADE. Moreover, understanding the underlying pathophysiological process and associations with vascular risk factors or CSVD markers is crucial to primary prevention and reducing the risk of recurrent ICH.

Our results found that the presence of IADE in patients with spontaneous ICH might be associated with CSVD markers for arteriolosclerosis rather than CAA because of their inverse relationship with the latter (Table 4 and Figure S2). Our findings suggest that patients with IADE are less likely to have CAA as an underlying pathology, but this finding requires further confirmation in other cohorts. Computed tomography angiography is commonly performed as a standard investigation in patients with ICH. Future research, therefore, might explore the potential benefits of including IADE in addition to the established Edinburgh computed tomography-based diagnostic criteria for lobar ICH associated with CAA to determine whether this could enhance the accuracy of diagnosis.

The present study thoroughly investigated a complete range of neuroimaging markers of CSVD, including well-defined hemorrhagic and nonhemorrhagic markers, and their correlations with IADE in a specific population with intracranial hemorrhage. However, we acknowledge some limitations, including the retrospective study design and small sample size that might result in inadequate statistical power to identify minor or modest associations. Second, because of the cross-sectional study design, the establishment of causal relationships is not possible. We also acknowledge the lack of uniformly set diagnostic criteria for IADE. It is important to acknowledge that previously proposed criteria for IADE used different imaging modalities to establish IADE, including computed tomography, MRI, or both.[6,20,22] Currently, there is no consensus definition for distinguishing VBD from a fusiform aneurysm, and using lumen-based time-of-flight MRA may be inadequate in challenging cases. Although time-of-flight MRA is widely used for the noninvasive assessment of the cerebrovascular system, potential artifacts associated with this technique include the overestimation of stenoses due to artifact cause by turbulent flow. To overcome this artifact, it is often necessary to perform a gadolinium contrast enhancement MRA. However, we intended to minimize this disadvantage by performing an interrater agreement in the present study. Due to a small proportion of IADE in this study, we could not account for factors such as sex and body weight in multivariate models, which might affect arterial diameter variations. Finally, we cannot generalize our results to all patients with IADE because we did not identify dolichoectasia of the anterior circulation.

CONCLUSIONS

In conclusion, IADE is a common intracranial large vessel arteriopathy found in about 12% of patients with ICH, a prevalence similar to that seen in ischemic stroke. Our study demonstrated independent associations between IADE and neuroimaging markers of arteriolosclerosis (periventricular WMHs, deep lacunes, and deep CMBs), but negative associations with cortical superficial siderosis, a marker of CAA. Hemodynamic alterations or shared pathways related to blood vessel structure and remodeling associated with longstanding hypertension are potential underlying pathophysiological mechanisms. Further studies are required to establish the utility of this large vessel arteriopathy as a marker for identifying ICH subtypes and prognosis in patients with ICH.

ARTICLE INFORMATION

Received September 24, 2024; accepted May 5, 2025.

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Acknowledgments

Mr Thiankhaw: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, and writing—original draft; Dr Panteleienko: data curation, methodology, and writing—review and editing; Ms Stewart: data curation, methodology, and writing—review and editing; Dr Oliver: data curation, methodology, and writing—review and editing; Dr Mallon: data curation, methodology, supervision, visualization, and writing—review and editing; Dr Ambler: formal analysis, methodology, supervision, visualization, and writing—review and editing; Dr Werring: conceptualization, investigation, methodology, supervision, visualization, and writing—review and editing.

Sources of Funding

This research was supported by researchers at the National Institute for Health and Care Research, University College London Hospitals Biomedical Research Centre.

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

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