Pre-existing White Matter Hyperintensity Lesion Burden and Diagnostic Certainty of Transient Ischemic Attack

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Goals: There are no validated biomarkers that allow for reliable distinction between TIA and other transient neurological symptoms that mimic TIA. We sought to determine whether the degree of pre-existing white matter hyperintensity (WMH) lesion burden relates to the diagnostic certainty of TIA in a cohort of patients presenting with transient neurological symptoms. *Materials and Methods*: We retrospectively analyzed 144 consecutive patients with available brain MRI to quantify and normalize the WMH volume for brain atrophy (adjusted white matter hyperintensity [aWMHV]). We first stratified subjects to probable (n = 62) versus possible (n = 82) TIA as per existing guidelines. Receiver-operating characteristic curves were used to determine a critical aWMHV-threshold (7.8 mL) that best differentiated probable from possible TIA. We then further stratified patients with possible TIA to likely (n = 52) versus unlikely (n = 30) TIA after independent chart review and adjudication. Finally, multivariable logistic and multinomial regression was used to determine whether the defined aWMHV independently related to probable and likely TIA after adjustment for pertinent confounders. *Findings*: With the exception of age ($P < .001$) and use of antiplatelets ($P = .017$), baseline characteristics were similar between patients with probable, likely, and unlikely TIA. In the fully adjusted multinomial model, the aWMHV cut-off greater than 7.8 mL (odds ratio 3.8, 95% confidence interval 1.3-10.9, $P = .012$) was significantly more frequent in patients with a probable TIA as compared to those with an unlikely TIA diagnosis. *Conclusions*: We provide proof-of-principle that WMH may serve as a neuroimaging marker of diagnostic certainty of TIA after neurological workup has been completed.

Key Words: Diagnosis—magnetic resonant imaging—stroke mimic—transient ischemic attack—white matter hyperintensity

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Introduction

Transient ischemic attack (TIA) represents a high-risk condition for near and long-term cerebrovascular events, cardiovascular complications, and death.[1] In contemporaneous clinical trials and registries incidence of stroke among patients with TIA or minor stroke has been found to range from 3.7% to 11.7%.[2-4] Accordingly, early and accurate identification of TIA is an important goal to initiate appropriate workup and secondary prophylaxis. The classic World Health Organization and National Institute of Neurological Disorders and Stroke definitions of TIA are primarily based on clinical features as a sudden focal neurologic deficit that resolves within 24 hours.[5,6] More recently, the Stroke Council of the American Heart Association introduced a tissue-based definition of TIA that requires absent evidence of acute infarction on neuroimaging.[7,8] According to this definition patients have no acute imaging finding to support the diagnosis of a TIA and the diagnosis rests on the clinician's interpretation of the patient's symptoms and overall clinical scenario.

However, clinical decision making may be biased by the treating physician's expertise contributing to low interobserver agreement for the clinical diagnosis of TIA. This may hamper differentiating TIAs from other conditions that are associated with transient neurological symptoms[9,10]; raising concerns that a subset of patients is misdiagnosed (false negatives or false positives) given the remaining diagnostic uncertainty.[9] This may have the unwanted consequence that TIA is either not recognized to require aggressive treatment to optimize secondary stroke prophylaxis or result in avoidable anxiety and exposure to unnecessary stroke prevention measures.[9] The reliability to detect cerebral infarcts with standard clinical MRI techniques depends on multiple factors including ischemia duration, infarct size, timing of imaging, as well as cerebral small vessel disease related stroke etiology.[9,11] Because the pre-existing white matter hyperintensity (WMH) lesion burden correlates with TIA-related risk factors,[12] it may be possible to leverage WMH to aid diagnosis of clinically defined TIA.

To test this hypothesis, we determined the pre-existing WMH lesion volume in patients with different diagnostic certainties (probable, likely, and unlikely) of their TIA as stratified according 2 approaches using (1) previously suggested practice guidelines as well as (2) the Precise Diagnostic Score (PREDISC).[13,14]

Materials and Methods

Study Cohort

Figure 1 summarizes the flow of patient exclusion. We retrospectively analyzed 144 consecutive patients who presented with transient neurological symptoms, without acute infarction or other acute pathology on brain MRI obtained within 48 hours from presentation, and in whom TIA was considered either the most likely diagnosis (probable TIA) or a possible differential diagnosis (possible TIA) after completion of the diagnostic workup. Subjects were recruited from our local stroke registry between January 2013 and April 2015. Analyses were conducted between November 2017 and February 2018. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (http://www.strobe-statement.org).

Clinical Characteristics, TIA Severity, and TIA Etiology

Patient demographics, laboratory data, comorbidities, and preadmission medications were abstracted from the medical record by trained physician abstractors. Members of the stroke team certified in National Institutes of Health Stroke Scale (NIHSS) scoring graded the deficit severity at presentation. Presence of a possible cardiovascular cause for the incident TIA was determined after completion of the stroke workup and defined as: (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia using NASCET criteria,[15] (2) major-risk cardioembolic source, (3) any other specific cause of stroke (eg, arterial dissection).[16,17] All other cases were considered to have no cardiovascular cause present (this included subjects considered to have a lacunar syndrome in the setting of absent cardiovascular cause).

Definition of TIA

In the absence of a universally accepted definition we defined TIA as rapidly developed clinical sign characterized by a transient episode of neurological dysfunction caused by focal brain or retinal ischemia, lasting less than 24 hours.[5,7,8]

To test our primary hypothesis, we first stratified TIA to probable TIA versus possible TIA based on previously suggested practice guidelines (Supplemental Table I).[13] In each case, the diagnosis of probable versus possible TIA was established by the treating board certified vascular neurologist and as adjudicated by the investigative team after independent review of the medical records and imaging data. Uncertain cases were resolved by consensus. In brief, TIA was considered *possible* if symptoms were compatible with both TIA and a competing etiology such as isolated vertigo, diplopia, dysarthria, dysphagia, loss of balance, drop attack, or isolated sensory symptoms that affected only part of a limb or only half the face.[13] TIA was considered *probable* in the abscence of a competing etiology and if patients had either an acute onset of at least 1 focal neurological deficit that included monocular blindness, aphasia, motor symptoms, sensory symptoms, homonymous hemianopia, cortical blindness, or had more than 1 symptom of possible TIA.[13] We then stratified possible TIA to (1) likely TIA and (2) unlikely TIA. For example, symptom progression in a stepwise or slowly gradual fashion was deemed indicative of an unlikely TIA.[13,18]

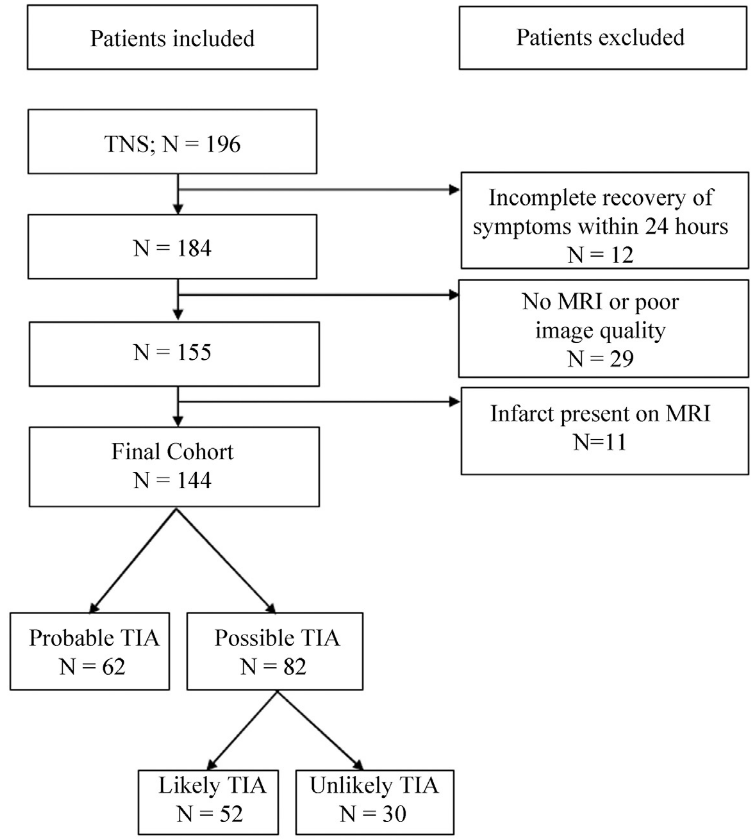

Figure 1. *Patient flowchart. TIA was classified according to published clinical practice guidelines.*[13] *TNS, transient neurological symptoms.*

Because TIA diagnosis solely based on clinicians' judgment may result in poor inter-rater agreement even among stroke specialists,[10,19-21] we additionally classified TIA diagnosis by using the previously developed PREDISC, which has been shown to improve inter-rater agreement.[14] In brief, PREDISC utilizes a structured approach to rate each patient on an 8-point scale that is composed of a clinical score (0-4 points) and an imaging score (0-4 points). The composite PREDISC classifies TIA likelihood as unlikely (0-1 point), possible (2 points), probable (3 points) and very likely (4-8 points).[14] Given our exclusion of patients with diffusion weighted imaging (DWI) lesion and because perfusion weighted imaging is not conducted in TIA patients, the PREDISC score in our cohort was based on the clinical score only (with a maximal score of 4).

Risk Factor Definitions

We determined the presence of hypertension (use of antihypertensive medications, or systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg on 2 separate occasions), hypercholesterolemia (use of lipid-lowering agents, or fasting blood total cholesterol level of ≥200 mg/dL or low density lipoprotein cholesterol [LDLc] of ≥130 mg/dL) and diabetes mellitus (history of fasting glucose ≥126 mg/dL or current use of hypoglycemic drugs) as defined according to the National Diabetes Data Group and World Health Organization.[22]

Cardiac studies were obtained at the treating physicians' discretion and included transthoracic echocardiography or transesophageal echocardiography, electrocardiography, and 30-day cardiac rhythm event monitoring. All patients underwent continuous 24-hour in-patient cardiac telemetry per institutional protocol. A chest radiograph was done if pulmonary disease or heart failure was suspected.

Neuroimaging Protocol

Brain MRI included T1-, T2-, and fluid-attenuated inversion recovery (FLAIR) sequences as well as DWI. MRI was performed on a 1.5 Tesla clinical scanner (Signa HD; GE Healthcare, Milwaukee, WI). DWI was obtained using echo-planar imaging with a repetition time of 8000 ms, an echo time of 102 ms, a field of view of 22 × 22 cm, image matrix of 128 × 128, slice thickness 5 mm with a 1-mm gap, and b values of 0 s/mm^2 and 1000 s/mm^2.[12] FLAIR was obtained with a repetition time of 9002 ms, an echo time of 143 ms, a field of view of 22 × 22 cm, image matrix of 256 × 224, and slice thickness 6 mm with a 1-mm gap.

Neuroimaging Review and Analysis

DWI was reviewed independently by experienced readers (N.H., M.N.) blinded to both clinical data and any follow-up scans. Patients with lesions that were hyperintense on DWI and hypo- or isointense on the apparent diffusion coefficient (ADC) maps were considered to have an acute ischemic infarct and were excluded. WMH was defined as white matter hyper-intensity on FLAIR images according to the STandards for ReportIng Vascular changes on nEuroimaging criteria.[23] Chronic white matter infarcts and infratentorial structures were excluded from analysis.[23]

MRIcron (http://www.mricro.com) was used to quantify the supratentorial intracranial volume (ICV), total brain volume (TBV), and WMH volume (WMHV) on FLAIR images. The WMHV was determined using a semi-automated process as previously described in detail.[24] TBV and ICV were determined by adding the manually outlined brain and intracranial areas on each slice, respectively; followed by multiplication by the slice thickness plus the interslice gap. To account for intersubject variation and brain atrophy, we calculated an adjusted WMHV (aWMHV) as follows: aWMHV = (WMHV × ICV × mean TBV)/(TBV × mean ICV). The mean TBV and mean ICV refer to the mean of the studied cohort and as calculated separately for men and women, respectively. Last, relative brain atrophy was calculated by (ICV−TBV)/ICV × 100.[25] Analyses of a full image dataset required approximately 20 minutes (10 minutes for WMHV and 10 minutes for brain volumetry). Prior to conducting any analyses, novel raters first received hands-on training in the use of MRIcron on 2 sample image sets. Thereafter, they conducted analyses of a set of 10 training images with review after each set by a trained investigator (M.N. or N.H.) to achieve iterative improvement in the lesion delineation. Finally, raters independently analyzed 10 randomly chosen images from an existing dataset (analyzed by a trained investigator) to determine inter-rater agreement of the volumetric analyses. Krippendorf's alpha greater than .8 was considered to indicate good inter-rater agreement and training expertise.[26] Lower agreement prompted retraining as needed.

To determine inter-rater agreement in the current dataset, 35 brains were independently analyzed by 2 investigators. There was overall excellent inter-rater correlation in the WMHV (r = .978, $P < .001$) and Bland-Altman analysis indicated minimal bias between raters (−.22 mL; 95% CI = −.60 mL to .15 mL; limits of agreement = −2.37 mL to 1.93 mL; not shown).

Statistical Analyses

Unless otherwise stated, continuous variables are reported as mean ± S.D. or median (25th-75th quartile). Categorical variables are reported as proportions. Between-group comparisons for continuous and ordinal variables were made with Mann-Whitney U test, Kruskal-Wallis one-way ANOVA on ranks with posthoc Dunn's test, 2-way ANOVA with posthoc Holm-Šidák test as appropriate. Categorical variables were compared using the χ^2 test. Bonferroni method was used to correct for multiple comparisons. Correlation analysis was performed using Spearman rank test.

In a first step, we constructed a multivariable logistic regression model to determine whether the aWMHV threshold was independently associated with a probable TIA diagnosis. We adjusted the model for factors associated ($P < .20$) with the diagnosis of probable TIA in univariate analyses (including age, history of hypertension and hyperlipidemia, as well as therapy with an HMG-CoA reductase inhibitor [statin] and antiplatelets). In addition, we included the presence of a cardiovascular cause into the model. To avoid model overfitting, variables were sequentially removed (likelihood ratio) from the models at a significance level of .1.

In a second step, we created multinomial logistic regression models to determine whether the aWMHV cut-off differed between unlikely TIA as compared to likely TIA and probable TIA, respectively. Models were adjusted for the same covariates included in the multivariable logistic regression. A parsimonious model was created by sequential manual removal of terms. 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 and unless stated otherwise a 2-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM-Armonk, NY).

Results

During the study period, 184 subjects were diagnosed as having either a probable or possible TIA. We excluded 40 subjects because they had no MRI or a poor quality MRI (n = 29; 15.8%) and who had evidence of acute infarction on DWI (n = 11), leaving 144 patients for analysis (Fig 1).

Baseline characteristics of the included patients as stratified by TIA category according to previously published practice guidelines[13] are summarized in Table 1. Overall, when dichotomized to probable versus possible TIA, baseline characteristics were similar between subgroups except that patients considered to have a probable TIA were older (P = .002), more frequently used statins (P = .029), as well as had a greater ICV (P = .047) and aWMHV (P = .002).

Factors significantly associated with greater aWMHV (Table 2) were older age ($P < .001$), history of prior stroke/TIA (P = .005), hypertension ($P < .001$), hyperlipidemia

Table 1. *Baseline characteristics of the studied patient population stratified by TIA category**

	All patients	Probable TIA	Possible TIA (n = 82)			
Characteristics	(n = 144)	(n = 62)	Likely TIA (n = 52)	Unlikely TIA (n = 30)	*P* value†	*P* value‡
Age, y	70 (55-79)	74 (61-82)	71 (57-79)	55 (43-67)	.002	<.001
Female sex	73 (50.7%)	29 (46.8%)	28 (53.8%)	16 (53.5%)	.501	.747
Admission NIHSS	1 (0-3)	1 (0-2)	0 (0-2)	2 (0-4)	.985	.143
Cardiovascular cause present	32 (22.2%)	15 (24.2%)	14 (26.9%)	3 (10%)	.687	.190
Pre-existing risk factors						
Hypertension	106 (73.6%)	50 (80.6%)	37 (71.2%)	37 (63.3%)	.127	.191
Diabetes	33 (22.9%)	14 (22.6%)	13 (25.0%)	6 (20.0%)	1.000	.903
Prior stroke or TIA	41 (28.5%)	21 (33.9%)	11 (21.2%)	9 (30.0%)	.264	.331
Peripheral artery disease	27 (18.8%)	10 (16.1%)	11 (21.2%)	6 (20.0%)	.525	.820
Hyperlipidemia	88 (61.1%)	42 (67.7%)	32 (61.5%)	14 (46.7%)	.171	.158
Atrial fibrillation	16 (11.1%)	7 (11.3%)	5 (9.6%)	4 (13.3%)	1.000	.889
Congestive heart failure	5 (3.5%)	1 (1.6%)	3 (5.8%)	1 (3.3%)	.391	.441
Coronary artery disease	30 (20.8%)	16 (25.8%)	10 (19.2%)	4 (13.3%)	.219	.386
Preadmission medications						
Statin	75 (52.1%)	39 (62.9%)	24 (46.2%)	12 (40.0%)	.029	.066
Antihypertensive	93 (64.6%)	43 (69.4%)	34 (65.4%)	16 (53.3%)	.379	.311
Antiglycemic	30 (20.8%)	12 (19.4%)	13 (25.0%)	5 (16.7%)	.836	.646
Antiplatelet	84 (58.3%)	42 (67.7%)	31 (59.6%)	11 (36.7%)	.060	.017
Anticoagulants	8 (5.6%)	3 (4.8%)	3 (5.8%)	2 (6.7%)	1.000	.902
ICV, mL	1163 (1086-1271)	1193 (1136-1282)	1149 (1077-1270)	1111 (1068-1267)	.047	.103
TBV, mL	955 (889-1063)	976 (905-1063)	932 (875-1059)	931 (895-1075)	.183	.348
aWMHV, mL	10.2 (6.4-16.9)	12.0 (8.0-21.6)	11.1 (5.4-16.9)	6.8 (4.6-9.9)	.002	<.001

aWMHV, adjusted white matter hyperintensity volume; ICV, intracranial volume; LAA, large artery atherosclerosis; TBV, total brain volume.
Data are n (%) or median (25th-75th quartile).
*TIA was classified according to previously published clinical practice guidelines.[13]
†Comparison between probable versus possible (combined likely and unlikely) TIA.
‡Comparison between probable versus likely versus unlikely TIA.

Table 2. *Bivariable relations with the aWMHV*

Covariate	aWMHV (mL; mean ± sd) Absent	Present	*P* value
Female sex	17.5 ± 18.8	13.1 ± 11.9	.224
Cardiovascular cause	14.2 ± 13.3	19.5 ± 22.6	.269
Pre-existing risk factors			
Hypertension	10.5 ± 17.3	17.1 ± 15	<.001
Diabetes	14.8 ± 15.9	17.3 ± 16	.156
Prior stroke or TIA	13.2 ± 12.9	20.8 ± 20.8	.005
Peripheral artery disease	15.1 ± 16.2	16.2 ± 14.6	.561
Hyperlipidemia	13.7 ± 17.8	16.4 ± 14.5	.011
Atrial fibrillation	15 ± 15.5	18.2 ± 19	.434
Congestive heart failure	15.3 ± 15.9	15.8 ± 17.3	.874
Coronary artery disease	13.8 ± 15.6	21.3 ± 15.7	.001
Preadmission medications			
Statin	12.4 ± 15	18.1 ± 16.3	.006
Antihypertensive	11.5 ± 16.5	17.5 ± 15.2	<.001
Antiglycemic	14.6 ± 15.7	18.1 ± 16.4	.103
Antiplatelet	11.3 ± 12.3	18.2 ± 17.5	.001
Anticoagulants	15.2 ± 16.1	17.8 ± 12.7	.160
Age, y	r = .597		<.001
Admission NIHSS	r = .028		.741

aWMHV, adjusted white matter hyperintensity volume.
All comparisons were made using Mann-Whitney U test and Spearman rank correlation analysis.

(P < .011), coronary artery disease (P = .001), as well as antihypertensives (P < .001) and antiplatelets (P = .001).

Area under the receiver-operating characteristic curves were plotted to determine the aWMHV and age cut-offs best predicting probable TIA in the entire cohort. Optimal thresholds (7.8 mL for aWMHV and 67 years for age) were determined by maximizing Youden's index (sensitivity + specificity−1). After adjustment, the aWMHV greater than 7.8 mL (OR 2.9; 95% CI 1.4-6.3; P = .006) and statin therapy (OR 2.0; 95% CI 1.0-4.0; P = .049) were independently associated with a diagnosis of probable TIA (goodness of fit χ^2 = .233, P = .890).

When trichotomized to probable, likely, and unlikely TIA as per previously published practice guidelines,[13] there was no significant difference in the baseline characteristics of patients with the exception of the aWMHV (P < .001, Fig 2A), age (P < .001), and use of antiplatelets (P = .017; Table 1). Specifically, subjects with unlikely TIA had significantly smaller aWMHV than subjects with a likely TIA diagnosis (6.8 mL [interquartile range (IQR) 4.8-9.9 mL] versus 11.1 mL [IQR 5.4-16.9 mL], P = .011). Similarly, significantly fewer subjects with unlikely TIA had aWMHV greater than 7.8 mL than subjects with a likely TIA diagnosis (36.7% versus 65.4%, P = .021).

In the fully adjusted multinomial regression, both aWMHV greater than 7.8 mL (OR 3.8, 95% CI 1.3-10.9, P = .012) and age greater than 67 years (OR 3.7, 95% CI 61.3-10.6, P = .017) were significantly more frequent in patients with a probable TIA as compared to those with an *unlikely* TIA diagnosis. There was no difference for aWMHV and age between subjects with probable versus *likely* TIA. Together, these results suggest that defining a critical aWMHV cut-off could differentiate subjects with unlikely TIA from those with a likely TIA or probable TIA.

To address the issue that our results may have been biased by the utilized clinical TIA-classification scheme, we conducted an additional set of analyses. First, we stratified TIA based on the absence versus presence of a cardiovascular cause for the incident TIA (Fig 2**B**). Overall, there was no difference between the aWMHV of patients with versus without a cardiovascular cause (11.7 mL [IQR 6.4-23.3 mL] versus 9.6 mL [IQR 6.4-16.3 mL], P = .269; Fig 2**B**). Importantly, the association of an increasing aWMHV with greater diagnostic certainty did not depend on the presence of a cardiovascular cause both for the dichotomized (Fig 2C) and trichotomized (Fig 2D) TIA classification. Results were not meaningfully affected when we reclassified patients with lacunar syndrome to have a "cardiovascular cause present" (not shown).

Second, we classified TIA likelihood according to the established PREDISC scale. Using the PREDISC classification scheme, we found that increasing WMH-lesion burden significantly correlated with a higher PREDISC score (r = .296, P <.001; Fig 3**A**) and patients with our defined aWMHV cut-off were significantly more frequently present with increasing PREDISC-determined TIA likelihood (P = .006; Fisher's exact test; Fig 3**B**).

Discussion

The main goal of our study was to determine whether the MRI-defined WMH lesion burden relates to the

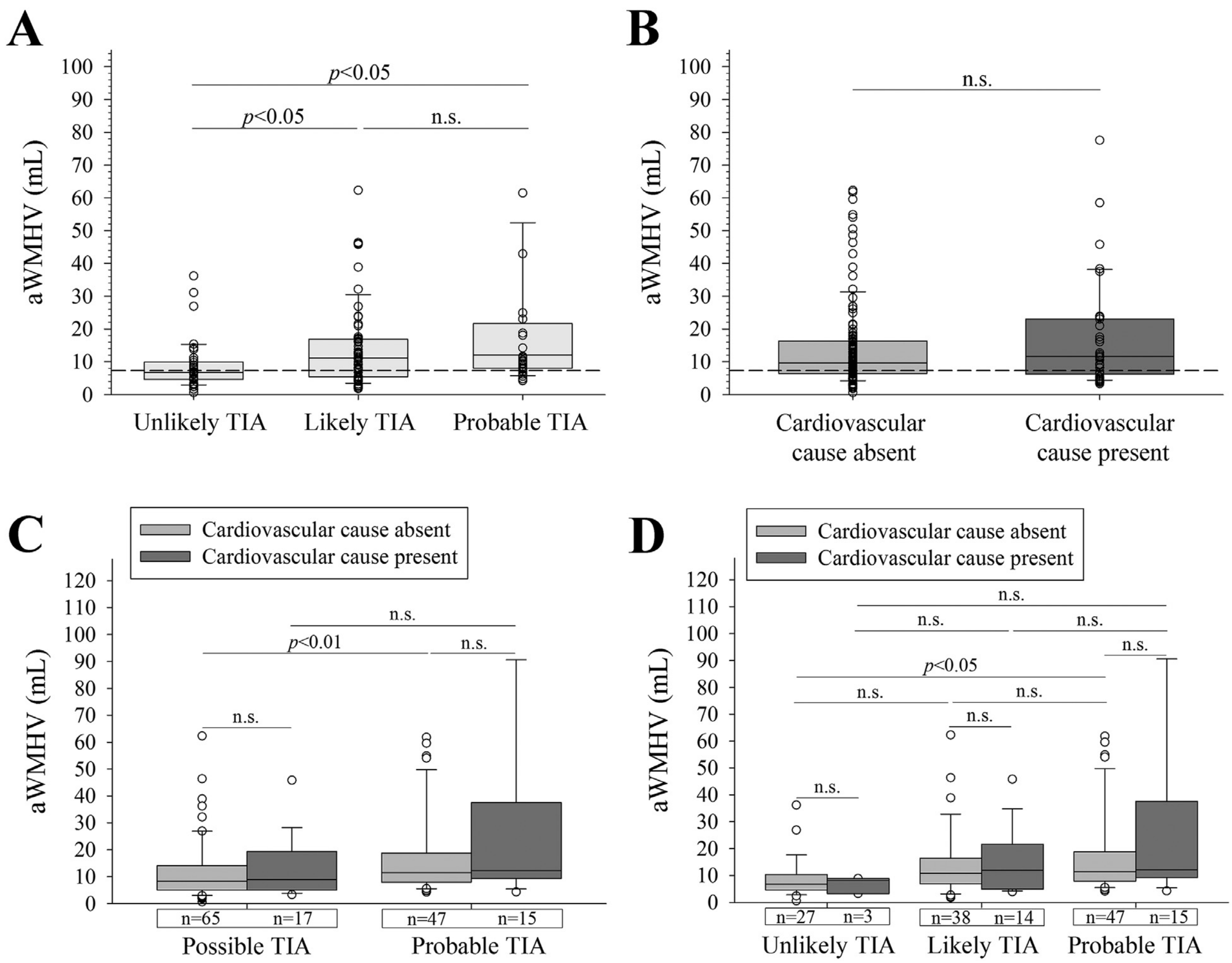

Figure 2. *Adjusted white matter hyperintensity volume (aWMHV) stratified by diagnostic certainty and cardiovascular cause presence of TIA according to published clinical practice guidelines.*[13] *(**A**) Increasing aWMHV with greater diagnostic certainty for TIA (P for trend = .0003; ANOVA on Ranks with posthoc Dunn's). (**B**) Similar aWMHV between subjects with versus without a cardiovascular cause (Mann-Whitney U test). (**C**) The association of an increasing aWMHV with greater diagnostic certainty did not depend on the presence of a cardiovascular cause (2-way ANOVA: P = .002 for diagnostic certainty effects [DF = 1, F = 9.6], P = .09 for cardiovascular cause effects [DF = 1, F = 2.9], and P = .20 for TIA category x cardiovascular cause interaction [DF = 1, F = 1.6]). (**D**) Results were similar when the diagnostic certainty was trichotomized (2-way ANOVA: P = .007 for diagnostic certainty effects [DF = 2, F = 5.1], P = .50 for cardiovascular cause effects [DF = 1, F = .5], and P = .33 for TIA category × cardiovascular cause interaction [DF = 2, F = 1.1]. Box plots are median ± interquartile range with whiskers indicating 5th/95th percentile (open circles in panels A and B depict the individual patients).*

diagnostic certainty of patients deemed to have a possible TIA. Indeed, we found that patients with probable TIA had significantly greater aWMHVs than subjects with a less certain (possible) diagnosis of TIA. Most important, our results indicated that the presence of a high WMH lesion burden related to a greater clinical diagnostic certainty of a TIA irrespective of a patient's age, vascular risk factor profile, medication regimen, as well as the presence of a presumed cause for the TIA.

Our results need to be viewed in light of our patient selection, which excluded patients that were unequivocally deemed to have a TIA mimic. Accordingly, our results extend only to subjects that were considered to have a TIA as a differential diagnosis as assessed by stroke physicians and after completion of the diagnostic workup. Nevertheless, among included patients in our cohort there remained uncertainty as to the diagnosis of TIA in as many as 57% of subjects, which is consistent with previously reported uncertainty in rendering a definite diagnosis of TIA.[10,27] Accordingly, our study addresses a common clinical scenario in a real-life patient population.

Our observation that patients with different levels of diagnostic certainty for their TIA had a similar risk factor profile is important for several reasons. First, these results are consistent with prior investigations that did not find significant differences between patients deemed to have a TIA versus those thought to have a nonischemic causes for their transient neurologic symptoms.[18] Second, this highlights that a patient's vascular risk factor profile is ill suited to help diagnose TIA in uncertain situations. This emphasizes the need to define novel biomarkers to improve diagnostic certainty of TIA, particularly since

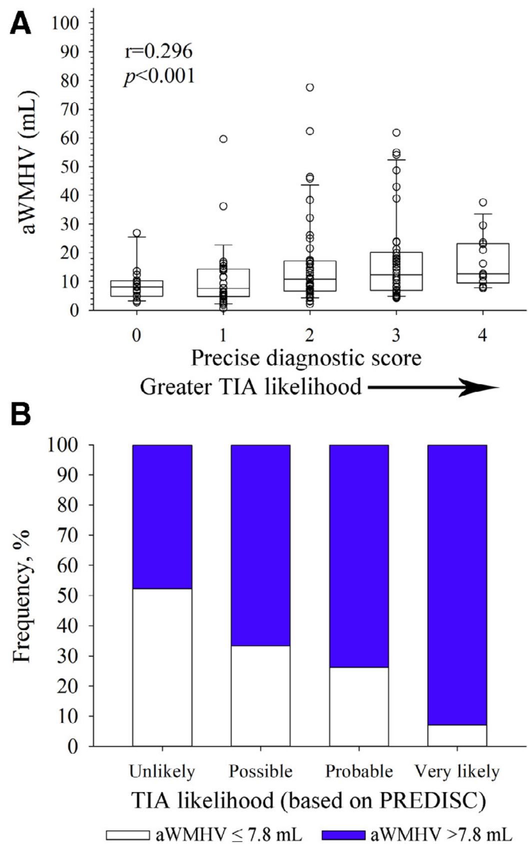

Figure 3. *Adjusted white matter hyperintensity volume (aWMHV) stratified by TIA likelihood according to the Precise Diagnostic Score (PREDISC).[14] (A) Positive correlation between the aWMHV and PREDISC (Spearman rank correlation test). Box plots are median ± interquartile range with whiskers indicating 5th/95th percentile (open circles represent individual patients). (B) Presence of an aWMHV >7.8mL significantly increased with greater TIA likelihood as categorized according to PREDISC (*P = .006*; Fisher's exact test).*

TIA is a high risk condition for subsequent ischemic stroke if not recognized and treated appropriately.[27,28]

In this respect the pre-existing WMH lesion burden is an attractive candidate imaging biomarker because it is accessible from routine clinical MRI and is common among patients with TIA with which it shares the same vascular risk factors.[29,30] Furthermore, WMH has been shown to affect the clinical presentation in the setting of acute cerebral ischemia.[12,31-34] Specifically, we previously demonstrated that among stroke patients with similar functional deficit severity at the time of their presentation those with a high WMH lesion burden had significantly smaller infarcts.[32] Accordingly, in the setting of a high WMH lesion burden smaller infarcts under the detection limit of MRI[35] would be expected to produce typical TIA deficits that can be more easily recognized as a probable TIA as determined by existing guidelines or the PREDISC scoring system.[13,14]

Indeed, we found a positive correlation between the WMH burden and diagnostic certainty using these 2 different approaches to assessing TIA likelihood. Using the same lesion cut-off that best distinguished probable from possible TIA we found that patients with unlikely TIA had significantly lower rates of high aWMHVs. These results provide proof-of-principle that it is possible to define a critical WMH cut-off that relates the diagnostic certainty of TIA. Nevertheless, whether our specific cut-off is ideal, and whether it enables to distinguish TIA from mimics, remains to be defined in future prospective studies. Although our approach to WMHV quantification is labor intensive and presently not widely available for clinical use, there is increasing availability of software solutions for brain parcellation to calculate volumes of interest in a semi- and even fully automated fashion that will enable utilization of WMH-derived metrics to improve diagnostic accuracy and aid decision making in the future.

Strengths of our study include quantification of the WMHV with adjustment for brain atrophy and gender-specific normalization, stratification of diagnostic certainty of TIA according to 2 published assessment tools, and after independent chart review with adjudication by the investigative team, as well as rigorous adjustment of the multivariable models using pertinent confounders. Limitations relate to its retrospective, cross-sectional design as well as the modest sample sizes in this study. This may have limited the power of our analyses. We only included subjects that had brain MRI available for analysis. Thus, our results may not fully translate to all patients. Lastly, in the absence of a gold standard for diagnosing TIA there remains some uncertainty regarding patient allocation in our cohort. Nevertheless, our approach and the studied patient cohort reflect a relevant and common clinical scenario, highlighting the clinical relevance of our study.

Conclusions

Worse pre-existing aWMHV relates to greater diagnostic certainty among subjects presenting with TIA irrespective of common vascular risk factors. Further study is needed to determine whether WMH may serve as a supplementary neuroimaging marker to improve diagnostic clarity when TIA remains uncertain after conclusion of the neurological workup.

Ethical Approval

Our investigation was approved by our Institutional Review Board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We were granted a Health Insurance Portability and Accountability Act waiver of informed consent.

Conflict of Interest

Dr Henninger serves on the advisory board of Omniox, Inc and Portola Pharmaceuticals, Inc. All other authors declare no competing interests.

Author Contributions

M.N., and N.H. were involved in the study design and drafted the article. M.N., M.A., Y.S., S.N., and N.H. acquired the data. N.H. conducted statistical analyses. M.N., M.A., and N.H. were involved in data interpretation. All authors commented on the manuscript for important intellectual content.

Data Sharing

The investigators will share anonymized data (with associated coding library) used in developing the results presented in this manuscript upon reasonable request to investigators who have received ethical clearance from their host institution.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.12.022.

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