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Markers of coagulation and hemostatic activation aid in identifying causes of cryptogenic stroke

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Abstract

Objective

To test the hypothesis that markers of coagulation and hemostatic activation (MOCHA) help identify causes of cryptogenic stroke, we obtained serum measurements on 132 patients and followed them up to identify causes of stroke.

Methods

Consecutive patients with cryptogenic stroke who met embolic stroke of undetermined source (ESUS) criteria from January 1, 2017, to October 31, 2018, underwent outpatient cardiac monitoring and the MOCHA profile (serum D-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomer) obtained ≥2 weeks after the index stroke; abnormal MOCHA profile was defined as ≥2 elevated markers. Prespecified endpoints monitored during routine clinical visits included new atrial fibrillation (AF), malignancy, venous thromboembolism (VTE), or other defined hypercoagulable states (HS).

Results

Overall, 132 patients with ESUS (mean age 64 ± 15 years, 61% female, 51% nonwhite) met study criteria. During a median follow-up of 10 (interquartile range 7–14) months, AF, malignancy, VTE, or HS was identified in 31 (23%) patients; the 53 (40%) patients with ESUS with abnormal MOCHA were significantly more likely than patients with normal levels to have subsequent new diagnoses of malignancy (21% vs 0%, $p < 0.001$), VTE (9% vs 0%, $p = 0.009$), or HS (11% vs 0%, $p = 0.004$) but not AF (8% vs 9%, $p = 0.79$). The combination of 4 normal MOCHA and normal left atrial size (n = 30) had 100% sensitivity for ruling out the prespecified endpoints.

Conclusion

The MOCHA profile identified patients with cryptogenic stroke more likely to have new malignancy, VTE, or HS during short-term follow-up and may be useful in direct evaluation for underlying causes of cryptogenic stroke.

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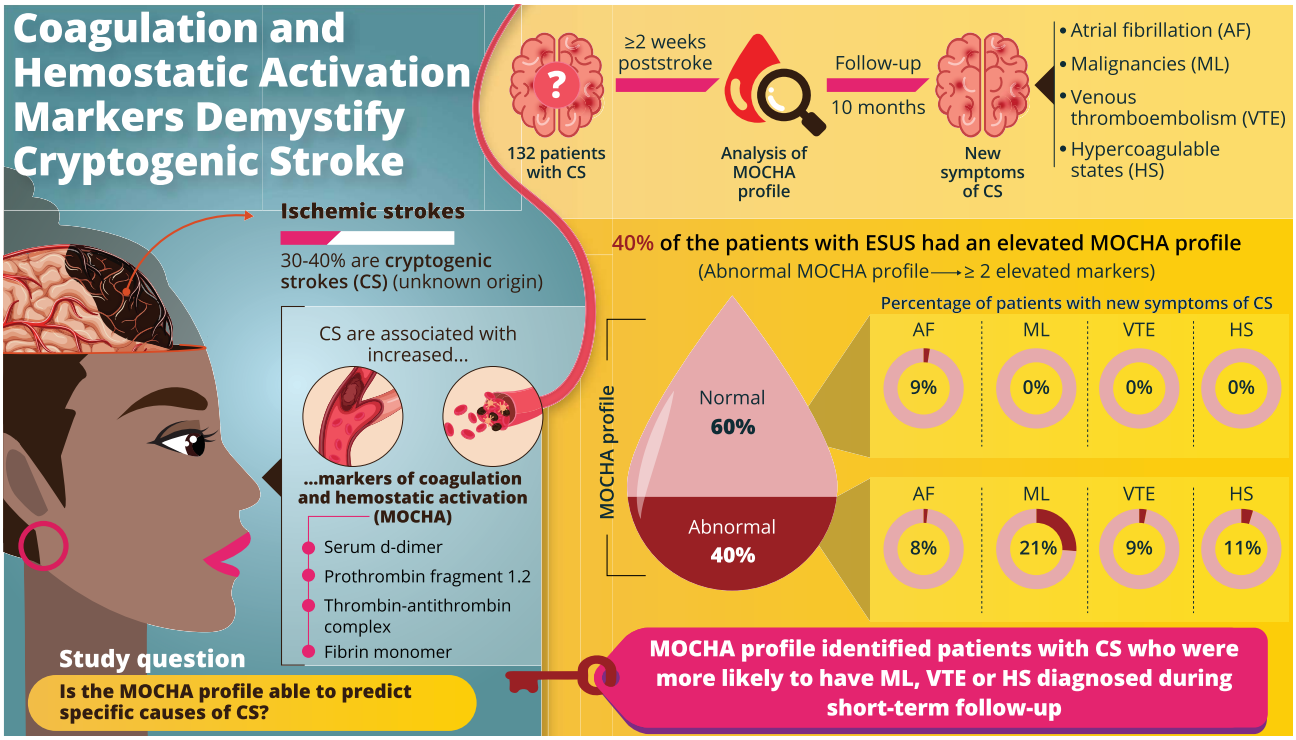
Glossary

AF = atrial fibrillation; **ARCADIA** = Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; **CS** = cryptogenic stroke; **ESUS** = embolic stroke of undetermined source; **ILR** = implantable loop recorder; **IQR** = interquartile range; **LA** = left atrial; **LAVI** = LA volume index; **MCOT** = mobile cardiac outpatient telemetry; **MOCHA** = markers of coagulation and hemostatic activation; **TTE** = transthoracic echocardiography; **VTE** = venous thromboembolism.



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Up to 30% to 40% of ischemic strokes are classified as cryptogenic in origin.[1] Recent studies suggest that cryptogenic stroke (CS) may have thromboembolic causes, including occult atrial fibrillation (AF), occult malignancies, paradoxical embolism, and hypercoagulable states, with an estimated recurrent stroke rate of 4%/y despite antiplatelet therapy.[1,2]

Left atrial (LA) structural abnormalities, including enlarged LA size, have been associated with a higher likelihood of having occult AF; however, the identification of other causes of CS has been limited.[3,4] Markers of coagulation and hemostatic activation (MOCHA) tests have previously been shown to be increased in patients with AF or malignancy. However, data on their use in patients with CS are limited.[5–10] The objective of our study was to evaluate whether the MOCHA profile could help identify a subgroup of patients with CS who are more likely to have occult AF, malignancy, venous thromboembolism (VTE), or other defined hypercoagulable states.

Methods

Participants

Consecutive patients with CS according to embolic stroke of undetermined source (ESUS) criteria[11] seen in the Emory Clinic from January 1, 2017, to October 31, 2018, were included in this analysis if they were ≥18 years of age and completed prolonged outpatient cardiac monitoring with either 30-day mobile cardiac outpatient telemetry (MCOT) or implantable loop recorder (ILR) (Reveal LINQ, Medtronic, Minneapolis, MN) according to our CS diagnostic algorithm.[10] All patients underwent brain imaging with a CT or MRI that displayed a nonlacunar brain infarct that excluded symptomatic extracranial and intracranial arterial stenosis or occlusion due to atherosclerosis, vasculitis, or dissection and excluded a documented cardioembolic source after 12-lead ECG, cardiac monitoring for ≥24 hours with automated rhythm detection, and echocardiography. The MOCHA profile was obtained on patients with CS and included serum levels of D-dimer (reference value <574 ng/mL), prothrombin fragment 1.2

(reference value 65–288 pmol/L), thrombin-antithrombin complex (reference value 1.0–5.5 μg/L), and fibrin monomer (reference value <7 μg/mL) ≥2 weeks after stroke onset.[10] For this analysis, we excluded patients on anticoagulation therapy at the time of MOCHA testing and patients with known malignancy, VTE, or hypercoagulable states.

Echocardiography

Standard 2D and Doppler transthoracic echocardiography (TTE) was performed on a GE Vivid 7 and E9 (General Electric, Milwaukee, WI) or Philips IE 33 (Philips, Andover, MA). We evaluated LA echocardiographic parameters obtained by TTE, including LA volume index (LAVI) and LA diameter. Normal LA size was defined as an LAVI <29 mL/m^2 or LA diameter of <4.0 cm. Mild, moderate, and severe LA dilation was defined as LAVI of 29 to 33, 34 to 40, and >40 mL/m^2, respectively; in patients with missing LAVI, we used categorical classification of the LA size (no, mild, moderate, severe enlargement) to impute average values of each category based on normative data.[12] A bubble study was performed to evaluate the presence of a patent foramen ovale and was considered positive if seen on TTE or transesophageal echocardiography. All echocardiography imaging was reviewed by a board-certified cardiologist.

Measurement of plasma concentrations of MOCHA markers

All assays were done with 3.2% citrated plasma. Plasma D-dimer levels were measured with high-sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, MA). Both prothrombin fragment 1.2 and thrombin antithrombin complexes were performed with the Enzygnost ELISA kit (Siemens Healthcare, Tarrytown, NY). Soluble fibrin monomer was performed with the latex immunoassay (Stago, Parsippany, NJ). All laboratory tests were performed by technicians blinded to patient clinical information.

Patient monitoring and follow-up

Outpatient clinic follow-up was done according to routine clinical practice. At clinic visits, patients with CS were encouraged to remain updated on age-appropriate cancer screenings as suggested by the US Preventive Services Task Force.[13] Cardiac monitoring reports were reviewed for evidence of new AF, and history was obtained to identify potential new diagnoses of AF, malignancy, VTE, or other defined hypercoagulable states. All AF diagnoses were verified by specialists, including a board-certified cardiac electrophysiologist for AF,[14–16] and malignancies or hypercoagulable disorders (antiphospholipid antibody syndrome, presence of genetic mutation, including factor V Leiden or prothrombin gene mutations 20210A, von Willebrand factor abnormality, nephrotic syndrome) were verified by board-certified oncologists/hematologists. No predefined screening for VTE or malignancy was established. In patients who developed symptoms concerning for VTE during follow-up, a lower extremity Doppler ultrasound was obtained. In patients who developed symptoms concerning for possible malignancy during follow-up, CT scans of the chest, abdomen, or pelvis were performed at the discretion of the patient's physician team.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Emory University Institutional Review Board.

Statistical analysis

This is a retrospective analysis of prospectively identified eligible patients. All continuous variables were assessed for normality of distribution; specifically, if the Shapiro-Wilk test p value was <0.05, medians and interquartile ranges (IQRs) were reported, and nonparametric statistical tests were performed. For pairwise nonparametric comparison, the Mann-Whitney U test was performed. For >2-group comparisons, the Kruskal-Wallis test was performed with post hoc pairwise comparisons using Bonferroni correction. Two-sample t tests were used for continuous variables, and the χ^2 or Fisher exact test was used for categorical variables. We assessed the number of elevated MOCHA in each patient on the basis of testing and quantified sensitivity, specificity, positive predictive value, and negative predictive value at 0, 1, 2, 3, and 4 elevated markers. On the basis of the results of our preliminary study,[10] an abnormal MOCHA profile was defined as ≥2 elevated markers above the reference range. Univariate analysis included age, race, sex, hypertension history, history of diabetes mellitus, smoking history, migraine history, risk of paradoxical embolism score, LAVI, LA diameter, and MOCHA for the individual endpoints. Variables with values of $p < 0.1$ were incorporated into the multivariable analysis. For all statistical comparisons, significance was defined as $p < 0.05$.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

During the study period, 132 patients met our study criteria. The mean age was 64 ± 15 years; 61% were female; and 51% were nonwhite (table 1). At baseline, 79% of patients had a history of hypertension, 21% had diabetes mellitus, and 44% had either former or active tobacco use. A history of ischemic stroke was present in 9.8% of patients. In our cohort, 64% completed a 30-day MCOT, and 46% underwent ILR monitoring, including 24% who underwent ILR placement after completing MCOT if it showed no significant arrhythmia. Echocardiographic parameters showed normal LA size in 56% of patients, mild LA dilation in 21%, moderate LA dilation in 12%, and severe LA dilation in 12%.

Over a median follow-up of 10 (IQR 7–14) months, 11 (8.3%) patients had newly diagnosed AF detected on outpatient cardiac monitoring, 11 (8.3%) with newly diagnosed malignancy (including breast, colon, prostate, bladder, renal,

Table 1 Baseline characteristics of the study population

Characteristics	Total (n = 132)	Composite outcome (n = 31)[a]	AF (n = 11)	Malignancy (n = 11)	VTE (n = 5)	Hypercoagulable disorders (n = 6)
Demographics						
Age, mean (SD), y	64 (15)	69 (14)	72 (10)	72 (12)	70 (22)	64 (18)
Female, n (%)	81 (61)	20 (65)	6 (55)	6 (55)	4 (80)	5 (83)
Race, n (%)						
Nonwhite	68 (51)	18 (58)	6 (55)	7 (64)	2 (40)	4 (67)
Comorbid conditions, n (%)						
Hypertension	105 (79)	27 (87)	11 (100)	10 (91)	4 (80)	4 (67)
Diabetes mellitus	28 (21)	6 (19)	1 (9)	3 (27)	1 (20)	1 (17)
Previous stroke	13 (9.8)	1 (3)	0 (0)	1 (9)	0 (0)	0 (0)
Any tobacco use	59 (44)	13 (42)	6 (55)	6 (55)	1 (20)	1 (17)
Migraine	31 (23)	2 (7)	0 (0)	0 (0)	1 (20)	1 (17)
30-d MCOT, n (%)	85 (64)	20 (65)	8 (73)	6 (55)	1 (20)	6 (100)
ILR, n (%)	60 (46)	14 (45)	5 (46)	4 (36)	3 (60)	3 (50)
LAVI, mean (SD), mL/m^2	31 (10)	35 (11)	41 (5)	33 (16)	35 (10)	26 (7)
LAD, mean (SD), cm	3.6 (0.72)	3.6 (0.70)	4.0 (0.46)	3.3 (0.61)	3.5 (1.2)	3.3 (0.25)
RoPE score, median (IQR)	4 (4–6)	4 (4–5)	4 (4–5)	4 (4–5)	4 (3–7)	5 (4–8)
Time from ESUS to MOCHA profile, median (IQR), d	42 (21–75)	32 (21–57)	23 (18–30)	32 (28–113)	60 (46–120)	44 (14–47)
Follow-up duration, median (IQR), mo	10 (7–14)	11 (8–14)	8 (3–13)	13 (7–17)	12 (11–20)	13 (11–15)

Abbreviations: AF = atrial fibrillation; ESUS = embolic stroke of undetermined source; ILR = implantable loop recorder; IQR = interquartile range; LAD = left atrial diameter; LAVI = left atrial volume index; MCOT = monitored cardiac outpatient telemetry; MOCHA = markers of coagulation and hemostatic activation; RoPE = risk of paradoxical embolism; VTE = venous thromboembolism.
[a] Two patients had >1 composite endpoint during follow-up.

acute myelocytic leukemia, and polycythemia vera), 5 (3.8%) with VTE, and 6 (4.5%) with defined hypercoagulable states (including antiphospholipid antibody syndrome, von Willebrand factor abnormality, nephrotic syndrome); 2 patients had >1 endpoint during follow-up, including 1 patient with AF and malignancy and 1 patient with malignancy and VTE (table 2). Of the 5 patients who had a VTE during follow-up, 1 patient had a patent foramen ovale on echocardiography. Overall, 31 (23%) patients had the composite outcome of new AF, malignancy, VTE, or defined hypercoagulable state.

MOCHA profile was obtained a median of 42 (IQR 21–75) days after CS. Overall, 53 (40%) patients had ≥2 elevated markers (table 2). Compared to patients with CS with normal MOCHA profile, those with abnormal MOCHA had significantly higher frequency of malignancy (21% vs 0%, $p < 0.001$), VTE (9% vs 0% $p = 0.004$), and defined hypercoagulable states (11% vs 0%, $p = <0.004$) but not AF (8% vs 9%, $p = 0.789$). Overall, patients with ≥2 elevated MOCHA had significantly higher rates of the composite outcome than patients with <2 abnormal markers (45% vs 9%, $p < 0.001$).

D-dimer, prothrombin fragment 1.2, and thrombin-antithrombin complex levels were significantly higher in patients with malignancy, VTE, and other hypercoagulable

Table 2 Endpoints stratified by MOCHA markers

Endpoints	Abnormal MOCHA profile (n = 53), n (%)	Normal MOCHA profile (n = 79), n (%)	*p* Value
AF	4 (8)	7 (9)	0.79
Malignancy	11 (21)	0 (0)	<0.001
VTE	5 (9)	0 (0)	0.009
Hypercoagulable disorder	6 (11)	0 (0)	0.004
Composite outcome	24 (45)[a]	7 (9)	<0.001

Abbreviations: AF = atrial fibrillation; MOCHA = markers of coagulation and hemostatic activation; VTE = venous thromboembolism.
[a] Two patients had >1 composite endpoint during follow-up.

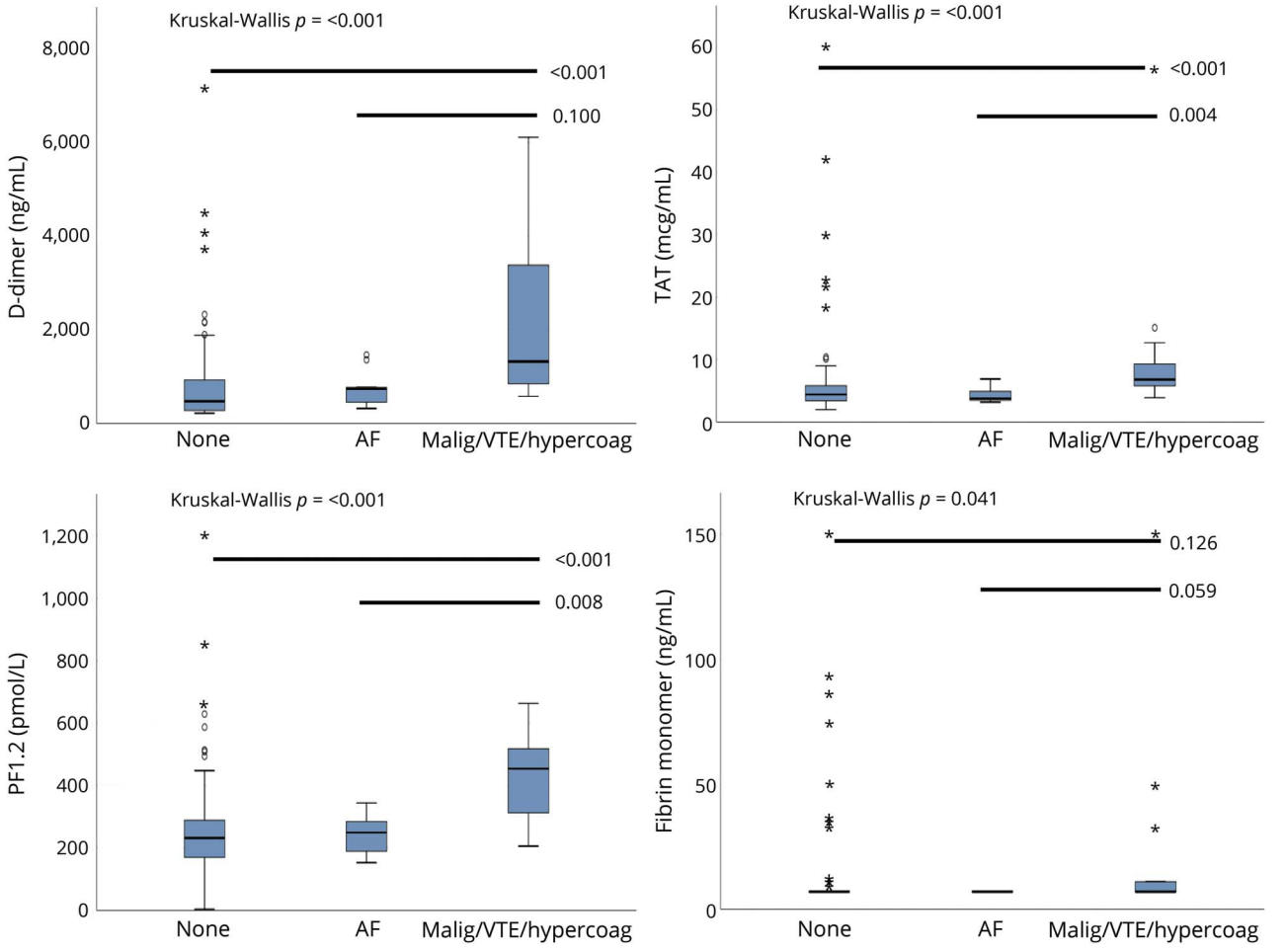
states compared to patients with no composite endpoint, whereas fibrin monomer levels showed no difference (p = 0.126) (figure 1). Prothrombin fragment 1.2 and thrombin-antithrombin complex levels, but not D-dimer (p = 0.1) or fibrin monomer (p = 0.059) levels, were also significantly higher in patients with malignancy, VTE, and other hypercoagulable states compared to patients diagnosed with AF during follow-up. Univariate analysis of the composite outcome showed a significant (p < 0.1) association with age (p = 0.05), number of MOCHA abnormalities (p < 0.001), LAVI (p = 0.051), and migraine history (p = 0.02), although in multivariable analysis, only MOCHA were significant (p = 0.017). Univariate analysis of malignancy showed a significant association with MOCHA (p = 0.001) and age (p = 0.075). However, in multivariable analysis, only MOCHA were significant (p = 0.003). Univariate analysis of AF showed a significant association with LA diameter (p = 0.032) and LAVI (p = 0.011), although no association was seen in multivariable analysis.

In patients with the combination of 4 normal MOCHA tests and normal LA size (n = 30), no patients had the composite endpoint (figure 2). Among patients with ≥2 elevated MOCHA and normal LA size (n = 29), 52% had the composite outcome, including 24% with malignancy, 10% with VTE, and 17% with defined hypercoagulable state; in patients with ≥2 elevated markers and LA enlargement (n = 24), 46% had the composite outcome, including 17% with AF, 17% with malignancy, 8% with VTE, and 4% with defined hypercoagulable state.

Discussion

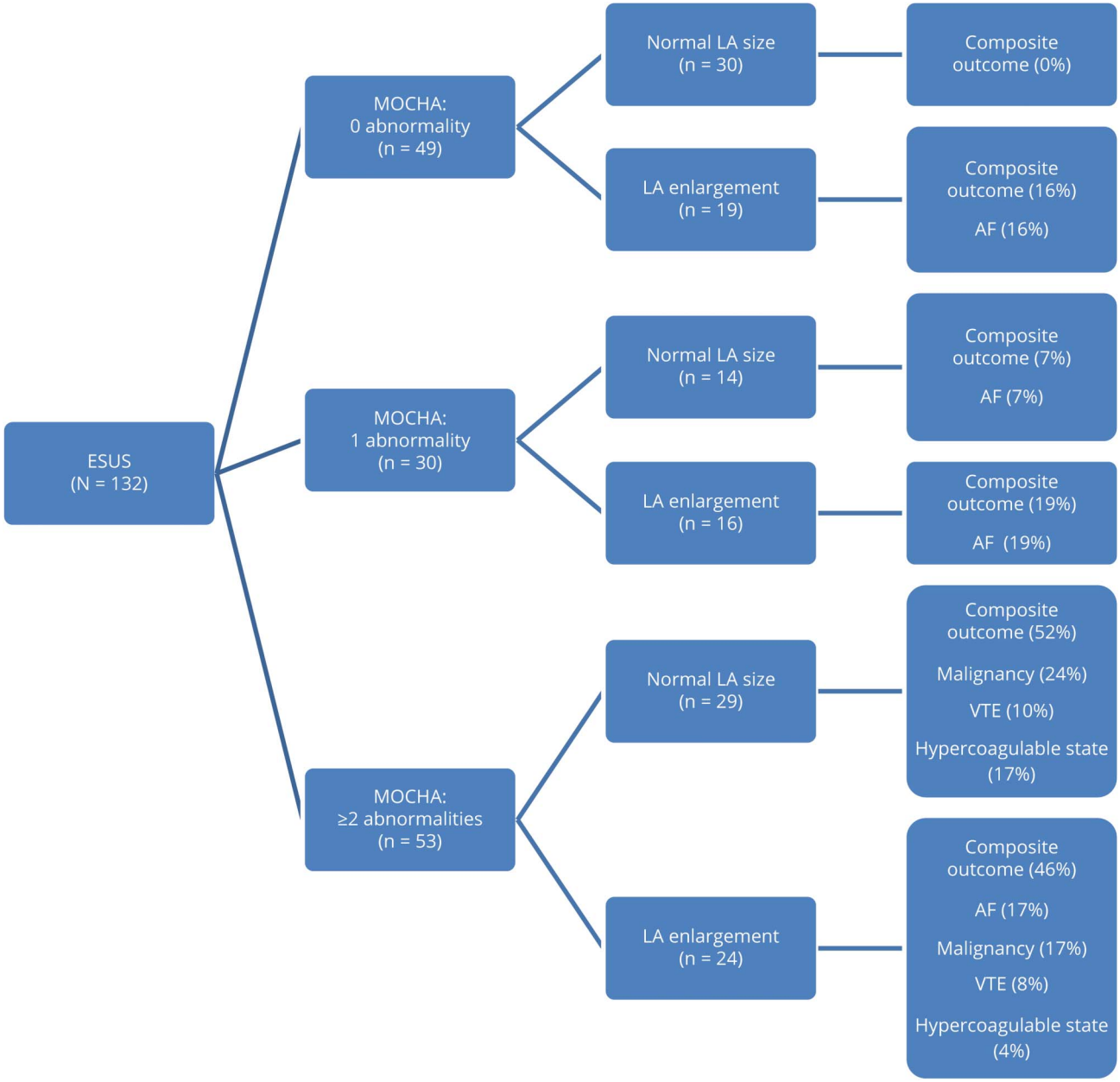
We found that patients with CS had a significant rate of newly diagnosed AF, malignancy, VTE, or defined hypercoagulable states, with 23% of patients having the composite outcome during follow-up. Nearly half of patients with CS with MOCHA elevation of ≥2 markers had the composite outcome and were significantly more likely to have new malignancy, VTE, or defined hypercoagulable states than patients with <2 MOCHA elevations. Contrary to our pilot data, an elevation of ≥2 MOCHA tests alone did not identify patients with CS as more likely to have a subsequent diagnosis of AF. Instead, we found

Figure 1 Individual markers and their association with clinical outcomes



Bars represent median values and interquartile range. Horizontal lines represent p values between categories. AF = atrial fibrillation; hypercoag = hypercoagulable states; malig = malignancy; PF1.2 = prothrombin fragment 1.2; TAT = thrombin-antithrombin complex; VTE = venous thromboembolism.

Figure 2 Flow diagram of composite outcome incorporating MOCHA and left atrial enlargement



AF = atrial fibrillation; ESUS = embolic stroke of undetermined source; LA = left atrium; MOCHA = markers of coagulation and hemostatic activation; VTE = venous thromboembolism.

that the use of LA measurements such as LA diameter and LAVI was a better predictor of subsequent AF. To predict the composite outcome, MOCHA and LA measurements appeared to be complementary and had high sensitivity for ruling out the composite outcome when patients had the combination of 4 normal MOCHA and normal LA size.

We chose to evaluate the MOCHA profile in our study because CS is thought to be mediated primarily through a thromboembolic event. Because the 4 markers in the panel are associated with coagulation activation or fibrinolysis, we anticipated that an elevation in these tests beyond 2 weeks after stroke would be a marker of an underlying persistent coagulopathic state. In addition, previous studies have shown the individual markers to be associated with elevations in AF, coronary artery disease, malignancy, and cardioembolic stroke.[5–10]

Our study has several important implications for the evaluation of patients with CS. First, noncardiac causes such as occult malignancy, VTE through a patent foramen ovale, or defined hypercoagulable states can contribute to CS, and the MOCHA profile was effective at identifying patients with these diagnoses. Second, a combination of normal MOCHA and normal LA size on echocardiography may be able to identify patients with CS

who are unlikely to have AF, malignancy, VTE, or other hypercoagulable state during follow-up.

All of our patients were placed on antiplatelet therapy after their CS according to current treatment guidelines. However, we chose to use the combined outcome of malignancy, VTE, hypercoagulable states, and AF because they were considered indications that might prompt clinicians to switch patients from antiplatelet to anticoagulation therapy, although randomized trial data evaluating the efficacy of anticoagulation vs antiplatelet therapy for secondary stroke prevention in the setting of malignancy are lacking. Furthermore, patients with CS with abnormal MOCHA on antiplatelet therapy who were transitioned to anticoagulation after having an endpoint in the study had normalization of all of their markers on repeat testing, suggesting that their hypercoagulable condition was suppressed with anticoagulation therapy.[10] Given the lack of benefit seen with anticoagulant treatment with dabigatran and rivaroxaban compared to aspirin in patients with ESUS,[17,18] evaluation of biomarkers after CS may be useful to identify patients who may require early anticoagulation, as is currently being evaluated in the Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) trial.[19]

Our study has several limitations. It is a retrospective analysis of prospectively identified patients with ESUS. While all patients were offered ILR, 55% declined having it placed, and this may have led to an underdetection of AF in our cohort. Patients were followed up for a median of 10 months, and a longer follow-up may have identified additional patients who had a composite endpoint. External validation in a larger cohort is warranted to assess for confounding variables.

The MOCHA profile may be useful in identifying the underlying cause of stroke in patients with CS. Whether the MOCHA profile can guide appropriate antithrombotic therapy in patients with CS requires evaluation in a larger cohort.

Study funding

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Disclosure

F. Nahab has a patent pending on the use of MOCHA to guide medical treatment in cardiovascular disease and stroke. V. Sharashidze, M. Liu, P. Rathakrishnan, S. El Jamal, A. Duncan, M. Hoskins, F. Marmarchi, S. Belagaje, N. Bianchi, T. Belair, L. Henriquez, K. Monah, and S. Rangaraju report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
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Michael Liu, BS	Emory University, Atlanta, GA	Data collection, data analysis, editing of manuscript
Priyadharshi Rathakrishnan, BS	Emory University, Atlanta, GA	Data collection, editing of manuscript
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