CHALLENGES IN ACUTE MINOR ISCHEMIC STROKE

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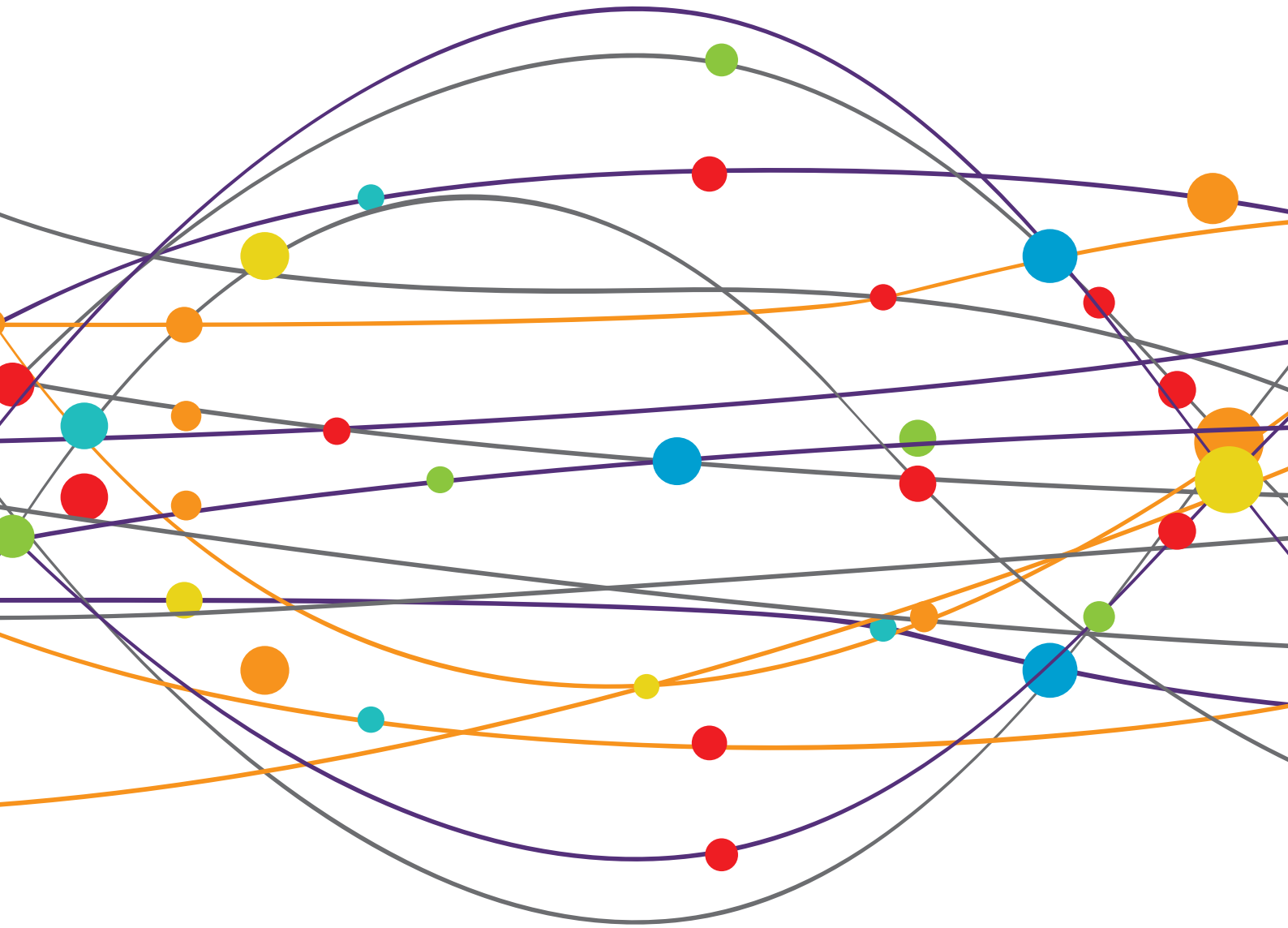

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CHALLENGES IN ACUTE MINOR ISCHEMIC STROKE

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EDITORIAL
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Editorial: Challenges in Acute Minor Ischemic Stroke

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Keywords: minor stroke, treatment, prognosis, epidemiology, thrombolysis, endovascular treatment

Editorial on the Research Topic

Challenges in Acute Minor Ischemic Stroke

More than half of acute ischemic stroke patients can present with minor symptoms, yet they don't necessarily all have a benign outcome with up to a third of these patients having a modified Rankin Scale of 2 or more at 90 days. In this series, we have focused on various challenges in managing patients with acute minor ischemic stroke, ranging from acute treatment to prognosis.

Whilst all our contributors should be congratulated on their excellent and in some cases very delicate work in the area, it is worth noting that various operational definitions of minor stroke have been and are still being used. The two most commonly used cut-offs were NIHSS ≤ 5 in hyper-acute settings and NIHSS ≤ 3 in TIA/minor stroke or in secondary prevention settings more generally.

One of the biggest challenges in managing patients with acute minor ischemic stroke is perhaps the decision for acute reperfusion therapies such as intravenous thrombolysis (IVT) or endovascular treatment (EVT). With regards to IVT, as summarized by the two comprehensive reviews from Ferrari et al., and from Slawski and Heit, decisions to treat are likely to be made weighing the potential gain of improved functional outcome against the increased risk of intracerebral hemorrhage on an individual basis. An overall benefit is more likely in those presenting with disabling symptoms or those with proven large vessel occlusion (LVO). Whilst an increase of IVT in minor ischemic stroke has been observed in high-income countries in recent years, we still have a number of areas to improve, including better pre-hospital recognition of such patients, ultimate choice of thrombolytic agent (Alteplase vs. Tenecteplase) and identifying patients with early neurological deterioration. Indeed, Tang et al. showed in their single center experience that about 10% of the patients who received IVT after presenting with a minor stroke still experienced early neurological deterioration, which were associated with high baseline systolic blood pressure and history of coronary heart disease.

Another well-recognized factor that is associated with early neurological deterioration and poor outcome in minor ischemic stroke is the presence of LVO, which leads to the discussion about the role of EVT, another aspect of acute reperfusion therapies. LVO is not rare as demonstrated by Duloquin et al. Using data from the well-established Dijon Stroke Registry, the authors found that ∼4% of patients with a mild ischemic stroke had LVO. Interestingly there was little evidence of any obvious predictors for LVO, showing the importance of timely arterial imaging in patients who presented with mild symptoms. With regards to EVT in such patients, Volbers et al. found in a retrospective cohort study that patients with minor deficits and LVO tended to have worse outcome compared to patients who presented initially with more severe deficits, especially in the context of secondary neurological deterioration, which was strongly associated with more proximal occlusion, suggesting that preventing such deterioration with EVT in high-risk patients might be one

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important way to improve functional outcome. They also showed that the approach starting with medical management first with rescue EVT after secondary neurological deterioration was associated with a poorer outcome, highlighting the importance of ongoing trials looking at immediate EVT vs. best medical treatment in patients with minor ischemic stroke and LVO, such as the Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW) trial and the Minor Stroke Therapy Evaluation (MOSTE) trial. Whilst we are still waiting for the trial results, it was encouraging to see some positive trends from prospective cohort studies, such as the study led by Liu et al. They found that patients with mild symptoms and acute LVO in the anterior circulation had a higher proportion of independent outcome if they received EVT compared to those that were treated medically.

Of course, a large proportion of patients with minor ischemic stroke do not necessarily require acute reperfusion therapy and for those with non-cardioembolic events, short-term use of dual antiplatelet treatment, commonly Aspirin and Clopidogrel, is recommended by guidelines. However, 10–20% of patients still had early recurrence despite being on dual antiplatelet therapy, partly due to high residual on-treatment platelet reactivity (HRPR). Whilst there have been very promising data on genetic testing to identify CYP2C19 loss-of-function carriers, who are likely to be Clopidogrel non-responders, clinical markers remain extremely helpful. Guo et al. showed elegantly that in acute ischemic stroke patients taking dual antiplatelet treatment, history of diabetes might be such a marker. They found that diabetes was associated with increased platelet reactivity and higher prevalence of HRPR to Clopidogrel. If proven in other larger and prospective studies, their research offers a potentially simple approach for more personalized treatment in the future.

Ultimately the most important aspect in managing minor stroke is to improve the short and longer term prognosis. On one hand, it was disappointing to see that the onset to door time was prolonged during the COVID-19 pandemic in patients presenting with transient ischemic attack (TIA) or minor stroke in some Japanese hospitals, as shown by Tanaka et al. Their research reminds us that better public education on recognition of more minor events is still urgently needed. On the other hand, it was encouraging to see from the Australian community-based study, The INternational comparison of Systems of care and patient outcomes In minor Stroke and TIA (INSIST) study led by Tomari et al., that perhaps owning to early implementation of antithrombotic treatment, the 1-year risk of stroke in patients with TIA or minor stroke in their region was lower than previously reported.

Whilst we have made great progress in improving outcomes after minor strokes, there is certainly still room for further improvement and future potential new treatment targets are always welcomed. Li et al. measured heart rate variability on ECG, which is a marker for autonomic function, and showed that low heart rate variability was associated with higher stroke recurrence and worse functional outcome at 90 days after TIA or minor stroke. More research is still needed to determine if autonomic function can be a potential new treatment target. Tan et al. investigated efficacy and safety of adherence to dl-3-n-Butylphthalide (NBP) treatment in patients with non-disabling minor stroke and TIA and found that compliance with NBP therapy was associated with better 90-day functional outcomes particularly in patients presenting with minor stroke, although there was some unexplained signal of an increased risk of recurrent stroke in the NBP compliant group, which warrants further research.

Finally, in additional to more conventional approaches mentioned above, health innovations and technology is also evolving in the area. A good example is illustrated by Wijesundera et al., who showed that vision and visuomotor performance can be rapidly measured with bedside iPad apps after minor stroke. Hopefully with continued efforts as demonstrated in this series of research, we will be able to do better at managing patients with minor stroke in the very near future.

AUTHOR CONTRIBUTIONS

LL wrote the initial draft and all authors contributed to the conceptualization and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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The Association Between Heart Rate Variability and 90-Day Prognosis in Patients With Transient Ischemic Attack and Minor Stroke

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Background: Low heart rate variability (HRV) is known to be associated with increased all-cause, cardiovascular, and cerebrovascular mortality but its association with clinical outcomes in patients with transient ischemic attack (TIA) or minor stroke is unclear.

Methods: We selected TIA and minor stroke patients from a prospective registration study. From each continuous electrocardiograph (ECG) record, each QRS complex was detected and normal-to-normal (N-N) intervals were determined. The standard deviation of all N-N intervals (SDNN) and the square root of the mean squared differences of successive N-N intervals (RMSSD) were calculated. Logistic regression analysis and Cox regression analysis were performed to assess the outcomes of patients at 90 days, and the odds and risk ratios (OR/HR) of each index quartile were compared.

Results: Compared with SDNN patients in the lowest quartile, neurological disability was significantly reduced in other quartile groups at 90 days, with significant differences [OR of group Q2 was 0.659; 95% confidence interval (CI), 0.482–0.900; $p = 0.0088$; OR of group Q3 was 0.662; 95% CI, 0.478–0.916; $p = 0.0127$; OR of group Q4 was 0.441; 95% CI, 0.305–0.639; $p < 0.0001$]. Compared with the lowest quartile, the recurrence rate of TIA or minor stroke in patients of the two higher quartiles (Q3 and Q4) of SDNN was significantly reduced at 90 days (HR of Q3 group was 0.732; 95% CI, 0.539–0.995; $p = 0.0461$; HR of Q4 group was 0.528; 95% CI, 0.374–0.745; $p = 0.0003$).

Conclusions: Based on our findings, autonomic dysfunction is an adverse indicator for neurological function prognosis and stroke recurrence 90 days after TIA or minor stroke.

Keywords: neurological function, prognosis, stroke, transient ischemic attack, heart rate variability, stroke recurrence

INTRODUCTION

Stroke is the second leading cause of death worldwide (1) and the leading cause of mortality and disability in China (2). About 40% of stroke survivors are disabled [modified Rankin Scale (mRS) score 3–5] between 1 month and 5 years after stroke (3). Depending on the circumstances of treatment, the rate of stroke recurrence 90 days after the first ischemic event ranges from 3.7 to 20% (4–6). Approximately 40% of recurrent stroke events are fatal within 30 days, which is nearly twice the 30-day case fatality of a first-ever stroke (7). According to the data of the Third China National Stroke Registry (CNSR-III), TIA and minor stroke (an National Institutes of Health Stroke Scale (NIHSS) score $\leq$ 5) account for about 73% of acute ischemic stroke cases. Both TIA and minor stroke are characterized by a high risk of early stroke recurrence (8). Currently, assessment tools have limitations in predicting the early recurrence of stroke (9–12). It is still challenging to stratify the risk and identify high-risk patients accurately in the early treatment stage of stroke.

Heart rate variability (HRV) is a commonly used quantitative marker for measuring autonomic nerve system (13). HRV is easy to obtain. It quantifies sympathetic-vagus regulation at the sinus level as a tool (14) for assessing overall heart health and autonomic nerve system function (13, 15). Dysfunction of the autonomic nerve system after stroke increases the risk of stroke recurrence and death (16–18). Therefore, exploitation of the predictive function of HRV in risk stratification tools has become an important measure to identify high-risk populations. Although correlation between autonomic nerve system function and stroke prognosis has been studied previously, the sample sizes were small (19, 20).

To date, no study has been done to evaluate how HRV is related to a comprehensive 90-day prognosis in patients with TIA or minor stroke. Using the CNSR-III database, this study focused on the correlation between HRV and 90-day outcomes in patients with TIA and minor stroke including neurological disability, stroke recurrence, and cardiovascular death.

METHODS

Study Population

The CNSR-III database is a nationwide prospective clinical registry of ischemic stroke or TIA in China based on etiology, imaging, and biology markers. The detailed study design of the CNSR-III trial has been described elsewhere (21). Briefly, between August 2015 and March 2018, the CNSR-III recruited consecutive patients with ischemic stroke or TIA from 201 hospitals that covered 22 provinces and four municipalities in China. Informed consent received from the patient or legally authorized representative (primarily spouse, parents, adult children, otherwise indicated). Clinical data were collected prospectively using an electronic data capture system by face-to-face interviews. Brain imaging, including brain magnetic resonance imaging (MRI) and computed tomography (CT), were completed at baseline. Blood samples were collected and biomarkers were tested at baseline. Face-to-face follow-up was conducted at 3 months, and telephone follow-up was conducted at 6 months and 1–5 years.

The registry recruited consecutive patients who met the following criteria: age >18 years; ischemic stroke or TIA; within 7 days from the onset of symptoms to enrolment; Acute ischemic stroke was diagnosed according to the World Health Organization (WHO) criteria (22) and confirmed by MRI or brain CT. Patients who had silent cerebral infarction with no manifestation of symptoms and signs or who refused to participate in the registry were excluded. The protocol of the CNSR-III trial was approved by the ethics committee at Beijing Tiantan Hospital affiliated to Capital Medical University (IRB Approval Number: KY2015-001-01) and all participating centers. In this study, minor stroke was defined as an NIHSS score $\leq$ 5.

There were 15,166 patients in CNSR-III, and 4,086 patients with an NIHSS score >5 were excluded. There were 11,080 patients with TIA and minor stroke (an NIHSS score $\leq$ 5). Six hundred and one patients with atrial fibrillation and atrial flutter ($n = 601$) or those with missing HRV data ($n = 5{,}171$) were excluded (including no 24-h ECG examination or HRV data generated during 24-h ECG examination). A total of 5,308 patients were eligible for the study. **Figure 1** shows a detailed flow chart for the study population selection from CNSR-III.

Baseline Variables

Age, sex, smoking history (never, occasionally, current, and past), drinking history (never, occasionally, current, and past), body mass index (BMI), heart rate on admission, blood pressure on admission, NIHSS (National Institute of Health stroke scale), medical history (including stroke, heart disease, hypertension, diabetes mellitus, and hyperlipidemia), mRS score before onset, medication history, secondary prevention treatment, and stroke etiology were all collected at the baseline.

During hospitalization, the patient received 24-h ECG, from which the SDNN and RMSSD were automatically obtained. SDNN is a global index of HRV, and reflects the standard deviation of the normal R-R intervals (N-N intervals) (23). RMSSD is the square root of the mean squared differences of successive N-N intervals. It is thought to reflect the activity of the parasympathetic nervous system (13).

Outcome Measures

Neurological function prognosis, stroke recurrence, and cardiovascular death were recorded 90 day after TIA or minor stroke. Disability after stroke was defined as an mRS score $\geq$ 3. Recurrent stroke was defined as new ischemic and recurrent hemorrhagic strokes (intracerebral and subarachnoid hemorrhages). Cardiovascular death was defined as ischemic stroke, hemorrhagic stroke, sudden cardiac death, acute myocardial infarction, death directly caused by heart failure, and other cardiovascular death [including cardiac arrhythmias unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention (unrelated to acute myocardial infarction), aortic aneurysm rupture, and peripheral arterial disease]. Each case fatality was either confirmed on a death certificate from the attending hospital or local citizen registry.

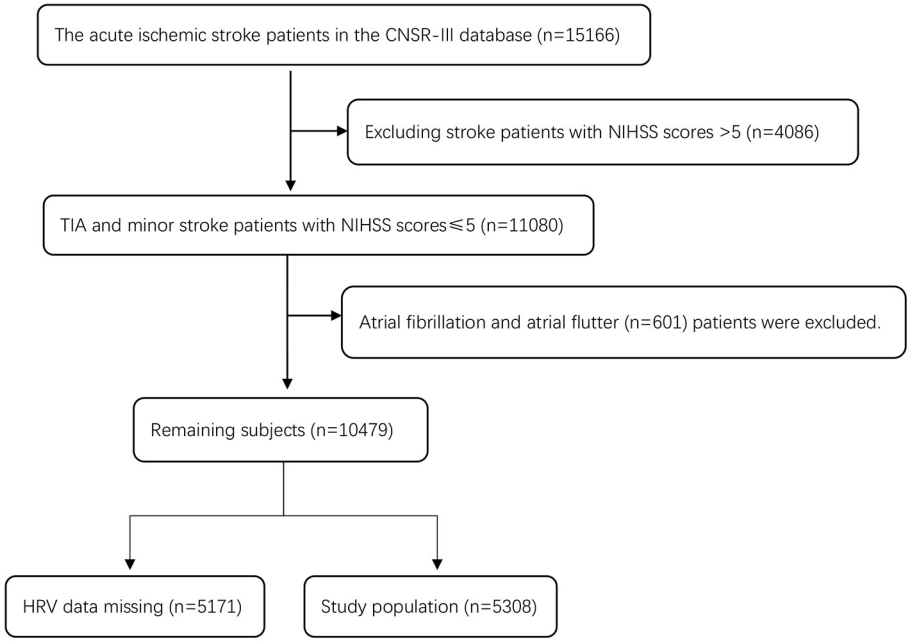

FIGURE 1 | Flowchart of patient selection from CNSR-III database.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation, and classification variables are expressed as a percentage. A quartile classification method was used for SDNN and RMSSD, with the lowest quartile as a reference for all comparisons. Baseline variables between different quartile groups were compared using a chi-square test for classification variables and Kruskal-wallis-test for continuous variables. Logistic regression analysis and Cox regression analysis were used to calculate the odds and risk ratios (OR/HR) and 95% confidence intervals (CIs). The adjusted clinical covariables included age, sex, smoking, alcohol consumption, previous stroke history, heart disease, hypertension, diabetes mellitus, lipid metabolic disorders, and other variables with a $p < 0.1$. A two-sided significance level of $P < 0.05$ was determined. All analyses were performed using SAS 9.4 software.

RESULTS

A total of 5,308 patients (mean age, 61.13 ± 10.81 years) were enrolled in the study: 69.11% males (mean age, 60.2 ± 10.8 years) and 30.89% females (mean age, 63.2 ± 10.4 years). SDNN was 108.32 ± 30.55 ms and RMSSD was 30.79 ± 15.05 ms. Among the patients, the prevalence of previous stroke/TIA, coronary heart disease, hypertension, diabetes mellitus, and dyslipidemia were 22.89% (1,215 cases), 10.70% (568 cases), 62.08% (3,296 cases), 22.92% (1,217 cases), and 8.16% (433 cases), respectively. The proportion of anti-platelet, anticoagulation, stains, antioxidant, hypoglycemic and antihypertensive drugs in secondary prevention were 97.98% (5,201 cases), 5.58% (296 cases), 95.65% (5,077 cases), 15.79% (838 cases), 24.89% (1,321 cases), 47.14% (2,502 cases), respectively.

Table 1 showed the descriptive statistics for the baseline variables in terms of SDNN quartiles. The group with a lower SDNN value tended to be older, with an increased proportion of women, faster heart rate, and higher systolic blood pressure at first admission. In the medical history, the prevalence of diabetes mellitus increased significantly in the group with a low SDNN value, and there was a significant difference between groups ($p < 0.0001$).

With a gradual increase of SDNN, the rate of neurological disability in patients with TIA or minor stroke decreased significantly 90 days after stroke. Compared with the lowest SDNN quartile, findings for the other three groups were as follows, [OR in group Q2 after correction, 0.659; 95% confidence interval (CI), 0.482–0.900; $p = 0.0088$; OR of group Q3, 0.662; 95% CI, 0.478–0.916; $p = 0.0127$; OR of group Q4, 0.441; 95% CI, 0.305–0.639; $p < 0.0001$]. With an increasing SDNN, stroke recurrence showed a decreasing trend. The recurrence rate of patients of the two higher quartiles of SDNN was significantly reduced at 90 days (HR of Q3 group after correction, 0.732; 95% CI, 0.539–0.995; $p = 0.0461$; HR of Q4 group after correction, 0.528; 95% CI, 0.374–0.745; $p = 0.0003$). No clear association was found between SDNN and cardiovascular death (**Table 2**). In addition, no association was found between RMSSD and 90-day neurological disability, recurrent stroke, or cardiovascular death (**Table 3**).

DISCUSSION

In the time domain measurement of HRV, SDNN reflects the overall condition of the autonomic nerve system, and a decrease of the SDNN usually indicates a relative superiority of the sympathetic nerve in the autonomic nervous system

TABLE 1 | Baseline characteristics for study sample by SDNN quartile (n = 5,308).

Characteristics	SDNN Quartile				
Category	**1**	**2**	**3**	**4**	***P*-value**
N	1,364	1,291	1,346	1,307	
Range, ms	<88	88–105.5	105.5–26	>126	
Age (years)	63.18 ± 10.86	61.58 ± 10.5	60.07 ± 10.36	59.62 ± 11.15	<0.0001
Male, *n* (%)	838 (61.44)	870 (67.39)	956 (71.03)	1,005 (76.83)	<0.0001
Cigarette smoking, *n* (%)					
Never	775 (56.82)	667 (51.67)	639 (47.47)	576 (44.07)	<0.0001
Occasionally	57 (4.18)	48 (3.72)	55 (4.09)	64 (4.90)	
Current	360 (26.39)	417 (32.30)	507 (37.67)	494 (37.80)	
Former	172 (12.61)	159 (12.32)	145 (10.77)	173 (13.24)	
Alcohol consumption, *n* (%)					
Never	822 (60.26)	680 (52.67)	676 (50.22)	641 (49.04)	<0.0001
Occasionally	266 (19.50)	303 (23.47)	343 (25.48)	313 (23.95)	
Current	180 (13.20)	220 (17.04)	239 (17.76)	259 (19.82)	
Former	96 (7.04)	88 (6.82)	88 (6.54)	94 (7.19)	
BMI, kg/m^2, mean (SD)	24.71 ± 3.33	24.88 ± 3.37	25.09 ± 3.15	24.8 ± 3.11	0.0100
Waistline	85 (79–95)	87 (79–95)	87 (80–96)	87 (79–95)	0.3528
Heart rate on admission, bpm, mean (SD)	76 (70–82)	76 (70–80)	75 (68–80)	72 (65–79)	<0.0001
Blood pressure on admission (mmHg)					
Right systolic BP, mmHg, mean (SD)	150 (138–166)	150 (134–165)	150 (135–165)	148 (133–163)	0.0049
Right diastolic BP, mmHg, mean (SD)	90 (80–97)	87 (80–99)	89 (80–98)	88 (80–97)	0.3011
Left systolic BP, mmHg, mean (SD)	150 (136–162.5)	149 (135–162)	149 (135–162)	145 (132–160)	0.0033
Left diastolic BP, mmHg, mean (SD)	86 (80–95)	86 (80–96)	86 (80–96)	85 (80–95)	0.3953
NIHSS score	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–3)	<0.0001
Medical history, *n* (%)					
Previous Stroke/TIA	352 (25.81)	280 (21.69)	279 (20.73)	304 (23.26)	0.0102
Previous heart disease	170 (12.46)	140 (10.84)	133 (9.88)	125 (9.56)	0.0657
Hypertension	872 (63.93)	799 (61.89)	836 (62.11)	789 (60.29)	0.2862
Diabetes mellitus	398 (29.18)	289 (22.39)	284 (21.10)	246 (18.82)	<0.0001
Dyslipidemia	99 (7.26)	111 (8.60)	110 (8.17)	113 (8.65)	0.5273
mRS score before onset					0.9001
0	1,031 (75.59)	999 (77.38)	1,042 (77.41)	995 (76.13)	
1	241 (17.67)	208 (16.11)	222 (16.49)	232 (17.75)	
2	54 (3.96)	55 (4.26)	53 (3.94)	53 (4.06)	
3	24 (1.76)	15 (1.16)	19 (1.41)	17 (1.30)	
4	13 (0.95)	14 (1.08)	9 (0.67)	8 (0.61)	
5	1 (0.07)	0 (0.00)	1 (0.07)	2 (0.15)	
Medication history					
Antiplatelet agents	218 (15.98)	195 (15.10)	190 (14.12)	200 (15.30)	0.5975
Anticoagulant agents	1 (0.07)	3 (0.23)	2 (0.15)	3 (0.23)	0.7149
Stains	133 (9.75)	119 (9.22)	105 (7.80)	136 (10.41)	0.1205
Hypoglycemic drugs	323 (23.68)	222 (17.20)	228 (16.94)	186 (14.23)	<0.0001
Antioxidant against lipid peroxidation	5 (0.37)	5 (0.39)	2 (0.15)	3 (0.23)	0.6080
Antihypertensive drugs	633 (46.41)	551 (42.68)	579 (43.02)	546 (41.78)	0.0801
β-blockers	41 (3.01)	30 (2.32)	21 (1.56)	25 (1.91)	0.0641
Inpatient therapy					
Dual antiplatelet therapy	186 (13.64)	198 (15.34)	196 (14.56)	165 (12.62)	0.2160
Anti-platelet therapy	1,332 (97.65)	1,267 (98.14)	1,319 (97.99)	1,283 (98.16)	0.7704
Anticoagulation treatment	85 (6.23)	84 (6.51)	72 (5.35)	55 (4.21)	0.0457
Stains	1,307 (95.82)	1,240 (96.05)	1,280 (95.10)	1,250 (95.64)	0.6635

(Continued)

TABLE 1 | Continued

Characteristics	SDNN Quartile				
Category	**1**	**2**	**3**	**4**	***P*-value**
Antioxidant treatment	226 (16.57)	198 (15.34)	211 (15.68)	203 (15.53)	0.8253
Hypoglycemic treatment	436 (31.96)	327 (25.33)	302 (22.44)	256 (19.59)	<0.0001
Antihypertensive treatment	690 (50.59)	603 (46.71)	611 (45.39)	598 (45.75)	0.0261
CCB	522 (38.27)	473 (36.64)	475 (35.29)	446 (34.12)	0.1362
ACEI or ARB	251 (18.40)	225 (17.43)	222 (16.49)	236 (18.06)	0.5816
Diuretic	29 (2.13)	28 (2.17)	28 (2.08)	41 (3.14)	0.2232
β-blockers	62 (4.55)	39 (3.02)	34 (2.53)	32 (2.45)	0.0055
α-blockers	2 (0.15)	3 (0.23)	1 (0.07)	1 (0.08)	0.6468
TOAST					0.0205
Large artery atherosclerosis;	379 (27.79)	311 (24.09)	307 (22.81)	315 (24.10)	
Cardioembolism	21 (1.54)	19 (1.47)	16 (1.19)	22 (1.68)	
Small vascular occlusion	307 (22.51)	329 (25.48)	346 (25.71)	309 (23.64)	
Other determination	27 (1.98)	18 (1.39)	15 (1.11)	9 (0.69)	
Undetermined	630 (46.19)	614 (47.56)	662 (49.18)	652 (49.89)	

SDNN, the standard deviation of all N-N intervals; BMI, body mass index; SD, standard deviation; BP, blood pressure; NIHSS, National Institute of Health stroke scale; TIA, transient ischemic attack; mRS, modified Rankin scale; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

TABLE 2 | Correlation of SDNN with the 90-day prognosis of ischemic stroke.

Outcomes	SDNN	Events *n* (%)	Model 1 unadjusted		Model 2 adjusted	
			OR/HR (95% CI)	***P*-value**	**OR/HR (95% CI)**	***P*-value**
Disability (mRS, 3–5)	Q1	123 (9.16)	Reference		Reference	
	Q2	73 (5.69)	0.599 (0.444–0.809)	0.0008	0.659 (0.482–0.900)	0.0088
	Q3	65 (4.88)	0.509 (0.373–0.694)	<0.0001	0.662 (0.478–0.916)	0.0127
	Q4	43 (3.32)	0.341 (0.239–0.487)	<0.0001	0.441 (0.305–0.639)	<0.0001
Recurrent stroke	Q1	104 (7.62)	Reference		Reference	
	Q2	84 (6.51)	0.846 (0.635–1.128)	0.2555	0.878 (0.657–1.173)	0.3779
	Q3	71 (5.27)	0.683 (0.505–0.924)	0.0133	0.732 (0.539–0.995)	0.0461
	Q4	49 (3.75)	0.481 (0.342–0.676)	<0.0001	0.528 (0.374–0.745)	0.0003
Cardiovascular death	Q1	5 (0.37)	Reference		Reference	
	Q2	3 (0.23)	0.631 (0.151–2.638)	0.5278	0.654 (0.154–2.785)	0.5658
	Q3	3 (0.22)	0.606 (0.145–2.536)	0.4930	0.668 (0.156–2.852)	0.5858
	Q4	2 (0.15)	0.417 (0.081–2.148)	0.2955	0.514 (0.097–2.730)	0.4349

Model 1: unadjusted. Model 2: adjusted for age, sex, smoking, alcohol consumption, body mass index, heart rate on admission, systolic and diastolic blood pressures on admission, NIHSS (National Institute of Health stroke scale) score, medical history, mRS score before onset, dual antiplatelet therapy, and stroke etiology (TOAST). HR can be interpreted as the comparison between quartiles 2, 3, and 4 with quartile 1 (reference). OR/HR can be interpreted as the comparison between quartiles 2, 3, and 4 with quartile 1 (reference).
SDNN, the standard deviation of all N-N intervals; OR, odds ratio; HR, hazard ratio; CI, confidence interval; mRS, modified Rankin scale.
SDNN: Q1 < 88 ms; Q2: 88–105.5 ms; Q3: 105.5–126 ms; Q4 >126 ms.

(24). Aging (25), female sex (25, 26), increased blood pressure, and diabetes mellitus (26, 27) all showed the characteristics of relative sympathetic nerve superiority in the autonomic nervous system, and thus with a decreased SDNN. This is consistent with our baseline data analysis results (**Table 1**). In this study, we found that with an increasing SDNN, the rate of neurological dysfunction in patients at 90 days after ischemic stroke decreased significantly. The recurrence rate of 90-day stroke was significantly reduced for participants in the two higher quartiles of SDNN.

Previous studies have shown that age, diabetes mellitus, and NIHSS scores are predictors of 90-day neurological disability (28, 29). But in this study, after correcting for confounding factors, we found that with an increasing SDNN, the rate of neurological dysfunction in patients 90 days after ischemic stroke decreased significantly. After the acute phase, patients with autonomic nerve system dysfunction need more help in their daily rehabilitation tasks (30). Poor adaptability of the cardiac autonomic nerve system in different rehabilitation training activities and poor rehabilitation dependence impact

TABLE 3 | Correlation of RMSSD with the 90-day prognosis of ischemic stroke.

Outcomes	RMSSD	Events *n* (%)	Model 1 unadjusted		Model 2 adjusted	
			OR/HR (95% CI)	*P*-value	OR/HR (95% CI)	*P*-value
Disability (mRS, 3–5)	Q1	88 (6.31)	Reference		Reference	
	Q2	68 (5.33)	0.836 (0.604–1.158)	0.2818	0.886 (0.632–1.243)	0.4841
	Q3	65 (4.93)	0.770 (0.554–1.071)	0.1202	0.838 (0.595–1.180)	0.3113
	Q4	83 (6.57)	1.044 (0.766–1.423)	0.7858	1.059 (0.765–1.465)	0.7298
Recurrent stroke	Q1	96 (6.79)	Reference		Reference	
	Q2	65 (5.06)	0.737 (0.538–1.009)	0.0572	0.745 (0.543–1.022)	0.0683
	Q3	74 (5.56)	0.814 (0.601–1.102)	0.1833	0.830 (0.612–1.126)	0.2317
	Q4	73 (5.72)	0.837 (0.617–1.135)	0.2524	0.855 (0.629–1.161)	0.3146
Cardiovascular death	Q1	7 (0.50)	Reference		Reference	
	Q2	0 (0.00)	-	-	-	-
	Q3	1 (0.08)	0.151 (0.019–1.231)	0.0775	0.142 (0.017–1.165)	0.0692
	Q4	5 (0.39)	0.791 (0.251–2.491)	0.6882	0.633 (0.196–2.042)	0.4442

Model 1: unadjusted. Model 2: adjusted for age, sex, smoking, alcohol consumption, body mass index, heart rate on admission, systolic and diastolic blood pressures on admission, NIHSS (National Institute of Health stroke scale) score, medical history, mRS score before onset, dual antiplatelet therapy, and stroke etiology (TOAST). OR/HR can be interpreted as the comparison between quartiles 2, 3, and 4 with quartile 1 (reference).

RMSSD, the square root of the mean squared differences of successive N-N intervals; OR, odds ratio; HR, hazard ratio; CI, confidence interval; mRS, modified Rankin scale.

RMSSD: Q1 < 20 ms; Q2: 20–27 ms; Q3: 27–38 ms; Q4 >38 ms.

the rehabilitation effects (30, 31). At the same time, autonomic nerve system dysfunction is not only associated with overall cognitive function, processing speed, executive function, and poor retrospective memory performance in patients (32, 33) but also associated with post-stroke depression (34). All of these might have a negative impact on the patients' positive initiative in rehabilitation training and their ability to follow the rehabilitation regimens, resulting in unsatisfactory rehabilitation results.

According to previous studies, age, blood pressure and diabetes mellitus were all risk factors for recurrence of TIA and minor stroke (35, 36). However, after adjusting for risk factors such as age, blood pressure, and diabetes mellitus, SDNN was still significantly correlated with stroke recurrence, suggesting that autonomic dysregulation was associated with stroke recurrence. There is a balance between the sympathetic and parasympathetic nervous systems, which is important for regulating cerebral blood flow. Dysfunction of the autonomic nervous system after stroke aggravated secondary brain injury through changes in hemodynamics (37) and non-hemodynamic factors. Changes in hemodynamics, such as increased blood pressure variability, impaired brain autoregulation, and cardiovascular complications, lead to secondary brain injury. Non-hemodynamic factors such as the production of inflammatory factors (38), hyperglycemia, and increased blood-brain barrier permeability (39), coagulation factor activation, and platelet activation (40, 41) also cause secondary brain damage. These all increase the risk of further vascular events, such as myocardial infarction, recurrent stroke, and deep vein thrombosis (40). In animal experiments, chronic stress increased sympathetic nerve activity to increase the heart rate of mice. It was found that vascular endothelial function was damaged and oxidative stress in the blood vessels and brain as well as the susceptibility to cerebral ischemia were increased (42), consequently increasing the area of brain injury. Lowering the heart rate can restore vascular endothelial function, reduce oxidative stress, increase capillary density and collateral circulation (43), protect ischemic brain injury (43), and reduce stroke volume (44). The above mechanisms may explain our findings, that is, sympathetic hyperexcitation leads to poor neurological outcomes and stroke recurrence, while sympathetic suppression leads to favorable neurological outcomes and a reduction in stroke recurrence.

Previous evidence had shown that 24-h SDNN was strongly associated with all-cause mortality (45). Low HRV predicted increased mortality, and the association could not be attributed to cardiovascular risk factors or underlying disease (23). The cardiac complications resulting from autonomic dysfunction in stroke patients were 2–6% of the total mortality rate 90 days after acute ischemic stroke (46). In our study, both SDNN and RMSSD were not associated with 90-day vascular death in patients. This is different from previous studies, which may be due to the study population difference. The study population we selected were TIA and minor stroke patients with an NIHSS score $\leq$5, with mild clinical symptoms, and a total mortality rate of 0.24%.

SDNN reflects the overall autonomic function, including sympathetic and parasympathetic activity, while RMSSD only reflects parasympathetic activity (13). The parasympathetic effect is transient, while there is a long period of sympathetic excitation after ischemic stroke (47). Therefore, considering that 90-day neurological dysfunction and stroke recurrence are both associated with sympathetic hyperexcitability after ischemic stroke, reducing sympathetic activity may improve the prognosis of ischemic stroke after 90 days. Vagal nerve stimulation (VNS) was also shown to reduce infarct volume and improve neurological outcome at 1 day after acute ischemic stroke in middle cerebral artery occlusion rats (48). The mechanism of protection with VNS may involve a

reduction in extracellular glutamate and reduced excitotoxicity during cerebral ischemia, and/or a reduction in inflammation and release of norepinephrine. Parasympathetic activation also increases cerebral blood flow and enhance neurogenesis. However, parasympathetic activation is an invasive technique, which limits its use in acute stroke treatment (49). Beta blockade (50), statin (51), external counter pulsation (52), tele-acupuncture (53) have all been reported to modulate autonomic nervous dysfunction although more research is needed to confirm these findings.

LIMITATIONS

Our research has some limitations. Firstly, CNSR-III is a prospective clinical registry study of ischemic stroke or TIA nationwide based on etiological classification, imaging, and biological markers. It is not a specific study on the correlation between HRV and stroke prognosis. Second, patients received 24-h Holter during the acute period of hospitalization for stroke, and we did not conduct statistics on the interval between the examination and stroke occurrence. Third, in this study, we mainly analyzed the correlation between autonomic nerve system function and short-term prognosis of patients with TIA and minor ischemic stroke. Considering that TIA has no lesions and the lesions of minor stroke are relatively small, the localization of the lesions has not been evaluated yet. The relationship between stroke location and HRV need be investigated.

CONCLUSION

This study shows that autonomic nerve system dysfunction (sympathetic hyperexcitability and/or decreased parasympathetic activity) is an adverse factor for 90-day neurological prognosis and stroke recurrence after TIA and minor stroke. Regulating autonomic nerve system function may be a potential new target for improving the 90-day prognosis in these patients and is worthy to be further investigated.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tiantan Hospital affiliated to Capital Medical University (IRB Approval Number: KY2015-001-01) and all participating centers. 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

CL conceived the study and wrote the first draft of the paper. YP and MW analyzed the data. XM and ZL critically edited the manuscript. YW supervised the study. All authors contributed to the article and approved the submitted version.

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REVIEW
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Treatment Challenges in Acute Minor Ischemic Stroke

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Patients with acute ischemic stroke may present with minor neurologic deficits. Acute treatment decisions depend on the disability imposed by the symptoms along with radiographic features. The presence of disabling neurologic deficits warrants intravenous thrombolysis, but the indications for endovascular therapy are less defined. The degree of disability, presence of a large vessel occlusion with perfusion mismatch, and collateral circulation status may all be factors in selecting patients for endovascular treatment. Identification of patients who are at risk for neurologic deterioration is critical to preventing poor outcomes in this patient population.

Keywords: stroke, low NIHSS score, endovascular treatment, intravenous thrombolysis, minor stroke

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BACKGROUND AND CURRENT STATUS OF MINOR ISCHEMIC STROKE TREATMENT

Clinical trials have shown that acute ischemic stroke can be treated with intravenous (IV) thrombolysis (1, 2) and/or endovascular thrombectomy (ET) (3–5). Treatment with thrombolysis is not without risk, and it is the physician's task to determine whether the benefit of treatment outweighs that risk for each individual patient. This risk-benefit assessment is aided by clinical scales that measure neurologic impairment and non-invasive brain imaging studies. The National Institutes of Health Stroke Scale (NIHSS) is a 42-point measure of stroke severity that is used throughout the US and elsewhere. In research and clinical practice, the NIHSS score is used to help guide treatment decisions and prognosis. Patients with a higher NIHSS score generally have a larger ischemic territory and worse outcomes if left untreated (6). In addition to the NIHSS score, neuroimaging is another key factor in making treatment decisions for thrombolysis. For all stroke patients a non-contrast head computed tomography (CT) is required for treatment with thrombolysis in order to exclude the presence of an intracranial hemorrhage and a large established ischemic infarction. Advanced imaging, such as CT or magnetic resonance (MR) perfusion, is an additional tool for more complex cases such as delayed presentation from symptom onset.

The NIHSS score and imaging are key to identifying patients who may benefit from IV thrombolysis treatment, though there are instances where these tools may be insufficient. Patients who present with mild symptoms and a low NIHSS score are an important example of how these screening tools may fail. The concept of "minor stroke" has been defined as NIHSS scores ≤ 5 by the American Stroke Association, but the score alone may not account for the disability incurred by certain symptoms as will be discussed below in more detail. The early clinical trials for IV thrombolysis and ET generally excluded patients with mild symptoms or no measurable deficit on the NIHSS (1, 7, 8). The presence of mild symptoms is one of the most commonly-cited reasons for not administering alteplase (9). Approximately 34% of acute ischemic stroke patients presenting with low NIHSS scores are not treated with alteplase (10) and another 30% who are otherwise

eligible for ET are also not treated (11). Furthermore, studies on the natural history of minor strokes with NIHSS $\leq$ 5 have demonstrated that 25% of patients will have residual disability at 3 months (12). These statistics illustrate how a significant minority of patients with mild stroke are considered ineligible for treatment despite the increased risk of poor outcome. There is a critical need for more data and better screening tools to identify which patients with minor stroke symptoms would benefit from treatment. In this review, we will discuss the challenges in acute minor ischemic stroke and future directions to improve patient care.

MINOR ISCHEMIC STROKE AND INTRAVENOUS THROMBOLYSIS

Prior to IV thrombolysis with alteplase, there are both clinical and radiographic criteria that should be met for treatment eligibility. Official guidelines put forth by the American Stroke Association recommend that patients with disabling symptoms, regardless of stroke severity measured by the NIHSS, should be treated with IV thrombolysis if they meet other standard criteria (13). This recommendation supports the use of alteplase in patients with low NIHSS so long as disabling symptoms are present. A large meta-analysis by Emberson et al. (14) pooled data from major trials, including NINDS, ECASS and IST, and over 6,000 patients were included. While only 10% of these patients had minor strokes with NIHSS 0–4 and disabling symptoms, there was a demonstrable benefit of treatment with alteplase compared to placebo with an odds ratio of 1.48 (1.07–2.06, 95% CI) for good outcome. This study informed the guideline recommendations.

The presence of disabling symptoms is a key factor in patient selection for IV thrombolysis; however, there is no unified definition in the literature for what constitutes "disabling symptoms." Even some clinical trials, such as ECASS III, did not specify this term in more detail (1). In our practice, patients with limb weakness, language impairment, vision impairment, and hemineglect are considered to have disabling symptoms that warrant treatment with IV thrombolysis. By contrast, there is more literature about what might be considered "non-disabling symptoms." In the NINDS-TPA trial, the investigators specifically noted that pure sensory symptoms, isolated ataxia, isolated dysarthria, and isolated facial weakness could be considered minor and non-disabling. A subsequent study found that application of this definition, rather than a particular score on the NIHSS, may better identify minor stroke patients who could do well without IV thrombolysis (12). Overall, qualifying symptoms as disabling or non-disabling can help distinguish which patients with mild stroke severity should be treated.

The ASA guidelines comment that patients with mild stroke severity (NIHSS scores $\leq$ 5) and no disabling symptoms should not receive alteplase (13). Rather, patients with mild symptoms might benefit from less aggressive medical treatment, including aspirin administration. The PRISMS trial was a randomized trial that compared IV thrombolysis with alteplase to aspirin (15). PRISMS was halted early, but the results suggested that acute ischemic stroke patients with low NIHSS scores of 0–5 and no disabling symptoms are unlikely to gain benefit from treatment with alteplase compared to aspirin (15). More recently, the use of dual-antiplatelet therapy in minor ischemic stroke or transient ischemic attack has gained favor based on evidence from two clinical trials (16, 17). Patients with NIHSS scores of 0–3 had significantly reduced risk of recurrent stroke when treated with aspirin and clopidogrel, with the most benefit gained within the first 21 days (18).

Imaging plays a supportive role in screening for patients who would benefit from alteplase. Routine non-contrast head CT is required prior to treatment to exclude cerebral hemorrhage or a large territory cerebral infarction but is unlikely to alter the decision for thrombolysis in the way that the presence of disabling symptoms might. However, advanced imaging plays a larger role in patients with delayed presentation or unknown time of symptom onset. The EXTEND trial evaluated alteplase treatment in patients with evidence of a salvageable penumbra on cerebral perfusion imaging between 4.5 and 9 h from symptom onset (19). Patients with NIHSS scores as low as 4 points were included, although these patients represented a minority of the overall cohort. A subgroup analysis of the data suggested that patients with NIHSS scores $<$ 10 may benefit from treatment when compared to placebo, but the study was underpowered to demonstrate a significant difference between these two groups (19). Further study to determine whether perfusion imaging can identify patients with mild stroke symptoms who might benefit from IV thrombolysis is warranted.

The WAKE-UP trial used MRI to identify stroke patients who are likely to benefit from IV thrombolysis when they present with an unknown time of symptom onset (20). Patients in this trial were enrolled if they had a mismatch between the ischemic core on DWI and corresponding hyperintense signal abnormality on FLAIR imaging, which suggests that their time from symptom onset is likely $\leq$4.5 h (after which FLAIR signal is typically hyperintense). WAKE-UP included patients with NIHSS scores as low as 4 as long as their symptoms were disabling. In a subgroup analysis, patients with NIHSS scores $<$ 10 and disabling symptoms had significantly improved outcomes compared to placebo. These findings underscore that neuroimaging may be used to guide IV thrombolysis treatment decisions in patients with more mild stroke symptoms.

In summary, patients presenting with minor stroke severity (NIHSS scores $\leq$ 5) and disabling symptoms may still benefit from treatment with alteplase. The presence of a disabling neurologic deficit is a key feature in screening for eligibility and is an important adjunct to the NIHSS. Imaging plays a supportive role in the earlier time window patients but is more informative in late window patients when the amount of core infarct or time from symptom onset needs to be better characterized. Currently there is insufficient evidence supporting treatment of minor stroke patients with thrombolysis in later time windows but further studies are warranted.

MINOR ISCHEMIC STROKE WITH LARGE VESSEL OCCLUSION

Endovascular thrombectomy is a well-established treatment for acute ischemic stroke patients with NIHSS score ≥ 6 and concomitant large vessel occlusion (LVO) of the internal carotid artery (ICA) or the first part of the middle cerebral artery (MCA-M1) (5). Patients with minor stroke severity were not included in the landmark randomized thrombectomy trials that were reported between 2015 and 2018. As a result, there is a paucity of data to guide ET treatment decisions in patients with minor stroke symptoms due to LVO. Current ASA guidelines reflect this scarcity of high-level evidence and state that ET may be reasonable in patients with NIHSS < 6 (13). There are no specific comments about disabling symptoms such as those described in the IV thrombolysis literature and recommendations, which introduces additional uncertainty in the treatment of these patients.

Given that the average NIHSS score of a patient with large vessel occlusion is 10 (21), one might question the frequency of patients with mild symptoms and LVO. In one study, about 13% of all acute ischemic stroke patients had an NIHSS of < 8 points and an LVO (22). Another study evaluated only patients with mild symptoms and found that within this group about 38% of patients had an LVO (23). Numerous other studies report varying percentages of mild ischemic stroke patients with LVO depending on the NIHSS cutoff (24, 25). These data illustrate that mild symptoms can be misleading and that there is a significant number of patients with low NIHSS scores who have a large vessel occlusion that would be amenable to thrombectomy treatment. One common cause for a patient to present with mild symptoms despite the presence of LVO is good collateral circulation that sustains the penumbra (tissue at-risk). It is important to recognize this subset of patients due to the potential for worse outcome should the collateral circulation collapse. Whether patients with mild stroke and LVO should be treated with endovascular thrombectomy remains highly debated and is a topic of ongoing randomized trials. An example case from our institution is shown in **Figure 1**.

MILD ISCHEMIC STROKE WITH LARGE VESSEL OCCLUSION AND EARLY NEUROLOGIC DETERIORATION

Strong collateral circulation often underlies mild ischemic stroke symptoms in the presence of an LVO. However, collaterals may reach a critical point and collapse with subsequent clinical worsening. This concept, termed early neurologic deterioration (END), describes worsening of stroke symptoms by four or more points on the NIHSS within 24 h of presentation and is not caused by intracranial hemorrhage (26). Recent data illustrated that approximately 12% of patients with mild stroke and LVO will progress to END despite treatment with alteplase (27). The vast majority who decline will do so within the first several hours of hospital presentation (28), which indicates that timely treatment is critical.

The risk of END is associated with several different factors. For example, the site of LVO has been well-described as a predictor of END in minor ischemic stroke. In one study, 30% of patients with occlusions involving the ICA terminus or tandem occlusion of the ICA and MCA-M1 suffered early deterioration. These patients had all been treated with intravenous thrombolysis as well (23). Patients with occlusions involving the ICA, ACA, MCA-M1, and basilar arteries were at least twice as likely to suffer early deterioration despite treatment with alteplase (23).

Another important factor associated with END is thrombus length. One study measured thrombus length on MRA, CT, or CTA and discovered that length is independently associated with END and the risk increases proportionately with increasing size (27). The investigators dichotomized length to demonstrate that thrombi measuring nine or more millimeters in size would yield three times greater odds of progressing to END (27). The authors suggested that larger thrombi were associated with END because early recanalization could not be achieved with IV thrombolysis alone. It has been previously demonstrated that patients with larger thrombi have suboptimal reperfusion rates after alteplase (29).

The potential for early neurologic deterioration in minor ischemic stroke patients with LVO poses a dilemma for providers. Although this pathway is overall uncommon, it may be more likely to occur with proximal cervical or cerebral artery occlusions and longer thrombi. If patients at risk of collateral circulation collapse and END could be accurately identified, these patients may be optimal to consider for thrombectomy treatment.

EVALUATING THE COLLATERAL CIRCULATION IN MINOR STROKE WITH LVO

To date, there is no convincing association between collateral circulation and early neurologic deterioration. Some perfusion imaging parameters can be used as a surrogate for collateral circulation and are of interest in predicting END. Hypoperfused tissue with a disproportionately large amount of Tmax > 10 s delay compared to Tmax > 6 s delay is known to be associated with poor collateral circulation (30). One might speculate that patients with larger Tmax > 10 s volumes could be at risk for END. Saleem et al. (28) evaluated several different factors related to collateral circulation including perfusion-dependency of symptoms and Tmax perfusion volumes at thresholds of 6 and 10 s in a cohort of 122 patients, but none was independently associated with END. In a retrospective cohort of 81 patients with minor symptoms and LVO, Lee et al. (31) noted that patients who declined were significantly more likely to have larger baseline core and penumbra volumes on CT perfusion. These studies are limited by their small size and retrospective design.

OUTCOMES IN PATIENTS WITH MINOR STROKE AND LVO

Data for outcomes in minor stroke treated with thrombectomy are limited to retrospective and observational cohorts. The

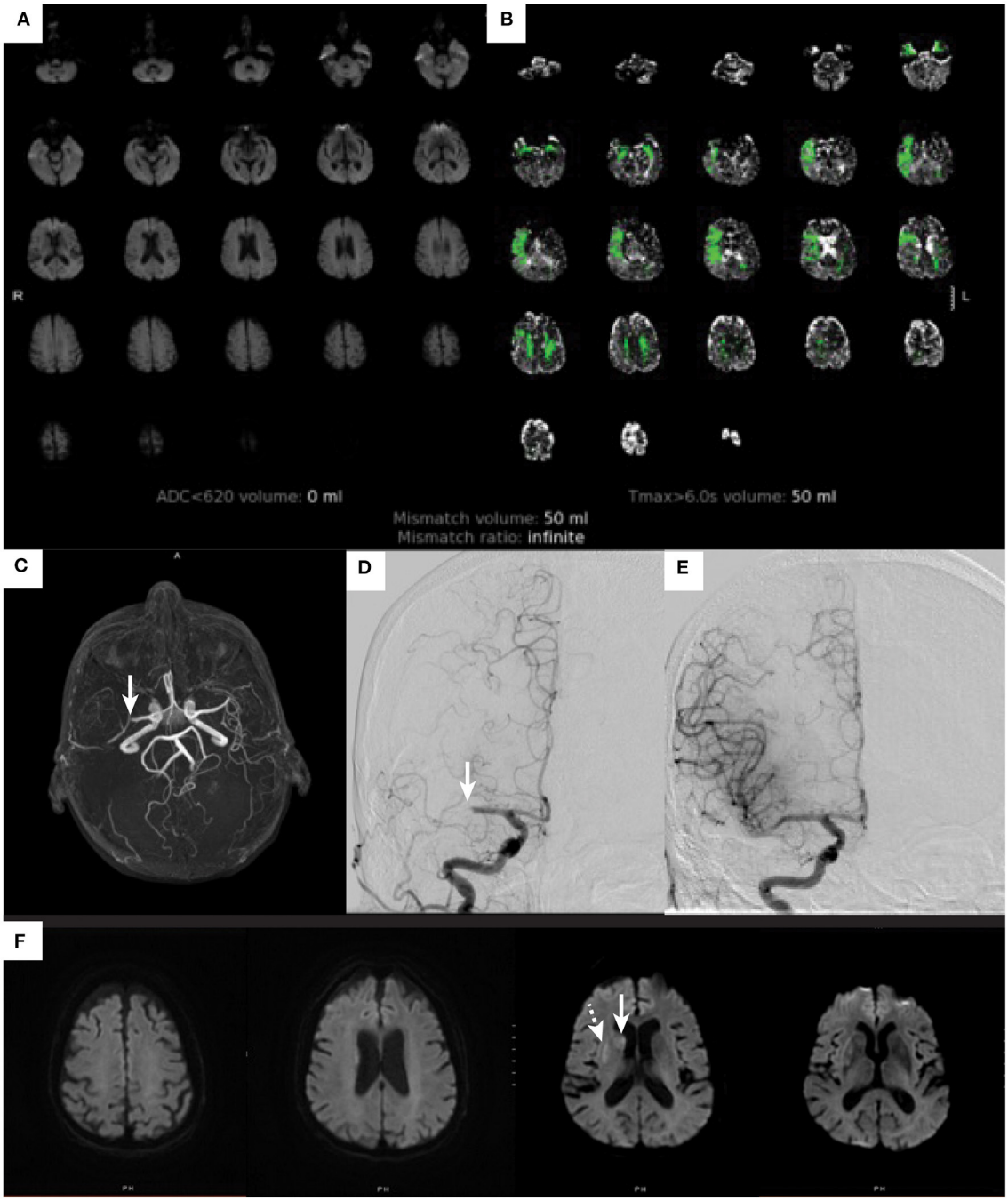

FIGURE 1 | Ischemic stroke in an elderly patients with mild symptoms. An 81-year-old woman with atrial flutter on apixaban, hypertension, hyperlipidemia, and baseline modified Rankin score of 0 developed acute onset left facial droop with dysarthria and left hand weakness. These symptoms lasted for about 20 min and then completely resolved by the time she arrived to the emergency department. On initial examination she had an NIHSS score of 0. She was not treated with IV alteplase due to resolution of symptoms. A diffusion-weighted image **(A)** does not show any evidence of cerebral infarction (ADC < 620 volume 0), and perfusion imaging **(B)** demonstrates a perfusion deficit within the right MCA territory (Tmax > 6 s volume 50 ml). An MR angiogram [arrow **(C)**] shows a right M1-MCA occlusion. The patient underwent a cerebral angiogram that identified the right M1-MCA occlusion [arrow **(D)**], which was successfully treated by thrombectomy with complete revascularization **(E)**. A post thrombectomy diffusion-weighted MRI **(F)** demonstrates small cerebral infarctions within the caudate (arrow) and putamen (dashed arrow).

most salient questions are (1) is EVT safe and feasible in this patient population and (2) is EVT more likely to yield improved outcomes compared to best medical therapy. A recent comprehensive meta-analysis published by McCarthy et al. included 24 different studies and found encouraging evidence for the overall safety of endovascular therapy (32). This finding is not surprising given that the technical aspects of the procedure would not differ among these patients and others with LVO.

However, there were some negative aspects to treatment with ET in a cohort of patients from our center. Patients treated with ET had a longer length of stay and were more likely to be discharged to a skilled nursing facility, although there was no detectable impact on the rate of good outcome as measured by modified Rankin Scale score ≤ 2 (65% in medical group and 56% in ET group, $p = 0.25$). Due to the retrospective nature of the study it is possible that the ET group may have included sicker patients. There were also baseline differences between the groups with fewer patients receiving alteplase and more tandem occlusions in the ET group (33).

The second question regarding superiority of ET compared to best medical management in minor stroke with LVO is less clear. One of the largest studies to date was published by Dargazanli et al. and included a cohort of 301 patients. Half of these patients received best medical therapy and the other half received up-front ET along with best medical therapy. There was no significant difference in the rate of excellent or favorable outcome between the two groups (22). A second cohort of similar size, however, demonstrated a significant benefit of up-front ET with a rate of good outcome reaching 84% compared to 70% in the medical therapy group (34). Other studies have more specifically compared IV thrombolysis with EVT and found no difference in the rate of good outcome (35).

A final point to consider is delayed endovascular therapy. The above studies evaluated up-front ET, but it might be reasonable to offer best medical therapy first and follow up with endovascular therapy if neurologic deterioration occurs. Seners et al. (27) identified a subset of patients with minor ischemic stroke and large vessel occlusion who received alteplase and subsequently developed END. Just over half of the patients who deteriorated were selected for rescue ET and the vast majority achieved successful reperfusion (82%). Compared to patients who deteriorated and did not receive any ET, those who underwent ET were three times more likely to have a good outcome (27). In this cohort overall, the patients who suffered END had worse outcomes but this was mitigated to some degree with rescue thrombectomy.

In conclusion, studies have demonstrated reasonable safety and feasibility of ET for patients with minor ischemic stroke symptoms and concomitant LVO. Whether ET provides any additional benefit beyond best medical management is not clear. The "wait and treat" approach might be a reasonable alternative to up-front intervention, and data show that rescue thrombectomy may be beneficial in this situation. However, the opportunity for a good outcome may be diminished in the event of early neurologic deterioration regardless of rescue thrombectomy. Resource availability further complicates ET treatment decision-making process. When patients with LVO and mild stroke symptoms are monitored at a smaller community hospital with a "wait and treat" approach, further treatment delays may be incurred should the patient require transfer to a thrombectomy-capable center upon deterioration. If patients at risk for END could be accurately identified, then transfer to a tertiary stroke center could be quickly initiated. In our hospital, we often transfer such patients from community hospitals to our facility, where they are closely monitored and neurointerventional physicians are on-call for immediately treatment should clinical deterioration occur.

AREAS OF UNCERTAINTY AND NEED

The ability to predict clinical decline is a critical factor in decision making for patients with minor stroke symptoms and LVO. Patients are likely to do well with best medical therapy unless they develop early neurologic deterioration, at which point they may be at risk for poor outcome regardless of rescue treatment. Perhaps patient selection for treatment should be performed in a manner similar to late-window thrombectomy where perfusion imaging plays an important role in selection for patients presenting 6–24 h from symptom onset (**Figure 2**) (3, 4). Both groups share an underlying pathophysiology of LVO with peri-ischemic tissue sustained by strong collateral circulation. With this idea in mind, some of the techniques used for late-window thrombectomy selection, such as perfusion imaging, could be shared in selecting patients with minor symptoms and LVO for ET.

As discussed earlier, thrombus length and location are some established predictors of END. There are other advanced imaging measures that could identify patients at risk of decline. For example, patients with more critically impaired perfusion at presentation could be considered high risk. Hypoperfusion severity could be measured by Tmax > 10 s volume or the hypoperfusion intensity ratio (HIR). Higher HIR values are known to be correlated with more rapid infarct progression (36, 37).

Grading the collateral circulation is another potential way to identify patients at risk for clinical decline. There are numerous collateral scoring systems that exist, each with strengths and weaknesses. The gold standard for rating pial collaterals is digital subtraction angiography (DSA). However, this technique is the most invasive method for collateral assessment, which renders it a poor screening tool. Single-phase CTA captures arterial filling over time after a bolus injection, while the more advanced multi-phase CTA characterizes blood flow in the arterial, peak venous, and late venous phases. Multi-phase CTA may provide a more nuanced evaluation of the collateral circulation and is validated to predict outcomes in acute ischemic stroke (38). Most patients presenting with acute ischemic stroke will undergo CTA as part of the initial diagnostic workup. Further study is needed to determine if CTA can serve a dual purpose as a screening tool for later decompensation. In DEFUSE 3, patients with good collateral scores graded by the Tan/Maas scales with single-phase CTA had smaller ischemic core volumes and decreased core volume growth (37). This subset of late-window patients could be similar to those with minor symptoms and LVO with strong collateral circulation.

Other studies have compared CTA-based collateral scoring with CT perfusion imaging for selecting patients who would most likely benefit from endovascular therapy. The two methods have similar capability of predicting outcomes in a late-window cohort (38) but these techniques have not been thoroughly explored in patients with LVO and minor stroke symptoms.

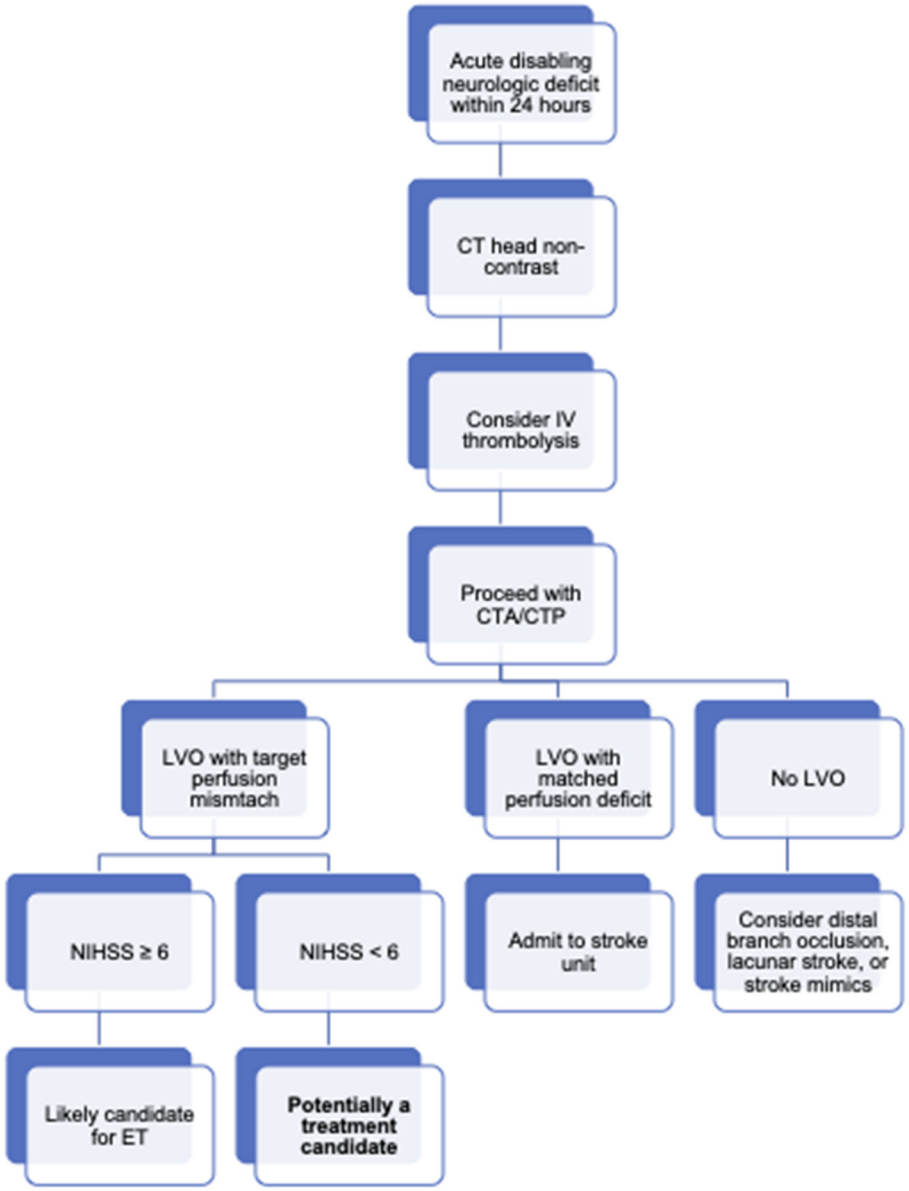

FIGURE 2 | Treatment diagram for patients with a LVO and mild stroke symptoms. Board overview of workflow for acute ischemic stroke patients at our institution. In general, patients with an acute neurologic deficit (even those scoring low on the NIHSS) will be taken for non-contrast head CT if stroke is clinically suspected. In the absence of intracranial hemorrhage or early ischemic changes, patients may be considered for thrombolysis if symptoms remain diabling and the patient is within 4.5 hours of symptoms onset. Extended window thrombolysis is considered on a case-by-case basis and is not depicted here. Patients treated with thrombolysis and patients not treated with thrombolysis but still suspected to have an acute stroke clinically are further imaged with CT angiography and perfusion. Identification of an LVO and a target perfusion mismatch profile (CBF < 30% volume of < 70 cc, mismatch ratio ≥ 1.8, mismatch volume ≥ 15 cc) leads to activation of the stroke interventional team. Patients with NIHSS scores of 6 or more points are usually treated with ET. Patients with NIHSS < 6 are considered.

CURRENT CLINICAL TRIALS

There are a number of trials investigating best management strategies for acute ischemic stroke with low NIHSS. The ENDOLOW study is currently recruiting patients with NIHSS 0–5 and objective neurological deficits who present within 8 h of symptom onset to be randomized to best medical therapy or ET. This trial requires imaging confirmation of an LVO (ICA, MCA M1, or proximal M2) and absence of a large core infarct judged by ASPECTS ≥ 6 or estimated ischemic core volume of <70 ml (determined by CT perfusion imaging as a CBF < 30% reduction). Crossover from the medical group to the endovascular group is permitted in the event of neurologic deterioration (Clinicaltrials.gov study number NCT04167527). The study design echoes that of late-window thrombectomy trials that relied on advanced imaging to identify the amount of salvageable tissue.

A second clinical trial, MOSTE, is currently enrolling in Europe. This study is randomizing patients with NIHSS < 6 or clinical stroke symptoms within 24 h of last known well to receive either best medical therapy or ET. Imaging criteria is broad and allows for patients with ASPECTS ≥ 6 with a confirmed LVO involving the ICA, MCA (M1 or M2 segments) (Clinicaltrials.gov study number NCT03796468). This study will likely capture a more heterogeneous patient population compared to the ENDOLOW study, but both studies will provide meaningful data for selecting patients for endovascular treatment.

Third, the TEMPO-2 study focuses on medical management in patients with NIHSS ≤ 5. Patients in TEMPO-2 are randomized within 12 h of symptom onset to either Tenecteplase or antiplatelet therapy. Uniquely, this study includes patients with transient ischemic attack in addition to patients with ongoing symptoms at the time of enrollment. Imaging requirements for enrollment include multi-phase CTA to determine the presence of complete or near-complete occlusion of any identifiable vessel supplying anterior or posterior circulations, or evidence of a focal perfusion abnormality that can be correlated with symptoms (Clinicaltrials.gov study number NCT02398656). This study takes a novel approach by favoring thrombolytic treatment based on imaging findings of LVO or perfusion changes. Inclusion of patients with no symptoms at all will provide an interesting view on treatment selection in this population.

Of note, none of these clinical trials has emphasized the need for disabling neurologic deficits. The presence of any deficit is considered meaningful in the context of a corresponding LVO, and the presence of a LVO is required for enrollment in each of these studies. Imaging clearly plays a larger role in screening for patients with low NIHSS who would still benefit from treatment.

CONCLUSIONS

Patients who present with acute ischemic stroke and low NIHSS are an important subgroup of the broader ischemic stroke population. Treatment decisions for IV thrombolysis and ET are different but rely on shared principles. The presence of disabling symptoms is a cornerstone consideration for both intravenous and endovascular therapy and would likely warrant treatment with alteplase at a minimum. On the other hand, patients with non-disabling symptoms are likely to do well without interventions. The benefit of endovascular therapy up-front has not been definitively established in patients with minor symptoms and large vessel occlusion. In the event of clinical decline, rescue thrombectomy may yield improved outcomes. Clinical trials are needed to understand the value of endovascular therapy in this patient population, and identification of patients likely to develop END would further aid in optimizing patient selection.

AUTHOR CONTRIBUTIONS

DS prepared the manuscript and figure. JH critically reviewed the manuscript and figure. Both authors contributed to the article and approved the submitted version.

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Efficacy and Safety of Adherence to dl-3-n-Butylphthalide Treatment in Patients With Non-disabling Minor Stroke and TIA—Analysis From a Nationwide, Multicenter Registry

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Background: Dl-3-n-Butylphthalide (NBP) has the potential to improve clinical outcomes in acute ischemic stroke patients by improving collateral circulation. We aimed to evaluate the efficacy and safety of NBP in patients with non-disabling minor ischemic stroke and transient ischemic attack (TIA).

Methods: The BRIDGE (the observation study on clinical effectiveness of NBP on patients with non-disabling ischemic cerebrovascular disease) is a prospective registry to monitor the efficacy and safety of NBP therapy in acute non-disabling ischemic stroke or high-risk TIA. Non-disabling minor ischemic stroke patients within 48 h were enrolled across 51 stroke centers in China. We divided patients into NBP compliance or non-compliance groups according to their adherence to NBP. The primary outcome was the favorable functional outcome at 90 days, defined as a modified Rankin scale (mRS) < 2.

Results: Between 10th October 2016 and 25th June 2019, 3,118 patients were included in this analysis. In multivariable analysis, after adjusting for common risk factors and demographic factors, NBP-compliance group has a higher proportion of favorable functional outcome (92.1 vs. 87.4%, adjusted odds ratio 2.00, 95% confidence interval, 1.50–2.65), and a higher stroke recurrence rate (2.40 vs. 0.31%, adjusted odds ratio 8.86, 95% confidence interval, 3.37–23.30) than the NBP-non-compliance group. There was no significant difference in death and intracranial hemorrhage rate between the two groups. In subgroup analysis, patients with National Institutes of Health Stroke Scale (NIHSS) scores from 3 to 5 who complied to NBP therapy had a higher rate of favorable functional outcomes than the NBP-non-compliance group. [88.82 vs. 76.21%, adjusted odds ratio 2.52 (1.81–3.50), adjusted interaction $P = 0.00$].

Conclusion: In non-disabling minor ischemic stroke or TIA patients, compliance with NBP therapy led to better 90-day functional outcomes despite a higher risk of recurrence, and this effect seems to be stronger in patients with NIHSS scores of 3–5. Further large randomized, double-blind controlled studies to analyse the association between NBP and functional outcome is warranted in the coming future.

Keywords: minor stroke, dl-3-n-butylphthalide, TIA, efficacy, modified rankin scale, non-disabling

INTRODUCTION

Studies have reported that minor stroke and high-risk TIA (ABCD2 score $\geq$ 4) may have a high risk of early stroke recurrence and a more unsatisfactory clinical outcome than expected (1–4). Although treatment of minor stroke and high-risk TIA has improved, the risk of stroke recurrence within 90 days of stroke onset has been reported to be as high as 10–20% (1–4). Randomized, double-blind controlled studies based on Chinese populations have reported a 90-day fatal or disability incidence of 6.03% and a 90-day stroke recurrence rate of 9.6% in patients with minor stroke [National Institutes of Health Stroke Scale (NIHSS), 0–3] or high-risk TIA (5).

Evaluating collateral circulation at an early stage will facilitate the selection of intravenous thrombolysis and endovascular therapy (6–8). More importantly, a robust collateral flow will compensate for blood supply in the ischemic area, reduce core infarct volume and revive the penumbra zone.

Dl-3-n-butylphthalide (NBP) is a synthetic compound based on l-3-n-butylphthalide extracted from the seeds of Apium graveolens Linn. Synthesized NBP has been approved to treat ischemic stroke patients with medium and small infarct foci in China (9). NBP improved collateral circulation by restoring the diameter of meningeal micro-arteries in the ischemic area and promoting blood vessel formation in mice (10, 11). Results of several multicenter randomized, double-blind, placebo-controlled trials evaluating oral NBP in patients with acute ischemic stroke showed significant improvements in neurological deficits and activity of daily living scales in the NBP -treated group compared with the placebo-controlled group, with a good safety profile (9, 12), and accepted by the Chinese guidelines for acute ischemic stroke (13). However, real-world, large-scale clinical studies of NBP therapy in patients with non-disabling minor stroke and high-risk TIA are still lacking.

This study aimed to analyze the efficacy and safety of NBP in patients with Non-disabling minor ischemic stroke and high-risk TIA.

METHODS

The BRIDGE Registry

The BRIDGE (the observation study on clinical effectiveness of NBP on patients with non-disabling ischemic cerebrovascular disease) is a prospective registry that was initiated in 2018 to monitor efficacy and safety of NBP therapy in acute non-disabling ischemic stroke (NIHSS $\leq$ 5 on admission) or high-risk TIA (ABCD2 score $\geq$ 4 on admission). For the BRIDGE registry, specific information on timing and dosing of NBP, antiplatelet and statin therapy, and other stroke risk factors was added to the standard questionnaire. Data presented were obtained by standardized questionnaires in the 51 participating hospitals, medical history (prior coronary interventions, congestive heart failure, diabetes mellitus, renal insufficiency), biochemical test results, stroke subtype, and brain imaging. The clinical research forms available for the study were centralized at NCRC-ND (The China National Clinical Research Center for Neurological Diseases) and recorded into the Electronic Data Capture System [EDC 1.0, Jianhe Jiuzhou (Beijing) Technology Co.]. All data were analyzed centrally at NCRC-ND, China. Local monitoring and audits of the data have been performed in 10% of randomly selected patients. The ethics committee has approved the registry study. The local ethics committee has approved the registry of each center. Trial registration: http://www.chictr.org.cn/ Identifier: ChiCTR-OPC-16008069.

Patient Selection

All patients with non-disabling ischemic stroke (NIHSS $\leq$ 5 on admission) or high-risk TIA (ABCD2 score $\geq$ 4 on admission) within 48 h of onset and treated with NBP were included on an intention-to-treat basis. Exclusion criteria include: (1) intracranial hemorrhage or vascular malformation, tumor, abscess, or other common non-ischemic brain diseases (e.g., multiple sclerosis); (2) iatrogenic stroke; (3) patients receiving early recanalization therapy (intravenous thrombolysis or endovascular thrombectomy); (4) pre-morbid mRS score >2; and (5) severe multi-organ failure; (6) patients with severe mental disorders and dementia; (7) patients who are pregnant or nursing or planning to become pregnant. All patients underwent cranial MRI during hospitalization to determine cerebral infarction diagnosis and exclude mimic stroke.

Procedure and NBP Medication Compliance

The 600 mg dose of NBP was taken as two capsules three times daily, each containing 100 mg of NBP. We invited all patients to take part in the study. Physicians contacted patients to obtain informed consent. All patients who agreed to participate in the study were instructed to take standard dose of NBP for 90 days and asked to complete a questionnaire at baseline; they were followed up every 30 for 90 days (**Figure 1**: flow progress diagram). For each month follow-up period, the patient received a pack of 180 capsules, and they were instructed to return the unused capsules at each visit. Nurses interviewed the patients. Patients were asked to record the duration of any lapses, the

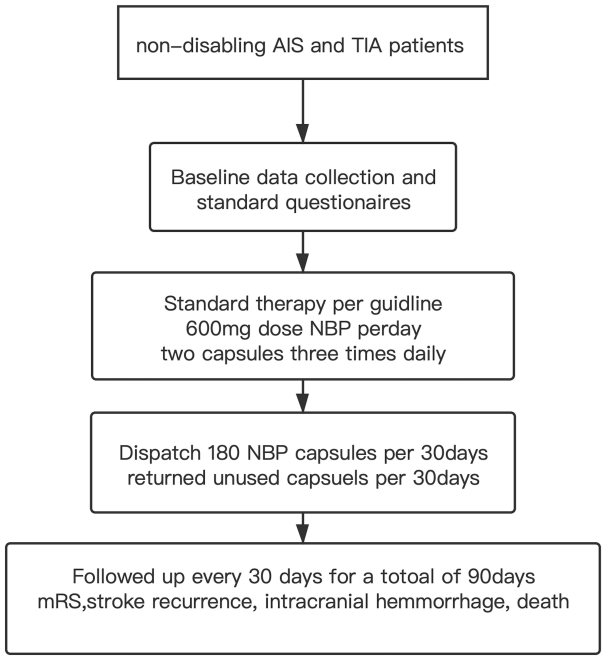

FIGURE 1 | Flow progress diagram.

altered dosages that may have been taken, and the frequency of omitting any single dose. The answers were recorded in a completed CRF form for double-checking of the unreturned pills by follow-up personnels. Compliance with medication was calculated as the number of nonreturned capsules divided by six times the number of days in the follow-up period. The daily capsule count was expressed as a percentage of the scheduled dose (14). NBP medicine compliance was defined as taking 80% or more of the prescribed NBP doses (15). We monitored the patient's adverse reactions in accordance with the usual follow-up requirements, and the patient's liver and kidney function monitoring is carried out during baseline and routine follow-up.

Sample Size

Assuming the proportion of good functional outcome (mRS0–1) in NBP-compliance group is 85%, and in NBP-non compliance group is 80%, power of 0.90, and a level of 0.05, we required 1,209 participants per group. To account for possible dropouts of 10%, we increased the sample to 2,688.

Statistical Methods

All statistical analyses were performed using SAS version 9.4, and continuous variables are expressed as mean and standard deviation or median and quartiles.

We present data as absolute numbers or percentages. The Pearson–Fisher χ^2 test compared the frequencies of categorical variables in the two treatment groups. The Mann–Whitney–Wilcoxon test compared continuous variables.

We compared the proportion of stroke recurrence at 90 days between the two groups using Fisher's exact probability test or χ^2 test. We calculated HRs and 95% confidence intervals using single-factor and multifactor Cox regression.

We compared the proportion of favorable outcomes (mRS $\leq$ 1) between the two groups using single-factor and multifactor regression analysis.

We used single and multivariable Cox regression to compare the proportion of death and intracranial hemorrhage between the two groups at 90 days and calculate HR and 95% confidence intervals. A propensity score for NBP-compliance treatment was created to adjust for baseline differences between NBP-compliance and NBP-non-compliance subjects. A logistic regression model with compliance -NBP treatment as the outcome was used to generate propensity scores for all subjects. Variables that are potential confound compliance for NBP were included in three models; model 1 (age and sex); model 2 (age, sex, history of hypertension, body mass index, history of diabetes, history of dyslipidemia, smoking, alcohol consumption, admission NIHSS score, and TOAST types); modle 3 (propensity score). All hypotheses were tested using a two-sided test with $\alpha = 0.05$. $P \leq 0.05$ was considered statistically significant.

RESULTS

Between 10th October 2016 and 25th June 2019, 4,592 consecutive patients with minor acute ischemic stroke or high-risk TIA within 48 h of onset were included in the BRIDGE registry. A total of 152 patients were excluded because of incomplete information, of which 12 were missing important baseline information (age, sex, height, and weight), and 140 were missing important follow-up information (mRS scores at discharge and day 90). A total of 2,966 cases were entered into the analytical dataset based on the definition of the analytical dataset (**Supplementary Figure 1**), of which there were 1,042 cases in the NBP-compliance group and 1,924 cases in the NBP-non-compliance group. **Table 1** shows the baseline characteristics in the two groups.

Of the 2,966 patients included in this study, 2,751 (92.7%) were treated with antiplatelet therapy, of which 1,229 (43.80%) were treated with aspirin only, 389 (13.11%) with clopidogrel only, 1,233 (41.57%) with dual antiplatelet, and 215 (7.25%) were not treated with any antiplatelet agents.

The mean age of the NBP-non-compliance and the NBP compliance group was 65.00 (56.00–73.00) and 64.00 (55.00–72.00) years. The median onset time from onset to hospital admission was 10.12 (3.00–24.00) h and 10.01 (2.52–24.00) h for the NBP-non-compliance group and the NBP compliance group, respectively. The median NIHSS score at admission was 2 for each of the two groups. The remaining baseline characteristics are detailed in **Table 1**.

Primary Outcomes

The proportion of patients with a favorable 90-day functional outcome (mRS 0–1) was higher in the NBP-compliance group (92.05%, 949 cases) than in the NBP-non-compliance group (87.42%, 1,626 cases) (OR = 1.67, 95% CI, 1.28–2.17, and $p = 0.0002$). In logistic regression model 1, after adjusting for age and sex, there was a significant difference in the proportion

TABLE 1 | Baseline characteristics between NBP compliance and NBP-non-compliance group.

Variate	ALL	NBP-non-compliance group (n = 1,924)	NBP compliance group (n = 1,042)	P
Age, years		65.00 (56.00–73.00)	64.00 (55.00–72.00)	0.0779
Male	1,935 (65.23%)	1,234 (64.14)	701 (67.27)	0.0868
Onset to admission time (h)		10.12 (3.00–24.00)	10.01 (2.52–24.00)	0.0283
Diabetes, *N* (%)	763 (25.72)	486 (25.26)	277 (26.58)	0.4311
Hypertension, *N* (%)	1,954 (65.88)	1,270 (66.01)	684 (65.64)	0.8412
Dyslipidemia, *N* (%)	2,707 (91.27)	1,762 (91.58)	945 (90.69)	0.4129
Stroke history, *N* (%)	110 (3.7)	70 (3.64)	40 (3.84)	0.7827
Smoke, *N* (%)	735 (24.78)	469 (24.38)	266 (25.53)	0.0175
Atrial fibrillation, *N* (%)	80 (2.70)	66 (3.43)	20 (1.92)	0.0192
Coronary heart disease, *N* (%)	374 (12.61)	229 (11.90)	145 (13.92)	0.1148
Previous anti-hypertension, *N* (%)	1,415 (47.71)	941 (48.91)	474 (45.49)	0.0751
Previous antiplatelet, *N* (%)	593 (20.00)	371 (19.28)	222 (21.31)	0.1886
NIHSS, median (IQR)	2.00 (1.00–4.00)	2.00 (1.00–3.00)	2.00 (1.00–4.00)	0.0003
Current medication therapy				
Antiplatelet, *N* (%)	2,751 (92.75)	714 (92.13)	2,037 (92.97)	0.4371
Anticoagulant, *N* (%)	240 (8.10)	61 (7.87)	179 (8.17)	0.7932
Stain therapy, *N* (%)	2,447 (82.50)	625 (80.65)	1,822 (83.16)	0.1135
Anti-hypertension, *N* (%)	1,297 (43.73)	359 (46.32)	938 (42.81)	0.0903

Values expressed as no./total no. (%) unless otherwise indicated. mRS, modified rankin scale; NIHSS, National Institutes of Health Stroke Scale.

of favorable functional outcomes between the two groups (OR = 1.63, 95% CI, 1.25–2.13, and $p = 0.0003$). In the logistic regression model 2, after adjusting for age, sex, history of hypertension, body mass index, diabetes, dyslipidemia, smoking, alcohol consumption, TOAST types, and admission NIHSS score, the proportion of favorable functional outcomes remained significantly different between the two groups (OR = 2.00, 95% CI, 1.50–2.65, and $p < 0.0001$; **Table 2**). After adjusting for propensity score in model 3, we found the similar results between the two groups [OR = 1.97 (1.5–2.59), $p < 0.0001$]. The distribution of the modified Rankin scale scores between NBP-compliance and NBP-non-compliance group was shown in **Figure 2**.

Key Secondary and Other Efficacy Outcomes

The recurrence rate of ischemic stroke within 90 days was significantly higher in the NBP-compliance group than the NBP-non-compliance group (2.4 vs. 0.31%, OR = 7.78, 95% CI, 3.19–18.95, and $P < 0.0001$; **Table 2**). The incidence of death within 3 months was 0 cases (0.00%) in the NBP-compliance group and 4 cases (0.21%) in the NBP-non-compliance group (**Table 2**). Among all TIA patients, only one patient had stroke recurrence, and this patient was in the NBP-compliance group ($p = 0.30$).

Bleeding Events

The primary safety endpoint major bleeding occurred rarely and was not different between the groups (0.29% NBP-compliance group and 0.0% NBP-non-compliance group).

Subgroup Analysis

The high proportion of 90-day favorable functional outcomes in the NBP-compliance group was consistent across the major subgroups, with interaction $p > 0.05$, except that the 90-day favorable functional outcome was better in the NIHSS (3–5) subgroup (88.82%, 453 cases) than in the NIHSS (0–2) subgroup (95.20%, 496 cases) (OR = 2.52, 95% CI, 1.81–3.50, and interaction $p = 0.00$), after adjustment for age, sex, history of hypertension, body mass index, diabetes, dyslipidemia, smoking, alcohol consumption, and admission NIHSS score (**Table 3**).

DISCUSSION

The principal result of this study is that compliance to NBP-treatment increased 90 days favorable functional outcome rate by 4.63% compared with the NBP-non-compliance patients (OR = 1.86, 95% CI, 1.41–2.45) in non-disabling ischemic stroke or TIA patients, suggesting that the regular use of NBP in patients with minor stroke and high-risk TIA may improve functional outcomes and reduce disability. A *post-hoc* subgroup analysis raises the hypothesis that patients with NIHSS scores 3–5 may achieve a higher proportion of favorable functional outcomes at 90 days among patients with NIHSS scores 0–5. This result suggests that NBP treatment may reduce the rate of disability in patients with potentially disabling minor strokes.

NBP Compliance and Functional Outcome

Our study suggested a recent substantial-high proportion of favorable functional outcomes (86.8%, 2,577/2,966) in patients with non-disabling minor ischemic stroke or TIA. However, cohort studies suggested about 30% of patients with minor stroke had a functional disability at 90 days after stroke despite

TABLE 2 | Outcome in the bridge trial according to compliance of nbp treatment.

	NBP-non -compliance group	NBP compliance group	No adjusted	*P*	Model 1	*P*	Model 2	*P*
	n (%)	*n* (%)	HR/OR (95% CI)		HR/OR (95% CI)		HR/OR (95% CI)	
mRS (0–1) 90-day	1,626 (87.42)	949 (92.05)	1.67 (1.28–2.17)	0.0002	1.63 (1.25–2.13)	0.0003	1.86 (1.41–2.45)	<0.0001
Stroke recurrence	6 (0.31)	25 (2.40)	7.78 (3.19–18.95)	<0.0001	7.65 (3.14–18.66)	<0.0001	7.85 (3.22–19.18)	<0.0001
Intracranial hemmorrhage	0 (0.00)	3 (0.29)	–	–	–	–	–	–
Death	4 (0.21)	0 (0.00)	–	–	–	–	–	–

Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, history of hypertension, body mass index, past history: history of diabetes, history of dyslipidemia, smoking, alcohol consumption, and admission NIHSS score.

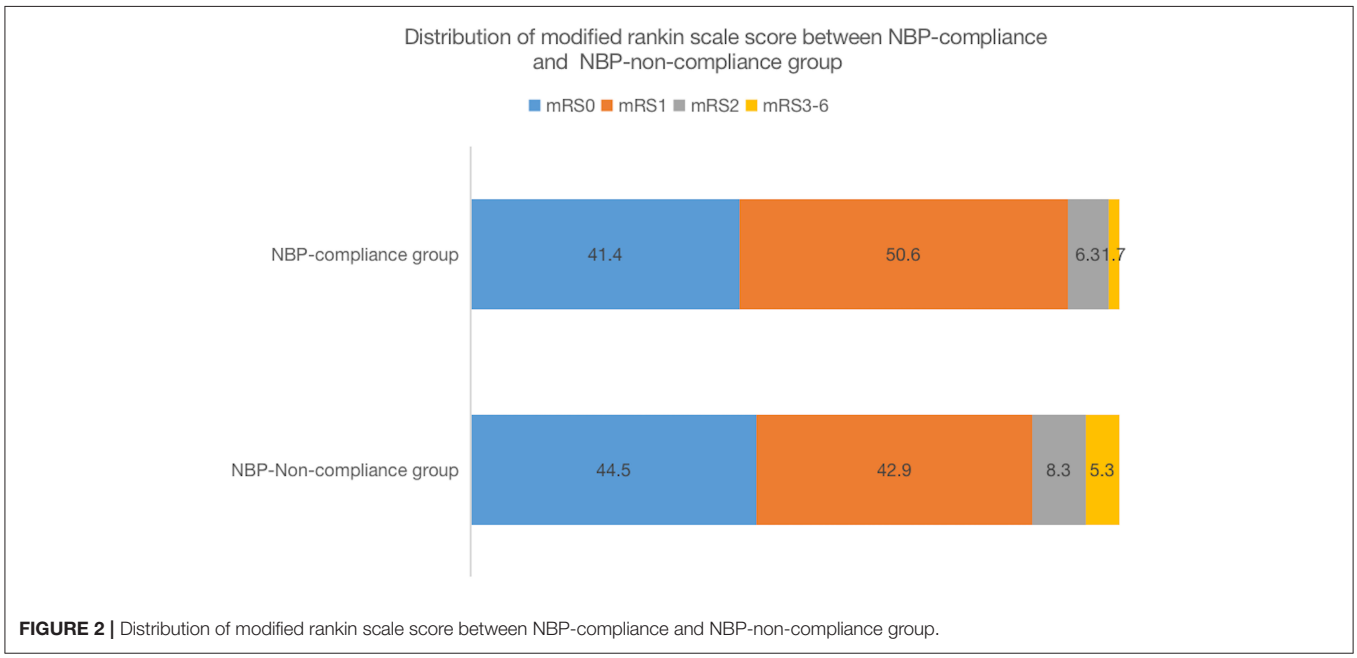

FIGURE 2 | Distribution of modified rankin scale score between NBP-compliance and NBP-non-compliance group.

nonsevere deficits at presentation (16, 17). The most likely reason for the discrepancy between previous cohort studies and the BRIDGE trial is the different inclusion criteria. Patients requiring intravenous thrombolysis and emergency revascularization were excluded from the present study; thus, many patients with potentially disabling stroke and large vessel stenosis or occlusion were excluded. Data from the United States showed that more than one-half of acute ischemic stroke hospitalizations had minor deficits, accounting for 4 of every 10 intravenous thrombolysis therapy (IVT) and 1 of every 10 mechanical thrombectomy treatments (18). A nationwide study in the United States, the excellent functional outcome only occurred in 48.2% of all minor strokes who underwent IVT or endovascular therapy (EVT) (18). The exclusion of EVT and IVT minor ischemic stroke or TIA patients from the present study might contribute to the substantial-high proportion of favorable functional outcomes. Only non-disabling minor stroke patients, rather than all minor stroke patients, were enrolled in this study was another contributor to the substantial-high favorable functional outcome rate. Our study suggested treatment with NBP, in addition to other standard treatments, may result in an additional good functional outcome in non-disabling ischemic stroke patients with no indication for EVT or IVT. This finding may be relevant to the pharmacological mechanism of NBP.

Mechanism of NBP in Stroke

NBP is a synthetic compound that has been approved for the treatment of ischemic stroke in China. The underlying mechanisms of the NBP-treatment efficacy have been reported in multiple studies. Animal experiments have shown that NBP can significantly improve the collateral circulation: rapidly opening the secondary collateral circulation, restoring the diameter of meningeal micro-arteries in the ischemic area and increasing blood flow velocity (19); establishing the tertiary collateral circulation, promoting the expression of VEGF and promoting vascular neovascularization (20). Recent animal studies have shown that daily intranasal NBP treatment can stimulate neurogenesis and angiogenesis in mice with ischemic

TABLE 3 | Subgroup analysis on favorable functional outcome at 90 days (mRS 0–1).

	NBP-non-compliance group, *n* (%)	NBP compliance group, *n* (%)	*Adjusted OR (95% CI)	*P* for interaction
Sex				
Male	680 (88.43)	418 (92.68)	2.06 (1.32–3.19)	0.4671
Female	372 (86.11)	183 (90.59)	1.59 (0.89–2.84)	
Age				
<60	343 (90.03)	215 (95.98)	3.01 (1.36–6.64)	0.1580
≥60	709 (86.46)	386 (89.98)	1.63 (1.10–2.42)	
BMI				
<25 kg/m^2	1,052 (87.59)	601 (92.04)	1.90 (1.34–2.70)	0.8304
≥25 kg/m^2	574 (87.10)	348 (92.06)	1.79 (1.13–2.84)	
Hypertension				
No	384 (87.67)	221 (94.04)	2.36 (1.25–4.47)	0.4183
Yes	668 (87.55)	380 (90.91)	1.75 (1.15–2.67)	
Diabetes				
No	818 (88.82)	449 (92.77)	1.80 (1.18–2.72)	0.8211
Yes	234 (83.57)	152 (89.94)	2.21 (1.14–4.31)	
Dyslipidemia				
No	69 (82.14)	52 (94.55)	3.92 (0.97–15.80)	0.2053
Yes	983 (88.00)	549 (91.81)	1.77 (1.23–2.54)	
Smoking				
Yes	799 (87.23)	445 (90.63)	1.60 (1.09–2.34)	0.0586
No	253 (88.77)	156 (96.30)	3.96 (1.55–10.09)	
Alcohol consumption				
No	807 (87.24)	438 (90.50)	1.61 (1.10–2.36)	0.0590
Yes	245 (88.77)	163 (96.45)	4.26 (1.67–10.85)	
Admission NIHSS score				
0	296 (97.69)	115 (96.64)	0.53 (0.15–1.92)	0.1151
1–5	1,330 (85.42)	834 (91.45)	1.82 (1.38–2.39)	
Admission NIHSS				
0–1	621 (96.43)	259 (95.57)	0.79 (0.38–1.61)	0.0185
2–5	1,005 (82.65)	690 (90.79)	2.04 (1.52–2.73)	
Admission NIHSS				
0–2	1,043 (95.25)	496 (95.20)	0.94 (0.58–1.55)	0.0016
3–5	582 (76.21)	453 (88.82)	2.52 (1.81–3.50)	

**Adjusted for age, sex, body mass index, past history: history of hypertension, history of diabetes, history of dyslipidemia, smoking, alcohol consumption, and admission NIHSS score.*

strokes (21). NBP might address different pathophysiological functions, including anti-oxidation, anti-inflammatory, anti-apoptosis, antithrombotic, and mitochondrial protection for acute ischemic stroke treatment (22).

Furthermore, another randomized clinical trial included 170 patients and found that NBP significantly increased circulating levels of endothelial progenitor cells in acute ischemic stroke patients and improved clinical outcomes (mRS at 90 days) (12).

NBP Compliance and Stroke Recurrence

Data from the CNSR study (the China National Stroke Registry) in China (from 2007 to 2008) showed that the 3-month recurrence rate of cerebrovascular disease (included ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage) among patients with minor stroke and TIA was 9.8% (23). However, the proportion of patients with minor stroke or TIA who had a 90-day recurrence was only 1.04% (31/2,966) in this study cohort, lower than in previous studies (23). This discrepancy could be attributed to several possible reasons. First of all, previous reports of stroke risk after TIA is highest in the first 7 days and in patients without immediate treatment (11.0%; 95% CI, 8.6–13.5%) (24). Over the past two decades, new treatment strategies and early management of TIA and minor strokes have significantly reduced stroke recurrence rates (25). The lowest risks were seen in studies of emergency treatment in specialist stroke services [0.9% (95% CI, 0.0–1.9)] (26–29) and the highest risks in population-based studies without urgent treatment [11.0% (8.6–13.5)] (30–32). There was substantial heterogeneity between studies. Furthermore, in a most recent

systematic review and meta-analysis of 206,455 patients in 68 unique studies during 5 decades, the subsequent risk of ischemic stroke was 4.7% within 90 days and the incidence was gradually decreased by the time of trials, among the study population recruited before 1999 was significantly higher (25). Second of all, the definition of stroke recurrence varies between studies, resulting in different incidences of observed stroke recurrence. One study showed a 90-day recurrence rate of 20/180 for patients with minor stroke and TIA, but a real new stroke (infarction at a new site) of only 2/180 was found at 30-day follow-up using MRI (33). Thirdly, the dual antiplatelet therapy in the present study (41.57%) and the combined treatment with NBP may also have contributed to the lower stroke recurrence rate. The present study found that the 90 days ischemic stroke recurrence rate was significantly higher in the NBP-compliance group than in the NBP-non-compliance group. However, due to the low overall event rate and the short follow-up period, we cannot rule out the possibility of an incidental finding. A large-scale study with a more extended follow-up period is needed to explore this finding.

Medication Adherence

In the present study, 80% was used as the cutoff value of NBP drug compliance. Previous observational studies that evaluated the relationship between medication compliance and outcome used 80–100% as an indicator of high medication compliance (15), and found that it was associated with better blood pressure control (34) and blood sugar control (35). Furthermore, pharmacy supplement data and patient self-reports are the most commonly used methods of compliance assessment which is similar to the present study (15).

Despite a higher rate of recurrences, patients in the compliance group had a greater proportion of functional outcomes than patients in the non-compliance group. This discrepancy is due to the fact that patients in the compliance group with recurrent strokes still have a good functional outcome after 90 days. In this study, both the NBP-compliance and non-compliance groups had recurrent stroke cases of 25 and 6, respectively. However, the proportion of 90-day good functional outcomes in the NBP-compliance group was 64.00% (16/25), compared with 33.33% (2/6) in the NBP-non-compliance group (**Supplementary Table 1**). We also noticed that in the NBP-compliance group, 36.00% (9/25) of stroke recurrence occurred in patients with baseline NIHSS0–1 and TIA in the NBP-non-compliance group, and 50.00% (3/6) in NBP compliance group. The interaction between baseline NIHSS score and 90-day functional outcomes might be related to the relatively high proportion of good functional outcomes in the NBP compliance group.

The strengths of this study are mainly that, (1) the data collected prospectively in 51 cities in China represent the Chinese population with non-disabling minor stroke and TIA. (2) This study was the largest data analysis based on the efficacy analysis of treatment with NBP in the Chinese non-disabling minor stroke and TIA population. (3) In patients who are not suitable for intravenous thrombolysis or acute endovascular thrombectomy therapy, NBP treatment might improve functional outcomes at 90 days, providing a potential alternative treatment for non-disabling minor stroke and TIA patients.

The limitations of this study are, (1) that the patients enrolled were not classified for stroke etiology, such as the proportion of patients with symptomatic large vessel occlusion, and minor ischemic strokes with large vessel occlusions may be associated with higher stroke recurrence and progression. (2) The present study used 90-day mRS as the primary outcome, and there is a possibility that a longer follow-up period may have identified more stroke recurrence. (3) The treatment strategy for both groups were determined by the physician based on the patient's condition. Potentially disabling patients or patients with large vessel occlusion have been excluded due to administration of thrombolytic therapy or endovascular thrombectomy, so the present study did not reflect the characteristics of the overall minor stroke and TIA patients cohort. Another shortcoming of this study is that patients who were not compliant with NBP may also be non-compliant with other medications. Adherence to antithrombotic, lipid-lowering, and antihypertensive drugs was ensured during follow-up in our study, but adherence to glucose-lowering drugs was not followed up in this study.

CONCLUSION

In this real-world experience, patients who complied with NBP therapy gained better short-term functional outcomes than those who did not, and the efficacy might even be more in those patients with NIHSS score from 3 to 5. Further large scale randomized controlled trial to explore the association between NBP therapy and non-disabling minor acute ischemic stroke or TIA outcomes is warranted in the coming future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Council of the First Affiliated Hospital of Jinan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZT and AX conceived and designed the study. YZ, SH, and YD performed the study. YZ and ZT analyzed the

data. ZT wrote the paper. AX gave suggestions how to design the study, edit the results, and write the manuscript. 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.2021.720664/full#supplementary-material

Supplementary Figure 1 | Trial flow diagram.

Supplementary Table 1 | Proportion of 90 day good functional outcomes in patients with stroke recurrence.

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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: Efficacy and Safety of Adherence to dl-3-n-Butylphthalide Treatment in Patients With Non-disabling Minor Stroke and TIA—Analysis From a Nationwide, Multicenter Registry

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Keywords: minor stroke, dl-3-n-butylphthalide, TIA, efficacy, modified rankin scale, non-disabling

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A Corrigendum on

Efficacy and Safety of Adherence to dl-3-n-Butylphthalide Treatment in Patients With Non-disabling Minor Stroke and TIA—Analysis From a Nationwide, Multicenter Registry
by Tan, Z., Zhao, Y., Yang, W., He, S., Ding, Y., and Xu, A. (2021). Front. Neurol. 12:720664. doi: 10.3389/fneur.2021.720664

In the original article, there was an error. The Results section contained an error regarding the number of subjects in the compliance and non-compliance NBP groups. The number of non-compliance patients was mistakenly listed as the number of compliance patients in the results section. Also, the number of patients in the non-compliance group was taken as the number of patients in the compliance group.

A correction has been made to Results, paragraph 1, lines 8 to 12, page 3.

A total of 2,966 cases were entered into the analytical dataset based on the definition of the analytical dataset (**Supplementary Figure 1**), of which there were 1,042 cases in the NBP-compliance group and 1,924 cases in the NBP-non-compliance group.

In the original article, there was an error. The second error is related to subgroup analysis. There was a discrepancy between the subgroup analyses described in this article and those shown in **Table 3** of NIHSS0-2 and NIHSS3-5. Our initial statistical analysis section contained an error related to our subgroup analysis, which we corrected, and then updated our table, but we did not update the Abstract and Subgroup Analysis sections.

A correction has been made to the Abstract, Results, lines 10 to 11.

…[88.82 vs. 76.21%, adjusted odds ratio 2.52 (1.81–3.50), adjusted interaction $P = 0.00$].

A correction has been made to Subgroup Analysis, lines 5 to 7, page 4.

…subgroup (88.82%, 453 cases) than in the NIHSS (0–2) subgroup (95.20%, 496 cases) (OR = 2.52, 95% CI, 1.81–3.50, and interaction $p = 0.00$).

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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Acute Stroke With Large Vessel Occlusion and Minor Clinical Deficits: Prognostic Factors and Therapeutic Implications

Bastian Volbers[1,2*], *Rebecca Gröger*[1], *Tobias Engelhorn*[2], *Armin Marsch*[1], *Kosmas Macha*[1], *Stefan Schwab*[1], *Arnd Dörfler*[2], *Stefan Lang*[2†] *and Bernd Kallmünzer*[1†]

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Background and Purpose: The optimal acute management of patients with large vessel occlusion (LVO) and minor clinical deficits on admission [National Institutes of Health Stroke Scale (NIHSS) ≤ 4] remains to be elucidated. The aim of the present study was to investigate the prognostic factors and therapeutic management of those patients.

Methods: In this retrospective cohort study, we investigated (1) all patients with acute ischemic stroke due to an LVO who underwent mechanical thrombectomy (MT) and (2) all patients with minor clinical deficits (NIHSS ≤ 4) on admission due to an LVO between January 2013 and December 2016 at the University Medical Center Erlangen. We dichotomized management of patients with minor deficits treated with MT for analysis according to immediate mechanical thrombectomy (IT) and initial medical management with rescue intervention (MM) in case of secondary deterioration. Primary endpoints were secondary deterioration, in-hospital mortality, and functional outcome on day 90 (dichotomized modified Rankin Scale 0–2: favorable, 3–6: poor).

Results: Two hundred twenty-three patients (83% with anterior circulation stroke, 13 (6%) with minor deficits) treated with MT and 88 patients with minor deficits due to LVO [13 (15%) treated with MT] were included. Secondary deterioration ($n = 19$) was independently associated with poor outcome in patients with minor deficits and LVO [odds ratio (OR), 0.060; 95% confidence interval (CI), 0.013–0.280], which in turn was associated with the occlusion site [especially M1 occlusion: 11 (58%) vs. 3 (4%) in patients without secondary deterioration, $p < 0.0001$]. IT ($n = 8$) was associated with a lower intrahospital mortality compared to MM ($n = 5$; 13 vs. 80%; OR, 0.036; 95% CI, 0.002–0.741). Seven of eight patients with IT survived until discharge, with 29% showing a favorable functional outcome on day 90.

Conclusions: Secondary deterioration is associated with poor outcome in patients with LVO and minor deficits, which in turn was associated with occlusion site. Future randomized controlled trials should assess whether selected patients, depending on occlusion site and associated characteristics, may benefit from MT.

Keywords: mechanical thrombectomy, minor stroke, large vessel occlusion (LVO), acute management of stroke, outcome

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INTRODUCTION

Recently, a series of randomized controlled trials (RCTs) could demonstrate that endovascular mechanical thrombectomy (MT) plus standard of care is superior to medical management alone in stroke patients with acute large vessel occlusion (LVO) (1). Up to 30% of patients with LVO may present with only minor clinical symptoms on admission (2). Evidence-based recommendations regarding the optimal management are lacking, as those patients were excluded from prospective trials or their number was markedly underrepresented (1, 3). Even if MT was shown to be effective irrespective of symptom severity on admission (1), observational studies still suggest a high risk of unfavorable outcome in those patients, mainly due to decompensating collaterals associated with secondary neurologic deterioration (4–6). Here, the occlusion site may be of importance (7). Nevertheless, only limited evidence from retrospective data exists regarding the efficacy of MT (8, 9), also in comparison to initial medical management with rescue intervention in case of secondary deterioration (10–12). However, mild stroke symptoms may not justify immediate MT in view of the procedure's invasiveness and potential serious adverse effects (13). Thus, patient selection may play a crucial role to identify patients with minor deficits and LVO who may benefit from an interventional treatment. In this retrospective study, we investigated characteristics, prognostic factors, and management of patients with LVO and minor clinical deficit on admission also in comparison to patients with moderate to severe deficits.

METHODS

Patient Selection

This study was approved by our institutional review board (University of Erlangen-Nuremberg Re.-No. 377_17 Bc). We retrospectively identified all patients who (1) underwent MT due to an LVO [internal carotid artery (without T), intracranial internal carotid artery-T, M1 and M2 segment of the middle cerebral artery, basilar artery and vertebral artery] or (2) showed minor clinical deficits [defined as National Institutes of Health Stroke Scale (NIHSS) $\leq$ 4 on admission] due to an LVO (as defined above) irrespective of any acute stroke treatment (no reperfusion therapy, thrombolysis, MT, or both) between January 2013 and December 2016 from our prospectively organized institutional database. Patients had been admitted either to our tertiary stroke center or to one of our collaborating primary hospitals and were then transferred for MT (drip and ship). Clinical characteristics on admission, comorbidities and preadmission status, treatment and medication, symptom-to-groin time, and clinical parameters during the in-hospital stay were recorded.

Patient Treatment

A trained stroke physician performed standardized clinical examination on admission and obtained the NIHSS. Neuroimaging was performed using computed tomography (CT) including CT angiography and CT perfusion or magnetic resonance imaging (MRI) including diffusion-weighted imaging, fluid attenuation inversion recovery, susceptibility weighted imaging, MRI angiography, and MRI perfusion to rule out an intracerebral hemorrhage, ensure LVO, and assess Alberta Stroke Program Early CT Score (14). Patients initially admitted to a primary care hospital were referred to our tertiary stroke center after diagnosis of LVO. Intravenous thrombolysis with recombinant tissue-type plasminogen activator was performed in accordance with recommendations of international guidelines (15, 16) due to the treating physician. The decision on MT was based on the agreement between the treating neurologist and the neurointerventionalist considering both clinical and imaging criteria.

Assessment of Outcome

Outcome variables were intrahospital mortality, modified Rankin Scale (mRS) on day 90 ["favorable outcome" (mRS 0–2) and "poor outcome" (mRS 3–6)] and secondary deterioration. Trained and certified physicians conducted phone interviews with patients or their next of kin to obtain day 90 mRS. Secondary deterioration was defined as an acute NIHSS increase of 4 or more points during the in-hospital stay (6). In patients with minor deficits, we assessed factors associated with outcome and secondary deterioration. In the MT cohort, we assessed factors associated with outcome also in relation to stroke severity on admission. Furthermore, we retrospectively divided patients with NIHSS $\leq$ 4 on admission into two groups for analysis: immediate mechanical thrombectomy (IT) or initial medical management with rescue intervention in case of secondary deterioration (MM) and correlated outcome with NIHSS on admission. If the decision to perform a thrombectomy was made in the context of the initial diagnostic workup, we defined this intention as "IT." If it was decided not to perform a thrombectomy after the initial diagnostic workup, but this decision was revised after secondary deterioration, we defined it as "MM." Furthermore, procedure-related complications and the occurrence of secondary intracerebral hemorrhage according to the ECASS-2 definition (17) and dichotomized final infarct size (greater than and less than one-third of corresponding artery territory) were investigated.

Statistics

IBM® SPSS® Statistics 21 software package (IBM Corp, Armonk, NY) was used. The significance level was set at $\alpha = 0.05$. Statistical tests were 2-sided. We used the Kolmogorov–Smirnov test to determine the distribution of data. Data were presented as mean and standard deviation (SD), as median and interquartile range (IQR, Mann–Whitney U test), or number (n) and percentage (Pearson χ^2 or Fisher exact test), as appropriate. We used univariate logistic regression to calculate mortality-related odds ratios. Clinically meaningful parameters with $p \leq 0.1$ in univariate testing were included in a multivariable logistic regression model for prediction of favorable outcome and secondary deterioration using stepwise backward inclusion (likelihood ratio). We excluded patients with missing outcome data from outcome-related analyses. For patients treated with MT, we performed an additional sensitivity analysis of functional outcome including only patients with anterior circulation LVO

and a baseline mRS 0–2 (defined as mRS during the week before admission). In the minor stroke group, we performed an additional sensitivity analysis of factors associated with secondary deterioration excluding patients with IT.

RESULTS

Patients' Characteristics and Outcome

Two hundred twenty-three patients treated with MT and 88 patients with minor deficits due to LVO were included (characteristics shown in **Table 1**). Thirteen patients with minor deficits due to LVO were treated with MT and thus were included in both groups. Functional outcome on day 90 was available in 89% of patients.

Patients Treated With MT ($n = 223$)

Location of vessel occlusion did not differ between patients with favorable and poor outcome ($\chi^2 = 9.879, p = 0.063$). Multivariate logistic regression revealed an association of favorable functional outcome on day 90 with NIHSS on admission [odds ratio (OR), 0.951; 95% confidence interval (CI), 0.908–0.995; $p = 0.028$], pre-stroke mRS (OR, 0.554; 95% CI, 0.382–0.804; $p = 0.002$), dichotomized infarct size (OR, 0.049; 95% CI, 0.010–0.236; $p < 0.0001$), and a diagnosis of hypertension (OR, 0.273; 95% CI, 0.099–0.753; $p = 0.012$). Intravenous thrombolysis showed a trend toward a favorable outcome (OR, 3.067; 95% CI, 0.816–11.531; $p = 0.097$).

Patients With LVO and NIHSS ≤ 4 on Admission ($n = 88$)

Sixty patients (68%) with LVO and minor deficits on admission had a favorable day 90 outcome. Higher baseline mRS, higher NIHSS on admission, secondary deterioration, M1 occlusion, and larger final infarct size were associated with poor functional outcome (**Table 2**). Multivariate logistic regression revealed baseline mRS (OR, 0.343; 95% CI, 0.163–0.722), initial NIHSS (OR, 0.496; 95% CI, 0.291–0.846), and secondary deterioration (OR, 0.060; 95% CI, 0.013–0.280) as independent predictors of poor functional outcome in patients with minor stroke and LVO on admission. Secondary deterioration was associated with higher baseline mRS, higher NIHSS on admission, and M1 occlusion, whereas vertebral artery occlusion was associated with a lower risk of secondary deterioration. An internal carotid artery occlusion was not associated with a secondary deterioration. An intracranial internal carotid artery-T occlusion was also not associated with a secondary deterioration in our cohort (**Table 3**). However, there was only one patient with ICA-T occlusion in our cohort, who was treated with IT. In the multivariate logistic regression, only M1 occlusion remained as a risk factor for secondary deterioration (OR, 29.9; 95% CI, 6.5–137.9). Comorbidities were associated neither with outcome nor with secondary deterioration. All three patients without secondary deterioration and M1 occlusion showed a reperfusion in control angiography. Two of them received intravenous thrombolysis in a primary stroke center and improved during transfer to our tertiary stroke center. One patient was treated with MT (IT group, see below). The sensitivity analysis without patients treated with IT ($n = 80$) revealed similar results while there was a trend toward an association of BA occlusion with secondary deterioration [4 (27%) patients with BA occlusion showed secondary deterioration, 5 (8%) did not, $p = 0.058$; further characteristics not shown]. However, all patients with secondary deterioration and BA occlusion showed a poor posterior communicating artery collateral flow and a large clot extent ($n = 4$), whereas in comparison patients without

TABLE 1 | Baseline characteristics of included patients.

Characteristics	Patients with MT ($n = 223$)	Patients with minor stroke and LVO ($n = 88$)
Age (IQR) (years)	75 (60–80)	67 (58–77)
Sex (female) (%)	120 (54)	22 (33)
Baseline mRS (IQR)	0 (0–2)	0 (0–1)
Hypertension (%)	180 (81)	74 (84)
Diabetes (%)	56 (25)	11 (13)
Hypercholesterinemia (%)	84 (38)	59 (67)
Renal insufficiency (%)	26 (12)	12 (14)
Atrial fibrillation (%)	113 (51)	25 (28)
Antiplatelet use (%)	186 (83)	32 (36)
Anticoagulation (VKA and DOAC) (%)	37 (17)	10 (11)
NIHSS on admission (IQR)	17 (13–21)	2 (1–3)
NIHSS 24 h (IQR)	25 (7–38; $n = 200$)	2 (1–4)
Secondary deterioration (acute NIHSS increase > 4 during in-hospital stay) (%)	15 (7, before MT)	19 (22)
MT (%)	223 (100)	13 (15)
Symptom to groin time (h)	5.8 (SD 7.4)	5.3 (IQR 9.1)
CT-ASPECTS on admission (IQR)	8 (7–9)	10 (9–10)
Intravenous thrombolysis (%)	171 (77)	15 (17)
Thrombolysis in primary care center (%)	61 (27)	3 (3)
Location of vessel occlusion		
Left-sided occlusion (anterior circulation) (%)	92 (50)	21 (45)
Internal carotid artery (without T) (%)	21 (9)	13 (15)
Intracranial internal carotid artery-T (%)	43 (19)	1 (1)
Middle cerebral artery: M1 (%)	107 (48)	14 (16)
Middle cerebral artery: M2 (%)	13 (6)	19 (22)
Posterior cerebral artery (%)	0 (0)	5 (6)
Vertebral artery (%)	3 (1)	25 (28)
Basilar artery (%)	36 (16)	11 (13)
Outcome parameters		
Infarct size greater than one-third of corresponding artery territory (%)	57 (26)	8 (9)
Symptomatic ICH (%)	7 (3)	2 (2)
Asymptomatic ICH (%)	17 (8)	0 (0)
Intrahospital mortality (%)	46 (21)	6 (7)
mRS on day 90 (IQR)	4 (2–6; $n = 192$)	2 (1–3)
Favorable outcome (mRS 0–2) (%)	54 (28; $n = 192$)	60 (68; $n = 87$)

Data are given as mean and SD, median and IQR, and n (%) as appropriate. Thirty-one patients did not have day 90 outcome data available. VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; ASPECT, Alberta Stroke Program Early CT Score; ICH, intracerebral hemorrhage; baseline mRS, mRS during the week before admission; minor stroke, NIHSS on admission ≤ 4.

TABLE 2 | Characteristics of patients with minor deficits (NIHSS ≤ 4 on admission) and LVO stratified for outcome (favorable = day 90 mRS 0–2; unfavorable = day 90 mRS 3–6).

Characteristics of patients with minor stroke (NIHSS on admission ≤ 4) and LVO ($n = 88$)	Favorable outcome (day 90 mRS 0–2; $n = 60$)	Unfavorable outcome (day 90 mRS 3–6; $n = 28$)	*p*-value
Age (IQR)$^{+}$ (years)	67 (56–85)	73 (59–78)	0.251
Sex (female) (%)*	20 (33)	9 (32)	0.999
Baseline mRS (IQR)$^{+}$	0 (0)	1 (0–3)	<0.0001
NIHSS on admission (IQR)$^{+}$	2 (0–3)	3 (2–4)	<0.0001
NIHSS 24 h (IQR) $^{+}$	1 (0–2)	7 (3–34)	<0.0001
Secondary deterioration (NIHSS increase > 4 during in-hospital stay; %)*	3 (5)	16 (57)	<0.0001
Time between admission and secondary deterioration (h) (IQR)*	4 (1.7)	5.3 (2.5–24.3)	0.507
MT (%)*	3 (5)	10 (36)	<0.0001
Intravenous thrombolysis (%)*	8 (13)	7 (25)	0.225
Location of vessel occlusion			
Left-sided occlusion (anterior circulation) (%)*	14 (45)	7 (44)	0.995
Internal carotid artery (without T, %)*	11 (18)	2 (7)	0.212
Intracranial internal carotid artery-T (%)*	0 (0)	1 (4)	0.318
Middle cerebral artery: M1 (%)*	4 (7)	10 (36)	0.001
Middle cerebral artery: M2 (%)*	16 (27)	3 (11)	0.104
Posterior cerebral artery (%)*	5 (8)	0 (0)	0.173
Vertebral artery (%)*	18 (30)	7 (25)	0.800
Basilar artery (%)*	5 (18)	6 (10)	0.491
Infarct size greater than one-third of corresponding artery territory (%)*	0 (0)	8 (29)	<0.0001
Symptomatic ICH (%)*	1 (2)	1 (4)	0.999
Asymptomatic ICH (%)*	0 (0)	0 (0)	0.999

*Data are given as median and IQR and n (%) as appropriate. * χ^2/Fisher exact. $^{+}$Non-parametric test (Wilcoxon rank-sum test). mRS, mRS during the week before symptom onset.*

TABLE 3 | Characteristics of patients with minor stroke (NIHSS on admission ≤ 4) due to LVO stratified for secondary deterioration (acute NIHSS increase > 4 points during in-hospital stay).

Characteristics [patients with minor stroke (NIHSS on admission ≤ 4) due to LVO, $n = 88$]	Secondary deterioration (acute NIHSS increase > 4; $n = 19$)	No secondary deterioration ($n = 69$)	*p*-value
Age (IQR)$^{+}$ (years)	72 (64–77)	67 (56–76)	0.199
Sex (female) (%)*	6 (32)	23 (33)	0.999
Baseline mRS (IQR)$^{+}$	1 (0–3)	0 (0–0.5)	0.014
NIHSS on admission (IQR)$^{+}$	3 (2–4)	1 (0–3)	0.001
NIHSS 24 h (IQR) $^{+}$	8 (5–20)	2 (0–3)	<0.0001
MT (%)*	9 (48)	4 (6)	<0.0001
Intravenous thrombolysis (%)*	6 (32)	9 (13	0.083
Location of vessel occlusion			
Left-sided occlusion (anterior circulation) (%)*	8 (57)	13 (39)	0.531
Internal carotid artery (%)*	1 (5)	12 (17)	0.283
Intracranial internal carotid artery-T (%)*	0 (0)	1 (1)	0.999
Middle cerebral artery: M1 (%)*	11 (58)	3 (4)	<0.0001
Middle cerebral artery: M2 (%)*	2 (11)	17 (25)	0.226
Posterior cerebral artery (%)*	0 (0)	5 (7)	0.352
Vertebral artery (%)*	1 (5)	24 (35)	0.019
Basilar artery (%)*	4 (21)	7 (10)	0.242
Infarct size greater than one-third of corresponding artery territory (%)*	7 (37)	1 (1)	<0.0001

*Data are given as median and IQR and n (%) as appropriate. * χ^2/Fisher exact. $^{+}$Non-parametric test (Wilcoxon rank-sum test). baseline mRS, mRS during the week before symptom onset.*

TABLE 4 | Characteristics of patients treated with MT with NIHSS ≤ 4 and >4 on admission.

Characteristics (patients treated with MT; $n = 223$)	NIHSS on admission ≤ 4 ($n = 13$)	NIHSS on admission > 4 ($n = 210$)	*p*-value
Age (IQR)$^+$ (years)	65 (58–75)	75 (62–81)	0.056
Sex (female) (%)*	2 (16)	118 (56)	0.004
Baseline mRS (IQR)$^+$	1 (0–2.5)	0 (0–2)	0.549
NIHSS on admission (IQR)$^+$	4 (2.5–4)	17 (13.8–22)	<0.0001
Symptom to groin time (h) (IQR)$^+$	5.3 (3.6–12.6)	3.9 (2.4–6.4)	0.169
CT-ASPECTS on admission (IQR)$^+$	9 (7.5–10)	8 (7–9)	0.410
Left-sided occlusion (anterior circulation) (%)*	5 (50)	87 (50)	0.999
Intravenous thrombolysis (%)*	7 (54)	164 (78)	0.082
Intrahospital mortality (%)*	5 (39)	41 (20)	0.149
mRS on day 90 (IQR; $n = 191$)$^+$	4.5 (2.5–6)	4 (2–6)	0.326
Favorable outcome (mRS 0–2) (%; $n = 191$)*	3 (25)	51 (29)	0.999
Symptomatic ICH (%)*	1 (8)	6 (3)	0.347
Asymptomatic ICH (%)*	0 (0)	17 (8)	0.606
Procedure-related complications (%)*	0 (0)	21 (10)	0.377
Infarct size greater than one-third of corresponding artery territory (%)*	4 (31)	53 (25)	0.744

*Data are given as median and IQR and n (%) as appropriate. Thirty-two patients did not have day 90 outcome data available. *χ^2/Fisher exact. $^+$Non-parametric test (Wilcoxon rank-sum test). baseline mRS, mRS during the week before symptom onset; ASPECTS, Alberta Stroke Program Early CT Score.*

secondary deterioration and BA occlusion mainly showed a short proximal occlusion with a strong posterior communicating artery collateral flow [$n = 5$, $p = 0.008$; two patients were treated with IT (see below)].

Patients With LVO Treated With MT: NIHSS ≤ 4 on Admission ($n = 13$) vs. NIHSS > 4 ($n = 210$)

Thirteen patients with NIHSS ≤ 4 on admission and LVO received MT (**Table 4**). Compared to patients with more severe deficits (NIHSS > 4), patients with low NIHSS scores on admission were more likely to be female. They also showed a trend toward a lower age and lower thrombolysis rates. There were no differences between both groups regarding the site of vessel occlusion ($\chi^2 = 2.668$, $p = 0.705$), comorbidities, medication, and secondary intracerebral hemorrhage rate (**Table 4**). The established association of symptom severity on admission (as quantified using the NIHSS score) with functional day 90 outcome (1) seems to inverse in treated patients with mild symptoms (NIHSS ≤ 4, **Figure 1A**) compared to moderately and severely affected stroke patients. Our sensitivity analysis showed consistent results ($n = 154$, characteristics not shown, **Figure 1B**): Patients with only minor neurologic deficits on admission despite an LVO treated with MT seem to have a worse functional day 90 outcome than patients with moderate stroke severity at baseline.

Immediate vs. Rescue Thrombectomy in Patients With LVO and NIHSS ≤ 4 on Admission ($n = 13$)

Thirteen patients with minor deficits and available outcome data were dichotomized to either IT (eight patients, IT) or initial medical management with rescue intervention after secondary clinical deterioration (five patients, MM). Relevant clinical and demographic characteristics (**Table 5**) and proportion of posterior circulation stroke did not differ between the IT and MM groups [2 (25%) and 1 (20%), $p = 0.999$]. Four patients in the IT group showed a secondary deterioration after decision to perform IT was made. Median time between admission and secondary deterioration was 6.8 h (IQR, 3.3–21.2) in the MM group, and median time between secondary deterioration and groin was 1.1 h (IQR, 0.8–1.7). IT was associated with a lower intrahospital mortality (OR, 0.036; 95% CI, 0.002–0.741) compared to MM (13 vs. 80%, $p = 0.032$). Twenty-nine percent of patients with available outcome data treated with IT had a favorable outcome on day 90.

DISCUSSION

In this observational study, patients with minor neurological deficits on admission despite LVO had a high risk of poor outcome, if secondary deterioration occurred. In those patients, rescue endovascular thrombectomy was associated with a poor outcome in our cohort. Secondary deterioration seems to be associated with occlusion site and associated factors, which may guide selection criteria for future RCTs to identify patients who may benefit from revascularization.

Until present, it remains unclear whether patients with LVO and minor clinical deficits on admission would benefit from IT compared to primarily medical management. The scenario of active collaterals that initially attenuate the hemodynamic effect of LVO applies for up to 30% of acute stroke patients with LVO and is associated with a high risk of poor outcome, mainly due to secondary deterioration (2, 5, 18). The major thrombectomy trials did not focus on those patients sufficiently (1, 3), and retrospective data revealed controversial results (9, 10, 12).

In our study, the group of patients with NIHSS ≤ 4 on admission and LVO treated with MT seems to show a disproportionately poor outcome compared to patients with moderate or severe deficits, especially in cases with initial medical management and secondary deterioration. Even if these findings support existing data regarding the high risk of unfavorable outcome in those patients, they also contradict the established efficacy of MT irrespective of the clinical status on admission (1, 3). As we found low rates of symptomatic secondary hemorrhage in those patients (13), we consider the fatal clinical course of patients with initial medical management, which was associated with a large final infarct size, as possible explanation. Accordingly, the proportion of patients with large final cerebral infarction did not differ between patients with

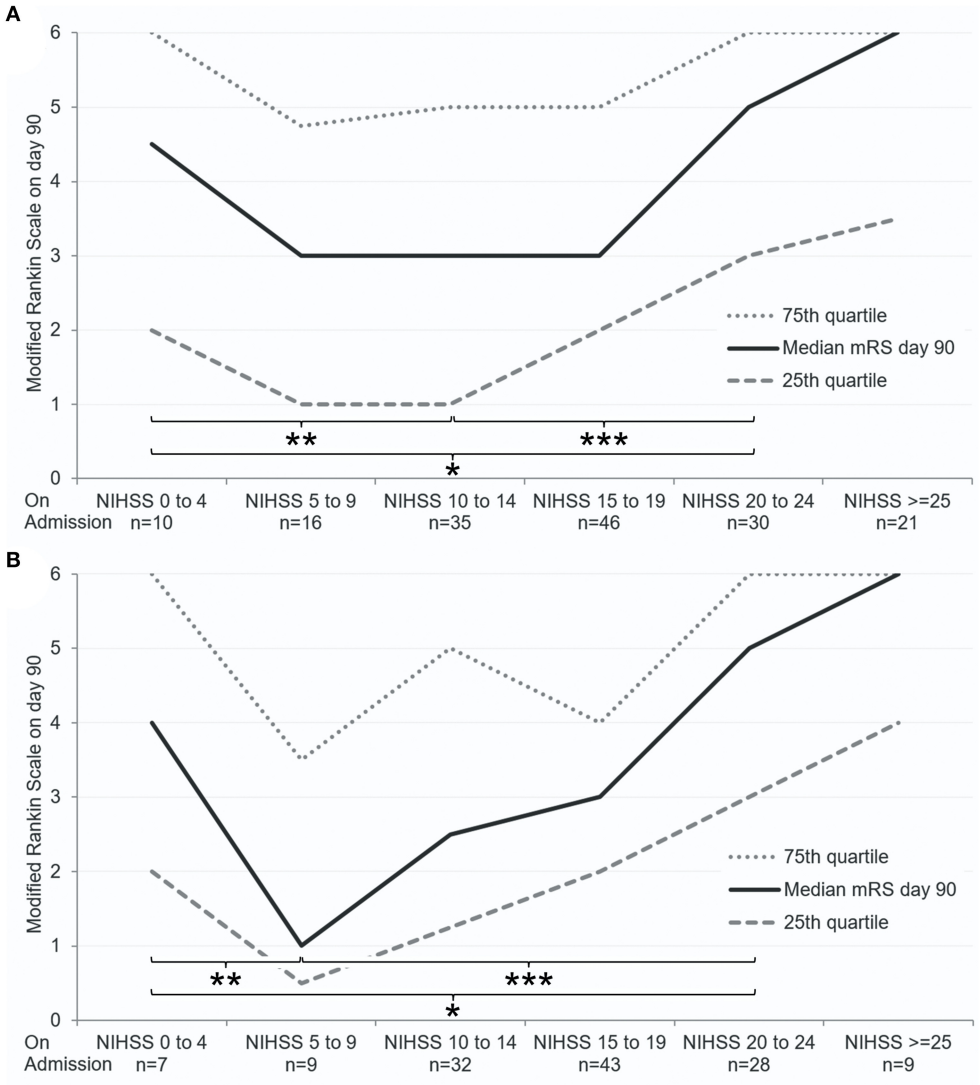

FIGURE 1 | Association of NIHSS on admission with functional outcome on day 90 in patients treated with MT. Only patients with baseline mRS 0–2 (during the week before admission) were included in this figure. **(A)** Including anterior and posterior circulation strokes ($n = 158$). **(B)** Including only anterior circulation strokes (cohort of sensitivity analysis, $n = 154$; 26 patients did not have day 90 outcome data). Median mRS (black line) and 25th and 75th quartiles (dotted gray lines) are displayed. $^{***}p < 0.05$, $^{**}p < 0.1$, $^{*}p > 0.1$ (Wilcoxon rank-sum test between indicated patient groups).

minor and moderate–severe stroke severity on admission. Especially, patients suffering secondary deterioration showed a higher rate of a large final cerebral infarction size. Therefore, the severity of the condition should not be underestimated on admission. Even patients with minor deficits on admission may need an appropriate diagnostic in the acute phase including vessel imaging to rule out an LVO. Thus, our results underline the well-established concept of early reperfusion therapy in stroke in general and the detrimental consequences of a secondary clinical worsening (1, 5). A limitation of this interpretation may be seen in certain imbalances between patients with minor stroke and patients with moderate to severe deficits in our cohort: There was a lower proportion of females in the minor stroke group, which may not explain the results, but should be kept in mind when interpreting our results. The trend toward a lower thrombolysis rate in our cohort treated with MT may also be associated with a poor outcome, whereas on the other hand, the trend toward a younger age in those patients may be associated with a favorable outcome (1). Because of the small sample size, we could not adjust for those variables in our analysis.

Furthermore, symptom onset to groin time was longer in patients treated with rescue MT. In the DAWN trial as well as in the DEFUSE-3 trial, a benefit of thrombectomy was found in patients up to 24 and 16 h after symptom onset, respectively (19, 20). However, both trials used strict selection criteria including a prominent clinical-core mismatch with an

TABLE 5 | Characteristics of patients with NIHSS on admission ≤ 4 (minor stroke) who were treated with MT dichotomized according to IT and MM.

Characteristics [patients with minor stroke (NIHSS on admission ≤ 4) who were treated with MT, *n* = 13]	IT group, *n* = 8	MM group, *n* = 5	*p*-value
Age (IQR)$^{+}$ (years)	60 (56–72)	70 (66–76)	0.106
Sex (female) (%)*	0 (0)	2 (40)	0.128
Baseline mRS (IQR)$^{+}$	0 (0–2.75)	1 (0.5–2.5)	0.438
NIHSS on admission (IQR)$^{+}$	4 (3–4)	3 (1–4)	0.135
Secondary deterioration (NIHSS increase > 4 before thrombectomy; %)*	4 (50)	5 (100)	0.105
NIHSS before thrombectomy (IQR)$^{+}$	6 (4–11)	15 (10–18)	0.019
Symptom to groin time (h) (IQR)$^{+}$	3.9 (2–5)	13.9 (9–24.5)	0.030
CT-ASPECTS on admission (IQR)$^{+}$	8.5 (7–10)	9 (7–10)	0.943
Intravenous thrombolysis (%)*	5 (62)	2 (40)	0.592
Intrahospital mortality (%)*	1 (13)	4 (80)	0.032
mRS on day 90 (IQR; *n* = 12)$^{+}$	4 (2–5)	6 (4–6)	0.148
Favorable outcome (mRS 0–2) (%; *n* = 12)*	2 (29, n = 7)	1 (20)	0.999
Symptomatic ICH (%)*	1 (13)	0 (0)	0.999
Asymptomatic ICH (%)*	0 (0)	0 (0)	0.999
Procedure-related complications (%)*	0 (0)	0 (0)	0.999
Infarct size greater than one-third of corresponding artery territory (%)*	2 (25)	2 (40)	0.999

*Data are given as median and IQR and n (%) as appropriate. One patient did not have day 90 outcome data available. * χ^2/Fisher exact. $^{+}$Non-parametric test (Wilcoxon rank-sum test). baseline mRS, mRS during the week before symptom onset; ASPECTS, Alberta Stroke Program Early CT Score.*

NIHSS of more than 10 prior to inclusion and perfusion imaging, respectively. Furthermore, patients with minor stroke were neither included in DAWN nor in DEFUSE-3 irrespective of secondary deterioration.

However, strict selection criteria may also play a crucial role to identify patients with minor deficits due to LVO who might benefit from thrombectomy or thrombolysis. In our minor stroke cohort, intravenous thrombolysis was not associated with outcome. Although we did not assess this association further, existing results have shown that thrombolysis may be associated with potential harm in patients presenting with an NIHSS score of 0–1 compared to patients with a score of 2–5 (21). Other results suggested that intravenous thrombolysis might also be associated with deterioration due to thrombus fragmentation in some patients with ICA occlusion (22). The efficacy of bridging thrombolysis in those patients also remains to be elucidated (23). Those results underline the necessity to select the right patient for the right treatment. Secondary deterioration seems to be strongly associated with outcome (6), which we could also show in our cohort. In turn, secondary deterioration seems to be associated with the occlusion site (6). Here, our results suggest an M1 occlusion as a strong predictor, whereas a vertrebral artery occlusion does not seem to be associated with secondary deterioration. Seners et al. found that in anterior circulation stroke patients with M2 occlusion had a lower risk of secondary deterioration than patients with M1 occlusion or carotid artery-T occlusion. It seems that the more distal the occlusion site could be found in patients with minor stroke, the lower was the associated risk of secondary deterioration (6). As we could include only one patient with carotid artery-T occlusion in our minor stroke cohort and did not differentiate distal from proximal M1 occlusions, we could not assess dedicated ORs for carotid artery-T occlusions and different M1 occlusion sites. Furthermore, the patient with carotid artery-T occlusion was treated with IT; thus, no conclusions regarding the prognostic value of carotid-t occlusions to predict secondary deterioration can be drawn from our data. However, in general, our data also support these findings that proximal middle cerebral artery occlusions are associated with higher risks of secondary deterioration than distal ones. On the other side, we found no association of internal carotid artery occlusions with secondary deterioration in patients with minor deficits, with only one patient (5%) showing a secondary deterioration. None of the patients with internal carotid artery occlusion and minor deficits on admission received MT; only one patient received thrombolysis (data not shown). Still 11 patients showed a favorable outcome. This raises the question whether patients with a mere internal carotid artery occlusion and minor deficits on admission should be treated with MT. As we could not assess collateral status and could include only a small number of those patients, our data cannot sufficiently answer this question, which should be addressed in future research. For patients with basilar artery occlusion, clot extent and collaterals seem to play a special role. However, because of small cohort size and a rather qualitative assessment, those results should be interpreted with care. Furthermore, our results suggest an association of the severity of clinical symptoms with deterioration even within the group of patients with minor deficits as defined, although we could not show this association in our multivariable logistic regression model any more. Again, because of the small cohort size, those results also have to be interpreted with care. Those factors may play a role when defining inclusion criteria for future RCTs to assess the efficacy

of a revascularization treatment in patients with minor deficits due to LVO.

There are several limitations to our study: The retrospective single-center design and the limited number of patients with mild clinical symptoms on admission treated with MT might compromise the generalizability of our results. Furthermore, comparative statistics should be interpreted with caution. Our cohort consisted of patients with LVO in both the anterior and posterior cerebral circulation. However, our sensitivity analysis showed consistent results. In the IT group, some patients showed neurologic deterioration before thrombectomy. However, treatment was not delayed, and the decision to perform MT was made before deterioration. During the study period, several influential trials on MT (1) have been published, which may have altered clinical practice. However, patients with minor deficits have not sufficiently been addressed in those trials. In accordance with others (24, 25), we defined minor stroke using an NIHSS score < 5. Other NIHSS cutoff values have been described to define a minor stroke, which may have altered our results. We did not perform a quantitative assessment of clot extent/thrombus length and collateral flow in patients with BA occlusion, which may limit our results. Also, no assessment of collateral flow could be performed in anterior circulation LVOs. This assessment was performed only comparatively. However, the small number of patients included for this assessment did not justify an elaborate quantitative assessment.

CONCLUSION

Patients with mild neurologic deficits on admission despite a large vessel occlusion might have a high risk of unfavorable outcome and a large final infarct size especially in cases of secondary deterioration. Initial medical management with rescue intervention after clinical deterioration was associated with a fatal clinical course in our cohort. Occlusion site and associated factors showed an association with secondary deterioration, which may guide selection of patients for clinical trials. Quick diagnosis is essential, and immediate recanalization of LVO may be addressed in future RCTs even in patients with minor stroke, if adequate inclusion criteria are applied.

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 Ethikkommission der Friedrich-Alexander-Universität Erlangen-Nürnberg Krankenhausstraße 12 91054 Erlangen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BV, RG, TE, AM, KM, SS, AD, SL, and BK: acquisition, analysis and interpretation of data for the work, revising the manuscript, and final approval of the version to be published. BV, SL, and BK: conception and design of the work and drafting the work. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Delays in Presentation Time Under the COVID-19 Epidemic in Patients With Transient Ischemic Attack and Mild Stroke: A Retrospective Study of Three Hospitals in a Japanese Prefecture

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Background: Coronavirus Disease 2019 (COVID-19) has spread worldwide with collateral damage and therefore might affect the behavior of stroke patients with mild symptoms seeking medical attention.

Methods: Patients with ischemic stroke who were admitted to hospitals within 7 days of onset were retrospectively registered. The clinical characteristics, including onset-to-door time (ODT), of patients with a transient ischemic attack (TIA)/mild stroke (National Institutes of Health Stroke Scale [NIHSS] score of $\leq$3 on admission) or moderate/severe stroke were compared between those admitted from April 2019 to March 2020 (pre-COVID-19 period) and from April to September 2020 (COVID-19 period). Multivariable regression analysis was performed to identify factors associated with the ODT.

Results: Of 1,100 patients (732 men, median age, 73 years), 754 were admitted during the pre-COVID-19 period, and 346 were admitted during the COVID-19 period. The number and proportion of patients with TIA/minor stroke were 464 (61.5%) in the pre-COVID-19 period and 216 (62.4%) during the COVID-19 period. Among patients with TIA/mild stroke, the ODT was longer in patients admitted during the COVID-19 period compared with that of the pre-COVID-19 period (median 864 min vs. 508 min, $p = 0.003$). Multivariable analysis revealed the COVID-19 period of admission was associated with longer ODT (standardized partial regression coefficient 0.09, $p = 0.003$) after adjustment for age, sex, route of arrival, NIHSS score on admission, and the presence of hypertension, diabetes mellitus, and wake-up stroke. No significant change in the ODT was seen in patients with moderate/severe stroke.

Conclusions: The COVID-19 epidemic might increase the ODT of patients with TIA/mild stroke.

Keywords: ischemic stroke, transient ischemic attack, mild stroke, COVID-19, onset-to-door time

INTRODUCTION

The novel Coronavirus Disease 2019 (COVID-19) has posed a great challenge to the global healthcare system. The reallocation of resources to support the treatment of patients with COVID-19 might have resulted in collateral damage to non-COVID-19-related life-threatening conditions (1). During the pandemic, the number of stroke patients seen in emergency departments has decreased considerably, with a significant reduction in intravenous thrombolysis and endovascular therapy (2–4). Prolongation in onset to hospital arrival time and a significant reduction in individuals arriving at hospitals within 4.5 h were also noted (5–7). In Japan, a state of emergency was declared from April 7 to May 25 2020 because of a massive increase in COVID-19 patients, which had a great impact on the management of acute ischemic stroke patients. Ota et al. (8) reported a rapid decrease in the number of emergent stroke admissions in the Tokyo metropolitan area after the declaration and the trend in restrictions of emergent stroke care systems continued after the declaration was lifted.

Concurrently, several studies showed this decline was more apparent in patients with TIA or mild-to-moderate stroke than for severe stroke (9–11). In a report by Ohara et al. (12), the number of overall stroke patients was decreased, despite increased numbers of stroke patients undergoing thrombectomy or surgery in Kobe City, indicating patients with mild neurological deficits refrained from visiting hospitals during the COVID-19 epidemic. These studies were mainly conducted in the first phase of the COVID-19 pandemic and it remains a rapidly evolving situation. TIA or mild stroke patients are at high risk of subsequent or recurrent ischemic stroke and urgent evaluation and treatment can greatly improve their outcomes (13, 14). Clarifying the impact of the COVID-19 epidemic on the behavior of patients with TIA/mild stroke seeking medical attention may help future public awareness campaigns. Therefore, in this study, we investigated the changes in the clinical characteristics, including onset-to-door time (ODT) in patients with TIA/mild stroke before and during the COVID-19 epidemic using data from three hospitals in Fukuoka Prefecture, Japan.

MATERIALS AND METHODS

Study Design

This was a retrospective study involving three urban hospitals with a stroke care unit located in Fukuoka and Kitakyushu, government-designated cities in Fukuoka Prefecture. Saiseikai Fukuoka General Hospital is a tertiary-level facility and Fukuoka City Hospital is a secondary-level emergency facility for the Fukuoka area including Fukuoka City and surrounding small cities and towns. Kokura Memorial Hospital is a secondary-level emergency facility for the Kitakyushu area. All three hospitals have 24/7 availability of computed tomography, magnetic resonance imaging, and neurologists and/or neurosurgeons to provide stroke care including recanalization therapy. The cohort comprised consecutive patients with acute ischemic stroke admitted within 7 days of onset between April 2019 and September 2020. Trained specialized stroke physicians in each hospital performed emergency evaluations, including imaging, and made decisions about intravenous thrombolysis and endovascular therapy. Patient eligibility for recanalization therapy was determined in accordance with Japanese guidelines (15, 16).

The study period was divided into two parts: pre-COVID-19 (from April 2019 to March 2020) and COVID-19 (from April to September 2020). The beginning of COVID-19 period was defined based on the surge in number of COVID-19 cases in Fukuoka Prefecture and the timing of a declaration of emergency state. On January 16 2020, the first case of COVID-19 was reported in Japan. There was a short delay in the number of cases in Fukuoka Prefecture compared with the Tokyo metropolitan area, but then the number of patients rapidly increased at the end of March 2020. A state of emergency was declared by the Japanese government on April 7 2020. On April 24 2020, the Japan Stroke Society issued a protocol for stroke care during the COVID-19 pandemic (17). According to the protocol, acute stroke treatment was performed under appropriate infection control measures at each institution. The number of new confirmed cases gradually decreased, and the state of emergency was lifted on May 25 2020. However, a second wave occurred in July 2020 (18). Although all three hospitals dedicated their medical resources to treating COVID-19 patients in response to the COVID-19 pandemic, the emergency acceptance of stroke cases was not suspended throughout the study period.

Patient clinical information was recorded in a web-based Research Electronic Data Capture database hosted at Kyushu University Hospital (19). Data were extracted from the hospital discharge record of the Diagnosis Procedure Combination, a mixed-case patient-classification system that includes the principal diagnosis coded according to the International Classification of Diseases and Injuries, 10th revision (ICD-10), which is linked to a hospital finance system (20). We identified patients hospitalized for acute ischemic stroke by using ICD-10 diagnosis codes related to ischemic stroke (I63.0–9) and TIA (G45.0–9) and excluding patients with scheduled admissions. This study was approved by the ethics committee of Kyushu University Hospital (2020-650) and by each facility involved.

Study Subjects

The following clinical information was systematically collected from medical records: age; sex; history of stroke; the presence of

hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, ischemic heart disease, or congestive heart failure; and maintenance hemodialysis. Route of arrival was categorized as direct walk-in, direct ambulance transport, walk-in with a referral from another medical facility, and transferred from another medical facility. In this study, patients with in-hospital stroke were excluded. Pre-stroke functional status was estimated using the modified Rankin Scale (mRS); pre-stroke disability was defined as an mRS of 3 or more. Because pre-stroke disability potentially affects a patient's behavior related to seeking medical attention and the severity of stroke symptoms on admission, patients with pre-stroke disability were excluded from the analysis. The ODT was defined as the time from onset of stroke or last-known well time to arrival. Wake-up stroke was defined as a stroke occurring during sleep and the last-known well time was bedtime. Acute ischemic lesions were evaluated on admission by computed tomography and/or magnetic resonance imaging including diffusion-weighted imaging. The severity of stroke symptoms was assessed with the National Institutes of Health Stroke Scale (NIHSS) score on admission. A clinical diagnosis of TIA was made if focal neurological symptoms attributable to a vascular etiology lasted for <24 h, without ischemic lesions observed on imaging (21). Minor stroke was defined as transient neurological symptoms or an NIHSS score of ≤3 on admission with at least one ischemic lesion (22).

Statistical Analysis

All statistical analyses were performed with JMP statistical software, version 9.0 (SAS Institute, Cary, NC, USA). Data were expressed as medians and interquartile ranges for continuous variables and counts and percentages for categorical variables.

First, we investigated the trend in the monthly proportions of patients with TIA/mild stroke among overall acute ischemic stroke cases using the Cochran–Armitage trend test. The number of new confirmed COVID-19 cases that were officially announced by Fukuoka Prefecture was also referenced.

Next, for patients with TIA/mild stroke, their clinical characteristics including the ODT were compared between pre-COVID-19 and COVID-19 periods, using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. Multivariable regression analysis was performed to investigate factors associated with the ODT, using forced entry and stepwise selection procedures. Age, sex, and the COVID-19 period of admission were forced in; other variables were chosen by stepwise selection with a significance level of $\alpha = 0.10$ for entry and $\alpha = 0.10$ for removal, including all variables in the univariate analysis. ODT values were transformed with the Box–Cox transformation to better approximate a normal distribution. The values were back-transformed to facilitate the interpretation of the effect. A similar analysis was performed for

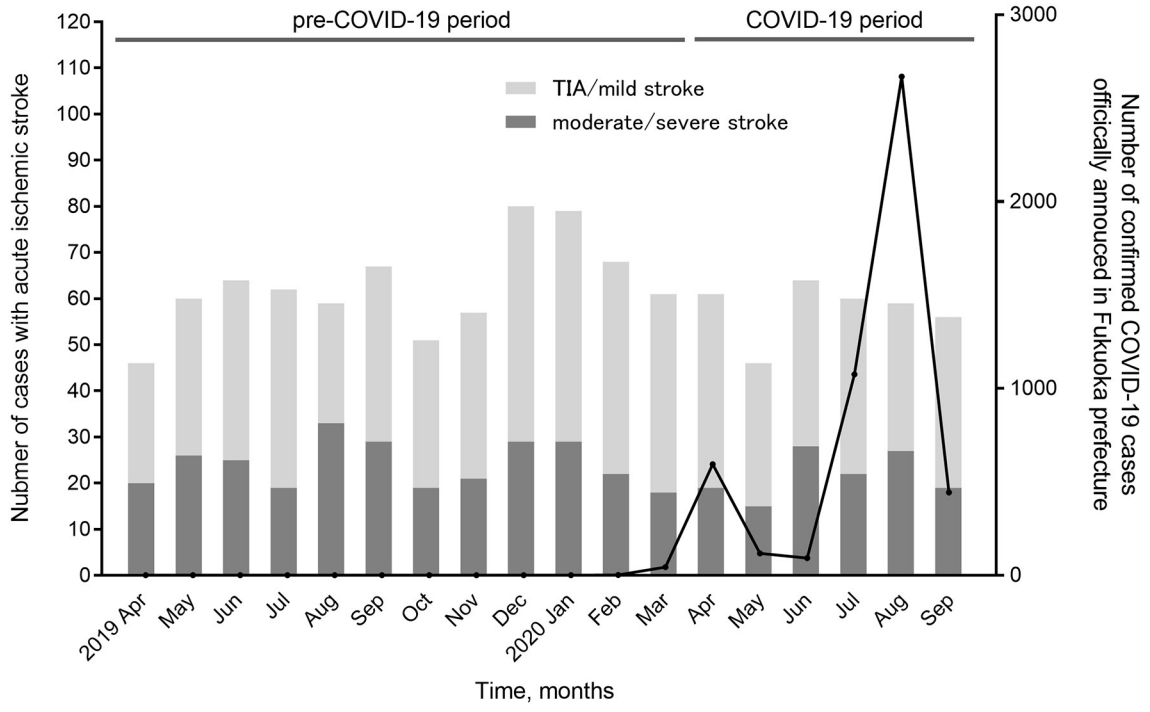

FIGURE 1 | Monthly proportions of patients with transient ischemic attack/mild stroke among overall acute ischemic stroke cases. No significant trend in the proportion of transient ischemic attack (TIA)/mild stroke among overall acute ischemic stroke cases was seen during the study period ($p = 0.231$, Cochran-Armitage trend test).

TABLE 1 | Characteristics of patients with transient ischemic attack/mild stroke.

Variables	Total ($n = 680$)	Pre-COVID-19 period ($n = 464$)	COVID-19 period ($n = 216$)	*p*-value
Sex, male	452 (66.5)	314 (67.7)	138 (63.9)	0.331
Age, years	72 (62–79)	72 (62–80)	71 (60–78)	0.143
History of stroke	132 (19.4)	91 (19.6)	41 (19.0)	0.847
Hypertension	520 (76.5)	350 (75.4)	170 (78.7)	0.349
Dyslipidemia	317 (46.6)	201 (43.3)	116 (53.7)	0.012
Diabetes mellitus	188 (27.6)	128 (27.6)	60 (27.8)	0.959
Atrial fibrillation	92 (13.5)	69 (14.9)	23 (10.6)	0.134
Ischemic heart disease	85 (12.5)	60 (12.9)	25 (11.6)	0.618
Congestive heart failure	26 (3.8)	16 (3.5)	10 (4.6)	0.520
Maintenance hemodialysis	33 (4.9)	26 (5.6)	7 (3.2)	0.250
Route of arrival				0.034
Direct walk-in	153 (22.5)	112 (24.1)	41 (19.0)	
Direct ambulance transport	232 (34.1)	164 (35.3)	68 (31.5)	
Walk-in with a referral from another medical facility	216 (31.8)	131 (28.2)	85 (39.4)	
Transferred from another medical facility	79 (11.6)	57 (12.3)	22 (10.2)	
Wake-up stroke	189 (27.8)	134 (28.9)	55 (25.5)	0.355
Onset-to-door time, min	602 (121–1,461)	508 (105–1,373)	864 (196–1,761)	0.003
Onset-to-door time ≤4.5 h	241 (35.4)	180 (38.8)	61 (28.2)	0.007
NIHSS score on admission	1 (0–2)	1 (0–2)	1 (0.25–2)	0.909
Intravenous thrombolysis	48 (7.1)	34 (7.3)	14 (6.5)	0.688
Endovascular therapy	2 (0.3)	2 (0.4)	0 (0)	1.000

Data are presented as the n (%) or median (interquartile range). NIHSS, National Institutes of Health Stroke Scale.

patients with diseases other than TIA/mild stroke, representing moderate/severe stroke. A p-value of < 0.05 was considered statistically significant.

RESULTS

Frequencies in TIA/mild Stroke Among Overall Acute Ischemic Stroke Cases During the Study Periods

Overall, 1,571 patients with acute ischemic stroke were admitted during the study period. Among them, 471 patients were excluded because of in-hospital stroke ($n = 100$), asymptomatic or arrived at ≥7 days after onset ($n = 98$), pre-stroke disability ($n = 184$), insufficient clinical information regarding the severity of stroke symptoms ($n = 18$), or an uncertain onset of stroke or last-known well time ($n = 71$). Finally, 1,100 patients (732 men, median age, 73 years) with ischemic stroke (754 admitted during the pre-COVID-19 period and 346 admitted during the COVID-19 period) were included in the analysis. The number and proportion of patients with TIA/minor stroke was 464 (61.5%) in the pre-COVID-19 and 216 (62.4%) in the COVID-19 periods. **Figure 1** shows the monthly proportions of patients with TIA/mild stroke among overall acute ischemic stroke cases. There was no significant trend in the proportion of TIA/mild stroke cases during the study period ($p = 0.231$ by Cochran-Armitage trend test). There was one case of stroke with newly confirmed COVID-19 after admission during the study period.

Changes in Clinical Characteristics During the COVID-19 Epidemic and the Impact of COVID-19 Epidemic on the ODT in Patients With TIA/Mild Stroke

Overall, 680 patients (452 men, median age of 72 years) with TIA/mild stroke (464 admitted during the pre-COVID-19 period and 216 admitted during the COVID-19 period) were included in the analysis. Compared with the pre-COVID-19 period, the route of arrival was different in the COVID-19 period ($p = 0.034$); direct walk-in and direct ambulance transport were decreased (19.0 vs. 24.1% and 31.5 vs. 35.3%, respectively) and walk-in with a referral from another medical facility was increased (39.4% vs. 28.2%). Patients admitted during the COVID-19 period were more likely to have dyslipidemia (53.7 vs. 43.3%, $p = 0.012$) and a longer ODT (median 864 vs. 508 min, $p = 0.003$) compared with those admitted during the pre-COVID-19 period (**Table 1**). Recanalization therapy was performed for 49 patients (7.2%) with mild stroke during the study period. Intravenous thrombolysis was performed in 34 patients (7.3%) during the pre-COVID-19 period and in 14 patients (6.5%) during the COVID-19 period. Endovascular therapy was performed in two patients (0.4%) in the pre-COVID-19 period. Multivariable analysis revealed that the COVID-19 period of admission was associated with a longer ODT (standardized partial regression coefficient [β] 0.09, $p = 0.003$), after adjustment for age, sex, route of arrival, hypertension, diabetes mellitus, NIHSS score on admission, and wake-up stroke (**Table 2**), corresponding

TABLE 2 | Multivariable regression analyses for the factors associated with onset-to-door time.

Variable	Unstandardized		Standardized	*t* value	*p*-value
	B	SE	β		
Intercept	2947.71	131.36		22.44	<0.001
COVID-19 period of admission	67.80	22.68	0.09	2.99	0.003
Wake-up stroke	294.70	24.12	0.37	12.22	<0.001
Route of arrival					
Direct walk-in (reference)					
Direct ambulance transport	−194.82	28.68	−0.26	−6.79	<0.001
Walk-in with a referral from another medical facility	207.48	29.05	0.27	7.14	<0.001
Transferred from another medical facility	−27.92	38.16	−0.02	−0.73	0.465
NIHSS on arrival	75.11	19.51	0.11	3.85	<0.001
Diabetes mellitus	60.69	23.76	0.08	2.55	0.011
Hypertension	46.89	25.59	0.06	1.83	0.067
Age	−0.22	1.69	0.00	−0.13	0.895
Sex, male	7.69	22.54	0.01	0.34	0.733
Adjusted R^2	0.433				

Onset-to-door time values were transformed by Box-Cox transformation (λ = 0) to better approximate a normal distribution. NIHSS, National Institutes of Health Stroke Scale; B, partial regression coefficient, SE, standard error.

to 83.0 min delay in original ODT. To exclude the potential impact of seasonal fluctuation on the number of patients with ischemic stroke and the proportion of patients with distinct stroke severity, we performed a sensitivity analysis by extracting 258 patients admitted between April 2019 and September 2020 from the pre-COVID-19 period dataset and compared them with patients in the COVID-19 period (between April 2020 and September 2020). This demonstrated an association between the COVID-19 period of admission and a longer ODT remained significant in the multivariable analysis (β 0.08, $p = 0.032$) (**Supplementary Table 1**), corresponding to 74.0 min delay in original ODT.

Analysis of Patients With Moderate/Severe Stroke in the Pre-COVID-19 and COVID-19 Periods

A similar analysis was performed for patients with moderate/severe stroke. Overall, 420 patients (280 men, median age of 76 years) with moderate/severe stroke (290 admitted during the pre-COVID-19 period and 130 admitted during the COVID-19 period) were included in the analysis. No significant changes in clinical characteristics including the ODT (median 434 vs. 471 min, $p = 0.952$) was observed between the pre-COVID-19 and COVID-19 periods (**Supplementary Table 2**). Intravenous thrombolysis and endovascular therapy were performed in 82 (28.3%) and in 40 (30.8%) patients during the pre-COVID-19 period and in 78 (26.9%) and 29 (22.3%) patients during the COVID-19 period.

DISCUSSION

This study clarified the changes in the clinical characteristics of patients with TIA/mild stroke admitted to thrombectomy-capable hospitals during the COVID-19 epidemic. The first major finding of this study was that under the COVID-19 epidemic, a prolongation of ODT occurred despite a comparable case volume and proportion of TIA/mild strokes among overall ischemic strokes during the study period. Similar delays have been described in other settings including acute coronary syndrome, testicular torsion, or pediatric appendicitis (23–27). Previous studies suggest that reluctance to seek medical attention shortly after symptom onset during the COVID-19 pandemic was related to the restrictions in healthcare systems as well as a decreased awareness/shift of attention of the patients, the desire not to overload the emergency healthcare systems, or the fear of in-hospital infection (28). Delays in seeking medical attention after TIA/mild stroke were reported by several studies even before the COVID-19 pandemic (29–32). In addition to the symptoms themselves, the perception and response of patients and people around them, and the referral process contributed to the pre-hospital delay. The independent association between the COVID-19 period of admission and a longer ODT in our study suggests the COVID-19 pandemic is a contributing factor to the delay in presentation time in patients with TIA/mild stroke as a social-psychological behavior modifier.

In contrast to a previous study (5), the ODT was not significantly changed during the COVID-19 epidemic in patients with moderate/severe stroke. However, this was in accordance with the other studies where patients with severe stroke or hemorrhagic stroke were affected less by the COVID-19 pandemic (8–12), indicating that patients and pre-hospital medical staff correctly recognized the need for the emergency care of severe stroke cases. Another possible reason is that emergency acceptance of severe stroke cases was not suspended throughout the study period in these three hospitals, which might be attributable to the relatively low number of COVID-19 cases in Fukuoka Prefecture compared with the Tokyo metropolitan area.

Therefore, a massive increase of COVID-19 cases may seriously affect the acute stroke care system.

The second major finding was that the route of arrival changed during the COVID-19 epidemic in patients with TIA/mild stroke: there was an increased frequency of walk-ins with a referral from another facility and a decreased frequency of direct walk-ins and ambulance transport. Although all three hospitals dedicated medical resources to treating COVID-19 patients by implementing infection prevention and control guidelines, patients might have preferred to visit family doctors or their usual or local medical facilities rather than be directly transported to the main hospitals. Our results are consistent with the results of a questionnaire survey reported by Yao et al. (33), where most patients with suspected TIA hesitated to go to a hospital because of the fear of in-hospital infection and complicated procedures, unless a dual attack occurred within a week. Patients with TIA/mild stroke admitted during the COVID-19 period more frequently had dyslipidemia. A similar trend was reported previously (34), although the diagnosis of dyslipidemia was done in the stroke units in this study. The reason for this is unclear but might result from an increase in the frequency of referrals with a detailed history provided by family doctors, or patients without underlying diseases or connections with family doctors refrained from visiting these hospitals directly during the COVID-19 epidemic.

The spread of COVID-19 infection continues globally and therefore, the impact of the COVID-19 pandemic on patients with TIA/mild stoke seeking medical attention may have increased further (35). Continuous research on the impact of the COVID-19 pandemic on patients with TIA/mild stroke seeking medical attention and clinical outcomes is needed. Considering that substantial numbers of patients with mild stroke were eligible for recanalization therapy, it is necessary to continue to increase awareness regarding the need for the urgent evaluation and treatment of TIA/mild stroke.

This study had several limitations. First, this was a retrospective study and was conducted in a small number of facilities with a limited number of patients. A detailed analysis regarding the changes in clinical characteristics within the COVID-19 period (e.g., during and after the state of emergency) could not be performed. Moreover, this study was from one region and might not represent the nationwide situation. Second, outcome data were lacking and the impact of a prolonged ODT on stroke outcomes remains unclear. Previous studies suggest patients with high-risk TIA/minor stroke may have a disadvantage in being treated later especially due to the later administration of secondary preventive treatments. Further study is warranted to elucidate associations between changes in clinical characteristics including the ODT and outcomes in patients with TIA/mild stroke. Third, $ABCD^2$ score and some clinical information that might be associated with seeking medical attention [e.g., bystanders, cognitive impairment, initial perception of symptoms, socioeconomic status, or area/infrastructure at residence (36, 37)] were not included in the analysis. Finally, changes in clinical characteristics during the COVID-19 epidemic in patients with pre-stroke disability or in-hospital stroke were not investigated.

CONCLUSIONS

COVID-19 epidemic might increase the ODT in patients with TIA/mild stroke. Public education regarding TIA/minor stroke should be continuously reinforced even during the COVID-19 pandemic.

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 the Ethics Committee of Kyushu University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KT, SM, and TY made substantial contributions to the concept and design of the study. KT, YN, KS, SN, and TH contributed to the acquisition, analysis, and interpretation of data. KT, SM, TY, RY, IN, and NI contributed to drafting the text and preparing the figures. All authors contributed to and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Mechanical Thrombectomy for Acute Stroke Due to Large-Vessel Occlusion Presenting With Mild Symptoms

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Purpose: To evaluate the safety and efficacy of mechanical thrombectomy (MT) for acute stroke due to large vessel occlusion (LVO), presenting with mild symptoms.

Methods: A prospective cohort study of patients with mild ischemic stroke and LVO was conducted. Patients were divided into two groups: MT group or best medical management (MM) group. Propensity score matching (PSM) was conducted to reduce the confounding bias between the groups. The primary outcome was functional independence at 90 days. The safety outcome was symptomatic intracranial hemorrhage (sICH). Univariate and multivariate logistic regression analyses were used to identify the independent factors associated with outcomes.

Results: Among the 105 included patients, 43 were in the MT group and 62 in the MM group. Forty-three pairs of patients were generated after PSM. There were no significant differences in sICH rates between two groups ($p = 1.000$). The MT group had a higher proportion of independent outcomes (83.7% MT vs. 67.4% MM; OR 2.483; 95% CI 0.886–6.959; $p = 0.079$) and excellent outcomes (76.7% MT vs. 51.2% MM; OR 3.150; 95% CI 1.247–7.954; $p = 0.013$) compared to the MM group, especially in patients with stroke of the anterior circulation ($p < 0.05$). Multivariate logistic regression analysis showed that small infarct core volume ($p = 0.015$) and MT treatment ($p = 0.013$) were independently associated with excellent outcomes.

Conclusions: Our results suggest that MT in stroke patients, presenting with mild symptoms, due to acute LVO in the anterior circulation may be associated with satisfactory clinical outcomes.

Clinical Trial Registration: ClinicalTrials.gov, identifier: NCT04526756.

Keywords: acute large vessel occlusion, thrombectomy, mild stroke, outcome, prognosis

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INTRODUCTION

Mechanical thrombectomy (MT) has been globally acknowledged as a standard treatment for patients with acute ischemic stroke patients (AIS) and large vessel occlusion (LVO). Some randomized trials (1–7) provided level 1a evidence for MT in patients with LVO in the anterior circulation (internal carotid artery and middle

cerebral artery M1) with a National Institutes of Health Stroke Scale (NIHSS) score of ≥6 (8, 9). However, mild stroke cannot be considered as a benign condition, with approximately one-third of patients becoming functionally dependent after 90 days (10–12). Large-scale prospective studies have shown that the NIHSS score is not a precise predictor of LVO in patients with AIS (13, 14), as nearly 10% patients with NIHSS score <6 suffered from LVO. Furthermore, patients with LVO presenting with a low NIHSS score were found to be a high risk of clinical worsening of the condition, leading to poor outcome (15). It is still unclear whether patients with minor stroke and LVO can benefit from MT. Several studies have focused on this topic, but the results are inconsistent (16–19). The aim of this prospective study is to evaluate the relationship between MT and the clinical outcome of acute LVO with mild symptoms.

MATERIALS AND METHODS

Study Design

We conducted a prospective cohort study on patients with LVO and mild symptoms from a comprehensive stroke center in Shanghai, China, between August 1, 2016, and March 31, 2020. The inclusion criteria were as follows: (1) time from onset or last seen well of the symptoms ≤24 h; (2) age ≥18 years; (3) NIHSS score <6; (4) LVO including middle cerebral artery M1, proximal M2 segment, intracranial internal carotid artery, basilar artery, and posterior cerebral artery P1 occlusion detected by computed tomography (CT) angiography (CTA); and (5) anterior circulation LVO with infarct core volume ≤50 ml and mismatch ratio >1.8. Patients with prior disability [the modified Rankin Scale (mRS) score of >2] and occlusive artery spontaneous recanalization before thrombectomy and those with neurological worsening in the medical management (MM) group with rescue MT were excluded.

The study was approved by the institutional ethics committee of Shanghai East Hospital, and a written informed consent was obtained from each participant.

Measurements

All patients underwent an initial imaging protocol including non-enhanced CT scan. When patients with mild stroke (NIHSS score <6) are considered as anterior circulation stroke presenting with cortical symptoms (such as mild aphasia, somnolence, slow-mindedness) or posterior circulation stroke presenting with continuous vertigo and bilateral pathological signs within 24 h, they were suspected with LVO and received the emergency whole-brain CT perfusion (CTP), which can obtain CTA and CTP images at the same time to judge whether there is LVO and penumbra. If they met the inclusion criteria mentioned above, patients were informed of the advantages and disadvantages of the MT and MM treatment and decided which treatment to receive. The study subjects were divided into two groups: MT group, and best MM group. The following data were collected: (1) demographics; (2) time of onset, admission, thrombolysis, CTP examination, puncture, and reperfusion; (3) medical history; and (4) NIHSS score before evaluation of MT.

Computed tomography perfusion/Computed tomography angiography images were acquired using a 320-slice CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). Computed tomography perfusion data were analyzed using a commercial software (MiStar; Apollo Medical Imaging Technology, Melbourne, Australia). Hypoperfusion volume and infarct core volume were calculated using previously validated thresholds [hypoperfused lesion: delay time (DT) >3 s, infarct core: relative cerebral blood flow (rCBF) <30%, severe hypoperfused lesion: DT >6 s] (20–22). The mismatch ratio was defined as the proportion of hypoperfusion volume to the infarct core volume (22). Acute cerebral collateral flow was quantified using the volume ratio of severely delayed contrast transit tissue (DT >6 s within the DT >3 s perfusion lesion) (23).

Solitaire stent placement and manual aspiration were performed as first-line endovascular treatment. When stent retriever thrombectomy failed, an intra-arterial recombinant tissue plasminogen activator (rtPA) was administered or a stent was placed. Successful revascularization was defined as a modified thrombolysis in cerebral infarction (TICI) grade 2b or 3 (24).

The mRS was assessed at 3 months *via* telephone by a trained staff who was unaware of the patients' treatment group. The mRS score was recorded as 6 at the 3-month follow-up when the patients died in the hospital. The primary outcome was defined as functional independence (mRS score of 0–2) at 90 days. We also evaluated excellent clinical outcomes (mRS score of 0–1) at 90 days, NIHSS score (a NIHSS score of 42 was assigned in case of death) and mRS score at 7 days, symptomatic intracranial hemorrhage (sICH), in-hospital mortality, and at 90 days as secondary outcomes. Symptomatic intracranial hemorrhage was defined according to the European Cooperative Acute Stroke Study (ECASS)-III criteria (25).

Statistical Analysis

Statistical analysis for categorical variables included the Chi-square test and Fisher's exact test when cell sizes were small. Quantitative data were described as mean ± standard deviation (SD) if normally distributed or the median, i.e., interquartile range (IQR), and analyzed using Student's *t*-test or the Mann–Whitney test. Logistic regression analysis was performed to identify the independent predictors of clinical outcomes. Variables with a *p*-value of <0.15 in the univariate analysis of the clinical outcome were included in the multivariate logistic regression. The Matchit package in R language was used to conduct the propensity score matching (PSM) analysis (nearest neighbor 1:1 matching). Other statistical analyses were conducted using SPSS version 22.0, for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Abbreviations: AIS, acute ischemic stroke; CT, computed tomography; CI, confidence interval; CTA, CT angiography; CTP, CT perfusion; DT, delay time; ECASS, European Cooperative Acute Stroke Study; IQR, interquartile range; LVO, large vessel occlusion; MT, mechanical thrombectomy; MM, medical management; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PSM, propensity score matching; rtPA, recombinant tissue plasminogen activator; rCBF, relative cerebral blood flow; SD, standard deviation; sICH, symptomatic intracranial hemorrhage; TICI, thrombolysis in cerebral infarction.

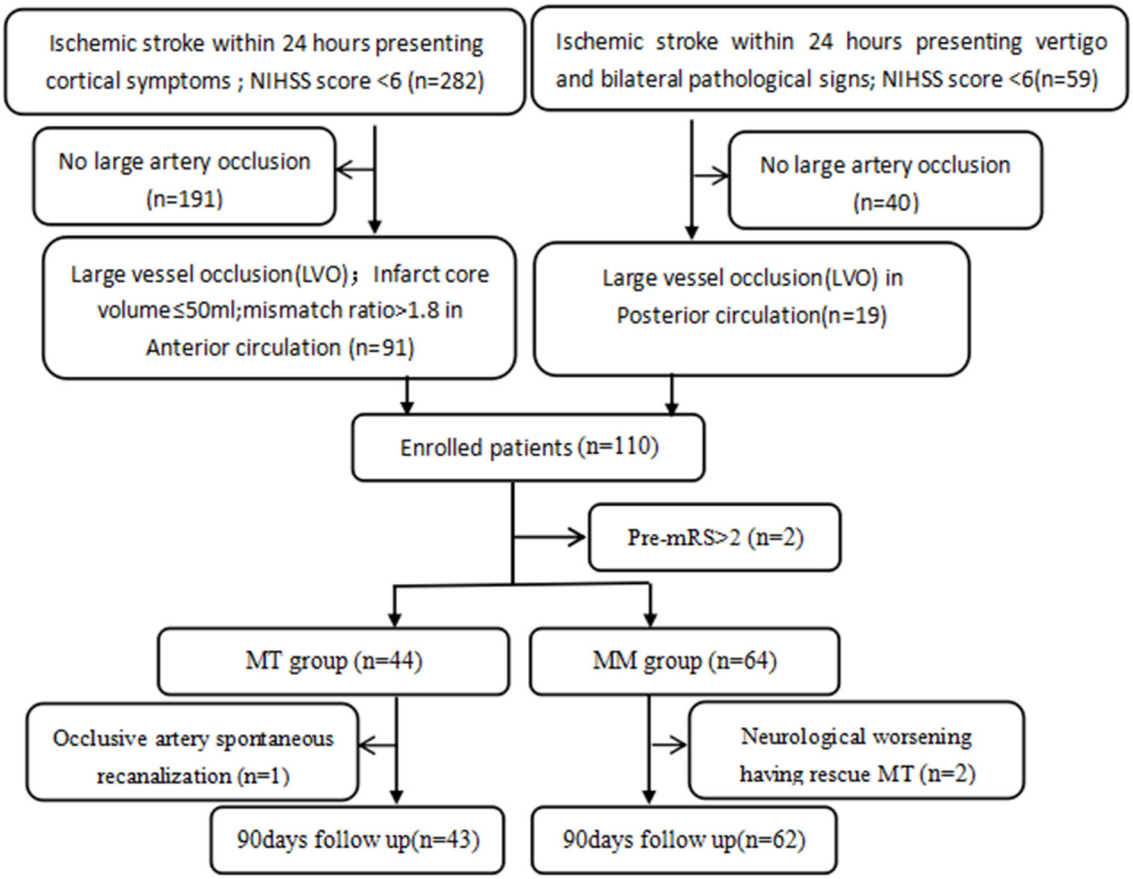

FIGURE 1 | The study flowchart. NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MT, mechanical thrombectomy; MM, medical management; LVO including middle cerebral artery M1, proximal M2 segment, intracranial internal carotid artery, basilar artery, and posterior cerebral artery P1 occlusion.

RESULTS

We initially identified 110 patients for this study. Of them, two patients were excluded because of a pre-stroke mRS >2, one in the MT group was excluded for spontaneous recanalization, and two patients in the MM group were excluded for rescue MT due to neurological worsening. Of the two excluded patients, one was excluded because he had acute occlusion of the contralateral middle cerebral artery during hospitalization, which was not related to this stroke. Another one was treated by interventional surgery due to the aggravation of cerebral infarction symptoms. We excluded this patient because we considered that there may be a correlation between thrombectomy and the prognosis. Thus, finally a total of 105 patients (64.8% male) with a mean age of 68.8 years (SD 11.7) and median NIHSS score of 5 (4,5) were included. Forty-three patients (41%) were placed in the MT group, and 62 (59%) patients were in the MM group. All 105 patients were followed up at 90 days. The summary of the study design is presented as a flowchart in **Figure 1**. Forty-three pairs of patients were generated after PSM.

Baseline demographics, medical history, and perfusion analyses results were comparable between the two groups. Before PSM, the MT group had more MCA-M1 (46.5 vs. 38.7%), less MCA-M2 (7 vs. 25.8%), and less posterior circulation occlusions (9.3 vs. 22.6%) than the MM group ($p = 0.004$). Moreover, these differences were reduced after PSM (**Table 1**).

With respect to clinical outcomes, Before PSM, patients in the MT group had a significantly higher proportion of independence (83.7 vs. 62.9%; OR 3.033; 95% CI 1.162–7.919; $p = 0.02$) and excellent clinical outcomes (76.7% MT vs. 45.2% MM; OR 4.007; 95% CI 1.685–9.531; $p = 0.001$) than the MM group at 90 days, especially in the anterior circulation group. Patients treated with MT also had lower NIHSS and mRS scores at 7 days than those in the MM group ($p < 0.05$). Symptomatic intracranial hemorrhage rates (7% MT vs. 4.8% MM group; $p = 0.687$), in-hospital mortality (9.3% MT vs. 4.7% MM group; $p = 0.714$), incidence of pulmonary infection (23.3% MT vs. 22.6% MM group; $p = 0.935$), and length of hospitalization (12 days vs. 11 days, $p = 0.131$) were comparable between the groups (**Table 2**). In the univariate analysis, female, pre-mRS = 0, small infarct core volume (≤15 ml), and MT were identified as predictors of good outcomes. Multivariate logistic regression showed that a small infarct core volume (OR 3.275, 95% CI 1.221–8.783, $p = 0.018$; OR 3.102, 95% CI 1.156–8.323, $p = 0.025$) and MT (OR 3.320,

TABLE 1 | Comparisons of baseline clinical profiles and CTP data between thrombectomy and medical management groups before and after PSM.

Characteristic		Before PSM			After PSM		
		MT group ($n = 43$)	MT group ($n = 62$)	*p*-value	MT group ($n = 43$)	MM group ($n = 43$)	*p*-value
Baseline demographic and clinical data							
Age, years, mean ± SD		66.51 ± 9.26	67.02 ± 13.18	0.829	66.51 ± 9.26	66.86 ± 12.65	0.884
Sex, male, *n* (%)		27 (62.8)	41 (66.1)	0.725	27 (62.8)	27 (62.8)	1.000
Medical history, *n* (%)							
Hypertension		27 (62.8)	45 (72.6)	0.288	27 (62.8)	29 (67.4)	0.651
Diabetes mellitus		8 (18.6)	14 (22.6)	0.623	8 (18.6)	10 (23.3)	0.596
Dyslipidemia		6 (14.0)	10 (16.1)	0.760	6 (14.0)	6 (14.0)	1.000
Ischemic stroke		7 (16.3)	8 (12.9)	0.627	7 (16.3)	7 (16.3)	1.000
Cardioembolic source		16 (37.2)	20 (32.3)	0.599	16 (37.2)	15 (34.9)	0.822
Smoking		15 (34.9)	23 (37.1)	0.816	15 (34.9)	14 (32.6)	0.820
Taking antiplatelet prior to stroke		8 (18.6)	12 (19.4)	0.923	8 (18.6)	8 (18.6)	1.000
Taking anticoagulant prior to stroke		3 (7.0)	3 (4.8)	0.687	3 (7.0)	3 (7.0)	1.000
Glucose at admission, mmol/L, median (IQR)		6.7 (5.9, 7.9)	6.95 (6.1, 8.9)	0.444	6.7 (5.9, 7.9)	6.6 (5.9, 8.9)	0.782
Intravenous rtPA, *n* (%)		19 (44.2)	26 (41.9)	0.819	19 (44.2)	20 (46.5)	0.829
DNT, min, median (IQR)		34 (28, 45)	34 (27, 48)	0.827	34 (28, 45)	32 (24.5, 46.5)	0.844
NIHSS before evaluation of thrombectomy, median (IQR)		5 (4, 5)	5 (3, 5)	0.138	5 (4, 5)	5 (4, 5)	0.835
Onset to door time, min, median (IQR)		121 (60, 309)	143 (60, 303)	0.604	121 (60, 309)	115 (59, 285)	0.900
Onset to CTP time, min, median (IQR)		219 (130, 415)	235 (151, 381)	0.555	219 (130, 415)	236 (148, 358)	0.832
Onset to puncture time, min, median (IQR)		360 (275, 543)	NA	NA	360 (275, 543)	NA	NA
Onset to clot first reperfusion time, min, median (IQR)		433 (345, 598)	NA	NA	433 (345, 598)	NA	NA
Local anesthesia, *n* (%)		20 (46.5)	NA	NA	20 (46.5)	NA	NA
Successful recanalization (TICI 2b/3), *n* (%)		42 (97.7)	NA	NA	42 (97.7)	NA	NA
Occlusion site	MCA M1, *n* (%)	20 (46.5)	24 (38.7)	0.004	20 (46.5)	18 (41.9)	0.001
	MCA M2, *n* (%)	3 (7.0)	16 (25.8)		3 (7.0)	10 (23.3)	
	Proximal ICA, *n* (%)	5 (11.6)	4 (6.5)		5 (11.6)	3 (7.0)	
	Terminal ICA or tandem occlusion, *n* (%)	11 (25.6)	4 (6.5)		11 (25.6)	2 (4.7)	
	BA or PCA P1, *n* (%)	4 (9.3)	14 (22.6)		4 (9.3)	10 (23.3)	
Baseline perfusion imaging data							
Infarct core, ml, median (IQR)		6 (3, 25)	6.5 (3, 18)	0.747	6 (3, 25)	7 (3, 18)	0.694
Penumbra, ml, median (IQR)		89 (32, 118)	63 (23, 103)	0.062	89 (32, 118)	73 (24, 103)	0.240
DT > 3 s, ml, median (IQR)		95 (37, 148)	75.5 (27, 123.3)	0.121	95 (37, 148)	95 (29, 125)	0.344
DT > 6 s, ml, median (IQR)		19.0 (4.6, 36.8)	11.5 (3.9, 31.9)	0.265	19.0 (4.6, 36.8)	11 (5, 35)	0.426
Mismatch ratio, median (IQR)		10.5 (4.6, 18.5)	7.8 (3.0, 16.9)	0.171	10.5 (4.6, 18.5)	8.7 (3.5, 18.6)	0.392
DT6/DT3 ratio, median (IQR)		0.22 (0.11, 0.33)	0.18 (0.08, 0.30)	0.542	0.22 (0.11, 0.33)	0.18 (0.05, 0.30)	0.402

Data are n (%), mean (SD), or median (IQR). p-values are based on chi-square, T-test, or Wilcoxon signed-rank test. PSM, propensity score matching; MT, mechanical thrombectomy; MM, medical management; rtPA, recombinant tissue plasminogen activator; DNT, door to needle time; NA, not applicable; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; DT, delay time; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery.

TABLE 2 | Clinical outcomes of patients between thrombectomy and medical management group before and after PSM.

Characteristic	Before PSM				After PSM			
	MT group ($n = 43$)	MT group ($n = 62$)	*p*-value	OR (95% CI)	MT group ($n = 43$)	MM group ($n = 43$)	*p*-value	OR (95% CI)
sICH, *n* (%)	3 (7.0)	3 (4.8)	0.687	1.475 (0.283–7.679)	3 (7.0)	2 (4.7)	1.000	1.538 (0.244–9.70)
Death in hospital, *n* (%)	4 (9.3)	4 (4.7)	0.714	1.478 (0.351–6.303)	4 (9.3)	3 (7.0)	1.000	1.368 (0.287–6.512)
Death at 90 days, *n* (%)	5 (11.6)	4 (6.5)	0.482	1.908 (0.481–7.561)	5 (11.6)	3 (7.0)	0.713	1.754 (0.392–7.852)
Pulmonary infection, *n* (%)	10 (23.3)	14 (22.6)	0.935	1.039 (0.412–2.619)	10 (23.3)	10 (23.3)	1.000	1.000 (0.368–2.720)
NIHSS score at 7 days, median (IQR)	2 (1.5)	4 (2.75.7.25)	0.042		2 (1.5)	4 (2.8)	0.058	
mRS at 7 days, median (IQR)	1 (1.3)	3 (1.4)	0.033		1 (1.3)	2 (1.4)	0.078	
mRS (0–1) at 90 days, *n* (%)	33 (76.7)	28 (45.2)	0.001	4.007 (1.685–9.531)	33 (76.7)	22 (51.2)	0.013	3.15 (1.247–7.954)
Anterior circulation	31 (79.5)	20 (41.7)	0.000	5.425 (2.065–14.255)	31 (79.5)	16 (48.5)	0.006	4.117 (1.463–11.584)
Posterior circulation	2 (50.0%)	8 (57.1)	1.000	0.750 (0.081–6.958)	2 (50.0)	6 (60)	1.000	0.667 (0.065–6.871)
mRS (0–2) at 90 days, *n* (%)	36 (83.7)	39 (62.9)	0.002	3.033 (1.162–7.919)	36 (83.7)	29 (67.4)	0.079	2.483 (0.886–6.959)
Anterior circulation	34 (87.2)	29 (60.4)	0.005	4.455 (1.479–13.420)	34 (87.2)	22 (66.7)	0.037	3.40 (1.039–11.124)
Posterior circulation	2 (50.0)	10 (71.4)	0.569	0.400 (0.041–3.900)	2 (50.0)	7 (70)	0.580	0.429 (0.04–4.637)
mRS at 90 days, median (IQR)	1 (0.1)	2 (0.3)	0.039		1 (0.1)	1 (0.3)	0.096	
Hospitalization days, day, median (IQR)	12 (11.15)	11 (9.15)	0.131		12 (11.15)	11 (8.15)	0.120	

Data are n (%), mean (SD), or median (IQR). P-values are based on chi-square, T test, or Wilcoxon signed-rank test; PSM, propensity score matching; MT, mechanical thrombectomy; MM, medical management; sICH, symptomatic intracranial hemorrhages; OR, odds ratio; CI, confidence interval; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; IQR, interquartile range.

TABLE 3 | Univariate and multivariate analysis of determinants of good outcome before and after PSM.

	Before PSM				After PSM			
	mRS (0–1) at 90 days				mRS (0–1) at 90 days			
Variables	**Unadjusted OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**	**Unadjusted OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Thrombectomy	4.01 (1.69–9.53)	0.001	4.44 (1.74–11.36)	0.002	3.15 (1.25–7.95)	0.013	3.61 (1.31–9.93)	0.013
Infarct core ≤15 ml	3.46 (1.43–8.36)	0.005	3.10 (1.16–8.32)	0.025	4.12 (1.54–11.50)	0.004	3.91 (1.30–11.74)	0.015
Gender, male	0.37 (0.16–0.88)	0.023	0.40 (0.16–1.04)	0.059	0.45 (0.17–1.18)	0.100	0.52 (0.18–1.49)	0.222
Pre-mRS = 1	0.17 (0.02–1.55)	0.159	0.35 (0.03–3.71)	0.038	0.17 (0.02–1.74)	0.131	0.37 (0.03–4.16)	0.417
	mRS (0–2) at 90 days				**mRS (0–2) at 90 days**			
Variables	**Unadjusted OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**	**Unadjusted OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Thrombectomy	3.03 (1.16–7.92)	0.020	3.32 (1.16–9.48)	0.025	2.48 (0.89–6.96)	0.079	2.95 (0.92–9.50)	0.070
Infarct core ≤15 ml	4.00 (1.61–9.96)	0.002	3.27 (1.22–8.88)	0.018	6.55 (2.22–19.28)	0.000	5.78 (1.81–18.42)	0.003
Gender, male	0.46 (0.17–1.20)	0.106	0.58 (0.20–1.63)	0.299	0.44 (0.14–1.35)	0.144	0.59 (0.17–2.04)	0.405
Pre-mRS = 1	0.09 (0.01–0.82)	0.023	0.16 (0.02–1.66)	0.124	0.09 (0.01–0.96)	0.044	0.20 (0.02–2.30)	0.195

Adjusted for sex, Pre-mRS, thrombectomy and infarct core ≤15 ml. PSM, propensity score matching; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval.

95% CI 1.163–9.479, $p = 0.025$; OR 4.442, 95% CI 1.737–11.359, $p = 0.002$) were associated with independence and excellent clinical outcome at 90 days (**Table 3**).

Similar results were obtained after PSM analysis. Patients in the anterior circulation stroke, MT group, had a significantly higher proportion of independence (87.2 vs. 66.7%; $p = 0.037$) and excellent clinical outcomes (79.5% MT vs. 48.5% MM; $p = 0.006$) than the MM group at 90 days (**Table 2**). Multivariate logistic regression showed that a small infarct core volume (OR 3.91, 95% CI 1.299–11.744, $p = 0.015$) and MT (OR 3.612, 95%

CI 1.314–9.927, $p = 0.013$) were associated with excellent clinical outcome at 90 days (**Table 3**).

DISCUSSION

This prospective cohort study of patients with mild ischemic stroke (NIHSS score < 6) and LVO showed that MT treatment was independently associated with good functional outcome at 90 days, especially in anterior circulation post-procedure. Similar rates of sICH, in-hospital mortality, and pulmonary infection between groups may contribute to concerns regarding the safety of MT.

It is still unclear whether patients with acute mild ischemic stroke due to LVO can benefit from thrombectomy. To the best of our knowledge, there have been no randomized controlled trials on this topic, and observational studies have shown conflicting results. Our findings supported the results of the retrospective study by Haussen et al. (19); compared to medical therapy, thrombectomy in patients with LVO with mild symptoms (NIHSS 0–5) was associated with improved clinical outcomes. A multicenter-matched analysis (18) with a larger sample size also showed similar results. In addition, a meta-analysis (26) conducted in 2018 demonstrated results in favor of thrombectomy in patients with LVO stroke with minor or mild symptoms (NIHSS $\leq$ 8). However, the patients in the thrombectomy group were considerably younger, which may have been a major confounder. In contrast, ETIS registry investigators (27) reported similar proportions of favorable functional outcomes at 3 months between urgent MT and medical treatment with possible delayed MT matched with propensity score, but with nearly 20% management crossover. Similar results were reported in another multicenter cohort study (17); however, there was a signal toward benefit from MT in M1 occlusions ($p = 0.07$) (17). A recent meta-analysis (16) demonstrated that there was no difference in clinical outcomes in patients with LVO and NIHSS score <6 treated with MT or best MM. Our research adds to the knowledge in this field with regard to the eastern Chinese population.

In terms of safety, we found no significant difference in the rate of sICH and mortality between the MT and MM groups, which is consistent with the findings of some matched cohort studies (18, 27). Goyal et al. in a meta-analysis (16) found that MT was associated with higher rates of asymptomatic ICH (OR, 11.07; 95% CI, 1.31–93.53; $p = 0.03$), but with a similar rate of sICH between the two groups. Sarraj et al. (17) observed that sICH rates were higher in the MT group and were associated with higher mortality. Multiple passes of MT might be related to an increased risk of sICH. Patients in this study were included from nearly 10 years ago, and the development of thrombectomy technique may be associated with a decreased rate of complications and mortality. Overall, sICH and other complications are still major concerns for MT in patients with mild stroke.

There are several possible reasons behind the positive results in this study. First, the higher recanalization rate in this study (up to 97.7%) was comparable to that in a meta-analysis by Goyal et al. (84.5%) (16) and that reported by Sarraj et al. (78%) (17). A higher recanalization rate might be associated with a better outcome in the MT group, which was also supported by a retrospective analysis of the BEYOND-SWIFT registry study (28). Better outcomes were observed in patients with successful reperfusion. Second, perfusion imaging was used to select patients. In China, there were no clear recommendations on the guidelines for thrombectomy in patients with LVO and mild stroke (29, 30). No recommendation was described in the 2015 guideline, and MT can be considered after careful analysis and screening in the 2018 guideline. Even though there were no common rules to make a treatment decision for such condition, patients with smaller infarct cores and larger penumbra might prefer thrombectomy. In addition, treatment decision might also be affected by insurance status and family culture. Even though we used multivariate logistic regression and PSM to adjust for these confounders, our results might still be affected by indication bias.

Strengths and Limitations

Our study was prospectively designed to explore the relationship between MT treatment in patients with mild stroke and associated functional outcomes. The baseline characteristics were almost balanced between groups providing ideally comparable populations. There were several limitations to this study, including the non-randomized study design with a limited sample size, which might have caused potential bias. The baseline NIHSS score in the MT group seemed higher than that in the MM group, and there were more patients with anterior circulation occlusion in the MT group. To overcome these drawbacks, PSM analysis was conducted to reduce the confounding bias. Also, we tried to adjust these imbalances with multivariate analysis. Furthermore, the study included both anterior and posterior circulation patients, which may reduce the credibility of the results. So we conducted a stratified analysis, suggesting that the benefit of thrombectomy is mainly reflected in the anterior circulation and there is no statistical difference between the two groups in the posterior circulation. Moreover, the power of the NIHSS score in evaluating the severity of posterior circulation and the reliability of perfusion imaging in the evaluation of posterior circulation is low, which may also have caused potential bias. Finally, not all patients presented with NIHSS <6 underwent emergency multimodal imaging to screen for LVO; only when stroke doctors considered that LVO cannot be completely excluded according to the patient's clinical symptoms would they give the patient multimodal imaging examination, which may lead to selection bias. Therefore, it is necessary to conduct a large multicenter randomized controlled trial comparing the MT with the best MM in patients with LVO presenting with minor symptoms.

CONCLUSIONS

This study suggested that MT in patients presenting with mild stroke symptoms and acute LVO may be related to good clinical outcomes, especially in the anterior circulation, with a similar risk

of sICH. This observational study adds evidence in support of thrombectomy in patients with mild stroke patients in the eastern Chinese population.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Shanghai East Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FL and HS conceived of and designed the study, wrote the first draft of the manuscript, and analyzed the data. GL designed the study and finalized the manuscript. All authors revised and approved the final manuscript.

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Characteristics and Outcomes of Intravenous Thrombolysis in Mild Ischemic Stroke Patients

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Objective: This study assessed the characteristics of intravenous thrombolysis (IVT) with respect to early neurological deterioration (END) and functional outcome in mild ischemic stroke patients.

Methods: Data were obtained from acute mild ischemic stroke patients (defined as having a National Institute of Health Stroke Score (NIHSS) $\leq$5) treated with IVT in our hospital from July 2017 to December 2020. END was defined as the NIHSS increased $\geq$1 over the baseline at 24 h after IVT. A modified Rankin scale (mRS) $\leq$1 at 3 months was considered as a favorable outcome, and an mRS $\geq$2 at 3 months was an unfavorable outcome.

Results: Two hundred thirty-three acute mild ischemic stroke patients (all patients underwent MRI and DWI restriction) with IVT were included in this study. Thirty-one patients experienced END, and 57 patients experienced an unfavorable outcome at 3 months. With multivariate analysis, END was associated with an elevated baseline systolic blood pressure (SBP) (OR = 1.324, 95% CI, 1.053–1.664, $p = 0.016$) and coronary heart disease (OR = 4.933, 95% CI, 1.249–19.482, $p = 0.023$). An unfavorable outcome at 3 months after IVT was independently associated with a baseline elevated SBP (OR = 1.213, 95% CI, 1.005–1.465, $p = 0.045$), baseline NIHSS (OR = 1.515, 95% CI, 1.186–1.935, $p = 0.001$), prior hyperlipemia (OR = 3.065, 95% CI, 1.107–8.482, $p = 0.031$), cardioembolic stroke (OR = 0.323, 95% CI, 0.120–0.871, $p = 0.025$), and END at 24 h (OR = 4.531, 95% CI, 1.950–10.533, $p < 0.001$) in mild ischemic stroke patients.

Conclusion: In mild ischemic stroke patients with IVT, an elevated baseline SBP and coronary heart disease were associated with END. The elevated baseline SBP, baseline NIHSS, a history of prior hyperlipemia, cardioembolic stroke, and END at 24 h after IVT were useful in predicting an unfavorable outcome at 3 months.

Keywords: mild ischemic stroke, thrombolysis, early neurological deterioration, unfavorable outcome, systolic blood pressure (SBP)

INTRODUCTION

Intravenous thrombolysis (IVT) has been proven to be an effective treatment for acute ischemic stroke patients when it is given within 4.5 h of stroke onset (1). More than half of acute ischemic stroke patients exhibit mild symptoms, including neurological deficits (2, 3). Currently, mild ischemic stroke has no uniform definition, but most studies define mild ischemic stroke as presenting a National Institute of Health Stroke Score (NIHSS) $\leq$5 (4, 5). Due to the risk of hemorrhagic transformation and not increasing the likelihood of a favorable outcome at 90 days (5), IVT is not recommended for mild non-disabled ischemic stroke patients within 4.5 h (6). However, approximately one-third of mild ischemic stroke patients without IVT have unfavorable outcome due to mild stroke (7). Some non-disabled patients who did not receive IVT in the appropriate time frame go on to develop early neurological deterioration (END) (8). Currently, there are no better-accepted treatments that can be given to lengthen the time window of IVT. However, previous research has found that mild ischemic stroke patients could be benefit from IVT (9–11). Although thrombolysis might increase the risk of hemorrhagic transformation, but its occurrence was statically insignificant and did not increase the mortality rate (9, 11). Therefore, this study was designed to identify factors that impacted END and the functional outcome of mild ischemic stroke patients after IVT, which could be useful in predicting a possible unfavorable outcome at 3 months.

METHODS

Patient Selection

The study was carried out between July 2017 and December 2020 in Shaoxing People's Hospital (Shaoxing Hospital, Zhejiang University School of Medicine). Initially, there were 282 acute, mild, and ischemic stroke patients receiving intravenous recombinant tissue plasminogen activator (alteplase 0.9 mg/kg up to a maximum of 90 mg, 10% of the total dosage as a bolus and the rest over 1 h) therapy in our hospital. We eliminated 49 patients (25 patients were stroke mimic, 2 patients were newly diagnosed lung cancer, 18 patients lacked follow-up data, and 4 patients lacked MRI images). Finally, 233 patients were enrolled in this study. Patients were selected using the following criteria: (1) is aged >18 years; (2) diagnosed with acute ischemic stroke (AIS) according to clinical symptoms, MRI, and DWI restriction; (3) had a baseline NIHSS $\leq$5; (4) received IVT within 4.5 h of AIS onset; and (5) underwent CT scans at 24 h after IVT. The exclusion criteria included the following: (1) the presence of existing contraindications for intravenous thrombolysis according to the standard IVT guidelines (12); (2) prior stroke or the presence of other diseases that resulted in a baseline mRS $\geq$1; (3) a long-term life expectancy of 3 months or less; (4) necessity of daily life need care because of other chronic system diseases, such as chronic heart failure, chronic obstructive pulmonary disease, and end-stage renal disease; (5) limb fracture affecting movement; and (6) lack of follow-up data.

Data Collection

A neurologist who was blinded to the patient's outcome reviewed the medical records to collect the following data: demographic characteristics, baseline NIHSS, baseline SBP, baseline DBP, history of smoking, hypertension, atrial fibrillation, coronary heart disease, diabetes, prior hyperlipemia, and prior stroke or transient ischemic attack (TIA). A history of prior hyperlipemia disease included hypertriglyceridemia and hypercholesterolemia. Coronary heart disease is defined as a patient having a history of acute coronary syndrome or angina pectoralis. Acute ischemic stroke subtypes were determined by using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (13). This study was approved by the Shaoxing Hospital, Zhejiang University School of Medicine Sciences Ethics Committee.

Neurological Outcomes

END was defined as an NIHSS at 24 h after IVT that was increased $\geq$1 over the baseline (14). There was a neurologist in charge of the follow-up. The mRS score at 3 months was all collected by phone. An mRS score $\leq$1 at 3 months was determined to be a favorable outcome after IVT, and an mRS score $\geq$2 at 3 months was an unfavorable outcome. Hemorrhage transformation was classified as hemorrhagic infarction types I and II and parenchymal hemorrhage types I and II according to the definition provided by the European Cooperative Acute Stroke Study (ECASS) (15). Symptomatic intracerebral hemorrhage (SICH) was defined as the presence of a neurological decline attributed to parenchymal hemorrhage type II with an NIHSS score increase of $\geq$4 after IVT (16).

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). Fisher's exact test was used to compare the dichotomous variables between groups, while the Mann–Whitney *U*-test was used for the continuous variables. Variables with a two-tailed *p*-value of <0.1 in univariate regression analyses were included in the binary multivariate logistic regression model to determine the independent risk factors of END at 24 h and functional outcome at 3 months after IVT. A two-tailed *p*-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Two hundred thirty-three mild AIS with IVT were included. No patients underwent thrombectomy. The mean age (±SD) was 60.08 ± 10.87 years. Eighty-four (36.1%) patients were female. The median baseline NIHSS was 2 (interquartile range, IQR, 1–4) among all patients: 31 (13.3%) patients experienced END, 9 (3.9%) patients experienced hemorrhagic transformation, and 2 (0.9%) of the nine exhibited SICH. Nine patients experienced stroke recurrence in 3 months. Fifty-seven (24.5%) patients experienced an unfavorable outcome at 3 months after

TABLE 1 | Characteristics of mild acute ischemic stroke patients with IVT with or without END at 24 h.

	END at 24 h *N* = 31	Non-END at 24 h *N* = 202	*p*-value
Age, IQR	68 (63–73)	67 (58–74)	0.979
Female, *N* (%)	14 (45.2)	70 (34.7)	0.315
ONT, (mean ± SD)	183.65 ± 66.64	178.60 ± 81.91	0.541
Baseline NIHSS, IQR	3 (2–5)	3 (2–4)	0.246
Baseline SBP, mmHg	157.19 ± 18.54	148.47 ± 18.15	**0.007**
Baseline DBP, mmHg	87.74 ± 8.53	84.28 ± 11.45	0.059
Smoking, *N* (%)	8 (26.7)	53 (27.3)	1.000
Hypertension, *N* (%)	22 (71)	138 (68.3)	0.838
Atrial fibrillation, *N* (%)	6 (19.4)	29 (14.4)	0.429
Coronary heart disease, *N* (%)	4 (12.9)	6 (3.0)	**0.031**
Diabetes, *N* (%)	7 (22.6)	45 (22.3)	1.000
Hyperlipemia, *N* (%)	2 (6.5)	20 (9.9)	0.747
Prior stroke or TIA, *N* (%)	4 (12.9)	36 (17.9)	0.615
TOAST criteria			
Large artery atherosclerosis, *N* (%)	11 (35.5)	52 (26.2)	0.286
Cardioembolic, *N* (%)	6 (19.4)	42 (20.8)	1.000
Lacunar, *N* (%)	9 (29.0)	70 (34.7)	0.684
Undetermined cause, *N* (%)	4 (12.9)	34 (16.8)	0.795
Other etiology, *N* (%)	1 (3.2)	3 (1.5)	0.437
Hemorrhagic transformation, *N* (%)	4(12.9)	5(2.5)	**0.020**
HI-I, *N* (%)	1 (3.2)	4 (2.0)	
HI-II, *N* (%)	0 (0)	1 (0.5)	
PH-I, *N* (%)	1 (3.2)	0 (0)	
PH-II, *N* (%)	2 (6.5)	0 (0)	
Symptomatic intracerebral hemorrhage, *N* (%)	2 (6.5)	0 (0)	**0.017**
3 mRS ≥ 2, *N* (%)	17 (54.8)	40 (19.8)	**<0.001**

SBP, systolic blood pressure; DBP, diastolic blood pressure; HI-I, hemorrhagic infarction type; HI-II, hemorrhagic infarction type II; PH-I, parenchymal hemorrhage type I; PH-II, parenchymal hemorrhage type II.

IVT. The demographics and baseline characteristics are shown in **Table 1**.

Early Neurological Deterioration

After univariate analysis is carried out, the mild AIS patients with END exhibited a higher baseline SBP (157.19 ± 18.54 vs. 148.47 ± 18.15, $p = 0.007$) and a higher baseline DBP (87.74 ± 8.53 vs. 84.28 ± 11.45, $p = 0.059$) compared with non-END patients. Moreover, the mild AIS patients with END presented a higher rate of coronary heart disease compared with the non-END group (12.9% vs. 3.0%, $p = 0.031$). Baseline SBP, DBP, and coronary heart disease were included in the binary logistic multivariate analysis. The results revealed that an elevated baseline SBP (OR = 1.324, 95% CI, 1.053–1.664, $p = 0.016$) and coronary heart disease (OR = 4.933, 95% CI, 1.249–19.482, $p = 0.023$) were independently associated with END at 24 h after IVT (**Table 2**).

TABLE 2 | Binary logistic analysis of risk factors of END at 24 h after IVT.

	OR	95% CI	*p*
Baseline SBP	1.324	1.053–1.664	**0.016**
Baseline DBP	1.107	0.727–1.684	0.636
Coronary heart disease	4.933	1.249–19.482	**0.023**

Neurologic Outcome

In this study, 57 (24.5%) mild AIS patients experienced an unfavorable outcome. Two patients experienced SICH and had an unfavorable outcome at 3 months. Based on univariate analysis, we observed that patients with unfavorable outcomes at 3 months had a higher baseline NIHSS (IQR, 3 (2–4) vs. 3 (2–5), $p = 0.001$), a higher baseline SBP (154.68 ± 17.27 vs. 147.99 ± 18.51, $p = 0.016$), and increased END (29.8% vs. 8.0%, $p < 0.001$) after IVT. In the TOAST classification, the unfavorable outcome group had a higher rate of large artery atherosclerosis (40.4% vs. 23.3%, $p = 0.017$) and a lower rate of cardioembolic stroke (10.5 vs. 23.9%, $p = 0.037$). However, there was no difference in the incidence of hemorrhagic transformation (5.3 vs. 3.4%, $p = 0.692$) between the two groups (**Table 3**). The variables with *p*-values M < 0.1 in the univariate analysis underwent binary logistic multivariate analysis. After large artery atherosclerosis of stroke and the presence of diabetes were adjusted for, the results demonstrated that the baseline elevated SBP (OR = 1.213, 95% CI, 1.005–1.465, $p = 0.045$), baseline NIHSS (OR = 1.515, 95% CI, 1.186–1.935, $p = 0.001$), prior hyperlipemia (OR = 3.065, 95% CI, 1.107–8.482, $p = 0.031$), cardioembolic stroke (OR = 0.323, 95% CI, 0.120–0.871, $p = 0.025$), and END at 24 h (OR = 4.531, 95% CI, 1.950–10.533, $p < 0.001$) after IVT were independently associated with unfavorable outcomes at 3 months in mild AIS patients (**Table 4**). SICH could not be included in the logistic analysis due to the small number of patients.

DISCUSSION

In this study, we demonstrated that an elevated baseline SBP and coronary heart disease were independently associated with END. In addition, an elevated baseline SBP, baseline NIHSS, prior hyperlipemia, cardioembolic stroke, and END at 24 h after IVT were useful for predicting an unfavorable outcome in mild AIS patients.

An elevated baseline SBP was an independent predictor of END and unfavorable outcomes at 3 months after IVT in mild AIS patients. After the occurrence of ischemic stroke, SBP might remain elevated to maintain constant cerebral perfusion (17). Current guidelines (12) recommend that blood pressure should be controlled (<180/105 mmHg) in the first 24 h after IVT. However, the relationship between blood pressure and functional outcome exhibits a U-shape (18, 19). Both high SBP and low SBP are correlated with unfavorable outcomes in ischemic stroke patients (18, 20, 21). On one hand, lower SBP might lead to unfavorable outcome by reducing cerebral hemodynamic reserve

TABLE 3 | Characteristics of mild acute ischemic stroke patients with IVT with or without favorable outcomes at 3 months.

	Favorable outcome at 3 months *N* = 176	Unfavorable outcome at 3 months *N* = 57	*p*-value
Age, IQR	66 (58–73)	69 (62–75)	0.107
Female, *N* (%)	61 (34.7)	23 (40.4)	0.433
ONT, (mean ± SD)	174.82 ± 80.27	193.04 ± 78.00	0.131
Baseline NIHSS, IQR	3 (2–4)	3 (2–5)	**0.001**
Baseline SBP, mmHg	147.99 ± 18.51	154.68 ± 17.27	**0.016**
Baseline DBP, mmHg	85.10 ± 11.18	83.61 ± 11.09	0.463
Smoking, *N* (%)	45 (26.9)	16 (28.1)	0.865
Hypertension, *N* (%)	118 (67.0)	42 (73.7)	0.413
Atrial fibrillation, *N* (%)	29 (16.5)	6 (10.5)	0.393
Coronary heart disease, *N* (%)	7 (4.0)	3 (5.3)	0.710
Diabetes, *N* (%)	34 (19.3)	18 (31.6)	**0.067**
Hyperlipemia, *N* (%)	13 (7.4)	9 (15.8)	**0.070**
Prior stroke or TIA, *N* (%)	27 (15.3)	13 (23.2)	0.222
TOAST criteria			
Large artery atherosclerosis, *N* (%)	41 (23.3)	23 (40.4)	**0.017**
Cardioembolic, *N* (%)	42 (23.9)	6 (10.5)	**0.037**
Lacunar, *N* (%)	60 (34.1)	19 (33.3)	1.000
Undetermined cause, *N* (%)	30 (17.0)	8 (14.0)	0.683
Other etiology, *N* (%)	3 1.7)	1 (1.8)	1.000
Hemorrhagic transformation, *N* (%)	6 (3.4)	3 (5.3)	0.692
HI-I, *N* (%)	5 (2.8)	0 (0)	
HI-II, *N* (%)	1 (0.6)	0 (0)	
PH-I, *N* (%)	0 (0)	1 (1.8)	
PH-II, *N* (%)	0 (0)	2 (3.5)	
Symptomatic intracerebral hemorrhage, *N* (%)	0 (0)	2 (3.5)	0.059
END at 24 h, *N* (%)	14 (8.0)	17 (29.8)	**<0.001**
Length of stay in hospital, IQR, day	8 (7–12)	12 (9–17)	**<0.001**

SBP, systolic blood pressure; DBP, diastolic blood pressure; HI-I, hemorrhagic infarction type; HI-II, hemorrhagic infarction type II; PH-I, parenchymal hemorrhage type I; PH-II, parenchymal hemorrhage type II.

TABLE 4 | Binary logistic analysis of risk factors of functional outcome at 3 months after IVT.

	OR	95% CI	*p*
Baseline SBP	1.213	1.005–1.465	**0.045**
Baseline NIHSS	1.515	1.186–1.935	**0.001**
Diabetes	1.551	0.728–3.305	0.256
Hyperlipemia	3.065	1.107–8.482	**0.031**
Large artery atherosclerosis	1.543	0.737–3.231	0.250
Cardioembolic	0.323	0.120–0.871	**0.025**
END at 24 h	4.531	1.950–10.533	**<0.001**

and cerebral hypoperfusion (22). On the other hand, higher SBP might be associated with unfavorable outcome due to cerebral edema, stroke recurrence, and hemorrhagic transformation (18). Yan et al. found that when the SBP was maintained within a range of 140–149 mmHg for the first 24 h after IVT, neurological deterioration was the lowest (19). In our study, the mean SBP in non-END patients was 148.47 ± 18.15 mmHg, which fell within the recommended 140–149 mmHg range.

The mechanism by which SBP contributes to END is unclear. Yan He et al. found that blood pressure was directly proportional to serum levels of MMP-9 and AQP-4 at 24 h after thrombolysis (19). Thus, they presumed that the SBP that occurred with END might be associated with oxidative stress-induced blood–brain barrier disruption and AQP-4 upregulation (19). Also, high SBP could increase the risk of cerebral edema, hemorrhagic transformation, and stroke recurrence, which are associated with unfavorable outcomes in ischemic stroke patients. We observed that END in mild AIS patients directly impacted the unfavorable outcome at 3 months after IVT. This result was consistent with a prior study (23).

Coronary heart disease is defined as the patient having a history of acute coronary syndrome or angina pectoralis. It is well known that ischemic stroke and coronary heart diseases have the same risk factors. It has been reported that coronary heart disease is correlated with an unfavorable outcome in AIS patients (24). Our study demonstrated that coronary heart disease was an independent predictor of END after IVT in mild AIS patients, but the underlying mechanism is unknown. In fact, there was no difference in ejection fraction of coronary heart disease patients between the END group and non-END group (66.00 ± 7.83% vs. 65.17 ± 4.54%, $p = 0.967$). It is notable that we observed 10 patients with coronary heart disease that included four (12.9%) in the END group and six (3.0%) in the non-END group. In the END group, three of the four coronary heart disease patients concurrently experienced cerebral vascular stenosis. Conversely, no patient experienced cerebral vascular stenosis in the other group. Therefore, we proposed that coronary heart disease associated with END was possibly related to the fact that the patients with coronary heart disease also had a high occurrence of cerebral vascular stenosis. This possibility could be confirmed in a future study.

In this study, the incidence of hemorrhagic transformation was 3.9% (9/233), and SICH was 0.9% (2/233). We found that hemorrhagic transformation did not affect the occurrence of an unfavorable outcome at 3 months after IVT in mild AIS patients. Although two SICH patients experienced an unfavorable outcome at 3 months, the incidence of SICH in mild AIS patients with IVT was not higher than other ischemic stroke patients with IVT. Previous studies demonstrated that IVT did not increase the risk of SICH in mild ischemic stroke patients (25).

Baseline NIHSS has been determined to be an independent predictor of unfavorable outcomes in mild ischemic stroke after IVT (26, 27), and the result in this study was the same as in these prior studies. For cardioembolic stroke, we found those patients had higher rate of favorable outcomes at 3

months after IVT. Similar studies were published (28, 29). It seemed that IVT was more effective in cardioembolic stroke. This result might be associated with the composition of the thrombus. The thrombus of cardioembolic stroke contains more fibrin and platelet, but other thrombi contain more red blood cells (28). Meanwhile, rt-PA has high banding affinity for fibrin and might be more prone to result in thrombus dissolution (28).

We also observed that hyperlipemia was associated with unfavorable outcomes in mild AIS patients. Hypertriglyceridemia and hypercholesterolemia were both included in hyperlipemia. A previous study confirmed that hypertriglyceridemia might be a predictor of END (30). However, high LDC-C early in the course of stroke has been associated with a favorable outcome at 3 months in mild ischemic stroke (31). The specific pathophysiological mechanism underlying this association remains unclear. Because of our retrospective design, we did not subdivide the patients with hypertriglyceridemia and hypercholesterolemia.

Our study is mainly limited by its retrospective design of single center. First, although we collected data using an established prospective stroke registry, a risk of selection bias is possible. Second, we found baseline SBP, baseline NIHSS, a history of prior hyperlipemia, cardioembolic stroke, and END at 24 h after IVT were associated with unfavorable outcome at 3 months in mild stroke patients. But our registry did not collect the outcome data of mild ischemic stroke patients without IVT. There might be other factors associated with unfavorable outcome of mild ischemic stroke patients without IVT, which will be collected and studied in our future work. Third, we found that coronary heart disease had a high occurrence of cerebral vascular stenosis and proposed that coronary heart disease associated with END was possibly related to this fact. But we have no complete data on large vessel stenosis of all included mild stroke patients. We could not get a conclusion on in this study on whether mild stroke patients with large vessel stenosis were more likely to experience END. This possibility could be confirmed in a future study that uses a larger sample size.

CONCLUSION

In this study, 24.5% of patients with mild ischemic stroke experienced an unfavorable outcome after IVT. The incidence of SICH was low (0.9%). Moreover, elevated baseline SBP was an independent predictor of END at 24 h and an unfavorable outcome at 3 months after IVT. Thus, blood pressure might be rigorously controlled for mild ischemic stroke patients during and after IVT. This conclusion needs to be confirmed with a larger sample size and the inclusion of additional blood pressure-related parameters in future work.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Ethics Committee of Shaoxing People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HT was responsible for setting this topic, designing protocol, statistical analysis, and writing papers. SY was responsible for designing protocol and statistical analysis. CW was responsible for data collection and assessing hemorrhagic transformation. YZ was responsible for data collection and follow-up work. All authors contributed to the article and approved the submitted version.

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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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Impact of Diabetes on Platelet Function in Acute Ischemic Stroke Patients Taking Dual Antiplatelet Therapy

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Objectives: Diabetes mellitus (DM) is a significant risk factor for ischemic stroke and associated with platelet reactivity. We aim to evaluate the effect of DM on platelet function in acute ischemic stroke patients taking dual antiplatelet therapy (DAPT).

Methods: We consecutively included patients with acute ischemic stroke taking DAPT. Platelet function was assessed by thromboelastography and the arachidonic acid (AA) or adenosine diphosphate (ADP) induced platelet inhibition rate were used to confirmed the high-residual on-treatment platelet reactivity (HRPR) to aspirin or clopidogrel. We classified patients into DM and non-DM groups. The association between DM and platelet function was assessed and the confounding factors were adjusted by propensity score matching (PSM) analysis. The independent risk factors of HRPR were determined by multivariate logistic regression analysis.

Results: A total of 1,071 acute ischemic stroke patients, 712 in the non-DM group and 359 in the DM group, were included. Patients with DM had a significantly higher maximum amplitude (63.0 vs. 62.0 mm, $P < 0.01$), ADP-induced clot strength (34.6 vs. 30.3 mm, $P < 0.01$) and clopidogrel HRPR rate (22.6% vs. 17.3%, $P = 0.038$) than those without DM. Among 662 patients after PSM, the maximum amplitude (63.1 vs. 62.5 mm, $P = 0.032$), ADP-induced clot strength (34.6 vs. 29.3 mm, $P < 0.01$) and clopidogrel HRPR rate (23.0% vs. 15.7%, $P = 0.018$) is still higher in the DM group. DM was an independent factor of clopidogrel HRPR (OR = 1.48, 95% CI: 1.03–2.07, $P < 0.05$).

Conclusions: In acute ischemic stroke patients taking DAPT, DM is associated with increased platelet reactivity and higher prevalence of clopidogrel HRPR.

Keywords: diabetes mellitus, dual antiplatelet therapy (DAPT), ischemic stroke, platelet function, thromboelastography (TEG)

INTRODUCTION

It is well-known that diabetes mellitus (DM) could increase the risk for cerebrovascular diseases. It has been reported that 25–45% of ischemic stroke patients have confirmed DM (1–3). Previous studies have suggested that DM substantially increases the risk for first ischemic stroke (4–6). In addition, DM is associated with increased mortality (7) and recurrence rate of ischemic stroke (8–10).

In the acute treatment and secondary prevention of ischemic stroke, aspirin and clopidogrel are the most widely used antiplatelet drugs in clinical practice. They not only significantly reduce the mortality and disability rate, but also effectively prevent stroke recurrence (11). However, 10–20% of ischemic stroke patients will have new vascular events in the first 3 months despite have received antiplatelet therapy (12–14). One possible reason is the high residual on-treatment platelet reactivity (HRPR), which means the reduced platelet inhibition rate and absence of antiplatelet effect (15).

Studies have found that HRPR may increase the prevalence of ischemic events in coronary heart disease and diabetes patients (16, 17), which may be due to generally higher aggregation activity of platelet and less responsiveness to antiplatelet drugs (18) in patients with DM. Most previous studies on platelet function have focused on individuals with cardiovascular disease. However, studies on the relationship between DM and platelet function in acute ischemic stroke patients taking dual antiplatelet therapy (DAPT) remain scarce. The present study aimed to evaluate whether DM had an effect on platelet function in acute ischemic stroke patients taking DAPT.

METHODS

Study Population

This study retrospectively included consecutive patients with acute ischemic stroke hospitalized in the Department of Neurology, Tongji Hospital, from September 2013 and May 2019. The inclusion criteria included: (1) ≥18 years old; (2) diagnosis of acute ischemic stroke on the basis of clinical symptoms and magnetic resonance imaging or computer tomography; (3) having received treatment of clopidogrel (75 mg/day) plus aspirin (100 mg/day) without a loading dose for at least 7 days before platelet function testing. Patients would be excluded if: (1) having medications within the past 3 months affecting blood coagulation function, such as cilostazol, warfarin, dabigatran, heparin, and factor Xa inhibitors (such as rivaroxaban); (2) a history of malignant tumors, digestive diseases, or severe liver, kidney, or blood-related diseases.

This study has been approved by the Tongji Hospital Ethics Committee (No. TJ-IRB20210107). The requirement of informed consent was waived since all data analyzed in this study were anonymized and cannot do any harm to the subjects.

Clinical Assessments

The demographic and clinical information included: age, sex, smoking (defined as a history of smoking ≥1 cigarette per day for 1 year or more), alcohol intake (defined as weekly alcohol intake exceeding 200 g for 1 year or more), a history of ischemic stroke/transient ischemic attack, hypertension, hyperlipidemia, coronary heart disease (defined as a history of myocardial infarction or angina pectoris) and DM (defined as a HbA1c ≥ 6.5%, or a 2 h plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test, or self-reported history of DM) (8, 19, 20). Laboratory test were conducted within 24 h of admission, included creatinine, eGFR, platelet indexes, fasting glucose, and glycosylated hemoglobin A1c (HbA1c). These data were obtained from the hospital medical records.

Measurement of Platelet Function

The platelet function was assessed using a thromboelastography (TEG) Analyzer 5000 (Haemonetics Corporation, USA) with assays taken within 1 h following blood sample collection. Peripheral venous whole blood was collected by venipuncture in vacutainer tubes containing 3.2% sodium citrate and sodium heparin (Becton–Dickinson, San Jose, CA) at least 7 days after patients had received DAPT and 12 h after the last dose in our study. The TEG was performed using standard methods in hospital laboratories according to manufacturers' instructions. Four channels were used to detect the effects of antiplatelet therapy with arachidonic acid (AA) and adenosine diphosphate (ADP) activators at 37°C. The maximum amplitude (MA) was designated as the maximum intensity obtained from a clot, which represented the maximum platelet function that observed in a blood sample. MA_{ADP} represented the ADP-induced clot strength, MA_{AA} was the AA-induced clot strength, MA_{fibrin} was the activator-induced clot strength (measurement of fibrin contribution), and $MA_{thrombin}$ was the thrombin-induced clot strength. The platelet inhibition rate induced by AA or ADP was calculated by computer software according to the following formula: Inhibition rate (%) = $[(MA_{thrombin} - MA_{ADP}$ or $MA_{AA})/(MA_{thrombin} - MA_{fibrin})] \times 100\%$, which represented the responsiveness to aspirin or clopidogrel. AA% < 50% can be considered as aspirin HRPR and ADP% < 30% or MA_{ADP} > 47 mm can be considered as clopidogrel HRPR (21, 22).

Statistical Analysis

Statistical analysis was performed using IBM SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as percentages and frequencies, whereas continuous data were presented as the mean ± the standard deviation (SD), or median [interquartile range] for data having a skewed distribution. To detect deviations from a normal distribution the Kolmogorov–Smirnov test was used. Comparisons between groups were evaluated using two-sided *t*-tests, the Mann–Whitney U test, or the Chi-square test according to the respective distribution. A *P*-value < 0.05 was considered statistically significant.

We classified all patients into DM and non-DM groups. Propensity score matching (PSM) analysis applied logistic regression to balance the distribution of possible confounding variables between groups, including age, hypertension, dyslipidemia, and coronary heart disease. Patients were matched between the groups using the nearest logit of the propensity score and a PSM ratio of 1:1. For further analysis,

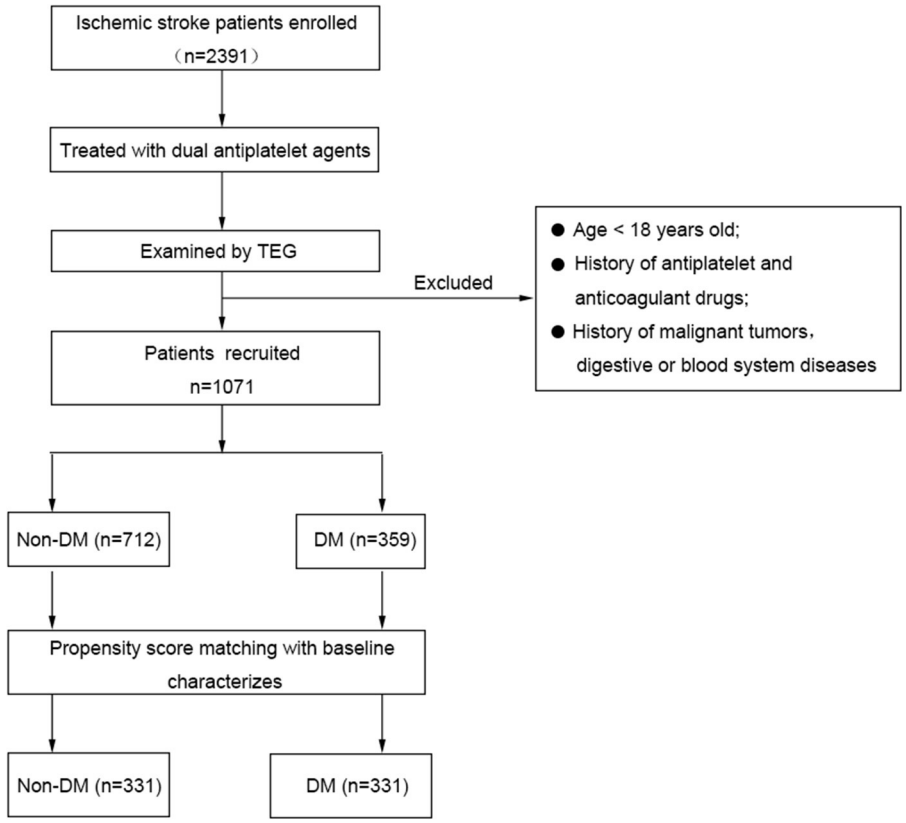

FIGURE 1 | Flowchart of patient recruitment.

patients were classified into HRPR and non-HRPR groups with respect to clopidogrel responsiveness. Different variables between the two groups ($P < 0.05$) were conducted multivariate logistic regression analysis to identify independent risk factors of clopidogrel HRPR. The results were expressed as odd ratios (ORs) with 95% confidence intervals (95% CI).

RESULTS

Demographics and Clinical Characteristics

We have included 1,071 patients with acute ischemic stroke in this study (**Figure 1**). The demographic and clinical data of DM group ($n = 712$) and non-DM group ($n = 359$) are presented in **Table 1**. No statistical differences were found in sex, cerebrovascular risk factors (smoking, alcohol intake, history of stroke/TIA), and platelet indices between the two groups. In addition, age, prevalence of cerebrovascular risk factors (hypertension, hyperlipidemia, coronary heart disease), creatinine, fasting glucose and HbA1c were significantly different between the DM and non-DM group ($P < 0.05$).

To reduce differences of baseline characteristics, the PSM was further analyzed to balance the distribution of variables between the groups (**Table 1**). After PSM, the total number of patients in each study group was 331. There were no significant differences in baseline characteristics between the two groups, except for creatinine, fasting glucose and HbA1c.

The Impact of DM on Platelet Function

Before PSM, we found that the median of MA (63.0 vs. 62.0 mm, $P < 0.05$) and MA_{ADP} (34.6 vs. 30.3 mm, $P < 0.05$) was significantly higher in the DM group and the ADP% (55.7% vs. 60.3%, $P < 0.05$) was significantly lower in the DM group compared with the non-DM group. No significant differences in the median levels of AA% were observed between the two groups (96.0% vs. 97.0%, $P > 0.05$).

After PSM, the difference in the median levels of MA (63.1 vs. 62.5 mm, $P < 0.05$), MA_{ADP} (34.6 vs. 29.3 mm, $P < 0.05$) and ADP% (55.8 vs. 67.4%, $P < 0.05$) between the DM and non-DM group (**Table 2**) remained. However, the median levels of AA% were significantly higher in the DM-group than those without (96.1% vs. 93.0%, $P < 0.05$).

Among all study populations 19.0% of patients exhibited clopidogrel HRPR. The prevalence rate of clopidogrel HRPR was significantly lower in the non-DM group compared with the DM group (17.3% vs. 22.6%, $P < 0.05$), but no difference in aspirin HRPR was found between the two groups (**Table 2**). The results were the same before and after PSM.

TABLE 1 | Patients' baseline characteristics before and after PS matching.

Characteristics	Before PS matching			After PS matching		
	Non-DM ($n = 712$)	DM ($n = 359$)	*P*-value	Non-DM ($n = 331$)	DM ($n = 331$)	*P*-value
Age (*y*)	56.0 [50.0–65.0]	60.0 [53.0–65.0]	**<0.001**	59.0 [53.0–65.0]	60.0 [53.0–65.0]	0.848
Male, *n* (%)	525 (73.7)	253 (70.5)	0.258	238 (71.9)	233 (70.4)	0.668
Smoking, *n* (%)	362 (50.8)	162 (45.1)	0.077	170 (51.4)	151 (45.6)	0.140
Alcohol intake, *n* (%)	302 (42.4)	140 (39.0)	0.283	145 (43.8)	129 (39.0)	0.207
Medical history, *n* (%)						
History of stroke/TIA	130 (18.3)	74 (20.6)	0.354	66 (19.9)	64 (19.3)	0.845
Hypertension	442 (62.1)	274 (76.3)	**<0.001**	253 (76.4)	253 (76.4)	1.000
Hyperlipidemia	58 (8.1)	58 (16.2)	**<0.001**	35 (10.6)	35 (10.6)	1.000
Coronary heart disease	48 (6.7)	46 (12.8)	**<0.001**	33 (10.0)	33 (10.0)	1.000
Laboratory data						
Creatinine (umol/L)	73.0 [64.0–85.0]	70.0 [59.0–83.0]	**0.008**	74.0 [64.0–86.0]	70.0 [59.0–83.0]	**0.004**
eGFR (ml/min/1.73 m^2)	94.6 [82.5–103.8]	94.6 [82.4–103.3]	0.719	91.0 [80.0–101.0]	95.0 [83.0–103.0]	0.049
Platelet count (*10^9/L)	213 [178–251]	210 [176–256]	0.530	212 [176–246]	213 [178–259]	0.377
PDW (fL)	13.1 [11.7–15.0]	13.3 [11.9–15.2]	0.197	13.0 [12.0–15.0]	13.0 [12.0–15.0]	0.235
MPV (L)	10.9 [10.1–11.7]	11.0 [10.3–11.8]	0.221	11.0 [10.0–12.0]	11.0 [10.0–12.0]	0.161
P-LCR (%)	32.2 [27.0–39.2]	33.2 [27.5–39.7]	0.213	32.0 [27.0–39.0]	33.0 [27.0–40.0]	0.162
Fasting glucose (mmol/L)	5.1 [4.8–5.5]	6.9 [5.6–8.8]	**<0.001**	5.0 [5.0–6.0]	7.0 [6.0–9.0]	**<0.001**
HbA1c (%)	5.6 [5.5–5.8]	7.3 [6.5–8.6]	**<0.001**	6.0 [5.0–6.0]	7.0 [7.0–9.0]	**<0.001**

Data given as n (%) or median [interquartile range]. PS, propensity score; DM, Diabetes mellitus; TIA, transient ischemic attack; eGFR, glomerular filtration rate; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio; HbAc1, glycosylated hemoglobin A1c. The bold values indicates P-value < 0.05.

TABLE 2 | Platelet reactivity, high residual on-treatment platelet reactivity (HRPR) before and after PS matching.

Variables	Before PS matching			After PS matching		
	Non-DM ($n = 712$)	DM ($n = 359$)	*P*-value	Non-DM ($n = 331$)	DM ($n = 331$)	*P*-value
MA (mm)	62.0 [58.1–65.6]	63.0 [59.8–66.3]	**0.002**	62.5 [58.5–65.5]	63.1 [59.9–63.1]	**0.032**
MA_{ADP} (mm)	30.3 [16.9–41.0]	34.6 [22.5–44.9]	**0.001**	29.3 [14.7–40.4]	34.6 [22.6–45.0]	**<0.001**
ADP% (%)	60.3 [39.9–84.3]	55.7 [36.7–80.1]	**0.039**	67.4 [42.2–87.1]	55.8 [36.7–80.2]	**0.004**
AA% (%)	97.0 [82.8–100]	96.0 [80.0–100]	0.306	93.0 [69.8–99.5]	96.1 [78.0–100.0]	**0.011**
Clopidogrel HRPR, *n* (%)	123 (17.3)	81 (22.6)	**0.038**	52 (15.7)	76 (23.0)	**0.018**
Aspirin HRPR, *n* (%)	89 (12.6)	43 (12.2)	0.818	51 (15.4)	41 (12.4)	0.268

Data given as n (%) or median [interquartile range]. PS, propensity score; DM, Diabetes mellitus; MA, maximum amplitude; MA_{ADP}, ADP-induced platelet-fibrin clot maximum amplitude; ADP%, inhibition rate of adenosine diphosphate (ADP); AA%, inhibition rate of arachidonic acid (AA); HRPR: high residual on-treatment platelet reactivity. The bold values indicates P-value < 0.05.

Risk Factors of Clopidogrel HRPR

Previous studies have demonstrated that clopidogrel HRPR is affected by many factors. Accordingly, we classified the patients into two groups (non-HRPR and HRPR). The demographic and clinical data of the two groups were compared. Age, sex, smoking, alcohol intake, DM, creatinine and HbA1c were significantly different between the groups (**Table 3**). After adjustment for potential confounders (age, sex, smoking, alcohol intake, creatinine and HbA1c), the DM (OR = 1.48, 95% CI: 1.03–2.07, $P < 0.05$) remained independent of the clopidogrel HRPR.

DISCUSSION

In this study, we found that patients with DM had higher levels of MA, MA_{ADP} and lower levels of ADP%. The clopidogrel HRPR rate was also higher in DM group than non-DM group. Additionally, after adjustment for potential confounders, DM remained an independent risk factor of HRPR following clopidogrel therapy. These results suggested that in acute ischemic stroke patients taking DAPT, DM is associated not only with an increase of platelet reactivity but also with a low responsiveness to clopidogrel.

Although it is widely recognized that DM could influence the platelet reactivity in patients following percutaneous transluminal coronary intervention (23, 24), the data examining the DM influences on platelet function in acute ischemic stroke patients taking DAPT have been sparse. Previous studies have found that in ischemic stroke patients receiving clopidogrel (75 mg) daily for 1 week, clopidogrel resistance is associated with DM (25). In a study involving 237 patients following recent

TABLE 3 | Risk factors for clopidogrel high residual on-treatment platelet reactivity (clopidogrel HRPR) in all patients.

Characteristics	All patients		
	Non-HRPR ($n = 867$)	HRPR ($n = 204$)	*P*-value
Age (*y*)	57.0 [50.0–65.0]	60.0 [53.0–66.0]	**<0.001**
Male, *n* (%)	661 (76.2)	117 (57.4)	**<0.001**
Smoking, *n* (%)	449 (51.8)	75 (36.8)	**<0.001**
Alcohol intake, *n* (%)	374 (43.1)	68 (33.3)	**0.001**
Medical history, *n* (%)			
History of stroke/TIA	158 (18.2)	46 (22.5)	0.157
Hypertension	577 (66.6)	139 (68.1)	0.665
Diabetes mellitus	278 (32.1)	81 (39.7)	**0.038**
Hyperlipidemia	88 (10.1)	28 (13.7)	0.139
Coronary heart disease	70 (8.1)	24 (11.8)	0.094
Laboratory data			
Creatinine (umol/L)	73.0 [63.0–84.3]	70.0 [57.0–84.0]	**0.008**
eGFR (ml/min/1.73 m^2)	94.8 [83.0–104.4]	94.3 [81.3–102.4]	0.719
Platelet count (*10^9/L)	213 [177–253]	210 [177–250]	0.530
PDW (fL)	13.2 [11.8–13.2]	13.2 [11.9–14.8]	0.197
MPV (L)	10.9 [10.2–11.7]	11.0 [10.3–11.7]	0.221
P-LCR (%)	32.5 [27.8–39.6]	33.0 [27.7–38.7]	0.213
Fasting glucose (mmol/L)	5.3 [4.8–6.3]	5.4 [5.0–6.6]	0.853
HbA1c (%)	5.8 [5.5–6.5]	5.9 [5.6–6.9]	**<0.001**

Data given as n (%) or median [interquartile range]. HRPR: high residual on-treatment platelet reactivity; TIA, transient ischemic attack; eGFR, glomerular filtration rate; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet large cell ratio; HbAc1, glycosylated hemoglobin A1c. The bold values indicates P-value < 0.05.

ischemic stroke or TIA treated receiving DAPT, DM was found to be associated with HRPR defined as aspirin resistance or clopidogrel resistance (26), which was different from our study. Our study provides further evidence that DM is associated with clopidogrel HRPR but not with aspirin HRPR.

In our study, AA-mediated platelet reactivity and aspirin HRPR were not affected by DM. The relationship between DM and aspirin HRPR remained controversies. As reported by previous studies (27), despite a high risk of aspirin HRPR in DM patients, DM itself does not contribute to a higher risk of aspirin HRPR and is more likely to be related to insulin resistance. In another study, it is found that aspirin resistance was more common among participants treated with low dose aspirin compared with higher doses (28). We speculate that different methods and time of platelet function tested, differences in aspirin dosing and frequency, and characteristics of the patient populations studied would affect the results of platelet function test. In future studies, we will try to explore which factors have effects on the relationship between DM and aspirin HRPR.

Studies have shown that clopidogrel HRPR is 4–30% in patients who use conventional doses of clopidogrel (29) and rises to 28% in ischemic cerebrovascular disease (30–32). Moreover, up to 40% of patients exhibiting clopidogrel HRPR may have recurring thrombotic events (33, 34). Therefore, the prediction and identification of patients with HRPR is a significant issue, as they may benefit from other antiplatelet drugs for the prevention of ischemic events and improvement of clinical outcomes. In our study, ADP-mediated platelet reactivity and clopidogrel HRPR was associated with DM. Therefore, the presence of DM should be considered in developing strategies for anti-platelet treatment of acute ischemic stroke patients.

The mechanism underlying increased platelet reactivity and clopidogrel HRPR in DM remains unclear. One possible reason is that chronic inflammatory reaction accompanies DM, which can upregulate the expression of cyclooxygenase-2 (COX-2) in vascular endothelial cells, monocyte-macrophages and other cells, leading to a significant increase in platelet activity (35, 36). In addition, DM patients have a high level of glycosylation of platelet surface membrane proteins, which competitively inhibits their acetylation and weakens the anti-platelet aggregation effect of clopidogrel (37).

Some limitations should be addressed. First, in this retrospective study, although most of the measured confounders were balanced between the two groups by PSM, bias may still exist. Confounding factors such as the use of proton pump inhibitors and the types of use, the use of statin, liver function or heterogeneity of metabolic genes (e.g., CYP2C19 gene type) may affect the responsiveness of clopidogrel drugs. However, we have included as many confounding factors as possible. Second, the degree of platelet aggregation and its response also depends on the type of diabetes. Type 2 diabetes has a higher ADP-induced aggregation rate than type 1, although due to the current sparsity of data conclusions are inconsistent. Third, our research subjects are Chinese patients, so generalizing these results to non-Asian patients may need careful interpretation and further research.

In conclusion, we found that in acute ischemic stroke patients taking DAPT, DM was associated with increased platelet activity and a greater prevalence of clopidogrel HRPR. Hence, it is necessary for us to stratify patients according to the presence or absence of DM and to choose a personalized treatment strategy to reduce the risk of ischemic events.

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 the Ethics Board of Tongji Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YG, YZ, and LW collected the clinical data. YG, DH, and JZ processed statistical data. YG, ZY, and HH drafted and

revised the manuscript. XL and HH designed and guided the 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.2021.712024/full#supplementary-material

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REVIEW
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Acute Ischemic Stroke With Mild Symptoms–To Thrombolyse or Not to Thrombolyse?

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Management of stroke with minor symptoms may represent a therapeutical dilemma as the hemorrhage risk of acute thrombolytic therapy may eventually outweigh the stroke severity. However, around 30% of patients presenting with minor stroke symptoms are ultimately left with disability. The objective of this review is to evaluate the current literature and evidence regarding the management of minor stroke, with a particular emphasis on the role of IV thrombolysis. Definition of minor stroke, pre-hospital recognition of minor stroke and stroke of unknown onset are discussed together with neuroimaging aspects and existing evidence for IV thrombolysis in minor strokes. Though current guidelines advise against the use of thrombolysis in those without clearly disabling symptoms due to a paucity of evidence, advanced imaging techniques may be able to identify those likely to benefit. Further research on this topic is ongoing.

Keywords: minor stroke, thrombolysis/thrombolytic agents, DAPT (dual antiplatelet therapy), very mild severity, rapidly improving stroke symptoms

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INTRODUCTION

A scenario known to every neurologist: a patient with acute onset mild stroke symptoms is admitted to the hospital. Imaging excludes an intracranial hemorrhage. Should intravenous thrombolysis be given? What are the risks and what are the benefits? It is frequently assumed that for those with mild stroke symptoms, risks of thrombolysis outweigh potential benefits. However, despite having "minor" symptoms, one-third of stroke patients were not functionally independent at 90 days when considered too mild to treat for intravenous thrombolysis (1–4). The purpose of this review is to provide an update on the acute treatment of patients with minor stroke with a special focus on intravenous thrombolysis.

DEFINITION OF STROKE WITH MILD SYMPTOMS

The definition of a stroke with mild symptoms or minor stroke (MS) is not standardized. Definitions are often based on the National Institutes of Health Stroke Scale (NIHSS) requiring a score ≤ 1 on every item (5) or utilize certain limits, mostly NIHSS ≤ 6 (6). Other definitions include whether symptoms are disabling or non-disabling, e.g., isolated aphasia or a severe distal paresis of the arm will give a low NIHSS score but are very disabling symptoms.

Further questions arise in differentiating minor stroke from a transient ischemic attack (TIA). In the acute phase, it is not possible to tell whether symptoms will persist or resolve spontaneously. The definition of a TIA from the American Heart and the American Stroke Association from 2002, "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction" (7) implies the use of an advanced imaging method to differentiate between TIA and minor stroke. This definition will build the basis for the 11th International Classification of Diseases (8). A majority of TIAs are of short duration, and once neurological deficits persist longer than 60 min they resolve in $< 15\%$ within 24 h (9). Furthermore, only 2% of patients that received placebo in the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study were free of symptoms 24 h later (10).

Those with rapidly improving symptoms are usually excluded from receiving thrombolysis therapy. Rapidly improving symptoms are those which improve spontaneously after presentation, but the definition is ambiguous. However, their outcomes are not predictable, with 30% of those with minor stroke or rapidly improving symptoms not fully functionally independent at hospital discharge (1).

DISABLING OR NON-DISABLING SYMPTOMS?

Determining whether symptoms are "disabling" or not is an important factor in the management of acute MS. A pooled metanalysis of nine trials could show that thrombolysis treatment resulted in a nearly 10% better chance of an excellent functional outcome after 3 months in patients with clearly disabling deficits such as aphasia or hemiparesis (11, 12).

For those with non-disabling symptoms, however, less evidence exists. Only one of these nine trials–the Third International Stroke Trial (IST-3) (13)–did not exclude patients with non-disabling symptoms.

IST-3 found evidence of benefit for thrombolysis for those presenting within 6 h of symptoms of stroke, however the benefit increased with increasing NIHSS and was less beneficial for those with minor stroke symptoms. Out of the 106 patients randomized with NIHSS ≤ 5, 60% showed a favorable outcome after 3 months.

Non-disabling symptoms include transient, fluctuating or persistent symptoms without unilateral motor weakness or language/speech disturbance (e.g., hemi-body sensory symptoms, monocular vision loss, binocular diplopia, hemifield vision loss, dysarthria, dysphagia, or ataxia). The PRISMS trial, a randomized controlled trial (RCT), showed that among patients with a low NIHSS and no disabling deficit, rtPA may not provide a benefit and might increase the risk of symptomatic intracranial hemorrhage (6). A clearly disabling deficit was operationally defined as a deficit that, if unchanged, would prevent the patient from performing basic activities of daily living (i.e., bathing, ambulating, toileting, hygiene, and eating) or returning to work. Judging how disabling a deficit will be in the future is challenging in the hyperacute stroke setting.

A further obstacle to thrombolysis treatment in minor stroke is that patients with minor stroke symptoms do not receive the priority of emergency medical services and in-hospital triage pathways leading to relevant time delays in onset-to-door and door-to-imaging times (14).

PREHOSPITAL RECOGNITION OF MINOR STROKE

The presentation of those with mild symptoms is frequently delayed compared to major stroke as it may not be recognized in the acute phase, leading to undertreatment. Public knowledge of stroke symptoms according to the FAST campaign is only about 70%, with the highest rate found in females and in the older and white population (15). Additionally, the mode of arrival at the hospital plays an important role. Patterns of emergency medical services pre-notification vary across countries. Data from a cohort study in New York showed that patients with minor stroke have longer door to needle times if the mode of arrival was without pre-notification (16).

The clinical significance of posterior circulation symptoms is often not recognized and, therefore, mostly remain undertreated in the acute phase. As in the NIHSS symptoms of the posterior circulation are underrepresented (e.g., vertigo, imbalance of gait), strokes in this territory are more likely to be defined as "minor" if a cut-off NIHSS score is used.

WAKE UP STROKE AND STROKE OF UNKNOWN ONSET

Those who wake up with stroke were traditionally excluded from revascularization therapies, due to unknown time of onset. Due to circadian rhythms there is diurnal variation in stroke onset, with a higher number occurring in the morning, which may be related to a surge in blood pressure (17). This suggests that the stroke may have occurred shortly before awakening, though the true time of onset is unknown. Modern imaging technologies, such as MRI DWI and FLAIR mismatch and or perfusion imaging, can help identify those who may benefit from thrombolysis or thrombectomy (18). The WAKE-UP trial showed that those with strokes evident from sleep with favorable MRI findings (DWI and FLAIR mismatch) who were treated with IV alteplase had significantly better functional outcomes, though more intracranial hemorrhages, than placebo at 90 days (19). The WAKE-UP trial included patients with all types of stroke severity, but the median NIHSS was of mild to moderate severity (median NIHSS 6, interquartile range 4–9). Analysis of patients with minor stroke has not been reported so far. Penumbral pattern identified using perfusion imaging is another recent radiological paradigm to identify those to benefit from reperfusion in the absence of onset time knowledge. Trials including ECASS4, EPITHET and EXTEND proved positively this concept for wake-up strokes and extended time window (4.5–9 h) thrombolysis (20).

Thrombolysis for wake-up stroke with minor symptoms has not been specifically studied. As mentioned previously, many stroke centers do not perform advanced imaging in those with NIHSS $\leq$ 6, and may be missing those with mismatch deficits or large vessel occlusions who could potentially benefit from thrombolysis. See also illustrative patient case in **Figure 2**.

CURRENT EVIDENCE OF USE OF THROMBOLYTIC AGENTS IN PATIENTS WITH MINOR STROKE

Current guidelines and recommendations state that for patients with acute minor disabling ischemic stroke of $<$ 4.5 h duration, intravenous thrombolysis with recombinant alteplase is recommended/ may be reasonable (21, 22). RCTs and observational studies addressing this topic so far showed promising results with a good functional outcome and a low complication rate (**Table 1**).

For patients with acute minor non-disabling ischemic stroke of $<$ 4.5 h duration, no intravenous thrombolysis is recommended. One exception may be patients with non-disabling symptoms and a large vessel occlusion. However, many acute stroke centers do not perform angiography for those with NIHSS $<$ 6 as part of their internal protocol, and many centers do not have access to advanced imaging such as CT perfusion. Therefore, an unknown proportion of stroke with minor symptoms who have large vessel occlusions amenable to intervention are being missed. TEMPO 1, a case series of 50 patients with mild symptoms and intracranial vessel occlusion, which showed that administration of tenecteplase-tissue-type plasminogen activator in minor stroke with intracranial occlusion is feasible and safe (24). Wang et al. found that intravenous thrombolysis benefits though with mild stroke symptoms (NIHSS $\leq$ 5) and large artery atherosclerosis, though not those who had a tandem proximal intracranial occlusion and cervical internal artery lesion (complete occlusion or severe stenosis $\geq$ 90%) (30). They found that LAA-type patients (as defined by TOAST criteria) had significantly favorable outcomes after treatment with thrombolysis compared to untreated patients, however no such benefits were observed in other stroke subtypes, such as cardioembolic, small vessel occlusion and undetermined. This suggests that CT or MR angiography might be helpful to choose patients for thrombolysis that present with stroke with minor symptoms.

ALTEPLASE OR TENECTEPLASE IN PATIENTS WITH MINOR STROKE

In recent years, the recombinant plasminogen activator tenecteplase is increasingly competing with the gold standard alteplase. The first publication of the EXTEND IA TNK study showed that higher perfusion rates and better clinical results can be achieved with tenecteplase in the 0.25 mg/kg dose than with alteplase in patients with an acute ischemic stroke (31). Tenecteplase was used as so-called bridging thrombolysis in the 4.5 h time window until the mechanical thrombectomy was performed. In addition, tenecteplase has advantages in handling, as it can be administered as single intravenous bolus and does not require a continuous infusion over 1 h, as alteplase does. The results of the EXTEND TNK study prompted the authors of the US guideline and the European Stroke Organization (ESO) to include tenecteplase in their recommendation as an alternative fibrinolytic (AHA/ASA Class IIb recommendation), although the AHA/ASA recommendation can also be considered to the 0.4 mg/kg dose for patients with less severe neurological impairments and if there are no large vessel occlusions (Level of Evidence: IIb) (22).

The second part of the EXTEND TNK study was recently published (32) which evaluated different doses of tenecteplase. The higher dose of tenecteplase (0.4 mg/kg) did not have any disadvantages in terms of safety: there were 16 and 22 death in the high and low dose groups, respectively. Symptomatic intracerebral hemorrhages 36 h after thrombolysis were numerically more frequent in the high dose group (7 vs. 2 patients), but four bleeding events in this group were associated with wire perforations during the endovascular procedure and were therefore not attributable to thrombolysis directly. The authors of the study report that the latter results are in contrast to an earlier study with the 0.40 mg/kg dose that was terminated prematurely for safety reasons, as some patients developed symptomatic intracranial hemorrhage. As a limitation, Campbell and colleagues point out that the study may not have been powered to reveal differences in efficacy. There was no restriction on clinical severity using NIHSS scores in these trials, but showed that probably a higher perfusion rate can be achieved with tenecteplase in patients with vessel occlusions. TEMPO 2 is an ongoing multicentre prospective randomized open label blinded-endpoint (PROBE) controlled trial of thrombolysis with low dose TEnecteplase vs. standard of care in Minor ischemic stroke with Proven acute symptomatic Occlusion (33). The hypothesis is that patients with mild (NIHSS $<=$ 5) or even non-disabling symptoms due to identifiable vessel occlusion will benefit from IVT as compared to standard antiplatelet therapy. Results are expected in 2024. In summary, currently no evidence exists that tenecteplase should be preferred to alteplase in acute treatment of minor stroke patients, though further research is ongoing.

TIME TRENDS OF USING INTRAVENOUS THROMBOLYSIS

In Austria, rates of rtPA treatment in patients with very mild symptoms (NIHSS 0-1) raised from 0.8% in 2006 to 3.5% in 2018 and for patients with a NIHSS 2–3 from 2.2% in 2006 to 17.2% in 2018 (34). Another large registry from 66 hospitals in Puerto Rico and Florida reported a substantial increase in thrombolysis rates of patients with minor stroke presenting within 4 h of stroke onset from 10% in 2010 to 25% in 2015 (14). The Get With the Guidelines Stroke database,

TABLE 1 | Randomized controlled trials and observational trials on thrombolysis in minor stroke.

Reference	Patient group	Study type	Inter-vention	Outcome	Key results	sICH	Mortality
IST 3 Sandercock et al. (13); Khatri et al. (23)	NIHSS ≤ 5 within 3 h of onset $n = 106$	International, multicentre, randomized, controlled	rtPA	Alive and independent at 6 month Oxford handicap scale (OHS) 0–2 and favorable outcome after 6 month (OHS 0–1)	Alive & Independent (OHS 0–2): 84 vs. 65%, aOR 3.3, 95% CI 1.2, 8.8 • Favorable outcome (OHS 0–1): 60 vs. 51%, aOR 1.9, 95% CI 0.8, 4.4	0%	0%
Emberson et al. (11)	NIHSS < 5 $n = 666$	Metaanalysis	rtPA	mRS 0–1 at 3 months	OR 1.48, CI: 1.07–2.06, favoring rtPA	0,9%	NA
TEMPO 1, Coutts et al. (24)	NIHSS < 5 $n = 50$	Phase 2, randomized, open label	0.1 mg/kg TNK 0.2 mg/kg TNK	Rate of expected serious adverse events.	No serious drug-related adverse events in 0.1 mg/kg group. In the 0.25 mg/ kg group, 1 sICH	0.25 mg/kg group: 4%	0.25 mg/kg group: 4%
PRISMS, Khatri et al. 2018 (6)	non-disabling NIHSS ≤ 5 $n = 313$	Phase 3b, randomized, blinded	rtPA	mRS 0–1 at 3 months	78.2% in the rtPA group vs. 81.5% in the aspirin group (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%)	3.2%	0.6%
Khatri et al. (25)	$n = 38$, NIHSS ≤ 5	Retrospective analysis from the NINDS trial	rtPA	mRS of 0–1 at 3 months	78.6% (CI 63.2–89.7%) of rtPA cases vs. 81.3% (CI 54.4–96.0%) of the placebo cases	2,4%	1 patient died
Sykora et al. 2021 (26)	$n = 703$, NIHSS 0–1	Retrospective	rtPA	mRS of 0-1 at 3 months	75.5% rtPA vs. 80.8% non-rt-PA group, adjusted OR 0.57, CI 0.4–0.81	1.4%	4.7%
Huisa et al. (27)	$n = 133$, NIHSS ≤ 5	Retrospective	rtPA	mRS of 0–1 at 3 months	57.6% of the rtPA group and 68.9% of the untreated group (OR 0.93, CI 0.39–2.2)	5%	5,1%
Urra et al. (28)	$n = 203$, NIHSS ≤ 5	Prospective observational	rtPA	mRS of 0–1 at 3 months	167 (82%) patients had excellent outcome; thrombolysis was associated with a greater proportion of patients who shifted down on the modified Rankin Scale score at 3 months (OR 2.66; CI 1.49–4.74, $p = 0.001$).	0%	1,7%
Greisenegger et al. (29)	$n = 890$, NIHSS ≤ 5	Retrospective	rtPA	mRS of 0–1 at 3 months	OR 1.49; CI 1.17–1.89; $P < 0.001$ favoring rtPA cases	2,5%	N/A

NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; rtPA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage.

which collects information from 1,783 hospitals across the United States, showed that the use of thrombolysis has increased from 45% in 2003 to 2005 to 82% in 2010 to 2011 (35). These substantial increases rtPA use in ischemic stroke patients with mild symptoms in different parts of the world document an increasing confidence in using this treatment according to the guidelines, which are regularly updated with regard to the minor stroke patient group.

Data from a prospective stroke thrombolysis registry in France (36) showed that a high rate (77%) of excellent outcome (3 month-modified Rankin Scale score ≤ 1) was observed in 1,035 minor stroke patients receiving thrombolysis. No symptomatic intracerebral hemorrhage occurred and the rate of any hemorrhagic transformation was 5%.

PATIENTS WITH VERY MILD SYMPTOMS

A recent analysis from a large nationwide stroke registry in Austria shows that in patients with very mild symptoms (NIHSS 0–1), treatment with intravenous thrombolysis did not increase the likelihood of an excellent outcome as compared with those managed conservatively. On the contrary, those receiving IVT were more likely to suffer early neurological deterioration (adjusted OR 8.84, CI 6.61–11.83), symptomatic intracranial hemorrhage (adjusted OR 9.32, CI 4.53–19.15) and lower rate of excellent outcome (mRS 0–1) at 3 months (adjusted OR 0.67, CI 0.5–0.9). Proposed explanations for this phenomenon may include large vessel occlusion, thrombus migration, reperfusion injury, or re-embolization (26). Indeed, up to a third of patients of patients with initially mild symptoms may harbor a large vessel

occlusion which may not respond well to IVT alone and may lead to secondary deterioration (37).

DUAL ANTIPLATELET THERAPY

If thrombolysis treatment is contraindicated or clinical assessment does preclude its use, current guidelines recommend dual antiplatelet therapy with Aspirin and Clopidogrel or Aspirin and Ticagrelor for a short time in patients with a minor stroke (NIHSS score $\leq$ 3) or high-risk TIA (ABCD2 score $\geq$ 4) (38). This treatment does not aim at vessel recanalization or rapid improvement of stroke symptoms, but rather to reduce early stroke recurrence.

The CHANCE study used a 300-mg clopidogrel (then 75 mg daily) and an aspirin loading dose of 75 to 300 mg followed by 75 mg daily within the first 24 h after TIA or minor stroke for a duration of 21 days (39). In the POINT trial 600-mg clopidogrel loading dose (then 75 mg daily) and an aspirin regimen of 50 to 325 mg daily started within in the first 12 h after TIA or minor stroke for up to 90 days was used (40). Additional analysis of the POINT trial could show that the effect of avoiding a recurrent stroke is primarily seen in the first 21 days, so that the recommendation is to treat these patients with a DAPT with loading doses immediately after TIA or minor stroke for no longer than 21 days. In both the CHANCE and POINT trials the benefits clearly outweighed the risk of bleeding.

In the THALES trial the use of ticagrelor (180-mg loading dose, then 90 mg twice daily) plus aspirin (300- to 325- mg loading does, then 75–100 mg daily) for 30 days was shown to be slightly superior to aspirin alone in preventing recurrent stroke with a significant increase in bleeding (41). In this study the preventive effect of the DAPT outweighed the risk of bleeding.

RCT's regarding the comparison of thrombolysis vs. DAPT in acute minor stroke patients are lacking. There is only one exploratory comparative analysis (42) showing a weak trend among intravenous thrombolysis, DAPT and Aspirin but not a significant difference in 90 day functional outcome in patients with minor stroke.

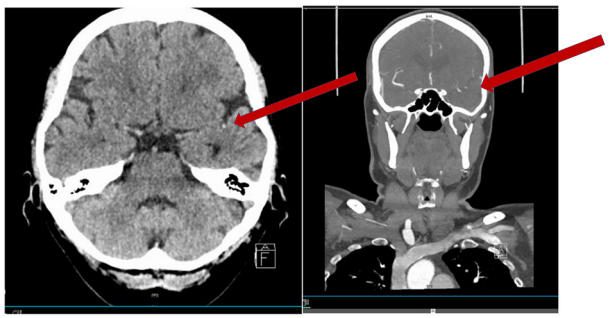

FIGURE 1 | Fifty-nine-year-old woman with an acute onset of aphasia (NIHSS 1 disabling). CT scan showing a hyperdense vessel sign in M2 (arrow). CTA showing the occlusion in M2 (short in length).

DISCUSSION

Traditionally those presenting acutely with stroke with minor symptoms have been excluded from thrombolysis due to concerns that risks of hemorrhage would outweigh the benefits. However, as we have discussed above those presenting lower NIHSS scores may still experience long term disability. Currently it is challenging to judge what patients are likely to benefit most from thrombolysis (with or without thrombectomy) treatment with the lowest risk of bleeding complications.

Patients with vessel occlusions (like patients in **Figures 1**, **2**) are likely to benefit from recanalizing treatments rather than (intensified) secondary prophylaxis with antiplatelets. Yet, in a majority of centers acute stroke treatment protocols do exclude patients with a low NIHSS from advanced imaging like MR/CT-angiography and perfusion. Therefore, the decision to initiate and organize these imaging modalities leads to time delays making thrombolysis less safe and efficient. Indeed, a recent study showed significant increased detection of LVO and increased frequencies of performed MTs after an in-house protocol change excluding the NIHSS criterion (43). Therefore, we would advocate that all patients presenting with stroke symptoms, including minor stroke symptoms, have angiography (typically CT) as part of their acute work up.

There is some data which suggests that minor strokes of certain etiologies–e.g., like strokes due to large artery

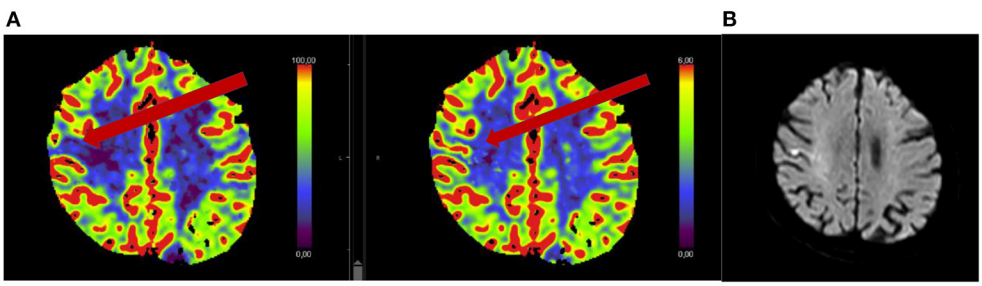

FIGURE 2 | Seventy-five year old woman with acute onset of mild left hemi-body weakness and sensory loss (NIHSS 3). Patient received intravenous thrombolysis and showed clinical improvement. Acute CT perfusion showed a mismatch between normal cerebral blood volume **(B)** and reduced cerebral blood flow **(A)**. Follow-up MRI performed 24 h after thrombolysis showed a small cortical ischemia.

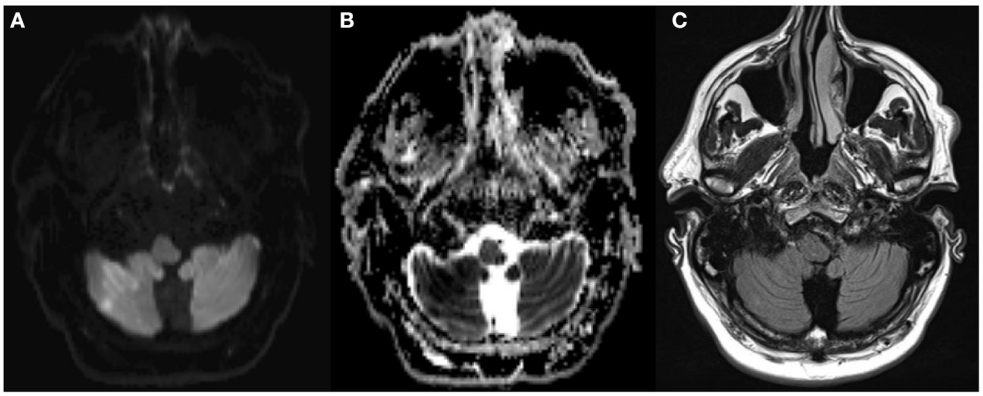

FIGURE 3 | Fifty-five year old man with acute onset of mild dysathria and ataxia of the trunk, unable to walk (NIHSS 1). MRI showed an acute infarction [DWI positive **(A)**, ADC negative **(B)**, FLAIR negative **(C)**] in the territory of the occluded right posterior inferior cerebellar artery. The patient was treated with rtPA 3 h and 46 min after stroke onset.

atherosclerosis (without large vessel occlusion) (30)–may benefit more from thrombolytic treatment.

Finally, the relevance of a neurological deficit can be extremely hard to judge in the acute stroke setting. Symptoms such as neglect, extinction, and cognitive deficits can be frequently under recognized in the emergency room. In particular, posterior circulation strokes tend to be misclassified as "minor stroke" (illustrative patient example **Figure 3**).

The NIHSS has limitations with respect to its use when comparing the neurologic severity of a posterior circulation stroke and anterior circulation stroke (44). A patient with an acute ischemic stroke in the posterior circulation might have a comparably low score like patients with an acute ischemic stroke in the anterior circulation but be bedridden due to severe ataxia and/or vertigo, underlining that patients with a posterior circulation stroke need the same diagnostic and therapeutic measures (e.g., iv thrombolysis) like patients with an anterior circulation stroke (45).

CONCLUSION

Patients with a minor stroke are by no means to be classified as benign and may result in lasting significant neurological deficits. Even though the use of IV thrombolysis in this setting has substantially increased world-wild, current guidelines still recommend the administration of thrombolysis only to minor stroke patients with clear disabling symptoms, due to lack of convincing data from large randomized-controlled trials. Advanced imaging might help to better estimate the risk-benefit ratio of thrombolysis treatment in acute ischemic stroke with minor symptoms. Further results of ongoing trials on this topic are expected shortly.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the manuscript, literature search and provided patients cases. All authors read and approved the final version of the manuscript.

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One-Year Risk of Stroke After Transient Ischemic Attack or Minor Stroke in Hunter New England, Australia (INSIST Study)

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Background: One-year risk of stroke in transient ischemic attack and minor stroke (TIAMS) managed in secondary care settings has been reported as 5–8%. However, evidence for the outcomes of TIAMS in community care settings is limited.

Methods: The INternational comparison of Systems of care and patient outcomes In minor Stroke and TIA (INSIST) study was a prospective inception cohort community-based study of patients of 16 general practices in the Hunter–Manning region (New South Wales, Australia). Possible-TIAMS patients were recruited from 2012 to 2016 and followed-up for 12 months post-index event. Adjudication as TIAMS or TIAMS-mimics was by an expert panel. We established 7-days, 90-days, and 1-year risk of stroke, TIA, myocardial infarction (MI), coronary or carotid revascularization procedure and death; and medications use at 24 h post-index event.

Results: Of 613 participants (mean age; 70 ± 12 years), 298 (49%) were adjudicated as TIAMS. TIAMS-group participants had ischemic strokes at 7-days, 90-days, and 1-year, at Kaplan-Meier (KM) rates of 1% (95% confidence interval; 0.3, 3.1), 2.1% (0.9, 4.6), and 3.2% (1.7, 6.1), respectively, compared to 0.3, 0.3, and 0.6% of TIAMS-mimic-group participants. At one year, TIAMS-group-participants had twenty-five TIA events (KM rate: 8.8%), two MI events (0.6%), four coronary revascularizations (1.5%), eleven carotid revascularizations (3.9%), and three deaths (1.1%), compared to 1.6, 0.6, 1.0, 0.3, and 0.6% of TIAMS-mimic-group participants. Of 167 TIAMS-group participants who commenced or received enhanced therapies, 95 (57%) were treated within 24 h

post-index event. For TIAMS-group participants who commenced or received enhanced therapies, time from symptom onset to treatment was median 9.5 h [IQR 1.8–89.9].

Conclusion: One-year risk of stroke in TIAMS participants was lower than reported in previous studies. Early implementation of antiplatelet/anticoagulant therapies may have contributed to the low stroke recurrence.

Keywords: transient ischemic attack, minor stroke, stroke-mimic syndrome, one-year risk of ischemic stroke, community-based study

INTRODUCTION

Transient ischemic attack and minor stroke (TIAMS) account for up to 58% of all cerebral ischemic events (1, 2). Although recurrent vascular event rates post-TIAMS have been declining over the past two decades (3, 4), 5–8% of patients have disabling stroke, 1.1–1.3% have coronary artery events, and 0.6–0.7% die from cardiovascular causes in the year following TIAMS (5–7). Short-term dual antiplatelet therapy (DAPT) is the current gold standard for secondary prevention in high-risk TIAMS patients with non-cardioembolic sources (8). For those with atrial fibrillation, non-vitamin K antagonist oral anticoagulants (NOACs) are indicated as the first line therapy (9).

While the majority of TIAMS studies have been conducted in secondary-care settings such as hospital or specialist-care units, many TIAMS are managed in community-care settings. Short- and long-term outcomes of TIAMS in community-care settings have undergone more limited study, related to the fact that distinguishing TIAMS from TIAMS-mimics is challenging for non-neurologists (10).

AIMS

In the INternational comparison of Systems of care and patient outcomes In minor Stroke and Tia (INSIST) study (11), we aimed, (a) to establish rates of stroke, TIA, myocardial infarction (MI), and death post-index event for TIAMS and TIAMS-mimic groups recruited from primary-care population and, (b) to compare recurrence rates of stroke and TIA between both groups, and (c) to document antiplatelet and anticoagulant treatments in both groups pre-index event, at 24 h post-index event, and after 1 year.

METHODS

Ethic approval was gained from Hunter New England Human Research Ethics Committee (Reference No. 12/04/18/4.02). The participants provided written informed consent.

INSIST was a community-based prospective cohort study. The methods have been reported in detail in the protocol paper (11). TIA was defined as a neurological episode self-resolving in $<$24 h. Minor stroke was defined as a neurological deficit lasting $>$24 h with National Institute of Health Stroke Scale (NIHSS) $\leq$5 at presentation.

Inclusion Criteria

- $\geq$18 years old.
- Suffered a possible TIAMS during the study period.
- Attended one of the participating practices.

Exclusion Criteria

- Unable to provide informed consent e.g., cognitive impairment.
- Moderate/severe stroke at presentation (symptoms lasting more than 24 h and NIHSS $>$5).
- TIAMS but delayed consulting a general practitioner (GP) and subsequently presented with stroke or major vascular event.

Study Population

We recruited consecutive patients between August 2012 and August 2016 from general practices in Hunter-Manning valleys regions of New South Wales, within the referral territory of acute neurovascular clinic at John Hunter Hospital (referral centre of Hunter New England Local Health District). Patients attended one of 16 general practices, of which 11 were in urban and five were in rural areas. Patients' eligibility was ascertained by multiple overlapping methods involving clinical records of general practices, after-hours GP service, the acute neurovascular clinic and emergency departments. The study population was possible TIAMS patients engaged with health systems at primary or secondary levels. While Australian evidence-based guidelines recommended optimal management of TIAMS to be urgent referral to acute specialist neurologist/stroke care (12), local practice was known to involve some TIAMS care being solely provided by GPs. Models of care included contributions from GPs, Emergency Departments, a dedicated Acute Neurovascular Clinic, inpatient admission, and specialist physicians or surgeons.

INSIST wasn't a community incidence study with ascertainment of all events (it didn't include events not presenting to medical care). Potential participants were recruited by invitation letters from the participating practices.

Data Collection

Participants underwent a baseline interview, and follow-up interviews at three- and 12-months post-baseline assessment. Further data were collected from medical records at the study conclusion. Patients not consenting to participation (non-responders) had de-identified outcome data collected, including subsequent TIA, stroke, MI, coronary or carotid revascularization and death at 12 months.

Outcome Measures

Outcomes were subsequent stroke, subsequent TIA, MI, coronary or carotid revascularization procedure, and death. Outcomes were assessed at 7-days, 90-days, and 1-year post-index event. Further outcomes were use of antiplatelet and anticoagulant medications pre-index event, at 24 h post-index event and after 1 year post-index event.

Adjudication

An expert panel adjudicated the index events and subsequent events as stroke, TIA, or TIAMS-mimic using data from phone interviews and examination of GP clinical records including imaging findings. Determinations were blinded and cross-referenced with the Hunter Region Heart and Stroke Register (13). The panel consisted of three clinicians; experienced stroke physicians (CRL, HZ, CG-E) and GPs (PM, MS, AD), with at least one of each at meetings. TIAMS and TIAMS-mimic groups were defined based on the index event adjudication.

Statistical Analysis

In descriptive analyses, continuous variables were summarized using mean with standard deviation or median with interquartile range (IQR). Clinical characteristics were compared between TIAMS and TIAMS-mimic participants using Pearson's chi-square test for categorical variables, Student's unpaired *t*-test for normally distributed continuous variables and Wilcoxon's rank sum test for non-normally distributed continuous variables.

Rates of the six events: subsequent stroke, TIA, MI, coronary or carotid revascularization and death within 7 days, 90 days, and 1 year, with 95% confidence intervals, were each estimated using the Kaplan-Meier (KM) estimator (6 events × 3 time points = 18 estimates). For subsequent stroke and TIA (considered separately), the time to event was compared between TIAMS and TIAMS-mimic group participants using log-rank tests. For participants who did not have a subsequent stroke or TIA within the defined study time, their survival time was right censored at final follow-up.

For each of the six events of interest, we also considered that the five alternative events may potentially alter the risk of the event of interest occurring and treated the alternative events as competing risks. For example, for the outcome of subsequent stroke, competing risks were defined as subsequent TIA, MI, carotid or coronary revascularization or death. For KM estimates and log-rank tests, this was achieved by censoring the survival time at the time of the competing risk for individuals experiencing a competing risk before the event of interest. Time to subsequent stroke and time to subsequent TIA were also compared between TIAMS and TIAMS-mimic group participants using competing risks regression (14) to estimate sub-distribution hazard ratios (SHR), defining competing risks as described above. The competing risks regression model was also used to plot the cumulative incidence of subsequent stroke and TIA.

Time from symptom onset to commencement or enhancement of antiplatelet or anticoagulant drugs was summarized using median with interquartile range. All statistical analysis was performed using STATA 15.0 (Stata Corp, Texas, USA) with significance level set at 0.05.

RESULTS

Between August 2012 and August 2016, 1,363 patients were ascertained to have suffered a possible TIAMS event, with 643

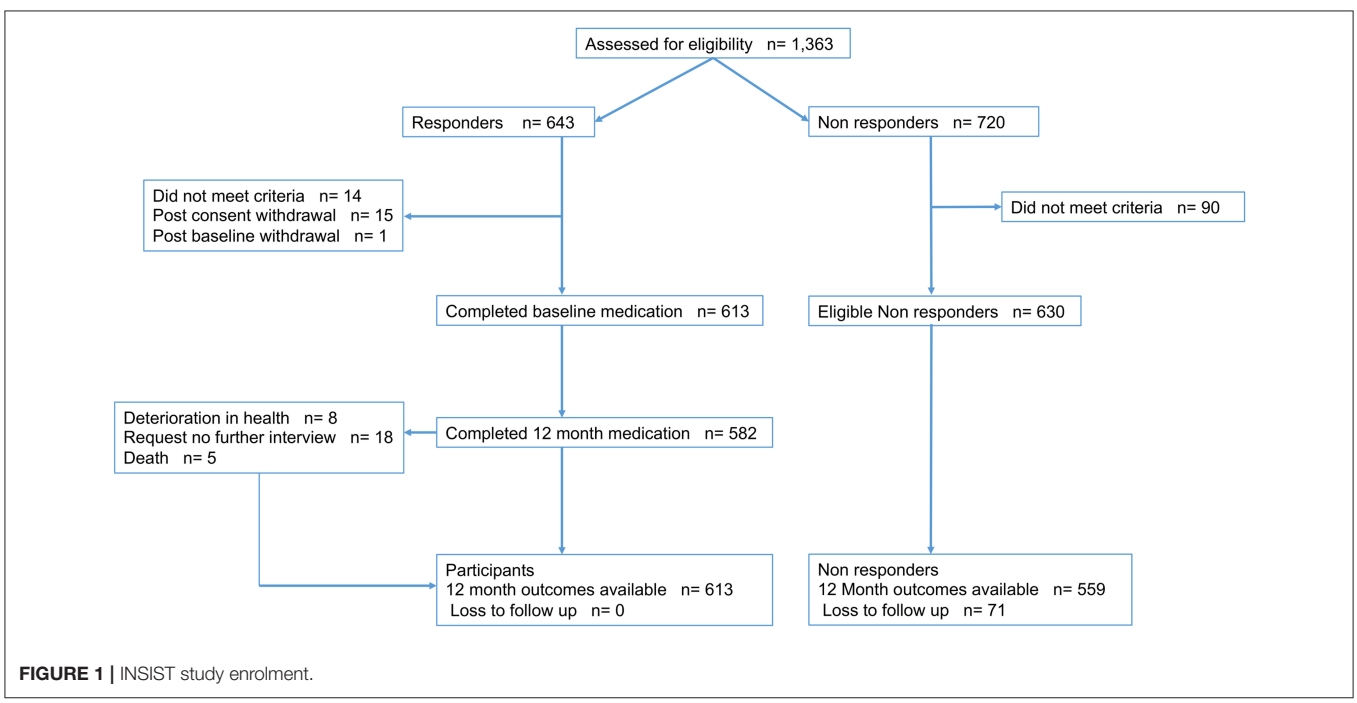

FIGURE 1 | INSIST study enrolment.

TABLE 1 | Clinical characteristics of participating patients.

	TIAMS $N = 298$	Mimics $N = 315$	*p*
Age, years	72 ± 11	68 ± 13	<0.001
Gender, men	171 (57)	107 (34)	<0.001
Premorbid modified rankin scale 0–2	265 (89)	285 (90)	0.53
Secondary/specialist management	221 (74)	177 (56)	<0.001
Medical history			
Hypertension	223 (75)	202 (64)	0.004
Hyperlipidaemia	166 (56)	155 (49)	0.11
Diabetes/pre-diabetes	86 (29)	70 (22)	0.059
Atrial fibrillation	67 (22)	35 (11)	<0.001
Heart failure	33 (11)	18 (5.7)	0.016
Carotid/peripheral vascular disease	37 (12)	13 (4.1)	<0.001
Cardiovascular disease	93 (31)	61 (19)	0.001
Previous TIA/stroke	76 (26)	52 (17)	0.006
Current smoker	19 (13)	17 (12)	0.61
ABCD2 score* ≥4	188 (64)	110 (35)	<0.001
Education <10 years	131 (44)	117 (37)	0.086
Living alone	78 (26)	70 (22)	0.25

Data are presented as mean ± standard deviation or absolute (percentage) values. TIAMS; transient ischemic attack and minor stroke.
**ABCD2 score; age, blood pressure, clinical features, duration of symptoms and history of diabetes.*

consenting to participation (response rate 47%) and 613 meeting the study criteria (**Figure 1**). Outcome data were available in all participants, while medication use at 12 months was available in 582 (90.5%). Of 720 non-responders, 559 had clinical outcomes collected. Of 613 participants enrolled into the study, 278 (45%) were men, the mean age was 70 years, 298 (49%) were classified as TIAMS (175 TIA and 123 minor stroke −118 ischemic and 5 hemorrhagic) and 315 (51%) as TIAMS-mimics. Median time from symptom onset to seeing the first doctor was 19 [IQR 2.75–100] hours. Of TIAMS-group participants, 188 (63%) had an ABCD2 score ≥ 4, and 221 (74%) had secondary care/specialist management (26% managed solely by GPs). For TIAMS-mimic-group participants, 138 (44%) were managed solely by GPs ($P < 0.001$) (**Table 1**).

Descriptive analyses also showed TIAMS-group participants were more likely to be older (72 vs. 68 years, $p < 0.001$), have vascular risk factors—hypertension (75 vs. 64%, $p = 0.004$), atrial fibrillation (22 vs. 11%, $p < 0.001$), heart failure (11 vs. 5.7%, $p = 0.016$), carotid/peripheral vascular disease (12 vs. 4.1%, $p < 0.001$), cardiovascular disease (31 vs. 19%, $p = 0.001$) and previous TIA/stroke (26 vs. 17%, $p = 0.006$). The most common diagnosis of TIAMS-mimics was migraine (27%), followed by syncope (15%), and vestibular disease (12%).

Clinical Outcomes

In the TIAMS group, there were three subsequent ischemic strokes (KM rate: 1%; 95% CI: 0.3, 3.1) and nine (3.0%; 1.6, 5.8) TIAs within 7 days post-index event, increasing to six (2.1%; 0.9, 4.6) and thirteen (4.4%; 2.6, 7.5) at 90 days, and to nine (3.2%; 1.7, 6.1) and twenty-five (8.8%; 6.0, 12.7) after 1 year (**Table 2**). Alternatively, the TIAMS-mimic group had one stroke and one TIA (0.3% each; 0.04, 2.2) within 7 days, increasing to two TIAs (0.6%; 0.2, 2.5) at 90 days, and two strokes (0.6%; 0.2, 2.5) and five TIAs (1.6%; 0.7, 3.8) after 1 year.

Rates of subsequent stroke and TIA were higher among TIAMS-group than TIAMS-mimic-group participants ($p = 0.020$ for stroke and $p < 0.001$ for TIA, from log-rank tests) (**Figure 2**). The estimated SHR with 95% CI for subsequent stroke in TIAMS-group vs. TIAMS-mimic-group participants, accounting for competing risks, was 4.8 (1.04, 22.3; $p = 0.045$) and for subsequent TIA was 5.5 (2.1, 14.3; $p = 0.001$); CIs were wide due to low event rates. The proportional hazards assumption was met for both models. There were two MI events in each group (KM rate: 0.6%) after 1 year. Four TIAMS-group and three TIAMS-mimic-group participants had coronary revascularization, and eleven TIAMS-group and one TIAMS-mimic-group participants underwent carotid revascularization. Three TIAMS-group and two TIAMS-mimic-group participants died from non-cardiovascular causes; **Table 2** shows KM rates for all events. No intracerebral or subarachnoid hemorrhage were recorded. Non-responders had five strokes (0.9%), seventeen TIAs (3.0%), seven MI events (1.3%), three coronary revascularization (0.5%), two carotid revascularization (0.3%), and seventeen deaths (3.0%) during the 12 months follow-up.

Secondary Prevention

Of 298 TIAMS-group participants, 133 (45%) were using antiplatelet therapy pre-index event, increasing to 178 (60%) at 24 h post-index event with 103 (35%) treated with aspirin alone (**Figure 3**). Of 315 TIAMS-mimic-group participants, 116 participants (37%) were using antiplatelet therapy pre-index event, increasing to 158 (50%) at 24 h with 121 (38%) treated with aspirin alone. There was a marked increase in DAPT in TIAMS group, increasing from 20 participants (6.7%) pre-index event to 44 (15%) at 24 h, compared to 14 participants (4.4%) increasing to 20 (6.7%) in TIAMS-mimic group. Anticoagulant therapy was used in 34 (11%) TIAMS-group participants pre-index event, increasing to 53 (18%) at 24 h post-index event, but was unchanged in TIAMS-mimic group with 22 (7%). NOACs use increased from four (1.3%) TIAMS-group participants pre-index event to 14 (4.7%) at 24 h, but was unchanged in TIAMS-mimic group with seven (2.2%). Of all participants, 275 (167 TIAMS and 108 mimics) commenced or received enhanced antiplatelet/anticoagulant therapy post-index event.

Of TIAMS-group participants who commenced or received enhanced therapies post-index event, 95 (57%) were treated within 24 h, compared to 48 (44%) of TIAMS-mimic group. Among the 275 participants managed with new or enhanced therapies, time from symptom onset to the therapies in TIAMS group was shorter than in TIAMS-mimic group (median 9.5 [IQR 1.8–89.9] hours vs. 31.7 [4.9–133.4] hours, $p < 0.001$).

TABLE 2 | Seven days, 90 days, and 1 year event outcomes after the index event.

	7 days				90 days				One year			
	TIAMS		Mimics		TIAMS		Mimics		TIAMS		Mimics	
	n (%)	[95% CI]	*n* (%)	[95% CI]	*n* (%)	[95% CI]	*n* (%)	[95% CI]	*n* (%)	[95% CI]	*n* (%)	[95% CI]
Ischemic stroke	3 (1.0)	[0.3, 3.1]	1 (0.3)	[0.04, 2.2]	6 (2.1)	[0.9, 4.6]	1 (0.3)	[0.04, 2.2]	9 (3.2)	[1.7, 6.1]	2 (0.6)	[0.2, 2.5]
TIA	9 (3.0)	[1.6, 5.8]	1 (0.3)	[0.04, 2.2]	13 (4.4)	[2.6, 7.5]	2 (0.6)	[0.2, 2.5]	25 (8.8)	[6.0, 12.7]	5 (1.6)	[0.7, 3.8]
Myocardial infarction	0	0	0	0	0	0	1 (0.3)	[0.05, 2.2]	2 (0.6)	[0.2, 3.1]	2 (0.6)	[0.2, 2.6]
Coronary revascularization	0	0	0	0	2 (0.7)	[0.2, 2.9]	2 (0.6)	[0.2, 2.5]	4 (1.5)	[0.6, 4.0]	3 (1.0)	[0.3, 3.0]
Carotid revascularization	1 (0.3)	[0.05, 2.4]	0	0	10 (3.5)	[1.9, 6.4]	0	0	11 (3.9)	[2.2, 6.9]	1 (0.3)	[0.05, 2.2]
Death	0	0	0	0	0	0	0	0	3 (1.1)	[0.4, 3.5]	2 (0.6)	[0.2, 2.6]

Data are presented as absolute values, (rates) and [95% CI].
CI, confidence interval; TIAMS, transient ischemic attack and minor stroke.

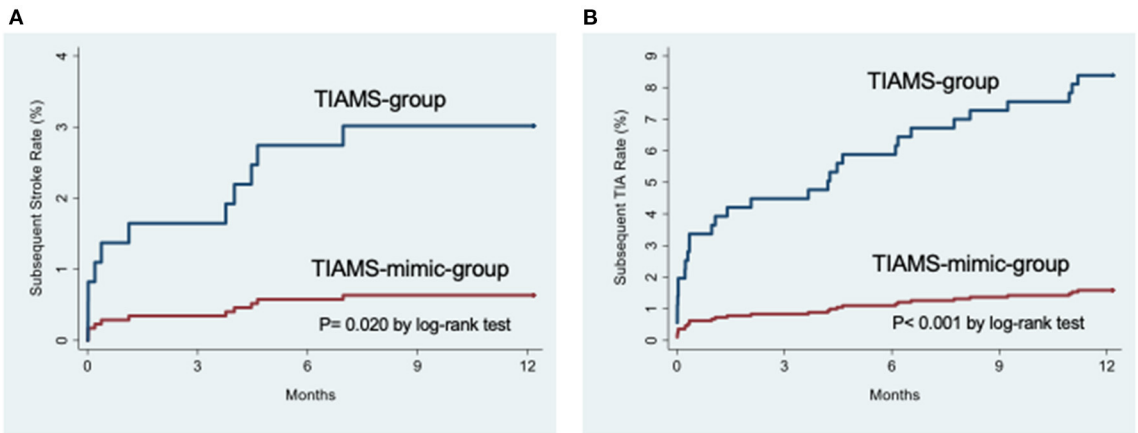

FIGURE 2 | (A) Cumulative incidence functions for subsequent stroke from the time of the index event. **(B)** Cumulative incidence functions for subsequent transient ischemic attack from the time of the index event.

DISCUSSION

We report a subsequent stroke rate in TIAMS participants at 7-days of 1% (95% CI: 0.3, 3.1), which can be compared to earlier studies of 2.1–3.4% (5, 15), a 90-days stroke risk of 2.1% (CI: 0.9, 4.6) compared to 1.2–7.4% (3–5, 15–17), and a 1-year rate of 3.2% (CI: 1.7, 6.1) compared to 5.1–8.1% (4, 5, 7). A subsequent TIA rate in TIAMS participants at 1-year of 8.8% was similar to previously reported 7.4% (5).

INSIST was an observational study of unselected patients of general practices including patients exclusively managed in general practices—but the proportion of participants with stroke recurrence appeared comparable or lower with those of study populations managed in secondary/specialist clinics [2.1% at 7-day (5), 1.2% (16), 2.1% (17), and 3.7% (5) at 90-day, and 5.1% at 1 year (5)].

We can hypothesize several reasons for the lower recurrence rate, but the most compelling is the prompt institution of antiplatelet/anticoagulant therapy post-index event. This was particularly so for aspirin in early post-TIAMS period (18). Time from symptom-onset to the therapies (median 9.5 hours [IQR 1.8–89.9]) was shorter than previously reported; time from seeking medical-attention to first-prescription (median 1 day [IQR 0–3]) (19). High community awareness in our study region may have led to the rapid treatment for TIAMS patients. National Prescribing Service MedicineWise Stroke Prevention Program implemented across Australia in 2009–2010 (20) might be correlated with high TIAMS awareness in GPs.

Another consideration is that our study population may have included TIAMS with better prognoses than previous studies. However, more than 60% of our TIAMS participants had an ABCD2 score $\geq$ 4, which was similar in the TIAregistry.org project (5) where systems were dedicated to urgent specialist evaluation. In the Framingham study with comprehensive community ascertainment of incident TIAs (4), 5.9% of participants at 90-days and 7.6% at 1-year had strokes. This suggests that TIAs with good prognoses being more likely to be managed in primary than secondary care, is unlikely to be a factor in our findings. The low incidence of stroke in non-responders suggests that our study did not lack TIAMS patients with poor prognoses at the enrolment.

Our findings provide further insight into GPs' approach to possible TIAMS. Aspirin in the TIAMS-mimic group at 24-h post-event was comparable to the TIAMS group. There

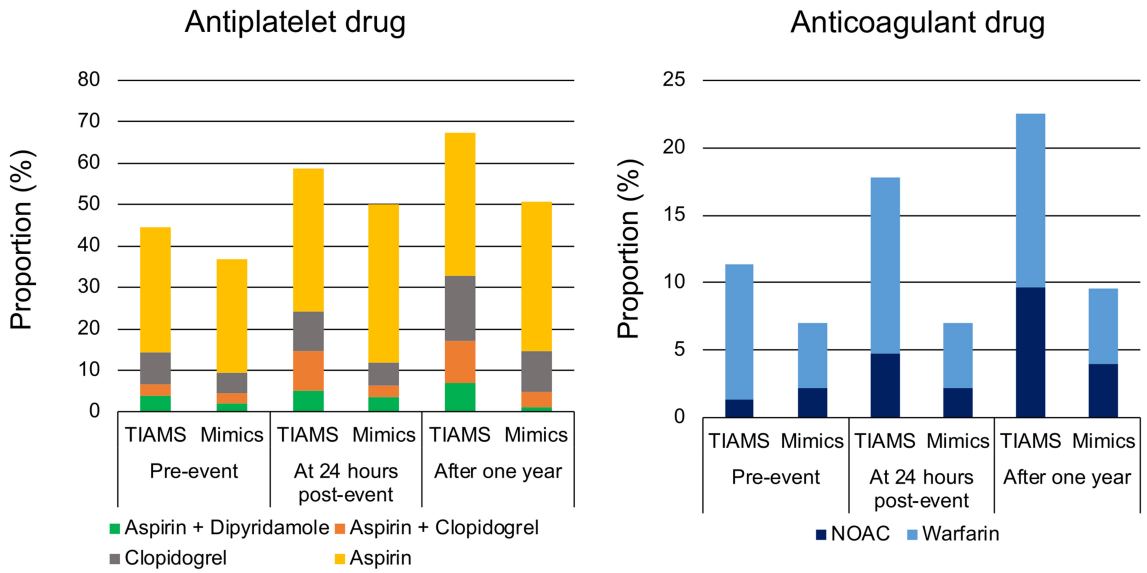

FIGURE 3 | Antiplatelet and anticoagulant drugs pre-index event, at 24 h post-index event and after 1 year in TIAMS- and TIAMS-mimic-group participants (these are simple proportions). TIAMS, transient ischemic attack and minor stroke; NOAC, non-vitamin K antagonist oral anticoagulant.

was no corresponding increase in DAPT or anticoagulant use. GPs recognize that TIAMS is a medical emergency and differentiation of TIAMS and TIAMS-mimics is difficult. Therefore, if GPs can't exclude TIAMS, they may elect a "minimalist" approach of aspirin-only management rather than DAPT (though noting that for much of our study period DAPT was not yet guideline-recommended). Aspirin use for TIAMS/TIAMS-mimics may represent a liberal instance of recommended urgent prescription at diagnosis for suspected TIA (21).

Study Strengths and Limitations

INSIST was a comprehensive community-based study, reflecting real-world TIAMS management by clinicians including exclusive management by GPs. Overlapping means of TIAMS/TIAMS-mimics ascertainment was rigorous. With 16 participating GP practices, including urban and rural settings, the results are broadly generalizable to the Australian general practice setting and to other health systems where GPs are gatekeepers to secondary care. There are several limitations. The response rate of 47% was modest, but it is a reasonable response rate for cohort studies (22). And we collected de-identified outcome data for non-responders. Medication data after 1 year was missing in 31 participants, however outcome data was complete. Reported HRs represented univariable estimates only because the event count was low, and we did not include any adjustment variables in the Cox model.

Implications for Practice

Australian guidelines recommend urgent specialist-care for suspected TIAMS at high risk (12). TIAMS outcomes in our study were favorable even with 26% of TIAMS participants managed solely by GPs. 35% of TIAMS participants treated with aspirin alone at 24 h post-index event may reflect the then-current guidelines without evidence for DAPT. The majority of TIAMS-mimic participants treated with aspirin alone may reflect diagnostic uncertainty among GPs. Lack of full confidence in the diagnosis may deter introduction of DAPT and transfer to specialist/secondary care. Therefore, GP access to specialists may be desirable for diagnostic or management advice. Given multiple barriers to access to specialist-care (23), an appropriate response may be institution of TIAMS "rapid response" telehealth service (24, 25).

CONCLUSION

We have established the recurrent stroke and major vascular event rates after TIAMS in a regional community-based Australian healthcare setting. The recurrence rate appears to be comparable with other TIAMS cohorts from specialist/secondary care settings. Rapid prescription of new or additional antiplatelet/anticoagulant drugs may have contributed to the low recurrence rate. However, our data suggest scope for improvements in the immediate management of TIAMS in the Australian regional healthcare setting.

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 Hunter New England Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL, DL, JV, PAB, DC, and PM: study design. HZ, CG-E, AD, NN, and MS: data collection. EH: statistical analysis. ST, CL, and PM: interpreted the data. ST, CL, JV, HD, PAB, NS, VF, PR, and PM: drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Large Vessel Occlusion in Patients With Minor Ischemic Stroke in a Population-Based Study. The Dijon Stroke Registry

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Introduction: Strategy for the acute management of minor ischemic stroke (IS) with large vessel occlusion (LVO) is under debate, especially the benefits of mechanical thrombectomy. The frequency of minor IS with LVO among overall patients is not well established. This study aimed to assess the proportion of minor IS and to depict characteristics of patients according to the presence of LVO in a comprehensive population-based setting.

Methods: Patients with acute IS were prospectively identified among residents of Dijon, France, using a population-based registry (2013–2017). All arterial imaging exams were reviewed to assess arterial occlusion. Minor stroke was defined as that with a National Institutes of Health Stroke Scale (NIHSS) score of <6. Proportion of patients with LVO was estimated in the minor IS population. The clinical presentation of patients was compared according to the presence of an LVO.

Results: Nine hundred seventy-one patients were registered, including 582 (59.9%) patients with a minor IS. Of these patients, 23 (4.0%) had a LVO. Patients with minor IS and LVO had more severe presentation [median 3 (IQR 2–5) vs. 2 (IQR 1–3), $p = 0.001$] with decreased consciousness (13.0 vs. 1.6%, $p<0.001$) and cortical signs (56.5 vs. 30.8%, $p = 0.009$), especially aphasia (34.8 vs. 15.4%, $p = 0.013$) and altered item level of consciousness (LOC) questions (26.1 vs. 11.6%, $p = 0.037$). In multivariable analyses, only NIHSS score (OR = 1.45 per point; 95% CI: 1.11–1.91, $p = 0.007$) was associated with proximal LVO in patients with minor IS.

Conclusion: Large vessel occlusion (LVO) in minor stroke is non-exceptional, and our findings highlight the need for emergency arterial imaging in any patients suspected of acute stroke, including those with minor symptoms because of the absence of obvious predictors of proximal LVO.

Keywords: stroke, ischemic stroke, registry, epidemiology, minor stroke, large vessel occlusion, population-based studies

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INTRODUCTION

The best strategy for the acute management of minor ischemic stroke (IS) is currently under debate. Indeed, in some cases, patients with minor symptoms at initial presentation of IS, defined as a National Institute of Health Stroke Scale (NIHSS) score of < 5, may have a large vessel occlusion (LVO). In such a situation, a strong collateral circulation is usually associated with a relatively preserved cerebral blood perfusion, but there is a subsequent risk of early neurological deterioration when the adaptive process is overtaken if patients are not recanalized (1). Recent guidelines from the European Stroke Organization (ESO) recommended to administer intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator (rt-PA) in patients with minor and disabling IS < 4.5 h duration (2), in accordance with the results of a meta-analysis of randomized clinical trials showing the effectiveness of rt-PA on the outcome of these patients (3). In addition, the benefits of mechanical thrombectomy (MT) in patients with minor IS and LVO is currently evaluated in dedicated clinical trials (4). However, there is no standardized definition of minor "disabling" stroke, and the evaluation relies on judgement of physicians in clinical practice. Moreover, the frequency of minor IS with LVO among overall patients is not well known.

Therefore, the aim of this study was to assess the proportion of minor IS and to depict characteristics of patients according to the presence of LVO, in a comprehensive population-based setting.

METHODS

Study Population and Case-Ascertainment Procedures

Data were obtained from the Dijon Stroke Registry (5–7), an ongoing prospective population-based study that complies with the criteria for conducting ideal incidence stroke studies (8), and the guidelines for the reporting of incidence and prevalence studies in neuroepidemiology according to Standards of Reporting of Neurological Disorders (9). The methodology of the Dijon Stroke Registry has been described extensively elsewhere (5–7). Briefly, case collection relies on multiple overlapping sources of information to identify hospitalized and not hospitalized cases of stroke among residents of the city of Dijon, France (156,000 inhabitants), including a review of medical records of all patients referred to the Dijon University Hospital where the only stroke unit in the country is located, a review of computerized hospital diagnostic codes using the International Classification of Diseases, Tenth Revision (ICD-10; I61; I62; I63; I64; G45; G46, and G81), a review of medical records from the departments of the private hospitals of the city and its suburbs, a cooperation with local general practitioners and private neurologists to identify stroke patients from home or nursing homes and Dijon residents who had a stroke when outside the city, a review of the medical records of patients identified from a computer-generated list of all requests for imaging to radiology centers in Dijon, and regular reviewing of death certificates to identify fatal strokes that occurred outside the hospital. The final adjudication of cases is systematically made by senior neurologists trained in stroke ascertainment according to the WHO diagnostic criteria (i.e., Rapidly developing clinical signs of focal, at time global, disturbance of cerebral function, lasting >24 h or leading to death with no apparent cause other than that vascular origin) (10).

For this study, analyses were restricted to patients with an acute IS between January 1, 2013 and December 31, 2017 and in whom data about arterial imaging (intracranial computed tomography angiography or magnetic resonance imaging) were available. The etiological classification of patients with IS was derived from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (11) as follows: large artery atheroma, cardioembolic IS, lacunar IS due to small vessels disease, IS from other identified cause, IS from undetermined cause, and IS from multiple possible causes. The classification was made by a stroke-trained neurologist investigator of the Dijon Stroke Registry based on medical records, including complementary exams performed during the diagnostic workup of IS.

Data Collection

As previously described, vascular risk factors, past medical history, and pre-stroke treatments were collected (7). Pre-stroke cognitive function (no cognitive impairment, mild cognitive impairment, and dementia) and functional status based on the premorbid modified Rankin Scale score were assessed. Pre-existing dependency was defined by a premorbid Rankin Scale score of >2. Stroke severity at onset was quantified using the NIHSS score obtained at the first clinical examination. Minor Stroke was defined as a NIHSS score of <6.

All cervical and intracranial arterial imaging exams were systematically reviewed by stroke-trained investigators to assess the presence and location of arterial occlusion responsible for the acute IS. A proximal LVO was defined as an occlusion site affecting the terminal intracranial internal carotid artery, M1 and M2 segments of the middle cerebral artery (including tandem occlusions), or A1 and A2 segment of the anterior cerebral artery, or the basilar artery. Patients with isolated extracranial internal carotid artery occlusion were not included in this group. In patients with minor IS and proximal occlusion, brain perfusion imaging including CT or MRI were reviewed when performed to assess the presence of a reduced cerebral perfusion in the territory of the occluded artery.

Statistical Analyses

Proportions and mean values of baseline characteristics were compared between groups (patients with minor stroke vs. patients with non-minor stroke; minor stroke patients with vs. without proximal LVO) using the Chi-2 test and the Mann-Withney test. A multivariate logistic regression analysis was performed to evaluate factors associated with minor stroke. In models, we introduced age, sex, and variables with a $p < 0.20$ in unadjusted

TABLE 1 | Characteristics of patients with minor ($n = 582$) vs. non-minor ischemic stroke (IS).

	Patients with minor stroke ($N = 582$)	Patients with non-minor stroke ($N = 389$)	*p* value
Age, mean ± SD, y	73.2 (16.3)	78.5 (14.7)	
Age, median (IQR), y	78 (64–86)	82 (69–90)	<0.001
Male, *n* (%)	289 (49.6)	168 (43.2)	0.048
Hypertension, *n* (%)	403 (69.2)	295 (76.0)	0.021
Diabetes mellitus, *n* (%)	118 (20.3)	78 (20.1)	0.937
Hypercholesterolemia, *n* (%)	212 (36.6)	139 (35.8)	0.802
Current smoking, *n* (%)			0.125
No	449 (77.1)	292 (75.1)	
Yes	88 (15.1)	42 (10.8)	
Unknown	45 (7.7)	55 (14.1)	
History of AF, *n* (%)	129 (22.2)	158 (40.8)	<0.001
Current alcohol consumption, *n* (%)	33 (6.0)	18 (5.2)	0.614
Coronary heart disease, *n* (%)	75 (13.0)	70 (18.1)	0.031
Chronic heart failure, *n* (%)	40 (7.0)	39 (10.1)	0.084
Peripheral artery disease, *n* (%)	40 (6.9)	28 (7.2)	0.857
Active cancer, *n* (%)	20 (3.5)	19 (5.1)	0.229
Previous TIA, *n* (%)	85 (14.6)	41 (10.5)	0.065
Previous stroke, *n* (%)	117 (20.1)	89 (22.9)	0.306
Prestroke treatments, n(%)			
Antiplatelets agents	193 (33.4)	135 (35.3)	0.552
Anticoagulants	87 (1.1)	69 (18.0)	0.223
Antihypertensive treatment	365 (63.2)	258 (67.4)	0.180
Statins	144 (24.9)	80 (20.9)	0.148
Antidiabetic treatment	102 (17.7)	62 (16.2)	0.556
NIHSS score at onset, median (IQR)	2 (1 – 3)	13 (8 – 19)	<0.001
Prestroke cognitive status, *n* (%)			<0.001
No cognitive impairment	497 (80.4)	252 (65.5)	
MCI	59 (10.2)	63 (16.4)	
Dementia	55 (9.5)	70 (18.2)	
Premorbid mRS score>2, *n* (%)	122 (21.0)	123 (31.8)	<0.001
Living in an institution, *n* (%)	41 (7.1)	62 (16.0)	<0.001
TOAST classification, *n* (%)			<0.001
LAA	61 (10.5)	51 (13.1)	
CE	143 (24.6)	175 (45.0)	
SVD	52 (8.9)	14 (3.6)	
Other	43 (7.4)	25 (6.4)	
Undetermined	255 (43.8)	114 (29.3)	
Multiples causes	28 (4.)	10 (2.6)	
Acute revascularisation therapy			
IV thrombolysis only	36 (6.2)	70 (18.0)	
Mechanical thrombectomy only	4 (0.7)	38 (9.8)	
Combined treatment	3 (0.5)	17 (4.4)	

AF, indicates atrial fibrillation; CE, cardioembolic; IQR, interquartile range; IV, intravenous; LAA, large artery atheroma; MCI, mild cognitive impairment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SVD, Small Vessel Disease; TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

models. Another multivariate logistic regression analysis was performed to evaluate factors associated with proximal LVO among patients with minor IS. In models, variables with a $p < 0.20$ were introduced. Statistical analysis was performed with STATA 13 software (StataCorp LP, College Station, TX)

Ethics

The Dijon Stroke Registry was approved using the following national ethics boards: The Comité d'Evaluation des Registres (French National Committee of Registers), Santé Publique France (French Institute for Public Health Surveillance), and the Commission Nationale Informatique et Liberté (French data

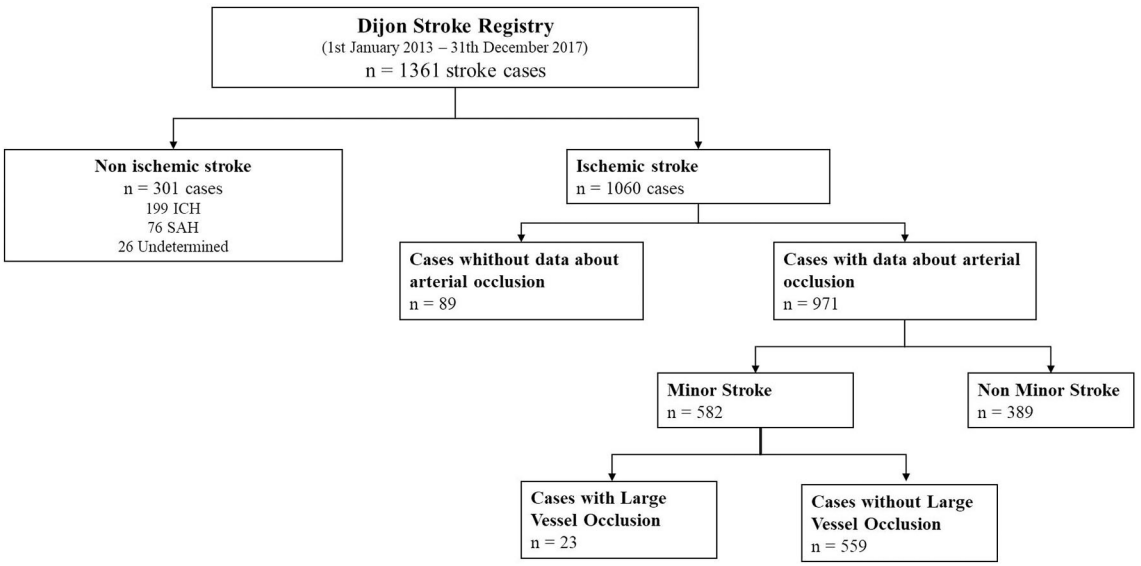

FIGURE 1 | Study flow chart.

protection authority). In accordance with the French legislation boards, the need for written patient consent was waived.

RESULTS

From January 1, 2013 to December 31, 2017, among the 1,060 recorded IS patients, 989 cases had available arterial imaging. In detail, 836 patients had a CT angiography, 456 had an MRI, and 683 patients had a US Doppler of cervical arteries, among whom 453 had a transcranial Doppler. The NIHSS score was available in 971 patients.

Among these patients, 582 (59.9%) suffered a minor stroke. Compared with non-minor stroke, minor stroke patients were younger (median age 78 vs. 82 years old, $p < 0.001$), had less frequent hypertension (69.2 vs. 76%, $p = 0.02$), atrial fibrillation (22.2 vs. 40.8%, $p < 0.01$), and history of coronary disease (13.0 vs. 18.1%, $p = 0.03$) (**Table 1**). In addition, pre-existing mild cognitive impairment (MCI) (10.2 vs. 16.4%) and dementia (9.5 vs. 18.2%) were less frequently observed in patients with minor stroke ($p < 0.001$) who were also less frequently functionally dependent (21.0 vs. 31.8%, $p < 0.001$) or institutionalized (7.1 vs. 16.0%, $p < 0.001$) before their stroke. IS etiology differed between patients with or without minor-stroke, with a greater proportion of cardioembolic IS observed among patients with non-minor stroke (45 vs. 24.6%). In multivariable analyses, past myocardial infarction (OR = 0.62; 95% CI:0.40−0.97, $p = 0.035$), MCI (OR = 0.58; 95% CI:0.36–0.95, $p = 0.029$), small vessel disease etiology (OR = 3.69; 95% CI: 1.76–7.74, $p = 0.001$), undetermined etiology (OR = 2.49; 95% CI: 1.52–4.06, $p < 0.001$), and IS with multiple causes (OR = 5.50; 95% CI: 1.97–15.34, $p = 0.001$) were associated with minor stroke.

A total of 174 cases of IS with a proximal LVO were recorded in our study population. Among the 389 patients with non-minor stroke, 149 (38.3%) had a proximal LVO. In contrast, among the 582 patients with minor stroke, 23 (4.0%) had a proximal LVO (**Figure 1**). In these patients, the M1 or M2 segment of the MCA was occluded in 6 and 14 cases, respectively, whereas in 3 cases, the site of occlusion was the basilar artery. Three patients had an NIHSS score of 0, one patient scored 1, four patients scored 2, five patients scored 3, three patients scored 4, and seven patients scored 5. Among the 20 patients with a proximal occlusion of the MCA, 13 had perfusion imaging with an onset-to-imaging time ranging from 36 at 330 min. In all cases, perfusion imaging showed a hypoperfusion corresponding to the territory of the occluded artery. Ten patients received acute recanalization therapy (7 IV thrombolysis, 1 mechanical thrombectomy, and 2 bridging therapy). Among the 13 patients who did not receive acute recanalization therapy, three had a clinical deterioration with an increase in NIHSS score of 4 points per patient, among whom 2 had beneficiated from a brain perfusion imaging.

In patients with minor IS, those with a proximal LVO more often had atrial fibrillation (43.5 vs. 21.4%, $p = 0.012$), a higher NIHSS score [median 3 (IQR 2–5) vs. 2 (IQR 1–3), $p = 0.001$], and a greater proportion of cardioembolic IS mechanism (**Table 2**). In multivariable analyses, only NIHSS score (OR = 1.45 per point; 95% CI: 1.11–1.91, $p = 0.007$) was associated with proximal LVO in patients with minor stroke.

By studying the different items of the NIHSS, patients with minor IS and proximal LVO more often had decreased consciousness (13 vs. 1.6%, $p<0.001$) and more often had cortical signs (56.5 vs. 30.8%, $p = 0.009$), especially aphasia (34.8 vs. 15.4%, $p = 0.013$) and altered item level of consciousness (LOC) Questions (26.1 vs. 11.6%, $p = 0.037$) (**Figure 2**).

In a sensitivity analysis, 441 patients (45.4%) had a minor IS, defined as that with an NIHSS score of ≤ 3. Among these patients,

TABLE 2 | Characteristics of minor ischemic stroke patients presenting with ($n = 23$) or without large vessel occlusion (LVO; $n = 557$).

	Patients without LVO ($N = 559$)	Patients with LVO ($N = 23$)	P Value
Age mean ± SD, y	73.4 ± 16.3	70.1 ± 17.8	0.287
Age median (IQR), y	78 (64–86)	72 (5–84)	
Male, *n* (%)	277 (49.6)	12 (52.2)	0.805
Hypertension, *n* (%)	389 (69.6)	14 (60.9)	0.375
Diabetes mellitus, *n* (%)	115 (20.6)	3 (13.0)	0.377
Hypercholesterolemia, *n* (%)	208 (37.4)	4 (17.4)	0.051
Current smoking, *n* (%)			0.361
Yes	85 (15.3)	3 (12.0)	
No	430 (76.8)	19 (84.0)	
Unknown	44 (7.9)	1 (4.0)	
History of AF, *n* (%)	119 (21.4)	10 (43.5)	0.012
Current alcohol consumption, *n* (%)	33 (6.3)	0 (0.0)	0.226
Coronary heart disease, *n* (%)	72 (13.0)	3 (13.0)	0.997
Chronic heart failure, *n* (%)	40 (7.3)	0 (0.0)	0.179
Peripheral artery disease, *n* (%)	39 (7.0)	1 (4.4)	0.618
Active cancer, *n* (%)	18 (3.3)	2 (8.7)	0.168
Previous TIA, *n* (%)	80 (14.3)	5 (21.7)	0.323
Previous stroke, *n* (%)	111 (19.9)	6 (27.3)	0.395
Prestroke treatments, *n* (%)			
Antiplatelets agents	185 (33.3)	8 (34.8)	0.885
Anticoagulants	84 (15.1)	3 (13.0)	0.783
Antihypertensive treatment	353 (63.6)	12 (52.2)	0.266
Statins	142 (25.6)	2 (8.7)	0.066
NIHSS score at onset, median (IQR)	2 (1–3)	3 (2–5)	0.001
Prestroke cognitive status, *n* (%)			0.567
No cognitive impairment	448 (80.3)	19 (82.6)	
MCI	58 (10.4)	1 (4.4)	
Dementia	52 (9.3)	3 (13.0)	
Premorbid mRS score>2, *n* (%)	117 (20.9)	5 (21.7)	0.926
Living in an institution, *n* (%)	41 (7.4)	0 (0.0)	0.177
TOAST classification, *n* (%)			0.011
LAA	60 (10.7)	1 (4.4)	
CE	130 (23.3)	13 (56.5)	
SVD	52 (9.3)	0 (0.0)	
Other	42 (7.5)	1 (4.4)	
Undetermined	247 (44.2)	8 (34.8)	
Multiple causes	28 (5.0)	0 (0.0)	

AF, indicates atrial fibrillation; CE, cardioembolic; IQR, interquartile range; IV, intravenous; LAA, large artery atheroma; MCI, mild cognitive impairment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SVD, Small Vessel Disease; TIA, Transient Ischemic Attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

13 (2.9%) had a proximal LVO. Of note, 3 out of 110 patients with a NIHSS score of 0 had a proximal LVO.

DISCUSSION

This study provided original data about the prevalence of proximal LVO in patients presenting with minor IS in a large population-based setting. We observed that ∼4% of patients with a mild clinical presentation had an LVO, thus representing those potentially eligible for mechanical thrombectomy. Although LVO in patients with minor IS was more frequently noticed in patients with atrial fibrillation and/or a cardioembolic etiology, only a greater NIHSS score was independently associated with LVO, which was explained by more frequent decreased consciousness, aphasia, or altered item LOC questions.

Different definitions are used to define the minor stroke in the literature. Fischer et al. suggested several definitions of minor stroke and concluded that a maximum score of 1 on every baseline NIHSS score, except level consciousness items, or a total NIHSS score of ≤3 could be the best

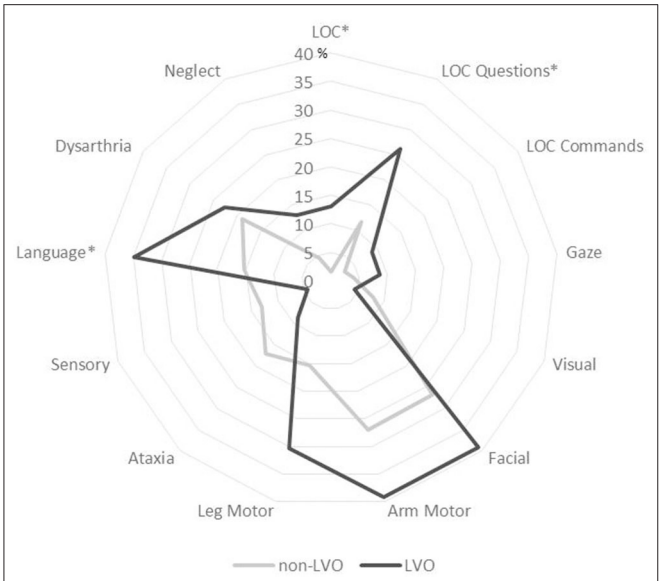

FIGURE 2 | Proportion of patients with minor ischemic stroke who have impairment in each item of National Institutes of Health Stroke Scale NIHSS score according to the presence of proximal large vessel occlusion (LVO). *$p < 0.05$.

definition (12). In the Oxford Vascular Study (OXVASC), a NIHSS score of <3 was used to define minor stroke (13). Regarding recent randomized clinical trials focusing on dual antiplatelet therapy in secondary prevention of IS patients, both Platelet-oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) (14) and Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) (15) trials considered minor stroke if the NIHSS score was $\leq$ 3. Conversely, in Acute Stroke Or Transient IsChaemic Attack TReated With Aspirin or Ticagrelor and Patient OutcomES (SOCRATES) (16) and The Acute Stroke or Transient Ischaemic Attack treated with Tricagelor and Tricagelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) (17) trials, minor stroke was defined as that with a NIHSS score of $\leq$ 5. Some authors suggested a definition of mild severity as a NIHSS score <5 (18, 19). Recent guidelines from the ESO on the use of dual antiplatelets therapy in minor IS used a NIHSS score $\leq$ 3 as a threshold (20, 21). However, for the management of IS with endovascular therapy, current recommendations used a NIHSS score of <6 for defining IS with mild symptoms (22, 23). Whether these patients should benefit from mechanical thrombectomy is a challenging issue. Therefore, we used this definition to assess the true prevalence of LVO in minor IS.

Minor IS, defined as a NIHSS score of < 6, accounted for ∼60% of overall IS patients in our population. So as to compare with the Oxford Vascular (OXVASC) study, we found a similar proportion of minor IS when considering a definition with a NIHSS score < 3 (45% in our study vs. 47% in the Oxford Vascular Study). This high rate of minor IS reflects the fact that, in both studies, we used a population-based setting rather than a hospital-based recruitment that would have led to higher clinical severity of included patients (24).

Our study provides new information on the prevalence of LVO in patients with minor IS. Although this prevalence was relatively low (4%), we did not find any factor associated with the presence of LVO in these patients, except the NIHSS score. However, the difference was very small, and, therefore, it is not useful for the discrimination between patients with vs. without occlusion. Consequently, our findings suggest that in a patient presenting with a clinical picture of minor stroke, it is impossible to easily predict the existence of a proximal LVO. This is important in the current context of discussion about the best therapeutic strategy in this patient, i.e., whether to administer IV thrombolysis and/or mechanical thrombectomy, and it should be considered that until proven otherwise, these patients may have a LVO and may therefore benefit from urgent brain and arterial imaging even if the neurological symptoms are mild. In addition, we noticed that all patients with minor IS and a proximal LVO of the anterior circulation had a hypoperfusion in the corresponding arterial territory when perfusion imaging was performed. A majority of these patients received IV thrombolysis despite the fact that the guidelines regarding the indication of this therapy were not established at the time this study was conducted. Of note, 2 out of 3 patients with proximal occlusion and a hypoperfusion and who did not receive IV thrombolysis had an early neurological deterioration. This suggests that brain perfusion imaging could be useful for the selection of minor IS patients eligible to acute revascularization therapy.

The major strength of our study is the use of a population-based registry and a relatively large sample size of patients. The reliability of the classification of patients as having or not having an LVO was ensured by a systematic review of all arterial imaging exams by stroke-trained investigators. However, our study was limited by a small number of cases with LVO, thus limiting the study power and additional subgroup analyses.

To conclude, LVO in minor stroke is non-exceptional, and our findings highlight the need for emergency arterial imaging in any patients suspected of acute stroke, including those with minor symptoms, because of the absence of obvious predictors of proximal LVO.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of restrictions due to national legislation. Requests to access the datasets should be directed to yannick.bejot@chu-dijon.fr.

AUTHOR CONTRIBUTIONS

GD: study concept and design, acquisition, analysis and interpretation of data, reviewing arterial imaging, and drafting and revising the manuscript for content. VC, PJ, MG, and CV: acquisition of data and critical revision of manuscript for

intellectual content. YB: study concept and design, acquisition, analysis and interpretation of data, study supervision, obtaining funding, and drafting and revising the manuscript for content. All authors contributed to the article and approved the submitted version.

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Vision and Visuomotor Performance Following Acute Ischemic Stroke

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Background: As measurable sensory and motor deficits are key to the diagnosis of stroke, we investigated the value of objective tablet based vision and visuomotor capacity assessment in acute mild-moderate ischemic stroke (AIS) patients.

Methods: Sixty AIS patients (65 ± 14 years, 33 males) without pre-existing visual/neurological disorders and acuity better than 6/12 were tested at their bedside during the first week post-stroke and were compared to 40 controls (64 ± 11 years, 15 males). Visual field sensitivity, quantified as mean deviation (dB) and visual acuity (with and without luminance noise), were tested on MRFn (Melbourne Rapid Field-Neural) iPad application. Visuomotor capacity was assessed with the Lee-Ryan Eye-Hand Coordination (EHC) iPad application using a capacitive stylus for iPad held in the preferred hand.Time to trace 3 shapes and displacement errors (deviations of >3.5 mm from the shape) were recorded. Diagnostic capacity was considered with Receiver Operating Characteristics. Vision test outcomes were correlated with National Institutes of Health Stroke Scale (NIHSS) score at the admission.

Results: Of the 60 AIS patients, 58 grasped the iPad stylus in their preferred right hand even though 31 had left hemisphere lesions. Forty-one patients (68%) with better than 6/12 visual acuity (19 right, 19 left hemisphere and 3 multi-territorial lesions) returned significantly abnormal visual fields. The stroke group took significantly longer (AIS: 93.4 ± 60.1 s; Controls: 33.1 ± 11.5 s, $p < 0.01$) to complete EHC tracing and made larger displacements (AIS: 16,388 ± 36,367 mm; Controls: 2,620 ± 1,359 mm, $p < 0.01$) although both control and stroke groups made similar numbers of errors. EHC time was not significantly different between participants with R ($n = 26$, 84.3 ± 55.3 s) and L ($n = 31$, 101.3 ± 64.7 s) hemisphere lesions. NIHSS scores and EHC measures showed low correlations (Spearman R: −0.15, L: 0.17). ROC analysis of EHC and vision tests found high diagnostic specificity and sensitivity for a fail at EHC time, or visual field, or Acuity-in-noise (sensivity: 93%, specificity: 83%) that shows little relationship to NIHSS scores.

Conclusions: EHC time and vision test outcomes provide an easy and rapid bedside measure that complements existing clinical assessments in AIS. The low correlation between visual function, NIHSS scores and lesion site offers an expanded clinical view of changes following stroke.

Keywords: acute ischemic stroke, eye-hand coordination, visual field, visual acuity-in-noise, vision, visuomotor function, Melbourne Rapid Field-Neural (MRFn), Lee-Ryan Eye-Hand Coordination Test (SLURP)

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INTRODUCTION

Stroke is defined as sudden onset focal (or global) disturbance of cerebral function, lasting more than 24 hours, or leading to death, and with no apparent cause other than that of vascular origin (1). Stroke is recognized as one of the leading causes of adult mortality and disability worldwide, affecting over 16 million people annually with nearly five million deaths and another six million people developing permanent disability (2). Post-stroke recovery is often associated with persistent symptoms of impaired cognition, sensory and motor disability that tend to be accompanied by anxiety/depression and fatigue (3–7). Upper limb function is often impaired acutely (8–10) leading to reduced manual and coordination of visually guided motor tasks contralateral to the site of the brain lesion (3, 11). Clinical trials have reported that ∼70% of referred stroke survivors post-hospitalization have ipsilaterally derived eye movement disorders (12–15) and reduced amplitude in micro-saccades which may affect visual sensitivity (16). We have also recently reported that ∼2/3 of mild-moderate severity first episode acute ischemic stroke (AIS) patients with no previous history of impaired vision, experience deteriorated visual acuity-in-noise (VAn) with contralateral visual field defects immediately (i.e., within 7 days) after stroke (17). Given the ubiquity of motor involvement in stroke, we set out to examine and quantify visuomotor performance in the same group of hospitalized AIS cases whose sensory visual capacity was reported in the past (17), and for this study, we added a motor eye-hand coordination task. We also wanted to establish whether the visuomotor changes would associate with changes in conscious perception, sensory vision loss or the hemisphere of lesion (motor) and be reflected in the NIHSS scores. According to Lyden 2017 (18), NIHSS is the "most widely used deficit rating scale in modern neurology" and a well-validated and reliable relative measure of consciousness, limb motor capacity and oculomotor function (19). Finally, we aim to ascertain the value of these rapid tests as diagnostic agents of stroke.

Vision was quantified in terms of high contrast visual acuity (VA) in the absence or presence of luminous noise (visual acuity-in-noise) to ascertain impairments to central attention mechanisms (20). This was achieved with readily available Melbourne Rapid Field-Neural (MRFn) iPad application that can be used for bedside testing and quantification of vision deficits (described in an earlier publication) (17). Visuomotor function in terms of eye-hand coordination (EHC) has been established using the Lee-Ryan eye-hand coordination (SLURP) app, designed by the University of New South Wales (21). The SLURP app was designed to quantify trace time, accuracy and the extent of displacement when tracing three familiar shapes on an iPad. We hypothesized that in patients with intact central vision, hemisphere of lesion would limit hand of preference and that the time and number of errors during item tracing would be much greater in AIS patients compared to age similar controls. Our secondary aim was to consider the correlation of vision and visuomotor function as found with MRFn and the EHC task and NIHSS scores (22) which encompasses clinical rankings of sensory and motor function in AIS. Finally, we have calculated the diagnostic value of these vision tests in radiologically identified AIS.

Abbreviations: MRFn App, Melbourne Rapid Field Neural App; SLURP, Test Lee-Ryan Eye-Hand Coordination Test; EHC, Eye-Hand Coordination; VA, Visual Acuity; Van, Visual Acuity-in-Noise.

MATERIALS AND METHODS

Ethics approval was provided by Sunshine Hospital (Western Health Ethics Committee HREC/16/WH/1) review board and the study was conducted in accordance with the tenets of the Declaration of Helsinki with all participants (or their carers) giving informed consent to participate. Clinical Trial registration: ACTRN12618001111268.

Participants

One hundred and sixty (29–95 years, 68 ± 14.5years, 88 males) sequentially presenting, acute ischemic stroke patients admitted to Sunshine Hospital, Melbourne, between June 2017 and July 2018 were invited to volunteer for a subjective assessment of their vision and a quantifiable objective measure of visuomotor function. Those who agreed, and who met our inclusion criteria (see **Figure 1**) (17): first episode AIS, intact (better than 6/12) central high contrast visual acuity and radiographic confirmation of lesion site with no existing ocular/neurological disease or previous stroke, had their data analyzed for vision and EHC outcomes in this study. Sixty first-episode AIS patients (29–88 years, mean: 65 ± 14 years, 33 males) met our inclusion criteria and had their data analyzed for vision and EHC outcomes in this study whereas 65 others were excluded (**Figure 1**).

All testing was performed during the first week (usually day 2 or 3) of any participant's hospital stay. Fifteen stroke patients with total upper limb paresis were excluded as they were unable to lift their preferred arm or grasp the iPad stylus. Four out of the 20 excluded stroke patients had existing eye disease due to advanced macular degeneration with large central scotomas and VA <6/12. These participants could not see adequately to perform the EHC task. Two patients were excluded due to co-morbid, neuro-motor disorder and Parkinson's disease (PD). Each showed significant hand tremor consistent with PD while holding the pen. All other AIS patients were capable of a stable hand grip of the iPad stylus with their preferred hand (right hand 58/60) as needed for the tracing task (**Figure 1**).

Stroke diagnosis and severity was determined at the time of admission by a stroke neurologist. Site of the infarction and vascular territory was established and confirmed with routine computer tomography (CT/CT angiography) or magnetic resonance imaging (MRI/MR angiography) of the brain (23–25). This information was used to confirm the site and extent of the lesion and facilitate a structure-function analysis with the EHC measures (26). NIHSS scores of the patients in this study were recorded at the time of admission and confirmed by two stroke neurologists.

Patients wore their habitual reading glasses for testing and were examined binocularly at their bedside using the MRFn and SLURP iPad applications (17, 21). The adequacy of current

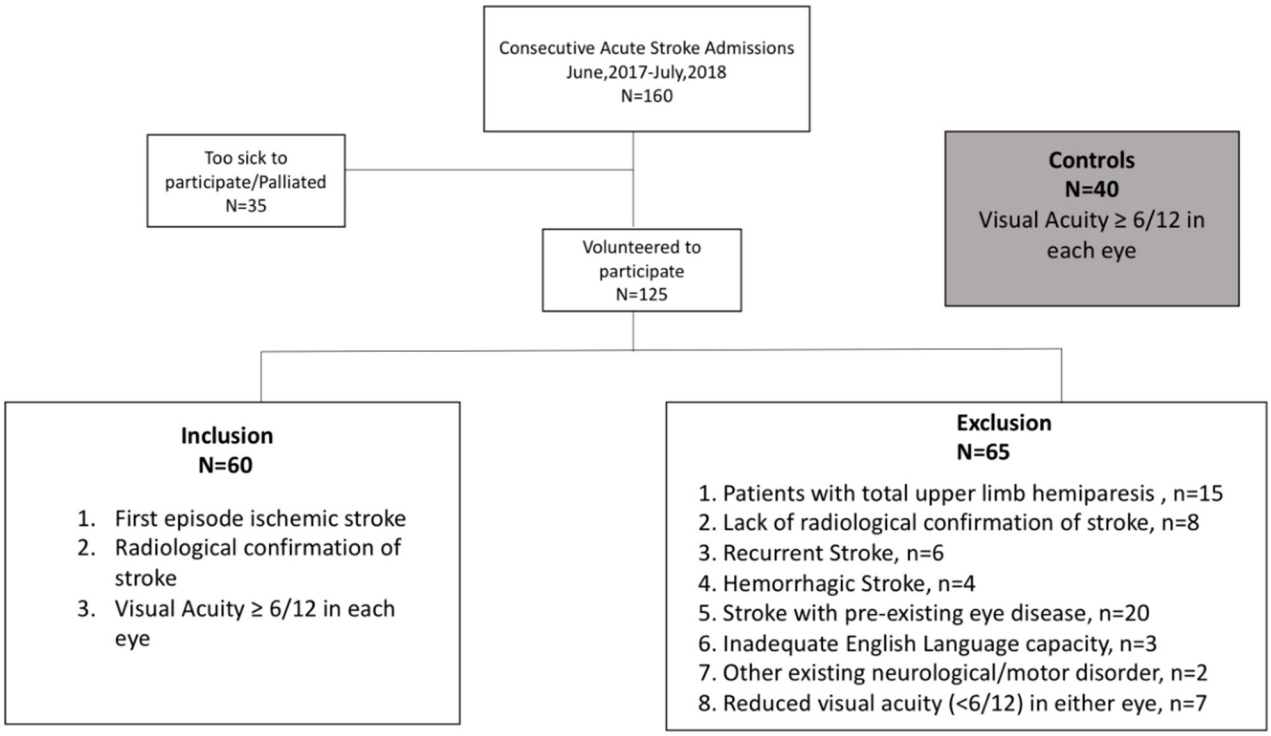

FIGURE 1 | Consort flowchart including exclusion and inclusion criteria for the recruitment of the participants to the study.

reading glasses was established by measuring near visual acuity as 6/12 or better using the MRFn app.

Forty age-similar healthy controls (29–85 years, mean:64 ± 11 years, 15 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, motor or neurological disorders, wore their habitual reading glasses for testing and provided normal near visual acuity (6/12 or better) prior to visuomotor assessment.

SLURP (Lee-Ryan Eye-Hand Coordination Test) iPad Application

The Lee-Ryan Eye-Hand Coordination (SLURP) test is available from Apple App Store for $2.10 USD—dated 13/08/2020—and was originally designed to provide a measure of visuomotor performance in children with amblyopia (21) on an iPad and in neurotypical adults whose results are similar to any of our age similar controls. We have chosen to use SLURP as a measure of EHC post-stroke due to its ease of use at a patient's bedside and evidence for its fast and sensitive assessment on a geriatric population (21, 27). As SLURP EHC test, is performed on a 2D setting, it is shown to assess attention and fine motor control with less demand on stereopsis compared to visuomotor tasks that involve grasping and bead threading where visually guided movements are adversely affected by eye movement impairments and visual deficits that reduce depth perception (28, 29). Hence SLURP EHC app objectively assesses both spatial and temporal accuracy of oculo-motor function that reflects cortical processing of visual attention and fine motor actions, in a generalized acute stroke population. There is no gold standard for measurement of EHC, however, previous studies (30–32) have suggested that the standard EHC measurement should involve the motor reaction time in any correlation of a visual task involving an interactive eye and hand modulating function in decision making. The methodology of EHC with SLURP subscribes to that. Other seminal EHC studies (33, 34) also use reaction time as the predominate marker of EHC assessment. Quantification of performance in SLURP is calculated by the time taken to trace a number of geometric or animal shapes shown on an iPad screen (**Figure 2**) and it is further measured by the number and nature of errors made while tracing each item (21). Tracing can be performed using an iPad stylus or by hand, with Junghans and Khuu (27) finding that the number of errors correlate with the type of stylus pen used for tracing. As a consequence, we adopted the Apple iPad rubber tip stylus pen (Capacitive Screen Touch Pencil Drawing Pen, for Apple iPad) in all cases to ensure consistency.

Testing Procedures

Measurements of near visual acuity, visual acuity in the presence of luminance noise jitter and visual field sensitivity of all participants were performed monocularly in ambient binocular hospital room lighting using the Melbourne Rapid Field-Neural

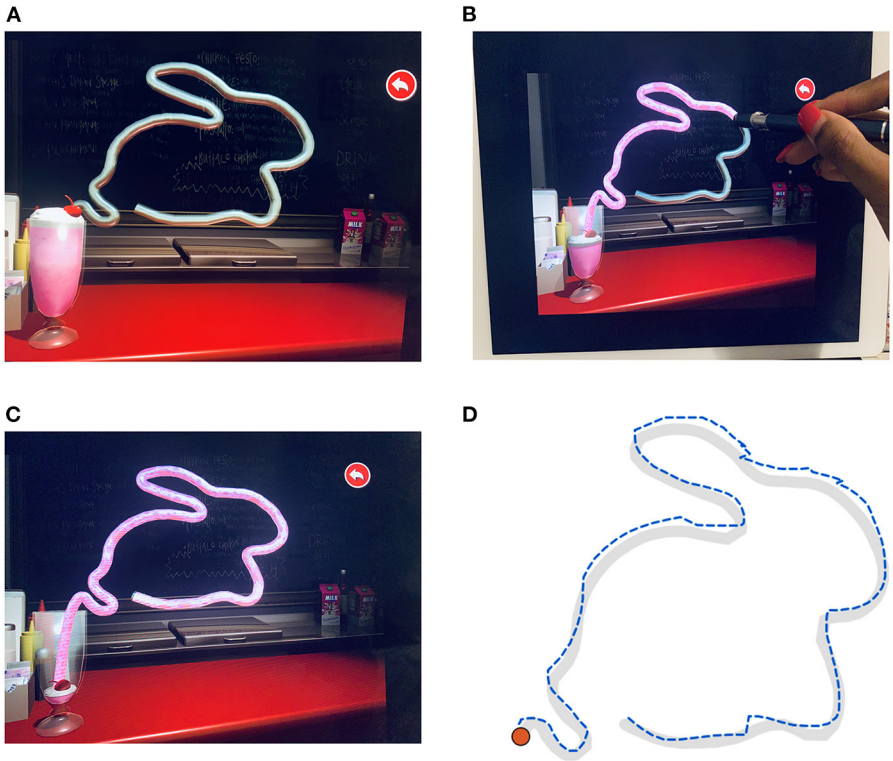

FIGURE 2 | The UNSW Lee-Ryan Eye Hand Coordination Test (SLURP) using the rabbit shape. **(A)** Geometric shape of the rabbit prior to start of task. Timing is initiated when the participant touches the red cherry spot at the top of the glass carrying the milkshake of panel. **(B)** Example of Rabbit trace in progress with the stylus iPad pen. Note that the milk shake enters the straw and defines the path that has been correctly traced up to that time. **(C)** Completed trace of Rabbit shape. **(D)** Example of a patient's trace of the rabbit shape. The desired trace path is shown in gray. The blue dashed line identifies the participant's trace with displacement errors displayed as contour realignments.

(MRFn) App where the methodology is detailed in a previous publication (17) and the outcomes are reproduced here with the approval of the editor of our past publication. For inclusion in the study, we required a near acuity better than 6/12 with habitual glasses (**Figure 1**) given that patients with worse near-acuity self-reported difficulty doing the EHC test. As the iPad is a calibrated source of light, external lighting has little impact on the visibility of targets (35) provided reflections off the screen are avoided. Screen brightness was set to maximum for 10 min prior to testing, to stabilize luminous output (36). All patients were asked to use their preferred hand to hold the Apple iPad pen (27).

The participants' task was to binocularly trace three shapes (circle, triangle and a rabbit) as quickly and as accurately as possible wearing normal near vision corrections and using the iPad stylus pen at a working distance of 33 cm with the iPad flat on a table (**Figure 2A**). Participants were told to initiate a trial by touching the "cherry shape" located at the top of the milkshake icon (**Figure 2A**). Verbal instructions regarding the task were given at the bedside and patients were requested to undertake a practice trial using the circle shape before commencement of formal testing to ensure they understood the nature of the task and were able to confidently and comfortably grasp the iPad stylus pen.

When the tracing is executed correctly (displacements within $\pm$ 3.5 mm) the straw outlining the shape becomes filled with "strawberry milk" (**Figure 2B**), thereby emptying the glass. Whenever the patient's tracing deviates from the shape path by $>$3.5 mm, the straw filling stops and a warning sound is activated. The patient was instructed to restart from where they last left off (end of milkshake in straw) as soon as possible after this sound and continue until they reach the end of the shape. The task algorithm returns time for completion, the number of deviation errors and the summed deviations beyond the 3.5 mm criterion.

Data Analysis

Comparisons between stroke and control groups were made for visual acuity, visual acuity-in-noise, the visual field mean deviation (MD) and the average foveal threshold of the affected central visual field. Visual acuity and visual acuity-in-noise were measured using the MRFn application as detailed in a previous publication (17). The mean deviation is returned by a pointwise comparison of thresholds (dB) to age-normals, stored in the MRFn database. Foveal thresholds (dB) represent the average retinal sensitivity of four foveal points located at about 0.8 degrees from fixation in each quadrant. Although both eyes were tested for vision, the foveal thresholds associated with the affected

TABLE 1 | Summary of visuomotor and NIHSS score results for controls and AIS groups.

	Controls ($n = 40$)	Stroke ($n = 60$)	R side stroke ($n = 26$)	L side stroke ($n = 31$)	Multi-territorial strokes ($n = 3$)
Age mean (years ± months)	64 ± 11	65 ± 14	60 ± 14	69 ± 13	64 ± 11
Gender (M:F)	15:25	33:27	13:13	19:12	0:3
NIHSS Score	N/A	4.0 ± 4.0	4.2 ± 4.1	4.0 ± 4.2	2.7 ± 1.5
EHC time (s)	33 ± 11.5	93 ± 60.1 Fail: $n = 40$, $p < 0.01$	84 ± 55.3 Fail: $n = 16$, $p < 0.01$	101 ± 64.7 Fail: $n = 22$, $p < 0.01$	90 ± 59.4 Fail: $n = 2$
EHC errors	22.4 ± 8.8	24.6 ± 17.3 Fail: $n = 13$, $p = 0.73$	20.7 ± 11.8 Fail: $n = 3$, $p = 0.63$	26.6 ± 19.3 Fail: $n = 8$, $p = 0.72$	37 ± 32.0 Fail: $n = 2$
EHC displacement (mm)	2,630 ± 1,354	16,634 ± 36,625 Fail: $n = 33$, $p < 0.01$	13,682 ± 22,907 Fail: $n = 15$, $p < 0.01$	18,434 ± 46,324 Fail: $n = 16$, $p < 0.01$	23,621 ± 24,206 Fail: $n = 2$

Fail identifies the number of AIS group beyond the 97.5th confidence limit of normal.

hemifield in both eyes of AIS patients (hemifield contralateral to the CT/MRI defined lesion) were analyzed for the AIS group and compared to the findings returned from the right hemifield of all controls (comparison to the fellow hemifield does not change our findings).

The total time for completion of the three shapes, total number of errors and the total displacement during the tracing of the SLURP task were recorded and have been analyzed in conjunction with hemisphere of lesion and NIHSS score. The results have been compared to an age-similar control group (29–85 years, 64 ± 11 years, 15 males) as age has been previously highlighted as a significant factor affecting task performance (27). See **Table 1** for descriptive statistics of controls.

Data for all variables are displayed as means and standard deviations with the 97.5th confidence limit of our age similar controls used as the criterion to identify "abnormal" outcomes for stroke participants. Statistical analysis and graphs were conducted using GraphPad Prism v7.00 for Windows www.graphpad.com. Cohort comparisons of visual capacity assessment in the form of visual acuity, field of vision and visuomotor spatio-temporal accuracy were made using a Student's *T*-test or non-parametric Mann-Whitney U test in cases where the data were not normally distributed. A conservative alpha value of 0.01 was employed to allow Bonferroni considerations. Correlations between variables were determined with non-parametric Spearman's rank correlation coefficient for our stroke population given the non-Gaussian distributions in all our data (visual acuity-in-noise, visual field mean deviation and EHC for controls and stroke cohorts) as The Kolmogorov-Smirnov test failed to find normality in controls and stroke groups. Igor Pro was used to produce multidimensional scatter plots. Receiver-operator-characteristics (ROC) were calculated to assess the diagnostic capability of each parameter.

RESULTS

Sixty of 160 (37.5%) mild-moderate (NIHSS Score: 4.0 ± 4.0) AIS participants were recruited and were able to perform the MRFn and EHC tasks at their bedside in a mean time of 7 and 2–5 min, respectively. Forty-one (68%) of the hospitalized AIS volunteers showed extensive visual field deficits. Of this group, 26 (43%) had right hemisphere lesions, 31 (52%) left hemisphere lesions and three participants (5%) had multi-territorial lesions. On average our patients had mild-moderate stroke manifestations as evident from the NIHSS scores (4.0 ± 4.0) for both Right (4.2 ± 4.1) and Left (4.0 ± 4.2) sided lesions (**Table 1**).

Of the 26 with right hemisphere lesions, 19 (73%) had visual field deficits, which included 16 left hemianopias (84% of the visual field deficits), 1 left quadrantanopia and 2 diffuse altitudinal losses. Among the 31 left hemisphere lesions, 19 (61%) showed visual field deficits with 13 having right hemianopias (68% of the visual field deficits), 2 right quadrantinopias and 4 diffuse altitudinal losses.

Visuomotor Performance in Terms of Time and Errors Made on EHC-SLURP Task

Despite significant hand motor limitations as assessed on NIHSS in 10/60 patients with a NIHSS score >9, only 2/10 were found not to choose to pick up the stylus with their previously dominant right hand. Both had restricted dominant arm movement post-stroke. One was radiologically defined with a frontal lobe infarct, in the areas around Broca's area in their left hemisphere and the other, had a lesion in the right hemisphere middle cerebral artery causing a posterior territory infarction.

The stroke patients completed tracing of the three shapes (circle, triangle, rabbit) with an average total time of 93 ± 6 0.1 s. Control patients required a significantly ($p < 0.01$) shorter average time of 33 ± 12.8 s to complete tracing of the same shapes in the same order (**Figure 3**). Both the circle [AUC: 0.92, (CI: 0.87–0.97), $p < 0.01$] and rabbit [AUC: 0.89, (CI: 0.82–0.95), $p < 0.0001$] show similar areas under the ROC curve. Although a significant increase in tracing time was found for each EHC task, we did not find a statistically significant difference in tracing time or tracing errors related to hemisphere of lesion (see **Table 1**; **Figure 3**).

Surprisingly, our EHC results find that the AIS and control groups make a similar number of average errors (controls: 22 ± 9; stroke: 25 ± 17, $p = 0.95$) during the tracing of all three shapes. Stroke patients, however, give significantly ($p < 0.01$)

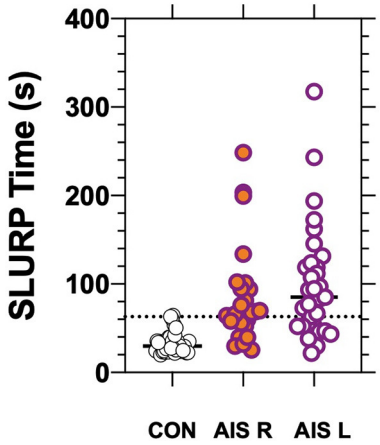

FIGURE 3 | Eye-hand coordination time for controls and AIS patients having Right ($p < 0.01$) or Left ($p < 0.01$) hemisphere lesions as confirmed radiologically. The bars show group/individual tracing time and the horizontal dotted line indicates the 97.5th percentile for control.

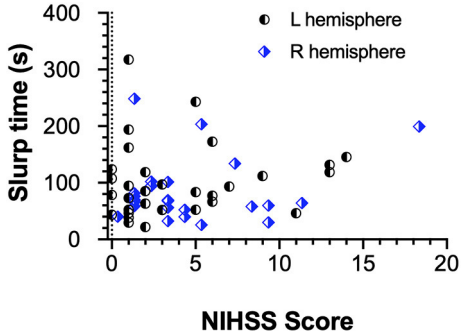

FIGURE 4 | EHC Time as a function of NIHSS Score and Hemisphere of lesion. The scatter plot shows a poor correlation between both parameters regardless of the affected hemisphere.

greater average displacements per error than controls (controls: 117.6 mm/error; stroke: 677.6 mm/error). As a consequence, stroke patients made significantly ($p < 0.01$) larger cumulative displacements (mm) during the tracing of the 3 shapes (16,388 ± 36,367 mm) relative to controls (2,620 ± 1,359 mm) consistent with their longer tracing times. Furthermore, stroke patients take significantly longer to return to the correct spatial location and restart tracing when they make an error (displacement/time: controls: 79.4 mm/s, stroke: 178.0 mm/s, $p < 0.01$). The total time taken for the completion of these tests by stroke patients showed a moderately positive correlation with both displacement (Spearmann's *r*: R: 0.78, L: 0.74) and number of errors (Spearmann's *r*: R: 0.66, L: 0.79) for cases with right or left hemisphere lesions.

Relationship Between NIHSS Scores and Vision and Visuomotor Function

As NIHSS scores reflect somato-sensory and motor capacity we compared these scores with vision outcomes and the total time taken for completion of the EHC tasks for all three shapes. The **Figure 4** demonstrates that most stroke patients with low NIHSS scores, perform the EHC in a shorter duration. However, statistically our results (**Figure 4**) show a low correlation between EHC total time and NIHSS score ($r = 0.09$) for the entire group and for the cohorts in terms of left or right hemisphere lesions (Spearman's R −0.15, L 0.17). Similarly, poor correlations were found for NIHSS scores and EHC errors (R −0.03, L 0.19) and NIHSS scores and total displacement (R 0.15, L 0.31) with both right and left hemisphere lesions respectively.

The NIHSS scores with visual acuity-in-noise ($r = 0.1$) and visual field loss ($r = -0.3$) return low correlations. **Figure 5** confirms the lack of correlation between mean deviation, EHC (SLURP) time and NIHSS score in **Figure 5A** or with Visual Acuity-in-Noise (VAn) in **Figure 5B**. It also demonstrates that the lesion location (hemisphere) does not mediate these processes.

The Role of Central Foveal Threshold on Visuomotor Performance

Although both the AIS and control groups had average high contrast visual acuity of 6/7.5, 62% of the AIS group showed a significant deterioration to 6/12 with visual acuity-in-noise whereas controls remained unaffected by the presence of luminance noise (17). Hence, as visual acuity-in-noise is a foveal task, we considered whether foveal thresholds might influence hemianopia. Significantly reduced foveal thresholds regardless of the side of the lesion (R = 18.4 dB and L = 18.0 dB) were present. However, EHC time in 13/19 left hemianopias and 16/19 right hemianopias return strong negative correlations with their EHC time (Spearmann's R: −0.57, L: −0.42) indicating that a reduced hemi-field sensitivity may underlie the poorer EHC task.

Lesion Effects on Expected Structure Function Relationships

The structure-function relationship between stroke and area of infarction was analyzed in terms of hemispheric localization of the stroke lesion and the time taken for completion of the EHC tasks (**Figure 6**). Surprisingly we find that lesions in most brain regions yield increases in tracking time for EHC performance (**Figure 6**). Our findings do not show any significant correlations between the hemisphere of lesion and the number of errors or the displacements made during the EHC task.

In **Figure 6**, the least impairment in EHC performance was found in our occipital lesion ($n = 7$, 67.1 ± 33.0 s) group in the right hemisphere, followed by "other lesion" cohorts in the right side ($n = 8$, 68.9 ± 16.3 s) which included 4 frontal lobe lesions, 3 parietal lobe lesions, 2 basal ganglia lesions, 2 pons lesions, 2 anterior cerebellar artery lesions, 1 internal carotid artery lesion, 1 prefrontal lesion, 1 internal capsule lesion and 1 corona radiata lesion.

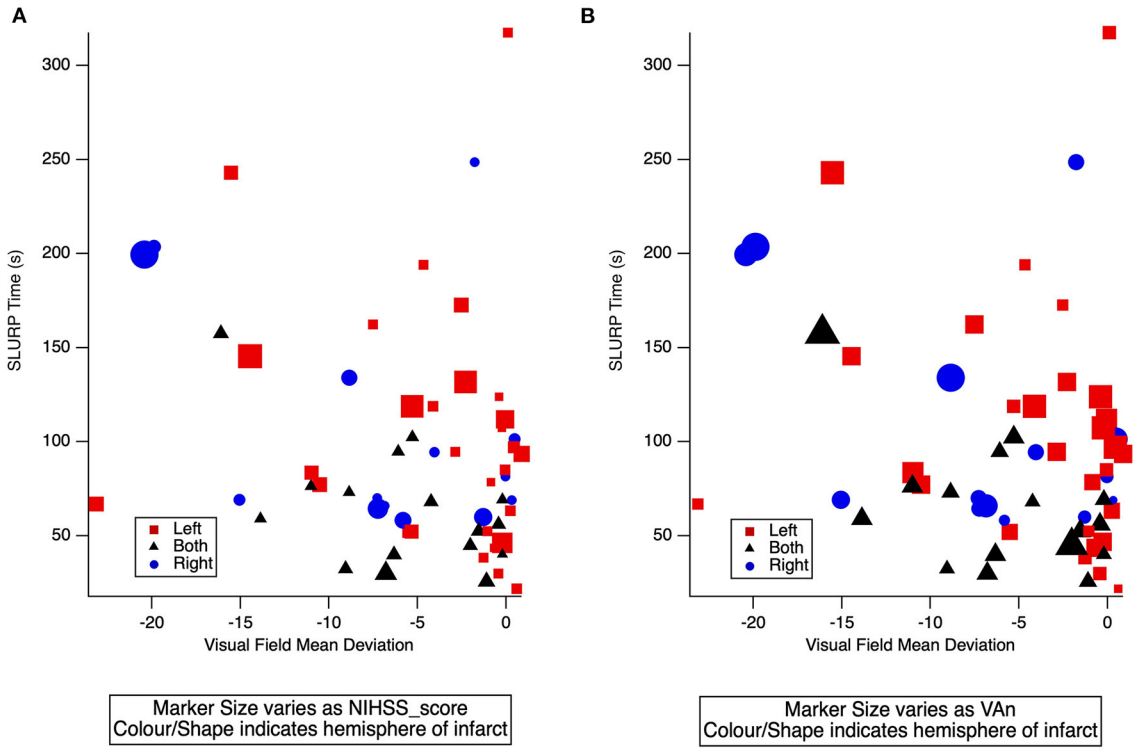

FIGURE 5 | (A) 3-D scatter plot of individual AIS patient EHC (SLURP) time and mean deviation of visual field sensitivity covarying with NIHSS score. **(B)** 3-D scatter plot of individual AIS patient EHC (SLURP) time and mean deviation of visual field sensitivity covarying with visual acuity-in-noise (VAn). Blue Circle: Right Hemisphere lesion, Red square: Left Hemisphere lesion, Black Triangle: a lesion in both hemispheres. Lesion site and severity of AIS is indicated by shape, color and size of spot respectively.

Value of Vision Tests in Identifying Cases of Early Stroke

Diagnostic accuracy of the MRFn visual field mean deviation, EHC time from the SLURP app, visual acuity (VA), visual acuity-in-noise and EHC time were evaluated by considering Receiver Operator Characteristics (ROC) (**Figure 7**). The ROC analyses shows a diagnostic specificity (98%) and sensitivity (67%), (AUC: 0.92, 95% CI: 0.86–0.97) for EHC time. Visual field mean deviation (AUC: 0.89, 95% CI: 0.83–0.95, has sensitivity: 68%, specificity: 94%). Visual acuity-in-noise returns a moderate AUC (AUC: 0.81, 95% CI: 0.72–0.89), with sensitivity (62%) and specificity (88%) whereas high contrast visual acuity had no diagnostic capacity in our mild stroke cases (AUC: 0.54, 95% CI: 0.43–0.66, sensitivity:20%, specificity:95% with performance that encompassed chance (diagonal line). Applying three tests (EHC time, Mean deviation, Acuity-in-noise) with an "OR" logic gives sensitivity (93%) and specificity (83%).

DISCUSSION

Vision Outcomes

As sensory-motor processing is a core diagnostic feature of AIS, vision and visuomotor capacity have been ascertained and quantified in 60 first event AIS patients with no prior history of visual anomalies during their first week of hospitalization. Assessments were made using the rapid SLURP EHC task (<2 min testing time) and the MRFn (<7 min testing time) apps. Although 41/60 of stroke sample showed significant visual field deficits, 37/60 presented a significant deterioration in visual acuity-in-noise and 40/60 showed a significant deterioration in the time taken to complete the visuomotor task and 18/41 with visual field deficits were unaware of any loss in vision. The presence of quantifiable visual deficits in 2/3 of AIS stroke population stand in line with the findings from previous studies where 92% of the 915 population of stroke patients referred for suspected vision problems, tested at a median of 22 days post-stroke presented some form of visual deficit, with the commonest being visual field deficits followed by visual attention deficits and eye movement deficits (13, 37).

Visuomotor Performance and the Role of Central Foveal Threshold on Visuomotor Performance

With our AIS cohort, 58/60 patients were capable of picking up, grasping, holding and using the iPad stylus pen in their preferred hand. They chose to use their previously dominant right hand even though 31/60 had confirmed lesions in the contralateral left hemisphere. Overall the AIS group were all able to trace the three prescribed shapes but the mean time for completion of the three items was significantly longer for the stroke group

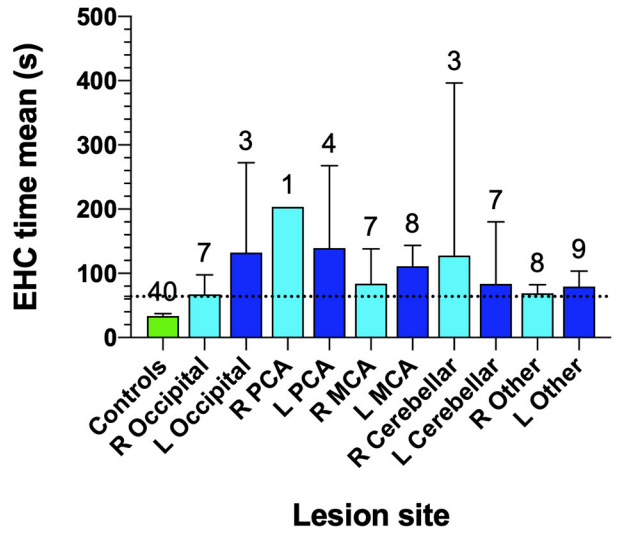

FIGURE 6 | Eye-hand coordination for controls and site of lesion in AIS patients. Cohort number is shown at the top of each bar. Bars identify mean EHC time for various lesion locations and error bars are SD. The horizontal dotted line identifies the 97.5th percentile for controls.

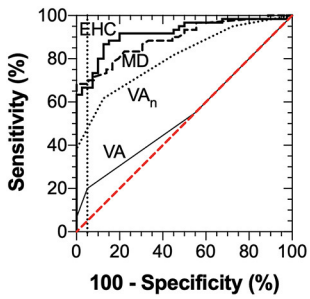

FIGURE 7 | ROC Analysis for visual acuity (AUC: 0.54, 95% CI: 0.43–0.66), visual acuity-in-noise (AUC: 0.81, 95% CI: 0.72–0.89), Mean Deviation of the visual field (AUC: 0.89, 95% CI: 0.83–0.95) and Eye-hand coordination (AUC: 0.92, 95% CI: 0.86–0.97) time.

than the age and vision matched healthy controls. Surprisingly the number of errors in tracing was similar for the stroke group to that of controls. However, the displacements per error of the stroke group were significantly larger and required longer time to relocate the stylus back to the task irrespective of hemisphere of lesion. See results illustrated in **Figure 4**.

Our results are consistent with previous studies that have shown that stroke patients require longer times to perform eye hand coordination tasks (3, 38, 39). Similar increases in time to perform a visuomotor task correctly has also been described in acquired traumatic brain injuries (40) and in the presence of impaired cognition in stroke (34). Such observations have been further associated with impaired proprioceptive judgments (41, 42) though previous results were predominantly considered for upper arm power and reaching action of the hand.

Our findings, for the same numbers of errors but significantly different displacements and relatively longer time to relocate to the pink "straw" path task of stroke patients compared to controls, is consistent with prior research showing that effective ocular-motor coordination requires optimal synergistic sensorimotor function of vision and proprioception (3, 43–45). Our findings also suggest that accuracy of motor control for familiar automatic routines is not grossly disturbed but rather that time and capacity to correct displacements following error requires conscious attention. Interestingly, our results would seem to indicate that optimal field of binocular vision was not entirely necessary to prevent tracing errors as 41/60 of our patients had quite severe visual field deficits with 31 having left hemisphere lesions. Previous research has demonstrated substantial foveal sparing (16) in the presence of hemianopia in stroke patients. However, consideration of foveal threshold sensitivity within the impaired visual field, i.e., hemianopia both on right and left, is significantly reduced with patients showing ∼18/30 dB visual field sensitivity and impacts on the timing to complete the EHC tasks.

Relationship Between NIHSS Scores and Vision and Visuomotor Function

Ten out of the 60 AIS patients demonstrated moderate motor impairment (46) with NIHSS scores >9. Of these 10 patients, 9/10 showed significant visual field deficits, 7/10 took significantly longer time for visuo-motor performance and 6/10 showed impaired visual-acuity-in noise. The low correlation between the NIHSS scores and EHC was unexpected and may be related to our small sample though the choice of all left hemisphere lesions patients to use their formerly preferred right hand irrespective of hemisphere of lesion argues against this. Rather the difference may be more related to the type of motor task and degree of familiarity and automatization associated with the manual movements requirements. Indeed our EHC tasks require well learnt automatized hand motor control rather than the NIHSS motor assessment requirement for voluntary control and organization of upper arm muscle power. Furthermore, NIHSS score encompasses ranking of sensory and motor function with prominent emphasis on motor components whereas EHC predominantly involves the fronto-parietal network with goal oriented fine motor action (3, 33) and less upper arm movement with the SLURP testing (21).

Lesion Effects on Expected Structure Function Relationships

Our findings indicate that right handed patients with left hemisphere lesions did not take significantly longer to complete EHC tracings than did right hemisphere lesion patients were most unexpected. Indeed, the significantly longer time for both the left and right hemisphere stroke patients to trace and complete a shape after deviating outside the outline suggests that stroke patients require a longer time to consciously re-plan and reprogram the recovery path than does motor control *per se* specially for those with right hemisphere lesions given that the right frontoparietal network is known to play a greater

role in attentional control of goal directed planning (47–49), and visuomotor actions. This interpretation was supported by **Figure 5** that shows the lack of correlation of EHC time with the NIHSS scores or hemisphere of lesion in our AIS participants.

An associated interpretation for our findings could be that the increased time taken in tracing the shapes in the "SLURP" EHC tasks, may reflect a generalized impairment in visually driven attention and conscious reprogramming of spatial relocation processing needed for visuomotor actions, as a direct result of an impairment in the fast conducting magnocellular driven foveal vision rather than stroke damage to motor function (50). Such an explanation is supported by the observation that as expected (13) the 5 patients with posterior cerebral artery (PCA) lesions and possible primary visual cortex and dorsal visual stream damage (1 Right hemisphere,1 Left occipital and 4 left PCA lesions) took greatest average durations to complete the item tracings (**Figure 4**) while most other stroke patients, irrespective of the site of the lesion or the hemisphere, required a similar amount of time to complete the tracings, which was significantly longer than control but less than in the PCA cases. Such a generalized AIS induced impairment in EHC further raises the possibility that widespread hemispheric oedema (51) in the days following an AIS episode is a contributing source of impairment for sensory-motor integration and reduced attention required for fast and precise previously automatic EHC (52).

Value of Vision Tests in Identifying Cases of Early Stroke

In terms of translatable findings and the diagnostic value of tablet based bedside vision tests in acute stroke management (18), our analysis of the ROC measures (**Figures 3**, **4**) indicate that the "time" taken to perform the tracing of the three SLURP items gives the most sensitive measure of visuomotor compromise. Both time and the "extent of the displacements" provide useful quantifiable measures of stroke and visuomotor performance in relation to hand stability (21) of the EHC task irrespective of hemisphere of lesion. In addition, our findings demonstrate that the visual acuity-in-noise, visual field deviation and EHC are better discriminants in aiding the diagnosis of acute stroke than the more generally used high contrast visual acuity which shows little diagnostic capacity.

Individual performance in tracing the three shapes has also been compared to determine if one shape might be more useful diagnostically than the other two. Interestingly, duration for circle tracing shows moderate sensitivity (57%) at a specificity of 95% in detecting an abnormality in EHC in relatively short time of 35.0 s in stroke patients at high correlations with both R (Spearmann's r 0.83) and L hemispheres (Spearmann's R 0.80). Both the circle and rabbit) show similar areas under the ROC curve indicating high diagnostic capacity. Thus, it would appear that using a single shape (rabbit or circle) could provide excellent diagnostic capacity with minimal test time, making this a clinically useful and rapid measure of visuomotor impairment. Such a rapid assay might be useful in home measurements and potentially in the ambulance and emergency department by the non-stroke team clinicians with added value to complement and aid in the diagnostic process. Recent studies have shown increased EHC deficits in the presence of hemianopias from stroke (53). We do not however claim that our findings of EHC deficits shown in SLURP are exclusive to stroke as we have not made comparisons with other similar groups such as acquired brain injury, Parkinson's disease, migraines and TIAs although not all acquired brain injury conditions are as likely to affect vision in the same way as for stroke patients.

LIMITATIONS

The generalizability of this study is limited by the size of the sample of mild-moderate AIS patients in a hospitalized environment that did not encourage testing of both hands to determine the effect on the non-dominant hand and contralateral hand. Most particularly small sample size made it difficult to compare hemispheric and lesion site effects on EHC duration in the hospital environment. A further limitation to our study is the lack of independent cohort groups such as migraine, other motor compromised disease such as Parkinson's disease, acquired brain injury and TIA patients to ascertain the ability of SLURP app to differentiate a stroke from such conditions that mimic stroke. Patient fatigue also limited testing of monocular as well as binocular effects of AIS on SLURP performance. A further limitation of the assessment of visuomotor function with the SLURP App is that the App operates in a two-dimensional plane which requires fine motor control rather than voluntary upper arm function and so is less of a test of upper arm movement and motor power than the holding of an arm extended palm down as undertaken with the NIHSS task. In addition, the SLURP App cannot be used in the presence of total upper limb paresis. On the other hand, SLURP app allows testing of focussed and sustained attention, ability to conform the hand to pick up and grasp the stylus and sophisticated manipulation of the hand and arm to enable tracing of the shapes. A further limitation to the theoretical interpretation is the lack of functional imaging, such as fMRI, to assess the extent of activation in visual attention networks during the performance of the impaired visual fields and during SLURP tracing by patients. However, despite these limitations, the translatable importance of the two Apps should be recognized in that the SLURP task is a sensitive quantifiable measure of the hand/grasp construct as in traditional EHC tests. The MRFn allows assessment of the most important sensory information in the form of vision that drives most cognitive and motor behavior and occupies the largest cortical and subcortical brain volume (48, 54).

Future Work

Further longitudinal follow up will be required to define the mechanisms and underlying structure-network-function relationships in visuomotor function in AIS. Large scale, multi center studies will be required to further validate and longitudinally monitor recovery of visuomotor function following stroke to establish relationships between more regionalized lesions, and impairment in the

goal directed parieto-frontal network activated during EHC tasks. Future studies with stroke mimics such as Parkinson's, migraines and TIA patients would also be required to explore the diagnostic value of SLURP in acute mild-moderate stroke.

CONCLUSION

Our findings and the methodology of the testing, demonstrate the translatable value of the iPad apps that can rapidly and sensitively quantify relative timing of residual visual capacity and motor sensory integration. In particular the SLURP app measures EHC that requires eye movement planning, visuomotor planning and executive functionality to achieve goal directed actions post-stroke. The MRFn and SLURP apps are patient friendly and together provide easy and fast (<9 min in total for most patients) clinical tools, that can be used to quantify and assess multiple brain functions required to plan, control and execute fine motor tasks following acquired brain injury such as stroke and could be used to monitor their recovery.

Our findings also demonstrate that EHC deficits occur irrespective of lesion site across most areas of the brain without a structure specific component indicating that AIS patients with good visual acuity (>6/12) do not show the expected specific lesion structure-function impairment with regard to residual visuomotor capacity. Indeed our results suggest that the ubiquitous cerebral dysfunction/oedema, that accompanies AIS (52), is likely to contribute significantly to many of the acute acquired deficits including ability to attend, planning movements and cognitive and affective status (6, 55, 56).

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 Sunshine Hospital, Western Health Ethics Committee, Melbourne, Australia, HREC/16/WH/1. 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, led acquisition and interpretation of all radiological data, NIHSS scores, and 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 and funded the study *via* internal grants, contributed to analysis, theoretical interpretation of the data, and 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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.757431/full#supplementary-material

Supplementary Table S1 | Raw data for controls and stroke participants.

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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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