DECISION SUPPORT IN CLINICAL PRACTICE FOR STROKE: CLINICIAN EXPERIENCES AND EXPECTATIONS

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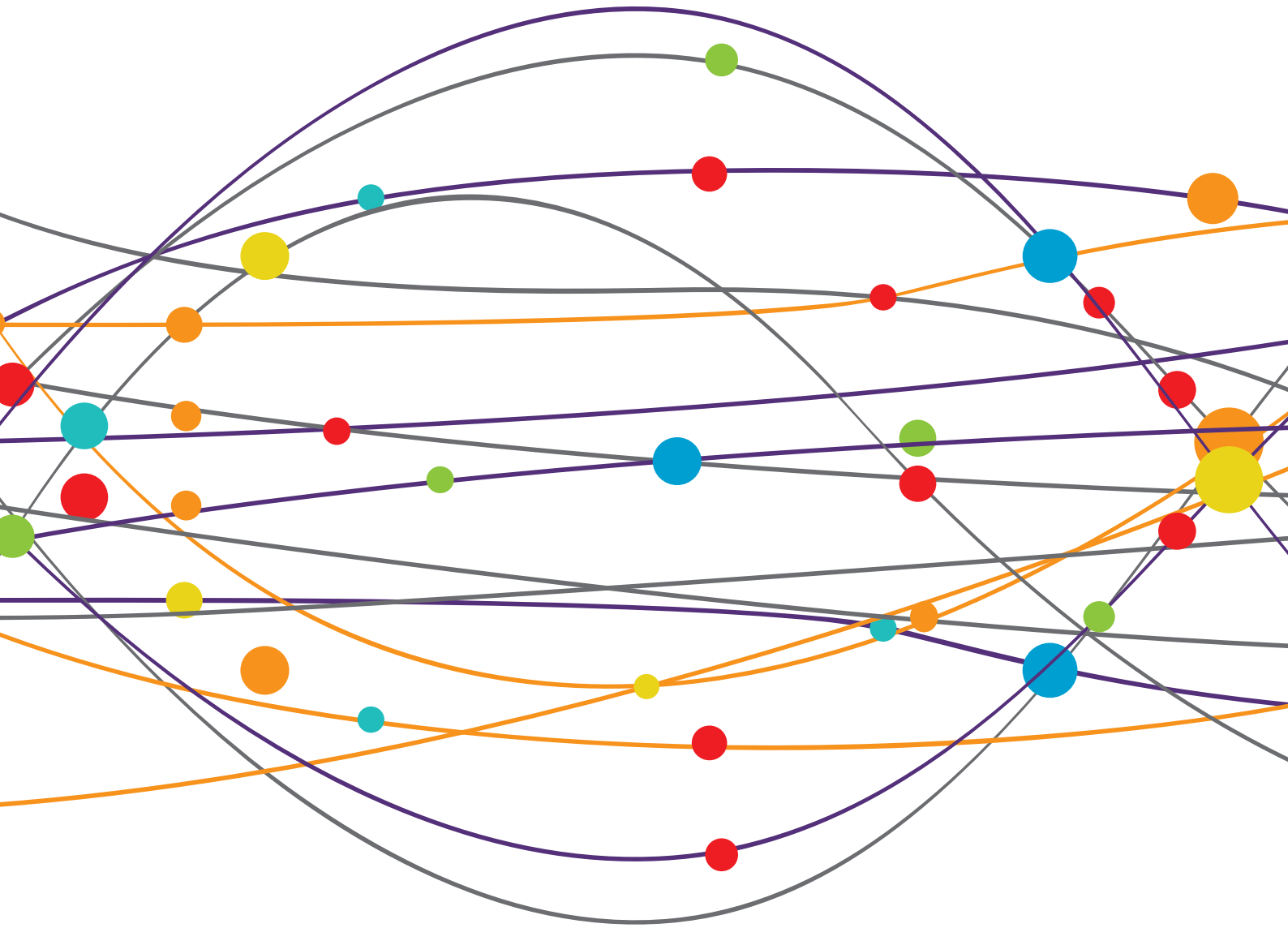

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DECISION SUPPORT IN CLINICAL PRACTICE FOR STROKE: CLINICIAN EXPERIENCES AND EXPECTATIONS

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Utility of Transthoracic Echocardiography in Diagnostic Evaluation of Ischemic Stroke

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Objective: Transthoracic echocardiography (TTE) is routinely performed as part of standard acute ischemic stroke (AIS) workup. However, the overall yield of TTE is unclear and many patients may undergo unnecessary investigations. This study aims to investigate the utility of TTE as part of AIS workup.

Methods: We collected data on consecutive patients with AIS who were admitted to our institution between 07/01/2016 and 09/30/2017. Patients were included based on neuroimaging-documented AIS, age >18 and neuroimaging studies. Primary endpoint was the proportion of cases in which TTE yielded relevant finding, defined as Atrial Septa Defect or Patent Foramen Ovale, left atrial enlargement, left ventricular thrombus or ejection fraction of <35%. Secondary endpoint was the proportion of patients who had a TTE-drive change in management.

Results: Among 548 AIS patients (median age 71 [59–81] years, 50% female), 482 (87%) underwent TTE. Clinically relevant findings were observed in 183 (38%) patients, leading to additional workup in 41 (8.5%). Further workup was associated with younger median age (58 [50–65] vs. 72 [62–81], $p < 0.0001$, and was less likely in suspected large vessel etiology ($p = 0.02$). Abnormal TTE lead to treatment change in 24 (5%) patients; 22/24 were started on anticoagulation. TTE results were less likely to influence treatment changes in older patients (71 [60–80] vs. 58 [49–69] years, $p = 0.02$) with known atrial fibrillation ($p = 0.01$).

Conclusion: Our findings suggest that despite widespread use, the overall yield of TTE in AIS is low. Stratifying patients according to their likelihood of benefitting from it will be important toward better resource utilization.

Keywords: transthoracic echocardiography, ischemic stroke, diagnostics, stroke diagnosis, stroke etiology, resource utilization

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INTRODUCTION

Identification of the etiology of acute ischemic stroke (AIS) is crucial for selecting optimal secondary preventative strategies. Since up to 30% of AIS can be attributed to a cardiac source (1), a cardiac workup including transthoracic echocardiography (TTE) is routinely performed to evaluate for clinically relevant findings including structural defects, left sided thrombi, or features suggestive of atrial fibrillation, such as enlarged left atrial appendages (2, 3). However, there are no clear guidelines regarding the utility of echocardiography in AIS, especially given the lack of data

on how management changes are made based on TTE results. The European Stroke Organization guidelines recommend the use of echocardiography only in selected patients, such as patients with evidence of cardiac disease on history, examination, or electrocardiogram (ECG), suspected cardiac source of embolism (e.g., infarctions in multiple cerebral or systemic arterial territories), suspected aortic disease or paradoxical embolism and for patients with no other identifiable causes of stroke) (4). On the other hand, the American Stroke Association (ASA) up until now made no specific recommendation (5, 6). The recently released in the 2018 AHA/ASA guidelines take a more direct stance and explicitly advise against routine use of echocardiography in patients with AIS (7). These recommendations have led to significant uncertainties for practitioners and have implications for cost reimbursements; the guidelines do not specify which patients are likely to benefit from TTE which is was the rationale for this study. We sought to investigate the utility of TTE as part of AIS workup with a retrospective study investigating the frequency of abnormal echocardiography findings and TTE-driven change in management.

METHODS

This was a single-center retrospective observational study of prospectively collected data on consecutive patients with AIS who were admitted to a tertiary academic center in the USA, between 07/01/2016 and 09/30/2017. The study was approved by the local institutional review board. Informed consent was not applicable. Patients were selected based on the following inclusion and exclusion criteria: Patients with confirmed acute ischemic stroke, age >18 years old and with available neuroimaging studies. Patients were excluded if sudden onset focal neurological deficits resulted from an entity other than ischemic stroke, including intracranial hemorrhage, trauma/concussion, brain tumors, seizures, migraines, encephalitis, cerebral venous thrombosis, or metabolic derangements and if there was lack of baseline imaging data.

We collected and analyzed the following clinicodemographic variables: age, sex, race, cardiovascular comorbidities (hypertension, diabetes, hypercholesterolemia, history of coronary artery disease (CAD), atrial fibrillation (AF), congestive heart failure (CHF), chronic kidney disease (CKD), prior stroke or transient ischemic attack. We also collected information on prior use antiplatelets, anticoagulants, statins and antihypertensive medications as well as laboratory testing obtained routinely as part of AIS workup: Hemoglobin A1c, total cholesterol, triglycerides, low density lipoprotein (LDL) and high-density lipoprotein (HDL). We reviewed brain imaging obtained as routine AIS work up. All patients received brain MRI, except for those with contraindication, who received CT scan only. Also, all patients with suspected AIS received head and neck vessel imaging, either CT or MR Angiography.

All patients ≤60 years of age had a bubble study. In older patients, a bubble study was performed on a case by case basis according to the preferences of the individual Vascular Neurologist. Data abstraction was performed by TTE report review. All TTE were read by trained cardiologists, blinded to the patients' neurologic status and stroke subtype. Data abstracted from the report view included findings deemed to be of potential diagnostic relevance. These included (1) left atrial enlargement, (2) patent foramen ovale (PFO)/atrial septal defect (ASD), (3) depressed ejection fraction (EF) (defined as EF of <35%) (8), intracardiac thrombus and valve vegetation or other valvular abnormality.

Stroke subtypes were classified into five categories based on etiology, using the TOAST classification (9), modified to include the more recently evolved concept of the embolic stroke of undetermined source (ESUS) (10): (1) large-artery atherosclerosis (LAA), (2) small vessel occlusion (SVO), (3) cardioembolism (CE), (4) stroke of other determined etiology, (5) ESUS. LAA was defined as brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis, and a stroke in its downstream supplied territory. SVO was defined as a lesion diameter of <20 mm (11) and located in a subcortical area or brainstem on DWI MRI. The ESUS category was defined as non-lacunar infarct following specific imaging criteria: either cortical infarct or, for subcortical infarcts, a diameter of ≥1.5 cm on CT or ≥2.0 cm on DWI MRI (12). In addition the absence of large vessel atherosclerosis by CTA or MRA, lack of documented atrial fibrillation during hospital or outpatient long-term cardiac monitoring and CE made less likely by echocardiography were mandated (12). CE was defined as patients with arterial occlusions presumably due to an embolus arising in the heart. This was based on brain imaging findings which are similar to those described for large-artery atherosclerosis, but without significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery as well as brain imaging findings of stroke in multiple vascular territories, and cardiac source for an embolus based on history of AF, systemic embolism, or TTE findings suggestive of cardiac etiology. Neuroimaging was reviewed independently by two neurologists blinded to TTE findings.

The primary endpoint was the proportion of cases in which TTE yielded a diagnostically relevant finding as defined above. Our secondary endpoint was the number of patients who had a change of management due to an abnormal TTE finding, which was defined as one of two categories: (a) further work up (transesophageal echocardiography, MRV of the pelvis, lower extremity Doppler ultrasound) and (b) treatment change, either the form of medication change or intervention (initiation of anticoagulation, PFO closure, cardiac surgery).

STATISTICAL ANALYSIS

Categorical and ordinal variables are presented as percentages and continuous variables as either mean ± standard deviation (SD) or median and interquartile range (IQR) depending on normality of distribution. Normality of distribution for continuous variables was tested with the Shapiro-Wilk test. We explored univariable associations between clinical, demographic

TABLE 1 | Summary of baseline cohort characteristics.

Clinicodemographic characteristics	Entire cohort, $N = 548$	No TTE 65 (11.9%)	TTE 483 (88.1%)	*p*-value
Age, median (IQR)	71 (59–81)	77 (64–86.5)	70 (59–80)	0.02
Female sex, *n* (%)	273 (49.8)	37 (57)	237 (49)	0.23
Race				0.09
White	357 (66)	51 (78)	306 (63.5)	
African American	79 (14)	4 (6)	75 (15.5)	
Hispanic	22 (4)	4 (5)	19 (4)	
Asian	12 (2)	2 (3)	10 (2)	
Other/Unknown	78 (14)	6 (8)	72 (15)	
Cardiovascular comorbidities				
Hypertension, *n* (%)	401 (73.1)	49 (75)	352 (73)	0.76
Diabetes, *n* (%)	174 (31.7)	19 (29)	155 (32)	0.67
Hypercholesterolemia, *n* (%)	289 (52.7)	32 (49)	257 (53)	0.54
Current smoking, *n* (%)	90 (16.5)	11 (17.2)	79 (16.5)	0.88
CHF, *n* (%)	45 (8.2)	5 (8)	40 (8)	0.87
Afib, *n* (%)	112 (20.4)	20 (31)	92 (19)	0.03
Coronary artery disease, *n* (%)	97 (17.7)	10 (15.4)	87 (18)	0.73
Prior Stroke or TIA, *n* (%)	77 (14)	5 (8)	72 (15)	0.13
CKD, *n* (%)	57 (10.4)	10 (15)	47 (10)	0.16
Laboratory values				
Hemoglobin A1C, median (IQR)	5.7 (5.3–6.7)	5.8 (5.45–6.3)	5.7 (5.3–6.7)	0.32
Total Cholesterol, mean (±SD)	161 (133.5–197.5)	158 (138–184)	163 (133–198.75)	0.55
Triglycerides, mean (±SD)	115 (84–155.5)	116 (84.5–159)	115 (84–154	0.75
HDL, mean (±SD)	45 (37–57)	44.5 (34.75–61)	45 (37–56)	0.74
LDL, mean (±SD)	90 (63.5–117)	85 (68–101.5)	90.5 (63–119)	0.5
Stroke subtypes				0.53
Large artery atherosclerosis, *n* (%)	127 (23.2)	13 (20)	114 (24)	0.64
Cardioembolic, *n* (%)	200 (36.5)	20 (31)	180 (37)	0.39
Small vessel/lacunar	79 (14.4)	10 (15)	69 (14)	0.85
ESUS	91 (16.6)	13 (20)	78 (16)	0.48
Other defined causes/crytptogenic	51 (9.3)	9 (14)	42 (9)	0.18
Medications				
Anticoagulation on presentation, *n* (%)	90 (16.4)	17 (26)	73 (15)	0.03
Antiplatelets on presentation, *n* (%)	266 (48.5)	27 (42)	239 (50)	0.4
Statins on presentation, *n* (%)	283 (51.6)	33 (51)	250 (52)	0.89
Antihypertensives, *n* (%)	378 (68.9)	47 (72)	331 (69)	0.66
Acute treatment				
tPA given, *n* (%)	98 (17.8)	5 (8)	93 (19)	0.02
Mechanical thrombectomy, *n* (%)	45 (8.2)	1 (1.5)	44 (9)	0.03

and imaging variables and our outcomes of interest (clinically relevant TTE finding, TTE-driven additional workup and TTE-driven medication change or intervention). We used the chi-squared test for categorical variable comparisons. For continuous variables we used Student's *t*-test or the non-parametric Mann-Whitney U test depending on normality of distribution. Subsequently we constructed multivariable logistic regression models, including variables with statistical significance in the univariable models (defined as two-sided $p < 0.05$) and calculated odds ratios and 95% confidence intervals. Given that stroke phenotyping into certain subtypes might have been affected by TTE findings, we built two multivariable models, one excluding stroke subtypes and a second including stroke subtypes, if they had reached statistical significance in the univariable analysis. Analyses were performed in JMP Pro 12 (SAS, Cary, NC, USA).

Baseline Cohort Characteristics

We identified 548 patients with AIS; 273 (49.8%) female, median age 71 (59–81) years. The baseline characteristics are summarized in **Table 1**. Our cohort comprised largely White (357, 66%) patients with the most common etiologies being CE (200; 36.5%) followed by LAA (127, 23.2%). Four hundred eighty-three (88%) patients received TTE as part of AIS workup. Differences between those who received TTE vs. those who did not are summarized in

Table 1. Patients who received TTE were younger (70 [59–80] vs. 77 [64–86.5] years; $p = 0.02$), less likely to have AF (92 [19%] vs. 20 [31%]; $p = 0.03$) and receive anticoagulation therapy (73 [15%] vs. 17 [26%]; $p = 0.03$) and more likely to have received intravenous thrombolysis (93 [19%] vs. 5 [8%]; $p = 0.02$) and mechanical thrombectomy (44 [9%] vs. 1[1.5%]; $p = 0.03$).

TTE With Findings of Potential Clinical Relevance

Echocardiographic findings of potential clinical significance were observed in 183 (38%) patients. The most frequent finding was left atrial enlargement, observed in 112 (23%) patients, followed by depressed EF (35 [7%] patients), PFO/ASD (35 [7%] patients), valve vegetations and other valvular abnormalities (10 [2%] patients) and intracardiac thrombus (5 [1%] patients). Characteristics of patients with and without clinically relevant findings are summarized in **Table 2**. In multivariable adjusted models, not including stroke subtypes, coronary artery disease (OR 1.95, 95% CI [1.21–3.15]; $p = 0.006$) and chronic kidney disease (OR 1.95, 95% CI [1.05–3.63]; $p = 0.03$) remained independently associated with higher odds of observing a clinically relevant echocardiographic finding. When including stroke subtypes in the multivariable model, presence of coronary artery disease remained associated with higher likelihood of clinically relevant finding (OR 1.9, 95% CI [1.17–3.11]; (0.01); conversely, LAA subtype was associated with lower odds (0.48 [0.27–0.81]; $p = 0.007$) (**Table 2**).

TTE Leading to Additional Diagnostic Workup

Forty-one (8.5%) patients had additional workup as a result of a TTE finding. The most common additional diagnostic test was lower extremity venous Doppler ultrasound, in 25 (5%) patients, followed by transesophageal echocardiogram (TEE) in 17 (3.5%) patients, and MR Venogram of the pelvis in 16 (3.3%) patients. Characteristics of patients with and without additional TTE-related diagnostic workup are presented in **Table 3**. Patients who underwent additional testing were younger (58 [50–65] vs. 72 [61.5–81]; $p < 0.0001$), less likely to have hypertension (21 [51%] vs. 331 [75%]; $p = 0.001$) and AF (3 [7%] vs. 89 [20%]; $p = 0.045$) (**Table 3**). In multivariable adjusted models excluding stroke subtypes, only age retained its significant, inverse association with odds of receiving further workup (OR 0.94, 95% CI [0.92–0.97]; $p < 0.0001$). When including stroke subtypes, age retained the same association with unaltered effect size, while in addition, LAA stroke was independently associated with lower likelihood of receiving further workup (OR 0.17, 95% CI [0.03–0.59]; $p = 0.003$) (**Table 3**).

Echocardiographic Findings Leading to Treatment Change

Twenty-four (5%) patients had treatment change as a direct result of a TTE finding. Twenty-two (4.5%) commenced anticoagulant therapy, while two (0.4%) had a PFO closure and cardiac surgical procedure, respectively (**Table 5**). Characteristics of patients without vs. with treatment change are summarized in **Table 4**. Younger age (58 [49–69] vs. 71 [60–80]; $p = 0.0003$, presence of diabetes (13 [54%] vs. 142 [31%]; $p = 0.02$) and CE stroke (16 [67%] vs. 164 [36%]; $p = 0.004$) were all associated with higher likelihood of treatment change. Conversely, no patients with LAA and small vessel/lacunar strokes had treatment changes (**Table 4**).

DISCUSSION

In our study population 38% of patients had clinically relevant TTE findings, and approximately 9% necessitated additional workup, which ultimately resulted in treatment change in 5%. While there appears to be redundancy regarding TTE as part of AIS work up, there are at least some patients, who appear to benefit from TTE. Patients who were most likely to benefit from TTE were younger, had cardioembolic stroke subtype, or had a history of cardiac disease. Patients who were least likely to benefit from TTE were older patients with established AF, and patients with LAA and lacunar/ SVO stroke etiology.

Until recently, there were no clear guidelines regarding the utility of TTE in AIS (5, 6). In the most recent revision of the American Heart Association guidelines for the early management of patients presenting with AIS, did the ASA make firm recommendations against the routine use of TTE in AIS, which has sparked controversy as there is no elaboration on which patient subgroups might benefit from TTE. The new recommendation eliminates the perceived need for TTE in all AIS patients, that had elevated the routine TTE use into "standard of care," which has very likely been a contributing factor to clinician overuse. On the other hand, many practicing clinicians have expressed concern that the updated recommendations adopt a simplistic stance that lacks granularity to appropriately stratify patients according to the likelihood of substantial benefit from TTE. In a challenging fiscal environment with health care organizations trying to reduce health care costs and prioritizing value and efficiency, performing a large number of redundant diagnostic tests will inevitably be targeted as wasteful. A more productive way of resource utilization would be to identify the patients that are much more likely to benefit, channel TTE usage toward them and educating physicians about targeted TTE use. Previous studies have shown that educating staff about the low yield of TTE in AIS resulted in a more cautious utilization and an overall decline in ordering echocardiograms (13).

TTE is performed with the intent to identify structural cardiac abnormalities of clinical relevance. Our study showed that clinically relevant findings are indeed relatively frequent, seen in 1/3 of patients. Our findings suggest that patients with LAA stroke subtype are the least likely to have a clinically relevant finding, suggesting that it might be reasonable to forgo TTE in this patient population. The importance of some of the TTE findings seems unequivocal; presence of valvular vegetation or intraventricular thrombus in the setting of multifocal acute infarcts would seal the diagnosis and management decision. Conversely, the pertinence of other findings is not entirely clear. This pertains in particular to left atrial enlargement which was the most common finding, seen in over 20% of our cohort. Traditionally, it has been viewed as indirect marker of occult

TABLE 2 | Comparisons between patients according to relevant findings on TTE.

Variables	No relevant findings 299 (62%)	Relevant findings 183 (38%)	*p*-value	Multivariable logistic regression model 1[a]		Multivariable logistic regression model 2[b]	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age, median (IQR)	71 (60–80)	70 (59–80)	0.91				
Female sex, *n* (%)	159 (53)	78 (42)	0.02	0.7 (0.48–1.02)	0.07	0.67 (.45–0.98)	0.04
Race			0.44				
White	185 (62)	121 (66)					
African American	52 (17)	23 (13)					
Hispanic	11 (4)	8 (4)					
Asian	8 (3)	2 (1)					
Other/Unknown	43 (14)	29 (16)					
Cardiovascular comorbidities							
Hypertension, *n* (%)	213 (71)	139 (76)	0.3				
Diabetes, *n* (%)	92 (31)	63 (34)	0.43				
Hypercholesterolemia, *n* (%)	156 (52)	101 (55)	0.56				
Current smoking, *n* (%)	45 (15)	34 (19)	0.37				
CHF, *n* (%)	22 (7)	18 (10)	0.35				
Afib, *n* (%)	52 (17)	40 (22)	0.28				
Coronary artery disease, *n* (%)	41 (14)	46 (25)	0.002	1.95 (1.21–3.15)	0.006	1.9 (1.17–3.11)	0.01
Prior Stroke or TIA, *n* (%)	50 (17)	22 (12)	0.19				
CKD, *n* (%)	22 (7)	25 (14)	0.02	1.95 (1.05–3.63)	0.03	1.79 (0.95–3.41)	0.07
Laboratory values							
Hemoglobin A1C, median (IQR)	5.7 (5.3–6.7)	5.7 (5.3–6.9)	0.67				
Total Cholesterol, mean (±SD)	167 (136–202.5)	158 (128–196)	0.051				
Triglycerides, mean (±SD)	115 (83–154)	113 (86–156)	0.91				
HDL, mean (±SD)	46.5 (37–58)	43 (35–54)	0.03				
LDL, mean (±SD)	92 (66–121)	88 (60–115)	0.09				
Stroke subtypes			<0.0001				
Large artery atherosclerosis, *n* (%)	88 (29)	26 (14)	0.0001			0.48 (0.27–0.81)	0.007
Cardioembolic, *n* (%)	90 (30)	90 (49)	<0.0001			1.52 (0.98–2.36)	0.06
Small vessel/lacunar	47 (16)	22 (12)	0.29				
ESUS	52 (17)	26 (14)	0.37				
Other defined causes	22 (7)	20 (11)	0.19				
Medications							
Anticoagulation on presentation, *n* (%)	37 (12)	36 (20)	0.03	1.69 (1.01–2.82)	0.04		0.2
Antiplatelets on presentation, *n* (%)	157 (53)	82 (45)	0.08				
Statins on presentation, *n* (%)	152 (51)	98 (53)	0.63				
Antihypertensives, *n* (%)	204 (68)	127 (69)	0.89				
Acute treatment							
tPA given, *n* (%)	62 (21)	31 (17)	0.3				
Mechanical thrombectomy, *n* (%)	27 (9)	17 (9)	1				

[a] *Multivariable model including variables that reached statistical significance (p-value < 0.05) in univariable analyses excluding stroke subtype.*
[b] *Variables included in model 1 plus stroke subtypes (if they reached statistical significance in univariable comparisons).*

atrial fibrillation (2, 3) although anticoagulation therapy is not advisable in the absence of confirmed atrial fibrillation. However, emerging evidence suggests that atrial enlargement, might be a biomarker of underlying thrombogenic atrial cardiopathy independent of atrial fibrillation with independent risk of recurrent cryptogenic or cardioembolic stroke (14, 15). The clinical relevance of this concept will be tested in the ongoing multicenter Phase III Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trial (NCT03192215), in which left atrial enlargement is being used among other inclusion criteria.

PFO is an additional finding that has sparked controversy in the past. Its high prevalence in the population (16), uncertainty regarding its implication as a causative factor and lack of efficacy with PFO closure (17) had limited the practicality of identifying a PFO. However, improved risk-stratification schemes (18) and

TABLE 3 | Comparisons between patients according to the need of subsequent work up.

	No additional workup 441 (91.5%)	Subsequent workup 41 (8.5%)	*p*-value	Multivariable logistic regression model* 1[a]		Multivariable logistic regression model* 2[b]	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age, median (IQR)	72 (61.5–81)	58 (50–65)	<0.0001	0.94 (0.92–0.97)	<0.0001	0.95 (0.92–0.97)	<0.0001
Female sex, *n* (%)	220 (50)	17 (41)	0.3				
Race			0.27				
White	284 (64)	22 (54)					
African American	65 (15)	10 (24)					
Hispanic	16 (4)	3 (7)					
Asian	10 (2)	0					
Other/Unknown	66 (15)	6 (15)					
Cardiovascular comorbidities							
Hypertension, *n* (%)	331 (75)	21 (51)	0.001	0.59 (0.29–1.22)	0.16	0.63 (0.3–1.32)	0.22
Diabetes, *n* (%)	142 (32)	13 (32)	0.96				
Hypercholesterolemia, *n* (%)	240 (54)	17 (41)	0.1				
Current smoking, *n* (%)	73 (17)	6 (15)	1				
CHF, *n* (%)	39 (9)	1 (2)	0.1				
Afib, *n* (%)	89 (20)	3 (7)	0.045	0.69 (0.16–2.14	0.28	0.6 (0.13–1.94)	0.42
Coronary artery disease, *n* (%)	84 (19)	3 (7)	0.09				
Prior Stroke or TIA, *n* (%)	68 (15)	4 (10)	0.49				
CKD, *n* (%)	44 (10)	3 (7)	0.58				
Laboratory values							
Hemoglobin A1C, median (IQR)	5.7 (5.3–6.7)	5.6 (5.4–6.9)	0.78				
Total Cholesterol, mean (±SD)	161 (132–198)	172 (140.5–208)	0.3				
Triglycerides, mean (±SD)	115 (84–154)	110 (83.5–159.5)	0.76				
HDL, mean (±SD)	45 (37–56)	46 (37–60)	0.66				
LDL, mean (±SD)	90 (63–116)	98.5 (70–125.75)	0.18				
Stroke subtypes			0.02				
Large artery atherosclerosis, *n* (%)	112 (25)	2 (5)	0.002			0.17 (0.03–0.59)	0.003
Cardioembolic, *n* (%)	164 (37)	16 (39)	0.87				
Small vessel/lacunar	63 (14)	6 (15)	1				
ESUS	66 (15)	12 (29)	0.025			1.31 (0.59–2.83)	0.49
Other defined causes	37 (8)	5 (12)	0.38				
Medications							
Anticoagulation on presentation, *n* (%)	69 (16)	4 (10)	0.3				
Antiplatelets on presentation, *n* (%)	227 (51)	12 (29)	0.008				
Statins on presentation, *n* (%)	234 (53.06)	16 (39)	0.09				
Antihypertensives, *n* (%)	310 (70)	21 (51)	0.02				
Acute treatment							
tPA given, *n* (%)	85 (19)	8 (20)	0.96				
Mechanical thrombectomy, *n* (%)	41 (9)	3 (7)	1				

**Outcome of interest: Need for subsequent workup.*

[a] *Multivariable model including variables that reached statistical significance (p-value < 0.05) in univariable analyses excluding stroke subtype.*

[b] *Variables included in model 1 plus stroke subtypes (if they reached statistical significance in univariable comparisons).*

findings from three recent randomized controlled trials (19–21) suggesting long-term benefit for PFO closure in select patients have of renewed interest in PFO detection. The most relevant question is whether TTE is practical as a useful PFO detection tool. It is known that TTE has high specificity but low sensitivity (22) and, indeed, in our cohort TTE identified a PFO only in 7% of the patients which is much lower than the prevalence reported in the literature (23, 24). On the other hand, TEE and transcranial Doppler, both of which have significantly higher sensitivity (22), present other limitations, including invasiveness, cost, need for specially trained personnel. Therefore, use of TTE as an initial screening tool in selected patients with embolic-appearing strokes and lack of other obvious stroke etiologies might be a reasonable strategy.

TABLE 4 | Comparisons between patients according to TTE role in treatment change.

	No treatment change 458 (95%)	Treatment change 24 (5%)	*p*-value	Multivariable logistic regression model* 1[a]		Multivariable logistic regression model* 2[b]	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age, median (IQR)	71 (60–80)	58 (49–69)	0.0003	0.95 (0.92–0.98)	0.004	0.95 (0.92–0.98)	0.003
Female sex, *n* (%)	230 (50)	7 (29)	0.04	1.89 (0.78–5.1)	0.53	1.89 (0.74–5.27)	0.19
Race			0.71				
White	290 (63)	16 (67)					
African American	70 (15)	5 (21)					
Hispanic	19 (4)	0 (0)					
Asian	10 (2)	0 (0)					
Other/Unknown	69 (15)	3 (12)					
Cardiovascular comorbidities							
Hypertension, *n* (%)	336 (73)	16 (67)	0.48				
Diabetes, *n* (%)	142 (31)	13 (54)	0.02	2.7 (1.14–6.54)	0.9	3.33 (1.33–8.62)	0.01
Hypercholesterolemia, *n* (%)	245 (53)	12 (50)	0.75				
Current smoking, *n* (%)	76 (17)	3 (12)	0.78				
CHF, *n* (%)	38 (8)	2 (8)	0.99				
Afib, *n* (%)	91 (20)	1 (4)	0.05	0.29 (0.016–1.54)	0.54	0.12 (0.006–0.66)	0.01
CAD, *n* (%)	80 (17)	7 (29)	0.17				
Prior stroke or TIA	68 (15)	4 (17)	0.8				
CKD, *n* (%)	45 (10)	2 (8)	0.81				
Laboratory values							
Hemoglobin A1C, median (IQR)	5.7 (5.3–6.6)	6.2 (5.6–9.2)	0.007				
Total Cholesterol, mean (±SD)	113 (84–154)	144 (88.5–162)	0.25				
Triglycerides, mean (±SD)	115 (84–154)	110 (83.5–159.5)	0.76				
HDL, mean (±SD)	45 (37–57)	41 (37.5–51)	0.23				
LDL, mean (±SD)	91 (63–119)	79.5 (61–125.5)	0.81				
Stroke subtypes			0.002				
Large artery atherosclerosis, *n* (%)	114 (25)	0	0.002			Unstable term	0.003
Cardioembolic, *n* (%)	164 (36)	16 (67)	0.004			3.14 (1.19–8.97)	0.02
Small vessel/lacunar	69 (15)	0	0.04			Unstable term	0.01
ESUS	72 (16)	6 (25)	0.25				
Other defined causes	40 (9)	2 (8)	1				
Medications							
Anticoagulation on presentation, *n* (%)	71 (16)	2 (8)	0.33				
Antiplatelets on presentation, *n* (%)	227 (50)	12 (50)	0.97				
Statins on presentation, *n* (%)	236 (51)	14 (58)	0.51				
Antihypertensives, *n* (%)	314 (69)	17 (71)	0.81				
Acute treatment							
tPA given, *n* (%)	88 (19)	5 (21)	0.84				
Mechanical thrombectomy, *n* (%)	42 (9)	2 (8)	1				

**Outcome of interest: Treatment change.*

[a] *Multivariable model including variables that reached statistical significance (p-value < 0.05) in univariable analyses excluding stroke subtype.*

[b] *Variables included in model 1 plus stroke subtypes (if they reached statistical significance in univariable comparisons).*

A more compelling estimate of the utility of routine TTE is whether it results in additional workup or therapeutic intervention. The proportions of patients were 8.5 and 5%, respectively which reveal that a considerable proportion of the studies performed might indeed be redundant. Although it might be difficult to identify patients likely to derive therapeutic or diagnostic benefit from TTE, it seems that at the very least it is feasible to identify patients whose management is least affected by TTE results. In our cohort none of the LAA and SVO stroke subtype patients had additional diagnostics or treatment change based on a TTE finding. This suggests that in patients whose strokes have been reliably phenotyped into these stroke subtypes, performing a TTE might be less impactful. Notably this simple observation applies to >1/3 of our patients who had a

TABLE 5 | Types of treatment change.

Type of treatment change	No. (%)
Initiation of anticoagulation	22 (4.5)
Initiation of cardiac meds	0
PFO closure	2 (0.4)
Cardiac surgical procedure	2 (0.4)

TTE, suggesting that with careful selection of target patients, the widespread TTE use could be appropriately curtailed.

Limitations of our study include a single center study design, as well as possibly practice bias, with younger patients prone to receiving both, more frequent further diagnostic testing and treatment change. For the etiologic classification we used the widely used TOAST classification. A different, more granular scheme, such as the *Causative Classification System for Ischemic Stroke (CCS)* might have yielded different distributions of stroke etiologies. Given that this might alter our estimation regarding the contribution of TTE in stroke diagnosis, it merits further elucidation in future studies (25). Our findings do not address the potential utility of TTE in managing post-stroke cardiorespiratory complications, which is driven by different, often critical clinical indications (26). There is also an inherent practical difficulty stemming from the fact that the intervention under study (TTE) is used, to some extent, to define some of the explanatory variables (stroke subtypes). At least two of the stroke categories (LAA and SVO) are defined based on brain and vascular imaging with minimal interference from TTE. We attempted to minimize it by including two different adjusted models, one including stroke subtype and one without; the adjusted model without stroke subtype is essentially agnostic to and unaffected by the TTE finding. In addition, our main outcome of interest (clinically relevant structural findings) is not affected by stroke subtype. However, this ultimately remains an important limitation, but one that is impossible to completely eliminate.

In conclusion, there might be redundancy in TTE utilization as part of AIS work up, but certain patients derive critical, treatment-defining benefit based on TTE findings. We must better define who these patients are, or at least start by identifying who are the least likely to benefit. Our study suggests that patients with LAA stroke subtype were the ones that consistently showed to have the least benefit from TTE. We consider our findings hypothesis-generating and do not advocate for limiting TTE use at the moment; external validation in different and larger cohorts including cost effectiveness analysis is needed.

DATA AVAILABILITY STATEMENT

Data that is not available with the article will be provided in an anonymized form by the corresponding author upon reasonable request from any qualified investigator. Indeed, if requested (e.g., for the purpose of a meta-analysis) data can be provided according to local IRB practices.

ETHICS STATEMENT

The Institutional Review Board of Beth Israel Deaconess Medical Center approved the study, but waived the need for approval for this study protocol as it is retrospective.

AUTHOR CONTRIBUTIONS

JH: design and conceptualization of the study, analysis and interpretation of the data, drafting the original manuscript. JY and MSa: data collection, revising the manuscript for intellectual content. SK: revising the manuscript for intellectual content. MSe: revising the manuscript for intellectual. VL: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript for intellectual content.

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JH and VL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. VL (Harvard Medical School) and JH (Harvard Medical School) conducted and are responsible for the data analysis.

REFERENCES

1. Ustrell X, Pellisé A. Cardiac workup of ischemic stroke. *Curr Cardiol Rev.* (2010) 6:175–83. doi: 10.2174/157340310791658721
2. Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J.* (2014) 35:1457–65. doi: 10.1093/eurheartj/eht500
3. Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, et al. Left atrial structure and function and clinical outcomes in the general population. *Eur Heart J.* (2013) 34:278–85. doi: 10.1093/eurheartj/ehs188
4. European Stroke Organisation Executive C, Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis.* (2008) 25:457–507. doi: 10.1159/000131083
5. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation.* (2007) 115:e478–534. doi: 10.1161/CIRCULATIONAHA.107.181486
6. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2013) 44:870–947. doi: 10.1161/STR.0b013e318284056a
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
8. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and

sinus rhythm. *N Engl J Med*. (2012) 366:1859–69. doi: 10.1056/NEJMoa1202299
9. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
10. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. (2014) 13:429–38. doi: 10.1016/S1474-4422(13)70310-7
11. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. (2013) 12:822–38. doi: 10.1016/S1474-4422(13)70124-8
12. Diener HC, Easton JD, Granger CB, Cronin L, Duffy C, Cotton D, et al. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *Int J Stroke*. (2015) 10:1309–12. doi: 10.1111/ijs.12630
13. Alberts MJ, Bennett CA, Rutledge VR. Hospital charges for stroke patients. *Stroke*. (1996) 27:1825–8. doi: 10.1161/01.STR.27.10.1825
14. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, et al. Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). *Stroke*. (2018) 49:980–6. doi: 10.1161/STROKEAHA.117.020059
15. Kamel H, Okin PM, Longstreth WT Jr, Elkind MS, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol*. (2015) 11:323–31. doi: 10.2217/fca.15.22
16. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. (1988) 318:1148–52. doi: 10.1056/NEJM198805053181802
17. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. (2013) 368:1083–91. doi: 10.1056/NEJMoa1211716
18. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology*. (2013) 81:619–25. doi: 10.1212/WNL.0b013e3182a08d59
19. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. (2017) 377:1022–32. doi: 10.1056/NEJMoa1610057
20. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med*. (2017) 377:1011–21. doi: 10.1056/NEJMoa1705915
21. Kasner SE, Thomassen L, Søndergaard L, Rhodes JF, Larsen CC, Jacobson J. Patent foramen ovale closure with GORE HELEX or CARDIOFORM Septal Occluder vs. antiplatelet therapy for reduction of recurrent stroke or new brain infarct in patients with prior cryptogenic stroke: design of the randomized Gore REDUCE Clinical Study. *Int J Stroke*. (2017) 12:998–1004. doi: 10.1177/1747493017701152
22. Katsanos AH, Psaltopoulou T, Sergentanis TN, Frogoudaki A, Vrettou AR, Ikonomidis I, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. (2016) 79:625–35. doi: 10.1002/ana.24609
23. Harvey JR, Teague SM, Anderson JL, Voyles WF, Thadani U. Clinically silent atrial septal defects with evidence for cerebral embolization. *Ann Intern Med*. (1986) 105:695–7. doi: 10.7326/0003-4819-105-5-695
24. Di Tullio M, Sacco RL, Venketasubramanian N, Sherman D, Mohr JP, Homma S. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke*. (1993) 24:1020–4. doi: 10.1161/01.STR.24.7.1020
25. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. (2005) 58:688–97. doi: 10.1002/ana.20617
26. Wira CR, Rivers E, Martinez-Capolino C, Silver B, Iyer G, Sherwin R, et al. Cardiac complications in acute ischemic stroke. *West J Emerg Med*. (2011) 12:414–20. doi: 10.5811/westjem.2011.2.1785

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BRIEF RESEARCH REPORT
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No Evidence of the "Weekend Effect" in the Northern New South Wales Telestroke Network

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Background: Admission outside normal business hours has been associated with prolonged door-to-treatment times and poorer patient outcomes, the so called "weekend effect. " This is the *first* examination of the weekend effect in a telestroke service that uses multi-modal computed tomography.

Aims: To examine differences in workflow and triage between in-hours and out-of-hours calls to a telestroke service.

Methods: All patients assessed using the Northern New South Wales (N-NSW) telestroke service from April 2013 to January 2019 were eligible for inclusion (674 in total; 539 with complete data). The primary outcomes measured were differences between in-hours and out-of-hours in door-to-call-to-decision-to-needle times, differences in the proportion of patients confirmed to have strokes or of patients selected for reperfusion therapies or patients with a modified Rankin Score (mRS $\leq$ 2) at 90 days.

Results: There were no significant differences between in-hours and out-of-hours in any of the measured times, nor in the proportions of patients confirmed to have strokes (67.6 and 69.6%, respectively, $p = 0.93$); selected for reperfusion therapies (22.7 and 22.6%, respectively, $p = 0.56$); or independent at 3 months (34.8 and 33.6%, respectively, $p = 0.770$). There were significant differences in times between individual hospitals, and patient presentation more than 4.5 h after symptom onset was associated with slower times (21 minute delay in door-to-call, $p = 0.002$ and 22 min delay in door-to-image, $p = 0.001$).

Conclusions: The weekend effect is not evident in the Northern NSW telestroke network experience, though this study did identify some opportunities for improvement in the delivery of acute stroke therapies.

Keywords: telestroke, weekend effect, thrombolysis, thrombectomy, door to needle time

INTRODUCTION

The John Hunter and Gosford Hospitals provide telestroke services to five rural hospitals within the Hunter New England Local Health District and the adjacent Mid-North Coast Local Health District (New South Wales, Australia), together representing ∼1.1 million inhabitants in an area over 143,000 km^2. John Hunter Hospital functions as the hub of the network, with Gosford Hospital providing Neurologist consultations via the network but not accepting patient transfers. The telestroke network aims to identify patient candidates for acute reperfusion therapies; thrombolysis, which is delivered at the spoke hospital and mechanical thrombectomy (MT) which requires transfer to John Hunter Hospital (1). Both therapies are time-sensitive and require developed acute stroke pathways to minimize door-to-thrombolysis (needle) (DTN) and door to groin puncture times (2–4).

After-hours presentation has been associated with prolonged DTN time and poorer patient outcomes (5–7), the so-called "weekend effect." Studies in the USA (8) and Germany (9) have indicated that telestroke services are less prone to the weekend effect, but this has not been examined telestroke services that offer mechanical thrombectomy (MT) nor any telestroke service that relies on multi-modal computed tomography (mCT) imaging for treatment decisions. Furthermore, previous studies in telestroke networks have been confined to patients who received thrombolysis, and did not examine differences in the accuracy of triage by spoke-site staff, which has implications for telestroke resource management. In this study, we aimed to determine whether admission in- or out-of business hours had a significant influence on door to needle timings and accuracy of emergency department triage or patient outcomes in our telestroke network. In secondary analyses we examined differences between individual hospitals, differences between groups of hospitals sorted by experience in the telestroke network and the effects of factors such as stroke severity and time from symptom onset to presentation on hospital timings. The latter was examined both before and after the criteria for reperfusion therapy was extended to 24-h.

METHODS

Ethics Approval

Ethics approval was gained from the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 13/02/20/5.06) with a posterior amendment (AU201712-15). Given the nature of the study (an audit of internal data) the requirement for individual patient consent was waived.

Northern NSW Telestroke Network

The telestroke network commenced with the first spoke hub (hospital A) in April 2013, followed by Hospital B (2014), and three other sites (hospitals C, D, and E) joined in 2017. Of these hospitals, only Hospital B has neurologists on site and routinely provides in-hours thrombolysis while the telestroke network primarily functions out-of-hours. The telestroke network offers 24/7 services to the rest of the hospitals, with Neurologist workforce being drawn from both John Hunter Hospital and Gosford District Hospital, while John Hunter Hospital also accepts patient transfers for MT. The distance from spoke to hub ranges from 167 to 423 km. As part of the network, the rural hospitals were equipped with telemedicine cameras, the physicians were trained in acute stroke triage, and multimodal CT (compendium of brain non-contrast computed tomography -NCCT-, CT angiography -CTA-, and CT perfusion -CTP-) was introduced and performed routinely. Patients presenting with neurological symptoms as defined by the FAST scale (10) within the relevant time-frame from symptom onset would receive multimodal CT imaging and be assessed via the telestroke service. From April 2013 to November 2017, the stroke call criteria required symptom onset within 4.5 h. From November 2017, after publication of the DAWN (2) and DEFUSE-3 (11) trials, the time window for stroke calls was expanded to 24 h. Acute imaging interpretation and final treatment decision are performed by the consulting telestroke Neurologist, with spoke-hospital staff delivering thrombolysis and/or arranging transfer to John Hunter hospital for MT as appropriate. In cases where the patient received both thrombolysis and MT, thrombolysis would be initiated at the spoke site prior to transfer. For more details about our telestroke workflow, we direct the reader to our previous results (1, 12).

Data Collection

All patients assessed using the Northern New South Wales (NSW) telestroke service from April 2013 to January 2019 were eligible for inclusion and were only excluded from the analysis if complete data were not available. Clinical data were retrospectively collected from April 2013 to June 2016 (46 patients, 8.5% of the total) and prospectively collected June 2016–January 2019. In addition to baseline demographics, past medical history, baseline National Institutes of Health Stroke Scale (NIHSS), treatment decision, final diagnosis, and several time points were collected. The DTN time was defined as the time between emergency department (ED) presentation and delivery of the bolus of thrombolytics. DTN was divided into three parts; the time between arrival at the ED and call to the telestroke neurologist ("door-to-call"), the time from the call to the decision (reperfusion treatment, yes or no) ("call-to-decision"), and the time from this decision to thrombolysis, where applicable ("decision-to-needle"). Door-to-image, defined as the time between arrival at ED to first image of brain CT was also collected. Patients who suffered a stroke in hospital were excluded from door-to-call and door-to-imaging analyses but were included in all others. The time between symptom onset (either witnessed onset or time last known well) and ED presentation was analyzed as <3 h, 3–4.5 h, and >4.5 h as 4.5 h is the currently licensed window for thrombolysis.

Final diagnosis was coded as stroke [confirmed ischemic lesion on multimodal CT or follow-up CT or magnetic resonance image (MRI)] or not confirmed stroke. Transient ischaemic attacks (TIAs) were not classed as confirmed stroke unless the transient perfusion deficit was visible on acute CTP and consistent with clinical presentation. Symptomatic intracranial hemorrhage was defined according to the Safe Implementation

TABLE 1 | Patient population characteristics in-hours vs. out-of hours and treated vs. non-treated with acute reperfusion therapy.

	In-hours patients	Out-of-hours patients	Patients receiving acute reperfusion therapy	Patients not receiving acute reperfusion therapy	All patients
Total number of patients (%, male)	256 (58%)	283 (59%)	122 (62%)	401 (57%)	539 (59%)
Age (Mean, range)	69 (29–96)	70 (23–95)	69 (29–92)	70 (23–96)	70 (23–96)
NIHSS (Median–IQR)	4 (2–8)	5 (2–10)	10 (6–17)	3 (1–7)	4 (2–9)

of Treatments in Stroke Monitoring Study (SITS-MOST) criteria (13). Telestroke calls were classified as "In-hours" (i.e., business hours) if the call was made between 8:00 a.m. and 5:00 p.m. local time Monday-Friday, excluding New South Wales public holidays. The rest of the calls were considered as "out-of-hours."

Statistical Analysis

All statistical analysis was performed on Stata version 14 (Statacorp, USA). Differences in triage between in-hours and out-of-hours were assessed by comparing the proportion of patients in each category who were confirmed to have stroke, and the proportion who received acute reperfusion therapy using Pearson's chi-squared test. Timings of the stroke workflow in the hub sites were assessed using linear regression. To examine the effect of hospital experience in the telestroke network, the three hospitals that have joined it most recently (hospitals C, D and E) were grouped together as "least experienced" while Hospital A was coded as "most experienced" Hospital B, with an intermediate level of experience was excluded from the analysis. Another regression analysis was performed with the patients since the time-window for acute therapies was expanded to 24 h to examine the effects of symptom onset to presentation time after this change in call criteria.

RESULTS

A total of 674 patients were assessed from April 2013 to January 2019; 135 were excluded due to incomplete data leaving 539 (80%) patients in this analysis. Of these, 256 (47.5%) were assessed in-hours and 283 (52.5%) out-of-hours; 20 calls related to patients already in hospital. One hundred and twenty-two patients (23.3%) underwent reperfusion therapies (75 thrombolysis, 25 thrombectomy, and 22 combined thrombolysis and thrombectomy) (**Table 1**). A total of two patients were treated who were not found to have confirmed stroke. After final work-up, one of these patients was still believed to be a stroke, while the other was diagnosed with an unspecified mimic. A total of two patients suffered symptomatic intracerebral hemorrhage (sICH) after reperfusion therapy (1.6% of those treated).

Triage efficacy was similar in-hours to out-of-hours, with 71.5% of patients confirmed to have stroke and 22.7% selected for reperfusion therapies in hours compared to 73.9% confirmed strokes and 22.3% selected for reperfusion therapy out of hours ($p = 0.560$ and 0.930, respectively) (**Table 2**). Patient outcomes were also similar between the two groups (34.7% 90-days mRS $\leq$ 2 in-hours vs. 33.6% out-of-hours, $p = 0.770$). Forty-six patients were thrombolysed in hours, with 51 thrombolysed out-of-hours. The median door-to-needle time was 91 min (IQR 71–110 min), being longer out-of-hours than in-hours (94 vs. 87 min, respectively). This pattern was the same for the decision to needle time (23 vs. 20 min) and the door to image time (56 vs. 53 min) although the call to decision time was slightly shorter out-of-hours (36.5 vs. 40.5 min). None of these differences were statistically significant after adjusting for other factors (hospital, onset-presentation time, stroke severity).

TABLE 2 | Patients confirmed to have suffered a stroke and treated with reperfusion therapy (thrombolysis or MT), in- vs. out-of-hours.

	In-hours *N* (% of in-hours calls)	Out-of-hours *N* (% of out-of-hours calls)	Total *N* (% of all calls)
Total number of patients	256	283	539
Confirmed stroke	171 (67.6%)	197 (69.6%)	370 (68.6%)
Treated with reperfusion therapy	58 (22.7%)	64 (22.6%)	122 (22.6%)
90-day mRS $\leq$ 2	89 (34.8%)	95 (33.6%)	184 (34.1%)

Effect of in-hours vs. Out-of-Hours

Patient arrival in-hours was not a statistically significant predictor of work-flow times, despite a trend for it to be associated with reduced times such as an estimated 10.2-minute decrease in door-to-call times (95% CI −1.8 to 22.2, $p = 0.097$), and an estimated 6.1-min (95% CI −6.16 to 18.35, $p = 0.329$) decrease in door-to-image and 4.33 min (95% CI −1.00 to 4.33, $p = 0.109$) decrease in decision-to-needle times compared to out-of-hours presentation. None of these differences were statistically significant (all $p > 0.05$); including the overall door to needle time (estimated 9.6 min, 95% CI −28.9 to 9.8, $p = 0.330$).

Onset to Presentation Time

A total of 296 patients presented within 3 h of onset, 31 between 3 and 4.5 h and 169 patients presented more than 4.5-h since the last time seen well. There was no significant difference in any of the acute stroke metrics (door-to-image, door-to-call, or decision-to-needle times) between patients admitted within 3 and 3–4.5 h after onset (all nominal $p > 0.05$; see **Table 3**). The presentation over 4.5 h was associated with significantly slower door-to-call and door-to-image times though not with a slower decision-to-needle time (see **Table 3**). There was a trend for a

TABLE 3 | Estimated effects on workflow times (from linear regression) of symptom-onset to presentation time for all patients.

Time from onset-ED		3–4.5 h	> 4.5 h
Door-to-call time	β (95% CI)	2.6 (−22.1 to 27.2)	21 (7.8 to 34.1)
	p	0.838	0.002
Call-to-decision time	β (95% CI)	−8.1 (−19.1 to 3.0)	5.24 (−0.6 to 11.1)
	p	0.15	0.08
Decision-to-needle time	β (95% CI)	−5.2 (−19.9 to 9.5)	2.7 (−6.8 to 12.1)
	p	0.485	0.573
Door-to-Image time	β (95% CI)	6.39 (−18.8 to 31.6)	22.1 (8.7 to 65.5)
	p	0.618	0.001

All estimates are relative to patients presenting within 3 h of symptom onset.

TABLE 4 | Estimated effects on workflow times (from linear regression) of symptom-onset to presentation time after the protocol was changed to include patients presenting up to 24-h after onset.

Time from onset-ED		3–4.5 h	>4.5 h
Door-to-call time	β (95% CI)	−13.8 (−43.4 to 14.8)	27.4 (13.0 to 41.7)
	p	0.343	<0.001
Call-to-decision time	β (95% CI)	−14.5 (−27.5 to −1.5)	6.9 (0.4 to 13.4)
	p	0.029	0.038
Decision-to-needle time	β (95% CI)	−0.4 (−18.5 to 17.8)	−1.4 (−13.1 to 10.2)
	p	0.967	0.809
Door-to-Image time	β (95% CI)	−13.7 (−42.8 to 15.4)	29.1 (14.5 to 43.6)
	p	0.356	<0.001

All estimates are relative to patients presenting within 3 h of symptom onset.

slower call-to-decision time (by an estimated 5.2 min, 95% CI −0.6 to 11.1, $p = 0.080$).

A specific analysis after expanding the call window to 24 h since onset was performed. This group comprised 407 patients in total, 63 treated with thrombolysis alone, 24 with MT alone and 19 with both therapies. Amongst this group, those presenting >4.5-h after onset still experienced significantly longer door-to-call, door-to-imaging and call-to-decision times (see **Table 4**); while those presenting 3–4.5 h after onset experienced a call-to-decision time faster than patients presenting within 3 h (by an estimated 14.5 min, 95% CI 1.5 to 27.5 min, $p = 0.029$).

Hospital Experience

Compared to Hospital A (the most experienced site), all sites except hospital C demonstrated significantly slower decision-to-needle times by ∼10–12 min (see **Table 5**). Hospital B demonstrated slower workflow across all of the times while hospital D demonstrated significantly faster door-to-imaging times than any other site (**Table 5**). Hospital experience (that is, admission to the most experienced site relative to the 3 least-experienced sites) was associated with significantly faster decision-to-needle times (by an estimated 14.3 min, 95%CI 5.8 to 22.8 min, $p = 0.001$) but not faster door-to-call, call-to-decision or door-to-image times (p-values of 0.217, 0.819, and 0.861, respectively, see **Supplementary Material** for further details).

Stroke Severity and Reperfusion Therapy

There was a trend for faster door-to-call times with more severe strokes, by ∼1.7 min for every unit increase in NIHSS, but this was not statistically significance once other factors such as the use of reperfusion therapy were adjusted for ($p = 0.081$). Patients who did receive reperfusion therapy tended to have more severe strokes than those who did not (see **Table 1**) and were assessed more quickly on average. The use of reperfusion therapy (either thrombolysis or MT) was consistently associated with faster door-to-call (by 16.8 min, 95% CI 0.6 to 32.9 min, $p = 0.043$) and door-to-imaging (by 25.3 min, 95% CI 8.8 to 41.8 min, $p = 0.003$) times but was not significantly associated with the call-to-decision time (estimate = 0.7 min faster, $p = 0.577$).

DISCUSSION

There were no differences in the accuracy or speed of triage for the telestroke service between in-hours and out-of-hours. The proportion of patients confirmed to have stroke, the proportion who received reperfusion therapy and the proportion who were independent at 90 days were all similar between both groups. The lack of variation in mRS outcomes between the two groups is consistent with previous studies (8, 9); differences in the rates of stroke diagnosis and reperfusion therapy have not previously been examined in a telestroke network. Differences in acute stroke metrics were not statistically significant between in- and out-of-hours, although there were differences between hospitals. These results are reasonably consistent with the single study that has examined door-to-needle times in a telestroke network (8), which found a small difference (1.6 min) in one of their workflow times (page-camera, for which our study has no correlate) but no difference in overall door-needle times. Both telestroke analyses contrast with previous studies in comprehensive stroke centers that did find a significant difference between in-hours and out-of-hours, both in Australia (14) and overseas (7). The hypothesized reasons for these differences have included extra time required for the stroke team to travel to the hospital after being called or having a smaller and/or less experienced staff working out-of-hours. Our telestroke service does not require the stroke team to travel to the hospital, eliminating this potential source of delay. With regard to staffing levels, the spoke hospitals in the Northern NSW telestroke network tend to have lean staffing levels at all times, thus the difference in available staff between in-hours and out-of-hours is minimal.

Previous studies on the weekend effect in telestroke networks have been limited to date; studies in the USA (8) and Germany (9) have examined differences in patient outcomes between in-hours and out-of-hours presentations, and the former examined differences in workflow-timings (finding no difference in door-to-needle times between the two groups). However, both of these studies were confined to patients who received thrombolysis. There are no studies we are aware of that examine the weekend effect in a telestroke network that includes MT as a treatment option, and hence triages patients presenting outside

TABLE 5 | Estimated differences in work-flow times relative to Hospital A after adjusting for other variables (*$P < 0.05$).

		Door-to-call time	Call-to-decision time	Decision-to-needle time	Door-to-imaging time
Hospital B	β	25.8	13.4	10.2	33.4
	(95% CI)	(6.9–44.7)	(5.0–21.8)	(2.2–18.3)	(14.1–52.8)
	P	0.008*	0.002*	0.014*	0.001*
Hospital C	β	2.9	2.3	6.1	0.2
	(95% CI)	(−25.6 to 1.3)	(−10.4 to 15.1)	(−9.0 to 21.2)	(−28.9 to 29.3)
	P	0.844	0.719	0.424	0.99
Hospital D	β	−1.6	−0.3	12.5	−17.8
	(95% CI)	(−18.7 to 15.5)	(−7.9 to 7.4)	(4.5 to 20.4)	(−35.1 to −0.4)
	P	0.856	0.94	0.003*	0.045*
Hospital E	β	17.0	1.3	10.2	18.8
	(95% CI)	(0.2 to 33.9)	(−6.2 to 8.8)	(3.5 to 17.0)	(1.6 to 35.9)
	P	0.048*	0.733	0.003*	0.032*

the typical thrombolysis window. Furthermore, no previous study has examined a telestroke service that uses CTP routinely (both the US and German telestroke networks primarily relied on NCCT and CTA), nor have differences in the accuracy of patient triage for the telestroke service been examined previously. The latter are potentially important for managing the telestroke workload.

The routine use of CTP may, in theory, have differential effects outside of normal business hours due to the availability (or lack thereof) of radiography staff trained in this procedure. The use of perfusion imaging (either CTP or MR-Perfusion) is important for the selection of patients for MT in the extended time-window of 6- to 24-h after symptom onset, into which a significant proportion of our patients fall once the lengthy transfer times between spokes and hub are accounted for. Our group has recently published a comprehensive analysis of the effects of mCT on clinical decision-making and outcomes in this telestroke network (12). Amongst 80 patients who met standard NCCT and clinical criteria for thrombolysis, 36 (45%) were not thrombolysed based on mCT criteria, 6 because mCT demonstrated a large established core (>70 mL) that was not visible on NCCT, while the remainder had very small or no lesions and 12 of these patients were subsequently diagnosed as stroke mimics. In keeping with our previous larger observational study (15), clinical outcomes in patients with no or very small lesions were excellent without treatment.

The delays associated with patients presenting more than 4.5 h after stroke onset probably indicate an incomplete awareness of the expanded window for stroke therapy despite specific training being performed. The delay in triaging patients admitted out of the classic thrombolysis window is likely to reduce the efficacy of reperfusion therapy when it is provided and hence degrade patient outcomes (16). This will need to be a key focus of future training within the telestroke network.

Patients who received reperfusion therapies (thrombolysis or MT) were triaged faster, resulting in door-to-call and door-to-imaging times ∼15 and 25 min, respectively, faster than patients who did not go on to receive such therapies. This suggests that staff are acting with more urgency when they judge that a patient may be suitable for reperfusion therapy early in the triage process. This may in part be due to greater stroke severity amongst patients who received reperfusion therapy, a hypothesis supported by the fact that stroke severity was an important confounder for the regression models without being statistically significant once reperfusion therapy had been corrected for.

The variation in timing between hospitals was considerable, and may account for an important proportion of the apparent difference between in-hours and out-of-hours timings given that hospital B, which demonstrated the slowest times across the board, also had the highest proportion of out-of-hours telestroke calls (66% out-of-hours vs. 53% across all sites, see **Supplementary Table 1**). Hospital B has local neurologists and primarily uses the telestroke service out-of-hours, or when the local Neurologists are unavailable. This may explain the slower timings at this hospital as well, since the local emergency staff works with two different models, leading to possible delays activating the telestroke team.

The effect of hospital experience was chiefly evident in differences in the decision-to-needle time. The spoke hospitals in the Northern NSW telestroke network tend to have relatively transient medical workforce, with a more stable nursing staff hence the accumulation of experience within a hospital primarily occurs within the nursing staff. This may be why the benefit of this experience is primarily demonstrated in the decision-to-needle time, which is influenced more by the efficiency of nursing staff than by the efficiency of the treating doctor.

The key strength of this study is the examination of a range of quality-of-care measures in addition to the standard patient outcomes, including the speed of work-flow for both patients who received reperfusion therapy and those who did not, the latter group having previously been excluded from examinations of the weekend effect in telestroke networks. The key weaknesses of the study lie in the fact that some of the data were collected retrospectively, and a considerable portion of patients were excluded due to incomplete data.

CONCLUSIONS

This study has demonstrated that presentation out-of-hours is not a barrier to effective and efficient use of the telestroke service, and has identified opportunities for improvement within the Northern NSW telestroke network, in particular with regard to patients admitted more than 4.5 h after symptom onset.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The full data-set contains potentially identifiable patient data. Requests to access the dataset can be made to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunter New England Health Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

In addition to these tasks, FM, PG-B, SG, TW, BO'B, JE, KA, CG-E, and NS collected and collated data for the article. TL and AP conducted statistical analyses and drafted the bulk of the article. AB and MP oversaw imaging protocols and the various hospitals and CG-E and NS oversaw the overall operation of the Telestroke network and CL oversaw the establishment of the network. All authors contributed to the drafting, editing, and final formation of the article on behalf of the Northern NSW Telestroke investigators.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00130/full#supplementary-material

REFERENCES

1. Demeestere J, Sewell C, Rudd J, Ang T, Jordan L, Wills J, et al. The establishment of a telestroke service using multimodal CT imaging decision assistance: "Turning on the fog lights". *J Clin Neurosci*. (2017) 37:1–5. doi: 10.1016/j.jocn.2016.10.018
2. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
3. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochr Database Syst Rev*. (2014) 2014:Cd000213. doi: 10.1002/14651858.CD000213.pub3
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. (2018) 49:e46–110. doi: 10.1161/STR.0000000000000172
5. Sorita A, Ahmed A, Starr SR, Thompson KM, Reed DA, Dabrh AM, et al. Off-hour presentation and outcomes in patients with acute ischemic stroke: a systematic review and meta-analysis. *Europ J Internal Med*. (2014) 25:394–400. doi: 10.1016/j.ejim.2014.03.012
6. Ogbu UC, Westert GP, Slobbe LC, Stronks K, Arah OA. A multifaceted look at time of admission and its impact on case-fatality among a cohort of ischaemic stroke patients. *J Neurol Neurosurg Psychiatry*. (2011) 82:8–13. doi: 10.1136/jnnp.2009.202176
7. Turner M, Barber M, Dodds H, Dennis M, Langhorne P, Macleod MJ, et al. Stroke patients admitted within normal working hours are more likely to achieve process standards and to have better outcomes. *J Neurol Neurosurg Psychiatry*. (2016) 87:138–43. doi: 10.1136/jnnp-2015-311273
8. Cossey TC, Jagolino A, Ankrom C, Bambhroliya AB, Cai C, Vahidy FS, et al. No weekend or after-hours effect in acute ischemic stroke patients treated by telemedicine. *J Stroke Cerebrovasc Dis*. (2019) 28:198–204. doi: 10.1016/j.jstrokecerebrovasdis.2018.09.035
9. Haeusler KG, Gerischer LM, Vatankhah B, Audebert HJ, Nolte CH. Impact of hospital admission during nonworking hours on patient outcomes after thrombolysis for stroke. *Stroke*. (2011) 42:2521–5. doi: 10.1161/STROKEAHA.110.612697
10. Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. *Stroke*. (2004) 35:1355–9. doi: 10.1161/01.STR.0000128529.63156.c5
11. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
12. Garcia-Esperon C, Soderhjelm Dinkelspiel F, Miteff F, Gangadharan S, Wellings T, O Brien B, et al. Implementation of multimodal computed tomography in a telestroke network: five-year experience. *CNS Neurosci Therap*. (2019). doi: 10.1111/cns.13224. [Epub ahead of print].
13. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. (2007) 369:275–82. doi: 10.1016/S0140-6736(07)60149-4
14. Tai YJ, Weir L, Hand P, Davis S, Yan B. Does a 'code stroke' rapid access protocol decrease door-to-needle time for thrombolysis? *Intern Med J*. (2012) 42:1316–24. doi: 10.1111/j.1445-5994.2011.02709.x
15. Bivard A, Lou M, Levi CR, Krishnamurthy V, Cheng X, Aviv RI, et al. Too good to treat? Ischemic stroke patients with small computed tomography perfusion lesions may not benefit from thrombolysis. *Ann Neurol*. (2016) 80:286–93. doi: 10.1002/ana.24714
16. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. (2016) 316:1279–88. doi: 10.1001/jama.2016.12266

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Blend Sign Is a Strong Predictor of the Extent of Early Hematoma Expansion in Spontaneous Intracerebral Hemorrhage

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Background and Purpose: It is unclear which imaging marker is optimal for predicting the extent of hematoma expansion (EHE). We aimed to compare the usefulness of the blend sign (BS) with that of other non-contrast computed tomography (NCCT) markers for predicting the EHE in patients with spontaneous intracerebral hemorrhage (sICH).

Methods: Patients with sICH admitted to our Neurology Emergency Department between September 2013 and January 2019 were enrolled. The EHE was calculated as the absolute increase in hematoma volume between baseline and follow-up CT (within 72 h). The EHE was categorized into four groups: "no growth," "minimal change" (≤5.1 ml), "moderate change" (5.1–12.5 ml), and "massive change" (>12.5 ml). Univariate and multivariate analyses were performed to investigate the relationship between the NCCT markers [BS, black hole sign (BHS), satellite sign, and island sign] and the EHE.

Results: A total of 1,111 sICH patients were included (median age: 60 years; 66.5% males). Multiple linear regression analysis showed that the presence of the BS and BHS was independently associated with the EHE, after adjusting for confounders ($P < 0.001$ and $P = 0.003$, respectively). The presence of the BS and BHS was positively correlated with growth category ($r = 0.285$ and $r = 0.199$, both Ps < 0.001). The BS demonstrated a better predictive performance for the EHE than did the BHS [area under the curve (AUC): 0.67 vs. 0.57; both Ps < 0.001].

Conclusions: In patients with acute sICH, the BS showed a better performance in predicting the EHE compared with other NCCT markers. This imaging marker may help identify patients at a high risk of significant hematoma expansion and may facilitate its early management.

Keywords: intracerebral hemorrhage, extent of hematoma expansion, functional outcome, blend sign, computed tomography

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INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) has become the leading cause of disability and death in China, and early hematoma expansion (HE) is an independent risk factor for early neurological deterioration and long-term functional outcomes (1). In a large meta-analysis, intracerebral hemorrhage (ICH) baseline volume, non-contrast computed tomography (NCCT) timing, and

antiplatelet and anticoagulant use were found to be independent predictors of intracerebral hematoma growth (2). HE occurs in 20–40% of all patients with sICH (3, 4), and previous reports have identified multiple factors that are associated with clinical outcomes following sICH, including age, baseline hematoma volume, HE, the presence of a neurological deficit, intraventricular hemorrhage (IVH), and hematoma location (4–6). Among these factors, hemorrhage volume is a significant predictor of poor outcome in patients with sICH (7), and this is an area of ongoing research. Davis et al. found that an increase in the hematoma volume by 10% increases the risk of death at 90 days by 5% and poor outcome by 16–18% (4). Conversely, an approximately 2–4 ml reduction in hematoma volume was associated with a 20–30% reduction in the risk of death (8). Thus, increased hemorrhage volume has been a major focus for potential therapeutic targets, as it is the only modifiable factor which is present in the majority of patients (9–12). Therefore, it is important to find markers associated with the extent of hematoma expansion (EHE).

The computed tomography angiography (CTA) spot sign is regarded as a useful predictor for HE and poor functional outcomes (13–17). However, CTA is not routinely used in many institutions (18). Recently, several NCCT markers have shown the ability to predict HE (19), such as the blend sign (BS) (20), black hole sign (BHS) (21), satellite sign (22), and island sign (23). Which imaging marker is better at predicting the EHE remains unclear. Therefore, the purpose of this study was to compare their performances in predicting the EHE.

METHODS

Study Population

We retrospectively evaluated consecutive sICH patients who were admitted to our Neurology Emergency Department between September 2013 and January 2019. The eligibility criteria for our study included patients aged >18 years old whose baseline NCCT and follow-up NCCT were performed within 6 and 72 h from symptom onset, respectively. We used the following exclusion criteria: (1) hemorrhage secondary to tumor, aneurysm, trauma, arteriovenous malformation, or hemorrhagic infarction; (2) surgical intervention for the hematoma performed prior to the follow-up CT scan; (3) multiple cerebral hemorrhages or primary IVH; and (4) a lack of hospitalization data and follow-up CT. In addition, macrovascular causes were detected using CTA. CTA was not performed routinely in all patients, but at the discretion of the clinical team. The management of patients followed the recommendations provided by the American Heart Association/American Stroke Association (AHA/ASA) guidelines. Our study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University.

Clinical Data

Clinical data such as age, sex, medical history (including smoking, alcohol consumption, and diabetes mellitus), admission platelet count, admission systolic blood pressure, time from onset to baseline CT (h), time from baseline CT to follow-up CT (h), and Glasgow Coma Scale (GCS) score were retrospectively collected. The Glasgow Outcome Scale (GOS) score was evaluated at discharge, and patients were dichotomized into favorable outcome (4–5 points) and poor outcome (1–3 points).

Image Acquisition and Analysis

The baseline and follow-up CT scans (120 kVp, 80 mA; section thickness, 5 mm) were performed using a standard clinical protocol. All CT images were acquired from the picture archiving and communication system (PACS) and saved in DICOM format for further evaluation. Volumetric calculation of the hematoma was completed through three-dimensional reconstruction of the regions of interest obtained by manually depicting the lesion circumference in multiple successive layers on baseline and follow-up NCCT imaging. All measurements were performed in a blinded fashion. Two experienced radiologists, who were blinded to the patients' clinical data, independently evaluated all baseline and follow-up CT images. Any disagreement between the two radiologists was resolved by consensus. Hematoma location and volume, the presence of the intraventricular extension (16), BHS (21), BS (20), island sign (23), and satellite sign (22) was assessed. Hematoma location was divided into deep, lobar, brain stem, and cerebellum (24), and deep ICH was defined as hematoma involving the thalamus or basal ganglia. Baseline hematoma volume was divided into four categories: <10, 10–20, 20–30, and ≥30 ml. The EHE was defined as an increase in hematoma volume between baseline and follow-up CT. The extent of hematoma growth was classified into four "clinically meaningful" grades: "no growth," "minimal change" (≤5 ml), "moderate change" (5.1–12.5 ml), and "massive change" (>12.5 ml) (8). In addition, follow-up CT was performed routinely within 72 h, but the exact timing of the follow-up CT was at the discretion of the clinical physician and time to deterioration of patients.

Statistical Analyses

Statistical analyses were performed using R software (version 3.6.0; The R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 24.0; IBM Corp., Armonk, NY, USA). Continuous variables were described as medians or means; categorical variables were expressed in percentages. We performed exploratory simple linear regression analysis to explore the association between patient characteristics and absolute growth, followed by multiple linear regression to determine the independent predictors of absolute hematoma growth. Variables with a $P < 0.05$ in univariate regression analyses were included in the multiple linear regression. Previous use of antiplatelet and anticoagulant medications, which were thought to be independent predictors associated with HE, was forced into the model. The absolute growth and imaging markers were compared using chi-square or Fisher's exact test and Student's *t*-test or Mann–Whitney *U*-test, as appropriate. The correlation analysis was performed using Kendall's tau-*b* test. Receiver operating characteristic analysis was performed to evaluate the value of the BS and BHS in predicting HE (>12.5 ml). Multivariate logistic regression analysis was performed to investigate whether the EHE was an independent

predictor of poor outcome in patients with ICH, adjusting for predictors of poor outcome that were previously used in the INTERACT1 study (8). The amount of missing data was low (<5%), and patients with missing values were not involved in the multivariate logistic regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1,111 sICH patients (739 males and 372 females) were included in our study. The median age of the patients was 60.90 years [interquartile range (IQR) 51–70 years]. Baseline characteristics are shown in (**Table 1**). Exploratory simple linear regression analysis revealed that sex, baseline volume, location of hemorrhage, time from onset to baseline CT, time from baseline CT to follow-up CT, systolic blood pressure, baseline GCS, and the presence of the satellite sign, BS, BHS, and island sign were all associated with the EHE (all *P*s < 0.05; **Table 2**). Multivariate analysis with multiple linear regression showed that the BS ($P < 0.001$) and BHS ($P = 0.003$) were independently associated with absolute growth after adjusting for sex, baseline volume, location of hemorrhage, time from onset to baseline CT, time from baseline CT to follow-up CT, systolic blood pressure, antiplatelet, anticoagulant, and baseline GCS (**Table 3**).

The BS and BHS showed a statistically significant association with absolute growth on follow-up CT (**Figure 1**). Compared with the non-BS group, patients with the BS had a significantly higher median hematoma growth (0.45 [0.39–2.29] vs. 5.10 [0.98–13.91] ml, $P < 0.001$; **Figure 1A**). Median growth was higher in the BHS group than in the non-BHS group (2.46 [0.27–7.96] vs. 0.58 [−0.38 to 2.62] ml, $P < 0.001$; **Figure 1B**). Patients with small baseline hematoma volumes were less likely to present the BS or BHS (both *P*s < 0.001; **Figure 2A**). (**Figure 2**) demonstrates the presence of a significant difference in the amount of hematoma growth between patients in the BS and non-BS groups for all baseline hematoma volumes (all *P*s < 0.01; **Figure 2B**). When we compare the BHS and non-BHS groups, significant differences were only observed in those with a baseline hematoma volume of up to 20 ml (**Figure 2C**).

On moving to the categories of higher hematoma growth from nil to >12.5 ml, the frequency of the BS and BHS increased from 7.5 to 42.2% and from 10.5 to 28.4%, respectively ($P < 0.001$; **Figures 3A,B**). Compared with that in "no growth" (7.5%), the incidence of BS was significantly higher in the "minimal change" (17.8%) or "moderate change" (36%) groups ($P < 0.001$). The "massive change" group showed the highest incidence of the BS (42.2%). The receiver operating characteristic analysis showed that the area under the curve (AUC) of the BS was 0.67 (95% CI 0.62–0.74) and that of the BHS was 0.57 (95% CI 0.51–0.64) in predicting HE (**Figure 4**). In addition, the BS and BHS showed positive correlations with the baseline hematoma category (BS: $r = 0.249$, $P < 0.001$; BHS: $r = 0.211$, $P < 0.001$). The BS and BHS also had positive correlations with the hematoma growth category (BS: $r = 0.285$, $P < 0.001$; BHS: $r = 0.199$, $P < 0.001$). After known predictors of outcome were adjusted for, compared to that in patients with "no growth," the change in hematoma growth was independently associated with higher odds of poor outcome following sICH (OR: 1.030 [95% CI 0.679–1.565], $P = 0.888$ for "minimal change," and OR: 2.227 [95% CI 1.222–4.060], $P = 0.009$ for "moderate change"). Patients with "massive change" had the highest risk of a poor outcome (OR: 2.534 [95% CI 1.296–4.955], $P = 0.007$, **Table 4**).

TABLE 1 | Baseline characteristics of the study cohort.

Demographic characteristics	Total (n = 1,111)
Age, years, median (IQR)	60.9 (51–70)
Male sex, *n* (%)	739 (66.5)
Systolic blood pressure, median (IQR)	161 (144–177)
Clinical characteristics	
History of diabetes mellitus, *n* (%)	140 (12.7)
History of smoking, *n* (%)	350 (31.8)
History of alcohol intake, *n* (%)	348 (31.6)
Antiplatelet, *n* (%)	19 (1.7)
Anticoagulant, *n* (%)	8 (0.7)
Platelet count, $\times 10^3/\mu$l, median (IQR)	202.5 (165–242)
Location	
Lobar, *n* (%)	82 (7.4)
Deep, *n* (%)	951 (85.6)
Brain stem, *n* (%)	49 (4.4)
Cerebellum, *n* (%)	29 (2.6)
GCS score, median (IQR)	13 (10–15)
Time from onset to first CT (h), median (IQR)	3 (2–4)
Time from the first to the follow-up CT (h), median (IQR)	19.5 (12–29.5)
Discharge GOS <4, *n* (%)	748 (67.3)
Baseline volume, median (IQR)	16.4 (8.9–27.1)
Presence of IVH, *n* (%)	386 (34.7)
Black hole sign, *n* (%)	173 (15.6)
Blend sign, *n* (%)	169 (15.2)
Satellite sign, *n* (%)	420 (37.8)
Island sign, *n* (%)	230 (20.7)

Continuous variables are presented as median (IQR); categorical variables are expressed in n (%).
CT, computed tomography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; IQR, interquartile range; IVH, intraventricular hemorrhage.

DISCUSSION

In our retrospective study of 1,111 patients with sICH, we compared the BS with several CT markers to predict the EHE. The main finding of this analysis was that the BS was better able to stratify the EHE than were other CT markers.

The INTERACT1 study showed an approximate linear relationship between HE and prognosis; every 1-ml increase in hematoma growth was associated with a 5% increase in the odds of a poor outcome (8). Studies have also shown that absolute HE definitions predict poor outcomes better than relative HE definitions (25). It is universally acknowledged that hematoma volume is the main determinant of poor outcome in patients with sICH (5, 6). A growth in hematoma volume of over 5 ml is clearly visible in clinical practice (8). In addition, baseline hematoma

TABLE 2 | Simple linear regression analysis of predictors of the extent of early hematoma expansion.

Predictors	*B*	*β*	95% CI of *B*	*P*-value
Sex, male	1.923	0.084	0.575–3.271	0.005
Age	−0.011	−0.012	−0.062–0.041	0.685
Systolic blood pressure	−0.036	−0.087	−0.061 to −0.011	0.004
Medical history				
History of diabetes mellitus	0.210	0.006	−1.715–2.134	0.831
History of smoking	0.805	0.035	−1.571–2.181	0.215
History of alcohol intake	0.805	0.032	−0.766–2.375	0.315
Antiplatelet	−2.628	−0.031	−7.552–2.296	0.295
Anticoagulant	23.039	0.180	15.608–30.470	<0.001
Platelet count	−0.010	−0.067	−0.019–0.001	0.026
Time from onset to first CT	−0.679	−0.090	−1.123 to −0.235	0.003
Time from the first to the follow-up CT	−0.127	−0.183	−0.167 to −0.087	<0.001
Location of hemorrhage	−0.993	−0.06	−0.968–0.018	0.046
Baseline hematoma volume	0.148	0.201	0.105 to 0.019	<0.001
Presence of IVH	0.515	0.023	−0.826–1.855	0.451
Baseline GCS score	−0.671	−0.203	−0.863 to −0.479	<0.001
Black hole sign	4.517	0.151	2.777–6.258	<0.001
Blend sign	6.969	0.231	5.240–8.699	<0.001
Satellite sign	1.924	0.086	0.612–3.236	0.004
Island sign	2.696	0.101	1.126–4.267	0.001

B, unstandardized coefficients; β, standardized coefficients; 95% CI, 95% confidence interval for B; CT, computed tomography; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage.

TABLE 3 | Multiple linear regression analysis of predictors of the extent of early hematoma expansion.

Predictors	*B*	*β*	95% CI	*P*-value
Sex, male	1.729	0.078	0.465–2.993	0.007
Systolic blood pressure	−0.023	−0.056	−0.046–0.001	0.047
Antiplatelet	−0.406	−0.005	−4.784–3.971	0.855
Anticoagulant	22.651	0.188	15.924–29.378	<0.001
Time from onset to first CT	−0.608	−0.083	−1.018 to −0.199	0.004
Time from the first to the follow-up CT	−0.067	−0.101	−0.105 to −0.023	0.001
Location of hemorrhage	−0.439	−0.035	−1.132–0.255	0.855
Baseline hematoma volume	−0.001	−0.001	−0.052–0.050	0.976
Baseline GCS score	−0.528	−0.162	−0.722 to −0.333	<0.001
Black hole sign	2.524	0.087	0.861–4.188	0.003
Blend sign	5.658	0.195	3.958–7.358	<0.001
Satellite sign	0.247	0.011	−1.325–1.819	0.758
Island sign	1.915	0.074	−0.022–3.852	0.053

Adjustment by sex, baseline volume, location of hemorrhage, time from onset to baseline CT, time from baseline CT to follow-up CT, systolic blood pressure, antiplatelet, anticoagulant, baseline GCS score.

B, unstandardized coefficients; β, standardized coefficients; 95% CI, 95% confidence interval for B; CT, computed tomography; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage.

volume is a significant predictor of HE, which is directly related to both the final hematoma volume and the clinical outcome (5, 26). In our study, the incidence of the BS and BHS was both positively correlated with baseline hematoma volume category. With an increase in the baseline hematoma growth category, the frequency of the BS and BHS increased from 2.8 to 29.9% and from 6.2 to 28.1%, respectively. The HE volume was divided into four groups, and we identified a positive correlation between the incidence of the BS and the HE volume category. Conversely, in the BHS-positive patients, there was a plateau in the frequency of BHS above the 5.1-ml hematoma growth volume category. We found that the presence of the BS may indicate a greater risk in the occurrence of the final hematoma volume. The BS represented ongoing, active bleeding in the hematoma (20, 27), and its low incidence in patients with a small baseline hematoma indicates a stable hematoma and lower risk of expansion. In contrast, a large baseline hematoma volume probably reflects multifocal bleeding sources within the hematoma.

In our study, we found that when the baseline hematoma volume was divided into four categories (<10, 10–20, 20–30, and >30 ml), a linear correlation was detected between the baseline hematoma volume and the BHS and BS. Furthermore, we demonstrated that larger initial hematoma volumes are more frequent for those with BHS and BS, and they are more likely to develop toward a larger hematoma volume. Median growth of the hematoma was significantly greater in patients with BHS and BS than in CT marker-negative patients; this supports the current hypotheses regarding the pathophysiology of sICH expansion (28–31). These CT markers were consistent features for larger hematomas and reflect the natural history of HE in sICH.

The clinical value of the BHS and BS in predicting HE and secondary neurological deterioration has been confirmed in multiple studies (32–37). The principle underlying the BHS and BS is that the hematoma is heterogeneous. However, it is necessary to improve the reliability of the heterogeneous hematoma in predicting HE. Barras et al. (28) found that heterogeneous density of a hematoma independently predicted HE, with growth occurring on a continuous scale. In a retrospective analysis (38), the BS and spot sign were highly predictive of poor functional outcomes. Furthermore, the multivariate analysis confirmed the BS as a reliable predictor of poor functional outcome in patients with sICH, after adjusting for several known risk factors. Notably, Yu et al. (34) obtained similar results in predicting HE. Similar to the BS, there was a close relationship between the CTA spot sign and the BHS. However, Sporns (36) demonstrated a high degree of association between the BS and spot sign ($\kappa = 0.701$) and a moderate degree of association between the BHS and spot sign ($\kappa = 0.424$). We hypothesize that these CT markers (the BHS and BS) are surrogates for a phenomenon similar to that mediating the spot sign and that that this represents ongoing, multifocal, active bleeding within the hematoma.

In our study, the BHS and BS exhibited favorable abilities to predict the EHE, with the BS performing slightly better than the BHS. We also directly compared the diagnostic performances of the BHS and BS and found that the AUC for the BS was

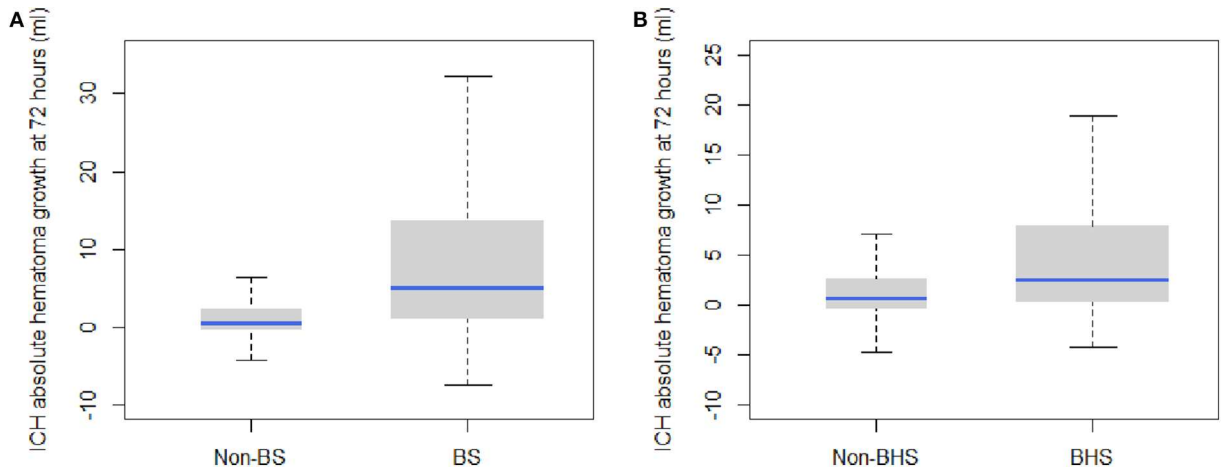

FIGURE 1 | Box plots of hematoma growth between the baseline and 72-h CT scans depict a greater hemorrhage volume growth in **(A)** the BS vs. non-BS scans ($P < 0.001$) and **(B)** the BHS vs. non-BHS scans ($P < 0.001$). BHS, black hole sign; BS, blend sign; CT, computed tomography.

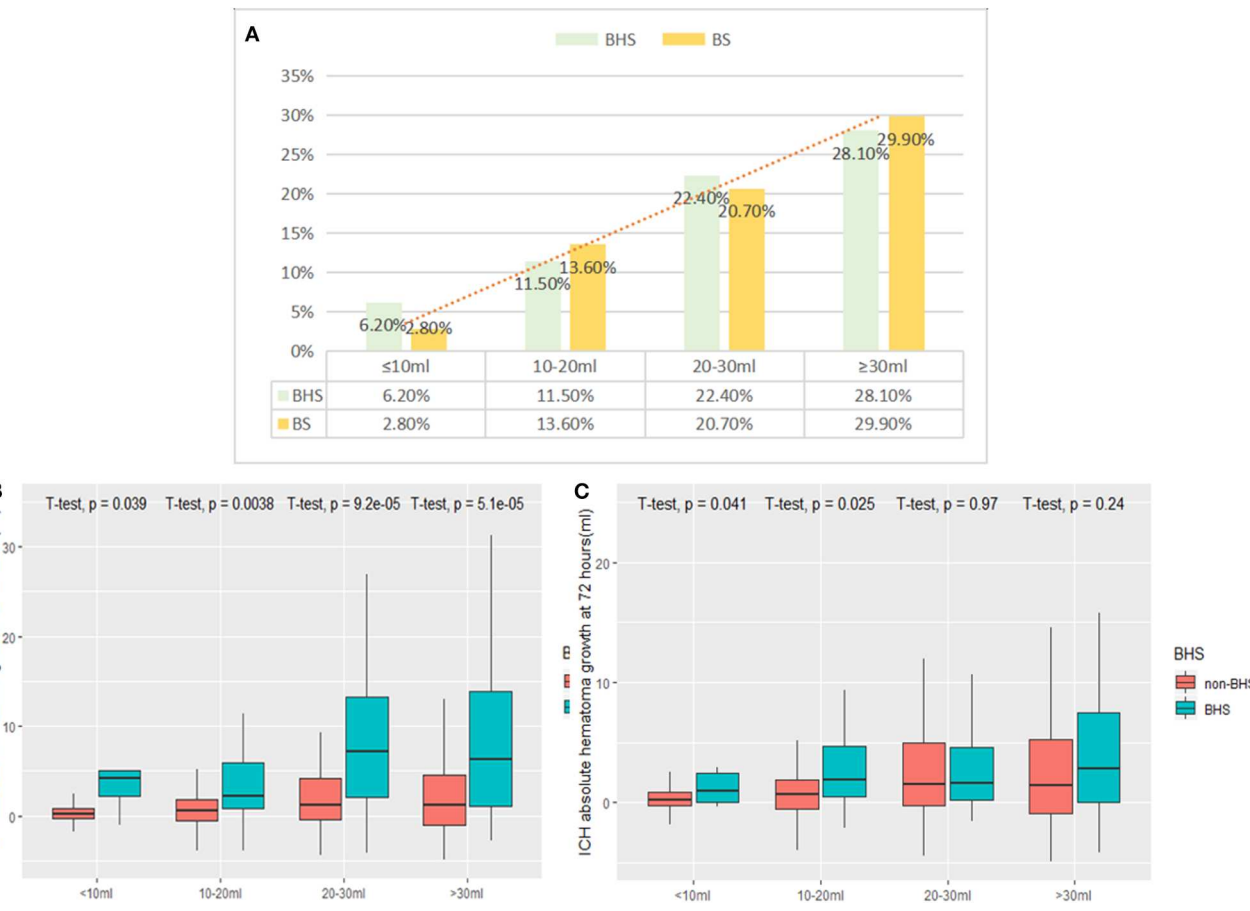

FIGURE 2 | (A) shows the frequency of the BS and BHS, stratified by baseline hematoma volume (both *P*s < 0.001). Differences between **(B)** the BS and non-BS and **(C)** the BHS and non-BHS scans are shown in the figure. BHS, black hole sign; BS, blend sign.

significantly higher than the AUC for the BHS in predicting HE. To explain these results, we compared hematoma growth between those with and without these CT markers, according to baseline hematoma volumes. Heterogeneous density on NCCT (39) and a larger baseline hematoma volume (26) may indicate active hemorrhage or multiple bleeding vessels, which lead to

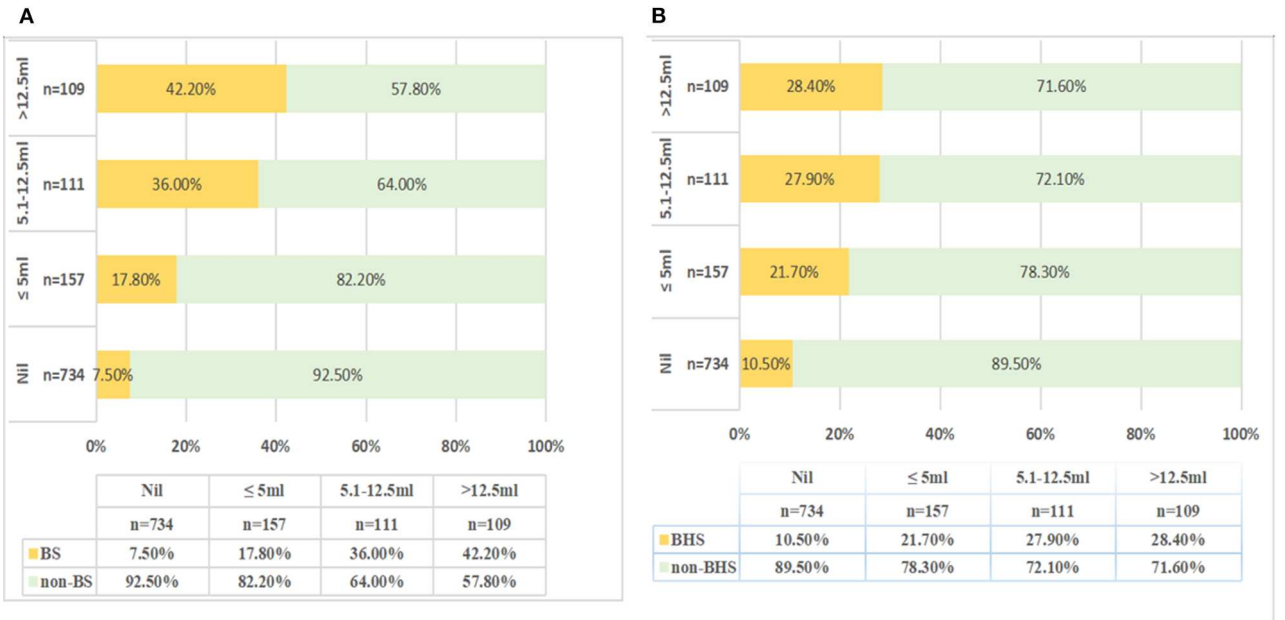

FIGURE 3 | The proportions (%) of the BS **(A)** and BHS **(B)** in the four groups stratifying the extent of hematoma growth. The *x*-axis refers to the percentage of the BS or BHS (%). $P < 0.001$. BHS, black hole sign; BS, blend sign; Nil, no growth.

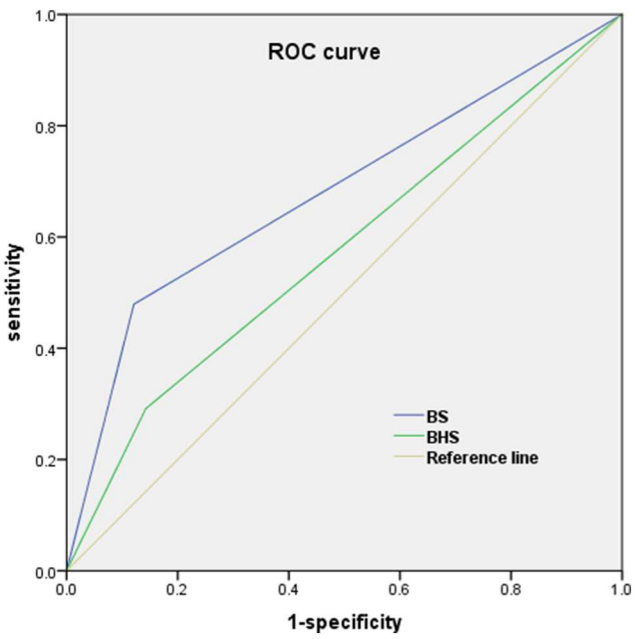

FIGURE 4 | The receiver operating characteristic (ROC) curve of the BS and BHS were used for predicting HE (>12.5 ml). The area under the curve for the BS was 0.67 and that for the BHS was 0.57. BHS, black hole sign; BS, blend sign.

an increased risk of the BS. The BS and BHS were found to be associated with a higher risk of postoperative rebleeding in sICH patients undergoing surgical intervention (33, 40, 41), and this also indirectly confirmed the underlying mechanisms of HE. Therefore, the presence of the BS combined with larger baseline hematoma volume could identify those patients most likely to benefit from anti-HE therapies.

HE was associated with poor functional outcome (4, 42), which can be influenced by therapy (43–45). However, it was unclear if the absolute growth led to poor outcomes in individuals. There is no universal consensus on a clinically meaningful definition of HE (11, 12, 46, 47). At present, >6 ml (48, 49) or >12.5 ml (9) absolute growth is the widely used definitions of HE. According to the method used by Youden, Dowlatshahi et al. (25) proposed the best cutoff value for absolute growth to be >3 ml in predicting poor outcome. Absolute hematoma growth was categorized into four groups on a continuous scale in the previous study, which, compared to the binary classification of HE, provided additional stratification by volume for the risk of poor outcome following HE.

In a previous study, Morotti et al. (50) established the BAT score (including the CT BS and time of baseline NCCT <2.5 h), which could predict HE and emphasized that the time from onset to NCCT <2.5 h was significantly correlated with HE. Ovesen et al. (51) indicated that the shorter the time from symptom onset to baseline CT, the higher the incidence of HE, especially in patients with a time to baseline CT of <3 h. A recent meta-analysis (2) found that the rate of decline was steepest 0.5–3 h after ICH symptom onset and that the median time from symptom onset to baseline CT scan was 2.2 (IQR 1.3–4.2). The proportion of patients with HE (defined as >6 ml) was 22%. Our study showed that time to baseline CT scan (median 3 h, IQR 2–4) was an independent predictor of EHE and that the incidence of HE (also defined as >6 ml) was 15.9% in patients with ICH. However,

TABLE 4 | Multivariate logistic regression analysis of predicting poor outcome.

Variable	Adjusted OR	95% CI	*P*-value
Sex, male	0.898	0.663–1.215	0.486
Age, year	1.016	1.004–1.029	0.009
Systolic blood pressure, mmHg	1.003	0.997–1.009	0.296
Time from onset to first CT, h	0.963	0.870–1.065	0.461
Time from the first to the follow-up CT, h	0.995	0.986–1.004	0.252
Location of hemorrhage			
Deep	1 [Reference]	1 [Reference]	1 [Reference]
Lobar	0.221	0.125–0.388	<0.001
Brain stem	0.108	0.048–0.240	<0.001
Cerebellum	0.340	0.143–0.809	0.015
Presence of IVH	1.191	0.867–1.635	0.281
Baseline hematoma volume, ml	1.044	1.029–1.059	<0.001
Baseline GCS score (≤8)	2.771	1.616–4.752	<0.001
Extent of hematoma expansion			
No growth (nil)	1 [Reference]	1 [Reference]	1 [Reference]
Minimal change (≤5 ml)	1.030	0.679–1.565	0.888
Moderate change (5.1–12.5 ml)	2.227	1.222–4.060	0.009
Massive change (>12.5 ml)	2.534	1.296–4.955	0.007

OR, odds ratios; 95% CI, 95% confidence interval; CT, computed tomography; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage.

some patients were at or beyond the time of greatest risk of HE in our cohort. A small number of patients who required early surgical intervention or abandonment of treatment were excluded. Moreover, patients with missing data were likely to have had more severe deficits or died early and might be considered to have a higher incidence of HE; therefore, excluding them contributed to underestimating the real performance. We recognized the potential for selection bias to influence our results. Therefore, we adjusted for these and other known confounding variables in the multivariate model.

Many patients with sICH are likely to have a poor outcome irrespective of the presence or absence of HE, and this is possibly due to the hematoma location, intraventricular extension, age, or large initial hematoma volume; none of these factors can be modified. There has been hope that poor outcomes and mortality related to high-volume hemorrhage could be ameliorated by interventions that aim to lower hemorrhage volume in patients with sICH. The results from the INTERACT1 study reaffirmed the importance of HE as a determinant of poor outcome and mortality. In our study, we found that an increase in the EHE was associated with an increase in the risk of a poor outcome. Conversely, smaller hematomas were less likely to produce poor outcomes, which is consistent with prior studies (8). Our study reinforces the association between EHE and clinical outcomes in patients with sICH. The most plausible explanation for these findings is that the absolute HE is directly proportional to the volume of the brain tissue destroyed. In addition, with the popularity of minimally invasive neurosurgical techniques, patients with a high risk of HE could receive more intensive neurological monitoring, and targeted surgical hematoma evacuation. Stratification of HE risk has important implications for the clinical care of patients with sICH.

Our study has several limitations. First, our study results were derived from a retrospective single-center analysis and lack data from formal orders for withdrawal of care, which require further validation. Second, the proportion of Chinese participants with deep ICH was higher than that among Western populations, which may limit the generalizability of our findings to other ethnic groups. Third, emergency CTA was not performed in all patients from our study population, which may have affected our results. Moreover, the presence of an underlying macrovascular abnormality was not detected at the time of the baseline NCCT. Thus, using the NCCT features to predict poor outcome and HE possibly influenced early treatment decisions. Fourth, given the retrospective design and in a study investigating emergencies, standardized therapeutic procedures were difficult to establish, and we were also not able to fully account for acute-phase therapies that may affect hematoma growth. Fifth, the exact timing of the follow-up CT was at the discretion of the clinical physician based on clinical judgment, patient preference, and treatment need, but we attempted to minimize this effect as much as possible by adjusting for the time of follow-up CT in the HE models. Finally, functional outcomes were assessed at discharge, which may not reflect the long-term outcomes for patients with sICH. Future studies using larger samples are needed to support our findings.

CONCLUSIONS

The CT BS showed a better performance in predicting the EHE in patients with sICH than did other NCCT markers. These markers may help identify patients at a high risk of HE and provide a potential target for anti-HE treatments for patients with acute sICH. Meanwhile, the lack of these markers may enable clinicians to identify patients at lower risk of HE being more suitable for admission to general neurology wards, especially in limited resource settings. Because patients without these markers appear to be relatively stable, anti-expansion treatment such as intensive blood pressure lowering or surgical intervention may offer little value.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will be made available on request to the corresponding author.

ETHICS STATEMENT

This study was performed in accordance with the recommendations of the Medical Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University. Written informed consent from all participation was waived. The protocol was approved by the Medical Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University.

AUTHOR CONTRIBUTIONS

YY and MZ contributed to the study conception and design. YY acquired the funding. MZ, JC, CZ, JL, CC, TZ, TX, and DZ collected the patients' data. CZ and MZ checked the data and performed statistical analyses. MZ drafted the article. YY and QC critically revised it. All authors reviewed the final manuscript and approved it to be submitted. We would like to thank Editage (www.editage.cn) for English language editing.

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REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the global burden of disease study 2010. *Lancet*. (2014) 383:245–54. doi: 10.1016/S0140-6736(13)61953-4
2. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. (2018) 17:885–94. doi: 10.1016/S1474-4422(18)30253-9
3. Yaghi S, Dibu J, Achi E, Patel A, Samant R, Hinduja A. Hematoma expansion in spontaneous intracerebral hemorrhage: predictors and outcome. *Int J Neurosci*. (2014) 124:890–3. doi: 10.3109/00207454.2014.887716
4. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. (2006) 66:1175–81. doi: 10.1212/01.wnl.0000208408.98482.99
5. Broderick JP, Brott TG, Duldner JE, Tomsick T. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. (1993) 24:987–93. doi: 10.1161/01.STR.24.7.987
6. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. (2001) 32:891–7. doi: 10.1161/01.STR.32.4.891
7. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med*. (2001) 344:1450–60. doi: 10.1056/NEJM200105103441907
8. Delcourt C, Huang Y, Arima H, Chalmers J, Davis SM, Heeley EL, et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology*. (2012) 79:314–9. doi: 10.1212/WNL.0b013e318260cbba
9. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke*. (2007) 38:1072–5. doi: 10.1161/01.STR.0000258078.35316.30
10. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke*. (2004) 35:1364–7. doi: 10.1161/01.STR.0000128795.38283.4b
11. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. (1998) 29:1160–6. doi: 10.1161/01.STR.29.6.1160
12. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. (1997) 28:2370–5. doi: 10.1161/01.STR.28.12.2370
13. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. *Cerebrovasc Dis*. (2013) 35:195–201. doi: 10.1159/000346599
14. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. (2007) 38:1257–62. doi: 10.1161/01.STR.0000259633.59404.f3
15. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. (2007) 68:889–94. doi: 10.1212/01.wnl.0000257087.22852.21
16. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol*. (2012) 11:307–14. doi: 10.1016/S1474-4422(12)70038-8
17. Heit JJ, Iv M, Wintermark M. Imaging of intracranial hemorrhage. *J Stroke*. (2017) 19:11–27. doi: 10.5853/jos.2016.00563
18. Caplan LR. Recognizing and preventing intracerebral hematoma expansion. *JAMA Neurol*. (2016) 73:914–5. doi: 10.1001/jamaneurol.2016.1899
19. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. *Stroke*. (2017) 48:1120–5. doi: 10.1161/STROKEAHA.116.015062
20. Li Q, Zhang G, Huang YJ, Dong MX, Lv FJ, Wei X, et al. Blend sign on computed tomography: novel and reliable predictor for early hematoma growth in patients with intracerebral hemorrhage. *Stroke*. (2015) 46:2119–23. doi: 10.1161/STROKEAHA.115.009185
21. Li Q, Zhang G, Xiong X, Wang XC, Yang WS, Li KW, et al. Black hole sign: novel imaging marker that predicts hematoma growth in patients with intracerebral hemorrhage. *Stroke*. (2016) 47:1777–81. doi: 10.1161/STROKEAHA.116.013186
22. Shimoda Y, Ohtomo S, Arai H, Okada K, Tominaga T. Satellite sign: a poor outcome predictor in intracerebral hemorrhage. *Cerebrovasc Dis*. (2017) 44:105–12. doi: 10.1159/000477179
23. Li Q, Liu QJ, Yang WS, Wang XC, Zhao LB, Xiong X, et al. Island sign: an imaging predictor for early hematoma expansion and poor outcome in patients with intracerebral hemorrhage. *Stroke*. (2017) 48:3019–25. doi: 10.1161/STROKEAHA.117.017985
24. Gerner ST, Kuramatsu JB, Moeller S, Huber A, Lucking H, Kloska SP, et al. Specific lobar affection reveals a rostrocaudal gradient in functional outcome in spontaneous intracerebral hemorrhage. *Stroke*. (2017) 48:587–95. doi: 10.1161/STROKEAHA.116.015890
25. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. (2011) 76:1238–44. doi: 10.1212/WNL.0b013e3182143317
26. Dowlatshahi D, Smith EE, Flaherty ML, Ali M, Lyden P, Demchuk AM, et al. Small intracerebral haemorrhages are associated with less haematoma expansion and better outcomes. *Int J Stroke*. (2011) 6:201–6. doi: 10.1111/j.1747-4949.2010.00563.x
27. Lei C, Geng J, Chen C, Chang X. Accuracy of the blend sign on computed tomography as a predictor of hematoma growth after spontaneous intracerebral hemorrhage: a systematic review. *J Stroke Cerebrovasc Dis*. (2018) 27:1705–10. doi: 10.1016/j.jstrokecerebrovasdis.2018.01.032
28. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke*. (2009) 40:1325–31. doi: 10.1161/STROKEAHA.108.536888
29. Greenberg CH, Frosch MP, Goldstein JN, Rosand J, Greenberg SM. Modeling intracerebral hemorrhage growth and response to anticoagulation. *PLoS ONE*. (2012) 7:e48458. doi: 10.1371/journal.pone.0048458
30. Flaherty ML, Haverbusch M, Sekar P, Kissela B, Kleindorfer D, Moomaw CJ, et al. Long-term mortality after intracerebral hemorrhage. *Neurology*. (2006) 66:1182–6. doi: 10.1212/01.wnl.0000208400.08722.7c

31. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol*. (1971) 30:536–50. doi: 10.1097/00005072-197107000-00015
32. Morotti A, Boulouis G, Romero JM, Brouwers HB, Jessel MJ, Vashkevich A, et al. Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. *Neurology*. (2017) 89:548–54. doi: 10.1212/WNL.0000000000004210
33. Wu G, Shen Z, Wang L, Sun S, Luo J, Mao Y. Post-operative re-bleeding in patients with hypertensive ICH is closely associated with the CT blend sign. *BMC Neurol*. (2017) 17:131. doi: 10.1186/s12883-017-0910-6
34. Yu Z, Zheng J, Ma L, Guo R, Li M, Wang X, et al. The predictive accuracy of the black hole sign and the spot sign for hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Neurol Sci*. (2017) 38:1591–7. doi: 10.1007/s10072-017-3006-6
35. Zheng J, Yu Z, Xu Z, Li M, Wang X, Lin S, et al. The accuracy of the spot sign and the blend sign for predicting hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Med Sci Monit*. (2017) 23:2250–7. doi: 10.12659/MSM.901583
36. Sporns PB, Schwake M, Kemmling A, Minnerup J, Schwindt W, Niederstadt T, et al. Comparison of spot sign, blend sign and black hole sign for outcome prediction in patients with intracerebral hemorrhage. *J Stroke*. (2017) 19:333–9. doi: 10.5853/jos.2016.02061
37. Li Q, Yang WS, Wang XC, Cao D, Zhu D, Lv FJ, et al. Blend sign predicts poor outcome in patients with intracerebral hemorrhage. *PLoS ONE*. (2017) 12:e0183082. doi: 10.1371/journal.pone.0183082
38. Sporns PB, Schwake M, Schmidt R, Kemmling A, Minnerup J, Schwindt W, et al. Computed tomographic blend sign is associated with computed tomographic angiography spot sign and predicts secondary neurological deterioration after intracerebral hemorrhage. *Stroke*. (2017) 48:131–5. doi: 10.1161/STROKEAHA.116.014068
39. Chen S, Zhao B, Wang W, Shi L, Reis C, Zhang J. Predictors of hematoma expansion predictors after intracerebral hemorrhage. *Oncotarget*. (2017) 8:89348–63. doi: 10.18632/oncotarget.19366
40. Yagi K, Tao Y, Hara K, Hirai S, Takai H, Kinoshita K, et al. Does noncontrast computed tomography scan predict rebleeding after endoscopic surgery for spontaneous intracerebral hemorrhage? *World Neurosurg*. (2019) 127:e965–71. doi: 10.1016/j.wneu.2019.04.010
41. Shen Z, Wang L, Wu G, Li Q, Ren S, Mao Y. Computed tomographic black hole sign predicts postoperative rehemorrhage in patients with spontaneous intracranial hemorrhage following stereotactic minimally invasive surgery. *World Neurosurg*. (2018) 120:e153–60. doi: 10.1016/j.wneu.2018.07.256
42. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology*. (2004) 63:461–7. doi: 10.1212/01.WNL.0000133204.81153.AC
43. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. (2008) 358:2127–37. doi: 10.1056/NEJMoa0707534
44. Mayer SA, Brun NC, Broderick J, Davis SM, Diringer MN, Skolnick BE, et al. Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care*. (2006) 4:206–14. doi: 10.1385/NCC:4:3:206
45. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. (2008) 7:391–9. doi: 10.1016/S1474-4422(08)70069-3
46. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. (1996) 27:1783–7. doi: 10.1161/01.STR.27.10.1783
47. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. (1997) 28:1–5. doi: 10.1161/01.STR.28.1.1
48. Thompson AL, Kosior JC, Gladstone DJ, Hopyan JJ, Symons SP, Romero F, et al. Defining the CT angiography 'spot sign' in primary intracerebral hemorrhage. *Can J Neurol Sci*. (2009) 36:456–61. doi: 10.1017/S0317167100007782
49. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, et al. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. *Stroke*. (2009) 40:2994–3000. doi: 10.1161/STROKEAHA.109.554667
50. Morotti A, Dowlatshahi D, Boulouis G, Al-Ajlan F, Demchuk AM, Aviv RI, et al. Predicting intracerebral hemorrhage expansion with noncontrast computed tomography: the BAT score. *Stroke*. (2018) 49:1163–9. doi: 10.1161/STROKEAHA.117.020138
51. Ovesen C, Christensen AF, Krieger DW, Rosenbaum S, Havsteen I, Christensen H. Time course of early postadmission hematoma expansion in spontaneous intracerebral hemorrhage. *Stroke*. (2014) 45:994–9. doi: 10.1161/STROKEAHA.113.003608

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Deciding Thrombolysis in AIS Based on Automated versus on WhatsApp Interpreted ASPECTS, a Reliability and Cost-Effectiveness Analysis in Developing System of Care

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Background: Automated ASPECTS has the potential of reducing interobserver variability in the determination of early ischemic changes. We aimed to assess the performance of an automated ASPECTS vs. ASPECTS interpreted for sent CT images on WhatsApp and to correlate these results with the outcome.

Materials and Methods: Patients with anterior circulation stroke who had baseline NCCT and underwent successful IV-thrombolysis were included. NCCT-ASPECTS was assessed by two neuroradiologists, and discrepancies were resolved by agreement. Two groups of patients were included; group 1, where treatment was decided after an automated ASPECTS interpretation that was provided by RAPID software, and group 2, where patients received IV-tPA after an assessment of CT images sent on WhatsApp.

Results: A total of 122 patients were included: 36 in group 1 and 86 in group 2. In group 2, the interobserver agreement for NCCT ASPECTS was moderate ($\kappa = 0.36$), as was the dichotomized data ($\kappa = 0.44$). IOA, however, improved (to $\kappa = 0.57$ and $\kappa = 0.64$) when the same CT images were interpreted on a workstation. In group 1, Automated ASPECTS showed excellent agreement ($\kappa = 0.80$) with agreement reads for workstation images. There were significantly ($P < 0.001$) increased odds of functional independence and fewer hemorrhagic complications with thrombolyzed patients in group 1.

Conclusions: Automated ASPECTS provided by the RAPID@IschemaView ASPECTS performs at a level equal to the agreement read of expert neuroradiologists, and this performance was severely degraded when WhatsApp captured CT images used for ASPECTS assessment. In our study, we found that automated ASPECTS might predict outcomes after IV thrombolysis.

Keywords: acute ischemic stroke, thrombolysis, automated ASPECTS, mRS, reliability, cost-effectiveness analysis

INTRODUCTION

ASPECTS was introduced in the year 2000 to assess the early ischemic changes in CT scans. It is a 10-point scoring system, with one point deducted for signs of early ischemic change in each defined region of the MCA territory (1).

CT-ASPECTS has been shown to predict the functional outcome and symptomatic intracranial hemorrhage after thrombolytic treatment (1, 2).

Consequently, the ASPECTS assessment has been increasingly incorporated into treatment decision making and has been used in several randomized clinical trials for endovascular treatment decision making (3, 4).

The major drawback of the ASPECTS evaluation is its modest interobserver agreement (IOA) and reproducibility. Early ischemic changes are often difficult to detect on NCCT, with low interobserver agreement for presence and extent (5–7).

Transmitting CT scans as instant messages captured and sent using smartphones has been shown to be highly reliable in neurosurgical emergencies (8).

Although scientific studies on the use of WhatsApp Messenger remain scarce in medical literature, increasing numbers of health professionals have adopted it as a communication interface and for the exchange of multimedia (9, 10). A debate is currently ongoing on the subject of its effect on transmitted image quality in the conversion from analog to digital formats to the degree of whether it is able to identify sufficient detail for an adequate diagnosis and initial treatment with better efficacy than other modalities used for the same purposes (11).

In acute ischemic stroke settings, both time and detail are imperative to confounding the incorporated role of ASPECTS in treatment decision-making process.

To our knowledge, this is the first study to evaluate the reliability of interpreting ASPECTS from three settings—source images, captured images on WhatsApp, and automated ASPECTS obtained from a software-based analysis (RAPID ASPECTS®) by iSchemaView (Menlo Park, USA www.ischemaview.com)—and to show the possible impact on the outcome after thrombolysis.

MATERIALS AND METHODS

Patient Selection

This study was approved by the local institutional review board (Alexandria University System, Alexandria). We retrospectively reviewed consecutive patients with AIS who presented to the primary stroke unit, which is one our institution-affiliated facilities for stroke care in the Alexandria stroke network (www.egyptianstroke.net). Between January 2018 and December 2019, 176 AIS patients who met the following inclusion criteria received IV-tPA: (1) time from symptom onset <4.5 h; (2) anterior circulation ischemic stroke; (3) baseline NCCT; (4) no contraindication for IV-tPA; and (5) ASPECT score $\geq$ 6 (ischemic changes $\leq$ 1/3 of MCA territory). There were several exclusion criteria: (1) intracranial hemorrhage; (2) pre-existing cerebral defects within the probable current ischemic area that could not reliably be distinguished from acute ischemic changes; and (3) severe motion or other artifacts impeding CT interpretation. To expedite stroke workflow, the thrombolysis decision is remotely taken by a stroke consultant through a closed WhatsApp group where clinical and laboratory data of the patients as well as NCCT images are uploaded by a stroke residency where interpretation of NCCT is carried out on the WhatsApp group by the neuroradiologist on duty. Other stroke neurologists, neurosurgeons, and ICU physicians all are within the same chat group and are notified by the decision. As of 2019, RAPID software (a computer-based automated scoring to assess early signs of brain ischemia) has been deployed in our institution to help develop a faster and more accurate stroke workflow as a part of developing the stroke service to include all reperfusion therapies for AIS. During our study period, we could identify two groups of patients: group 1 consisted of 36 AIS patients receiving the IV-tPA based on the automated ASPECTS processed by the RAPID system, while group 2 consisted of 86 AIS patients receiving treatment based on the decision made using the NCCT images sent via the WhatsApp group.

All clinical data for both groups of patients included the patients' age, sex, baseline NIHSS scores, the time from stroke onset/last well-known, door to need time, time from CT to needle, data on receiving intravenous tissue plasminogen activator, and 90-day mRS when available. mRS scores <3 were used to indicating a functional independence outcome.

Image Acquisition

CT image acquisition was performed using a Brilliance 64-slice CT scanner (Philips Healthcare, Netherland). Helical NCCT (120 kV, 100–350 auto-mA) was performed using a 5-mm section thickness from the foramen magnum through the vertex.

WhatsApp Data Transmission

Clear regulations and standardization of medical data sharing are lacking, and the use of Whatsapp(TM) remains a "gray area." We tried to reduce variation in the image quality transmitted via WhatsApp, where all transferred NECT images were captured by one universal smartphone—the "resident's phone" (Iphone 8 plus; 8MP camera). The transmitted images were either made up of a full range of series with customized slice thickness (1mm) generated by CT workstation software for printing or a video clip spanning the entire CT study. However, other factors, such as the "camera view angle" and "image light intensity," that could affect image quality could not be avoided in this study, and this might downgrade the efficiency of the WhatsApp method for transmitting CT images when deciding on AIS treatment compared to a decision based on transferred automated dicom files through dedicated software.

On the other hand, in WhatsApp-transmitted images, trying to reduce concerns regarding the identification of patients from non-anonymized shared data was considered in the current study where all data were transmitted to a closed group on WhatsApp that included only physicians who are involved in the treatment workflow of the patient. However, other privacy concerns could

Abbreviations: AIS, acute ischemic stroke; IQR, interquartile range; IV-tPA, Intravenous tissue plasminogen activator.

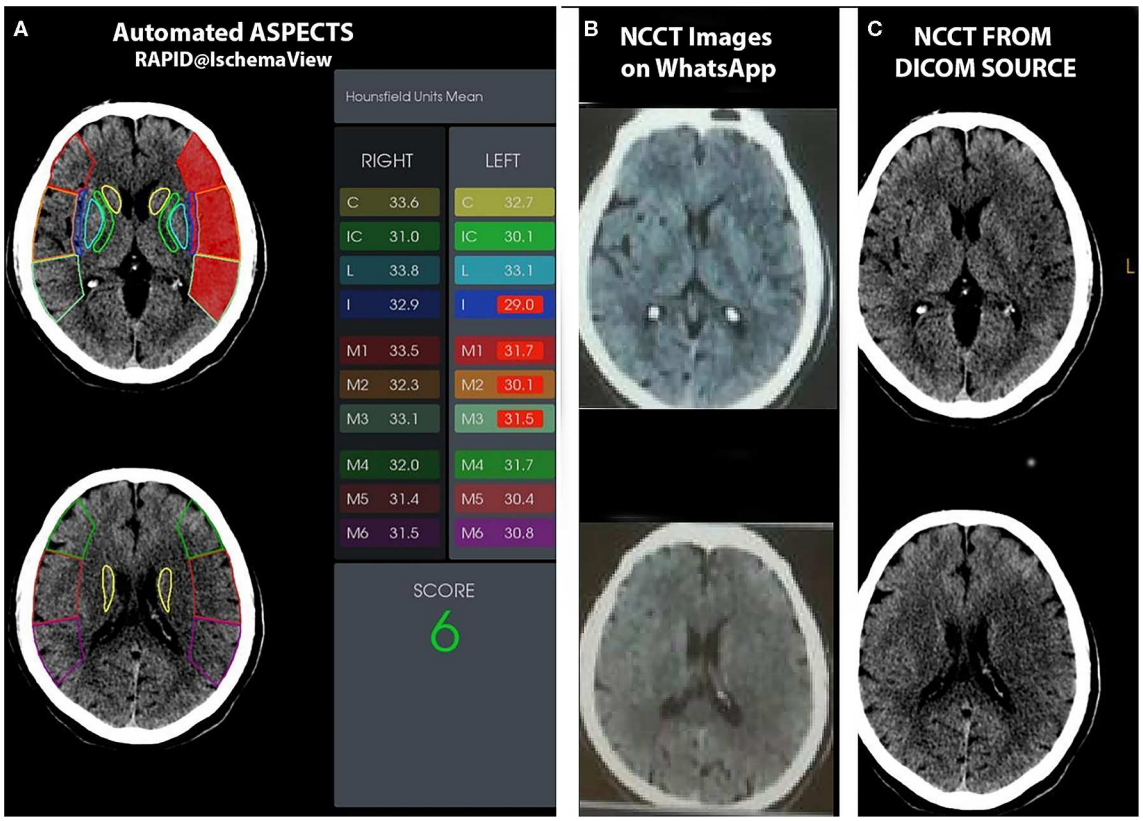

FIGURE 1 | A 70-year-old man who presented with right hemiparesis, dysphasia with right UMN facial weakness, and an NIHSS score of 16. He underwent IV thrombolysis with a door to needle time of 40 min. Automated ASPECTS **(A)**, Axial NCCT images uploaded to the WhatsApp group **(B)**, and axial NCCT images processed by NR on workstation **(C)** are shown. For the two human readers, one scored 6 and the other 7 (agreement ASPECTS, 6). **(B)** Automated software assigned an ASPECTS of 6.

not be avoided, such as the fact that images sent through the app will be immediately downloaded into the recipient's smartphone photo library unless that setting is manually switched off. All messages are stored on a server in the US, which means they are not compliant with UK data protection legislation and the General Data Protection Regulation (GDPR). We did not anonymize the process of transmitting the images for the sake of the time factor, which is crucial in AIS treatment.

Image Analysis (Figure 2)

Two neuroradiologists years with more than 10 years' experience independently reviewed all baseline NCCTs and assigned an ASPECTS using a 10-point scale (1). Discrepancies between two readers were resolved using an agreement read in a separate reading session.

In addition, an automated software-based analysis RAPID ASPECTS® by iSchemaView (Menlo Park, USA). Axial isotropic sequences from the NCCT for each patient were uploaded to the software, and the automated ASPECTS was calculated without human interaction.

For both group of patients, the neuroradiologists and automated ASPECTS were then exported to an IBM SPSS software V23 spreadsheet (IBM corporation; Giza, Egypt) for analysis.

Finally, we used a cost-effectiveness analysis to compare the use of the automated ASPECTS interpretation (RAPID ischemaView) and the traditional ASPECTS interpretation of the sent NCCT images on the WhatsApp group.

A CEA decision tree model was created by TreeAge Pro 2019 (TreeAge Software, inc.) to evaluate the cost-utility analysis for both traditional and automated interpretation of ASPECTS CT., where we assumed that 90 days of follow-up could be one of the three possibilities, using mRS to reflect clinical outcome after IV-tPA: either 1-functional independence; 0–2 mRS; 2- functional dependence; 3–5 mRS; or 6 mRS - death. For cost utility, we refer you to **Table 1**.

Statistical Analysis

Clinical and demographic data were presented as mean (SD) or median (interquartile range) as appropriate. ASPECTS values were presented as median (interquartile range). Comparison of ASPECTS was performed using both the raw/original scores and dichotomized ASPECTS using ≥ 6 and <6 as a cutoff. The interobserver agreement between two neuroradiologists was performed using a weighted κ test with a calculation of the 95% CI. Agreement and correlation among neuroradiologist agreement reads and automated ASPECTS were performed using the intraclass correlation coefficient with 95% CI.

TABLE 1 | Characteristics of 122 patients who received IV-tPA in both groups.

	WhatsApp ($n = 86$) group 2	RAPIDsoftware ($n = 36$) group 1	*P*
Age (Mean)	58.2 ± 9.4	60.9 ± 10.5	0.172
Door to needle (min)	52.3 ± 16.0	36.8 ± 11.8	0.001
Male	46 (53.4%)	13 (36.3%)	0.080
HTN	36 (41.9%)	20 (55.6%)	0.166
DM	32 (37.2%)	12 (33.3%)	0.684
Smoker	11(12.8%)	9 (25%)	0.097
Dyslipidemia	9 (10.5%)	4 (11.1%)	0.916
AF/arrythmias	14 (16.3%)	9 (25%)	0.261
IHD	30 (34.9%)	12 (33.3%)	0.869
Hgic transformation	18 (2 0.9%)	2 (5.6%)	0.036
Dyas90mRS (0–3)	35 (40.7%)	23 (63.9%)	0.030
Dichotomized ASPECTS ≥6	34 (94.4%)	75 (87.2%)	0.3

Clinical and imaging variables and functional outcome (using a 90-day mRS >2 as a cutoff) were compared between both groups using a combination of *t*-tests and χ^2 tests as appropriate.

RESULTS

Demographic and Clinical Data

A total of 122 patients were included (59 men, 63 women; mean age, 59 ± 9.8 years). The mean of the door to needle time was 47.8 ± 16.5 min. The median and interquartile range (IQR) of the NIHSS were 11 and 8–14. Stroke etiology was cardioembolic in 27.9% of cases. A total of 58/122 patients (47.5%) achieved mRS <3 at 90-days follow-up. The median and (IQR) of the final agreement ASPECTS (inferred from source Dicom images) were 8 and 6–9.

Table 1 shows the basic characteristics of AIS patients in both groups of patients. A higher rate of hemorrhagic complications was seen in thrombolysis decided based on the NCCT shared on WhatsApp (20 vs. 5.5%, $P = 0.036$). By dichotomizing the 90-day outcome by using mRS < 3 as a cutoff value, indicating functional independence, a higher incidence of getting functional independence was observed in thrombolysis based on automated ASPECTS CT interpretation (40.7 vs. 63.9%, $P = 0.022$). Additionally, a 14-min reduction in the DTN time was observed in the group of AIS patients with automated ASPECTS interpretation (median of 50 and 36 min in group 1 and group 2, respectively).

Human Interpretation

In group 2, where the NCCT was delivered via WhatsApp ($n = 86$), an NCCT file that was uploaded to the WhatsApp group was read by two neuroradiologists to interpret the ASPECTS. Similarly, both were involved blindly (without knowing localizing information) to rate the ASPECTS of the NCCT dicom source images on the workstation for each patient.

The median for ASPECTS rated from CT images sent on WhatsApp was 7 (IQR, 6–7) for reader 1 and 7 (IQR, 6–8) for reader 2. The interobserver agreement was fair with $\kappa = 0.36$ (95% CI, 0.02–0.58). For the dichotomized ASPECTS (ASPECTS ≥6 or <6), the interobserver agreement was improved to $\kappa = 0.44$ (95% CI, 0.14–0.64).

When readers were involved in interpreting ASPECTS from the source of the images on the workstation for the same patients, the median for ASPECTS was 7 (IQR, 5–7) for reader 1 and 7 (IQR, 6–8) for reader 2, and the IOA was improved to moderate with $\kappa = 0.57$ (95% CI, 0.33–0.72). Similarly, for the dichotomized ASPECTS (ASPECTS ≥6 or <6), IOA was improved with $\kappa = 0.69$ (95% CI, 0.51–0.79). In the dichotomized agreement read, a total of 75 patients had ASPECTS ≥6 and 11 patients had ASPECTS <6.

Automated ASPECTS of NCCT

In group 2, where 36 patients received IV-tPA based on automated ASPECTS generated by RAPID@ IschemaView software, the median was 7 (IQR, 6–8) for automated ASPECTS. The source Dicom images were blindly evaluated by both readers in an agreement session in which, for the final agreement read, the median for ASPECTS was 7 (IQR, 7–9).

By dichotomizing Automated ASPECTS, a total of 35 patients had eASPECTS ≥6, while 1 had eASPECTS <6.

Comparing the ASPECTS values, which were interpreted automatically by RAPID@ IschemaView software and humanly from source workstation images for the same patients (human agreement reads), we saw excellent agreement ($\kappa = 0.80$; 95% CI, 0.60–0.90) for the dichotomized scores. In only one patient, the software underestimated the extent of early ischemic changes by providing an automated ASPECTS >6, while the score was <6 by agreement read.

Cost Effectiveness Analysis (Figure 2)

The rate-adjusted total costs of the treatment decision based on automated interpretation and WhatsApp are summarized and extrapolated from our hospital cost (IV-tPA, cost of RAPID@IschemaView software, other stroke treatment and investigation, prolonged stay from complications, and death) in the **Table 1**.

The use of WhatsApp to assess the ASPECTS had a total mean per patient cost of LE 16,126.48, and 0.37 QALYs, while automated ASPECTS had a total mean per patient cost of LE 12,646.48, and 0.73 QALYs. The incremental cost of WhatsApp supported ASPECTS interpretation over automated ASPECTS interpretation was LE 3,480.00. The estimated ICER for RAPID assessment vs. WhatsApp assessment of treatment decision was LE 9,738.35.

DISCUSSION

If regions of hypodensity encompass more than one-third of the affected cerebral hemisphere, IV thrombolysis is contraindicated and should not be administered (12). A *post-hoc* analysis of the European Cooperative Acute Stroke Study (ECASS) suggested that the extent of hypoattenuation on head CT was a predictor of response to thrombolysis and the risk of hemorrhagic transformation (13).

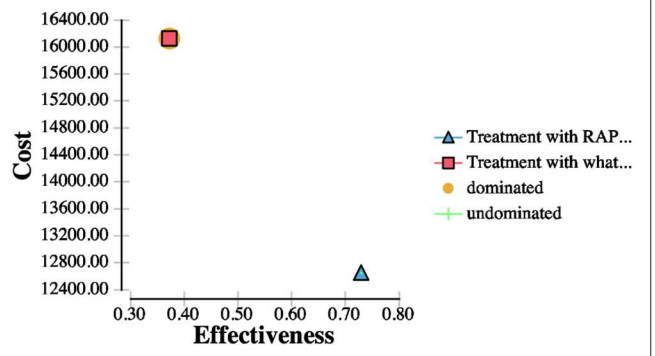

FIGURE 2 | This figure demonstrates a CEA analysis curve for thrombolysis based on automated ASPECTS vs. ASPECTS interpretation on WhatsApp.

In early NNCT of AIS, judging the extent and degree of ischemia compared to infarction is not always straightforward. Even among experienced neuroradiologists and neurologists, the interrater agreement to determine whether ischemia affects less than or greater than one-third of the middle cerebral artery (MCA) territory is only moderate (κ.4) (14).

This draws attention to the effect of a quantitative approach in judging the extent of ischemia, and this includes the use of ASPECTS and the possibility for it to be integrated into the decision-making process for reperfusion therapy in patients with AIS, similarly to its use in deciding MT in LVO stroke guidelines (15). The current study reaffirmed the concern of interobserver variability for ASPECTS assessment by showing only fair interobserver agreement (κ = 0.57), even for experienced neuroradiologists. This was attributed to factors such as physician training and experience, time pressure, personal bias of expected findings (for example, from the ordering or treatment teams), and other factors that have been noted as potential reasons for the variability of ASPECTS (16–18). In the current study, this agreement severely dropped (κ = 0.36) when the assessment was for images sent on WhatsApp; this may be explained by the shortcomings of the image quality, which could affect the interpretation ability of that images. Marginal improvement in interobserver agreement (κ = 0.69) has been shown in our study when dichotomized ASPECTS (≥6 or <6) was used in agreement with other studies (19, 20). This Human variability in ASPECTS assessment could be the reason behind the contradiction between studies in linking ASPECTS assessment to predicting the clinical outcome (21, 22). In current studies excluding large core ischemia (hypoattenuation in >1/3 of MCA territory quantitatively equal to ASEPCTS <6), receiving IV-thrombolysis increased odds of functional independence and decreased odds of hemorrhagic complications in the more reliably selected patients based on automated ASPECTS interpretation of the early CT, which is similar to results of a study by Pfaff et al. (21). This improvement in reliability through the use of automated software has been shown in different studies, and the success of such software was achieved by addressing variability associated with human interpretation through software packages trained on deep learning algorithms (18, 21, 23–26). As shown by Maegerlein et al. (18), in the current study, there was excellent agreement (κ = 0.80) between dichotomized ASPECTS interpreted by RAPID and in the agreement reading of ASPECTS from source images on a workstation. The assessment of captured CT images on smartphones has several disadvantages that might hamper accurate interpretation of them. The quality of capturing files from a workstation onto a smartphone might be unfavorably affected by screen reflection from the workstation's monitor, lack of image stabilization, and the occasional loss of focus. Compared with a workstation, a smartphone has a smaller screen size, and image quality and resolution are obviously inferior. Standard, commonly used features available on a PACS for evaluating a CT image, such as manipulating the image by zooming in and out and changing the window level between soft tissue and bone, are not available when viewing a captured CT images on a smartphone. A CT image shown on a PACS can be readily scrolled through. Scrolling through captured CT images on a smartphone, while possible, is cumbersome compared with scrolling on a PACS. This may explain the discrepancy between neuroradiologists when they interpreted the ASPECTS value from source images on a workstation and from captured and sent images on WhatsApp. Consequently it is plausible to use automated ASPECTS to standardize NCCT interpretation in the acute setting, avoiding variability associated with individual human interpretation and ensuring that all patients receive equivalent care and are triaged with appropriate treatment options like in other studies (27).

In 2020, over 2 billion WhatsApp [a freeware, cross-platform messaging, and Voiceover IP (VoIP) service] users were reported worldwide. It has become the primary means of instant messaging in clinical and non-clinical settings in many countries and specialties. Its frequent use in stroke workflow could be due to its live-chat feature, i.e., instantaneous communication with all stroke team with transmitting and sharing a patient's CT images and clinical data with a real-time notification service. Remote viewing images on smartphones and tablets with specialized applications have been shown to be effective for rapidly visualizing radiologic images and for urgent decision making with regards to patient care in different domains of medicine (28, 29). The US Food and Drug Administration (FDA) has given multiple indications to the RAPID@IschemaView neuroimaging platform for the use of selecting stroke patients most likely to benefit from endovascular thrombectomy (30). However, these applications may appear to be costly and cumbersome because they require a prearranged setup, such as cloud computing or a visualization server at the source, and the installation and registration of the application at the receiving ends' smartphone. In the current study, a cost-effective analysis showed the use of rapid software with high reliability in screening patients presenting with acute stroke to determine eligibility for alteplase treatment is cost effective and warrants consideration as an alternative to routine practice compared to that using WhatsApp, which is a cheaper way of communication but is not cost effective and conducive to better healthcare. Like in several reports that support a favorable association between higher ASPECTS and good functional outcome (31, 32), we showed the use of an

automated ASPECTS group [in group 1: median 7 (IQR, 6–8)] to exclude those patients with hypoattenuation in >1/3 of MCA territory (which quantitatively equal to ASEPCTS <6) was predictive of functional outcome. In the current study, there was no statistical difference between both groups of patients with regards to dichotomized ASPECTS score (ASPECTS ≥ 6/<6) in the agreement session (with improved k), neither with regards to initial median NIHSS or the basic clinical data, which make this discrepancy in outcome might ought to the higher reliability of automated ASPECTS (by RAPID@IschemaVeiw, used in current study) in interpreting ASPECTS for thrombolysis decision. That results which could not be affirmed in others studies were dated before the era of automated ASPECTS to include patients for thrombolysis (16, 33). There are several limitations to our study. The sample size was relatively small, and further validation studies with larger sample sizes are required to validate the practical application of our automated software as a stand-alone tool in the triage of patients with AIS for thrombolysis. A retrospective design can introduce unknown bias. Another issue is that no standardization was required for the quality of images captured for CT and shared on WhatsApp, but this could be of value to the current study to document the traditional style of communicating AIS workflow through a WhatsApp chat.

CONCLUSION

We showed that interpretation of automated ASPECTS by the RAPID@IschemaView ASPECTS software package performs equally well with the agreement read of expert neuroradiologists, and this performance was severely degraded when WhatsApp captured CT images used for ASPECTS assessment. In our study, we showed that automated ASPECTS might predict outcomes following IV thrombolysis.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to yassinossama@yahoo.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Alexandria University Ethical Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed equally to drafting the work and revising it critically for important intellectual content. OM has substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work, and contributed to drafting the work, revising it critically for important intellectual content. Final approval of the version to be published.

REFERENCES

1. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS study group. Alberta stroke programme early CT score. *Lancet*. (2000) 355:1670–4. doi: 10.1016/S0140-6736(00)02237-6
2. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study I. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for stroke effectiveness study. *CMAJ*. (2005) 172:1307–12. doi: 10.1503/cmaj.1041561
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
4. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061
5. Finlayson O, John V, Yeung R, Dowlatshahi D, Howard P, Zhang L, et al. Interobserver agreement of ASPECT score distribution for noncontrast CT, CT angiography, and CT perfusion in acute stroke. *Stroke*. (2013) 44:234–6. doi: 10.1161/STROKEAHA.112.665208
6. Mak HK, Yau KK, Khong PL, Ching AS, Cheng PW, Au-Yeung PK, et al. Hypodensity of >1/3 middle cerebral artery territory versus Alberta Stroke Programme Early CT Score (ASPECTS): comparison of two methods of quantitative evaluation of early CT changes in hyperacute ischemic stroke in the community setting. *Stroke*. (2003) 34:1194–6. doi: 10.1161/01.STR.0000069162.64966.71
7. Wardlaw JM, Dorman PJ, Lewis SC, Sandercock PA. Can stroke physicians and neuroradiologists identify signs of early cerebral infarction on CT? *J Neurol Neurosurg Psychiatry*. (1999) 67:651–3. doi: 10.1136/jnnp.67.5.651
8. Waran V, Bahuri NF, Narayanan V, Ganesan D, Kadir KA. Video clip transfer of radiological images using a mobile telephone in emergency neurosurgical consultations (3G multi-media messaging service). *Br J Neurosurg*. (2012) 26:199–201. doi: 10.3109/02688697.2011.605482
9. Graziano F, Maugeri R, Iacopino DG. Telemedicine versus whatsApp: from tradition to evolution. *Neuroreport*. (2015) 26:602–3. doi: 10.1097/WNR.0000000000000393
10. Thota RS, Divatia JV. WhatsApp: what an app! *Indian J Crit Care Med*. (2015) 19:363–5. doi: 10.4103/0972-5229.158288
11. Giordano V, Koch HA, Mendes CH, Bergamin A, de Souza FS, do Amaral NP. WhatsApp messenger is useful and reproducible in the assessment of tibial plateau fractures: inter- and intra-observer agreement study. *Int J Med Inform*. (2015) 84:141–8. doi: 10.1016/j.ijmedinf.2014.11.002
12. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist*. (2015) 5:110–21. doi: 10.1177/1941874415578532
13. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. (2009) 7:CD000213. doi: 10.1002/14651858.CD000213.pub2
14. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology*. (1997) 205:327–33. doi: 10.1148/radiology.205.2.9356611
15. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. (2018). 49:e46–110. doi: 10.1161/STR.0000000000000158
16. McTaggart RA, Jovin TG, Lansberg MG, Mlynash M, Jayaraman MV, Choudhri OA, et al. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography

and MRI: reader agreement, modality agreement, and outcome prediction. *Stroke.* (2015) 46:407–12. doi: 10.1161/STROKEAHA.114.006564

17. Kobkitsuksakul C, Tritanon O, Suraratdecha V. Interobserver agreement between senior radiology resident, neuroradiology fellow, and experienced neuroradiologist in the rating of Alberta Stroke Program Early Computed Tomography Score (ASPECTS). *Diagn Interv Radiol.* (2018) 24:104–7. doi: 10.5152/dir.2018.17336
18. Maegerlein C, Fischer J, Monch S, Berndt M, Wunderlich S, Seifert CL, et al. Automated calculation of the Alberta stroke program early CT score: feasibility and reliability. *Radiology.* (2019) 291:141–8. doi: 10.1148/radiol.2019181228
19. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, et al. Alberta stroke program early CT scoring of CT perfusion in early stroke visualization and assessment. *AJNR Am J Neuroradiol.* (2007) 28:1975–80. doi: 10.3174/ajnr.A0689
20. Gupta AC, Schaefer PW, Chaudhry ZA, Leslie-Mazwi TM, Chandra RV, Gonzalez RG, et al. Interobserver reliability of baseline noncontrast CT Alberta stroke program early CT score for intra-arterial stroke treatment selection. *AJNR Am J Neuroradiol.* (2012) 33:1046–9. doi: 10.3174/ajnr.A2942
21. Pfaff J, Herweh C, Schieber S, Schonenberger S, Bosel J, Ringleb PA, et al. e-ASPECTS correlates with and is predictive of outcome after mechanical thrombectomy. *AJNR Am J Neuroradiol.* (2017) 38:1594–9. doi: 10.3174/ajnr.A5236
22. Demeestere J, Scheldeman L, Cornelissen SA, Heye S, Wouters A, Dupont P, et al. Alberta stroke program early CT score versus computed tomographic perfusion to predict functional outcome after successful reperfusion in acute ischemic stroke. *Stroke.* (2018) 49:2361–7. doi: 10.1161/STROKEAHA.118.021961
23. Herweh C, Ringleb PA, Rauch G, Gerry S, Behrens L, Mohlenbruch M, et al. Performance of e-ASPECTS software in comparison to that of stroke physicians on assessing CT scans of acute ischemic stroke patients. *Int J Stroke.* (2016) 11:438–45. doi: 10.1177/1747493016632244
24. Nagel S, Sinha D, Day D, Reith W, Chapot R, Papanagiotou P, et al. e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients. *Int J Stroke.* (2017) 12:615–22. doi: 10.1177/1747493016681020
25. Kuang H, Najm M, Chakraborty D, Maraj N, Sohn SI, Goyal M, et al. Automated ASPECTS on noncontrast CT scans in patients with acute ischemic stroke using machine learning. *AJNR Am J Neuroradiol.* (2019) 40:33–8. doi: 10.3174/ajnr.A5889
26. Guberina N, Dietrich U, Radbruch A, Goebel J, Deuschl C, Ringelstein A, et al. Detection of early infarction signs with machine learning-based diagnosis by means of the Alberta Stroke Program Early CT score (ASPECTS) in the clinical routine. *Neuroradiology.* (2018) 60:889–901. doi: 10.1007/s00234-018-2066-5
27. Sundaram VK, Goldstein J, Wheelwright D, Aggarwal A, Pawha PS, Doshi A, et al. Automated ASPECTS in acute ischemic stroke: a comparative analysis with CT perfusion. *AJNR Am J Neuroradiol.* (2019) 40:2033–8. doi: 10.3174/ajnr.A6303
28. Zennaro F, Grosso D, Fascetta R, Marini M, Odoni L, Di Carlo V, et al. Teleradiology for remote consultation using iPad improves the use of health system human resources for paediatric fractures: prospective controlled study in a tertiary care hospital in Italy. *BMC Health Serv Res.* (2014) 14:327. doi: 10.1186/1472-6963-14-327
29. Ozdalga E, Ozdalga A, Ahuja N. The smartphone in medicine: a review of current and potential use among physicians and students. *J Med Internet Res.* (2012) 14:e128. doi: 10.2196/jmir.1994
30. MENLO PARK C–BW. *FDA Additionally Clears RAPID^{TM} Imaging Platform for Use in Selecting Acute Stroke Patients for Clot Removal BUSINESS WIRE: BUSINESS WIRE.* (2019). Available online at: https://www.businesswire.com/news/home/20190115005169/en/FDA-Additionally-Clears-RAPIDTM-Imaging-Platform-Selecting (accessed April 19 2020)
31. Olive-Gadea M, Martins N, Boned S, Carvajal J, Moreno MJ, Muchada M, et al. Baseline ASPECTS and e-ASPECTS correlation with infarct volume and functional outcome in patients undergoing mechanical thrombectomy. *J Neuroimaging.* (2019) 29:198–202. doi: 10.1111/jon.12564
32. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, et al. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta stroke program early CT score in ECASS II. *Stroke.* (2006) 37:973–8. doi: 10.1161/01.STR.0000206215.62441.56
33. Weir NU, Pexman JH, Hill MD, Buchan AM, investigators C. How well does ASPECTS predict the outcome of acute stroke treated with IV tPA? *Neurology.* (2006) 67:516–8. doi: 10.1212/01.wnl.0000228221.44334.73

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Motivational Strategies for Stroke Rehabilitation: A Descriptive Cross-Sectional Study

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Background: The addition of motivational strategies to a rehabilitation program is thought to enhance patient adherence and improve outcomes. However, little is known about how rehabilitation professionals motivate stroke patients during rehabilitation. The primary objective of this study was to provide a comprehensive and quantitative list of motivational strategies for stroke rehabilitation. In addition, we aimed to examine (1) whether professionals with more clinical experience used a higher number of motivational strategies, (2) the purpose for using each strategy, and (3) the information considered when choosing strategies.

Methods: This descriptive, cross-sectional study was conducted using a web survey with a convenience sample of 407 rehabilitation professionals including physicians, nurses, physical therapists, occupational therapists, and speech-language-hearing therapists.

Results: We received data for 362 participants. Fifteen strategies were found to be used by more than 75% of the respondents to motivate their patients. Almost all of the respondents reported that they actively listened to and praised their patients to increase patient adherence to rehabilitation programs. Respondents with more clinical experience tended to use a higher number of motivational strategies (rho = 0.208, $p < 0.001$). For 11 of the 15 strategies selected by more than 75% of the respondents, the highest percentage of respondents reported that they used the strategies to make rehabilitation worthwhile for their patients. The majority of respondents reported that they decided which motivational strategy to use by considering comprehensive information regarding the patient health condition, environmental factors, and personal factors.

Conclusions: The comprehensive list of motivational strategies obtained may be useful for increasing patient adherence to rehabilitation, especially for professionals with less clinical experience. Furthermore, our findings regarding the purpose for using each strategy and the information considered when choose strategies might help rehabilitation professionals to optimally utilize the motivational strategy list.

Keywords: cerebrovascular disease, cluster analysis, motivation, motivational model, strategy

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INTRODUCTION

Studies on stroke rehabilitation have recommended the use of intensive and repetitive task-specific practice, as well as aerobic exercise (1). Given that the independent efforts of the patient are necessary to sustain these practices and exercises, patient motivation is frequently used as a determinant of rehabilitation outcome (2). High adherence to a rehabilitation program is thought to be indicative of motivation (2, 3), and a lack of motivation is one of the perceived barriers to physical activity and exercise training after stroke (4–7). Therefore, the addition of motivational strategies to rehabilitation programs may effectively enhance patient adherence, producing better outcomes (8).

Motivational strategies such as feedback (9, 10), counseling (11), and information provision (12) have positive effects on recovery after stroke. An international randomized clinical trial found that praise and positive feedback were effective for improving walking speed during inpatient rehabilitation (9). Feedback using virtual reality has been found to be beneficial in improving motivation, upper limb function, and activities of daily living (10, 13). Furthermore, counseling and information provision have been found to have a positive impact on mood (11, 12). However, few reports have comprehensively investigated strategies used by medical professionals to motivate patients undergoing stroke rehabilitation.

Maclean et al. (3) conducted a semi-structured interview of medical professionals to determine how they increase patient motivation with respect to stroke rehabilitation. The researchers reported that setting rehabilitation goals, providing information about rehabilitation, and accessing and using the patient's cultural norms appeared to have a positive effect on motivation (3). However, it is difficult to generalize these findings to the general population due to the small sample size and in-depth interview method used (14).

As opposed to semi-structured interviews, the findings from quantitative surveys are generalizable to a larger population (14). Therefore, the primary objective of this study was to provide a comprehensive list of motivational strategies that medical professionals use for stroke rehabilitation in Japan based on quantitative survey data. A list of motivational strategies is likely to be useful in increasing patient adherence to rehabilitation programs. Based on our clinical experience, we hypothesized that motivational skills could be acquired through clinical experience. In addition, understanding the purpose of each motivational strategy and the information that is evaluated when choosing strategies may contribute to effective utilization of the list. Thus, our secondary objectives were to examine (1) whether rehabilitation professionals with greater clinical experience used more motivational strategies, (2) the purpose for using each strategy, and (3) the information considered when choosing motivational strategies.

MATERIALS AND METHODS

Study Design

This study had a descriptive cross-sectional design. We used a convenience sampling web-based survey to obtain quantitative results from the participant perspective. The study protocol was approved by the appropriate ethics committee at the Hamamatsu University School of Medicine (approval number: 18-136). Informed consent was obtained from all participants.

Participants

Eligible participants were rehabilitation professionals including physicians, nurses, physical therapists, occupational therapists, speech-language-hearing therapists, or clinical psychologists currently working in rehabilitation. Participants were recruited with the cooperation of the 33rd conference of the Comprehensive Rehabilitation Ward Association and the 48th Annual Meeting of the Nagano Physical Therapy Association. To recruit participants, we set up a booth with laptops at each of the above-mentioned conferences. Professionals who were interested in participating in the study were able to access the survey website using the provided laptops. In addition, we distributed leaflets to professionals and displayed posters containing a brief description of the study and a hyperlink to the survey in front of the booth. Respondents were able to access the survey website using their own laptops, tablets, or smartphones. The first page of the survey informed participants about the total number of questions, the approximate time required to complete the survey, and the aim of the study. Participants were asked to report their professional category and years of experience working in stroke rehabilitation. Those who met the eligible criteria proceeded to the next page.

Survey Instrument

We consulted existing guidelines and followed a checklist when preparing the survey (15, 16). We chose to use a voluntarily accessed survey format developed using the Google Forms tool (Google LLC, Mountain View, CA, USA). Among the individuals who completed the survey, 50 were selected via a draw to receive an honorarium of 1,000 yen (∼US $9.00).

The survey items regarding motivational strategies were developed based on the clinical experience of the authors, the findings of related literature (2–5, 7, 9, 11, 12, 17–20), and data obtained from semi-structured interviews with five professionals about motivational strategies for stroke rehabilitation (21). Stroke rehabilitation experts were asked to review the items for clarity, relevance, and topic coverage (22). We carried out a pilot test with a group of 10 rehabilitation professionals to determine whether the respondents understood the questions and instructions, and whether the meaning of the questions was the same for all respondents (16). The survey took an average of 15 min to complete. According to the qualitative feedback obtained from the semi-structured interviews with the 10 respondents, we made some minor grammatical changes to the survey. Consequently, we prepared a list of 22 motivational strategies (**Table 1**). In the first section of the survey, respondents were shown the list of motivational strategies and asked if they used each strategy in their clinical practice. Respondents were also asked to respond to an open-ended question at which point they were invited to

TABLE 1 | List of motivational strategies.

Motivational strategy	Representation in the manuscript
Active listening	Active listening
Allowing the patient to use a newly acquired skill	Allowing the patient to use a newly acquired skill
Applying patient preferences to practice and exercise tasks	Application of patient's preferences
Control of task difficulty	Control of task difficulty
Explaining the necessity of a practice	Explaining the necessity of a practice
Goal-oriented practice	Goal-oriented practice
Goal setting	Goal setting
Group rehabilitation	Group rehabilitation
Engaging in enjoyable communication with the patient	Enjoyable communication
Providing the patient positive evaluation and encouragement	Praise
Proposing conditions for exchange (e.g., promising to undertake the patient's favorite practice after achieving his/her least favorite practice)	Proposing conditions for exchange
Providing a suitable rehabilitation environment	Providing a suitable rehabilitation environment
Providing exercise and practice with game properties	Practice with game properties
Providing medical information	Providing medical information
Providing opportunities for the patient to identify possible treatments	Providing opportunities to identify possible treatments
Providing practice tasks relating to the patient's experience and lifestyle	Practice related to patient's experience
Providing variations of rehabilitation programs to sustain interest	Providing variations of the program
Recommending the presence of a family member during rehabilitation	Family member present
Respect for self-determination	Respect for self-determination
Sharing the criteria for evaluation	Sharing the criteria for evaluation
Specifying the amount of practice and exercise that will be required	Specifying the amount of practice required
Using tools such as a diary or graph that enables the patient to track his/her progress	Using progress-confirming tools

Motivational strategies are arranged in alphabetical order.

propose additional motivational strategies that were not included in the list.

In the second section, for each motivational strategy that a respondent reported using, they were asked to state their aim when using that strategy. Specifically, they were asked to select from the following four purposes: (1) to increase the patient's interest in rehabilitation; (2) to make rehabilitation more worthwhile for the patient; (3) to help the patient gain confidence in performing a rehabilitation task; and (4) to increase patient satisfaction with the rehabilitation program. These purposes were based on the four sub-components of motivation proposed by the Attention, Relevance, Confidence, and Satisfaction (ARCS) model (23, 24). The ARCS model is a problem-solving approach that is used when designing motivational aspects of learning environments with the goal of stimulating and sustaining students' motivation to learn (23). In the third section, respondents were shown 11 items related to the patient health status, environmental factors, and personal factors (**Table 2**) (25). They were asked to select all of the items that they considered when deciding which motivational strategy to use. Finally, respondents were asked to report their gender, primary affiliation, and the phase of stroke recovery of the patients with which they most frequently worked.

TABLE 2 | Information used when determining how to motivate a patient with stroke.

Information
Cognitive function (e.g., higher brain dysfunction and dementia)
Comorbidities (e.g., psychological disorder, diabetes mellitus, and infection)
Demographic characteristics such as age and sex
Diagnosis (e.g., ischemic or hemorrhagic, lesion site, and recurrence)
Human environment (e.g., key person and family)
Patient's reaction to a presented motivational strategy
Personality
Physical function (e.g., muscle weakness, limited range of motion, and sensory dysfunction)
Severity of activity limitations
Severity of participation restrictions
Social environment (e.g., economic condition and employment status)

Information arranged in alphabetical order.

Sample Size

We used the Cochran sample size formula to calculate the sample size. We set an alpha level a priori at 0.05, an acceptable error level of 5%, and a confidence interval of 95% (26). Consequently, a minimum of 384 participants were required. Assuming that the data from approximately 5% of the participants would be excluded from analysis, we aimed to recruit a total of 400 participants.

Statistical Analysis

We used descriptive statistics to characterize the study sample and summarize the participant responses. The normality of distribution was tested using the Shapiro-Wilk test. We used

Pearson's product-moment correlation coefficient or Spearman's rank correlation coefficient to test whether respondents with more experience used more motivational strategies. In addition, we used a stepwise multiple regression analysis to examine the relationship between the years of clinical experience and the number of motivational strategies used by each respondent, while controlling for potentially confounding variables. We included the respondents' gender, professional category, primary affiliation, and the patient phase of stroke recovery in the model as covariates. Dummy variables were used to incorporate categorical variables such as gender and professional category into the regression model. For the motivational strategies that were used by at least 75% of respondents (27), we conducted a hierarchical cluster analysis using Ward's method with a squared Euclidean distance to group them according to the purpose of use. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 25.0 (International Business Machines Corp., NY, USA). Any p values < 0.05 were considered statistically significant.

Reporting

This study was reported according to the recommended best practices and guidelines in the literature for the reporting of survey research (16, 22).

RESULTS

The survey was conducted from February to July 2019. Approximately 4,150 rehabilitation professionals attended the two conferences. Among them, 407 professionals accessed the survey. Therefore, the response rate was ∼9.8%. Forty-five respondents were excluded because they did not meet the eligibility criteria, withdrew consent to participate, or had missing data. Consequently, 362 respondents completed the survey. The flow of participants is shown in **Figure 1**. **Table 3** shows the characteristics of the respondents. The majority of the respondents were physical therapists (51.1%), had <5 years of clinical experience (36.2%), were female (53.0%), were employed in a hospital (91.2%), and worked with patients with subacute stroke (71.3%). No clinical psychologists participated in the survey.

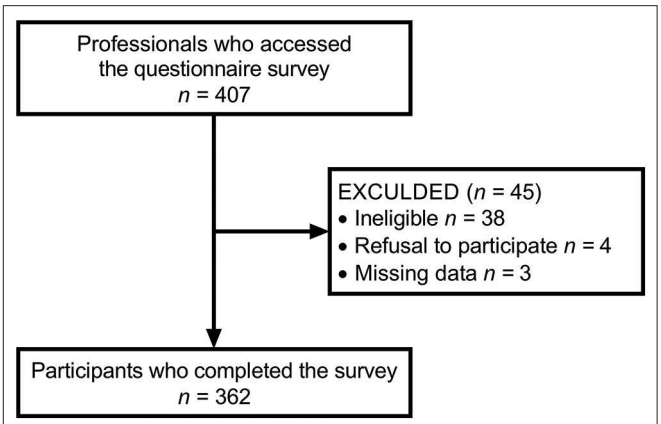

FIGURE 1 | Flow diagram of the participant selection process.

TABLE 3 | Respondent characteristics ($n = 362$).

Variable	Value
Professional category	
Physical therapist	185 (51.1)
Nurse	82 (22.7)
Occupational therapist	74 (20.4)
Speech-language-hearing therapist	13 (3.6)
Physician	8 (2.2)
Years of experience in stroke rehabilitation	
Less than 5 years	131 (36.2)
5–9 years	90 (24.8)
10–14 years	79 (21.8)
15–19 years	31 (8.6)
20 years or more	31 (8.6)
Sex	
Female	192 (53.0)
Male	170 (47.0)
Primary affiliation	
Hospital	333 (92.0)
Geriatric health services facility or nursing home	16 (4.4)
Others	13 (3.6)
Phase of stroke recovery of the patients	
Subacute	258 (71.2)
Chronic	46 (12.7)
Acute	44 (12.2)
Others	14 (3.9)

Values are presented as number (%).

Which Strategies Do Rehabilitation Professionals use to Motivate Their Patients?

The percentages of respondents who used each of the presented motivational strategies are shown in **Figure 2**. The majority of the respondents (98.3%) selected "active listening" and "praise." "Enjoyable communication," "providing a suitable rehabilitation environment," "goal setting," "explaining the necessity of a practice," and "respect for self-determination" were also selected by more than 90% of the respondents (95.3–91.7%). The majority of the respondents reported that they used "control of task difficulty," "family member present," "goal-oriented practice," "providing medical information," "application of patient preferences," "practice related to patient's experience," "providing opportunities to identify possible treatments," and "specifying the amount of practice required" (89.2–76.0%). Thus, 15 out of the 22 presented strategies were selected by more than 75% of the respondents. Between 69.3 and 66.9% of the respondents reported that they used "allowing the patient to use a newly acquired skill," "sharing the criteria for evaluation," and "providing variations of the program." Less than half of the respondents selected "practice with game properties," "proposing conditions for exchange," "using progress-confirming tools," and

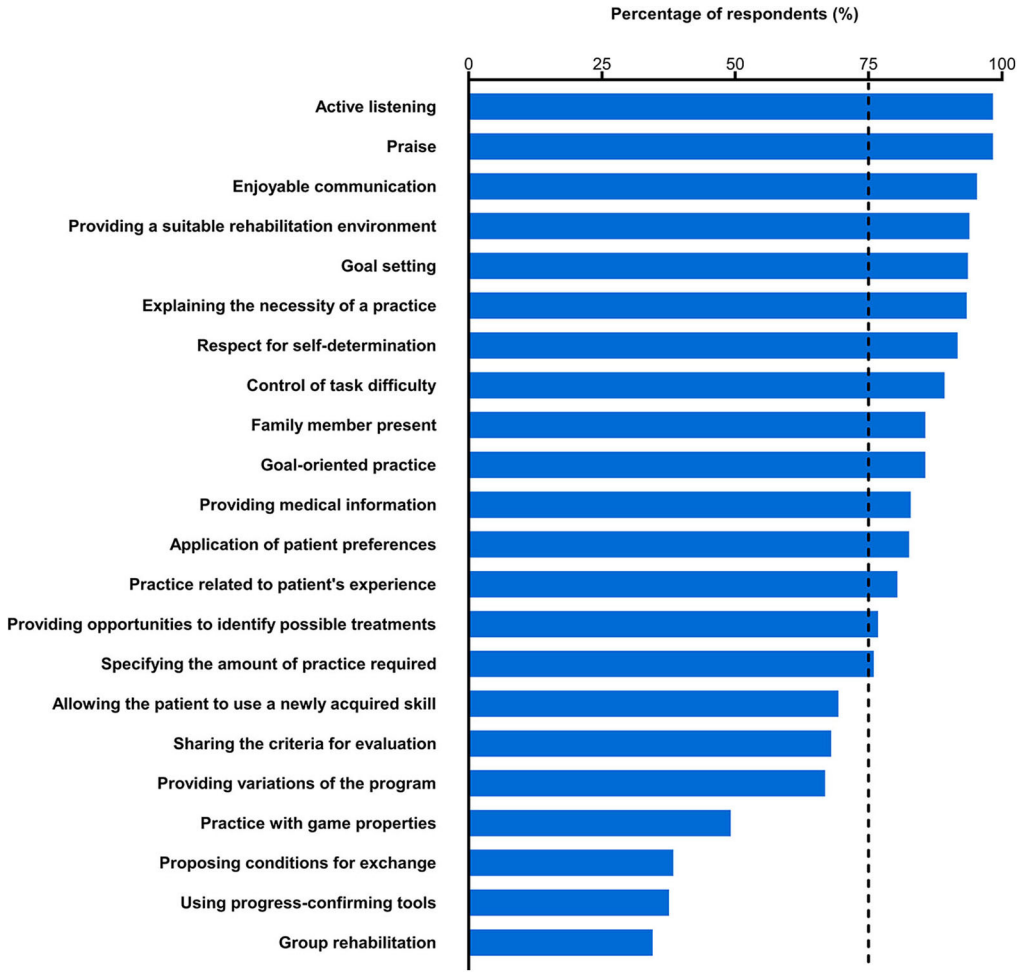

FIGURE 2 | Percentage of respondents who reported that they used each presented motivational strategy during stroke rehabilitation. The vertical dashed line represents 75% of the respondents. The motivational strategies are arranged in descending order by the percentage of respondents who stated that they used each strategy.

"group rehabilitation" (49.2–34.5%). The results by professional category are shown in **Supplemental Figure 1**. The numbers of motivational strategies selected by at least 75% of the respondents who were nurses, physical therapists, and occupational therapists were 10, 15, and 18, respectively. The respondents proposed four additional motivational strategies (**Supplemental Table 1**). Respondents with more clinical experience tended to use a larger number of motivational strategies (rho = 0.208, 95% confidence interval = 0.105, 0.308, $p < 0.001$) (**Figure 3**). In addition, even when controlling for potentially confounding variables, the relationship between years of clinical experience and the number of motivational strategies used by each respondent remained significant ($t = 2.027$, $p = 0.043$).

For What Purpose Do Rehabilitation Professionals use Each Motivational Strategy?

For 11 of the 15 motivational strategies that were used by at least 75% of the respondents, the highest percentage of respondents reported that they used the strategies to make rehabilitation worthwhile for their patients (51.3–31.6%) (**Figure 4A**). For "control of task difficulty" and "praise," the most common purpose was to help the patient gain confidence in performing a rehabilitation task (45.4 and 35.5%, respectively). The largest proportion of respondents who used "enjoyable communication" and "application of patient preferences" reported that they used these strategies to increase the patient's interest in rehabilitation (49.3 and 39.4%, respectively).

The hierarchical cluster analysis produced three motivational strategy clusters (**Figure 4B**). The first cluster included seven motivational strategies, such as "family member present" and "providing a suitable rehabilitation environment." For six of these seven strategies, more than 30% of the respondents reported that they used the strategies to help the patients gain confidence in performing a rehabilitation task. The second cluster included six motivational strategies, such as "providing opportunities to identify possible treatments" and "explaining the necessity of a practice."

Most of the respondents used these to make rehabilitation worthwhile for their patient. The third cluster comprised two strategies that the largest percentage of respondents reported having used to increase the patient's interest in rehabilitation.

FIGURE 3 | Correlation between the number of motivational strategies used by each respondent and years of rehabilitation practice.

What Information Is Considered When Rehabilitation Professionals Choose Motivational Strategies?

Each of the presented 11 items was selected by more than 75% of respondents as information that they considered when deciding which motivational strategy to use (**Figure 5**). Almost all of the respondents selected "patient's reaction to a presented motivational strategy" and "personality" (97.5%), whereas the lowest percentage of respondents selected "diagnosis" (75.4%). Furthermore, approximately half of the respondents selected all of the 11 presented items (49.1%). The results for each professional category are shown in **Supplemental Figure 2**. More than 75% of the respondents who were physicians and nurses selected all 11 of the presented items. More than 75% of the respondents who were physical therapists and occupational therapists selected all of the items except for "diagnosis," whereas more than 75% of the respondents who were speech-language-hearing therapists selected all of the items excluding "social environment," "comorbidities," and "diagnosis."

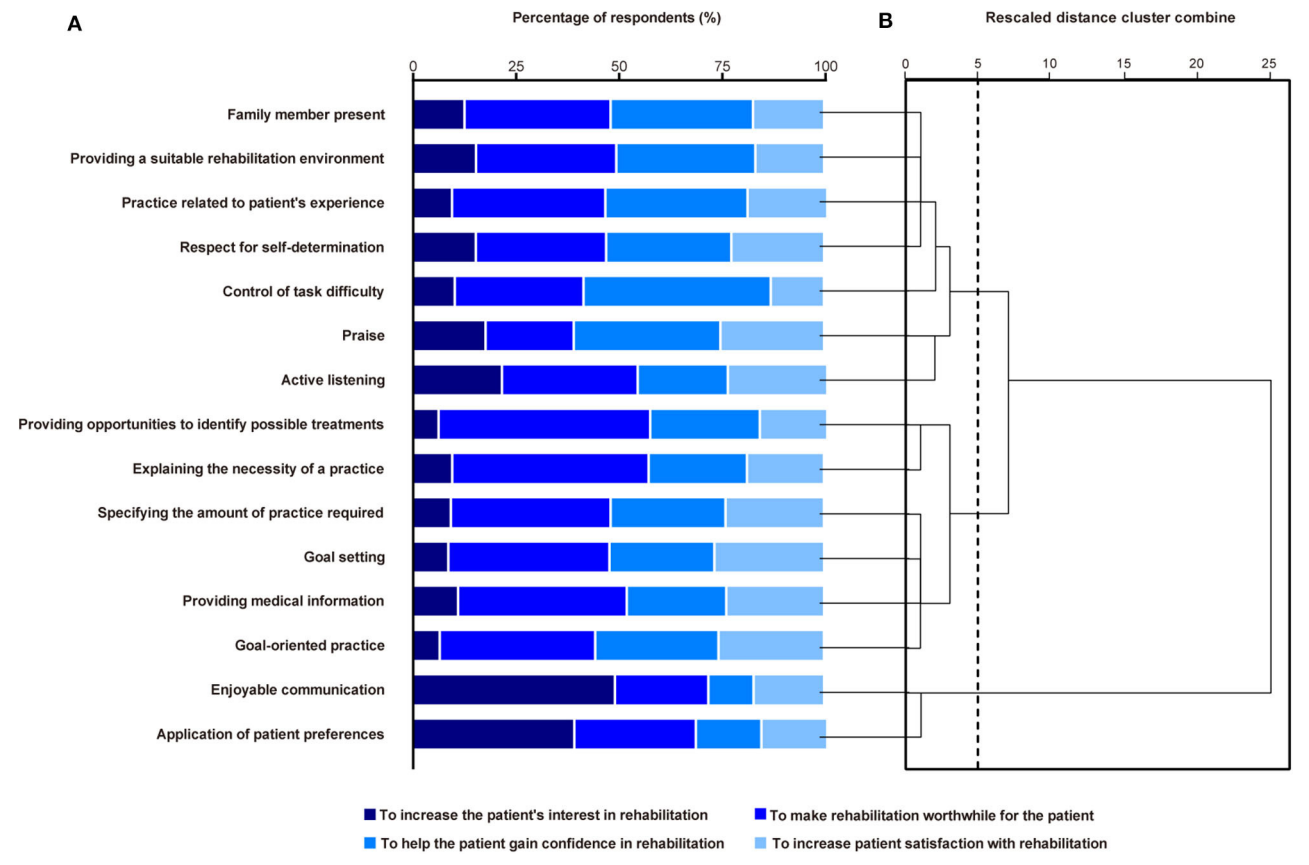

FIGURE 4 | The purpose of using each motivational strategy used by at least 75% of the respondents **(A)**. The order corresponds to **(B)**. A dendrogram showing the three distinct clusters identified based on hierarchical cluster analysis via Ward's method **(B)**. The vertical dashed line indicates the optimal number of groups.

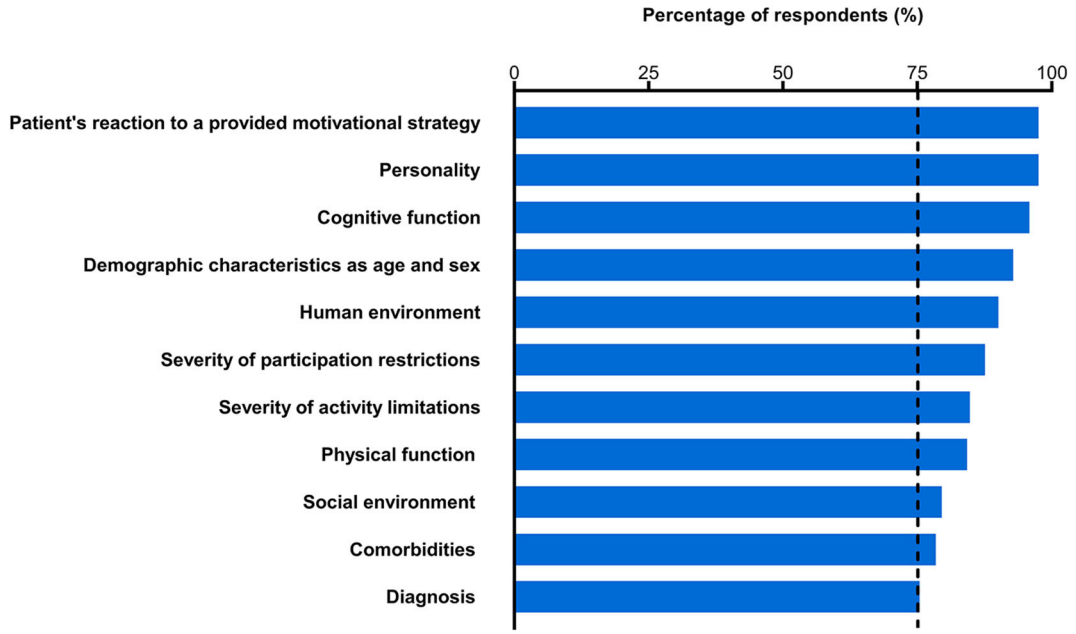

FIGURE 5 | Percentage of respondents who reported considering each type of information when deciding which motivational strategy to use. The vertical dashed line represents 75% of the respondents. Information is arranged in descending order by the percentage of respondents.

DISCUSSION

As a result of the present study, we generated a comprehensive list of motivational strategies used during stroke rehabilitation in Japan based on quantitative survey data. We identified 15 motivational strategies used by more than 75% of the rehabilitation professionals who participated in the study. The results support our hypothesis that rehabilitation professionals acquire skills to motivate stroke patients via clinical experience. Furthermore, our survey generated data regarding the purpose of using each motivational strategy and the information that professionals consider when they choose motivational strategies. To our knowledge, the present study is the first comprehensive survey-based investigation of strategies used to motivate stroke patients during rehabilitation. We prepared the survey in accordance with existing guidelines (15, 16) and conducted pretesting procedures, such as expert reviews and pilot testing, to establish content and response process validity (22). We expected that these procedures would enhance the reliability and generalizability of our findings.

Which Strategies Do Rehabilitation Professionals use to Motivate Their Patients?

Active listening is one of the core communication skills used in counseling (11, 28). A systematic review reported that counseling has a positive effect on mood in stroke patients (11, 12). Praise can induce positive mood and increase motivation to perform a motor skill, resulting in improved performance (29–31). Moreover, daily feedback with praise has been reported to be effective in improving walking speed in stroke inpatients (9). Almost all of the respondents in our study reported that they actively listened to and praised their stroke patients to increase patient motivation regarding rehabilitation.

Our results suggest that the majority of the surveyed rehabilitation professionals recognized that the communication skills of the medical professional, rehabilitation environment, setting of goals, provision of information, and the presence of family members during practice could affect patient motivation regarding rehabilitation. These findings are consistent with those of Maclean et al. (3). Communication training programs for clinicians have been shown to increase patient satisfaction, levels of motivation for goal setting and action, and health-related quality of life (32). Sonoda et al. (33) found that providing a specific rehabilitation environment for stroke inpatients increased the amount of physical activity that they engaged in during activities of daily living. Furthermore, providing information about rehabilitation and insuring that a family member is present during rehabilitation may be effective in improving a patient's mood and encouraging them to become more active (12, 34).

Respect for self-determination, control of task difficulty, and provision of a goal-oriented practice were motivational strategies that were selected by more than 75% of the respondents. Self-determination contributes to the facilitation and maintenance of intrinsic motivation (35). The difficulty of a practice task is thought to have an important impact on the effectiveness of rehabilitation, as inappropriate levels of difficulty can lead the patient to become bored or frustrated (36). Indeed, gradual increases in task difficulty and goal-oriented practice have been recommended to facilitate functional motor recovery during

stroke rehabilitation (1). Through clinical practice, rehabilitation professionals may have observed the effectiveness of these motivational strategies for increasing patient adherence to rehabilitation programs.

We found that the following four strategies were reportedly used by less than half of the respondents to motivate their patients: providing practice with game properties, proposing conditions for exchange, using progress-confirming tools, and providing group rehabilitation. The reasons why these particular motivational strategies were not used remain unclear. Environmental and time constraints, professional lack of confidence regarding the practice, and lack of perceived effectiveness may prevent rehabilitation professionals from using specific motivational strategies (37). In addition, some respondents may not have selected these strategies because they did not understand the accompanying motivational effects, even if they did use these strategies in clinical practice.

For What Purpose Do Rehabilitation Professionals use Each Motivational Strategy?

In clinical settings, rehabilitation professionals may be required to select strategies according to the cause of a patients' lack of motivation. Therefore, we examined the reasons for using each motivational strategy. For 11 of the 15 strategies used by the majority of respondents, the highest percentage of respondents reported that they used the strategy to make rehabilitation worthwhile for their patient. Lack of knowledge about the potential benefits of training may decrease patient adherence to rehabilitation (19). Therefore, professionals may emphasize patient comprehension regarding the benefits and significance of practices to motivate patients regarding rehabilitation.

Our hierarchical cluster analysis revealed three groups of motivational strategies. Strategies that center on the value of rehabilitation for patients, such as explaining the necessity of a practice and exercise, are expected to motivate patients with poor understanding regarding the benefits of rehabilitation. For patients with low confidence regarding their practice tasks, strategies focused on increasing patient confidence, such as control of task difficulty and praise, may be effective for increasing patient motivation. Moreover, engaging in enjoyable conversation and applying patient preferences to practice tasks are likely to increase patient interest and prevent patient boredom during rehabilitation. There were no strategies that were used by the majority of respondents to increase patient satisfaction with rehabilitation. However, more than a quarter of the respondents reported that they used goal setting, goal-oriented practice, and praise to increase patient satisfaction with rehabilitation. These strategies may be effective in motivating patients who are not satisfied with rehabilitation. Thus, our findings may help rehabilitation professionals to choose strategies from the list according to the cause of a patients' lack of motivation.

What Information Is Considered When Rehabilitation Professionals Choose Motivational Strategies?

Maclean et al. (3) reported that compared with younger patients, older unmotivated stroke patients did not respond as well to encouragement. Thus, rehabilitation professionals may benefit from choosing motivational strategies according to the characteristics of each patient. Our results suggest that the majority of rehabilitation professionals choose motivational strategies based on comprehensive data regarding a patient's health condition, environmental factors, and personal factors. Patient personality type and responses to motivational strategies suggested by the professional seem to be regarded as especially essential information. Our findings may assist rehabilitation professionals in deciding which motivational strategy to use and contribute to the effective utilization of the motivational strategy list.

We also examined the participant responses by professional category (**Supplemental Figure 2**). We observed some differences in the responses among the different specializations. For example, while more than 75% of the physicians and nurses who participated answered that they utilized information regarding "diagnosis" when they decided which motivational strategies to use, this type of information was selected as useful by less than 75% of physical therapists, occupational therapists, and speech-language-hearing therapists. As physicians and nurses are responsible for medical management, they may be more likely to consider patient diagnosis as an important factor when choosing motivational strategies. These results may support our data indicating that different types of specialists use different strategies for motivation (**Supplemental Figure 1**). However, the sample of physicians and speech-language-hearing therapists in the present study was small. Thus, careful interpretation of the results by each professional category is necessary.

As mentioned above, our results showed that the different strategies were used for different purposes (**Figure 4**). For example, "control of task difficulty" and "praise" were most frequently used to help patients gain confidence in performing a rehabilitation task (45.4 and 35.5%, respectively), whereas the largest proportion of respondents who used "enjoyable communication" and "application of patient preferences" reported that they used these strategies to increase the patient's interest in rehabilitation (49.3 and 39.4%, respectively). However, our data suggested that many of these motivational strategies were used for one or more different purposes. For example, although the most common purpose for using "control of task difficulty" was to help patients gain confidence in performing a rehabilitation task (45.4%), the respondents also reported other purposes (10.4% to increase the patient's interest in rehabilitation; 31.2% to make rehabilitation worthwhile for the patient; 12.9% to increase patient satisfaction with rehabilitation). These different purposes for using motivational strategies might depend on the patient condition (e.g., age, comorbidities, and severity of stroke) and/or environmental factors. In the present study, we investigated the factors that are taken into consideration when rehabilitation professionals

choose motivational strategies (**Figure 5**). However, we did not conduct concrete classifications of strategies according to the patient condition and environmental factors. Thus, future studies are needed to evaluate the motivational strategies that rehabilitation professionals use according to the patient condition and environmental factors.

LIMITATIONS

Several limitations to this study should be mentioned. First, the actual response rate of the present survey was low (∼9.8%, 407 out of 4150), and we utilized a convenience sampling method. Therefore, the results of this survey may not accurately represent the actual use of motivational strategies for stoke rehabilitation in professionals in Japan. Unfortunately, the characteristics of the nonparticipants in this survey were unavailable. We recruited participants by distributing leaflets and displaying posters, and participation was voluntarily. As a result, the nonparticipants in this study may have been less interested in the motivation of patients compared with the participants. Accordingly, the results should be interpreted with caution because the rate of use of each motivational strategy may be higher in our sample than in the general population of rehabilitation professionals. We recommend that further studies employ a stratified random sampling method to increase the range of occupations of the respondents and the generalizability of the results (38).

A secondary limitation is a weakness of generalizability of the study. Maclean et al. (3) reported that goal setting and providing medical information were thought to have a positive effect on patient motivation. In addition, Dobkin et al. (9) found that praise and positive feedback were effective for improving walking speed in patients with stroke. Thus, the present results are partly consistent with the previous qualitative (2, 3, 17, 18) and experimental reports (9, 12, 13, 34, 36) from Western countries. The advantage of this study was that it represents the first extensive survey to quantitatively investigate the actual motivational strategies used in stroke rehabilitation. However, as all of the participants were recruited in Japan, whether our findings are generalizable to rehabilitation professionals outside of Japan remains unclear. An international survey of motivational strategies used for stroke rehabilitation would improve the external validity of our findings.

Third, there may have been a perceived lack of differentiation between the motivational strategies. As our list of motivational strategies comprised specific examples about motivating a patient, some of the presented motivational strategies may have overlapped with one another (8), potentially confusing the respondents. However, we designed the motivational strategy list to show specific motivational strategies so that it would be easy to use in a clinical environment. Fourth, the responses obtained from the survey may not reflect the actual practices of the professionals. Instead, responses may have been affected by inaccurate recall or reflect the beliefs or desires of the respondents (39). However, we believe that our web-based survey carried a low participant burden and enabled more complete population coverage for sampling (39, 40). Finally, as this study had a cross-sectional design, we are unable to comment on the causal relationship between patient recovery and quantity and type of motivational strategies used. Nevertheless, our findings may be useful for examining the effect of motivational strategies on functional outcomes in the future.

CONCLUSIONS

We generated a comprehensive and qualitative list of motivational strategies used for stroke rehabilitation in Japan, and found that our 15 motivational strategies were used by the majority of rehabilitation professionals. In addition, we obtained data regarding the purpose for using each motivational strategy and the information considered when choosing motivational strategies. These findings may enhance the effective utilization of our motivational strategy list in stroke rehabilitation.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee at the Hamamatsu University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KO contributed to the study concept and design, development of the survey, acquisition of data, analysis and interpretation of data, obtaining of funding, and drafting and revising the manuscript for content. MS contributed to the development of the survey, acquisition of data, and revising of the manuscript for content. YO contributed to the study concept and design, development of the survey, and revising of the manuscript for content. ST contributed to the study concept and design, development of the survey, acquisition of data, analysis and interpretation of data, study supervision, obtaining of funding, and drafting and revising of the manuscript for content. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00553/full#supplementary-material

REFERENCES

1. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2016) 47:e98–e169. doi: 10.1161/STR.0000000000000098
2. Maclean N, Pound P, Wolfe C, Rudd A. Qualitative analysis of stroke patients' motivation for rehabilitation. *BMJ.* (2000) 321:1051–4. doi: 10.1136/bmj.321.7268.1051
3. Maclean N, Pound P, Wolfe C, Rudd A. The concept of patient motivation: A qualitative analysis of stroke professionals' attitudes. *Stroke.* (2002) 33:444–8. doi: 10.1161/hs0202.102367
4. Damush TM, Plue L, Bakas T, Schmid A, Williams LS. Barriers and facilitators to exercise among stroke survivors. *Rehabil Nurs.* (2007) 32:253–60. doi: 10.1002/j.2048-7940.2007.tb00183.x
5. Nicholson S, Sniehotta FF, van Wijck F, Greig CA, Johnston M, McMurdo ME, et al. A systematic review of perceived barriers and motivators to physical activity after stroke. *Int J Stroke.* (2013) 8:357–64. doi: 10.1111/j.1747-4949.2012.00880.x
6. Morris J, Oliver T, Kroll T, Macgillivray S. The importance of psychological and social factors in influencing the uptake and maintenance of physical activity after stroke: A structured review of the empirical literature. *Stroke Res Treat.* (2012) 2012:195249. doi: 10.1155/2012/195249
7. Rimmer JH, Wang E, Smith D. Barriers associated with exercise and community access for individuals with stroke. *J Rehabil Res Dev.* (2008) 45:315–22. doi: 10.1682/JRRD.2007.02.0042
8. McGrane N, Galvin R, Cusack T, Stokes E. Addition of motivational interventions to exercise and traditional physiotherapy: A review and meta-analysis. *Physiotherapy.* (2015) 101:1–12. doi: 10.1016/j.physio.2014.04.009
9. Dobkin BH, Plummer-D'Amato P, Elashoff R, Lee J, Group S. International randomized clinical trial, stroke inpatient rehabilitation with reinforcement of walking speed (SIRROWS), improves outcomes. *Neurorehabil Neural Repair.* (2010) 24:235–42. doi: 10.1177/1545968309357558
10. Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev.* (2017) 11:CD008349. doi: 10.1002/14651858.CD008349.pub4
11. Cheng D, Qu Z, Huang J, Xiao Y, Luo H, Wang J. Motivational interviewing for improving recovery after stroke. *Cochrane Database Syst Rev.* (2015) 6:CD011398. doi: 10.1002/14651858.CD011398.pub2
12. Forster A, Brown L, Smith J, House A, Knapp P, Wright JJ, et al. Information provision for stroke patients and their caregivers. *Cochrane Database Syst Rev.* (2012) 11:CD001919. doi: 10.1002/14651858.CD001919.pub3
13. Popović MD, Kostić MD, Rodić SZ, Konstantinović LM. Feedback-mediated upper extremities exercise: increasing patient motivation in poststroke rehabilitation. *Biomed Res Int.* (2014) 2014:520374. doi: 10.1155/2014/520374
14. Queirós A, Faria D, Almeida F. Strengths and limitations of qualitative and quantitative research methods. *Eur J Educ Stud.* (2017) 3:2017.
15. Gehlbach H, Artino AR Jr. The survey checklist (Manifesto). *Acad Med.* (2018) 93:360–6. doi: 10.1097/ACM.0000000000002083
16. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care.* (2003) 15:261–6. doi: 10.1093/intqhc/mzg031
17. Simpson LA, Eng JJ, Tawashy AE. Exercise perceptions among people with stroke: Barriers and facilitators to participation. *Int J Ther Rehabil.* (2011) 18:520–30. doi: 10.12968/ijtr.2011.18.9.520
18. Nicholson SL, Greig CA, Sniehotta F, Johnston M, Lewis SJ, McMurdo ME, et al. Quantitative data analysis of perceived barriers and motivators to physical activity in stroke survivors. *J R Coll Physicians Edinb.* (2017) 47:231–6. doi: 10.4997/JRCPE.2017.304
19. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2014) 45:2532–53. doi: 10.1161/STR.0000000000000022
20. Dobkin BH. Behavioral self-management strategies for practice and exercise should be included in neurologic rehabilitation trials and care. *Curr Opin Neurol.* (2016) 29:693–9. doi: 10.1097/WCO.0000000000000380
21. Oyake K, Kondo K, Tanaka S. Categorization of motivational strategies in rehabilitation based on ARCS model. In: *Proceedings of the 34th Annual Conference of Japan Society for Educational Technology.* Miyagi (2018). p. 28–30.
22. Artino AR Jr, Durning SJ, Sklar DP. Guidelines for reporting survey-based research submitted to academic medicine. *Acad Med.* (2018) 93:337–40. doi: 10.1097/ACM.0000000000002094
23. Keller JM. Development and use of the ARCS model of instructional design. *J Instr Dev.* (1987) 10:2. doi: 10.1007/BF02905780
24. Keller JM. *Motivational Design for learning and Performance*. New York, NY: Springer (2010) doi: 10.1007/978-1-4419-1250-3
25. Ustun TB, Chatterji S, Bickenbach J, Kostanjsek N, Schneider M. The international classification of functioning, disability and health: a new tool for understanding disability and health. *Disabil Rehabil.* (2003) 25:565–71. doi: 10.1080/0963828031000137063
26. Bartlett EJI, Joe KW, Chadwick HC. Determining appropriate sample size in survey research. *ITLPJ.* (2001) 19:43–50.
27. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol.* (2014) 67:401–9. doi: 10.1016/j.jclinepi.2013.12.002
28. McGrane N, Cusack T, O'Donoghue G, Stokes E. Motivational strategies for physiotherapists. *Phys Ther Rev.* (2014) 19:136–42. doi: 10.1179/1743288X13Y.0000000117
29. Blumenfeld PC, Pintrich PR, Meece J, Wessels K. The formation and role of self perceptions of ability in elementary classrooms. *ESJ.* (1982) 82:401–20. doi: 10.1086/461278
30. Henderlong J, Lepper MR. The effects of praise on children's intrinsic motivation: A review and synthesis. *Psychol Bull.* (2002) 128:774–95. doi: 10.1037/0033-2909.128.5.774
31. Sugawara SK, Tanaka S, Okazaki S, Watanabe K, Sadato N. Social rewards enhance offline improvements in motor skill. *PLoS ONE.* (2012) 7:e48174. doi: 10.1371/journal.pone.0048174
32. Michimata A, Suzukamo Y, Izumi S. Development of clinicians' communication skills influences the satisfaction, motivation, and quality of life of patients with stroke. *Int J Phys Med Rehabil.* (2013) 1:174. doi: 10.4172/2329-9096.1000174
33. Sonoda S, Saitoh E, Nagai S, Kawakita M, Kanada Y. Full-time integrated treatment program, a new system for stroke rehabilitation in Japan: Comparison with conventional rehabilitation. *Am J Phys Med Rehabil.* (2004) 83:88–93. doi: 10.1097/01.PHM.0000107481.69424.E1
34. Prakash V, Shah MA, Hariohm K. Family's presence associated with increased physical activity in patients with acute stroke: an observational study. *Braz J Phys Ther.* (2016) 20:306–11. doi: 10.1590/bjpt-rbf.2014.0172

35. Ryan RM, Deci EL. Intrinsic and extrinsic motivations: classic definitions and new directions. *Contem Educ Psychol.* (2000) 25:54–67. doi: 10.1006/ceps.1999.1020
36. Pan L, Song A, Wang S, Duan S. Experimental study on upper-limb rehabilitation training of stroke patients based on adaptive task level: a preliminary study. *Biomed Res Int.* (2019) 2019:2742595. doi: 10.1155/2019/2742595
37. Holden J, Davidson M, O'Halloran P. Motivational strategies for returning patients with low back pain to usual activities: a survey of physiotherapists working in Australia. *Man Ther.* (2015) 20:842–9. doi: 10.1016/j.math.2015.04.005
38. Bhardwaj P. Types of sampling in research. *J Pract Cardiovasc Sci.* (2019) 5:157–63. doi: 10.4103/jpcs.jpcs_62_19
39. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *J Public Health (Oxf).* (2005) 27:281–91. doi: 10.1093/pubmed/fdi031
40. Archer SK, Wellwood I, Smith CH, Newham DJ. Dysphagia therapy in stroke: A survey of speech and language therapists. *Int J Lang Commun Disord.* (2013) 48:283–96. doi: 10.1111/1460-6984.12006

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ORIGINAL RESEARCH
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A SCANO Nomogram for Individualized Prediction of the Probability of 1-Year Unfavorable Outcomes in Chinese Acute Ischemic Stroke Patients

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Background and Purpose: Accurate prediction of functional outcomes after stroke would provide evidence for reasonable poststroke management. This study aimed to develop and validate a nomogram for individualized prediction of 1-year unfavorable outcomes in Chinese acute ischemic stroke (AIS) patients.

Methods: We gathered AIS patients at the National Advanced Stroke Center of Nanjing First Hospital (China) between August 2014 and May 2017 within 12 h of symptom onset. The outcome measure was 1-year unfavorable outcomes (modified Rankin Scale 3–6). The patients were randomly stratified into the training (66.7%) and testing (33.3%) sets. With the training data, pre-established predictors were entered into a logistic regression model to generate the nomogram. Predictive performance of the nomogram model was evaluated in the testing data by calculating the area under the receiver operating characteristic curve (AUC-ROC), Brier score, and a calibration plot.

Results: A total of 807 patients were included into this study, and 262 (32.5%) of them had unfavorable outcomes. Systolic blood pressure, Creatinine, Age, National Institutes of Health Stroke Scale (NIHSS) score on admission, and fasting blood glucose were significantly associated with unfavorable outcomes and entered into the SCANO nomogram. The AUC-ROC of the SCANO nomogram in the testing set was 0.781 (Brier score: 0.166; calibration slope: 0.936; calibration intercept: 0.060).

Conclusions: The SCANO nomogram is developed and validated in Chinese AIS patients to firstly predict 1-year unfavorable outcomes, which is simple and convenient for the management of stroke patients.

Keywords: nomogram, prediction, functional outcome, stroke, ischemic stroke

INTRODUCTION

Acute ischemic stroke (AIS) continues to be an important cause of morbidity and mortality worldwide, which can bring heavy economic burden for patients and their families (1, 2). Consequently, clinicians will be faced with a great challenge regarding unfavorable outcomes in these patients. Better identification of AIS patients with unfavorable outcomes could be useful to develop preventive strategies and reduce the risk of morbidity and mortality after stroke.

Some prognostic scores (3–5) and several nomograms (6–8) have identified some demographic and clinical characteristics to predict 3-month clinical outcomes for AIS patients. However, model for predicting 1-year unfavorable outcomes in AIS patients was not found. On the one hand, most of the functional improvements tend to be achieved during the first 3 months after stroke. Although the patients with AIS recover rapidly during the first few weeks, there are some additional recovery between 3 and 6 months (9, 10). On the other hand, between 3 and 12 months, one in six patients with AIS deteriorate in functional outcomes (11). Therefore, the models for predicting 3-month outcomes may be limited because these models could not be suitable for all patients. Furthermore, as the strongest predictors of 3-month unfavorable outcomes (3, 6, 12–14), the correlation of National Institutes of Health Stroke Scale (NIHSS) score with the outcomes varies with the time passed from the onset of cerebral ischemia (15). This also affects the predictive performance when these models were used to predict 1-year outcomes. As a result, these prognostic scores and nomograms cannot be extrapolated to predict 1-year unfavorable outcomes, and it is meaningful to establish a model to predict 1-year unfavorable outcomes.

Therefore, the present research aimed to develop and validate a nomogram by using a limited number of easily available variables to predict 1-year unfavorable outcomes for Chinese AIS patients.

METHODS

Study Population

We conducted a retrospective analysis on the basis of data prospectively gathered from 1,831 consecutive AIS patients admitted at the National Advanced Stroke Center (NASC) of Nanjing First Hospital (China) from August 2014 to May 2017 within 12 h of symptom onset. We excluded patients with intracranial hemorrhage (ICH) on baseline brain computed tomography (CT) scan, lack of 1-year modified Rankin Scale (mRS) score, age $<$ 18 years, and NIHSS score on admission unknown for the present study. All variables with 20% missing values or more for further analysis were excluded.

All clinical, anamnestic, and demographic characteristics were recorded at the time of admission, including the following data: age, sex, NIHSS score on admission, systolic blood pressure (SBP), diastolic blood pressure, platelet count, international normalized ratio (INR), creatinine, fasting blood glucose (FBG), triglyceride (TG), low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), medical history such as hypertension, and previous cerebral hemorrhage. Owing to the U-shape characteristic of SBP (16–18), SBP was divided into two groups: Group 1 with SBP between 100 and 180 mmHg and Group 2 with SBP $<$ 100 or $>$180 mmHg.

The unfavorable outcomes were defined as mRS 3–6, 1 year after stroke. Certified assessors evaluated the baseline NIHSS and 1-year mRS during a face to face or via telephone follow-up with the patients, their relatives, or their general practitioners.

Statistical Analysis

The data were randomly stratified into the training and testing sets by the software package R version 3.5.2 (R Development Core Team, Auckland, New Zealand): two-thirds of the data were used for model development, whereas the remaining one-third were used to evaluate the performance of the model.

Continuous variables were represented as median value and interquartile range, and the differences between various groups were explored using the Mann–Whitney *U*-test. Categorical variables were instead expressed as number of events and percentage, dividing the number of events by the total number excluding missing and unknown cases. The differences between proportions were assessed by Fisher's exact test or the χ^2 test, when appropriate.

To generate the nomogram, the variables with a probability value $<$ 0.10 in the univariate analysis or thought to be independent predictors of ischemic stroke were entered into a logistic regression model. A final model selection was carried out by a backward stepwise selection process with the Akaike information criterion. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CIs) for each of the variable included in the model were finally calculated. Collinearity of combinations of variables that entered the multivariate logistic regression analysis was evaluated by the variation inflation factors (VIFs; $<$2 being considered nonsignificant) and condition index ($<$30 being considered nonsignificant).

The performance of the model was assessed in the testing data by discrimination (the ability of a proposed model to separate patients with different outcomes) and calibration (the relative distance of predictions from actual outcome). The discrimination of the nomogram model was assessed by the area under the receiver operating characteristic curve (AUC-ROC), whereas calibration was valued by the Hosmer–Lemeshow test, the Brier score, and a calibration plot. A 45° line indicates perfect calibration when the predictive value of the model perfectly matches the patient's actual risk. In all analyses, $p < 0.05$ was considered statistically significant.

The statistical analysis was performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) and Stata version 13.0 (StataCorp, College Station, TX, USA) statistical software. The software package R was used for model visualization.

RESULTS

After patients were excluded for NIHSS score on admission unknown (n = 143; 7.8%) and lack of 1-year mRS score

TABLE 1 | Clinical, demographic, and laboratory data of study population stratified according to 1-year favorable or unfavorable outcome after acute ischemic stroke in Chinese patients.

	Favorable outcome (mRS 0–2)	Unfavorable outcome (mRS 3–6)	*P*-value
Patients, *n*	545	262	
Age, years, median (IQR)	67 (59–75)	76 (67–82)	$P = 0.000^{\dagger *}$
Sex, *n* (%)			$P = 0.000^{*}$
Male	398 (73.0)	159 (60.7)	
Female	147 (27.0)	103 (39.3)	
Medical history, *n* (%)			
Hypertension	387 (71.0)	194 (74.0)	$P = 0.368$
Hyperlipidemia	26 (4.8)	9 (3.4)	$P = 0.383$
Atrial fibrillation	48 (8.8)	56 (21.4)	$P = 0.000^{*}$
Valvular heart disease	6 (1.1)	6 (2.3)	$P = 0.191$
Peripheral vascular disease	1 (0.2)	2 (0.8)	$P = 0.516$
Transient ischemic attack	4 (0.7)	0 (0)	$P = 0.310$
Previous cerebral infarction	105 (19.3)	60 (22.9)	$P = 0.231$
Previous cerebral hemorrhage	9 (1.7)	3 (1.1)	$P = 0.806$
Previous carotid endovascular treatment or endarterectomy	2 (0.4)	3 (1.1)	$P = 0.401$
Drinking, *n* (%)			$P = 0.359$
Never drinker	423 (77.6)	210 (80.2)	
Former drinker	25 (4.6)	15 (5.7)	
Current drinker	97 (17.8)	37 (14.1)	
Smoking, *n* (%)			$P = 0.003^{*}$
Never smoker	376 (69.0)	191 (72.9)	
Former smoker	27 (5.0)	25 (9.5)	
Current smoker	142 (26.1)	46 (17.6)	
Baseline data			
NIHSS score on admission, median (IQR)	3 (1–5)	8 (3–14)	$P = 0.000^{\dagger *}$
SBP, *n* (%)			$P = 0.006^{*}$
>100 and <180 mmHg	511 (93.8)	231 (88.2)	
≤100 or ≥180 mmHg	34 (6.2)	31 (11.8)	
DBP, mmHg, median (IQR)	84 (80–91)	82 (78–92)	$P = 0.576^{\dagger}$
Platelet count, 10^9/L, median (IQR)	186 (156–223)	188 (148–223)	$P = 0.660^{\dagger}$
INR, median (IQR)	0.98 (0.94–1.04)	1.01 (0.97–1.07)	$P = 0.000^{\dagger *}$
Creatinine, umol/L, median (IQR)	73.30 (61.00–86.00)	80.60 (65.00–101.00)	$P = 0.000^{\dagger *}$
FBG, mmol/L, median (IQR)	5.23 (4.68–6.44)	6.06 (5.00–8.23)	$P = 0.000^{\dagger *}$
TC, mmol/L, median (IQR)	4.20 (3.61–4.89)	4.17 (3.45–4.98)	$P = 0.494^{\dagger}$
TG, mmol/L, median (IQR)	1.36 (0.97–1.92)	1.14 (0.83–1.62)	$P = 0.000^{\dagger *}$
LDL, mmol/l, median (IQR)	2.64 (2.10–3.23)	2.59 (2.04–3.09)	$P = 0.191^{\dagger}$
HbA1c, %, median (IQR)	5.88 (5.50–6.70)	6.10 (5.60–7.10)	$P = 0.017^{\dagger *}$
Endovascular therapy, *n* (%)	56 (10.3)	44 (16.8)	$P = 0.007^{*}$
intravenous thrombolysis, *n* (%)	112 (20.6)	83 (31.7)	$P = 0.000^{*}$

mRS, indicates modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratios; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HbA1c, Glycated hemoglobin.

†Calculated using Mann–Whitney U-test.

*included into the multiple logistic regression models.

TABLE 2 | Significant predictors of 1-year unfavorable outcome after acute ischemic stroke in Chinese patients.

	OR	Error	Wald	*P* value	95% CI
Age	1.050	0.011	4.88	$P = 0.000^{*}$	1.030–1.071
NIHSS score on admission	1.172	0.024	7.62	$P = 0.000^{*}$	1.125–1.221
Creatinine	1.011	0.004	3.02	$P = 0.003^{*}$	1.004–1.017
FBG	1.111	0.045	2.62	$P = 0.009^{*}$	1.027–1.202
SBP	2.375	0.881	2.33	$P = 0.020^{*}$	1.148–4.912

NIHSS, indicates National Institutes of Health Stroke Scale; FBG, fasting blood glucose; SBP, systolic blood pressure; OR, odds ratio; CI, confidence interval.

$^{*}p < 0.05$ was considered as significant in the multivariate logistic model.

($n = 881$; 48.1%), 807 patients entered our study (median age 70 years; interquartile range: 62–79 years). The comparison of the characteristics of the patients between the included and excluded patients is shown in **Table S1**. The characteristics of the patients were well balanced between the training ($n = 537$, 66.5%) and testing ($n = 270$, 33.5%) sets (**Table S2**). The proportion of patients with unfavorable outcomes was 32.5% (262/807), and 10.5% (85/807) died within the follow-up period (mRS score = 6).

The clinical, anamnestic, demographic, and laboratory data of the patients in the favorable outcome cohorts ($n = 545$) and unfavorable outcome cohorts ($n = 262$) are shown in **Table 1**. Age, sex, NIHSS score on admission, SBP, INR, creatinine, FBG, TG, HbA1c, history of atrial fibrillation and smoking, endovascular therapy, and intravenous (IV) thrombolysis were found to be significant in the univariate analysis.

In multivariate analysis, age (OR: 1.050, $p < 0.0001$), NIHSS score on admission (OR: 1.172, $p < 0.0001$), creatinine (OR: 1.011, $p = 0.003$), FBG (OR: 1.111, $p = 0.009$), and SBP (OR: 2.375, $p = 0.020$) were finally entered into a logistic regression model to construct the SCANO nomogram for predicting the probability of unfavorable outcomes after the acute ischemic event (**Table 2**, **Figure 1**). No significant statistical collinearity was observed for any of the five pre-established variables that entered the multivariate logistic regression analysis. The logistic regression model resulted in the following: $\mathrm{Log}[p(x)/1-p(x)] = -6.763 + (0.049 \times \text{age}) + (0.159 \times \text{NIHSS score on admission}) + (0.105 \times \text{FBG}) + (0.010 \times \text{creatinine}) + (0.865 \times \text{SBP} \geq 180 \text{ or } \leq 100)$, where $p(x)$ was the probability of 1-year unfavorable outcomes.

The nomogram was established by distributing a graphic preliminary score to each of the five predictors with a point range from 0 to 100, which was then summed to compute the total score and finally transited into an individual probability of 1-year unfavorable outcomes (from 5 to 95%). The lower total score of the nomogram indicated the lower likelihood of unfavorable outcomes, whereas the higher total score was linked with the higher likelihood of unfavorable outcomes. For example, a 60-year-old (about 35 points) stroke patient, with creatinine of 75 μmol/L (about 14 points) and FBG of 5 mmol/L (about 6 points), admitted with a NIHSS score of 3 (about

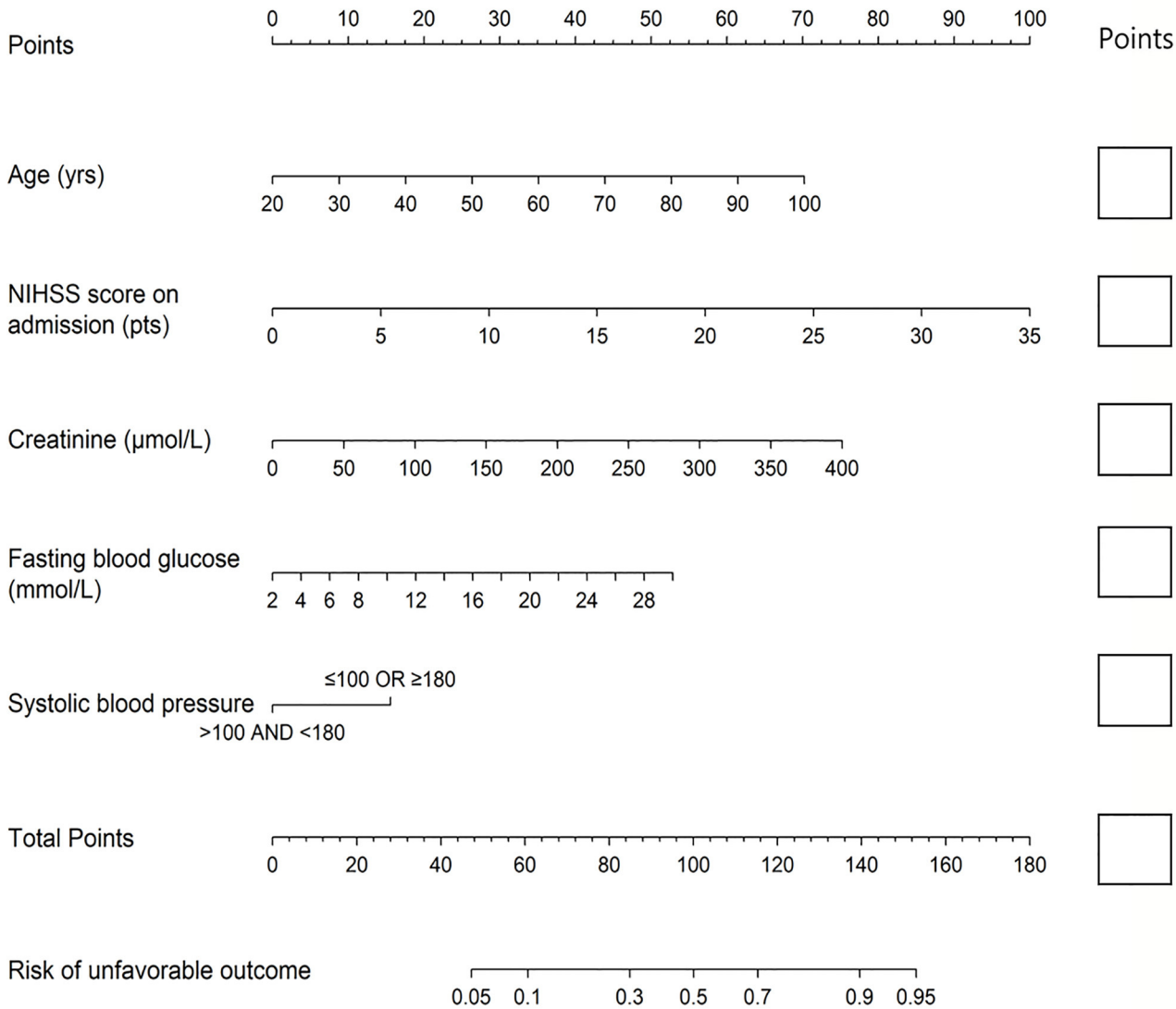

FIGURE 1 | The nomogram used for predicting 1-year unfavorable outcomes in Chinese AIS patients. The final score (i.e., total points) is calculated as the sum of the individual score of each of the five variables included in the nomogram. AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale.

10 points) and SBP of 120 (0 points), would have a total nomogram score of 65 and <20% probability of unfavorable outcomes. Conversely, a 70-year- old (about 44 points) stroke patient, admitted with a NIHSS score of 15 (about 42.5 points), creatinine of 150 μmol/L (28 points), FBG of 12 mmol/L (18 points), and SBP of 185 (about 15 points), would have a total nomogram score of 147.5 and >90% probability of unfavorable outcomes.

The discrimination of the SCANO nomogram was good, with an AUC–ROC of 0.802 (95% CI: 0.761–0.843) in the training set (**Figure 2A**) and 0.781 (95% CI: 0.721–0.840) in the testing set (**Figure 2B**). The Hosmer–Lemeshow goodness-of-fit test showed good calibration of the nomogram in the training ($p = 0.437$) and testing ($p = 0.178$) sets. The calibration plot revealed adequate fit of the model predicting the risk of 1-year unfavorable outcomes in the training (**Figure 3A**) and testing (**Figure 3B**) sets. The calibration slope, calibration intercept, and Brier score in the testing data were 0.936, 0.060, and 0.166, respectively.

In the testing data, there were 39 (14.4%) patients with a risk probability < 10%, and only two of these had an unfavorable outcome (0.21 specificity, 0.97 sensitivity, 0.37 positive predictive value, and 0.93 negative predictive value). The number of a risk probability < 40% was 198 (73.3%), 38 of whom (19.2%) had unfavorable outcomes (0.88 specificity, 0.60 sensitivity, 0.70 positive predictive value, and 0.82 negative predictive value). Finally, the patients with a high-risk probability

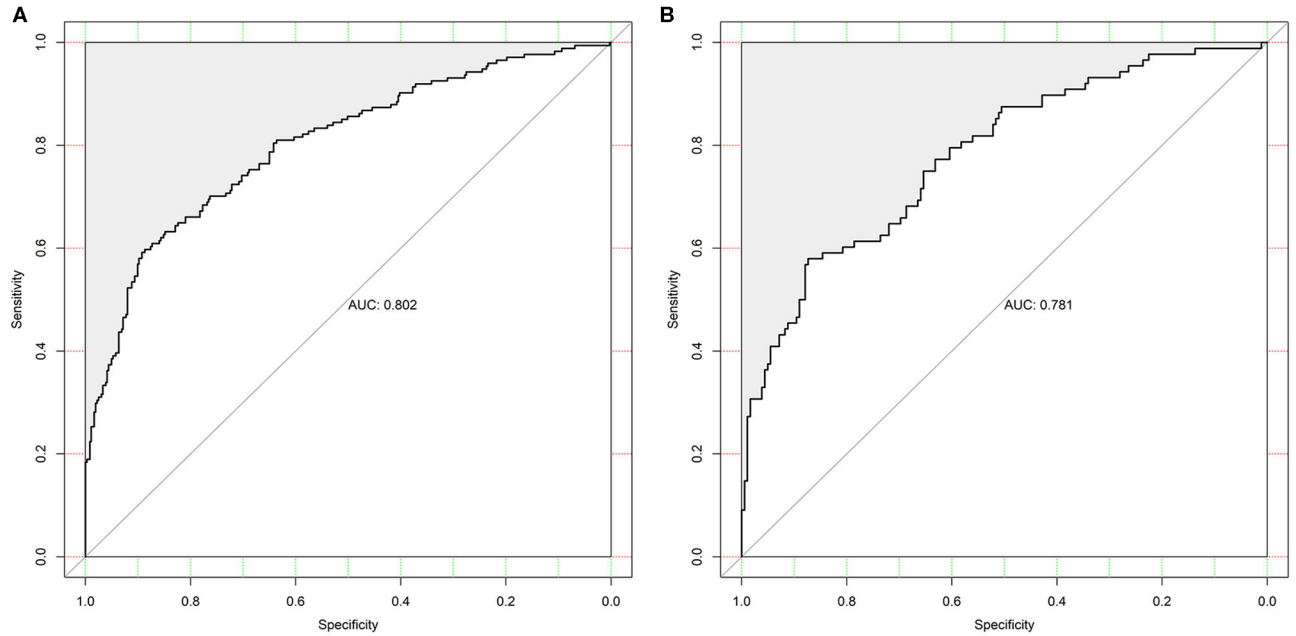

FIGURE 2 | The ROC curve of the nomogram used for predicting 1-year unfavorable outcomes in Chinese AIS patients. **(A)** The ROC curve in the training set. **(B)** The ROC curves in the testing set. ROC, receiver operating characteristic; AIS, acute ischemic stroke.

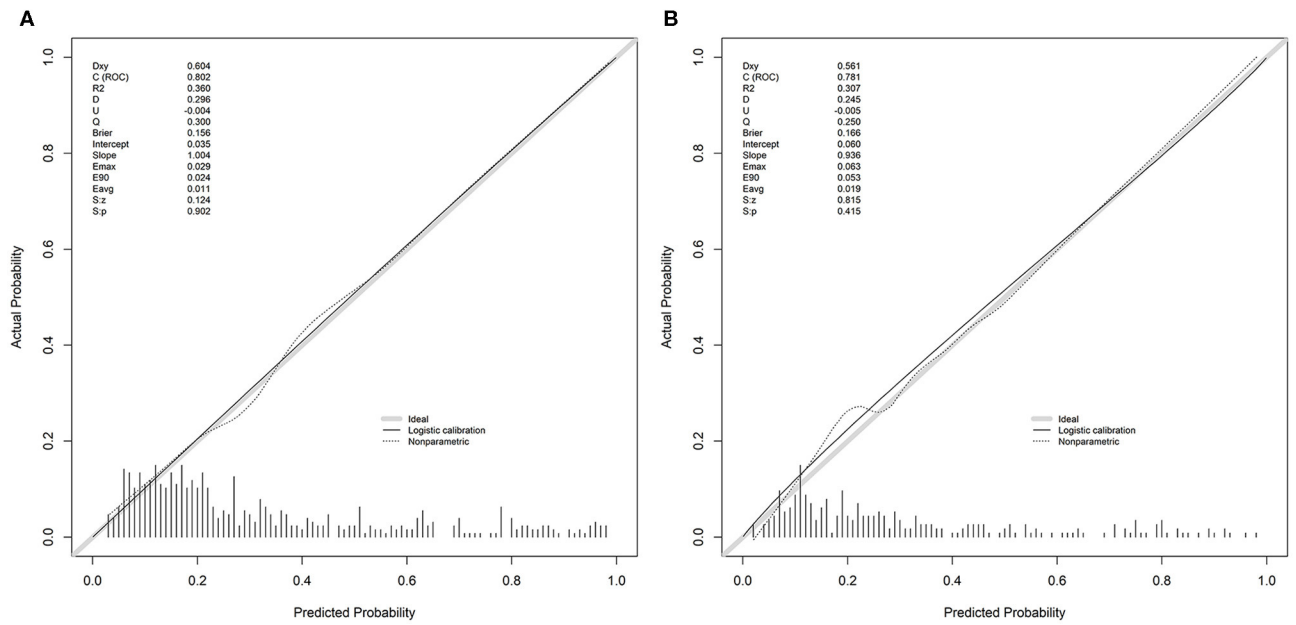

FIGURE 3 | The calibration plot for the nomogram used for predicting 1-year unfavorable outcomes in Chinese AIS patients. **(A)** The calibration plot in the training set. **(B)** The calibration plot in the testing set. Dashed line is reference line where an ideal nomogram would lie. The dotted line is the performance of nomogram, whereas the solid line corrects for any bias in nomogram. AIS, acute ischemic stroke.

(i.e., >80%) were 18/270 (6.7%), the vast majority of whom (16/18; 88.9%) had an unfavorable prognosis (0.99 specificity, 0.24 sensitivity, 0.91 positive predictive value, and 0.73 negative predictive value).

DISCUSSION

Stroke is a major cause of death and lifelong disability worldwide (1, 2). As a public health problem, early prediction of unfavorable

outcomes of AIS patients should be an important reference for accurate clinical and therapeutic management and has the potential to enhance clinical care and rehabilitation. So far, there are some reports on 3-month unfavorable outcomes after stroke (4, 5, 19, 20), and previous studies have attempted to use the nomogram to predict 3-month unfavorable outcomes for AIS patients (6–8). However, to date, there is no nomogram to predict unfavorable outcomes in the longer term, and the SCANO nomogram was developed and validated in Chinese AIS patients to firstly predict 1-year unfavorable outcomes, which is advantageous by providing individualized risk assessment in a user-friendly and dynamic manner. Furthermore, we emphasize that we have included only the five common variables, which are available in clinical practice. In addition, our nomogram may be more easily and quickly employed in a clinical practice if used with related software on a computer or a handheld device.

Our study showed that age, creatinine, FBG, NIHSS score on admission, and SBP were significantly independent predictors of unfavorable outcomes in Chinese AIS patients. Firstly, consistent with previous studies (4, 6, 12), our study showed that age and NIHSS score on admission were significant and independent predictors of unfavorable outcomes in Chinese AIS patients. Indeed, the NIHSS score manifests a more severe stroke, which can be more likely associated with unfavorable outcomes, whereas age can generally bring about a less intense recovery. Secondly, serum creatinine concentration is generally considered as an index of renal function. However, the relationship between renal function and stroke outcomes is controversial (21, 22). Future studies regarding to the mechanisms of creatinine in the pathogenesis of stroke are needed. Thirdly, the results of our study showed a relationship between admission SBP and unfavorable outcomes, which was described as a distinct U-shaped relation in the previous studies (16–18). Finally, hyperglycemia in ischemic stroke patients could predict unfavorable outcomes independently, possibly owing to increased blood–brain barrier disruption with higher hemorrhagic risk (23, 24) or increased lactic acid production in ischemic tissue leading to a greater infarct size (25).

Consequently, we have developed and validated a nomogram on the basis of the combination of these five variables, and we observed relatively high predictive accuracy (AUC, 0.781) of unfavorable outcomes. Importantly, a risk probability $>$ 80% derived from the nomogram displayed a remarkably positive predictive value (i.e., 0.91), which can predict accurately unfavorable outcomes. On the other hand, a risk probability $<$ 10% was associated with 0.93 negative predictive value, thus enabling to exclude accurately the possibility of developing unfavorable outcomes. Therefore, the SCANO nomogram may provide more detailed information to facilitate the early identification of patients with high probability of unfavorable outcomes and to discuss prognosis with patients and their families.

There are some limitations that might have an impact on the interpretation of our results. Firstly, this is characterized by the inherent disadvantage of any retrospective single-center study such as collection and entry bias, and possible residual confounding. For example, there were some cases that were lost to follow-up. It is unclear whether we have overestimated or underestimated the unfavorable outcomes after AIS. However, most of models to predict functional outcomes of ischemic stroke were built in this way. Secondly, patient populations with limited geographical or ethnicity area have been a concern in the development of predictive models, and racial differences may have affected the unfavorable outcomes (26). External validation, especially in different populations, is the future work for this predictive model. Finally, data of known neurobiological predictors such as infarct size (27) were not available in our study. Notwithstanding these limitations, to our knowledge, the present study is the first attempt to develop and validate a nomogram to predict 1-year unfavorable outcomes in a cohort of AIS patients in agreement with the current guidelines.

CONCLUSION

The SCANO nomogram may be a reliable and easy-to-use tool to firstly predict 1-year unfavorable outcomes, which is developed and validated in Chinese AIS patients. External validations are needed to ensure its value in predicting the 1-year outcomes for AIS patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All patients have given their written informed consent and the scientific use of the data obtained from the Nanjing First Hospital Stroke Registry was approved by the Ethics Committees of Nanjing First Hospital in accord with the Helsinki declaration and internal protocol.

AUTHOR CONTRIBUTIONS

ML and JZo conceived, designed, and supervised the study. FW, CS, XuL, CH, and JZh acquired the data. XiL and ZhiZ analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis. XiL, LN, and ZheZ drafted the manuscript. JZo, ML, ZhiZ, and JL critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00531/full#supplementary-material

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation.* (2018) 137:e67. doi: 10.1161/CIR.0000000000000573
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation.* (2019) 139:e56–528. doi: 10.1161/CIR.0000000000000659
3. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology.* (2012) 78:1916–22. doi: 10.1212/WNL.0b013e318259e221
4. Strbian D, Meretoja A, Ahlhelm FJ, Pitkäniemi J, Lyrer P, Kaste M, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. *Neurology.* (2012) 78:427–32. doi: 10.1212/WNL.0b013e318245d2a9
5. Saposnik G, Fang J, Kapral MK, Tu JV, Mamdani M, Austin P, et al. The iScore predicts effectiveness of thrombolytic therapy for acute ischemic stroke. *Stroke.* (2012) 43:1315–22. doi: 10.1161/STROKEAHA.111.646265
6. Song B, Liu Y, Nyame L, Chen X, Jiang T, Wang W, et al. A COACHS nomogram to predict the probability of three-month unfavorable outcome after acute ischemic stroke in chinese patients. *Cerebrovasc Dis.* (2019) 47:80–7. doi: 10.1159/000497243
7. Turcato G, Cervellin G, Cappellari M, Bonora A, Zannoni M, Bovi P, et al. Early function decline after ischemic stroke can be predicted by a nomogram based on age, use of thrombolysis, RDW and NIHSS score at admission. *J Thromb Thrombolysis.* (2017) 43:394–400. doi: 10.1007/s11239-016-1456-y
8. Cappellari M, Turcato G, Forlivesi S, Zivelonghi C, Bovi P, Bonetti B, et al. STARTING-SICH nomogram to predict symptomatic intracerebral hemorrhage after intravenous thrombolysis for stroke. *Stroke.* (2018) 49:397–404. doi: 10.1161/STROKEAHA.117.018427
9. Wondergem R, Pisters MF, Wouters EJ, Olthof N, de Bie RA, Visser-Meily JMA, et al. The course of activities in daily living: who is at risk for decline after first ever stroke? *Cerebrovasc Dis.* (2017) 43:1–8. doi: 10.1159/000451034
10. Lee KB, Lim SH, Kim KH, Kim KJ, Kim YR, ChangWN, et al. Six-month functional recovery of stroke patients: a multi-time-point study. *Int J Rehabil Res.* (2015) 38:173–80. doi: 10.1097/MRR.0000000000000108
11. Ullberg T, Zia E, Petersson J, Norrving B. Changes in functional outcome over the first year after stroke: an observational study from the Swedish stroke register. *Stroke.* (2015) 46:389–94. doi: 10.1161/STROKEAHA.114.006538
12. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* (2014) 384:1929–35. doi: 10.1016/S0140-6736(14)60584-5
13. Weimar C, Konig IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. *Stroke.* (2004) 35:158–62. doi: 10.1161/01.STR.0000106761.94985.8B
14. Vora NA, Shook SJ, Schumacher HC, Tievsky AL, Albers GW, Wechsler LR, et al. A 5-item scale to predict stroke outcome after cortical middle cerebral artery territory infarction: validation from results of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. *Stroke.* (2011) 42:645–9. doi: 10.1161/STROKEAHA.110.596312
15. Saver JL, Altman H. Relationship between neurologic deficit severity and final functional outcome shifts and strengthens during first hours after onset. *Stroke.* (2012) 43:1537–41. doi: 10.1161/STROKEAHA.111.636928
16. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke.* (2002) 33:1315–20. doi: 10.1161/01.STR.0000014509.11540.66
17. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med.* (2004) 255:257–65. doi: 10.1046/j.1365-2796.2003.01291.x
18. Keezer MR, Amy YX, Zhu B, Wolfson C, Côté R. Blood pressure and antihypertensive therapy as predictors of early outcome in acute ischemic stroke. *Cerebrovasc Dis.* (2008) 25:202–8. doi: 10.1159/000113857
19. Martins AI, Sargento-Freitas J, Silva F, Jesus-Ribeiro J, Correia I, Gomes JP, et al. Recanalization modulates association between blood pressure and functional outcome in acute ischemic stroke. *Stroke.* (2016) 47:1571–6. doi: 10.1161/STROKEAHA.115.012544
20. Sposato LA, Cohen G, Wardlaw JM, Sandercock P, Lindley RI, Hachinski V. Effect of right insular involvement on death and functional outcome after acute ischemic stroke in the IST-3 trial (Third International Stroke Trial). *Stroke.* (2016) 47:2959–65. doi: 10.1161/STROKEAHA.116.014928
21. Nugroho AW, Arima H, Miyazawa I, Fujii T, Miyamatsu N, Sugimoto Y, et al. The association between glomerular filtration rate estimated on admission and acute stroke outcome: the Shiga Stroke Registry. *J Atheroscler Thromb.* (2014) 25:570–9. doi: 10.5551/jat.42812
22. Yang J, Arima H, Zhou J, Zhao Y, Li Q, Wu G, et al. Effects of low estimated glomerular filtration rate on outcomes after stroke: a hospital-based stroke registry in China. *Eur J Neurol.* (2014) 21:1143–5. doi: 10.1111/ene.12311
23. Kamada H, Yu F, Nito C, Chan PH. Influence of hyperglycemia on oxidative stress and matrix metalloproteinase-9 activation after focal cerebral ischemia/reperfusion in rats: relation to blood-brain barrier dysfunction. *Stroke.* (2007) 38:1044–9. doi: 10.1161/01.STR.0000258041.75739.cb
24. Ennis SR, Keep RF. Effect of sustained-mild and transient-severe hyperglycemia on ischemia-induced blood-brain barrier opening. *J Cereb Blood Flow Metab.* (2007) 27:1573–82. doi: 10.1038/sj.jcbfm.9600454
25. Suh SW, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, et al. Glucose and NADPH oxidase drive neuronal superoxide formation in stroke. *Ann Neurol.* (2008) 64:654–63. doi: 10.1002/ana.21511
26. Burke JF, Freedman VA, Lisabeth LD, Brown DL, Haggins A, Skolarus LE. Racial differences in disability after stroke: results from a nationwide study. *Neurology.* (2014) 83:390–7. doi: 10.1212/WNL.0000000000000640
27. Cappellari M, Turcato G, Forlivesi S, Micheletti N, Tomelleri G, Bonetti B, et al. Introduction of direct oral anticoagulant within 7 days of stroke onset: a nomogram to predict the probability of 3-month modified Rankin Scale score>2. *J Thromb Thrombolysis.* (2018) 46:292–8. doi: 10.1007/s11239-018-1700-8

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CORRECTION
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Corrigendum: A SCANO Nomogram for Individualized Prediction of the Probability of 1-Year Unfavorable Outcomes in Chinese Acute Ischemic Stroke Patients

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A Corrigendum on

A SCANO Nomogram for Individualized Prediction of the Probability of 1-Year Unfavorable Outcomes in Chinese Acute Ischemic Stroke Patients

by Li, X., Wang, F., Zhao, Z., Sun, C., Liao, J., Li, X., et al. (2020). Front. Neurol. 11:531. doi: 10.3389/fneur.2020.00531

In the published article there was an error regarding the affiliation for Jianjun Zou and Zheng Zhao. Instead of having affiliation 1 and affiliation 2, Jianjun Zou and Zheng Zhao have only affiliation 2.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Efficacy and Safety of Intravenous Thrombolysis on Acute Branch Atheromatous Disease: A Retrospective Case–Control Study

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Background and Objective: Branch atheromatous disease (BAD) is distinctive from large-artery atherosclerosis and small-vessel disease, which is single subcortical infarction caused by the occlusion of perforator's orifice. This study aimed to indicate whether intravenous thrombolysis (IVT) with alteplase could prevent early neurological deterioration (END) and improve functional outcome for patients with BAD within 4.5 h after symptom onset.

Methods: We retrospectively analyzed data collected from patients with BAD who were admitted to our hospital from January 2015 to August 2019. To investigate the efficacy and safety of IVT, subjects were classified into alteplase and control groups. A propensity score matching analysis was performed to control substantial heterogeneity of subgroup. The coprimary outcomes were END that is defined as an increase of ≥2 points in the National Institutes of Health Stroke Scale (NIHSS) score within 7 days after stroke, and favorable outcome at 3 months after stroke that defined by a score of 0–1 point on the modified Rankin scale (mRS).

Results: A total of 135 patients were eventually enrolled in this study ($n = 51$ for the alteplase group and $n = 84$ for the control group). Additionally, 42 pairs of subjects were successfully matched by propensity score matching. Intravenous alteplase within 4.5 h after stroke onset reduced the incidence of END [unadjusted odds ratio (OR), 3.32; 95% confidence interval (CI), 1.06–10.37] and improved the clinical outcome at 3 months after stroke, with more patients achieving favorable functional prognosis (mRS, 0–1 point; unadjusted OR, 0.25; 95% CI, 0.10–0.62). Patients in the alteplase group were more likely to be independent (mRS, 0–2 points) at 3 months after stroke (unadjusted OR, 0.33; 95% CI, 0.12–0.90). The rate of death or dependence (mRS, ≥4 points) in the alteplase group was also markedly lower than that in the control group (unadjusted OR, 4.06; 95% CI, 1.03–16.02).

Conclusion: Our findings indicated that intravenous thrombolysis may be a safe and effective therapy for patients with BAD.

Keywords: acute stroke, branch atheromatous disease, early neurological deterioration, intravenous thrombolysis, antiplatelet treatment, propensity score matching

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INTRODUCTION

Branch atheromatous disease (BAD) was first described as a mechanism alternative to lipohyalinosis and considered the arteriopathy closely associated with pathogenesis of single subcortical infarction (1). It is a common subtype of intracranial atherosclerotic stroke, particularly in Asian countries (2), and its prevalence was reported as high as 10.4–18.3% (3, 4). Radiographically, BAD can be misdiagnosed as lacunar infarction, while it is quite different from lacunar infarction in physiopathology. Lacunar infarction is pathologically characterized by fibrinoid degeneration or lipohyalinosis of penetrating artery (5), while BAD is caused by parent arterial disease occluding the perforator's orifice (2). Clinically, early neurological deterioration (END) was reported to frequently occur in BAD patients and often resulted in severe disability (6–8). However, to date, no optimal therapeutic approach for BAD has been presented.

Intravenous thrombolysis (IVT) with alteplase has been approved for treating acute ischemic stroke, regardless of stroke subtype (9, 10). The majority of patients with BAD was classified as minor stroke, while patients with minor stroke typically does not receive IVT. It has been previously reported that IVT neither improves clinical outcome nor prevents END in such patients, while the results of these studies could not be generalized because of their small sample size and lack of control group (11, 12). Whether IVT can effectively treat BAD has still remained elusive. In the present study, we aimed to assess whether IVT can be more effective than usual care in preventing END and improving clinical outcome for patients with BAD within 4.5 h after symptom onset.

MATERIALS AND METHODS

This is a retrospective case–control study, which was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Wuhan, China) and was carried out in compliance with the Declaration of Helsinki. The need to informed consent was waived.

Study Subjects

This retrospective study was performed based on clinical data consecutively collected from patients with BAD who were admitted to Zhongnan Hospital of Wuhan University from January 2015 to August 2019. Inclusion criteria were as follows: subjects who (1) were treated within 4.5 h after symptom onset, (2) received intravenous alteplase or/and antiplatelet therapy, (3) completed follow-up process at 3 months after stroke, and (4) were diagnosed by diffusion-weighted imaging (DWI). Exclusion criteria were as follows: subjects who (1) were treated beyond 4.5 h after symptom onset, (2) received intravenous urokinase, (3) failed to complete magnetic resonance imaging (MRI) or had poor imaging quality, or (4) did not complete follow-up at 3 months after stroke. **Figure 1** shows the flowchart of selection of eligible study subjects. Moreover, as illustrated in **Figure 2**, BAD-related infarctions were previously defined as follows (6, 11–15): (1) infarcts with a diameter $\geq$15 mm that involves $\geq$3 axial slices on DWI in the blood-supply region of lenticulostriate artery, or lesions extending to the ventral pontine surface in the blood-supply region of paramedian pontine artery; (2) neither evidence of large arterial stenosis (>50%) or occlusion, nor evidence of cardiogenic embolism.

Demographic characteristics, including age and sex, as well as clinical data, involving onset-to-needle time (ONT), baseline National Institutes of Health Stroke Scale (NIHSS) score, blood pressure at admission, baseline blood glucose levels, NIHSS score at discharge, and length of stay at hospital were recorded. Risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, history of smoking, atrial fibrillation, and history of ischemic stroke were recorded as well. The clinical data were collected by two neurologists (CN and ZK).

Therapeutic Approach

Subjects were classified into alteplase and control groups. Alteplase with a standard dose of 0.9 mg/kg was administered to patients in the alteplase group within 4.5 h after stroke onset. After confirmed no cerebral hemorrhage by non-contrast computed tomography (CT) at 24 h after intravenous alteplase, 75 mg of clopidogrel and 100 mg of aspirin were given by once daily. In the control group, 300 mg of clopidogrel and 100 mg of aspirin were initially given, followed by 75 mg of clopidogrel and 100 mg of aspirin once daily. After 21 days of undergoing dual-antiplatelet therapy, patients in the two groups were treated with aspirin or clopidogrel alone for a long time (16, 17). To avoid potential selection bias, a limited number of BAD patients who underwent mono-antiplatelet therapy were included in the current study. All patients would discontinue antiplatelet therapy if intracerebral hemorrhage was confirmed.

Imaging Assessment

According to the American Heart Association/American Stroke Association (AHA/ASA) guideline for the early management of acute ischemic stroke (18), CT/MRI scans were performed at the time of admission prior to any treatment. The MRI of all subjects was carried out within 48 h after stroke onset, with T1WI + T2WI + DWI + T2Flair + magnetic resonance angiography (MRA) sequences, which were obtained using Siemens 3.0 T MRI scanner (Siemens AG, Munich, Germany). The BAD was diagnosed by two neurologists (XW and YL) with more than 5 years of diagnostic experience. If there was a discrepancy in their diagnoses, another senior neurologist made the final decision. The intrarater reliability of BAD was tested in 20 subjects by a single assessor with kappa (κ) coefficient equal to 0.92.

Clinical Outcomes and Safety Variables

The modified Rankin scale (mRS) score, which ranges from 0 (no symptom) to 6 (death), was assessed at 3 months after stroke by trained neurologists (YL, CN, and ZK) who were unaware of the therapeutic measures. Besides, the severity of initial stroke was measured using NIHSS, which was conducted daily by members of our team. The coprimary outcomes were END, which was

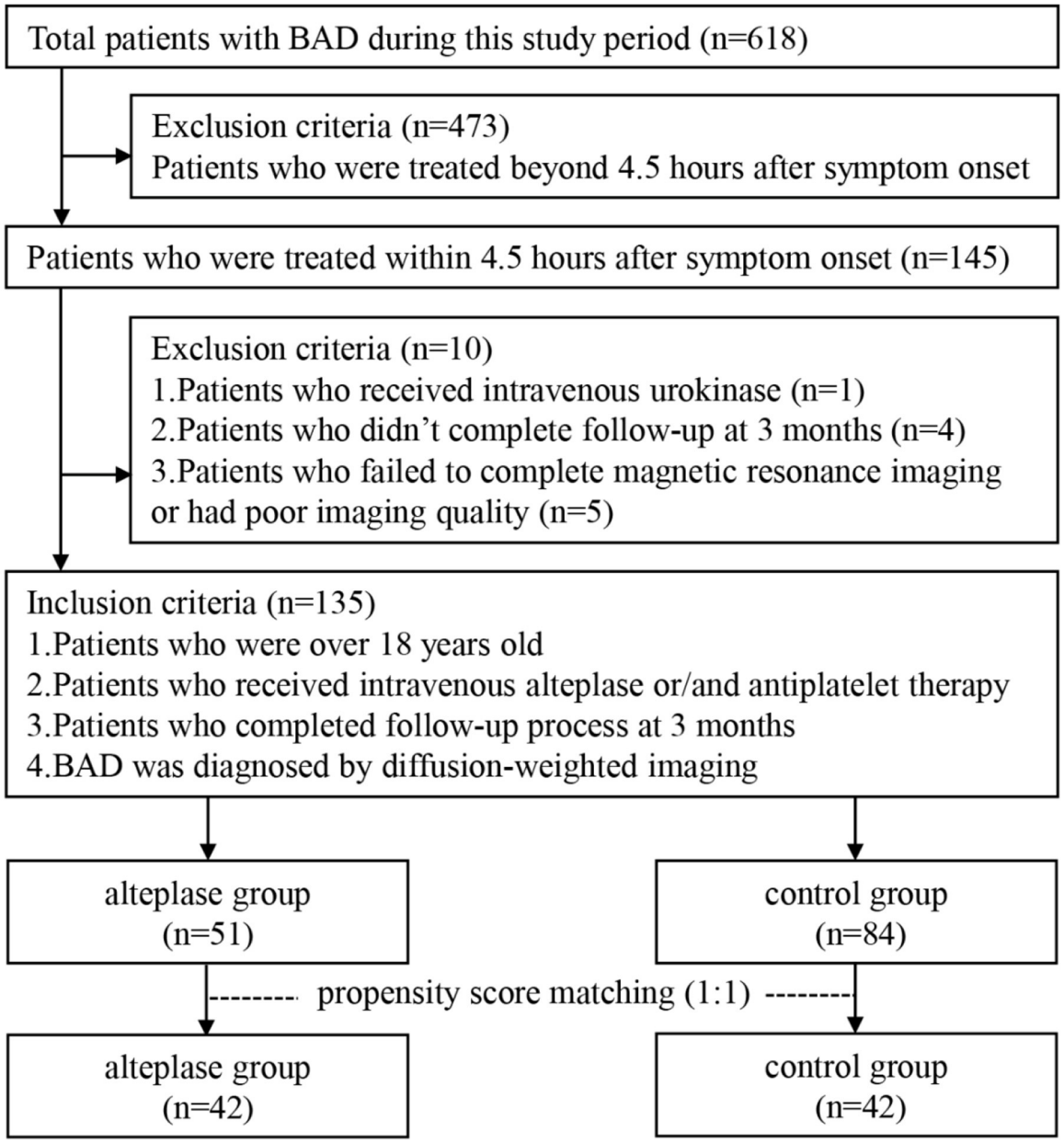

FIGURE 1 | Flowchart of selection of eligible study subjects. BAD, branch atheromatous disease.

defined as an increase of ≥2 points in the NIHSS score within 7 days after stroke (3, 11) and favorable outcome at 3 months after stroke, which was defined by a score of 0–1 point on the modified Rankin Scale (19). Safety variables were death or dependence defined as the mRS score of ≥4 points at 3 months after stroke and the incidence of symptomatic intracranial hemorrhage (sICH) and parenchymal hemorrhage type 2 (PH-2) according to the European Cooperative Acute Stroke Study II (ECASS II), including hemorrhagic infarction classifications HI 1 and HI 2 and parenchymal infarction classifications PH-1 and PH-2 (20).

Statistical Analysis

Baseline characteristics were analyzed by the Student's *t*-test, the Mann–Whitney *U*-test, chi-squared test, or Fisher's exact test. We stratified the following variables for multivariate regression analysis: the baseline NIHSS score (1–3, 4–6, or>6 points), age (≤70 or >70 years old), and onset-to-needle time (≤3 or 3–4.5 h). To minimize the effects of selection bias, propensity score matching analysis was undertaken. Matching factors included all unbalanced variables ($P \leq 0.1$). One-to-one nearest-neighbor matching with a caliper of 0.1 was used to create two matched groups from the derived propensity score. The coprimary

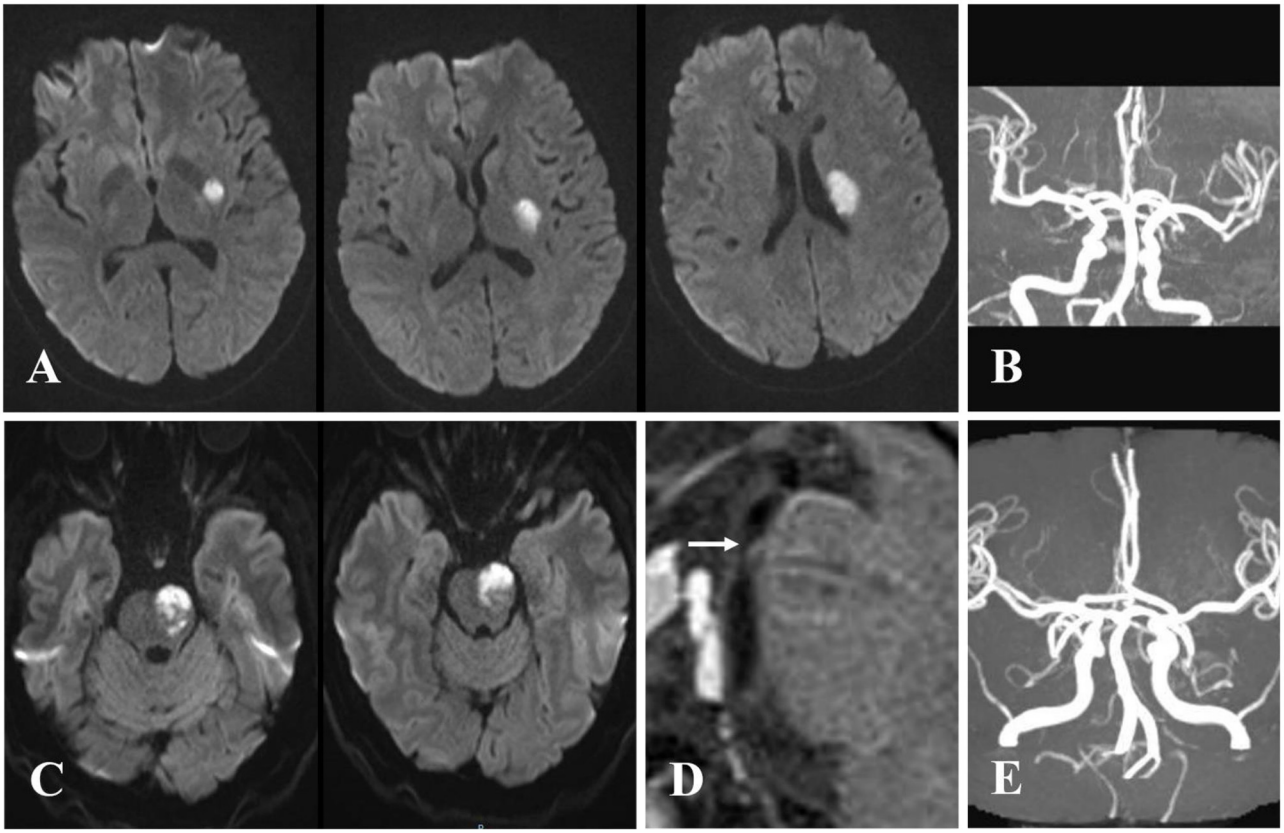

FIGURE 2 | Examples of cases with branch atheromatous disease (BAD). Case 1: A 57-year-old woman with right-sided weakness. **(A)** Diffusion-weighted imaging (DWI) showing cerebral stroke in the area of lenticulostriate artery. **(B)** Magnetic resonance angiography (MRA) illustrating no significant stenosis of parent artery. Case 2: A 61-year-old man with right-sided weakness and dysarthria. **(C)** DWI showing infarction extended to the ventral pontine surface in the area of paramedian pontine artery. **(D)** Vessel wall magnetic resonance imaging (VWMRI) depicting junctional plaque in the orifice of paramedian pontine artery. **(E)** MRA displaying no significant stenosis of basilar artery.

outcomes were the unadjusted odds ratio (OR) for END and favorable outcome (mRS score, 0–1 point), using binary logistic regression analysis to assess the odds ratio and its 95% confidence interval (CI). For safety variables, we also fitted a binary logistic regression model to evaluate the odds ratio and its 95% CI. $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS 23.0 software (IBM, Armonk, NY, USA).

RESULTS

Baseline Characteristics

Between January 2015 and August 2019, a total of 145 BAD patients within 4.5 h after stroke onset were consecutively enrolled in this study. According to the mentioned inclusion and exclusion criteria, 135 patients were included for final analysis ($n = 51$ for alteplase group, $n = 84$ for control group), and 10 patients were excluded (**Figure 1**). There was no significant di?erence in baseline characteristics and clinical outcomes between patients who were included and those who were excluded (**Supplementary Table 1**).

In the original cohort, patients in the alteplase group were more severely affected at admission, with a higher baseline NIHSS score (median, 7 vs. 4, $P < 0.001$), and had a lower rate of ischemic stroke history (5.9 vs. 17.9%, $P = 0.047$). Other patients' baseline characteristics showed no statistically significant difference (**Table 1**). A total of 42 pairs of subjects in the two groups were successfully matched by propensity score matching. All patients' baseline characteristics were comparable in our matched cohort (**Table 1**).

Outcomes in the Original Cohort

Thirty-five patients (25.9%) suffered from END in our unmatched cohort, which had longer length of stay at hospital and worse functional outcome (**Supplementary Table 2**). In univariate logistic regression analysis, there was significant difference in incidence of END between the two groups (unadjusted OR, 2.55; 95% CI, 1.05–6.16; $P = 0.038$). In multivariable logistic regression analysis, after adjusted for baseline NIHSS score and history of ischemic stroke, patients in the alteplase group had more favorable functional outcome [28 of 51 (54.9%) vs. 40 of 84 (47.6%); adjusted OR, 0.30; 95% CI,

TABLE 1 | The demographics and clinical characteristics of patients with branch atheromatous disease.

Variables	Unmatched Cohort			Matched Cohort		
	Alteplase Group ($n = 51$)	Control Group ($n = 84$)	*P*-value	Alteplase Group ($n = 42$)	Control Group ($n = 42$)	*P*-value
Age, mean ± SD, year	59.1 ± 12.2	64.2 ± 12.5	0.834	59.3 ± 11.9	63.7 ± 14.7	0.168
Male, *n* (%)	32 (62.7)	60 (71.4)	0.294	25 (59.5)	32 (76.2)	0.102
Risk factors						
Hypertension, *n* (%)	34 (66.7)	51 (60.7)	0.487	27 (64.3)	26 (61.9)	0.821
Hyperlipidemia, *n* (%)	25 (49.0)	36 (42.9)	0.485	22 (52.4)	17 (40.5)	0.274
Diabetes, *n* (%)	11 (21.6)	26 (31.0)	0.236	11 (26.2)	14 (33.3)	0.474
Smoking, *n* (%)	17 (33.3)	22 (26.2)	0.375	11 (26.2)	9 (21.4)	0.606
History of ischemic stroke, *n* (%)	3 (5.9)	15 (17.9)	0.047	3 (7.1)	5 (11.9)	0.713
Blood pressure at admission						
SBP, mean ± SD, mmHg	152.2 ± 21.1	154.1 ± 23.4	0.371	150 (138, 166)	155 (126, 180)	0.213
DBP, median (IQR), mmHg	88 (76, 99)	85 (76, 99)	0.414	89 (76, 95)	89 (76, 104)	0.629
Baseline blood glucose, median (IQR), mmol/L	5.4 (5.0, 6.3)	5.8 (5.1, 7.0)	0.370	5.4 (5.0, 6.3)	5.9 (5.3, 7.3)	0.181
Onset-to-needle time, median (IQR), hours	3 (3, 4)	3 (2, 4)	0.648	3 (2, 4)	3 (2, 4)	0.790
Baseline NIHSS score, median (IQR)	7 (4, 9)	4 (3, 6)	<0.001	5 (4, 8)	5 (4, 7)	0.664
NIHSS score at discharge, median (IQR)	2 (0, 5)	4 (2, 6)	0.009	2 (0, 4)	4 (3, 8)	<0.001
Hospital stay, median (IQR), days	9 (6, 12)	11 (9, 14)	0.005	9 (6, 11)	12 (9, 15)	0.001
Infarct site						
The lenticulostriate artery, *n* (%)	37 (72.5)	59 (70.2)	0.774	30 (71.4)	30 (71.4)	1.000
The paramedian pontine artery, *n* (%)	14 (27.5)	25 (29.8)	0.774	12 (28.6)	12 (28.6)	1.000
Dual antiplatelet treatment, *n* (%)	48 (94.1)	79 (94.0)	0.987	39 (92.9)	41 (97.6)	0.616

SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure.

0.12–0.74; $P = 0.009$]. The rate of death or dependence (mRS ≥ 4 points at 3 months after stroke) in the alteplase group was lower than that in the control group, whereas no significant difference was noted (adjusted OR, 3.14; 95% CI, 0.90–10.91; $P = 0.072$). At 3 months after stroke, a 91-year-old man in the control group died of pulmonary infection secondary to stroke, while no death happened in the alteplase group. There were two (3.9%) cases with PH-2 in the alteplase group, while no case of intracerebral hemorrhage was observed in the control group. One of the two cases had cerebral hemorrhage with no clinical symptoms, and the other had sICH in the infarcted region with severe disability (**Table 2** and **Figure 3**).

Outcomes in the Matched Cohort

As mentioned earlier, to control substantial heterogeneity of subgroup, a propensity score matching analysis was carried out, which resulted in inclusion of 42 pairs of subjects in the matched cohort. Patients in the alteplase group remarkably improved in both primary and secondary outcomes compared with the control group. Favorable outcome (mRS, 0–1 point) at 3 months after stroke was found in 28 (66.7%) of 42 patients in the alteplase group compared with 14 (33.3%) of 42 patients in the control group (unadjusted OR, 0.25; 95% CI, 0.10–0.62; $P = 0.003$), and END was observed in 5 (11.9%) of 42 patients in the alteplase group compared with 13 (31.0%) of 42 patients in the control group (unadjusted OR, 3.32; 95% CI, 1.06–10.34; $P = 0.039$). Patients in the alteplase group were more likely to be independent (mRS, 0–2 points) at 3 months after stroke (unadjusted OR, 0.33; 95% CI, 0.12–0.90; $P = 0.031$). The rate of death or dependence (mRS, ≥ 4 points) in the alteplase group was also markedly lower than that in the control group (unadjusted OR, 4.06; 95% CI, 1.03–16.02; $P = 0.045$). There was one case of sICH with severe disability in the alteplase group, while one case died in the control group (**Table 2** and **Figure 3**).

DISCUSSION

In 1989, Caplan initially put forward the concept of BAD and elucidated its pathomechanism, which was an occlusion or stenosis at the orifice of one or several penetrating arterial branches due to microatheroma or junctional plaque (21). However, BAD remains an underused concept in clinical practice and research in Western countries for decades (15). In contrast, BAD is a well-known disease in Asian countries, especially in Japan, China, and South Korea. Owing to routine imaging techniques that are unable to depict small vessel changes, features used to define BAD are mostly indirect, consisting of vascular territory and morphological characteristics of the ischemic lesion. The definition of BAD has not been fully set up yet, but it is universally accepted that BAD is a single

TABLE 2 | Study outcomes.

Outcomes	Alteplase Group	Control Group	Binary Logistic Regression Analysis	
Unmatched cohort	**(*n* = 51)**	**(*n* = 84)**	**Adjusted OR (95% CI)**	***P*-value**
Primary outcomes				
mRS ≤ 1 at 3 months, *n* (%)†	28 (54.9)	40 (47.6)	0.30 (0.12, 0.74)	0.009
Early neurological deterioration, *n* (%)‡	8 (15.7)	27 (32.1)	2.55 (1.05, 6.16)	0.038
Secondary and safety outcomes				
mRS ≤ 2 at 3 months, *n* (%)†	40 (78.4)	62 (73.8)	0.43 (0.16, 1.12)	0.084
mRS ≥ 4 at 3 months, *n* (%)†	5 (9.8)	13 (15.5)	3.14 (0.90, 10.91)	0.072
Intracranial hemorrhage, *n* (%)	2 (3.9)*	0	–	–
Death, *n* (%)	0	1 (2.0)	–	–
Matched cohort	**(*n* = 42)**	**(*n* = 42)**	**Unadjusted OR (95% CI)**	***P*-value**
Primary outcomes				
mRS ≤ 1 at 3 months, *n* (%)	28 (66.7)	14 (33.3)	0.25 (0.10, 0.62)	0.003
Early neurological deterioration, *n* (%)	5 (11.9)	13 (31.0)	3.32 (1.06, 10.37)	0.039
Secondary and safety outcomes				
mRS ≤ 2 at 3 months, *n* (%)	35 (83.3)	26 (61.9)	0.33 (0.12, 0.90)	0.031
mRS ≥ 4 at 3 months, *n* (%)	3 (7.1)	10 (23.8)	4.06 (1.03, 16.02)	0.045
Intracranial hemorrhage, *n* (%)	2 (5.0)*	0	–	–
Death, *n* (%)	0	1 (2.5)	–	–

mRS, modified Rankin scale score; OR, odds ratio.

† These models were adjusted for baseline NIHSS score and history of ischemic stroke.

‡ Univariate logistic regression analysis was performed due to the failure of fitting a multivariate model adjusted for baseline NIHSS score and history of ischemic stroke.

**There were two cases (3.9%) of parenchymal hemorrhage type 2 according to the criteria of ECASS II in the alteplase group, one of the two cases had symptomatic intracranial hemorrhage in the infarcted region and left severe disability.*

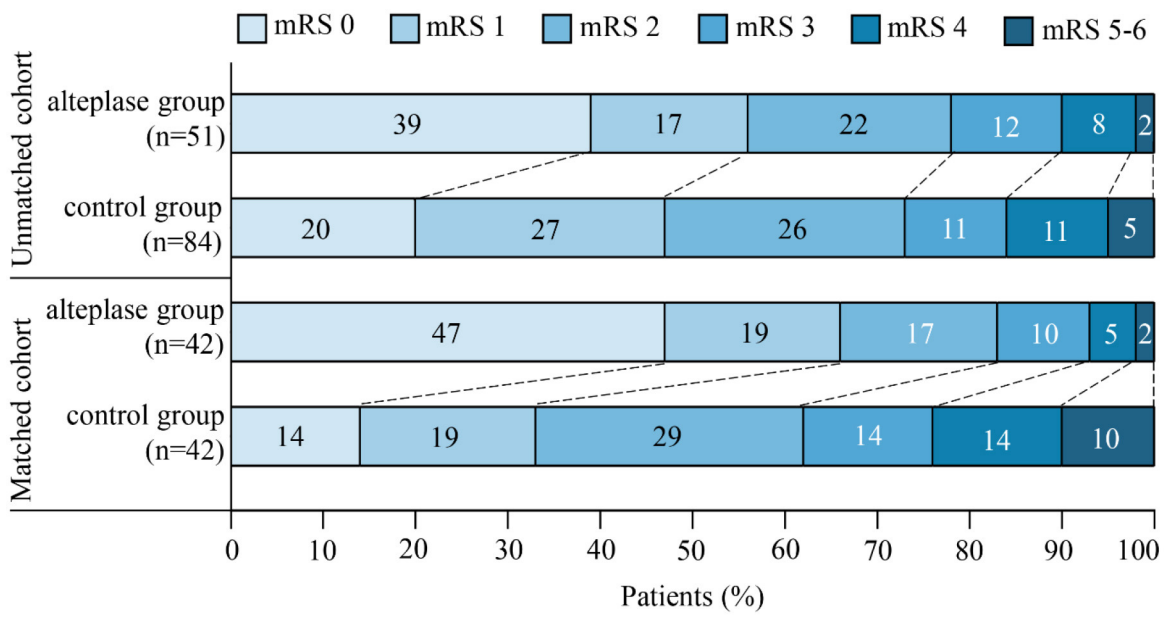

FIGURE 3 | The distribution of scores on the modified Rankin scale (mRS) at 3 months after stroke was in favor of intravenous thrombolysis. The mRS scores ranged from 0 to 6, in which higher scores indicated more severe disability.

subcortical infarction larger than lacunar stoke and lack of severe stenosis (≥50%) of the parent artery that supplies the regions of deep perforators, mainly the lenticulostriate arteries and pontine paramedian arteries (22). In recent years, the majority of clinical studies have followed the diagnostic criteria (12–15); however, these criteria neither reflect infarcts in the territories of other perforating arteries, nor explain the coexistence of BAD and large artery atherosclerosis. In spite of these shortcomings, no better alternative can be found based on the routine imaging techniques. Therefore, we attempted to follow the above-mentioned criteria in the present study.

The physiopathological mechanisms of BAD are complicated and have not been fully elucidated yet. Previous etiological classifications of stroke, such as Trial of Org 10172 in Acute Stroke Treatment (TOAST) (23) and Oxfordshire Community Stroke Project (OCSP) (24) are not appropriate for BAD. BAD was initially considered as a subtype of lacunar infarction by Caplan (21). However, at present, it is generally believed that BAD is distinctive from large-artery atherosclerosis and small-vessel disease. Ryoo et al. (2) demonstrated that BAD is a common and unique subtype of intracranial atherosclerotic stroke (ICAS) and has unique radiological features compared with non-BAD ICAS. Another research (22) revealed that BAD was relatively common among the embolic stroke of undetermined source (ESUS) patients and was classified as a subtype of ESUS.

In recent years, numerous scholars have demonstrated that the fluctuation or progression of neurological function is closely associated with BAD (6, 7, 22). According to different defined criteria, the prevalence of END may noticeably vary, ranging from 17 to 75% in different studies (15, 22). Neurological deterioration mainly involves motor function and often causes severe disabilities. Regrettably, a limited number of researches have concentrated on the treatment of BAD due to no international consensus about BAD classifying it as a subtype of stroke in previous etiological classifications. Although the NINDS trial demonstrated that alteplase has similar positive effect on all stroke subgroups (25), BAD treated with alteplase was found ineffective in recently conducted researches (11, 12). The current study indicated that IVT within 4.5 h after stroke onset reduced the incidence of END (unadjusted OR, 3.32; 95% CI, 1.06–10.37) and improved the clinical outcome at 3 months after stroke, with more patients achieving favorable outcome (mRS, 0–1 point; unadjusted OR, 0.25; 95% CI, 0.10–0.62), which is consistent with findings of the NINDS trial (26).

In PubMed database, only two articles concentrated on the efficacy and safety of IVT in treatment of BAD. Park et al. (11) retrospectively studied 35 patients with BAD (9 in tPA group and 26 in non-tPA group) and found that there were no statistical differences in END ($P = 0.886$) and mRS score at 3 months after stroke ($P = 0.781$) between the two groups. However, the prevalence of END in total patients (68.6%) was remarkably higher than most of BAD-related studies (12, 26–28). Subjects' poor clinical outcome may be attributed to mono-antiplatelet therapy with clopidogrel owing to higher portion of Asian individuals who are less sensitive to clopidogrel due to CYP2C19 loss-of-function alleles (29, 30). Deguchi et al. (12) assessed treatment outcomes of tissue plasminogen activator (t-PA) for hyperacute BAD within 3 h after symptom onset and demonstrated that using t-PA infusion for BAD, symptoms transiently improved, while the rate of symptom deterioration was considerable. In the present study with a medium sample size ($n = 135$), in contrast, our data unveiled that intravenous alteplase reduced the incidence of END and improved functional outcome of BAD patients. Our results may be attributable to the following reasons: first, a standard dose of alteplase (0.9 mg/kg) was given to our subjects. Whether low or standard dose of alteplase have the same efficacy on acute stroke remains controversial (31), but the majority of guidelines recommended a standard dose of alteplase for treating stroke (32). Second, dual-antiplatelet treatment was administrated to the majority of our subjects in two groups. Previous studies pointed out the efficacy of dual-antiplatelet treatment for lacunar stroke and small vessel disease. Kimura et al. (33) found that clinical progression of BAD was significantly reduced with ultra-early combination antiplatelet therapy. Berberich et al. (34) demonstrated that dual-antiplatelet therapy improved functional outcome of patients with progressive lacunar strokes.

Mortality and the incidence of sICH were insignificant in the current research. Only one patient (2%) in the alteplase group suffered from sICH according to the ECASS II criteria, which resulted in severe disability (mRS, 4 points at 3 months after stroke). Susceptibility weighted imaging (SWI) showed that this case had >10 cerebral microbleeds (CMBs) in his subcortex and brain stem. A research reported that increasing CMBs burden was closely associated with sICH after IVT treatment for acute stroke (35). Therefore, IVT is not an appropriate therapeutic approach for the mentioned patient.

There were several limitations in the current study. First, the diagnosis of BAD was carried out according to DWI data after IVT. The embolic occlusion of proximal large artery followed by alteplase-induced recanalization may come into an image that is line with BAD. Owing to the patients with cardiogenic embolism or severe arterial stenosis (≥50%) who were excluded from this study, the probability of that situation was quite low. Second, a number of variables in baseline data between the two groups were unbalanced. The propensity score matching analysis could only adjust for some confounding factors, while it could not eliminate the effect of all hidden biases. Third, this was a single-center retrospective study; the universal applicability of our results needs further study.

In conclusion,our results showed that BAD may be effectively treated with intravenous thrombolysis. However, further multicenter, prospective, randomized studies should be conducted to confirm our findings.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee, Zhongnan Hospital of Wuhan University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

XW wroted and proofed the manuscript. YaL, CN, and ZK conducted follow-up and collected the data. YaL and QW conducted statistical analysis. DS, HL, and YuL revised the manuscript. BM proposed the concept and designed this study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00581/full#supplementary-material

Supplementary Table 1 | Baseline characteristics and outcomes were compared between included and excluded groups.

Supplementary Table 2 | Baseline characteristics and outcomes were compared between END and non-END groups.

REFERENCES

1. Nah HW, Kang DW, Kwon SU, Kim JS. Diversity of single small subcortical infarctions according to infarct location and parent artery disease: analysis of indicators for small vessel disease and atherosclerosis. *Stroke.* (2010) 41:2822–7. doi: 10.1161/STROKEAHA.110.599464
2. Ryoo S, Lee MJ, Cha J, Jeon P, Bang OY. Differential vascular pathophysiologic types of intracranial atherosclerotic stroke: a high-resolution wall magnetic resonance imaging study. *Stroke.* (2015) 46:2815–21. doi: 10.1161/STROKEAHA.115.010894
3. Nakase T, Yoshioka S, Sasaki M, Suzuki A. Clinical evaluation of lacunar infarction and branch atheromatous disease. *J Stroke Cerebrovasc Dis.* (2013) 22:406–12. doi: 10.1016/j.jstrokecerebrovasdis.2011.10.005
4. Kwan MW, Mak W, Cheung RT, Ho SL. Ischemic stroke related to intracranial branch atheromatous disease and comparison with large and small artery diseases. *J Neurol Sci.* (2011) 303:80–4. doi: 10.1016/j.jns.2011.01.008
5. Fisher CM. Lacunes: Small, deep cerebral infarcts. *Neurology.* (1998) 50:841. doi: 10.1212/WNL.50.4.841-a
6. Yamamoto Y, Ohara T, Hamanaka M, Hosomi A, Tamura A, Akiguchi I. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. *J Neurol Sci.* (2011) 304:78–82. doi: 10.1016/j.jns.2011.02.006
7. Jeong HG, Kim BJ, Yang MH, Han MK, Bae HJ. Neuroimaging markers for early neurologic deterioration in single small subcortical infarction. *Stroke.* (2015) 46:687–91. doi: 10.1161/STROKEAHA.114.007466
8. Miyamoto N, Tanaka Y, Ueno Y, Kawamura M, Shimada Y, Tanaka R, et al. Demographic, clinical, and radiologic predictors of neurologic deterioration in patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis.* (2013) 22:205–10. doi: 10.1016/j.jstrokecerebrovasdis.2011.07.018
9. Group NIoNDaSr-PSS. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* (1995) 333:1581–7. doi: 10.1056/NEJM199512143332401
10. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): a randomised controlled trial. *Lancet.* (2012) 379:2352–63. doi: 10.1016/S0140-6736(12)60768-5
11. Park MG, Oh EH, Kim BK, Park KP. Intravenous tissue plasminogen activator in acute branch atheromatous disease: does it prevent early neurological deterioration? *J Clin Neurosci.* (2016) 33:194–7. doi: 10.1016/j.jocn.2016.04.011
12. Deguchi I, Hayashi T, Kato Y, Nagoya H, Ohe Y, Fukuoka T, et al. Treatment outcomes of tissue plasminogen activator infusion for branch atheromatous disease. *J Stroke Cerebrovasc Dis.* (2013) 22:e168–72. doi: 10.1016/j.jstrokecerebrovasdis.2012.10.012
13. Zhou L, Yao M, Peng B, Zhu Y, Ni J, Cui L. Atherosclerosis might be responsible for branch artery disease: evidence from white matter hyperintensity burden in acute isolated pontine infarction. *Front Neurol.* (2018) 9:840. doi: 10.3389/fneur.2018.00840
14. Liao S, Deng Z, Wang Y, Jiang T, Kang Z, Tan S, et al. Different mechanisms of two subtypes of perforating artery infarct in the middle cerebral artery territory: a high-resolution magnetic resonance imaging study. *Front Neurol.* (2018) 9:657. doi: 10.3389/fneur.2018.00657
15. Petrone L, Nannoni S, Del Bene A, Palumbo V, Inzitari D. Branch atheromatous disease: a clinically meaningful, yet unproven concept. *Cerebrovasc Dis.* (2016) 41:87–95. doi: 10.1159/000442577
16. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* (2013) 369:11–9. doi: 10.1056/NEJMoa1215340
17. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk tia. *N Engl J Med.* (2018) 379:215–5. doi: 10.1056/NEJMoa1800410
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2018) 49:e46–e110. doi: 10.1161/STR.0000000000000163
19. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* (1988) 19:604–7. doi: 10.1161/01.STR.19.5.604
20. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ecass ii). Second European-Australasian acute stroke study investigators. *Lancet.* (1998) 352:1245–51. doi: 10.1016/S0140-6736(98)08020-9
21. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. *Neurology.* (1989) 39:1246–50. doi: 10.1212/WNL.39.9.1246
22. Uchiyama S, Toyoda K, Kitagawa K, Okada Y, Ameriso S, Mundl H, et al. Branch atheromatous disease diagnosed as embolic stroke of undetermined source: a sub-analysis of navigate esus. *Int J Stroke.* (2019) 14:915–22. doi: 10.1177/1747493019852177
23. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
24. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet.* (1991) 337:1521–6. doi: 10.1016/0140-6736(91)93206-O
25. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* (1995) 333:1581–7.

26. Suto Y, Nakayasu H, Maeda M, Kusumi M, Kowa H, Awaki E, et al. Long-term prognosis of patients with large subcortical infarctions. *Eur Neurol.* (2009) 62:304–10. doi: 10.1159/000235943
27. Sun LL, Li ZH, Tang WX, Liu L, Chang FY, Zhang XB, et al. High resolution magnetic resonance imaging in pathogenesis diagnosis of single lenticulostriate infarction with nonstenotic middle cerebral artery, a retrospective study. *BMC Neurol.* (2018) 18:51. doi: 10.1186/s12883-018-1054-z
28. Yamamoto Y, Nagakane Y, Makino M, Ohara T, Koizumi T, Makita N, et al. Aggressive antiplatelet treatment for acute branch atheromatous disease type infarcts: a 12-year prospective study. *Int J Stroke.* (2014) 9:E8. doi: 10.1111/ijs.12200
29. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: A systematic review and meta-analysis. *Circulation.* (2017) 135:21–33. doi: 10.1161/CIRCULATIONAHA.116.024913
30. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, et al. Association between cyp2c19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA.* (2016) 316:70–8. doi: 10.1001/jama.2016.8662
31. Liao X, Wang Y, Pan Y, Wang C, Zhao X, Wang DZ, et al. Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. *Stroke.* (2014) 45:2354–8. doi: 10.1161/STROKEAHA.114.005989
32. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2019) 50:e344–e418. doi: 10.1161/STR.0000000000000211
33. Kimura T, Tucker A, Sugimura T, Seki T, Fukuda S, Takeuchi S, et al. Ultra-early combination antiplatelet therapy with cilostazol for the prevention of branch atheromatous disease: a multicenter prospective study. *Cerebrovasc Dis Extra.* (2016) 6:84–95. doi: 10.1159/000450835
34. Berberich A, Schneider C, Reiff T, Gumbinger C, Ringleb PA. Dual antiplatelet therapy improves functional outcome in patients with progressive lacunar strokes. *Stroke.* (2019) 50:1007–9. doi: 10.1161/STROKEAHA.118.023789
35. Charidimou A, Turc G, Oppenheim C, Yan S, Scheitz JF, Erdur H, et al. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis. *Stroke.* (2017) 48:2084–90. doi: 10.1161/STROKEAHA.116.012992

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Acquired Visual Deficits Independent of Lesion Site in Acute Stroke

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Most clinical diagnoses of stroke are based on the persistence of symptoms relating to consciousness, language, visual-field loss, extraocular movement, neglect (visual), motor strength, and sensory loss following acute cerebral infarction. Yet despite the fact that most motor actions and cognition are driven by vision, functional vision *per se* is seldom tested rigorously during hospitalization. Hence we set out to determine the effects of acute stroke on functional vision, using an iPad application (Melbourne Rapid Field-Neural) that can be used to assess vision (visual acuity and visual field sensitivity) at the bedside or in the emergency ward in about 6 min per eye. Our convenience sample comprised 60 (29–88 years, 65 ± 14 years, 33 males) of 160 sequentially presenting first episode, acute (<7 days) ischemic stroke patients at Sunshine Hospital, Melbourne. One hundred patients were excluded due to existing eye disease, inadequate radiological confirmation, inability to comply with English directions or too ill to participate. Stroke cases were compared with 37 (29–85 years, 64 ± 12 years,14 males) similar-aged controls using a Mann-Whitney *U*-test. A significant loss in visual field sensitivity was measured in 68% of stroke cases (41/60, Mean Deviation: Stroke: −5.39 ± 6.26 dB, Control: 0.30 ± 0.60 dB, MWU = 246, $p < 0.0001$). Surprisingly, 44% (18/41) of these patients were unaware of their field loss. Although high contrast visual acuity was unaffected in most (55/60) patients, visual acuity-in-noise was reduced in 62% (37/60, Stroke: mean 6/12−2, log MAR 0.34 ± 0.21 vs. Control: mean 6/7·5–2, log MAR 0.14 ± 0.10; MWU = 470, $p < 0.0001$). Visual field defects were associated with all occipital, parietal and posterior cerebellar artery strokes while 9/15 middle cerebral artery lesions and 11 lesions in other brain regions were also associated with visual field defects. Our findings demonstrate that ∼2/3 of acute first episode ischemic stroke patients experience acquired vision deficits, often unrelated to the confirmed lesion site. Our results also imply that visual dysfunction may be associated with a more generalized cerebral dysfunction while highlighting the need for bedside testing of vision for every stroke patient and demonstrating the translational clinical value of the "Melbourne Rapid Field- Neural" iPad application.

Clinical Trial: http://www.ANZCTR.org.au/ACTRN12618001111268.aspx.

Keywords: visual function, acute stroke, visual field, visual acuity-in-noise, ischemic, vision, Melbourne Rapid Field-Neural (MRFn)

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INTRODUCTION

Stroke is categorized by the World Health Organization as rapidly developing clinical signs of focal cerebral dysfunction due to vascular compromise, lasting more than 24 h, or leading to death (1, 2). Stroke is the leading cause of adult disability and the second leading cause of death worldwide (3). The American Stroke Association guidelines for the early management of acute ischemic stroke assessment emphasize testing of the level of consciousness, motor strength, items relating to confrontation visual field measurements, horizontal eye movements and visual inattention (4). However, visual function *per se* is seldom examined rigorously in the emergency room or during initial hospitalization for stroke (5), despite the central role vision plays in driving most human brain functions such as eye movements (6), attention (7), cognition (8), emotional responses (9), motor actions (6), and occupying larger volumes of cortical and subcortical regions in the human brain than do motor functions (10, 11).

Previous studies have reported that ∼92% of the 915 stroke patients (5), who were referred to hospital eye clinics in the UK within a median of 22 days and up to 3 months post-stroke, have been reported as having some form of a visual deficit (12) with post chiasmal lesions in the lateral geniculate body (1%) (13), optic tract (6%), in the optic radiations (33%), and occipital lobes (54%). The commonest persistent visual deficits included visual field loss (hemianopia, quadrantanopia) (5), perceptual (visual inattention/neglect) (14) and eye movement disorders (5). Unfortunately, the recruitment criteria for the study of Rowe and colleagues (5) did not mention the number of unselected patients screened, nor the number with pre-existing eye diseases that may have confounded the effects of acute stroke on vision.

Ptosis has also been identified as a common indicator of transient ischemic attacks and midbrain infarctions (15) while impaired saccades, smooth pursuits (16), and nystagmus are reported to be more prevalent following frontal lobe, cerebellar and brainstem infarctions (17). Other stroke related visual anomalies have also been reported to be under diagnosed as ocular misalignment and gaze deficits can be subtle and patients are often unaware or asymptomatic for these changes (18, 19), with two-thirds of patients showing unilateral visual neglect following acute right hemisphere parietal stroke (20). Furthermore, the application of a battery of three bedside oculomotor tests (HINTS) measuring head impulse, nystagmus, and test of skew have proven accurate and reliable for the identification of acute stroke following acute vertigo presentations (21).

Indeed an acute stroke test battery (4) measuring distance visual acuity in each eye (22, 23), visual neglect (20), and ocular misalignment has been proposed recently (24). The battery includes tests for diplopia, pupil dysfunction, nystagmus and eye movement deficiency as well as more subtle tropia, phoria, and extraocular motor function in the cardinal positions of gaze, given that the cranial nerves III, IV and VI are supplied by a myriad of arteriole blood vessels on the same side as the eye such that they are susceptible to ocular motor dysfunction in ischemic conditions (24). However, the battery is not yet established as a regular neurological routine and most current bedside visual field assessments are performed using hand/finger confrontation (25) even though this method has been reported as having limited value for the detection of visual field loss (26, 27).

Confrontation continues to be used for bedside screening of stroke patients due to the difficulty of applying commercial visual field devices that require a degree of patient mobility and head/face coordination for testing (28). As a consequence, the nature of acquired visual field deficit in the acute phase of stroke (<72 h) has not been evaluated rigorously to date, though the advent of modern technology, and in particular tablet devices, afford ideal interfaces and test platforms for the testing of vision in hospitalized patients by their bedside (26, 29). A newly developed iPad tablet application for measuring visual field integrity known as Melbourne Rapid Field-Neural (MRFn) has recently been validated against the gold standard Humphrey Visual Field Analyzer (30) making it an useful tool to measure the integrity of functional vision across the visual fields of both eyes in hospitalized patients. The MRFn app also comes with the ability to test high contrast visual acuity with a Landolt C and visual acuity in noise (i.e., visual stimulus is embedded in a background of white noise) aimed at measuring threshold perception following the decomposition of the contrast of the target (30, 31). Therefore, measuring visual acuity performance in background noise provides useful insights into the neural mechanisms and computations needed to solve visual recognition (32–34) as demonstrated in the psychophysical testing of neurotypical and psychiatry patients with major depressive disorder (35).

Thus, the aim of this study was to utilize the MRFn (Melbourne Rapid Field-Neural) iPad application to measure visual acuity with high contrast targets, visual acuity-in-noise and visual field integrity in first episode hospitalized ischemic acute stroke patients with no prior history of ocular disorder. We hypothesize a decrement in vision post stroke acutely.

MATERIALS AND METHODS

The clinical ethics has been approved by the local review board (Western Health Ethics Committee HREC/16/WH/1) and was conducted in accordance with the tenets of the Declaration of Helsinki with all participants (or their carers) providing informed consent.

Participants

Our convenience sample of cases comprised 160 sequentially presenting, stroke patients (29–95 years, 68 ± 14.5years, 89 males) admitted to Sunshine Hospital, Melbourne, between June 2017 and July 2018. Patients were invited to volunteer for a subjective assessment of vision (visual acuity [high contrast and in noise] and visual fields) and those who agreed and, who met our inclusion criteria (i.e., first episode ischemic stroke with radiological confirmation, the availability of current habitual reading glasses) (**Figure 1**) were tested while wearing their

Abbreviations: MRFn App, Melbourne Rapid Field Neural App.

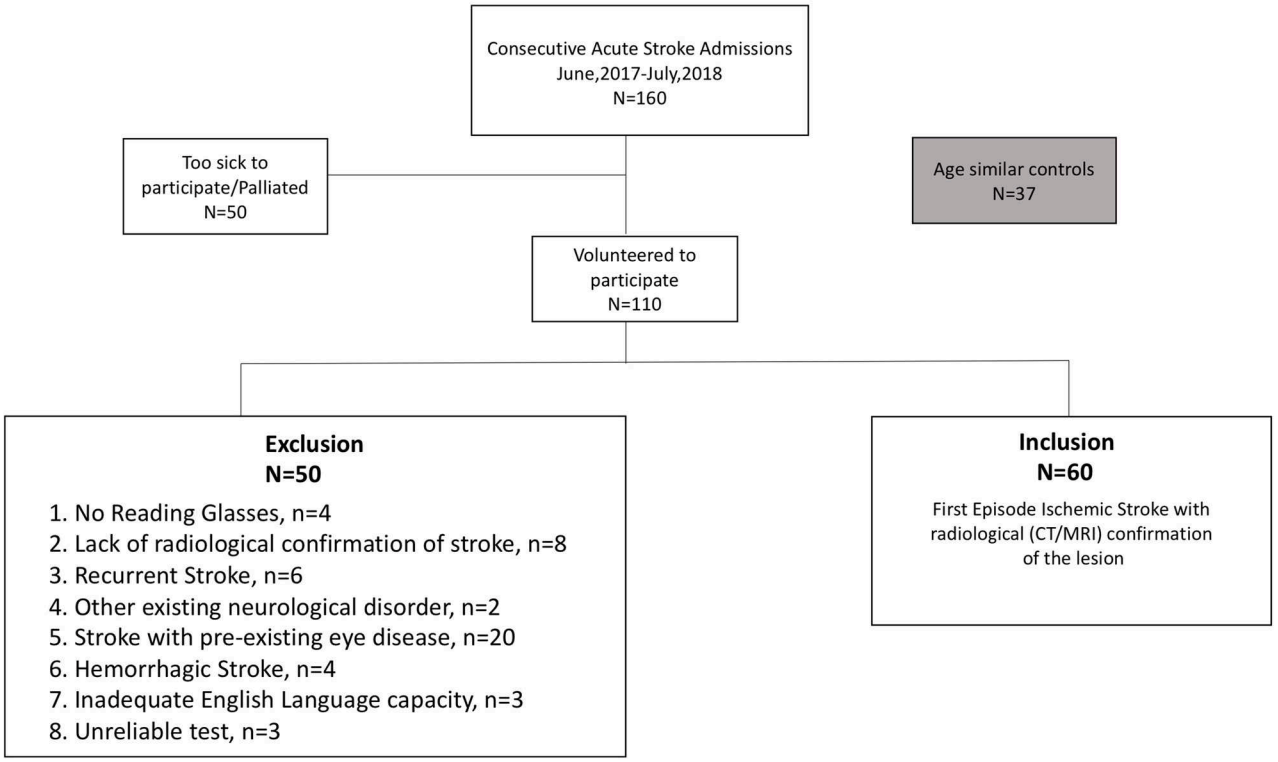

FIGURE 1 | Consort diagram (36).

habitual reading spectacles at their bedside using the Melbourne Rapid Field-Neural (MRFn) application. Refractions were not performed at the hospital rather their verbal history was used to determine the adequacy of current reading glasses. All testing was performed during the first week (usually day 2 or day 3) of hospital stay. Sixty first episode acute ischemic stroke patients (29–88 years, 65 ± 14 years, 33 males) met our inclusion criteria and had their data analyzed for this study. One hundred patients (63%) were excluded from analysis for the exclusion criteria shown in **Figure 1**.

Thirty-seven age-similar healthy controls (29–85 years, 64 ± 12 years,14 males) were recruited following a comprehensive routine eye examination at an optometry practice of one of the authors (CW) after providing informed written consent for participation. These participants showed no evidence of current or past ocular and neurological disorders and were wearing their habitual reading glasses.

Stroke diagnosis and localization of the vascular source of the lesion was determined at the time of admission by a neurologist with routine Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). The greater spatial resolution of MRI was utilized to identify small volume ischemic changes often associated with minor strokes (37). This information was used to confirm the diagnosis and facilitate a structure-function analysis with the visual capacity (38).

Melbourne Rapid Field-Neural iPad (MRFn) Application

The Melbourne Rapid Field application (GLANCE Optical Pty Ltd, Melbourne, Australia) measures visual acuity and visual field thresholds across the central visual field using an iPad tablet (12.9 inches iPad Pro) (39). Stroke cases sat on the hospital bed or on a bedside chair during the testing whereas controls performed the test on a bench in a clinical optometry practice at 33–38 cm working distance. The visual field test pattern used by MRFn is a reduced 24-2 Humphrey Field Analyser (HFA) test grid with 4 extra spots added to the fovea (**Figure 2**) (30). Spot size scaling results in a fixed threshold of 30 dB (**Figure 2**) at all locations (30). Previous studies find the MRFn returns outcomes that are strongly correlated to HFA thresholds on both a global and regional basis (40, 41).

In visual field testing, patients were required to respond to the presence of a spot by either tapping the screen or the spacebar of the iPad keyboard. All chose to tap the keyboard space bar indicating adequate manual control. We found one patient with a frontal lobe lesion who had difficulty tapping the space bar and preferred to tap the screen directly to complete testing. There were two other subjects who adopted their non-dominant hand for motor tasks after the stroke and used it for the visual assessment, all other participants used their dominant hand. Reliability (false positive, false negative and fixation loss) was routinely polled during testing.

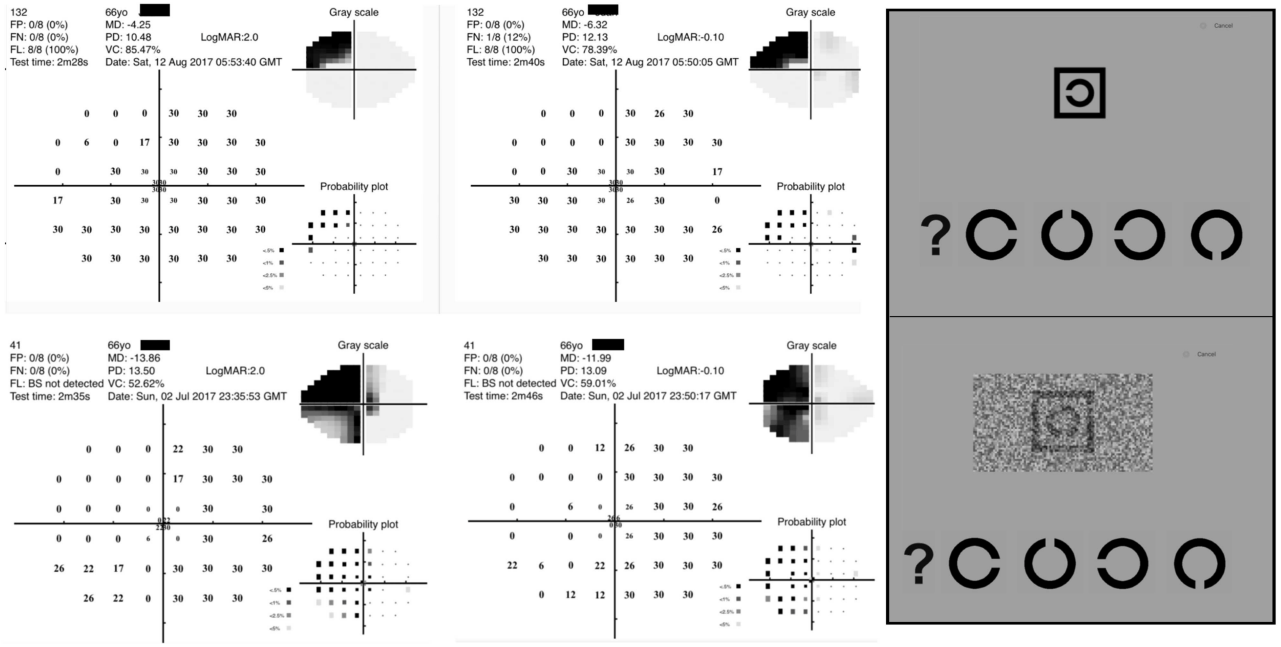

FIGURE 2 | Diagnostic features of the Melbourne Rapid Field Neural (MRFn) test. **(Left)** Visual field outcomes for two acute stroke patients. **(Right)** Screen capture of the acuity optotypes used in the test (high contrast acuity-top, visual acuity-in-noise-bottom) with the response options at the bottom of the each presented optotypes.

The visual acuity test presents a high contrast "Landolt C" target (**Figure 2**) on a bright background (130 cd/sq.m) as well as the same "Landolt C" target embedded in luminance noise, generated using a psychometric model accounting for true acuity and noise in the visual system, with the reduction of the contrast sensitivity of the background spatial vision by 10% of the high contrast "Landolt C" optotype (42). Visual acuity-in noise has not been previously tested in acute stroke, but given the past reports for abnormality of noise-related tasks in acquired neurological disorders and in stroke cases well-after the onset of stroke (43, 44), we tested our acute stroke cohort expecting some may have difficulty recognizing visual targets immersed in noise.

Testing Procedures

Visual acuity and the visual fields of both eyes of all study participants were measured monocularly in ambient hospital room lighting. The lighting has been found to have little impact on test outcomes (45) provided reflections off the screen are avoided. Screen brightness was set to maximum for 10 min prior to testing, to stabilize luminous output (46). Verbal instruction on test performance was given at the bedside and patients were allowed a practice trial before starting the test.

As most participants were naive to tablet perimetry, the preferred eye was tested first with operator feedback for training and learning of how to do the test. This eye was retested after the training phase before testing the fellow eye.

Data Analysis

Comparisons between stroke and control groups were made for visual acuity, visual acuity-in-noise, and the mean deviation (MD) of the visual field. The mean deviation is determined from a pointwise comparison of contrast thresholds (dB) to age-related normals provided by the MRFn App. The time taken to complete vision assessments was also recorded.

Although both eyes were tested, the eye ipsilateral to the CT/MRI defined lesion was analyzed in the stroke group and compared to the RE (Right Eye) of controls (comparison to the fellow eye does not change our findings).

Non-parametric statistics (Mann–Whitney *U*-tests) were employed given the heterogeneity and variability of data in the stroke group (**Figure 3**). All group data are shown as box-and-whisker plots, with whiskers identifying the total range of the data set. The 99th percentile of controls was used as the criterion to identify "abnormal" outcomes. Levene's test was used to compare group variances. Statistical analysis was conducted using GraphPad Prism v7.00 for Windows www.graphpad.com.

RESULTS

Of the 160 stroke presentations (**Figure 1**) MRFn testing could be performed and was successfully completed in 108 (68%) patients. Of these, 48 cases did not meet our inclusion criteria (first episode ischemic stroke with radiological confirmation, **Figure 1**) leaving 60 cases of acute ischemic stroke for analysis. First episode acute stroke patients were able to perform the tests accurately at their bedside, in under 5.4 ± 0.8 min per eye. Control patients completed all tests in under 4.0 ± 0.3 min per eye.

High contrast visual acuity (VA) was not significantly affected by acute ischemic stroke (**Figure 3**). Only 5 patients (8%) showed a one-line reduction in VA (mean 6/7·5+1, log MAR 0.09 ±

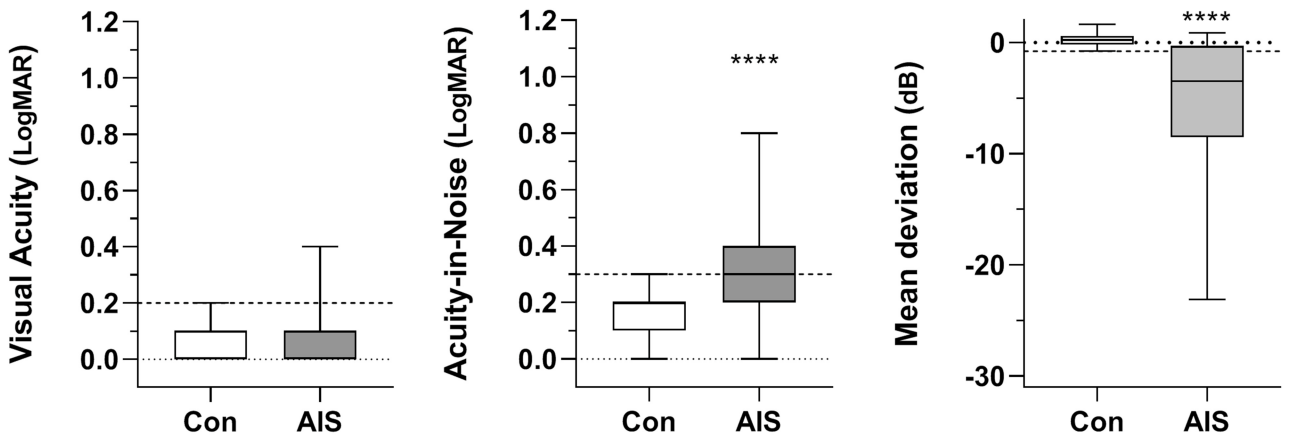

FIGURE 3 | Box-and-whisker plots for visual acuity, visual acuity-in-noise and the Mean Deviation of the visual field for the control (Con) and acute ischemic stroke (AIS) groups. Horizontal dashed lines in each panel show 99th percentile for control data. Significant differences between groups (MWU, $P < 0.0001$) have been identified with asterisks (****).

0.10) relative to controls (mean 6/6-3, log MAR 0.07 ± 0.06: MWU = 1,045, $p = 0.30$).

Statistically significant deterioration was found in the visual acuity-in-noise of 37/60 stroke cases (62%) despite having normal high contrast acuity (Stroke: mean 6/12-2, log MAR 0.34 ± 0.21 vs. Control: mean 6/7·5-2, log MAR 0.14 ± 0.10; MWU = 470, $p < 0.0001$). The stroke group also showed much larger variability in acuity-in-noise outcomes (range: 6/6–6/38; log MAR 0.0–0.8) compared to the maximum range of control patients (6/6 to 6/12; log MAR 0.0 to 0.3, Levene's F-ratio = 4.52, **Figure 3**).

Forty-one out of the 60 stroke patients (68%, $p < 0.0001$) showed acquired visual field defects in terms of their Mean Deviation. Fifty percent of patients (i.e., 30/60) had acquired homonymous hemianopias and five (5/60, 8.3%) showed quadrantanopic defects. Three (3/60, 5%) demonstrated altitudinal defects with diffuse loss of visual field sensitivity (**Tables 1**, **2**). The control group showed an average Mean Deviation value of 0.30 ± 0.60 dB whereas the 41 stroke patients who had a significant visual field loss (**Figure 3**) gave a group Mean Deviation of −5.39 ± 6.26 dB (MWU = 246, $p < 0.001$).

In the right hemisphere, 17/26 and in the left hemisphere 18/31 presented visual field losses in the form of a hemianopia, quadrantanopia or an altitudinal loss. All right hemispheric vascular based lesions showed twice as greater visual field losses compared to left hemisphere (**Table 1**). Despite the presence of substantial hemianopic and quadrantanopic visual field losses, eighteen of the 41 (44%) patients with visual field loss were unaware of any limitation to their vision. (See **Tables 1**, **2** for more detailed information on vision function in individual lesion regions.)

The CT and MRI-scans showed that the commonest site of lesion among the 60 patients was a middle-cerebral artery lesion ($n = 15$, 25%), followed by cerebellar artery disorders ($n = 10$, 17%), occipital lobe infarcts ($n = 9$, 15%), posterior cerebral artery lesions ($n = 6$, 10%) and parietal lesions ($n = 3$, 5%). Multi-territorial infarcts were noted in three patients (5%) and the locus for the other 14 cases have been detailed in **Tables 1**, **2**.

DISCUSSION

To the best of our knowledge, few studies have quantified the incidence and nature of acquired visual deficits in acute ischemic stroke patients (<7 days) with no previous history of visual abnormality (26). The key features of our findings are that most patients (except for 5 cases) with radiologically confirmed first episode ischemic stroke, retain near normal high contrast visual acuity, although given we did not rigorously refract participants but had them wear their habitual reading glasses, we cannot dismiss the possibility that these 5 patients show high contrast visual acuity loss due to uncorrected refractive error. On the other hand, 62% of our patient sample showed deficits in visual acuity-in-noise and 68% showed visual field loss. These changes could not have arisen from an uncorrected refractive state. Besides, although the majority of stroke patients presented with varying clinical symptoms including sudden onset unilateral numbness, loss of motor sensation, and hemiparesis, 44% (18 out of 41) of our patients were unaware of their visual field defect or of their altered visual capacity (i.e., acuity-in-noise).

Our results also demonstrate the clinical potential of using tablet based applications to obtain a quantified measure of visual capacity (visual field, visual acuity and acuity-in-noise) in a relatively short duration (<6 min per eye) in an acute stage of a cerebrovascular injury by testing at the bedside of the patient.

In terms of a structure-function analysis, many ischemic lesions throughout the brain can induce acute visual defects (47). As expected, all occipital lesions ($n = 9/60$) and posterior cerebral artery strokes ($n = 15/60$) induced visual field deficits. All 3 parietal cortex lesions (Right hemisphere: 2, Left hemisphere:

TABLE 1 | Vascular territories of lesion sites and corresponding visual deficits.

Site of Lesion R side: $n = 14$ L side: $n = 20$	Total patients ($n = 34$)	Hemianopia ($n = 15$)	Quadrantanopia ($n = 1$)	Altitudinal defect ($n = 3$)	VF: MD ± SD (dB)	HC VA: mean ± SD (snellen), (mean: log MAR)	VA noise: mean ± SD (snellen), (mean: log MAR)
Middle Cerebral Artery: $n = 15$							
• R side	7	4	0	1	−6.61 ± 7.29	0.10 ± 0.00,6/7.5	0.34 ± 0.18,6/12
• L side	8	3	1	0	−3.71 ± 4.94	0.10 ± 0.00,6/7.5	0.33 ± 0.15,6/12
Posterior Cerebral Artery: $n = 6$							
• R side	2	2	0	0	−20.43 ± 0.77	0.10 ± 0.00,6/7.5	0.80 ± 0.00,6/48
• L side	4	4	0	0	−11.56 ± 9.97	0.10 ± 7.79,6/7.5	0.30 ± 0.22,6/12
Cerebellar Artery: $n = 10$							
• R side	3	1	0	1	−2.01 ± 1.93	0.10 ± 0.00,6/7.5	0.23 ± 0.20,6/9.5
• L side	7	1	0	1	−1.52 ± 3.28	0.10 ± 0.00,6/7.5	0.21 ± 0.15,6/9.5
Anterior Cerebral Artery: $n = 2$							
• R side	1	0	0	0	−4.23	0.00,6/6	0.10,6/7.5
• L side	1	0	0	0	0.23	0.00,6/6	0.30,6/12
Internal Carotid Artery: $n = 1$							
• R side	1	0	0	0	−5.83	0.00,6/6	0.10,6/7.5

(Based on CT/MRI).

TABLE 2 | Neuro anatomical Lesion from CT/MRI scans and corresponding visual deficits.

Site of Lesion R side: $n = 12$ L side: $n = 11$ Multiterritorial: $n = 3$	Total patients ($n = 26$)	Hemianopia ($n = 14$)	Quadrantanopia ($n = 4$)	Altitudinal defect ($n = 1$)	VF: MD ± SD (dB)	HC VA: mean ± SD (snellen), (mean: log MAR)	VA noise: mean ± SD (snellen), (mean: log MAR)
Frontal Lobe: $n = 4$							
• R side	2	1	0	0	−0.61 ± 1.32	0.10 ± 0.00,6/7.5	0.15 ± 0.21,6/9.5
• L side	2	0	1	0	−2.79 ± 3.61	0.10 ± 2.20,6/7.5	0.10 ± 2.67,6/7.5
Parietal Lobe: $n = 3$							
• R side	1	1	0	0	−7.23	0.10,6/7.5	0·30,6/12
• L side	2	2	0	0	−5.91 ± 6.53	0.10 ± 0.00,6/7.5	0.30 ± 0.40,6/12
Occipital Lobe: $n = 9$							
• R side	6	5	1	0	−5.05 ± 10.19	0.10 ± 0.00,6/7.5	0.52 ± 0.31,6/15
• L side	3	2	1	0	−6.59 ± 3.81	0.10 ± 0.0,6/7.5	0.40 ± 0.26,6/15
Pre Frontal Lobe: $n = 1$, R side	1	0	0	0	−0.42	0.10, 6/7.5	0.30, 6/12
Corona Radiata: $n = 1$, L side	1	0	0	0	−0.07	0.20, 6/9.5	0.50,6/18
Internal Capsule: $n = 1$, L side	1	0	0	0	−0.24	0.00, 6/6	0.64, 6/24
Pons: $n = 2$, R side	2	0	0	0	−2.67 ± 3.71	0.05 ± 0.07, 6/7.5	0.25 ± 0.07, 6/9.5
Basal ganglia: $n = 2$,L side	2	2	0	0	−5.91 ± 6.53	0.10 ± 0.00, 6/7.5	0.30 ± 0.40, 6/12
Multiterritorial (R & L): $n = 3$	3	1	1	1	−6.10 ± 8.70	0.10 ± 0.17, 6/7.5	0.57 ± 0.32, 6/24

1) also produced visual deficits. Unexpectedly, ∼33% (20/60) of cases who had lesions in other regions (**Tables 1**, **2**) of the brain were also associated with visual field deficits and showed an acuity-in-noise impairment. Among them, nine of the 15 middle cerebral artery strokes and four of the 10 cerebellar artery strokes produced visual field defects (**Table 1**). Two strokes in the left basal ganglia, two out of 4 frontal lobe strokes, and 3 multi-territorial infarcts also caused visual loss (**Table 1**). The three multi-territorial infarcts involved more than one site of lesion from brain imaging. Interestingly all parietal strokes and the two multi-territorial infarcts which also had parietal lobe involvement produced visual field defects. Although hemineglect is commonly associated with parietal cortex lesions (48), we did not assay for this possibility in the current cohort of patients and cannot comment on its presence.

Our findings are similar to those of Rowe et al. who undertook vision assessment 22 days (median) after stroke (range 0–2,543 days) in patients identified during hospitalization as needing ophthalmic referral. Of these patients 63% had previously shown visual field loss during confrontation test whereas only 37% of cases showed visual field deficits when tested on automated static or manual kinetic (Goldmann) methods (49). From these findings, Rowe et al., concluded that 52% of 915 cases had visual field loss (49). We quantified visual field loss in 68% of our cases who did not have pre-existing eye disease.

Rowe et al. (5) have previously advocated the need for vision testing following stroke. The high prevalence of quantifiable visual defects in acute ischemic stroke cases as noted in our study and that of past works (26), coupled with the lack of awareness for such loss, highlights the need for digital appliances that can quantify these losses. The novel MRFn App is an easy, rapid, and sensitive bedside diagnostic tool for routine use in acute neurological assessments and for tracking recovery or change in the patient.

The immediate impact that acute ischemic stroke *per se* has on visual acuity has not previously been reported even though other neurological diseases such as multiple sclerosis (50) and idiopathic intracranial hypertension (51) are known to be associated with visual acuity loss. Interestingly, 27 out of the 37 patients (73%) who showed deterioration in visual acuity-in-noise also showed evidence of abnormal visual fields but preservation of high contrast acuity.

Clinically, visual acuity is a measure of the ability of the foveal visual system to discriminate a letter or optotype from background spatial information. Visual acuity-in-noise measures the ability to discriminate and identify the targets in the presence of added background white noise (52). The addition of luminance noise imputes to a stronger masking effect for the optotypes, and thus more complex processing of the visual information (31). This is likely the cause of the one line reduction in visual acuity in our controls (mean: 6/7.5-2) in the presence of the noise elements (53, 54). In our stroke group, however, we found a 2-line deterioration in the visual acuity-in noise with mean of 6/12-2. This involves all parietal strokes, occipital strokes, and the multi-territorial strokes with parietal lobe involvement whereas we did not find such a marked visual acuity-in-noise impairment in controls.

The possibility that the visual acuity-in-noise optotypes and visual field loss are measuring similar neuroanatomical processes can be rejected given that patients who showed deterioration in visual acuity-in-noise and visual field sensitivity had regional diversity of lesions (**Tables 1**, **2**) corrupting any commonality in their structure-function relationship (47, 55). Recognition of an acuity target involves the distinction of a static optotype from its background (52). The addition of luminance noise elements raises the threshold of retinal sensitivity as well as the subsequent neural processing needed for stimulus identification (56). This visual processing originates in the primary visual cortex, and involves the dorsal stream via the parietal cortex, for visually guided spatial location and orientation of objects (57). Similarly, ventral processing, which also arises from the primary visual cortex, involves the temporal lobe, and functions in object recognition and the discrimination of object details (58). Thus, it is not surprising that visual acuity-in-noise is affected by stroke as it likely requires processing and possibly integration from extensive cortical regions. The recent work of Cavanaugh et al. (43) in patients who have cortical blindness noted elevated intrinsic noise that affected performance in these patients well-after the acute stroke event (up to 276 months).

It is possible to deduce that the use of visual acuity-in-noise along with high contrast visual acuity at the bedside, has the potential to aid in the diagnosis of ischemic stroke and differentiate these effects from ocular disease. High contrast visual acuity will be typically affected by eye disease and given that visual acuity-in-noise is a sequential processing of this information by cortical inputs through both the dorsal and ventral pathways, these should also be affected due to the reduced ocular input. In our study, our controls returned 0.1 log MAR (6/7.5) for both forms of acuity, whereas stroke cases had an average high contrast acuity of 0.1 log MAR (6/7.5) and an acuity-in-noise of 0.3 log MAR (6/12) implying discrete non-ocular causes for this loss. Patients who had radiologic lesions in their occipital lobes also manifested intact high contrast visual acuity (**Table 2**).

As 44% of the patients were unaware of their visual field loss, it is also unlikely many would show subjective symptoms of a reduced visual acuity-in-noise as it is a subtle mechanism detected through the testing of target specific features. Although the presence of significant ischemia/brain edema may require longer times (6) for the identification of surrounding objects, we did not place any time constraints on subject response and do not believe that longer observation times would have affected outcomes.

Limitations of our study include the non-identified source of cortical dysfunction, through functional MRI (59), diffusion tensor imaging (60), EEG or psychophysics associated with processes mediated by other cortical regions such as hemispatial neglect (61) or visuomotor processing (62). However, as both of the latter have been reportedly affected by stroke, albeit in a minority of patients, the prospect of loss in cases of generalized cortical involvement is possible. Furthermore, we were unable to identify an association in visual field deficits and visual acuity in noise and hemisphere of lesion. Future studies using functional connectivity (63) MRI may be able to establish this.

Future studies will be required to better establish the mechanisms of functional connectivity associated with cortical defects following acute stroke and during the post stroke recovery phase, especially in visuomotor processing, or attention mechanisms between the right and left side brain hemispheres underlying hemispatial neglect (20) using larger sample sizes for indicators of generalized edema and if, visual acuity-in-noise and some aspect of visual field defects, in the absence of structure-functional relationship, recover over time.

Longitudinal studies with the MRFn app and MRI imaging will elucidate these changes in adaptation, visual attention, and

neuroplasticity as well as provide information regarding any therapeutic response in post-stroke patients.

CONCLUSION

Our findings indicate that acute stroke induces significant vision loss in 2/3 of hospitalized patients, quantifiable as early as 48-h after stroke, and often unrelated to the confirmed lesion site. Visual acuity-in-noise and visual field deficits have emerged as rapid and sensitive biomarkers of acute ischemic brain dysfunction. Our results imply that visual dysfunction may be associated with a more generalized cerebral dysfunction while highlighting the need for bedside testing of vision for every stroke patient and demonstrating the translational clinical value of the "Melbourne Rapid Field-Neural" iPad application as a low cost, rapid, rigorous and easy to administer functional vision test for use in acute stroke patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local review board (Western Health Ethics Committee HREC/16/WH/1) and was conducted in accordance with the tenets of the Declaration of Helsinki with all participants (or their carers) providing informed consent. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CW was involved in planning, design of the experiments, was responsible for recruitment of patients and all aspects of data collection, contributed to analysis of the data, prepared figures and tables, authored and reviewed the paper, and approved the final draft as part of her doctoral research. TW as Head of Hospital Department of Neurology managed ethical concerns, facilitated patient access and recruitment, was involved in design of experiments, led acquisition and interpretation of all radiological data, contributed to drafting of manuscript, and final approval. AV contributed to design of experiments, led data analysis, preparation of figures and interpretation of visual field results, co-authored and reviewed drafts of the manuscript, and approved the final version. SC conceptualized, designed, funded the study via internal grants, contributed to analysis, theoretical interpretation of the data, drafting of manuscript, and final approval. CW, AV, and SC had full access to all the data in the study. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American heart association/american stroke association. *Stroke.* (2013) 44:2064–89. doi: 10.1161/STR.0b013e318296aeca
2. Josephson SA, Hills NK, Johnston SC. NIH stroke scale reliability in ratings from a large sample of clinicians. *Cerebrovasc Dis.* (2006) 22:389–95. doi: 10.1159/000094857
3. World Health Organisation. *Global Health Estimates 2016: Deaths by Cause, Age, Sex by Country and and Region, 2000-2016.* (2018). Available online at: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html (accessed May 20, 2019).
4. Furie KL, Jayaraman MV. 2018 guidelines for the early management of patients with acute ischemic stroke. *Stroke.* (2018) 49:509–10. doi: 10.1161/STROKEAHA.118.020176
5. Rowe F, Brand D, Jackson CA, Price A, Walker L, Harrison S, et al. Visual impairment following stroke: do stroke patients require vision assessment? *Age Ageing.* (2009) 38:188–93. doi: 10.1093/ageing/afn230
6. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. The influence of time after stroke on brain activations during a motor task. *Ann Neurol.* (2004) 55:829–34. doi: 10.1002/ana.20099
7. Pessoa L. To what extent are emotional visual stimuli processed without attention and awareness? *Curr Opin Neurobiol.* (2005) 15:188–96. doi: 10.1016/j.conb.2005.03.002
8. Woutersen K, Guadron L, van den Berg AV, Boonstra FN, Theelen T, Goossens J. A meta-analysis of perceptual and cognitive functions involved in useful-field-of-view test performance. *J Vis.* (2017) 17:11. doi: 10.1167/17.14.11
9. Kawasaki H, Kaufman O, Damasio H, Damasio AR, Granner M, Bakken H, et al. Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. *Nat Neurosci.* (2001) 4:15–6. doi: 10.1038/82850
10. Martín MB, Santos-Lozano A, Martín-Hernández J, López-Miguel A, Maldonado M, Baladrón C, et al. Cerebral versus ocular visual impairment: the impact on developmental neuroplasticity. *Front Psychol.* (2016) 7:1958. doi: 10.3389/fpsyg.2016.01958
11. Kreiman G, Koch C, Fried I. Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat Neurosci.* (2000) 3:946–53. doi: 10.1038/78868
12. Rowe FJ, Hepworth LR, Howard C, Hanna KL, Cheyne CP, Currie J. High incidence and prevalence of visual problems after acute stroke: an epidemiology study with implications for service delivery. *PLoS ONE.* (2019) 14:e0213035. doi: 10.1371/journal.pone.0213035
13. Tsuda H, Yoshizawa T. Localized infarction of the lateral geniculate body. *Intern Med.* (2014) 53:1891–2. doi: 10.2169/internalmedicine.53.2695
14. Albert ML. A simple test of visual neglect. *Neurology.* (1973) 23:658–64. doi: 10.1212/WNL.23.6.658
15. Sugawara E, Nakamura H, Endo M, Tanaka F, Takahashi T. Isolated unilateral ptosis due to paramedian midbrain infarction. *J Stroke Cerebrovasc Dis.* (2015) 24:e121–3. doi: 10.1016/j.jstrokecerebrovasdis.2015.01.027

16. Pedersen RA, Troost BT. Abnormalities of gaze in cerebrovascular disease. *Stroke.* (1981) 12:251–4. doi: 10.1161/01.STR.12.2.251
17. Bogousslavsky J, Meienberg O. Eye-movement disorders in brain-stem and cerebellar stroke. *Arch Neurol.* (1987) 44:141–8. doi: 10.1001/archneur.1987.00520140013011
18. Jones SA, Shinton RA. Improving outcome in stroke patients with visual problems. *Age Ageing.* (2006) 35:560–5. doi: 10.1093/ageing/afl074
19. Pollock L. Managing patients with visual symptoms of cerebro-vascular disease. *Eye News.* (2007) 7:23–6.
20. Stone SP, Halligan PW, Greenwood RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Ageing.* (1993) 22:46–52. doi: 10.1093/ageing/22.1.46
21. Newman-Toker DE, Curthoys IS, Halmagyi GM. Diagnosing stroke in acute vertigo: the hints family of eye movement tests and the future of the "Eye ECG". *Semin Neurol.* (2015) 35:506–21. doi: 10.1055/s-0035-1564298
22. Lauda F, Neugebauer H, Reiber L, Jüttler E. Acute silent brain infarction in monocular visual loss of ischemic origin. *Cerebrovasc Dis.* (2015) 40:151–6. doi: 10.1159/000437274
23. Varma DD, Cugati S, Lee AW, Chen CS. A review of central retinal artery occlusion: clinical presentation and management. *Eye.* (2013) 27:688–97. doi: 10.1038/eye.2013.25
24. Ciuffreda KJ, Kapoor N, Rutner D, Suchoff IB, Han ME, Craig S. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. *Optometry.* (2007) 78:155–61. doi: 10.1016/j.optm.2006.11.011
25. Johansen A, White S, Waraisch P. Screening for visual impairment in older people: validation of the cardiff acuity test. *Arch Gerontol Geriatr.* (2003) 36:289–93. doi: 10.1016/S0167-4943(02)00175-9
26. Quinn TJ, Livingstone I, Weir A, Shaw R, Breckenridge A, McAlpine C, et al. Accuracy and feasibility of an android-based digital assessment tool for post stroke visual disorders-the stroke vision app. *Front Neurol.* (2018) 9:146. doi: 10.3389/fneur.2018.00146
27. Spofforth J, Codina C, Bjerre A. Is the 'visual fields easy' application a useful tool to identify visual field defects in patients who have suffered a stroke? *Ophthalmol Res Int J.* (2017) 7:1–10. doi: 10.9734/OR/2017/34947
28. Cassidy TP, Bruce DW, Gray CS. Visual field loss after stroke: confrontation and perimetry in the assessment of recovery. *J Stroke Cerebrovasc Dis.* (2001) 10:113–7. doi: 10.1053/jscd.2001.25457
29. Nordfang M, Uhre V, Robotham RJ, Kerry SJ, Frederiksen JL, Starrfelt R. A free and simple computerized screening test for visual field defects. *Scand J Psychol.* (2019) 60:289–94. doi: 10.1111/sjop.12546
30. Kong YX, He M, Crowston JG, Vingrys AJ. A comparison of perimetric results from a tablet perimeter and humphrey field analyzer in glaucoma patients. *Transl Vis Sci Technol.* (2016) 5:2. doi: 10.1167/tvst.5.6.2
31. Lu ZL, Dosher BA. Characterizing human perceptual inefficiencies with equivalent internal noise. *J Opt Soc Am A Opt Image Sci Vis.* (1999) 16:764–78. doi: 10.1364/JOSAA.16.000764
32. Levi DM, Klein SA, Chen I. What is the signal in noise? *Vision Res.* (2005) 45:1835–46. doi: 10.1016/j.visres.2005.01.020
33. Dosher BA, Lu ZL. Perceptual learning reflects external noise filtering and internal noise reduction through channel reweighting. *Proc Natl Acad Sci USA.* (1998) 95:13988–93. doi: 10.1073/pnas.95.23.13988
34. Dosher BA, Lu ZL. Mechanisms of perceptual learning. *Vision Res.* (1999) 39:3197–221. doi: 10.1016/S0042-6989(99)00059-0
35. Zomet A, Amiaz R, Grunhaus L, Polat U. Major depression affects perceptual filling-in. *Biol Psychiatr.* (2008) 64:667–71. doi: 10.1016/j.biopsych.2008.05.030
36. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet.* (2008) 371:281–3. doi: 10.1016/S0140-6736(07)61835-2
37. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, et al. Diffusion MRI in patients with transient ischemic attacks. *Stroke.* (1999) 30:1174–80. doi: 10.1161/01.STR.30.6.1174
38. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatr.* (2005) 76:1528–33. doi: 10.1136/jnnp.2004.059261
39. Vingrys AJ, Healey JK, Liew S, Saharinen V, Tran M, Wu W, et al. Validation of a tablet as a tangent perimeter. *Transl Vis Sci Technol.* (2016) 5:3. doi: 10.1167/tvst.5.4.3
40. Prea SM, Kong YXG, Mehta A, He M, Crowston JG, Gupta V, et al. Six-month longitudinal comparison of a portable tablet perimeter with the humphrey field analyzer. *Am J Ophthalmol.* (2018) 190:9–16. doi: 10.1016/j.ajo.2018.03.009
41. Nesaratnam N, Thomas PBM, Kirollos R, Vingrys AJ, Kong GYX, Martin KR. Tablets at the bedside - iPad-based visual field test used in the diagnosis of intrasellar haemangiopericytoma: a case report. *BMC Ophthalmol.* (2017) 17:53. doi: 10.1186/s12886-017-0445-z
42. Felius J, Wang YZ, Birch EE. The accuracy of the amblyopia treatment study visual acuity testing protocol. *J Aapos.* (2003) 7:406–12. doi: 10.1016/j.jaapos.2003.07.009
43. Cavanaugh MR, Zhang R, Melnick MD, Das A, Roberts M, Tadin D, et al. Visual recovery in cortical blindness is limited by high internal noise. *J Vis.* (2015) 15:9. doi: 10.1167/15.10.9
44. Hayes RD, Merigan WH. Mechanisms of sensitivity loss due to visual cortex lesions in humans and macaques. *Cereb Cortex.* (2007) 17:1117–28. doi: 10.1093/cercor/bhl021
45. Zele AJ, Smith VC, Pokorny J. Spatial and temporal chromatic contrast: Effects on chromatic discrimination for stimuli varying in L- and M-cone excitation. *Vis Neurosci.* (2006) 23:495–501. doi: 10.1017/S0952523806232012
46. Bodduluri L, Boon MY, Ryan M, Dain SJ. Impact of gamification of vision tests on the user experience. *Games Health J.* (2017) 6:229–36. doi: 10.1089/g4h.2016.0100
47. Sathian K, Crosson B. Structure-function correlations in stroke. *Neuron.* (2015) 85:887–89. doi: 10.1016/j.neuron.2015.02.031
48. Corbetta M, Shulman GL. Spatial neglect and attention networks. *Annu Rev Neurosci.* (2011) 34:569–99. doi: 10.1146/annurev-neuro-061010-113731
49. Rowe FJ, Wright D, Brand D, Jackson C, Harrison S, Maan T, et al. A prospective profile of visual field loss following stroke: prevalence, type, rehabilitation, and outcome. *Biomed Res Int.* (2013) 2013:719096. doi: 10.1155/2013/719096
50. Balcer LJ, Raynowska J, Nolan R, Galetta SL, Kapoor R, Benedict R, et al. Validity of low-contrast letter acuity as a visual performance outcome measure for multiple sclerosis. *Mult Scler.* (2017) 23:734–47. doi: 10.1177/1352458517690822
51. Chen JJ, Thurtell MJ, Longmuir RA, Garvin MK, Wang JK, Wall M, et al. Causes and prognosis of visual acuity loss at the time of initial presentation in idiopathic intracranial hypertension. *Invest Ophthalmol Vis Sci.* (2015) 56:3850–9. doi: 10.1167/iovs.15-16450
52. Kukkonen H, Rovamo J, Näsänen R. Masking potency and whiteness of noise at various noise check sizes. *Invest Ophthalmol Vis Sci.* (1995) 36:513–8.
53. Allard R, Cavanagh P. Crowding in a detection task: external noise triggers change in processing strategy. *Vision Res.* (2011) 51:408–16. doi: 10.1016/j.visres.2010.12.008
54. Hall C, Wang S, Bhagat R, McAnany JJ. Effect of luminance noise on the object frequencies mediating letter identification. *Front Psychol.* (2014) 5:663. doi: 10.3389/fpsyg.2014.00663
55. Born RT, Bradley DC. Structure and function of visual area MT. *Annu Rev Neurosci.* (2005) 28:157–89. doi: 10.1146/annurev.neuro.26.041002.131052
56. Young LK, Smithson HE. Critical band masking reveals the effects of optical distortions on the channel mediating letter identification. *Front Psychol.* (2014) 5:1060. doi: 10.3389/fpsyg.2014.01060
57. Hebart MN, Hesselmann G. What visual information is processed in the human dorsal stream? *J Neurosci.* (2012) 32:8107–9. doi: 10.1523/JNEUROSCI.1462-12.2012
58. Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends Cogn Sci.* (2013) 17:26–49. doi: 10.1016/j.tics.2012.10.011
59. Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med.* (2005) 54:1377–86. doi: 10.1002/mrm.20642

60. Grand S, Tahon F, Attye A, Lefournier V, Le Bas JF, Krainik A. Perfusion imaging in brain disease. *Diagn Interv Imaging.* (2013) 94:1241–57. doi: 10.1016/j.diii.2013.06.009
61. Verdon V, Schwartz S, Lovblad KO, Hauert CA, Vuilleumier P. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain.* (2010) 133:880–94. doi: 10.1093/brain/awp305
62. Pavlova EL, Lindberg P, Khan A, Ruschkowski S, Nitsche MA, Borg J. Transcranial direct current stimulation combined with visuo-motor training as treatment for chronic stroke patients. *Restor Neurol Neurosci.* (2017) 35:307–17. doi: 10.3233/RNN-160706
63. Buckner RL, Krienen FM, Yeo BT. Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci.* (2013) 16:832–7. doi: 10.1038/nn.3423

Conflict of Interest: AV is a founding director of Glance Optical Pty Ltd, the maker of Melbourne Rapid Field-Neural (MRFn) App.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Air vs. Road Decision for Endovascular Clot Retrieval in a Rural Telestroke Network

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Background and Purpose: Telestroke aims to increase access to endovascular clot retrieval (ECR) for rural areas. There is limited information on transfer workflow for ECR in rural settings. We sought to describe the transfer metrics for ECR in a rural telestroke network with respect to decision making.

Methods: A retrospective cohort study was employed on consecutive patients transferred to the comprehensive stroke center (CSC) for ECR in a rural hub-and-spoke telestroke network between April 2013 and October 2019, by road or air. Key time-based metrics were analyzed.

Results: Sixty-two patients were included. Mean age was 66 years [standard deviation (SD), 14] and median National Institutes of Health Stroke Scale 13 [interquartile range (IQR), 8–18]. Median rural-hospital-door-to-CSC-door (D2D) was 308 min (IQR, 254–351), of which 68% was spent at rural hospitals [door-in-door-out (DIDO); 214 min; IQR, 171–247]. DIDO was longer for air transfers than road ($P = 0.004$), primarily because of a median 87 min greater decision-to-departure time (Decision-DO, $P < 0.001$). In multiple linear regression analysis, intubation but not thrombolysis was associated with significantly longer DIDO. The distance at which the extra speed of an aircraft made up for the delays involved in booking an aircraft was 299 km from the CSC.

Conclusions: DIDO is longer for air retrievals compared with road. Decision-DO represents the most important component of DIDO, being longer for air transfers. Systems for rapid transportation of rural ECR candidates need optimization for best patient outcomes, with decision support seen as a potential tool to achieve this.

Keywords: telemedicine, decision, retrieval, thrombectomy, rural

INTRODUCTION

Endovascular clot retrieval (ECR) is the standard of care in the treatment of acute stroke patients with large vessel occlusion (LVO) (1). It has been shown to be major benefits in selected patients up to 24 h (2, 3), but earlier treatment leads to greater benefit (4–6). This presents logistical challenges in Australia, because patients from widely dispersed geographic regions are eligible for this treatment, but it is offered only in limited metropolitan centers (7, 8).

Telestroke is being increasingly used in Australia to help overcome geographical disparities in access to acute stroke care (9–11). Optimal implementation of ECR through telestroke requires efficient workflow from primary hospital to the comprehensive stroke center. Door-in-door-out (DIDO) time at the primary hospital has been thought to have the greatest impact on outcome for patients with LVO being transferred for ECR, among modifiable factors (12–14). A recent study in metropolitan Australia proposed that the target time for DIDO should be shortened to 45 min (15, 16).

Despite the fact that about 29% of Australia's population live in rural and remote areas, with people in very remote areas having a mortality rate almost 1.4 times as high as in major cities (17), there is a paucity of data on transfer workflow specific to rural Australia to guide further development of ECR in these areas. We aimed to describe the transfer metrics for ECR from rural hospitals to a regional comprehensive stroke center in a telestroke network in rural Australia, with respect to key points in clinical decision making.

Clinical decision making in stroke care is complex (18), with there being a correlation between decision delay in acute stroke and both pre-hospital and in-hospital delays (19–21). In addition to transfer workflow, we extended our study to look at the relationship between transfer metrics and clinical decision making so that the results might be more readily adapted to modify routine clinical practice and potentially identify areas for decision support. We sought to compare different transport modalities. Our main hypothesis was that DIDO for air transfers would be longer than for road transfers.

METHODS

Setting

A "hub and spoke" telestroke network was developed to support delivery of reperfusion therapy (thrombolysis and ECR) as a 24/7 service to six rural (spoke) hospitals in the Hunter New England and Mid-North Coast local health districts of New South Wales, Australia. The comprehensive stroke center hub based at John Hunter Hospital (JHH) in Newcastle, Australia, covers a population of over 1.1 million people distributed over an area of 143,120 km^2 (slightly larger than England). The average distance between the spoke sites and the hub is 227 km (range 167–423 km). All six spoke sites have advanced imaging (including brain CT angiography and CT perfusion) capability needed to select patients for reperfusion therapies, with all spoke sites capable of administering thrombolysis. The rural spoke hospitals were equipped with telehealth cameras, and the local physicians were trained in the face, arm, speech, time (FAST) scale. Only one of the spoke hospitals had neurologists or stroke physicians on staff who could guide local decisions about in-hours thrombolysis. All other decisions about reperfusion therapy in the acute phase were made by the telestroke neurologist at the hub (JHH) after reviewing the imaging and if required assessing the patient remotely through the telehealth cameras. Neurologists at Gosford District Hospital also participated in the telestroke roster, although only JHH accepted patients for ECR.

The decision to transfer for ECR was made by the telestroke neurologist on an individualized basis taking into account standard clinical, imaging, and patient factors. From November 2017, the time window for ECR was expanded to 24 h in image-selected patients following the release of pivotal ECR trial results (2, 3). When it was deemed necessary to give thrombolysis with ECR, thrombolysis was always initiated at the spoke hospital prior to transfer for ECR. Repeat imaging was not routinely performed at the hub because of the commitment to transfer patients across very large distances after the decision for transfer was made and the good baseline selection of patients using advanced imaging (22). Road transfers occurred by road ambulance directly from the spoke hospital to JHH. Air transfers by helicopter occurred from the rural airport servicing the respective spoke hospital to the helipad at JHH. Air transfers by fixed wing occurred from the rural airport servicing the respective spoke hospital to the regional airport based 26 km from JHH, after which the transfer to JHH took place by road ambulance. All connecting transfers to the rural airports from the respective spoke hospitals in order to facilitate air retrievals occurred by road ambulance. For more details of the telestroke setup, we direct the reader to our published experience (22, 23).

Study Design and Data Collection

We employed a retrospective cohort study design, where transfer metrics were collected on consecutive telestroke patients transferred to JHH for ECR between April 2013 and October 2019. Clinical data were collected prospectively from June 2016 and retrospectively prior to that. Patients were transferred by road or air (helicopter or fixed wing), depending on availability and hospital distance.

Data collected included baseline demographics, past medical history, National Institutes of Health Stroke Scale (NIHSS), advanced imaging characteristics, acute treatment decision, and mode of retrieval.

Outcome Measures and Analyses

Time metrics included DIDO, defined as the duration of time from arrival to departure at the rural hospital. DIDO was divided into two segments, door-in-to-decision (DI-Decision) and decision-to-door-out (Decision-DO). Decision was defined as the time that the telestroke neurologist at JHH contacted the rural hospital regarding the decision to transfer. Door-to-door (D2D) was the time from arrival at the rural hospital to arrival at the comprehensive stroke center. We also examined the total time from decision to arrival at JHH, and from arrival at the spoke site to arrival at JHH, correcting for the distance between spoke and hub.

Statistical Analysis

All statistical analyses were conducted in Stata Version 14.0 (StataCorp, USA). Univariate and multivariate linear regressions were performed to estimate the effect of each variable in the form of a coefficient with respect to DIDO, DI-Decision, and Decision-DO times. Adjusting each model for individual spoke site could not be done, as each spoke site had a small number of patients and almost exclusively used either air transport or road transport, making these effects difficult to separate reliably in this data set. Further, we needed to separate delays associated with air transfers from delays related to sites with reduced experience. Thus, spoke sites were grouped by experience into more experienced sites (those with more than 10 transfers) and less experienced sites (those with 10 or fewer transfers). This would also serve to correct for potentially faster triage and treatment at more experienced sites.

Ethics approval was gained from the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 13/02/20/5.06 and AU201712-15).

RESULTS

Between April 2013 and October 2019, 1,087 patients were assessed by telestroke, of which 568 (52%) had confirmed ischemic strokes (when mimics and hemorrhages were excluded). Of all patients with confirmed strokes, 175 had LVO (31%). Of these patients with LVO, 75 (43%) were transferred with a view to receiving ECR. Twelve of these patients were transferred to other ECR centers owing to logistic factors relating to transport, weather, or unavailability of ECR at JHH. One patient was transferred to JHH who did not eventually receive ECR owing to established infarct found on repeat brain imaging performed at JHH due to severe unexpected delays during that transfer. A sample of 62 patients who underwent ECR at JHH was finally included in this analysis (**Table 1**). Mean age was 66 years [standard deviation (SD), 14 years], 34 (55%) were male, and median NIHSS was 13 [interquartile range (IQR), 8 to 18]. There were 42 air transfers (33 by helicopter and 9 by fixed wing) and 20 road transfers. The groups were well-matched overall.

Transfer Metrics

Median D2D time was 308 min (IQR, 254 to 351). Median DIDO time was 214 min (IQR, 171 to 247). On average, 68% (SD, 10%) of D2D time was spent at the spoke hospital, and only 32% (SD, 10%) in transit. Median DI-Decision time was 70 min (IQR, 54 to 92). Median Decision-DO time was 130 min (IQR, 82 to 182). Median time from ED arrival at spoke sites to first telestroke neurologist contact was 26 min (IQR, 16 to 43).

Comparison of Air and Road Transfers

Spoke sites nearest to JHH transferred patients primarily by road, whereas more distant sites transferred patients primarily by air, with only two patients transferred by the method not normally used by their respective spoke site (**Table 2**).

Air transfer was associated with a delay of 64 min in DIDO time ($P = 0.004$). This was entirely due to its association with longer Decision-DO times by 87 min ($P < 0.001$).

TABLE 1 | Baseline characteristics of different groups.

	All transfers	Road transfers	Air transfers	*P*
Number (No.) of patients	62	20	42	
Age, mean [SD], years	66 (14)	69 (11)	65 (15)	0.27
Sex				
Men, No. (%)	34 (55%)	11 (55%)	23 (55%)	0.99
Women, No. (%)	28 (45%)	9 (45%)	19 (45%)	
Medical history, No. (%)				
Hypertension	28 (45%)	10 (50%)	18 (43%)	0.60
Hypercholesterolemia	10 (16%)	1 (5%)	9 (21%)	0.10
Diabetes mellitus	8 (13%)	3 (15%)	5 (12%)	0.25
Prior stroke/TIA	8 (13%)	3 (15%)	5 (12%)	0.73
Atrial fibrillation	13 (21%)	2 (10%)	11 (26%)	0.14
Ischemic heart disease	9 (15%)	4 (20%)	5 (12%)	0.40
Smoker	10 (16%)	6 (30%)	4 (10%)	0.04
Prestroke mRS, No. (%)				
0–2	61 (98%)	20 (100%)	41 (98%)	0.49
3–4	1 (2%)	0 (0%)	1 (2%)	
NIHSS score, median [IQR]	13 (8-18)	9 (6-16)	14 (10-18)	0.25
Intubated, No. (%)	4 (6%)	0 (0%)	4 (10%)	0.15
Thrombolyzed, No. (%)	25 (40%)	5 (25%)	20 (48%)	0.09
Occlusion location, No. (%)				
ICA	4 (6%)	1 (5%)	3 (7%)	0.75
M1 MCA	37 (60%)	13 (65%)	24 (57%)	0.55
M2 MCA	7 (11%)	4 (20%)	3 (7%)	0.14
Basilar	5 (8%)	1 (5%)	4 (10%)	0.54

ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

TABLE 2 | Distribution of transfers for rural spoke sites.

Hospital	Distance to John Hunter Hospital (km)	Road transfers	Air transfers	Total transfers
Taree	167	19	1	20
Tamworth	219	0	8	8
Armidale	267	0	12	12
Port Macquarie	198	1	10	11
Coffs Harbour	319	0	10	10
Moree	423	0	1	1
More experienced group (>10 transfers)		20	23	43
Less experienced group (≤10 transfers)		0	19	19

Separate univariate regressions of the time from decision to arrival at JHH against distance for air travel and road travel were performed and plotted (**Figure 1**). Extrapolating from these regressions suggested that the distance at which the extra speed of an aircraft made up for the delays involved in booking an aircraft was 299 km.

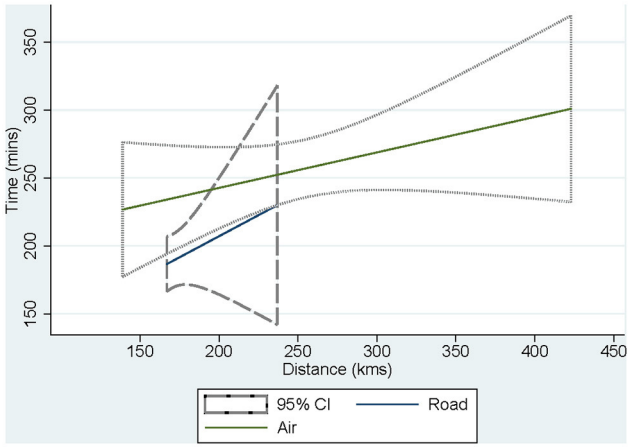

FIGURE 1 | Comparison through univariate regression analysis of decision to arrival time at John Hunter Hospital for air and road transfers by distance. Extrapolating from these separate regressions suggested that the distance at which the extra speed of an aircraft made up for the delays involved in booking an aircraft was 299 km.

TABLE 3 | Effects of selected variables on components of DIDO in adjusted analysis.

Variable	DIDO coefficient (min) (95% CI) *P*	DI-Decision coefficient (min) (95% CI) *P*	Decision-DO coefficient (min) (95% CI) *P*
Experience (>10 patients transferred)	8.2 (−39.1 to 55.6) $P = 0.73$	0.9 (−29.7 to 31.5) $P = 0.95$	17.0 (−16.1 to 50.2) $P = 0.31$
Air transport	63.5 (20.8 to 106.2) $P = 0.004$	−15.7 (−43.3 to 12.0) $P = 0.26$	87.4 (56.3 to 118.5) $P < 0.001$
Intubated Note $N = 4$, all transported by air	242.3 (165.0 to 319.7) $P < 0.001$	229.2 (179.2 to 279.3) $P < 0.001$	14.6 (−42.1 to 71.2) $P = 0.61$
Thrombolyzed	11.0 (−26.2 to 48.2) $P = 0.56$	−26.3 (−50.4 to −2.3) $P = 0.033$	33.8 (7.1 to 60.5) $P = 0.014$
Adjusted R^2	0.5134	0.6523	0.4313
P overall model	<0.001	<0.001	<0.001

DIDO, door-in-door-out; DI-Decision, door-in-to-decision; Decision-DO, decision-to-door-out.

Other Factors Which Might Influence Workflow

Differences in the level of experience between individual hospitals, that is, between the more experienced and less experienced sites (**Table 2**), were not significant with respect to key transfer metrics.

Intubation was associated with a delay of 242 min in DIDO and a delay of 229 min in the DI-Decision time but was not significantly associated with the Decision-DO time ($P = 0.61$, **Table 3**).

Thrombolysis was associated with faster DI-Decision times by 26 min but slower Decision-DO times by 34 min, which canceled each other out with respect to DIDO times (meaning thrombolysis was not significantly associated with DIDO, $P = 0.56$).

DISCUSSION

We found that air transfer was associated with a significant delay in DIDO time as compared with road. The main reason for this appeared to be the longer Decision-DO with air travel, which was probably attributable to multiple logistical factors that increased the complexity of organizing air retrieval. Our study indicates that Decision-DO appears to be a key component of DIDO, which has special relevance to the rural telestroke setup. While training and systems are already being used to minimize the DI-Decision time, which was also found to be too long in our study, Decision-DO in particular represents an important target for future optimization of transfer workflow for ECR in our area.

Our analysis suggests that the critical distance at which the speed of air travel makes up for the delays in booking aircraft is ∼300 km in our telestroke network, although there is considerable uncertainty about the exact figure, owing to a lack of overlap in the distances covered by air transfers compared with road transfers. Nevertheless, this figure may serve in future as a guide to base decisions about allocation of retrieval resources. For instance, when applied to other health service networks with comparable demographics and infrastructure to ours, transfers below a similar threshold may be prioritized for road rather than air retrieval (24–27).

We discovered that DIDO in our study was 214 min, more than double that published in other metropolitan Australian networks (15, 16). Potential reasons for our relatively long DIDO time include the much larger distances needed to be traversed by retrieval services in our network (hence affecting transport arrival times to rural spoke sites) as well as the resource and workforce limitations inherent in the rural setting.

Intubation was associated with a significant delay in DIDO, whereas thrombolysis was not. Our results are in line with previous studies in which thrombolysis did not have a detrimental impact on workflow of ECR transfers (14–16). However, although thrombolysis had no clear effect on DIDO in our study, it was associated with longer Decision-DO, which was compensated by shorter DI-Decision. This indicates that patients who are identified as potentially suitable for thrombolysis are triaged and treated quickly in our rural spoke sites relative to those who present later. The fact that the Decision-DO time is extended suggests that the process of thrombolysis may actually delay transfers slightly. This effect might be potentially reduced by using tenecteplase instead of alteplase for thrombolysis, which is just a bolus dose and not an infusion.

Although there may be too many variables in the telestroke-guided retrieval process to fully control for, our study raises a few potential roles for decision support in this process, with the overarching goal of reducing delays. One such role might be to integrate the entire retrieval process, so there is a uniform approach for all transfers. For example, once the decision to transfer for ECR has been made in a particular case,

a decision support system may work via a platform that helps to coordinate the retrieval process in real time and generate the most appropriate transfer strategy (taking into account factors such as distance, current weather conditions, availability of aircraft and landing stations, and need for intubation before transfer).

Another role for decision support might be in helping to activate the retrieval service. Ideally, the retrieval system could be activated for suspected LVO patients even before the formal decision by the telestroke neurologist. For example, decision support could facilitate ED and ambulance staff to activate the retrieval pathway even prior to consultation with the telestroke neurologist if certain clinical or imaging criteria are met, with the capacity to abort the transfer later if needed. This may serve to reduce Decision-DO in our population, although its implementation is likely to be hindered by transport limitations.

Besides the limited generalizability of our results due to small sample size and heterogeneity of our rural spoke sites, it was beyond the scope of our analysis to measure patient outcomes. Although we did not specifically look at patient outcomes, we instead studied key time metrics associated with DIDO, and by inference, the optimization of these metrics would likely serve to improve patient outcomes. The basis for this is that it is already well-established that delays in DIDO equate to delayed recanalization and hence are detrimental to patient outcomes (12). For similar reasons, we could not adequately compare helicopter and fixed wing retrievals. Some of our data were collected retrospectively. We were unable to account for less predictable factors, which could potentially affect transfers such as the effects of peak-hour traffic, aircraft availability, and refueling protocols.

In conclusion, DIDO in rural areas is longer than described in metropolitan areas. DIDO is longer for air retrievals compared with road. Decision-DO time represents the most important component of DIDO and hence a potential target for future interventions to improve transfer workflow. Decision-DO varies depending upon transport modality, being longer for air travel than road. Systems for rapid transportation of rural ECR candidates need optimization to minimize delays to treatment and ensure best patient outcomes, with decision support seen as a potential tool to achieve this.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The full data-set contains potentially identifiable patient data. Request to access the data can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunter New England Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SG: took the lead in writing the manuscript, in consultation with NS, CG-E, and TL. NS and CG-E: made an equal contribution to the article as joint senior authors and conceived the framework for the project with input from CL and together oversaw the overall operation of the telestroke network. In addition, TL, FM, PG-B, TW, BO'B, JE, KA, CG-E, and NS: collected and collated data for the article. TL conducted the statistical analyses. MP and AB: oversaw the imaging protocols. All authors contributed to designing and writing and the conception of the manuscript on behalf of the Northern NSW Telestroke investigators.

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REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, etal. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
2. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, etal. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
3. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, etal. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
4. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, etal. Drip and ship versus direct to endovascular thrombectomy: the impact of treatment times on transport decision-making. *Eur Stroke J.* (2018) 3:126–35. doi: 10.1177/2396987318759362
5. Sarraj A, Mlynash M, Savitz SI, Heit JJ, Lansberg MG, Marks MP, etal. Outcomes of thrombectomy in transferred patients with ischemic stroke in the late window: a subanalysis from the DEFUSE 3 trial. *JAMA Neurol.* (2019) 76:682–9. doi: 10.1001/jamaneurol.2019.0118

6. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, etal. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. (2016) 316:1279–88. doi: 10.1001/jama.2016.13647
7. Campbell BCV. Advances in stroke medicine. *MJA*. (2019) 210:367–74. doi: 10.5694/mja2.50137
8. Janssen PM, Venema E, Dippel DWJ. Effect of workflow improvements in endovascular stroke treatment: a systematic review and meta-analysis. *Stroke*. (2019) 50:665–74. doi: 10.1161/STROKEAHA.118.021633
9. Levine SR, Gorman M. Telestroke: the application of telemedicine for stroke. *Stroke*. (1999) 30:464–9. doi: 10.1161/01.STR.30.2.464
10. Bagot KL, Cadilhac DA, Hand PJ, Vu M, Bladin CF. Telemedicine expedites access to optimal acute stroke care. *Lancet*. (2016) 388:757–8. doi: 10.1016/S0140-6736(16)31360-5
11. Saler M, Switzer JA, Hess DC. Use of telemedicine and helicopter transport to improve stroke care in remote locations. *Curr Treat Options Cardiovasc Med*. (2011) 13:215–24. doi: 10.1007/s11936-011-0124-y
12. McTaggart RA, Moldovan K, Oliver LA, Dibiasio EL, Baird GL, Hemendinger ML, etal. Door-in-Door-out time at primary stroke centers may predict outcome for emergent large vessel occlusion patients. *Stroke*. (2018) 49:2969–74. doi: 10.1161/STROKEAHA.118.021936
13. Ranasinghe I, Turnbull F, Tonkin A, Clark RA, Coffee N, Brieger D. Comparative effectiveness of population interventions to improve access to reperfusion for ST-segment-elevation myocardial infarction in Australia. *Circ Cardiovasc Qual Outcomes*. (2012) 5:429–36. doi: 10.1161/CIRCOUTCOMES.112.965111
14. Regenhardt RW, Mecca AP, Flavin SA, Boulouis G, Lauer A, Zachrison KS, etal. Delays in the air or ground transfer of patients for endovascular thrombectomy. *Stroke*. (2018) 49:1419–25. doi: 10.1161/STROKEAHA.118.020618
15. Choi PMC, Tsoi AH, Pope AL, Leung S, Frost T, Loh PS, etal. Door-in-door-out time of 60 minutes for stroke with emergent large vessel occlusion at a primary stroke center. *Stroke*. (2019) 50:2829–34. doi: 10.1161/STROKEAHA.119.025838
16. Ng FC, Low E, Andrew E, Smith K, Campbell BCV, Hand PJ. Deconstruction of interhospital transfer workflow in large vessel occlusion: real-world data in the thrombectomy era. *Stroke*. (2017) 48:1976–9. doi: 10.1161/STROKEAHA.117.017235
17. Australian Institute of Health and Welfare. *Australia's Health*. (2018). Australia's health series no. 16. AUS 221.
18. Saposnik G, Johnston SC. Decision making in acute stroke care. *Stroke*. (2014) 45:2144–50. doi: 10.1161/STROKEAHA.114.005462
19. Mellor RM, Bailey S, Sheppard J, Carr P, Quinn T, Boyal A etal. Decisions and delays within stroke patients' route to the hospital: a qualitative study. *Ann Emerg Med*. (2015) 65:279–87. doi: 10.1016/j.annemergmed.2014.10.018
20. Faiz KW, Sundseth A, Thommessen B, Ronning OM. Factors related to decision delay in acute stroke. *J Stroke Cerebrovasc Dis*. (2014) 23:534–9. doi: 10.1016/j.jstrokecerebrovasdis.2013.05.007
21. Hsia AW, Castle A, Wing JJ, Edwards DF, Brown NC, Higgins TM etal. Understanding reasons for delay in seeking acute stroke care in an underserved urban population. *Stroke*. (2011) 42:1697–1701. doi: 10.1161/STROKEAHA.110.604736
22. Garcia-Esperon C, Soderhjelm Dinkelspiel F, Miteff F, Gangadharan S, Wellings T, O'Brien B, et al. Implementation of multimodal computed tomography in a telestroke network: five-year experience. *CNS Neurosci Ther*. (2020) 26:367–73. doi: 10.1111/cns.13224
23. Demeestere J, Sewell C, Rudd J, Ang T, Jordan L, Wills J, etal. The establishment of a telestroke service using multimodal CT imaging decision assistance: "Turning on the fog lights." *J Clin Neurosci*. (2017) 37:1–5. doi: 10.1016/j.jocn.2016.10.018
24. Svenson JE, O'Connor JE, Lindsay MB. Is air transport faster? A comparison of air versus ground transport times for interfacility transfers in a regional referral system. *Air Med J*. (2006) 25:170–2. doi: 10.1016/j.amj.2006.04.003
25. Diaz MA, Hendey GW, Bivins HJ. When is the helicopter faster? A comparison of helicopter and ground ambulance transport times. *J Trauma*. (2005) 58:148–53. doi: 10.1097/01.TA.0000124264.43941.41
26. Munford BJ, Beehan SJ. Development of a model for air medical service utilisation. In: *ADAC/International Society of Aeromedical Services AIRMED 96 Congress Report*. Munich (1996). p. 597–602.
27. Ramadas R, Hendel S, MacKillop A. Civilian aeromedical retrievals (the Australian experience). *BJA Educ*. (2016) 16:186–90. doi: 10.1093/bjaed/mkv040

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Functional Outcome Prediction in Ischemic Stroke: A Comparison of Machine Learning Algorithms and Regression Models

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Background and Purpose: Stroke-related functional risk scores are used to predict patients' functional outcomes following a stroke event. We evaluate the predictive accuracy of machine-learning algorithms for predicting functional outcomes in acute ischemic stroke patients after endovascular treatment.

Methods: Data were from the Precise and Rapid Assessment of Collaterals with Multi-phase CT Angiography (PROVE-IT), an observational study of 614 ischemic stroke patients. Regression and machine learning models, including random forest (RF), classification and regression tree (CART), C5.0 decision tree (DT), support vector machine (SVM), adaptive boost machine (ABM), least absolute shrinkage and selection operator (LASSO) logistic regression, and logistic regression models were used to train and predict the 90-day functional impairment risk, which is measured by the modified Rankin scale (mRS) score > 2. The models were internally validated using split-sample cross-validation and externally validated in the INTERRSeCT cohort study. The accuracy of these models was evaluated using the area under the receiver operating characteristic curve (AUC), Matthews Correlation Coefficient (MCC), and Brier score.

Results: Of the 614 patients included in the training data, 249 (40.5%) had 90-day functional impairment (i.e., mRS > 2). The median and interquartile range (IQR) of age and baseline NIHSS scores were 77 years (IQR = 69–83) and 17 (IQR = 11–22), respectively. Both logistic regression and machine learning models had comparable predictive accuracy when validated internally (AUC range = [0.65–0.72]; MCC range = [0.29–0.42]) and externally (AUC range = [0.66–0.71]; MCC range = [0.34–0.42]).

Conclusions: Machine learning algorithms and logistic regression had comparable predictive accuracy for predicting stroke-related functional impairment in stroke patients.

Keywords: machine learning, acute ischemic stroke, functional outcome, clinical risk prediction, discrimination calibration

INTRODUCTION

Prognostic risk scores that use patient characteristics to predict functional outcomes in stroke patients are of increasing importance for aiding clinical decisions in stroke management (1). Examples of these prognostic tools include Ischemic Stroke Predictive Risk Score (ISCORE) (2), the Acute Stroke Registry, and Analysis of Lausanne (ASTRAL) (3) and Dense Artery, mRS, Age, Glucose, Onset-to-Treatment, and NIHSS (DRAGON) (4), among others. These models combine multiple predictors to provide insight into the relative or absolute risk of functional impairment for each patient and a simple risk scoring system that allows for their use in busy clinical settings (5–8). These scores are particularly of interest in both routine clinical practice and policy administration for discharge planning, quality improvement, management of prognostic expectations in stroke patients, and resource allocation (9).

One characteristic feature of these prognostic risk scores is that they are mostly developed based on regression models and have shown moderate to good discriminatory accuracy (AUC range = [66 and 88%]) for predicting 90-day functional outcomes in ischemic stroke patients (10). However, these risk scores are inherently limited to a number of reasons. First, existing scores are mostly developed on a highly selective population obtained from randomized controlled trials, which are not representative of the population of stroke patients being seen in acute care settings. Second, the risk scores are mostly developed using a small set of clinical predictors, ignoring the available rich information on patients' clinical, imaging, and behavioral characteristics that may be predictive of the outcome of interest. Third, these risk scores are rarely validated in other external cohorts; they tend to demonstrate poor predictive accuracy even when validated in external cohorts.

Machine learning (ML) algorithms constitute a promising class of methods for developing prognostic models. In recent times, there has been an increased focus on ML algorithms and their potential to revolutionize clinical research, especially in precision medicine. ML algorithms explore both linear and non-linear interactions among predictors while maximizing the information in them to improve the accuracy of outcome predictions. Despite its attractive features and touted potentials, there is still limited uptake of ML for developing prognostic risk scores for stroke patients (10).

In this study, we examine the predictive performance of ML algorithms for predicting a 90-day functional impairment risk after acute ischemic stroke. We hypothesized that the predictive performance of ML would be comparable to the regression-based risk prediction models.

METHODS

The study is reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist for prediction model development and validation (11).

Data Sources

This study used prospectively collected multicenter observational studies of ischemic stroke patients to develop and validate the ML algorithms for predicting the patient-specific risk of functional impairment. These data sources are described as follows, and the ethics approval were sought from the University of Calgary Conjoint Health Research Ethics Board (REB14-2012 and REB14-2015).

Precise and Rapid Assessment of Collaterals With Multi-Phase CT Angiography (PROVE-IT) (12)

PROVE-IT is a prospective multi-center hospital-based cohort study of 614 patients with acute ischemic stroke presenting within 12 h of stroke symptom onset with evidence of intracranial occlusion on routine computed tomography angiography CTA and treated with intravenous alteplase and/or intra-arterial therapy. Patients underwent baseline unenhanced CT, multiphase CT angiography, and perfusion CT. Both demographic, clinical, and imaging data were collected on study participants across these centers. The primary outcome was patients' 90-day functional status measured by the mRS. The study was conducted over a 3-year period. Details about this study have been published elsewhere (12).

Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV tPA Using Serial CT Angiography (INTERRSeCT) (13)

INTERRSeCT is a prospective multi-center hospital-based cohort of patients treated with intravenous alteplase comparing the rates of early recanalization in 684 patients. Patient eligibility included the following: presentation to the emergency department with symptoms consistent with ischemic stroke 12 h from last known well, age at least 40 years, and a baseline CTA (before alteplase bolus, if given) with evidence of a symptomatic intracranial thrombus. This study compared rates of early recanalization by location of primary intracranial or extracranial artery occlusion. The primary radiological outcome was recanalization, while the primary clinical outcome was functional independence, as measured by the mRS (range, 0 [no symptoms] to 6 [death]) at 90 days. Details about this study have been published elsewhere (13). A subset of 507 patients were included in this study, and the rest of the patients were excluded for being a participant in the PROVE-IT study.

Data from both study cohorts are not publicly available because of data protection laws imposed by University of Calgary Conjoint Health Research Ethics. But datasets might be available from the institutional CHRED for research who meet the criteria for access to confidential data.

Statistical Analysis

Descriptive statistics were used to compare patients' demographic and clinical characteristics in both training and validation datasets. Similarly, descriptive analyses of patients'

characteristics by 90-day functional status (i.e., mRS $>$ 2 vs. mRS $\leq$ 2) were conducted for each training and validation cohorts. Univariate associations between each categorical/continuous predictor variable and 90-day function outcome were assessed using the chi-square test and Wilcoxon rank-sum tests, respectively. For each cohort, predictors on which missing data were more than 50%, and/or predictors for which the ratio of the levels of categorical features are more than 4:1 in either cohorts were excluded from the analyses. Median imputation method was used to impute missing data in both cohorts. In addition, given the slight imbalance in the distribution of patients by functional outcome, an under-sampling of majority subgroup (mRS $\leq$ 2 subgroup) was adopted to mitigate the influence of class imbalance on the accuracy of the investigated models in both cohorts.

Functional impairment risk prediction models developed based on support vector machine, random forest, C5.0 decision tree, adaptive boost machine, classification and regression tree, least absolute shrinkage, and selection operator (LASSO) logistic regression, and conventional logistic regression models were trained using under-sampled data from the PROVE-IT study and validated in the INTERRSeCT study. For each cohort, model predictors were scaled to ensure comparability of accuracy across several models. Specifically, predictor scaling was performed in each shuffle in the outer loop and that imputed and scales values were based on the training set both for both cohorts. Two variable selection strategies were adopted for deriving the most accurate risk prediction model for all the ML and regression algorithms, namely; (1) clinical expert knowledge, and (2) automated variable selection. Model predictors were selected based on the knowledge of the literature by two stroke neurologists on our team (BKM, MDH) and their presence in both PROVE-IT and INTERRSeCT cohorts. These predictors included age, NIHSS, treatment received, blood glucose, systolic blood pressure, diastolic blood pressure, hypertension, and diabetes. On the other hand, an automated variable selection method based on rank ordering of the full set of predictors was used to predict 90-day functional outcome. In both approaches, a grid search of the optimal hyper parameter (i.e., hyper parameter tuning) was used to train and derive the most accurate models common to both PROVE-IT and INTERRSeCT cohorts) for each type of model. For LASSO regression, a L1 regularization that shrinks the coefficients effect size of the less important variables toward zero. For random forest, classification and regression trees, and C5.0 decision tree, the optimal number of trees was obtained by grid search while avoiding model overfitting and optimal accuracy. The optimal accuracy of the support vector machine and adaptive boost were obtained by tuning the hyper-parameters using a grid search cross-validation. For the conventional logistic regression, backward elimination was used to determine the most parsimonious model.

Furthermore, predictors in the training data were ranked according to their relative contribution to the prediction of 90-day functional outcomes using a variety of variable importance metrics. For random forest model, the mean decrease in Gini coefficient, which measures how each variable contributes to the homogeneity of the nodes and leaves, was used to rank the variables. Variables with larger Gini index were considered more important (14). For support vector machine and adaptive boosting, the relative importance of each predictor was evaluated based on their unique contribution, as measured by AUC, to the prediction of 90-day functional outcome. On the other hand, the mean decrease in impurity of each surrogate variables at each node was used to evaluate the relative contribution of the predictors in C5.0 and classification and regression trees. For LASSO and the conventional logistic regression models, the magnitude of the standardized logistic regression coefficients was used rank order the predictors according to their importance (15). The absolute values of the importance metrics for all the predictors were scaled to unit norm, in order to ensure comparable rank ordering across all the investigated models (16).

Furthermore, the predictive accuracy of both ML and logistic regression models were assessed using both internal cross-validation (PROVE-IT) and external validation (INTERRSeCT). In the former, the prediction models were trained using data obtained from the PROVE-IT study via a repeated 3-fold cross-validation method. Specifically, the PROVE-IT dataset was randomly split, with two-thirds of the data used for model development and the remaining one-third for internal validation. This process was repeated 500 times by sampling the original data with replacement. In the latter, predictors in the INTERRSeCT data were scaled using parameters from the PROVE-IT study before validating the trained in this cohort.

The predictive performance of each model was examined using sensitivity, specificity, the area under the receiver operating characteristic curve (AUC), and Mathew's correlation coefficient (MCC). MCC measures the strength of association between observed and predicted binary classification. MCC values ranges between -1 and $+1$; the former represents total disagreement between observed and predicted binary classifications, while the latter represents perfect agreement (i.e., perfect prediction) (17, 18).

Moreover, both brier scores and calibration plots were used to assess the calibration performance of all the models trained and validated in the PROVE-IT and INTERSECT cohorts, respectively (19). In contrast, calibration curves for all the ML and regression-based algorithms based on automated and clinical expert knowledge predictor selection methods were plotted. A perfectly calibrated model should have all the points line on a 45^0 diagonal line to the x- and y-axes; the greater the deviation of the calibration curve from this diagonal line, the poorer the model calibration. The development and validation of models was checked against the recommendations for reporting in the TRIPOD statement (see Appendix A in **Supplementary Material**). Statistical significance was evaluated at $\alpha = 0.05$. All the analyses were conducted using several packages (20–26) in R software v 3.6.1 (27).

RESULTS

Table 1 describes the demographic and clinical characteristics of patients between PROVE-IT and INTERRSeCT study cohorts. Of the 614 patients in the PROVE-IT study, all the study predictors

TABLE 1 | Descriptive characteristics of PROVE-IT and INTERRSeCT study participants.

Participants' characteristics	PROVE-IT ($N_1 = 614$)	INTERRSeCT ($N_2 = 507$)	*P*-value
Age (median, IQR)	73 (63–80)	71 (63–79)	0.68
Sex (*n*, % Male)	322 (52.4%)	264 (52.1%)	0.48
Diastolic blood pressure (median, IQR)	82 (74–93)	80 (71–90)	0.62
Systolic blood pressure (median, IQR)	150 (135–170)	147 (131–169)	0.45
Blood glucose (median, IQR)	6.4 (5.6–7.8)	6.5 (5.8–7.9)	0.39
NIHSS (median, IQR)	13 (6–19)	14 (8–19)	0.46
Treatment (*n*, % Intervention)	291 (47.3%)	192 (37.9%)	0.56
History of atrial fibrillation (*n*, % Yes)	184 (29.9%)	161 (31.8%)	0.27
Diabetes (*n*, % No)	511 (83.2%)	421 (83.0%)	0.34
Hypertension (*n*, % Yes)	422 (68.7%)	302 (59.6%)	0.35
International normalize ratio (median, IQR)	1 (1–1.2)	1(1–1.1)	0.60
Creatinine (median, IQR)	81 (67.8–96)	78 (66–93.4)	0.97
Platelet count (median, IQR)	207 (171–253)	195 (57–137)	0.67
Hematocrit (median, IQR)	0.43 (0.39–0.47)	0.41 (0.38–0.44)	0.92

IQR, Interquartile range; NIHSS, National Institute of Stroke Severity Scale; mRS, modified Rankin Scale.

TABLE 2 | Descriptive characteristics of patients in PROVE-IT study.

Participants' characteristics	mRS > 2 ($N_1 = 249$)	mRS ≤ 2 ($N_2 = 365$)	*P*-value
Age(median, IQR)	77 (69–83)	70 (59–77)	< 0.01
Sex (*n*, % Male)	127 (51%)	195 (53.4%)	0.56
Diastolic blood pressure (median, IQR)	85 (77–95)	80 (72–92)	0.09
Systolic blood pressure (median, IQR)	154 (140–172)	150 (130–170)	0.08
Blood glucose (median, IQR)	6.8 (5.8–8.1)	6.2 (5.6–7.5)	< 0.01
NIHSS (median, IQR)	17 (11–22)	9 (5–15)	< 0.01
Treatment (*n*, % Intervention)	128 (51.1%)	163(44.7%)	0.11
History of atrial fibrillation (*n*, % Yes)	92 (36.9%)	92 (25.2%)	0.002
Diabetes (*n*, % No)	202 (81.1%)	309 (84.7%)	0.25
Hypertension (*n*, % Yes)	190 (76.3%)	232 (63.5%)	< 0.01
International normalized ratio (median, IQR)	1.09 (1.0–1.20)	1.0 (1.0–1.1)	< 0.01
Creatinine (median, IQR)	83 (65–101)	80 (69–91)	0.23
Platelet count (median, IQR)	210 (169–257)	206 (172–249)	0.83
Hematocrit (median, IQR)	0.42 (0.38–0.47)	0.43 (0.41–0.48)	0.03

IQR, Interquartile Range; NIHSS, National Institute of Health Stroke Severity Scale; mRS, Modified Rankin scale.

had no more than 10% missing values, except for imaging. Similarly, of the 507 patients in the INTERRSeCT study, all the study predictors had less than 10% missing values, except for imaging, hemoglobin, partial thromboplastin time, and history of hemoglobin (See Appendix B in **Supplementary Material**). In addition, history of congestive heart failure, history of heart disease, and smoking had skewed distributions across their categorical levels. These seven variables were excluded from our main analyses. There were no significant differences between both cohorts with respect to patients' demographical and clinical characteristics. **Tables 2**, **3** describes the demographic and clinical characteristics of patients according to their 90-day functional outcome in PROVE-IT and INTERRSeCT cohorts, respectively. In both cohorts, patients with mRS > 2 tend to be older patients ($p < 0.01$) with more severe stroke ($p < 0.01$), and comorbid hypertension ($p < 0.01$).

TABLE 3 | Descriptive characteristics of patients in the INTERRSeCT Study.

Participants' characteristics	mRS > 2 ($N_1 = 239$)	mRS ≤ 2 ($N_2 = 268$)	*P*-value
Age (median, IQR)	77 (68–83)	68 (59–75)	< 0.01
Sex (*n*, %Male)	112 (46.8%)	152 (56.7%)	0.03
Diastolic blood pressure (median, IQR)	80 (70–90)	81 (72–90)	0.71
Systolic blood pressure (median, IQR)	150 (134–171)	145 (130–162)	0.02
Blood glucose (median, IQR)	6.6 (5.9–8.1)	6.4 (5.80–7.55)	0.07
NIHSS (median, IQR)	17 (12–20)	10 (6–17)	< 0.01
Treatment (*n*, % Intervention)	86 (35.9%)	106 (39.5)	0.40
History of atrial fibrillation (*n*, % Yes)	88 (36.8%)	73 (27.2%)	0.02
Diabetes (*n*, % No)	192 (80.3%)	229 (85.4%)	0.12
Hypertension (*n*, % Yes)	154 (64.4%)	148 (55%)	0.04
Creatinine (median, IQR)	78 (65–96)	78 (66–91.1)	0.72
International normalized ratio (median, IQR)	1.02 (1.0–1.10)	1.0 (1.0–1.10)	0.09
Platelet Count (median, IQR)	93 (57–142)	97 (55.8–130.3)	0.88
Hematocrit (median, IQR)	0.4 (0.37–0.43)	0.42 (0.39–0.44)	< 0.01

IQR, Interquartile Range; NIHSS, National Institute of Health Stroke Severity Scale; mRS, Modified Rankin scale.

Figures 1, **2** describe the relative importance of the predictor variables with respect to the prediction of 90-day functional outcomes in ischemic stroke patients for ML and logistic regression models in imputed PROVE-IT data. Age and NIHSS were ranked as the two most important predictors of 90-day functional outcomes for almost all the models, regardless of the predictor selection strategy. But there are variations in the rank ordering other less important variables across all the investigated models.

Table 4 describes the predictive accuracy of investigated models in the PROVE-IT data when the predictors were selected based on automated variable selection and clinical expert knowledge. There were negligible differences in the accuracy of ML and regression-based models, regardless of the variable selection method adopted. For example, for models trained using predictors derived from clinical expert knowledge, the average AUC and MCC for LASSO logistic regression were 0.71 (95%CI = [0.53, 0.71]) and 0.43(95%CI = [0.32, 0.55]); whereas the average AUC and MCC for random forest were 0.67 (95%CI = [0.61, 0.73]) and 0.34 (95%CI = [0.22, 0.46]). Similar patterns were observed for both sensitivity and specificity values across the models. Moreover, when these models were validated

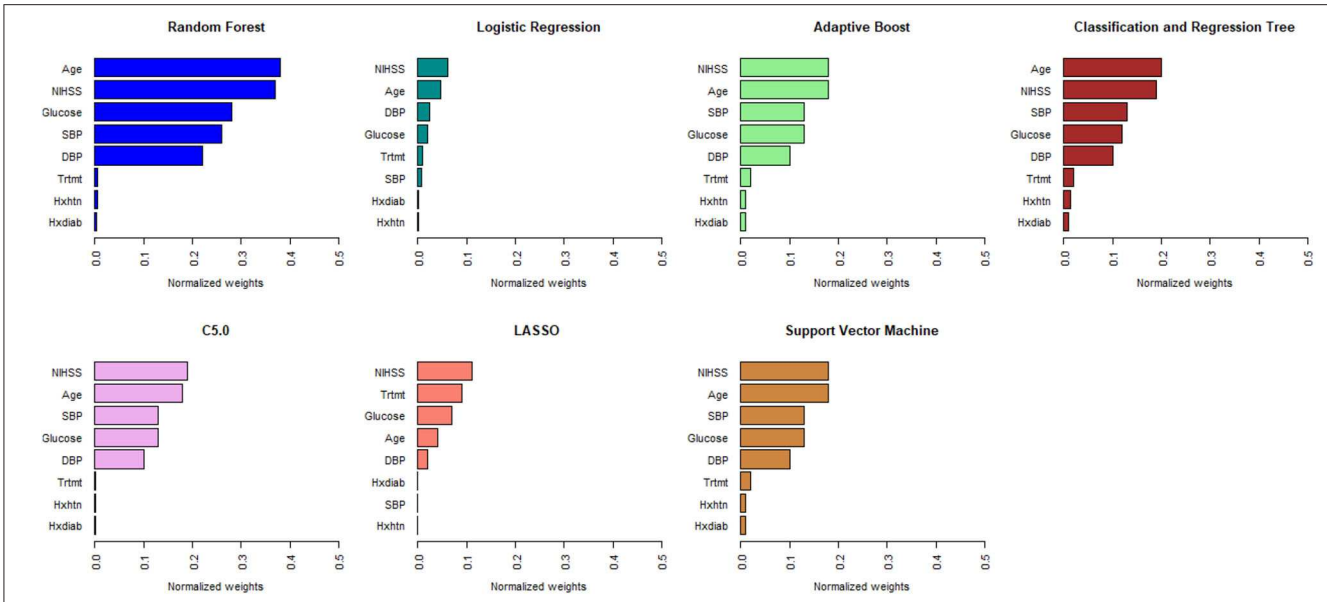

FIGURE 1 | Rank ordering of machine learning and regression model predictors (selected based on clinical expert knowledge). NIHSS, National Institute of Health and Stroke Scale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; Trtmt, Treatment; Hxdiab, History of Diabetes; Hxhtn, History of Hypertension; LASSO, Least Absolute Shrinkage Selection Operator.

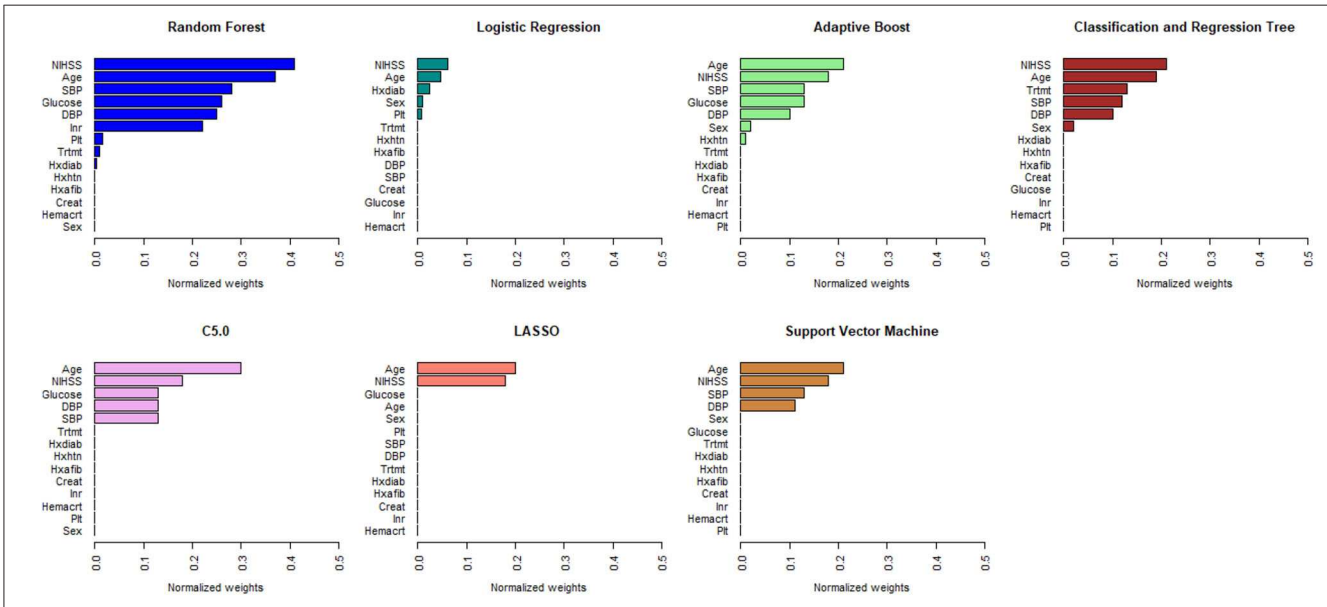

FIGURE 2 | Rank ordering of machine learning and regression-based model predictors (automated variable selection). NIHSS, National Institute of Health and Stroke Scale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; Trtmt, Treatment; Hxdiab, History of Diabetes; Hxhtn, History of Hypertension; Hxafib, History of Atrial Fibrillation; Plt, Partial Thromboplastin Time; Inr, International Normalize Ratio; Creat, Creatinine; Hemacrt, Hematocrit; LASSO, Least Absolute Shrinkage Selection Operator.

externally in the INTERRSeCT cohort (**Table 5**), similar patterns of negligible differences in the AUCs and MCCs of ML and logistic regression algorithms were reported, regardless of the variable selection strategies adopted.

Moreover, there were no significant differences in Brier scores for ML and regression-based models across both training and validation cohorts, regardless of the variable selection strategy adopted (**Tables 4**, **5**). But graphical examination of calibration for LASSO logistic and conventional logistic regression models showed that both models had fairly good calibration in high-risk individuals but they slightly under-estimated or over-estimated the risk of poor functional outcome (mRS > 3) in low risk in

TABLE 4 | Predictive accuracy (95%CI) of regression and ML models in PROVE-IT data (internal validation).

Predictive accuracy metric	RF	SVM	C5.0	ABM	CART	LR	LASSO
Automated variable selection							
Sensitivity	0.67 (0.57–0.77)	0.62 (0.51–0.72)	0.66 (0.56–0.76)	0.74 (0.64–0.83)	0.76 (0.66–0.84)	0.73 (0.63–0.83)	0.73 (0.63–0.82)
Specificity	0.58 (0.47–0.68)	0.63 (0.52–0.73)	0.71 (0.61–0.80)	0.60 (0.50–0.71)	0.54 (0.43–0.64)	0.70 (0.60–0.79)	0.70 (0.60–0.79)
AUC	0.63 (0.56–0.70)	0.62 (0.55–0.70)	0.69 (0.62–0.76)	0.67 (0.60–0.74)	0.65 (0.58–0.72)	0.72 (0.65–0.78)	0.72 (0.65–0.79)
MCC	0.26 (0.11–0.39)	0.25 (0.11–0.37)	0.38 (0.24–0.51)	0.35 (0.21–0.49)	0.31 (0.16–0.44)	0.43 (0.30–0.56)	0.43 (0.30–0.56)
Brier score	0.34 (0.30–0.45)	0.34 (0.30–0.45)	0.28 (0.25–0.38)	0.30 (0.21–0.48)	0.32 (0.28–0.42)	0.26 (0.21–0.35)	0.26 (0.21–0.35)
Clinical expert knowledge							
Sensitivity	0.64 (0.55–0.72)	0.61 (0.51–0.71)	0.68 (0.59–0.76)	0.66 (0.57–0.75)	0.62 (0.53–0.71)	0.62 (0.53–0.71)	0.62 (0.53–0.71)
Specificity	0.70 (0.60–0.79)	0.77 (0.67–0.84)	0.69 (0.59–0.78)	0.74 (0.64–0.82)	0.71 (0.69–0.79)	0.80 (0.72–0.87)	0.80 (0.72–0.87)
AUC	0.67(0.61–0.73)	0.69 (0.63–0.75)	0.69 (0.63–0.75)	0.70 (0.64–0.76)	0.67 (0.61–0.73)	0.71(0.66–0.77)	0.71 (0.66–0.77)
MCC	0.34 (0.22–0.46)	0.38 (0.26–0.50)	0.37 (0.24–0.49)	0.40 (0.28–0.52)	0.33 (0.21–0.47)	0.43 (0.32–0.55)	0.43 (0.32–0.55)
Brier score	0.33 (0.27–0.39)	0.31 (0.26–0.38)	0.31 (0.25–0.37)	0.30 (0.24–0.36)	0.34 (0.28–0.39)	0.29 (0.24–0.35)	0.29 (0.24–0.35)

95%CI, 95% Confidence Interval; AUC, Area under the receiver operating characteristic curve; RF, Random Forest; SVM, Support Vector Machine; C5.0, C5.0 Decision Tree; ABM, Adaptive Boost Machine; CART, Classification and Regression Tree; LR, Logistic Regression; LASSO, Least Absolute Shrinkage and Selection Operation; MCC, Matthews Correlation Coefficient.

TABLE 5 | Predictive accuracy (95%CI) of regression and ML models in INTERRSeCT data (external validation).

Predictive accuracy metric	RF	SVM	C5.0	ABM	CART	LR	LASSO
Automated variable selection							
Sensitivity	0.70 (0.64–0.76)	0.65 (0.59–0.71)	0.76 (0.70–0.81)	0.68 (0.61–0.74)	0.77 (0.71–0.82)	0.83 (0.78–0.88)	0.71 (0.60–0.79)
Specificity	0.71 (0.65–0.77)	0.77 (0.71–0.82)	0.58 (0.51–0.65)	0.70 (0.60–0.79)	0.60 (0.54–0.67)	0.56 (0.49–0.62)	0.67 (0.61–0.73)
AUC	0.70 (0.66–0.75)	0.71 (0.65–0.75)	0.66 (0.63–0.72)	0.67 (0.65–0.73)	0.69 (0.64–0.73)	0.69 (0.65–0.73)	0.67 (0.60–0.73)
MCC	0.41 (0.29–0.54)	0.42 (0.29–0.53)	0.34 (0.15–0.44)	0.38 (0.16–0.43)	0.38 (0.14–0.41)	0.40 (0.29–0.52)	0.39 (0.20–0.50)
Brier score	0.32 (0.28–0.41)	0.32 (0.29–0.42)	0.32 (0.28–0.41)	0.32 (0.29–0.42)	0.33 (0.30–0.43)	0.30 (0.27–0.39)	0.30 (0.27–0.39)
Clinical expert knowledge							
Sensitivity	0.67 (0.61–0.73)	0.67 (0.61–0.73)	0.67 (0.60–0.73)	0.56 (0.49–0.62)	0.66 (0.60–0.72)	0.81 (0.75–0.85)	0.71 (0.65–0.77)
Specificity	0.71 (0.65–0.76)	0.72 (0.66–0.78)	0.75 (0.69–0.80)	0.78 (0.73–0.83)	0.69 (0.62–0.75)	0.60 (0.54–0.66)	0.69 (0.63–0.75)
AUC	0.66 (0.58–0.73)	0.67 (0.65–0.74)	0.63 (0.58–0.67)	0.68 (0.63–0.72)	0.67 (0.63–0.72)	0.68 (0.65–0.72)	0.69 (0.65–0.73)
MCC	0.38 (0.22–0.55)	0.39 (0.27–0.55)	0.42 (0.28–0.51)	0.35 (0.21–0.53)	0.35 (0.21–0.54)	0.41 (0.29–0.55)	0.40 (0.29–0.53)
Brier score	0.31 (0.25–0.37)	0.26 (0.22–0.38)	0.35 (0.27–0.36)	0.25 (0.21–0.32)	0.25 (0.21–0.38)	0.27(0.25–0.36)	0.27(0.24–0.35)

95%CI, 95% Confidence Interval; AUC, Area under the receiver operating characteristic curve; RF, Random Forest; SVM, Support Vector Machine; C5.0, C5.0 Decision Tree; ABM, Adaptive Boost Machine; CART, Classification and Regression Tree; LR, Logistic Regression; LASSO, Least Absolute Shrinkage and Selection Operation; MCC, Matthews Correlation Coefficient.

individuals. In contrast, the calibration slopes for classification and regression tree exhibited moderate departures from the diagonal line, suggesting moderately poor calibration. But the random forest, C5.0 decision tree, support vector machine and adaptive boosting significantly over-estimated and/or under-estimated the probability of poor functional outcomes in low risk and high risk individuals (See **Figures 3**, **4**).

DISCUSSION

This study examined the predictive accuracy of regression-based and ML models for predicting functional outcomes in stroke patients. Our analyses revealed that ML algorithms and logistic regression models had comparable predictive accuracy when validated internally and externally. Our findings buttress current evidence from other published studies (28–33) that already showed that the logistic regression and ML algorithms had comparable predictive accuracy in empirical clinical studies. A recently published systematic review found no evidence of the superior predictive performance of ML models over logistic regression models in clinical studies (32). Also, Van Os et al. (33) also explored the use of ML algorithms for predicting 90-day functional outcomes in MR CLEAN registry, a Dutch database of stroke patients who received endovascular treatment, and concluded that ML algorithms did not exhibit superior predictive accuracy over logistic regression models. These studies, while similar to ours in their use of feature selection predictor selection, relied on a relatively larger sample size than ours ($N >$ 1,000) but lacked validation of their prediction algorithms in external cohorts.

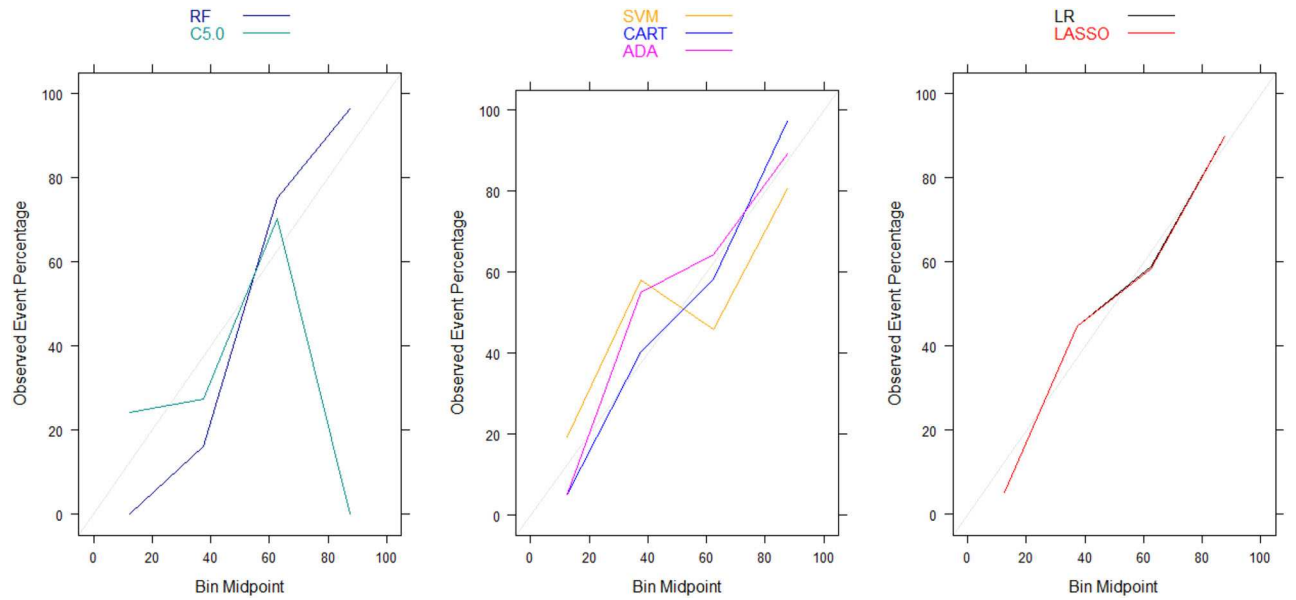

FIGURE 3 | Calibration plots for externally validated ML and regression-based models based on predictors derived via clinical expert knowledge. RF, Random Forest; SVM, Support Vector Machine; C5.0, C5.0 Decision Tree; ADA, Adaptive Boost Machine; CART, Classification and Regression Tree; LR, Logistic Regression; LASSO, Least Absolute Shrinkage and Selection Operation.

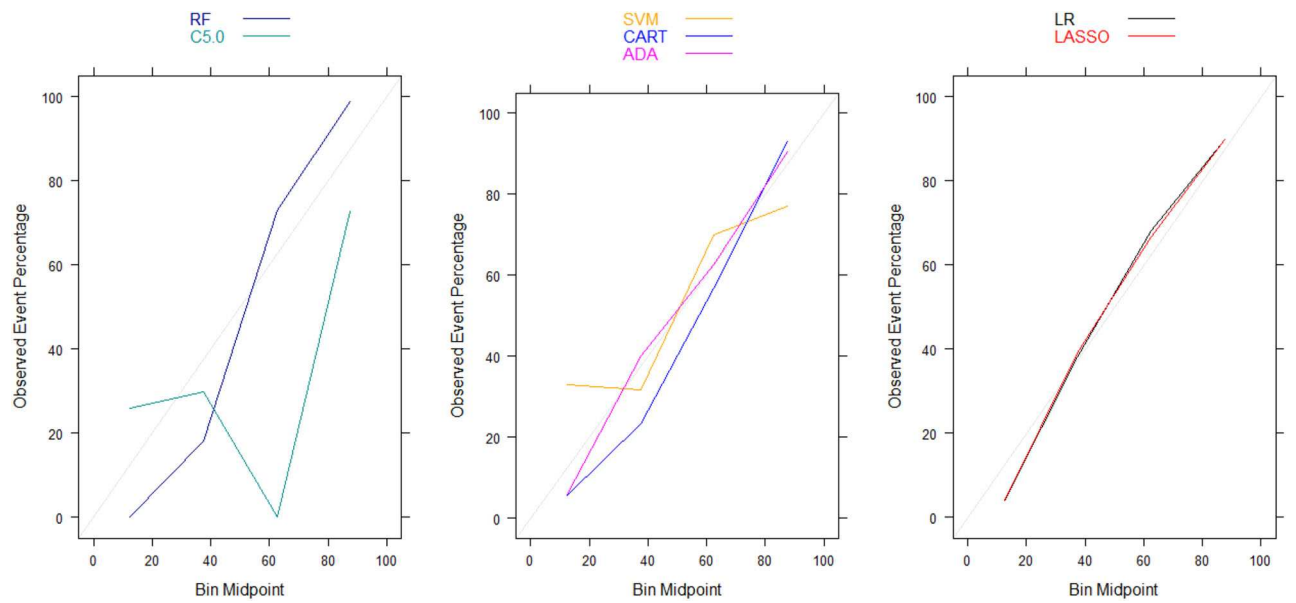

FIGURE 4 | Calibration plots for externally validated ML and regression-based models based on automated predictor selection. RF, Random Forest; SVM, Support Vector Machine; C5.0, C5.0 Decision Tree; ADA, Adaptive Boost Machine; CART, Classification and Regression Tree; LR, Logistic Regression; LASSO, Least Absolute Shrinkage and Selection Operation.

Moreover, our calibration plots revealed that logistic regression models had good calibration but ML algorithms had poorer calibration despite having comparable Brier scores. In fact, the majority of the ML algorithms had either overfitting or under-fitting problems in correctly predicting patients' functional outcomes despite having Brier scores and AUCs that are comparable to those in logistic regression models. This highlights the inherent limitation of interpreting Brier score, which is a composite measure of both discrimination and calibration, in terms of calibration alone (19). Therefore, our conclusions about the calibration of ML algorithms are based on the calibrations curves rather than Brier scores. This is consistent with recommendations by Rufibach (19) who cautioned against erroneous interpretation of the low Brier score as indicative

of good calibration. On the other hand, our evaluation of the relative importance of the predictor variables in risk prediction models based on ML and logistic regression revealed that age and stroke severity (measured by NIHSS) were the most important predictors of 90-day functional outcome that are common across all the models. This is consistent with findings from existing prognostic risk scores for predicting functional outcomes in ischemic stroke (3, 34–36), many of which have identified stroke severity (measured by NIHSS) and age as most important predictors of 90-day functional outcomes in ischemic stroke patients.

A unique strength of this study is the examination of both the discrimination and calibration of the investigated ML and regression-based risk prediction models. Unlike most clinical prediction studies that lack external validation of their findings, the external validation of these ML and regression-based functional impairment risk prediction models developed in another observational stroke registry is also a unique feature of this study. Despite these strengths, this study is not without its limitations, which might have influenced our study conclusions. First, this study focused primarily on regression and ML models for predicting binary outcomes to derive more accurate estimates of functional impairment risk. Our conclusions are based on empirical analysis of observational cohorts of acute stroke patients. This might limit the generalizability of findings to other populations. For example, both PROVE-IT and INTERRSeCT are small-sampled hospital cohorts and study predictors are those collected in acute care settings. Other important post-acute care risk factors, such as social support, imaging, and stroke rehabilitation, which are known to be predictive of 90-day functional impairment risk, were either not at our disposal or had significant missing data (37, 38). Future research will examine the robustness of our conclusions in large observational cohorts and through the use of computer simulations to study the performance of these models under a variety of different data analytic conditions. Second, our choice of PROVE-IT study cohort as the training cohort was driven by our initial access to this multicenter prospective observational study led by members of our team (BKM, MDH) and the relatively smaller rate of missing observations in PROVE-IT. It is possible that our conclusions might be different if INTERRSeCT study was used to train and develop the models while PROVE-IT study is used for external validation. Third, we have adopted mRS02 as the binary cut off point for good outcomes. It is possible that our study conclusions might be sensitive to others definitions of the good outcome functional outcomes (e.g., mRS01, or mRS03). Finally, median imputation method to impute missing observations in both cohorts was used. Future research will use sensitivity analyses will examine the robustness of our study conclusions to different types of imputation methods such as the multiple imputation chain equation methods.

In conclusion, ML and regression-based models have comparable predictive accuracy in predicting functional outcomes in stroke patients. We recommend that the choice between among these classes of models should be guided by important considerations as study design characteristics, data quality, and its utility in clinical settings.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data from both study cohorts are not publicly available because of data protection laws imposed by University of Calgary Conjoint Health Research Ethics (UCalgary CHREB). But datasets might be available from the UCalgary CHREB for researchers who meet the criteria for access to confidential data. Requests to access these datasets should be directed to docbijoymenon@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Calgary Conjoint Health Research Ethics Board (REB14-2012 and REB14-2015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00889/full#supplementary-material

REFERENCES

1. Abu-Hanna A, Lucas PJ. Prognostic models in medicine. *Methods Inform Med.* (2001) 40:1–5. doi: 10.1055/s-0038-1634456

2. Kim YD, Choi HY, Jung YH, Yoo J, Nam HS, Song D, et al. The ischemic stroke predictive risk score predicts early neurological deterioration. *J Stroke Cerebrovasc Dis.* (2016) 25:819–24. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.003

3. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke. *Neurology.* (2012) 78:1916LP−22. doi: 10.1212/WNL.0b013e318259e221
4. Wang A, Pednekar N, Lehrer R, Todo A, Sahni R, Marks S, et al. DRAGON score predicts functional outcomes in acute ischemic stroke patients receiving both intravenous tissue plasminogen activator and endovascular therapy. *Surg Neurol Int.* (2017) 8:149. doi: 10.4103/2152-7806.210993
5. Kissela B, Lindsell CJ, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, et al. Clinical prediction of functional outcome after ischemic stroke the surprising importance of periventricular white matter disease and race. *Stroke.* (2009) 40:530–6. doi: 10.1161/STROKEAHA.108.521906
6. Reid JM, Gubitz GJ, Dai D, Kydd D, Eskes G, Reidy Y, et al. Predicting functional outcome after stroke by modelling baseline clinical and CT variables. *Age Ageing.* (2010) 39:360–6. doi: 10.1093/ageing/afq027
7. Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. *Am J Neuroradiol.* (2010) 31:1192–6. doi: 10.3174/ajnr.A2050
8. Grech R, Galvin PL, Power S, O'Hare A, Looby S, Brennan P, et al. Outcome prediction in acute stroke patients considered for endovascular treatment: a novel tool. *Interv Neuroradiol.* (2014) 20:312–24. doi: 10.15274/INR-2014-10029
9. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ.* (2009) 338:b375. doi: 10.1136/bmj.b375
10. Fahey M, Crayton E, Wolfe C, Douiri A. Clinical prediction models for mortality and functional outcome following ischemic stroke: a systematic review and meta-analysis. *PLoS ONE.* (2018) 13:1–13. doi: 10.1371/journal.pone.0185402
11. Localio AR, Stack CB. TRIPOD: a new reporting baseline for developing and interpreting prediction models. *Ann Intern Med.* (2015) 162:73–4. doi: 10.7326/M14-2423
12. Al-Ajlan FS, Qazi E, Kim CK, Venkatesan EP, Wilson L, Menon BK. Multimodality CT based imaging to determine clot characteristics and recanalization with intravenous TPA in patients with acute ischemic stroke. *Neurovasc Imaging.* (2017) 3:2. doi: 10.1186/s40809-017-0026-9
13. Menon BK, Najm M, Al-Ajlan F, Puig Alcantara J, Dowlatshashi D, Calleja A, et al. IV tPA recanalization rates by site of occlusion and time after tPA bolus-main results of the interrsect multinational multicenter prospective cohort study. *Stroke.* (2017) 48:186. doi: 10.1161/STROKEAHA.118.021579
14. Sandri M, Zuccolotto P. A bias correction algorithm for the Gini variable importance measure in classification trees. *J Comput Graph Stat.* (2008) 17:611–28. doi: 10.1198/106186008X344522
15. Kuhn M, Wing J, Weston S, Williams A, Keefer C, Engelhardt A, et al. Package 'caret'. *R J.* (2020).
16. Zihni E, Madai VI, Livne M, Galinovic I, Khalil AA, Fiebach JB, et al. Opening the black box of artificial intelligence for clinical decision support: a study predicting stroke outcome. *PLos ONE.* (2020) 15:e0231166. doi: 10.1371/journal.pone.0231166
17. Chicco D, Jurman G. The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. *BMC Genomics.* (2020) 21:6. doi: 10.1186/s12864-019-6413-7
18. Matthews BW. Comparison of the predicted and observed secondary structure of T4 phage lysozyme. *Biochim Biophys Acta Protein Struct.* (1975) 405:442–51. doi: 10.1016/0005-2795(75)90109-9
19. Rufibach K. Use of brier score to assess binary predictions. *J Clin Epidemiol.* (2010) 63:938–9.
20. Karatzoglou A, Meyer D, Hornik K. Support vector machines in R. *J Stat Softw.* (2006) 15:1–29.
21. RColorBrewer S, Liaw MA. *Package 'randomForest'*. Berkeley, CA: University of California. (2018).
22. Kuhn M, Weston S, Coulter N, Culp M, Quinlan R. *C50: C5.0 Decision Trees and Rule-Based Models.* (2012). R package version 0.1.0. Available online at: https://CRAN.R-project.org/package=C50
23. Alfaro E, Gamez M, Garcia N. adabag: An R package for classification with boosting and bagging. *J Stat Softw.* (2013) 54, 1–35.
24. Therneau TM, Atkinson B, Ripley MB. *rpart: Recursive Partitioning and Regression Trees.* (2019). R package version 4.1. 5. Available online at: https://CRAN.R-project.org/package=rpart
25. Friedman J, Hastie T, Tibshiranii R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw.* (2010) 33:1–22.
26. Kuhn M. Building predictive models in R using the caret package. *J Stat Soft.* (2008) 28:1–28. doi: 10.18637/jss.v028.i05
27. Fox J, Leanage A. R and the journal of statistical software. *J Stat Softw.* (2016) 73:1–13. doi: 10.18637/jss.v073.i02
28. Heo J, Yoon JG, Park H, Kim YD, Nam HS, Heo JH. Machine learning–based model for prediction of outcomes in acute stroke. *Stroke.* (2019) 50:1263–5. doi: 10.1161/STROKEAHA.118.024293
29. Sung SM, Kang YJ, Cho HJ, Kim NR, Lee SM, Choi BK, et al. Prediction of early neurological deterioration in acute minor ischemic stroke by machine learning algorithms. *Clin Neurol Neurosurg.* (2020) 195:105892. doi: 10.1016/j.clineuro.2020.105892
30. Nusinovici S, Tham YC, Yan MY, Ting DS, Li J, Sabanayagam C, et al. Logistic regression was as good as machine learning for predicting major chronic diseases. *J Clin Epidemiol.* (2020) 122:56–69. doi: 10.1016/j.jclinepi.2020.03.002
31. Kuhle S, Maguire B, Zhang H, Hamilton D, Allen AC, Joseph KS, et al. Comparison of logistic regression with machine learning methods for the prediction of fetal growth abnormalities: a retrospective cohort study. *BMC Pregnancy Childbirth.* (2018) 18:1–9. doi: 10.1186/s12884-018-1971-2
32. Jie MA, Collins GS, Steyerberg EW, Verbakel JY, van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol.* (2019) 110:12–22. doi: 10.1016/j.jclinepi.2019.02.004
33. Van Os HJ, Ramos LA, Hilbert A, van Leeuwen M, Van Walderveen MA, Kruyt ND, et al. Predicting outcome of endovascular treatment for acute ischemic stroke: potential value of machine learning algorithms. *Front Neurol.* (2018) 9:784. doi: 10.3389/fneur.2018.00784
34. Liu X, Lv Y, Wang B, Zhao G, Yan Y, Xu D. Prediction of functional outcome of ischemic stroke patients in northwest China. *Clin Neurol Neurosurg.* (2007) 109:571–7. doi: 10.1016/j.clineuro.2007.05.008
35. König IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke.* (2008) 39:1821–6. doi: 10.1161/STROKEAHA.107.505867
36. Sajobi TT, Menon BK, Wang M, Lawal O, Shuaib A, Williams D, et al. Early trajectory of stroke severity predicts long-term functional outcomes in ischemic stroke subjects: results from the ESCAPE Trial (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing ct to recanalization times). *Stroke.* (2016) 48:105–10. doi: 10.1161/STR.0000000000000127
37. Saxena SK, Ng TP, Yong D, Fong NP, Koh G. Functional outcomes in inpatient rehabilitative care of stroke patients: predictive factors and the effect of therapy intensity. *Qual Primary Care.* (2006) 14: 145–53.
38. Stier N, Vincent N, Liebeskind D, Scalzo F. Deep learning of tissue fate features in acute ischemic stroke. In: 2015 *IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. IEEE (2015). p. 1316–21.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Validation of 10-Year Stroke Prediction Scores in a Community-Based Cohort of Chinese Older Adults

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A stroke prediction model based on the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) project was developed. We compared its predictive ability with the revised Framingham Stroke Risk Score (R-FSRS) for 5-year stroke incidence in a community cohort of Chinese adults, namely the Beijing Longitudinal Study of Aging (BLSA). Calibration, discrimination, and recalibration were used to compare the predictive ability between the two prediction models. Category-less net reclassification improvement (NRI) and integrated discrimination improvement (IDI) values were also assessed. During a mean follow-up duration of 5.1 years, 106 incidents of fatal or non-fatal strokes occurred among 1,203 participants aged 55–84 years. The R-FSRS applied to our cohort underestimated the 5-year risk for stroke in men and women. China-PAR performed better than the R-FSRS in terms of calibration (men, R-FSRS: χ^2-value 144.2 [$P < 0.001$], China-PAR: 10.4 [$P = 0.238$]; women, R-FSRS: 280.1 [$P < 0.001$], China-PAR: 12.5 [$P = 0.129$]). In terms of discrimination, R-FSRS and China-PAR models performed modestly in our cohort (C-statistic 0.603 [95% CI: 0.560–0.644] for men using China-PAR and 0.568 [95% CI: 0.524–0.610] using the R-FSRS; the corresponding numbers for women were 0.602 [95% CI: 0.564–0.639] and 0.575 [95% CI: 0.537–0.613). The recalibrated China-PAR model significantly improved the discrimination in C statistics and produced higher category-less NRI and IDI for stroke incidence than the R-FSRS. Although China-PAR fairly estimated stroke risk in our cohort, it did not sufficiently identify adults at high risk of stroke. Caution would be exercised by practitioners in applying the original China-PAR to Chinese older adults. Further studies are needed to develop an adequate prediction model based on the recalibrated China-PAR or to find new risk markers which could upgrade this model.

Keywords: stroke, risk factors, prediction score, primary prevention, cohort study

INTRODUCTION

Stroke is the second most prevalent cause of death and disability (1), particularly in the aged population, which presents a large proportion of the Chinese population, with population aging having significantly increased stroke incidence (2). The prevalence and incidence of stroke have increased in China over the past 3 decades. Current statistics demonstrate that an estimated 2.4 million incidents of strokes occur annually, adding to the pool of 11.1 million stroke survivors who return to community after treatment at the acute stage (3). Thus, an effective screening tool is required for identifying adults at high risk of stroke for primary prevention, which might be the best choice for cost/benefit balance in managing stroke.

Several multivariate risk prediction models have been developed following the original Framingham Stroke Risk Score (FSRS), which is based on various vascular risk factors for predicting the risk of initial stroke (4–8). The FSRS has been the most widely used tool worldwide, and the revised Framingham Stroke Risk Score (R-FSRS), which is the most recent version to reflect the temporal trends, was published in 2017 (8). However, most prediction models have been developed based on Western populations. Therefore, applying these models to the Chinese population might not be appropriate. In 2019, Xing et al. (9) established a new stroke prediction model aimed at predicting stroke risk among Chinese individuals included in the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) project. The China-PAR stroke risk models were developed based on a middle-aged cohort (40–79 years, mean age 48.6 years) and included factors such as age and age-related diseases. However, whether these findings are generalizable in elderly populations of the community is unknown.

The present study aimed to assess the external validity of the China-PAR stroke risk models in a community cohort of Chinese adults aged 55 years and over, namely the Beijing Longitudinal Study of Aging (BLSA), and to compare this prediction model with the R-FSRS.

MATERIALS AND METHODS

Study Population

We used data from the BLSA to validate the R-FSRS and China-PAR 10-year stroke prediction models. The study design has already been reported elsewhere (10, 11). The BLSA was a prospective population-based cohort study to investigate health conditions in residents aged 55 years and over in Beijing, China. Briefly, a stratification-random clustering procedure was applied to the sample to ensure representativeness in terms of the average age, education, and economic level. The present study was based on the survey conducted in 2009. Among all 2468 participants aged 55 years and older, 2089 (84.6%) completed the follow-up survey with a mean follow-up time of 4.8 years.

The R-FSRS was developed to assess the risk of stroke in individuals aged 55–84 years with no history of stroke (8). The China-PAR was mainly developed based on Chinese individuals aged 35–74 years to predict the 10-year risk of stroke (12). In order to make the samples as comparable as possible, we excluded participants aged 85 years or older. Among all participants, 1,203 were eligible for analysis after excluding those with history of stroke ($n = 297$), aged over 84 years ($n = 153$), and with missing data on measurements of blood specimens ($n = 815$; **Supplementary Figure 1**).

Risk Factors Measurement

All enrolled participants were asked to complete the baseline assessment, which consisted of answering a questionnaire and undergoing a physical examination, a fasting blood sample collection.

All enrolled participants were asked to complete a questionnaire survey conducted by well-trained medical students using standardized methods. The questionnaire covered a wide range of variables, including demographic characteristics; life-style habits (smoking and drinking status); history of stroke, heart disease, hypertension, diabetes, hyperlipidemia, and other chronic diseases related to aging; and the use of medication.

Before the examination, each subject was asked to rest for $\geq$20 min. The sitting blood pressure (BP) was measured twice on the right arm in 2–5-min intervals, and the mean of the two measurements was calculated and use for the analysis. BP was measured using a standard mercury sphygmomanometer. The measurements of height and body weight were also collected for each subject.

Blood samples were collected from the subjects in the morning after an overnight fast, centrifuged to collected the serum, stored in a refrigerator at 2–8°C, and transferred to a central laboratory (IPE Center for Clinical Laboratory, Beijing, China), which performed all analyses within 24 h. Total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, fasting blood glucose (FBG), and high-sensitivity C-reactive protein levels were determined by a Hitachi 7600 automatic analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan).

Follow-up and Study Outcomes

In December of 2014, a follow-up survey was performed to investigate the outcomes of each subject who underwent the 2009 baseline assessment. A door-to-door survey was conducted by well-trained graduate students of medicine. Information on possible new cases of stroke and deaths that occurred during the follow-up period was collected. The study subjects' medical and health insurance in local medical clinics were also reviewed by the physicians who participated in the follow-up survey. The local government death records kept at the Center for Disease Control (CDC), were also reviewed to collect the date and causes of death. In China, the CDC is in charge of death statistics, and the underlying causes of death are coded according to the principles of the 10th version of the International Classification of Diseases (ICD-10). Codes I63.0-I63.9 and I60.0-I62.9 represent fatal stroke. The study outcome was defined as stroke occurrence.

Definitions

Hypertension was defined following the Joint National Committee guideline (JNC VII) (13) to include subjects with systolic BP (SBP) $\geq$ 140 mmHg or/and diastolic BP (DBP)

≥ 90 mmHg, or those with a history of hypertension or taking anti-hypertension medications. The diagnosis of diabetes was based on the American Diabetes Association criteria as FBG ≥ 7.0 mmol/L (126 mg/dL) (14), having a history of diabetes, or taking hypoglycemic medication. Smokers included current and ex-smokers for those who had quit smoking for > 2 years.

Prediction Models

We calculated the stroke risk for each BLSA participant using the published models of the R-FSRS (15) and China-PAR 10-year stroke risk models (9). **Supplementary Table 1** presents the predictor variables used in the R-FSRS and China-PAR models. Although family history of stroke was used in the China-PAR 10-year stroke risk model, it was not assessed in the BLSA. Therefore, for this factor, missing values were attributed to all participants. All participants in the BLSA data lived in northern China, and, therefore, no Cox hazard regression coefficient could be estimated. For these analyses, the 5-year baseline survival rate was replaced to predict the 5-year stroke risk based on the 10-year risk models.

To compare the performance of the two prediction models, three versions of each model were used to calculate the 5-year stroke risk for every participant (16). The three versions of the prediction models differed in terms of baseline survival rate, the means of the risk factors, andthe Cox hazard regression coefficients of risk factors. The original versions of the prediction models used these parameters based on the original research, thus possibly overestimating or underestimating the stroke risk of participants. Therefore, the adjusted versions could optimize data fit. We used the mean values of risk factors and baseline survival rate, which were derived from BLSA data in the adjusted versions. In theory, we could produce a suitable prediction model by adopting coefficients of risk factors to compensate for different background incidence rates in different populations (17). To represent the best possible risk function for BLSA data, we updated the mean values of risk factors to represent the current prevalence, updated the baseline survival rate of stroke to represent current rates, and updated cox hazard regression coefficients to represent current associations in the recalibrated prediction models. The cox hazard regression coefficients for components in the models were compared (**Supplementary Tables 2**, **3**).

Statistical Analysis

Risk factors are summarized for sex-specific groups as mean (SD) for continuous variables and percentile for categorical variables. Chi-square test or Fisher's exact test was used for comparing categorical variables, and the *t*-test or the Kruskal–Wallis test for comparing continuous variables. The Kaplan–Meier product-limit method was used to estimate the survival rate.

Calibration and discrimination were used to evaluate the predictive capabilities of all prediction models. Calibration, which measured how closely the predicted stroke risk fit the observed stroke risk, was assessed using the Hosmer–Lemeshow goodness-of-fit test. Values of χ^2 more than 20 were considered to indicate significant lack of calibration ($P < 0.01$).

Discrimination of all prediction models was assessed using C statistics. Differences in C statistics between the two prediction models were evaluated using the method by DeLong et al. Category-less net reclassification improvement (NRI) and integrated discrimination improvement (IDI) values were also assessed (18).

RESULTS

Baseline and Follow-Up Information

Of the 1,203 participants in our analysis, 537 (44.6%) were men; the mean age of participants was 68.6 years. The overall and sex-specific baseline characteristics of the participants selected for this analysis are summarized in **Table 1**. Compared with women, men were older and had lower total cholesterol values (all $P < 0.05$). The proportions of participants with diabetes and of those taking antihypertensive medication were smaller among men than among women, whereas the proportion of current smokers was substantially greater among the former (all $P < 0.05$).

By the end of 2014, follow-up was conducted for a total of 6,139 person-years.

During a mean follow-up duration of 5.1 years, 106 incidents of fatal or non-fatal strokes (in 50 men and 56 women) occurred. The follow-up rate was 87.5%, with 150 participants lost to follow up. The 5-year cumulative incidence of stroke was 1,851.9 per 100,000 person-years and 1,628.3 per 100,000 person-years in men and women, respectively.

Calibration

We found that the China-PAR performed better than the R-FSRS in terms of calibration (men: R-FSRS: χ^2 value 144.2 [$P < 0.001$], China-PAR: 10.4 [$P = 0.238$]; women: 280.1 [$P < 0.001$], and 12.5 [$P = 0.129$]). The calibration plots indicated that the R-FSRS underestimated the expected stroke rate among men and women compared to the observed rates (**Figures 1A,B**). Compared with the original R-FSRS, the adjusted R-FSRS showed improved model calibration (men: χ^2 value 39.5 [$P < 0.001$]); women: χ^2 value 31.7 [$P < 0.001$]); however, this model still slightly overestimated stroke risk among men and underestimated stroke risk among women (**Figures 1C,D**). Calibration plots (**Figures 1E,F**) showed that the recalibrated R-FSRS model did not underestimate or overestimate stroke events among men and women (all calibration χ^2 values < 20). As also shown in **Figure 2**, both the adjusted and recalibrated China-PAR performed well in the calibration analysis (all calibration χ^2 values < 20). In addition, the recalibrated China-PAR had the lowest calibration χ^2 values in all prediction models.

Discrimination

As shown in **Table 2**, the R-FSRS and China-PAR models performed modestly in our cohort (C statistic: 0.603 [95% CI: 0.560–0.644] for men using China-PAR and 0.568 [95% CI: 0.524–0.610] using the R-FSRS; the corresponding values for women were 0.602 [95% CI: 0.564–0.639] and 0.575 [95% CI: 0.537–0.613]). C-statistic values of the adjusted China-PAR and R-FSRS were similar to those of the original models. **Figure 3** displays the differences in C statistics between the China-PAR,

TABLE 1 | Baseline of characteristics of study participants by sex.

Characteristics	Total	Men ($n = 537$)	Women ($n = 666$)	*P*-value
Age, mean (SD), year	68.63 (7.62)	69.21 (7.73)	68.15 (7.49)	0.016
Age ≥ 65, *n* (%)	795 (66.1)	366 (68.2)	429 (64.4)	0.102
SBP, mean (SD), mmHg	138.7 (19.99)	138.18 (19.58)	139.17 (20.31)	0.392
Waist circumference, mean(SD), cm	90.8 (10.67)	88.94 (9.73)	91.08 (10.69)	0.307
Total cholesterol, mean(SD), mg/dl	227.45 (44.12)	214.48 (39.01)	237.91 (45.24)	<0.001
HDL-C, mean (SD), mg/dl	47.38 (10.60)	46.72 (10.99)	47.90 (10.24)	0.054
Urban, *n* (%)	800 (66.5)	362 (67.4)	438 (65.8)	0.58
Antihypertensive treatment, *n* (%)	464 (38.6)	171 (31.8)	293 (44.0)	<0.001
Diabetes, *n* (%)	194 (16.1)	73 (13.6)	121 (18.2)	0.033
DM if <65 year, *n* (%)	54 (4.5)	18 (3.4)	36 (5.4)	0.094
DM if ≥65 year, *n* (%)	140 (11.6)	55 (10.2)	85 (12.8)	0.205
Smoking, *n* (%)	296 (24.6)	246 (45.8)	50 (7.5)	<0.001
History of CVD, *n* (%)	187 (15.5)	77 (14.3)	110 (16.5)	0.337

SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; CVD, cardiovascular disease.

R-FSRS, and recalibrated prediction models. There were no significant differences in C statistics for stroke between the China-PAR and R-FSRS for both sexes. The performance of the recalibrated China-PAR model was excellent as suggested by C statistics (men: 0.748 [95% CI: 0.709–0.784]; women: 0.761 [95% CI: 0.727–0.793. According to the China-PAR model, the recalibrated China-PAR showed a significant improvement in performance C statistics from 0.603 to 0.748 (C statistics difference: 0.145, 95% CI: 0.062–0.229) in men and from 0.602 to 0.761 (C statistics difference: 0.159, 95% CI: 0.079–0.240) in women. In contrast, C statistics for the performance of the recalibrated R-FSRS for men improved from 0.568 to 0.648 (C statistics difference: 0.081, 95% CI: 0.009–0.152). Although the R-FSRS and China-PAR models both updated the mean values of risk factors, survival rate of stroke, and cox coefficients in order to represent the best possible risk function for BSLA data, the recalibrated China-PAR could better identify individuals at a high risk of stroke than did the recalibrated R-FSRS (men: C statistics, 0.748 vs. 0.648, C statistics difference: 0.100, 95% CI: 0.024–0.176; women: C statistics: 0.761 vs 0.621,; C statistics difference: 0.140, 95% CI: 0.051–0.230). There was no significant difference in C-statistic values between the recalibrated and original R-FSRS (C statistics: 0.621 vs. 0.575, C statistics difference: 0.046, 95% CI: −0.010 to 0.101) in women.

The category-less NRI for China-PAR, R-FSRS, and their recalibrated versions were calculated from the difference in the estimated risk of stroke moving up and down among these prediction models (**Table 3**). Compared with the R-FSRS model, the China-PAR model could not improve risk classification for the 5-year stroke risk, as evidenced by the category-less NRI in men (0.004 [95% CI: −0.004 to 0.012]) and in women (0.007 [95% CI: −0.003 to 0.016]). However, the IDIs were improved both in men (0.018 [95% CI: 0.0020–0.033]) and in women (0.014 [95% CI: 0.001–0.027]). Similar results were observed when comparing the recalibrated with the original R-FSRS. The recalibrated China-PAR models were more likely than the original China-PAR models to provide higher category-free NRI among men (0.617 [95% CI: 0.342–0.894]) and women (0.611 [95% CI: 0.344–0.879]). This discrimination improvement was also confirmed by IDI among men (0.056 [95% CI: 0.023–0.090]) and women (0.092 [95% CI: 0.054–0.130]). Reclassification analyses also showed higher category-free NRI and IDI for 5-year stroke incidence when comparing the recalibrated China-PAR to the recalibrated R-FSRS models.

DISCUSSION

The China-PAR stroke risk prediction model is the most recent tool to identify high-risk stroke adults in China (9). The validity of this risk model among samples of different age ranges has not been studied. To our knowledge, no previous study has compared the performances of the R-FSRS and China-PAR 10-year stroke risk models for the 5-year risk of stroke in a prospective community-based cohort of residents aged 55–84 years without known stroke at baseline. Compared with the R-FSRS model, the China-PAR model showed a better calibration and similar discriminative ability for the 5-year risk of stroke in our cohort. In contrast, the R-FSRS model underestimated the 5-year stroke. The recalibration analysis significantly improved the discriminative ability of China-PAR.

The FSRS, which is widely used for primary prevention of stroke, was established in 1991 to evaluate the 10-year risk of stroke in the western population aged 55–84 years (19). The FSRS was updated as R-FSRS to reflect the present situation of risk factors of stroke (8). Several studies have revealed conflicting results when applying these predictive models to different cohorts. The Reasons for Geographic and Racial Differences in Stroke study found that the use of the FSRS leads to overestimation in predicting stroke risk among black and white participants (20). An overestimation was also reported in the Three-City study, which validated the FSRS among French adults aged 65 years or older (16). The FSRS and R-FSRS were predictive of incident stroke in the Rotterdam study, which included 7966 stroke-free subjects (15). Similar results were also observed when

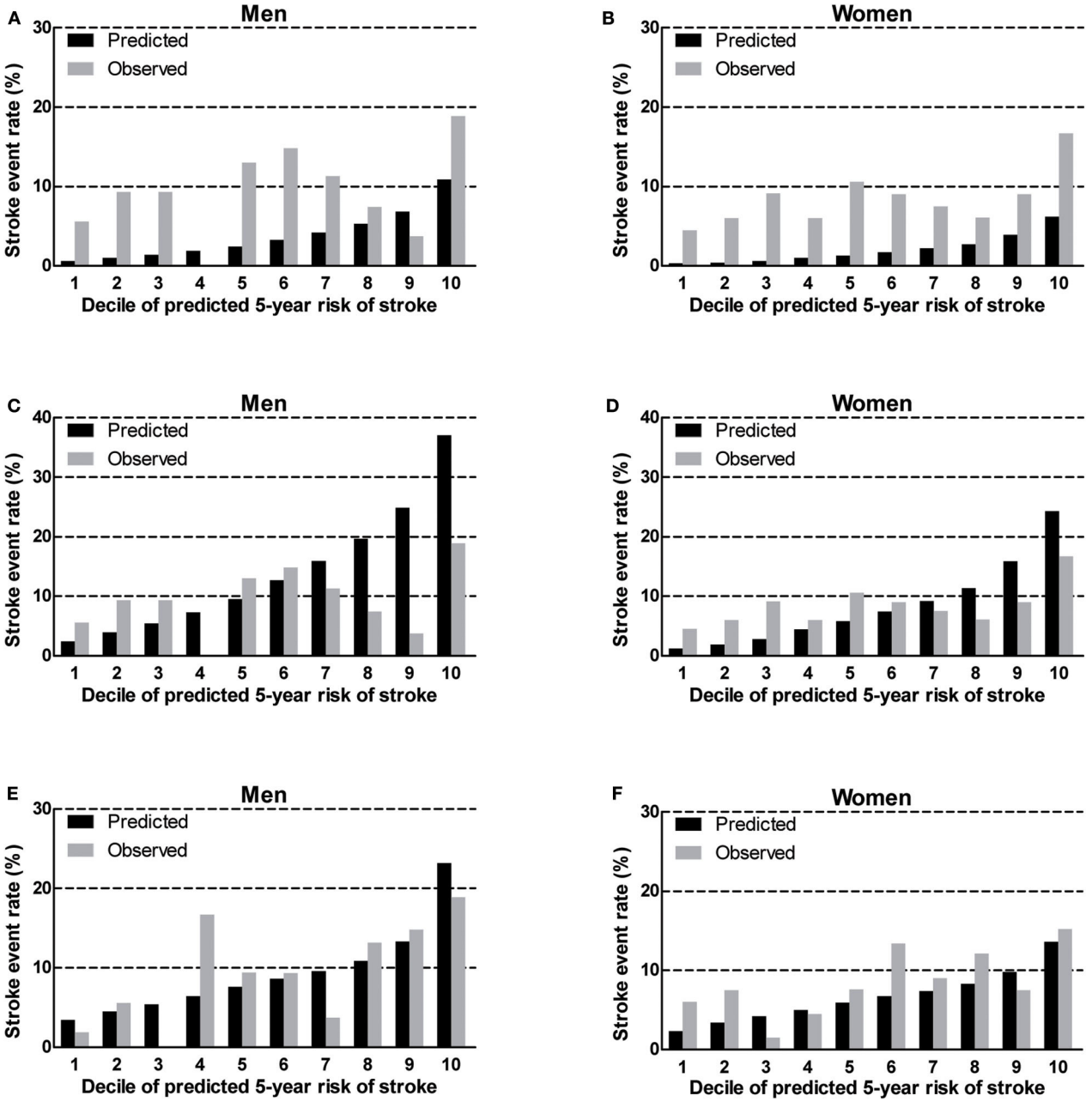

FIGURE 1 | Calibration of the original R-FSRS **(A,B)**, adjusted R-FSRS **(C,D)**, and recalibrated R-FSRS **(E,F)** in BLSA men and women. R-FSRS, revised Framingham Stroke Risk Scores; BLSA, Beijing Longitudinal Study of Aging.

evaluating stroke risk among participants of the Multi-Ethnic Study of Atherosclerosis (21). There are limited studies showing different results regarding the performance of these stroke risk models among Chinese individuals. The CIMIC study validated the R-FSRS among 34,357 Chinese participants aged 55-74 years at baseline recruited between 2007 and 2008 (9). The result revealed that discrimination was moderate based on C statistics (men: 0.668; women: 0.686), while calibration was poor in men (χ^2 value: 120.3) and women (χ^2 value: 123.7). The 5-year risk of stroke was underestimated by 43.1% for men and 50.7% for women. An underestimation of stroke risk using the R-FSRS model was also noted in the current study. However, recalibration analysis by BLSA data corrected this underestimation. This might be attributed to ethnic heterogeneities, distinct risk factors of stroke burden, and different treatment rates for risk factors between Chinese and Western populations (22–25). Furthermore, differences in the stroke incidence rate could be the direct factor explaining this result. In China, the age-standardized

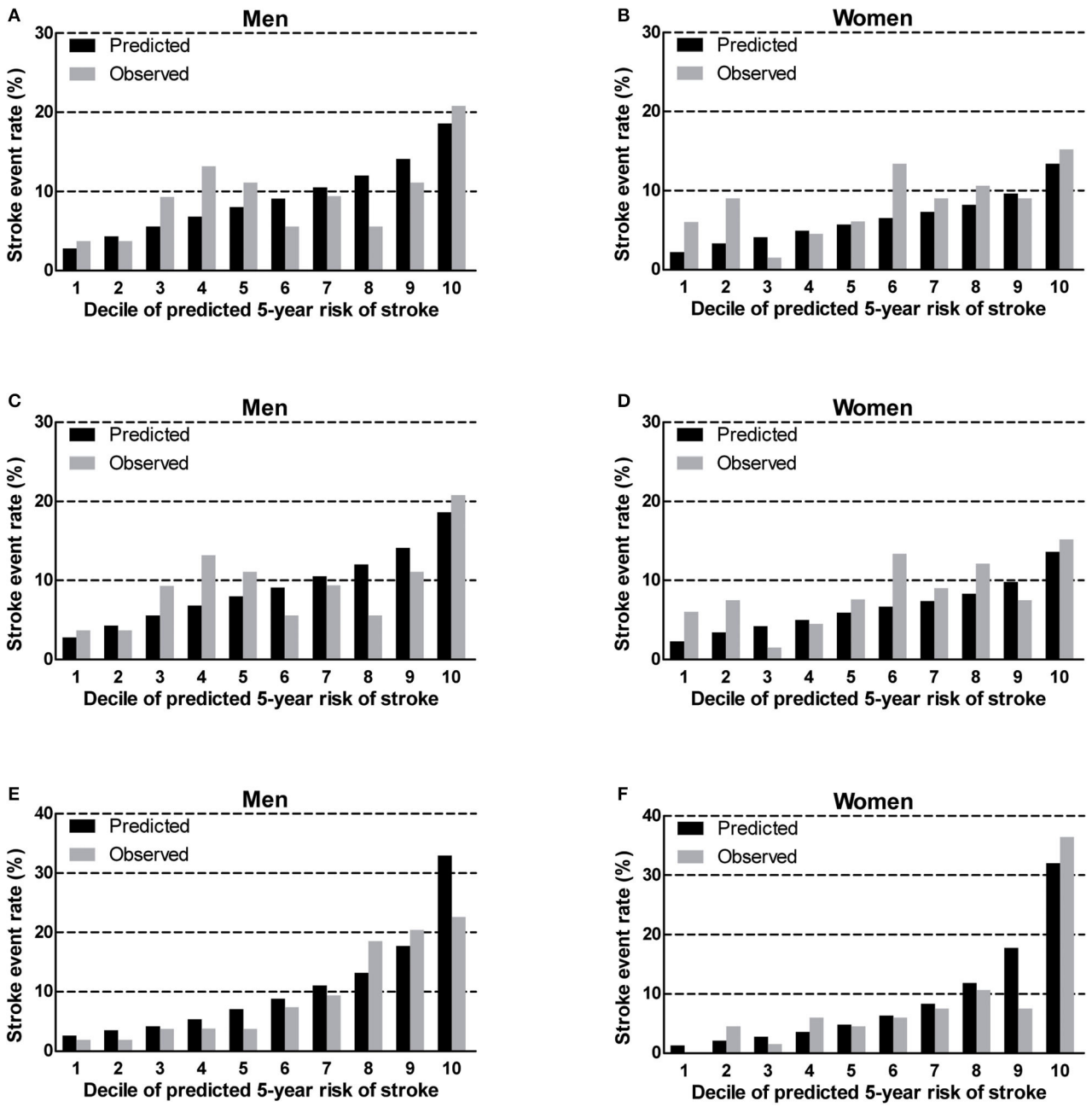

FIGURE 2 | Calibration of the original China-PAR **(A,B)**, adjusted China-PAR **(C,D)**, and recalibrated China-PAR **(E,F)** in BLSA men and women. China-PAR, Prediction for ASCVD Risk in China; BLSA, Beijing Longitudinal Study of Aging.

stroke incidence rate, estimated at 247 per 100,000 person-years, suggests that the absolute stroke incidence rate in China is the highest in the world (3).

Our results indicate that the calibration χ^2 value is lower in the case of China-PAR than of the R-FSRS. In contrast, the China-PAR model may not have sufficient discriminatory ability (C statistics) to identify individuals at high risk of stroke in our cohort. Several factors might explain this moderate discriminatory ability. First, although the China-PAR model was developed in 2019, data on the derivation cohort were collected in 1998, whereas BLSA data were gathered in 2008. In fact, the predictive model might be slightly outdated because the management of stroke risk factors has considerably evolved during the past 20 years. Second, BLSA participants were older than China-PAR participants (68.6 vs. 48.6 years). In addition, BLSA participants had a higher mean SBP, higher total cholesterol levels and waist circumference; had lower mean HDL-C levels; used more antihypertensive medication; were more

TABLE 2 | Validation of 5-year stroke risk prediction by the three versions of R-FSRS and China-PAR in men and women.

Models	Kaplan–Meier adjusted events (*n*)	Predicted Events (*n*)	Calibration χ^2 values	*P*-value	Discrimination C statistic (95%CI)
MEN					
R-FSRS	54.8	20.3	144.166	<0.001	0.568 (0.524–0.610)
Adjusted R-FSRS	54.8	74.2	39.493	<0.001	0.568 (0.524–0.610)
Recalibrated R-FSRS	54.8	49.7	16.481	0.036	0.648 (0.606–0.689)
China-PAR	54.8	43.3	10.405	0.238	0.603 (0.560–0.644)
Adjusted China-PAR	54.8	49.2	9.375	0.312	0.603 (0.560–0.644)
Recalibrated China-PAR	54.8	60.87	6.334	0.610	0.748 (0.709–0.784)
WOMEN					
R-FSRS	59.9	13.6	280.054	<0.001	0.575 (0.537–0.613)
Adjusted R-FSRS	59.9	55.98	31.743	<0.001	0.575 (0.537–0.613)
Recalibrated R-FSRS	59.9	43.36	11.926	0.155	0.621 (0.583–0.658)
China-PAR	59.9	69.7	12.524	0.129	0.602 (0.564–0.639)
Adjusted China-PAR	59.9	44.56	16.047	0.042	0.604 (0.566–0.642)
Recalibrated China-PAR	59.9	60.3	9.796	0.280	0.761 (0.727–0.793)

R-FSRS, revised Framingham Stroke Risk Scores; China-PAR, Prediction for ASCVD Risk in China.

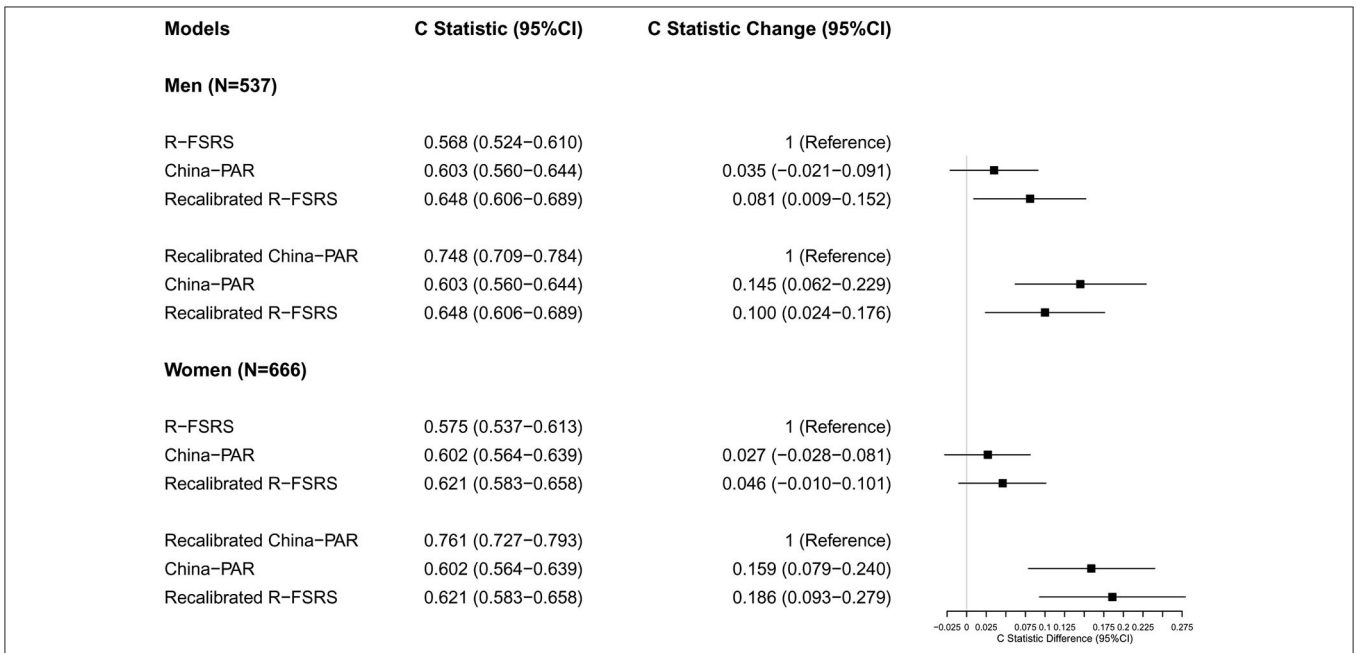

FIGURE 3 | Differences in C statistics between the China-PAR, R-FSRS, and recalibrated prediction models in BLSA men and women. R-FSRS, revised Framingham Stroke Risk Scores; China-PAR, Prediction for ASCVD Risk in China; BLSA, Beijing Longitudinal Study of Aging.

often smokers; and more of them had diabetes. Third, the R-FSRS was derived and validated in participants without stroke at baseline. Thus, the present study excluded participants with a history of stroke, and, since the China-PAR was established in cohorts without history of myocardial infarction (MI) and stroke, this could have influenced its performance. It thus may be unfair to compare the China-PAR with the R-FSRS in our cohort. Nevertheless, prevalent cardiovascular disease is a risk factor included in the R-FSRS. Moreover, both these prediction models consider stroke as their primary endpoint and were established for predicting personalized stroke risk among adults free of MI and stroke (China-PAR) or adults free of stroke (R-FSRS). Therefore, it is reasonable to compare the discriminative ability of the China-PAR and the R-FSRS for stroke incidence in the primary prevention cohort.

Compared with the China-PAR study, the follow-up duration of the BLSA was relatively shorter. Moreover, the C statistic of the China-PAR model for predicting the 5-year risk of stroke was reduced from 0.792 to 0.716 in men and from 0.802 to 0.715 in women among participants aged 55 years and older

TABLE 3 | Category-less NRI and IDI between R-FSRS, China-PAR, and their recalibrated versions.

	Men		Women	
	Event	**Nonevent**	**Event**	**Nonevent**
FSRS > China-PAR (Downward)	0	1	0	2
FSRS < China-PAR (Upward)	50	486	56	608
Overall	50	487	56	610
NRI	1	−0.996	1	−0.993
Total NRI (95%CI)	0.004 (−0.004–0.012)		0.007 (−0.003–0.016)	
IDI (95%CI)	0.018 (0.0020–0.033)		0.014 (0.001–0.027)	
R-FSRS > Recalibrated R-FSRS (Downward)	1	17	2	3
FSRS < Recalibrated FSRS (Upward)	49	466	54	606
Overall	50	483	56	609
NRI	0.960	−0.922	0.928	−0.989
Total NRI (95%CI)	0.038 (−0.047–0.123)		−0.058 (−0.156–0.040)	
IDI (95%CI)	0.027 (0.007–0.048)		0.008 (0.001–0.016)	
China-PAR > Recalibrated China-PAR (Downward)	17	312	23	433
China-PAR < Recalibrated China-PAR (Upward)	33	167	33	167
Overall	50	479	56	610
NRI	0.320	0.297	0.179	0.436
Total NRI (95%CI)	0.617 (0.342–0.894)		0.611 (0.344–0.879)	
IDI (95%CI)	0.056 (0.023–0.090)		0.092 (0.054–0.130)	
Recalibrated FSRS > Recalibrated China-PAR (Downward)	2	61	16	331
Recalibrated FSRS < Recalibrated China-PAR (Upward)	48	421	40	276
Overall	50	482	56	610
NRI	0.920	−0.739	0.429	0.090
Total NRI (95%CI)	0.175 (0.051–0.298)		0.517 (0.268–0.767)	
IDI (95%CI)	0.074 (0.040–0.108)		0.098 (0.159–0.137)	

IDI, integrated discrimination index; NRI, net reclassification improvement; R-FSRS, revised Framingham Stroke Risk Scores; China-PAR, Prediction for ASCVD Risk in China.

in the validation cohort of the China-PAR study (9). The recalibrated China-PAR model predicted a stroke incidence rate that was reasonably close to the observed one and meaningfully improved the ability to identify individuals at high risk of developing stroke in the future among BLSA participants. This also suggests that the recalibrated China-PAR model could be extended to apply to individuals aged 55-84 years in northern China. These findings suggest that a recalibration analysis reflecting the characteristics of the current population might be an effective solution. Moreover, the original prediction models should be developed for similar populations, in terms of same race, lifestyle, and so on. However, most clinicians might have trouble to recalibrate prediction risk models for their population. Therefore, caution should be exercised by practitioners when applying the original China-PAR model to Chinese older adults, as its ability to identify individuals at high risk of stroke is insufficient. Therefore, additional risk factors of stroke risk besides age are needed in Chinese older adults. Markers of atherosclerosis might be a choice (21, 26–28). Further work should be done to evaluate the value of such makers in improving the discriminative ability of models to predict stroke even in older populations.

The current study has several strengths, including the relatively large sample size, representativeness of local residents, and standardized processes for collecting baseline and follow-up information. Our study contains the following limitations. First, nearly one third of the participants in the BLSA cohort had missing data on laboratory measurements, which is common in cohort studies (12, 29). However, compared with individuals with missing data, those with complete data were younger and fewer of them had DM, which might have led to an underestimation of the prediction scores (**Supplementary Table 4**). Second, participants with atrial fibrillation (AF) and parental history of stroke were not included in our cohort, and these parameters were set to 0 when calculating risk by risk models; thus the risk of stroke might be underestimated. However, such an impact could be limited due to the low prevalence of AF among Chinese individuals (30). A parental history of stroke has been suggested as a predictor of stroke events (31). Nevertheless, it was used in the China-PAR stroke risk model only for men, while the predictive ability could be slightly influenced in men in our cohort, and it is a stronger risk factor in early onset stroke (age < 55) (32, 33); thus, it may not be so important that participants without such history are missing from our cohort. Third, the adjudication of stroke fatality using ICD coding on death certificates may have good specificity but likely suboptimal sensitivity (34). Finally, due to the relatively short follow-up period, the modest discrimination ability of the prediction models in our cohort should be interpreted with

caution. Additional research is required to confirm whether the performance of these prediction models could be improved with longer follow-up duration.

CONCLUSION

The present study revealed that the R-FSRS underestimates the 5-year absolute risk of stroke in a community-based Chinese population aged 55–84 years. Regardless of the fact that the China-PAR fairly predicted the risk of stroke, it showed a modest discrimination ability for incident of stroke. The recalibration process reasonably improved the discrimination ability of China-PAR. Further studies are needed to develop an adequate prediction model based on the recalibrated China-PAR and to identify new risk markers which could upgrade this model.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Xuanwu Hospital, Capital Medical University, Beijing, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XF, SG, and JC contributed conception and design of the study. HL, CW, ZZ, XG, and CL organized the database. YZ and XW performed the statistical analysis. YZ wrote the first draft of the manuscript. XF and JC wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00986/full#supplementary-material

REFERENCES

1. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:459–80. doi: 10.1016/S1474-4422(18)30499-X
2. Egorova N, Liem F, Hachinski V, Brodtmann A. Predicted brain age after stroke. *Front Aging Neurosci.* (2019) 11:348. doi: 10.3389/fnagi.2019.00348
3. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, incidence, and mortality of stroke in China clinical perspective. *Circulation.* (2017) 135:759–71. doi: 10.1161/CIRCULATIONAHA.116.025250
4. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke.* (1994) 25:40–3. doi: 10.1161/01.STR.25.1.40
5. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ.* (2013) 346:f2573. doi: 10.1136/bmj.f2573
6. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *Circulation*. (2014) 129:S49–73. doi: 10.1161/01.cir.0000437741.48606.98
7. Parmar P, Krishnamurthi R, Ikram MA, Hofman A, Mirza SS, Varakin Y, et al. The Stroke Riskometer(TM) App: validation of a data collection tool and stroke risk predictor. *Int J Stroke.* (2015) 10:231–44. doi: 10.1111/ijs.12411
8. Dufouil C, Beiser A, McLure LA, Wolf PA, Tzourio C, Howard VJ, et al. Revised Framingham stroke risk profile to reflect temporal trendsclinical perspective. *Circulation.* (2017) 135:1145–59. doi: 10.1161/CIRCULATIONAHA.115.021275
9. Xing X, Yang X, Liu F, Li J, Chen J, Liu X, et al. Predicting 10-year and lifetime stroke risk in Chinese population. *Stroke.* (2019) 50:2371–8. doi: 10.1161/STROKEAHA.119.025553
10. Gu X, Fang X, Hua Y, Tang Z, Ji X, Guan S, et al. Association between kidney dysfunction and carotid atherosclerosis in community-based older adults in China. *Angiology.* (2016) 67:252–8. doi: 10.1177/0003319715586505
11. Wang C, Song X, Mitnitski A, Yu P, Fang X, Tang Z, et al. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. *J Gerontol A Biol Sci Med Sci.* (2013) 68:338–46. doi: 10.1093/gerona/gls166
12. Tang X, Zhang D, He L, Wu N, Si Y, Cao Y, et al. Performance of atherosclerotic cardiovascular risk prediction models in a rural Northern Chinese population: results from the Fangshan Cohort Study. *Am Heart J.* (2019) 211:34–44. doi: 10.1016/j.ahj.2019.01.009
13. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JJ, et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA.* (2003) 289:2560–72. doi: 10.1001/jama.289.19.2560
14. Standards of medical care in diabetes—2011. *Diabetes Care.* (2011) 34(Suppl 1):S11–61. doi: 10.2337/dc11-S011
15. Bos D, Ikram MA, Leening MJG, Ikram MK. The revised Framingham stroke risk profile in a primary prevention population. *Circulation.* (2017) 135:2207–9. doi: 10.1161/CIRCULATIONAHA.117.028429
16. Bineau S, Dufouil C, Helmer C, Ritchie K, Empana JP, Ducimetiere P, et al. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. *Stroke.* (2009) 40:1564–70. doi: 10.1161/STROKEAHA.108.532325
17. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in northern and southern European populations: a reanalysis of the seven countries study for a European coronary risk chart. *Heart.* (2000) 84:238–44. doi: 10.1136/heart.84.3.238
18. Pencina MJ, D'Agostino RS, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated

discrimination improvement for normal variables and nested models. *Stat Med.* (2012) 31:101–13. doi: 10.1002/sim.4348
19. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* (1991) 22:312–8. doi: 10.1161/01.STR.22.3.312
20. McClure LA, Kleindorfer DO, Kissela BM, Cushman M, Soliman EZ, Howard G. Assessing the performance of the Framingham stroke risk score in the reasons for geographic and racial differences in stroke cohort. *Stroke.* (2014) 45:1716–20. doi: 10.1161/STROKEAHA.114.004915
21. Peter F, Will L, David H, Joseph Y. Revised Framingham stroke risk score, nontraditional risk markers, and incident stroke in a multiethnic cohort. *Stroke.* (2018) 49:363–9. doi: 10.1161/STROKEAHA.117.018928
22. Xu Y. Prevalence and control of diabetes in Chinese adults. *JAMA.* (2013) 310:948. doi: 10.1001/jama.2013.168118
23. Chan F, Adamo S, Coxson P, Goldman L, Gu D, Zhao D, et al. Projected impact of urbanization on cardiovascular disease in China. *Int J Public Health.* (2012) 57:849–54. doi: 10.1007/s00038-012-0400-y
24. Yang W, Xiao J, Yang Z, Ji L, Jia W, Weng J, et al. Serum lipids and lipoproteins in Chinese men and women. *Circulation.* (2012) 125:2212–21. doi: 10.1161/CIRCULATIONAHA.111.065904
25. Gao Y, Chen G, Tian H, Lin L, Lu J, Weng J, et al. Prevalence of hypertension in china: a cross-sectional study. *PLoS One.* (2013) 8:e65938. doi: 10.1371/journal.pone.0065938
26. Wang D, Wang J, Jin C, Ji R, Wang A, Li X, et al. asymptomatic extracranial artery stenosis and the risk of cardiovascular and cerebrovascular diseases. *Sci Rep.* (2016) 6:33960. doi: 10.1038/srep33960
27. Zhang Y, Fang X, Hua Y, Tang Z, Guan S, Wu X, et al. Carotid artery plaques, carotid intima-media thickness, and risk of cardiovascular events and all-cause death in older adults: a 5-year prospective, community-based study. *Angiology.* (2018) 69:120–9. doi: 10.1177/0003319717716842
28. Yano Y, O Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, et al. Association of coronary artery calcium score vs age with cardiovascular risk in older adults. *Jama Cardiol.* (2017) 2:986. doi: 10.1001/jamacardio.2017.2498
29. Yatsuya H, Iso H, Li Y, Yamagishi K, Kokubo Y, Saito I, et al. Development of a risk equation for the incidence of coronary artery disease and ischemic stroke for middle-aged Japanese-Japan public health center-based prospective study. *Circ J.* (2016) 80:1386–95. doi: 10.1253/circj.CJ-16-0081
30. Wang Z, Chen Z, Wang X, Zhang L, Li S, Tian Y, et al. The disease burden of atrial fibrillation in China from a National Cross-sectional Survey. *Am J Cardiol.* (2018) 122:793–8. doi: 10.1016/j.amjcard.2018.05.015
31. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GBJ, McPherson R, et al. 2012 Update of the Canadian Cardiovascular Society Guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol.* (2013) 29:151–67. doi: 10.1016/j.cjca.2012.11.032
32. Tian T, Jin G, Yu C, Lv J, Guo Y, Bian Z, et al. Family history and stroke risk in china: evidence from a large cohort study. *J Stroke.* (2017) 19:188–95. doi: 10.5853/jos.2016.01270
33. Ilinca A, Kristoffersson U, Soller M, Lindgren AG. Familial aggregation of stroke amongst young patients in Lund Stroke Register. *Eur J Neurol.* (2016) 23:401–7. doi: 10.1111/ene.12881
34. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of diagnostic codes for acute stroke in administrative databases: a systematic review. *PLos One.* (2015) 10:e135834. doi: 10.1371/journal.pone.0135834

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Perioperative Blood Pressure Control in Carotid Artery Stenosis Patients With Carotid Angioplasty Stenting: A Retrospective Analysis of 173 Cases

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Zheng L, Li J, Liu H, Guo H, Zhao L, Bai H, Yan Z and Qu Y (2020) Perioperative Blood Pressure Control in Carotid Artery Stenosis Patients With Carotid Angioplasty Stenting: A Retrospective Analysis of 173 Cases. Front. Neurol. 11:567623. doi: 10.3389/fneur.2020.567623

Background: Carotid angioplasty stenting (CAS) is a currently widely used surgical treatment of carotid artery stenosis. However, the influences of the perioperative blood pressure (BP) on patients' prognosis remain unclear.

Objective: The present study was designed to explore the effects of different perioperative BP control strategies on CAS patients' prognosis.

Methods: One hundred seventy-three consecutive patients admitted between January 2016 and April 2019 were reviewed retrospectively. The outcomes of patients with different systolic BP (<120, 120–130, and >130 mmHg) before CAS and within 24 h after CAS were compared. The primary outcomes were the incidence of secondary cerebral infarction (CI) and intracranial hemorrhage (ICH) after CAS. The secondary outcome was the incidence of unfavorable discharge and in-hospital death. The unfavorable discharge was defined as modified Rankin Scale (mRS) score 3–5 at discharge.

Results: There was no significant difference between the incidences of ICH ($P = 0.803$) and CI ($P = 0.410$) in patients with different BP before CAS. The patients with post-CAS BP values of >130 mmHg had a 37.67-fold increased risk (95% CI: 6.79–209.01) of ICH compared with others, while no significant difference was observed on the incidence of CI ($P = 0.174$) among patients with different post-CAS BP values. The patients with post-CAS BP values of >130 mmHg also had a significantly higher incidence of unfavorable discharge ($P = 0.002$) and in-hospital death ($P = 0.001$) compared with others.

Conclusion: High BP (>130 mmHg) within 24 h after CAS significantly increases the risks of secondary cerebral hemorrhage, unfavorable discharge, and in-hospital death. Thus, the BP should be controlled below 130 mmHg in the first 24 h after CAS.

Keywords: cerebral infarction, intracranial hemorrhage, carotid angioplasty stenting, carotid artery stenosis, blood pressure control

INTRODUCTION

Stroke has become the leading cause of death worldwide (1–3). Even worse, the absolute numbers of strokes will continue to increase worldwide for a long time along with the increasing of the aging population and the high prevalence of smoking and hypertension (4, 5), and most importantly due to the increasing incidence of stroke in younger persons aged <65 years (6, 7). In addition, the proportion of ischemic strokes is increasing in many developing countries such as China (4, 8). Currently, about 85% of strokes are cerebral ischemia, which is characterized by a sudden loss of neurological function due to insufficient blood supply to the brain (9).

Carotid artery stenosis is a well-documented risk factor for cerebrovascular diseases such as acute ischemic stroke or transient ischemic attack (10). It is reported that atherosclerotic disease of the extracranial internal carotid artery is responsible for 20–25% of ischemic strokes (11). The evidence of the optimal treatment strategies for different patients is still insufficient (10, 12). For asymptomatic carotid artery stenosis patients with stenosis <70%, medical therapy and control of risk factors are the currently recommended treatment strategies. However, for symptomatic patients with stenosis of more than 50% or asymptomatic patients with stenosis of more than 70%, surgical treatment could be considered (13–15).

Current surgical treatments for carotid stenosis include carotid endarterectomy (CEA) and carotid angioplasty stenting (CAS) (16). Although CEA has been established as the gold standard treatment for symptomatic severe carotid stenosis, CAS, as a less-invasive procedure, has been performed as an alternative to CEA (17, 18). Breakthroughs have been made since the treatment of endovascular recanalization for the symptomatic internal carotid artery stenosis patients in the subacute to chronic stage was first reported (19). Compared with CEA, CAS has advantages in the treatment of chronic carotid artery stenosis in some clinical situations (12, 20–23). For example, CAS patients can recover quickly and have shorter hospital stays. Besides, CAS can be performed on patients with severe stenosis of the internal carotid artery. Moreover, tandem lesions can be treated simultaneously.

Cerebral hyperperfusion syndrome (CHS), which could further lead to cerebral swelling or intracranial hemorrhage (ICH), occurs on 1.1–6.8% of intracranial arterial stenosis patients after CAS (24–26). The pathophysiology of CHS is characterized by the increase of cerebral blood flow due to the dysregulation of the cerebral vascular system and hypertension (27). Therefore, controlling post-CAS blood pressure (BP) at a low level could reduce the risk of CHS and ICH (28). However, excessive lowering of BP may aggravate the cerebral ischemia. Currently, the standard of BP control after CAS is still controversial.

Thus we conducted this retrospective study of 173 CAS patients at Tangdu Hospital from January 2016 to April 2019 to explore the effect of different perioperative BP control strategies on the risk of post-CAS ICH, cerebral infarction (CI), and prognosis of CAS patients.

MATERIALS AND METHODS

Study Design and Population

The present study was designed to compare the incidence rate of CI, ICH, unfavorable discharge [modified Rankin Scale (mRS) 3–5], and in-hospital death in carotid artery stenosis patients with different perioperative BP after CAS. This study was approved by the Biological and Medical Ethics Committee of Tangdu Hospital (No. TDLL-20181205) and performed in Tangdu Hospital strictly following the Declaration of Helsinki (29). The medical records of all patients who underwent CAS at Tangdu Hospital between January 2016 and April 2019 were retrospectively reviewed.

Then, the participants were selected according to the following criteria.

Inclusion Criteria

1. 18–80 years old.
2. Symptomatic patients with stenosis more than 50% or asymptomatic patients with stenosis more than 70% (demonstrated by digital subtraction angiography).
3. Without newly emerging ischemic stroke within 2 weeks.
4. Underwent CAS during the hospitalization.

Exclusion Criteria

1. Definite contraindications against BP control (such as renal failure and hypovolemic shock).
2. A tendency of severe bleeding (such as a peptic ulcer or gastrointestinal bleeding).
3. A history of CEA or occlusion after stenting.
4. A history of ICH within 30 days.
5. Concurrent serious severe heart or lung dysfunction.

Treatment

All patients obtained standard treatment in accordance with the recommendations of the American Heart Association/American Stroke Association (AHA/ASA). Medical histories were recorded after admission in a timely manner. Neurological status was documented on admission using the National Institutes of Health Stroke Scale (NIHSS) by certified neurologists. Routine radiological examination and blood tests were performed during the perioperative period. The strategies of BP control were specified based on the physician's judgment of the clinical status of patients.

Surgical Procedures

All of the surgeries were performed by a well-trained vascular surgery team with more than 10 years of experience. All patients received antiplatelet medication (aspirin 100 mg/day and clopidogrel 75 mg/day) for at least 5 days before the surgery, which were performed under local anesthesia. A dose of 3,000 IU heparin was given by intravenous bolus injection intraoperatively to each patient. Cerebral angiography was performed before CAS to measure the stenosis degree according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. A protective distal filter device (EV3) was carefully deployed in the normal vessel distal to the stenosis. A balloon with a diameter of 4–6 mm was performed for pre- or post-dilation if needed. Then, a self-expanding stent was deployed over the lesion.

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed both before and after the surgery to assess ICH and CI.

Data Collection and Outcomes Evaluation

General characteristics (such as sex, age, etc.) were collected from the patient information management department of our hospital. Past medical history (smoking, alcohol, hypertension, coronary artery disease, hyperlipidemia, and diabetes), degree of stenosis, and contralateral lesions were obtained from medical documentation and cerebral angiography report in our hospital. The preoperative severity of disease was evaluated by the preoperative NIHSS score, which was also collected from medical documentation. The baseline BP values were obtained as the mean values of three random systolic BP (SBP) in the last 24 h before CAS, and the post-CAS BP levels were acquired as the mean values of every hourly SBP in the first 24 h after CAS. If ICH or CI occurs within 24 h post-CAS, the subsequent BP values would be excluded from the analysis. All the BP records were collected from medical documentation. The outcomes of patients with different systolic BP (<120 mmHg, 120–130 mmHg, and >130 mmHg) before CAS and within 24 h after CAS were compared.

The primary outcomes were the incidence rate of ICH and CI after CAS during the hospitalization, which were assessed by CT or MRI scan. ICH was defined as punctate or confluent hyper-densities consistent with blood within the parenchyma of the cerebral hemispheres or within the subarachnoid space as demonstrated on CT imaging (30). CI was defined as episode of neurological dysfunction caused by focal cerebral based on CT or MRI (31). Spotty CI was ruled out, and carotid ultrasound was performed post procedure to assess thrombosis or occlusion of the carotid artery. All assessments were finished separately by two investigators after carefully comparing the cerebral imaging before and after CAS. The secondary outcomes were in-hospital death and unfavorable discharge, which was defined as mRS score 3–5 at discharge.

Statistical Analysis

Statistical calculations were performed using SPSS version 23.0 (IBM, Armonk, USA). The chi-squared tests and Fisher's exact tests were used to analyze the comparison of categorical data, which were displayed as percentages. Wilcoxon signed-rank tests were used to analyze the comparison of continuous data, which were presented as median scores with interquartile ranges because of non-normal data distributions. Multivariate logistic regression analysis was used to detect the risk factors of ICH,

TABLE 1 | General characteristics in each group.

Characteristics	Total	<120 mmHg	120–130 mmHg	>130 mmHg	*P*-value
Gender (female)	33/173	17.4% (20/115)	15.0% (6/40)	38.9% (7/18)	0.097
Age (years)		62.9 ± 8.7	63.2 ± 9.0	65.2 ± 11.1	0.749
Grade of hypertension		2 (0–3)	3 (2–3)	2.5 (2–3)	0.154
Diabetes mellitus		20.0% (23/115)	17.5% (7/40)	38.9% (7/18)	0.179
Coronary artery disease		13.0% (15/115)	12.5% (5/40)	11.1% (2/18)	1
Hyperlipidemia		27.0% (31/115)	32.5% (13/40)	38.9% (7/18)	0.502
Alcoholic		22.6% (26/115)	25.0% (10/40)	22.2% (4/18)	0.96
Smoking		48.7% (56/115)	45.0% (18/40)	33.3% (6/18)	0.501
Bilat lesions		9.6% (11/115)	17.5% (7/40)	22.2% (4/18)	0.159
Stenosis (NASCET, %)		79.1 ± 8.1%	81.4 ± 7.9%	85.4 ± 8.8%	0.006
Preoperative NIHSS score		0 (0–0)	0 (0–1)	0 (0–2.25)	0.426
Postoperative MRI		47.0% (54/115)	55.0% (22/40)	27.8% (5/18)	0.161
Spotty infarction		79.6% (43/54)	72.9% (16/22)	40.0% (2/5)	0.129

NIHSS, National Institutes of Health Stroke Scale; MRI, Magnetic Resonance Imaging; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

TABLE 2 | The incidence of post-CAS CI, ICH, unfavorable discharge, and in-hospital death in the patients with different baseline BP and post-CAS BP.

		<120 mmHg	120–130 mmHg	>130 mmHg	*P*-value
Baseline BP	CI	0% (0/24)	7.9% (6/76)	4.1% (3/73)	0.410
	ICH	4.2% (1/24)	7.9% (6/76)	9.6% (7/73)	0.803
24 h BP	CI	3.5% (4/115)	7.5% (3/40)	11.1% (2/18)	0.174
	ICH	2.6% (3/115)	5.0% (2/40)	50% (9/18)	<0.0001
	Unfavorable discharge	1.7% (2/115)	0% (0/40)	22.2% (4/18)	0.002
	In-hospital death	0% (0/115)	0% (0/40)	16.7% (3/18)	0.001

CI, Cerebral Infarction; ICH, Intracranial Hemorrhage.

CI, unfavorable discharge, and in-hospital death. Statistical test results were recognized as significant when the *P*-value was <0.05.

RESULTS

Patient Numbers

Two hundred eighty-eight consecutive patients with carotid artery stenosis who underwent CAS admitted to our hospital between January 2016 and April 2019 were retrospectively reviewed. Among them, 115 patients were excluded due to the lack of clinical or cerebral imaging data; then, a total of 173 patients met the inclusion criteria and were enrolled in this study.

General Characteristics

Among the 173 included patients, 140 were male and 33 were female. The age of the patients ranged from 39 to 81, and the average age was 63.2 ± 9.0. The average degree of stenosis was 80.3 ± 8.3%. Among the 115 excluded patients, 97 were male and 18 were female. The age of the patients ranged from 42 to 80, and the average age was 63.7 ± 7.7. The average degree of stenosis was 78.5 ± 8.5%. There was no significant difference in the demographic and baseline characteristics among the BP groups divided according to the post-CAS systolic BP levels (**Table 1**).

OUTCOME ASSESSMENT

After CAS, 14 (8.1%) patients suffered different types of ICH, which included 1 subarachnoid hemorrhage, 1 contralateral intracerebral microhemorrhage, 1 bilateral subdural hemorrhage, 1 posterior cerebral circulation hemorrhage, 6 intracerebral microhemorrhages, and 4 intracerebral hemorrhages. Nine (5.2%) patients suffered CI. Three (1.73%) patients died before discharge. Besides, unfavorable discharge occurred in six (3.47%) cases (**Table 2**). Among the 115 excluded patients, the incidence of ICH or CI cannot be identified due to the lack of clinical or cerebral imaging data. No one died or suffered unfavorable discharge.

Among the three BP groups divided according to the baseline BP levels, there were no significant differences in the incidence of both CI ($P = 0.410$) and ICH ($P = 0.803$). However, among the three BP groups divided according to the post-CAS BP levels, there were significant differences on the incidence of ICH ($P < 0.0001$), unfavorable discharge ($P = 0.002$), and in-hospital death ($P = 0.001$), whereas there was no significant difference on the incidence of CI ($P = 0.174$) (**Table 2**).

Within different postoperative BP groups, the >130 mmHg group had a significantly higher incidence of ICH ($P < 0.0001$ vs. the <120 mmHg group, $P < 0.0001$ vs. the 120–130 mmHg group), unfavorable discharge ($P = 0.003$ vs. the <120 mmHg group, $P = 0.007$ vs. the 120–130 mmHg group), and in-hospital death ($P = 0.002$ vs. the <120 mmHg group, $P = 0.026$ vs. the 120–130 mmHg group) than that in the other two groups. However, there was no significant difference on the incidence of ICH ($P = 0.604$) and unfavorable discharge ($P = 1$) between the <120 mmHg group and the 120–130 mmHg group (**Table 3**).

TABLE 3 | The difference in the incidence of post-CAS, ICH, unfavorable discharge, and in-hospital death between different post-CAS BP groups.

P-value	<120 mmHg vs. 120–130 mmHg	<120 mmHg vs. >130 mmHg	120 mm−130 mmHg vs. >130 mmHg
ICH	0.604	<0.0001	<0.0001
Unfavorable discharge	1	0.003	0.007
In-hospital death	NA	0.002	0.026

ICH, Intracranial Hemorrhage; NA, Not Applicable.

TABLE 4 | Multivariate logistic regression of potential influentially factors on the post-CAS ICH.

		OR (95% CI)	*P*-value
24 h BP (Reference is ≤130 mmHg)	>130 mmHg	37.67 (6.79–209.01)	<0.0001
Baseline BP		0.977 (0.91–1.05)	0.516
Age		0.938 (0.86–1.02)	0.130
Grade of hypertension		1.12 (0.59–2.12)	0.740
Bilat lesions (Reference is No)	Yes	1.67 (0.30–9.29)	0.560
Stenosis (NASCET)		1.194 (1.063–1.342)	0.003
Preoperative NIHSS score		0.54 (0.18–1.66)	0.282

NIHSS, The National Institutes of Health Stroke Scale; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

TABLE 5 | Logistic regression of risk factors of unfavorable discharge and in-hospital death.

	Unfavorable discharge		In-hospital death	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Hemorrhage				
NO	1.00		1.00	
YES	31.40 (5.13–192.59)	<0.0001	26.33 (2.23–311.69)	0.009
Infarction				
NO	1.00		1.00	
YES	11.43 (1.78–73.30)	0.01	10.13 (0.83–123.75)	0.07

After adjusting for confounding variables including age, baseline BP, the grade of hypertension, bilat lesions, degree of stenosis (NASCET), and preoperative NIHSS score, multivariate logistic regression analysis showed that the patients with post-CAS BP of >130 mmHg had a 37.67-fold increased risk (95% CI: 6.79–209.01) of post-CAS ICH compared with those with post-CAS BP of ≤130 mmHg (**Table 4**).

Furthermore, the patients with post-CAS ICH had a 31.40-fold increased risk (95% CI: 5.13–192.59) of unfavorable discharge and a 26.33-fold increased risk (95% CI: 2.23–311.69) of in-hospital death, compared with others. Meanwhile, the patients with post-CAS CI had an 11.43-fold increased risk (95% CI: 1.78–73.30) of unfavorable discharge and a tendency of an increase of the risk (OR: 10.13, 95% CI: 0.83–123.75) of in-hospital death, compared with others (**Table 5**).

Typical cases of post-CAS ICH and CI are shown in **Figure 1**. Case #1 was a patient with a 99% stenosis in the proximal segment

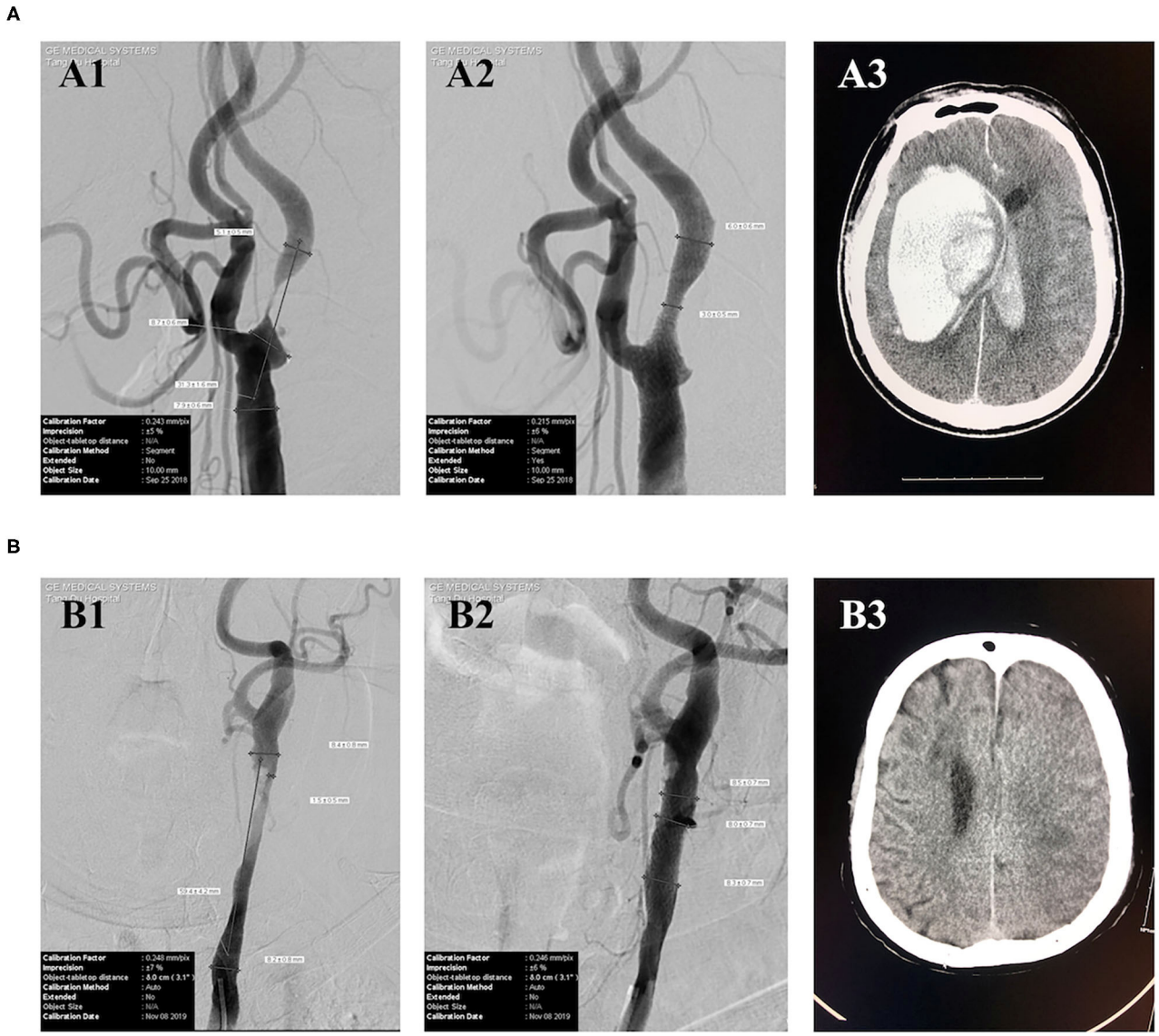

FIGURE 1 | Typical cases of post-CAS ICH and CI. **(A)** Case #1 **(A1)** DSA showed a 99% stenosis in the proximal segment of the right internal carotid artery. **(A2)** DSA showed a 50% residual stenosis in the proximal segment of the right internal carotid artery after CAS. **(A3)** CT performed 25 h after CAS showed a huge right intracerebral hematoma. **(B)** Case #2 **(B1)** DSA showed an 82% stenosis in the left carotid artery. **(B2)** DSA showed a nearly 0% residual stenosis in the left carotid artery after CAS. **(B3)** CT scan performed 58 h after CAS showed a left massive CI.

of the right internal carotid artery. The baseline BP, immediate post-CAS BP, and average BP within 24 h after CAS were 125/75, 123/83, and 156/82 mmHg, respectively. This patient had symptoms of headache, nausea, and vomiting after CAS. The CT scan performed 25 h after CAS showed a huge right intracerebral hematoma (**Figure 1A3**), which was considered to be caused by poor post-CAS BP control and CHS. This patient eventually died in the hospital. Case #2 was a patient with an 82% stenosis in the left carotid artery. The baseline BP, immediate post-CAS BP, and average BP within 24 h after CAS were 125/61, 115/74, and 101/61 mmHg, respectively. The CT scan performed 58 h after CAS showed a massive left CI (**Figure 1B3**). Carotid ultrasound post-procedure excluded thrombosis or occlusion of the carotid artery. This patient eventually suffered unfavorable discharge.

DISCUSSION

The present study was designed to explore the effects of different perioperative BP control strategies on CAS patients' prognosis. We found that the post-CAS BP was significantly correlated with ICH, unfavorable discharge, and in-hospital death, while there was no significant association with CI in CAS patients, although baseline BP did not appear to have an effect on the incidence of

both CI and ICH. The patients with post-CAS BP values of >130 mmHg had a 37.67-fold increased risk of ICH compared with others, and patients who suffered ICH had a 31.40-fold increased risk of unfavorable discharge and 26.33-fold increased risk of in-hospital death. These results suggest that the systolic pressure within 24 h after CAS should be controlled below 130 mmHg to avoid post-CAS ICH.

CAS has been demonstrated to be valuable in the treatment of chronic carotid artery stenosis. Post-CAS ICH is characterized with early occurrence, high disability, and mortality. As the most common cause, the mechanisms of post-CAS CHS might include: (1) the failure of vessels' autoregulatory mechanisms during the sudden increase of cerebral blood flow after revascularization in long-standing hypoperfused tissues, (2) the disturbance of baroreflex secondary to revascularization, and (3) the disturbance of the trigeminovascular system (32). Thus, maintaining hemodynamic stability may be an important way to prevent post-CAS CHS and ICH. However, most of the previous literature about CHS and ICH was concentrated on the difference of post-surgery ICH incidence between CAS and CEA (30, 33–35). Some other studies were focused on the predictive risk factors of CHS and ICH after CAS (36–38). Besides, as ischemic post-CAS stroke, the mechanisms of CI can be classified as (1) carotid-embolic, (2) hemodynamic, (3) thrombosis or occlusion of the carotid artery, (4) hyperperfusion, (5) cardio-embolic, (6) multiple, or (7) undetermined (39). A previous study showed that hemodynamic disturbance was an important mechanism, and careful attention to BP control could lower the incidence of ischemic post-CAS stroke (31). There is still limited clinical evidence on how to prevent ICH and CI after CAS, which is one of the primary issues in the management of patients and can directly improve the patient's prognosis.

In 1999, a literature first reported ICH after CAS and pointed out that attention should be paid to perioperative BP (40). In 2017, A meta-analysis showed that periprocedural hypertension was the most common risk factor of CHS and ICH (32). Another literature (39) proved that careful attention to BP control could lower the incidence of procedural stroke. In addition, previous studies have reached a common conclusion that post-CAS BP should be controlled below a certain level (41–44). However, it is still unclear whether lower BPs increase the risk of post-CAS CI. Although the present study showed that difference between the incidence of CI in each post-surgery BP group had no statistical significance, we provided a more specific strategy of BP control after CAS than the previous studies.

This study has several limitations. At first, the incidence of post-CAS ICH in this study was 8.1%, which was much higher than the incidence range of 0.36–4.5% reported in previous studies (26, 38). The incidence may be enlarged by two reasons. One is the selection bias inherent in a retrospective study, which is characterized by excluding 115 patients in whom no one died or suffered unfavorable discharge in this study, despite the lack of clinical or cerebral imaging data. Another is that we have included six intracerebral microhemorrhage patients who suffered no CHS symptoms in the analysis, while most of the previous studies focused on ICH in the context of CHS. Besides, the 5.2% incidence of CI is similar to the 4.3% of a previous study (30). Although we have excluded spotty CI to be directly related to the operation by MRI and assessed thrombosis or occlusion of the carotid artery by carotid ultrasound post-procedure, it is difficult to identify whether post-CAS CI was caused by carotid-embolic or hemodynamics. The reason we did not find significant association between post-CAS BP and CI may be the lack of essential cerebral imaging data and the small sample size of retrospective study. Last, the characteristics of a single-center study and the lack of randomization due to the retrospective design may not make the results generalizable. Thus, prospective multi-center randomized controlled clinical trials with a larger sample size and adequately pre-defined radiological examination protocol are needed.

In conclusion, the baseline systolic BP has no significant influence on post-CAS ICH and CI, while the BP within 24 h after CAS is closely related to the post-CAS ICH and patients' prognosis and should be controlled lower than 130 mmHg.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the biological and medical ethics committee of Tangdu Hospital (No. TDLL-20181205).

AUTHOR CONTRIBUTIONS

All authors of this work met ICMJE criteria for authorship and made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, drafting, critical revising, and final approval of this manuscript.

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REFERENCES

1. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH, Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. *Lancet Neurol.* (2007) 6:456–64. doi: 10.1016/S1474-4422(07)70004-2
2. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* (2008) 371:1612–23. doi: 10.1016/S0140-6736(08)60694-7
3. Liu L, Wang D, Wong KS, Wang Y. Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke.* (2011) 42:3651–4. doi: 10.1161/STROKEAHA.111.635755

4. Kinlay S. Changes in stroke epidemiology, prevention, and treatment. *Circulation.* (2011) 124:e494–6. doi: 10.1161/CIRCULATIONAHA.111.069633
5. Kunst AE, Amiri M, Janssen F. The decline in stroke mortality: exploration of future trends in 7 Western European countries. *Stroke.* (2011) 42:2126–30. doi: 10.1161/STROKEAHA.110.599712
6. Group GBDNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* (2017) 16:877–97. doi: 10.1016/S1474-4422(17)30299-5
7. Hankey GJ. Stroke. *Lancet.* (2017) 389:641–54. doi: 10.1016/S0140-6736(16)30962-X
8. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation.* (2017) 135:759–71. doi: 10.1161/CIRCULATIONAHA.116.025250
9. Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke. *Lancet.* (2018) 392:1247–56. doi: 10.1016/S0140-6736(18)31874-9
10. Barrett KM, Brott TG. Stroke caused by extracranial disease. *Circ Res.* (2017) 120:496–501. doi: 10.1161/CIRCRESAHA.117.310138
11. Alcalde-Lopez J, Zapata-Arriaza E, Cayuela A, Moniche F, Escudero-Martinez I, Ortega-Quintanilla J, et al. Safety of early carotid artery stenting for symptomatic stenosis in daily practice. *Eur J Vasc Endovasc Surg.* (2018) 56:776–82. doi: 10.1016/j.ejvs.2018.07.026
12. Levy EI, Mocco J, Samuelson RM, Ecker RD, Jahromi BS, Hopkins LN. Optimal treatment of carotid artery disease. *J Am Coll Cardiol.* (2008) 51:979–85. doi: 10.1016/j.jacc.2007.10.052
13. Raman G, Moorthy D, Hadar N, Dahabreh IJ, O'Donnell TF, Thaler DE, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. *Ann Intern Med.* (2013) 158:676–85. doi: 10.7326/0003-4819-158-9-201305070-00007
14. Abbott AL, Paraskevas KI, Kakkos SK, Golledge J, Eckstein HH, Diaz-Sandoval LJ, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. *Stroke.* (2015) 46:3288–301. doi: 10.1161/STROKEAHA.115.003390
15. Kapila V, Jetty P, Basile VS, Dubois L. Management of transient ischemic attack or nondisabling stroke related to extracranial internal carotid artery stenosis. *CMAJ.* (2019) 191:E418–22. doi: 10.1503/cmaj.180735
16. Roffi M, Cremonesi A. Carotid artery stenting vs. endarterectomy for carotid stenosis. *Lancet.* (2010) 376:327; author reply 327–8. doi: 10.1016/S0140-6736(10)61177-4
17. Brott TG, Hobson RWII, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting vs. endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* (2010) 363:11–23. doi: 10.1056/NEJMoa0912321
18. Gonzales NR, Demaerschalk BM, Voeks JH, Tom M, Howard G, Sheffet AJ, et al. Complication rates and center enrollment volume in the carotid revascularization endarterectomy vs. stenting trial. *Stroke.* (2014) 45:3320–4. doi: 10.1161/STROKEAHA.114.006228
19. Terada T, Okada H, Nanto M, Shintani A, Yoshimura R, Kakishita K, et al. Endovascular recanalization of the completely occluded internal carotid artery using a flow reversal system at the subacute to chronic stage. *J Neurosurg.* (2010) 112:563–71. doi: 10.3171/2009.6.JNS09125
20. Kao HL, Lin MS, Wang CS, Lin YH, Lin LC, Chao CL, et al. Feasibility of endovascular recanalization for symptomatic cervical internal carotid artery occlusion. *J Am Coll Cardiol.* (2007) 49:765–71. doi: 10.1016/j.jacc.2006.11.029
21. Lin MS, Lin LC, Li HY, Lin CH, Chao CC, Hsu CN, et al. Procedural safety and potential vascular complication of endovascular recanalization for chronic cervical internal carotid artery occlusion. *Circ Cardiovasc Interv.* (2008) 1:119–25. doi: 10.1161/CIRCINTERVENTIONS.108.772350
22. Doig D, Brown MM. Carotid stenting vs. endarterectomy. *Annu Rev Med.* (2012) 63:259–76. doi: 10.1146/annurev-med-081210-101714
23. White CJ. Carotid artery stenting. *J Am Coll Cardiol.* (2014) 64:722–31. doi: 10.1016/j.jacc.2014.04.069
24. Schoser BG, Heesen C, Eckert B, Thie A. Cerebral hyperperfusion injury after percutaneous transluminal angioplasty of extracranial arteries. *J Neurol.* (1997) 244:101–4. doi: 10.1007/s004150050057
25. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. *J Am Coll Cardiol.* (2004) 43:1596–601. doi: 10.1016/j.jacc.2003.12.039
26. Moulakakis KG, Mylonas SN, Sfyroeras GS, Andrikopoulos V. Hyperperfusion syndrome after carotid revascularization. *J Vasc Surg.* (2009) 49:1060–8. doi: 10.1016/j.jvs.2008.11.026
27. Farooq MU, Goshgarian C, Min J, Gorelick PB. Pathophysiology and management of reperfusion injury and hyperperfusion syndrome after carotid endarterectomy and carotid artery stenting. *Exp Transl Stroke Med.* (2016) 8:7. doi: 10.1186/s13231-016-0021-2
28. van Mook WN, Rennenberg RJ, Schurink GW, Van Oostenbrugge RJ, Mess WH, Hofman PA, et al. Cerebral hyperperfusion syndrome. *Lancet Neurol.* (2005) 4:877–88. doi: 10.1016/S1474-4422(05)70251-9
29. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* (2013) 310:2191–4. doi: 10.1001/jama.2013.281053
30. Galyfos G, Sianou A, Filis K. Cerebral hyperperfusion syndrome and intracranial hemorrhage after carotid endarterectomy or carotid stenting: a meta-analysis. *J Neurol Sci.* (2017) 381:74–82. doi: 10.1016/j.jns.2017.08.020
31. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2013) 44:2064–89. doi: 10.1161/STR.0b013e318296aeca
32. Abreu P, Nogueira J, Rodrigues FB, Nascimento A, Carvalho M, Marreiros A, et al. Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: systematic review and meta-analysis. *Acta Neurochir (Wien).* (2017) 159:2089–97. doi: 10.1007/s00701-017-3328-4
33. Timaran CH, Veith FJ, Rosero EB, Modrall JG, Valentine RJ, Clagett GP. Intracranial hemorrhage after carotid endarterectomy and carotid stenting in the United States in 2005 *J Vasc Surg.* (2009) 49:623–8; discussion 628–9. doi: 10.1016/j.jvs.2008.09.064
34. McDonald RJ, Cloft HJ, Kallmes DF. Intracranial hemorrhage is much more common after carotid stenting than after endarterectomy: evidence from the National Inpatient Sample. *Stroke.* (2011) 42:2782–7. doi: 10.1161/STROKEAHA.111.618769
35. Hussain MA, Alali AS, Mamdani M, Tu JV, Saposnik G, Salata K, et al. Risk of intracranial hemorrhage after carotid artery stenting vs. endarterectomy: a population-based study. *J Neurosurg.* (2018) 129:1522–9. doi: 10.3171/2017.8.JNS171142
36. Matsumoto S, Nakahara I, Higashi T, Iwamuro Y, Watanabe Y, Takahashi K, et al. Near-infrared spectroscopy in carotid artery stenting predicts cerebral hyperperfusion syndrome. *Neurology.* (2009) 72:1512–8. doi: 10.1212/WNL.0b013e3181a2e846
37. Lee KJ, Kwak HS, Chung GH, Song JS, Hwang SB. Leptomeningeal collateral vessels are a major risk factor for intracranial hemorrhage after carotid stenting in patients with carotid atherosclerotic plaque. *J Neurointerv Surg.* (2016) 8:512–6. doi: 10.1136/neurintsurg-2014-011634
38. Zhang L, Dai D, Li Z, Duan G, Zhang YW, Yang P, et al. Risk factors for hyperperfusion-induced intracranial hemorrhage after carotid artery stenting in patients with symptomatic severe carotid stenosis evaluation. *J Neurointerv Surg.* (2019) 11:474–8. doi: 10.1136/neurintsurg-2018-013998
39. Huibers A, Calvet D, Kennedy F, Czuriga-Kovacs KR, Featherstone RL, Moll FL, et al. Mechanism of procedural stroke following carotid endarterectomy or carotid artery stenting within the International Carotid Stenting Study (ICSS) randomised trial. *Eur J Vasc Endovasc Surg.* (2015) 50:281–8. doi: 10.1016/j.ejvs.2015.05.017
40. McCabe DJ, Brown MM, Clifton A. Fatal cerebral reperfusion hemorrhage after carotid stenting. *Stroke.* (1999) 30:2483–6. doi: 10.1161/01.STR.30.11.2483
41. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. *Catheter Cardiovasc Interv.* (2007) 69:690–6. doi: 10.1002/ccd.20693

42. Ogasawara K, Sakai N, Kuroiwa T, Hosoda K, Iihara K, Toyoda K, et al. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. *J Neurosurg.* (2007) 107:1130–6. doi: 10.3171/JNS-07/12/1130
43. Cronenwett JL, Kraiss LW, Cambria RP. The society for vascular surgery vascular quality initiative. *J Vasc Surg.* (2012) 55:1529–37. doi: 10.1016/j.jvs.2012.03.016
44. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting vs. endarterectomy for carotid-artery stenosis. *N Engl J Med.* (2016) 374:1021–31. doi: 10.1056/NEJMoa1505215

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Predicting 6-Month Unfavorable Outcome of Acute Ischemic Stroke Using Machine Learning

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Background and Purpose: Accurate prediction of functional outcome after stroke would provide evidence for reasonable post-stroke management. This study aimed to develop a machine learning-based prediction model for 6-month unfavorable functional outcome in Chinese acute ischemic stroke (AIS) patient.

Methods: We collected AIS patients at National Advanced Stroke Center of Nanjing First Hospital (China) between September 2016 and March 2019. The unfavorable outcome was defined as modified Rankin Scale score (mRS) 3–6 at 6-month. We developed five machine-learning models (logistic regression, support vector machine, random forest classifier, extreme gradient boosting, and fully-connected deep neural network) and assessed the discriminative performance by the area under the receiver-operating characteristic curve. We also compared them to the Houston Intra-arterial Recanalization Therapy (HIAT) score, the Totaled Health Risks in Vascular Events (THRIVE) score, and the NADE nomogram.

Results: A total of 1,735 patients were included into this study, and 541 (31.2%) of them had unfavorable outcomes. Incorporating age, National Institutes of Health Stroke Scale score at admission, premorbid mRS, fasting blood glucose, and creatinine, there were similar predictive performance between our machine-learning models, while they are significantly better than HIAT score, THRIVE score, and NADE nomogram.

Conclusions: Compared with the HIAT score, the THRIVE score, and the NADE nomogram, the RFC model can improve the prediction of 6-month outcome in Chinese AIS patients.

Keywords: cerebral ischemia, machine learning, prediction, unfavorable outcome, stroke

INTRODUCTION

Globally, stroke is a leading cause of mortality and disability (1). In developing countries, the prevalence of stroke is increasing as the population ages. Patients who survive stroke have an increased economic burden due to post-stroke care (2). Therefore, accurate prediction of functional outcome after stroke would provide evidence for reasonable post-stroke management and thus improve the allocation of health care resources.

The prognostic prediction requires the processing of patients' clinical data, such as demographic information, clinical features, and laboratory tests results. Then, the model is developed to predict prognosis base on existing data. Several prognostic models have been developed to predict the clinical outcome after stroke, such as Houston Intra-arterial Recanalization Therapy (HIAT) score, Totaled Health Risks in Vascular Events (THRIVE) score and NADE nomogram (3–5). They are generally based on regression model with the assumption of a linear relationship between variables and the outcomes. The THRIVE score and HIAT score were developed based on Whites or Blacks, not Asians. Compared with White patients, the average age of Asian patients was younger (6, 7). In addition, several studies have observed worse survival in Whites with stroke compare to other race (8, 9). Importantly, the long-term outcomes of stroke were significantly different by race (7). Thus, it is difficult for these models to achieve accurate predictive performances on the Chinese population.

Machine-learning (ML) approaches have been widely used in medical fields (10). Recently, it has shown effective capability in disease prediction, especially in the analysis of large datasets with a multitude of variables (11–13). ML uses computer algorithms to build a model from labeled data and to make data-driven predictions. It enables the computer to process complex non-linear relationships between variables and outcomes, which may be hard to be detected by conventional regression models (14). Such advantages increase the accuracy of prediction model. ML includes multiple algorithms, such as logistic regression (LR), random forest classifier (RFC), support vector machine (SVM), fully-connected deep neural network (DNN), and extreme gradient boosting (XGBoost). The optimal selection of algorithm should be in accordance with the characteristics of the dataset. Meanwhile, the popularity of electronic patient record (EPR) systems and wide availability of structured patient data make sophisticated computer algorithms implemented at the bedside a reality.

In this study, we aim to develop the models using ML method to predict 6-month unfavorable outcomes in Chinese stroke patients, and then compare the performance of ML-based methods with existing clinical prediction scores.

METHODS

Study Population and Clinical Baseline Characteristic

We retrospectively conducted an analysis using a cohort of acute ischemic stroke (AIS) patients who were admitted within 7 days of the onset of symptoms. The cohort included 3,231 consecutive AIS patients admitted at National Advanced Stroke Center of Nanjing First Hospital (China) between September 2016 and March 2019. The exclusion criteria were patients with missing data on pretreatment variables or long-term clinical outcome, signs of intracranial hemorrhage on baseline brain computed tomography scan, age < 18 years. We discarded all variables with 25% missing values or more for further analysis.

All clinical, anamnestic, and demographic characteristics were recorded at the time of admission, including the following data: age, sex, body mass index, National Institute of Health stroke scale (NIHSS) at admission, premorbid modified Rankin Scale (mRS), interval from onset to hospital within 4.5 h, systolic blood pressure, diastolic blood pressure, platelet count, urea nitrogen, creatinine, fasting blood glucose (FBG), and medical history such as hypertension, previous cerebral infarction, and so on. NIHSS at admission and premorbid mRS were presented as continuous variables in all models to increase model efficiency, and the ordinal scores were assumed to be linear. Unfavorable outcome was defined as mRS 3–6, 6 months after stroke. During face-to-face or *via* telephone follow-up with the patients using structured interview, their relatives or their general practitioners, certified neurologists, evaluated the baseline NIHSS and mRS scores.

Statistical Analysis

The AIS patients were randomly stratified (8:2) into the training set for developing models, and the testing was set for evaluating the models' performance, which meant that the sampling was in proportion to the original dataset. We initially compared the clinical characteristics of patients with 6-month favorable and unfavorable outcomes in the training set. Continuous variables were reported as median value and interquartile range, and the various groups were explored for differences using the Mann–Whitney *U*-test. Categorical variables were instead expressed as number of events and percentage, dividing the number of events by the total number excluding missing and unknown cases. To compare categorical variables, Fisher's exact test or the χ^2 test were used. To identify which variables were independently associated with poor outcome, all potential variables with $p < 0.10$ in the univariable analysis or thought to be independent predictors of ischemic stroke were entered into a multivariable LR with a backward stepwise. Variables with $p < 0.05$ were considered statistically significant, and all p were two-sided. Finally, our models were developed based on ML, including age, premorbid mRS, NIHSS at admission, creatinine, and FBG. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) and Stata version 13.0 (StataCorp, College Station, TX, USA).

Model Development

According to Wolpert's "No Free Lunch Theorem," no one technique will be most accurate in every case, and so comparisons of techniques in different research areas and datasets may yield different results (15). Therefore, we used 5 ML algorithms: LR, SVM, RFC, XGBoost, and DNN because they are widely and successfully used for clinical data (16–20).

As a standard way of estimating the performance of the model, the k-fold cross-validation method is more reliable than simply

holding out the validation set by giving the variance of the performance and has been used in various reports (16–19). The 5-fold cross-validation was used for the model derivation and internal evaluation by dividing the training set into five mutually exclusive parts, four of which were used as training data to generate the model and one for evaluation as inner validation data; this process was repeated five times to generate five different but overlapping training data and five unique validation data. Due to the long training time and high resource consumption of DNN, we used a random partition of 10% data as a validation set instead of 5-fold cross-validation to optimize the model. In the training step, we optimized model hyperparameters with a grid search algorithm. During the searching process, we set the area under the curve (AUC) of receiver operating characteristic (ROC) as the score.

Model Evaluation

After the models were derived, the sensitivity, specificity, accuracy, and AUC were calculated for the testing data. The performances of different models were compared by ROC analysis and Delong test.

For evaluating the superiority of prediction capability for the ML models, we calculated THRIVE score, HIAT score, and NADE nomogram on the same patient group. Although there were some other scores, they were not included because the database lacked information for the calculation (21, 22). In addition, we also developed 2 ML models (LR and RFC models) using 21 variables with $p < 0.10$ in a univariable analysis as a reference. After derivation of the models, we calculated the contribution of each variable: the absolute value of the standardized regression coefficient for LR and information gain (which was estimated by the decrease in impurity) for RFC. The five ML models were developed and validated with open-source packages in Python software (version 3.7): Scikit-learn, keras, and XGboost.

RESULTS

Patient Characteristics

A total of 3,379 patients were registered to the cohort during the study period. After excluding 1,213 patients with unavailable 6-month mRS scores, 200 patients with unavailable NIHSS at admission, 108 patients with unavailable FBG, and 123 patients with missing other laboratory tests or clinical data, 1,735 patients were finally included (**Figure 1**). Comparison of demographic variables between the included and excluded patients is shown in **Supplementary Table 1**. The median age of the 1,735 patients was 68 (IQR:60–78) years, and 67.1% were men. The proportion of patients with unfavorable outcome was 31.2% (541/1,735), and 12.0% (208/1,735) died within the follow-up period (mRS score = 6). The characteristics of the patients were well-balanced between the training (n = 1,388, 80%) and testing (n = 347, 20%) sets (**Supplementary Table 2**).

Feature Selection

The 21 variables with $p < 0.10$ in the univariable analysis or thought to be independent predictors of ischemic stroke (the variables list is shown under **Table 1**) entered into the LR. After multivariate LR analysis, age, NIHSS at admission, premorbid mRS, FBG, and creatinine remained independent predictors of 6-month unfavorable outcome.

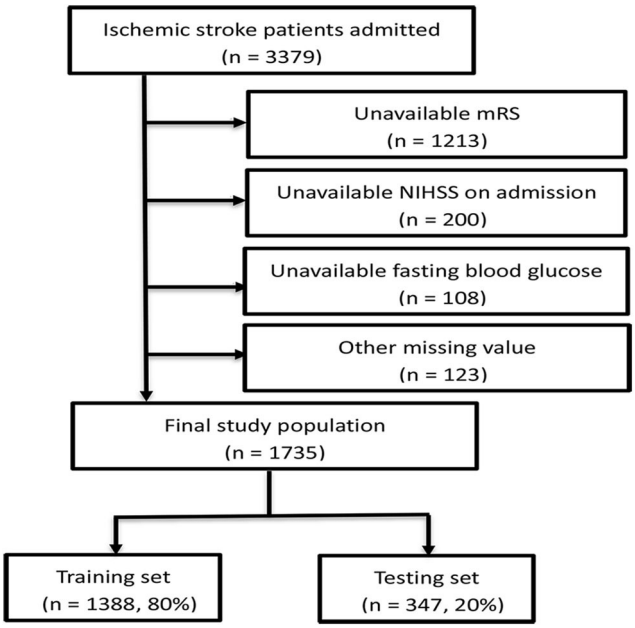

FIGURE 1 | Flow chart illustrating patient selection. mRS, modified Rankin Scale; NIHSS, National Institute of Health stroke scale.

Model Performance

The AUC of each model on the training and inner validation sets is provided in **Table 2**. The AUC of each model on the testing set is given as follows (**Table 3**, **Figure 2**): LR 0.857 [95% CI, 0.814–0.900], SVM 0.865 [0.823–0.907], RFC 0.862 [0.820–0.904], XGBoost 0.858 [0.815–0.901], and DNN 0.867 [0.827–0.908]. *P*-values for AUC of RFC compared with LR, SVM, XGBoost, and DNN were 0.885, 0.930, 0.898, and 0.848, respectively. Although there was no difference in AUC between the ML models, we chose the RFC model to compare with previously reported models.

The RFC model performed significantly better than the THRIVE score [AUC 0.862 [0.820–0.904] vs. 0.771 [0.721–0.822]; $p = 0.007$], HIAT score [AUC 0.862 [0.820–0.904] vs. 0.686 [0.630–0.743]; $p < 0.0001$], and NADE nomogram [AUC 0.862 [0.820–0.904] vs. 0.813 [0.763–0.862]; $p = 0.011$] (**Figure 3**). The sensitivity of RFC model is 0.657, while specificity is 0.883.

After we developed LR and RFC model with 21 variables, the performance of ML models did not differ from these models with five variables [0.857 [0.814–0.900] vs. 0.866 [0.825–0.907], $p = 0.755$ and 0.862 [0.820–0.904] vs. 0.874 [0.835–0.912], $p = 0.665$] (**Table 3**, **Figure 4**). Furthermore, we calculated the six most important variables in LR and RFC model using 21 variables. Age, NIHSS at admission, premorbid mRS, FBG, and creatinine also appeared as the most important variables (**Table 4**).

TABLE 1 | Clinical, demographic and laboratory data of the patients in the training set stratified according to 6-month favorable or unfavorable outcome after acute ischemic stroke.

	Favorable outcome (mRS 0–2)	Unfavorable outcome (mRS 3–6)	*P*-value
Patients, n	955	433	
Age, years, median (IQR)	66 (58–74)	77 (68–83)	< 0.0001#*
Sex, n (%)			< 0.0001*
Male	682 (71.4)	254 (58.7)	
Female	273 (28.6)	179 (41.3)	
Onset-to-admission delay <4.5 h, n (%)	236 (24.7)	127 (29.3)	0.070*
Medical history, n (%)			
Hypertension	650 (68.1)	317 (73.2)	0.053*
Diabetes mellitus	248 (26.0)	143 (33.0)	0.007*
Hyperlipidemia	29 (3.0)	6 (1.4)	0.069*
Coronary artery disease	100 (10.5)	77 (17.8)	< 0.0001*
Atrial fibrillation	75 (7.9)	95 (21.9)	< 0.0001*
Previous cerebral infarction	123 (12.9)	102 (23.6)	< 0.0001*
Valvular heart disease	13 (1.4)	8 (1.8)	0.492
Smoking, n (%)			< 0.0001*
Never smoker	394 (41.3)	255 (58.9)	
Former smoker	129 (13.5)	66 (15.2)	
Current smoker	432 (45.2)	112 (25.9)	
Drinking, n (%)			< 0.0001*
Never drinker	525 (55.0)	307 (70.9)	
Former drinker	84 (8.8)	47 (10.9)	
Current drinker	346 (36.2)	79 (18.2)	
Baseline data			
Premorbid mRS, median (IQR)	0 (0–0)	0 (0–2)	< 0.0001#*
NIHSS at admission, median (IQR)	3 (2–5)	10 (5–16)	< 0.0001#*
BMI, kg/m^2, median (IQR)	24.38 (22.38–26.64)	24.03 (21.60–26.37)	0.046#*
Pulse, times/min, median (IQR)	76 (70–80)	76 (70–84)	0.005#*
Systolic BP, mmHg, median (IQR)	140 (130–160)	142 (130–160)	0.350#
Diastolic BP, mmHg, median (IQR)	84 (80–94)	83 (78–95)	0.533#
Platelet count, 10^9/L, median (IQR)	195 (159–234)	188 (150–238)	0.159#
Urea nitrogen, mmol/L, median (IQR)	5.23 (4.4–6.34)	6.12 (4.71–7.75)	< 0.0001#*
Creatinine, μmol/L, median (IQR)	71 (59–83)	76 (62–97)	< 0.0001#*
FBG, mmol/L, median (IQR)	5.08 (4.50–6.21)	6.40 (5.05–7.99)	< 0.0001#*
TC, mmol/L, median (IQR)	4.41 (3.76–5.16)	4.41 (3.64–5.18)	0.574#
TG, mmol/L, median (IQR)	1.31 (0.96–1.86)	1.18 (0.84–1.59)	< 0.0001#*
LDL, mmol/l, median (IQR)	2.71 (2.13–3.31)	2.76 (1.96–3.27)	0.470#
HDL, mmol/l, median (IQR)	1.05 (0.9–1.23)	1.08 (0.9–1.26)	0.165#
Endovascular therapy, n (%)	72 (7.5)	55 (12.7)	0.002*
IV thrombolysis, n (%)	208 (21.8)	119 (27.5)	0.020*

mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institute of Health stroke scale; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IV, intravenous.

#calculated using Mann-Whitney U-test.

**included into the multiple logistic regression models (P < 0.1).*

DISCUSSION

To the best of our knowledge, this is the first study that develops prediction models with ML methods for the 6-month clinical outcome of AIS patients. For predicting 6-month unfavorable functional outcome in Chinese AIS patients, our study suggested that the RFC model is more accurate than the HIAT score, the THRIVE score, and the NADE nomogram. End users in clinical practice will be able to perform more accurate evaluation of long-term outcome for AIS patients when our models are fed five easily accessible variables. Thus, it interests clinical physicians because of importance of outcome prediction for patients and their families. Although, there are some criticisms about ML techniques because they are black

TABLE 2 | The area under the curve (AUC) of training set and inner validation set.

Models	Training set (95% CI)	Inner validation set (95% CI)
LR	0.867 (0.847–0.888)	0.862 (0.812–0.911)
SVM	0.874 (0.855–0.894)	0.871 (0.840–0.901)
RFC	0.897 (0.880–0.915)	0.866 (0.831–0.902)
XGBoost	0.890 (0.872–0.908)	0.867 (0.833–0.901)
DNN	0.877 (0.858–0.897)	0.860 (0.825–0.896)
LR*	0.874 (0.853–0.894)	0.865 (0.833–0.897)
RFC*	0.899 (0.881–0.917)	0.865 (0.835–0.894)

LR, logistic regression; SVM, support vector machine; RFC, random forest classifier; XGBoost, extreme gradient boosting; DNN, fully-connected deep neural network.
**indicates model developed with 21 variables.*

TABLE 3 | Scores for each model in the testing set.

Models	AUC (95% CI)	Specificity	Sensitivity	Precision	Accuracy
LR	0.857 (0.814–0.900)	0.912	0.620	0.761	0.821
SVM	0.865 (0.823–0.907)	0.912	0.602	0.756	0.816
RFC	0.862 (0.820–0.904)	0.883	0.657	0.717	0.813
XGBoost	0.858 (0.815–0.901)	0.895	0.630	0.731	0.813
DNN	0.867 (0.827–0.908)	0.891	0.556	0.811	0.821
LR*	0.866 (0.825–0.907)	0.921	0.593	0.780	0.821
RFC*	0.874 (0.835–0.912)	0.950	0.500	0.818	0.810

AUC, the area under the curve; LR, logistic regression; SVM, support vector machine; RFC, random forest classifier; XGBoost, extreme gradient boosting; DNN, fully-connected deep neural network.
**indicates model developed with 21 variables.*

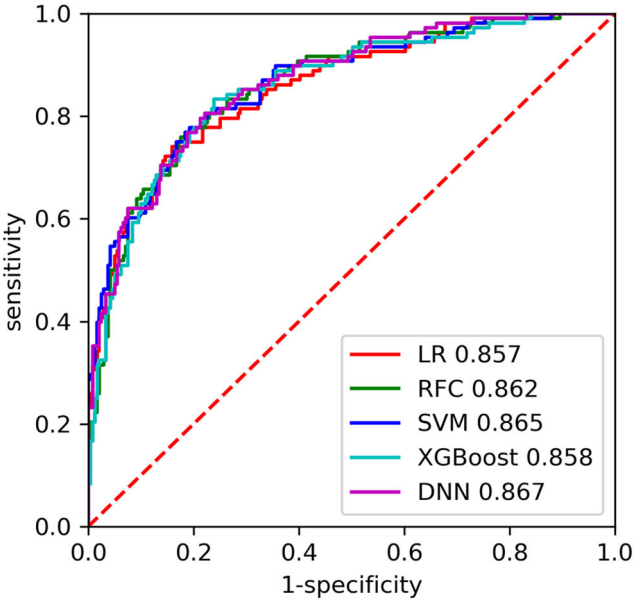

FIGURE 2 | The receiver operating characteristic (ROC) curves of the machine learning (ML) models on the testing set. LR, logistic regression; SVC, support vector machine; RFC, random forest classifier; XGBoost, extreme gradient boosting; DNN, fully-connected deep neural network.

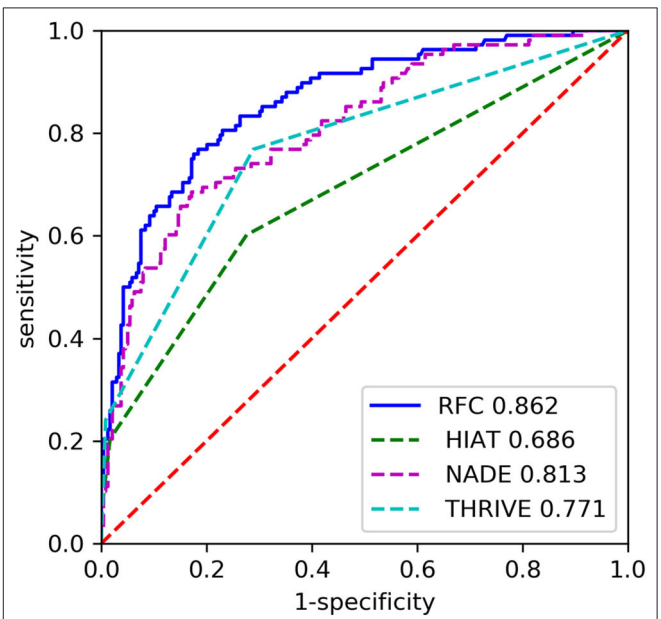

FIGURE 3 | The receiver operating characteristic (ROC) curves of the random forest classifier (RFC) and previous models on the testing set. HIAT, Houston Intra-Arterial Therapy score; THRIVE, Totaled Health Risks in Vascular Events score; NADE, NIHSS score on admission, age, previous diabetes mellitus and creatinine.

boxes (23). Importantly, our model should be used together with, rather than instead of, clinical judgment. Combining machines plus physicians reliably enhances system performance. Hence, we should strongly consider the RFC model if accuracy is paramount.

As a popular ensemble method, RFC has been successfully applied in medical fields due to its ability to build predictive models with high certainty and little necessity of model optimization. In particular, the important advantages were shown in the RFC model compared with other methodologies, including the ability to handle highly non-linearly correlated data, robustness to noise, and tuning simplicity (24). In our research, some strategies to avoid overfitting were performed, and our results showed no signs of obvious overfitting in the RFC model. Additionally, to ensure an unbiased and robust performance, 5-fold cross-validation was iteratively used. The preceding characteristic features may make our model useful in real-world practice.

Several previous prognostic models have been developed to predict the clinical outcome after stroke, such as the HIAT score, the THRIVE score, and the NADE nomogram (3–5). The HIAT score identified three predictors of a 3-month unfavorable outcome in intra-arterial recanalization therapy, that is age $>$ 75 years, NIHSS $>$ 18, and baseline glucose level $\geq$ 150 mg/dL. It respectively, has an AUC value of 0.69 and 0.73 in two cohorts (3). The THRIVE score identified age, NIHSS, hypertension, diabetes mellitus, and atrial fibrillation

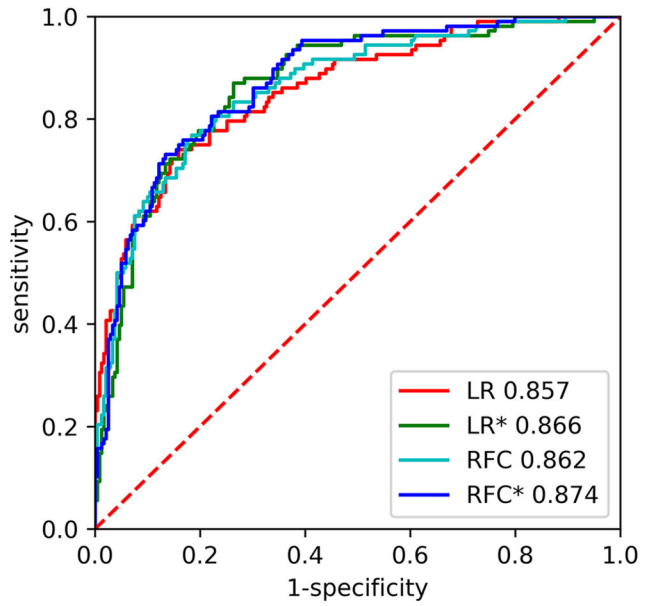

FIGURE 4 | The receiver operating characteristic (ROC) curves of the random forest classifier (RFC) and logistic regression (LR) on the testing set. * indicates model developed with 21 variables.

TABLE 4 | Top 6 important features in the models with 21 variables.

NO.	LR*	RFC*
1	NIHSS at admission	NIHSS at admission
2	Premorbid mRS	Age
3	Age	Premorbid mRS
4	Fasting blood glucose	Fasting blood glucose
5	Creatinine	Urea nitrogen
6	Sex	Creatinine

LR, logistic regression; RFC, random forest classifier; NIHSS, National Institute of Health stroke scale; mRS, modified Rankin Scale.
**indicates model developed with 21 variables.*

are independently associated with a 3-month poor outcome (4). It was well-validated with a large sample size from the Virtual International Stroke Trials Archive and had an AUC of 0.75 (25). The NADE nomogram was developed to predict 6-month unfavorable outcome after AIS (5). NIHSS at admission, age, previous diabetes mellitus, and creatinine were found to be significant predictors. The AUC value of the NADE nomogram was 0.791. In our study, only five variables—age, NIHSS on admission, premorbid mRS, FBG, and creatinine—were included into our models. NIHSS and premorbid mRS indicated that stroke severity and degree of dependence in the daily activities influenced the stroke outcome. Blood glucose has been proven to be not only associated with stroke outcome but also a risk factor of symptomatic intracerebral hemorrhage after thrombolysis therapy (26). Creatinine is an indicator of renal function. However, the relationship between renal function and stroke outcomes is controversial (27, 28). Indeed, after excluding some less important and even misleading variables for stroke outcome, ML models based on 5 and 21 variables have achieved similar performance. This illustrates that the five variables we selected contained almost all useful information in the original data. In addition, variable importance derived from the RFC and LR with 21 variables also provides insight for the importance of individual variables in prediction performance.

There are some limitations in our study. First, our population was from a single hospital. The generalizability of the predictive models needs to be tested in patients treated at other institutions and by other surgeons. Second, there were some cases that were lost to follow-up. Especially, of total 1,213 cases excluded from this study for loss of 6-month follow-up, 944 cases (78%) were lost between May 2017 and March 2018, accounting for 85% of the AIS patients during that period. It is unclear whether we have overestimated or underestimated the unfavorable outcome after AIS. But we believe this centralized loss of data may have less impact on the results. Finally, data of known neurobiological predictors of 3-month outcome such as infarct size (29) were not available in our study. Future prospective studies will have to assess whether incorporating novel predictors may improve the accuracy of predictive model.

CONCLUSIONS

To sum up, the comparison with the previous models demonstrated that it is feasible to apply the RFC model to stroke patient management, which achieves optimal performance compared with the HIAT score, THRIVE score, and NADE nomogram. Moreover, the RFC model is easy to use and robust. These advanced characteristics may contribute to reliable and practical applications in clinical practice.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Approval from the ethics committee of Nanjing First Hospital was obtained.

AUTHOR CONTRIBUTIONS

XL and JZo concepted, designed, and supervised the study. JZh, YL, FW, XZ, JY, and YZ acquired the data. XL and ZZ analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis. XL, XP, MW, CS, ZZ, and SW drafted the manuscript. JZo and CJ critically revised the manuscript for important intellectual content.

All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.539509/full#supplementary-material

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American heart association. *Circulation.* (2018) 137:e67. doi: 10.1161/CIR.0000000000000573
2. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, et al. Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ.* (2019) 20:107–34. doi: 10.1007/s10198-018-0984-0
3. Hallevi H, Barreto AD, Liebeskind DS, Morales MM, MartinSchild SB, Abraham AT, et al. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. *Stroke.* (2009) 40:1780–5. doi: 10.1161/STROKEAHA.108.535146
4. Flint AC, Cullen SP, Faigeles BS, Rao, VA. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. *Am J Neuroradiol.* (2010) 31:1192–6. doi: 10.3174/ajnr.A2050
5. Sun C, Li X, Song B, Chen X, Nyame L, Liu Y, et al. A NADE nomogram to predict the probability of 6-month unfavorable outcome in Chinese patients with ischemic stroke. *BMC Neurol.* (2019) 19:274. doi: 10.1186/s12883-019-1464-6
6. Tsai CF, Brenda T, Sudlow C. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. *Neurology.* (2013) 81:264–72. doi: 10.1212/WNL.0b013e31829bfde3
7. Qian F, Fonarow GC, Smith EE, Xian Y, Pan W, Hannan EL, et al. Racial and ethnic differences in outcomes in older patients with acute ischemic stroke. *Circ Cardiovasc Qual Outcomes.* (2013) 6:284–92. doi: 10.1161/CIRCOUTCOMES.113.000211
8. Kumar N, Khera R, Pandey A, Garg N. Racial differences in outcomes after acute ischemic stroke hospitalization in the united states. *J Stroke Cerebrovasc Dis.* (2016) 25:1970–7. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.049
9. Xian Y, Holloway RG, Noyes K, Shah MN, Friedman B. Racial differences in mortality among patients with acute ischemic stroke: an observational study. *Ann Intern Med.* (2011) 54:152–9. doi: 10.7326/0003-4819-154-3-201102010-00004
10. Kamal H, Lopez V, Sheth SA. Machine learning in acute ischemic stroke neuroimaging. *Front Neurol.* (2018) 9:945. doi: 10.3389/fneur.2018.00945
11. Goldstein BA, Navar AM, Carter RE. Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. *Eur Heart J.* (2017) 38:1805–14. doi: 10.1093/eurheartj/ehw302
12. Meyer A, Zverinski D, Pfahringer B, Kempfert J, Kuehne T, Sündermann SH, et al. Machine learning for real-time prediction of complications in critical care: a retrospective study. *Lancet Respir Med.* (2018) 6:905–14. doi: 10.1016/S2213-2600(18)30300-X
13. Goto T, Jo T, Matsui H, Fushimi K, Hayashi H, Yasunaga H. Machine learning-based prediction models for 30-day readmission after hospitalization for chronic obstructive pulmonary disease. *COPD.* (2019) 16:338–43. doi: 10.1080/15412555.2019.1688278
14. Deo RC. Machine learning in medicine. *Circulation.* (2015) 132:1920–30. doi: 10.1161/CIRCULATIONAHA.115.001593
15. Wolpert DH. *The Supervised Learning No-Free-Lunch Theorems. Soft Computing and Industry*. London: Springer (2002). p. 25–42. doi: 10.1007/978-1-4471-0123-9_3
16. Montazeri M, Montazeri M, Montazeri M, Beigzadeh A. Machine learning models in breast cancer survival prediction. *Technol Health Care.* (2016) 24:31–42. doi: 10.3233/THC-151071
17. Garg R, Prabhakaran S, Holl JL, Luo Y, Faigle R, Kording K, et al. Improving the accuracy of scores to predict gastrostomy after intracerebral hemorrhage with machine learning. *J Stroke Cerebrovasc Dis.* (2018) 27:3570–4. doi: 10.1016/j.jstrokecerebrovasdis.2018.08.026
18. Churpek MM, Yuen TC, Winslow C, Meltzer DO, Kattan MW, Edelson DP. Multicenter comparison of machine learning methods and conventional regression for predicting clinical deterioration on the wards. *Crit Care Med.* (2016) 44:368–74. doi: 10.1097/CCM.0000000000001571
19. Nishi H, Oishi N, Ishii A, Ono I, Ogura T, Sunohara T, et al. Predicting clinical outcomes of large vessel occlusion before mechanical thrombectomy using machine learning. *Stroke.* (2019) 50:2379–88. doi: 10.1161/STROKEAHA.119.025411
20. Abedi V, Goyal N, Tsivgoulis G, Hosseinichimeh N, Hontecillas R, Bassaganya-Riera J, et al. Novel screening tool for stroke using artificial neural network. *Stroke.* (2017) 48:1678–81. doi: 10.1161/STROKEAHA.117.017033
21. Liggins JTP, Yoo AJ, Mishra NK, Wheeler HM, Straka M, Leslie-Mazwi TM, et al. A score based on age and DWI volume predicts poor outcome following endovascular treatment for acute ischemic stroke. *Int J Stroke.* (2015) 10:705–9. doi: 10.1111/ijs.12207
22. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology.* (2012) 78:1916–22. doi: 10.1212/WNL.0b013e318259e221
23. Rudin C. Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. *Nat. Mach. Intellig.* (2019) 1:206–15. doi: 10.1038/s42256-019-0048-x
24. Caruana R, Niculescu-Mizil, A. An empirical comparison of supervised learning algorithms. In: *Proceedings of the 23rd International Conference on Machine Learning* (Pittsburgh, PA: ACM) (2006). p. 161–8. doi: 10.1145/1143844.1143865
25. Flint AC, Faigeles BS, Cullen SP, Kamel H, Rao VA, Gupta R, et al. THRIVE score predicts ischemic stroke outcomes and thrombolytic hemorrhage risk in VISTA. *Stroke.* (2013) 44:3365–9. doi: 10.1161/STROKEAHA.113.002794
26. Rocco A, Heuschmann PU, Schellinger PD, Köhrmann M, Diedler J, Sykora M, et al. Glycosylated hemoglobin A1 predicts risk for symptomatic hemorrhage after thrombolysis for acute stroke. *Stroke.* (2013) 44:2134–8. doi: 10.1161/STROKEAHA.111.675918
27. Nugroho AW, Arima H, Miyazawa I, Fujii T, Miyamatsu N,Sugimoto Y, et al. The association between glomerular filtration rate estimated on admission and acute stroke outcome: the Shiga stroke registry. *J Atheroscler Thromb.* (2018) 23:570–9. doi: 10.5551/jat.42812
28. Yang J, Arima H, Zhou J, Zhao Y, Li Q, Wu G, et al. Effects of low estimated glomerular filtration rate on outcomes after stroke: a hospital-based stroke registry in China. *EurJ Neurol.* (2014) 21:1143–5. doi: 10.1111/ene.12311
29. Cappellari M, Turcato G, Forlivesi S, Micheletti N, Tomelleri G, Bonetti B, et al. Introduction of direct oral anticoagulant within 7 days of stroke

onset: a nomogram to predict the probability of 3-month modified Rankin scale score> 2. *J Thromb Thrombolysis.* (2018) 46:292–8. doi: 10.1007/s11239-018-1700-8

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Optimizing Patient Selection for Interhospital Transfer and Endovascular Therapy in Acute Ischemic Stroke: Real-World Data From a Supraregional, Hub-and-Spoke Neurovascular Network in Germany

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Background: Interhospital transfer for endovascular treatment (EVT) within neurovascular networks might result in transfer of patients who will not undergo EVT (futile transfer). Limited evidence exists on factors associated with the primary patient selection for interhospital transfer from primary stroke centers (PSCs) to comprehensive stroke centers (CSCs), or EVT-workflow parameters that may render a transfer futile.

Methods: A prospective, registry-based study was performed between July 1, 2017 and June 30, 2018, at a hub-and-spoke neurovascular network in southwest Germany, comprising 12 referring PSCs and one designated CSC providing round-the-clock EVT at the University Hospital Tübingen. Patients with acute ischemic stroke due to suspected large artery occlusion (LAO) were included upon emergency interhospital transfer inquiry (ITI).

Results: ITI was made for 154 patients, 91 (59%) of whom were transferred to the CSC. Non-transferred patients (41%) had significantly higher premorbid modified Rankin scale scores (mRS) compared to transferred patients [median (IQR): 2 (1–3) vs. 0 (0–1), $p < 0.001$]. Interhospital transfer was denied due to: distal vessel occlusion (44.4%), or non-verifiable LAO (33.3%) in computed tomography angiography (CTA) upon teleconsultation by CSC neuroradiologists; limited Stroke-Unit or ventilation capacity (9.5%), or limited neuroradiological capacity at the CSC (12.7%). The CT-to-ITI interval was significantly longer in patients denied interhospital transfer [median (IQR): 43 (29–56) min] compared to transferred patients [29 (15–55), $p = 0.029$]. No further differences in EVT-workflow, and no differences in the 3-month mRS outcomes were

noted between non-transferred and transferred patients [median (IQR): 2 (0–5) vs. 3 (1–4), $p = 0.189$]. After transfer to the CSC, 44 (48%) patients underwent EVT. The Alberta stroke program early CT score [ORadj (95% CI): 1.786 (1.573–2.028), $p < 0.001$] and the CT-to-ITI interval [0.994 (0.991–0.998), $p = 0.001$] were significant predictors of the likelihood of EVT performance.

Conclusion: Our findings show that hub-and-spoke neurovascular network infrastructures efficiently enable access to EVT to patients with AIS due to LAO, who are primarily admitted to PSCs without on-site EVT availability. As in real-world settings optimal allocation of EVT resources is warranted, teleconsultation by experienced endovascular interventionists and prompt interhospital-transfer-inquiries are crucial to reduce the futile transfer rates and optimize patient selection for EVT within neurovascular networks.

Keywords: endovascular therapy, recanalization, acute ischemic stroke, neurovascular network, mechanical thrombectomy

INTRODUCTION

Endovascular recanalization therapy (EVT) has become standard of care in acute ischemic stroke (AIS) due to large artery occlusion (LAO) (1). The recent expansion of the therapeutic EVT time window, following the publication of the Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) (2) and the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) (3) trial results, has led to a substantial increase in the number of EVT-eligible patients. In the face of rising healthcare demands, an optimal allocation of EVT resources—especially when EVT is provided within extended hub-and-spoke neurovascular networks—is warranted.

Currently, the operational workflow in most supraregional neurovascular networks (4, 5) entails acute AIS management, including administration of intravenous thrombolysis, at primary stroke centers (PSCs) followed by emergency interhospital patient transfer to comprehensive stroke centers (CSCs) when EVT is required. Although a growing number of studies have dealt with reasons for unsuccessful EVT in patients transferred from PSCs to CSCs (i.e., the "drip-and-ship" strategy) (6) compared to patients directly transferred to the nearest CSC (i.e., the "mothership" strategy) (7, 8), little is known regarding factors that determine the decision-making processes for patient-transfer within neurovascular networks. As current EVT registries, including the German Stroke Registry Endovascular Treatment (GSR-ET) (9, 10), only capture data of transferred patients with intention-to-treat with EVT at the CSCs, real-world evidence on patient selection for interhospital transfer are lacking.

Here we sought to identify factors associated with the primary patient selection following the request for emergency interhospital transfer for EVT within a large, supraregional neurovascular network. We aimed to evaluate the neurovascular network's capacity and operational workflow, and analyze factors associated with the decision to perform EVT, along with EVT and clinical outcomes in non-transferred and transferred patients. We hypothesized that data analyses of our prospective registry would yield results that contribute to quality improvement, enhancing the efficiency of decision-making and acute AIS care within the neurovascular network.

METHODS

Patient level data was acquired from prospective databases and transfer records from a hub-and-spoke neurovascular network in southwest Germany (Centre for neurovascular diseases Tübingen; "Zentrum für neurovaskuläre Erkrankungen Tübingen": ZNET), comprising 12 referring PSCs and one designated CSC, that provides round-the-clock EVT at the University Hospital Tübingen. Consecutive patients presenting to PSCs, between July 1, 2017 and June 30, 2018, with AIS due to suspected LAO were included in the study upon emergency inter-hospital transfer inquiry (ITI) for EVT.

According to the ZNET standard operating procedures, and in line with operational protocols of supraregional neurovascular networks covering large rural and semi-rural areas (5), stroke patients were primarily admitted to the nearest PSC without bypassing hospitals by the ambulance service. Initial computed tomography (CT) imaging, including non-contrast CT (NCT) and CT angiography (CTA), was performed at the PSCs and eligible AIS patients underwent on-site intravenous thrombolysis. Adhering to the EVT guidelines in force at the time the study was conducted (1), ITI was made when a patient was considered eligible for EVT (with or without prior intravenous thrombolysis), according to the "drip-and-ship" paradigm. Eligibility criteria for ITI within the ZNET included: (a) anterior circulation LAO, within 6 h of symptom onset; (b) posterior circulation LAO, within 24 h of symptom onset; (c) any LAO in wake-up AIS or AIS with unknown symptom onset, and Alberta stroke program early CT score (ASPECTS) >6 (11). Non-accessible vessel occlusion was determined to include occlusions distal to the M2 segment, or any anterior or posterior cerebral

artery segment. In the presence of contraindications for CTA that could cause significant delays in patient transfer (e.g., contrast agent allergy, potentially requiring patient stabilization after CTA), ITI could be made based on NCT when a patient presented with severe neurological deficits (12) and/or hyperdense artery sign on NCT (13). Evaluation of ITI followed on a case-by-case basis after assessment of clinical parameters, including premorbid modified Rankin scale (pmRS) score and National Institutes of Health Stroke Scale (NIHSS) score on admission. A telemedicine consultation was performed by a team of senior stroke neurologists and interventional neuroradiologists at the CSC, based on the real-time transmitted, cloud-based CT imaging data. If emergency patient transfer was decided, ambulance crew was recruited for air or road transport, on the principle of fastest-available-route for secondary transportation to the CSC. If emergency transfer within the ZNET was denied due to limited CSC Stroke Unit/Neurological ICU (NICU), ICU ventilation or neuroradiological (i.e., endovascular suite) capacity, ITI for emergency patient transfer to other neighboring hospitals with EVT availability was decided on individual basis. For patients transferred to the study CSC, CT imaging was performed on admission (o/a), including NCT, CTA, and CT perfusion (CTP) with cerebral blood flow (CBF) and cerebral blood volume (CBV) perfusion maps. Presence of concomitant vessel stenosis was diagnosed based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (14). CBF-CBV mismatch was visually assessed as described previously (2, 3). The final decision for EVT was made based on clinical and imaging findings by an interdisciplinary team of senior stroke neurologists and interventional neuroradiologists.

Based on the decisions to "ship" and perform EVT, 3 AIS patient groups were analyzed: (a) No-transfer group: Patients for whom ITI was made, but no transfer followed; (b) No-EVT group: transferred patients, who were considered unsuitable for EVT o/a to the CSC; (c) EVT group: transferred patients, who underwent EVT. Analysis was performed to determine clinical characteristics and process-related factors, including the time metrics: Symptom-onset-to-PSC-CT, Symptom-onset-to-intravenous-thrombolysis and PSC-CT-to-ITI, that could be associated with the decision to "ship." For transferred patients, the time metrics PSC-CT-to-CSC-CT and CSC-CT-to-groin were also analyzed. Revascularization success was evaluated based on final angiograms. Successful recanalization was defined as modified treatment in cerebral infarction (mTICI) score $\geq$ 2b−3 for anterior circulation LAO (15) or Arterial Occlusive Lesion scale score = 3 for posterior circulation LAO (16). Clinical outcome was assessed by mRS at 90 days after the index event by phone calls or outpatient visits. If mRS 90 was not available, the mRS at discharge was carried forward.

The study was approved by the institutional ethics committee (Ethics Committee at the University Hospital of Tübingen, protocol number 767/2018BO2). Individual informed consent was waived for this study, since use of routine treatment data for research purposes is covered by a clinic-wide consent.

STATISTICAL ANALYSES

Differences between baseline variables in patient demographics and clinical characteristics were assessed using chi-square tests or two-tailed independent-sample Mann–Whitney *U* tests (due to non-normal distribution) depending on data characteristics, i.e., categorical vs. continuous variables, respectively. In the first part of the analysis, all observations were included. Patients for whom ITI was made, but no transfer followed comprised the "no-transfer group." Transferred patients, who were unsuitable for EVT ("No-EVT group") and patients, who underwent EVT ("EVT group"), jointly comprised the "transfer group." Analysis was performed to determine clinical characteristics, imaging parameters and process-related factors associated with the decision to "ship." A multiple regression analysis was conducted to assess the relationship between time metrics that were significantly different between transferred and non-transferred patients (i.e., PSC-CT-to-ITI time) and relevant patient characteristics (including age, pmRS, NIHSS o/a to the PSC, and presence of distal vessel occlusion).

In the second part of the analysis, differences in group characteristics were examined between the "No-EVT" and "EVT" patient groups. Analysis was performed to determine factors associated with the decision to perform EVT. A logistic regression analysis was used to calculate the odds of EVT performance including covariates significantly different at baseline or considered clinically relevant (i.e., PSC-CT-to-ITI time and ASPECTS). A Pearson product-moment correlation was run to determine the relationship between PSC-CT-to-ITI time and ASPECTS. We calculated the "Number-needed-to-ship" (NNS), defined as the number of patients needed to transfer to the CSC during the study period for one patient to undergo EVT (NNS=number of transferred patients/number of EVT patients).

In the third part of the analysis, EVT and clinical outcomes at 3 months (mRS) after the index event were analyzed as described previously. The significance level for all procedures was determined as $p < 0.05$. All statistical analyses were computed with IBM SPSS Statistics v.23 (IBM, NY, USA).

RESULTS

Comparison of Patients Denied Interhospital Transfer (No-Transfer Group) vs. Patients Transferred to the CSC With Intention-to-Treat With EVT (Transfer Group)

During the study period, emergency ITI for EVT was made for a total of 154 patients, who presented with AIS due to suspected LAO in 12 referring PSCs. Of those, 63 patients (41%), who were denied transfer to the CSC comprised the "no-transfer group" vs. 91 patients (59%), who were transferred to the CSC with intention-to-treat with EVT and comprised the "transfer group."

TABLE 1 | Baseline characteristics of non-transferred vs. transferred patients.

Patient Characteristics	All ($n = 154$)	Non-transferred ($n = 63$)	Transferred ($n = 91$)	p-Values
Age, median (IQR)	77 (66–84)	80 (64–86)	75 (66–83)	0.199[§]
Female, n (%)	84 (54.5)	35 (55.6)	49 (53.8)	0.834[#]
PSC Hospitals				
Distance in km, median (IQR)	47 (18–61)	47 (18–61)	47 (18–61)	0.182[§]
Baseline Parameters				
NIHSS o/a, median (IQR)	11 (5–16)	9 (3–15)	13 (5–17)	0.074[§]
pmRS, median (IQR)	0 (0–2)	2 (1–3)	0 (0–1)	<0.001*[§]
ASPECTS at PSC, median (IQR)	10 (10–10)	10 (10–10)	10 (10–10)	0.378[§]
Stroke time metrics and management				
i.v. Thrombolysis, *n* (%)	84 (54.5)	21 (33.3)	63 (69.2)	<0.001*[#]
Onset-to-thrombolysis, median (IQR)	98 (72–133)	85 (73–131)	100 (71–135)	0.790[§]
Symptom-onset-to-CT in min, median (IQR)	69 (54–118)	72 (57–128)	67 (52–91)	0.115[§]
CTA within 15 min, *n* (%)	106 (68.8)	43 (68.3)	63 (69.2)	0.950[#]
PSC-CT-to-ITI in min, median (IQR)	37 (23–55)	43 (29–56)	29 (15–55)	0.029*[§]
ITI between 8 a.m. and 8 p.m., *n* (%)	65 (42.2)	25 (39.7)	40 (44)	0.893[#]
Baseline CT imaging				
Extracranial Stenosis NASCET above 70%, *n* (%)	10 (6.5)	2 (3.2)	8 (8.8)	0.164[#]
Extracranial Occlusion, *n* (%)	18 (11.7)	6 (9.5)	12 (13.2)	0.487[#]
Intracranial Occlusion, *n* (%)	119 (77.3)	36 (57.1)	83 (91.2)	<0.001*[#]
Cervical ICA Occlusion, *n* (%)	19 (12.3)	5 (7.9)	14 (15.4)	0.167[#]
Intracranial ICA Occlusion with Carotid-T, *n* (%)	7 (4.5)	1 (1.6)	6 (6.6)	0.148[#]
Intracranial ICA Occlusion without Carotid-T, *n* (%)	4 (2.6)	0 (0)	4 (4.4)	0.092[#]
Tandem occlusion ICA/MCA, *n* (%)	14 (9.1)	1 (1.6)	13 (14.3)	0.007*[#]
Proximal M1 Occlusion, *n* (%)	55 (35.7)	3 (4.8)	52 (57.1)	<0.001*[#]
Distal M1 Occlusion, *n* (%)	24 (15.6)	9 (14.3)	15 (16.5)	0.712[#]
M2 Occlusion, *n* (%)	31 (20.1)	18 (28.6)	13 (14.3)	0.030*[#]
Extracranial VA Occlusion, *n* (%)	1 (0.6)	0 (0)	1 (1.1)	0.404[#]
BA Occlusion, *n* (%)	9 (5.8)	1 (1.6)	8 (8.8)	0.061[#]
PCA Occlusion, *n* (%)	10 (6.5)	10 (15.9)	0 (0)	<0.001*[#]
Infratentorial Occlusion, *n* (%)	12 (7.8)	1 (1.6)	11 (12.1)	0.017*[#]
Vessel Tortuosity, *n* (%)	39 (25.3)	18 (28.6)	21 (23.1)	0.441[#]

[§]*Mann–Whitney U tests.*

[#]*Chi-Square tests.*

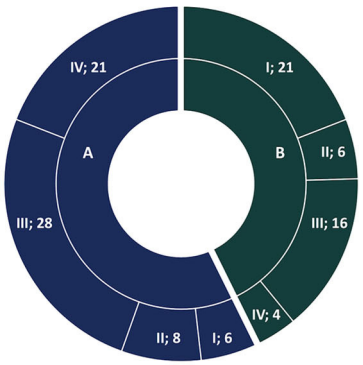
**Denotes significance $p < 0.05$.*

IQR, interquartile range; PSC, Primary stroke center; NIHSS, National Institutes of Health Stroke Scale; pmRS, premorbid modified Rankin scale score; ASPECTS, Alberta stroke program early CT score; ITI, interhospital transfer inquiry; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery.

Patients' characteristics at baseline are depicted in **Table 1**.

No statistically significant differences with respect to age, gender, or cardiovascular risk factors existed in non-transferred vs. transferred patients (**Supplementary Material**). Baseline NIHSS scores o/a to the PSCs were similar between groups, but non-transferred patients had significantly higher pmRS scores compared to transferred patients [median (IQR): 2 (1–3) vs. 0 (0–1), $p < 0.001$]. Significantly more transferred patients underwent intravenous thrombolysis compared to non-transferred patients ($p < 0.001$). The reasons for withholding intravenous thrombolysis included significantly higher rates of combined dual antiplatelet and direct oral anticoagulants (DOAC) in non-transferred patients ($p = 0.031$) and higher frequencies of demarcated ischemia o/a or admission outside the 4.5-h time window among non-transferred (25.4%) compared to transferred (13.2%) patients ($p = 0.053$) (**Supplementary Material**). In the subgroup of patients who underwent thrombolysis, the Symptom-onset-to-intravenous-thrombolysis time (in min) was similar between groups.

The reasons against interhospital transfer for the "no-transfer group" group are summarized in **Figure 1**. Six (9.5%) patients were denied interhospital transfer due to limited bed capacity at NICU or ICU ventilation capacity at the CSC, and 8 (12.7%) patients were denied transfer due to limited neuroradiological capacity. Upon teleconsultation, 28 (44.4%) patients were denied transfer due to non-accessible (i.e., distal)



	Arguments against IT (Group A) or EVT (Group B)	number	% of total	% of subgroup	
I	NICU or ICU capacity	6	5	10	Group A (n=63)
II	Interventional neuroradiology capacity	8	7	13	
III	Site of vascular occlusion not reachable	28	25	44	
IV	No LAO verifiable	21	19	33	
I	ASPECTS <6	21	19	45	Group B (n=47)
II	Site of vascular occlusion not reachable	6	5	13	
III	Spontaneous/post-thrombolysis vessel recanalization	16	15	34	
IV	No LAO verifiable	4	4	8	

Abbreviations: IT: Interhospital transfer; EVT: endovascular therapy; (N)ICU: (Neurological) Intensive Care Unit; LAO: large artery occlusion; ASPECTS: Alberta stroke programme early CT score.

FIGURE 1 | Reasons against interhospital patient transfer or endovascular therapy (EVT) in non-transferred and transferred patients who did not undergo EVT, respectively. In each diagram section, the number of patients is denoted next to the argument category for non-transferred (blue) or transferred no-EVT (green) patients, e.g., I; 6 denotes that point I (absent NICU or ICU capacity) was the reason against interhospital transfer (IT) in 6 non-transferred patients.

vessel occlusion. In 21 (33.3%) cases the suspicion of underlying LAO in CTA could not be verified by the CSC neuroradiologists on teleconsultation.

No significant between-group differences were noted with respect to the geographical distance (in km) between the PSCs and CSC, and no biases in patient selection were detected when the rates of non-transferred vs. transferred patients were compared for each referring PSC (**Supplementary Material**). Also, no between-group differences existed concerning the rates of non-transferred vs. transferred patients, based on whether ITI was made during (or outside) working hours (i.e., between 8:00 a.m. and 8:00 p.m.).

Regarding procedural parameters, PSC-CT-to-ITI time (in min) was significantly prolonged in non-transferred compared to transferred patients [median (IQR): 43 (29–56) vs. 29 (15–55), $p = 0.029$]. The equation of the multiple regression analyses, that assessed the relationship between PSC-CT-to-ITI time and patient characteristics, including age, pmRS, NIHSS o/a to the PSC, and presence of distal vessel occlusion, was significant $F(4, 73) = 3.407$, $p = 0.013$, with an $R^2 = 0.157$. Advanced age ($b = 0.251$, $p = 0.032$) and higher pmRS ($b = 0.229$, $p = 0.047$) were significantly associated with prolonged PSC-CT-to-ITI time, while NIHSS o/a to the PSC ($b = -0.002$, $p = 0.990$) and distal vessel occlusion ($b = 0.055$, $p = 0.628$) were not related to the PSC-CT-to-ITI time. Symptom-onset-to-PSC-CT (in min) and ASPECT scores were comparable between groups. Although the rates of CTA performance were similar between groups, only 69% of all patients underwent CTA within 15 min after NCT.

With respect to the site of vessel occlusion, significantly more patients in the "transfer group" had intracranial occlusion ($p < 0.001$), tandem occlusion [i.e., internal carotid artery (ICA) and middle cerebral artery (MCA)] ($p = 0.007$), proximal M1 occlusion ($p < 0.001$) and infratentorial vessel occlusion ($p = 0.017$). Contrarily, significantly more patients from the "no-transfer group" had M2 occlusions ($p = 0.03$) and posterior cerebral artery (PCA) occlusions ($p < 0.001$).

Comparison of Patients Considered Ineligible for EVT After Interhospital Transfer (No-EVT Group) vs. Patients Who Underwent EVT (EVT Group)

Among the 91 patients transferred to the CSC, 47 (52%) patients were considered ineligible for EVT and comprised the "No-EVT group" vs. 44 (48%) patients, who underwent EVT and comprised the "EVT group." Accordingly, the NNS was 2 (=91 transferred patients/44 EVT patients). Patients' characteristics are depicted in **Table 2**.

No significant between-group differences with respect to age, gender, cardiovascular risk factors and comorbidities, NIHSS o/a to the CSC and pmRS scores were noted (**Supplementary Material**). The rates of intravenous thrombolysis and the Symptom-onset-to-intravenous-thrombolysis time (in min) in patients who underwent thrombolysis were similar between No-EVT and EVT patients.

The reasons against EVT performance for the No-EVT group are summarized in **Figure 1**. Twenty-one (44.7%) patients were considered ineligible for EVT due to ASPECTS < 6 o/a to the CSC, and 6 (12.8%) patients were considered ineligible for EVT due to distal vessel occlusion. In 16 (34%) cases no LAO existed o/a to the CSC, either due to spontaneous recanalization or recanalization following intravenous thrombolysis, and in 4 (8.5%) cases no LAO could be verified upon arrival at the CSC [in cases where no CTA had been performed at the PSCs and interhospital transfer was decided based on severity of neurological deficits—with NIHSS ≥ 14 (12) and/or hyperdense artery sign on NCT (13)].

No significant between-group differences were noted with respect to the geographical distance (in km) between the

TABLE 2 | Baseline characteristics of No-EVT (ineligible for EVT) vs. EVT patients.

Patient characteristics	All ($n = 91$)	No-EVT ($n = 47$)	EVT ($n = 44$)	p-values
Age, median (IQR)	75 (66–83)	74 (66–82)	76 (66–83)	0.812[§]
Female, *n* (%)	49 (53.8)	26 (55.3)	23 (52.3)	0.771[#]
PSC Hospitals				
Distance in km, median (IQR)	47 (18–61)	47 (33–61)	47 (18–61)	0.752[§]
Air-transportation, *n* (%)	16 (17.6)	8 (17.0)	8 (18.2)	0.884[#]
Baseline Parameters				
NIHSS at CSC, median (IQR)	5 (1–13)	6 (1–16)	5 (2–11)	0.659[§]
pmRS, median (IQR)	0 (0–1)	0 (0–1)	0 (0–0)	0.071[§]
ASPECTS at CSC, median (IQR)	9 (7–10)	7 (5–10)	10 (9–10)	0.001*[§]
Stroke time metrics and management				
i.v. Thrombolysis, *n* (%)	63 (69.2)	31 (66.0)	32 (72.7)	0.484[#]
Onset-to-thrombolysis, median (IQR)	100 (71–135)	100 (75–130)	90 (60–149)	0.577[§]
Symptom-onset-to-CT in min, median (IQR)	67 (52–91)	70 (54–83)	67 (46–143)	0.625[§]
CTA within 15 min, *n* (%)	63 (69.2)	32 (68.1)	31 (70.5)	0.679[#]
PSC-CT-to-ITI in min, median (IQR)	43 (24–65)	43 (30–86)	41 (19–59)	0.001*[§]
PSC-CT-to-CSC-CT in min, median (IQR)	125 (97–159)	125 (96–161)	125 (96–160)	0.704[§]
CT Imaging at CSC				
CTP Mismatch, *n* (%)	56 (61.5)	13 (27.7)	43 (97.7)	<0.001*[#]
Extracranial Stenosis NASCET above 70%, *n* (%)	8 (8.8)	3 (6.4)	5 (11.4)	0.402[#]
Extracranial Occlusion, *n* (%)	12 (13.2)	9 (19.1)	3 (6.8)	0.082[#]
Intracranial Occlusion, *n* (%)	83 (91.2)	39 (83.0)	44 (100)	0.004*[#]
Cervical ICA Occlusion, *n* (%)	14 (15.4)	11 (23.4)	3 (6.8)	0.028*[#]
Intracranial ICA Occlusion with Carotid-T, *n* (%)	6 (6.6)	5 (10.6)	1 (2.3)	0.108[#]
Intracranial ICA Occlusion without Carotid-T, *n* (%)	4 (4.4)	0 (0)	4 (9.1)	0.035*[#]
Tandem Occlusion ICA/MCA, *n* (%)	13 (14.3)	8 (17.0)	5 (11.4)	0.441[#]
Proximal M1 Occlusion, *n* (%)	52 (57.1)	27 (57.4)	25 (56.8)	0.952[#]
Distal M1 Occlusion, *n* (%)	15 (16.5)	5 (10.6)	10 (22.7)	0.120[#]
M2 Occlusion, *n* (%)	13 (14.3)	9 (19.1)	4 (9.1)	0.171[#]
Extracranial VA Occlusion, *n* (%)	1 (1.1)	1 (2.1)	0 (0)	0.331[#]
BA Occlusion, *n* (%)	8 (8.8)	5 (10.6)	3 (6.8)	0.520[#]
PCA Occlusion, *n* (%)	0 (0)	0 (0)	0 (0)	–
Infratentorial Occlusion, *n* (%)	11 (12.1)	8 (17.0)	3 (6.8)	0.136[#]
Vessel Tortuosity, *n* (%)	21 (23.1)	16 (34.0)	5 (11.4)	0.010*[#]

[§] *Mann-Whitney U tests;* [#] *Chi-Square tests,* [*] *denotes significance p<0.05.*

IQR, interquartile range; PSC, Primary stroke center; NIHSS, National Institutes of Health Stroke Scale; CSC, Comprehensive stroke center; pmRS, premorbid modified Rankin scale score; ASPECTS, Alberta stroke program early CT score; ITI, interhospital transfer inquiry; CTP, CT perfusion; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery.

PSCs and CSC or the type of transportation (air or road transport). Also, no biases in patient selection were detected when the rates of EVT were compared for each referring PSC (**Supplementary Material**).

Regarding procedural parameters, PSC-CT-to-ITI time (in min) was significantly prolonged in the No-EVT compared to the EVT group [median (IQR): 43 (30–86) vs. 41 (19–59), $p = 0.001$]. Symptom-onset-to-PSC-CT (in min) and PSC-CT-to-CSC-CT (in min) were comparable between groups. Similar rates in CTA performance within 15 min after NCT (at the PSC) were observed between groups. Significantly higher ASPECT scores (at the CSC) were noted in the EVT compared to the No-EVT group [median (IQR): 10 (9–10) vs. 7 (5–10), $p = 0.001$]. The rates of CTP mismatch were significantly higher in the EVT compared to the No-EVT group ($p < 0.001$).

With respect to the site of vessel occlusion, significantly more patients in the EVT group had intracranial occlusion ($p = 0.004$) or intracranial ICA occlusion without occlusion of the carotid-T ($p = 0.035$). Contrarily, significantly more No-EVT patients had cervical ICA occlusions ($p = 0.028$) and vessel tortuosity in the CTA ($p = 0.01$).

Predictors for Decision to Perform EVT After Patient Transfer to the CSC

The logistic regression model for assessment of the effect of ASPECT score o/a to the CSC and the PSC-CT-to-ITI

time (in min) on the likelihood of EVT performance was statistically significant, $\chi^2(2) = 148.7$, $p < 0.001$. The model explained 34.1% (Nagelkerke's R^2) of the variance in EVT performance and correctly classified 71.6% of the cases (no multicollinearity was noted, tolerance = 0.946, VIF = 1.057). Higher ASPECT score [adjusted OR (ORadj) (95% CI): 1.786 (1.573–2.028), $p < 0.001$] was significantly associated with higher likelihood of EVT performance. Conversely, longer PSC-CT-to-ITI [0.994 (0.991–0.998), $p = 0.001$] was significantly associated with lower likelihood of EVT performance o/a to the CSC. A significant negative correlation was noted between PSC-CT-to-ITI time and ASPECTS o/a to the CSC ($r = -0.233$, $p < 0.001$).

EVT Outcomes and Functional Outcome at 3 Months After AIS

Recanalization was achieved in 39 (88%) of EVT patients. Secondary intracerebral hemorrhage after EVT was noted in 7 (16%) patients. In terms of functional outcome at 90 days after the index event, after exclusion of patients with spontaneous recanalization o/a to the CSC, no significant differences were noted between No-EVT and EVT patients [median (IQR): 4 (2–5) vs. 3 (2–4), $p = 0.138$]. A subgroup analysis of patients with M1-occlusions revealed significant differences of functional outcome at 90 days, with No-EVT patients having higher mRS at 90 days compared to the EVT group [median (IQR): 5 (4–5) vs. 3 (2–4), $p = 0.003$]. No significant between-group differences in functional outcome at 90 days existed for the subgroups of patients with M2 occlusions ($p = 0.352$) and cervical ICA occlusions ($p = 0.209$). Also, no significant differences were noted in mRS outcome at 90 days between non-transferred and transferred patients [median (IQR): 2 (0–5) vs. 3 (1–4), $p = 0.189$].

DISCUSSION

We analyzed the operational workflow of EVT implementation and AIS service organization within a large, supraregional neurovascular network. Our findings indicate that the current infrastructures efficiently enable access to EVT for patients with AIS due to LAO, who are primarily admitted to PSCs without on-site EVT availability (5). During the study period, the majority (59%) of patients for whom emergency request for interhospital transfer was made were admitted to the CSC with intention-to-treat with EVT, 69.2% of whom underwent intravenous thrombolysis at the PSCs. Among non-transferred patients, interhospital transfer was denied due to inaccessible (i.e., distal) vessel occlusion or non-verifiable LAO upon teleconsultation in 44.4 and 33.3% of the cases, respectively. These results corroborate the role that PSCs hold in primary AIS care, including intravenous thrombolysis administration, and in candidate selection for EVT (4). Also, taking into consideration the finite EVT resources within high-volume neurovascular networks, these data emphasize the real-world significance of prompt teleconsultation by experienced interventionalists prior to interhospital patient transfers.

Since limited NICU/ICU or neuroradiological capacity at the CSC were the reasons against interhospital transfer in 9.5 and 12.7% of non-transferred patients, respectively, we investigated workflow parameters, including procedural time metrics, that could be optimized to improve resource allocation within the neurovascular network. Our results showed similar Symptom-onset-to-PSC-CT and Symptom-onset-to-intravenous-thrombolysis times between non-transferred and transferred patients. However, the PSC-CT-to-ITI times (i.e., the intervals spanning between CT performance and ITI) were significantly longer in patients denied interhospital transfer compared to transferred patients, while prolonged PSC-CT-to-ITI time was associated with advanced patient age and higher pmRS. These findings strongly suggest that, in clinical practice, workflow optimization may play a catalytic role in patient selection. In accord with previous real-world thrombectomy studies (4), our results underline the importance of early-on time-metrics monitoring, along with the need for regular training interventions (17) for workflow improvement starting from the stages of primary patient admission to the PSCs.

With respect to imaging studies, although no differences were noted in the CTA performance rates between non-transferred and transferred patients, only 69% of all patients admitted with AIS to the PSCs underwent CTA within 15 min of NCT. CTA delays comprise a detrimental, but modifiable factor when it comes to identification of patients that may benefit from EVT (18). Since multimodal CT imaging, including NCT, CTA and PCT, does not delay acute AIS management (19, 20), the integration of uniform AIS imaging protocols in the standard operating procedures of neurovascular networks is pivotal.

Within the study hub-and-spoke neurovascular network, we operationalized a quality assurance framework evaluating to what extent patient selection for interhospital transfer was aligned with contemporary EVT guidelines. In line with current EVT recommendations (21), non-transferred patients had higher premorbid mRS scores compared to transferred patients. Additionally, more non-transferred patients had distal (i.e., M2 and PCA) occlusions compared to transferred patients, whereas transferred patients had more frequently extracranial, vertebrobasilar, and proximal intracranial (i.e., M1) occlusions. Although these findings are in accordance with current EVT guidelines (1, 21), regular adjustment of patient selection criteria is warranted to ensure prompt translation of EVT research advances into clinical practice. Evidence from the MR CLEAN registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), for example, recently showed that prestroke-dependent patients can benefit from EVT to a similar extent as prestroke-independent patients (22). Additionally, EVT in distal vessel occlusion has recently become possible by use of modern EVT devices (23). Continuous adjustment of neurovascular networks' organization is, hence, imperative to facilitate up-to-date AIS care.

Comparing the interhospital transfer and EVT performance rates among transferred patients from the various referring PSCs, no biases in patient selection were detected. Although most EVT registries have, so far, neglected non-transferred patients (9), acquisition of pre-transfer data is crucial, especially in terms of assessment of PSCs' access to EVT and healthcare policy-making within neurovascular networks. Among transferred patients, the transportation times were comparable between patients excluded from EVT and EVT patients. These findings demonstrate that within the study neurovascular network timely access to EVT is facilitated for patients referred from the various PSCs.

During the study period, we found a NNS ("Number-needed-to-ship") of 2, as 48% of transferred patients underwent EVT, whereas 52% were considered ineligible for EVT o/a to the CSC. In the majority (44.7%) of patients who were considered ineligible for EVT, ASPECTS was <6 o/a to the CSC, while absence of LAO o/a to the CSC or inaccessible vessel occlusion accounted for the remaining number of excluded cases. These results are comparable with data published from other EVT registries, reporting rates of futile transfers of 45% (6). We consider NNS an important measure for assessment of a neurovascular networks' efficiency in primary patient selection and performance across all stages of EVT implementation (i.e., with lower NNS indicating accurate primary patient selection at the PSCs, well-regulated interhospital transfer and patient selection for EVT at the CSC).

Consequently, we investigated factors associated with the NNS. Our analyses revealed that prolonged PSC-CT-to-ITI time is associated with significantly lower ASPECTS o/a to the CSC and significantly reduces the odds of EVT performance (i.e., thereby increasing the NNS). Conversely, higher ASPECTS was significantly associated with the decision to perform EVT. Since a large proportion of transferred patients (44.7%) were excluded from EVT o/a to the CSC due to ASPECTS < 6, we hypothesize that adjunctive neuroprotective therapies, such as hyperbaric oxygenation (24), during primary care at the PSCs or during interhospital transfer could improve NNS. This hypothesis is currently being tested in a randomized clinical trial at the study CSC (ClinicalTrials.gov Identifier: NCT03500939).

Regarding EVT outcomes, successful recanalization was achieved in 88% of EVT patients, a rate that is within the upper range of rates reported from large EVT trials and registries (15, 25–27). Among transferred patients, patients who underwent EVT had a trend for better functional outcome at 3 months after the index event compared to patients excluded from EVT. Yet, this difference was significant only in the subgroup of patients presenting with M1 occlusion, favoring patients who underwent EVT. The 3-month functional outcomes in our study are also comparable to those obtained from studies evaluating the "drip-and-ship" over the "mothership" strategy (6), which suggest comparable clinical outcomes in patients undergoing mechanical thrombectomy according to the "drip-and-ship" or the "mothership" model (28), especially for PSCs located at considerable distance from the CSCs (29). Since at group level, however, the high recanalization rates in our study were not equally reflected in clinical outcome improvement, further research in patient selection for EVT is warranted. Finally, the comparable 3-month clinical outcomes between transferred and non-transferred patients support the efficiency of patient selection for interhospital transfer, i.e., with both patient groups receiving optimal care resulting in comparable outcomes despite the fact that transferred patients initially presented with more severe strokes in the presence of LAO. In non-transferred patients, underlying stroke etiologies other than LAO, including small vessel disease [i.e., which is associated with good functional outcome after stroke (30)], and distal vessel occlusions [i.e., which due to thrombus characteristics tend to respond to intravenous thrombolysis (31)] may further account for the comparable functional outcomes between groups.

Limitations

We acknowledge possible limitations of the present study. First, as the present data were derived from a single neurovascular network with variable referral processes of the cooperating PSCs, additional real-world evidence is required to evaluate the generalizability of our results. Second, although the available time metrics reflect to a large extent the procedural stages involved in EVT implementation, monitoring of further time metrics [e.g., PSC-door-in-door-out and PSC-door-to-CSC-door times (4)] should be operationalized within neurovascular networks. Third, due to the limited number of patients in this study, data integration in predictive algorithms was not possible. Nonetheless, real-world data assimilation in predictive-decision models is crucial in order to improve patient selection, decision making over optimal transportation strategy (i.e., "drip-and-ship" over the "mothership") and resource allocation within neurovascular networks (7).

CONCLUSION

In conclusion, we provide evidence that the hub-and-spoke neurovascular network infrastructures efficiently enable access to EVT to patients with AIS due to LAO, who are primarily admitted to PSCs without on-site EVT availability. Our findings have important implications for neurovascular networks' service organization, as they point out that operational workflow should be monitored and optimized across all stages of EVT implementation, starting from the stages of primary admission to the PSCs. In particular, our findings show that delays in interhospital-transfer-inquiries can majorly compromise patient selection for interhospital transfer and render a transfer futile. Due to the crucial role of teleconsultation in real-world settings, major effort should be directed toward establishing uniform AIS imaging protocols across neurovascular networks, including multimodal CT imaging, to facilitate appropriate patient selection for EVT. Finally, regular auditing and training interventions are warranted to improve resource allocation within high-volume neurovascular networks.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee at the University Hospital of Tübingen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM and M-IS conceived the present study. AM, VS, DB, and M-IS acquired the data, analyzed/interpreted the data, and drafted the manuscript. FH and UE acquired the neuroradiological data and critically reviewed the manuscript. UZ and SP supervised and critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.600917/full#supplementary-material

REFERENCES

1. Sacks D, Baxter B, Campbell BCV, Carpenter JS, Cognard C, Dippel D, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke: from the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO). *J Vasc Interv Radiol*. (2018) 29:441–53. doi: 10.1016/j.jvir.2017.11.026
2. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
3. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
4. Ng FC, Low E, Andrew E, Smith K, Campbell BCV, Hand PJ, et al. Deconstruction of interhospital transfer workflow in large vessel occlusion: real-world data in the thrombectomy era. *Stroke*. (2017) 48:1976–9. doi: 10.1161/STROKEAHA.117.017235
5. Feil K, Remi J, Kupper C, Herzberg M, Dorn F, Kunz WG, et al. Drip and ship for mechanical thrombectomy within the Neurovascular Network of Southwest Bavaria. *Neurology*. (2020) 94:e453–63. doi: 10.1212/WNL.0000000000008753
6. Sablot D, Dumitrana A, Leibinger F, Khlifa K, Fadat B, Farouil G, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: analysis of a 6-year prospective registry. *J Neurointerv Surg*. (2019) 11:539–44. doi: 10.1136/neurintsurg-2018-014206
7. Schlemm L, Endres M, Scheitz JF, Ernst M, Nolte CH, Schlemm E. Comparative evaluation of 10 prehospital triage strategy paradigms for patients with suspected acute ischemic stroke. *J Am Heart Assoc*. (2019) 8:e012665. doi: 10.1161/JAHA.119.012665
8. Schlemm L, Endres M, Nolte CH. Bypassing the closest stroke center for thrombectomy candidates: what additional delay to thrombolysis is acceptable? *Stroke*. (2020) 51:867–75. doi: 10.1161/STROKEAHA.119.027512
9. Alegiani AC, Dorn F, Herzberg M, Wollenweber FA, Kellert L, Siebert E, et al. Systematic evaluation of stroke thrombectomy in clinical practice: The German Stroke Registry Endovascular Treatment. *Int J Stroke*. (2019) 14:372–80. doi: 10.1177/1747493018806199
10. Wollenweber FA, Tiedt S, Alegiani A, Alber B, Bangard C, Berrouschot J, et al. Functional outcome following stroke thrombectomy in clinical practice. *Stroke*. (2019) 50:2500–6. doi: 10.1161/STROKEAHA.119.026005
11. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. (2001) 22:1534–42.
12. Scheitz JF, Abdul-Rahim AH, MacIsaac RL, Cooray C, Sucharew H, Kleindorfer D, et al. Clinical selection strategies to identify ischemic stroke patients with large anterior vessel occlusion: results from SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry). *Stroke*. (2017) 48:290–7. doi: 10.1161/strokeaha.116.014431
13. Mair G, Boyd EV, Chappell FM, von Kummer R, Lindley RI, Sandercock P, et al. Sensitivity and specificity of the hyperdense artery sign for arterial obstruction in acute ischemic stroke. *Stroke*. (2015) 46:102–7. doi: 10.1161/strokeaha.114.007036
14. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. (1998) 339:1415–25. doi: 10.1056/NEJM199811123392002
15. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. (2013) 44:2650–63. doi: 10.1161/STROKEAHA.113.001972
16. Jung C, Yoon W, Ahn SJ, Choi BS, Kim JH, Suh SH. the revascularization scales dilemma: is it right to apply the treatment in cerebral ischemia scale in posterior circulation stroke? *AJNR Am J Neuroradiol*. (2016) 37:285–9. doi: 10.3174/ajnr.A4529

17. Bohmann FO, Kurka N, du Mesnil de Rochemont R, Gruber K, Guenther J, Rostek P, et al. Simulation-based training of the rapid evaluation and management of acute stroke (STREAM)—a prospective single-arm multicenter trial. *Front Neurol.* (2019) 10:969. doi: 10.3389/fneur.2019.00969
18. Douglas V, Shamy M, Bhattacharya P. Should CT angiography be a routine component of acute stroke imaging? *Neurohospitalist*. (2015) 5:97–8. doi: 10.1177/1941874415588393
19. Salottolo KM, Fanale CV, Leonard KA, Frei DF, Bar-Or D. Multimodal imaging does not delay intravenous thrombolytic therapy in acute stroke. *AJNR Am J Neuroradiol*. (2011) 32:864–8. doi: 10.3174/ajnr.A2394
20. Bal S, Menon BK, Demchuk AM, Hill MD. Routine CT angiography in acute stroke does not delay thrombolytic therapy. *Can J Neurol Sci*. (2012) 39:499–501. doi: 10.1017/s0317167100014025
21. Mokin M, Ansari SA, McTaggart RA, Bulsara KR, Goyal M, Chen M, et al. Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee. *J Neurointerv Surg*. (2019) 11:215–20. doi: 10.1136/neurintsurg-2018-014640
22. Goldhoorn RB, Verhagen M, Dippel DWJ, van der Lugt A, Lingsma HF, Roos Y, et al. Safety and outcome of endovascular treatment in prestroke-dependent patients. *Stroke*. (2018) 49:2406–14. doi: 10.1161/STROKEAHA.118.022352
23. Grossberg JA, Rebello LC, Haussen DC, Bouslama M, Bowen M, Barreira CM, et al. Beyond large vessel occlusion strokes: distal occlusion thrombectomy. *Stroke*. (2018) 49:1662–8. doi: 10.1161/STROKEAHA.118.020567
24. Poli S, Baron JC, Singhal AB, Hartig F. Normobaric hyperoxygenation: a potential neuroprotective therapy for acute ischemic stroke? *Expert Rev Neurother*. (2017) 17:1131–4. doi: 10.1080/14737175.2017.1376657
25. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
26. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
27. Heider DM, Simgen A, Wagenpfeil G, Dietrich P, Yilmaz U, Muhl-Benninghaus R, et al. Why we fail: mechanisms and co-factors of unsuccessful thrombectomy in acute ischemic stroke. *Neurol Sci*. (2020) 41:1547–55. doi: 10.1007/s10072-020-04244-5
28. Adams KM, Burns PA, Hunter A, Rennie I, Flynn PA, Smyth G, et al. Outcomes after thrombectomy in belfast: mothership and drip-and-ship in the real world. *Cerebrovasc Dis*. (2019) 47:231–7. doi: 10.1159/000500849
29. Milne MS, Holodinsky JK, Hill MD, Nygren A, Qiu C, Goyal M, et al. Drip 'n ship versus mothership for endovascular treatment: modeling the best transportation options for optimal outcomes. *Stroke*. (2017) 48:791–4. doi: 10.1161/STROKEAHA.116.015321
30. Mustanoja S, Meretoja A, Putaala J, Viitanen V, Curtze S, Atula S, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: descriptive subtype analysis. *Stroke*. (2011) 42:102–6. doi: 10.1161/strokeaha.110.597534
31. Seners P, Turc G, Maïer B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: a systematic review and meta-analysis. *Stroke*. (2016) 47:2409–12. doi: 10.1161/strokeaha.116.014181

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Reduced Impact of Endovascular Thrombectomy on Disability in Real-World Practice, Relative to Randomized Controlled Trial Evidence in Australia

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Background and Aims: Disability-adjusted life years (DALYs) are an important measure of the global burden of disease that informs patient outcomes and policy decision-making. Our study aimed to compare the DALYs saved by endovascular thrombectomy (EVT) in the Australasian-based EXTEND-IA trial vs. clinical registry data from EVT in Australian routine clinical practice.

Methods: The 3-month modified Rankin scale (mRS) outcome and treatment status of consecutively enrolled Australian patients with large vessel occlusion (LVO) stroke were taken from the International Stroke Perfusion Imaging Registry (INSPIRE). DALYs were calculated as the summation of years of life lost (YLL) due to premature death and years lived with a disability (YLD). A generalized linear model (GLM) with gamma family and log link was used to compare the difference in DALYs for patients receiving/not receiving EVT while controlling for key covariates. Ordered logit regression model was utilized to compare the difference in functional outcome at 3 months between the treatment groups. Cox regression analysis was undertaken to compare the difference in survival over an 18-year time horizon. Estimated long-term DALYs saved based on the EXTEND-IA randomized controlled trial (RCT) results were used as the comparator.

Results: INSPIRE patients who received EVT treatment only achieved nominally better functional outcomes than the non-EVT group ($p = 0.181$) at 3 months. There was no significant survival gain from EVT over the first 3 months of stroke in both INSPIRE and EXTEND-IA patients. However, measured against no EVT in the long-term, EVT in INSPIRE was associated with no significant survival gain [hazard ratio (HR): 0.92, 95% confidence interval (CI): 0.78–1.08, $p = 0.287$] compared with the survival benefit

extrapolated from the EXTEND-IA trial (HR: 0.42, 95% CI: 0.22–0.82, $p = 0.01$]. Offering EVT to patients with LVO stroke was also associated with fewer DALYs lost (11.04, 95% CI: 10.45–11.62) than those not receiving EVT in INSPIRE (12.13, 95% CI: 11.75–12.51), a reduction of −1.09 DALY (95% CI: −1.76 to −0.43, $p = 0.002$). The absolute magnitude of the treatment effect was lower than that seen in EXTEND-IA (−2.72 DALY reduction in EVT vs non-EVT patients).

Conclusions: EVT for the treatment of LVO in a registry of routine care was associated with significantly lower DALYs lost than medical care alone, but the saved DALYs are less than those reported in clinical trials, as there were major differences in the baseline characteristics of the patients.

Keywords: thrombectomy, disability adjusted life year (DALY), INSPIRE registry, real-world data analysis, randomized controlled clinical trial (RCT)

INTRODUCTION

Endovascular thrombectomy (EVT) is associated with significantly improved disability-free survival compared with the previous standard of care, intravenous thrombolysis (IVT) (1–6). One of these positive normal time window EVT trials, EXTEND-IA, in which selection by perfusion imaging demonstration of "target mismatch" was mandatory, reported that EVT led to a doubling of the number of people living disability free (generalized odds ratio (OR) 2.0, 95% confidence interval (CI): 1.2–3.8, $p = 0.006$ on ordinal analysis of modified Rankin scale (mRS) score) (6). However, analysis based on routine clinical practice following implementation of trial evidence is not always the same as that observed in randomized controlled trials (RCTs). Patients may be treated outside of the strict trial criteria. For example, most trials of EVT had an age limit for inclusion. In a real-world study, elderly patients who received EVT experienced higher rates of hemorrhage (40.7 vs. 9.3%, $p < 0.001$) without significantly improved functional outcomes than a matched medical management cohort (7). A previous study that examined the Disability-adjusted life years (DALYs) lost based on the EXTEND-IA RCT, which utilized perfusion imaging selection to identify patients with large vessel occlusion (LVO) stroke for EVT, reported that EVT led to significantly fewer lifetime DALYs lost than non-EVT (−2.72 DALY, $p = 0.02$) (8). However, DALY estimation from this study may not be generalizable to real-world practice as perfusion imaging selection (or the criteria if performed) for EVT is not rigidly adhered to (or not performed at all in some countries).

DALYs were developed to measure the relative and total global burden of all diseases using a common metric, which integrates both mortality (years of life lost (YLL) due to premature death) and morbidity (years of healthy life lost due to living with a disability) (9). As an important metric of disease burden, the DALYs can be used as the basis for resource allocation and priority setting for stroke prevention, evidence-based healthcare planning for acute stroke management, and post-stroke rehabilitation services (10). They have been referenced extensively in global health debates and decision-making (11). DALYs can reveal the likely impact of stroke on a patient over their remaining lifetime rather than at a single time point. Stroke, as the leading cause of adult disability in Australia and worldwide, leads to significantly more DALYs lost (116.4 million) annually than coronary heart disease (82 million) (12, 13).

Even though there is controversy around the use of DALYs as an outcome measure (14), they remain an important index to quantify the disease burden (15). Given the important role that DALYs play in informing policy decision-making, this study aims to improve the evidence based on comparing the DALYs saved from EVT in LVO stroke patients with LVO to assess the impact of the implementation of EVT into routine clinical care compared with the benefits reported in EXTEND-IA in Australia. Other important clinical outcomes including 3-month mRS score and overall survival were also analyzed and compared.

METHODS

Study Population

We accessed the International Stroke Perfusion Imaging Registry (INSPIRE), a registry of patients with stroke, to source the baseline and 90-day clinical and imaging data for all Australian patients with LVO defined as occlusions of the internal carotid artery (ICA) and proximal segment (M1, M2) of the middle cerebral artery over a 5-year period (2015–2019), regardless of the baseline characteristics (e.g., volume of infarct core, etc.) (16, 17). Routine multimodal computed tomography (CT: non-contrast CT, perfusion CT, and CT angiography) was performed on patients presenting with acute neurological deficits. Eligible patients received thrombolysis prior to EVT. In routine clinical practice, EVT is offered to patients with (i) the presence of a LVO that is potentially retrievable, (ii) reasonable pre-stroke function (mRS 0–3), and (iii) limited medical comorbidities. In particular, if the patient was within 6 h of onset, perfusion imaging criteria, such as used in EXTEND-IA, was not used to exclude patients from therapy. Unless contraindicated, magnetic resonance imaging (MRI) at 24 h post-stroke was standard practice, in which case repeat imaging was carried out with multimodal CT. The National Institute of Health Stroke Severity (NIHSS), the primary index for stroke severity, was assessed

immediately before treatment and 24 h imaging. In INSPIRE, 24-h Thrombolysis in Cerebral Infarction (TICI) Score is adopted as reperfusion grades with 2b−3 being successful reperfusion (18). All patients were assessed at 90 days post-stroke onset for functional outcome using the mRS.

Written informed consent for participation in the study was provided by all the patients. The Hunter New England Area Health Service Human Research Ethics Committee reviewed and approved the study protocol in 2012.

Estimation of DALY

A DALY is calculated as the summation of two components: YLL due to premature death and years lived with a disability (YLD). Lower DALYs indicate more disability-free life years after the index stroke (one DALY indicates 1 year of disability-free life lost).

YLL due to premature death are calculated as the difference in life expectancy of an age-, sex-matched person from the general Australian population and a stroke patient in a certain mRS category. Patients post-stroke have a higher hazard ratio (HR) of dying from all-cause mortality determined by their mRS score at 3 months. All-cause mortality of the general Australian population for each age and gender was adjusted by the corresponding HR to estimate the life expectancy for patients with stroke (19). The life table for the general Australian population and the formula to recalculate the life expectancy for stroke patients were sourced from the Australian Bureau of Statistics (ABS) (20).

YLD are calculated by multiplying the life expectancy of a stroke patient by a disability weight. The disability weights based on mRS score were sourced from the study by Hong and Saver (21). In the base case, DALYs were not adjusted by age weight nor discounted, in accordance with the recommendation of the World Health Organization (19). However, in the sensitivity analysis, DALYs were discounted at an annual rate of 3%, and age weighting was applied to examine the robustness of base case results (19). Using individual patient-level data from INSPIRE, DALYs (and the two components—YLL and YLD) were calculated for each patient based on their 3-month mRS score. The detailed calculations are provided in the **Supplementary Document**.

Statistical Analysis

Descriptive analysis was undertaken of the baseline characteristics of Australian patients receiving EVT vs. no EVT using INSPIRE data and compared with their respective groups in the Australasian-based EXTEND-IA trial. EXTEND-IA was selected as the comparator since it offers the optimal comparability of EVT/no EVT patients with INSPIRE, by reporting the long-term DALY outcome using patient-level data and comparing patients treated in the same centers and similar medical systems by the same healthcare providers across the country. Differences in baseline characteristics within INSPIRE and between INSPIRE and EXTEND-IA were tested using *T*-test or Wilcoxon rank-sum test depending on the distribution of the variable (22). Within INSPIRE, (i) ordered logit regression model was utilized to compare the difference in functional outcome at 3 months between the treatment groups (23); (ii) Cox regression model (survival analysis) was undertaken to explore the difference in the projected survival over 18 years (from 3-month post-stroke onset) between the two treatment groups (8). These analyses were also performed in a subgroup of patients with intracranial ICA or M1 occlusions as this is the group with the strongest evidence of benefit from thrombectomy. Eighteen years were considered sufficient to capture the difference in survival in the current study given the older age of many stroke patients. The time-to-death for each individual was extracted from the reconstructed life table for patients with stroke but was censored at 18 years post the index stroke. Where a patient died due to stroke (mRS = 6) prior to month 3, they were assigned the maximal survival of 3 months. In the Cox regression model, onset age, gender, baseline NIHSS, baseline infarct core volume, and baseline penumbra volume were adjusted, which are in line with the analysis from EXTEND-IA. Survival gain and DALYs saved due to EVT within INSPIRE were compared with similar outcomes (i.e., survival and DALYs saved from both EVT and no EVT treatment groups) estimated from EXTEND-IA (6).

To estimate the difference in DALYs, YLL and YLD between the two treatment groups, a generalized linear model (GLM) with gamma distribution and log link was adopted given the non-normal distribution of the DALY and its two components. The selection of gamma distribution and link function was informed by a modified Park test and link test (24). DALY was the dependent variable, whereas the treatment status, onset age, gender (male/female), time from stroke onset to hospital arrival (min), baseline NIHSS, baseline penumbra volume, and IVT treatment (Y/N) were entered as covariates. DALYs saved (i.e., between-group difference in DALYs) due to EVT from INSPIRE and EXTEND-IA were directly compared. To further test the difference in DALYs lost within INSPIRE by age, onset age was also coded as a dummy variable and was included in the GLM analysis. Bootstrapping with 2,000 iterations was undertaken to further examine the robustness of results from GLM analysis. All the analyses were performed using the STATA V16 statistical package (StataCorp 2019, Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX, USA) and Microsoft Excel.

RESULTS

Study Populations

In total, from INSPIRE, 178 LVO patients (mean age of 69.7 years, 53% male) received EVT vs. 584 LVO patients (mean age of 71.9 years, 52% male) who had medical treatment alone during the study period (2015–19). The age distribution of patients from the two treatment groups is shown in **Supplementary Figure 1**. The median baseline NIHSS was 16 and 15 in the two groups with similar interquartile ranges (IQRs). The baseline core volume was not significantly different between the two groups, whereas patients who received EVT had significantly higher penumbra volume at baseline (88 ml in the EVT group vs. 68 ml in the non-EVT group, $p < 0.001$). Approximately 48.3% of patients in the EVT group had thrombolysis prior to EVT compared with 59.3% in the non-EVT group, and 83% of patients received EVT within 6 h of stroke onset. Patients who received EVT

treatment only achieved nominally better functional outcomes than the non-EVT group ($p = 0.181$) at 3 months and when controlled for both time from stroke onset to hospital arrival and successful reperfusion at 24 h (i.e., TICI 2b/3), and the results were consistent ($p = 0.382$). Baseline characteristics and 3-month mRS outcomes of the study population are summarized in **Table 1** and **Supplementary Figure 2**. Three-month mRS outcomes for subgroups with ICA or M1 occlusions, provided in **Supplementary Table 1**, show that EVT was associated with significantly better functional outcomes than patients not receiving EVT ($p = 0.017$).

In comparison, the EXTEND-IA RCT recruited patients with a mean age of 69 years (SD = 12), median NIHSS score of 15 (IQR: 12–19), and 49% males (6). The median baseline core and perfusion lesion volumes were 12 vs. 18 ml and 106 vs. 115 ml in the EVT and no EVT treatment groups, respectively. Generally, patients receiving EVT in both INSPIRE and EXTEND-IA were comparable in terms of some key baseline characteristics. However, there were proportionally less patients with M2 occlusions offered EVT, higher proportion with large infarct core (thus smaller proportion with target mismatch), and longer time from stroke onset to hospital arrival in INSPIRE.

TABLE 1 | Baseline characteristics of the LVO study population from INSPIRE and EXTEND-IA.

	INSPIRE		EXTEND-IA RCT	
	EVT (*N* = 178)	**No EVT (*N* = 584)**	**EVT (*N* = 35)**	**No EVT (*N* = 35)**
Age (mean, SD)	69.7 (14.76)	71.9 (13.52)	68.6 (12.3)	70.2 (11.8)
Male gender (*N*, %)	95 (53.4%)	301 (51.5%)	17 (49%)	17 (49%)
Baseline NIHSS (median, IQR)	16 (11–21)	15 (10–18)	17 (13–20)	13 (9–19)
Baseline core volume (median, IQR)	18 (7–36)	18 (7–40)	12 (4–32)	18 (4–29)
Perfusion lesion volume (median, IQR)	112 (74–151)	83 (49–133)	106 (76–137)	115 (72–158)
Treatment type (*N*, %)				
EVT + tPA	86 (48.3%)	0	35 (100%)*	0
EVT only	92 (51.7%)	0	0	0
tPA only	0	346 (59.3%)	0	35 (100%)
Target mismatch	156 (87.6%)	452 (77.4%)	100%	100%
Core volume ≥70 ml	11 (6.2%)	68 (11.6%)	0%	0%
Median time from onset to hospital arrival	95 (43–148)	112 (53–171)	78 (54–112)	80 (56–115)
Median time from onset to tPA	156 (120–187)	171 (127–211)	127 (93–162)	145 (105–180)
Successful reperfusion (*N*, %)	90 (74.4%)**	242 (53.7%)**	35 (100%)	13 (37%)
Occlusion site (*N*, %)				
ICA	53 (29.8%)	151 (25.9%)	11 (31%)	11 (31%)
M1	115 (64.6%)	310 (53.1%)	20 (57%)	18 (51%)
M2	10 (5.6%)	123 (21.0%)	4 (11%)	6 (17%)
Three-month mRS				
mRS 0	27 (15.2%)	93 (15.9%)	9 (26%)	6 (17%)
mRS 1	39 (21.9%)	96 (16.4%)	9 (26%)	4 (11%)
mRS 2	19 (10.7%)	68 (11.6%)	7 (20%)	4 (11%)
mRS 3	41 (23.0%)	76 (13.0%)	6 (17%)	4 (11%)
mRS 4	15 (8.4%)	85 (14.6%)	1 (3%)	6 (17%)
mRS 5	8 (4.5%)	60 (10.3%)	0 (0%)	4 (11%)
mRS 6	29 (16.3%)	106 (18.2%)	3 (9%)	7 (20%)

Age, gender, baseline NIHSS, volumes of infarct core and perfusion lesion, and occlusion locations are not significantly different for patients who received EVT between INSPIRE and EXTEND-IA participants.

**On the basis of intention-to-treat principle; **57 patients in the EVT and 133 patients in the no EVT group did not have the 24-h TICI outcome. The proportion of successful reperfusion was significantly different between the EVT and no EVT groups within INSPIRE ($p < 0.0001$).*

Baseline core volume, perfusion lesion volume, and penumbra volume are expressed in ml.

EVT, endovascular thrombectomy; IQR, interquartile range; SD, standard deviation; ICA, internal carotid artery; tPA, tissue plasminogen activator.

Survival Analysis

Based on the published HR of mortality by mRS score for stroke patients, the Cox regression model showed that INSPIRE EVT was associated with nominally reduced probability of death (HR: 0.92, 95% CI: 0.78–1.08, $p = 0.287$, **Figure 1**). Older age, being male, and higher baseline volume of baseline infarct core contributed to decreased probability of survival ($p < 0.05$), whereas baseline NIHSS ($p = 0.146$) was not statistically significant for the probability of survival (**Supplementary Table 2**). The subgroup analysis including patients with ICA or M1 occlusions suggested that EVT led to a reduced probability of mortality (HR: 0.82, 95% CI: 0.71–0.96, $p = 0.012$) with older age, male gender, and higher baseline NIHSS accounting for lowered probability of survival (**Supplementary Figure 3**).

The long-term estimation based on the EXTEND-IA data reported that EVT was associated with a better probability of survival with a HR of 0.42 (95% CI: 0.22–0.82, $p = 0.01$) than corresponding controls with no EVT (8).

DALYs Lost

EVT in INSPIRE LVO patients was associated with fewer DALYs lost (11.04, 95% CI: 10.45–11.62) than those not receiving EVT (12.13, 95% CI: 11.75–12.51) or a difference in reduction of 1.09 DALYs (95% CI: −1.76 to −0.43, $p = 0.002$). Similar results were also observed for YLL and YLD, with corresponding avoided YLL of −0.68 (95% CI: −1.18−0.18, $p = 0.009$) and YLD of −0.47 (95% CI: −0.98 to 0.03, $p = 0.074$). The raw distribution of DALYs by treatment groups is presented in **Supplementary Figure 4**. In the scenario where the age weighting and discounting were applied, the difference in DALYs saved was smaller (as future life years were discounted) (**Table 2**). The unadjusted difference in EXTEND-IA DALYs was 2.72 ($p = 0.02$) (8). In summary, the between-group difference in DALYs reduction due to EVT was less in the INSPIRE population (1.09 DALY saved) than that in the EXTEND-IA RCT (2.72 DALY saved).

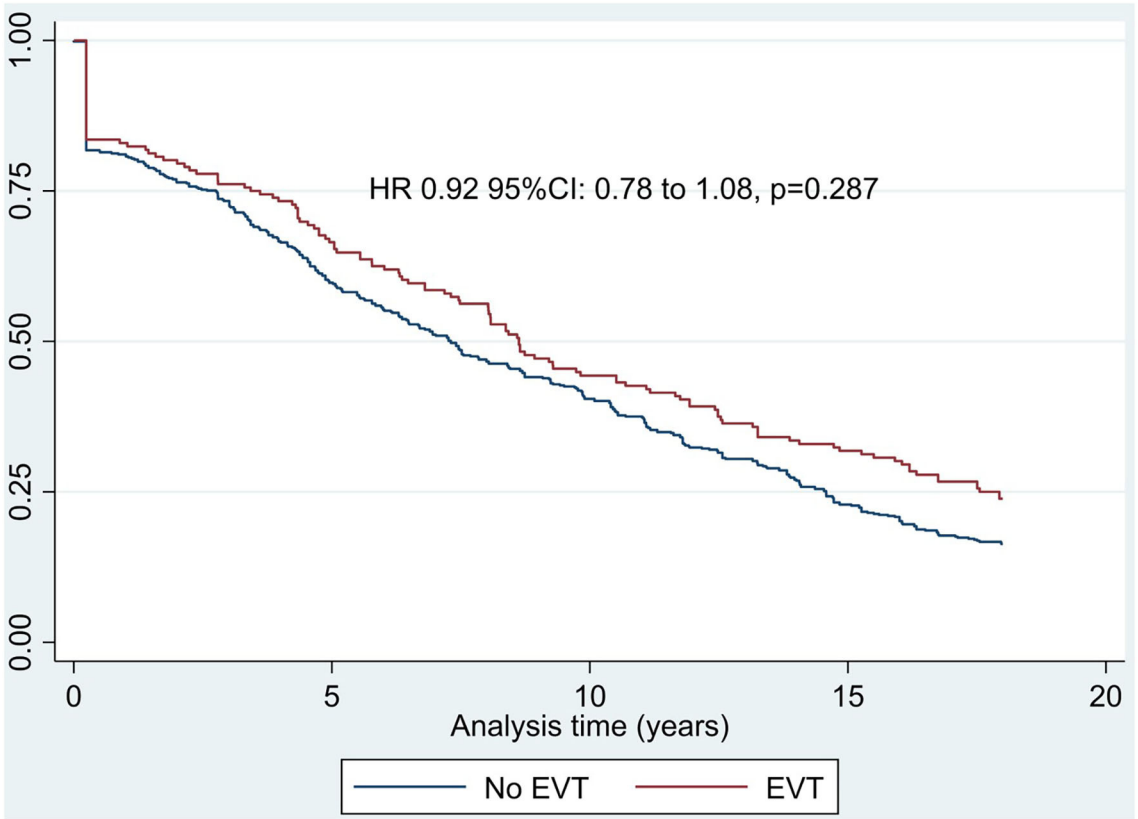

FIGURE 1 | Cox proportional hazards regression for the long-term modeled survival.

TABLE 2 | Results of disability-adjusted life years by endovascular thrombectomy status from INSPIRE and EXTEND-IA.

	INSPIRE				EXTEND-IA RCT			
	YLL		YLD		DALY		DALY	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
EVT	8.77 (8.35, 9.20)	2.61 (2.36, 2.86)	2.66 (2.14, 3.18)	1.74 (1.36, 2.13)	11.04 (10.45, 11.62)	3.96 (3.64, 4.27)	5.5 (3.2, 8.7)	2.0 (0.94, 3.6)
No EVT	9.45 (9.19, 9.72)	2.98 (2.82, 3.14)	3.13 (2.67, 3.60)	2.10 (1.72, 2.47)	12.13 (11.75, 12.51)	4.59 (4.37, 4.81)	8.9 (4.7, 13.8)	3.5 (1.6, 5.8)
Between-group difference	−0.68 (−1.18, −0.18)	−0.37 (−0.67, −0.07)	−0.47 (−0.98, 0.03)*	−0.35 (−0.70, −0.01)	−1.09 (−1.76, −0.43)	−0.63 (−0.99, −0.27)	−2.72 (N.A.)	−1.27 (N.A.)

EVT, endovascular thrombectomy; YLL, years of life lost; YLD, years lived with a disability; DALY, disability-adjusted life year; N.A., not available.
**Not statistically significant (p = 0.074).*

Sensitivity Analysis

The analysis by age group showed that in the INSPIRE population, DALYs saved decreased by age due to the lesser impact on remaining life expectancy (**Figure 2**). The larger difference in DALYs saved −1.90 (95% CI: −3.15 to −0.65) was observed in the youngest age group (<50 years), whereas this difference reduced to −0.57 (95% CI: −0.95 to −0.20) in the oldest age category (>80 years) (**Table 3**).

The bootstrapping revealed results consistent with the base case results from GLM analysis (**Table 4**). The differences in INSPIRE DALYs between the treatment groups were −0.97 (95% CI: −1.60 to −0.34, $p = 0.002$) in the unadjusted analysis and −0.55 (95% CI: −0.88 to −0.23, $p = 0.001$) in the adjusted analysis (**Figure 3**).

DISCUSSION

This study demonstrated that the clinical outcomes of LVO patients who undergo EVT LVO in Australia (i.e., INSPIRE)

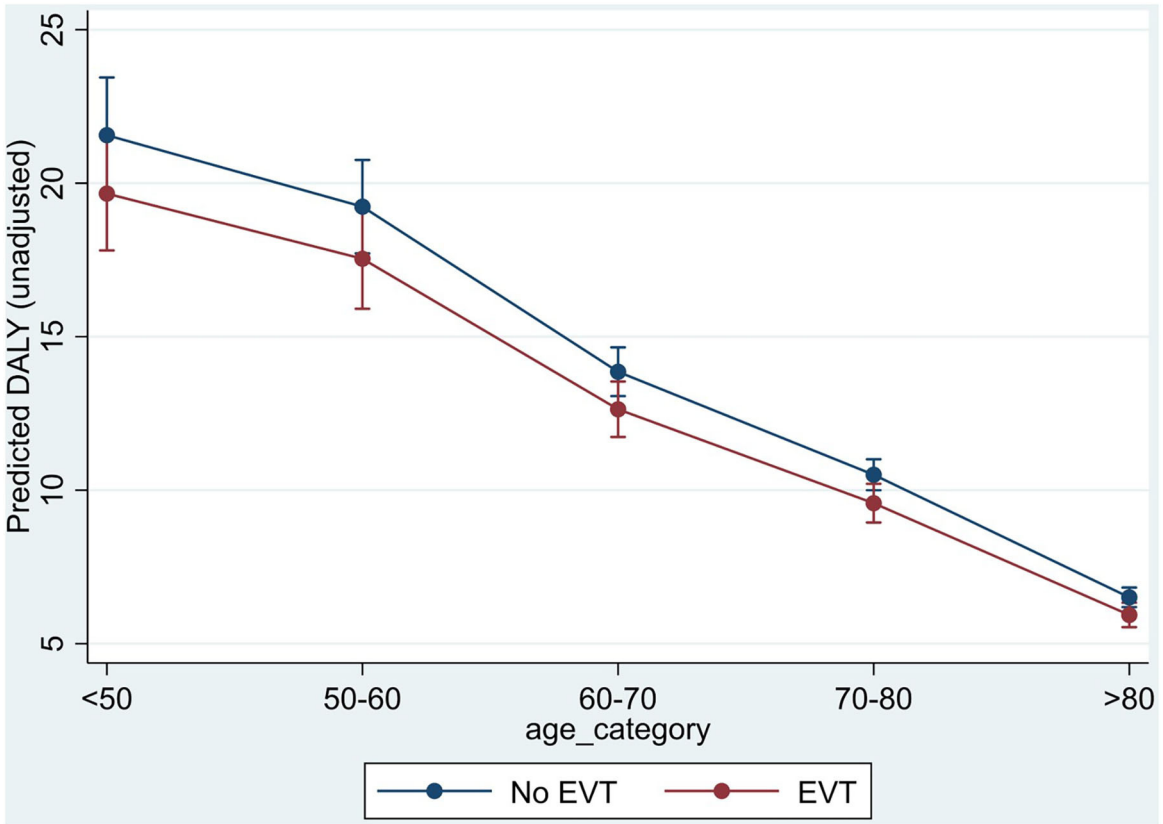

FIGURE 2 | Difference in disability-adjusted life years by age category.

TABLE 3 | Results of disability-adjusted life years by age category from INSPIRE.

Age category	EVT_INSPIRE	No EVT_INSPIRE	Between-group difference (DALY saved)
<50	19.66 (17.81, 21.51)	21.56 (19.68, 23.44)	−1.90 (−3.15, −0.65)
50–60	17.54 (15.91, 19.17)	19.23 (17.71, 20.76)	−1.70 (−2.80, −0.60)
60–70	12.64 (11.73, 13.54)	13.86 (13.06, 14.65)	−1.22 (−2.02, −0.43)
70–80	9.58 (8.95, 10.21)	10.50 (10.00, 11.01)	−0.93 (−1.53, −0.33)
>80	5.94 (5.54, 6.33)	6.51 (6.19, 6.83)	−0.57 (−0.95, −0.20)

EVT, endovascular thrombectomy; DALY, disability-adjusted life year.

resulted in less than half of the DALYs saved compared with those selected for enrollment in EXTEND-IA. However, EVT still resulted in significantly better DALY outcomes than those patients treated with/without thrombolysis in the INSPIRE. The saved INSPIRE DALYs from EVT were greater in the younger age group due to their longer life expectancy. The sensitivity analysis using a bootstrapping technique yielded similar results as the base case analysis with a slightly smaller difference in saved DALYs.

The smaller between-group difference in DALYs saved after EVT in INSPIRE compared with EXTEND-IA occurred despite generally comparable baseline characteristics including age, occlusion site, baseline NIHSS, ischemic core, and perfusion lesion volume (6). The primary reason for the discrepancy is that a higher proportion of patients randomized to EVT in the EXTEND-IA trial achieved much better functional outcomes proportionally at 3 months than observed from the current registry data: over 72% of patients achieved a mRS score $\leq$2, whereas this proportion was only 48% in the real-world data (6), probably due to offering EVT to extended time window patients (i.e., around 17% of patients received EVT beyond 6 h of the normal time window) or patients without a target mismatch (i.e., $\sim$12% of EVT patients did not have a target mismatch, and 6% of patients had a core volume >70 ml) in INSPIRE. Indeed, the outcomes achieved in EXTEND-IA are exceptionally high by any standard and indicate rigorous adherence to computed tomography perfusion (CTP) mismatch criteria, as opposed to MR CLEAN, for example, which did not use CTP selection, and the corresponding 3-month mRS 0–2 was 32.6% (3). It is worth noting that the key driver for the post-stroke survival and DALYs avoided was the HR of mortality according to the 3-month mRS score (i.e., higher mRS score is associated with higher HR in

TABLE 4 | Sensitivity analysis from bootstrapping INSPIRE.

	Unadjusted		Adjusted	
	INSPIRE between-group difference	***p*-value**	**INSPIRE between-group difference**	***p*-value**
YLL	−0.63 (95% CI: −1.12, −0.15)	0.011	−0.36 (95% CI: −0.66, −0.06)	0.018
YLD	−0.27 (95% CI: −0.56, 0.01)	0.063	−0.16 (95% CI: −0.32, −0.00)	0.046
DALY	−0.97 (95% CI: −1.60, −0.34)	0.002	−0.55 (95% CI: −0.88, −0.23)	0.001

YLL, years of life lost; YLD, years lived with a disability; DALY, disability-adjusted life year.

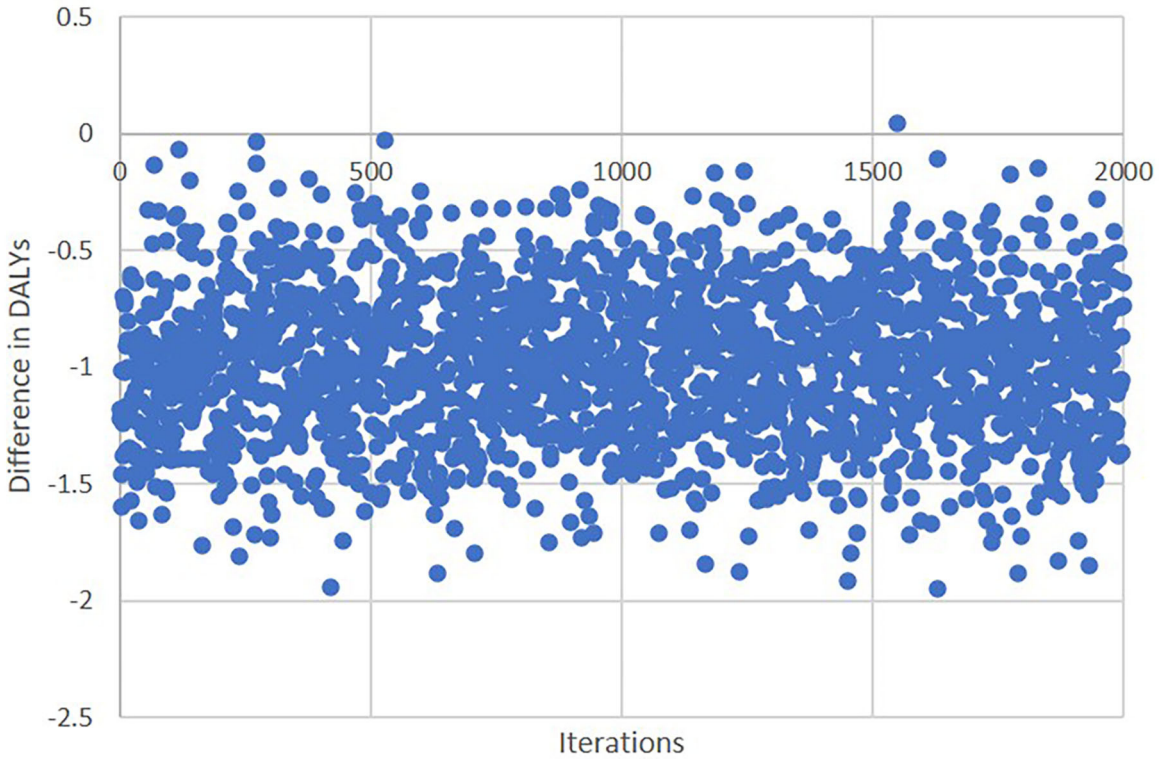

FIGURE 3 | Sensitivity analysis for difference in disability-adjusted life years from bootstrapping.

terms of overall mortality). The substantial difference in the proportion of patients with favorable mRS score (≤2) between the RCT and the real-world post-EVT (i.e., patients with severe disability are more likely to die in the following years than those with mild disability) resulted in the difference in the YLL and subsequently led to increased YLD due to the higher disability weight associated with poorer mRS outcome.

The survival analysis and 3-month outcomes did not show that INSPIRE EVT was significantly better than the no EVT treatment group. However, when restricting the analysis to patients with ICA or M1 occlusion, both analyses suggested that INSPIRE EVT was associated with better probability of survival and mRS outcome. One possible explanation for this is that the non-EVT patients from INSPIRE had the highest proportion of M2 occlusions (21%), whereas INSPIRE EVT patients had the lowest proportion of M2 occlusions (5.6%), in comparison with the proportions from EXTEND-IA (between 11 and 17%). Patients with M2 occlusion inherently have a better prognosis than patients with more proximal occlusion (25). The high proportion of M2 occlusion patients in the no EVT group from INSPIRE probably contributed to the non-significant difference in both survival and 3-month mRS outcomes for EVT vs no EVT in INSPIRE.

This study also showed that younger patients generated greater DALY savings regardless of the treatment received; this is echoed by the significant economic burden of stroke due to young patients primarily due to productivity losses (26–28). The substantial burden of young stroke warrants national policy consideration and a targeted campaign to raise awareness of the disease in this young age group.

Quantification of DALYs from real-life data bears two policy implications: (i) the DALY estimation based on tightly controlled research trial data is not directly generalizable to everyday clinical practice. In the real-world, the selection of patients who receive EVT may not be exactly the same as the eligibility criteria for the trials, which leads to the variation in the functional outcomes. (ii) Resource allocation, guideline formulation, and priority setting in stroke treatment and prevention should preferably be based on real-world data given the potential risk of overestimation of intervention benefit from the trials. In addition, using the incremental cost due to EVT from EXTEND-IA and the DALY reduction between the EVT and no EVT groups from INSPIRE, it was estimated that the incremental cost effectiveness ratio (ICER) was A$8,838 (95% CI: $5,454–$22,726). This result suggests that with the uncertainty considered in the economic analysis, the EVT procedure may not necessarily be cost-effective in some developing countries (i.e., the upper bound of the ICER may well exceed the willingness to pay per DALY threshold).

Our study has several key strengths. Firstly, the analysis was based on routine clinical practice registry data for stroke including both EVT and intravenous alteplase treatment over the past 5 years from most of the states/territories in Australia. However, there is no doubt that this still represents a minority of patients treated with EVT in all Australian centers over the study period. Secondly, INSPIRE participants not only include those who received EVT meeting CTP mismatch criteria from trials, such as EXTEND-IA, but also incorporate a minority of patients outside of these criteria who were treated with EVT at clinicians' discretion. Thirdly, individual patient-level data facilitated the analysis that adjusted for baseline characteristics (age, gender, baseline NIHSS, baseline penumbra volume, and time from stroke onset to hospital arrival) to accurately estimate the difference in DALYs avoided between the two groups. This study, however, is not without limitations. Any recurrent stroke and other cardiovascular events beyond 3 months were not simulated in the long-term when estimating life expectancy. Given these events would impact on the patients from both treatment groups (although it could be argued that patients with better mRS outcome would have lower risk of experiencing follow-up adverse cardiovascular events), this is considered to not favor EVT. Second, the differences in patient characteristics between the INSPIRE and the EXTEND-IA including more patients with large infarct core, absence of target mismatch, and longer time from stroke onset to hospital arrival in INSPIRE may restrict comparability. However, the INSPIRE group represents the experience of EVT and standard care without EVT in the real-world where differences in characteristics do exist for patients from both treatment groups, compared with the two randomized groups in EXTEND-IA. Lastly, we are not able to comment on unmeasured patient factors (i.e., premorbid mRS that was not mandated in the INSPIRE) that may have excluded a patient from a trial, such as EXTEND-IA, but led to their inclusion in INSPIRE as part of everyday practice. While this point leads to the strength of this analysis on the implementation of the evidence, we are unable to identify the key drivers of these influencing factors.

The recently published DIRECT-MT and SKIP trials assessed whether EVT alone was inferior to the alteplase prior to EVT, with the former demonstrating the non-inferiority (mRS shift, adjusted OR: 1.07, 95% CI: 0.81–1.40, $p = 0.04$) (29–31). It would be of research interest to compare the long-term health gains from bridging alteplase in real-world from INSPIRE vs. DIRECT-MT/SKIP RCTs. However, we expect the cost implications of such direct treatment, where there is limited clinical change, to be minimal since the majority of costs arise from the long-term care of patients.

CONCLUSIONS

EVT was associated with significant savings in DALYs compared with usual care/IVT in real-world Australian practice, but the benefit was smaller than that seen in EXTEND-IA. The incomplete translation of the EXTEND-IA results into real-world practice is likely related to multiple factors including patient selection.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethics consideration. Requests to access the datasets should be directed to Associate Professor Andrew Bivard, abivard@unimelb.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Hunter New England Area Health Service Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG and AB conceived and designed the study. LG, ET, and MM conducted the analysis. LG drafted the manuscript. MP, NS, CL, KB, TK, BY, CC, LL, PC, and AB contributed to the data collection and provided important input to the study. All authors consent to submit the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.593238/full#supplementary-material

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
3. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
5. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* (2015) 372:2285–95. doi: 10.1056/NEJMoa1415061
6. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
7. Alawieh A, Chatterjee A, Feng W, Porto G, Vargas J, Kellogg R, et al. Thrombectomy for acute ischemic stroke in the elderly: a 'real world' experience. *J NeuroIntervent Surg.* (2018) 10:1209–17. doi: 10.1136/neurintsurg-2018-013787
8. Campbell BCV, Mitchell PJ, Churilov L, Keshtkaran M, Hong KS, Kleinig TJ, et al. Endovascular thrombectomy for ischemic stroke increases disability-free survival, quality of life, and life expectancy and reduces cost. *Front Neurol.* (2017) 8:657. doi: 10.3389/fneur.2017.00657
9. World Health Organization. *Global Burden of Disease*. (2015). Available online at: http://www.who.int/trade/glossary/story036/en/. (last accessed May 13, 2020).
10. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:439–58. doi: 10.1016/S1474-4422(19)30034-1
11. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2197–223. doi: 10.1016/S0140-6736(12)61689-4
12. Deloitte Access Economics. *Stroke in Australia - No Postcode Untouched*. (2017) (Last accessed December 3, 2019).
13. World Health Organisation. *Global Burden of Coronary Heart Disease*. Available online at: https://www.who.int/cardiovascular_diseases/en/cvd_atlas_13_coronaryHD.pdf.
14. European Consortium in Healthcare Outcomes and Cost-Benefit Research. *European Guideline for cost-Effectiveness Assessments of Health Technologies*. Availabel online at: https://echoutcome.eu/wp-content/uploads/2020/06/Echoutcome__Leaflet_Guidelines___final.pdf. (2013).
15. GBD 2019 Universal Health Coverage Collaborators. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* (2020) 396:1250–84. doi: 10.1016/S0140-6736(20)30750-9
16. Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. *Radiology.* (2013) 267:543–50. doi: 10.1148/radiol.12120971
17. Lin L, Bivard A, Kleinig T, Spratt NJ, Levi CR, Yang Q, et al. Correction for delay and dispersion results in more accurate cerebral blood flow ischemic core measurement in acute stroke. *Stroke.* (2018) 49:924–30. doi: 10.1161/STROKEAHA.117.019562
18. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke.* (2003) 34:e109–37. doi: 10.1161/01.STR.0000082721.62796.09
19. Hong KS, Saver JL. Years of disability-adjusted life gained as a result of thrombolytic therapy for acute ischemic stroke. *Stroke.* (2010) 41:471–7. doi: 10.1161/STROKEAHA.109.571083
20. Australian Bureau of Statistics, 3302.0.55.001 - Life Tables, States, Territories and Australia, 2016-2018. Available online at: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.0.55.0012016-2018?OpenDocument.
21. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: WHO global burden of disease project disability weights for each level of the modified Rankin Scale. *Stroke.* (2009) 40:3828–33. doi: 10.1161/STROKEAHA.109.561365
22. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. *Ann Math Statist.* (1947) 18:50–60. doi: 10.1214/aoms/1177730491
23. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM, Oxford Vascular Study. Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology.* (2018) 91:e1951–e60. doi: 10.1212/WNL.0000000000006554
24. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Econ.* (2001) 20:461–94. doi: 10.1016/S0167-6296(01)00086-8
25. Lima FO, Furie KL, Silva GS, Lev MH, Camargo EC, Singhal AB, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. *JAMA Neurol.* (2014) 71:151–7. doi: 10.1001/jamaneurol.2013.5007
26. Sultan S, Elkind MSV. The growing problem of stroke among young adults. *Curr Cardiol Rep.* (2013) 15:421–21. doi: 10.1007/s11886-013-0421-z
27. Smajlovic D. Strokes in young adults: epidemiology and prevention. *Vasc Health Risk Manag.* (2015) 11:157–64. doi: 10.2147/VHRM.S53203
28. George MG. Risk factors for ischemic stroke in younger adults: a focused update. *Stroke.* (2020) 51:729–35. doi: 10.1161/STROKEAHA.119.024156
29. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med.* (2020) 382:1981–93. doi: 10.1056/NEJMoa2001123
30. Suzuki K, Kimura K, Takeuchi M, Morimoto M, Kanazawa R, Kamiya Y, et al. The randomized study of endovascular therapy with versus without intravenous tissue plasminogen activator in acute stroke with ICA and M1 occlusion (SKIP study). *Int J Stroke.* (2019) 14:752–5. doi: 10.1177/1747493019840932
31. Nogueira RG, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? *Stroke.* (2020) 51:3182–6. doi: 10.1161/STROKEAHA.120.030796

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ORIGINAL RESEARCH
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What Is the "Optimal" Target Mismatch Criteria for Acute Ischemic Stroke?

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We aimed to compare Perfusion Imaging Mismatch (PIM) and Clinical Core Mismatch (CCM) criteria in ischemic stroke patients to identify the effect of these criteria on selected patient population characteristics and clinical outcomes. Patients from the INternational Stroke Perfusion Imaging REgistry (INSPIRE) who received reperfusion therapy, had pre-treatment multimodal CT, 24-h imaging, and 3 month outcomes were analyzed. Patients were divided into 3 cohorts: endovascular thrombectomy (EVT), intravenous thrombolysis alone with large vessel occlusion (IVT-LVO), and intravenous thrombolysis alone without LVO (IVT-nonLVO). Patients were classified using 6 separate mismatch criteria: PIM-using 3 different measures to define the perfusion deficit (Delay Time, Tmax, or Mean Transit Time); or CCM-mismatch between age-adjusted National Institutes of Health Stroke Scale and CT Perfusion core, defined as relative cerebral blood flow <30% within the perfusion deficit defined in three ways (as above). We assessed the eligibility rate for each mismatch criterion and its ability to identify patients likely to respond to treatment. There were 994 patients eligible for this study. PIM with delay time (PIM-DT) had the highest inclusion rate for both EVT (82.7%) and IVT-LVO (79.5%) cohorts. In PIM positive patients who received EVT, recanalization was strongly associated with achieving an excellent outcome at 90-days (e.g., PIM-DT: mRS 0-1, adjusted OR 4.27, $P = 0.005$), whereas there was no such association between reperfusion and an excellent outcome with any of the CCM criteria (all $p > 0.05$). Notably, in IVT-LVO cohort, 58.2% of the PIM-DT positive patients achieved an excellent outcome compared with 31.0% in non-mismatch patients following successful recanalization ($P = 0.006$).

Conclusion: PIM-DT was the optimal mismatch criterion in large vessel occlusion patients, combining a high eligibility rate with better clinical response to reperfusion. No mismatch criterion was useful to identify patients who are most likely response to reperfusion in non-large vessel occlusion patients.

Keywords: ischemic stroke, perfusion, target mismatch, intravenous thrombolysis, endovascular thrombectomy

INTRODUCTION

Selection of patients using target mismatch can identify acute ischemic stroke patients who are most likely to benefit from intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT) in an extended time window (1–3). However, the exact patient selection criteria remain a controversial topic. The DEFUSE3 (3) and EXTEND IA (4) using Perfusion Imaging Mismatch (PIM), which preferentially enroll patients with a largely treatable penumbra and small ischemic core. The DAWN trial (1) applied a Clinical-Core Mismatch (CCM) where an age-adjusted National Institutes of Health Stroke Scale (NIHSS) score was used as a surrogate for the total perfusion deficit, in combination with a small age-adjusted ischemic core define mismatch. However, various thresholds calculated by different post-processing algorithms, defining penumbra and core, has been reported. The most common set of thresholds defining penumbra and core are time to peak of the residual function (Tmax) $>$ 6 s and relative cerebral blood flow (rCBF) $<$30%, or delay time (DT) $>$3 s and rCBF $<$30% (5). When calculating Mean Transit Time (MTT), Tmax and CBF by singular value deconvolution (sSVD), the algorithm assumes no delay in blood flow from proximal arteries to the ischemic region, as, almost invariably in ischemic stroke, there is delay and dispersion of the contrast between the more proximal arterial input function (AIF) and the ischemic region (6). The sSVD is a delay-sensitive algorithm, resulting in underestimation of CBF and overestimation of MTT (6–8). This is highly clinically relevant as different definitions of the perfusion deficit may affect reperfusion treatment eligibility. It is a challenge to determine which mismatch criteria are superior to others in term of optimally identifying excellent reperfusion responders and excluding those who are either likely to be harmed or who have a good natural history regardless of treatment, in routine clinical practice.

Therefore, in this study we aimed to: (i) to compare the various PIM and CCM criteria using different definitions of perfusion deficit; and (ii) assess the ability of each criterion to identify acute stroke patients who are most likely to respond to reperfusion treatment in different subgroups of acute ischemic stroke patients. We hypothesized: (i) that there would be considerable differences in the proportion of patients selected with each mismatch criterion; and (ii) that the presence of PIM or CCM positivity may not uniformly predict response to reperfusion treatment in different sub-groups of acute ischemic stroke patients.

METHODS

Patients

Consecutive acute ischemic stroke patients presenting to 14 centres between 2012 and 2017 were prospectively recruited into the INternational Stroke Perfusion Imaging REgistry (INSPIRE). From the INSPIRE database, patients with anterior circulation ischemic stroke were included in this study if they fulfilled the following criteria:

(i) Received reperfusion therapy: Endovascular Thrombectomy (EVT) or Intravenous Thrombolysis (IVT) based on institutional guidelines.
(ii) Underwent pre-treatment multimodal CT including non-contrast CT, CTP, CT angiography (CTA).
(iii) Underwent 24-h imaging with MRI or multimodal CT.

Stroke severity was assessed at baseline and 24-h using NIHSS. Functional outcome was assessed at day-90 using the modified Rankin Scale (mRS). Patients were divided into two binary outcomes: excellent clinical outcome (mRS of 0-1 VS. mRS of 2-6), and good clinical outcome (mRS of 0-2 VS. mRS of 3-6). Symptomatic Intracranial Hemorrhage (sICH) was defined as type 2 parenchymal haematoma on follow-up imaging with more than 4-point increase in NIHSS or leading to death (9).

Patient Cohorts

Patients were divided into 3 cohorts. Cohort A (EVT) consisted of patients who received EVT. Cohort B (IVT-LVO) consisted of patients receiving IVT alone with Large Vessel Occlusion. LVO was defined as occlusion of the internal carotid artery (ICA) and M1 segment of Middle Cerebral Artery (MCA) only. Cohort C (IVT-nonLVO) consisted of IVT only patients without LVO, including MCA occlusions beyond M1, anterior cerebral artery occlusions (and/or CTP patterns consistent with distal occlusions not easily visualized on CTA).

Imaging Acquisition and Analysis

All patients underwent pre-treatment multimodal CT and 24-h MRI or multimodal CT (if MR-incompatible) (10).

All CTP were post-processed with MIStar (Apollo Medical Imaging Technology, Melbourne, Australia) with both standard Single Value Deconvolution (sSVD, which is delay-sensitive), and also by delay and dispersion corrected Single Value Deconvolution (ddSVD, which is delay-insensitive) (11, 12). The software automatically performs motion correction and selects an arterial input function (AIF) from an unaffected artery (most often the anterior cerebral artery). Then the AIF was confirmed

by experienced analysts (C.C, a neuroscientist with >6 years experience of perfusion imaging; and A.B, a neuroscientist with >10 years experience). The sSVD method generates maps of: standard cerebral blood volume (CBV), standard CBF, standard MTT and Tmax. Tmax is calculated from the time to peak of the impulse residual function (IRF) curve, where Tmax=0 reflects normal blood supply in normal tissue without delay and dispersion. DT was calculated using ddSVD method to correct for the potential arterial delay and dispersion effects caused by stroke and arterial stenosis by generating an arterial transport function from each voxel IRF (13).

Threshold Setting to Define Perfusion Deficit and Ischemic Core

Dual threshold setting was used to define perfusion deficit and ischemic core, with upper threshold defining the perfusion deficit and lower threshold defining ischemic core. Three thresholds were used according to previously published thresholds to define perfusion deficit: (i) MTT >145% of contralateral normal tissue (derived from sSVD) (14), (ii) Tmax >6 s (derived from sSVD) (3, 4, 15), (iii) DT> 3 s (derived from ddSVD) (11, 16). The threshold of rCBF <30% was applied to measure ischemic core within each of the perfusion deficit defined by the above thresholds (17). Mismatch ratio was defined as the perfusion deficit divide by the infarct core volume; mismatch volume was defined as the perfusion deficit volume minus the ischemic core volume.

For the EVT cohort, recanalization status was graded by Thrombolysis in Cerebral Infarction (TICI) grading system post-procedure Digital Subtraction Angiography (DSA). For IVT patients, recanalization status was graded by comparing follow-up MRA/CTA to acute CTA, evaluating the restoration of the previously occluded artery with Thrombolysis in Myocardial Infarction scoring system. For this study, we classified recanalization status as either (i) recanalization = TICI 2b, 2c, or 3 on DSA or TIMI 3 on follow-up MRA/CTA, or (ii) no recanalization = TICI 0, 1, or 2a on DSA, or TIMI 0, 1, 2 on follow-up MRA/CT. Collateral supply to the mismatch area was classified as 1 = good, 2 = moderate, 3 = poor using the Miteff grading system (18).

Mismatch Profile Definition

Each patient was then classified using 6 separate mismatch criteria according to previously used mismatch criteria using the following methods and thresholds:

Perfusion Imaging Mismatch Profile (PIM-DT/PIM-Tmax/PIM-MTT)

PIM – mismatch between perfusion deficit and ischemic core: Mismatch ratio >1.8, mismatch volume >15 ml, core volume <70 ml, as determined by 3 different measures to define the perfusion deficit (DT >3 s, Tmax >6 s, or MTT >145%), and ischemic core defined as rCBF <30% constrained to the territory of the perfusion deficit defined in three ways as above;

Clinical Core Mismatch Profile (CCM-DT/CCM-Tmax/CCM-MTT)

CCM - mismatch between age-adjusted NIHSS and CTP core: NIHSS ≥10 and ischemic core volume <31 ml (age <80), or NIHSS ≥20 and ischemic core volume 31–51 ml (age <80); or NIHSS ≥10 and ischemic core volume <21 ml (age ≥80); as ischemic core volume determined by rCBF<30% constrained to the territory of the perfusion deficit defined in three ways (DT >3 s, Tmax >6 s, orMTT >145%).

Statistical Analysis

Descriptive results and quantitative baseline patient characteristics were presented as median and Interquartile Range (IQR). Comparisons of continuous variables between groups were performed with Wilcoxon rank-sum test. Categorical variables were presented as proportions. Categorical variables were compared by chi-square, or Fisher's exact test as appropriate. The proportions of patients selected by each mismatch criterion were compared groups 2 by 2 as assessed by McNemar Test for discordant pairs. In patients with the same mismatch profile, differences of outcome variables (rate of mRS0-1, rate of mRS0-2, sICH and mortality rate) were compared between patients with and without recanalization. Furthermore, in patients with the same recanalization status, differences of outcome variables were compared between patients with and without target mismatch. Separate univariate logistic regression was constructed to assess the relationship between recanalization and excellent outcome/good outcome in patients with and without target mismatch utilizing each mismatch criterion. This was followed by multiple logistic regressions adjusting for age, and baseline core volume.

All the statistical analyses were performed for 3 cohorts of patients separately. Significant level was set at $P < 0.05$. Statistical analyses were performed with STATA 13.0 (Stata Corp, College Station, Texas, USA).

RESULTS

During the study period, a total of 2,205 patients were enrolled in INSPIRE. A total of 994 patients were eligible for this study after various exclusions (patient inclusion was detailed in **Figure 1**). Cohort A consisted of 208 EVT patients (147 of the 208 EVT patients also received IVT); Cohort B consisted of 458 IVT-LVO patients; Cohort C consisted of 328 IVT-non LVO patients. Patients without an LVO had smaller baseline perfusion lesion, greater likelihood of good collaterals and a higher rate of excellent outcome (mRS 0-1 ate day-90) compared with patients with an LVO treated with EVT and/or IVT (**Table 1**). In patients with an LVO, EVT resulted in a higher rate of recanalization compared to IVT alone (78 vs. 47%, **Table 1**).

EVT Cohort

Of the patients treated with EVT, 82.7% (172/208) met the PIM-DT criterion, which had the highest proportion of eligible patients. The proportions of patients selected by each mismatch criterion were significantly lower when compared with PIM-DT (**Table 2**, illustrative example of the disagreement between

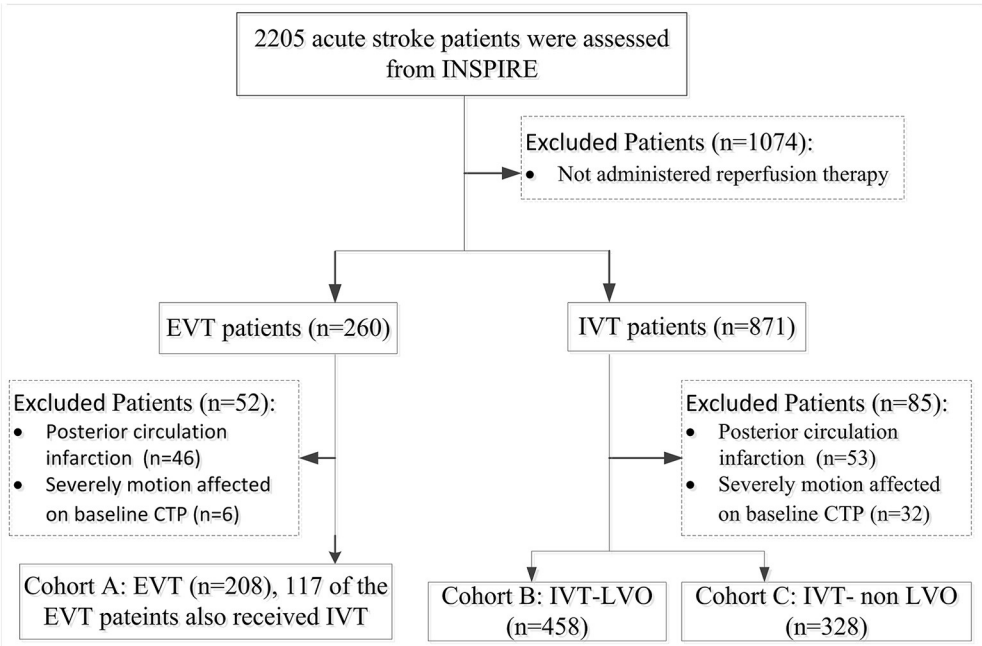

FIGURE 1 | Flowchart of Patients Inclusion. INSPIRE, INternational Stroke Perfusion Imaging REgistry; EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-non-LVO, Intravenous Thrombolysis patients with no Large Vessel Occlusion, Vessel Occlusion.

TABLE 1 | Clinical and imaging characteristics.

Parameter	EVT (*n* = 208)	IVT-LVO (*n* = 458)	IVT-non-LVO (*n* = 328)
Age, median (IQR)	70 (59, 78)	73 (64, 81)	71 (60, 82)
Sex (male %)	59	53	60
Baseline NIHSS median (IQR)	15 (11-19)	15 (12-18)	8 (6-12)
24 h NIHSS median (IQR)	10 (3-17)	11 (5-7)	3 (1-6)
Median 90-days mRS (IQR)	3 (1-4)	3 (1-5)	1 (0, 1)
mRS 0-1 at 90-days, (%)	35	30	61
mRS 0-2 at 90-days, (%)	44	42	74
Median baseline ischemic core (rCBF <30% within DT >3s) (IQR), mL	20 (9, 42)	20 (7, 40)	3 (1-40)
Median baseline perfusion deficit volume (DT >3 s) (IQR), mL	109 (66,154)	95 (55, 144)	17 (5, 44)
Median 24 h infarct volume (IQR), mL	39 (14, 94)	35 (12, 107)	3 (1-12)
Median onset to lysis time (IQR), minutes	148 (95, 255)	153 (82, 315)	155 (96,206)
Onset to recanalization time (EVT patients)	271 (109, 645)	–	–
Occlusion location			
ICA (%)	32	28	–
M1 (%)	57	72	–
M2 (%)	11	–	42
M3 (%)	–	–	15
ACA (%)	–	–	5
No visible occlusion (%)	–	–	38
Recanalization rate (%)	78	47	87
mRS 0-1 in patient with recanalization, (%)	57	55	67
mRS 0-1in patient without recanalization, (%)	15	6	3
sICH (%)	5	4	1

EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Score; mRS, modified Rankin Scale; rCBF, relative cerebral blood flow; DT, delay time; M1, M1segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; ICA, internal carotid artery; sICH, symptomatic intracranial hemorrhage.

mismatch criteria in **Figure 2**). Between 32% (66/208 from CCM-DT) and 61% (127/208 from CCM-MTT) of patients were excluded due to the age-adjusted NIHSS/core cut off when using the CCM criteria. A total of 28% (58/208) of the patients were excluded due to the large core (infarct core volume ≥70 mL) when assessed with PIM-MTT, 20% (42/208) when assessed with PIM-Tmax, and 12% (24/208) when assessed with PIM-DT (**Table 2**).

Recanalization was strongly associated with achieving an excellent outcome and good outcome at 90-days in patients meeting the PIM (DT/Tmax/MTT) criteria (e.g., PIM-DT + patients, mRS 0-1 adjusted OR: 4.27 95% CI: 1.53, 11.91, $P = 0.005$, **Tables 3A,B**). Whereas, there was no such association between recanalization and excellent or good outcome at 90-days in target mismatch patients classified by any of the CCM criteria (**Tables 3A,B**). Additionally, patients meeting the PIM (DT/Tmax/MTT) mismatch criteria had a higher rate of excellent outcome after recanalization (e.g., PIM-DT+ patient, 43.4%, 59/136 with recanalization, vs. 13.9%, 5/36 without recanalization, $P = 0.001$, **Tables 4A,B**). Importantly, PIM-DT was the only mismatch criterion that showed target mismatch patients had a higher rate of excellent or good outcome compared with non-target mismatch patients after recanalization (e.g., 43.4%, 59/136 PIM-DT+ patients with recanalization vs. 26.9%, 7/26 PIM-DT- patients with recanalization, $P = 0.013$, **Table 4A**).

IVT-LVO Cohort

In the cohort of LVO patients treated with IVT only, 79.5% (364/458) met the PIM–DT, which had the highest proportion of eligible patients. The proportions of patients selected by the other mismatch criteria were also significantly lower than PIM-DT (**Table 2**). When using the CCM criteria, between 35% (162/458 from CCM-DT) and 54% (246/458 from CCM-MTT) of the patients were excluded due to the age-adjusted NIHSS/core cut off. A total of 28% (118/458) of the patients were excluded due to large core (core volume ≥70 mL) when assessing with PIM-MTT, whilst 17% (76/458) when assessing with PIM-Tmax and 11% (49/458) using PIM-DT criterion (**Table 2**).

In contrast to the EVT cohort, recanalization was associated with an excellent and good outcome at day-90 in patients with and without target mismatch regardless of the type of mismatch criteria used (**Tables 3A,B**). The target mismatch patients with recanalization had a higher rate of excellent and good outcome compared with target mismatch patients without recanalization, regardless of the type of mismatch criteria used (e.g., rate of mRS 0-1: 58.2% in PIM-DT+ with recanalization vs. 7.7% in PIM-DT+ without recanalization, $P < 0.0001$, **Tables 4A,B**). A similar relationship was also seen in non-target mismatch patients (e.g., rate of mRS 0-1: 31.0% in PIMDT- with recanalization vs. 3.1% in PIM-DT- without recanalization, $P < 0.0001$, **Tables 4A,B**).

TABLE 2 | Disagreement between mismatch criteria and detail of exclusion.

			Number of patients were excluded by each reason, n (%)				
	Mismatch (+), n (%)	***P*-value**	**Large core**	**Small penumbra**	**Mismatch ratio < 1.8**	**Age/core cut off**	**Low NIHSS**
EVT (*n* = 208)							
PIM-DT	172 (82.7)	–	24 11.5)	12 (5.8)	0 (0)	–	–
PIM-Tmax	142 (68.3)	<0.0001	42 (20.2)	18 (8.7)	0 (0)	–	–
PIM-MTT	149 (71.6)	0.0023	58 (27.9)	1 (0.5)	0 (0)	–	–
CCM-DT	114 (54.8)	<0.0001	–	–	–	66 (31.7)	28 (13.5)
CCM-Tmax	74 (35.6)	<0.0001	–	–	–	106 (51.0)	28 (13.5)
CCM-MTT	53 (25.5)	<0.0001	–	–	–	127 (61.1)	28 (13.5)
IVT-LVO (*n* = 458)							
PIM-DT	364 (79.5)	–	49 (10.7)	5 (1.1)	1 (0.2)	-	-
PIM-Tmax	310 (67.7)	<0.0001	76 (16.6)	45 (9.8)	27 (5.9)	-	-
PIM-MTT	333 (72.7)	0.0003	118 (25.8)	5 (1.1)	1 (0.2)	-	-
CCM-DT	211 (46.1)	<0.0001	–	–	–	162 (35.4)	84 (18.3)
CCM-Tmax	174 (38.0)	<0.0001	–	–	–	200 (43.7)	84 (18.3)
CCM-MTT	128 (27.9)	<0.0001	–	–	–	246 (53.7)	84 (18.3)
IVT-nonLVO (*n* = 328)							
PIM-DT	152 (46.3)	<0.0001	1(0.3)	173 (52.7)	2 (0.6)	–	–
PIM-Tmax	120 (36.6)	<0.0001	5(1.5)	191 (58.2)	12 (3.7)	–	–
PIM-MTT	249 (75.9)	–	12 (3.7)	61 (18.3)	6 (1.8)	–	–
CCM-DT	117 (35.7)	<0.0001	–	–	–	11 (3.3)	200 (61.0)
CCM-Tmax	105 (32.0)	<0.0001	–	–	–	23 (7.0)	200 (61.0)
CCM-MTT	82 (25.0)	<0.0001	–	–	–	46 (1.4)	200 (61.0)

EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; PIM, Perfusion Imaging Mismatch; CCM, Clinical Core Mismatch; Significant level was set at P < 0.05, when the proportion of each mismatch criteria compared with the mismatch criteria had the highest proportion in each patient cohort, separately.

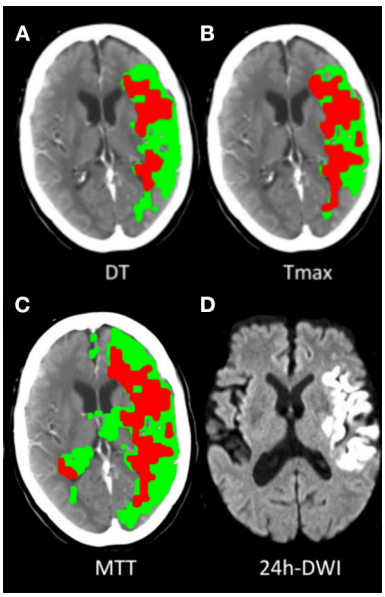

FIGURE 2 | Illustrative examples of target mismatch classified by 3 PIM criteria. A 67-year-old case, acute left middle cerebral artery (MCA) M1 segment occlusion with sudden onset of right-side hemiparesis (baseline NIHSS 24), underwent endovascular thrombectomy, had successful recanalization (TICI 2c) and had mRS 1 at 90-day. **(A)** Classified as target mismatch by PIM-DT, with mismatch ratio 2.2, perfusion deficit volume 119 mL, CTP core volume 55 mL (defined as DT >3S and rCBF<30%). **(B)** Classified as non-target mismatch by PIM-Tmax, with mismatch ratio 1.5, perfusion deficit volume 116 mL, CTP core volume 78 mL (defined as Tmax >6S and rCBF<30%). **(C)** Classified as non-target mismatch by PIM-MTT, with mismatch ratio 1.8, perfusion deficit volume 166 mL, CTP core volume 98 mL (defined as MTT >145% and rCBF<30%). **(D)** 24-h DWI detected 46 mL infarct core.

However, PIM-DT was the only mismatch criterion that showed target mismatch patients had a higher rate of excellent outcome compared with non-target mismatch patients after recanalization. A total of 58.2 % (114/196) PIM-DT+ patients achieved an excellent outcome at day-90 after recanalization, compared with only 31.0% (9/29) in PIM-DT- patients (P = 0.006, **Table 4A**). Furthermore, PIM-DT was again the only criterion that showed a reduced rate of sICH in PIM-DT+ patients with recanalization (1%, 2/196) compared with PIM-DT+ patients without (7.7%, 13/168, P = 0.006, **Table 4A**).

IVT-Non-LVO Cohort

In the cohort of IVT patients without an LVO, 75.9% (249/328) met the PIM-MTT criterion, which had the highest proportion of eligible patients. The proportions of patients selected by each mismatch profile were significantly smaller when compared with PIM-MTT (**Table 2**). The majority of non-target mismatch patients (61%, 200/328) were excluded due to low NIHSS when using the CCM criteria. A significant number of patients (19%, 61/328 from PIM-MTT; 58%, 191/328 from PIM-Tmax; and 53%, 173/328 from PIM-DT) were classified as non-mismatch due to small penumbral volume ($\leq$ 15 mL, **Table 2**).

Recanalization was associated with excellent and good outcome in patients with and without target mismatch regardless of mismatch criteria (**Tables 3A,B**). In IVT patients without an LVO, the adjusted OR of excellent outcome after recanalization (compared to no recanalization) in PIM-MTT+ patients was 5.01 (95% CI 1.93, 13.03, P = 0.001 **Table 3**), whereas in PIM-MTT- patients the adjusted OR of an excellent clinical outcome with recanalization was 7.64 (95% CI 0.82, 70.52, P = 0.043, **Table 2**). Mortality and sICH were not associated with recanalization in patients with and without target mismatch regardless of the type of mismatch criteria (**Table 4A**). There was no significant difference in the percentage of an excellent or good outcome at day-90, between target mismatch and non-target mismatch patients with recanalization, regardless of the type of mismatch criteria used (**Tables 4A,B**).

DISCUSSION

This study assessed a range of PIM and CCM criteria in a large ischemic stroke cohort from INSPIRE. It demonstrated that PIM-DT was the optimal target mismatch criterion to identify "excellent" responders to recanalization for LVO patients, treated with either EVT or IVT. The PIM-DT criterion had the highest proportion of eligible target mismatch patients and was the only of the six criteria to distinguish responders from non-responder to reperfusion in LVO patients.

For LVO patients receiving EVT and/or IVT, the CCM criterion was a more restrictive selection criterion compared to the PIM criteria regardless of the post-processing method used to define perfusion deficit and ischemic core. A large number of patients (32% to 61%) were excluded due to the age-adjusted NIHSS/core cut off. The strict age-adjusted NIHSS/core cut-off excluded patients with a relatively small ischemic core volume who might well-still benefit from reperfusion therapy (19). This is highly relevant to everyday practice and individual patient since the rates of excellent or good outcome after recanalization were similar between patients with and without CCM.

Both the DAWN (1) and DEFUSE 3 (3) trials demonstrated significant treatment benefits of thrombectomy extending to a later time window, despite different target mismatch criteria being applied. Clinical core mismatch was used in the DAWN trial, which has strict age-adjusted NIHSS/pre-treatment core volume cut off. In contrast, the DEFUSE 3 trial required perfusion imaging mismatch, a discrepancy between penumbra and ischemic core. However, patients who were excluded from the clinical core mismatch (due to large pre-treatment core) but met the perfusion imaging mismatch were shown to still benefit from reperfusion treatment (19). These two different patient selection techniques produced similar trial results which resulted in significant global practice change. However, it is clear that there is some refinement that can be done, where patients at the peripherals or even just edging into exclusion may benefit from treatment, but to less of an extent to those who are eligible. The challenge will be to definitely identify where the futility margin exists, and perhaps where harm even starts. Compounding this challenge is the issue that the thresholds to

TABLE 3A | The relationship between mismatch predicting mRS 0-1 in patients with recanalization.

	EVT		IVT-LVO		IVT-nonLVO	
Mismatch	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**	***P***
PIM-DT						
yes	4.27 (1.53, 11.91)	0.005	9.77 (4.83, 19.78)	<0.0001	4.91 (1.34, 17.97)	0.016
no	1.01 (0.14, 7.13)	0.992	9.32 (2.37, 35.90)	0.001	4.79 (1.38, 16.65)	0.014
PIM-Tmax						
yes	4.37 (1.58, 12.12)	0.025	14.39 (5.32, 38.93)	<0.0001	4.75 (1.03, 21.84)	0.045
no	3.25 (0.34, 31.07)	0.306	8.99 (4.02, 20.10)	<0.0001	7.52 (2.32, 24.29)	0.001
PIM-MTT						
Yes	5.66 (1.75, 18.26)	0.004	9.93 (4.96, 19.86)	<0.0001	5.01 (1.93, 13.03)	0.001
No	1.99 (0.41, 9.65)	0.394	22.03 (4.78, 101.45)	<0.0001	7.64 (0.82, 70.52)	0.043
CCM-DT						
Yes	5.74 (1.22, 27.02)	0.027	11.16 (4.95, 15.23)	<0.0001	6.15 (1.56, 24.24)	0.009
No	3.78 (1.28, 11.19)	0.016	7.96 (3.06, 20.71)	<0.0001	3.12 (0.94, 10.40)	0.044
CCM-Tmax						
Yes	6.24 (0.62, 62.88)	0.120	11.17 (4.62, 26.99)	<0.0001	5.69 (1.36, 23.94)	0.018
No	3.73 (1.34, 10.38)	0.012	10.35 (4.34, 24.68)	<0.0001	4.37 (1.42, 13.580)	0.011
CCM-MTT						
Yes	4.56 (1.75, 11.94)	0.310	9.73 (3.49, 27.14)	<0.0001	6.86 (1.25, 37.38)	0.026
No	5.43 (2.12, 13.93)	0.460	11.99 (5.55, 25.90)	<0.0001	4.74 (1.67, 13.41)	0.003

mRS 0-1, modified Rankin Score 0-1 at 90-days; EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; PIM, Perfusion Imaging Mismatch; CCM, Clinical Core Mismatch.

TABLE 3B | The relationship between mismatch predicting mRS 0-2 in patients with recanalization.

	EVT		IVT-LVO		IVT-nonLVO	
Mismatch	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**	***P***	**Adjusted OR (95%CI)**	***P***
PIM-DT						
Yes	6.69 (2.42, 18.50)	<0.0001	12.67 (7.41, 21.67)	<0.0001	2.69 (0.93, 7.73)	0.067
No	1.88 (0.29, 12.12)	0.503	5.15 (1.41, 18.79)	<0.0001	6.99 (1.54, 31.61)	0.012
PIM-Tmax						
Yes	5.90 (2.17, 16.04)	<0.0001	11.15 (6.34, 19.58)	<0.0001	2.04 (0.63, 6.66)	0.234
No	6.12 (0.69, 54.13)	0.103	13.48 (5.30, 34.25)	<0.0001	7.48 (2.29, 24.38)	0.001
PIM-MTT						
Yes	7.17 (2.27, 22.69)	0.001	12.04 (7.00, 20.69)	<0.0001	4.47 (1.86, 10.76)	0.001
No	4.10 (0.94, 17.98)	0.061	12.78 (4.60, 35.49)	<0.0001	2.72 (0.40, 18.37)	0.303
CCM-DT						
Yes	9.10 (1.96, 42.25)	0.005	10.72 (5.46, 21.03)	<0.0001	7.28 (2.14, 24.72)	0.001
No	3.86 (1.20, 12.39)	0.023	11.87 (5.71, 24.67)	<0.0001	1.47 (0.42, 5.16)	0.546
CCM-Tmax						
Yes	8.67 (0.94, 80.06)	0.057	9.96 (4.83, 20.52)	<0.0001	7.18 (1.94, 26.58)	0.003
No	6.05 (2.19, 16.68)	0.001	13.68 (7.11, 26.32)	<0.0001	2.13 (0.71, 6.4)	0.175
CCM-MTT						
Yes	2.73 (0.27, 27,99)	0.396	10.62 (4.48, 25.14)	<0.0001	7.80 (1.72, 35.4)	0.008
No	7.31 (2.79, 19.11)	<0.0001	13.14 (7.39, 23.39)	<0.0001	2.99 (1.12, 7.99)	0.029

mRS 0-2, modified Rankin Score 0, 1, 2 at 90-days; EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; PIM, Perfusion Imaging Mismatch; CCM, Clinical Core Mismatch.

TABLE 4A | Outcomes based on target mismatch profile and recanalization status.

		EVT			IVT-LVO			IVT-nonLVO		
Mismatch	**RECAN**	**mRS 0-1 (%)**	**Mortality rate (%)**	**sICH (%)**	**mRS 0-1 (%)**	**Mortality rate (%)**	**sICH (%)**	**mRS 0-1 (%)**	**Mortality rate (%)**	**sICH (%)**
PIM-DT										
Yes	Yes	43.4*	9.6*	3.7	58.2*	3.21*	1.0*	63.3*	1.1	1.4
Yes	No	13.9	30.6	5.6	7.7	21.5	7.7	28.6	0.0	0.0
	P	0.001	0.003	0.451	<0.0001	<0.0001	0.006	0.019	0.952	0.946
No	Yes	26.9	26.9	11.5	31.0*	11.4*	7.7	62.1*	4.8	2.4
No	No	20.0	50.0	0	3.1	34.2	5.8	22.2	16.7	6.7
	P	0.514	0.178	0.364	<0.0001	<0.0001	0.701	0.002	0.088	0.393
PIM-Tmax										
Yes	Yes	46.5*	8.2*	3.6	57.8*	3.7*	2.3	61.1	0.0	0
Yes	No	18.8	28.1	6.2	7.3	20.6	7.4	39.4	9.1	0
	P	0.005	0.006	0.408	<0.0001	<0.0001	0.148	0.184	0.169	1
No	Yes	28.9	21.2*	7.7	44.2*	6.3*	3.8	63.1*	4.4	2.7
No	No	7.1	50.0	0	5.2	30.5	6.9	19.1	9.5	5.9
	P	0.085	0.045	0.376	<0.0001	<0.0001	0.371	<0.0001	0.28	0.433
PIM-MTT										
Yes	Yes	42.2*	10.7*	4.1	58.1*	3.3*	4.1	65.1*	3.5	1.6
Yes	No	14.3	32.1	7.1	8.4	18.2	7.7	29.2	4.2	3.8
	P	0.004	0.008	0.391	<0.0001	<0.0001	0.254	0.001	0.918	0.336
No	Yes	36.6	17.1	7.3	41.3*	9.8*	0	53.4*	2.4	3.3
No	No	16.7	38.9	0	2.6	40.0	6.2	12.5	25.0	0
	P	0.109	0.072	0.328	<0.0001	<0.0001	0.101	0.045	0.063	0.981
CCM-DT										
Yes	Yes	35.8*	10.5	4.3	61.9*	3.6*	4.2	53.6*	6.6	0
Yes	No	10.6	26.3	5.3	9.7	14.7	3.1	17.6	11.7	0
	P	0.031	0.075	0.605	<0.0001	<0.0001	0.734	0.008	0.608	1
No	Yes	46.3*	14.9*	6.0	46.7*	6.7*	1.5*	67.4*	1.5	2.9
No	No	18.5	40.7	3.7	4.3	35.1	9.8	33.3	6.7	8.3
	P	0.018	0.012	0.553	<0.0001	<0.0001	0.03	0.009	0.268	0.366
CCM-Tmax										
Yes	Yes	30.8	12.3	4.6	62.2*	3.2*	3.8	52.2*	5.9	0
Yes	No	11.1	33.3	11.1	10.5	17.7	3.9	20.0	13.3	0
	P	0.209	0.125	0.412	<0.0001	0.002	0.971	0.043	0.301	1
No	Yes	47.4*	12.4*	5.2	48.8*	6.4*	2.3	67.4*	2.0	2.8
No	No	16.2	35.1	2.7	4.5	31.5	8.6	29.4	5.9	7.1
	P	0.001	0.005	0.270	<0.0001	<0.0001	0.065	0.002	0.357	0.383
CCM-MTT										
Yes	Yes	22.9	14.6	2.1	57.8*	2.9*	3.5	52.9*	3.9	0
Yes	No	20.0	40.0	0	10.5	21.3	5.1	16.7	8.3	0
	P	0.685	0.196	0.906	<0.0001	<0.0001	0.697	0.028	0.476	1
No	Yes	48.3*	11.4*	6.1	53.3*	5.9*	2.8	65.6*	3.1	2.5
No	No	14.6	34.2	4.9	5.1	28.8	7.7	30.0	10.0	6.2
	P	<0.0001	0.003	0.559	<0.0001	<0.0001	0.101	0.002	0.171	0.402

*RECEN, recanalization; sICH, symptomatic intracerebral haemorrhagic; EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; PIM, Perfusion Imaging Mismatch; CCM, Clinical Core Mismatch. *Denote a significant difference present when compared with patients with the same mismatch profile, but without recanalization.*

measure penumbra and core vary from different post-processing algorithms or software (11) which result in large discrepancies between vendors. The specific thresholds (Tmax > 6 s and rCBF<30%) used in the DEFUSE 3 and EXTEND-IA trial were calculated by sSVD, which are known to overestimate of the perfusion deficit (7, 8, 11). Without delay and dispersion correction, 15% of the patients who would potentially benefit for reperfusion treatment might be excluded when applying perfusion imaging mismatch criteria.

For patients without an LVO who received IVT, the PIM-MTT had a reasonable rate of eligibility, compared with other criteria. This may be due to the overestimation of the perfusion deficit that leads to a high rate of inclusion (20, 21). The MTT is less sensitive to spontaneous reperfusion as CBV may be increased more than

TABLE 4B | Outcomes based on target mismatch profile and recanalization status.

		EVT	IVT-LVO	IVT-nonLVO
Mismatch	**Recanalization**	**mRS0-2 (%)**	**mRS0-2 (%)**	**mRS0-2 (%)**
PIM-DT				
Yes	Yes	54.4*	72.7*	76.7
Yes	No	13.9	17.9	57.1
	P	<0.0001	<0.0001	0.061
No	Yes	42.3	51.7*	77.5*
No	No	20.0	7.7	27.3
	P	0.197	<0.0001	0.001
PIM-Tmax				
Yes	Yes	58.2*	72.7*	78.4*
Yes	No	18.8	19.9	31.3
	P	<0.0001	<0.0001	<0.0001
No	Yes	40.4*	65.4*	75.0
No	No	7.1	9.4	62.5
	P	0.016	<0.0001	0.232
PIM-MTT				
Yes	Yes	53.7*	72.6*	77.9*
Yes	No	14.3	18.2	46.2
	P	<0.0001	<0.0001	0.001
No	Yes	48.8*	60.9*	72.7
No	No	16.7	8.9	50.0
	P	0.018	<0.0001	0.257
CCM-DT				
Yes	Yes	49.5*	75.4*	75*
Yes	No	10.5	23.7	35.3
	P	0.001	<0.0001	0.003
No	Yes	56.7*	64.5*	78.3
No	No	18.5	9.3	60.0
	P	0.001	<0.0001	0.107
CCM-Tmax				
Yes	Yes	44.6	74.5*	73.1*
Yes	No	11.1	23.7	33.3
	P	0.055	<0.0001	0.005
No	Yes	57.7*	66.9*	78.9
No	No	16.2	10.8	58.8
	P	<0.0001	<0.0001	0.065
CCM-MTT				
Yes	Yes	37.5	70.1*	72.6*
Yes	No	20.0	13.6	33.3
	P	0.404	<0.0001	0.014
No	Yes	58.8*	70.4*	78.5*
No	No	14.6	19.3	55
	P	<0.0001	<0.0001	0.025

*EVT, endovascular Thrombectomy; IVT-LVO, Intravenous Thrombolysis patients with Large Vessel Occlusion; IVT-nonLVO, Intravenous Thrombolysis patients without Large Vessel Occlusion; PIM, Perfusion Imaging Mismatch; CCM, Clinical Core Mismatch. *Denote a significant difference present when compared with patients with the same mismatch profile, but without recanalization.*

CBF due to spontaneous reperfusion leading to prolonged MTT whereas DT and Tmax will be lower as they are direct measures of reperfusion (22). However, none of the mismatch criterion was able to identify the non-LVO patients who most likely benefit from reperfusion therapy, since there was no significant difference in the rate of excellent or good clinical outcomes between patient with and without mismatch after recanalization. It is likely that some patients in the IVT-non-LVO cohort with a distal perfusion deficit, but no clear vessel occlusion on CTA, might have been undergoing spontaneous recanalization and reperfusion before imaging. Thus, these patients may have begun with target mismatch but by the time of imaging were non-mismatch. The majority of the patients (87%) in non LVO group achieved recanalization. These groups of patients have a high rate of spontaneous reperfusion and hence will have a good clinical outcome with or without thrombolysis (23, 24), with the majority of the patients (70%) without an LVO having a baseline perfusion deficit of < 15 mL.

Some limitations of the study need to be acknowledged. This is an observational study using data from INSPIRE, which is a large dataset collected from multiple sites. Whilst sites are strongly encouraged to recruit consecutive patients, this is not always possible and there may be recruitment biases which cannot be measured. In particular, the information about whether the mismatch criteria used in assisting decision-making was not available, there may be undocumented factors behind the treatment decision making. "Furthermore, there might be some unmeasured bedside bias influencing the reperfusion treatment decision making because of clinical judgment in case selection for reperfusion treatment remain variability. The current study only included anterior circulation ischemic stroke patients. The results are un-likely to be relevant to patients with posterior circulation ischemic stroke. It is important to acknowledge that our findings are specific to a particular post-processing imaging technique, and as such, our results might not be directly translated to other perfusion software currently used (25, 26). Nevertheless, the underlying principles of the algorithms (sSVD/ddSVD) using in different software are the same, we would expect that the PIM calculated with delay insensitive method would be the optimal target mismatch criterion that can identify patients with LVO most likely response to reperfusion therapy. Moreover, we used perfusion imaging from different scanners, which might slightly influence the results of imaging analysis. We assessed each of the mismatch criteria in the same patient cohort to reduce the influence from using perfusion imaging from different scanners.

In conclusion, the PIM-DT was the optimal target mismatch criterion to identify LVO patients most likely to have an excellent response to EVT and/or IVT. PIM-DT combined a relatively high rate of eligibility with high rates of response to recanalization (and with less sICH). In contrast, none of the mismatch criteria was useful to identify recanalization responders in non-LVO patients.

DATA AVAILABILITY STATEMENT

Anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunter New England Health District ethics committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC, MP, and AB: study design, acquisition, analysis and interpretation of data, drafted the manuscript, revised it critically for important intellectual content, and approved the final version. CL, NS, LL, TK, KB, RA, and MK: acquisition and interpretation of data, revised the manuscript critically for important intellectual content, and approved the final version. XC, QD, BO'B, PS, PC, SB, CY, JY, PW, and WQ: data acquisition, revised the manuscript critically for important intellectual content, and approved the final version.

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REFERENCES

1. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
2. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med.* (2019) 380:1795–803. doi: 10.1056/NEJMoa1813046
3. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
4. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* (2015) 372:1009–18. doi: 10.1056/NEJMoa1414792
5. Vagal A, Wintermark M, Nael K, Bivard A, Parsons M, Grossman AW, et al. Automated CT perfusion imaging for acute ischemic stroke: pearls and pitfalls for real-world use. *Neurology.* (2019) 93:888–98. doi: 10.1212/WNL.0000000000008481
6. Kudo K, Sasaki M, Ogasawara K, Terae S, Ehara S, Shirato H. Difference in tracer delay-induced effect among deconvolution algorithms in CT perfusion analysis: quantitative evaluation with digital phantoms. *Radiology.* (2009) 251:241–9. doi: 10.1148/radiol.2511080983
7. Lin L, Bivard A, Kleinig T, Spratt NJ, Levi CR, Yang Q, et al. Correction for delay and dispersion results in more accurate cerebral blood flow ischemic core measurement in acute stroke. *Stroke.* (2018) 49:924–30. doi: 10.1161/STROKEAHA.117.019562
8. Kudo K, Christensen S, Sasaki M, Ostergaard L, Shirato H, Ogasawara K, et al. Accuracy and reliability assessment of CT and MR perfusion analysis software using a digital phantom. *Radiology.* (2013) 267:201–11. doi: 10.1148/radiol.12112618
9. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* (2008) 359:1317–29. doi: 10.1056/NEJMoa0804656
10. Tian H, Parsons MW, Levi CR, Lin L, Aviv RI, Spratt NJ, et al. Influence of occlusion site and baseline ischemic core on outcome in patients with ischemic stroke. *Neurology.* (2019) 92:e2626–43. doi: 10.1212/WNL.0000000000007553
11. Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. *Radiology.* (2013) 267:543–50. doi: 10.1148/radiol.12120971
12. Chen C, Bivard A, Lin L, Levi CR, Spratt NJ, Parsons MW. Thresholds for infarction vary between gray matter and white matter in acute ischemic stroke: a CT perfusion study. *J Cereb Blood Flow Metab.* (2017) 39:536–46. doi: 10.1177/0271678X17744453
13. Yang Q. *Method and System for Mapping Tissue Status of Acute Stroke Patent US8942451B2.* Apollo Medical Imaging Technology Pty Ltd, Melbourne, VIC (2015).
14. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke.* (2006) 37:979–85. doi: 10.1161/01.STR.0000209238.61459.39
15. Lansberg MG, Lee J, Christensen S, Straka M, De Silva DA, Mlynash M, et al. RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Stroke.* (2011) 42:1608–14. doi: 10.1161/STROKEAHA.110.609008
16. Bivard A, Huang X, McElduff P, Levi CR, Campbell BC, Cheripelli BK, et al. Impact of computed tomography perfusion imaging on the response to tenecteplase in ischemic stroke: analysis of 2 randomized controlled trials. *Circulation.* (2017) 135:440–8. doi: 10.1161/CIRCULATIONAHA.116.022582
17. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke.* (2011) 42:3435–40. doi: 10.1161/STROKEAHA.111.618355
18. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. *Brain.* (2009) 132:2231–8. doi: 10.1093/brain/awp155
19. Leslie-Mazwi TM, Hamilton S, Mlynash M, Patel AB, Schwamm LH, Lansberg MG, et al. DEFUSE 3 non-DAWN patients. *Stroke.* (2019) 50:618–25. doi: 10.1161/STROKEAHA.118.023310
20. Nogueira RG, Kemmling A, Souza LM, Payabvash S, Hirsch JA, Yoo AJ, et al. Clinical diffusion mismatch better discriminates infarct growth than mean transit time-diffusion weighted imaging mismatch in patients with middle cerebral artery-M1 occlusion and limited infarct core. *J Neurointerv Surg.* (2017) 9:127–30. doi: 10.1136/neurintsurg-2014-011602
21. Yu Y, Han Q, Ding X, Chen Q, Ye K, Zhang S, et al. Defining core and penumbra in ischemic stroke: a voxel- and volume-based analysis of whole brain CT perfusion. *Sci Rep.* (2016) 6:20932. doi: 10.1038/srep20932
22. Lin L, Cheng X, Bivard A, Levi CR, Dong Q, Parsons MW. Quantifying reperfusion of the ischemic region on whole-brain computed tomography perfusion. *J Cereb Blood Flow Metab.* (2016) 37:2125–36. doi: 10.1177/0271678X16661338
23. Bivard A, Lou M, Levi CR, Krishnamurthy V, Cheng X, Aviv RI, et al. Too good to treat? Ischemic stroke patients with small computed tomography perfusion lesions may not benefit from thrombolysis. *Ann Neurol.* (2016) 80:286–93. doi: 10.1002/ana.24714
24. Tian H, Parsons MW, Levi CR, Cheng X, Aviv RI, Spratt NJ, et al. Intravenous Thrombolysis may not improve clinical outcome of acute ischemic stroke patients without a baseline vessel occlusion. *Front Neurol.* (2018) 9:405. doi: 10.3389/fneur.2018.00405
25. Wintermark M, Albers GW, Broderick JP, Demchuk AM, Fiebach JB, Fiehler J, et al. Acute stroke imaging research roadmap II. *Stroke.* (2013) 44:2628–39. doi: 10.1161/STROKEAHA.113.002015

26. Austein F, Riedel C, Kerby T, Meyne J, Binder A, Lindner T, et al. Comparison of perfusion CT software to predict the final infarct volume after thrombectomy. *Stroke*. (2016) 47:2311–7. doi: 10.1161/STROKEAHA.116.013147

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Association Between Ultrasound Parameters and History of Ischemic or Hemorrhagic Stroke in Patients With Moyamoya Disease

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Objective: To explore the association between ultrasound parameters and previous ischemic or hemorrhagic stroke in patients with moyamoya disease (MMD), and develop an ultrasound-based nomogram to identify stroke in patients with MMD.

Methods: We prospectively enrolled 52 consecutive patients (92 hemispheres) with MMD at the Beijing Tiantan Hospital. Thirty-six patients (65 hemispheres) were assigned to the training dataset from September 2019 to February 2020, and 16 patients (27 hemispheres) were assigned to the validation dataset from March 2020 to July 2020. Multivariate logistic regression analysis was applied to identify ultrasound parameters associated with previous history of ipsilateral stroke in patients with MMD, and a nomogram was subsequently constructed to identify stroke in patients with MMD. The performance of the nomogram was evaluated with respect to discrimination, calibration, and clinical usefulness.

Results: Multivariate analysis indicated that the flow volume (FV) of the extracranial internal carotid artery (EICA) and the peak systolic velocity (PSV) of the posterior cerebral artery (PCA) were independently associated with ipsilateral stroke in patients with MMD, a nomogram incorporating these two parameters was constructed to identify stroke patients. The area under the receiver operating characteristic (AUROC) curves was 0.776 (95% CI, 0.656–0.870) in the training dataset and 0.753 (95% CI, 0.550–0.897) in the validation dataset suggested that the model had good discrimination ability. The calibration plot showed good agreement in both the two datasets. The decision curve analysis (DCA) revealed that the nomogram was clinically useful.

Conclusions: Ultrasound parameters of EICA and PCA are independently associated with history of previous ipsilateral ischemic or hemorrhagic stroke in patients with MMD. The present ultrasound-based nomogram might provide information to identify MMD patients with high risk of stroke.

Future long-term follow-up studies are needed to prove the predictive value in other independent cohorts.

Clinical Trial Registration: http://www.chictr.org.cn/index.aspx. Unique Identifier: ChiCTR1900026075.

Keywords: moyamoya disease, stroke, ultrasound, nomogram, extracranial internal carotid artery, posterior cerebral artery

INTRODUCTION

Moyamoya disease (MMD), which is a rare disease with unknown etiology, predisposes some patients to stroke. It is characterized by progressive stenosis of the terminal portions of the internal carotid arteries and their proximal branches. Reduced blood flow in the main vessels of the intracranial anterior circulation leads to compensatory development of abnormal vascular network (1, 2). Leptomeningeal collateral vessels from the posterior cerebral artery (PCA) are regarded as the main collateral vessels in patients with MMD, and transdural collaterals from the branches of external carotid artery (ECA), including middle meningeal artery, maxillary artery (MA), superficial temporal artery (STA) can also compensate for ischemia in the brain (1, 3, 4). Cerebral ischemia and intracranial bleeding are the main hazards of MMD (2, 5). Studies have shown that regular imaging examination in patients with unilateral MMD can significantly reduce the burden of stroke and improve the clinical prognosis (2, 6).

Digital subtraction angiography (DSA) is the traditional gold standard for pre-operative diagnosis and post-operative prognostic evaluation of MMD, nevertheless, there is concern regarding the invasiveness, high cost of the procedure and the associated exposure to radiation. In situations when DSA is not readily available, magnetic resonance angiography (MRA) combined with magnetic resonance imaging (MRI) is considered as an alternative tool (7), but MRA combined with MRI is expensive, time-intensive and the process is complicated. None of these methods are suitable for the long-term and dynamic monitoring of MMD. Ultrasound is a non-invasive, convenient, and economical method, that has been used in the pre-operative examination and post-operative prognostic evaluation of MMD (8–10). The hemodynamic parameters of extracranial internal carotid artery (EICA), PCA, STA, MA can be easily detected by ultrasound. However, there is a lack of systematic research on the association between ultrasound parameters and stroke in patients with MMD. Therefore, in this study, we used ultrasound to detect the hemodynamic parameters of the EICA, STA, MA, and PCA to identify ipsilateral stroke in patients with MMD.

MATERIALS AND METHODS

Patient Data

We prospectively enrolled consecutive patients diagnosed with MMD based on the guidelines for MMD (7) between September 2019 and July 2020 at the Beijing Tiantan Hospital. The exclusion criteria for our study were: (1) patients who refused ultrasound examination; (2) patients with poor temporal acoustic bone window; (3) MMD patients with diseases that affect cardiac output; (4) patients who underwent prior bypass surgery; (5) patients lack of DSA, CT or MRI examination, or the interval between these examinations and ultrasound was more than 1 month, or during this period, patients exhibited new symptoms or clinical manifestations of sudden aggravation. From September 2019 to February 2020 and March 2020 to July 2020 eligible patients were assigned to training and validation datasets, respectively.

Informed consents were obtained from all eligible patients (or their parents or legal guardians for children under 18 years of age), and this study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University.

Clinical Data

Clinical information, including age, sex, clinical manifestations, radiological findings, history of hypertension, diabetes, hyperlipidemia, smoking, and drinking were recorded. Based on the clinical manifestations on admission, the 92 hemispheres from 52 patients were diagnosed as stroke or non-stroke by the following methods: (1) stroke was defined as patients who had already experienced ischemic stroke or hemorrhagic stroke. Ischemic stroke was a new symptomatic neurological deterioration that was confirmed by MRI as cerebral infarction and could not be attributed to non-ischemic causes. Hemorrhagic stroke was defined as blood permeated into the brain parenchyma that was confirmed by CT (11). (2) Non-stroke was defined as patients who had demonstrated no signs of cerebral infarction or hemorrhage. All the clinical manifestations were confirmed by a neurosurgeon with over 5 years of experience.

Radiological Evaluations

The criteria of collateral circulation were defined by Liu et al. (12). Anterior collateral circulation was assessed based on Suzuki stage (1, 2), Suzuki stage I to VI corresponded to scores of 6 to 1, respectively. Six points corresponded to stage I: narrowing of the internal carotid artery (ICA) apex; 5 points corresponded to stage II: initiation of moyamoya collaterals; 4 points corresponded to stage III: progressive stenosis of the ICA with intensification of moyamoya collaterals; 3 points corresponded to stage IV: development of ECA collaterals; 2 points corresponded to stage V: reduction of moyamoya vessels and intensification of ECA collaterals; and 1 point corresponded to stage VI: complete occlusion of the ICA and disappearance of moyamoya collaterals.

Posterior collateral circulation was assessed according to the anatomical extent of pial collateral blood from the PCA territory

to the middle cerebral artery (MCA) and anterior cerebral artery (ACA) territory (12). Scoring of leptomeningeal collateral networks from the PCA to ACA territory was as following: (1) 1 point: blood supply to the cortical border area between the ACA and PCA territory; and (2) 2 points: blood supply over the central sulcus. Scoring of leptomeningeal collateral networks from the PCA to MCA territory was as following: (1) 1 point: the parieto-occipital branch or the anterior temporal branch of the PCA anastomoses to the MCA; (2) 2 points: blood supply extended to the sylvian fissure; and (3) 3 points: blood supply extended to the occlusion (M1 or proximal M2 segments of the MCA). A score of 0 point was assigned if there were no leptomeningeal anastomoses.

The grading score of the collateral circulation was the sum of the above anterior and posterior collateral circulation scores, it was graded as follows: grade I, 0 to 4 points; grade II, 5 to 8 points; and grade III, 9 to12 points.

Ultrasound Examination

Ultrasound parameters were measured by 2 independent experienced sonographers (SZ and YL), blinded to the radiographic findings and clinical data. Ultrasound examination was performed using a sonographic scanner (EPIQ 7, Philips Medical Systems, Bothell, WA).

Extracranial Internal Carotid Artery

Carotid ultrasound was performed using a 3–12 MHz linear array probe. The patients assumed a supine position with the head slightly turned to the opposite side. The examiner adjusted the depth, grayscale, and focus according to the condition of each patient. The diameter (D) of the EICA was measured at 1–2 cm above the carotid sinus. Then color and pulse doppler were used to measure the time-averaged mean velocity (TAMV). The gain, pulse-repetition frequency, and wall filter were corrected to appropriate condition, the doppler sample size was adjusted to the same width as the vessel, the doppler angle was $<60^{\circ}$, and after at least three cardiac cycles, the TAMV was measured. The flow volume (FV) was obtained according to the formula $FV = TAMV \times [(D/2)^2 \times \pi]$ (13, 14). The level of the FV in EICA was categorized as "<50 ml/min," "50–99 ml/min," "100–149 ml/min," "150–199 ml/min," or ">200 ml/min."

Superficial Temporal Artery

The STA was examined using a 3–12 MHz linear array probe. The patient assumed a supine position with the head turned to the opposite side. The probe was placed before the ear at the trunk of the STA. The examiner adjusted the depth, grayscale, and focus according to the condition of each patient. Color and pulse doppler were subsequently used to measure the peak systolic velocity (PSV) of the STA. The gain, pulse-repetition frequency, and wall filter were corrected to appropriate condition, the doppler sample size was adjusted to about 1/3 of the STA, and the doppler angle was $<60^{\circ}$. Then, the PSV of the STA was measured. The level of the PSV in STA was categorized as "<50 cm/s" or "50–99 cm/s."

Maxillary Artery

The MA was examined with a 1–5 MHz convex transducer. The patient assumed a supine position with the head turned to the opposite side. The probe was placed at the mandibular angle and pointed toward the tip of the nose. The examiner adjusted the depth, grayscale, and focus according to the condition of each patient. Color and pulse doppler were subsequently used to measure the PSV of the MA. The gain, pulse-repetition frequency, and wall filter were corrected to appropriate condition, the doppler sample size was adjusted to about 1/3 of the MA, and the doppler angle was $<60^{\circ}$. Then, the PSV of MA was measured. The level of the PSV in MA was categorized as "<50 cm/s," "50–99 cm/s," or "100–149 cm/s."

Posterior Cerebral Artery

Transcranial color-coded sonography (TCCS) was performed using a 1.5–3.0 MHz phased array probe. The P2 segment of the PCA was detected through the transtemporal window. Color and pulse doppler were used to measure the PSV of the PCA. The patient assumed a lateral position. The examiner adjusted the parameters of the sonographic scanner according to the condition of each patient. The depth of insonation was adjusted to 60–70 mm, the doppler sample size was 3–5 mm, the doppler angle was $<60^{\circ}$. Then, the PSV of the PCA was measured. The level of the PSV in PCA was categorized as "<50 cm/s," "50–99 cm/s," "100–149 cm/s," "150–199 cm/s," or ">200cm/s."

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY). Continuous variables were described as medians (interquartile ranges), ranked variables and categorical variables were described as percentages. The Mann-Whitney *U*-test was used for continuous variables and ranked variables; the chi-square test was used for categorical variables. Weighted kappa (κ) was used to assess the interrater reliability of ultrasound parameters between the 2 sonographers in the training dataset. As for ultrasound parameters we used the parameters measured by the first rater. Multivariate logistic regression analysis was applied to identify ultrasound parameters associated with previous history of ipsilateral stroke in patients with MMD. The rms package for R software 3.6.1 was used to establish a nomogram incorporating the independent associated parameters. Then, a validation dataset was used for verification. The discrimination ability of the nomogram was evaluated using the area under the receiver operating characteristic (AUROC) curves. The consistency between the observed and the assessed probability of stroke was evaluated by calibration curve. The Hosmer-Lemeshow-test was performed to verify the suitability of the nomogram (15, 16). Meanwhile, decision curve analysis was performed to evaluate the clinical applicability of the model. All calculated *P*-values were 2-tailed, and a P-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

During the study period, of 205 patients with MMD, 13 patients refused ultrasound examination, 8 patients with poor temporal acoustic bone window, 10 patients with diseases that affect cardiac output, 48 patients underwent prior bypass surgery and 74 patients lack of DSA, CT, or MRI examination, or the interval between these examinations and ultrasound was more than 1 month, or during this period, patients exhibited new symptoms or clinical manifestations of sudden aggravation were excluded. Finally, 52 patients (92 hemispheres) met the inclusion criteria were included in the analysis. Among them, from September 2019 to February 2020, 36 patients (65 hemispheres) were assigned to the training dataset, from March 2020 to July 2020, 16 patients (27 hemispheres) were assigned to the validation dataset. Of 52 eligible patients, 12 patients had unilateral hemispheric involvement and 40 patients had bilateral hemispheric involvement. The demographics, clinical history, angiographic findings and ultrasound parameters of patients with MMD in the training and validation datasets were shown in **Table 1**. Stroke accounted for 38.5% (25/65) in the training dataset, and 40.7% (11/27) in the validation dataset. There were no differences in the above data between the two datasets.

TABLE 1 | Baseline characteristics of eligible patients.

Characteristics	Training dataset ($n = 65$ hemispheres)	Validation dataset ($n = 27$ hemispheres)	*P*-value
Age, years	38.0 (28.5–46.0)	37.0 (34.0–45.0)	0.725
Sex, male, *n* (%)	30 (46.2)	12 (44.4)	0.881
Clinical history, *n* (%)			
Hypertension	15 (23.1)	6 (22.2)	0.929
Diabetes	4 (6.2)	2 (7.4)	0.825
Hyperlipidemia	5(7.7)	1 (3.7)	0.809
Smoking	5 (7.7)	2 (7.4)	0.508
Drinking	5 (7.7)	2 (7.4)	0.508
Stroke, *n* (%)	25 (38.5)	11 (40.7)	0.838
Suzuki stage, *n* (%)			0.877
I	5 (7.7)	3 (11.1)	
II	15 (23.1)	6 (22.2)	
III	21 (32.3)	8 (29.6)	
IV	12 (18.5)	5 (18.5)	
V	11 (16.9)	4 (14.8)	
VI	1 (1.5)	1 (3.7)	
Collateral circulation, *n* (%)			0.241
Grade I	13 (20)	3 (11.1)	
Grade II	44 (67.7)	19 (70.4)	
Grade III	8 (12.3)	5 (18.5)	
Ultrasound parameters			
$EICA_{FV}$ (ml/min)			
<50	15 (23.1)	6 (22.2)	0.772
50–99	15 (23.1)	6 (22.2)	
100–149	14 (21.5)	9 (33.3)	
150–199	12 (18.5)	3 (11.1)	
>200	9 (13.8)	3 (11.1)	
PCA_{PSV} (cm/s)			0.862
<50	7 (10.8)	1 (3.7)	
50–99	19 (29.2)	9 (33.3)	
100–149	22 (33.8)	11 (40.7)	
150–199	11 (16.9)	4 (14.8)	
>200	6 (9.2)	2 (7.4)	
STA_{PSV} (cm/s)			0.871
<50	13 (20)	5 (18.5)	
50–99	52 (80)	22 (81.4)	
MA_{PSV} (cm/s)			0.359
<50	17 (26.1)	6 (22.2)	
50–99	42 (64.6)	16 (59.3)	
100–149	6 (9.2)	5 (18.5)	

$EICA_{FV}$, flow volume of extracranial internal carotid artery; PCA_{PSV}, peak systolic velocity of posterior cerebral artery; STA_{PSV}, peak systolic velocity of superficial temporal artery; MA_{PSV}, peak systolic velocity of maxillary artery.

Interrater Reliability of Ultrasound Parameters Between 2 Sonographers

The interrater reliability between 2 sonographers was good for the FV of the EICA (κ: 0.79, 95 % CI: 0.70–0.89) and the PSV of the MA (k: 0.76, 95 % CI: 0.62–0.91); The interrater reliability was excellent for the PSV of the STA (k: 0.82, 95 % CI: 0.65–0.99) and the PSV of the PCA (k: 0.83, 95 % CI: 0.74–0.93).

Multivariate Logistic Regression Analysis of Associated Ultrasound Parameters for Previous History of Ipsilateral Stroke in Patients With MMD

Univariate analysis revealed that the FV of the EICA and the PSV of the PCA were associated ultrasound parameters for previous history of ipsilateral stroke in patients with MMD. Multivariate analysis revealed that when the variables were not adjusted in model 1, the FV of the EICA (OR = 0.511, 95% CI: 0.319–0.821, $P = 0.005$) and the PSV of the PCA (OR = 0.550, 95% CI:0.313–0.966, $P = 0.037$) were independent associated ultrasound parameters for stroke. After adjusting for age and sex in model 2, the FV of the EICA (OR = 0.476, 95% CI: 0.282–0.804, $P = 0.005$) and the PSV of the PCA (OR = 0.545, 95% CI: 0.311–0.955, $P = 0.034$) were still independent associated ultrasound parameters for stroke (**Table 2**). By using these ultrasound parameters, we constructed a model to identify stroke in patients with MMD.

Construction of the Nomogram

A nomogram was constructed based on the independent associated ultrasound parameters identified by the multivariable analysis to differentiate between stroke and non-stroke patients with MMD (**Figure 1**). With the nomogram, the identification ability could be calculated by summing the points of each variable, and then locating the sum on the total points axis. In a representative case, a 33-year-old woman with MMD, the FV of the right EICA was 36.1 ml/min (100 points), the PSV of the right PCA was 69.8 cm/s (67 points), and the sum was 167

TABLE 2 | Logistic regression for ultrasound parameters to identify stroke in patients with MMD.

Variables	Univariable analysis		Multivariable analysis			
			Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years	1.007 (0.973–1.042)	0.691				
Male sex	0.960 (0.351–2.626)	0.937				
History of risk factors						
Hypertension	1.088 (0.334–3.541)	0.889				
Diabetes	1.652 (0.218–12.545)	0.627				
Hyperlipidemia	1.072 (0.166–6.912)	0.941				
Smoking	2.591 (0.401–16.721)	0.317				
Drinking	2.591 (0.401–16.721)	0.317				
Ultrasound parameters						
$EICA_{FV}$	0.495 (0.314–0.779)	0.002	0.511 (0.319–0.821)	0.005	0.476 (0.282–0.804)	0.005
STA_{PSV}	0.672 (0.197–2.293)	0.525				
MA_{PSV}	0.857 (0.356–2.064)	0.731				
PCA_{PSV}	0.520 (0.307–0.879)	0.015	0.550 (0.313–0.966)	0.037	0.545 (0.311–0.955)	0.034

OR, odds ratio; 95% CI, 95% confidence interval; $EICA_{FV}$, flow volume of extracranial internal carotid artery; PCA_{PSV}, peak systolic velocity of posterior cerebral artery; STA_{PSV}, peak systolic velocity of superficial temporal artery; MA_{PSV}, peak systolic velocity of maxillary artery.

[a] *Unadjusted.*

[b] *Adjusted for age and sex.*

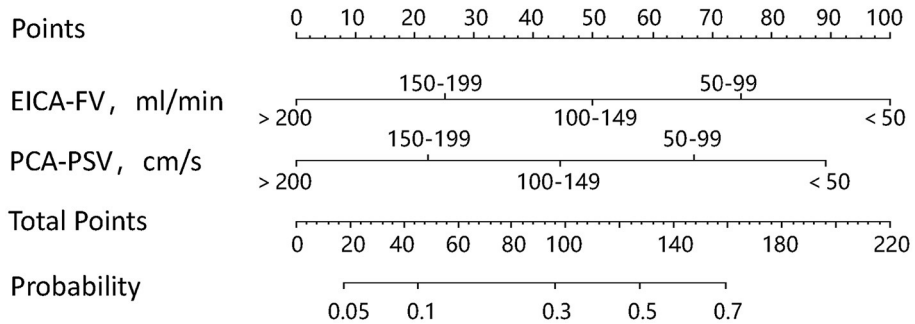

FIGURE 1 | The nomogram used to identify stroke in patients with MMD. To use the nomogram, first, find the value of each variable, draw a vertical line to the points axis to find the corresponding points, add the points of each variable to get the total points, and then, draw a vertical line from the total points axis to find the probability of stroke.

points, which could be converted into >70% probability of right hemisphere stroke (**Figure 2**).

Performance of the Nomogram

The AUROC curves was 0.776 (95% CI, 0.656–0.870) in the training dataset and 0.753 (95% CI, 0.550–0.897) in the validation dataset suggested that the model had good discrimination ability (**Figures 3A**, **4A**). The *P*-value of the Hosmer-Lemeshow test was 0.311 and 0.296 in the training and validation datasets, respectively, indicating a good fit of the model. The calibration curve of the nomogram showed good consistency between the observed and assessed outcomes in both the training and

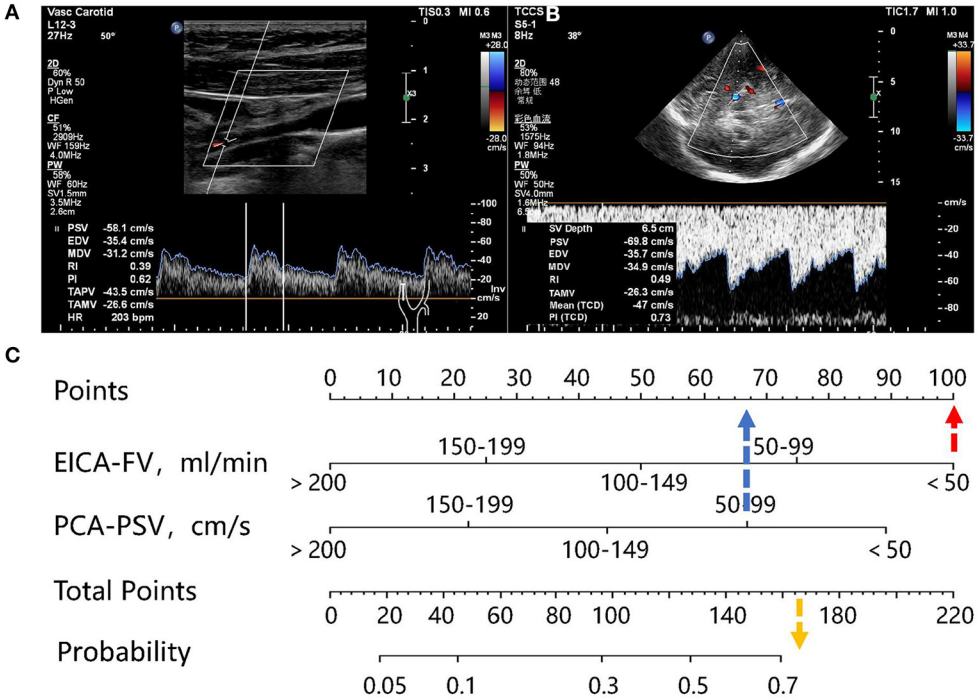

FIGURE 2 | Representative case. **(A)** A 33-year-old woman with MMD. Carotid ultrasonography showed that the diameter of right EICA was 0.19 cm, the TAMV was 21.2 cm/s, and the FV was 36.1 ml/min. **(B)** The TCCS showed that the PSV of the PCA was 69.8 cm/s. **(C)** the FV of the right EICA was 36.1 ml/min, corresponding to100 points, the PSV of right PCA was 69.8 cm/s, corresponding to 67 points, and the sum was 167 points, which can be converted to a probability of >70%.

validation datasets (**Figures 3B**, **4B**). The decision curve analysis (DCA) indicated that when the threshold probability ranged from 0.1 to 0.75, clinicians or patients could obtain a net benefit by using this nomogram to differentiate between stroke and non-stroke patients with MMD, and that the nomogram was therefore clinically useful (**Figure 5**).

DISCUSSION

In this study, we constructed an easy-to-use nomogram incorporating the FV of the EICA and the PSV of the PCA to identify previous history of ipsilateral stroke in patients with MMD. The discrimination ability of the nomogram was evaluated by using the AUROC, with an AUROC of 0.5 being defined as meaningless; 0.5–0.7 being defined as fair; 0.7–0.9 being defined as good; and >0.9 being defined as excellent. Our nomogram showed good discrimination and good calibration in both the training and validation datasets. The DCA indicated that the nomogram was clinically useful.

The clinical manifestations and outcomes of patients with MMD are heterogeneous. Digital subtraction angiography (DSA) is the traditional gold standard for pre-operative diagnosis and post-operative prognostic evaluation of MMD. According to DSA findings, the severity of the disease is often divided into six progressive stages, which is called as Suzuki stage and were defined by Suzuki and Takaku in 1969 (1). However, DSA is invasive and requires exogenous contrast agent and ionizing radiation. Although it has improved our understanding of MMD, it is not an ideal method for long-term monitoring and assessing risk of poor clinical outcomes in patients with MMD.

Ultrasound is a non-invasive, repeatable, and economical technique, that has been used to screen MMD, detect moyamoya spontaneous anastomosis pre-operatively and evaluate the prognosis post-operatively (8–10). Hong et al. used ultrasound to explore the FV of the EICA in MMD patients, the results showed that the FV of the EICA is inversely correlated with Suzuki stage (17). Yasuda evaluated the ratio of the diameter of the EICA to that of the common carotid artery by using carotid ultrasound and cerebral angiography, and the results confirmed that the lower the ratio, the more likely a patient is to experience ipsilateral cerebral vascular events (18). Our study coincided with previous studies. We found that the FV of the EICA is an independent associated parameter for previous history of ipsilateral stroke in patients with MMD. The FV of the EICA is the product of the cross-sectional area and the time-averaged mean velocity (13, 14). As MMD progresses, the diameter of the EICA gradually decreases, which is known as the bottle neck sign (18, 19), leading to a decrease in the cross-sectional area of the EICA. As stenosis of the terminal portions of the ICA progresses, the increased vascular resistance at the distal portions leads to decreased velocity of the EICA, which eventually results in a reduction in the FV of the EICA. Due to the reduced FV of the EICA, the ACA and MCA territory are susceptible to

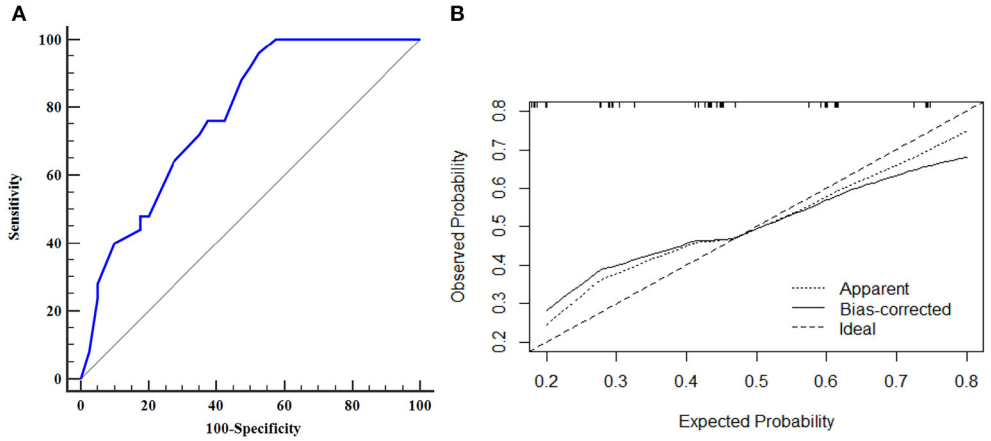

FIGURE 3 | ROC curve and calibration plot of the nomogram in the training dataset. **(A)** ROC curve of the nomogram, AUROC was 0.776 (95% CI, 0.656–0.870); **(B)** Calibration plot of the nomogram in the training dataset.

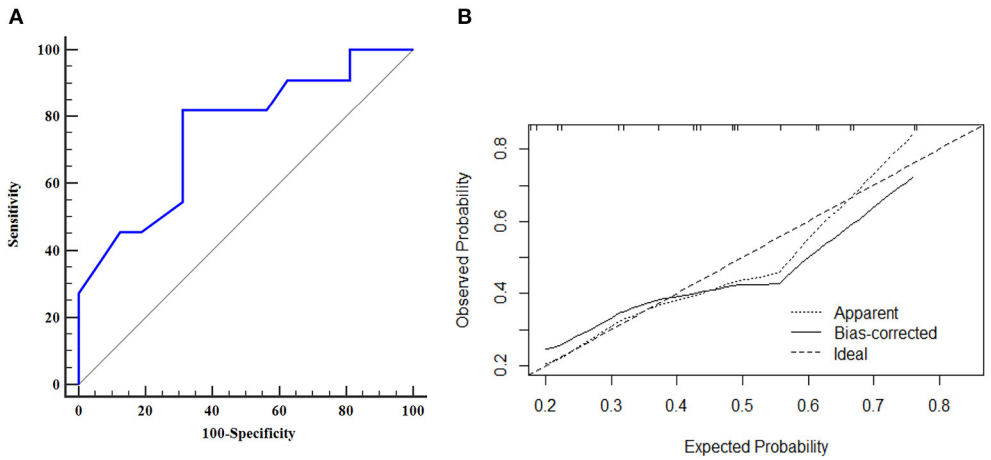

FIGURE 4 | ROC curve and calibration plot of the nomogram in the validation dataset. **(A)** ROC curve of the nomogram, AUROC was 0.753 (95% CI, 0.550–0.897); **(B)** Calibration plot of the nomogram in the validation dataset.

hypoperfusion (20). Hypoperfusion increases the susceptibility to ischemia, abnormal hemodynamics can lead to ischemic stroke (13). Cerebral hemorrhage is an adverse consequence of a compensatory response to cerebral ischemia, rupture of the fragile moyamoya vessels and Willis aneurysm under abnormally increased hemodynamic stress can result in hemorrhagic stroke (21). Therefore, the FV of the EICA decreased as Suzuki stage advanced, the FV of the EICA is an independent associated parameter for previous history of ipsilateral stroke in patients with MMD.

However, in some cases, the Suzuki stage may not correlate with clinical severity, because the main blood vessels of anterior circulation occlusions may be compensated by collateral vessels. Leptomeningeal collaterals from the PCA are regarded as the main collateral vessels, and transdural collaterals from the ECA can also compensate for ischemia in the brain (1, 3, 22, 23). Previous studies have shown that the more extensive the collateral vessels produced by the PCA supply the ACA and MCA territory, the less likely a patient is to suffer from ischemic stroke and parenchymal hemorrhage (12, 24, 25). Our research seems to be consistent with previous studies. In our study, TCCS was used to detect the PSV of the PCA. Although TCCS cannot directly and stereoscopically display the lumen structure of intracranial vessels or the density of abnormal moyamoya vessels, but it can reflect the compensation from the PCA to anterior circulation by measuring the flow velocity. We found that the PSV of the PCA is an independent associated parameter for previous history of ipsilateral stroke in patients with MMD. In our study, we chose the P2 segment of the PCA to explore hemodynamic changes, because in some cases, the PCA is partially or completely derived from the ICA, with the P1 segment being absent or exhibiting dysplasia. The P1 segment of the PCA mainly supplies the thalamus and basal ganglia. In addition, stenosis and occlusion of the PCA initially occurs in its proximal segment. Therefore, study

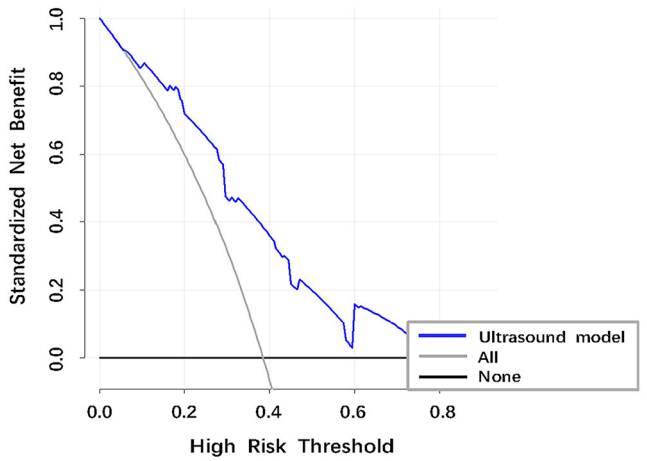

FIGURE 5 | Decision curve analysis (DCA) of the ultrasound model to identify stroke in patients with MMD. The vertical axis was the standardized net benefit. The horizontal axis was the corresponding risk threshold. The DCA showed that if the threshold probability ranged from 0.10 to 0.75, using the nomogram to identify stroke in patients provided a net benefit.

of the P2 segment is more meaningful (26, 27). We found that the higher the PSV of the PCA, the less likely a patient is to experience a stroke in the ipsilateral hemisphere. The cause of this is that a high PSV of the PCA can lead to abundant collateral circulation. If the P1 segment of the PCA is narrowed, the P2 segment presents with low-velocity blood flow, it cannot form abundant collateral circulation. Therefore, the higher the PSV of PCA, the more collateral circulation formed by the PCA, resulting in lower stroke occurrence in patients with MMD (27). We also measured the PSV of the STA and MA in patients with MMD, However, these parameters were not found to be statistically significant in the univariate and multivariate analyses.

Recently, Liu et al. proposed a new MMD grading system to assess clinical symptoms by combining Suzuki stage with the leptomeningeal system from the PCA. This new MMD grading system correlates well with hemodynamic status and clinical symptoms, and contributes to risk stratification and prognostic predictions in patients with MMD (13). In our study, we constructed a nomogram to identify stroke in patients with MMD incorporating ultrasound parameters of the PCA and EICA, which has good discrimination and calibration. These findings indicated that the nomogram might become an important method for identification of stroke in patients with MMD, clinicians might take targeted individual preventive and control measures.

Our study has some limitations. First, because the incidence of MMD is low, our sample size was relatively small. We divided the patients into stroke group and non-stroke group according to their clinical manifestations, but did not further divide the patients into ischemic stroke group, hemorrhagic stroke group, transient ischemic attack group, and asymptomatic group. Second, this study was a single-center study, and there was no ultrasound examination before stroke onset in patients with MMD. Therefore, Further validation with prospective registration and long-term follow-up is needed to prove the predictive ability of our findings.

CONCLUSIONS

Ultrasound parameters of EICA and PCA are associated with previous history of ipsilateral stroke in patients with MMD. The present ultrasound-based nomogram may provide information to identify MMD patients with high risk of stroke, large-scale and prospective longitudinal cohort studies are needed to validate its predictability.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SZ, PG, YL, and JW: conception and design. SZ, PG, YL, JW, ZS, JZ, and LH: acquisition of data. SZ and PG: analysis and interpretation of data. SZ: drafting the article. WH: approved the final version of the manuscript on behalf of all authors. LC, DZ, and WH: study supervision. All authors critically revising the article and reviewed submitted version of manuscript.

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REFERENCES

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol.* (1969) 20:288–99. doi: 10.1001/archneur.1969.00480090076012
2. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med.* (2009) 360:1226–37. doi: 10.1056/NEJMra0804622
3. Yamada I, Himeno Y, Suzuki S, Matsushima Y. Posterior circulation in moyamoya disease: angiographic study. *Radiology*. (1995) 197:239–46. doi: 10.1148/radiology.197.1.7568830
4. Suzuki J, Kodama N. Moyamoya disease–a review. *Stroke.* (1983) 14:104–9. doi: 10.1161/01.STR.14.1.104
5. Kuroda S, Houkin K. Moyamoya disease: current concepts and future perspectives. *Lancet Neurol.* (2008) 7:1056–66. doi: 10.1016/S1474-4422(08)70240-0

6. Smith ER, Scott RM. Progression of disease in unilateral moyamoya syndrome. *Neurosurg Focus*. (2008) 24:E17. doi: 10.3171/FOC/2008/24/2/E17
7. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir*. (2012) 52:245–66. doi: 10.2176/nmc.52.245
8. Seo WK, Choi CW, Kim CK, Oh K. Contrast-enhanced color-coded doppler sonography in moyamoya disease: a retrospective study. *Ultrasound Med Biol*. (2018) 44:1281–85. doi: 10.1016/j.ultrasmedbio.2018.01.002
9. Chen L, Xu B, Wang Y, Liao Y, Pan H, Wang Y. Preoperative evaluation of moyamoya spontaneous anastomosis of combined revascularization donor vessels in adults by duplex ultrasonography. *Br J Neurosurg*. (2018) 32:412–17. doi: 10.1080/02688697.2017.1406450
10. Yeh SJ, Tang SC, Tsai LK, Chen YF, Liu HM, Chen YA, et al. Ultrasonographic changes after indirect revascularization surgery in pediatric patients with Moyamoya disease. *Ultrasound Med Biol*. (2016) 42:2844–51. doi: 10.1016/j.ultrasmedbio.2016.07.016
11. Amarenco P, Lavallée PC, Monteiro Tavares L, Labreuche J, Albers GW, Abboud H, et al. Five-year risk of stroke after TIA or minor ischemic stroke. *N Engl J Med*. (2018) 37:2182–90. doi: 10.1056/NEJMoa1802712
12. Liu ZW, Han C, Zhao F, Qiao PG, Wang H, Bao XY, et al. Collateral circulation in Moyamoya disease: a new grading system. *Stroke*. (2019) 50:2708–15. doi: 10.1161/STROKEAHA.119.024487
13. Scheel P, Ruge C, Petruch UR, Schöning M. Color duplex measurement of cerebral blood flow volume in healthy adults. *Stroke*. (2000) 31:147–50. doi: 10.1161/01.STR.31.1.147
14. Dörfler P, Puls I, Schliesser M, Mäurer M, Becker G. Measurement of cerebral blood flow volume by extracranial sonography. *J Cereb Blood Flow Metab*. (2000) 20:269–71. doi: 10.1097/00004647-200002000-00007
15. Rouzier R, Coutant C, Incitti R, Natowicz R, Chahine G, Uzan S, et al. Breast cancer: nomograms to predict pathologic response after preoperative chemotherapy. *J Med Liban*. (2009) 57:89–92.
16. Graesslin O, Abdulkarim BS, Coutant C, Huguet F, Gabos Z, Hsu L, et al. Nomogram to predict subsequent brain metastasis in patients with metastatic breast cancer. *J Clin Oncol*. (2010) 28:2032–7. doi: 10.1200/JCO.2009.24.6314
17. Hong JM, Hong YH, Lee SJ, Lee SE, Lee JS, Shin DH, Hemodynamic contribution of transdural collateral flow in adult patients with moyamoya disease. *Neurol Sci*. (2016) 37:1969–77. doi: 10.1007/s10072-016-2700-0
18. Yasuda C, Arakawa S, Shimogawa T, Kanazawa Y, Sayama T, Haga S, et al. Clinical significance of the champagne bottle neck sign in the extracranial carotid arteries of patients with Moyamoya disease. *AJNR Am J Neuroradiol*. (2016) 37:1898–902. doi: 10.3174/ajnr.A4815
19. Yasaka M, Ogata T, Yasumori K, Inoue T, Okada Y, Bottle neck sign of the proximal portion of the internal carotid artery in moyamoya disease. *J Ultrasound Med*. (2006) 25:1547–52. doi: 10.7863/jum.2006.25.12.1547
20. Fan AP, Khalighi MM, Guo J, Ishii Y, Rosenberg J, Wardak M, et al. Identifying hypoperfusion in Moyamoya disease with arterial spin labeling and an (O)-water positron emission tomography/magnetic resonance imaging normative database. *Stroke*. (2019) 50:373–80. doi: 10.1161/STROKEAHA.118.023426
21. Lv X. Hemorrhagic factors of Moyamoya disease. *AJNR Am J Neuroradiol*. (2019) 40:1672–3. doi: 10.3174/ajnr.A6217
22. Kuroda S, Hashimoto N, Yoshimoto T, Iwasaki Y. Radiological findings, clinical course, and outcome in asymptomatic moyamoya disease: results of multicenter survey in Japan. *Stroke*. (2007) 38:1430–5. doi: 10.1161/STROKEAHA.106.478297
23. Strother MK, Anderson MD, Singer RJ, Du L, Moore RD, Shyr Y, et al. Cerebrovascular collaterals correlate with disease severity in adult North American patients with Moyamoya disease. *AJNR Am J Neuroradiol*. (2014) 35:1318–24. doi: 10.3174/ajnr.A3883
24. Mugikura S, Takahashi S, Higano S, Shirane R, Kurihara N, Furuta S, et al. The relationship between cerebral infarction and angiographic characteristics in childhood moyamoya disease. *AJNR Am J Neuroradiol*. (1999) 20:336–43.
25. Funaki T, Takahashi JC, Takagi Y, Yoshida K, Araki Y, Kikuchi T, et al. Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease. *J Neurosurg Pediatr*. (2013) 12:626–32. doi: 10.3171/2013.9.PEDS13111
26. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ihara I, Yamagata S, Study of the posterior circulation in moyamoya disease. Part 2: visual disturbances and surgical treatment. *J Neurosurg*. (1986) 65:454–60. doi: 10.3171/jns.1986.65.4.0454
27. Wang JZ, He W, Zhang D, Yu LB, Zhao YH, Cai JX, Changing ischemic lesion patterns and hemodynamics of the posterior cerebral artery in Moyamoya disease. *J Ultrasound Med*. (2019) 38:2621–30. doi: 10.1002/jum.14959

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Scoring Model to Predict Functional Outcome in Poor-Grade Aneurysmal Subarachnoid Hemorrhage

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Background: Patients with poor-grade aneurysmal subarachnoid hemorrhage (aSAH), defined as World Federation of Neurosurgical Societies (WFNS) grades IV–V have high rates of disability and mortality. The objective of this study was to accurately prognosticate the outcomes of patients with poor-grade aSAH by developing a new scoring model.

Methods: A total of 147 poor-grade aSAH patients in our center were enrolled. Risk variables identified by multivariate logistic regression analysis were used to devise a scoring model (total score, 0–9 points). The scores were estimated on the basis of β coefficients. A cohort of 68 patients from another institute was used to validate the model.

Results: Multivariate logistic regression analysis revealed that modified Fisher grade >2 [odds ratio [OR], 2.972; $P = 0.034$], age ≥65 years (OR, 3.534; $P = 0.006$), conservative treatment (OR, 5.078; $P = 0.019$), WFNS grade V (OR, 2.638; $P = 0.029$), delayed cerebral ischemia (OR, 3.170; $P = 0.016$), shunt-dependent hydrocephalus (OR, 3.202; $P = 0.032$), and cerebral herniation (OR, 7.337; $P < 0.001$) were significant predictors for poor prognosis [modified Rankin Scale [mRS] ≥3]. A scoring system was constructed by the integration of these factors and divided the poor-grade aSAH patients into three categories: low risk (0–1 points), intermediate risk (2–3 points), and high risk (4–9 points), with predicted risks of poor prognosis of 11, 52, and 87%, respectively ($P < 0.001$). The area under the curve in the derivation cohort was 0.844 (95% CI, 0.778–0.909). The AUC in the validation cohort was 0.831 (95% CI, 0.732–0.929).

Conclusions: The new scoring model can improve prognostication and help decision-making for subsequent complementary treatment in patients with aSAH.

Keywords: scoring system, prognosis, poor-grade, aneurysmal subarachnoid hemorrhage, model

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INTRODUCTION

Intracranial aneurysms are abnormal protrusions of the intracranial arterial wall arising from various causes (1, 2). The prevalence rate of intracranial aneurysms in the global population (mean age, 50 years) is up to 3.2% (3). A previous report described that approximately, 1–2% of these aneurysms will rupture (4). According to statistics,

the global incidence of aneurysmal subarachnoid hemorrhage (aSAH) is 9–11 per 100,000 people/year. Furthermore, poor-grade aSAH [World Federation of Neurological Surgeons [WFNS] grades IV–V] accounts for 18–30% of all aSAH cases (5, 6). A meta-analysis by Han et al. (7) reported a 26% mortality rate for poor-grade aSAH. At present, most related literature indicates that the disability rate for poor-grade aSAH exceeds 60% (8).

Regarding prognosis prediction, the International Subarachnoid Aneurysm Trial (ISAT) could achieve an accurate prediction of 60-day mortality after aSAH (9). Meanwhile, the Subarachnoid Hemorrhage International Trialists (SAHIT) model successfully predicted long-term outcomes and was used to counsel patients with aSAH and their family members (10). An external validation of the SAHIT model using the Barrow Ruptured Aneurysm Trial (BRAT) cohort revealed that its area under the curve (AUC) for unfavorable outcomes was 0.734 (11). It is worth pointing out that these studies included patients exposed to different subgroups of various treatment procedures, and that most of them were good-grade aSAH patients eligible for surgical treatment. Although good-grade and poor-grade aSAH patients differ in disease progression and survival prognosis (5, 12), previous studies typically combined these patients for analysis without detailed stratification (9–11). Therefore, the previous predictive models have some limitations for the accurate prediction of outcomes in poor-grade aSAH patients. The objective of the present study was to devise a new scoring system that can evaluate the prognosis of patients with poor-grade aSAH intuitively.

MATERIALS AND METHODS

Study Design

The derivation cohort comprised poor-grade aSAH patients who were treated in the Department of Neurosurgery at our center from January 2013 to January 2019. The validation cohort was composed of aSAH patients treated in the Department of Neurosurgery at another institute from January 2016 to January 2019. The inclusion criteria were: (1) aSAH diagnosed by computed tomography (CT) or lumbar puncture in the medical center; (2) aneurysm confirmed as the cause of SAH on digital subtraction angiography (DSA), three-dimensional CT angiography, or magnetic resonance angiography; (3) WFNS grade IV and V; (4) signed informed consent from family members of patients to cooperate with clinical treatment procedures; and (5) patients without surgical treatment in referral centers. The exclusion criteria were: (1) traumatic, mycotic, or arteriovenous malformation-related aneurysms or SAH of unknown etiology; (2) WFNS grade less than or equal to III; (3) absence of important medical information for patients; and (4) patients treated with medical instruments or drugs that were not approved. The STROBE statement guideline has been implemented in this manuscript.

Clinical Therapeutic Protocol

All patients admitted under emergency conditions received early resuscitation, early CT angiography, multidisciplinary consensus consultation, conservative treatment, or surgical treatment. A multidisciplinary team of neurosurgeons and anesthesiologists made therapeutic decisions on the basis of the clinical conditions and family members' consent. The treatment mode in our study was divided into two categories: (1) the conservative group: patients who received pure medicinal conservative treatment or patients who received other basic surgical methods without treatment of the underlying aneurysm, such as external drainage surgery, hematoma evacuation, and decompressive craniectomy; and (2) the clipping or coiling group: patients who underwent primary aneurysm embolization or clipping alone, or combined with a basic surgical operation involving coiling or clipping. Patients underwent surgical treatment in accordance with an early treatment strategy (within 72 h). All aSAH patients were treated with routine SAH treatments, including mannitol, anticonvulsants, triple-H (hypervolemia/hypertension/hemodilution) treatment, and nimodipine treatment. Antiplatelets were administered to prevent thrombosis after stent-assisted embolization.

Clinical Data and Variable Definitions

The clinical variables were collected retrospectively from the hospital database. Patient's baseline information and imaging information were collected by two doctors separately, and any conflicting items were evaluated again by a senior doctor. Age was divided into two subcategories in accordance with the cutoff age of 65 years. The modified Fisher grade was divided into two subcategories in accordance with the cutoff value of grade 2. A wide-necked aneurysm was defined as an aneurysm with a neck width $\geq$4 mm or a neck ratio exceeding 1:2. Cerebral herniation was diagnosed based on CT results and corresponding signs, including deterioration of consciousness disturbance, some focal signs, oculomotor palsy, respiratory distress, and decorticate or decerebrate rigidity (13). Among the complications, shunt-dependent hydrocephalus (SDH) was defined as clinical deterioration occurring on the 14th day after aSAH and no other causes were found except for hydrocephalus, at the same time, it was observed in CT that the ventricular size progressively increased and the Evans index exceeded 0.30 (14). Epilepsy was defined as rhythmic jerking, with or without preceding tonic spasms, that was focal or generalized in nature, with or without loss of consciousness. Even one late seizure was considered to be post-stroke epilepsy (15, 16). Aneurysm rebleeding was defined as a sudden clinical deterioration accompanied by increased subarachnoid, intracerebral, or ventricular blood flow on subsequent CT scans (17). Cerebral vasospasm (CVS) was defined as arterial stenosis

Abbreviations: aSAH, Aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies; OR, Odds ratio; CI, Confidence interval; ICU, Intensive care unit; DCI, Delayed cerebral ischemia; CVS, Cerebral vasospasm; GOS, Glasgow Outcome Scale; IVH, Intraventricular hemorrhage; ICH, Intracerebral hemorrhage; CT, Computed tomography; mRS, Modified Rankin score; ISAT, International Subarachnoid Aneurysm Trail; SAHIT, Subarachnoid Hemorrhage International Trialists; BRAT, Barrow Ruptured Aneurysm Trial; CLSD, Continuous lumber subarachnoid drainage; AUC, Area under the curve; WBC, White blood cell count; SDH, Shunt-dependent hydrocephalus; PASHPSS, Poor-Grade Aneurysmal Subarachnoid Hemorrhage Prognostic Scoring System.

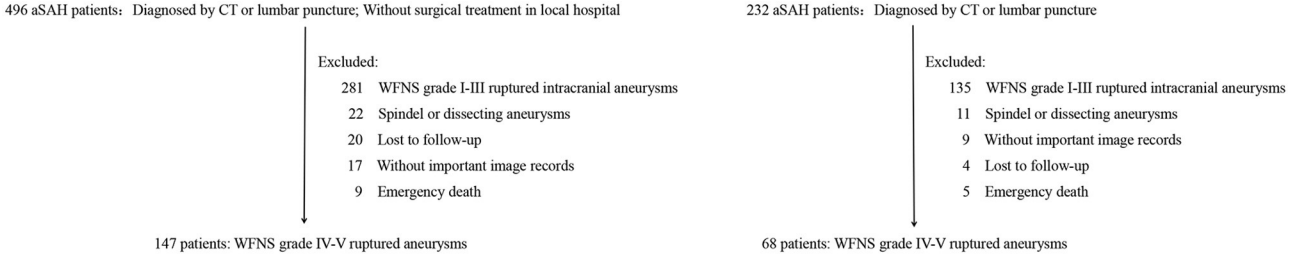

FIGURE 1 | Study flow diagram.

found on the CT angiography examination when the patient's clinical symptoms deteriorated, or vasospasm was detected during DSA (18). Delayed cerebral ischemia (DCI) was defined as: (1) occurrence of focal neurological impairment or decrease of $\geq$ 2 points on the Glasgow Coma Scale that could not be attributed to another cause, such as cerebral rebleeding or encephaledema; or (2) a new low-density area not seen on the previous CT scan and not attributable to other causes such as surgical treatment, or a low-density shadow after absorption of a hematoma (19).

Outcome Measures

A dynamic follow-up evaluation was performed at 6 months after discharge by neurosurgeons in accordance with the modified Rankin score (mRS) via telephone call or outpatient appointment. The assessment of neurological prognosis mainly focused on whether or not the patients presented with self-care ability. Functional prognosis was classified as good (mRS scores 0–2) or poor (mRS scores 3–6).

Statistical Analysis

Data were analyzed using the SPSS Version 23.0 software (IBM, Armonk, NY). Continuous variables were reported as mean $\pm$ standard deviation and compared between favorable and poor outcomes using an unpaired *t*-test. Categorical variables were reported as proportion and percentile and analyzed by the chi-square or Fisher exact test, as appropriate. Univariate and multivariate logistic regression analyses were performed using poor outcomes as the outcome variable in the derivation cohort. Variables with $P \leq 0.1$ in the univariate analyses were entered into the multivariate logistic regression analysis with stepwise backward selection. Risk variables independently associated with prognosis were entered into the new scoring model. The points for individual factors were assigned on the basis of their corresponding β coefficients in the multivariate analysis. The discrimination of the prognostic model was assessed by the AUC in a receiver operating characteristic curve analysis. The Hosmer–Lemeshow goodness-of-fit test and a calibration plot were used to evaluate the calibration of the prediction model.

RESULTS

Basic Information of Patients

The detailed processes for the selection and exclusion of patients in the derivation group and validation group are shown in **Figure 1**. In total, 147 patients were included in the derivation study and 68 patients were included in the validation cohort.

In the derivation cohort, 55 (37%) patients were male and 92 (63%) were female. Among these patients, the age range was 37–87 years, the mean age was 61.3 $\pm$ 11.5 years, and ∼39% were aged $\geq$65 years. The baseline characteristics of the 147 patients with poor-grade aSAH are presented in **Table 1**. In total, 124 (84.3%) patients received surgical therapies including coiling (29.2%) and clipping (55.1%), and 23 (15.7%) patients received conservative treatment. In addition, there was no significant statistical difference between the treatment approach and the WFNS grade ($P = 0.110$). The distribution of mRS scores among the 147 poor-grade aSAH patients with different treatments is shown in **Figure 2A**. As shown in **Figures 2B–E**, patients who received coiling or clipping had a better prognosis than patients who received conservative treatment, but there was no significant difference in prognosis between patients who received coiling or clipping. There were 114 (77.6%) poor-grade aSAH patients with a modified Fisher grade >2 and 85 (57.8%) patients with WFNS grade V. The distribution of mRS scores among the 147 poor-grade aSAH patients with different modified Fisher grades is shown in **Figure 2F**. The influences of different modified Fisher grades on the prognosis of patients are shown in **Figures 2G–J**. During the 6-month follow-up after discharge, 85 patients (58%) had poor outcomes.

Of the 68 patients in the validation cohort, 25 (36.7%) patients were aged $\geq$65 years. A total of 44 (64.7%) poor-grade aSAH patients had a modified Fisher grade >2 and 40 (58.8%) patients presented with WFNS grade V. Forty-nine (72%) patients underwent surgical therapies. At the 6-month follow-up after discharge, 38 (56%) patients had poor outcomes. Specific data for the validation cohort are presented in **Table 1**.

Univariate Analyses of Poor Outcomes

The associations between clinical variables and poor outcomes identified by univariate analyses are shown in **Table 1**. Poor prognosis was associated with age $\geq$65 years ($P = 0.027$), intraventricular hemorrhage (IVH) ($P = 0.005$), WFNS grade V ($P < 0.001$), conservative treatment ($P = 0.009$), modified Fisher grade >2 ($P = 0.001$), emergence of cerebral herniation ($P < 0.001$), aneurysm rebleeding ($P = 0.004$), CVS ($P = 0.041$), and DCI ($P = 0.030$). Medical histories of patients and data for aneurysms were not significantly correlated with clinical outcomes.

TABLE 1 | Demographic and baseline characteristics of the study population and univariate analysis results of modeling cohorts.

Variable	Derivation cohort		*P*-value (Modeling cohort)	Validation cohort	
	Favorable outcome %/Mean ± SD	Poor outcome %/Mean ± SD		Favorable outcome %/Mean ± SD	Poor outcome %/Mean ± SD
No. of patients	**62 (42%)**	**85 (58%)**		**30 (44%)**	**38 (56%)**
Demographic characters					
Age (years)			**0.027**		
<65	44 (71%)	45 (53%)		22 (73%)	21 (55%)
≧65	18 (29%)	40 (47%)		8 (27%)	17 (45%)
Gender			0.147		
Male	19 (31%)	36 (42%)		10 (33%)	16 (42%)
Female	43 (69%)	49 (58%)		20 (67%)	22 (58%)
Medical history					
Hyperlipidemia	19 (31%)	26 (31%)	0.994	7 (23%)	11 (29%)
Hypertension	32 (52%)	54 (64%)	0.148	18 (60%)	22 (58%)
Diabetes mellitus	14 (23%)	28 (33%)	0.170	8 (27%)	14 (37%)
Cerebrovascular disease	8 (13%)	11 (13%)	0.995	5 (17%)	8 (21%)
Alcohol consumption	13 (21%)	28 (33%)	0.110	8 (27%)	10 (26%)
Smoking	15 (24%)	21 (25%)	0.943	10 (33%)	9 (24%)
Radiologic imaging and laboratory examination					
WBC ≧ 15 × 10^9	30 (48%)	42 (49%)	0.902	13 (43%)	19 (50%)
ICH	21 (34%)	34 (40%)	0.448	10 (33%)	18 (47%)
IVH	41 (66%)	73 (86%)	**0.005**	16 (53%)	28 (74%)
Ventricular casting	10 (16%)	21 (25%)	0.195	4 (13%)	8 (21%)
Modified Fisher grade			**0.001**		
2	23 (37%)	12 (14%)		15 (50%)	9 (24%)
3	13 (21%)	32 (38%)		5 (17%)	11 (29%)
4	26 (42%)	41 (48%)		10 (33%)	18 (47%)
WFNS			**<0.001**		
IV	38 (61%)	24 (28%)		15 (50%)	13 (34%)
V	24 (39%)	61 (72%)		15 (50%)	25 (66%)
Aneurysm morphology					
Wide-necked aneurysm	31 (50%)	49 (58%)	0.317	13 (43%)	19 (50%)
Multiple aneurysms	8 (13%)	16 (19%)	0.338	5 (17%)	10 (26%)
Aneurysm size (mm)	5.9 ± 3.3	6.1 ± 3.7	0.860	6.5 ± 2.5	6.7 ± 3.1
Location of aneurysm			0.435		
ICA	13 (21%)	10 (12%)		6 (20%)	5 (13%)
ACA	6 (10%)	10 (12%)		4 (13%)	3 (8%)
AComA	12 (19%)	21 (25%)		8 (27%)	8 (21%)
MCA	15 (24%)	15 (17%)		5 (17%)	9 (24%)
PComA	11 (18%)	16 (19%)		5 (17%)	8 (21%)
PC	5 (8%)	13 (15%)		2 (6%)	5 (13%)
Treatment					
Therapeutic strategy			**0.009**		
Coiling	19 (31%)	24 (28%)		16 (53%)	11 (29%)
Clipping	39 (63%)	42 (49%)		9 (30%)	13 (34%)
Conservative treatment	4 (6%)	19 (23%)		5 (17%)	14 (37%)
CLSD	21 (34%)	28 (33%)	0.906	7 (23%)	9 (24%)
Complication					
Acute hydrocephalus	12 (19%)	20 (24%)	0.545	7 (23%)	10 (26%)
SDH	8 (13%)	22 (26%)	**0.054**	7 (23%)	12 (32%)

(Continued)

TABLE 1 | Continued

Variable	Derivation cohort		*P*-value (Modeling cohort)	Validation cohort	
	Favorable outcome %/Mean ± SD	Poor outcome %/Mean ± SD		Favorable outcome %/Mean ± SD	Poor outcome %/Mean ± SD
Aneurysm rebleeding	1 (2%)	13 (15%)	**0.004**	0	8 (21%)
Epilepsy	4 (7%)	9 (11%)	0.383	1 (3.3%)	3 (8%)
Pulmonary infection	32 (52%)	50 (59%)	0.385	16 (53%)	21 (55%)
Intracranial infection	33 (53%)	40 (47%)	0.460	13 (43%)	16 (42%)
CVS	7 (11%)	21 (25%)	**0.041**	7 (23%)	16 (42%)
DCI	13 (21%)	32 (38%)	**0.030**	6 (20%)	11 (29%)
Cerebral herniation	6 (10%)	38 (45%)	**<0.001**	2 (7%)	16 (42%)

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; WFNS, world federation of neurosurgical societies; CLSD, continuous lumbar subarachnoid drainage; SDH, shunt-dependent hydrocephalus; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; ICA, internal carotid artery; ACA, anterior cerebral artery; AComA, Anterior communicating artery; MCA, middle cerebral artery; PComA, posterior communicating artery; PC, posterior cerebral circulation. P values less than 0.1 are shown in bold.

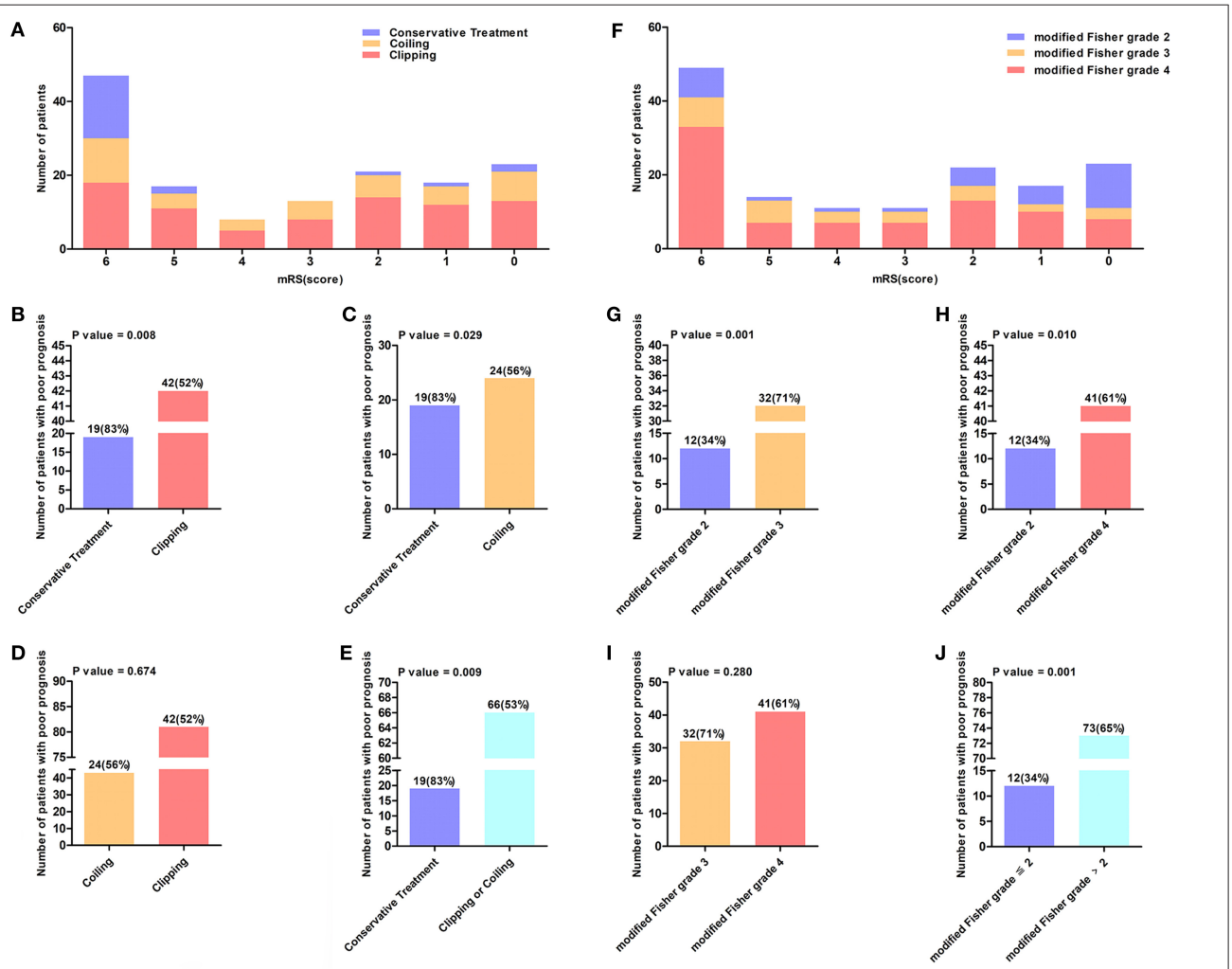

FIGURE 2 | (A) The distribution of mRS score of 147 poor-grade aSAH patients who accepted different treatment methods. The value above the histogram shows the number of patients with poor prognosis and their percentage, for instance, the interpretation of 19 (83%) in **(B)** is that 19 (83%) patients had a poor outcome among 23 patients who received conservation treatment. **(B–E)** Reflects the influence of different treatment methods on the prognosis of patients. **(F)** Shows the distribution of mRS score of 147 poor-grade aSAH patients in different modified Fisher grade. **(G–J)** Reflects the influence of different modified Fisher grade groups on the prognosis of patients.

TABLE 2 | Multivariate logistic regression model for poor prognosis risk of poor-grade aSAH.

Variable included in model	S.E	OR	95%CI	*P*
Modified Fisher grade (grade 3, 4)	0.515	2,972	1.083–8.156	0.034
Age (≥ 65)	0.457	3.534	1.442–8.662	0.006
Therapeutic strategy (conservation)	0.694	5.078	1.303–19.790	0.019
WFNS (grade V)	0.444	2.638	1.104–6.300	0.029
DCI	0.478	3.170	1.242–8.090	0.016
SDH	0.542	3.202	1.107–9.263	0.032
Cerebral herniation	0.565	7.337	2.426–22.192	< 0.001
Hosmer and Lemeshow test				
X^2				6.525
Degree of freedom				8
P				0.589

TABLE 3 | Poor-Grade Aneurysmal Subarachnoid Hemorrhage Prognostic Scoring System (PASHPSS) derived from the β coefficients.

Variable included in model	Categories	β coefficient	Score
Modified Fisher grade			
	Below grade 2	0 (reference)	0
	Grade 3, 4	1.09	1
Age			
	< 65	0 (reference)	0
	≥ 65	1.26	1
Therapeutic strategy			
	Coiling or clipping	0 (reference)	0
	Conservation	1.63	2
WFNS			
	Grade IV	0 (reference)	0
	Grade V	0.97	1
DCI			
	Non-DCI	0 (reference)	0
	DCI	1.15	1
SDH			
	Non-SDH	0 (reference)	0
	SDH	1.16	1
Cerebral herniation			
	Non-cerebral herniation	0 (reference)	0
	Cerebral herniation	1.99	2

Multivariate Regression Analysis of Poor Outcome

Ten variables with $P < 0.1$ in the univariate analyses were entered into the multivariate logistic regression analysis (**Table 2**). The results showed that age ≥65 years (OR, 3.534; $P = 0.006$), modified Fisher grade >2 (OR, 2,972; $P = 0.034$), cerebral herniation (OR, 7.337; $P < 0.001$), WFNS grade V (OR, 2.638; $P = 0.029$), SDH (OR, 3.202; $P = 0.032$), conservative treatment (OR, 5.078; $P = 0.019$), and DCI (OR, 3.170; $P = 0.016$) were independent risk factors for poor outcomes. The Hosmer–Lemeshow test reflected a satisfactory degree of consistency between the predicted risk of the model and the actual risk ($P = 0.589$; **Table 2**).

TABLE 4 | Risk of poor prognosis for low, intermediate, and high-risk individuals according to the PASHPSS risk score.

Risk stratification	Score	Observed risk (validation cohort)	Predicted risk	OR (95% CI)
Low risk stratification	0–1	19%	11%	1 (reference)
Moderate risk stratification	2–3	48%	51%	8.6 (2.2–18.7)
High risk stratification	4–9	81%	87%	54.2 (13.2–221.9)

Development of the Scoring System

By integration of the seven independent risk factors, namely modified Fisher grade >2, age ≥65 years, conservative treatment, WFNS grade V, DCI, SDH, and cerebral herniation, a scoring system designated Poor-Grade Aneurysmal Subarachnoid Hemorrhage Prognostic Scoring System (PASHPSS) was constructed (**Table 3**). On the basis of the β coefficients in the multivariate analysis, scores of 2 were assigned to cerebral herniation and conservative treatment, and scores of 1 were assigned to the other five risk factors; otherwise, a score of 0 points was assigned. In accordance with the sum of the scores (range, 0–9), the new model divided poor-grade aSAH patients into three prognostically different categories (**Table 4**): low risk category, 11% prediction risk of poor prognosis in patients with total scores of 0–1 point; intermediate risk category, 51% prediction risk of poor prognosis in patients with total scores of 2–3 points; high risk category, 87% prediction risk of poor prognosis in patients with total scores of ≥4 points.

Discrimination and Calibration of the Scoring System

In the derivation cohort, the AUC of the PASHPSS was 0.844 (95% CI: 0.778–0.909; **Figure 3**), and the Hosmer–Lemeshow test showed good calibration ($P = 0.589$). In the validation cohort, the PASHPSS also showed good discrimination with an AUC of 0.831 (95% CI, 0.732–0.929; **Figure 3**) and good calibration by the Hosmer–Lemeshow test ($P = 0.984$). Also in the validation cohort, the observed risks in the three risk categories were close to the predicted risks (**Table 3**): low risk category, actual observed risk of poor prognosis was 19%; intermediate risk category, actual observed risk of poor prognosis was 48%; high risk category, actual observed risk of poor prognosis was 81%.

DISCUSSION

As a serious cerebrovascular disease, poor-grade aSAH has high rates of mortality and disability. In this study, the rates of poor prognosis of patients in the modeling cohort and validation cohort both exceeded 55%. Although active and effective treatments can be provided, some aSAH patients still

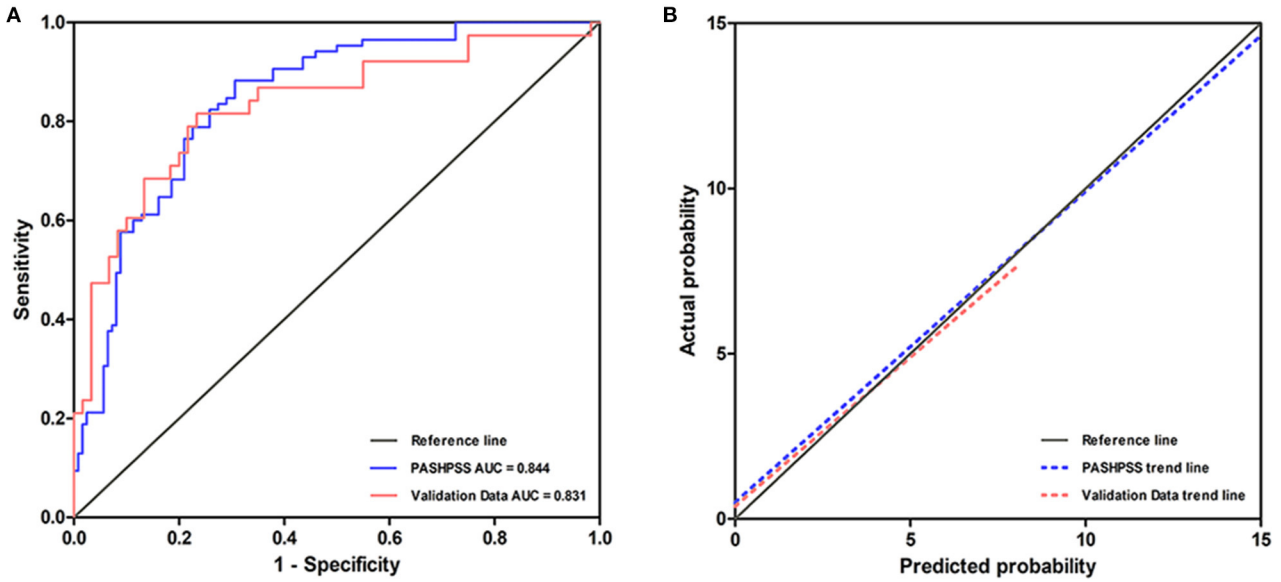

FIGURE 3 | (A) The AUC of the PASHPSS is 0.844 (95% CI, 0.778–0.909) in our center's derivation data, while it is 0.831 (95% CI, 0.732–0.929) in validation data. **(B)** A slope of 1 (45 degrees) with an intercept of 0 represents perfect calibration, the deviation from the reference line is smaller, the calibration is better. PASHPSS has a good calibration in derivation cohort and validation cohort.

present with neurological dysfunctions and life disorders that have great impacts on society and family members (1, 4, 6, 8). It is necessary to explore the relevant risk factors and evaluate the prognosis of these patients. Several modifiable and non-modifiable risk factors for poor prognosis in poor-grade aSAH patients are currently known, with the most common risk factors being elderly age, cerebral herniation, WFNS grade V, and higher modified Fisher grade (9, 10, 12, 20–24). These risk factors were also identified in the present study.

The choice of treatment method is significantly related to the prognosis of patients with poor-grade aSAH. In a systematic review of 815 patients with aSAH, researchers reported that the rates of good prognosis in patients with clipping, embolization, and conservative treatment were 45.3, 36.3, and 9.0%, respectively (25). In our study, the rate of poor prognosis in patients with clipping or coiling was significantly lower than that in patients with conservative treatment, but there was no statistically significant difference in prognosis between patients with clipping or embolization. Combining our center's experience with previous literature on poor-grade aSAH patients, more aggressive treatment of the underlying aneurysm by surgery is associated with a better therapeutic prognosis than conservative treatment.

Post-operative complications play important roles in the prognosis of poor-grade aSAH patients. As a critical complication, aneurysmal rebleeding usually causes a sharp increase in intracranial pressure, damages the nerve function, and increases the risk of death in the short term (26–28). CVS is generally considered a risk factor for poor prognosis. However, immediate vasospasm is usually difficult to detect, and nimodipine is routinely used in clinical practice to prevent its occurrence, leading to an overall reduction in the incidence of CVS (29). A more commonly observed and easily detected complication during clinical treatment is DCI caused by CVS, which is a strong independent risk factor for poor prognosis in patients with poor-grade aSAH (19, 30, 31). DCI continues to be an important cause of cognitive impairment and disability after aSAH despite aggressive management (32–34). A single-center study on 888 aSAH patients found that SDH was a strong independent risk factor for unfavorable functional outcomes (35). Our final results confirmed predictive roles for the above-mentioned factors.

Some other risk factors have also been raised in recent articles, but have not been widely recognized. IVH was considered as a risk factor for poor outcomes in many reports (36). IVH was identified in our univariate analyses, but subsequently eliminated in the multivariate regression analysis. The possible reason may be that IVH caused impairment of cerebrospinal fluid absorption by blocking arachnoid villi and brain capillaries, thereby affecting the prognosis by developing into chronic hydrocephalus (37, 38). Whether or not aneurysm location and size are predictive factors for poor prognosis of aSAH patients remains inconclusive (24). These inconsistent results may be explained by treatment selection biases in different studies. In the present study, there was no correlation between aneurysm location and size and long-term prognosis. In a multicenter study on poor-grade aSAH patients, Zhao et al. (21) demonstrated that wide-necked aneurysms and post-operative pneumonia were also poor prognostic factors. However, these two risk factors were not identified in our study. Leukocytosis (WBC $>15 \times 10^9$ /L) was regarded as a predictive factor for poor prognosis in a 9-year cohort study (22), but was not reported in other articles.

Although the current literature on poor-grade aSAH patients has focused on reporting risk factors for prognosis, prognostic predictive models for poor-grade aSAH patients are rare. A recent systematic review assessed 11 clinical prediction models

for aSAH patients and found that the most common factors associated with outcomes were age (8 of 11 studies), neurologic grade on admission (10 of 11 studies), and amount of blood detected by CT examination on admission (6 of 11 studies) (24). Although the WFNS and modified Fisher grade scales were commonly used, both scales are not completely reliable in patients because of the subjective nature of the parameters on which the models were built (39). For example, the WFNS and Hunt–Hess scales are generally unreliable in intubated patients. Furthermore, in two articles that established predictive scores in poor-grade aSAH patient populations, the factors were applied, but no additional risk factors were added to circumvent the errors caused by the inter-rater and intra-rater variabilities (22, 23). Undeniably, more valuable risk variables added into a risk score can improve its predictivity. Treatment methods, SDH, and DCI are three factors that affect the long-term neurological prognosis and cognitive impairment of patients, and their roles in predicting the prognosis of patients are worthy of recognition (19, 35, 37, 40). Our PASHPSS showed significantly improved discrimination compared with other risk scores by including these risk factors. For example, the AUC of the SAHIT model was 0.734 (11), while the AUC of the WAP score for poor-grade aSAH patients was 0.74 (23). Meanwhile, the AUC of the PASHPSS was 0.844, which can be regarded as excellent, especially when predicting the prognosis of poor-grade aSAH patients.

At present, several studies have proposed prognosis models for poor-grade aSAH patients, but most of these models have limitations in reporting calibration, discrimination, and external validation. Clinicians generally do not use existing models for the prediction of prognosis in poor-grade aSAH patients, even though their internal effectiveness is not inferior to the PASHPSS (22–24), partly because they lack external validity. However, the PASHPSS showed good discrimination in the validation data. Specifically, its AUC was 0.831, meaning that the system still performed well when it was applied to a new patient cohort.

The present study shows that the PASHPSS developed with identified risk factors can predict the future risk of poor prognosis in aSAH patients very well. Furthermore, it can help guide clinical decisions and patient consultations, and may also reduce the cost of treatment by ensuring effective resource allocation. Such benefits may be particularly important in the management of patients with poor-grade aSAH.

LIMITATIONS

Some limitations of our risk score need to be discussed. First, the statistical data were retrospectively collected. Second, the results of the study only represent the subgroup of poor-grade aSAH patients. Therefore, the scoring model is applicable to the prediction of poor prognosis among poor-grade aSAH patients only. With regard to functional neurologic outcomes, we selected 6 months after discharge as the follow-up point on the basis of the critical period for neurological recovery. However, if data on long-term follow-up can be acquired, the prediction of prognosis will be more accurate. Furthermore, the modeling data were acquired from a single center, which may lead to some inevitable bias in the analysis and conclusions.

CONCLUSIONS

The obtained results have allowed us to draw the following conclusions. The main risk factors affecting the prognosis of patients with poor-grade aSAH are modified Fisher grade, elderly age, therapeutic schedule, WFNS grade, DCI, SDH, and cerebral herniation. The PASHPSS is an efficient tool for predicting the prognosis of poor-grade aSAH, can be easily measured, and is helpful for decision-making on subsequent complementary treatment and in reducing the cost of treatment by ensuring effective resource allocation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethics approval has been obtained from the ethics committee of First Affiliated Hospital of Zhejiang University. Non-essential identifiable details have been omitted from all manuscripts. The patients next of kin provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS and JY contributed to writing the manuscript, acquisition of the data, and analysis and interpretation of the data. SH contributed to the acquisition of follow-up data and preliminary revision of the manuscript content. RM corrected the English language used in the manuscript. KH contributed to the acquisition of the data and preliminary revision of the manuscript content. XP contributed to preliminary revision of the manuscript content. GY provided the external validation data. ZX, LZ, ZL, and DC contributed to the literature review. JP and RZ contributed to the critical revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. De Rooij NK, Linn FH, Van Der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry.* (2007) 78:1365–72. doi: 10.1136/jnnp.2007.117655
2. Wiebers D, Whisnant JP, Huston J, Meissner I, Brown RD, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet.* (2003) 362:103–10. doi: 10.1016/S0140-6736(03)13860-3
3. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2015) 46:2368–400. doi: 10.1161/STR.0000000000000070
4. Ellis JA, Nossek E, Kronenburg A, Langer DJ, Ortiz RA. Intracranial aneurysm: diagnostic monitoring, current interventional practices, and advances. *Curr Treat Options Cardiovasc Med.* (2018) 20:94. doi: 10.1007/s11936-018-0695-y
5. Steiner T. Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G, et al. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis.* (2013) 35:93–112. doi: 10.1159/000346087
6. Howard. BM, Barrow. DL. Outcomes for patients with poor-grade subarachnoid hemorrhage: to treat or not to treat? *World Neurosurgery.* (2016) 85:125–9. doi: 10.1016/j.wneu.2015.10.034
7. Han Y, Ye F, Long X, Li A, Xu H, Zou L, et al. Ultra-Early treatment for poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *World Neurosurg.* (2018) 115:e160–71. doi: 10.1016/j.wneu.2018.03.219
8. Wartenberg KE. Critical care of poor-grade subarachnoid hemorrhage. *Curr Opin Crit Care.* (2011) 17:85–93. doi: 10.1097/MCC.0b013e328342f83d
9. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol.* (2010) 25:261–6. doi: 10.1007/s10654-010-9432-x
10. Jaja BNR, Saposnik G, Lingsma HF, Macdonald E, Thorpe KE, Mamdani M, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. *BMJ.* (2018) 360:j5745. doi: 10.1136/bmj.j5745
11. Mascitelli JR, Cole T, Yoon S, Nakaji P, Albuquerque FC, Mcdougall CG, et al. External validation of the subarachnoid hemorrhage international trialists (SAHIT) predictive model using the barrow ruptured aneurysm trial (BRAT) cohort. *Neurosurgery.* (2020) 86:101–6. doi: 10.1093/neuros/nyy600
12. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet.* (2002) 360:1267–74. doi: 10.1016/S0140-6736(02)11314-6
13. Riveros Gilardi B, Munoz Lopez JI, Hernandez Villegas AC, Garay Mora JA, Rico Rodriguez OC, Chavez Appendini R, et al. Types of cerebral herniation and their imaging features. *Radiographics.* (2019) 39:1598–610. doi: 10.1148/rg.2019190018
14. Suzuki H, Kinoshita N, Imanaka-Yoshida K, Yoshida T, Taki W. Cerebrospinal fluid tenascin-C increases preceding the development of chronic shunt-dependent hydrocephalus after subarachnoid hemorrhage. *Stroke.* (2008) 39:1610–2. doi: 10.1161/STROKEAHA.107.505735
15. Lin CL, Dumont AS, Lieu AS, Yen CP, Hwang SL, Kwan AL, et al. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* (2003) 99:978–85. doi: 10.3171/jns.2003.99.6.0978
16. Engel J Jr. Report of the ILAE classification core group. *Epilepsia*. (2006) 47:1558–68. doi: 10.1111/j.1528-1167.2006.00215.x
17. Schuss P, Hadjiathanasiou A, Borger V, Wispel C, Vatter H, Guresir E. Poor-Grade aneurysmal subarachnoid hemorrhage: factors influencing functional outcome–a single-center series. *World Neurosurg.* (2016) 85:125–9. doi: 10.1016/j.wneu.2015.08.046
18. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? *Stroke.* (2009) 40:1963–8. doi: 10.1161/STROKEAHA.108.544700
19. Vergouwen MD, Vermeulen M, Van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke.* (2010) 41:2391–5. doi: 10.1161/STROKEAHA.110.589275
20. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet.* (2015) 385:691–7. doi: 10.1016/S0140-6736(14)60975-2
21. Zhao B, Yang H, Zheng K, Li Z, Xiong Y, Tan X, et al. Preoperative and postoperative predictors of long-term outcome after endovascular treatment of poor-grade aneurysmal subarachnoid hemorrhage. *J Neurosurg.* (2017) 126:1764–71. doi: 10.3171/2016.4.JNS152587
22. Szklener S, Melges A, Korchut A, Zaluska W, Trojanowski T, Rejdak R, et al. Predictive model for patients with poor-grade subarachnoid haemorrhage in 30-day observation: a 9-year cohort study. *BMJ Open.* (2015) 5:e007795. doi: 10.1136/bmjopen-2015-007795
23. Zheng K, Zhong M, Zhao B, Chen SY, Tan XX, Li ZQ, et al. Poor-Grade aneurysmal subarachnoid hemorrhage: risk factors affecting clinical outcomes in intracranial aneurysm patients in a multi-center study. *Front Neurol.* (2019) 10:123. doi: 10.3389/fneur.2019.00123
24. Jaja BN, Cusimano MD, Etminan N, Hanggi D, Hasan D, Ilodigwe D, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. *Neurocrit Care.* (2013) 18:143–53. doi: 10.1007/s12028-012-9792-z
25. Ohkuma H, Shimamura N, Naraoka M, Katagai T. Aneurysmal subarachnoid hemorrhage in the elderly over age 75: a systematic review. *Neurol Med Chir.* (2017) 57:575–83. doi: 10.2176/nmc.ra.2017-0057
26. Van Donkelaar CE, Bakker NA, Veeger NJ, Uyttenboogaart M, Metzemaekers JD, Luijckx GJ, et al. Predictive factors for rebleeding after aneurysmal subarachnoid hemorrhage: rebleeding aneurysmal subarachnoid hemorrhage study. *Stroke.* (2015) 46:2100–6. doi: 10.1161/STROKEAHA.115.010037
27. Larsen CC, Astrup J. Rebleeding after aneurysmal subarachnoid hemorrhage: a literature review. *World Neurosurg.* (2013) 79:307–12. doi: 10.1016/j.wneu.2012.06.023
28. Lu VM, Graffeo CS, Perry A, Carlstrom LP, Rangel-Castilla L, Lanzino G, et al. Rebleeding drives poor outcome in aneurysmal subarachnoid hemorrhage independent of delayed cerebral ischemia: a propensity-score matched cohort study. *J Neurosurg.* (2019) 133:360–8. doi: 10.3171/2019.4.JNS19779
29. Findlay JM, Nisar J, Darsaut T. Cerebral vasospasm: a review. *Can J Neurol Sci.* (2016) 43:15–32. doi: 10.1017/cjn.2015.288
30. Al-Mufti F, Roh D, Lahiri S, Meyers E, Witsch J, Frey HP, et al. Ultra-early angiographic vasospasm associated with delayed cerebral ischemia and infarction following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* (2017) 126:1545–51. doi: 10.3171/2016.2.JNS151939
31. Leclerc JL, Blackburn S, Neal D, Mendez NV, Wharton JA, Waters MF, et al. Haptoglobin phenotype predicts the development of focal and global cerebral vasospasm and may influence outcomes after aneurysmal subarachnoid hemorrhage. *Proc Natl Acad Sci USA.* (2015) 112:1155–60. doi: 10.1073/pnas.1412833112
32. Wang X, Han C, Xing D, Wang C, Ding X. Early management of poor-grade aneurysmal subarachnoid hemorrhage: a prognostic analysis of 104 patients. *Clin Neurol Neurosurg.* (2019) 179:4–8. doi: 10.1016/j.clineuro.2019.02.003
33. Etminan N, Vergouwen Md, Rl. M. Angiographic vasospasm versus cerebral infarction as outcome measures after aneurysmal subarachnoid hemorrhage. *Acta Neurochirurgica.* (2013) 115:33–40. doi: 10.1007/978-3-7091-1192-5_8
34. Kreiter KT, Copeland D, Bernardini GL, Bates JE, Peery S, Claassen J, et al. Predictors of cognitive dysfunction after subarachnoid hemorrhage. *Stroke.* (2002) 33:200–8. doi: 10.1161/hs0102.101080
35. Paisan GM, Ding D, Starke RM, Crowley RW, Liu KC. Shunt-Dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: predictors and long-term functional outcomes. *Neurosurgery.* (2018) 83:393–402. doi: 10.1093/neuros/nyx393

36. Nguyen HS, Li L, Patel M, Kurpad S, Mueller W. Radiodensity of intraventricular hemorrhage associated with aneurysmal subarachnoid hemorrhage may be a negative predictor of outcome. *J Neurosurg.* (2018) 128:1032–6. doi: 10.3171/2016.11.JNS152839
37. De Oliveira JG, Beck J, Setzer M, Gerlach R, Vatter H, Seifert V, et al. Risk of shunt-dependent hydrocephalus after occlusion of ruptured intracranial aneurysms by surgical clipping or endovascular coiling: a single-institution series and meta-analysis. *Neurosurgery.* (2007) 61:924–33; discussion 933–24. doi: 10.1227/01.neu.0000303188.72425.24
38. Lai L, Morgan MK. Predictors of in-hospital shunt-dependent hydrocephalus following rupture of cerebral aneurysms. *J Clin Neurosci.* (2013) 20:1134–8. doi: 10.1016/j.jocn.2012.09.033
39. Degen LA, Dorhout Mees SM, Algra A, Rinkel GJ. Interobserver variability of grading scales for aneurysmal subarachnoid hemorrhage. *Stroke.* (2011) 42:1546–9. doi: 10.1161/STROKEAHA.110.601211
40. Van Donkelaar CE, Dijkland SA, Van Den Bergh WM, Bakker J, Dippel DW, Nijsten MW, et al. Early circulating lactate and glucose levels after aneurysmal subarachnoid hemorrhage correlate with poor outcome and delayed cerebral ischemia: a two-center cohort study. *Crit Care Med.* (2016) 44:966–72. doi: 10.1097/CCM.0000000000001569
41. Jie S, Jianbo Y, Sicong H, Rajneesh M, Kaiyuan H, Xinfa P, et al. *A Scoring Model to Predict the Prognosis of Patients With Poor-Grade Aneurysmal Subarachnoid Hemorrhage Research Square 2020.* (2020) Available online at: https://researchsquare.com/article/rs-69333/v1 (accessed Sep 2, 2020).

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