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ABSTRACT

BACKGROUND AND PURPOSE: Prehospital stroke scales may help identify patients likely to have large-vessel occlusion to facilitate rapid triage to thrombectomy-capable stroke centers. Scale misclassification may result in inaccurate decisions and possible harm. Pre-existing leukoaraiosis has been shown to attenuate the association between deficit type and stroke severity. We sought to determine whether leukoaraiosis affects the predictive ability of 5 commonly used large-vessel occlusion scales.

MATERIALS AND METHODS: We retrospectively analyzed 274 consecutive patients with stroke with available brain MR imaging and vessel imaging. We used the following large-vessel occlusion scales: the 3-Item Stroke Scale; Field Assessment Stroke Triage for Emergency Destination; Rapid Arterial Occlusion Evaluation; Vision, Aphasia, Neglect score; and Cincinnati Prehospital Stroke Severity Scale. For diagnostic scale accuracy, we assessed sensitivity, specificity, positive predictive value, negative predictive value, and $\kappa$. Multivariable logistic regression was used to determine the predictive ability of the scales after adjustment for leukoaraiosis and potential confounders.

RESULTS: In unadjusted analyses, all scales predicted the presence of large-vessel occlusion ($n = 46$, $P < .01$ each), though diagnostic accuracy was attenuated among patients with moderate-to-severe leukoaraiosis. After adjustment, the Field Assessment Stroke Triage for Emergency Destination (OR = 3.2; 95% CI, 1.1–9.5; $P = .033$) and Rapid Arterial Occlusion Evaluation (OR = 3.7; 95% CI, 1.3–10.8; $P = .015$), but not the 3-Item Stroke Scale (OR = 5.4; 95% CI, 0.86–33.9; $P = .073$), Vision, Aphasia, Neglect score (OR = 2.5; 95% CI, 0.8–7.2), and Cincinnati Prehospital Stroke Severity Scale (OR = 2.8; 95% CI, 1.0–8.0), predicted large-vessel occlusion.

CONCLUSIONS: The diagnostic accuracy of the tested large-vessel occlusion scales was attenuated in the presence of moderate-to-severe leukoaraiosis. This information that may aid the design of future studies that require large-vessel occlusion scale screening of patients who are likely to have concomitant leukoaraiosis.

ABBREVIATIONS: CPSSS = Cincinnati Prehospital Stroke Severity Scale; EST = endovascular stroke therapy; FAST-ED = Field Assessment Stroke Triage for Emergency Destination; LVO = large-vessel occlusion; RACE = Rapid Arterial Occlusion Evaluation; 3I/SS = 3-Item Stroke Scale; VAN = Vision, Aphasia, Neglect

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Recent endovascular stroke therapy (EST) trials have shown significantly improved outcomes among patients with large-vessel occlusion (LVO). Reliable prehospital identification of patients with LVO and transfer to an EST-capable center are critical because earlier treatment is associated with more favorable outcome.

Although the ideal prehospital triage of patients with potential LVO remains uncertain, several clinical scales have been developed to aid identification of patients likely to have an LVO before vascular imaging is available, such as in the prehospital setting or during telestroke consultations. However, these scales have the potential to misclassify patients. Several factors may attenuate diagnostic accuracy of stroke scales, including stroke location in the posterior circulation, atypical presentation, and the presence of stroke mimics. Inaccurate LVO prediction may delay patient transfer to an endovascular center (false-negatives) with an increased risk for a worse outcome. Conversely, unwarranted patient transfer to an EST-capable hospital (false-positives) may overburden the relatively few available EST-capable centers. It is important to understand factors that
may increase the risk for misclassification to improve prediction accuracy.

Pre-existing leukoaraiosis is identified in most patients with stroke on brain MR imaging as white matter hyperintensities. Prior studies have shown that leukoaraiosis alters the classic association between the NIHSS deficit and hemispheric lateralization, relates to greater-than-expected NIHSS scores in relation to the acute infarct extent, and worsens outcome after EST. Because most available LVO scales are based on the NIHSS, we sought to determine whether leukoaraiosis severity affects the diagnostic accuracy of several previously developed prehospital stroke scales. We hypothesized that the diagnostic scale performance is reduced among patients with stroke with moderate-to-severe pre-existing leukoaraiosis. Clarifying this issue may aid clinical study design and choice of LVO scales to more reliably identify patients with stroke with LVO in the prehospital setting when neuroimaging data are unavailable, and it is expected that a substantial proportion of screened patients will have advanced leukoaraiosis.

MATERIALS AND METHODS

Study Cohort

We retrospectively analyzed 274 consecutive patients with acute ischemic stroke shown on brain MR imaging who were included in the University of Massachusetts Memorial Medical Center Stroke Registry between January 2013 and January 2014. Patient demographics, laboratory data, comorbidities, premorbid medications, and stroke pathogenesis (using the Causative Classification System for Ischemic Stroke as previously described) after completion of diagnostic evaluation were collected on all patients. NIHSS scores were assessed at the time of presentation by members of the stroke team certified in the NIHSS. Only patients with complete details on all NIHSS subcategories were included (On-line Fig 1). All patients underwent head CT and either CTA (n = 249) or MRA (n = 25) at admission. Ten patients underwent both CTA and MRA. To reliably determine the white matter lesion burden (leukoaraiosis), we only included patients with available brain MR imaging. Our investigation was approved by our Institutional Review Board (No. H00006964), and a Health Insurance Portability and Accountability Act waiver of informed consent was granted. We adhere to the Standards for Reporting Vascular Changes on Neuroimaging criteria and graded according to the Fazekas scale as previously described in detail. We have previously shown substantial interrater reliability with an intraclass correlation coefficient of 0.969 (95% CI, 0.943–0.983). In addition, we dichotomized the degree of leukoaraiosis according to the median Fazekas scale score to 0–2 (n = 145, absent-to-mild leukoaraiosis) versus 3–6 (n = 129, moderate-to-severe leukoaraiosis) for statistical purposes.

Leukoaraiosis Grading

In all patients, leukoaraiosis was defined on MR imaging as supratentorial white matter FLAIR hyperintensity lesions according to the Standards for Reporting Vascular Changes on Neuroimaging criteria and graded according to the Fazekas scale as previously described in detail. We used the total Fazekas score scale calculated by adding the periventricular and subcortical scores. We have previously shown substantial interrater reliability with an intraclass correlation coefficient of 0.969 (95% CI, 0.943–0.983). In addition, we dichotomized the degree of leukoaraiosis according to the median Fazekas scale score to 0–2 (n = 145, absent-to-mild leukoaraiosis) versus 3–6 (n = 129, moderate-to-severe leukoaraiosis) for statistical purposes.

Definition of Large-Vessel Occlusion

Large-vessel occlusion was defined on the admission CTA or MRA as the presence of an apparent occlusion of the intracranial internal carotid artery and proximal middle cerebral artery (M1). The included prehospital stroke scales were not designed to assess the presence of occlusion in the distal MCA (M2), basilar, and intracranial vertebral arteries. Therefore, occlusion in these vessels was considered non-LVO for this study, and only considered in the exploratory analyses. All images were reviewed by a neuroradiologist as part of the routine clinical work-up. The site of the LVO was abstracted from the radiologic report and by cross-validating with the original scans by one of the authors (Y.M.), who was masked to clinical data. Discrepant interpretations were resolved by consensus after review by a second neurologist (N.H.).

Prehospital Stroke Scales

To determine the impact of pre-existing leukoaraiosis on LVO prediction, we examined 5 previously published scales that could be reliably reconstructed by abstraction from the admission NIHSS score sheet and the detailed neurologic examination documented in our medical records. We used the following addi-
Table 1: Baseline characteristics (unadjusted) of the studied patient population as stratified by the presence-versus-absence of proximal LVOa

| Characteristics                  | All Patients (n = 274) | LVO (n = 46) | No LVO (n = 228) | P Value |
|----------------------------------|------------------------|--------------|------------------|---------|
| Age (yr)                         | 69 (60–80)             | 68 (58–77)   | 70 (60–81)       | .347    |
| Female sex                       | 126 (46%)              | 24 (52%)     | 102 (45%)        | .418    |
| Admission NIHSS score            | 5 (2–10)               | 14 (4–17)    | 4 (2–9)          | <.001   |
| Prestroke mRS                    | 0 (0–1)                | 0 (0–1)      | 0 (0–1)          | .774    |
| LVO stroke scale scores          |                        |              |                  |         |
| 3I/SS                            | 1 (0–2)                | 2 (1–3)      | 1 (0–2)          | <.001   |
| VAN                              | 0 (0–2)                | 3 (0–4)      | 0 (0–2)          | <.001   |
| CPSSS                            | 0 (0–1)                | 1 (0–3)      | 0 (0–1)          | .001    |
| FAST-ED                          | 2 (0–4)                | 4 (2–6)      | 1 (0–3)          | <.001   |
| RACE                             | 2 (0–4)                | 5 (7–17)     | 1 (0–3)          | <.001   |
| Laboratory data                  |                        |              |                  |         |
| Admission glucose level (mg/dL)  | 119 (100–142)          | 120 (105–143)| 119 (99–142)    | .515    |
| Admission creatinine level (mg/dL)| 0.95 (0.78–1.20)      | 0.90 (0.73–1.0)| 0.97 (0.79–1.20)| .090    |
| HbA1c level (%)                  | 5.7 (5.7–6.5)          | 6.0 (5.6–6.3)| 5.9 (5.7–6.6)   | .794    |
| LDLc level (mg/dL)               | 93 (72–123)            | 89 (65–111)  | 94 (74–123)      | .274    |
| Neuroimaging                     |                        |              |                  |         |
| Fazekas scale score (0–2)        | 129 (48%)              | 30 (65%)     | 99 (43%)         | .009    |
| Pre-existing risk factors        |                        |              |                  |         |
| Hypertension                     | 210 (77%)              | 34 (74%)     | 176 (77%)        | .703    |
| Hyperlipidemia                   | 152 (56%)              | 26 (57%)     | 132 (58%)        | .076    |
| Diabetes                         | 75 (27%)               | 11 (24%)     | 64 (28%)         | .594    |
| Prior stroke or TIA              | 59 (22%)               | 6 (13%)      | 53 (23%)         | .168    |
| Atrial fibrillation              | 42 (15%)               | 8 (17%)      | 34 (15%)         | .823    |
| Coronary artery disease          | 58 (21%)               | 4 (9%)       | 54 (24%)         | .028    |
| Congestive heart failure         | 20 (7%)                | 1 (2%)       | 19 (8%)          | .215    |
| Peripheral arterial disease      | 18 (7%)                | 1 (2%)       | 17 (8%)          | .221    |
| Preadmission medications         |                        |              |                  |         |
| Statin                           | 124 (45%)              | 19 (41%)     | 105 (46%)        | .689    |
| Antihypertensive                 | 185 (67%)              | 32 (70%)     | 153 (67%)        | .863    |
| Antiglycemic                     | 53 (19%)               | 9 (20%)      | 44 (19%)         | 1.000   |
| Antipla telets                   | 145 (53%)              | 24 (52%)     | 121 (53%)        | 1.000   |
| Oral anticoagulant               | 19 (7%)                | 4 (9%)       | 15 (7%)          | .749    |

Note: —HbA1c indicates glycated hemoglobin A1c; LDLc, low-density lipoprotein cholesterol.

a Proximal LVO is defined as an occlusion of the internal carotid artery or middle cerebral artery M1 segment. Data are No. (%) or median (25th–75th percentile).

RESULTS

Of 502 patients with ischemic stroke, 274 fulfilled the study criteria and were included in the analysis (On-line Fig 1).

Baseline characteristics of included patients stratified by the presence of LVO are summarized in Table 1. Overall, 46 patients had a proximal LVO (17%), and 228 (83%) patients had no LVO. Baseline characteristics of the included patients were well-balanced except for a higher NIHSS (P < .001) and Fazekas scale score (P = .009) among patients with LVO. The relative tional prespecified rules for derivation of the scores because we previously found that severe leukoaraiosis substantially attenuates the classic hemispheric lateralization of the NIHSS deficit15: If both sides were weak, the weaker side determined the sign scored; and if both sides were equally weak, the presence of the sign was scored.

The Field Assessment Stroke Triage for Emergency Destination (FAST-ED) was calculated on the basis of the presence of facial palsy (scored 0–1), arm weakness (0–2), speech changes (0–2), eye deviation (0–2), and denial/neglect (0–2). A score of ≥4 was considered suggestive of LVO.7 The Rapid Arterial Occlusion Evaluation (RACE) was calculated on the basis of the presence of facial palsy (0–2), arm motor function (0–2), leg motor function (0–2), gaze (0–1), and aphasia or agnosia (0–2). A score ≥5 was considered indicative of LVO.8 The Vision, Aphasia, Neglect (VAN) score was calculated on the basis of the presence of arm motor weakness (0–1) plus the presence of visual disturbance (blindness, field cut, diplopia [0–1]), aphasia (0–1), and neglect (including forced gaze deviation [0–1]). In the absence of arm weakness, the patient received a score of zero. A score ≥2 was considered indicative of LVO. The Cincinnati Prehospital Stroke Severity Scale (CPSSS) was calculated on the basis of the presence of conjugate gaze deviation, (0–2), arm weakness (0–1), and impaired consciousness (0–1). A score of ≥2 was considered indicative of LVO.10 The 3-Item Stroke Scale (3I/SS) was calculated on the basis of the level of consciousness (0–2), gaze deviation (0–2), and hemiparesis (0–2). A score ≥4 was considered indicative of LVO.2

Statistics

 Unless otherwise stated, continuous variables are reported as mean ± SD or median (25th–75th percentile). Categorical variables are reported as proportions. Between-group comparisons for continuous and ordinal variables were performed with the Mann-Whitney U test. Categorical variables were compared using the χ2 test or Fisher exact test as appropriate. To determine the diagnostic accuracy of the LVO scales, we calculated the area under receiver operating curves (C statistics, ordinal scales) as well as sensitivity, specificity, positive predictive value, negative predictive value, and κ (dichotomized scales each) with corresponding 95% CIs.

We created multivariable logistic regression models to determine whether the tested LVO scale cutoffs predicted large-artery occlusion (dependent variable) independent of leukoaraiosis (as determined by the Fazekas scale score). All models were adjusted for factors known to be associated with leukoaraiosis, including age, sex, and preadmission mRS and a history of hypertension, stroke/TIA, and atrial fibrillation. In addition, models were adjusted for the Fazekas scale score × LVO Scale Interaction to determine whether the leukoaraiosis burden differentially modified the predictive ability of the tested scales. Variables were sequentially removed (likelihood ratio) from the models at a significance level of 0.1 to avoid model overfitting. Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess model fit.

Two-sided significance tests were used throughout; unless stated otherwise, a 2-sided P < .05 was considered statistically significant. All statistical analyses were performed with SPSS, Version 22 (IBM, Armonk, New York).
The NIHSS scores and types of arterial occlusion in the included patients are summarized in the Figure.

On-line Fig 2 shows the percentage of LVO cases that would have gone unidentified across different LVO score thresholds. On average, more cases would have gone unnoticed in patients with moderate-to-severe leukoaraiosis compared with those with only absent-to-mild leukoaraiosis.

Table 2 summarizes the diagnostic accuracy of the established LVO scale cutoffs both in the entire cohort and when stratified by leukoaraiosis burden. Overall, the diagnostic accuracy was modest in the entire cohort and further attenuated among patients with moderate-to-severe leukoaraiosis.

We calculated the area under receiver operating curve to examine the diagnostic performance of the 5 tested prehospital LVO scales for the presence of a proximal LVO as an ordinal variable in the entire cohort as well as stratified by leukoaraiosis burden (On-line Fig 3A–C). All scales predicted LVO in the entire cohort (P < .01 each, Table 3) and in patients with absent-to-mild leukoaraiosis (P < .001 each). However, none predicted LVO among patients with moderate-to-severe leukoaraiosis (P > .05 each). Results did not meaningfully change when the definition of LVO was liberalized to include MCA-M2, vertebral artery, and basilar artery occlusions (On-line Fig 3D–F). Last, results were similar in exploratory analyses excluding patients with small subcortical infarcts as well as those with posterior circulation infarcts (not shown).

Finally, on multivariable logistic regression with adjustment for leukoaraiosis and potential confounders, we found that despite an overall similar direction of association of all scales, only the FAST-ED and RACE scales predicted LVO (Table 3). In all models, leukoaraiosis severity was independently associated with the presence of LVO (P < .05 each). No Leukoaraiosis × LVO Scale Interaction was found in the examined models.

**DISCUSSION**

The goal of our study was to determine whether the diagnostic accuracy of previously validated prehospital LVO stroke scales is affected by the presence of leukoaraiosis—knowledge that may aid investigators in choosing scales that allow more reliable patient screening in the prehospital setting. Using a hospital-based acute ischemic stroke cohort, we found that the diagnostic accuracy of several LVO scales was attenuated among patients with severe leukoaraiosis. After we adjusted for leukoaraiosis severity and potential confounders, only 2 of the 5 tested scales (FAST-ED and RACE) predicted LVO.

Prehospital stroke scales have been developed to aid stroke recognition and prediction of LVO by non-stroke specialists when neuroimaging information is unavailable. Our results may aid the clinical study design when prehospital patient screening involves LVO scales, and it is expected that a substantial proportion of patients are likely to have leukoaraiosis. If confirmed, our data suggest that in such a setting, scales like the FAST-ED and RACE may be advantageous because they appeared less impervious to leukoaraiosis-related misclassification. Furthermore, LVO scales are increasingly used to render decisions regarding immediate patient transfer to EST-capable hospitals when LVO is suspected, including in the setting of telemedicine consultations. In this setting, our results may be impactful when a plain head CT is reviewed (and provides information on leukoaraiosis severity) but no CTA was obtained due to lack of resources or imme-
Arguably, the presence of severe leukoaraiosis has been repeatedly shown to confer an increased risk of poor outcome in patients with LVO, including those undergoing EST.25,26 Leukoaraiosis has been repeatedly shown to confer an increased risk of poor outcome in patients with LVO, including those undergoing EST.25,26

### Table 2: Diagnostic accuracy of prehospital stroke scales in predicting LVO stratified by leukoaraiosis severity

| Scale | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | χ² |
|-------|-----------------|-----------------|---------|---------|----|
| 3/SS ≥ 4 | 22 (11–36) | 90 (86–94) | 31 (19–47) | 85 (83–87) | 0.14 (0–0.28) |
| VAN ≥ 2 | 70 (54–82) | 63 (57–69) | 28 (23–33) | 91 (87–94) | 0.20 (0.10–0.30) |
| CPSSS ≥ 2 | 41 (27–57) | 79 (74–84) | 29 (19–47) | 87 (84–90) | 0.18 (0.05–0.33) |
| RACE ≥ 5 | 50 (35–65) | 85 (80–89) | 40 (31–51) | 89 (86–92) | 0.32 (0.18–0.46) |
| FAST-ED ≥ 4 | 57 (41–71) | 79 (73–84) | 35 (27–43) | 90 (83–87) | 0.28 (0.15–0.41) |

Absence-to-mild leukoaraiosis (Fazekas score, 0–2; n = 129)

| Scale | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | χ² |
|-------|-----------------|-----------------|---------|---------|----|
| 3/SS ≥ 4 | 50 (21–79) | 88 (80–94) | 33 (18–52) | 94 (89–96) | 0.09 (0–0.27) |
| VAN ≥ 2 | 73 (54–88) | 68 (58–77) | 41 (32–50) | 89 (82–94) | 0.32 (0.16–0.48) |
| CPSSS ≥ 2 | 37 (20–56) | 87 (79–93) | 46 (30–63) | 82 (77–86) | 0.25 (0.06–0.45) |
| RACE ≥ 5 | 53 (34–72) | 91 (83–96) | 64 (46–78) | 87 (81–90) | 0.47 (0.29–0.65) |
| FAST-ED ≥ 4 | 57 (37–75) | 84 (75–90) | 52 (38–65) | 86 (81–91) | 0.39 (0.09–0.57) |

Moderate-to-severe leukoaraiosis (Fazekas score, 3–6; n = 145)

### Table 3: Multivariable logistic regression analysis for the ability of previously defined clinical stroke scale cutoffs to predict large-vessel occlusion in the examined cohort

| Stroke Scale | Crude OR (95% CI) | P Value | Adjusted OR (95% CI)* | P Value |
|--------------|-------------------|---------|-----------------------|---------|
| 3/SS ≥ 4     | 4.736 (1.513–14.826) | <.001   | 5.389 (0.856–33.908) | .073    |
| VAN ≥ 2      | 3.918 (1.979–7.760) | <.001   | 2.468 (0.845–7.206)  | .098    |
| CPSSS ≥ 2    | 2.710 (1.388–5.290) | <.003   | 2.794 (0.973–8.028)  | .056    |
| RACE ≥ 5     | 5.706 (2.881–11.299) | <.001   | 3.236 (1.099–9.527)  | .033    |
| FAST-ED ≥ 4  | 4.749 (2.447–9.217) | <.001   | 3.740 (1.291–10.839) | .015    |

*Each model was adjusted for leukoaraiosis burden (as determined by the Fazekas scale score) as well as Leukoaraiosis × Stroke Scale Interaction. When additionally entered into the model, the prestroke modified Rankin Scale, age, sex, hypertension, history of stroke/transient ischemic attack, and atrial fibrillation were not retained in the final step of the analysis. In all analyses, leukoaraiosis and stroke scales were entered as dichotomized variables. When all analyses were repeated by entering the Fazekas scale score and stroke scale scores as ordinal variables, the VAN (P = .029), CPSSS (P = .024), FAST-ED (P = .003), RACE (P = .002), and 3/SS (P = .006) scores predicted LVO independent of the leukoaraiosis burden (not shown). There was no Leukoaraiosis × Stroke Scale Interaction in any of the examined models (P > .05, each).

### CONCLUSIONS

Our results indicate that the presence of moderate-to-severe leukoaraiosis attenuates the diagnostic accuracy of available LVO scales and that the RACE and FAST-ED scales appeared more resilient to the confounding effects of leukoaraiosis. If confirmed in a larger cohort, this information may aid the design of studies that require prehospital LVO scale screening of patients likely to have concomitant leukoaraiosis.

### DISCLOSURES

Brian Silver—UNRELATED: Consultancy: Women’s Health Initiative, National Institutes of Health; Employment: Joint Commission, Expert testimony, Comments: medicolegal malpractice, Patients (Planned, Pending or Issued): transcranial magnetic stimulation; Payment for Development of Educational Presentations: Ebix, MedLink, Medscape. Aijit Puri—UNRELATED: Consultancy: Stryker, Codman, Payment for Lectures Including Service on Speakers Bureau: Stryker, Stock/Stock Options: InNeuroCo. Nils Henninger—UNRELATED: Employment: Joint Commission; Consulting: transcranial magnetic stimulation, Payment for Development of Educational Presentations: Ebix, MedLink, Medscape. Scott Nielson—UNRELATED: Employment: Joint Commission, Board Membership: Stryker, Comments: Advisory Board Member, Other: Oak Ridge Associated Universities, Comments: ad hoc reviewer. *Money paid to the institution.
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