Standard clinical and imaging-based small vessel disease parameters associated with mild stroke versus non-mild stroke

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ABSTRACT

BACKGROUND: Mild stroke has variable outcomes, and there is an ongoing debate regarding whether the administration of thrombolytics improves outcomes in this subgroup of stroke patients. Having a better understanding of the features of mild stroke may help identify patients who are at risk of poor outcomes.

OBJECTIVE: The objective of this study is to evaluate the association of clinical and imaging-based small vessel disease features (white matter hyperintensities and cerebral microbleeds) with stroke severity and clinical outcomes in patients with mild stroke.

METHODS: In this retrospective study, mild stroke was defined as a National Institute of Health stroke scale (NIHSS) score <5. Clinical, laboratory and imaging data were compared between patients with mild stroke versus non-mild stroke (NIHSS≥5). Multivariate logistic regression analysis was performed to identify predictors of mild stroke and poor discharge outcome.

RESULTS: Among 296 patients included in the study, 131 patients (44%) had mild stroke. On multivariate analysis, patients with mild stroke were three times more likely to have sensory symptoms [odds ratio (OR) = 2.9; 95% confidence interval (CI) = (1.2-6.8)] and four times more likely to have stroke due to small vessel disease (OR = 3.7; 95%CI = 1.4-9.9). Among patients with mild stroke, higher age (OR = 1.1; 95%CI = 1.02-1.1), presence of cerebral microbleed (OR = 4.5; 95%CI = 1.5-13.8), vertigo (OR = 7.3; 95%CI = 1.2-45.1) and weakness (OR = 5.0; 95%CI = 1.2-20.3) as presenting symptoms were more likely to have poor discharge outcome.

CONCLUSION: Sensory symptoms and stroke due to small vessel disease are more common in mild stroke than non-mild stroke. Among patients with mild stroke, presence of cerebral microbleeds on imaging and symptoms of muscle weakness are associated with poor discharge outcome. Larger studies are needed to assess the impact of cerebral microbleed on mild stroke outcomes and risk stratify the benefit of thrombolytics in this group.

KEYWORDS: Ischemic stroke, mild stroke, outcomes

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Introduction

Stroke is the second leading cause of mortality worldwide.[1,2] It has an annual mortality rate of 5.5 million and causes chronic disability in 50% of survivors.[1] The treatment of moderate and severe stroke with thrombolytics is more straightforward with definitive guidelines and recommendations from the American Heart Association/American Stroke Association (AHA/ASA). However, the current AHA/ASA guidelines do not recommend alteplase for patients with mild, non-disabling stroke symptoms as the efficacy and safety benefit has not been clearly demonstrated.[3,4]

Despite extension of the alteplase treatment window from 3 to 4.5 hours from symptom onset, majority of patients do not receive alteplase as a result of delay in reaching the hospital in a timely manner.[5,6] Prehospital stroke workflow optimization such as improving emergency medical service response to a stroke with their education of stroke symptoms and prehospital stroke notification with single call activation of the stroke team have improved rates of intravenous thrombolysis and reduced door-to-needle time.[7] Among those who do make it to the hospital within the treatment time window, 30-40% are excluded because of mild symptoms or symptoms that are rapidly improving.[5,6] Although the benefit of alteplase has not been demonstrated in patients with mild non-disabling stroke, previous observational studies suggest that it should not be withheld under the guise that deficits are nondisabling as the

risks of alteplase are low and a substantial number of patients have a poor outcome.[5,8-11]

In a previous study on mild stroke, the total National Institutes of Health stroke scale (NIHSS) score rather than the type of neurological deficit scored as part of a patient's low baseline NIHSS score predicted poor outcome at 3 months.[8] While pre-existing small vessel disease features such as white matter hyperintensity (WMH) and cerebral microbleeds (CMB) have been shown to be associated with poor clinical outcomes in stroke,[12,13] their impact in mild stroke population is less clear. In a prior study involving high risk transient ischemic attack and mild stroke (NIHSS≤3), WMH was not associated with poor clinical outcome.[14] Prior studies have reported the association of CMB with good as well as poor clinical outcomes in patients with mild stroke.[15,16]

A systematic study of clinical and imaging features of small vessel disease in patients with mild stroke may help identify those more likely to have a poor outcome and who may benefit from thrombolytics. Our study objective was to evaluate the clinical and imaging-based small vessel disease features associated with stroke severity and clinical outcomes in mild stroke patients.

Methods

Data Source and Study Design

This is a retrospective observational study of consecutive acute ischemic stroke patients admitted to a tertiary comprehensive stroke center from July 1, 2015 to June 30, 2016. The Institutional Review Board at the University of Florida (IRB# 201601625) approved the study. Informed consent for the study was waived by the IRB and the study followed the tenets of Helsinki declaration.

Study Population

At our stroke center, stroke patients are routinely evaluated with a non-contrast computed tomography (CT) head, CT angiogram head and neck, and sometimes a CT perfusion scan of the brain. Stroke patients also routinely get a magnetic resonance imaging (MRI) of the brain if there are no contraindications for the MRI and if the patient is clinically stable and not claustrophobic. Patients were included in the study if they had a diagnosis of ischemic stroke based on the presence of restricted diffusion lesion on diffusion-weighted imaging (DWI). Patients were excluded if they had an uninterpretable DWI scan, diagnosis of transient ischemic attack, or clinical diagnosis of ischemic stroke without a DWI lesion. The following data elements were abstracted from the patients chart — (1) clinical – demographics, medical history, clinical symptoms at presentation, vital signs, admission NIHSS score, treatment with alteplase or mechanical thrombectomy; (2) laboratory data - lipid profile and hemoglobin A1c; (3) discharge data - complications during hospitalization, modified Rankin scale (mRS) score at the time of discharge, discharge disposition, and TOAST (Trial of Org 10172 in Acute Stroke Treatment) etiological classification.[17] Intracranial atherosclerosis was considered as large artery disease for TOAST classification. Patients with an admission NIHSS score from 0 to 4 were categorized as having mild stroke. The study dataset was divided into two groups — mild stroke (NIHSS <5) and non-mild stroke (NIHSS ≥5).

Imaging Protocol

MRI images were obtained from 1.5 T Avanto or 3T Verio Siemens scanners as described in our previous study.[18] Stroke protocol MRI included DWI, fluid-attenuated inversion recovery imaging (FLAIR), and susceptibility-weighted imaging (SWI) sequences. Typical parameters for DWI were repetition time/echo time (TR/TE) = 4100/102 or 7300/80 or 8200/89 with b = 0 and 1000 s/mm^2, 4-5 mm thickness; for FLAIR, TR/TE = 9000/90 or 9000/126, 4 mm thickness; and for SWI, TR/TE = 28/20 or 49/40, 3 mm thickness.

Imaging Assessment

Two investigators evaluated all DWI, SWI, and FLAIR images independently blinded to clinical history. Discrepancies in image reads were resolved by consensus. The DWI lesions were categorized based on the distribution of lesions in a particular vascular territory.

A meta-analysis reported that moderate to severe WMH was associated with poor 90-day functional outcome and mortality.[12] To assess the impact of WMH severity on clinical outcomes in patients with mild stroke, WMH was graded on FLAIR sequence using the semi-quantitative Fazekas rating scale.[19] The deep WMH (D-WMH) was graded on a scale of 0-3: 0–no lesion, 1–punctate foci, 2–beginning confluence of foci, and 3–large confluent areas. Similarly, the periventricular WMH (PV-WMH) was graded from 0-3: 0–no lesion, 1–caps or pencil-thin lining, 2–smooth halo, and 3–irregular periventricular hyperintensities extending into the deep white matter.[19] The total Fazekas score (sum of scores for D-WMH and PV-WM) was dichotomized as 0-3 (mild) versus 4-6 (severe) for analysis.

The CMBs were evaluated using the Microbleed Anatomical Rating Scale (MARS) which has been reported to have good inter-rater reliability for the presence of definite microbleeds.[20] As described in our previous study, circular, and homogenously hypointense lesions measuring 2-10 mm in diameter on SWI were identified as CMB.[18] The CMB mimics as described in MARS criteria were excluded. To exclude mimics such as calcium deposits, the hypointensities in the basal ganglia seen on MRI were compared to admission CT head.[18] Hypointense lesions mimicking small vessels were followed through sequential slices.

Hemorrhagic transformation (HT) was graded using the Heidelberg bleeding classification system.[21] Hemorrhagic infarct (HI) was classified as HI-1 (scattered small petechiae) and HI-2 (confluent petechiae) without mass effect. Parenchymal hematoma (PH) was classified as PH-1 (hematoma occupying <30% of the infarcted tissue without substantive mass effect) and PH-2 (hematoma occupying ≥30% of the infarcted tissue with clear mass effect). Intraventricular hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, and remote PH from the infarct area were included in PH category for analysis. The MRI brain performed during hospitalization was used to evaluate both CMB and HT.

Statistical Analysis

Group wise comparison was performed to delineate differences in clinical and imaging features between mild vs non-mild stroke patients. The clinical features assessed were demographics, medical history, presenting symptoms, vital signs, treatment with alteplase or mechanical thrombectomy, stroke related complications, TOAST classification, and pertinent laboratory data. The imaging parameters included vascular territory of the DWI stroke lesion, assessment of WMH and CMBs. Categorical variables were reported as percentages and analyzed with Chi-square test or Fisher's exact test. Continuous variables were reported as mean (±standard deviation) or median (interquartile range) and analyzed with univariate simple linear regression. Multivariate logistic regression analysis was performed to evaluate the clinical and imaging factors associated with mild stroke. Clinical (demographics, medical history, social history, presenting symptoms, and TOAST etiological classification) and imaging factors that were significant in univariate analysis were included as covariates. Total Fazekas score and presence of CMB were added as covariates as the study was particularly focused on these imaging features in mild stroke. Assumption testing was performed to assess the multivariate logistic regression model. There was no evidence of multicollinearity of above predictors included in the analysis. There were no outliers.

The primary outcome evaluated was discharge disposition – good discharge outcome vs poor discharge outcome. Discharge to home or home with home health care services were considered as good discharge outcomes. Poor discharge outcomes were defined as discharge to acute inpatient rehabilitation, skilled nursing facility, long-term care facility, hospice, or death. Secondary outcome evaluated was radiologically defined HT assessed on SWI. Multivariate logistic regression analysis was performed to identify factors associated with poor discharge outcome among patients with mild stroke. Patients with mild stroke were evaluated for the distribution of NIHSS score, discharge disposition, and HT stratified by alteplase use.

Model goodness-of-fit was expressed by C-statistic. The alpha level for statistical significance was .05. Odds ratio (OR) and 95% confidence intervals (CI) were reported for the results of the multivariate logistic regression models. Statistical analysis was performed using SAS version 9.4 SAS Institute Inc, Cary, NC.

Results

Baseline Clinical and Imaging Characteristics

Among 296 patients included in the study, 131 patients (44%) had mild stroke. Patients with mild stroke were on average younger (mean ± standard deviation: 65 ± 14 vs 69 ± 15 years; P = .02), compared to patients with non-mild stroke. There were no differences in gender, race, medical or social history between the two groups, except for higher rates of hypertension in patients with mild stroke compared to those with non-mild stroke (82% vs 72%, P = .03, Table 1).

Compared to non-mild stroke, patients with mild stroke were more likely to present with sensory symptoms (34% vs 13%, P<.0001) and vertigo (13% vs 5%, P = .02) and less likely to present with complaints of weakness (70% vs 87%, P = .0002), aphasia (18% vs 45%, P<.0001), and altered mental status (11% vs 21%, P = .03, Table 1). The distribution of abnormal NIHSS components among patients with mild stroke are as follows: level of consciousness (LOC), 1a = 0%; LOC questions, 1b = 4%; LOC commands, 1c = 0%; best gaze, 2 = 5%; visual, 3 = 9%; facial palsy, 4 = 33%; weakness of arm or leg, 5 or 6 = 29%; limb ataxia, 7 = 15%; sensory, 8 = 26%; aphasia, 9 = 10%; dysarthria, 10 = 34%; and extinction, 11 = 4%. When compared to patients with non-mild stroke, patients with mild stroke were more likely to have small vessel occlusion and less likely to have cardio-embolism as a cause of stroke. (Table 1).

Patients with mild stroke were less likely to have an involvement of anterior cerebral artery (5% vs 13%, P = .01), M1 segment of the middle cerebral artery (MCA) (8% vs 45%, P<.0001), or multiple vascular territories (9% vs 21%, P = .007, Table 2) but more likely to have a posterior cerebral artery territory stroke (27% vs 14%, P = .006). There were no differences in D-WMH, PV-WMH and total Fazekas score, categorized as mild (score 0-3) vs severe (score 4-6), between the two groups (Table 2). There was no difference in the number of patients with CMB between the two groups.

Clinical and Imaging Factors Associated With Mild Stroke

On multivariate analysis, patients with mild stroke were three times more likely to have sensory symptoms (OR = 2.9; 95% CI = 1.2-6.8) and four times more likely to have a stroke due to small vessel disease (OR = 3.7; 95% CI = 1.4-9.9). However, they were less likely to have weakness (OR = .3; 95% CI = .2-.7), aphasia (OR = .4; 95%CI = .2-.8), and M1 segment of middle cerebral artery territory stroke (OR = .2; 95%CI = .1-.4). Figure 1 shows the ROC area for the multivariate regression model. Figure 2 shows the plots with OR and 95% CI for the main results of the study Table 3.

Table 1. Clinical Characteristics.

VARIABLE	NON-MILD STROKE N = 165 (56%)	MILD STROKE YES N = 131 (44%)	*P* VALUE
Age, in years, mean (SD)	69 (15)	65 (14)	.02*
Age category, n (%)			
1. 18-45 years	13 (8)	13 (10)	.08
2. 46-65 years	50 (30)	55 (42)	
3. 66-80 years	61 (37)	43 (33)	
4. >80 years	41 (25)	20 (15)	
Sex, female, n (%)	80 (49)	65 (50)	.85
Race, n (%)			
1. White	136 (82)	96 (73)	.06
2. Non-white	29 (18)	35 (27)	
Past medical history, n (%)			
1. Hypertension	118 (72)	108 (82)	.03*
2. Diabetes mellitus	50 (30)	47 (36)	.31
3. Hyperlipidemia	55 (33)	53 (40)	.21
4. Stroke	36 (22)	31 (24)	.71
5. Atrial fibrillation	34 (21)	16 (12)	.06
6. Coronary artery disease	33 (20)	27 (21)	.90
7. Congestive heart failure	13 (8)	12 (9)	.69
8. Peripheral vascular disease	6 (4)	1 (1)	.14
Social history, n (%)			
1. Tobacco use	74 (45)	73 (56)	.06
2. Alcohol use	47 (28)	50 (38)	.08
Presenting symptoms, n (%)			
1. Weakness	144 (87)	91 (70)	.0002*
2. Sensory symptoms	22 (13)	45 (34)	<.0001*
3. Aphasia	74 (45)	24 (18)	<.0001*
4. Dysarthria	92 (56)	63 (48)	.19
5. Vision changes	25 (15)	23 (18)	.58
6. Difficulty walking	50 (30)	31 (24)	.20
7. Vertigo	9 (5)	17 (13)	.02*
8. Seizures	4 (2)	4 (3)	.74
9. Altered mental status	35 (21)	15 (11)	.03*
Vital signs, median (IQR)			
1. Systolic blood pressure, mmHg	151 (135-170)	156 (142-173)	.16
2. Diastolic blood pressure, mmHg	85 (72-98)	83 (71-93)	.40
3. Body mass index, kg/m^2	27 (23-32)	29 (25-34)	.22
TOAST classification, n (%)			
1. Large artery disease	30 (18)	26 (20)	<.0001*
2. Cardioembolism	57 (35)	22 (17)	
3. Small vessel occlusion	16 (10)	46 (35)	
4. Other determined etiology	16 (10)	10 (8)	
5. Undetermined etiology	46 (28)	27 (21)	
Complications, n (%)			
1. Urinary tract infection	22 (13)	13 (10)	.47
2. Pneumonia	17 (10)	2 (2)	.002*
Lipid profile, mg/dl, median (IQR)			

(Continued)

Table 1. Continued.

VARIABLE	NON-MILD STROKE N = 165 (56%)	MILD STROKE YES N = 131 (44%)	*P* VALUE
1. Low density lipoprotein	94 (67-119)	105 (72-130)	.10
2. High density lipoprotein	45 (38-55)	44 (34-56)	.21
3. Total cholesterol	170 (132-201)	177 (149-206)	.97
4. Triglycerides	94 (68-136)	114 (85-178)	.006*
Hemoglobin A1c, %, median (IQR)	5.9 (5.5-6.7)	6.0 (5.5-7.2)	.40
Alteplase use, n (%)	66 (40)	18 (14)	<.0001*
Mechanical thrombectomy, n (%)	25 (15)	0 (0)	<.0001*

SD = standard deviation; IQR = interquartile range.
*P ≤ .05

Table 2. Imaging Characteristics.

VARIABLE	NON-MILD STROKE N = 165 (56%)	MILD STROKE N = 131 (44%)	*P* VALUE
Vascular territory, n (%)			
1. Anterior cerebral artery	22 (13)	6 (5)	.01*
2. Middle cerebral artery			
a. M1	75 (45)	11 (8)	<.0001*
b. M2	60 (36)	58 (44)	.17
c. Lenticulostriate	23 (14)	21 (16)	.62
3. Anterior choroidal artery	8 (5)	6 (5)	.91
4. Posterior cerebral artery	23 (14)	35 (27)	.006*
5. Vertebral artery	16 (10)	9 (7)	.38
6. Basilar artery	19 (12)	20 (15)	.34
7. Multiple vascular territories	34 (21)	12 (9)	.007*
Fazekas scale score, n (%)[a]			
1. Periventricular hyperintensity			
a. Score 0	25 (15)	23 (18)	.63
b. Score 1	60 (37)	44 (34)	
c. Score 2	46 (28)	43 (33)	
d. Score 3	32 (20)	20 (15)	
2. Deep white matter hyperintensity			
a. Score 0	37 (23)	31 (24)	.27
b. Score 1	75 (46)	54 (42)	
c. Score 2	35 (21)	38 (29)	
d. Score 3	16 (10)	7 (5)	
3. Total fazakas score			
a. Score 0-3	112 (69)	83 (64)	.38
b. Score 4-6	51 (31)	47 (36)	
Cerebral microbleeds present, n (%)[b]	44 (28)	41 (32)	.46

IQR = interquartile range.
[a]n = 163 Non-mild stroke and n = 130 Mild stroke.
[b]n = 157 Non-mild stroke and n = 128 Mild stroke.
*P ≤ .05.

Outcomes

Patients with mild stroke were more likely to have good discharge outcome (73% vs 20%, P<.0001) and less likely to have HT (Table 4) compared with non-mild stroke. Among patients with mild stroke, higher age (OR = 1.1; 95% CI = 1.02-1.1), presence of CMB (OR = 4.5; 95% CI = 1.5-13.8), vertigo (OR = 7.3; 95% CI = 1.2-45.1) and weakness (OR = 5.0; 95% CI = 1.2-20.3) as presenting symptoms were associated with poor discharge outcome. Patients with aphasia (OR = .1; 95% CI = .01-.7) were less likely to have poor discharge outcome (Table 5). Figure 3 shows the ROC area for the selected model.

Among patients with mild stroke, there was no difference in good discharge outcome, discharge mRS, or HT in patients who received alteplase compared to those who did not receive alteplase (Table 6). However, mild stroke patients were more likely to receive alteplase with each point increase in NIHSS score from 0 to 4 (P = .006).

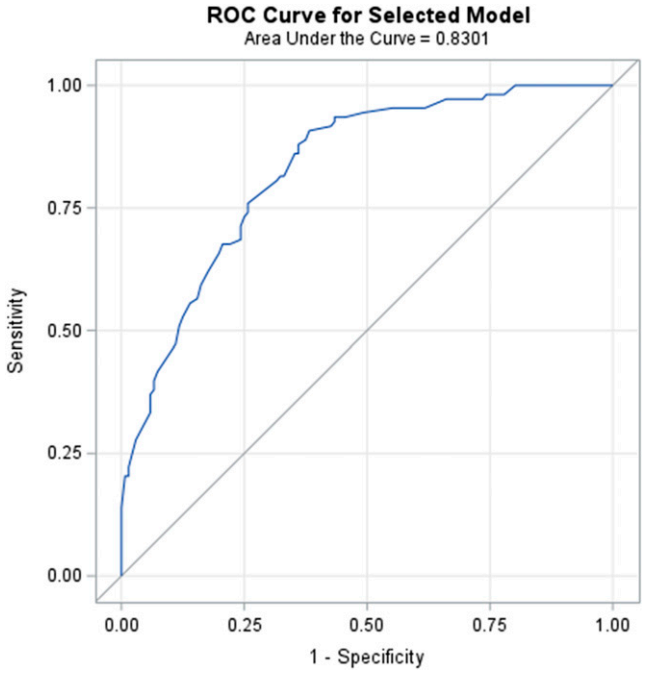

Figure 1. ROC curve for multivariate analysis for association of clinical and imaging factors with mild stroke.

Discussion

Our study highlights the clinical and imaging features of patients with mild stroke. Compared to non-mild stroke, patients with mild stroke were more likely to have sensory symptoms and stroke due to small vessel disease etiology and less likely to have weakness as a presenting symptom. Among patients with mild stroke, presence of CMB and weakness as a presenting symptom were associated with poor discharge outcome.

In our study, presenting symptoms were abstracted from the chief complaint and history of presenting illness at the time of retrospective chart review. We found that 70% of patients with mild stroke presented with a reported symptom of muscle weakness compared to 29% (for arm or leg weakness) found on objective NIHSS assessment. This difference in weakness as a presenting symptom compared with abnormal NIHSS examination finding is likely due to multiple factors. Patients may have arm or leg weakness that is not severe enough to cause a drift to be documented in NIHSS. If the weakness involves only the hand it may not be detected or accounted for in NIHSS assessment. In addition, some patients may report abnormal sensation and ataxia as heaviness or weakness.

Of all the stroke symptoms, weakness was the most common presenting symptom and it was more common in the non-mild stroke group than the mild stroke group (87% vs 70%).

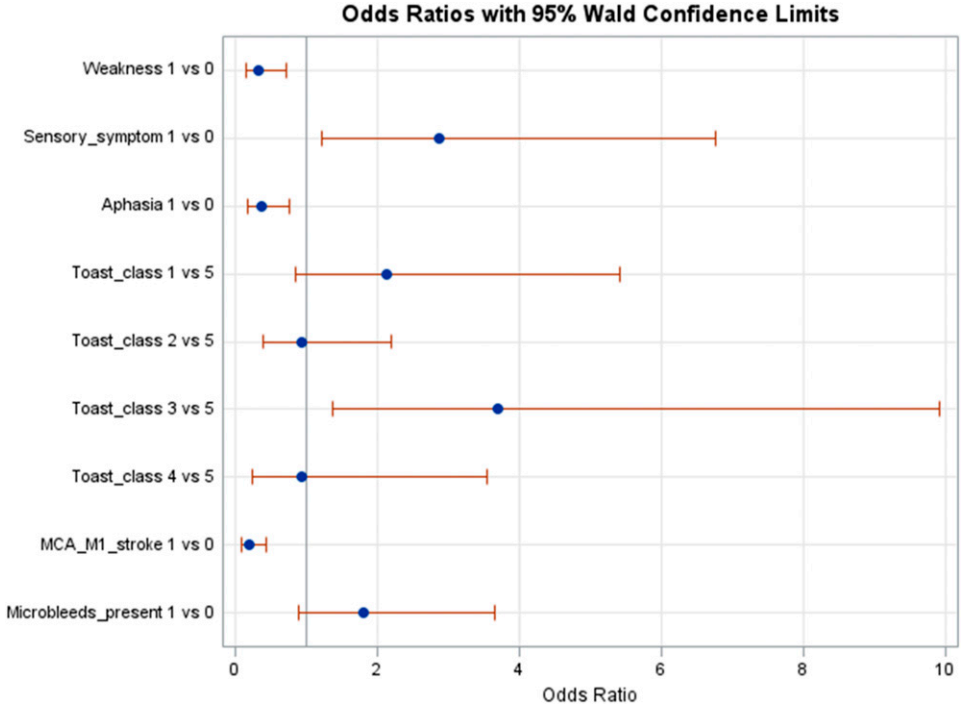

Figure 2. Plots showing odds ratio and 95% Wald confidence limits for the predictors of mild stroke. Toast class 1 = large artery disease, class 2 = cardioembolism, class 3 = small vessel occlusion, class 4 = other determined etiology, class 5 = undetermined etiology.

Table 3. Multivariate logistic regression analysis for predictors of mild stroke.

VARIABLE	OR (95% CI)	*P* VALUE
Weakness	.3 (.2-.7)	.005
Sensory symptoms	2.9 (1.2-6.8)	.0164
Aphasia	.4 (.2-.8)	.0077
Middle cerebral artery (M1) vascular territory	.2 (.1-.4)	.0001
TOAST class (small vessel disease vs undermined)	3.7 (1.4-9.9)	.0091
Presence of cerebral microbleed	1.8 (.9-3.7)	.0958
Model c-statistic .83		

Hosmer and Lemeshow Goodness of Fit Test, P = .56.

Table 4. Outcomes of stroke.

VARIABLE	NON-MILD STROKE N = 165 (56%)	MILD STROKE N = 131 (44%)	*P* VALUE
Discharge disposition, n (%)			
1. Home	11 (7)	43 (33)	<.0001*
2. Home with home health care services	22 (13)	53 (40)	
3. Acute inpatient rehabilitation	76 (46)	26 (20)	
4. Skilled nursing facility	19 (12)	9 (7)	
5. Long term care facility	10 (6)	0 (0)	
6. Hospice	8 (5)	0 (0)	
7. Death	19 (12)	0 (0)	
Good discharge outcome	33 (20)	96 (73)	<.0001*
Discharge mRS, median (1QR)	4 (2-5)	1 (1,2)	<.0001*
Hemorrhagic transformation, n (%)			
1. No hemorrhage	107 (68)	121 (95)	<.0001*
2. Hemorrhagic infarction (1 or 2)	36 (23)	7 (5)	
3. Parenchymal hematoma (1 or 2)	14 (9)	0 (0)	

*P ≤ .05.

Table 5. Multivariate Logistic Regression Analysis for Predictors of Poor Discharge Outcome Among Mild Stroke.

VARIABLE	OR (95% CI)	*P* VALUE
Age	1.1 (1.02-1.1)	.0085
Weakness	5.0 (1.2-20.3)	.0236
Aphasia	.1 (.01-.5)	.0112
Vertigo	7.3 (1.2-45.1)	.0318
Cerebral microbleed	4.5 (1.5-13.8)	.0081
Model c-statistic .81		

Hosmer and Lemeshow Goodness of Fit Test, P = .52.

However, on multivariate analyses, patients with mild stroke were 70% less likely to have weakness (OR = .3) as a presenting symptom. In a study of 6263 minor stroke patients by Wang et al,[22] motor symptoms were found in 66%, sensory complaints in 25%, and vertigo in 24%.[22] Another study by Majidi et al.[11] demonstrated that dysarthria (50%) and motor deficits (33%) were the two most common presenting symptoms of mild stroke followed by sensory deficit (27%) and aphasia (23%).[11]

Patients with rapidly improving stroke symptoms and mild stroke are frequently excluded from receiving alteplase based on current guidelines. This is likely due to exclusion of patients with mild deficits in previous alteplase trials and one clinical trial (PRISMS) that studied non-disabling mild strokes showed no benefit of alteplase.[3,4,23] However, patients with mild stroke can have poor outcome.[5,6,24,25] To better define this patient population, 'The Re-examining Acute Eligibility for Thrombolysis (TREAT) Task Force' defined rapidly improving stroke symptoms as total NIHSS ≤5 and absence of complete hemianopsia, severe aphasia, visual or sensory extinction, weakness limiting sustained effort against gravity (NIHSS ≥2 for component 5 and 6), and any deficits considered potentially disabling in the view of the patient and practitioner.[26] Spokoyny

et al.,[6] evaluated patients with mild stroke defined by the TREAT Task Force criteria for outcomes. They found that patients treated with alteplase had higher NIHSS scores (maximum total NIHSS ≤5) and were more likely to have arm weakness and aphasia. Patients considered too mild to treat and did not receive alteplase were 25-30% more likely to have poor 90-day outcome (mRS >1).[6]

Small vessel disease etiology was more frequent in mild stroke than non-mild stroke group (35% v 10%) in our study. It is comparable to the frequencies reported in the PRISMS study (34.8% in alteplase group and 38.5% in placebo group).[4] Patients with acute stroke due to small vessel disease can have fluctuating symptoms. Due to the unpredictable nature of such fluctuations, patients who initially present with non-disabling symptoms can progress to disabling symptoms resulting in poor functional outcome. This further adds to the complexity of predicting outcomes in mild stroke based on initial presenting symptoms. In one study of stroke with low NIHSS scores, distal paresis (hand) and gait disorder were common disabling deficits.[27] Due to the limitation of NIHSS in identifying disabling weakness when NIHSS = 0 for motor arm or leg component, a thorough assessment of strength on neurological examination as well as a patient's perception of their disability could help identify those who may potentially benefit from alteplase.

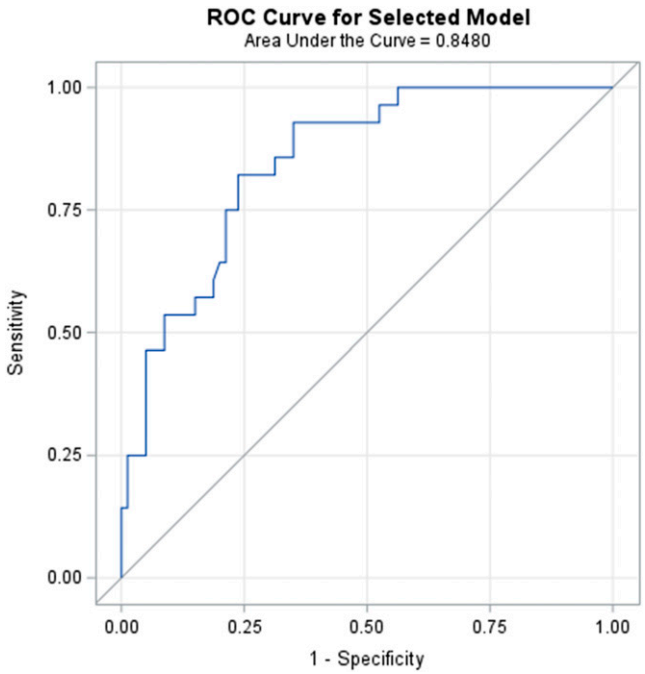

Figure 3. ROC curve for multivariate analysis to identify factors associated with poor discharge outcome among patients with mild stroke.

As reported in two prior studies, we did not find an association of WMH with discharge outcome in patients with mild stroke.[14,16] In one of these studies, WMH was associated with poor discharge outcome only in the presence of intracranial stenosis/occlusion.[14] Our study was limited by lack of assessment of vessel imaging but we evaluated the vascular territory based on distribution of the stroke lesions on DWI. Presence of CMB was four-times more likely associated with poor discharge outcome in our study. In a prior study of patients with mild stroke, patients with CMB were 3.4 times more likely to have unfavorable outcome defined as mRS 3-6 at 3 months.[16] However, in another study there was no difference in favorable outcome (mRS 0-2 at 3 months) in patients with no CMBs vs those with 1-4, 5-9 and ≥10 CMBs.[15] Although the reason for lack of significance is unclear, it is possible that analysis of four CMB groups (0, 1-4, 5-9, ≥10CMBs) in the prior study[15] might have influenced the study results. Our study evaluated two CMB groups (present vs absent CMB).

In a study that evaluated the role of aphasia on discharge location after stroke, patients with deficits in auditory and written word comprehension were more likely to be discharged to an institution (inpatient rehabilitation or skilled nursing facility) and those with impairment of naming, reading or repetition had no difference in home vs institution discharge.[28] It is possible that in our clinical practice, patients having isolated aphasia without weakness are more likely to be discharged home for outpatient speech therapy.

Table 6. National Institutes of Health Stroke Scale Score and Outcomes Stratified by Alteplase use in Mild Stroke.

VARIABLE	MILD STROKE ALTEPLASE NO N = 113	MILD STROKE ALTEPLASE YES N = 18	*P* VALUE
NIH stroke scale score, n (%)			.006*
1. Total score 0	24 (21)	0 (0)	
2. Total score 1	30 (27)	1 (6)	
3. Total score 2	19 (17)	4 (22)	
4. Total score 3	23 (20)	5 (28)	
5. Total score 4	17 (15)	8 (44)	
Good discharge outcome, n (%)	81 (72)	15 (83)	.30
Discharge mRS, median (IQR)	1 (1,2)	1 (1,2)	.68
Hemorrhagic transformation, n (%)	5 (4)	2 (11)	.25

*P ≤ .05.

This could have contributed to our study findings of aphasia being less likely to be associated with discharge to an institution. They also have good prognosis as one study reported resolution of aphasia in 90% of mild stroke patients by 6 months. Patients with aphasia and weakness likely have non-mild stroke leading to discharge to an institution. Although M1 segment occlusion of MCA is less common in mild stroke these patients are prone to worsening. In a prior study of patients with minor stroke (NIHSS ≤5) in the SITS International Stroke Thrombolysis Register, non-hemorrhagic early neurologic deterioration was observed in 30% of patients with terminal internal carotid artery or tandem internal carotid and MCA occlusion and in 9 % of M1 MCA occlusion compared with 3% among those with no occlusion despite treatment with intravenous thrombolytics.[29] Therefore, such patients should be treated with alteplase in the treatment window if they present with any disabling deficits despite having a mild stroke. They should also be monitored with serial neurological assessments for eligibility for mechanical thrombectomy.[29]

A systematic analysis of clinical and small vessel disease-based imaging features of mild stroke is a major strength of our study. Since some mild stroke-like symptoms particularly isolated sensory symptoms, dysarthria and dizziness may not be a stroke, we included only patients confirmed to have stroke on DWI in our study. Due to retrospective nature of the study, data elements were abstracted from the patient's electronic medical records. Structured templates for admission and discharge notes were used by the residents and stroke fellows for documentation in the electronic medical records. Because data entered by several trainees were analyzed there could be some inter-trainee differences in the documentation. We performed only a visual assessment of WMH severity based on Fazekas scale and did not perform a precise WMH volume calculation. Other small vessel disease imaging features such as lacunes and enlarged perivascular spaces were not analyzed in our study. In addition, our study is limited by small numbers and lack of follow-up outcome at 3 months.

Conclusion

Sensory symptoms and stroke due to small vessel disease are more common in mild stroke than non-mild stroke. Among patients with mild stroke, presence of CMB on imaging and symptom of muscle weakness are associated with poor discharge outcomes. Larger studies are needed to assess the impact of CMB on mild stroke outcomes and risk stratify the benefit of thrombolytics in this group.

Author contributions

Amreen Farooqui: Data curation, Investigation, Methodology, Writing - original draft, Writing - review and editing, Yoram A Roman Casul: Data curation, Methodology, Writing - original draft, Writing - review and editing, Varun Jain: Data curation, Methodology, Writing - original draft, Writing - review and editing, Nandakumar Nagaraja: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review and editing.

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