JoS
JOURNAL OF STROKE

Geometry of Terminal Internal Carotid Artery Bifurcation May Be Associated With Middle Cerebral Artery Plaque Ulceration: A Three-Dimensional Rotational Angiography Study

Xinyi Leng,[1] Bonaventure Y.M. Ip,[1] Sze Ho Ma,[1] Wai Ting Lui,[1] Vincent H.L. Ip,[1] Florence S.Y. Fan,[1] Howan Leung,[1] Vincent C.T. Mok,[1] Simon C.H. Yu,[2] Thomas W. Leung[1]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
[2]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Dear Sir:

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke. In patients with symptomatic ICAD, ICAD plaque ulceration as revealed through three-dimensional rotational angiography (3DRA) was associated with repetitive infarctions downstream, indicating possibly repetitive embolization.[1] Hence, plaque ulceration represents a vulnerable plaque type in ICAD, and it is imperative to study the contributing factors.

Previous studies have revealed the effects of carotid bifurcation geometry, in addition to systemic risk factors, on atherosclerosis in proximal internal carotid artery (ICA).[2,3] Regarding ICAD, there is some evidence of the association between proximal artery geometry and early-stage atherosclerosis (e.g., non-stenotic plaque) in middle cerebral artery (MCA).[4] However, it would be more clinically relevant to study such associations in patients with advanced ICAD (e.g., high-grade, symptomatic lesions), which bear a much higher stroke risk. In this study, we therefore aimed to investigate the association between terminal ICA bifurcation geometry and MCA-M1 plaque ulceration in patients with symptomatic, high-grade, atherosclerotic MCA-M1 stenosis.

In a prospective, cross-sectional study, patients with ischemic stroke or transient ischemic attack within 1 month, attributed to high-grade (60%–99%), atherosclerotic MCA-M1 stenosis confirmed through 3DRA, were recruited. Patients with an ipsilateral hypoplastic anterior cerebral artery (ACA) were excluded. More inclusion/exclusion criteria are provided in Supplementary Methods. This study was approved by the local Ethics Committee (Reference No. 2011.021), and all patients provided written informed consent.

Ulcerative MCA-M1 plaque was defined as the invagination of contrast beneath the endoluminal lining or a >90˚ slope at the upstream or downstream plaque shoulder.[1] Non-ulcerative plaques were defined as lesions with a smooth or irregular plaque surface.[1] We measured the distance of the plaque from the MCA origin and assessed the geometric features at the terminal ICA bifurcation in 3DRA, including the diameters at the MCA origin, ACA origin, and terminal ICA, and MCA-ACA angle (Figure 1 and Supplementary Methods). We calculated the area ratios of MCA versus ACA origin, MCA origin versus terminal ICA, and MCA+ACA origins versus terminal ICA.

Continuous and categorical variables were respectively described using median (interquartile range, IQR) and numbers (percentage) and compared between patients with ulcerative and non-ulcerative plaques, using Wilcoxon rank sum tests and chi-square or Fisher's exact tests. The geometric features of ICA bifurcation with a $P<0.05$ in univariate analyses were analyzed using multivariate logistic regression for their independent associations with ulcerative MCA-M1 plaque, adjusting for age, sex in Model 1, plus cardiovascular risk factors in Model 2, and plus percent luminal stenosis in MCA-M1 in Model 3. All analyses were conducted using IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY, USA), with a two-sided $P<0.05$ considered to represent statistical significance.

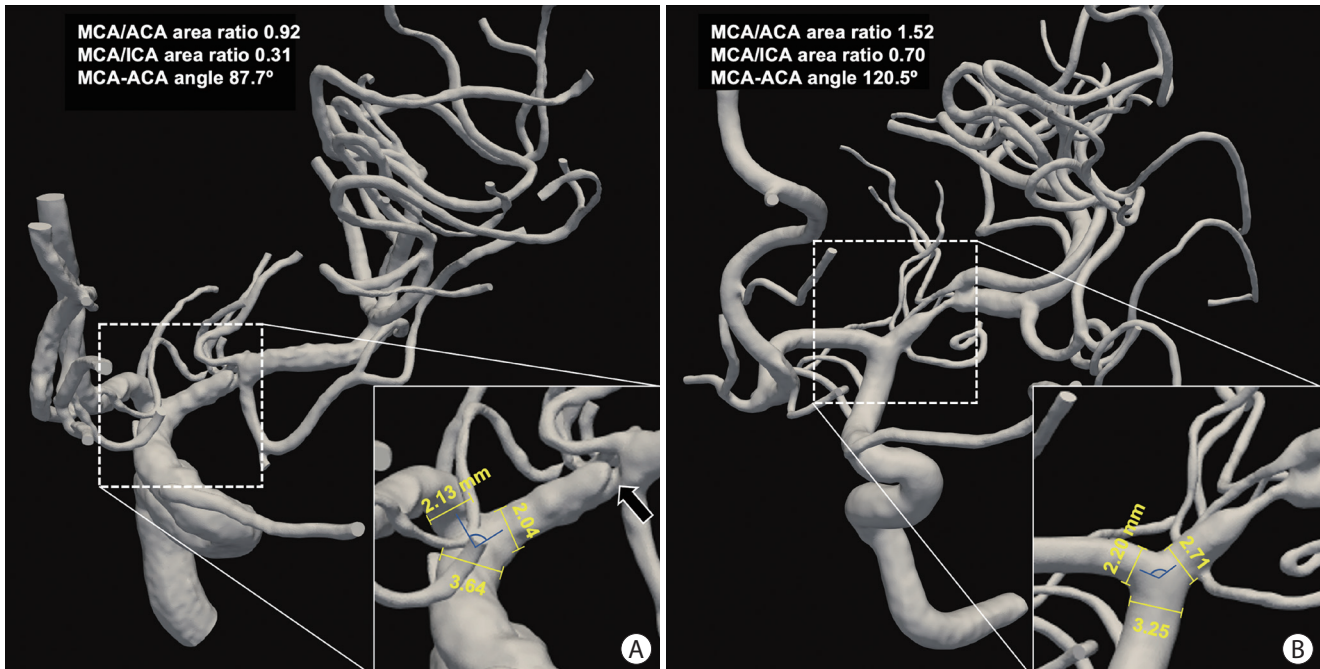**Figure 1.** Illustration of terminal ICA bifurcation geometry in 2 patients with ulcerative and non-ulcerative MCA-M1 plaques. (A) In a patient with an ulcerative (black arrow) MCA-M1 plaque of 83% luminal stenosis, the diameters of MCA origin, ACA origin, and terminal ICA were 2.04, 2.13, and 3.64 mm, respectively, and the MCA/ACA and MCA/ICA area ratios were 0.92 and 0.31, respectively, with an MCA-ACA angle of 87.7°. (B) In a patient with a non-ulcerative MCA-M1 plaque of 88% luminal stenosis, the diameters of MCA origin, ACA origin, and terminal ICA were 2.71, 2.20, and 3.25 mm, respectively, and the MCA/ACA and MCA/ICA area ratios were 1.52 and 0.70, respectively, with an MCA-ACA angle of 120.5°. ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

A flowchart is provided in Supplementary Figure 1. Among the 154 patients (median age 59 years; 65.6% males) recruited, 50 (32.5%), 84 (54.5%), and 20 (13.0%), respectively, had smooth, irregular, and ulcerative MCA-M1 plaques. Of the 20 patients with ulcerative plaques, the ulceration was located at the proximal, middle, and distal one-thirds of the plaques in 7, 7, and 6 patients, respectively. The median MCA-M1 luminal stenosis was 75% (IQR 71%–84%). The age, sex, common cardiovascular risk factors, prior ischemic stroke or transient ischemic attack, fasting blood test results (glycosylated hemoglobin, glucose, lipids), and MCA-M1 luminal stenosis were similar between patients with ulcerative and non-ulcerative MCA-M1 plaques (Supplementary Table 1).

Diameters of terminal ICA (medians 3.3 vs. 3.3 mm), MCA origin (2.5 vs. 2.6 mm), and ACA origin (2.1 vs. 2.0 mm); (MCA+ACA)/ICA area ratio (0.94 vs. 1.03); or distance of the plaque from MCA origin (4.4 vs. 4.7 mm) were not significantly different between patients with ulcerative and non-ulcerative MCA-M1 plaques (all $P>0.05$) (Supplementary Table 2). However, the MCA/ACA (1.36 vs. 1.71; $P=0.007$) and MCA/ICA area ratios (0.51 vs. 0.65; $P=0.029$), and MCA-ACA angle (103.1° vs. 113.2°; $P=0.046$) were smaller in patients with ulcerative MCA-M1 plaques than in those with non-ulcerative MCA-M1 plaques (Supplementary Table 2 and Supplementary Figure 2).

Smaller MCA/ACA and MCA/ICA area ratios were independently associated with ulcerative MCA-M1 plaques ($P<0.05$ in all multivariate logistic regression models) (Table 1). The association between a smaller MCA-ACA angle and ulcerative MCA-M1 plaque was attenuated in multivariate regression ($0.05<P<0.1$) (Table 1). Figure 1 illustrates two cases with ulcerative and non-ulcerative MCA-M1 plaques, with different geometric features at the terminal ICA bifurcation.

In summary, in this study, using 3DRA with a high spatial resolution for depicting intracranial arteries and ICAD lesions, we established an association between smaller MCA caliber relative to ACA and ICA and smaller MCA-ACA angle with MCA-M1 plaque ulceration, in patients with symptomatic, high-grade MCA-M1 stenosis, independent of systemic confounders and MCA-M1 luminal stenosis. These findings are partially consistent with a carotid bifurcation study, wherein smaller proximal ICA caliber relative to distal common carotid artery was associated with more severe ICA stenosis.[2] However, the same study also associated a larger carotid bifurcation angle with more severe ICA stenosis,[2] contrary to our findings. The differences in the anatomical features at carotid bifurcation and distal ICA bifurcation may partly explain the inconsistent findings among these two studies and other previous studies when proximal ICA contains the bulb area (with focally enlarged vessel lumen) and the distal resistance in

JoS

Leng et al.   ICA Bifurcation Geometry and MCA Plaque Ulceration

Table 1. Multivariate logistic regression analyses of the independent associations between three geometric metrics and MCA-M1 plaque ulceration

Geometric features	Model 1 (adjusted for age and sex)		Model 2 (Model 1+cardiovascular risk factors)		Model 3 (Model 2+MCA-M1 luminal stenosis)	
	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
MCA/ACA area ratio	0.35 (0.16–0.81)	0.013	0.34 (0.14–0.81)	0.015	0.30 (0.12–0.77)	0.012
Per 0.1 decrease	1.11 (1.02–1.21)		1.12 (1.02–1.22)		1.13 (1.03–1.24)	
MCA/ICA area ratio	0.05 (0.003–0.89)	0.041	0.05 (0.002–0.94)	0.045	0.05 (0.002–0.90)	0.043
Per 0.1 decrease	1.35 (1.01–1.79)		1.36 (1.01–1.82)		1.36 (1.01–1.84)	
MCA-ACA angle (°)	0.97 (0.94–1.00)	0.084	0.97 (0.94–1.00)	0.078	0.97 (0.94–1.00)	0.079
Per 10° decrease	1.35 (0.96–1.88)		1.37 (0.97–1.93)		1.36 (0.97–1.92)	

MCA, middle cerebral artery; aOR, adjusted odds ratio; CI, confidence interval; ACA, anterior cerebral artery; ICA, internal carotid artery.

external carotid artery differs from ICA. Another reason could be the different stages of atherosclerosis investigated in individual studies. For instance, a larger bifurcation angle would generally increase the area of low and oscillatory wall shear stress (WSS), which is atherogenic in the early stages.[5] In contrast, with a sudden, significant decrease in the vessel caliber from distal ICA to proximal MCA and a smaller degree of deviation in the flow direction (i.e., smaller MCA-ACA angle), there could be relatively high flow velocities and velocity gradient and hence high WSS in MCA-M1. This may increase plaque vulnerability and lead to plaque rupture (i.e., ulceration) in advanced atherosclerosis, which could partly explain the findings in the current study. Indeed, in our previous studies using a computational fluid dynamics model to simulate blood flow and quantify WSS across symptomatic ICAD of 50%–99% stenosis based on computed tomography angiography, we did observe significant associations of elevated WSS with multiple cortical or territorial infarcts at the index stroke and a higher risk of recurrent stroke with similar infarct patterns. Such infarct patterns suggest artery-to-artery embolism as a stroke mechanism that may be caused by plaque rupture.[6,7] Another study using high-resolution vessel wall MRI to depict MCA plaque characteristics and four-dimensional MRI to quantify focal WSS corroborated our previous findings. It showed that plaque enhancement was associated with the highest WSS, located mostly at the upstream shoulder, in MCA plaques with downstream infarct patterns related to artery-to-artery embolism.[8]

In conclusion, the geometry at the terminal ICA bifurcation was associated with MCA-M1 plaque ulceration, independent of cardiovascular risk factors and MCA-M1 luminal stenosis. This may help identify patients at a high risk of plaque ulceration. Further longitudinal, rheological studies across populations and subjects with different stages of ICAD may reveal the hemodynamic mechanisms and the possible effects on the risk of stroke recurrence. Vessel wall imaging for plaque components could also aid in understanding the mechanisms underlying such associations.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.00129.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: XL, TWL. Study design: XL, TWL. Methodology: XL, SCHY, TWL. Data collection: all authors. Statistical analysis: XL. Writing—original draft: XL. Writing—review & editing: all authors. Funding acquisition: XL, TWL. Approval of final manuscript: all authors.

References

1. Leung TW, Wang L, Zou X, Soo Y, Pu Y, Ip HL, et al. Plaque morphology in acute symptomatic intracranial atherosclerotic disease. *J Neurol Neurosurg Psychiatry* 2020;92:370-376.
2. Phan TG, Beare RJ, Jolley D, Das G, Ren M, Wong K, et al. Carotid artery anatomy and geometry as risk factors for carotid atherosclerotic disease. *Stroke* 2012;43:1596-1601.

3. Jiang P, Chen Z, Hippe DS, Watase H, Sun B, Lin R, et al. Association between carotid bifurcation geometry and atherosclerotic plaque vulnerability: a Chinese atherosclerosis risk evaluation study. *Arterioscler Thromb Vasc Biol* 2020;40:1383-1391.

4. Liu YT, Zhang ZM, Li ML, Gao S, Feng F, Xu WH. Association of carotid artery geometries with middle cerebral artery atherosclerosis. *Atherosclerosis* 2022;352:27-34.

5. Spanos K, Petrocheilou G, Karathanos C, Labropoulos N, Mikhailidis D, Giannoukas A. Carotid bifurcation geometry and atherosclerosis. *Angiology* 2017;68:757-764.

6. Leng X, Lan L, Ip HL, Abrigo J, Scalzo F, Liu H, et al. Hemodynamics and stroke risk in intracranial atherosclerotic disease. *Ann Neurol* 2019;85:752-764.

7. Feng X, Fang H, Ip BYM, Chan KL, Li S, Tian X, et al. Cerebral hemodynamics underlying artery-to-artery embolism in symptomatic intracranial atherosclerotic disease. *Transl Stroke Res* 2024;15:572-579.

8. Woo HG, Kim HG, Lee KM, Ha SH, Jo H, Heo SH, et al. Wall shear stress associated with stroke occurrence and mechanisms in middle cerebral artery atherosclerosis. *J Stroke* 2023;25:132-140.

Correspondence: Thomas W. Leung
Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China
Tel: +852-35053846
E-mail: drtleung@cuhk.edu.hk
https://orcid.org/0000-0001-8193-0709

Supplementary Methods

Inclusion criteria

Patients who suffered an acute ischemic stroke or transient ischemic attack within 1 month, attributed to high-grade (60%–99%), atherosclerotic M1 middle cerebral artery (MCA-M1) stenosis confirmed through three-dimensional rotational angiography (3DRA) between May 2007 and July 2022, were recruited. The 3DRA was performed as clinically indicated; for instance, 3DRA could be performed for a diagnostic purpose and/or guiding a decision for angioplasty/stenting treatment, when a patient with previously documented high-grade stenosis in noninvasive neurovascular imaging exams suffered stroke relapse despite medical treatment. The 3DRA could also be performed when a patient with documented high-grade stenosis in noninvasive neurovascular imaging exams was recruited to a clinical trial on stenting versus medical treatment for high-grade, symptomatic intracranial atherosclerotic stenosis (ChiCTR-TRC-06000689).

The stroke etiology and relevance to the MCA-M1 lesion were determined by neurologists, based on clinical syndromes, imaging features, and concurrent cardiovascular risk factors.

Exclusion criteria

Exclusion criteria included (1) probable non-atherosclerotic MCA-M1 stenosis, e.g., moyamoya disease, vasculitis, or dissection; (2) evidence of possible cardioembolism, e.g., atrial fibrillation, valvular heart disease, or recent myocardial infarction; (3) concurrent >50% stenosis of ipsilateral common carotid artery and extracranial internal carotid artery; and (4) an ipsilateral hypoplastic anterior cerebral artery.

Measurement of the MCA–anterior cerebral artery angle

The MCA-anterior cerebral artery (ACA) angle was defined as the angle between the centerlines of proximal MCA and ACA, measured in the plane when the centerlines of terminal internal carotid artery (ICA) and proximal MCA and ACA had the smallest angle deviations from this plane among all planes. In ideal situations, terminal ICA and proximal MCA and ACA segments could be in this same plane, but in most cases, these arterial segments are not completely straight.

JoS

Leng et al.   ICA Bifurcation Geometry and MCA Plaque Ulceration

Supplementary Table 1. Demographics, cardiovascular risk factors, and MCA-M1 luminal stenosis in patients with non-ulcerative versus ulcerative MCA-M1 plaques

Characteristics	Overall (n=154)	Non-ulcerative plaques (n=134)	Ulcerative plaques (n=20)	P
Age (yr)	59 (53–67)	60 (53–67)	59 (55–66)	0.955
Male sex	101 (65.6)	87 (64.9)	17 (73.9)	0.656
Ever-smoker	77 (50.0)	66 (49.3)	12 (52.2)	0.632
History of dyslipidemia	105 (68.2)	94 (70.1)	14 (60.9)	0.175
History of hypertension	89 (57.8)	79 (59.0)	12 (52.2)	0.449
History of diabetes	42 (27.3)	38 (28.4)	6 (26.1)	0.434
Prior ischemic stroke or TIA	35 (22.7)	31 (23.1)	4 (20.0)	0.755
Systolic blood pressure (mm Hg)	149 (135–165)	150 (135–164)	144 (134–174)	0.824
Diastolic blood pressure (mm Hg)	82 (74–90)	81 (74–90)	84 (64–100)	0.665
Laboratory test results				
Glycosylated hemoglobin (%)*	6.0 (5.6–6.8)	6.0 (5.6–6.7)	6.1 (5.8–6.8)	0.417
Fasting blood glucose (mmol/L)*	5.5 (5.1–6.7)	5.5 (5.0–6.6)	5.9 (5.2–6.8)	0.547
Low-density lipoprotein cholesterol (mmol/L)*	3.3 (2.6–3.9)	3.3 (2.5–4.0)	3.4 (2.9–3.9)	0.525
High-density lipoprotein cholesterol (mmol/L)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.1 (1.0–1.3)	0.868
Triglycerides (mmol/L)	1.4 (1.1–1.9)	1.4 (1.1–1.9)	1.3 (1.0–1.8)	0.599
Percent luminal stenosis in MCA-M1 (%)	75 (71–84)	75 (71–85)	76 (71–83)	0.806

Values are medians (interquartile range) or numbers (%); Wilcoxon rank sum tests were used for comparison of continuous variables and chi-square or Fisher's exact tests for categorical variables.
MCA, middle cerebral artery; TIA, transient ischemic attack.
*Data were missing in 5, 1, and 1 cases for glycosylated hemoglobin, fasting blood glucose, and low-density lipoprotein cholesterol, respectively.

Supplementary Table 2. Geometric characteristics at terminal ICA bifurcation in patients with non-ulcerative versus ulcerative MCA-M1 plaques

Geometric features	Non-ulcerative plaques (n=134)	Ulcerative plaques (n=20)	P
Diameter of MCA origin (mm)	2.6 (2.3–2.9)	2.5 (2.0–2.6)	0.075
Diameter of ACA origin (mm)	2.0 (1.7–2.3)	2.1 (1.8–2.3)	0.246
Diameter of terminal ICA (mm)	3.3 (2.9–3.7)	3.3 (3.0–3.6)	0.823
MCA/ACA area ratio	1.71 (1.29–2.51)	1.36 (0.97–1.68)	0.007
MCA/ICA area ratio	0.65 (0.51–0.75)	0.51 (0.42–0.68)	0.029
(MCA+ACA)/ICA area ratio	1.03 (0.87–1.16)	0.94 (0.82–1.09)	0.226
MCA-ACA angle (°)	113.2 (103.6–125.0)	103.1 (95.1–120.3)	0.046
Distance between the starting point of MCA-M1 plaque and the MCA origin (mm)	4.7 (0–8.7)	4.4 (0.2–6.3)	0.871

Values are medians (interquartile range); Wilcoxon rank sum tests were used for all comparisons in the table.
ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.
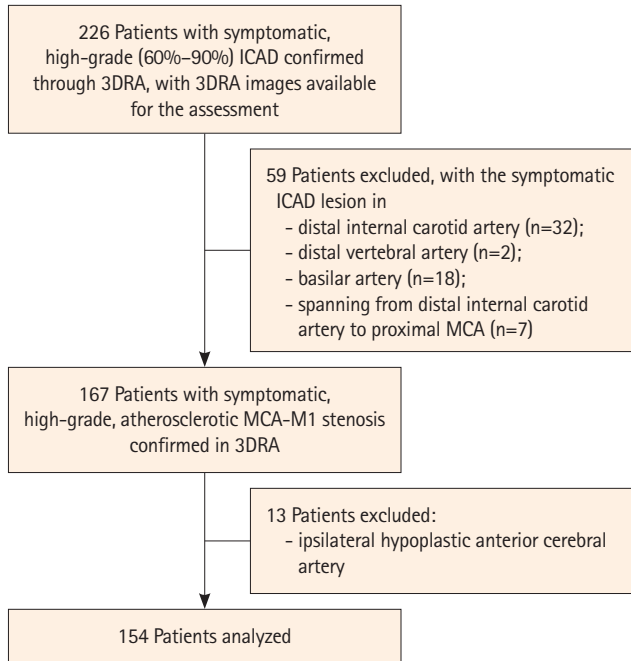
Supplementary Figure 1. Flowchart for patient screening. ICAD, intracranial atherosclerotic disease; 3DRA, three-dimensional rotational angiography; MCA, middle cerebral artery.
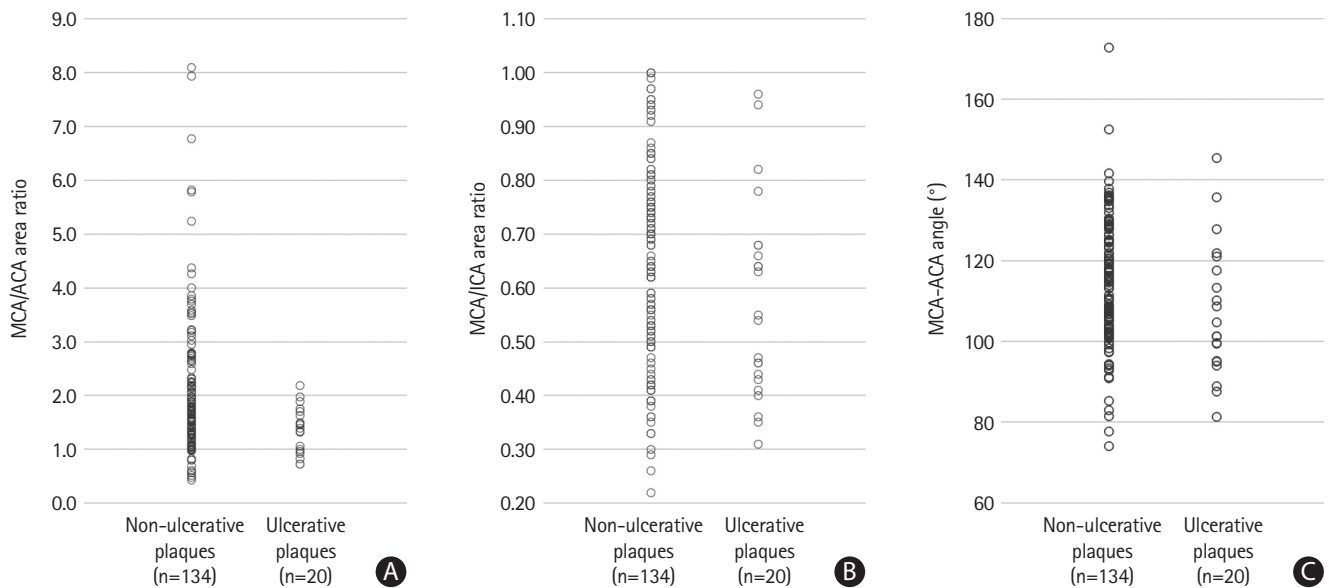
Supplementary Figure 2. Scatterplots showing MCA/ACA and MCA/ICA area ratios and MCA-ACA angle in patients with non-ulcerative and ulcerative MCA-M1 plaques. Smaller MCA/ACA (medians 1.36 vs. 1.71; P=0.007) and MCA/ICA area ratios (0.51 vs. 0.65; P=0.029) and MCA-ACA angle (103.1° vs. 113.2°; P=0.046) were observed in patients with ulcerative MCA-M1 plaques than in those with non-ulcerative MCA-M1 plaques. MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery.