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Clinical Evaluation, Treatment and Prognostication of Ischemic Stroke Patients

Edited by
Benjamin YQ Tan

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Benjamin YQ Tan

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Article

Impact of Traditional and Non-Traditional Lipid Parameters on Outcomes after Intravenous Thrombolysis in Acute Ischemic Stroke

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Abstract: Contradicting evidence exists regarding the role of lipids in outcomes following intravenous (IV) thrombolysis with tissue plasminogen activator (tPA). Restricted cubic spline curves and adjusted logistic regression were used to evaluate associations of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and LDL-C/HDL-C ratio with poor functional outcome, symptomatic intracranial hemorrhage (SICH) and 90-day mortality, among 1004 acute ischemic stroke (AIS) patients who received IV tPA in a comprehensive stroke center. Quartile (Q) 1, Q2 and Q3 of HDL-C were associated with increased odds of poor functional outcome (adjusted odds ratio (adjOR) 1.66, 95% CI 1.06–2.60, $p = 0.028$, adjOR 1.63, 95% CI 1.05–2.53, $p = 0.027$, adjOR 1.56, 95% CI 1.01–2.44, $p = 0.048$) compared to Q4. Q2 and Q4 of non-HDL-C were associated with increased odds of SICH (adjOR 4.28, 95% CI 1.36–18.90, $p = 0.025$, adjOR 5.17, 95% CI 1.64–22.81, $p = 0.011$) compared to Q3. Q1 and Q2 of LDL-C was associated with increased odds of mortality (adjOR 2.57, 95% CI 1.27–5.57, $p = 0.011$ and adjOR 2.28, 95% CI 1.10–5.02, $p = 0.032$) compared to Q3. In AIS patients who received IV tPA, low LDL-C was associated with increased odds of mortality while HDL-C may be protective against poor functional outcome.

Keywords: ischemic stroke; intravenous thrombolysis; tissue plasminogen activator; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; symptomatic intracranial hemorrhage

1. Introduction

Stroke incidence and stroke-related mortality increased substantially from 1990 to 2019, and the stroke burden will continue to increase globally, especially in underdeveloped countries [1]. In Singapore, a study reported an increased prevalence of stroke risk factors and the increased crude incidence rate of stroke among those younger than 65 [2]. There has been conflicting evidence on how lipid parameters affect post-thrombolysis outcomes [3,4], with non-traditional lipid parameters like non-HDL-C suggested to have similar functions as LDL-C in predicting hemorrhagic transformation (HT) [5]. Pre-stroke statin use was

also shown to influence ischemic stroke outcomes [6].Hence, we aimed to explore the general associations of selected traditional and non-traditional lipid parameters with post-thrombolysis outcomes, to compare their clinical utility in prognostication. One significance of this study is to facilitate determination of cholesterol target levels in achieving optimal post-stroke recovery. Lastly, there are varied results on the relationship between lipid parameters and large artery atherosclerosis (LAA) stroke subtype. Bang et al. found that higher non-HDL-C and TG, but not LDL-C, was associated with LAA. Several studies have also shown that LDL-C may not best predict atherosclerotic vascular risk [7]. However, Hindy et al. suggested LDL-C lowering likely reduces LAA risk [8]. These should be further assessed to evaluate the utility of targeting lipid parameters for LAA stroke prevention.

2. Materials and Methods

2.1. Study Design

In this study, we included consecutive patients who received IV tPA from September 2006 to June 2018. All these patients had no contraindications to IV tPA use. The study obtained ethics approval from the National Healthcare Group-Domain Specific Review Board (NHG DSRB Ref: 2010/00509). Patients were assessed by a neurologist for eligibility to receive intravenous thrombolysis according to institutional protocol and American Heart Association/American Stroke Association guidelines at a standard dose of 0.9 mg/kg body weight [9]. All thrombolysed stroke patients underwent standard non-contrast head computed tomography and computed tomography brain and neck angiography. Patients who were deemed as unsuitable for IV-tPA, or who underwent endovascular thrombectomy were excluded from the study. Patients that were included had valid lipid parameters of TC, HDL-C and TG collected in fasting conditions, in mmol/litre, that were taken within 24 h of their AIS admission as per our institution protocol (Figure 1).

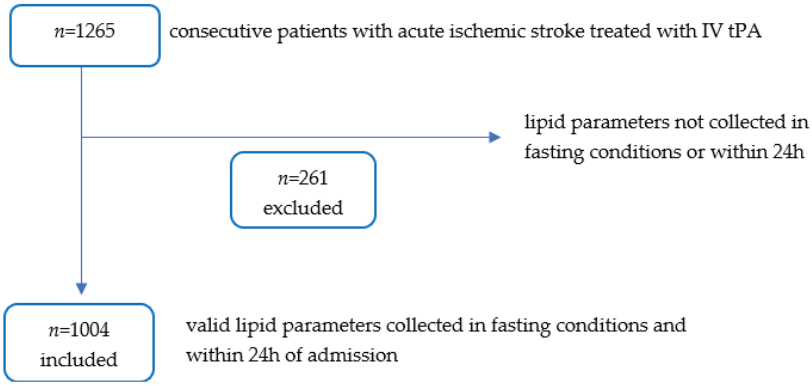

Figure 1. Flow Diagram Illustrating Only Patients with Valid Lipid Parameters were Analysed.

LDL-C was calculated by the Friedewald equation (TC-HDL-C-TG/5) [10], while some had LDL-C collected directly. Non-HDL-C levels were calculated by subtracting HDL-C levels from TC. LDL-C/HDL-C ratio was calculated by dividing LDL-C by HDL-C. Other baseline demographics, clinical parameters and ischemic stroke characteristics were collected and tabulated within 24 h of AIS admission. Diabetes mellitus (DM) was defined as pre-existing diagnosis of diabetes mellitus or an admitting fasting blood glucose level greater than or equal to 7.0 mmol/L or an HbA1c greater than or equal to 6.5% [11]. The severity of stroke at presentation was assessed using the National Institute of Health Stroke Scale (NIHSS) [12]. This assessment was made by credentialed nurses as part of the acute stroke response team. The presence of Large Vessel Occlusion (LVO) was defined as occlusions of the first and second segment of the middle cerebral artery (MCA), M1 and M2, the Internal Carotid Artery (ICA) and as well as its terminus, tandem occlusions involving ICA-MCA, or occlusion of the basilar artery. The Trial of ORG 10172 in Acute Stroke

Treatment (TOAST) criteria was used by the treating stroke neurologist to classify stroke subtypes [13]. Investigations to evaluate the TOAST mechanism included: vessel imaging with either computed tomography angiography (CTA), magnetic resonance angiography (MRA), transcranial doppler (TCD), carotid duplex or a combination of these, as well as Holter monitoring and transthoracic echocardiography.

The primary outcome measured was poor functional outcome (90-day modified Rankin Scale (mRS) of 3–6). Secondary outcomes measured were symptomatic intracranial hemorrhage (SICH) and 90-day all-cause mortality. SICH was based on the European Cooperative Acute Stroke Study (ECASS) II definition [14]. The 90-day mRS was evaluated during follow-up visit to the stroke clinic. If not, mRS was evaluated via telephone call instead.

2.2. Data Analysis

Analyses were performed using SPSS for Windows version 27.0 (SPSS Inc, Chicago, IL, USA) and R version 4.0.5. Restricted cubic splines with 5 knots were plotted to visually assess the univariate associations between the lipid parameters and the three outcomes. These served qualitative and descriptive purposes only. Since non-linear (U-shaped/inverse U-shaped/J-shaped/reverse tick) associations were found, lipid parameters were divided into quartiles for analysis. Descriptive statistics for continuous variables were presented as mean (SD) when normality and homogeneity assumptions were satisfied, otherwise as median (interquartile range) (IQR), and n (%) for categorical variables. Differences in continuous variables were assessed using 2 sample t-test when normality and homogeneity assumptions were satisfied; otherwise, Mann-Whitney U test was used where data was not distributed normally. Chi-square or Fisher's exact test was used for categorical variables. Covariates that were selected a priori for variable adjustment were gender, age, hypertension, atrial fibrillation, large vessel occlusion, diabetes mellitus, admitting NIHSS and admitting SBP. Logistic regression assessed the associations between lipid levels and outcomes, and with LAA. Results were presented as adjusted odds ratio (adjOR) with 95% confidence interval (CI). Statistical significance was set at two-sided $p < 0.05$.

3. Results

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.1. Baseline Characteristics and Associations of Lipid Parameters with LAA

1265 consecutive patients with ischemic stroke treated with IV tPA were analyzed and 1004 patients with valid lipid assessments were included in this study. Of 1004 patients, 589/986 (59.7%) were male, 586/883 (66.4%) were of Chinese ethnicity, 596/916 (65.1%) experienced a LVO and 190/1004 (18.9%) had AF. There were 657/1004 (65.4%) patients with history of with hypertension, 526/1004 (52.4%) with hyperlipidemia, and 306/1004 (30.5%) with diabetes mellitus. Median age was 66 (IQR 56–77) years while median admitting NIHSS was 15 (IQR 8–21). Median LDL-C, non-HDL-C, TC, HDL-C and LDL-C/HDL-C were 2.86 (IQR 2.18–3.50) mmol/L, 3.43 (IQR 2.70–4.19) mmol/L, 4.62 (IQR 3.86–5.36) mmol/L, 1.12 (IQR 0.95–1.32) mmol/L and 2.49 (IQR 1.84–3.30) respectively. In accordance with the TOAST classification, 322/975 (33.0%) had LAA stroke, 341/975 (35.0%) had cardioembolic (CE) stroke, 168/975 (17.2%) had small vessel occlusion (SVO), 10/975 (1.0%) had stroke of other determined etiology and 134/975 (13.7%) had cryptogenic stroke (Table 1).

Table 1. Baseline Characteristics of Study Population.

	Total (n = 1004)
Age (years)	66 [56,77]
Gender (male)	589/986 (59.7)
Race	
Chinese	586/883 (66.4)
Malay	188/883 (21.3)
Indian	62/883 (7.0)
Others	47/883 (5.3)
Lipid parameters	
LDL-C (mmol/L)	2.86 [2.18, 3.50]
Non-HDL-C (mmol/L)	3.43 [2.70, 4.19]
HDL-C (mmol/L)	1.12 [0.95, 1.32]
TC (mmol/L)	4.62 [3.86, 5.36]
LDL-C/HDL-C Ratio	2.49 [1.84, 3.30]
Stroke parameters	
Admitting NIHSS	15 [8,21]
Admitting SBP (mmHg)	152 [136,168]
Admitting DBP (mmHg)	82 [72,92]
Large vessel occlusion	596/916 (65.1)
Comorbidities	
Smoker	148 (14.7)
Hypertension	657 (65.4)
Hyperlipidemia	526 (52.4)
Diabetes mellitus	306 (30.5)
Atrial fibrillation	190 (18.9)
Stroke Subtype (TOAST)	
LAA	322/975 (33.0)
CE	341/975 (35.0)
SVO	168/975 (17.2)
Stroke of other determined etiology	10/975 (1.0)
Cryptogenic	134/975 (13.7)
Glucose level	
Fasting glucose (mmol/L)	5.90 [5.20, 7.30]
HbA1C (%)	6.00 [5.60, 6.90]

Values are median [IQR] for numerical variables and n/total (%) or n (%) for categorical variables. Abbreviations: mRS modified Rankin Scale, LDL-C high-density lipoprotein cholesterol, non-HDL-C non-high-density lipoprotein cholesterol, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, NIHSS National Institutes of Health Stroke Scale, SBP systolic blood pressure, DBP diastolic blood pressure, TOAST Trial of ORG 10172 in Acute Stroke Treatment, LAA large-artery atherosclerosis, CE cardioembolic, SVO stroke of other determined etiology, HbA1c Hemoglobin A1c.

Comparing LAA and non-LAA groups, median LDL-C, non-HDL-C, LDL-C/HDL-C ratio, as well as white blood cell (WBC) count, neutrophils, platelets, admitting NIHSS and presence of LVO were significantly higher in the LAA compared to non-LAA group (Table S1). Regarding lipid parameters and associations with LAA, after adjustment for gender, age, hypertension, atrial fibrillation, large vessel occlusion, diabetes mellitus, admitting NIHSS and admitting SBP, the following results were obtained. Q4 of LDL-C was associated with increased odds of LAA (adjusted odds ratio (adjOR) 1.69, 95% CI 1.07–2.69, $p = 0.024$) compared to Q1. Q2 and Q4 of non-HDL-C was significantly associated with increased odds of LAA (adjOR 1.64, 95% CI 1.04–2.60, $p = 0.035$ and adjOR 1.75, 95% CI 1.10–2.80, $p = 0.018$ respectively) compared to Q1. Q3 of HDL-C was associated with increased odds of LAA (adjOR 1.84, 95% CI 1.16–2.95, $p = 0.010$) compared to Q4. Lastly, Q3 and Q4 of LDL-C/HDL-C were associated with increased odds of LAA (adjOR 1.88, 95% CI 1.18–3.00, $p = 0.008$ and adjOR 1.71, 95% CI 1.07–2.77, $p = 0.027$ respectively) compared to Q1 (Table 2).

Table 2. Lipid Parameters and Associations with LAA.

	LAA			
	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
LDL-C:				
Q1	1.0	-	1.0	-
Q2	1.28 (0.87–1.88)	0.209	1.42 (0.90–2.25)	0.130
Q3	1.03 (0.69–1.51)	0.898	1.27 (0.79–2.05)	0.323
Q4	1.64 (1.13–2.40)	0.010	1.69 (1.07–2.69)	0.024
Non-HDL-C:				
Q1	1.0	-	1.0	-
Q2	1.39 (0.95–2.04)	0.093	1.64 (1.04–2.60)	0.035
Q3	1.09 (0.74–1.62)	0.657	1.25 (0.78–2.01)	0.355
Q4	1.62 (1.11–2.37)	0.013	1.75 (1.10–2.80)	0.018
TC:				
Q1	1.03 (0.70–1.52)	0.874	0.93 (0.59–1.47)	0.767
Q2	1.0	-	1.0	-
Q3	1.11 (0.76–1.62)	0.603	1.11 (0.71–1.74)	0.645
Q4	1.30 (0.89–1.90)	0.170	1.28 (0.82–1.99)	0.277
HDL-C				
Q1	1.44 (0.98–2.13)	0.067	1.27 (0.79–2.04)	0.320
Q2	1.30 (0.88–1.93)	0.183	1.30 (0.81–2.08)	0.276
Q3	1.76 (1.19–2.60)	0.005	1.84 (1.16–2.95)	0.010
Q4	1.0	-	1.0	-
LDL-C/HDL-C:				
Q1	1.0	-	1.0	-
Q2	1.10 (0.74–1.63)	0.646	1.26 (0.79–2.02)	0.333
Q3	1.67 (1.14–2.46)	0.009	1.88 (1.18–3.00)	0.008
Q4	1.69 (1.16–2.49)	0.007	1.71 (1.07–2.77)	0.027

Abbreviations: OR: Odds Ratio, 95% CI 95% Confidence Interval, Q1 first quartile, Q2 s quartile, Q3 third quartile, Q4 fourth quartile, LAA large-artery atherosclerosis, LDL-C high-density lipoprotein cholesterol, non-HDL-C non-high-density lipoprotein cholesterol, TC total cholesterol, HDL-C high-density lipoprotein cholesterol. Variables adjusted for in multivariate analysis include gender, age, hypertension, atrial fibrillation, large vessel occlusion, diabetes mellitus, admitting NIHSS and admitting SBP. The quartiles for non-HDL-C were Q1: ≤2.7mmol/L, Q2: >2.7–3.43 mmol/L, Q3: >3.43–4.19 mmol/L, Q4: >4.19mmol/L. The quartiles for LDL-C were Q1: ≤2.18 mmol/L; Q2: >2.18–2.86 mmol/L, Q3: >2.86–3.50 mmol/L, Q4: >3.50 mmol/L. The quartiles for TC were Q1: ≤3.85 mmol/L, Q2: >3.85–4.63 mmol/L, Q3: >4.63–5.36 mmol/L, Q4: >5.36 mmol/L. The quartiles for HDL-C were Q1: ≤0.95 mmol/L, Q2: >0.95–1.12 mmol/L, Q3: >1.12–1.32 mmol/L, Q4: >1.32 mmol/L. The quartiles for LDL/HDL ratio were Q1: ≤1.84, Q2: >1.84–2.49, Q3: >2.49–3.30, Q4: ≥3.30.

3.2. Stroke Outcomes

Of 1004 patients, 479/995 (48.1%) experienced poor functional outcomes (mRS 3–6), 48/1003 (4.8%) suffered SICH and 117/990 (11.8%) died. (Table 3) There was no statistically significant difference in prevalence of these three outcomes between the LAA and non-LAA group (Table S2).

Table 3. Stroke Outcomes.

Stroke Outcomes	Total (*n* = 1004)
Poor functional outcome (90-day mRS 3–6)	479/995 (48.1)
SICH	48/1003 (4.8)
90-day mortality	117/990 (11.8)

Values are *n*/total (%). Abbreviations: mRS modified Rankin Scale, SICH symptomatic intracranial hemorrhage.

3.3. Associations of Lipid Parameters with Poor Functional Outcome, SICH and Mortality

When evaluating the following relationships between lipid parameters and outcomes measured, variables adjusted for in the multivariate model include gender, age, hypertension, atrial fibrillation, large vessel occlusion, diabetes mellitus, admitting NIHSS and admitting SBP.

3.3.1. Poor Functional Outcome

Restricted cubic spline curves showed a 'reverse tick' relationship between LDL-C, non-HDL-C and TC with poor functional outcome (Figure 2).

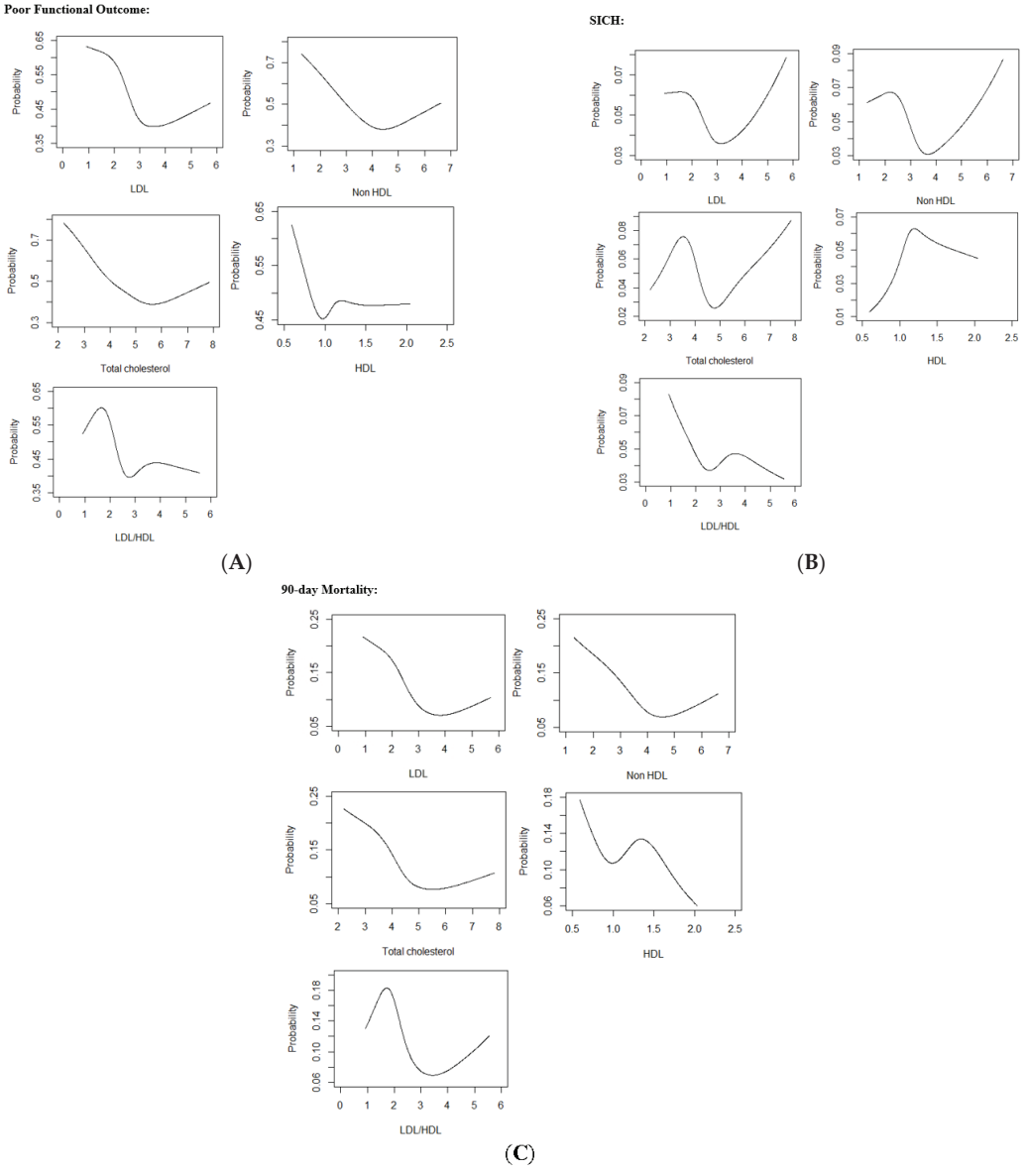

Figure 2. (**A**) Restricted Cubic Spline Curves relating Lipid Parameters with Poor Functional Outcome (**B**) Restricted Cubic Spline Curves relating Lipid Parameters with SICH (**C**) Restricted Cubic Spline Curves relating Lipid Parameters with Mortality.Abbreviations: LDL low-density lipoprotein cholesterol, HDL high-density lipoprotein cholesterol, LDL/HDL low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, SICH symptomatic intracranial hemorrhage.

In multivariate analysis, Q1, Q2 and Q3 of HDL-C were significantly associated with increased odds of poor functional outcome (adjOR 1.66, 95% CI 1.06–2.60, $p = 0.028$, adjOR 1.63, 95% CI 1.05–2.53, $p = 0.027$ and OR 1.56, 95% CI 1.01–2.44, $p = 0.048$ respectively) when compared to Q4. Q2 and Q4 of LDL-C/HDL-C ratio were associated increased odds of poor functional outcome (adjOR 1.56, 95% CI 1.02–2.41, $p = 0.043$, OR: 1.78, 95% CI 1.16–2.76, $p = 0.009$ respectively) when compared to Q3 (Table 4).

Table 4. Association of Lipid Parameters with Poor Functional Outcome, SICH and Mortality.

	Poor Functional Outcome (mRS 3–6)					
	Univariate Analysis			**Multivariate Analysis**		
	OR	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
LDL-C:						
Q1	2.18	1.52–3.12	<0.001	1.33	0.87–2.03	0.196
Q2	1.19	0.83–1.70	0.339	1.0	-	-
Q3	1.00	0.70–1.43	0.997	1.11	0.72–1.70	0.647
Q4	1.0	-	-	1.12	0.73–1.71	0.607
Non-HDL-C:						
Q1	2.56	1.79–3.68	<0.001	1.30	0.84–2.03	0.241
Q2	1.51	1.06–2.15	0.024	1.05	0.69–1.62	0.809
Q3	1.0	-	-	1.0	-	-
Q4	1.16	0.81–1.66	0.421	1.19	0.78–1.83	0.416
TC:						
Q1	2.38	1.66–3.42	<0.001	1.38	0.90–2.14	0.141
Q2	1.37	0.96–1.95	0.082	1.05	0.69–1.62	0.810
Q3	1.0	-	-	1.0	-	-
Q4	1.08	0.76–1.54	0.672	1.10	0.72–1.68	0.651
HDL-C:						
Q1	1.09	0.77–1.56	0.626	1.66	1.06–2.60	0.028
Q2	1.09	0.76–1.54	0.646	1.63	1.05–2.53	0.027
Q3	1.0	-	-	1.56	1.01–2.44	0.048
Q4	1.04	0.72–1.49	0.839	1.0	-	-
LDL-C/HDL-C Ratio:			<0.001			
Q1	2.31	1.61–3.32	<0.001	1.27	0.81–1.97	0.294
Q2	2.00	1.40–2.87	-	1.56	1.02–2.41	0.043
Q3	1.0	-	0.069	1.0	-	-
Q4	1.39	0.98–2.00		1.78	1.16–2.76	0.009

	Symptomatic Intracranial Hemorrhage (SICH)					
	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
LDL-C:						
Q1	2.37	0.99–6.27	0.062	1.84	0.71–5.37	0.227
Q2	1.62	0.63–4.48	0.324	1.41	0.52–4.21	0.514
Q3	1.0	-	-	1.0	-	-
Q4	2.10	0.86–5.63	0.115	2.22	0.85–6.47	0.117
Non-HDL-C:						
Q1	3.59	1.27–12.80	0.026	3.19	0.99–14.30	0.078
Q2	3.88	1.38–13.75	0.017	4.28	1.36–18.90	0.025
Q3	1.0	-	-	1.0	-	-
Q4	3.93	1.40–13.93	0.016	5.17	1.64–22.81	0.011

Table 4. *Cont.*

TC:						
Q1	4.92	1.58–21.55	0.013	3.58	1.12–15.96	0.052
Q2	5.28	1.71–22.98	0.009	4.46	1.43–19.59	0.021
Q3	1.0	-	-	1.0	-	-
Q4	5.68	1.86–24.62	0.006	5.29	1.69–23.33	0.010
HDL-C:						
Q1	1.0	-	-	1.0	-	-
Q2	2.82	1.15–7.93	0.032	3.07	1.23–8.75	0.022
Q3	1.82	0.67–5.43	0.253	2.08	0.74–6.34	0.173
Q4	2.68	1.07–7.63	0.045	2.26	0.85–6.74	0.116
LDL-C/HDL-C Ratio:						
Q1	2.23	0.97–5.54	0.068	1.49	0.63–3.83	0.378
Q2	1.40	0.56–3.67	0.479	1.07	0.41–2.89	0.897
Q3	1.0	-	-	1.0	-	-
Q4	1.54	0.62–3.99	0.355	1.55	0.61–4.14	0.367
	Mortality					
	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
LDL-C:						
Q1	3.43	1.93–6.42	<0.001	2.57	1.27–5.57	0.011
Q2	2.19	1.18–4.19	0.015	2.28	1.10–5.02	0.032
Q3	1.0	-	-	1.0	-	-
Q4	1.46	0.75–2.89	0.272	1.96	0.89–4.49	0.101
Non-HDL-C:						
Q1	2.25	1.29–4.03	0.005	1.06	0.54–2.14	0.669
Q2	1.94	1.10–3.51	0.025	1.55	0.79–3.14	0.204
Q3	1.0	-	-	1.0	-	-
Q4	1.01	0.53–1.94	0.968	1.10	0.53–2.34	0.744
TC:						
Q1	2.60	1.50–4.63	<0.001	1.44	0.77–2.76	0.266
Q2	1.65	0.92–3.02	0.097	1.16	0.60–2.30	0.657
Q3	1.0	-	-	1.0	-	-
Q4	1.08	0.57–2.05	0.818	1.04	0.51–2.15	0.904
HDL-C:						
Q1	1.19	0.67–2.11	0.553	1.16	0.62–2.21	0.639
Q2	1.36	0.78–2.38	0.280	1.38	0.75–2.55	0.296
Q3	1.0	-	-	1.10	0.57–2.10	0.784
Q4	1.16	0.65–2.07	0.623	1.0	-	-
LDL-C/HDL-C Ratio:						
Q1	2.28	1.29–4.15	0.005	1.55	0.80–3.14	0.204
Q2	2.27	1.29–4.13	0.006	2.51	1.30–5.05	0.008
Q3	1.0	-	-	1.0	-	-
Q4	1.06	0.55–2.06	0.857	1.46	0.68–3.17	0.338

Abbreviations: OR odds ratio, 95% CI 95% confidence interval, SICH symptomatic intracranial hemorrhage, mRS modified Rankin Scale, Q1: first quartile, Q2: second quartile, Q3: third quartile and Q4: fourth quartile. LDL-C high-density lipoprotein cholesterol, non-HDL-C non-high-density lipoprotein cholesterol, TC total cholesterol, HDL-C high-density lipoprotein cholesterol. Variables adjusted for in multivariate analysis include gender, hypertension, atrial fibrillation, large vessel occlusion, diabetes mellitus, age, admitting NIHSS and admitting SBP. The quartiles for non-HDL-C were Q1: ≤2.7mmol/L, Q2: >2.7–3.43 mmol/L, Q3: >3.43–4.19mmol/L, Q4: >4.19mmol/L. The quartiles for LDL-C were Q1: ≤2.18mmol/L; Q2: >2.18–2.86 mmol/L, Q3: >2.86–3.50 mmol/L, Q4: >3.50 mmol/L. The quartiles for TC were Q1: ≤3.85mmol/L, Q2: >3.85–4.63mmol/L, Q3: >4.63–5.36mmol/L, Q4: >5.36mmol/L. The quartiles for HDL-C were Q1: ≤0.95 mmol/L, Q2: >0.95–1.12 mmol/L, Q3: >1.12–1.32 mmol/L, Q4: >1.32 mmol/L. The quartiles for LDL/HDL ratio were Q1: ≤1.84, Q2: >1.84–2.49, Q3: >2.49–3.30, Q4: ≥3.30.

3.3.2. SICH

Restricted cubic spline curve showed a U-shaped association between non-HDL-C and LDL-C with SICH. (Figure 2) The lipid parameters that had significant non-linear relationships with SICH were non-HDL-C and TC. In multivariate analysis, Q2 and Q4 of non-HDL-C were significantly associated with SICH (adjOR 4.28, 95% CI 1.36–18.90, $p = 0.025$ and adjOR 5.17, 95% CI 1.64–22.81, $p = 0.011$ respectively) when compared to Q3. Similarly, Q2 and Q4 of TC were significantly associated with increased odds SICH (adjOR 4.46, 95% CI 1.43–19.59, $p = 0.021$ and adjOR 5.29, 95% CI 1.69–23.33, $p = 0.010$ respectively) when compared to Q3. Q2 of HDL-C remained significantly associated with increased odds of SICH (adjOR 3.07, 95% CI 1.23–8.75, $p = 0.022$) when compared to Q1 (Table 4).

3.3.3. 90-Day Mortality

Restricted cubic spline curves showed a 'reverse tick' relationship of LDL-C, non-HDL-C and TC with mortality. (Figure 2) In multivariate analysis, Q1 and Q2 of LDL-C were significantly associated with increased odds of mortality (adjOR 2.57, 95% CI 1.27–5.57, $p = 0.011$ and adjOR 2.28, 95% CI 1.10–5.02, $p = 0.032$) when compared to Q3. Q2 of LDL-C/HDL-C was associated with increased odds of mortality (adjOR 2.51, 95% CI 1.30–5.05, $p = 0.008$) when compared to Q3. No significant associations were found to relate non-HDL-C, TC and HDL-C with mortality on multivariate analysis (Table 4). Results of logistic regressions that adjusted for age and gender only, and age, gender, admitting NIHSS and LVO, are illustrated in the Supplementary Material (Tables S4 and S5).

4. Discussion

It was found that firstly, low HDL-C was associated with poor functional outcome, and secondly, a U-shaped relationship was found between non-HDL-C and SICH. Finally, low LDL-C was also found to be associated with increased mortality.

4.1. Lipid Parameters and Functional Neurological Outcome

We found that high HDL-C tended to be protective against poor functional outcome. This corroborates with a past Japanese study that found higher HDL-C and increased odds of favourable functional outcome after tPA thrombolysis [15]. This can be explained by how HDL reduces neuronal injury after ischemic stroke, possibly through anti-oxidative or anti-inflammatory pathways [16]. By suppressing inflammatory responses, HDL-C could promote neurological recovery because inflammatory cells and responses like neutrophils and neutrophil accumulation have been shown to cause poorer neurological outcome [17]. Next, our study found that the relationship between LDL-C/HDL-C and functional outcome may be non-linear, expanding on a previous Chinese study of 763 AIS patients treated with tPA, that demonstrated a LDL-C/HDL-C ratio cut-off of <2.71 was associated with higher risk of poor outcome [18]. Higher LDL-C/HDL-C was also found to be protective against mRS >2 at 3 months [19]. However, the relationship between LDL-C/HDL-C and functional outcome after ischemic stroke thrombolysis continues to be inconclusive.

4.2. Lipid Parameters and SICH

When investigating relationships with SICH, we found a U-shaped and non-linear relationship of non-HDL-C and TC with SICH respectively. Previously, a Chinese study found that lower non-HDL-C resulted in greater risk of hemorrhagic transformation [5], but other studies were unable to validate this association [3,20]. Conclusions on associations between TC and SICH were also varied [21,22]. Our finding of a U-shaped relationship between non-HDL-C and SICH where increased risk of SICH occurs at either moderately low or high non-HDL concentrations could explain the discrepancy in prior studies' results. Postulated mechanisms include how low cholesterol reflects poor general health and undernourishment that predisposes individuals to hemorrhagic transformation unrelated to cholesterol pathways [23]. High non-HDL-C could increase risk of SICH through the development of arterial stiffness, which independently increases the risk of hemorrhagic transformation in

thrombolysis-treated stroke patients [24]. Next, some studies have suggested a correlation between lower LDL-C and increased SICH risk [25,26]. In our study, non-HDL-C, but not LDL-C, was significantly associated with SICH. This is a surprising finding because LDL-C is a major component of non-HDL-C. However, other lipoproteins which contribute to non-HDL-C, such as very-low-density lipoproteins, intermediate-density lipoproteins and lipoprotein(a) could affect SICH occurrence. For instance, lipoprotein(a) was found to reduce bleeding risk in the brain due to its hemostatic properties [27]. Past studies have also demonstrated significant differences in the predictive ability of non-HDL-C and LDL-C on major adverse cardiac events (MACE) [28], reinstating the different roles of non-HDL-C and LDL-C in cardiovascular and cerebrovascular events.

4.3. LDL-C and Mortality

Our study found low LDL-C was significantly associated with increased odds of 90-day all-cause mortality after multivariate adjustment. This association has also been previously suggested outside of stroke—in a systematic review involving 68094 elderly patients, an inverse association between LDL-C and all-cause mortality was found, hypothesized by how low LDL-C increased vulnerability to fatal illnesses [29]. In our study, patients with low LDL-C had more comorbidities, (Table S3) which likely increased mortality predisposition. Hence, it was proposed that low LDL-C is an indirect indicator of severe illness rather than the cause of increased mortality [30]. Another explanation, although speculative, is the interaction between low LDL-C with dysbiosis and changes to bile acid metabolism that eventually leads to mortality [31]. The finding of low LDL-C increasing mortality may also be attributed to AIS patients without prior statin use, supported by Cheng et al. who found that low LDL-C was associated with higher mortality rates in statin-naïve acute ischemic stroke [32]. This finding is therefore generalized without comparison between statin, non-statin or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use.

4.4. Analysis of Lipid Parameters with LAA Subtype

This study also found that LDL-C, non-HDL-C, HDL-C and LDL-C/HDL-C were significantly associated with LAA after multivariate adjustment. Previous studies found elevated LDL-C a risk factor for atherothrombotic infarct, and LDL-C higher in LAA than other stroke subtypes [33,34]. Our finding of high LDL-C and increased odds of LAA can be explained by LDL-C's association with intracranial and extracranial stenosis [35]. Next, our study found that higher HDL-C may be more desirable than moderate HDL-C levels in protection against LAA, reasoned by how HDL-C increases LDL-C reverse transport, delivers antioxidants to LDL-C and decreases susceptibility of LDL-C to oxidation in endothelium, slowing the process of atherosclerosis [36]. Lastly, our finding of high LDL-C/HDL-C ratio and association with increased odds of LAA can be explained by the atherogenicity of LDL-C and atheroprotection by HDL-C, supporting the previous finding of LDL-C/HDL-C ratio and its association with increased intima-media thickness, a measure of subclinical atherosclerosis [37]. Thus, high LDL-C/HDL-C ratio may be a useful indicator of atherosclerosis to help identify patients at higher risk of LAA stroke.

5. Strengths and Limitations

Our study is a comprehensive report detailing associations of selected lipid parameters with post-thrombolysis outcomes, representing a relatively large cohort size (1004 patients analysed) compared to previous thrombolysis studies. However, this study was a single institution retrospective cohort study that solely evaluated intravenous thrombolysis patients. This may limit the generalisability of results to other cohorts, warranting more prospective studies on lipid parameters and ischemic stroke outcomes. We would like to acknowledge the possibility of Type I error in the multivariate analyses in which significant associations may no longer hold true after Bonferroni correction. Excessive correction of statistical level of significance may also increase the likelihood of Type II error as a trade-off to reduce Type I error, which may increase false negatives. The multivariate

relationship between HDL-C and poor functional outcome is to be interpreted with caution as no significant relationship was found on univariate analysis, in which the possible reasons can be explained statistically by Lo et al. and Wang et al. [38,39]. Hence further studies in this area are required to confirm this association. Our study did not distinguish statin and non-statin users or evaluated use of other lipid-lowering agents, nor compare antithrombotic drug use which could theoretically affect SICH risk. Comorbidities like chronic kidney disease could be a confounder that should be explored in future studies. We would suggest future studies compare ischemic stroke outcomes between intravenous thrombolysis, intra-arterial thrombolysis and mechanical thrombectomy cohorts, and evaluate the role of other non-traditional lipid measures like TG/HDL-C and TC/HDL-C ratio in these treatment options.

6. Conclusions

In AIS patients who received IV tPA, low LDL-C was associated with increased odds of mortality while HDL-C may be protective against poor functional outcome.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11237148/s1: Table S1: Baseline Characteristics of LAA vs. non-LAA Stroke Mechanisms; Table S2: Stroke Outcomes of LAA vs. non-LAA Mechanisms; Table S3: Baseline Characteristics of Study Population by LDL-C Quartiles; Table S4: Association of Lipid Parameters with Poor Functional Outcome, SICH and Mortality (Adjustment for Age and Gender only); Table S5: Association of Lipid Parameters with Poor Functional Outcome, SICH and Mortality (Adjustment for Age, Gender, Admitting NIHSS and Large Vessel Occlusion).

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References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* **2021**, *20*, 795–820. [CrossRef] [PubMed]
2. Tan, B.Y.Q.; Tan, J.T.C.; Cheah, D.; Zheng, H.; Pek, P.P.; De Silva, D.A.; Ahmad, A.; Chan, B.P.L.; Chang, H.M.; Kong, K.H.; et al. Long-Term Trends in Ischemic Stroke Incidence and Risk Factors: Perspectives from an Asian Stroke Registry. *J. Stroke* **2020**, *22*, 396–399. [CrossRef] [PubMed]
3. Rocco, A.; Sykora, M.; Ringleb, P.; Diedler, J. Impact of statin use and lipid profile on symptomatic intracerebral haemorrhage, outcome and mortality after intravenous thrombolysis in acute stroke. *Cerebrovasc. Dis.* **2012**, *33*, 362–368. [CrossRef] [PubMed]
4. Nardi, K.; Engelter, S.; Strbian, D.; Sarikaya, H.; Arnold, M.; Casoni, F.; Ford, G.A.; Cordonnier, C.; Lyrer, P.; Bordet, R.; et al. Lipid Profile in Thrombolysis Study, G. Lipid profiles and outcome in patients treated by intravenous thrombolysis for cerebral ischemia. *Neurology* **2012**, *79*, 1101–1108. [CrossRef] [PubMed]
5. Wang, Y.; Song, Q.; Cheng, Y.; Wei, C.; Ye, C.; Liu, J.; Wu, B.; Liu, M. Association between non-high-density lipoprotein cholesterol and haemorrhagic transformation in patients with acute ischaemic stroke. *BMC Neurol.* **2020**, *20*, 47. [CrossRef]
6. Hong, K.S.; Lee, J.S. Statins in Acute Ischemic Stroke: A Systematic Review. *J. Stroke* **2015**, *17*, 282–301. [CrossRef]

7. Bang, O.Y.; Saver, J.L.; Liebeskind, D.S.; Pineda, S.; Ovbiagele, B. Association of serum lipid indices with large artery atherosclerotic stroke. *Neurology* **2008**, *70*, 841–847. [CrossRef]
8. Hindy, G.; Engstrom, G.; Larsson, S.C.; Traylor, M.; Markus, H.S.; Melander, O.; Orho-Melander, M.; Stroke Genetics, N. Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes: A Mendelian Randomization Study. *Stroke* **2018**, *49*, 820–827. [CrossRef]
9. Powers, W.J.; Rabinstein, A.A.; Ackerson, T.; Adeoye, O.M.; Bambakidis, N.C.; Becker, K.; Biller, J.; Brown, M.; Demaerschalk, B.M.; Hoh, B.; et al. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* **2019**, *50*, e344–e418. [CrossRef] [PubMed]
10. Friedewald, W.T.; Levy, R.I.; Fredrickson, D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.* **1972**, *18*, 499–502. [CrossRef]
11. American Diabetes, A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* **2021**, *44* (Suppl. 1), S15–S33. [CrossRef] [PubMed]
12. Lyden, P.; Brott, T.; Tilley, B.; Welch, K.M.; Mascha, E.J.; Levine, S.; Haley, E.C.; Grotta, J.; Marler, J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* **1994**, *25*, 2220–2226. [CrossRef] [PubMed]
13. Adams, H.P., Jr.; Bendixen, B.H.; Kappelle, L.J.; Biller, J.; Love, B.B.; Gordon, D.L.; Marsh, E.E., 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* **1993**, *24*, 35–41. [CrossRef]
14. Hacke, W.; Kaste, M.; Fieschi, C.; von Kummer, R.; Davalos, A.; Meier, D.; Larrue, V.; Bluhmki, E.; Davis, S.; Donnan, G.; et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* **1998**, *352*, 1245–1251. [CrossRef]
15. Makihara, N.; Okada, Y.; Koga, M.; Shiokawa, Y.; Nakagawara, J.; Furui, E.; Kimura, K.; Yamagami, H.; Hasegawa, Y.; Kario, K.; et al. Effect of serum lipid levels on stroke outcome after rt-PA therapy: SAMURAI rt-PA registry. *Cerebrovasc. Dis.* **2012**, *33*, 240–247. [CrossRef] [PubMed]
16. Paterno, R.; Ruocco, A.; Postiglione, A.; Hubsch, A.; Andresen, I.; Lang, M.G. Reconstituted high-density lipoprotein exhibits neuroprotection in two rat models of stroke. *Cerebrovasc. Dis.* **2004**, *17*, 204–211. [CrossRef] [PubMed]
17. Lambertsen, K.L.; Finsen, B.; Clausen, B.H. Post-stroke inflammation-target or tool for therapy? *Acta Neuropathol.* **2019**, *137*, 693–714. [CrossRef]
18. Luo, Y.; Chen, J.; Yan, X.L.; Jin, H.; Sun, X.; Guo, Z.N.; Yang, Y. Association of Non-Traditional Lipid Parameters with Hemorrhagic Transformation and Clinical Outcome After Thrombolysis in Ischemic Stroke Patients. *Curr. Neurovasc. Res.* **2020**, *17*, 736–744. [CrossRef]
19. Liu, L.; Yin, P.; Lu, C.; Li, J.; Zang, Z.; Liu, Y.; Liu, S.; Wei, Y. Association of LDL-C/HDL-C Ratio with Stroke Outcomes Within 1 Year After Onset: A Hospital-Based Follow-Up Study. *Front. Neurol.* **2020**, *11*, 408. [CrossRef]
20. Wang, G.; Jing, J.; Wang, A.; Zhang, X.; Zhao, X.; Li, Z.; Wang, C.; Li, H.; Liu, L.; Wang, Y.; et al. China National Stroke Registry, I.I.I. Non-High-Density Lipoprotein Cholesterol Predicts Adverse Outcomes in Acute Ischemic Stroke. *Stroke* **2021**, *52*, 2035–2042. [CrossRef]
21. Lv, G.; Wang, G.Q.; Xia, Z.X.; Wang, H.X.; Liu, N.; Wei, W.; Huang, Y.H.; Zhang, W.W. Influences of blood lipids on the occurrence and prognosis of hemorrhagic transformation after acute cerebral infarction: A case-control study of 732 patients. *Mil. Med. Res.* **2019**, *6*, 2. [CrossRef] [PubMed]
22. Messe, S.R.; Pervez, M.A.; Smith, E.E.; Siddique, K.A.; Hellkamp, A.S.; Saver, J.L.; Bhatt, D.L.; Fonarow, G.C.; Peterson, E.D.; Schwamm, L.H. Lipid profile, lipid-lowering medications, and intracerebral hemorrhage after tPA in get with the guidelines-stroke. *Stroke* **2013**, *44*, 1354–1359. [CrossRef] [PubMed]
23. Bang, O.Y.; Saver, J.L.; Liebeskind, D.S.; Starkman, S.; Villablanca, P.; Salamon, N.; Buck, B.; Ali, L.; Restrepo, L.; Vinuela, F.; et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. *Neurology* **2007**, *68*, 737–742. [CrossRef]
24. Acampa, M.; Camarri, S.; Lazzerini, P.E.; Guideri, F.; Tassi, R.; Valenti, R.; Cartocci, A.; Martini, G. Increased arterial stiffness is an independent risk factor for hemorrhagic transformation in ischemic stroke undergoing thrombolysis. *Int. J. Cardiol.* **2017**, *243*, 466–470. [CrossRef] [PubMed]
25. Lin, S.F.; Chao, A.C.; Hu, H.H.; Lin, R.T.; Chen, C.H.; Chan, L.; Lin, H.J.; Sun, Y.; Lin, Y.Y.; Chen, P.L.; et al. Taiwan Thrombolytic Therapy for Acute Ischemic Stroke Study, G. Low Cholesterol Levels Increase Symptomatic Intracranial Hemorrhage Rates After Intravenous Thrombolysis: A Multicenter Cohort Validation Study. *J. Atheroscler. Thromb.* **2019**, *26*, 513–527. [CrossRef] [PubMed]
26. Yang, N.; Lin, M.; Wang, B.G.; Zeng, W.Y.; He, Y.F.; Peng, H.Y.; Zeng, J.; Wu, Z.Y.; Zhong, Y. Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 673–678.
27. Langsted, A.; Kamstrup, P.R.; Nordestgaard, B.G. High Lipoprotein(a) and Low Risk of Major Bleeding in Brain and Airways in the General Population: A Mendelian Randomization Study. *Clin. Chem.* **2017**, *63*, 1714–1723. [CrossRef]
28. Wongcharoen, W.; Sutthiwutthichai, S.; Gunaparn, S.; Phrommintikul, A. Is non-HDL-cholesterol a better predictor of long-term outcome in patients after acute myocardial infarction compared to LDL-cholesterol?: A retrospective study. *BMC Cardiovasc. Disord.* **2017**, *17*, 10. [CrossRef]

29. Ravnskov, U.; Diamond, D.M.; Hama, R.; Hamazaki, T.; Hammarskjold, B.; Hynes, N.; Kendrick, M.; Langsjoen, P.H.; Malhotra, A.; Mascitelli, L.; et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: A systematic review. *BMJ Open* **2016**, *6*, e010401. [CrossRef]
30. Johannesen, C.D.L.; Langsted, A.; Mortensen, M.B.; Nordestgaard, B.G. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: Prospective cohort study. *BMJ* **2020**, *371*, m4266. [CrossRef]
31. Sung, K.C.; Huh, J.H.; Ryu, S.; Lee, J.Y.; Scorletti, E.; Byrne, C.D.; Kim, J.Y.; Hyun, D.S.; Ko, S.B. Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users. *J. Clin. Med.* **2019**, *8*, 1571. [CrossRef] [PubMed]
32. Cheng, K.H.; Lin, J.R.; Anderson, C.S.; Lai, W.T.; Lee, T.H.; Group, S. Lipid Paradox in Statin-Naive Acute Ischemic Stroke but Not Hemorrhagic Stroke. *Front. Neurol.* **2018**, *9*, 541. [CrossRef] [PubMed]
33. Imamura, T.; Doi, Y.; Arima, H.; Yonemoto, K.; Hata, J.; Kubo, M.; Tanizaki, Y.; Ibayashi, S.; Iida, M.; Kiyohara, Y. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: The Hisayama study. *Stroke* **2009**, *40*, 382–388. [CrossRef]
34. Lv, P.; Jin, H.; Liu, Y.; Cui, W.; Peng, Q.; Liu, R.; Sun, W.; Fan, C.; Teng, Y.; Sun, W.; et al. Comparison of Risk Factor between Lacunar Stroke and Large Artery Atherosclerosis Stroke: A Cross-Sectional Study in China. *PLoS ONE* **2016**, *11*, e0149605. [CrossRef]
35. Lei, C.; Wu, B.; Liu, M.; Chen, Y. Risk factors and clinical outcomes associated with intracranial and extracranial atherosclerotic stenosis acute ischemic stroke. *J. Stroke Cerebrovasc. Dis.* **2014**, *23*, 1112–1117. [CrossRef] [PubMed]
36. Mackness, M.I.; Abbott, C.; Arrol, S.; Durrington, P.N. The role of high-density lipoprotein and lipid-soluble antioxidant vitamins in inhibiting low-density lipoprotein oxidation. *Biochem. J.* **1993**, *294 Pt 3*, 829–834. [CrossRef]
37. Enomoto, M.; Adachi, H.; Hirai, Y.; Fukami, A.; Satoh, A.; Otsuka, M.; Kumagae, S.; Nanjo, Y.; Yoshikawa, K.; Esaki, E.; et al. LDL-C/HDL-C Ratio Predicts Carotid Intima-Media Thickness Progression Better Than HDL-C or LDL-C Alone. *J. Lipids* **2011**, *2011*, 549137. [CrossRef] [PubMed]
38. Lo, S.K.; Li, I.T.; Tsou, T.S.; See, L. [Non-significant in univariate but significant in multivariate analysis: A discussion with examples]. *Changgeng Yi Xue Za Zhi* **1995**, *18*, 95–101. [PubMed]
39. Wang, H.; Peng, J.; Wang, B.; Lu, X.; Zheng, J.Z.; Wang, K.; Tu, X.M.; Feng, C. Inconsistency Between Univariate and Multiple Logistic Regressions. *Shanghai Arch. Psychiatry* **2017**, *29*, 124–128. [CrossRef]

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Shoulder Joint Hybrid Assistive Limb Treatment for Chronic Stroke Patients with Upper Limb Dysfunction

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Abstract: Upper extremity dysfunction after stroke affects quality of life. Focusing on the shoulder joint, we investigated the safety and effectiveness of rehabilitation using a shoulder joint hybrid assistive limb (HAL). Eight patients with chronic stroke and upper extremity functional disability were enrolled and used a shoulder joint HAL, which assisted shoulder movement based on the user's intention, through myoelectric activation of the shoulder flexor. Ten training sessions of 30–40 min each were performed to assist voluntary movement of upper limb elevation on the affected side through triggering the deltoid muscle. All patients completed the interventions without shoulder pain. Surface electromyography evaluation indicated post-intervention improvement in coordinated movement of the affected upper extremity. Significant improvements in voluntary and passive shoulder joint range of motion were obtained after the intervention, suggesting improvement in shoulder muscle strength. A significant decrease in the modified Ashworth scale and improvements in functional scores in the upper limb were also observed. Along with safe use for our study patients, the shoulder HAL provided appropriate motor learning benefits. Improvements in shoulder joint function and whole upper limb function were observed, suggesting that HAL could be an optimal treatment method.

Keywords: hybrid assistive limb (HAL); shoulder; rehabilitation; robotic rehabilitation; stroke; upper limb impairment

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1. Introduction

Upper extremity dysfunction due to stroke significantly affects activities of daily living, influencing quality of life [1]. It has been reported that approximately 50% of patients with stroke continue to experience upper limb dysfunction six months after stroke onset, and approximately 60% of those with severe or complete paralysis are unable to perform any movement with their affected limbs [2–4]. Recent advances in imaging examinations, such as functional magnetic resonance imaging and near-infrared spectroscopy, have shown that brain plasticity or reorganization can be expected after stroke. Recently, robotic rehabilitation has emerged as a training method to improve patients' limb dysfunction post-stroke [5,6]. The hybrid assistive limb (HAL) is an exoskeletal robot that controls and assists movements based on bioelectrical activity generated through voluntary movements. By means of generating feedback to the central nervous system, it has been hypothesized that this device stimulates functional recovery through inducing plasticity in the impaired central nervous system [7]. There are four types of HAL, namely, lower limb, single joint

(for elbow and knee joints), and lumbar types. One study that used a single joint HAL for the elbows reported improvements in upper limb motor function in patients with stroke [8]. Focusing on shoulder dysfunction after stroke, we previously conducted training using a shoulder joint HAL developed by our research group in patients with stroke. Furthermore, we published a case report showing that this training could be performed safely, while improving shoulder joint function and coordinated movements of the upper limb on the affected side [9]. Rehabilitation therapy focusing on the shoulder joint is extremely important, as improving shoulder joint function not only improves activities of daily living, such as changing clothes, but also ameliorates distal control of the upper extremity and prevents shoulder pain [10–12]. In this study, we aimed to determine the utility of shoulder joint HAL training applied in eight patients with chronic stroke and moderate-to-severe upper limb dysfunction.

2. Materials and Methods

2.1. Patients

Eight patients (six males, two females) were enrolled in this study. Patients' clinical data are shown in Table 1. The mean patient age (± standard deviation) was 68.4 ± 8.38 (range, 53–84) years. The mean time from stroke onset was 5.86 ± 6.40 (range, 0.93–19.7) years. All patients showed moderate-to-severe hemiplegia with a shoulder flexion manual muscle test (MMT) score of ≤2. Their grip power was <50% on the affected side compared with the unaffected upper limb and three patients were unable to complete grip dynamometer measurements. In Patient 8, bilateral grip power measurements could not be measured as the unaffected upper limb had been amputated at the hand level due to trauma in childhood. This study was conducted in accordance with the Declaration of Helsinki, with approval from the Ethics Committee of the Tsukuba University Faculty of Medicine (approval no.: TCRB18-38). All patients provided written informed consent for participation and publication, including the use of any accompanying images.

Table 1. Patient characteristics.

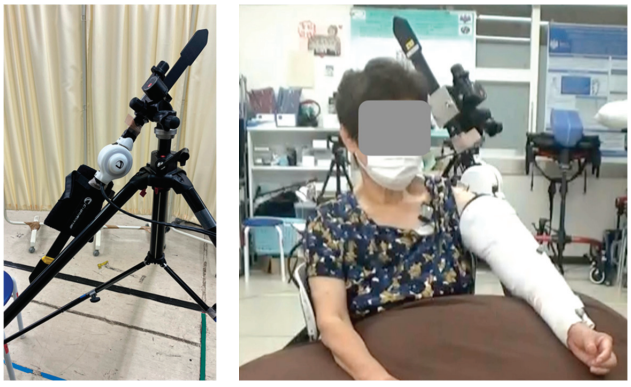
Number	Age	Sex	Disease	Side	From Onset (Year)	Shoulder MMT		Grip Strength (kg)	
						Affected Side	Unaffected Side	Affected Side	Unaffected Side
1	53	Female	SAH	Rt	1.98	2	5	0	17.8
2	84	Male	ICH	Rt	8.24	2	5	8.1	31.3
3	67	Male	CI	Lt	0.93	2	5	9.7	26.3
4	68	Male	ICH	Rt	8.65	2	5	0	33.4
5	71	Male	CI	Lt	1.60	2	5	6.7	30.3
6	68	Male	CI	Lt	4.57	2	5	15.7	35.1
7	67	Male	ICH	Lt	1.20	2	5	11	27.5
8	69	Female	CI	Lt	19.7	2	5	0	-

CI, cerebral infarction; ICH, intracranial hemorrhage; Lt, left; MMT, manual muscle testing; Rt, right; SAH, subarachnoid hemorrhage.

2.2. HAL Intervention

We set up the single-joint HAL in accordance with previous studies [5,6]. In brief, the proximal section of the HAL was fixed to a tripod using an attachment, and the distal section was fitted to the patient's upper arm with a belt for the elbow joint, which was attached to the HAL (Figure 1a). The elbow was extended to its full range of motion (ROM); the forearm was placed in a slightly externally rotated position to prevent external rotation of the humerus and was immobilized near the wrist joint using a splint and bandage (Figure 1b). Flexion electrodes were placed on the skin of the anterior deltoid fibers and triggered for upper limb elevation. Instead of using the electrodes as triggers, relaxation of the shoulder flexor muscle and gravity functioned to trigger extension. The ground was

placed on the bone touching the site where the bone was palpable, without interfering with the surface electromyography device.



(**a**) (**b**)

Figure 1. Images of the shoulder joint HAL device. (**a**) Single-joint HAL fixed to a tripod with attachments, (**b**) shoulder joint HAL fixed with splints and an elastic bandage. HAL, hybrid assistive limb.

The upper limb raising angle during training was measured prior to fitting the HAL, and the shoulder joint ROM was initiated at approximately 20° less than the ROM at the shoulder joint and then gradually increased while observing the training condition. Two methods were used to adjust the actual angle: (i) adjustment of the HAL, and (ii) adjustment using a tripod attachment. The HAL angle could be adjusted from 0° to 120°, and was used for adjustment. When the HAL assist angle of 120° was considered to be insufficient, a further increase in the angle of elevation was obtained through changing the tilt of the HAL itself using a tripod attachment.

All eight patients who participated in the study underwent a total of 10 HAL training sessions, with each session lasting 30–40 min, with at least one week between each intervention. The actual training time for upper extremity raising was approximately 20–30 min, including breaks, after approximately 5–20 min for electrode preparation and HAL placement and removal.

During training, a therapist stabilized the medial side of the patients' forearms to avoid excessive internal rotation or flexion of the upper limbs during the raising of the upper limbs. The direction of upper limb elevation was evaluated while observing the raising of the scapular plane, which needs to be considered to prevent excessive interference between the humerus and scapula (Figure 2). The pace of each exercise was set so that patients could fully extend their arms one at a time to avoid vigorous raising and then repeat raising the upper arm.

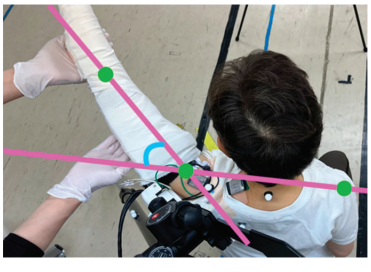


Figure 2. Images showing scapular elevation.

Upper extremity elevation at a 30–45° angle between the line connecting the bilateral acromion and the line connecting the acromion to the elbow joint is optimal to avoid interference between the scapula and humerus.

2.3. Assessments

2.3.1. Safety

Medical interviews and situational examinations were conducted to assess all participants for adverse symptoms, such as shoulder pain, occurrence of additional physical dysfunction, and the presence of serious adverse events. Serious adverse events were defined as any undesirable medical event that occurred while wearing the HAL or during the training period, or when at home, which required hospitalization for treatment or resulted in permanent or significant disability or dysfunction.

2.3.2. Efficacy

Evaluations were conducted one week prior to the start of training and one week following the end of training.

Shoulder Joint Function

Shoulder joint ROM during voluntary and passive shoulder flexion was assessed to evaluate the shoulder joint function on the affected side, and a manual muscle test (MMT) was performed to evaluate muscle strength during shoulder flexion.

Surface Electromyography

Wireless surface electromyography devices were placed on the trapezius, deltoid, infraspinatus, pectoralis major, biceps brachii, and triceps brachii muscles of the impaired side, and the Trigo™ Lab wireless surface electromyography system (Delsys Inc., Boston, MA, USA) was used to evaluate muscle activity before and during HAL training, while raising the upper limb of the affected side. The obtained values were band-pass filtered (30–400 Hz), rectified and integrated over a 50 ms local time window, and divided into cycles of repeated upper limb raising exercises, after which the average activity pattern per cycle without and with HAL was obtained. We subsequently compared the activity patterns of each muscle with and without HAL at the first and tenth intervention sessions according to the peak of the averaged patterns, respectively.

Motion Analysis

An optical three-dimensional motion analyzer (MX System, Vicon Motion Systems Ltd., Oxford, UK) was used to analyze motion during elevation of the upper limb on the affected side. Surface markers were placed on the spinous processes of C7 and T10, at the shoulder peak and the lateral epicondyle of the humerus. The trunk axis was defined as the line from C7 to T10, and the humeral axis was defined as the line from the shoulder peak to the lateral epicondyle of the humerus. The angle between these axes was calculated and detected as the angular velocity based on the time from the drooped position to the point of maximum reach.

Upper Limb Function and Activity

The upper limb function on the affected side was evaluated using the sum of modified Ashworth scale (MAS) scores in the affected upper limb (range, 0–28; shoulder flexion, elbow flexion, extension forearm rotation and extraversion, and wrist flexion and extension), and Fugl Meyer assessment—upper extremity (FMA-UE), action research arm test (ARAT), and box and block test (BBT) scores. Grip strength in the sitting position was measured to indicate hand function. A digital measuring device capable of measuring at $\geq$5 kg was used and, if measurement was not possible, the evaluation was performed at 0 kg.

2.4. Statistical Analysis

All data are presented as mean ± standard deviation. A Wilcoxon signed rank test was applied to examine shoulder joint ROM, MAS scores, upper limb function scores (FMA-UE, ARAT, BBT), and surface electromyography (EMG) data in each muscle. Statistical significance was set at 5%. JMP ver. 17.0.0 software was used for all statistical analyses.

3. Results

3.1. Safety

All patients performed the 10 shoulder HAL training interventions without any apparent adverse events, including shoulder pain. The mean duration of the 10 motion training sessions was 112 ± 33.7 days (77–168 days). The average time of shoulder joint elevation per training session was 156.1 ± 31.4 min; the average time of the first training session was 93.1 ± 34.4 min, and the average time of the tenth training session was 196.3 ± 40.3 min.

3.2. Efficacy

3.2.1. Shoulder Joint Function

The results for shoulder joint ROM pre- and post-intervention are shown in Figure 3. Pre-intervention, voluntary shoulder joint ROM measurements were: flexion, 60.0° ± 11.6°; abduction, 64.4° ± 13.2°; and 69.4° ± 14.5° of scapular plane movement, and passive ROM measurements were: flexion, 106.3° ± 18.7°; abduction, 93.8° ± 12.5°, and 108.8° ± 16.2° of scapular plane movement. Post-intervention, voluntary shoulder joint ROM measurements were: flexion, 85.6° ± 15.0° (p = 0.008); abduction, 77.5° ± 12.5° (p = 0.008); and 87.5° ± 12.5° of scapular plane movement (p = 0.047). Passive shoulder joint ROM measurements were: flexion, 118.1° ± 14.9° (p = 0.008); abduction, 105.0° ± 18.1° (p = 0.031); and 118.8° ± 13.4° (p = 0.047) of scapular plane movement. All parameters showed significant improvement compared with pre-intervention measurements.

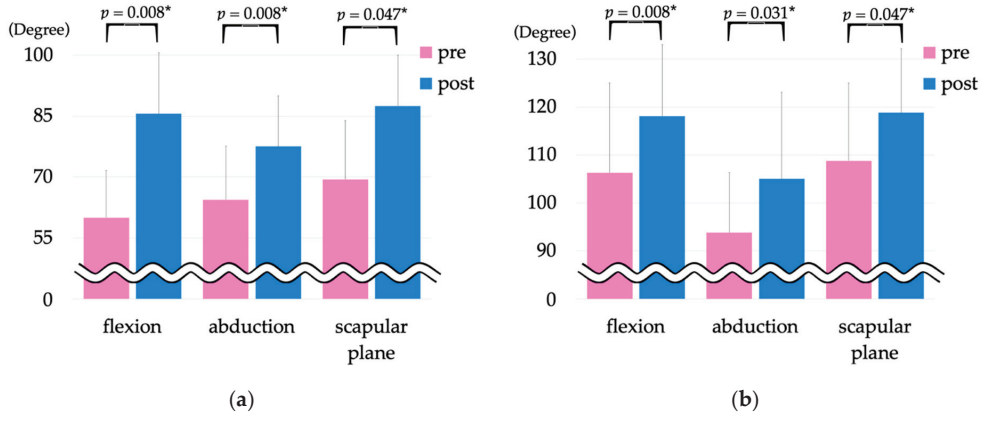


Figure 3. Shoulder joint ROM pre- and post-intervention. (**a**) Voluntary shoulder joint range of motion pre- and post-intervention, (**b**) passive shoulder joint ROM pre- and post-intervention. * Indicates $p < 0.05$. ROM, range of motion.

Pre-intervention, all eight patients had an MMT score of 2 for both flexion movements. Post-intervention, two patients showed improvement, with flexion scores improving to 4 in Patients 1 and 5.

3.2.2. Surface Electromyography

The results of surface EMG before and during the initial training with and without HAL are shown in Figure 4. We compared surface EMG findings during initial upper

extremity raising of the affected side with and without HAL. These showed a significant decrease in mean activity in the deltoid muscle from $8.77 \times 10^{-5} \pm 4.04 \times 10^{-5}$ without HAL to $6.34 \times 10^{-5} \pm 3.75 \times 10^{-5}$ when wearing HAL. No significant changes were observed in the other muscles.

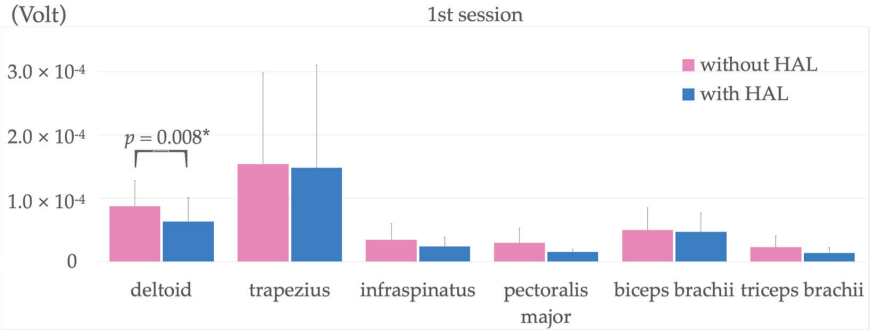


Figure 4. Comparison of surface EMG activity during upper limb raising before and after HAL application in the first training intervention. * $p < 0.05$. HAL, hybrid assistive limb.

The surface EMG findings before and during HAL application at the tenth training session are shown in Figure 5. We compared surface EMG findings during raising the affected upper limb with and without HAL at the tenth session. These showed that mean activity significantly decreased from $8.98 \times 10^{-5} \pm 3.79 \times 10^{-5}$ without HAL in the deltoid muscle to $4.88 \times 10^{-5} \pm 2.45 \times 10^{-5}$ when wearing HAL ($p = 0.016$). Furthermore, a significant decrease from $2.21 \times 10^{-4} \pm 2.31 \times 10^{-4}$ to $1.37 \times 10^{-4} \pm 1.56 \times 10^{-4}$ was observed in the trapezius muscle ($p = 0.008$) and a decrease from $3.62 \times 10^{-5} \pm 2.29 \times 10^{-5}$ to $2.29 \times 10^{-5} \pm 1.70 \times 10^{-5}$ in the infraspinatus muscle ($p = 0.039$) when wearing HAL compared with not wearing HAL, respectively.

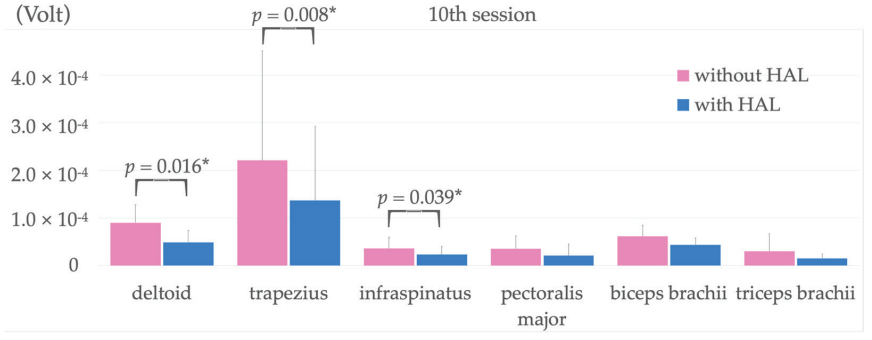


Figure 5. Comparison of surface EMG activity during upper limb raising before and after HAL application in the tenth training intervention session. * $p < 0.05$. HAL, hybrid assistive limb.

A significant decrease was observed in the deltoid muscle activity when wearing the HAL compared with prior to wearing the HAL, with no significant change observed in other muscles.

There was a significant decrease in the deltoid, trapezius, and infraspinatus muscle activity when wearing the HAL compared with prior to wearing the HAL, with no significant change noted in the other muscles.

3.2.3. Motion Analysis

The maximum angular velocity during upper extremity elevation pre- and post-intervention showed a significant improvement in angle degree per second from 102.2 ± 41.6 to 140.7 ± 46.8 (p = 0.039) in flexion and from 104.9 ± 50.5 to 140.5 ± 45.3 (p = 0.023) in the scapular plane (Figure 6). We showed upper extremity elevation in Movies S1 and S2.

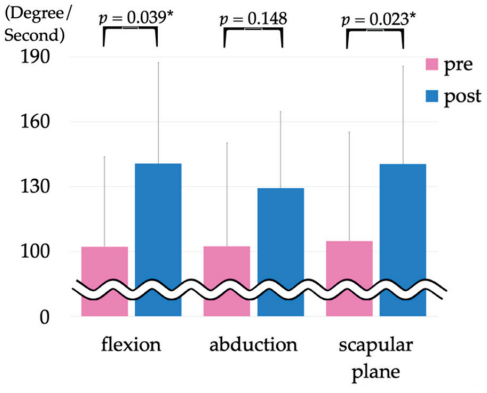


Figure 6. Motion analysis of raising the affected side of the upper limb in the standing position without HAL. * $p < 0.05$. HAL, hybrid assistive limb.

The maximum angular velocity during flexion and scapular elevation was significantly improved post-intervention compared with pre-intervention.

3.2.4. Upper Limb Function and Activity

The total MAS score in the upper limb showed a significant decrease from 9.1 ± 2.3 pre-intervention to 5.4 ± 2.9 post-intervention (p = 0.008). The results of FMA-UE test pre- and post-intervention are shown in Figure 7. The pre-intervention FMA-UE score was 29.9 ± 11.1, which significantly improved to 35.5 ± 12.1 post-intervention (p = 0.016).

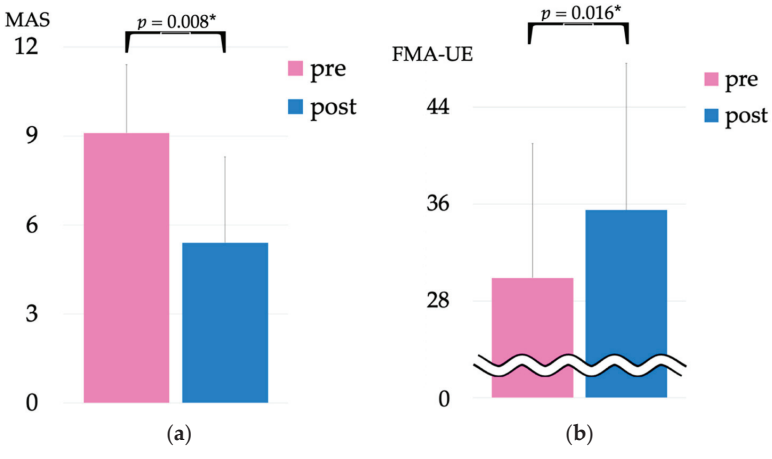


Figure 7. Comparison of MAS (**a**) and FMA-UE (**b**) scores pre- and post-intervention. * $p > 0.05$. FMA-UE, Fugl Meyer assessment upper extreme; MAS, modified Ashworth scale. Both MAS and FMA-UE scores significantly improved post-intervention.

The results of ARAT and BBT scores pre- and post-intervention are shown in Figure 8. Pre-intervention, the ARAT score was 11.5 ± 12.7, which significantly improved to 16.25 ± 14.6 post-intervention ($p = 0.016$). Pre-intervention, the BBT score was 7.8 ± 14.9, which improved to 9.9 ± 14.2 post-intervention but without statistical significance ($p = 0.125$). Three of eight patients had hand function difficulties, and their BBT scores were 0 both pre- and post-intervention.

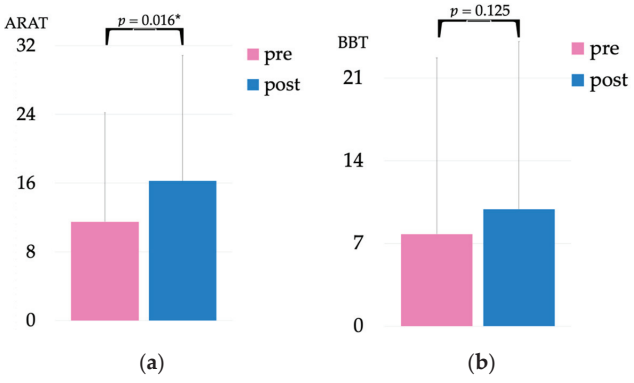


Figure 8. Comparison of ARAT (**a**) and BBT (**b**) scores pre- and post-intervention. * $p < 0.05$. ARAT, action research arm test; BBT, box and block test.

Post-intervention grip strength did not improve significantly; however, two of the three patients who had pre-intervention difficulty achieving a measurement could achieve a post-intervention measurement, with Patient 1 improving grip strength to 7.4 kg and Patient 4 improving grip strength to 9 kg.

4. Discussion

In this study, we aimed to test the safety and effectiveness of a shoulder joint HAL through using HAL to treat patients with stroke and moderate-to-severe upper limb dysfunction. In all eight patients, we observed shoulder joint contracture and muscle weakness on the affected side but training the upper limb to rise using the shoulder joint HAL could be performed safely without shoulder pain. Due to its instability, the shoulder joint is prone to shoulder pain when an upper limb is affected and, once hemiplegic shoulder joint pain develops, it is challenging to resolve and can significantly affect patient's quality of life [2,13]. Therefore, in conventional training, avoiding shoulder flexion beyond 90° is recommended to prevent shoulder pain [14,15]. Our study findings indicate that this technique can be safely performed if the shoulder MMT score is maintained at a muscle strength of at least 2, even if a relatively severe limitation in shoulder joint ROM is observed.

Limb dysfunction after stroke is problematic, not only in terms of muscle weakness, but also in terms of coordinated muscle movements. HAL treatment has the possibility of improving coordination through motor learning [16]. We have also used HAL for elbow extension training for patients with spastic cerebral palsy, with a focus on achieving elbow flexor and extensor movement separately. Coactivity between biceps and triceps brachii decreased following HAL sessions and active elbow extension improved [17]. Previously, we published reports showing improved coordinated movement in a patient with chronic stroke and in patients after C5 palsy [9,18,19].

In this study concerning evaluation of shoulder joint ROM, surface EMG played a central role in motion analysis. The shoulder joint has a high degree of freedom, accompanied with various types of muscle movement. Previous studies have utilized different methods to analyze shoulder movements. Tigrini et al. evaluated motion intention through pattern recognition methods in relation to upper limb surface EMG [20,21]. Rivela et al. evaluated the surface EMG of trunk muscles other than upper limb muscles [22,23]. Additionally,

several studies examined patients with shoulder disarticulation, focusing on the shoulder joint itself [23–25]. In our study, we selected the trunk muscles, including the trapezius, deltoid, infraspinatus, and pectoralis major muscles as well as upper limb muscles, such as biceps brachii and triceps brachii muscles, to evaluate surface EMG with and without HAL, based on previous studies [17,18,26].

Surface EMG findings showed co-activation of the trapezius, infraspinatus, and deltoid muscles when the upper limb was raised without the HAL in both the first and tenth sessions. In contrast, during the initial upper limb raising with HAL, only the deltoid muscles showed a decrease in activation. However, during the tenth training session, a significant decrease in activation was observed in the trapezius and infraspinatus muscles compared with upper limb raising without HAL, suggesting reduced co-activation of these muscles during upper limb raising with HAL. In a previous report [26], in which healthy participants performed upper limb raising with HAL, there was more contraction of the deltoid, trapezius, and infraspinatus muscles with HAL than without. These results suggest that HAL treatment for the shoulder joint in the present study improved muscle coordination during upper limb raising, and that treatment using the shoulder HAL for patients with chronic stroke and upper limb dysfunction may have the same motor learning effect as shown in previous reports [9,16–19]. Post-intervention, our study patients also showed improvement in muscle tone of the entire upper extremity, which we consider also contributed to improvement in coordinated movement.

To evaluate efficacy, patients in the chronic phase six months after stroke onset were included to exclude recovery of function and movement due to natural progression after stroke [27]. After shoulder HAL intervention, both voluntary and passive shoulder joint ROM significantly improved, and motion analysis showed that the patients were able to raise the affected upper extremity higher and more quickly, suggesting improved peri-shoulder muscle strength. The MMT is only a reference evaluation, as it is affected by automatic ROM as well as by muscle strength; however, two of eight patients showed improvement (from 2 to 4), which suggested an improvement in muscle strength. Tests to assess upper extremity function and movement, namely, the FMA and ARAT, also showed significant score improvement post-intervention, which indicates that there was improvement in the upper limb as a whole, along with improved shoulder joint function. Moreover, two of eight patients showed improvements in grip strength, which they had been unable to perform pre-intervention, indicating an improvement in hand function. Overall, our results show that shoulder HAL is a safe and effective treatment for patients with chronic stroke and moderate-to-severe upper limb dysfunction.

Limitations

The limitations of this study are as follows. First, to be cautious and to closely monitor the development of shoulder pain, this intervention was performed 10 times with at least one week between each intervention. Therefore, the 10 interventions were completed in an average of 112 days, resulting in a low intervention frequency. Second, the intervention targeted patients in the chronic phase to remove the influence of spontaneous recovery after stroke and an average of 5.86 years had passed from stroke onset to intervention. Third, the study environment was not conducive to effective rehabilitation for patients with stroke, as rehabilitation after stroke is more effective when undertaken at a shorter time from stroke onset and the amount of rehabilitation is more effective when performed 5–7 days per week [28]. Therefore, it is necessary to consider when and how to perform shoulder HAL treatment in future, as training may be more effective if intervention studies are conducted earlier and more frequently. Finally, when selecting our study patients, we focused on shoulder joint function only. As such, pre-intervention grip strength measurements could not be achieved in three of eight patients and hand function was often sub-optimal in the other patients. Upper limb movement is effective only when the patient can perform "grip and release" and "pinch and release" hand movements, in addition to reaching movements of the shoulder and elbow joints, and ARAT and BBT evaluations are based on

this assumption [29,30]. Upper limb dysfunction after stroke varies from patient to patient, and it is important to decide which training should be administered to which patients [31]. Our study results suggest that HAL can improve shoulder joint function and also improve upper limb function and movement.

5. Conclusions

We used shoulder joint elevation training using a single-joint HAL in eight patients with chronic stroke and moderate-to-severe upper limb dysfunction. Shoulder joint ROM improved, suggesting an increase in muscle output of the peri-articular muscles of the shoulder joint. In addition, improvements in muscle tone of the entire upper limb were observed, and significant improvements in FMA-UE and ARAT scores were also obtained, indicating improvements in function and movement of the affected upper limb. These findings suggest that the shoulder HAL may be an effective rehabilitation strategy for upper limb dysfunction after stroke.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12031215/s1. Movie S1. Elevation of the affected side of the upper limb with shoulder flexion pre-intervention in Patient 5. Movie S2. Elevation of the affected side of the upper limb with shoulder flexion post-intervention in Patient 5.

Author Contributions: Conceptualization, Y.S., Y.H. and M.Y.; Methodology, M.T., Y.S., H.K. and Y.H.; Validation, Y.S., H.K., Y.H. and M.Y.; Formal analysis, H.K.; Investigation, M.T., Y.S., H.K., S.K., Y.K. and Y.O.; Data curation, M.T.; Writing—original draft, M.T.; Writing—review & editing, M.T., Y.S., H.K., S.K., Y.K., Y.O., Y.H. and M.Y. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Tsukuba University Faculty of Medicine (approval no.: TCRB18-38).

Informed Consent Statement: Informed consent was obtained from all participants.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lloyd-Jones, D.; Adams, R.J.; Brown, T.M.; Carnethon, M.; Dai, S.; De Simone, G.; Ferguson, T.B.; Ford, E.; Furie, K.; Gillespie, C.; et al. Executive summary: Heart disease and stroke statistics—2010 update: A report from the American Heart Association. *Circulation* **2010**, *121*, 948–954. [CrossRef]
2. Broeks, J.G.; Lankhorst, G.J.; Rumping, K.; Prevo, A.J. The long-term outcome of arm function after stroke: Results of a follow-up study. *Disabil. Rehabil.* **1999**, *21*, 357–364. [CrossRef] [PubMed]
3. Lai, C.H.; Sung, W.H.; Chiang, S.L.; Lu, L.H.; Lin, C.H.; Tung, Y.C.; Lin, C.H. Bimanual coordination deficits in hands following stroke and their relationship with motor and functional performance. *J. Neuroeng. Rehabil.* **2019**, *16*, 101. [CrossRef] [PubMed]
4. Kwakkel, G.; Kollen, B.J.; van der Grond, J.; Prevo, A.J. Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke. *Stroke* **2003**, *34*, 2181–2186. [CrossRef] [PubMed]
5. Marshall, R.S.; Perera, G.M.; Lazar, R.M.; Krakauer, J.W.; Constantine, R.C.; Delapaz, R.L. Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke* **2000**, *31*, 656–661. [CrossRef]
6. Bertani, R.; Melegari, C.; De Cola, M.C.; Bramanti, A.; Bramanti, P.; Calabrò, R.S. Effects of robot-assisted upper limb rehabilitation in stroke patients: A systematic review with meta-analysis. *Neurol. Sci.* **2017**, *38*, 1561–1569. [CrossRef]
7. Saita, K.; Morishita, T.; Arima, H.; Hyakutake, K.; Ogata, T.; Yagi, K.; Shiota, E.; Inoue, T. Biofeedback effect of hybrid assistive limb in stroke rehabilitation: A proof of concept study using functional near infrared spectroscopy. *PLoS ONE* **2018**, *13*, e0191361. [CrossRef]
8. Okuno, T.; Takeuchi, T.; Takeda, E.; Izumi, Y.; Kaji, R. Clinical uses of a robot (hybrid-assisted limb or HAL™) in patients with post-stroke spasticity after botulinum toxin injections. *J. Med. Investig.* **2021**, *68*, 297–301. [CrossRef]

9. Taketomi, M.; Shimizu, Y.; Kadone, H.; Hada, Y.; Yamazaki, M. Hybrid Assistive Limb Intervention for Hemiplegic Shoulder Dysfunction Due to Stroke. *Cureus* **2021**, *13*, e19827. [CrossRef]
10. Kamkar, A.; Irrgang, J.J.; Whitney, S.L. Nonoperative management of secondary shoulder impingement syndrome. *J. Orthop. Sports Phys. Ther.* **1993**, *17*, 212–224. [CrossRef]
11. Lindgren, I.; Lexell, J.; Jönsson, A.C.; Brogårdh, C. Left-sided hemiparesis, pain frequency, and decreased passive shoulder range of abduction are predictors of long-lasting poststroke shoulder pain. *PMR* **2012**, *4*, 561–568. [CrossRef]
12. Olczak, A.; Truszczyńska-Baszak, A. Influence of the passive stabilization of the trunk and upper limb on selected parameters of the hand motor coordination, grip strength and muscle tension, in post-stroke patients. *J. Clin. Med.* **2021**, *10*, 2402. [CrossRef] [PubMed]
13. Pong, Y.P.; Wang, L.Y.; Wang, L.; Leong, C.P.; Huang, Y.C.; Chen, Y.K. Sonography of the shoulder in hemiplegic patients undergoing rehabilitation after a recent stroke. *J. Clin. Ultrasound* **2009**, *37*, 199–205. [CrossRef] [PubMed]
14. Ludewig, P.M.; Cook, T.M. Alterations in shoulder kinematics and associated muscle activity in people with symptoms of shoulder impingement. *Phys. Ther.* **2000**, *80*, 276–291. [CrossRef]
15. Patel, R.M.; Gelber, J.D.; Schickendantz, M.S. The weight-bearing shoulder. *J. Am. Acad. Orthop. Surg.* **2018**, *26*, 3–13. [CrossRef] [PubMed]
16. Puentes, S.; Kadone, H.; Watanabe, H.; Ueno, T.; Yamazaki, M.; Sankai, Y.; Marushima, A.; Suzuki, K. Reshaping of bilateral gait coordination in hemiparetic stroke patients after early robotic intervention. *Front. Neurosci.* **2018**, *12*, 719. [CrossRef]
17. Shimizu, Y.; Kadone, H.; Kubota, S.; Ueno, T.; Sankai, Y.; Hada, Y.; Yamazaki, M. Voluntary elbow extension-flexion using single joint Hybrid Assistive Limb (HAL) for patients with spastic cerebral palsy: Two case reports. *Front. Neurol.* **2019**, *10*, 2. [CrossRef]
18. Kubota, S.; Kadone, H.; Shimizu, Y.; Takahashi, H.; Koda, M.; Miura, K.; Watanabe, H.; Suzuki, K.; Hada, Y.; Sankai, Y.; et al. Robotic shoulder rehabilitation with the hybrid assistive limb in a patient with delayed recovery after postoperative C5 palsy: A case report. *Front. Neurol.* **2021**, *12*, 676352. [CrossRef]
19. Lafitte, M.N.; Kadone, H.; Kubota, S.; Shimizu, Y.; Tan, C.K.; Koda, M.; Hada, Y.; Sankai, Y.; Suzuki, K.; Yamazaki, M. Alteration of muscle activity during voluntary rehabilitation training with single-joint Hybrid Assistive Limb (HAL) in patients with shoulder elevation dysfunction from cervical origin. *Front. Neurosci.* **2022**, *16*, 817659. [CrossRef]
20. Tigrini, A.; Pettinari, L.A.; Verdini, F.; Fioretti, S.; Mengarelli, A. Shoulder Motion Intention Detection Through Myoelectric Pattern Recognition. *IEEE Sens. Lett.* **2021**, *5*, 1–4. [CrossRef]
21. Tigrini, A.; Scattolini, M.; Mengarelli, A.; Fioretti, S.; Morettini, M.; Burattini, L.; Verdini, F. (Eds.) Role of the Window Length for Myoelectric Pattern Recognition in Detecting User Intent of Motion. In Proceedings of the 2022 IEEE International Symposium on Medical Measurements and Applications (MeMeA), Messing, Italy, 22–24 June 2022. [CrossRef]
22. Rivela, D.; Scannella, A.; Pavan, E.E.; Frigo, C.A.; Belluco, P.; Gini, G. Analysis and Comparison of Features and Algorithms to Classify Shoulder Movements from sEMG Signals. *IEEE Sens. J.* **2018**, *18*, 3714–3721. [CrossRef]
23. Rivela, D.; Scannella, A.; Pavan, E.E.; Frigo, C.A.; Belluco, P.; Gini, G. (Eds.) Processing of surface EMG through pattern recognition techniques aimed at classifying shoulder joint movements. In Proceedings of the 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Milan, Italy, 25–29 August 2015. [CrossRef]
24. Sharba, G.K.; Wali, M.K.; Ai-Timemy, A.H. Real-time classification of shoulder girdle motions for multifunctional prosthetic hand control: A preliminary study. *Int. J. Artif. Organs* **2019**, *42*, 508–515. [CrossRef] [PubMed]
25. Nsugbe, E.; Al-Timemy, A.H. Shoulder girdle recognition using electrophysiological and low frequency anatomical contraction signals for prosthesis control. *CAAI Trans. Intell. Technol.* **2022**, *7*, 81–94. [CrossRef]
26. Makihara, T.; Kadone, H.; Onishi, S.; Kubota, S.; Hada, Y.; Shimizu, Y.; Kawamoto, H.; Sankai, Y.; Yamazaki, M. Shoulder motion assistance using a single-joint Hybrid Assistive Limb® robot: Evaluation of its safety and validity in healthy adults. *J. Orthop. Surg.* **2017**, *25*, 2309499017727951. [CrossRef] [PubMed]
27. Nakayama, H.; Jørgensen, H.S.; Raaschou, H.O.; Olsen, T.S. Recovery of upper extremity function in stroke patients: The Copenhagen Stroke Study. *Arch. Phys. Med. Rehabil.* **1994**, *75*, 394–398. [CrossRef]
28. Pollock, A.; Baer, G.; Campbell, P.; Choo, P.L.; Forster, A.; Morris, J.; Pomeroy, V.M.; Langhorne, P. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst. Rev.* **2014**, *2014*, CD001920. [CrossRef]
29. Hsieh, C.L.; Hsueh, I.P.; Chiang, F.M.; Lin, P.H. Inter-rater reliability and validity of the action research arm test in stroke patients. *Age Ageing* **1998**, *27*, 107–113. [CrossRef]
30. Slota, G.P.; Enders, L.R.; Seo, N.J. Improvement of hand function using different surfaces and identification of difficult movement post stroke in the Box and Block Test. *Appl. Ergon.* **2014**, *45*, 833–838. [CrossRef]
31. Jolkkonen, J.; Kwakkel, G. Translational hurdles in stroke recovery studies. *Transl. Stroke Res.* **2016**, *7*, 331–342. [CrossRef]

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MDPI

Systematic Review

Functional and Mortality Outcomes with Medical and Surgical Therapy in Malignant Posterior Circulation Infarcts: A Systematic Review

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Abstract: Background: There remains uncertainty regarding optimal definitive management for malignant posterior circulation infarcts (MPCI). While guidelines recommend neurosurgery for malignant cerebellar infarcts that are refractory to medical therapy, concerns exist about the functional outcome and quality of life after decompressive surgery. Objective: This study aims to evaluate the outcomes of surgical intervention compared to medical therapy in MPCI. Methods: In this systematic review, MEDLINE, Embase and Cochrane databases were searched from inception until 2 April 2021. Studies were included if they involved posterior circulation strokes treated with neurosurgical intervention and reported mortality and functional outcome data. Data were collected according to PRISMA guidelines. Results: The search yielded 6677 studies, of which 31 studies (comprising 723 patients) were included for analysis. From the included studies, we found that surgical therapy led to significant differences in mortality and functional outcomes in patients with severe disease. Neurological decline and radiological criteria were often used to decide the timing for surgical intervention, as there is currently limited evidence for preventative neurosurgery. There is also limited evidence for the superiority of one surgical modality over another. Conclusion: For patients with MPCI who are clinically stable at the time of presentation, in terms of mortality and functional outcome, surgical therapy appears to be equivocal to medical therapy. Reliable evidence is lacking, and further prospective studies are rendered.

Keywords: stroke; posterior circulation; neurosurgery; medical therapy

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1. Introduction

Stroke has become increasingly prevalent, with the mean global lifetime risk of stroke increasing from 22.8% in 1990 to 24.9% in 2016 [1]. Ischemic strokes account for approximately 80% of all strokes, 20% of which are posterior circulation strokes that involve the vertebral arteries, basilar artery, posterior cerebral arteries and their branches [2,3].

Posterior circulation strokes tend to have a worse prognosis than their anterior circulation counterparts, and this is partly due to the important structures located there and partly due to the difficulty in diagnosis that results in longer onset-to-door time [4]. The presentation is oftentimes non-specific, with dizziness, vertigo and vomiting as the

only symptoms [5]. In addition, as compared to the anterior cranial fossa, the smaller confines of the posterior fossa rapidly lead to mass effect, brainstem compression and increased mortality.

In extensive posterior circulation infarcts, mass effect with brainstem and fourth ventricle compression, hydrocephalus and brainstem herniation can occur [3]. Medical management for this includes osmotic therapy and other ancillary measures, such as elevating the head of the bed, hypothermia, barbiturates and corticosteroids [5]. However, these are typically temporising measures until the resolution of the mass effect occurs or there is definitive decompressive surgical treatment [5]. Neurosurgical therapy for MPCI includes extraventricular drainage (EVD), suboccipital decompressive craniectomy (SDC), SDC with necrosectomy and SDC with EVD.

There is evidence for early decompressive surgery in anterior circulation malignant middle cerebral artery infarcts [6,7]; however, evidence in MPCI is limited and warrants further review. While the American Heart Association/American Stroke Association guidelines recommend craniectomy in those with MPCI that are refractory to medical therapy [5], the evidence for this is sparse [8], as there are no randomized controlled trials on posterior circulation strokes and existing meta-analysis on this topic does not include the latest published data [9–11]. To date, effective and sustaining conservative treatments for malignant posterior infarcts are widely in practice. Surgery is currently the mainstay for the rapid decompression of the posterior fossa such that any viable brain cells can be preserved timely, especially for patients with MPCI who are unstable. However, there is another group of MPCI patients who are relatively more stable but with the risk of deterioration that can be managed conservatively.

This paper aims to provide a narrative review of the surgical interventions against medical therapy for the treatment of MPCI in patients who are relatively stable and to investigate the optimal type and timing of neurosurgical interventions for MPCI.

2. Methods

The conduct and reporting of this study adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The study protocol has been published in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021247737).

2.1. Search Strategy

The following databases, MEDLINE, EMBASE and the Cochrane Library, were searched from inception until 2 April 2021 using a search strategy designed in conjunction with a medical information specialist (Medical Library, National University of Singapore). The MEDLINE search used keywords synonymous with "ischemic stroke", "cerebellar infarction", "posterior cerebral infarction", "vertebral infarction", "basilar infarction", "occipital infarction", "cerebral infarction", "craniotomy", "craniectomy", "surgical decompression", "ventriculostomy" and "ventriculoperitoneal shunt". The detailed search strategy is available in Supplementary Table S1. References of included studies and grey literature sources, such as Google Scholar, were also hand-searched.

2.2. Inclusion and Exclusion Criteria

Studies were included if they involved patients with acute ischemic stroke involving the posterior circulation who later underwent neurosurgical intervention. Neurosurgical intervention was defined as any combination of ventriculostomy, cerebral shunting, ventricular drains, craniotomy or craniectomy, with or without necrosectomy. Randomized controlled trials, observational studies and case series with sufficient death and functional outcome data were included.

The following study designs were excluded: non-English studies without an accompanying English translation, conference abstracts, review articles, pre-clinical studies, studies involving paediatric populations, studies involving participants who only suffered from

haemorrhagic stroke and studies where the indication for neurosurgery was only after medical therapy had failed.

2.3. Study Selection

Screening was conducted through Covidence (Melbourne, VIC, Australia), an online systematic review tool recommended by Cochrane. The studies were reviewed independently by two authors (N.A. Lim and H.Y. Lin) through two rounds of screening using their titles/abstracts and full texts. Disagreements were resolved through consensus.

2.4. Data Extraction

The following information was independently extracted from each article: authorship, year of publication, journal, country, hospital, study design, study period and aims. The following patient demographical data were extracted: number of participants, sex and age. Data on the following comorbidities were extracted: hypertension, hyperlipidemia, atrial fibrillation and cardiac data (myocardial infarction, coronary artery disease, congestive heart failure, ischemic heart disease and coronary disease). Pre-intervention parameters were collected, namely bilateral stroke, hydrocephalus, time from symptom onset to neurosurgical intervention and Glasgow Coma Scale (GCS) at admission and pre-operatively.

Post-intervention findings such as the following were also collected: GCS, Glasgow Outcome Scale (GOS), mRS and number of deaths. Death was defined as 1 and 6 on the GOS and mRS, respectively, or extracted from the text. Deaths at all reported time points were included, which ranged from time of discharge to 57.6 months [13]. Good functional outcome was defined as mRS 0–2, GOS 4–5 and Barthel Index 91–100 or extracted from text (Table 1A,B).

2.5. Risk of Bias Assessment

Risk of bias of the studies were independently assessed by two authors (N.A. Lim and H.Y. Lin) using the Newcastle–Ottawa Scale [14]; the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical case-control study [15]; and the JBI Critical Appraisal Checklist for Case Series [16] for observational studies, case-control studies and case series, respectively.

2.6. Reporting Bias Assessment

The relevant authors were contacted if there was missing data that was essential for our analysis.

Table 1. (**A**) General characteristics of studies of patients with posterior ischemic stroke who are treated surgically or medically. (**B**) General characteristics of studies of patients with posterior ischemic stroke who are treated surgically only.

(A)

Study Title	Authors	Study Design	Country	Definition of Good Functional Outcome	Number of Patients Treated Surgically	Number of Patients Treated Medically	Follow-Up Duration (Months)
Cerebellar infarction with obstructive hydrocephalus	Taneda et al., 1982 [17]	Retrospective cohort study	Japan	Completely recovered	10	5	Unreported
Surgical and medical management of patients with massive cerebellar infarctions: results of the German–Austrian Cerebellar Infarction Study.	Jauss et al., 1999 [18]	Cohort study	Germany	mRS ≤ 2	48	36	Mean: 3
Space occupying cerebellar infarction	Hornig et al., 1994 [19]	Retrospective cohort study	Germany	mRS ≤ 1	36	16	Unreported
Neurosurgical management of cerebellar haematoma and infarct	Mathew et al., 1995 [20]	Retrospective cohort study	UK	GOS: unspecified by author. Assumed to be GOS ≥ 4	16	34	Unreported
Neuroimaging in deteriorating patients with cerebellar infarcts and mass effect	Koh et al., 2000 [21]	Retrospective cohort study	USA	mRS ≤ 2	9	26	Median: 16 (range: 1–105)
Management of acute cerebellar infarction: one institution's experience	Raco et al., 2003 [22]	Retrospective case series	Italy	GOS: unspecified by author. Assumed to be GOS ≥ 4	19	25	Unreported
Neurosurgical management of massive cerebellar infarct outcome in 53 patients	Mostofi, 2013 [23]	Retrospective cohort study	French West Indies	Unreported by author. Unable to determine	25	28	Unreported
Predicting Surgical Intervention in Cerebellar Stroke: A Quantitative Retrospective Analysis	Taylor et al., 2020 [24]	Retrospective cohort study	USA	Unreported by author. Unable to determine	21	65	Unreported

Table 1. *Cont.*

(B)						
Study Title	**Authors**	**Study Design**	**Country**	**Definition of Good Functional Outcome**	**Number of Patients Treated Surgically**	**Follow-Up Duration (Months)**
Treatment of cerebellar infarction by decompressive suboccipital craniectomy	Chen et al., 1992 [25]	Case series	Germany	Barthel Index; unspecified by author. Assumed to be BI = 100	11	Mean: 42.9
Management of cerebellar infarction with associated occlusive hydrocephalus	Bertalanffy et al., 1992 [26]	Case series	Germany	Unreported	10	Unreported
Monitoring therapeutic efficacy of decompressive craniotomy in space occupying cerebellar infarcts using brain-stem auditory evoked potentials	Krieger et al., 1993 [27]	Case series	Germany	Unreported by author. Unable to determine	11	Unreported
Is decompressive craniectomy for acute cerebral infarction of any benefit?	Koh et al., 2000 [28]	Case series	Singapore	GOS ≥ 4	3	Mean: 7 (range: 3–17)
Clinical outcome following surgical treatment for bilateral cerebellar infarction.	Tsitsopoulos et al., 2011 [13]	Case series	Denmark	mRS ≤ 2	10	Median: 57.6 (range: 15–118)
Endoscopic third ventriculostomy for occlusive hydrocephalus caused by cerebellar infarction	Baldauf et al., 2006 [29]	Case series	Germany	Unreported by author. Unable to determine	10	Mean: 43
Controversy of surgical treatment for severe cerebellar infarction	Kudo et al., 2007 [30]	Case series	Germany	GOS	25	Unreported
Occlusive hydrocephalus associated with cerebellar infarction treated with endoscopic third ventriculostomy: report of 5 cases	Yoshimura, et al., 2007 [31]	Case series	USA	GOS; undefined. Assumed to be GOS ≥ 4	5	Mean: 3

Table 1. *Cont.*

Long-term outcome after suboccipital decompressive craniectomy for malignant cerebellar infarction.	Pfefferkorn T et al., 2009 [32]	Case series	Germany	mRS ≤ 3	57	Unreported
Long-term outcome after surgical treatment for space-occupying cerebellar infarction: experience in 56 patients.	Jüttler et al., 2009 [33]	Case series	Germany	mRS ≤ 2	56	Unreported
Hydrocephalus in posterior fossa lesions: ventriculostomy and permanent shunt rates by diagnosis	Mangubat et al., 2009 [34]	Case series	USA	Unreported by author. Unable to determine	4	Unreported
Endoscopic third ventriculostomy in patients with secondary triventricular hydrocephalus from a haemorrhage or ischaemia in the posterior cranial fossa	Vindigni et al., 2010 [35]	Case series	Italy	GOS; undefined. Assumed to be GOS ≥ 4	19	Mean: 6
Surgical treatment of patients with unilateral cerebellar infarcts: clinical outcome and prognostic factors.	Tsitsopoulos et al., 2011 [36]	Case series	Germany	mRS ≤ 2	32	Unreported
Ventriculosubgaleal shunt in the management of obstructive hydrocephalus caused by cerebellar infarction	Moussa et al., 2013 [37]	Case series	Germany	Unreported by author. Unable to determine	10	Mean: 6
Lesions on DWI and the Outcome in Hyperacute Posterior Circulation Stroke	Lee et al., 2014 [38]	Case series	South Korea	mRS ≤ 2	9	Mean: 3
Preventive suboccipital decompressive craniectomy for cerebellar infarction: a retrospective matched case control study	Kim et al., 2016 [39]	Case-control	South Korea	mRS ≤ 2	84	Mean: 12

Table 1. *Cont.*

Neurologic Outcome After Decompressive Craniectomy: Predictors of Outcome in Different Pathologic Conditions	Goedemans et al., 2017 [40]	Case series	Amsterdam	GOS ≥4	10	Mean: 12
Strokectomy and Extensive Cerebrospinal Fluid Drainage for the Treatment of Space-Occupying Cerebellar Ischemic Stroke	Tartara et al., 2018 [41]	Case series	Germany	mRS ≤ 2	11	Mean: 33.8 (range 12–58)
Long-term functional outcome after decompressive suboccipital craniectomyfor space-occupying cerebellar infarction	Lindeskog et al., 2019 [42]	Case series	Denmark	mRS ≤ 3	22	Mean: 12
Evaluation of clinical significance of decompressive suboccipital craniectomy on the prognosis of cerebellar infarction	Suyama et al., 2019 [43]	Case series	Japan	mRS; unspecified by author. Assumed to be Mrs ≤ 2	14	Mean: 3
Posterior Fossa Surgery for Stroke: Differences in Outcomes Between Cerebellar Hemorrhage and Infarcts	Lee et al., 2020 [10]	Case series	Germany	mRS ≤3	50	Mean: 44.5 ± 33.9
Cerebellar Necrosectomy Instead of Suboccipital Decompression: A Suitable Alternative for Patients with Space-Occupying Cerebellar Infarction	Hernández-Durán et al., 2020 [44]	Case series	Germany	GOS ≥ 4	34	Unreported
The impact of emergent suboccipital craniectomy upon outcome and prognosis of massive cerebellar infarction: A single institutional study	Mattar et al., 2021 [45]	Case series	Egypt	mRS ≤ 2	42	Mean: 3

BI, Barthel index; EVD, Extraventricular drainage; GOS, Glasgow Outcome scale; mRS, modified Rankin scale.

3. Results

Our search yielded 6673 studies after deduplication. Following the title/abstract and full-text screen, 31 articles [10,13,17–45] were included for analysis. (Figure 1).

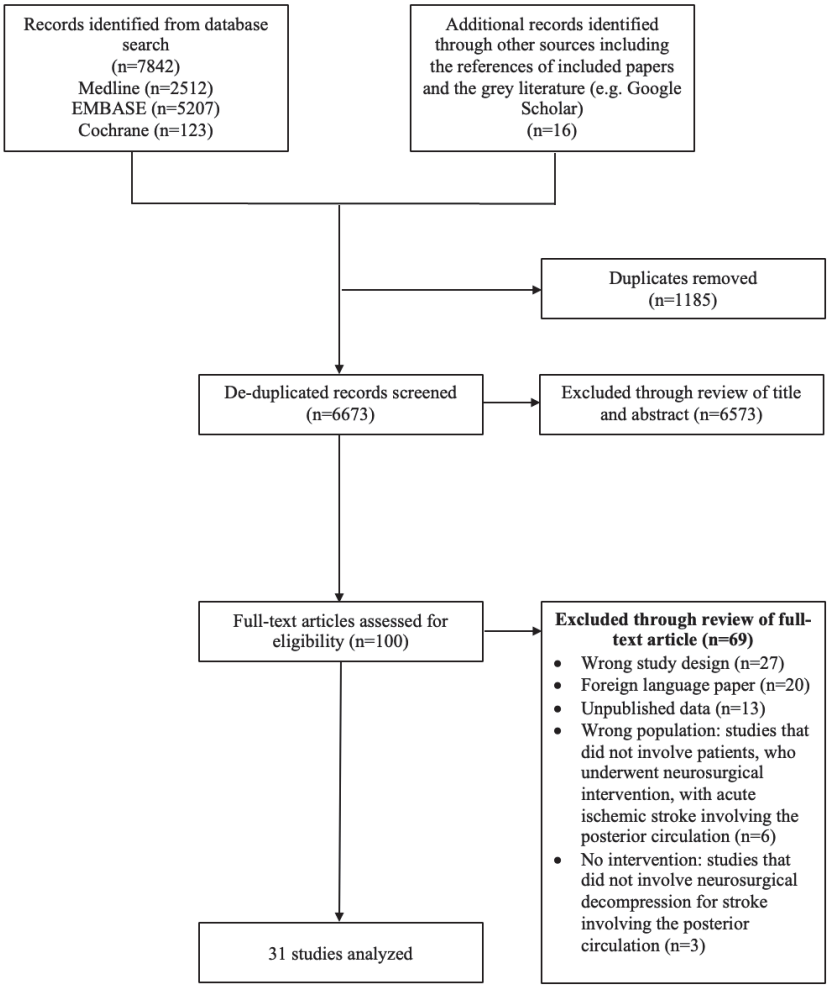

Figure 1. PRISMA flow diagram of included studies.

The main characteristics of the studies are summarized in Table 1A,B. Of the 31 studies included, 8 studies were observational studies that compared neurosurgery and medical therapy. The focus of this review will be on 419 patients included in these 8 dual-arm studies. Among these patients, 184 of them were treated with neurosurgery and 235 were treated with medical therapy. A total of 20 neurosurgical patients and 29 medically managed patients died. Further information containing the biodata, GCS on admission and outcome measures of the patients in the dual-arm and single-arm studies are summarized in Tables 2 and 3, respectively. Information about the age, pre-operative GCS, comorbidities and outcome measures of all patients who underwent neurosurgery in all the studies are summarized in Table 4.

Table 2. Pre-intervention characteristics and post-intervention outcomes of patients with posterior circulation stroke, treated surgically or medically.

Author and Year	**Raco et al., 2003 [22]**						**Mathew et al., 1995 [20]**					
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**
Number, n (%)	8 (18%)	4 (9.1%)	0	5 (11%)	Treatment-limiting decision: 2 (4.5%)	25 (57%)	7 (14%)	2 (4%)	0	0	Treatment-limiting decision: 3 (6%) Management change: 4 (8%)	34 (68%)
Comorbidities	Recent cardiac infarction: 6 Atrial flutter: 2 Endocarditis with vegetations: 2 Patent foramen ovale: 1						Unreported					
Radiological findings	*Presence of hydrocephalus*						*Presence of hydrocephalus*					
	8	0	0	5	0	0	Total: 19					
	Presence of brainstem compression						*Presence of brainstem compression*					
	Unreported						Total: 26					
Male, n (%)	24 (55%)						Unreported					
Age in years ± SD (range)	Median: 56 (9–83)						Mean: 57 (26–85)					
GCS on admission	GCS 3: 2 GCS 6: 2 GCS 9–12: 15 GCS 13: 15 GCS 14: 7 GCS 15: 3						Median: 14 (4–15)					
Good functional outcome, n (%)	8 (18%)	1 (2.3%)	-	4 (9.1%)	0	24 (55%)	6 (12%)	1 (2%)	-	-	Management change: 2 (4%)	34 (68%)
Death, n (%)	0	2 (4.5%)	-	1 (2.3%)	Treatment-limiting decision: 2 (4.5%)	1 (2.3%)	1 (2%)	1 (2%)	-	-	Treatment-limiting decision: 3 (6%) Management change: 2 (4%)	0

Table 2. *Cont.*

Author and Year	**Hornig et al., 1994** [19]						**Jauss et al., 1992** [18]					
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**
Number, n (%)	2 (3.8%)	0	8 (15%)	4 (7.7%)	SDC + EVD + necrosectomy: 22 (42%)	16 (31%)	14 (17%)	30 (36%)	0	4 (4.8%)	0	36 (43%)
Comorbidities	Arterial hypertension: 33 Diabetes: 21 Hypercholesterolemia: 5 Unilateral/bilateral vertebral artery stenosis: 10 Unilateral/bilateral vertebral artery occlusion: 2 Nonrheumatic atrial fibrillation: 14 Myocardial infarction: 3						Unreported					
Radiological findings	*Presence of hydrocephalus*						*Presence of hydrocephalus*					
	Total: 42						Unreported					
	Presence of brainstem compression						*Presence of brainstem compression*					
	Total: 39						Unreported					
Age in years ± SD (range)	Mean: 61.2 ± 10.1						Mean: 54.5 ± 17.3	Mean: 57.4 ± 12	-	-	-	Mean: 61.2 ± 10.3
GCS on admission	Unreported						Unreported					
Good functional outcome, n (%)	18 (35%)					11 (21%)	10 (12%)	22 (26%)	-	-	-	30 (36%)
Death, n (%)	6 (12%)					2 (3.8%)	unreported					
Author and Year	**Mostofi, 2013** [23]						**Koh et al., 2000** [28]					
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**
Number, n (%)	6 (11%)	16 (30%)	0	3 (5.7%)	0	28 (53%)	6 (17%)	2 (5.7%)	0	1 (2.9%)	0	26 (74%) (2 patients with treatment limiting decision)
Comorbidities	Unreported						Large artery disease: 13 Cardioembolism: 12					
Radiological findings	*Presence of hydrocephalus*						*Presence of hydrocephalus*					
	Unreported						Total among surgical group: 9					6
	Presence of brainstem compression						*Presence of brainstem compression*					
	Unreported						Total among surgical group: 7					2

Table 2. *Cont.*

Male, n (%)	32 (60%)						Unreported					
Age in years ± SD (range)	Mean: 58.7 (SD unreported)						Unreported					
GCS on admission	Mean: 9.5	Mean: 9.43	-	Mean: 6	-	Mean: 11.6	Unreported					
Good functional outcome, n (%)	unreported						2 (5.7%)	0	-	0	-	14 (40%)
Death, n (%)	2 (3.8%)					4 (7.5%)	0					1 (2.9%)
Author and Year	**Taneda et al., 1982** [17]						**Taylor et al., 2020** [24]					
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**Medical Only**
Number, n (%)	0	10 (67%)	0	0	0	5 (20%)	2 (2.3%)	0	12 (14%)	9 (10%)	0	65 (76%)
Comorbidities	Unreported								Obese, BMI ≥ 30: 37 Hypertension: 63 Diabetes: 37 Coronary artery disease: 21 Congestive heart failure: 16 Prior cerebrovascular accident: 16 Chronic kidney disease: 8 Alcohol abuse: 22 Tobacco abuse: 23 Hyperlipidemia: 35			
Radiological findings	*Presence of hydrocephalus*								*Presence of hydrocephalus*			
	Total: 15								Total among surgical group: 11			5
	Presence of brainstem compression								*Presence of brainstem compression*			
	Unreported								Total among surgical group: 10			8
Male, n (%)	-	9 (60%)	-	-	-	4 (27%)	12 (14%)					41 (48%)
Age in years ± SD (range)	-	Mean: 55.1 (40–66)	-	-	-	Mean: 67.6 (41–80)	Median: 58.5 IQR: 52–65					
GCS on admission	-	unreported	-	-	-	unreported	Median: 14 (IQR: 10–15)					Median: 15 (IQR: 10–15)
Good functional outcome, n (%)	-	7 (47%)	-	-	-	0	-	-	-	-	-	-
Death, n (%)	-	1 (6.7%)	-	-	-	5 (20%)	4 (4.7%)					16 (19%)

ETV, Endoscopic third ventriculostomy; EVD, Extraventricular drainage; GCS, Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation; SDC, suboccipital decompressive craniotomy.

Table 3. Post-intervention characteristics and post-intervention outcomes of patients with posterior circulation stroke, treated by surgery only.

Author and Year	Tsitsopoulos et al., 2010 [36]					Baldauf et al., 2006 [29]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	0	0	10 (100%)	0	0	0	0	0	ETV: 7 (70%) ETV + EVD: 2 (20%) ETV + SDC: 1 (10%)
Male, n (%)	-	-	-	8 (80%)	-	-	-	-	-	6 (60%)
Age in years ± SD (range)	-	-	-	Mean: 54.9 ± 13	-	-	-	-	-	Mean: 61.8 (SD unreported)
GCS on admission	-	-	-	Mean: 12.3 ± 3.1	-	-	-	-	-	Mean: 11.2 (SD unreported)
Good functional outcome, n (%)	-	-	-	6 (60%)	-	-	-	-	-	unreported
Death, n (%)	-	-	-	1 (10%)	-	-	-	-	-	0
Author and Year	**Koh et al., 2000** [21]					**Pfefferkorn et al., 2009** [32]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	3 (100%)	0	0	0	47 (82%)	57 (100%)	0	0	Infarct evacuation: 32/57 (56%)
Male, n (%)	-	1 (33%)	-	-	-	-	34	-	-	-
Age in years ± SD (range)	-	Mean: 53.6 (SD unreported)	-	-	-	-	Mean: 59.2 ± 12.9	-	-	-
GCS on admission	-	Mean: 12.3 (SD unreported)	-	-	-	-	unreported	-	-	-
Good functional outcome, n (%)	-	2 (66%)	-	-	-	-	27 (47%)	-	-	-
Death, n (%)	-	1 (33%)	-	-	-	-	16 (28%)	-	-	-
Author and Year	**Jüttler et al., 2009** [33]					**Lee et al., 2020** [10]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	9 (16%)	-	8 (14%)	39 (70%)	0	0	0	0	50 (100%)	0
Male, n (%)	37 (66%)	-	-	-	38 (76%)	-				
Age in years ± SD (range)	Median: 60 (30–76)	-	-	-	Mean: 57.3 ± 12	-				
GCS on admission	Median: 14.5 (3–15)	-	-	-	Unreported	-				

Table 3. *Cont.*

Good functional outcome, n (%)	4 (7.1%)	-	4 (7.1%)	12 (21%)	-	-	-	-	30 (60%)	-
Death, n (%)	2 (3.6%)	-	1 (1.8%)	9 (16%)	-	-	-	-	21 (42%)	-
Author and Year	**Tsitsopoulos et al., 2011** [13]					**Chen et al., 1992** [25]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	0	0	32 (100%)	0	0	0	0	2 (18%)	SDC + EVD + necrosectomy: 9 (82%)
Male, n (%)	-	-	-	24 (75%)	-	-	-	-	7 (64%)	
Age in years ± SD (range)	-	-	-	64.3 ± 9.9	-	-	-	-	Mean: 54 (36–73)	
GCS on admission	-	-	-	Median: 12.2 (7–15)	-	-	-	-	Mean: 12.9	
Good functional outcome, n (%)	-	-	-	19 (59%)	-	-	-	-	2 (18%)	
Death, n (%)	-	-	-	10 (31%)	-	-	-	-	0	
Author and Year	**Moussa et al., 2013** [37]					**Tartara et al., 2018** [41]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	5 (50%)	0	5 (50%)	0	0	2 (18%)	0	9 (82%)	0
Male, n (%)	7 (70%)	6 (55%)								
Age in years ± SD (range)			15 ≤ Age < 30 years: 6 30 ≤ Age < 45 years: 3 Age ≥ 45 years: 1					Mean: 64.7 ± 9.1		
GCS on admission			GCS 3–9 n = 5 GCS 10–12 n = 3 GCS 13–15 n = 2					Mean: 13.6 ± 1.1		
Good functional outcome, n (%)			Unreported			-	2 (18%)	-	7 (64%)	-
Death, n (%)	-	2 (20%)	-	0	-	-	0	-	1 (9.1%)	-
Author and Year	**Kudo et al., 2007** [30]					**Krieger et al., 1993** [27]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	3 (12%)	2 (8%)	0	3 (12%)	EVD + necrosectomy: 14 (56%) Necrosectomy only: 3 (12%)	0	0	0	11 (100%)	0

Table 3. *Cont.*

Male, n (%)			21 (84%)			-	-	-	8 (73%)	-
Age in years ± SD (range)			Mean age Group A: 72 ± 6 Group B: 61 ± 15			-	-	-	Mean: 52 (30–69)	-
GCS on admission			Unreported			-	-	-	Unreported	-
Good functional outcome, n (%)			11 (44%)			-	-	-	Unreported	-
Death, n (%)			3 (12%)			-	-	-	4 (36%)	-
Author and Year			**Suyama et al., 2019** [43]					**Lindeskog et al., 2018** [42]		
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	5 (36%)	0	9 (64%)	0	0	0	0	22 (100%)	0
Male, n (%)			12(86%)			-	-	-	16 (73%)	-
Age in years ± SD (range)			Mean: 65 ± 12			-	-	-	Median: 53 (IQR: 45–62)	-
GCS on admission			Unreported			-	-	-	Median: 8 (IQR: 5–10)	-
Good functional outcome, n (%)			10 (71%)			-	-	-	12 (55%)	-
Death, n (%)			2 (14%)			-	-	-	7 (32%)	-
Author and Year			**Mattar et al., 2021** [45]					**Hernández-Durán, 2020** [44]		
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	42 (100%)	0	0	0	0	0	0	0	Necrosectomy only: 34 (100%)
Male, n (%)	-	36 (86%)	-	-	-	-	-	-	-	18 (53%)
Age in years ± SD (range)	-	Mean: 66 ± 13	-	-	-	-	-	-	-	Median: 70 (28–84)
GCS on admission	-	Unreported	-	-	-	-	-	-	-	Median: 11 (3–15)
Good functional outcome, n (%)	-	25 (60%)	-	-	-	-	-	-	-	26 (76%)
Death, n (%)	-	6 (14%)	-	-	-	-	-	-	-	7 (21%)
Author and Year			**Goedemans et al., 2017** [40]					**Yoshimura et al., 2007** [31]		
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	10 (100%)	0	0	0	0	0	0	0	ETV: 5 (100%)

Table 3. *Cont.*

Male, n (%)			Unreported			-	-	-	-	3 (60%)	
Age in years ± SD (range)			Unreported			-	-	-	-	Mean: 71.8 (47–92)	
GCS on admission			Unreported			-	-	-	-	Mean: 12.8 (8–15)	
Good functional outcome, n (%)	-	-	5 (50%)	-	-	-	-	-	-		3 (60%)
Death, n (%)	-	-	Unreported	-	-	-	-	-	-		1 (20%)
Author and Year			**Lee et al., 2014** [38]						**Mangubat et al., 2009** [34]		
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**		**Others**
Number, n (%)	0	9 (100%)	0	0	0	4 (100%)	0	0	0		0
Male, n (%)	-	Unreported	-	-	-	Unreported	-	-	-		-
Age in years ± SD (range)	-	Unreported	-	-	-	Unreported	-	-	-		-
GCS on admission	-	Unreported	-	-	-	Unreported	-	-	-		-
Good functional outcome, n (%)	-	2 (22%)	-	-	-	Unreported	-	-	-		-
Death, n (%)	-	Unreported	-	-	-	4 (100%)	-	-	-		-
Author and Year			**Vindigni et al., 2010** [35]						**Bertalanffy et al., 1992** [26]		
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**		**Others**
Number, n (%)	12 (63%)	0	0	0	ETV: 7 (37%)	6 (60%)	0	0	0		Ventriculo–arterial shunt: 3 (30%) Ventriculo–peritoneal shunt: 1 (10%)
Male, n (%)			Unretrievable			2 (20%)	-	-	-		Ventriculo–arterial shunt: 1 (10%) Ventriculo–peritoneal shunt: 1 (10%)
Age in years ± SD (range)	Mean: 62.3 (52–73)	-	-	-	Mean: 50.4 (23–67)			Mean: 61.8 (SD unreported)			
GCS on admission			Unreported					Unreported			
Good functional outcome, n (%)	6 (32%)	-	-	-	3 (16%)			Unreported			
Death, n (%)	1 (5.3%)	-	-	-	1 (5.3%)	1 (10%)	-	-	-		Ventriculo–arterial shunt: 1 (10%) Ventriculo–peritoneal shunt: 1 (10%)

Table 3. *Cont.*

Author and Year	Kim et al., 2016 [39]				
Treatment Groups	**EVD Only**	**SDC Only**	**SDC with Necrosectomy Only**	**SDC and EVD**	**Others**
Number, n (%)	0	84 (100%)	0	0	0
Male, n (%)	0	52 (62%)	-	-	-
Age in years ± SD (range)	-	Mean age Preventive SDC group: 59.0 ± 11.6 Non-preventive SDC group: 59.4 ± 10.9	-	-	-
GCS on admission	-	Mean GCS Preventive SDC group: 12.1 ± 4.1 Non-preventive SDC group: 12.0 ± 3.8	-	-	-
Good functional outcome, n (%)	-	45 (54%)	-	-	-
Death, n (%)	-	6 (7.1%)	-	-	-

ETV, Endoscopic third ventriculostomy; EVD, Extraventricular drainage; GCS, Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation; SDC, suboccipital decompressive craniotomy.

Table 4. Summary of characteristics of all patients who underwent neurosurgery.

Study	Number of Patients	Number of Deaths	Mean Age (Years)	Mean Pre-Operative GCS	Proportion of Good Functional Outcome (%)	Proportion of Patients with Hyper-tension (%)	Proportion of Patients with Diabetes Mellitus (%)	Proportion of Patients with Dyslipidemia (%)	Proportion of Patients with Atrial Fibrillation (%)	Proportion of Patients with Heart Disease * (%)	Proportion of Patients with Previous Stroke (%)	Proportion of Patients with Bilateral Stroke (%)	Proportion of Patients with Hydro-cephalus (%)
Baldauf et al., 2006 [29]	10	0	61.8	11.2	NA	50	NA	NA	70	NA	NA	NA	100
Bertalanffy et al., 1992 [26]	10	3	61.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	100
Chen et al., 1992 [25]	11	0	54	6.27	2	27.3	NA	NA	NA	NA	NA	27.3	NA
Goedemans et al., 2017 [40]	10	NA	NA	NA	5	NA	NA	NA	NA	NA	NA	NA	NA
Hernández-Durán et al., 2020 [44]	34	7	70	7.5	26	NA	NA	NA	NA	NA	NA	26.5	55.9
Hornig et al., 1994 [19]	36	6	NA	NA	18	NA	NA	NA	NA	NA	NA	NA	NA
Jauss et al., 1992 [18]	48	NA	56.55	NA	32	NA	NA	NA	NA	NA	NA	NA	NA
Jüttler et al., 2009 [33]	56	14	60	13	20	NA	NA	NA	NA	NA	NA	14.3	NA
Kim et al., 2016 [39]	84	6	59.27	NA	45	40.5	34.5	25	41.7	3.57	13.1	42.9	NA
Koh et al., 2000 [21]	9	0	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	100
Koh et al., 2000 [28]	3	1	53.57	4	2	NA	NA	NA	NA	NA	NA	0	NA
Krieger et al., 1993 [27]	11	4	52	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kudo et al., 2007 [30]	25	3	63	6.4	11	NA	NA	NA	NA	NA	NA	NA	NA
Lee et al., 2014 [38]	9	NA	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	NA
Lee et al., 2020 [10]	50	21	57.3	NA	30	NA	NA	NA	NA	NA	NA	48	NA
Lindeskog et al., 2019 [42]	22	7	53	8	12	18.2	4.55	13.6	9.09	4.55	NA	27.3	NA
Mangubat et al., 2009 [34]	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mathew et al., 1995 [20]	16	7	NA	NA	9	NA	NA	NA	NA	NA	NA	NA	NA

Table 4. *Cont.*

Study	Number of Patients	Number of Deaths	Mean Age (Years)	Mean Pre-Operative GCS	Proportion of Good Functional Outcome (%)	Proportion of Patients with Hyper-tension (%)	Proportion of Patients with Diabetes Mellitus (%)	Proportion of Patients with Dyslipidemia (%)	Proportion of Patients with Atrial Fibrillation (%)	Proportion of Patients with Heart Disease * (%)	Proportion of Patients with Previous Stroke (%)	Proportion of Patients with Bilateral Stroke (%)	Proportion of Patients with Hydro-cephalus (%)
Mattar et al., 2021 [45]	42	6	66	NA	25	NA	NA	NA	NA	NA	NA	21.4	73.8
Mostofi et al., 2013 [23]	25	2	59.67	5.33	NA	NA	NA	NA	NA	NA	NA	NA	NA
Moussa et al., 2013 [37]	10	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pfefferkorn et al., 2009 [32]	57	16	59.2	NA	27	80	32	30	NA	NA	NA	37	NA
Raco et al., 2003 [22]	19	5	NA	NA	13	NA	NA	NA	NA	NA	NA	NA	NA
Suyama et al., 2019 [43]	14	2	65	NA	10	35.7	7.14	NA	14.3	14.3	21.4	57.1	85.7
Taneda et al., 1982 [17]	10	1	55.1	NA	7	NA	NA	NA	NA	NA	NA	0	NA
Tartara et al., 2018 [41]	11	1	64.7	9.27	9	NA	NA	NA	NA	NA	NA	18.2	NA
Taylor et al., 2020 [24]	21	4	55	10	NA	71.4	52.4	47.6	NA	28.6	28.6	33.3	52.4
Tsitsopoulos et al., 2011 [13]	10	1	54.9	8.9	6	20	10	10	20	10	NA	50	70
Tsitsopoulos et al., 2011 [36]	32	10	64.3	9	19	46.9	18.8	NA	18.8	15.6	NA	25	90.6
Vindigni et al., 2010 [35]	19	2	50.4	NA	9	31.6	NA	NA	36.8	NA	NA	0	NA
Yoshimura et al., 2007 [31]	5	1	71.8	9.8	3	NA	NA	NA	20	NA	NA	20	NA

NA, Not applicable as data were unreported by study. * Heart disease included myocardial infarction, coronary artery disease, congestive heart failure, ischemic heart disease and coronary disease.

3.1. Medical versus Surgical Treatment

3.1.1. Choice of Surgical Treatment vs. Medical Treatment

Generally, most patients receiving exclusively conservative, or medical, treatment tended to be younger [20] or have better Glasgow Coma Scale levels [20,23] than those patients for surgical intervention. However, patients presenting initially in deep comas tended to be the exception to this rule, with some institutions [20,22] opting for conservative treatment given these patients' poor prognosis.

The treatment algorithms guiding the timing and choice of surgical treatment differed between institutions and was often left up to the discretion of individual physicians [19]. For the majority of institutions [18], the decision for surgical intervention was made based on the decline in neurological examination in conjunction with radiological criteria, such as fourth ventricular compression [13] or hydrocephalus [13,24,29]. Jauss et al. [18] found that surgery was universally performed among comatose patients, whereas treatment regimens were more diverse among patients with somnolence or stupor.

Some studies then investigated whether these clinical features used in decision making were significant predictors for surgery. Taylor et al. [24] also found that clinical features of documented brainstem compression and hydrocephalus were significant predictors. This was concordant with the findings of Koh et al. [21], who also noted an association with basal cistern compression.

3.1.2. Comparing Functional Outcomes between Medical and Surgical Treatment

Studies largely agreed [18,24] that there was no significant difference in admission or discharge neurologic examination or functional status between surviving patients going through either neurosurgical or conservative management. One study by Hornig et al. [19] found that there was only a difference in functional outcome in the group of patients who were stuporous, comatose or had cardiorespiratory compromise, and surgery for this group of patients provided better functional outcomes compared to those who did not undergo surgery. This distinction between severe and limited disease was echoed by a small study by Mostofi et al. [23], which found that patients with massive ischemic cerebellar infarct, defined as ischemic volume above 5 cm^3 and/or when there was hydrocephalus or brain stem compression, showed improvements in GCS when operated on (GCS at zero and four weeks for operated patients: 9.4 to 12.68) versus a decline when not operated on (GCS at zero and four weeks for non-operated patients: 11.36 to 10.92).

This was contradicted by a small case series of 15 patients by Taneda et al. [17], where 9 of 10 surgically operated patients survived, with the last patient dying of a perforated duodenal ulcer unrelated to the neurological insult. In that series, all five of the conservatively treated patients died.

3.1.3. Comparing Mortality Rates between Medical and Surgical Treatment

For the pooled data of 419 patients from eight studies, patients treated by neurosurgery had 3% higher odds of dying at all recorded time points as compared to patients treated by medical therapy (OR = 1.03, [95% CI: 0.31–3.43], $p = 0.96$). However, this result was not statistically significant, and there was also substantial heterogeneity among the studies ($I^2 = 54\%$) (Figure 2).

With neurosurgical intervention for patients with large infarcts [23] with neurologic deterioration [28] or mass effect [23,28], mortality rates dropped from 66% [23] to approximately 20% [19,23,28]. However, as noted by Jauss et al. [18], for patients who were awake or drowsy and somnolent or experiencing stupor in consciousness, there was no significant difference after 3 months in outcomes between craniotomies, ventricular drainage and medical treatment. Similar findings were reported by Hornig et al. [19] in patients with early or intermediate clinical stages as well.

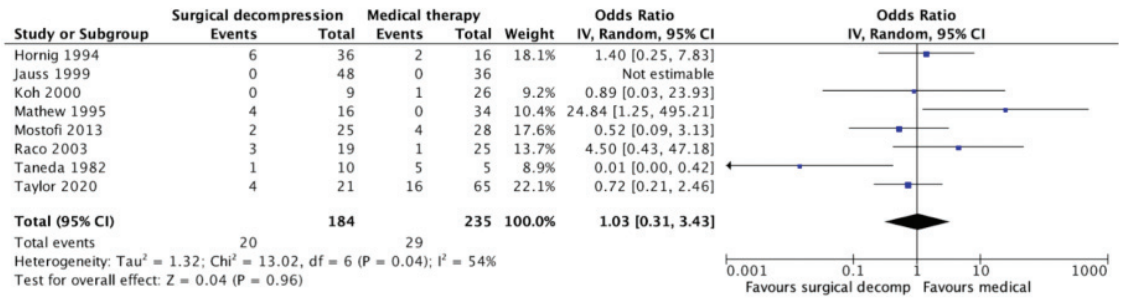

Figure 2. Forest plot with odds ratio (OR) and the corresponding 95% confidence interval (CI) for death in patients undergoing neurosurgical vs. medical therapy [17–20,22–24,28]. Events: death.

3.2. Surgical Treatment

3.2.1. Timing of Surgical Treatment

While most authors opted for surgical deterioration after clinical [18] or radiological deterioration [13,24,29], Kim et al. [39] opted for preventative craniectomies in patients with large infarcts, which was defined as a cerebellar infarction volume ratio between 0.25 and 0.33 on initial or routine follow-up radiographic findings. This was to account for patients who appeared clinically stable during the initial 72 h but would have a higher risk of delayed edema and deterioration later on. In this retrospective-matched case-control study involving 28 patients [39], preventative suboccipital decompressive craniectomy was found to have significantly better outcomes at discharge and at 12 months, and fewer deaths at 12 months.

Mattar et al. [45] also found that a short time from the onset of symptoms to surgery was significantly associated with better functional outcomes at 3 months. However, these findings were not adjusted for other variables, such as premorbid function, and this was a retrospective study without controls.

In contrast, in a retrospective study of 57 and 23 patients, respectively, Pfefferkorn et al. [32] and Lindeskog et al. [42] found that there was no significant association between time interval to surgery and outcomes.

Therefore, until there are prospective controlled studies on this topic, there remains little evidence for early or preventative craniectomies in the absence of clinical or radiological signs of deterioration.

3.2.2. Choice of Surgical Intervention

Studies that were included used various combinations of EVD, SDC, SDC with necrosectomy, endoscopic third ventriculostomy (ETV), ventriculo–arterial shunts and ventriculo–peritoneal shunts. Authors [22,28] often opted for a pathophysiology-directed approach and opted for external ventricular drainage in patients with hydrocephalus. In one institution [29] with neuroendoscopic experience, endoscopic third ventriculostomy was sometimes used instead.

Juttler et al. [33] found that there was no significant difference in long-term survival and survival time in those who died between patients who were treated by SDC only, EVD only and SDC with EVD. Evidence for which treatment provided better functional outcomes was mixed, with patients treated by SDC with EVD showing better outcomes at discharge as compared to those treated by EVD alone, but long-term outcomes favouring SDC as compared to EVD alone.

When compared with pooled results from a meta-analysis [11] on SDC in cerebellar infarcts, Hernández-Durán et al. [44] found that there was no significant difference in outcomes or deaths between patients undergoing necrosectomy via osteoplastic craniotomy and patients undergoing SDC.

There is currently limited evidence for which type of neurosurgical intervention results in better outcomes. Further research should be conducted on this topic.

3.3. Assessment of Publication Bias

The risk of bias assessments were also assessed and summarized. Of the eight cohort studies, four were found to have poor overall quality using the Newcastle–Ottawa Scale. The remaining 24 case series and one case-control study were rated according to the Joanna Briggs Institute (JBI) Critical Appraisal Checklist (Supplementary Table S2a–c).

4. Discussion

Surgical therapy for malignant posterior circulation infarcts appears to have limited impact on functional outcomes and reducing mortality, except in patients with severe disease who are at a high risk of deterioration from raised intracranial pressure. Patients with posterior circulation strokes are at risk of rapid deterioration and damage to the autonomic nervous system due to the tight anatomical space in the posterior fossa and the close proximity to the brainstem. Interestingly, there are also recent studies suggesting that hypertension and diabetes are more strongly associated with posterior as compared to anterior circulation strokes. Patients with posterior circulation strokes are postulated to be more vulnerable to the atherosclerosis in metabolic diseases as the posterior circulation has finer and shorter perforating branching vessels [46–48]. Nonetheless, more studies are still required to explore the differences in the mechanisms and risk factors of anterior and posterior circulation strokes. Control of any existing metabolic diseases is a priority in managing patients with posterior circulation strokes.

Most authors advocate for neurosurgical intervention with the onset of symptoms, as opposed to preventative or early neurosurgical intervention. To identify severely ill patients who may benefit from neurosurgical intervention, we recommend the close monitoring of the level of arousal and for the presence of new brainstem signs, in accordance with guidelines from the American Heart Association [5]. Certain radiological criteria, such as fourth ventricular compression [13], hydrocephalus [13,24,29] or basal cistern compression [21], may also indicate a need for neurosurgical intervention.

American guidelines recommend decompressive craniectomy for patients with MPCI that have evidence of raised intracranial pressure and are imminently deteriorating. Temporizing medical therapies can also be considered. However, the overall evidence for the surgical vs. medical treatment for patients with MPCI who are still clinically stable is still weak [5]. Recent European guidelines have suggested that it should only be considered and not recommended, as there still remains uncertainty about whether such surgery improves outcomes [49]. This study aggregates preliminary evidence that surgical therapy may reduce mortality as compared to medical therapy in patients with MPCI who are clinically stable at the time of presentation, but its impact on functional outcomes is generally not significant, except in severe disease. Nonetheless, high quality trials will need to be performed to validate these findings. Moreover, there is a need to evaluate which type of neurosurgical intervention leads to better outcomes, which is beyond the scope of this study.

Limitations

Study heterogeneity was significant, due to limited consensus on the threshold or protocol for neurosurgical treatment and different baseline characteristics of the patients. Outcome measures were variably reported, with differing times for follow-up, differing time-points when death was reported and varying definitions of good functional outcome. Further research is required to address these gaps.

There was also limited high quality data, as no large-scale randomized controlled trials were conducted on this topic. Therefore, the studies were mainly retrospective observational papers, with only one prospective study [18]. The sample sizes of the studies were also small, with the largest study involving 86 patients [24].

5. Conclusions

For patients with malignant posterior circulation stroke, in terms of mortality and functional outcome, surgical therapy appears to be equivocal to medical therapy. For patients with severe disease, surgery could be superior to medical therapy. There is a lack of quality data, and more randomized control trials are rendered following this review.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12093185/s1.

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Abbreviations

ETV	Endoscopic third ventriculostomy
EVD	Extraventricular drainage
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
JBI	Joanna Briggs Institute
MPCI	Malignant posterior circulation infarcts
mRS	Modified Rankin Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SDC	Suboccipital decompressive craniectomy

References

1. Feigin, V.L.; Nguyen, G.; Cercy, K.; Johnson, C.O.; Alam, T.; Parmar, P.G.; Abajobir, A.A.; Abate, K.H.; Abd-Allah, F.; GBD 2016 Lifetime Risk of Stroke Collaborators; et al. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *N. Engl. J. Med.* **2018**, *379*, 2429–2437. [PubMed]
2. Mehndiratta, M.; Pandey, S.; Nayak, R.; Alam, A. Posterior Circulation Ischemic Stroke—Clinical Characteristics, Risk Factors, and Subtypes in a North Indian Population. *Neurohospitalist* **2012**, *2*, 46–50. [CrossRef] [PubMed]
3. Schulz, U.G.; Fischer, U. Posterior Circulation Cerebrovascular Syndromes: Diagnosis and Management. *J. Neurol. Neurosurg. Psychiatry* **2017**, *88*, 45–53. [CrossRef] [PubMed]
4. Sommer, P.; Posekany, A.; Serles, W.; Marko, M.; Scharer, S.; Fertl, E.; Ferrari, J.; Lang, W.; Vosko, M.; Szabo, S.; et al. Is Functional Outcome Different in Posterior and Anterior Circulation Stroke? *Stroke* **2018**, *49*, 2728–2732. [CrossRef] [PubMed]
5. Wijdicks, E.F.M.; Sheth, K.N.; Carter, B.S.; Greer, D.M.; Kasner, S.E.; Kimberly, W.T.; Schwab, S.; Smith, E.E.; Tamargo, R.J.; Wintermark, M.; et al. Recommendations for the Management of Cerebral and Cerebellar Infarction with Swelling: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* **2014**, *45*, 1222–1238. [CrossRef]
6. Vahedi, K.; Hofmeijer, J.; Juettler, E.; Vicaut, E.; George, B.; Algra, A.; Amelink, G.J.; Schmiedeck, P.; Schwab, S.; Rothwell, P.M.; et al. Early Decompressive Surgery in Malignant Infarction of the Middle Cerebral Artery: A Pooled Analysis of Three Randomised Controlled Trials. *Lancet Neurol.* **2007**, *6*, 215–222. [CrossRef]
7. Hofmeijer, J.; Kappelle, L.J.; Algra, A.; Amelink, G.J.; van Gijn, J.; van der Worp, H.B. Others Surgical Decompression for Space-Occupying Cerebral Infarction (the Hemicraniectomy After Middle Cerebral Artery Infarction with Life-Threatening Edema Trial [HAMLET]): A Multicentre, Open, Randomised Trial. *Lancet Neurol.* **2009**, *8*, 326–333. [CrossRef]

8. Honeybul, S.; Gillett, G.R.; Ho, K.M.; Janzen, C.; Kruger, K. Is Life Worth Living? Decompressive Craniectomy and the Disability Paradox. *J. Neurosurg.* **2016**, *125*, 775–778. [CrossRef]
9. Kürten, S.; Munoz, C.; Beseoglu, K.; Fischer, I.; Perrin, J.; Steiger, H.-J. Decompressive Hemicraniectomy for Malignant Middle Cerebral Artery Infarction Including Patients with Additional Involvement of the Anterior And/or Posterior Cerebral Artery Territory-Outcome Analysis and Definition of Prognostic Factors. *Acta Neurochir.* **2018**, *160*, 83–89. [CrossRef]
10. Lee, L.; Loh, D.; Kam King, N.K. Posterior Fossa Surgery for Stroke: Differences in Outcomes Between Cerebellar Hemorrhage and Infarcts. *World Neurosurg.* **2020**, *135*, e375–e381. [CrossRef]
11. Ayling, O.G.S.; Alotaibi, N.M.; Wang, J.Z.; Fatehi, M.; Ibrahim, G.M.; Benavente, O.; Field, T.S.; Gooderham, P.A.; Macdonald, R.L. Suboccipital Decompressive Craniectomy for Cerebellar Infarction: A Systematic Review and Meta-Analysis. *World Neurosurg.* **2018**, *110*, 450–459.e5. [CrossRef] [PubMed]
12. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *Int. J. Surg.* **2021**, *88*, 105906. [CrossRef] [PubMed]
13. Tsitsopoulos, P.P.; Tobieson, L.; Enblad, P.; Marklund, N. Clinical Outcome Following Surgical Treatment for Bilateral Cerebellar Infarction. *Acta Neurol. Scand.* **2011**, *123*, 345–351. [CrossRef] [PubMed]
14. Wells, G.; Shea, B.; O'Connell, D.; Robertson, J.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta- Analysis. Available online: http://www3.med.unipmn.it/dispense_ebm/2009-2010/Corso%20Perfezionamento%20EBM_Faggiano/NOS_oxford.pdf (accessed on 11 November 2021).
15. Moola, S.; Munn, Z.; Tufanaru, C.; Aromataris, E.; Sears, K.; Sfetic, R.; Currie, M.; Lisy, K.; Qureshi, R.; Mattis, P.; et al. *Chapter 7: Systematic Reviews of Etiology and Risk. JBI Reviewer's Manual*; JBI: Abelaide, Australia, 2019.
16. Munn, Z.; Barker, T.H.; Moola, S.; Tufanaru, C.; Stern, C.; McArthur, A.; Stephenson, M.; Aromataris, E. Methodological Quality of Case Series Studies: An Introduction to the JBI Critical Appraisal Tool. *JBI Evid. Synth.* **2020**, *18*, 2127–2133. [CrossRef]
17. Taneda, M.; Ozaki, K.; Wakayama, A.; Yagi, K.; Kaneda, H.; Irino, T. Cerebellar Infarction with Obstructive Hydrocephalus. *J. Neurosurg.* **1982**, *57*, 83–91. [CrossRef]
18. Jauss, M.; Krieger, D.; Hornig, C.; Schramm, J.; Busse, O. Surgical and Medical Management of Patients with Massive Cerebellar Infarctions: Results of the German-Austrian Cerebellar Infarction Study. *J. Neurol.* **1999**, *246*, 257–264. [CrossRef]
19. Hornig, C.R.; Rust, D.S.; Busse, O.; Jauss, M.; Laun, A. Space-Occupying Cerebellar Infarction. Clinical Course and Prognosis. *Stroke* **1994**, *25*, 372–374. [CrossRef]
20. Mathew, P.; Teasdale, G.; Bannan, A.; Oluoch-Olunya, D. Neurosurgical Management of Cerebellar Haematoma and Infarct. *J. Neurol. Neurosurg. Psychiatry* **1995**, *59*, 287–292. [CrossRef]
21. Koh, M.G.; Phan, T.G.; Atkinson, J.L.; Wijdicks, E.F. Neuroimaging in Deteriorating Patients with Cerebellar Infarcts and Mass Effect. *Stroke* **2000**, *31*, 2062–2067. [CrossRef]
22. Raco, A.; Caroli, E.; Isidori, A.; Salvati, M. Management of Acute Cerebellar Infarction: One Institution's Experience. *Neurosurgery* **2003**, *53*, 1061–1065, discussion 1065–1066. [CrossRef]
23. Mostofi, K. Neurosurgical Management of Massive Cerebellar Infarct Outcome in 53 Patients. *Surg. Neurol. Int.* **2013**, *4*, 28. [CrossRef]
24. Taylor, D.R.; Basma, J.; Jones, G.M.; Lillard, J.; Wallace, D.; Ajmera, S.; Gienapp, A.J.; Michael, L.M., 2nd. Predicting Surgical Intervention in Cerebellar Stroke: A Quantitative Retrospective Analysis. *World Neurosurg.* **2020**, *142*, e160–e172. [CrossRef]
25. Chen, H.J.; Lee, T.C.; Wei, C.P. Treatment of Cerebellar Infarction by Decompressive Suboccipital Craniectomy. *Stroke* **1992**, *23*, 957–961. [CrossRef]
26. Bertalanffy, H.; de Vries, J. Management of Cerebellar Infarction with Associated Occlusive Hydrocephalus. *Clin. Neurol. Neurosurg.* **1992**, *94*, 19–23. [CrossRef]
27. Krieger, D.; Adams, H.P.; Rieke, K.; Hacke, W. Monitoring Therapeutic Efficacy of Decompressive Craniotomy in Space Occupying Cerebellar Infarcts Using Brain-Stem Auditory Evoked Potentials. *Electroencephalogr. Clin. Neurophysiol.* **1993**, *88*, 261–270. [CrossRef]
28. Koh, M.S.; Goh, K.Y.; Tung, M.Y.; Chan, C. Is Decompressive Craniectomy for Acute Cerebral Infarction of Any Benefit? *Surg. Neurol.* **2000**, *53*, 225–230. [CrossRef]
29. Baldauf, J.; Oertel, J.; Gaab, M.R.; Schroeder, H.W.S. Endoscopic Third Ventriculostomy for Occlusive Hydrocephalus Caused by Cerebellar Infarction. *Neurosurgery* **2006**, *59*, 539–544, discussion 539–544. [CrossRef]
30. Kudo, H.; Kawaguchi, T.; Minami, H.; Kuwamura, K.; Miyata, M.; Kohmura, E. Controversy of Surgical Treatment for Severe Cerebellar Infarction. *J. Stroke Cerebrovasc. Dis.* **2007**, *16*, 259–262. [CrossRef]
31. Yoshimura, K.; Kubo, S.; Nagashima, M.; Hasegawa, H.; Thminaga, S.; Yoshimine, T. Occlusive Hydrocephalus Associated with Cerebellar Infarction Treated with Endoscopic Third Ventriculostomy: Report of 5 Cases. *Minim. Invasive Neurosurg.* **2007**, *50*, 270–272. [CrossRef]
32. Pfefferkorn, T.; Eppinger, U.; Linn, J.; Birnbaum, T.; Herzog, J.; Straube, A.; Dichgans, M.; Grau, S. Long-Term Outcome after Suboccipital Decompressive Craniectomy for Malignant Cerebellar Infarction. *Stroke* **2009**, *40*, 3045–3050. [CrossRef]
33. Jüttler, E.; Schweickert, S.; Ringleb, P.A.; Huttner, H.B.; Köhrmann, M.; Aschoff, A. Long-Term Outcome after Surgical Treatment for Space-Occupying Cerebellar Infarction: Experience in 56 Patients. *Stroke* **2009**, *40*, 3060–3066. [CrossRef] [PubMed]

34. Mangubat, E.Z.; Chan, M.; Ruland, S.; Roitberg, B.Z. Hydrocephalus in Posterior Fossa Lesions: Ventriculostomy and Permanent Shunt Rates by Diagnosis. *Neurol. Res.* **2009**, *31*, 668–673. [CrossRef] [PubMed]
35. Vindigni, M.; Tuniz, F.; Ius, T.; Cramaro, A.; Skrap, M. Endoscopic Third Ventriculostomy in Patients with Secondary Triventricular Hydrocephalus from a Haemorrhage or Ischaemia in the Posterior Cranial Fossa. *Minim. Invasive Neurosurg.* **2010**, *53*, 106–111. [CrossRef]
36. Tsitsopoulos, P.P.; Tobieson, L.; Enblad, P.; Marklund, N. Surgical Treatment of Patients with Unilateral Cerebellar Infarcts: Clinical Outcome and Prognostic Factors. *Acta Neurochir.* **2011**, *153*, 2075–2083. [CrossRef] [PubMed]
37. Moussa, W.M.; Farhoud, A. Ventriculosubgaleal Shunt in the Management of Obstructive Hydrocephalus Caused by Cerebellar Infarction. *Alex. J. Med.* **2013**, *49*, 105–110. [CrossRef]
38. Lee, H.M.; Kim, M.; Suh, S.-I.; Kim, J.H.; Oh, K.; Koh, S.-B.; Seo, W.-K. Lesions on DWI and the Outcome in Hyperacute Posterior Circulation Stroke. *Can. J. Neurol. Sci.* **2014**, *41*, 187–192. [CrossRef]
39. Kim, M.J.; Park, S.K.; Song, J.; Oh, S.-Y.; Lim, Y.C.; Sim, S.Y.; Shin, Y.S.; Chung, J. Preventive Suboccipital Decompressive Craniectomy for Cerebellar Infarction: A Retrospective-Matched Case-Control Study. *Stroke* **2016**, *47*, 2565–2573. [CrossRef]
40. Goedemans, T.; Verbaan, D.; Coert, B.A.; Kerklaan, B.J.; van den Berg, R.; Coutinho, J.M.; van Middelaar, T.; Nederkoorn, P.J.; Vandertop, W.P.; van den Munckhof, P. Neurologic Outcome After Decompressive Craniectomy: Predictors of Outcome in Different Pathologic Conditions. *World Neurosurg.* **2017**, *105*, 765–774. [CrossRef]
41. Tartara, F.; Bongetta, D.; Colombo, E.V.; Bortolotti, C.; Cenzato, M.; Giombelli, E.; Gaetani, P.; Zenga, F.; Pilloni, G.; Ciccone, A.; et al. Strokectomy and Extensive Cerebrospinal Fluid Drainage for the Treatment of Space-Occupying Cerebellar Ischemic Stroke. *World Neurosurg.* **2018**, *115*, e80–e84. [CrossRef]
42. Lindeskog, D.; Lilja-Cyron, A.; Kelsen, J.; Juhler, M. Long-Term Functional Outcome after Decompressive Suboccipital Craniectomy for Space-Occupying Cerebellar Infarction. *Clin. Neurol. Neurosurg.* **2019**, *176*, 47–52. [CrossRef]
43. Suyama, Y.; Wakabayashi, S.; Aihara, H.; Ebiko, Y.; Kajikawa, H.; Nakahara, I. Evaluation of Clinical Significance of Decompressive Suboccipital Craniectomy on the Prognosis of Cerebellar Infarction. *Fujita Med. J.* **2019**, *5*, 21–24.
44. Hernández-Durán, S.; Wolfert, C.; Rohde, V.; Mielke, D. Cerebellar Necrosectomy Instead of Suboccipital Decompression: A Suitable Alternative for Patients with Space-Occupying Cerebellar Infarction. *World Neurosurg.* **2020**, *144*, e723–e733. [CrossRef]
45. Abdelbari Mattar, M.; Maher, H.; Zakaria, K.W. The Impact of Emergent Suboccipital Craniectomy upon Outcome & Prognosis of Massive Cerebellar Infarction: A Single Institutional Study. *Interdiscip. Neurosurg.* **2021**, *25*, 101223.
46. Nagao, T.; Sadoshima, S.; Ibayashi, S.; Takeya, Y.; Fujishima, M. Increase in Extracranial Atherosclerotic Carotid Lesions in Patients with Brain Ischemia in Japan. An Angiographic Study. *Stroke* **1994**, *25*, 766–770. [CrossRef]
47. Subramanian, G.; Silva, J.; Silver, F.L.; Fang, J.; Kapral, M.K.; Oczkowski, W.; Gould, L.; O'Donnell, M.J. Investigators of the Registry of the Canadian Stroke Network Risk Factors for Posterior Compared to Anterior Ischemic Stroke: An Observational Study of the Registry of the Canadian Stroke Network. *Neuroepidemiology* **2009**, *33*, 12–16. [CrossRef]
48. Kim, J.S.; Nah, H.-W.; Park, S.M.; Kim, S.-K.; Cho, K.H.; Lee, J.; Lee, Y.-S.; Kim, J.; Ha, S.-W.; Kim, E.-G.; et al. Risk Factors and Stroke Mechanisms in Atherosclerotic Stroke: Intracranial Compared with Extracranial and Anterior Compared with Posterior Circulation Disease. *Stroke* **2012**, *43*, 3313–3318. [CrossRef]
49. van der Worp, H.B.; Hofmeijer, J.; Jüttler, E.; Lal, A.; Michel, P.; Santalucia, P.; Schönenberger, S.; Steiner, T.; Thomalla, G. European Stroke Organisation (ESO) Guidelines on the Management of Space-Occupying Brain Infarction. *Eur. Stroke J.* **2021**, *6*, XC–CX. [CrossRef]

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Assessing the Relationship between LAMS and CT Perfusion Parameters in Acute Ischemic Stroke Secondary to Large Vessel Occlusion

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Abstract: Background: The Los Angeles Motor Scale (LAMS) is a rapid pre-hospital scale used to predict stroke severity which has also been shown to accurately predict large vessel occlusions (LVOs). However, to date there is no study exploring whether LAMS correlates with the computed tomography perfusion (CTP) parameters in LVOs. Methods: Patients with LVO between September 2019 and October 2021 were retrospectively reviewed and included if the CTP data and admission neurologic exams were available. The LAMS was documented based on emergency personnel exams or scored retrospectively using an admission neurologic exam. The CTP data was processed by RAPID (IschemaView, Menlo Park, CA, USA) with an ischemic core volume (relative cerebral blood flow [rCBF] < 30%), time-to-maximum (Tmax) volume (Tmax > 6 s delay), hypoperfusion index (HI), and cerebral blood volume (CBV) index. Spearman's correlations were performed between the LAMS and CTP parameters. Results: A total of 85 patients were included, of which there were 9 intracranial internal carotid artery (ICA), 53 proximal M1 branch middle cerebral artery M1, and 23 proximal M2 branch occlusions. Overall, 26 patients had LAMS 0–3, and 59 had LAMS 4–5. In total, LAMS positively correlated with CBF < 30% (Correlation Coefficient (CC): 0.32, $p < 0.01$), Tmax > 6 s (CC:0.23, $p < 0.04$), HI (CC:0.27, $p < 0.01$), and negatively correlated with the CBV index (CC:−0.24, $p < 0.05$). The relationships between LAMS and CBF were < 30% and the HI was more pronounced in M1 occlusions (CC:0.42, $p < 0.01$; 0.34, $p < 0.01$ respectively) and proximal M2 occlusions (CC:0.53, $p < 0.01$; 0.48, $p < 0.03$ respectively). The LAMS also correlated with a Tmax > 6 s in M1 occlusions (CC:0.42, $p < 0.01$), and negatively correlated with the CBV index in M2 occlusions (CC:−0.69, $p < 0.01$). There were no significant correlations between the LAMS and intracranial ICA occlusions. Conclusions: The results of our preliminary study indicate that the LAMS is positively correlated with the estimated ischemic core, perfusion deficit, and HI, and negatively correlated with the CBV index in patients with anterior circulation LVO, with stronger relationships in the M1 and M2 occlusions. This is the first study showing that the LAMS may be correlated with the collateral status and estimated ischemic core in patients with LVO.

Keywords: ischemic stroke; perfusion imaging; diagnosis; collateral status

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1. Introduction

Stroke is one of the leading causes of death and disability, with ischemic stroke being the most common [1]. Of those, ischemic strokes, due to large vessel occlusion (LVO), contribute disproportionally to post-stroke dependence and death [2]. Mechanical thrombectomy (MT) has proven to improve functional outcomes in patients with LVO [3], and earlier reperfusion has been associated with better outcomes [4]. Therefore, the ability

to quickly recognize patients with LVO in the field would be beneficial and allow those patients to be taken directly to comprehensive stroke centers, decreasing the time to reperfusion, and improving outcomes [5,6]. Several rapid pre-hospital stroke scales, used by emergency personnel, have been shown to predict LVOs [7].

The Los Angeles Motor Scale (LAMS) is one such rapid pre-hospital scale that was developed to predict stroke severity [8] and is useful when considering whether patients should be diverted to comprehensive stroke centers. Studies have shown that the LAMS has a strong correlation with admission National Institutes of Health Stroke Scale (NIHSS) and is comparable, if not superior, to other utilized pre-hospital stroke scales [9]. Moreover, the LAMS has good accuracy in predicting LVOs [10]. An increased LAMS severity with a score of 4–5 double the likelihood of LVOs compared to a LAMS score of 0–3 [9].

A comprehensive baseline computed tomography (CT) imaging–comprised of non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP)–is widely utilized for triaging patients presenting with acute ischemic stroke (AIS) secondary to anterior circulation LVO for MT. The addition of CTP to comprehensive baseline imaging increases the sensitivity for detecting ischemic core compared to NCCT only [11] while offering additional data in evaluating a patient's collateral status (CS) and eligibility for MT [12]. Poor CS is associated with an increased risk of post-MT complication and overall worse functional outcomes [13,14]. The hypoperfusion index (HI) and cerebral blood volume (CBV) index are parameters obtained from CTP that correlate with the collateral status and infarct growth, and guide decisions for MT [15–19]. There are no current studies exploring the relationship between pre-hospital stroke scales and CTP parameters.

Our preliminary study aimed to explore the relationship between the LAMS score and baseline CTP parameters. Such a relationship may suggest a biological correlation between the LAMS and collateral status and ischemic core.

2. Methods

2.1. Population

The data for the study population was collected through the Johns Hopkins Hospital Comprehensive Stroke Center Database. This study was approved through the Johns Hopkins School of Medicine institutional review board (JHU-IRB00269637). In this retrospective multicenter analysis, we identified consecutive patients from 1 September 2019 to 1 April 2021 who underwent NCCT, CTA, and CTP with confirmed anterior circulation LVO on CTA (defined as distal intracranial internal carotid artery (ICA), M1, and proximal M2 segments of the middle cerebral artery (MCA). Patients were excluded from the analysis if CTP was obtained >24 h after admission or after a mechanical thrombectomy procedure or if patients were incorrectly classified as having LVO (e.g., internal carotid artery stenosis).

2.2. Data Collection

Patients were included in the study if they had an LVO, CTP with available post-processed parameters, and a documented neurologic exam before the time of imaging. The baseline and clinical data collected for each patient included demographics, risk factors for AIS (including coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, prior stroke, smoking status, and body mass index (BMI), a baseline LAMS score, and a site of occlusion. When the LAMS score or admission NIHSS data was unavailable, the scores were estimated based on admission neurologic exam and history [8]. The LAMS score ranged from 0 to 5 based on the addition of the following components: 0 or 1 for facial strength (normal or droop); 0, 1, or 2 for arm strength (normal, drifts down, falls rapidly), and 0, 1, or 2 for grip strength (normal, weak, no grip). Patients were stratified into the LAMS 0–3 versus 4–5 for the primary analysis [20]. The vessel-based subgroup analysis was also performed for distal intracranial ICA, M1, and proximal M2 segments respectively.

2.3. Imaging

The NCCT was acquired on the Siemens Flash and/or Drive (Siemens Healthineers, Erlangen, Germany) with the following parameters: The helical mode at a 5 mm slice thickness (ST) (120 kVp, 365 mAs, rotation time 1 s, acquisition time 6–8 s, collimation 128 × 0.6 mm, pitch value 0.55, scan direction CC).

The CT ASPECTS score was obtained from documented experienced neuroimaging interpreters. If ASPECTS was unavailable, CT imaging was reviewed independently by a board-certified neuroradiologist to determine the ASPECTS score (VY, 6 years of experience).

The CTP was performed on a Siemens Flash and/or Drive (Siemens Healthineers, Erlangen, Germany) with the following parameters: The injection of 50 mL non-ionic iodinated contrast with 30 mL saline flush at 5–6 mL/s with a coverage of 70–100 mm at 5 mm slice thickness, 70 kVP, 200 effective mAs, rotation time 0.25 s, average acquisition time 60 s, collimation 48 × 1.2 mm, pitch value 0.7, 4D range 114 mm × 1.5 s. The CTP images are then post-processed using RAPID commercial software (IschemaView, Menlo Park, CA, USA) for generating Tmax maps. HI is then automatically calculated as a ratio of the calculated Tmax > 10 s delay volume divided by a Tmax > 6 s delay volume in mL (Tmax > 6 s) in the affected hemisphere. The ischemic core on the CTP is quantitatively estimated by the relative cerebral blood volume (rCBF) < 30% volume in mL (rCBF < 30%). Tissue at risk is defined as a Tmax > 6 s. Mismatch volume is defined as the difference between the Tmax > 6 s and the rCBF < 30%. The mismatch ratio is calculated as the Tmax > 6 s divided by the rCBF < 30%. The CBV index is automatically calculated by RAPID as the ratio of mean rCBV values within the Tmax >6 s region with the mean CBV in normal brain regions. The target mismatch profile for CTP is defined based on the prior study by Lansberg et al. [12].

2.4. Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, IL, USA, 2021. The quantitative data was described as mean ± SD (standard deviation) and then compared using an independent t-test after being tested for normality using the Shapiro-Wilk test. The qualitative data were described as numbers and percentages and compared using the Chi-squared test and Fisher's Exact test for variables with small, expected numbers. The correlation coefficients (CC) of the LAMS with the CTP parameters were calculated using the Spearman correlation test. The level of significance was taken at p-value ≤ 0.05, otherwise was non-significant.

3. Results

Eighty-five patients were included. Twenty-eight (32.9%) were scored with a LAMS 0–3 with 57 (67.1%) in the LAMS 4–5 category.

Eighty-five patients had LAMS, ASPECTS, and CTP parameters available for analysis (Figure 1). Patients with mismatch ratios of infinity were excluded from the LAMS mismatch ratio correlation, resulting in 46 out of 85 (54.1%) available for analysis of this parameter. In total, 84 out of 85 patients (98.8%) with a Tmax > 6 s and HI, and 66 out of 85 (77.6%) with CBV indices were available for review. Table 1 compares patients with a LAMS score of 0–3 to those with a score of 4–5. The groups were comparable demographically except for age, with patients scoring 4–5 being older (LAMS 0–3, 63.1 ± 14.23 years old versus LAMS 4–5, 71.02 ± 14.4 years old, $p = 0.02$). Please refer to Table 1 for additional details.

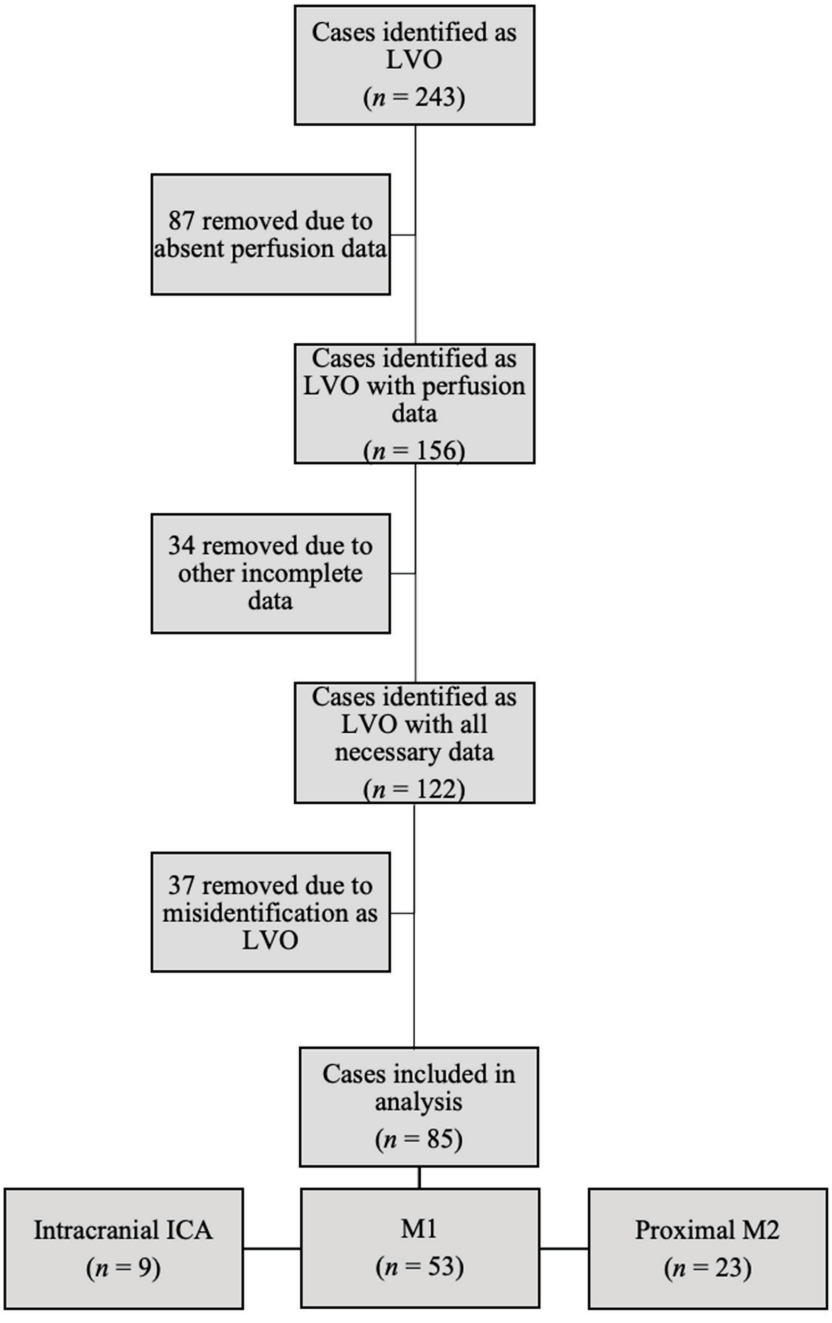

Figure 1. Flow chart of retrospective chart review to identify patients with LVO, admission neurologic exam, and perfusion data. LVO = large vessel occlusion; ICA = internal carotid artery; M1 = M1 branch of middle cerebral artery (MCA), M2 = M2 branch of MCA.

Table 1. Descriptive statistics among the studied cases and comparison according to LAMS score.

Variables		All Cases (N = 85)	LAMS Score		*p*-Value
			0–3 (N = 28)	4–5 (N = 57)	
Age (years), Mean ± SD		68.6 ± 14.7	63.1 ± 14.23	71.02 ± 14.4	⌂ 0.02 *
Sex (*n*, %)	Male	40 (47.1%)	13 (50%)	27 (45.7%)	# 0.97
	Female	45 (52.9%)	13 (50%)	32 (54.23%)	
Race (*n*, %)	African	44 (51.8%)	14 (53.8%)	30 (50.84%)	§ 0.89
	White/Caucasian	36 (42.4%)	10 (38.4%)	26 (44.06%)	
	Others	5 (5.9%)	2 (7.6%)	3 (5.08%)	
Atrial Fibrillation, (*n*, %)		28 (32.9%)	6 (23.1%)	22 (37.3%)	# 0.86
Diabetes, (*n*, %)		25 (29.4%)	6 (23.1%)	19 (32.2%)	# 0.87
Dyslipidemia, (*n*, %)		30 (35.3%)	10 (38.5%)	20 (33.9%)	# 0.12
HTN, (*n*, %)		60 (70.6%)	14 (53.8%)	46 (78.0%)	# 0.14
Prior CVA, (*n*, %)		17 (20.0%)	4 (15.4%)	13 (22.0%)	§ 0.92
CKD, (*n*, %)		8 (9.4%)	4 (15.4%)	4 (6.8%)	§ 0.13
Smoking history, (*n*, %)		16 (18.8%)	4 (15.4%)	12 (20.3%)	§ 0.74
CAD, (*n*, %)		16 (18.8%)	6 (23.1%)	10 (16.9%)	§ 0.83
ASPECTS, Mean ± SD		7.4 ± 2.5	7.8 ± 2.4	7.3 ± 2.6	⌂ 0.41
Time parameters, minutes Median (IQR)	Last known well to door	230 (70, 642)	148 (74, 736)	262 (70, 592)	ˆ 0.98
	Door to CT	29 (18, 44)	28 (18, 37)	30 (21, 45)	ˆ 0.35
	Last known well to CT	274.5 (98, 683)	198 (87, 796)	302 (112, 635)	ˆ 0.88

§ Fishers Exact test. # Chi square test. ⌂ Independent t-test. ˆ Mann-Whitney U test. * Significant (0.050). LAMS = Los Angeles Motor Scale; HTN = hypertension; CVA = cerebrovascular accident; CKD = chronic kidney disease, CAD = coronary artery disease; CT = computed tomography; IQR = interquartile range.

The 85 patients included in the study were comprised of nine distal intracranial ICA (9/85, 10.5%); 53 M1 (62.3%); and 23 proximal M2 (23/85, 27.1%) occlusions.

There were significant small to moderate positive correlations between the LAMS score and CBF <30% (mL) (CC 0.32, $p < 0.01$), Tmax > 6 s (CC:0.23, $p < 0.04$), and HI (CC:0.27, $p < 0.01$), and small negative correlation with the CBV index (CC:−0.24, $p < 0.05$) with the CBV index based on a post-processed analysis from a widely used commercial software platform (Table 2). There was no significant correlation between the LAMS score and imaging parameters when the intracranial ICA occlusions were isolated (Table 3).

Table 2. Correlation between LAMS score with imaging parameters for all cases.

Total Cases (*n* = 85)	Descriptive (*n*)	*p* Value	Correlation Coefficient
CBF < 30% (mL)	24.94 ± 42.6(85)	0.01 *	0.32
Tmax > 6 s (mL)	113.61 ± 83.4(84)	0.04 *	0.23
Mismatch Volume (mL)	88.67 ± 77.7(84)	0.36	0.10
Mismatch ratio	6.34 ± 7.03(46)	0.98	−0.01
Hypoperfusion Index	0.375 ± 0.25(84)	0.01 *	0.27
ASPECTS	7.45 ± 2.57(85)	0.38	−0.10
CBV Index (rCBV Tmax > 6 s)	0.70 ± 0.19(66)	0.05 *	−0.24
LAMS score	3.85 ± 1.5(85)	0	1

* Significant (0.050). CBF = cerebral blood flow, CBV = cerebral blood volume.

Table 3. Correlation between LAMS with imaging parameters for intracranial ICA occlusions.

Intracranial ICA Only (n = 9)	Descriptive (n)	p Value	Correlation Coefficient
CBF < 30% (mL)	62.63 ± 82.66 (11)	0.81	0.08
Tmax > 6 s (mL)	200.81 ± 137.16 (11)	0.43	0.27
Mismatch Volume (mL)	138.18 ± 144.6 (11)	0.65	0.15
Mismatch ratio	4.43 ± 4.07 (8)	0.95	0.03
Hypoperfusion Index	0.55 ± 0.22 (11)	0.86	0.06
ASPECTS	5.18 ± 3.45 (11)	0.40	0.29
CBV Index (rCBV Tmax > 6 s)	0.655 ± 2.87 (9)	0.56	−0.23
LAMS score	3 ± 1.67 (11)	0	1

* Significant (0.050).

3.1. M1 Segmental Subgroup Analysis

In patients with M1 occlusions, the LAMS score was moderate to positively correlated with a CBF < 30% (CC:0.42, $p < 0.01$), Tmax > 6 s (CC:0.42, $p < 0.01$), and HI (0.34, $p < 0.01$), and negatively correlated with ASPECTS (CC:−0.30, $p < 0.03$) (Table 4).

Table 4. Correlation between LAMS with imaging parameters for M1 occlusions.

M1 (n = 53)	Descriptive (n)	p Value	Correlation Coefficient
CBF < 30% (mL)	19.8 ± 31.4 (52)	0.01 *	0.42
Tmax > 6 s (mL)	113 ± 66.2 (52)	0.01 *	0.42
Mismatch Volume (mL)	93.8 ± 61.3 (52)	0.28	0.24
Mismatch ratio	7.98 ± 8.42 (27)	0.57	−0.12
Hypoperfusion Index	0.33 ± 0.25 (52)	0.01 *	0.34
ASPECTS	7.69 + 2.39 (52)	0.03 *	−0.30
CBV Index (rCBV Tmax > 6 s)	0.73 ± 0.14 (40)	0.39	−0.14
LAMS score	4.06 ± 1.29 (52)	0	1

* Significant (0.050).

3.2. Proximal M2 Segment Subgroup Analysis

In patients with proximal M2 occlusions, the LAMS score was moderate to strongly positively correlated with a CBF < 30% and HI (CC:0.53, $p < 0.01$; 0.48, $p < 0.03$ respectively). The LAMS score was strongly negatively correlated with the CBV index (CC:−0.69, $p < 0.01$) (Table 5). There was no correlation between the LAMS and ASPECTS scores in the M2 occlusions.

In summary, in patients with M1 or proximal M2 occlusions, the LAMS score is positively correlated with a CBF < 30% and HI. In patients with M2 occlusions, the LAMS score is further positively correlated with a Tmax > 6 s, and in patients with M1 occlusions, the LAMS is further negatively correlated with the ASPECTS score. In patients with intracranial ICA occlusions, no significant correlation between the LAMS score and the perfusion imaging parameters were demonstrated.

Table 5. Correlation between LAMS score with imaging parameters for proximal M2 occlusion.

Proximal M2 (n = 23)	Descriptive (n)	p Value	Correlation Coefficient
CBF < 30% (mL)	17.7 ± 26.8 (21)	0.01 *	0.53
Tmax > 6 s (mL)	67.6 ± 43.9 (21)	0.69	0.09
Mismatch Volume (mL)	49.9 ± 45.1 (21)	0.21	−0.29
Mismatch ratio	3.72 ± 2.92 (11)	0.57	−0.20
Hypoperfusion Index	0.37 ± 0.25 (21)	0.03 *	0.48
ASPECTS	8.05 ± 1.88 (22)	0.53	−0.14
CBV Index (rCBV in Tmax > 6 s)	0.68 ± 0.23 (17)	0.01 *	−0.69
LAMS score	3.77 ± 1.77 (22)	0	1

* Significant (0.050).

4. Discussion

We demonstrate that the LAMS score showed weak to moderate significant positive correlations with an rCBF < 30, a Tmax > 6 s, and HI in all patients with LVOs, though when affected vessels were analyzed separately, there were no correlations in patients with ICA occlusions. The results indicate that a rapid pre-hospital stroke scale may help determine which patients within the anterior circulation LVO subset also have a larger ischemic core and poor CS, an important biological correlation. After stratifying by the LVO segment (intracranial ICA, M1, and proximal M2), the results show that these relationships are most pronounced in MCA occlusions. There is no significant correlation between the LAMS score and the CTP imaging parameters in distal intracranial ICA occlusions, however, the sample size of patients with intracranial ICA occlusions was small. Future research should include a larger sample of patients with intracranial ICA occlusions to assess for a possible relationship. The positive correlation between the LAMS and HI index and the negative correlation of the CBV index specifically support the potential relationship between the LAMS and CS.

Poor CS has been shown to be associated with a larger core infarct size on admission [21] and larger 24-h infarct volumes [22]. Further, poor CS is associated with a higher ischemic core growth rate, meaning that patients with poor CS have less time to save salvageable tissue [23]. Previous research has shown that patients with poor CS are more likely to have high admission NIHSS scores [13]. Our results are in line with the correlation between the admission NIHSS and the admission LAMS score [8]. The LAMS, however, can be completed more rapidly than the NIHSS by emergency personnel. Therefore, being able to use the LAMS score to potentially predict CS is important for the rapid triaging of patients to stroke centers where treatment can be offered. This may help to prioritize transport to a comprehensive stroke center rather than the nearest hospital due to the faster ischemic core growth rate in patients with poor CS [23].

The moderate to strong correlations between the LAMS and a CBF < 30% indicate that the LAMS may also predict an ischemic core. In addition, the admission NIHSS has been associated with an ischemic core volume, with a lower NIHSS correlating with a smaller ischemic core [24]. Our results are in line with the correlation between the admission NIHSS and the admission LAMS score [8]. Interestingly, there was no correlation between the LAMS and ASPECTS. Prior research has shown that a CT ASPECTS score does not predict functional outcomes, while the CTP ASPECTS using a threshold of CBF < 30% for the core is predictive of functional outcomes [25]. A simple stroke scale, which may predict a CBF < 30% and collateral status, may therefore provide more information than an ASPECTS score as to which patients will benefit from thrombectomy. This is further supported by research showing that patients, even with a low CT ASPECTS, benefit from thrombectomy [26,27].

There are several limitations to this preliminary study. First, the LAMS scores, when unavailable from EMS personnel, were obtained retrospectively based on admission exams. These exams were usually performed by the consulting neurologist as opposed to EMS personnel. However, the entry LAMS score has been shown to have good convergent validity with the admission NIHSS and admission physical exam when retroactively scored [8]. Patients with a LAMS score of 4–5 were older than patients with a LAMS score of 0–3, and studies have shown that age correlates with poor CS [28]. Therefore we may expect older patients to have a higher LAMS based on our results. A further limitation of this study was the small sample size and the restriction of the sample of stroke patients with LVO. This study is predicated on the accuracy of the LAMS predicting LVOs, but we cannot know with certainty at the time of the LAMS if the patient in fact has an LVO. Future studies should compare the accuracy of the LAMS in predicting LVOs and CS in all suspected stroke patients. Nevertheless, our study shows a good correlation with surrogates for CS in this population and, therefore, may suggest that the LAMS has a biological correlation with CS, especially in MCA occlusions. The data more robustly supports the practice of using the LAMS to detect LVO in the field, which is especially important when considering triage to a comprehensive stroke center [29]. This information would be further useful in patients presenting within 6 h of treatment onset, as it may be reasonable to bypass advanced imaging and go directly to the angiography suite in patients with a higher LAMS, given the risk of poor CS and early ischemia. This approach has been shown to decrease transfer times [30,31] and higher rates of clinical improvement at 24 h [31]. Finally, given the relationship between poor CS with worse outcomes in patients with LVOs [14,32–35], future research should explore the utility of the LAMS in predicting recanalization and overall clinical outcomes with a larger prospective study.

In summary, this is the first study exploring the relationship between a rapid pre-hospital stroke scale and cerebral perfusion parameters. The results show that the LAMS may be correlated with CS and the ischemic core in patients with LVO. More research needs to be performed to validate these results. Nevertheless, these results suggest that a simple pre-hospital scale such as the LAMS may have value beyond LVO detection by providing information on the ischemic core and CS at the time of presentation. Poor CS specifically is associated with higher rates of infarct growth [23], and patients with poor CS should be transported to a comprehensive stroke center quickly to improve functional outcomes by decreasing the time to reperfusion [5]. The ability of a rapid scale, such as the LAMS to predict CS, is therefore extremely useful in selecting patients in which primary stroke centers should be bypassed. Future studies should build on these results to assess the utility of the LAMS in triaging stroke patients in the field for the timely transfer to a comprehensive stroke center for appropriate intervention.

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References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* **2021**, *20*, 795–820. [CrossRef] [PubMed]
2. Malhotra, K.; Gornbein, J.; Saver, J.L. Ischemic Strokes Due to Large-Vessel Occlusions Contribute Disproportionately to Stroke-Related Dependence and Death: A Review. *Front. Neurol.* **2017**, *8*, 651. [CrossRef] [PubMed]
3. Goyal, M.; Menon, B.K.; Van Zwam, W.H.; Dippel, D.W.; Mitchell, P.J.; Demchuk, A.M.; Dávalos, A.; Majoie, C.B.; van Der Lugt, A.; De Miquel, M.A. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* **2016**, *387*, 1723–1731. [CrossRef] [PubMed]
4. Saver, J.L.; Goyal, M.; Van der Lugt, A.; Menon, B.K.; Majoie, C.B.; Dippel, D.W.; Campbell, B.C.; Nogueira, R.G.; Demchuk, A.M.; Tomasello, A. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA* **2016**, *316*, 1279–1289. [CrossRef]
5. Hong, J.B.; Diprose, W.K.; Wang, M.T.M.; Meyer, J.; Kilfoyle, D.; Brew, S.; Barber, P.A. Bypass of Primary Stroke Centers Compared With Secondary Transfer for Endovascular Thrombectomy. *Stroke Vasc. Interv. Neurol.* **2022**, *2*, e000390. [CrossRef]
6. Mohamad, N.F.; Hastrup, S.; Rasmussen, M.; Andersen, M.S.; Johnsen, S.P.; Andersen, G.; Simonsen, C.Z. Bypassing primary stroke centre reduces delay and improves outcomes for patients with large vessel occlusion. *Eur. Stroke J.* **2016**, *1*, 85–92. [CrossRef]
7. Zhao, H.; Coote, S.; Pesavento, L.; Churilov, L.; Dewey, H.M.; Davis, S.M.; Campbell, B.C.V. Large Vessel Occlusion Scales Increase Delivery to Endovascular Centers Without Excessive Harm From Misclassifications. *Stroke* **2017**, *48*, 568–573. [CrossRef] [PubMed]
8. Llanes, J.N.; Kidwell, C.S.; Starkman, S.; Leary, M.C.; Eckstein, M.; Saver, J.L. The Los Angeles Motor Scale (LAMS): A new measure to characterize stroke severity in the field. *Prehospital Emerg. Care* **2004**, *8*, 46–50. [CrossRef] [PubMed]
9. Noorian, A.R.; Sanossian, N.; Shkirkova, K.; Liebeskind, D.S.; Eckstein, M.; Stratton, S.J.; Pratt, F.D.; Conwit, R.; Chatfield, F.; Sharma, L.K.; et al. Los Angeles Motor Scale to Identify Large Vessel Occlusion. *Stroke* **2018**, *49*, 565–572. [CrossRef]
10. Nazliel, B.; Starkman, S.; Liebeskind, D.S.; Ovbiagele, B.; Kim, D.; Sanossian, N.; Ali, L.; Buck, B.; Villablanca, P.; Vinuela, F.; et al. A brief prehospital stroke severity scale identifies ischemic stroke patients harboring persisting large arterial occlusions. *Stroke* **2008**, *39*, 2264–2267. [CrossRef]
11. Shen, J.; Li, X.; Li, Y.; Wu, B. Comparative accuracy of CT perfusion in diagnosing acute ischemic stroke: A systematic review of 27 trials. *PLoS ONE* **2017**, *12*, e0176622. [CrossRef]
12. Lansberg, M.G.; Christensen, S.; Kemp, S.; Mlynash, M.; Mishra, N.; Federau, C.; Tsai, J.P.; Kim, S.; Nogueria, R.G.; Jovin, T.; et al. Computed tomographic perfusion to Predict Response to Recanalization in ischemic stroke. *Ann. Neurol.* **2017**, *81*, 849–856. [CrossRef] [PubMed]
13. Fanou, E.M.; Knight, J.; Aviv, R.I.; Hojjat, S.P.; Symons, S.P.; Zhang, L.; Wintermark, M. Effect of Collaterals on Clinical Presentation, Baseline Imaging, Complications, and Outcome in Acute Stroke. *Am. J. Neuroradiol.* **2015**, *36*, 2285. [CrossRef] [PubMed]
14. Souza, L.C.S.; Yoo, A.J.; Chaudhry, Z.A.; Payabvash, S.; Kemmling, A.; Schaefer, P.W.; Hirsch, J.A.; Furie, K.L.; González, R.G.; Nogueira, R.G.; et al. Malignant CTA collateral profile is highly specific for large admission DWI infarct core and poor outcome in acute stroke. *AJNR Am. J. Neuroradiol.* **2012**, *33*, 1331–1336. [CrossRef] [PubMed]
15. Guenego, A.; Marcellus, D.G.; Martin, B.W.; Christensen, S.; Albers, G.W.; Lansberg, M.G.; Marks, M.P.; Wintermark, M.; Heit, J.J. Hypoperfusion Intensity Ratio Is Correlated With Patient Eligibility for Thrombectomy. *Stroke* **2019**, *50*, 917–922. [CrossRef]
16. Guenego, A.; Fahed, R.; Albers, G.W.; Kuraitis, G.; Sussman, E.S.; Martin, B.W.; Marcellus, D.G.; Olivot, J.M.; Marks, M.P.; Lansberg, M.G.; et al. Hypoperfusion intensity ratio correlates with angiographic collaterals in acute ischaemic stroke with M1 occlusion. *Eur. J. Neurol.* **2020**, *27*, 864–870. [CrossRef]
17. MacLellan, A.; Mlynash, M.; Kemp, S.; Ortega-Gutierrez, S.; Heit, J.J.; Marks, M.P.; Lansberg, M.G.; Albers, G.W. Perfusion Imaging Collateral Scores Predict Infarct Growth in Non-Reperfused DEFUSE 3 Patients. *J. Stroke Cerebrovasc. Dis.* **2022**, *31*, 106208. [CrossRef] [PubMed]
18. Arenillas, J.F.; Cortijo, E.; García-Bermejo, P.; Levy, E.I.; Jahan, R.; Liebeskind, D.; Goyal, M.; Saver, J.L.; Albers, G.W. Relative cerebral blood volume is associated with collateral status and infarct growth in stroke patients in SWIFT PRIME. *J. Cereb. Blood Flow Metab.* **2018**, *38*, 1839–1847. [CrossRef] [PubMed]
19. Mlynash, M.; Lansberg, M.G.; Kemp, S.; Christensen, S.; Yennu, A.; Heit, J.J.; Marks, M.P.; Albers, G.W. Abstract WP79: Combination of Tmax and Relative CBV Perfusion Parameters More Accurately Predicts CTA Collaterals Than a Single Perfusion Parameter in DEFUSE 3. *Stroke* **2019**, *50* (Suppl. S1), AWP79. [CrossRef]
20. Stead, T.G.; Banerjee, P.; Ganti, L. Real-World Field Performance of the Los Angeles Motor Scale as a Large Vessel Occlusion Screen: A Prospective Muticentre Study. *Cerebrovasc. Dis.* **2023**, *50*, 543–550. [CrossRef] [PubMed]
21. Xia, Q.; Wang, X.; Zhang, Z.; Fang, Q.; Hu, C. Relationship between CT angiography-derived collateral status and CT perfusion-derived tissue viability. *Clin. Radiol.* **2019**, *74*, 956–961. [CrossRef]
22. Rao, V.A.-O.; Mlynash, M.; Christensen, S.; Yennu, A.; Kemp, S.; Zaharchuk, G.; Heit, J.A.-O.; Marks, M.P.; Lansberg, M.G.; Albers, G.W. Collateral status contributes to differences between observed and predicted 24-h infarct volumes in DEFUSE 3. *J. Cereb. Blood Flow Metab.* **2020**, *40*, 1966–1974. [CrossRef]
23. Lin, L.; Yang, J.; Chen, C.; Tian, H.; Bivard, A.; Spratt, N.J.; Levi, C.R.; Parsons, M.W. Association of Collateral Status and Ischemic Core Growth in Patients with Acute Ischemic Stroke. *Neurology* **2021**, *96*, e161–e170. [CrossRef] [PubMed]

24. Cao, W.; Ling, Y.; Yang, L.; Wu, F.; Zhang, H.; Cheng, X.; Dong, Q. Association of Admission NIHSS Score with Infarct Core Volume and Target Mismatch of Infarct Core/Penumbra Volume on CT Perfusion in Acute Ischaemic Stroke. *Cerebrovasc. Dis.* **2021**, *50*, 700–706. [CrossRef]
25. Demeestere, J.; Scheldeman, L.; Cornelissen, S.A.; Heye, S.; Wouters, A.; Dupont, P.; Christensen, S.; Mlynash, M.; Albers, G.W.; Lansberg, M.; et al. Alberta Stroke Program Early CT Score Versus Computed Tomographic Perfusion to Predict Functional Outcome after Successful Reperfusion in Acute Ischemic Stroke. *Stroke* **2018**, *49*, 2361–2367. [CrossRef]
26. Huo, X.; Ma, G.; Tong, X.; Zhang, X.; Pan, Y.; Nguyen, T.N.; Yuan, G.; Han, H.; Chen, W.; Wei, M.; et al. Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *N. Engl. J. Med.* **2023**, *388*, 1272–1283. [CrossRef]
27. Sarraj, A.; Hassan, A.E.; Abraham, M.G.; Ortega-Gutierrez, S.; Kasner, S.E.; Hussain, M.S.; Chen, M.; Blackburn, S.; Sitton, C.W.; Churilov, L.; et al. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. *N. Engl. J. Med.* **2023**, *388*, 1259–1271. [CrossRef] [PubMed]
28. Wiegers, E.J.A.; Mulder, M.J.H.L.; Jansen, I.G.H.; Venema, E.; Compagne, K.C.J.; Berkhemer, O.A.; Emmer, B.J.; Marquering, H.A.; van Es, A.C.G.M.; Sprengers, M.E.; et al. Clinical and Imaging Determinants of Collateral Status in Patients with Acute Ischemic Stroke in MR CLEAN Trial and Registry. *Stroke* **2020**, *51*, 1493–1502. [CrossRef]
29. Haight, T.; Tabaac, B.; Patrice, K.-A.; Phipps, M.S.; Butler, J.; Johnson, B.; Aycock, A.; Toral, L.; Yarbrough, K.L.; Schrier, C.; et al. The Maryland Acute Stroke Emergency Medical Services Routing Pilot: Expediting Access to Thrombectomy for Stroke. *Front. Neurol.* **2021**, *12*, 663472. [CrossRef] [PubMed]
30. Jadhav, A.P.; Kenmuir, C.L.; Aghaebrahim, A.; Limaye, K.; Wechsler, L.R.; Hammer, M.D.; Starr, M.T.; Molyneaux, B.J.; Rocha, M.; Guyette, F.X.; et al. Interfacility Transfer Directly to the Neuroangiography Suite in Acute Ischemic Stroke Patients Undergoing Thrombectomy. *Stroke* **2017**, *48*, 1884–1889. [CrossRef] [PubMed]
31. Ribo, M.; Boned, S.; Rubiera, M.; Tomasello, A.; Coscojuela, P.; Hernández, D.; Pagola, J.; Juega, J.; Rodriguez, N.; Muchada, M.; et al. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. *J. Neurointerv. Surg.* **2018**, *10*, 221–224. [CrossRef]
32. Broocks, G.; Kemmling, A.; Meyer, L.; Nawabi, J.; Schön, G.; Fiehler, J.; Kniep, H.; Hanning, U. Computed Tomography Angiography Collateral Profile Is Directly Linked to Early Edema Progression Rate in Acute Ischemic Stroke. *Stroke* **2019**, *50*, 3424–3430. [CrossRef] [PubMed]
33. Lee, T.J.; Roh, H.G.; Kim, J.H.; Lee, S.B.; Park, J.J.; Lee, H.J.; Jeon, Y.S.; Choi, J.W.; Chun, Y.I.; Jung, Y.J.; et al. Collateral and permeability imaging derived from dynamic contrast material-enhanced MR angiography in prediction of PH 2 hemorrhagic transformation after acute ischemic stroke: A pilot study. *Neuroradiology* **2021**, *63*, 1471–1479. [CrossRef] [PubMed]
34. Feng, X.; Ye, G.; Cao, R.; Qi, P.; Lu, J.; Chen, J.; Wang, D. Identification of Predictors for Hemorrhagic Transformation in Patients with Acute Ischemic Stroke After Endovascular Therapy Using the Decision Tree Model. *Clin. Interv. Aging* **2020**, *15*, 1611–1624. [CrossRef] [PubMed]
35. Huang, X.; Yang, Q.; Shi, X.; Xu, X.; Ge, L.; Ding, X.; Zhou, Z. Predictors of malignant brain edema after mechanical thrombectomy for acute ischemic stroke. *J. Neurointerv. Surg.* **2019**, *11*, 994. [CrossRef] [PubMed]

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Association between Triglyceride-Glucose Index and Early Neurological Outcomes after Thrombolysis in Patients with Acute Ischemic Stroke

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Abstract: Background: The triglyceride-glucose (TyG) index is a novel biomarker of insulin resistance which might plausibly influence endogenous fibrinolysis and thus early neurological outcomes in patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis using recombinant tissue-plasminogen activator. Methods: We included consecutive AIS patients within 4.5 h of symptom onset undergoing intravenous thrombolysis between January 2015 and June 2022 in this multi-center retrospective observational study. Our primary outcome was early neurological deterioration (END), defined as $\geq$2 (END_2) or $\geq$ 4 (END_4) National Institutes of Health Stroke Scale (NIHSS) score worsening compared to the initial NIHSS score within 24 h of intravenous thrombolysis. Our secondary outcome was early neurological improvement (ENI), defined as a lower NIHSS score at discharge. TyG index was calculated using the log scale of fasting triglyceride (mg/dL) $\times$ fasting glucose (mg/dL)/2. We evaluated the association of END and ENI with TyG index using a logistic regression model. Results: A total of 676 patients with AIS were evaluated. The median age was 68 (Interquartile range, IQR (60–76) years old), and 432 (63.9%) were males. A total of 89 (13.2%) patients developed END_2, 61 (9.0%) patients developed END_4, and 492 (72.7%) experienced ENI. In multivariable logistic regression analysis, after adjustment for confounding factors, TyG index was significantly associated with increased risks of END_2 (categorical variable, vs. lowest tertile, medium tertile odds ratio [OR] 1.05, 95% confidence interval, CI 0.54–2.02, highest tertile OR 2.94, 95%CI 1.64–5.27, overall $p < 0.001$) and END_4 (categorical variable, vs. lowest tertile, medium tertile OR 1.21, 95%CI 0.54–2.74, highest tertile OR 3.80, 95%CI 1.85–7.79, overall $p < 0.001$), and a lower probability of ENI (categorical variable, vs. lowest tertile, medium tertile OR 1.00, 95%CI 0.63–1.58, highest tertile OR 0.59, 95%CI 0.38–0.93, overall $p = 0.022$). Conclusions: Increasing TyG index was associated with a higher risk of END and a lower probability of ENI in patients with acute ischemic stroke treated with intravenous thrombolysis.

Keywords: acute ischemic stroke; early neurological deterioration; early neurological improvement; intravenous thrombolysis; triglyceride-glucose index

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1. Introduction

Intravenous thrombolysis treatment remains a first-line approach for acute ischemic stroke (AIS) [1,2]. Despite the beneficial effects of intravenous thrombolysis using recombinant tissue-plasminogen activator for AIS patients, about one-third may experience unfavorable early neurological outcomes [3,4]; 13.8% (95% confidence interval, [CI] 10.0% to 17.7%) of patients experienced early neurological deterioration (END) [5], and 20.9% had failure of early neurological improvement (ENI) [6]. Previous studies showed that END was related to unfavorable stroke outcomes, while ENI was associated with favorable prognosis [6–8]. Therefore, identifying factors for early neurological outcomes including END and ENI in the AIS population could provide important prognostic information with relevance for stroke management.

Insulin resistance is considered a main pathophysiological mediator of metabolic syndrome [9]. Despite the established importance of insulin resistance in cardiovascular and cerebrovascular disease [10], evidence of the link between insulin resistance and acute ischemic stroke outcomes is scarce [11]. Insulin resistance might be relevant to acute recanalization therapy through its associations with thrombosis and inflammation, with abnormal endogenous fibrinolysis and increased platelet activation. The hyperinsulinemic-euglycemic clamp test is the gold standard for evaluating insulin resistance. However, this labor-intensive and time-consuming procedure is not routinely measured in clinical practice [12]. Recently, the triglyceride-glucose (TyG) index, which is calculated using serum triglyceride and fast blood glucose levels, has been used as a reliable and novel biomarker of insulin resistance [13]. Aggravating data showed that the TyG index is related to arterial stiffness [14], a higher risk of the cardiocerebrovascular diseases and unfavorable outcomes in patients with cardiocerebrovascular disease [15,16]. Previous studies showed that elevated triglyceride and blood glucose levels were related to the incidence of END and adversely associated with ENI in ischemic stroke population [5,17,18]. Moreover, data from the UK Biobank cohort involving 273,368 individuals showed that the TyG index was superior to blood glucose and triglycerides alone in predicting stroke occurrence, suggesting that the TyG index may potentially be a good biomarker of insulin resistance to predict stroke outcomes [19]. We hypothesized that a higher baseline TyG index is associated with an increased risk of END and a lower probability of ENI in AIS patients who received intravenous thrombolysis. Therefore, we investigated the association of TyG index with the risk of END and ENI after intravenous thrombolysis in a retrospective observational study.

2. Methods

2.1. Study Design and Participants

We included consecutive adult AIS patients undergoing intravenous thrombolysis within 4.5 h at three certified stroke centers of Fujian Medical University between January 2015 and June 2022 in this multi-center retrospective cohort study. The exclusion criteria were as follows: (1) discharged within 24 h; (2) receiving arterial thrombolytic treatment; (3) interrupted intravenous thrombolysis due to prompt neurological function improvement or serious side effects.

2.2. Data Acquisition

Two authors extracted data regarding baseline demographic characteristics, vascular risk factors (smoking, drinking, history of stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and coronary artery disease), pre-stroke medication-use history (antiplatelet, anticoagulation, statin, antihypertensive, and hypoglycemic agents), clinical features (admission stroke onset severity, admission systolic blood pressure and diastolic blood pressure, onset to treatment time, stroke subtypes), and laboratory findings. Stroke severity (presenting deficit severity) was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtypes were classified into atherosclerosis (A), small

vessel disease (S), cardioembolic (C), and others (O) [20]. Patients with missing data regarding the component of the TyG index and outcomes were excluded.

2.3. Triglyceride Glucose (TyG) Index Evaluation

Blood samples were collected after fasting for 8 to 12 h. Serum triglyceride and glucose levels were assessed with an automatic biochemical analyzer (Cobas c-system, Roche, Switzerland), and expressed in milligrams per deciliter (mg/dL). The TyG index was calculated using the log scale of fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2, as previously described [21].

2.4. Outcomes

Trained clinicians assessed the neurological deficit using the NIHSS score before and after intravenous thrombolysis. Our primary outcome was END. We applied two well-validated (available) definitions: (i) ≥2 NIHSS-point worsening (END_2); and (ii) ≥4 NIHSS-point worsening (END_4) compared to the initial NIHSS score within 24 h after intravenous thrombolysis [22,23]. Our secondary outcome was ENI, defined as a lower NIHSS score at discharge [6].

2.5. Statistical Analysis

Categorical variables were expressed as absolute counts with percentages. Continuous variables were expressed as means (standard deviation, SD) if normally distributed, or medians (interquartile range, IQR) if not normally distributed. TyG index was treated as both a three-level group (lowest as reference) and a continuous variable. A general linear model and chi-squared test were used to calculate the p for trend between variables for continuous and categorical TyG index data, respectively. To summarize the differences in baseline characteristics in patients with and without END or ENI, continuous variables were compared using the Student's t-test, the Mann–Whitney U-test, analysis of variance or the Kruskal–Wallis test, as appropriate, and categorical variables were compared using the chi-squared test or Fisher's exact test. We calculated the absolute risks and absolute risk differences between different TyG index tertile groups for early neurological outcomes. Five conventional multivariate adjusted logistic regression models were applied to assess the association of END or ENI with TyG index. Model 1: by incorporating those with $p < 0.1$ for END or ENI in the univariable analysis in addition to age and sex. Model 2: by incorporating the identified suitable minimally sufficient adjustment sets using a directed acyclic graph (DAG) [24] to minimize potential bias from intermediate variables when assessing the effect of the TyG index on END or ENI. Model 3: by incorporating those with $p < 0.1$ in different TyG index tertile groups in addition to age and sex. Model 4: by incorporating baseline NIHSS score and prespecified vascular risk factors (hypertension, atrial fibrillation, and coronary artery disease) that were shown to be related to the odds of END or ENI in addition to age and sex [5,25,26]. Model 5: by incorporating those variables that are associated with both exposure and outcome variables with $p < 0.1$ in the univariable analysis into the multivariable analysis. Considering the components of the TyG index, the fasting blood glucose, history of diabetes dyslipidemia, and previous hypoglycemic use were not simultaneously introduced along with the TyG index into the multivariable analysis. To test whether the effect of TyG index on END or ENI occurrence varied between age group (<65 vs. ≥65 years), sex (male vs. female), diabetes (yes vs. no), and stroke onset severity (baseline NIHSS <6 vs. ≥6), the interaction terms TyG-by-age, TyG-by-sex, TyG-by-NIHSS, and TyG-by-diabetes history were used as covariates. A priori p-value < 0.05 was considered significant for interactions. We conducted subgroup analyses, including age (<65 vs. ≥65 years), sex (male vs. female), baseline NIHSS (<6 vs. ≥6), and diabetes (yes vs. no). We conducted a sensitivity analysis limited to patients not receiving thrombectomy treatment after intravenous thrombolysis. Previous studies showed that symptomatic intracerebral hemorrhage (sICH) was a predictor for END, and END after thrombolysis treatment may be caused by sICH occurrence [6,27]. We further conducted a

sensitivity analysis by defining END separately from sICH. We also conducted a separate analysis, investigating the relationship between continuous TyG index and continuous delta NIHSS (24 h NIHSS score-baseline NIHSS score). All variables with a p-value < 0.05 were considered statistically significant in this study. All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Characteristics

From January 2015 through June 2022, a total of 765 adult AIS patients underwent intravenous thrombolysis at three stroke centers (Figure 1). We excluded 89 patients based on the following criteria: eight were discharged within 24 h, five underwent intra-arterial thrombolytic therapy, and three experienced interrupted intravenous thrombolysis; in addition, data of fast glucose and triglyceride to calculate the TyG index were missing in 73 patients. Thus, 676 patients who met the inclusion criteria were included in the final analysis. The median age was 68 [IQR 60–76] years old, and 432 (63.9%) were males. There were no significant differences in median age (68 [IQR 60–76] vs. 65 [IQR 56–76] years) and sex (male: 63.9% vs. 64.8%) between those included and excluded. In those included, stroke onset severity was generally mild to moderate, with a median initial NIHSS score of 6 (IQR 3–12). The median time from symptom onset to thrombolysis treatment was 180 (IQR 120–210) min. The mean value of the TyG index was 8.62 ([SD] 0.70). A total of 28 (4.1%) sICH based on the European Cooperative Acute Stroke Study (ECASS III) definition occurred. A total of 89 (13.2%) patients developed END_2, 61 (9.0%) developed END_4, and 492 (72.7%) experienced ENI at discharge (Table 1). The baseline characteristics of different TyG index groups are summarized in Table 1. Patients with a higher TyG index were more likely to be younger (vs. lowest tertile 70 (62–77), medium tertile 68 (59–75), highest tertile 67 (59–74) years old, overall $p = 0.064$;) and regular alcohol users (vs. lowest tertile 12 (5.3%), medium tertile 24 (10.6%), highest tertile 26 (11.7%), overall $p = 0.034$), and had higher proportions of diabetes mellitus [(vs. lowest tertile 31 (13.7%), medium tertile 48 (21.1%), highest tertile 63 (28.3%), overall $p < 0.001$)] and dyslipidemia [(vs. lowest tertile 42 (18.6%), medium tertile 55 (24.2%), highest tertile 110 (49.3%), overall $p < 0.001$)]. Laboratory findings including fasting blood glucose, triglyceride, total cholesterol, and low-density lipoprotein were significantly higher in patients with a higher TyG index (overall $p < 0.05$).

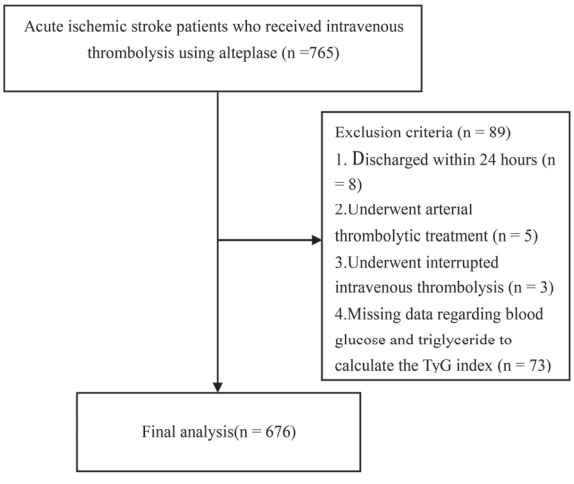

Figure 1. Flow chart. Abbreviations: TyG = Triglyceride-glucose.

Table 1. Baseline characteristics of different TyG index groups.

Variable	Total (n = 676)	Tertile I (Lowest) (n = 226)	Tertile II (Medium) (n = 227)	Tertile III (Highest) (n = 223)	*p* for Trend
Demographic characteristics					
Age, y, median (IQR)	68 (60–76)	70 (62–77)	68 (59–75)	67 (59–74)	0.064
Sex, n (%)					0.118
Male, n (%)	432 (63.9)	89 (39.4)	83 (36.6)	72 (32.3)	
Female, n (%)	244 (36.1)	137 (60.6)	144 (63.4)	151 (67.7)	
Vascular risk factors					
Current smoker, n (%)	198 (29.3)	61 (27.0)	64 (28.2)	73 (32.7)	0.153
Regular alcohol user, n (%)	62 (9.2)	12 (5.3)	24 (10.6)	26 (11.7)	0.034
Previous stroke, n (%)	102 (15.1)	41 (18.1)	33 (14.5)	28 (12.6)	0.098
Hypertension, n (%)	448 (66.3)	143 (63.3)	156 (68.7)	149 (66.8)	0.426
Diabetes, n (%)	142 (21.0)	31 (13.7)	48 (21.1)	63 (28.3)	<0.001
Dyslipidemia, n (%)	207 (30.6)	42 (18.6)	55 (24.2)	110 (49.3)	<0.001
Atrial fibrillation, n (%)	210 (31.1)	78 (34.5)	68 (30.0)	64 (28.7)	0.183
Coronary artery disease, n (%)	81 (12.0)	20 (8.8)	30 (13.2)	31 (13.9)	0.099
Medication use history					
Previous antiplatelet, n (%)	75 (11.1)	29 (12.8)	27 (11.9)	19 (8.5)	0.147
Previous anticoagulants, n (%)	14 (2.1)	1 (0.4)	10 (4.4)	3 (1.3)	0.495
Previous statin, n (%)	50 (7.4)	24 (10.6)	15 (6.6)	11 (4.9)	0.021
Previous antihypertension, n (%)	264 (39.1)	85(37.6)	99 (43.6)	80 (35.9)	0.711
Previous hypoglycemic agents, n (%)	81 (12.0)	20 (8.8)	25 (11.0)	36 (16.1)	0.018
Clinical assessment					
Initial NIHSS score, median (IQR)	6 (3–12)	7 (3–12)	6 (4–12)	6 (3–12)	0.527
Discharge NIHSS score, median (IQR)	3 (1–7)	3 (1–6)	3 (1–7)	2 (0–7)	0.221
SBP, mmHg, mean ± SD	149 ± 23	150 ± 25	148 ± 22	149 ± 22	0.726
DBP, mmHg, median (IQR)	89 (80–98)	90 (80–98)	87 (80–98)	90 (80–99)	0.285
OTT, minute, median (IQR)	180 (120–210)	180 (120–210)	180 (120–211)	180 (120–210)	0.928
Thrombectomy treatment, n (%)	93 (13.8)	30 (13.3)	33 (14.5)	30 (13.5)	1.000
24 h sICH, n (%)	28 (4.1)	9 (4.0)	4 (1.8)	15 (6.7)	0.147
Any ICH, n (%)	127(18.9)	45 (19.9)	39 (17.2)	43 (19.3)	0.862
ASCO Stroke subtype					0.454
Atherosclerosis, n (%)	250 (37.0)	72(31.9)	92 (40.5)	86 (38.6)	
Cardioembolic, n (%)	211 (31.2)	78 (34.5)	70 (30.8)	63 (28.3)	
Small vessel disease, n (%)	70 (10.4)	25 (11.1)	20 (8.8)	25 (11.2)	
Other causes, n (%)	145 (21.4)	51 (22.6)	45 (19.8)	49 (22.0)	
Laboratory data					
FBG, mg/dL, median (IQR)	102.9 (88.6–124.3)	93.2 (84.2–107.6)	101.7 (88.7–115.5)	119.3 (100.1–164.8)	<0.001
TG, mg/dL, median (IQR)	99.2 (69.1–144.4)	60.3 (46.0–73.5)	105.4 (88.6–121.3)	174.4 (133.2–231.2)	<0.001
TC, mg/dL, median (IQR)	173.3 (144.4–200.7)	165.4 (132.7–191.0)	168.4 (142.9–195.1)	186.5 (159.4–214.8)	<0.001
LDL, mg/dL, median (IQR)	114.1 (87.1–139.2)	106.2 (78.1–125.7)	114.1 (89.4–136.7)	130.3 (98.1–150.2)	<0.001
Early Neurological Outcome					
END_2	89 (13.2)	21 (9.3)	21 (9.3)	47 (21.1)	<0.001
END_4	61 (9.0)	13 (5.8)	14 (6.2)	34 (15.2)	<0.001
ENI	492 (72.7)	171 (75.7)	171 (75.3)	150 (67.3)	0.046

Abbreviations: TyG = Triglyceride-glucose; IQR = Interquartile range; NIHSS = National Institute of Health Stroke Scale; SBP = systolic blood pressure; SD = Standard deviation; DBP = diastolic blood pressure; OTT = onset to treatment time; sICH = symptomatic intracerebral hemorrhage; ICH = intracerebral hemorrhage; FBG = fasting blood glucose; TG = triglyceride; TC = total cholesterol; LDL = low-density lipoprotein; END = early neurological deterioration; ENI = early neurological improvement.

3.2. TyG Index and END

Table 2 summarizes the differences in baseline characteristics in patients with and without END. Patients with END_2 were older (70 [IQR 62–76] vs. 68 [IQR 59–75], $p = 0.048$), more likely to have atrial fibrillation (49 [55.1%] vs. 161 [27.4%], $p < 0.001$), coronary artery disease (17 [19.1%] vs. 64 [10.9%], $p = 0.026$), and diabetes (27 [30.3%] vs. 115 [19.6%], $p = 0.020$). Pre-stroke hypoglycemic agents (18 [20.2%] vs. 63 [10.7%], $p = 0.010$) were more frequently used in patients with END_2 compared to those without. Patients with

END_2 more frequently underwent bridging thrombectomy treatment than those without (28 [31.5%] vs. 65 [11.1%], $p < 0.001$). Patients with END_2 had a higher initial NIHSS score (8 [IQR 4–12] vs. 6 [IQR 3–12], $p = 0.102$), and a higher fast blood glucose level [mg/dl] (121.9 [IQR 95.2–177.7] vs. 101.3 [IQR 87.9–119.2], $p < 0.001$). Stroke subtypes in patients with and without END are significantly different ($p < 0.001$). Similar findings were detected in patients with and without END_4 (Table 2).

Table 2. Differences in baseline characteristics in patients with and without END.

Variable	Without END_2 (n = 587)	With END_2 (n = 89)	*p* Value	Without END_4 (n = 615)	With END_4 (n = 61)	*p* Value
Demographic characteristics						
Age, y, median (IQR)	68 (59–75)	70 (62–76)	0.048	68 (59–76)	70 (67–76)	0.019
Sex, n (%)			0.790			0.784
Male, n (%)	374 (63.7)	58 (65.2)		394 (64.1)	38 (62.3)	
Female, n (%)	213 (36.3)	31 (34.8)		221 (35.9)	23 (37.7)	
Vascular risk factors						
Current smoker, n (%)	170 (29.0)	28 (31.5)	0.629	181 (29.4)	17 (27.9)	0.798
Regular alcohol user, n (%)	54 (9.2)	8 (9.0)	0.949	59 (9.6)	3 (4.9)	0.228
Previous stroke, n (%)	94 (16.0)	8 (9.0)	0.084	95 (15.4)	7 (11.5)	0.408
Hypertension, n (%)	383 (65.2)	65 (73.0)	0.148	406 (66.0)	42 (68.9)	0.655
Diabetes, n (%)	115 (19.6)	27 (30.3)	0.020	120 (19.5)	22 (36.1)	0.002
Dyslipidemia, n (%)	179 (30.5)	28 (31.5)	0.854	193 (31.4)	14 (23.0)	0.173
Atrial fibrillation, n (%)	161 (27.4)	49 (55.1)	<0.001	168 (27.3)	42 (68.9)	<0.001
Coronary artery disease, n (%)	64 (10.9)	17 (19.1)	0.026	67 (10.9)	14 (23.0)	0.006
Medication use history						
Previous antiplatelet, n (%)	63 (10.7)	12 (13.5)	0.441	66 (10.7)	9 (14.8)	0.340
Previous anticoagulants, n (%)	13 (2.2)	1 (1.1)	0.784	13 (2.1)	1 (1.6)	0.804
Previous statin, n (%)	45 (7.7)	5 (5.6)	0.491	46 (7.5)	4 (6.6)	0.793
Previous antihypertension, n (%)	228 (38.8)	36 (40.4)	0.772	239 (38.9)	25 (41.0)	0.746
Previous hypoglycemic agents, n (%)	63 (10.7)	18 (20.2)	0.010	66 (10.7)	15 (24.6)	<0.001
Clinical assessment						
Initial NIHSS score, median (IQR)	6 (3–12)	8 (4–12)	0.102	6 (3–12)	12 (7–15)	<0.001
Discharge NIHSS score, median (IQR)	4 (2–9)	16 (8–24)	<0.001	4 (2–9)	18 (15–29)	<0.001
SBP, mmHg, mean ± SD	149 ± 22	151 ± 26	0.621	149 ± 22	151 ± 28	0.476
DBP, mmHg, median (IQR)	89 (80–98)	90 (80–90)	0.533	89 (80–98)	87 (78–99)	0.922
OTT, minute, median (IQR)	180 (120–210)	169 (120–228)	0.513	180 (120–210)	160 (120–220)	0.206
Thrombectomy treatment, n (%)	65 (11.1)	28 (31.5)	<0.001	68 (11.1)	25 (41.0)	<0.001
24 h sICH, n (%)	0 (0.0)	28 (31.5)	<0.001	0 (0.0)	28 (45.9)	<0.001
Any ICH, n (%)	87 (14.8)	40 (44.9)	<0.001	92 (15.0)	45 (57.4)	<0.001
ASCO Stroke subtype			<0.001			<0.001
Atherosclerosis, n (%)	222 (37.9)	28 (32.5)		232 (37.7)	18 (29.5)	
Cardioembolic, n (%)	167 (27.3)	44 (50.6)		172 (28.0)	39 (63.9)	
Small vessel disease, n (%)	60 (8.5)	10 (9.6)		67 (10.9)	3 (4.9)	
Other causes, n (%)	138 (26.3)	7 (7.2)		144 (23.4)	1 (1.6)	
Laboratory data						
FBG, mg/dL, median (IQR)	101.3 (87.9–119.2)	121.9 (95.2–177.7)	<0.001	100.8 (87.8–119.2)	136.5 (110.3–201.6)	<0.001
TG, mg/dL, median (IQR)	97.5 (69.1–144.4)	103.6 (77.9–143.4)	0.305	99.2 (69.1–147.0)	98.3 (77.0–129.3)	0.712
TC, mg/dL, median (IQR)	173.2 (144.2–200.0)	175.3 (145.4–207.3)	0.643	173.4 (144.7–200.7)	168.6 (138.1–199.9)	0.649
LDL, mg/dL, median (IQR)	113.3 (86.4–138.7)	120.3 (95.1–141.9)	0.178	113.7 (87.0–139.4)	118.3 (92.8–139.2)	0.757
TyG index, mean ± SD	8.58 ± 0.69	8.87 ± 0.68	<0.001	8.59 ± 0.69	8.90 ± 0.68	<0.001
TyG tertiles			<0.001			<0.001
Lowest, n (%)	205 (34.9)	21 (23.6)		213 (34.6)	13 (21.3)	
Medium, n (%)	206 (35.1)	21 (23.6)		213 (34.6)	14 (23.0)	
Highest, n (%)	176 (30.0)	47 (52.8)		189 (30.7)	34 (55.7)	

Abbreviations: END = early neurological deterioration; IQR = interquartile range; NIHSS = National Institute of Health Stroke Scale; SBP = systolic blood pressure; SD = standard deviation; DBP = diastolic blood pressure; OTT = onset to treatment time; sICH = symptomatic intracerebral hemorrhage; ICH = intracerebral hemorrhage; FBG = fasting blood glucose; TG = triglyceride; TC = total cholesterol; LDL = low-density lipoprotein; TyG = Triglyceride-glucose.

Patients who developed END_2 included 21 (23.6%) in the lowest tertile (range 6.78–8.30), 21 (23.6%) in the medium tertile (range 8.31–8.86), and 47 (52.8%) in the highest tertile (range 8.89–11.64), compared to 205 (34.9%), 206 (35.1%) and 176 (30.0%), respectively, in those without END_2 (overall $p < 0.001$). The risk of END_2 increases with increasing TyG index (continuous variable [per unit increase]; odds ratios: OR 1.77, 95%, CI 1.30–2.42, $p < 0.001$). The absolute risks for END_2 in the lowest, medium, and highest tertile groups were 9.3%, 9.3%, and 21.1%, respectively. The absolute risk difference for END_2 (highest vs. lowest) was 11.8% (95% CI, 5.2–18.3%). Similarly, the absolute risks for END_4 increased with increasing TyG index, while decreasing with increasing TyG index for ENI (Table S1). In the multivariable model 1, adjustment for age, sex, atrial fibrillation, coronary artery disease, initial NIHSS score, ASCO subtypes, and previous stroke use did not change the association between TyG index and the END_2 risk (categorical variable, vs. lowest tertile, medium tertile OR 1.05, 95% CI 0.54–2.02, highest tertile OR 2.94, 95%CI 1.64–5.27, overall $p < 0.001$; continuous variable [per unit increase], OR 1.91, 95% CI 1.38–2.66, $p < 0.001$). The DAG algorithm identified a minimal set of confounders: age, sex, current smoker, and regular alcohol user (Figure 2). Adjustment for this set did not alter the association between a higher TyG index and an increased risk of END_2 (Table 3). This association remained in models 3,4, and 5 (Table S2). We performed a post hoc analysis by combining the lowest and medium groups due to the similar probabilities of END_2 in these two groups (both 23.6%). The results show that a TyG index in the highest tertile was associated with a higher risk of END_2 when compared to the lowest and medium groups (adjusted OR 2.87, 95%CI 1.78–4.62, $p < 0.001$, Table 3). Similar findings regarding the association between TyG index and END_4 risk are shown in Tables 4 and S3.

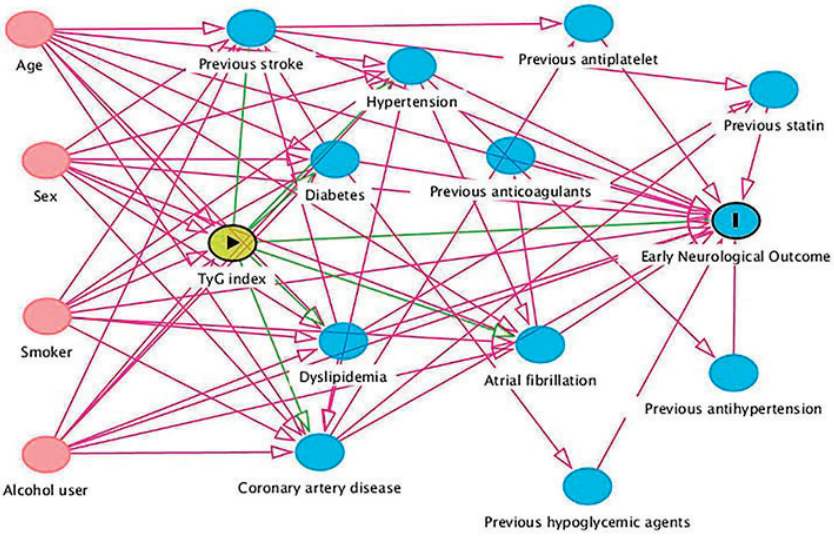

Figure 2. Directed acyclic graph for selection of minimal set of confounders. Abbreviations: TyG = Triglyceride-glucose.

Table 3. Association between TyG index and END_2.

	Unadjusted		Model 1		Model 2	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
TyG index	1.77 (1.30–2.42)	<0.001	1.91 (1.38–2.66)	<0.001	1.88 (1.37–2.58)	<0.001
TyG tertiles		<0.001		<0.001		<0.001
Lowest	Ref		Ref		Ref	
Medium	1.00 (0.53–1.88)		1.05 (0.54–2.02)		1.06 (0.56–2.02)	
Highest	2.61 (1.50–4.53)		2.94 (1.64–5.27)		2.82 (1.61–4.95)	
TyG binary classification						
Lowest to medium	Ref		Ref		Ref	
Highest	2.61 (1.66–4.11)	<0.001	2.87 (1.78–4.62)	<0.001	2.74 (1.73–4.33)	<0.001

Model 1 = adjusted for age, sex, atrial fibrillation, coronary artery disease, initial NIHSS score, ASCO subtypes, and previous stroke; Model 2 = adjusted for the minimally sufficient adjustment sets using a directed acyclic graph: age, sex, current smoker, regular alcohol user. Abbreviations: TyG = The triglyceride-glucose; END = early neurological deterioration; OR = odds ratios; CI = confidence interval; sICH = symptomatic intracerebral hemorrhage; NIHSS = National Institute of Health Stroke Scale. ASCO: A (atherosclerosis) S (small vessel disease) C (cardioembolic) O (other causes).

Table 4. Association between TyG index and END_4.

	Unadjusted		Model 1		Model 2	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
TyG index	1.80 (1.26–2.57)	0.001	2.07 (1.40–3.07)	<0.001	1.99 (1.37–2.87)	<0.001
TyG tertiles		<0.001		<0.001		<0.001
Lowest	Ref		Ref		Ref	
Medium	1.08 (0.49–2.35)		1.21 (0.54–2.74)		1.20 (0.55–2.62)	
Highest	2.95 (1.51–5.75)		3.80 (1.85–7.79)		3.37 (1.71–6.65)	
TyG binary classification						
Lowest to medium	Ref		Ref		Ref	
Highest	2.84 (1.67–4.84)	<0.001	3.45 (1.94–6.12)	<0.001	3.08 (1.79–5.30)	<0.001

Model 1 = adjusted for age, sex, atrial fibrillation, coronary artery disease, initial NIHSS score, ASCO subtypes; Model 2 = adjusted for the minimally sufficient adjustment sets using a directed acyclic graph: age, sex, current smoker, regular alcohol user. Abbreviations: TyG = Triglyceride-glucose; END = early neurological deterioration; OR = odds ratios; CI = confidence interval; sICH = symptomatic intracerebral hemorrhage; NIHSS = National Institute of Health Stroke Scale; ASCO: A (atherosclerosis) S (small vessel disease) C (cardioembolic) O (other causes).

A sensitivity analysis limited to patients without endovascular thrombectomy treatment showed that TyG index was associated with both END_2 (continuous variable [per unit increase], multivariable adjusted OR 1.74, 95%CI 1.19–2.55, $p = 0.004$) (Table S4) and END_4 risk (continuous variable [per unit increase], multivariable-adjusted OR 1.78, 95%CI 1.10–2.88, $p = 0.019$) (Table S5). However, it was no longer significant when treating TyG index as a categorical variable for the risk of END_4 (Table S5). Another sensitivity analysis by defining END separately from sICH yielded similar results to those derived from the main analysis (Tables S6 and S7). Subgroup analyses showed that there were no significant interactions between TyG index and variables including age (<65 vs. ≥65 years), diabetes (yes vs. no), and stroke onset severity (baseline NIHSS <6 vs. ≥6) for the risk of END_2 and END_4 (all p for interaction > 0.05). There was a significant interaction between TyG index and sex (male vs. female) for the risk of END_2 and END_4 (Figure S1A,B).

3.3. TyG Index and ENI

Differences in baseline characteristics in patients with and without ENI were shown in Table S8. Patients who had ENI included 171 (34.8%) in the lowest tertile, 171 (34.8%) in the medium tertile, and 150 (30.5%) in the highest tertile, compared to 55 (29.9%), 56 (30.4%), and 73 (39.7%), respectively, in those without ENI (overall $p = 0.077$). The odds of ENI decrease with increasing TyG index (continuous variable [per unit increase], OR 0.78, 95% CI 0.61–0.99, $p = 0.04$). In the multivariable model 1, TyG index showed a trend for a lower probability of ENI (categorical variable, vs. lowest tertile, medium tertile OR

1.00, 95%CI 0.63–1.58, highest tertile OR 0.59, 95%CI 0.38–0.92, overall $p = 0.022$; continuous variable [per unit increase], OR 0.73, 95% CI 0.56–0.94, $p = 0.015$). This association remained in other multivariable models (Table S9), but was lost when limited to patients who did not receive endovascular thrombectomy treatment (Table S10). Subgroup analysis showed that there were no significant interactions between the TyG index and variables including age (<65 vs. ≥65 years), sex (male vs. female), diabetes (yes vs. no), and stroke onset severity (baseline NIHSS <6 vs. ≥6) for the odds of ENI (all p for interaction > 0.05, Figure S1C).

3.4. TyG Index and NIHSS Score Change

Regarding the relationship between continuous TyG index and continuous delta NIHSS (24h NIHSS score-baseline NIHSS score), our data showed that the TyG index was associated with delta NIHSS (unadjusted Beta 0.116, $p = 0.003$, adjusted for the minimal sufficient adjustment set including age, sex, current smoker, and regular alcohol user, adjusted Beta 0.123, $p = 0.001$).

4. Discussion

The current study showed that a higher TyG index, a novel biomarker of insulin resistance, is associated with an increased probability of END and decreased odds of ENI in AIS patients who received intravenous thrombolysis; this suggests a role for insulin resistance in the unfavorable early neurological outcome in this population.

The potential role of the TyG index in AIS prognosis has been noted. A multi-center observational study showed that a higher TyG index was associated with 90-day unfavorable functional outcomes in AIS patients who received intravenous thrombolysis [28]. Moreover, TyG index was associated with a higher risk of in-hospital mortality in critically-ill stroke [29], and early stroke recurrence [30]. To our knowledge, whether TyG index is related to unfavorable early neurological functional outcomes is poorly understood. Our data showed that a higher TyG index (particularly being at the top tertile) was associated with a higher probability of developing END and lower odds of achieving ENI at discharge in AIS patients who received intravenous thrombolysis. In line with our finding, a previous study showed that TyG index was associated with END occurrence in patients with single subcortical infarctions [30]. However, that study included AIS patients within 72h of symptom onset applying only one END definition; therefore, the actual frequency of END might be underestimated [30]. Our study adds to previous studies by showing that the association between TyG index and END was consistent when applying two well-validated definitions for END. Moreover, when defining END separately from sICH, the association of END with TyG index remained in our cohort (Tables S6 and S7), since patients who had sICH were older, more likely to have vascular risk factors, higher blood glucose, and a more severe onset (Table S11). Another retrospective cohort study showed that TyG index was inversely associated with ENI (adjusted OR 0.68, 95% CI 0.52–0.89, $p = 0.004$) in AIS patients who received intravenous alteplase thrombolysis [31], which might also support our findings. The aforementioned findings may indicate that the TyG index is probably a biomarker for unfavorable early neurological functional outcomes. It is worth noting that the abovementioned studies were heterogeneous in study population and design; further large-sample size prospective studies are needed to validate the relationship between the TyG index and END risk.

There are several possible explanations for the relationship between TyG index and unfavorable early neurological outcomes after intravenous thrombolysis. First, patients with higher insulin resistance have elevated blood levels of fibrinolysis inhibitors, such as plasminogen activator inhibitors, which may reflect an impairment of endogenous fibrinolytic capacity [32]. Second, insulin resistance is also known to correlate with the worsening response to intravenous thrombolysis [33,34]. Insulin resistance may affect the structure of the offending clot itself, rendering it denser and more resistant to lysis in patients with AIS who received reperfusion treatments [35].

Our findings suggested a sex difference in the association between TyG index and END risk. Possible explanations might include sex disparities in glucose metabolism. For example, impaired glucose tolerance might be more prevalent in women [36]. Moreover, experimental data showed that endogenous estrogen may play a role in higher insulin sensitivity in a female rodent model [37]. Clinical evidence also demonstrated that menopausal hormone therapy may improve insulin sensitivity for postmenopausal women [38]. The above mentioned studies may highlight the need for a sex-specific risk management strategy.

The strengths of our study include using different models to validate the association between TyG index and END risk in a multicenter sample with two-well validated definitions of END. This study has some limitations. First, this is a retrospective observational study with a moderate sample size, inevitably introducing selection bias. Second, this study only included Chinese stroke patients; our findings may therefore not be generalizable to other populations. Third, because of practical limitations derived from our clinical setting, no direct measure to assess insulin resistance was used in our cohort. However, previous studies have shown that the TyG index has high sensitivity and specificity for assessing insulin resistance, suggesting that TyG index could be useful as a surrogate to identify insulin resistance [39]. Lastly, the early measurement may overestimate the prevalence of insulin resistance, since insulin resistance measurement is time-dependent during the acute ischemic stroke onset.

5. Conclusions

In conclusion, insulin resistance represented by increased TyG index is associated with higher odds of END and lower odds of ENI in acute ischemic stroke patients who received intravenous thrombolysis. Targeting the TyG index could be a potential obtainable biomarker for risk stratification in this stroke population during routine clinical practice.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12103471/s1, Figure S1: Interactions between the TyG index and END or ENI; Table S1: Absolute risks for early neurological outcomes in different TyG index tertile groups; Table S2: Association between TyG index and END_2; Table S3: Association between TyG index and END_4; Table S4: Association between TyG index and END_2 by limited to patients who did not receive thrombectomy treatment; Table S5: Association between TyG index and END4 by limited to patients who did not receive thrombectomy treatment; Table S6: Association between TyG index and END2 apart from sICH; Table S7: Association between TyG index and END_4 apart from sICH; Table S8: Differences in baseline characteristics in patients with and without ENI; Table S8: Differences in baseline characteristics in patients with and without ENI; Table S10: Association between TyG index and ENI by limited to patients who did not receive thrombectomy treatment; Table S11: Baseline characteristics in patients with and without early sICH.

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Abbreviations

TyG: Triglyceride-glucose; AIS: acute ischemic stroke; END: early neurological deterioration; ENI: early neurological improvement; NIHSS: National Institutes of Health Stroke Scale; SD: Standard deviation; IQR: Interquartile range; DAG: directed acyclic graph; OR: odds ratios; CI: confidence interval; ASCO: A (atherosclerosis) S (small vessel disease) C (cardioembolic) O (other causes). sICH: symptomatic intracerebral hemorrhage; ECASS: European Cooperative Acute Stroke Study.

References

1. Powers, W.J.; Rabinstein, A.A.; Ackerson, T.; Adeoye, O.M.; Bambakidis, N.C.; Becker, K.; Biller, J.; Michael, B.; Demaerschalk, B.M.; Hoh, B.; et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* **2018**, *49*, e46–e110. [CrossRef] [PubMed]
2. Neurology, C.; Society, C.S. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Chin. J. Neurol.* **2018**, *51*, 666–682.
3. Emberson, J.; Lees, K.R.; Lyden, P.; Blackwell, L.; Albers, G.; Bluhmki, E.; Brott, T.; Cohen, G.; Davis, S.; Donnan, G.; et al. Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke A meta-analysis of individual patient data from randomised trials. *Lancet* **2014**, *384*, 1929–1935. [PubMed]
4. Whiteley, W.N.; Emberson, J.; Lees, K.R.; Blackwell, L.; Albers, G.; Bluhmki, E.; Brott, T.; Cohen, G.; Davis, S.; Donnan, G.; et al. Stroke Thrombolysis Trialists' Collaboration. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke A secondary analysis of an individual patient data meta-analysis. *Lancet Neurol.* **2016**, *15*, 925–933. [CrossRef]
5. Seners, P.; Turc, G.; Oppenheim, C.; Baron, J.C. Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke A systematic review with pathophysiological implications. *J. Neurol. Neurosurg. Psychiatry* **2015**, *86*, 87–94. [CrossRef]
6. Weyland, C.S.; Mokli, Y.; Vey, J.A.; Kieser, M.; Herweh, C.; Schönenberger, S.; Bendszus, M.; Möhlenbruch, M.A.; Ringleb, P.A.; Nagel, S. Predictors for Failure of Early Neurological Improvement After Successful Thrombectomy in the Anterior Circulation. *Stroke* **2021**, *52*, 1291–1298. [CrossRef]
7. Wang, W.; Jiang, B.; Sun, H.; Ru, X.; Sun, D.; Wang, L.; Wang, L.; Jiang, Y.; Li, Y.; Wang, Y.; et al. NESS-China Investigators. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480,687 Adults. *Circulation* **2017**, *135*, 759–771. [CrossRef]
8. Yeo, L.L.; Paliwal, P.; Teoh, H.L.; Seet, R.C.; Chan, B.P.; Wakerley, B.; Liang, S.; Rathakrishnan, R.; Chong, V.F.; Ting, E.Y.S.; et al. Early and continuous neurologic improvements after intravenous thrombolysis are strong predictors of favorable long-term outcomes in acute ischemic stroke. *J. Stroke Cerebrovasc. Dis.* **2013**, *22*, e590–e596. [CrossRef]
9. Nagpal, M.; De, D.; Handa, S.; Pal, A.; Sachdeva, N. Insulin Resistance and Metabolic Syndrome in Young Men with Acne. *JAMA Dermatol.* **2016**, *152*, 399–404.
10. Holden, S.E.; Currie, C.J. Endogenous hyperinsulinaemia and exogenous insulin A common theme between atherosclerosis, increased cancer risk and other morbidities. *Atherosclerosis* **2012**, *222*, 26–28. [CrossRef]
11. Lee, M.; Saver, J.L.; Hong, K.S.; Song, S.; Chang, K.H.; Ovbiagele, B. Effect of pre-diabetes on future risk of stroke Meta-analysis. *BMJ* **2012**, *344*, e3564. [CrossRef] [PubMed]
12. Tam, C.S.; Xie, W.; Johnson, W.D.; Cefalu, W.T.; Redman, L.M.; Ravussin, E. Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care* **2012**, *35*, 1605–1610. [CrossRef] [PubMed]
13. Alizargar, J.; Bai, C.H.; Hsieh, N.C.; Wu, S.V. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. *Cardiovasc. Diabetol.* **2020**, *19*, 8. [CrossRef] [PubMed]
14. Lee, S.B.; Ahn, C.W.; Lee, B.K.; Kang, S.; Nam, J.S.; You, J.H.; Kim, M.J.; Kim, M.K.; Park, J.S. Association between triglyceride glucose index and arterial stiffness in Korean adults. *Cardiovasc. Diabetol.* **2018**, *17*, 41. [CrossRef] [PubMed]

15. Ma, X.; Dong, L.; Shao, Q.; Cheng, Y.; Lv, S.; Sun, Y.; Shen, H.; Wang, Z.; Zhou, Y.; Liu, X.; et al. Triglyceride glucose index for predicting cardiovascular outcomes after percutaneous coronary intervention in patients with type 2 diabetes mellitus and acute coronary syndrome. *Cardiovasc. Diabetol.* **2020**, *19*, 31. [CrossRef]
16. Kim, J.; Shin, S.J.; Kang, H.T. The association between triglyceride-glucose index, cardio-cerebrovascular diseases, and death in Korean adults: A retrospective study based on the NHIS-HEALS cohort. *PLoS ONE* **2021**, *16*, e0259212. [CrossRef]
17. Kwon, H.M.; Lim, J.S.; Park, H.K.; Lee, Y.S. Hypertriglyceridemia as a possible predictor of early neurological deterioration in acute lacunar stroke. *J. Neurol. Sci.* **2011**, *309*, 128–130. [CrossRef]
18. Nair, S.B.; Somarajan, D.; Pillai, R.K.; Balachandran, K.; Sathian, S. Predictors of Early Neurological Deterioration Following Intravenous Thrombolysis: Difference between Risk Factors for Ischemic and Hemorrhagic Worsening. *Ann. Indian Acad Neurol.* **2022**, *25*, 627–633.
19. Si, S.; Li, J.; Li, Y.; Li, W.; Chen, X.; Yuan, T.; Liu, C.; Li, H.; Hou, L.; Wang, B.; et al. Causal Effect of the Triglyceride-Glucose Index and the Joint Exposure of Higher Glucose and Triglyceride With Extensive Cardio-Cerebrovascular Metabolic Outcomes in the UK Biobank: A Mendelian Randomization Study. *Front. Cardiovasc. Med.* **2021**, *7*, 583473. [CrossRef]
20. Gökçal, E.; Niftaliyev, E.; Asil, T. Etiological classification of ischemic stroke in young patients A comparative study of TOAST, CCS, and ASCO. *Acta Neurol. Belg.* **2017**, *117*, 643–648. [CrossRef]
21. Simental-Mendía, L.E.; Rodríguez-Morán, M.; Guerrero-Romero, F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab. Syndr. Relat. Disord.* **2008**, *6*, 299–304. [CrossRef]
22. Vynckier, J.; Maamari, B.; Grunder, L.; Goeldlin, M.B.; Meinel, T.R.; Kaesmacher, J.; Hakim, A.; Arnold, M.; Gralla, J.; Seiffge, D.J.; et al. Early Neurologic Deterioration in Lacunar Stroke: Clinical and Imaging Predictors and Association with Long-term Outcome. *Neurology* **2021**, *16*, 1212. [CrossRef]
23. Seners, P.; Hassen, W.B.; Lapergue, B.; Arquizan, C.; Heldner, M.R.; Henon, H.; Perrin, C.; Strambo, D.; Cottier, J.P.; Sablot, D.; et al. MINOR-STROKE Collaborators. Prediction of Early Neurological Deterioration in Individuals With Minor Stroke and Large Vessel Occlusion Intended for Intravenous Thrombolysis Alone. *JAMA Neurol.* **2021**, *78*, 321–328. [CrossRef]
24. Knüppel, S.; Stang, A. DAG Program: Identifying Minimal Sufficient Adjustment Sets. *Epidemiology* **2010**, *21*, 159. [CrossRef]
25. Gong, P.; Zhang, X.; Gong, Y.; Liu, Y.; Wang, S.; Li, Z.; Chen, W.; Zhou, F.; Zhou, J.; Jiang, T.; et al. A novel nomogram to predict early neurological deterioration in patients with acute ischaemic stroke. *Eur. J. Neurol.* **2020**, *27*, 1996–2005. [CrossRef]
26. Seners, P.; Turc, G.; Tisserand, M.; Legrand, L.; Labeyrie, M.A.; Calvet, D.; Meder, J.F.; Mas, J.L.; Oppenheim, C.; Baron, J.C.; et al. Unexplained early neurological deterioration after intravenous thrombolysis Incidence, predictors, and associated factors. *Stroke* **2014**, *45*, 2004–2009. [CrossRef]
27. Simonsen, C.Z.; Schmitz, M.L.; Madsen, M.H.; Mikkelsen, I.K.; Chandra, R.V.; Leslie-Mazwi, T.; Anderse, G. Early neurological deterioration after thrombolysis: Clinical and imaging predictors. *Int. J. Stroke* **2016**, *11*, 776–782. [CrossRef] [PubMed]
28. Lin, S.F.; Hu, H.H.; Chao, H.L.; Ho, B.L.; Chen, C.H.; Chan, L.; Lin, H.J.; Sun, Y.; Lin, Y.Y.; Chen, P.L.; et al. Triglyceride-Glucose Index and Intravenous Thrombolysis Outcomes for Acute Ischemic Stroke: A Multicenter Prospective-Cohort Study. *Front. Neurol.* **2022**, *13*, 737441. [CrossRef] [PubMed]
29. Zhang, B.; Liu, L.; Ruan, H.; Zhu, Q.; Yu, D.; Yang, Y.; Men, X.; Lu, Z. Triglyceride-Glucose Index Linked to Hospital Mortality in Critically Ill Stroke: An Observational Multicentre Study on eICU Database. *Front. Med.* **2020**, *7*, 591036. [CrossRef] [PubMed]
30. Nam, K.W.; Kwon, H.M.; Lee, Y.S. High triglyceride-glucose index is associated with early recurrent ischemic lesion in acute ischemic stroke. *Sci. Rep.* **2021**, *11*, 15335. [CrossRef]
31. Toh, E.M.S.; Lim, A.Y.L.; Ming, C.; Yeo, L.L.L.; Sia, C.H.; Tan, B.W.Q.; Leow, A.S.T.; Ho, J.S.Y.; Chan, B.P.L.; Sharma, V.K.; et al. Association of triglyceride-glucose index with clinical outcomes in patients with acute ischemic stroke receiving intravenous thrombolysis. *Sci. Rep.* **2022**, *12*, 1596. [CrossRef] [PubMed]
32. Palomo, I.; Alarcón, M.; Moore-Carrasco, R.; Argilés, J.M. Hemostasis alterations in metabolic syndrome (Review). *Int. J. Mol. Med.* **2006**, *18*, 969–974. [CrossRef] [PubMed]
33. Alessi, M.C.; Juhan-Vague, I. Metabolic syndrome, haemostasis and thrombosis. *Thromb. Haemost.* **2008**, *99*, 995–1000. [PubMed]
34. Calleja, A.I.; García-Bermejo, P.; Cortijo, E.; Bustamante, R.; Martínez, E.R.; Sarmiento, E.G.; Fernández-Herranz, R.; Arenillas, J.F. Insulin resistance is associated with a poor response to intravenous thrombolysis in acute ischemic stroke. *Diabetes Care* **2011**, *34*, 2413–2417. [CrossRef] [PubMed]
35. Carter, A.M.; Cymbalista, C.M.; Spector, T.D.; Grant, P.J. EuroCLOT Investigators. Heritability of clot formation, morphology, and lysis the EuroCLOT study. *Arterioscler Thromb. Vasc. Biol.* **2007**, *27*, 2783–2789. [CrossRef]
36. Juutilainen, A.; Kortelainen, S.; Lehto, S.; Rönnemaa, T.; Pyörälä, K.; Laakso, M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care* **2004**, *27*, 2898–2904. [CrossRef]
37. Tiano, J.P.; Mauvais-Jarvis, F. Importance of oestrogen receptors to preserve functional β–cell mass in diabetes. *Nat. Rev. Endocrinol.* **2012**, *8*, 342–351. [CrossRef]

38. Duncan, A.C.; Lyall, H.; Roberts, R.N.; Petrie, J.R.; Perera, M.J.; Monaghan, S.; Hart, D.M.; Connell, J.M.C.; Lumsden, M.A. The effect of estradiol and a combined estradiol/progestagen preparation on insulin sensitivity in healthy pos-menopausal women. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 2402–2407. [CrossRef]
39. Sánchez-García, A.; Rodríguez-Gutiérrez, R.; Mancillas-Adame, L.; González-Nava, V.; González-Colmenero, A.D.; Solis, R.C.; Álvarez-Villalobos, N.A.; González-González, J.G. Diagnostic Accuracy of the Triglyceride and Glucose Index for Insulin Resistance: A Systematic Review. *Int. J. Endocrinol.* **2020**, *2020*, 4678526. [CrossRef]

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Posterior Circulation Stroke Patients Receive Less Reperfusion Therapy Because of Late Arrival and Relative Contraindications: A Retrospective Study

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Abstract: Background. Reperfusion treatment (RT) is administered to individuals with posterior circulation strokes (PCS) later and less frequently. We aimed to study the impact of demographic and clinical factors on the decision for RT in PCS. Methods. We conducted a retrospective analysis of the data from 500 subjects admitted to the tertiary stroke centre's emergency department between 2018 and 2020 due to PCS. Demographic and clinical factors were analysed among three groups: the RT group, the group with no RT because of absolute contraindications (ACI), and the group with no RT because of relative contraindications (RCI). Results. Of the patients, 202 (40.3%) were female. The median NIHSS was four (4), and the subjects' median age was 69 (18). RT was performed on 120 (24%) subjects. FAST symptoms (OR—5.62, 95% CI [2.90–12.28]) and higher NIHSS (OR—1.13, 95% CI [1.09–1.18]) at presentation, atrial fibrillation (OR—1.56, 95% CI [1.02–2.38]), hypertension (OR—2.19, 95% CI [1.17–4.53]) and diabetes (OR—1.70, 95% CI [1.06–2.71]) increased the chance of RT. Late arrival was the most prevalent ACI for 291 (58.2%) patients. FAST-negative subjects (OR—2.92, 95% CI [1.84–4.77]) and males (OR—1.58, 95% CI [1.11–2.28]) had a higher risk of arriving late. Because of RCI, 50 (10%) subjects did not receive RT; the majority were above 80 and had NIHSS ≤ 5. Subjects with RCI who received the RT had a higher NIHSS (4 vs. 3, $p < 0.001$), higher hypertension (59 (92.2%) vs. 35 (77.8%), $p = 0.032$) and heart failure (23 (35.9%) vs. 7 (15.6%), $p = 0.018$) prevalence. There was a trend for less RT in females with RCI. Conclusions. Late arrival was the most common barrier to RT, and the male gender increased this risk. because of relative contraindications, 10% of subjects were not considered for RT. The presence of FAST symptoms, vascular risk factors, and a higher NIHSS increased the chance of RT.

Keywords: posterior circulation stroke; reperfusion therapy; thrombolysis; thrombectomy; relative contraindications; late arrival; FAST; BEFAST; stroke recognition; decision-making

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1. Introduction

Posterior circulation strokes (PCS) occur in approximately 20% of all ischemic strokes [1]. However, the reported percentage of PCS among the patients treated with reperfusion therapy (RT) is lower—5–19% [2]. Specific anatomic and hemodynamic properties of the posterior circulation, such as lower flow velocities, different vessel calibre, and even different clot structures, result in distinct stroke aetiology and clinical course, compared to the anterior circulation [3,4].

PCS presents with typical symptoms listed in the FAST stroke recognition tool (face asymmetry, arm weakness, speech disturbance) less frequently. FAST tends to miss 40% of PCS, while the BEFAST tool, comprising balance and eye symptoms, is more sensitive [5,6]. PCS manifest with non-typical symptoms, like vomiting and seizures [7], more frequently compared to anterior circulation strokes (ACS). Patients with PCS are at risk of belated arrival at the hospital [8], and thrombolysis rates are lower in this group [9]. PCS patients are managed slower and receive RT later than those with ACS [10,11].

Not all the PCS symptoms are included in the National Institutes of Health Stroke Scale (NIHSS), sometimes resulting in a hesitancy to apply RT in PCS. Due to the non-typical presentation and relatively low NIHSS scores, weighting RT effectiveness and safety is quite complicated in some cases. Although the risk of symptomatic intracerebral haemorrhage in PCS is lower than in ACS, the dilemma of RT risk and benefit always exists, especially when NIHSS scores are low [12,13]. In such cases, decision-making might be guided by subtle, often subjective factors, not covered by the guidelines.

In light of these findings, it seems reasonable to identify the reasons for the scarcity of RT in PCS patients and the factors contributing to the decision to withhold RT. In this study, we aimed to analyse demographic and clinical factors influencing the decision for RT in PCS.

2. Materials and Methods

This retrospective observational single-centre study was conducted at Vilnius University Hospital Santaros Klinikos—a comprehensive stroke centre with a catchment population of 945,000. The research population included 500 subjects admitted due to ischemic PCS from January 2018 to December 2020. We did not continue further recruitment of the patients during the COVID-19 pandemic because it could result in longer times for treatment and arrival. This would make the data inappropriate for use after the pandemic.

The inclusion criteria were the following:

1. Ischemic PCS diagnosis. PCS diagnosis was confirmed in every subject either using neuroimaging (ischemia on the plain computerized tomography (CT) scan, posterior circulation vessel occlusion on the CT angiography, hypoperfusion in the posterior circulation territory on the CT perfusion or diffusion-weighted imaging-positive lesion in the posterior circulation, all of these needed to correspond to clinical symptoms), or based on typical clinical symptoms (e.g., alternating brainstem syndrome).
2. Aged 18 years old or older. There was no upper age limit for inclusion.
3. Hospitalised at the same centre.

The exclusion criteria were the following:

1. Transfer to other hospitals after the initial evaluation in the emergency department.
2. Unclear stroke territory.
3. Both ACS and PCS were detected.

We analysed clinical and demographic factors that influenced the suitability for the RT, including absolute and relative contraindications (ACI and RCI, respectively), according to the hospital protocol (Table 1).

Table 1. Absolute contraindications for the reperfusion therapy in the study.

Absolute Contraindication	Study Label
Suitable for intravenous thrombolysis (IVT) only, treatment cannot be applied within 4.5 h (6 h in the case of basilar artery occlusion)	Late arrival
Suitable for mechanical thrombectomy (MT) only, treatment cannot be applied within 24 h	
Using warfarin, INR $\geq$ 1.7	Anticoagulant use
Direct oral anticoagulants used in less than 48 h	
Low-molecular-weight heparin used in less than 12 h	
Heparin use with APTT two times higher than the upper normal range limit and impossible to reverse in time	
mRS > 2 points	mRS > 2

Table 1. *Cont.*

Absolute Contraindication	Study Label
Established stroke occupying more than 1/3 of the middle cerebral artery territory on the plain head CT	Established ischemia
Unfavourable penumbra-core ratio according to the ESO-ESMINT guidelines [14]	
Major bleeding within the past 3 weeks	Recent major bleeding
Major surgery within the past 3 weeks	Recent major surgery
ICH history	ICH history

This table represents absolute contraindications according to the hospital protocol and the labels used to classify them in the study. APTT—activated partial thromboplastin time, CT—computerised tomography, ESMINT—European Society for Minimally Invasive Neurological Therapy, ESO—European Stroke Organisation, ICH—intracerebral haemorrhage, INR—international normalised ratio, IVT—intravenous thrombolysis, mRS—Modified Rankin scale, MT—mechanical thrombectomy.

Subjects treated with intravenous thrombolysis (IVT), mechanical thrombectomy (MT) or both methods (bridging therapy (BT) were included in the RT group, and subjects who did not receive any RT were included in the non-RT group. The non-RT group was further divided into two subgroups: subjects who had ACI according to the hospital reperfusion treatment protocol (ACI group), and subjects who did not receive RT despite not having any ACI. This group did not receive RT due to factors that were not established as clear ACI in the hospital protocol, and the group was labelled as the relative contraindications group (RCI group). RCI included minor stroke (NIHSS $\leq$ 5 points), age > 80 years, ischemic stroke history within the past 3 months, intracranial aneurysm, and presenting with a seizure. The cases of posterior cerebral artery occlusion were discussed with the interventional radiologists who performed MT. Some of those cases were reported as "technically risky interventions". If MT was not performed due to this, the case was classified as a relative contraindication. The criteria used for the inclusion of subjects into the particular subgroup are presented in Table 2.

Table 2. Subgroup classification criteria.

RT Group: Any RT Method Applied	Non-RT Group: No RT Applied	
	ACI Subgroup	RCI Subgroup
Subjects who were treated with: 1. IVT 2. MT 3. IVT + MT (BT)	Subjects who were not treated with RT due to ACI, according to the hospital protocol: 1. Arrived too late to be treated with RT. 2. Any anticoagulant use preventing the patient from receiving RT. 3. mRS > 2 points. 4. Established stroke occupying more than 1/3 of the middle cerebral artery territory on the plain head CT or unfavourable penumbra-core ratio according to the ESO-ESMINT guidelines. 5. Major bleeding or surgery within the past 3 weeks. 6. History of ICH.	Subjects who were not treated with the RT in the absence of the ACI, according to the hospital protocol, such as: 1. NIHSS $\leq$ 5 points. 2. Age > 80 years. 3. Ischemic stroke history within the past 3 months. 4. Unruptured intracranial aneurysm. 5. Presenting with a seizure.

If the subject had several ACI, only the most important, determinant contraindication was registered (e.g., if a subject was late and had established infarct on plain CT, such a case was classified as belated arrival). In the RCI group, if the subject had several RCIs, all of them were registered.

Some subjects who had RCI received RT. We compared the baseline characteristics and outcomes between the subjects with RCI who received the RT and those who did not. Outcomes compared were lethal outcome during the hospitalization (labelled as an early lethal outcome), early ambulatory outcome defined as mRS 0–3 points (able to walk) on discharge from the stroke centre, and in-patient complications: intracranial or another major bleeding, recurrent stroke, myocardial infarction, infection, delirium.

Baseline characteristics included demographic data (sex, age), clinical symptoms at presentation, baseline NIHSS score, medical history (arterial hypertension (AH), congestive heart failure NYHA B or worse (CHF), history of stroke or transient ischemic attack (TIA), myocardial infarction (MI), diabetes mellitus (DM), and atrial fibrillation (AF).

All patients were examined by a neurology consultant on admission. The decision for RT was based on clinical and imaging findings. IVT was performed within 4.5 h after symptom onset and 6 h in the case of basilar artery occlusion (BAO). For IVT, a 0.9 mg/kg dose of alteplase was used (a maximum dose of 90 mg), with 10% of the dose given as a bolus in 1–2 min and the rest given as an intravenous infusion for 1 h. Mechanical thrombectomy was performed within 6 h of onset and within 24 h in the case of BAO. If the subject arrived later than the recommended timeframe for the RT, the case was classified as a late arrival.

Data were analysed using R software version 4.2.1. (R Core Team (2022)). Baseline characteristics are reported using descriptive statistics. The normality was assessed using the Shapiro-Wilk test; all qualitative variables were not normally distributed. The chi-square test was used to compare qualitative variables between groups, and the Wilcoxon test was used to compare quantitative variables between two groups. The accepted level of statistical significance was <0.05. Univariate logistic regression was used to analyse the odds ratios with a 95% confidence interval. The study power was 0.879 (calculated with G-Power software, version 3.1.9.2.).

The study was approved by the Vilnius Regional Bioethics Committee (approval Nr. 1170, 19 December 2019) and the Lithuania Bioethics Committee (approval Nr. L-14-03/1, L-14-03/2, L-14-03/3, L-14-03/4, L-14-03/5, L-14-03/6, 18 April 2014).

3. Results

3.1. Baseline Characteristics

The median age was 69 (18) years, the median NIHSS on admission was four (4) points, and 202 (40.3%) subjects were female. The number of FAST-positive (FAST+) subjects was 372 (74.4%). Other subjects were FAST-negative: 53 (10.6%) presented with ataxia, 23 (4.6%) with vision disturbance only (visual field deficit or double vision), and 39 (7.8%) presented with both ataxia and eye symptoms, resulting in 487 (97.4%) BEFAST-positive (BEFAST+) subjects in total. The most frequent symptom at presentation was ataxia (63.6%), followed by paresis (54.2%) and speech disturbance (51.8%). The prevalence of all symptoms is listed in Figure 1.

RT was performed on 120 (24%) subjects: 72 (14.4%) were treated with IVT, 37 (7.4%) with MT, and 11 (2.2%)—with BT. Subjects in the RT group had higher NIHSS (7 vs. 3, $p < 0.001$), and more of them were FAST + (92.6% vs. 68.8%, $p < 0.001$) and BEFAST+ (100% vs. 96.6%, $p = 0.039$). In the RT group, there was a higher frequency of AF (42.1% vs. 32.2%, $p = 0.045$), AH (90.9% vs. 81.8%), and DM (29.8% vs. 19.3%) (Table 3).

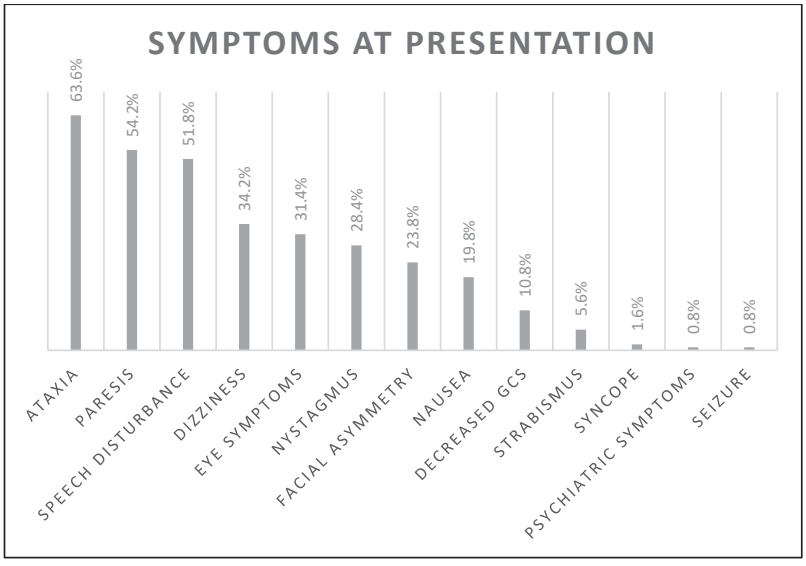

Figure 1. The prevalence of all symptoms on admission is presented in the figure. Eye symptoms include any visual disturbance: amblyopia, hemianopia, scotoma, diplopia. Decreased GCS—decreased level of consciousness measured using the Glasgow Coma Scale.

Table 3. Comparison of baseline characteristics in subjects who were and were not treated with reperfusion therapy.

Factor	RT Group	Non-RT Group	*p*-Value
Atrial fibrillation	51 (42.1%)	122 (32.2%)	0.045 *
Age	69 (15)	69 (19)	0.528
Hypertension	110 (90.9%)	310 (81.8%)	0.017 *
Anticoagulant use	14 (11.6%)	65 (17.2%)	0.143
Antiplatelet use	19 (15.7%)	70 (18.5%)	0.488
BEFAST+	120 (100%)	366 (96.6%)	0.039 *
Diabetes	36 (29.8%)	73 (19.3%)	0.015 *
Female sex	49 (40.5%)	153 (40.4%)	0.980
FAST+	112 (92.6%)	260 (68.6%)	<0.001 *
Heart failure	37 (30.6%)	90 (23.7%)	0.133
History of stroke or transient ischaemic attack	19 (15.7%)	85 (22.4%)	0.113
History of myocardial infarction	24 (19.8%)	78 (20.6%)	0.859
NIHSS	7 (7)	3 (3)	<0.001 *
Ongoing malignancy	4 (3.3%)	26 (6.9%)	0.152

Quantitative and numeric ordinal data (age in years and NIHSS in points) are presented as the median and interquartile range (IQR). Qualitative data are presented as an absolute number (percentage). * Significant differences are denoted with an asterisk. BEFAST+—at least one of the following symptoms: loss of balance, visual or eye disturbance, face asymmetry, arm weakness, speech disturbance; FAST+—at least one of the following symptoms: face asymmetry, arm weakness, speech disturbance; NIHSS—National Institutes of Health Stroke Scale, RT—reperfusion therapy.

3.2. Contraindications

330 (66%) subjects had ACI to RT. The most frequent ACI was late arrival: 291 (58.2%) subjects arrived later than the recommended timeframe for the appropriate RT. In 50 (10%) subjects, RT was not applied due to RCI only. Age > 80 years and NIHSS ≤ 5 points were the most frequent reasons to withhold RT. In this group, 15 (30%) subjects had more than one RCI. Of the subject with RCI, 49 (98%) were BEFAST+. Two (4%) of them did not have a disabling deficit (only isolated dizziness or isolated mild speech disturbance). The detailed structure of contraindications is presented in Table 4.

Table 4. Contraindications for RT in PCS subjects.

ACI		RCI	
Belated arrival	291 (58.2%)	NIHSS ≤ 5 points	38 (9.6%)
Anticoagulant use	22 (4.4%)	Age > 80 years	19 (4.8%)
mRS > 2 points	9 (1.8%)	High subjective risk of MT	6 (1.2%)
Recent major bleeding	3 (0.6%)	Stroke in 3 months	1 (0.2%)
Established infarct on plain CT	3 (0.6%)	Intracranial aneurysm	1 (0.2%)
Recent major surgery	1 (0.2%)	Seizure	1 (0.2%)
ICH history	1 (0.2%)	More than 1 RCI	15 (3.0%)

Absolute and relative contraindications for reperfusion therapy are listed in the table. The percentage of the total study population is denoted in round brackets. ACI—absolute contraindications, CT—computerized tomography, MT—mechanical thrombectomy; ICH—intracerebral haemorrhage, mRS—Modified Rankin scale, NIHSS—National Institutes of Health Stroke Scale, PCS—posterior circulation stroke, RCI—relative contraindications, RT—reperfusion therapy.

Having balance or visual symptoms without FAST symptoms was associated with an almost three-fold increase in the risk of late arrival (OR—2.92, 95% CI [1.84–4.77]). Male sex was another significant risk factor (OR—1.58, 95% CI [1.11–2.28]). Factors decreasing the risk of late arrival were the presence of FAST symptoms (OR—0.31, 95% CI [0.19–0.49]), a higher NIHSS score (OR—0.88 for each point, 95% CI [0.85–0.92]), AF (OR—0.51, 95% CI [0.35–0.74]) and heart failure (OR—0.51, 95% CI [0.34–0.76]) (Table 5). The last two may not have been independent risk factors confounded by the NIHSS, as they were higher in AF and HF subjects (five in AF and HF subjects vs. three in non-AF and non-HF subjects, $p < 0.001$).

Table 5. Association of demographic and clinical factors with the risk of belated arrival.

Factor	B	Std. Error	*p*-Value	OR (Exp B)	95% CI
AF	−0.68	0.19	<0.001 *	0.51	0.35–0.74 *
Age ≥ 80 years	−0.24	0.21	0.248	0.78	0.51–1.19
AH	−0.47	0.26	0.067	0.62	0.37–1.02
Balance or vision disturbance	1.07	0.24	<0.001 *	2.92	1.84–4.77 *
DM	−0.16	0.22	0.451	0.85	0.55–1.30
FAST+	−1.16	0.24	<0.001 *	0.31	0.19–0.49 *
HF	−0.68	0.21	0.001 *	0.51	0.34–0.76 *
History of stroke or TIA	−0.13	0.22	0.572	0.88	0.57–1.37

Table 5. *Cont.*

Factor	B	Std. Error	*p*-Value	OR (Exp B)	95% CI
Male sex	0.46	0.18	0.012 *	1.58	1.11–2.28 *
NIHSS (risk reduction for each additional point)	−0.12	0.02	<0.001 *	0.88	0.85–0.92 *

Data are presented as odds ratio and 95% confidence interval. * Significant differences are denoted with an asterisk. AF—atrial fibrillation, AH—arterial hypertension, CI—confidence interval, DM—diabetes mellitus, FAST+—at least one of the following symptoms: face asymmetry, arm weakness, speech disturbance; HF—heart failure, NIHSS—National Institutes of Health Stroke Scale, OR—odds ratio, Std. Error—Standard Error; TIA—transient ischemic attack.

3.3. Reperfusion Therapy

Being FAST+ was the most significant factor for receiving RT (OR—5.62, 95% CI [2.90–12.28]). Other factors increasing the chance of receiving RT were higher NIHSS (OR—1.13 for each point, 95% CI [1.09–1.18]), history of AF (OR—1.56, 95% CI [1.02–2.38]), AH (OR—2.19, 95% CI [1.17–4.53]) and DM (OR—1.70, 95% CI [1.06–2.71]) (Table 6).

Table 6. Association of demographic and clinical factors with the chance of receiving RT.

Factor	B	Std. Error	*p*-Value	OR (Exp B)	95% CI
AF	−0.84	0.61	0.171	1.56	1.02–2.38 *
Age ≥ 80 years	−0.22	0.26	0.402	0.81	0.48–1.32
AH	0.79	0.34	0.022 *	2.19	1.17–4.53 *
Balance or vision disturbance	−1.56	0.37	<0.001 *	0.21	0.10–0.41 *
DM	0.53	0.24	0.026 *	1.70	1.06–2.71 *
FAST+	1.73	0.36	<0.001 *	5.62	2.90–12.28 *
HF	0.36	0.23	0.118	1.44	0.91–2.25
History of stroke or TIA	−0.43	0.28	0.126	0.65	0.37–1.11
Male sex	−0.02	0.21	0.912	0.98	0.64–1.49
NIHSS (chance increase for each additional point)	0.12	0.02	<0.001 *	1.13	1.09–1.18 *

Data are presented as odds ratio and 95% confidence interval. * Significant differences are denoted with an asterisk. AF—atrial fibrillation, AH—arterial hypertension, CI—confidence interval, DM—diabetes mellitus, FAST+—at least one of the following symptoms: face asymmetry, arm weakness, speech disturbance; HF—heart failure, MI—myocardial infarction, NIHSS—National Institutes of Health Stroke Scale, OR—odds ratio, RT—reperfusion therapy, TIA—transient ischemic attack.

Although some subjects did not receive RT due to RCI, such as age and minor stroke, others with the same RCI were treated with RT. To clarify whether there were any additional factors influencing the decision, we compared baseline characteristics between RT and RCI groups, including only the subjects who had the most common RCI, i.e., being 80 years of age or older and having a minor stroke, defined as NIHSS $\leq$ 5. There were 64 subjects with the aforementioned RCI in the RT group. They had significantly higher NIHSS (four vs. three, $p < 0.001$) and higher prevalence of AH (92.2% vs. 77.8%, $p = 0.032$) and HF (35.9% vs. 15.6%, $p = 0.018$) than the RCI group. There was a trend for lower female prevalence in the RT group with RCI (39.1% vs. 57.8%, $p = 0.054$). None of the outcomes, including early in-hospital mortality, early ambulatory outcomes, or complication rates, differed between the groups (Table 7).

Table 7. Baseline characteristics and outcomes in subjects with relative contraindications, compared between the RT and RCI groups.

Factor/Outcome	RT Group (N = 64)	RCI Group (N = 45)	*p*-Value
AF	29 (45.3%)	16 (35.6%)	0.308
AH	59 (92.2%)	35 (77.8%)	0.032 *
Antiplatelet use	13 (20.3%)	12 (26.7%)	0.437
BEFAST+	64 (100%)	44 (97.8%)	0.231
DM	16 (25%)	8 (17.8%)	0.370
FAST+	55 (85.9%)	34 (75.6%)	0.168
HF	23 (35.9%)	7 (15.6%)	0.018 *
History of MI	15 (23.4%)	8 (17.8%)	0.476
Ongoing malignancy	3 (4.7%)	1 (2.2%)	0.500
Female sex	25 (39.1%)	26 (57.8%)	0.054 *
History of stroke or TIA	9 (14.1%)	9 (20%)	0.411
Age	76 (19%)	76 (19%)	0.751
NIHSS	4 (3)	3 (3)	<0.001 *
Early ambulatory outcome	26 (40.6%)	19 (42.2%)	0.868
Delirium	7 (10.9%)	4 (8.9%)	0.727
Intracranial haemorrhage	0 (0%)	0 (0%)	0.068
Another bleeding	0 (0%)	1 (2.2%)	0.231
Myocardial infarction	2 (3.1%)	1 (2.2%)	0.777
Infection	17 (26.6%)	9 (20%)	0.429
Lethal outcome	3 (4.7%)	0 (0%)	0.141
Recurrent stroke	3 (4.7%)	0 (0%)	0.141

Quantitative and numeric ordinal data are presented as median (IQR). Qualitative data are presented as an absolute number (percentage). * Significant differences are denoted with an asterisk. AF—atrial fibrillation, AH—arterial hypertension, BEFAST+—at least one of the following symptoms: loss of balance, visual or eye disturbance, face asymmetry, arm weakness, speech disturbance; DM—diabetes mellitus, FAST+—at least one of the following symptoms: face asymmetry, arm weakness, speech disturbance; HF—heart failure, MI—myocardial infarction, NIHSS—National Institutes of Health Stroke Scale, RCI—relative contraindications, RT—reperfusion therapy, TIA—transient ischemic attack.

4. Discussion

4.1. Discussion

The most frequent obstacle to receiving RT was belated arrival in more than half of the subjects. This finding confirms the results of other studies that revealed that PCS is a risk factor for late arrival and not receiving RT [8]. More PCS subjects arrived in time and received RT when they were FAST-positive. These findings can reflect two aspects.

First of all, after numerous educational campaigns, stroke symptoms listed in the FAST test might be better recognized by society and clinicians [15–17]. Nevertheless, about 20% of PCS subjects did not have FAST symptoms but had balance impairment, vision disturbance, or both of them. An Austrian study of PCS patients shows that PCS is associated with significant delays in prehospital and intra-hospital management. These findings show that there is room for improvement by initiating further educational campaigns, now using the BEFAST tool.

Furthermore, in those patients who arrived timely, the clinician's decision might have been biased, as ataxia and visual symptoms are sometimes underscored by the NIHSS [18]. Such strokes might be classified as minor strokes, causing doubt and incertitude about the risks and benefits of RT. Nevertheless, ataxia and vision disturbance are disabling symptoms, and, ideally, modified NIHSS scores for posterior circulation should be used to

estimate potential disability [19–21]. Moreover, recent data highlight the effectiveness of RT even on such subtle outcomes as vision and cognitive functions [22].

Ten percent of subjects were not recognized as suitable for RT with no strict contraindications. However, RT happened in a large proportion of subjects with the same RCI, and, again, the most significant factor that differed between the groups who received RT and did not was the median NIHSS score (four vs. three). Nevertheless, many so-called "minor strokes" were present in both groups. One can argue that only the subjects with non-disabling deficits were not thrombolysed, but only 13 subjects from the whole cohort were BEFAST-negative, and nobody from the BEFAST-positive cohort presented with isolated facial asymmetry, which means that they all had disabling symptoms. These findings clearly show the subjective component of the assessment that is always present on top of guidelines.

Thrombolysis in minor strokes is a constant matter of debate between stroke physicians. Some authors report that RT does not have a beneficial impact on the outcomes of minor strokes [23], while others are more optimistic [24], especially when large-vessel occlusion is present [25]. Unfortunately, the outcomes measured are usually mortality, mRS and NIHSS, and those are quite crude. To draw a reliable conclusion about minor stroke outcomes, it would be beneficial to investigate other aspects, including cognitive functions, fatigue, autonomic dysfunction [26] and other often underestimated stroke symptoms.

We can hypothesise that RCI "age >80" could be a vague description of the subjective clinician's impression of the subject's frailty. It is known that frailty increases the probability of poor outcomes [27–29], and sometimes it is hard to predict if the frail patient will benefit from RT. Although RT in the elderly is another questionable concept among clinicians, age should not be a contraindication for RT per se [30].

Subjects diagnosed with AF, AH, and DM were treated with RT more frequently. While AF might not be an independent risk factor because of the confounding with the NIHSS, AH and DM were not associated with higher NIHSS scores. We hypothesise that the presence of vascular risk factors made subjects and clinicians more vigilant about stroke. In our opinion, RT could have been withheld in the RCI group because of the uncertainty about the diagnosis. In such cases, additional cardiovascular risk factors encouraged the clinician to suspect stroke and make the choice in favour of RT.

Although males were late for RT more frequently, there was a trend to withhold RT in females with RCI for RT. That finding reconfirms the results of previous studies regarding sex differences in stroke RT, showing that women are receiving less RT than men, even after adjusting for confounders [31–33]. It is another illustration of the subjectivity of the decision-making process.

A study from Portugal identified that social factors such as poverty, lack of stroke awareness, or difficulties in requesting immediate medical help put patients at higher risk of late admission for RT [8]. Given this, we should aim to increase awareness of PCS symptoms by educating society about stroke symptoms with the help of the BEFAST tool. The data from the tertiary centre in Helsinki revealed that PCS patients have hypertension history less often and presented with non-typical symptoms, such as seizure, vomiting and headache more often than the ACS patients [7]. We encourage clinicians to consider the possibility of stroke even when the patient does not have traditional cardiovascular risk factors or presents with atypical symptoms. Testing for specific PCS symptoms that are not represented by classical NIHSS, such as axial ataxia and dysphagia, might be helpful. It is beneficial to remember that thrombolysis in stroke mimics is safe [34,35] and that IVT is recommended in minor strokes if the deficit is disabling [30]. In our opinion, it would be beneficial to analyse the impact of routine use of the BEFAST tool by paramedics and in the Accident and Emergency Department on large cohorts in future.

4.2. Strengths and Limitations of the Study

Our study is limited by its retrospective design. Moreover, some of the PCS patients transferred to other centres were not included because the exact diagnosis and follow-up

would be complicated. However, it does not make our findings less relevant. All transferred subjects were not suitable for the RT, so the real number of subjects with contraindications could be even higher. We did not analyse the impact of smoking status and dyslipidaemia on the chance of receiving RT because data about these factors were lacking. We also did not stratify our population according to stroke aetiology or type of admission (self-presented or paramedics). These problems should be investigated in future studies.

The strengths of the study are sufficient sample size and reliable clinical examination; every subject was examined by a neurology consultant on admission. It is also important that the majority of subjects had a radiologically confirmed PCS diagnosis.

5. Conclusions

Late arrival was the most common ACI to RT, and the male gender increased this risk. PCS patients with existing FAST symptoms, vascular risk factors, and higher NIHSS scores were more likely to be selected for reperfusion therapy. Ataxia or visual symptoms reduced the chance of receiving RT. Ten percent of subjects did not undergo RT due to relative contraindications. When only relative ineligibility criteria were present, RT was more often performed in the presence of higher NIHSS scores and vascular risk factors. There was a trend towards less frequent RT in female patients with relative contraindications.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data is available on request due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Tao, W.D.; Liu, M.; Fisher, M.; Wang, D.R.; Li, J.; Furie, K.L.; Hao, Z.L.; Lin, S.; Zhang, C.F.; Zeng, Q.T.; et al. Posterior versus anterior circulation infarction: How different are the neurological deficits? *Stroke* **2012**, *43*, 2060–2065. [CrossRef]
2. Keselman, B.; Gdovinová, Z.; Jatuzis, D.; Melo, T.P.E.; Vilionskis, A.; Cavallo, R.; Frol, S.; Jurak, L.; Koyuncu, B.; Nunes, A.P.; et al. Safety and outcomes of intravenous thrombolysis in posterior versus anterior circulation stroke results from the Safe Implementation of Treatments in Stroke registry and meta-analysis. *Stroke* **2020**, *51*, 876–882. [CrossRef]
3. Lindsberg, P.J.; Pekkola, J.; Strbian, D.; Sairanen, T.; Mattle, H.P.; Schroth, G. Time window for recanalization in basilar artery occlusion. *Neurology* **2015**, *85*, 1806–1815. [CrossRef]
4. Berndt, M.; Poppert, H.; Steiger, K.; Pelisek, J.; Oberdieck, P.; Maegerlein, C.; Zimmer, C.; Wunderlich, S.; Friedrich, B.; Boeckh-Behrens, T.; et al. Thrombus Histology of Basilar Artery Occlusions: Are There Differences to the Anterior Circulation? *Clin. Neuroradiol.* **2021**, *31*, 753–761. [CrossRef]
5. Aroor, S.; Singh, R.; Goldstein, L.B. BE-FAST (Balance, Eyes, Face, Arm, Speech, Time): Reducing the Proportion of Strokes Missed Using the FAST Mnemonic. *Stroke* **2017**, *48*, 479–481. [CrossRef]
6. Chen, X.; Zhao, X.; Xu, F.; Guo, M.; Yang, Y.; Zhong, L.; Weng, X.; Liu, X. A Systematic Review and Meta-Analysis Comparing FAST and BEFAST in Acute Stroke Patients. *Front. Neurol.* **2022**, *12*, 765069. [CrossRef] [PubMed]
7. Puustjärvi, V.; Strbian, D.; Tiainen, M.; Curtze, S.; Tatlisumak, T.; Sairanen, T. Recognition of posterior circulation stroke. *Acta Neurol. Scand.* **2015**, *131*, 389–393. [CrossRef]
8. Sobral, S.; Taveira, I.; Seixas, R.; Vicente, A.C.; Duarte, J.; Goes, A.T.; Durán, D.; Lopes, J.; Rita, H.; Nzwalo, H. Late Hospital Arrival for Thrombolysis after Stroke in Southern Portugal: Who Is at Risk? *J. Stroke Cerebrovasc. Dis.* **2019**, *28*, 900–905. [CrossRef] [PubMed]
9. Sand, K.M.; Næss, H.; Nilsen, R.M.; Thomassen, L.; Hoff, J.M. Less thrombolysis in posterior circulation infarction—A necessary evil? *Acta Neurol. Scand.* **2017**, *135*, 546–552. [CrossRef]
10. Halúsková, S.; Herzig, R.; Krajíčková, D.; Hamza, A.; Krajina, A.; Chovanec, V.; Lojík, M.; Raupach, J.; Renc, O.; Šimůnek, L.; et al. Acute management should be optimized in patients with less specific stroke symptoms: Findings from a retrospective observational study. *J. Clin. Med.* **2021**, *10*, 1143. [CrossRef] [PubMed]

11. Sommer, P.; Seyfang, L.; Posekany, A.; Ferrari, J.; Lang, W.; Fertl, E.; Serles, W.; Töll, T.; Kiechl, S.; Greisenegger, S. Prehospital and intra-hospital time delays in posterior circulation stroke: Results from the Austrian Stroke Unit Registry. *J. Neurol.* **2017**, *264*, 131–138. [CrossRef]
12. Wang, Y.; Tong, X.; Liao, X.; Pan, Y.; Cao, Y.; Wang, C.; Liu, L.; Zheng, H.; Zhao, X.; Wang, C.; et al. Intravenous thrombolysis is more safe and effective for posterior circulation stroke Data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China). *Medicine* **2016**, *95*, e3848.
13. Sung, S.F.; Chen, C.H.; Chen, Y.W.; Tseng, M.C.; Shen, H.C.; Lin, H.J. Predicting symptomatic intracerebral hemorrhage after intravenous thrombolysis: Stroke territory as a potential pitfall. *J. Neurol. Sci.* **2013**, *335*, 96–100. [CrossRef] [PubMed]
14. Turc, G.; Bhogal, P.; Fischer, U.; Khatri, P.; Lobotesis, K.; Mazighi, M.; Schellinger, P.D.; Toni, D.; de Vries, J.; White, P.; et al. European Stroke Organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. *J. Neurointerv. Surg.* **2019**, *15*, e8. [CrossRef]
15. Gordon, C.; Bell, R.; Ranta, A. Impact of the national public "FAST" campaigns. *N. Z. Med. J.* **2019**, *132*, 48–56.
16. Nordanstig, A.; Asplund, K.; Norrving, B.; Wahlgren, N.; Wester, P.; Rosengren, L. Impact of the Swedish National Stroke Campaign on stroke awareness. *Acta Neurol. Scand.* **2017**, *136*, 345–351. [CrossRef]
17. Wolters, F.J.; Paul, N.L.M.; Li, L.; Rothwell, P.M. Sustained impact of UK FAST-test public education on response to stroke: A population-based time-series study. *Int. J. Stroke* **2015**, *10*, 1108–1114. [CrossRef]
18. Martin-Schild, S.; Albright, K.C.; Tanksley, J.; Pandav, V.; Jones, E.B.; Grotta, J.C.; Savitz, S.I. Zero on the NIHSS does not equal the absence of stroke. *Ann. Emerg. Med.* **2011**, *57*, 42–45. [CrossRef]
19. Alemseged, F.; Rocco, A.; Arba, F.; Schwabova, J.P.; Wu, T.; Cavicchia, L.; Ng, F.; Ng, J.L.; Zhao, H.; Williams, C.; et al. Posterior National Institutes of Health Stroke Scale Improves Prognostic Accuracy in Posterior Circulation Stroke. *Stroke* **2022**, *53*, 1247–1255. [CrossRef] [PubMed]
20. Wiśniewski, A.; Filipska, K.; Piec, K.; Jaskólski, F.; Ślusarz, R. Introducing Adam's Scale of Posterior Stroke (ASPOS): A Novel Validated Tool to Assess and Predict Posterior Circulation Strokes. *Brain Sci.* **2021**, *11*, 424. [CrossRef] [PubMed]
21. Olivato, S.; Nizzoli, S.; Cavazzuti, M.; Casoni, F.; Nichelli, P.F.; Zini, A. e-NIHSS: An Expanded National Institutes of Health Stroke Scale Weighted for Anterior and Posterior Circulation Strokes. *J. Stroke. Cerebrovasc. Dis.* **2016**, *25*, 2953–2957. [CrossRef]
22. Strambo, D.; Bartolini, B.; Beaud, V.; Marto, J.P.; Sirimarco, G.; Dunet, V.; Saliou, G.; Nannoni, S.; Michel, P. Thrombectomy and Thrombolysis of Isolated Posterior Cerebral Artery Occlusion: Cognitive, Visual, and Disability Outcomes. *Stroke* **2020**, *51*, 254–261. [CrossRef]
23. Huang, Q.; Ma, Q.; Jia, J.; Wu, J. Intravenous thrombolysis for minor stroke and rapidly improving symptoms: A quantitative overview. *Neurol. Sci.* **2014**, *35*, 1321–1328. [CrossRef]
24. Duan, C.; Xiong, Y.; Gu, H.Q.; Wang, S.; Yang, K.X.; Hao, M.; Zhao, X.; Meng, X.; Wang, Y. Outcomes in minor stroke patients treated with intravenous thrombolysis. *CNS Neurosci. Ther.* **2023**, *29*, 2308–2317. [CrossRef]
25. Duan, C.; Xiong, Y.; Gu, H.; Wang, S.; Yang, K.; Hao, M.; Feng, X.; Zhao, X.; Meng, X.; Wang, Y. Intravenous thrombolysis versus antiplatelet therapy in minor stroke patients with large vessel occlusion. *CNS Neurosci. Ther.* **2023**, *29*, 1615–1623. [CrossRef]
26. Heldner, M.R.; Seners, P.; Li, L. Editorial: Challenges in Acute Minor Ischemic Stroke. *Front. Neurol.* **2022**, *13*, 896716. [CrossRef]
27. McEnhill, P.; Torsney, K.M.; Rajkumar, C. Does frailty predict post stroke mortality? *Age Ageing* **2020**, *49*, 535–536. [CrossRef]
28. Joyce, N.; Atkinson, T.; Mc Guire, K.; Ivan Wiggam, M.; Gordon, P.L.; Kerr, E.L.; Patterson, C.E.; McILmoyle, J.; Roberts, G.E.; Flynn, P.A.; et al. Frailty and stroke thrombectomy outcomes—An observational cohort study. *Age Ageing* **2022**, *51*, afab260. [CrossRef]
29. Tiainen, M.; Martinez-Majander, N.; Virtanen, P.; Räty, S.; Strbian, D. Clinical frailty and outcome after mechanical thrombectomy for stroke in patients aged ≥80 years. *J. Stroke Cerebrovasc. Dis.* **2022**, *31*, 106816. [CrossRef]
30. Berge, E.; Whiteley, W.; Audebert, H.; De Marchis, G.M.; Fonseca, A.C.; Padiglioni, C.; de la Ossa, N.P.; Strbian, D.; Tsivgoulis, G.; Turc, G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur. Stroke J.* **2021**, *6*, I–LXII. [CrossRef] [PubMed]
31. Reeves, M.; Bhatt, A.; Jajou, P.; Brown, M.; Lisabeth, L. Sex differences in the use of intravenous rt-pa thrombolysis treatment for acute ischemic stroke: A meta-analysis. *Stroke* **2009**, *40*, 1743–1749. [CrossRef]
32. Bushnell, C.; Howard, V.J.; Lisabeth, L.; Caso, V.; Gall, S.; Kleindorfer, D.; Chaturvedi, S.; Madsen, T.E.; Demel, S.L.; Lee, S.-J.; et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. *Lancet Neurol.* **2018**, *17*, 641–650. [CrossRef] [PubMed]
33. Strong, B.; Lisabeth, L.D.; Reeves, M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: A systematic review and meta-analysis. *Neurology* **2020**, *95*, e11–e22. [CrossRef] [PubMed]
34. Keselman, B.; Cooray, C.; Vanhooren, G.; Bassi, P.; Consoli, D.; Nichelli, P.; Peeters, A.; Sanak, D.; Zini, A.; Wahlgren, N.; et al. Intravenous thrombolysis in stroke mimics: Results from the SITS International Stroke Thrombolysis Register. *Eur. J. Neurol.* **2019**, *26*, 1091–1097. [CrossRef]
35. Zinkstok, S.M.; Engelter, S.T.; Gensicke, H.; Lyrer, P.A.; Ringleb, P.A.; Artto, V.; Putaala, J.; Haapaniemi, E.; Tatlisumak, T.; Chen, Y.; et al. Safety of thrombolysis in stroke mimics: Results from a multicenter cohort study. *Stroke* **2013**, *44*, 1080–1084. [CrossRef] [PubMed]

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The Stream Device—A Retrospective Review of 51 Cases

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Abstract: Mechanical thrombectomy is the gold-standard treatment for patients that have suffered large-vessel occlusion (LVO) stroke. Various different stent-retrievers, aspiration catheters, and techniques have been developed to perform this procedure. We present our initial results regarding the Stream device. Materials and Methods: We performed a retrospective review of a prospectively maintained database at our high-volume centre to identify all patients treated with the Stream device between February 2021 and January 2023. We recorded baseline demographics, NIHSS, ASPECT scores, eTICI scores, complications, and 90-day mRS. Results: We identified 51 patients, 49.0% of whom were male (n = 25), with a median age of 73 (range: 51–89) and a median NIHSS score of 17 (range 4–22), and 68.6% received IV tPA. The median ASPECT score was 10 (range 6–10). Hyperdense clots were seen in 34 cases (66.7%), with a mean clot length of 12 $\pm$ 6.2 mm (range 2–26 mm). Clots were located in the anterior circulation in 49 patients. The standard Stream device was used in 78.4% of cases, with Stream 17 being used in 19.6% of cases. The FPE was observed in 25.5% of cases (n = 13), with the mFPE being seen in 31.4% of cases (n = 16). A final eTICI score of $\geq$2b was achieved in 90.2% of cases (n = 46), and eTICI 2c/3 was seen in 84.3% of cases (n = 43). Furthermore, 24 h CT scans showed that the median ASPECT score was 8 (range 0–10). Good functional outcomes at 90 days (mRS $\leq$ 2) were achieved in 21.6% of cases (n = 11). Conclusions: The Stream device shows acceptable rates of FPE and mFPE compared to existing devices. Further larger studies are required alongside an understanding of the optimal technique for this device's use.

Keywords: stream device; mechanical thrombectomy; ischaemic stroke

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1. Introduction

Mechanical thrombectomy (MT) has become the gold-standard treatment for acute ischaemic stroke (AIS) caused by large-vessel occlusion (LVO), with studies further demonstrating the efficacy of this procedure in treating patients presenting beyond 6 h [1,2], in relation to posterior circulation, and, more recently, in treating patients with large-core strokes (with ASPECT scores of 3–5) [3–5]. A variety of studies assessing the impact of MT in more distal locations are currently underway, with the expectation that the indications for MT will continue to expand.

Recent advances in our understanding related to clot pathophysiology and structure, clot/stent interactions, and clot/vessel wall interactions have improved our knowledge base regarding ischaemic stroke [6–10]. Over the last decade, there has been a significant improvement in our understanding of the various clot types [6], the interaction between stent-retrievers and clots [7–9], and how both stent-retrievers and clots interact with the vessel wall and in combination during retrieval [10]. This improvement in our understanding has led to the development of stent-retrievers with novel designs [11–15], with the synchronous development of novel aspiration catheters [16–18] and various techniques for optimising the MT procedure and first-pass recanalisation.

Manually controlled, expandable, braided devices have been clinically used for the treatment of aneurysms [19–23] and, more recently, cerebral vasospasm [24,25]; however, their development and use in AIS are more recent occurrences. The Stream (Perflow Medical, Tel Aviv, Israel) device is a novel device with a braided structure that, via an actuator at the handle, can be expanded or contracted by the operator.

Currently, there are no publications that have examined the safety and efficacy of this novel device. In this article, we present our initial experience of the use of the Stream device to treat patients with AIS.

2. Materials and Methods

2.1. The Stream Device

The Stream device is a dynamic neuro-thrombectomy braided net, or an adjustable stent retriever, which is controlled by a proximal handle (Figure 1). At the distal end of the device, there is a 10–13 mm (depending on the device model) atraumatic, radiopaque wire tip. There are 6–8 (depending on the device model) paired wires that form the expandable Cerebral Net™, and these can be expanded from 0.4 to 6 mm depending on the model of device chosen. The actuator control handle has two operation modes: auto-lock mode for stepwise radial expansion and free mode for continuous adjustments that can also provide tactile feedback. In auto-lock mode, each 'click' of the handle results in an incremental controlled expansion of the device. There are currently three models:

- Stream;
- Stream XL;
- Stream 17.

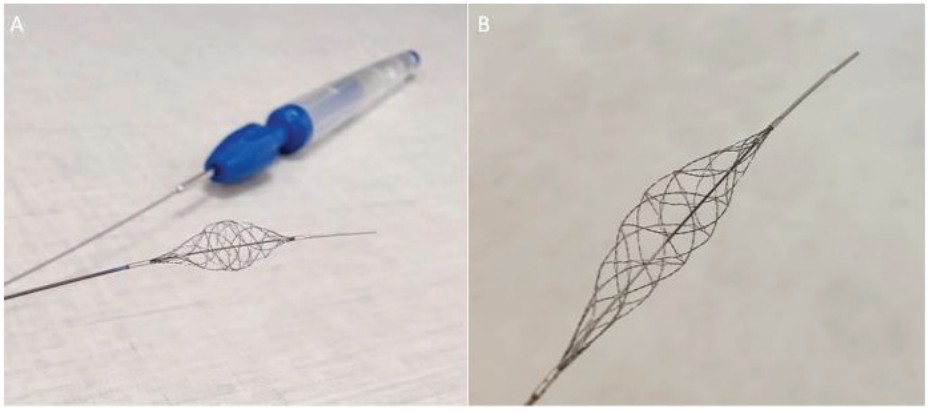

Figure 1. The Stream device consists of an actuator handle that allows for the precise control of the Cerebral Net ((**A**) and magnified image in (**B**)). At the distal end of the device, there is an atraumatic, radiopaque wire tip (**B**).

Stream and Stream XL are compatible with 0.021-inch-inner-diameter microcatheters, whereas Stream 17 is designed for 0.017-inch-inner-diameter microcatheters. In terms of length, Stream has a maximum braid length of 33 mm, Stream XL has a maximum braid length of 38 mm, and Stream 17 has a maximum braid length of 25 mm. The overall effective length of the Stream is 193 cm.

2.2. Patient Selection

We performed a retrospective review of prospectively maintained databases at a high-volume centre to identify all patients treated with the Stream device between February 2021 and January 2023. The retrospective nature of this study precluded the requirement of ethical approval at the participating centre.

2.3. Study Population

The inclusion criteria included the following:

- Age $\geq$ 18;
- National Institutes of Health Stroke Scale (NIHSS) score of $\geq$4;
- ASPECT score $\geq$ 5;
- LVO on CT angiography;
- Pre-morbid mRS of 0–2;
- Life expectancy of >6 month.

The Stream device was the first device used for treatment of the intracranial occlusion.

Patients were excluded if another device or technique (aspiration) was used as the initial strategy for the MT procedure or if there was an incomplete dataset (aside from the 90-day mRS).

All patients underwent non-enhanced CT and CT Angiograms from the arch to the vertex prior to the MT procedure. Patients were eligible for MT if their ASPECT score was $\geq$5, their baseline mRS was $\leq$2, and their life expectancy was greater than 6 months (in the case of a known underlying malignancy), with no upper limit on age. All patients were given IV tPA if they met the criteria.

2.4. Endovascular Procedure

Patients were treated either with local anaesthesia or general anaesthesia as per local standard practice.

The exact equipment used varied between the different operators; however, a distal aspiration catheter, typically a 6 Fr Sofia (Microvention, Aliso Viejo, CA, USA), was used in all cases and was typically introduced via a standard guide catheter such as a NeuronMax (Penumbra, Alameda, CA, USA).

Successful reperfusion was defined as eTICI $\geq$ 2b (67%). In addition, first-pass effect (FPE) and modified FPE were defined as eTICI $\geq$ 2c and as eTICI $\geq$ 2b, respectively, after the first thrombectomy attempt.

2.5. Post-Procedure

Post procedure, using non-enhanced CT imaging was routinely performed at 24 $\pm$ 6 h unless there was a sudden deterioration in a patient's consciousness level, prompting an earlier scan. In cases of intracranial or extracranial stenting, a CTA was also performed.

The 90-day mRS was recorded via telephone interview or clinic review conducted by a trained stroke physician.

The data recorded included the demographics (age, gender, underlying medical conditions, admission NIHSS score, etc.), use of IV tPA, radiological findings (including the ASPECT score prior to MT), clot location, endovascular procedural information, and relevant timing. The eTICI score was recorded after the first pass of the device and at the end of the procedure alongside any complications and the 90-day mRS where available.

3. Results

3.1. Baseline Demographics

In total, 51 patients met our inclusion and exclusion criteria. The median age of the participants was 73 (range 51–89), and 49.0% were male (n = 25). Pre-existing hypertension was common (n = 40, 78.4%), diabetes mellitus was less common (n = 13, 25.5%), and atrial fibrillation was noted in just over half of the patients (n = 26, 51%). All patients were recorded as having a baseline mRS of 0 prior to the MT procedure. The results are summarised in Table 1.

Table 1. Baseline demographics and medical data.

Baseline Data	*n* = 51
Demographics	
Age	Median 73 (range 51–89)
Female	51% (*n* = 26)
Co-Morbidities	
Smoking	20 (39.2%)
Hypertension	40 (78.4%)
Diabetes Mellitus	13 (25.5%)
Atrial Fibrillation	26 (51%)
Pre-Morbid mRS	
0	51 (100%)

3.2. Clinical and Angiographic Results

The median NIHSS score at presentation was 17 (range 4–22), and 68.6% received IV tPA prior to MT. The most common suspected cause of a stroke was thought to be cardioembolic (52.9%). Right-sided LVOs were more frequently seen (56.9%), and eight cases involved tandem lesions (15.7%). The median ASPECT score upon conducting a plain CT scan was 10 (range 6–10). Hyperdense clots were seen in 34 cases (66.7%), with a mean clot length of 12 ± 6.2 mm (range 2–26 mm). The vast majority of clots were located in the anterior circulation, with only two posterior basilar occlusions (3.9%).

The results are summarized in Table 2.

Table 2. Baseline clinical and imaging data, including suspected cause of stroke, NIHSS score, clot location, and ASPECT score.

Stroke Data	
NIHSS	Median 17 (range 4–22)
IV tPA	35 (68.6%)
Suspected Cause	
Cardioembolic	27 (52.9%)
Large-artery Atherosclerosis	6 (11.8%)
Mixed	5 (9.8%)
ESUS (Embolic Stroke of Undetermined Source)	13 (25.5%)
Imaging Findings	
Side	
R	29 (56.9%)
L	20 (39.2%)
Mid	2 (3.9%)
Tandem Lesion	
Y	8 (15.7%)
Clot Location	
ICA	16 (31.4%)
M1	29 (56.9%)
M2	4 (7.8%)
BA	2 (3.9%)
Hyperdense Clot	34 (66.7%)
Clot Length	12 ± 6.2 mm (range: 2–26 mm)
ASPECT Score	Median 10 (range: 6–10)

3.3. Procedural Outcomes

The vast majority of patients were operated on under local anaesthesia (n = 49, 96.1%). The standard Stream device was used as the first-line device in the majority of procedures (n = 40, 78.4%), with the smaller Stream 17 used in 19.6% of cases (n = 10). The first-pass effect (FPE) was seen in 25.5% of cases (n = 13), with a modified FPE seen in 31.4% (n = 16) (Figures 2 and 3). Distal embolisation was seen in 5.9% (n = 3) of cases, and an embolus in new territory was not seen in any cases.

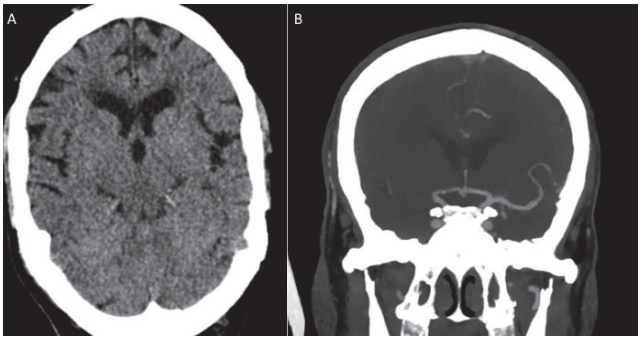

Figure 2. A male patient with 2 h history of acute left-sided weakness and an NIHSS score of 17. Non-contrast CT scan (**A**) revealed some subtle loss of grey–white matter differentiation involving the lentiform nucleus (ASPECT score 9), and CT angiography confirmed a right terminal ICA and M1 occlusion (**B**).

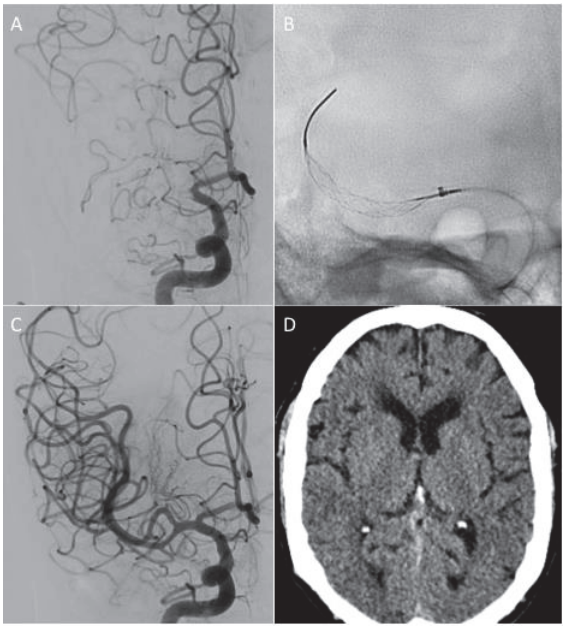

Figure 3. Angiography confirmed the terminal right ICA and M1 occlusion (**A**). The thrombus was crossed using a Headway 21 microcatheter, and a Stream device was expanded for 5 min (**B**). Withdrawal into the aspiration catheter was performed, during which the first-pass effect was observed (eTICI 2c) (**C**). Non-contrast CT scan of the head performed at 24 h demonstrated no evidence of haemorrhage and an ASPECT score of 8 (**D**).

In 19.6% (n = 10) of cases, Stream could not be used to remove the occlusion, and bailout with alternative devices/techniques was required. An intracranial stent was permanently implanted in one of these cases (1.9%). Carotid stents were implanted in two cases (3.9%).

The median number of passes when only Stream was used was 2 (range: 1-4), with a mean number of passes equal to 2.0 $\pm$ 0.92. At the end of the procedure, after all the devices and techniques had been used, a final eTICI score of $\geq$2b was achieved in 90.2% of cases (n = 46), with eTICI 2c/3 seen in 84.3% (n = 43) of cases. The results are summarised in Table 3.

Table 3. Procedural data including the model of Stream used, type of anaesthesia, angiographic result following MT, and distal and new-territory embolisation.

Procedural Data	
Anaesthesia	
LA	49 (96.1%)
GA	2 (3.9%)
Distal Aspiration Catheter	51 (100%)
Stream	
Stream	40 (78.4%)
Stream XL	1 (2%)
Stream 17	10 (19.6%)
Angiographic Results	
Median No. of passes	2 (range 1–8)
Median No. of passes with Stream	2 (range 1–4)
FPE (eTICI 2c/3)	13 (25.5%)
Modified FPE (eTICI $\geq$ 2b)	16 (31.4%)
Final eTICI	
0–2a	5 (9.8%)
2b	3 (5.9%)
2c	4 (7.8%)
3	39 (76.5%)
Distal Embolisation	3 (5.9%)
Embolisation to New territory	0
Bailout Required	n = 10
Resistant Clot	5 (9.8%)
Device Damage	4 (7.8%)
Intracranial Stent Implanted	1 (1.9%)
Carotid Stent Implanted	2 (3.9%)

3.4. Follow-up Imaging and Clinical Results

A follow-up CT scan performed at 24 h was available for all patients. The median ASPECT score was 8 (range 0–10). Subarachnoid haemorrhage was seen in eight patients (15.7%), and seven patients developed sICH (13.7%), three of whom also had SAH. The 90-day mRS was available for all patients, and a good functional outcome (mRS 0–2) was achieved in 21.6% of cases (n = 11), with an mRS of 6 in 43.1% of cases. The results are summarised in Table 4.

Table 4. Angiographic and clinical follow-up data.

Follow-up (n = 51)	
ASPECT	Median 8 (range 0–10)
sICH	7 (13.7%)
SAH	8 (15.7%)
90-day mRS	
0–2	11 (21.6%)
3–5	18 (35.3%)
6	22 (43.1%)

4. Discussion

In our initial experience with the Stream device, we observed a similar rate of efficacy with respect to FPE and mFPE when compared to other frequently used stent-retrievers such as the Solitaire (Medtronic) [26–29] and Trevo (Stryker) stent-retrievers [30–32], whose efficacy averages between 25 and 40%.

The Stream device has several potential technical advantages that come into effect during a mechanical thrombectomy. Unlike standard stent-retrievers, this device is under the direct control of the operating physician in the sense that it does not automatically expand like a standard device. Therefore, if the Stream device has been unsheathed in a sub-optimal position, it can be repositioned to optimise the clot/device interaction. Although one can achieve the same result with standard stent-retrievers, a potential drawback is that they will immediately expand upon unsheathing, and this will not only compress the clot but also result in microthrombi that have the potential to travel distally [10]. Similarly, the closed nature of the distal end of the Stream device's braided net may also act as a distal clot catcher that prevents, at least to a degree, the loss of distal thrombi during the expansion of the device, as was recently demonstrated with another device [33]. Interestingly, in our study, distal emboli were only seen in 5.9% of cases despite having been reported in ≈25% of cases for devices with distal clot catchers [12]. It is also noteworthy that the average clot length in the three cases where distal clot embolisation occurred was 17.7 ± 6.8 mm, which was considerably longer than the average clot length of 11.6 ± 6.1 mm in the cases in which no distal embolisation was seen. This may be due to the fact that distal embolisation may, at least in part, be due to the stent-retriever's length-to-clot-length ratio as has been suggested by Belachew et al. [34]. The fact that the Stream device shortens during expansion may mean that for longer clots, a longer device should be chosen in order to optimise the device/clot interaction, and further studies are required in order to determine if this holds true for the Stream device as it appears to for other devices [35–37].

The radial force of a stent-retriever is generally fixed and decreases at increasing diameters. Although techniques for increasing the radial force of standard stent-retrievers have been developed, such as the 'push and fluff' technique, these are unlikely to lead to very significant increases in the radial force developed. It has previously been shown that the migration of stent-struts into a clot is determined, at least in part, by the radial force exerted as well as the size of the pores [38]. The radially expandable devices do not share this limitation, and, in fact, the radial force can be increased with manual expansion in a similar manner to, but to a much lesser degree, angioplasty balloons. Conversely, the radial force can also be decreased during the procedure in case excessive resistance is felt. This allows the operator to expand and size the device according to the target vessel; importantly, this can be adapted during the thrombus's retrieval. This feature may be of particular importance in platelet-rich white thrombi, which prove resistant to standard mechanical thrombectomy approaches. Even in the event of a failure to remove these clots, valuable information can be gleaned from the attempt, as the Stream device is visible along its entire length and, as such, the exact location of the clot can be determined if bailout angioplasty and stenting are to be considered.

In our experience, we have only performed a standard unsheathing and expansion of the Stream device; however, there is some evidence to suggest that repeated inflation and deflation may offer an advantage. In the study conducted by Kara et al. [39], using the Tigertriever, the first-pass recanalisation (mTICI $\geq$ 2b) rate using a repeated inflation and deflation technique was 47.8% compared to 31.6% when using a standard unsheathing and expansion technique. The authors believe that this might have been due to a combination of factors. Repeated inflation and over inflation may result in the greater enlargement of the cells, allowing more clot fragments to be entrapped within the lumen of the device. The authors also suggest that oversizing causes better apposition of the stent to the vessel wall, which enhances stent–clot interaction. We believe that a further potential reason for this improved recanalisation can be the fact that static expansion will not only potentially compress the clot but also increase the frictional forces between the clot and the vessel

wall, whereas repeated inflation and deflation may 'pull' the clot away from the vessel wall with each deflation and hence aid in overcoming these frictional forces during retrieval. It remains to be seen whether the repeated expansion technique results in improved recanalisation rates; however, this warrants further investigation with larger cohorts as well as bench-side studies.

Our study has several limitations that are inherent to retrospective observational studies. We did not follow a predefined study protocol that included a fixed number of attempts with the Stream device before switching to a different device/technique, and we did not standardise the other pieces of equipment used. The eTICI scores and follow-up imaging procedures were not adjudicated by an independent core lab.

5. Conclusions

The Stream device showed acceptable rates of FPE and mFPE compared to existing devices. Further larger studies are required alongside an understanding of the optimal technique for this device's use.

Author Contributions: K.K. (Karlis Kupcs)—data collection, editing, and guarantor; P.S.—data collection, editing, and revision; K.K. (Katrina Kupca)—data collection, editing, and revision; P.B.—manuscript preparation, editing, and revision. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethics committee approval is not required for a retrospective study of this nature.

Informed Consent Statement: Informed consent was obtained from all individual patients who were able to provide consent. For patients that could not provide consent, the thombectomy procedures were discussed with their next of kin/available family members and consent was obtained by the operating team and stroke physicians.

Conflicts of Interest: P.B.—consulting agreements Phenox, Cerenovus, Balt, Neurovasc Technologies, Brainomix, Perflow Medical, Perfuze, PockIt Diagnositcs, Vesalio, and BT. The remaining authors declare no conflict of interest.

References

1. Nogueira, R.G.; Jadhav, A.P.; Haussen, D.C.; Bonafe, A.; Budzik, R.F.; Bhuva, P.; Yavagal, D.R.; Ribo, M.; Cognard, C.; Hanel, R.A.; et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N. Engl. J. Med.* **2018**, *378*, 11–21. [CrossRef] [PubMed]
2. Albers, G.W.; Marks, M.P.; Kemp, S.; Christensen, S.; Tsai, J.P.; Ortega-Gutierrez, S.; McTaggart, R.A.; Torbey, M.T.; Kim-Tenser, M.; Leslie-Mazwi, T.; et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N. Engl. J. Med.* **2018**, *378*, 708–718. [CrossRef] [PubMed]
3. Sarraj, A.; Hassan, A.E.; Abraham, M.G.; Ortega-Gutierrez, S.; Kasner, S.E.; Hussain, M.S.; Chen, M.; Blackburn, S.; Sitton, C.W.; Churilov, L.; et al. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. *N. Engl. J. Med.* **2023**, *388*, 1259–1271. [CrossRef] [PubMed]
4. Uchida, K.; Shindo, S.; Yoshimura, S.; Toyoda, K.; Sakai, N.; Yamagami, H.; Matsumaru, Y.; Matsumoto, Y.; Kimura, K.; Ishikura, R.; et al. Association Between Alberta Stroke Program Early Computed Tomography Score and Efficacy and Safety Outcomes With Endovascular Therapy in Patients With Stroke From Large-Vessel Occlusion: A Secondary Analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism-Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT). *JAMA Neurol.* **2022**, *79*, 1260–1266. [CrossRef] [PubMed]
5. Huo, X.; Ma, G.; Tong, X.; Zhang, X.; Pan, Y.; Nguyen, T.N.; Yuan, G.; Han, H.; Chen, W.; Wei, M.; et al. Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *N. Engl. J. Med.* **2023**, *388*, 1272–1283. [CrossRef] [PubMed]
6. Staessens, S.; Denorme, F.; Francois, O.; Desender, L.; Dewaele, T.; Vanacker, P.; Deckmyn, H.; Vanhoorelbeke, K.; Andersson, T.; De Meyer, S.F. Structural Analysis of Ischemic Stroke Thrombi: Histological Indications for Therapy Resistance. *Haematologica* **2020**, *105*, 498–507. [CrossRef] [PubMed]
7. Dumitriu LaGrange, D.; Bernava, G.; Reymond, P.; Wanke, I.; Vargas, M.I.; Machi, P.; Lövblad, K.-O. A High Resolution Scanning Electron Microscopy Analysis of Intracranial Thrombi Embedded along the Stent Retrievers. *Sci. Rep.* **2022**, *12*, 8027. [CrossRef] [PubMed]

8. Tsumoto, T.; Tsurusaki, Y.; Tokunaga, S. Interaction between the Stent Strut and Thrombus Characterized by Contrast-Enhanced High-Resolution Cone Beam CT during Deployment of the Solitaire Stent Retriever. *J. Neurointerv. Surg.* **2017**, *9*, 843–848. [CrossRef]
9. Autar, A.S.A.; Hund, H.M.; Ramlal, S.A.; Hansen, D.; Lycklama, À.; Nijeholt, G.J.; Emmer, B.J.; de Maat, M.P.M.; Dippel, D.W.J.; van der Lugt, A.; et al. High-Resolution Imaging of Interaction Between Thrombus and Stent-Retriever in Patients with Acute Ischemic Stroke. *J. Am. Heart Assoc.* **2018**, *7*, e008563. [CrossRef]
10. Liu, Y.; Gebrezgiabhier, D.; Reddy, A.S.; Davis, E.; Zheng, Y.; Arturo Larco, J.L.; Shih, A.J.; Pandey, A.S.; Savastano, L.E. Failure Modes and Effects Analysis of Mechanical Thrombectomy for Stroke Discovered in Human Brains. *J. Neurosurg.* **2021**, *136*, 197–204. [CrossRef]
11. Brouwer, P.A.; Yeo, L.L.L.; Holmberg, A.; Andersson, T.; Kolloch, J.; KuntzeSöderqvist, Å.; Ohlsson, M.; Holmin, S.; Mpotsaris, A.; Gontu, V.K.; et al. Thrombectomy Using the EmboTrap Device: Core Laboratory-Assessed Results in 201 Consecutive Patients in a Real-World Setting. *J. Neurointerv. Surg.* **2018**, *10*, 964–968. [CrossRef] [PubMed]
12. Omrani, O.; Hafezi-Bakhtiari, N.; DeSouza, P.; Nikola, C.; Wong, K.; Lansley, J.; Dhillon, P.; Makalanda, L.; Chan, N.; Harrison, T.; et al. The Initial Experience with the Embotrap III Stent-Retriever in a Real World Setting. *Interv. Neuroradiol. J. Peritherapeutic Neuroradiol. Surg. Proced. Relat. Neurosci.* **2022**, 15910199221142096. [CrossRef] [PubMed]
13. Zaidat, O.O.; Bozorgchami, H.; Ribó, M.; Saver, J.L.; Mattle, H.P.; Chapot, R.; Narata, A.P.; Francois, O.; Jadhav, A.P.; Grossberg, J.A.; et al. Primary Results of the Multicenter ARISE II Study (Analysis of Revascularization in Ischemic Stroke With EmboTrap). *Stroke* **2018**, *49*, 1107–1115. [CrossRef] [PubMed]
14. Bajrami, A.; Ertugrul, O.; Senadim, S.; Erdem, E.; Baltacioglu, F.; Geyik, S. First Pass Results of Mechanical Thrombectomy with Two-Drop Zone NeVaTM Device. *Interv. Neuroradiol. J. Peritherapeutic Neuroradiol. Surg. Proced. Relat. Neurosci.* **2022**, 15910199221135308. [CrossRef] [PubMed]
15. Akpinar, C.K.; Ozdemir, A.O.; Gurkas, E.; Bilgic, A.B.; Aykac, O.; Inanc, Y.; Giray, S. Favorable First-Pass Recanalization Rates with NeVa^{TM} Thrombectomy Device in Acute Stroke Patients: Initial Clinical Experience. *Interv. Neuroradiol. J. Peritherapeutic Neuroradiol. Surg. Proced. Relat. Neurosci.* **2021**, *27*, 107–113. [CrossRef]
16. Makalanda, L.; Lansley, J.; Wong, K.; Spooner, O.; Bhogal, P. The Q and A-The MIVI Q Catheters for Aspiration Thrombectomy-Initial Experience from London. *J. Clin. Med.* **2021**, *10*, 5844. [CrossRef] [PubMed]
17. de Rueda, M.E.; Ballenilla Marco, F.; Garmendia Lopetegui, E.; Pumar, J.M.; Zamarro, J.; García-Villalba, B.; Díaz-Pérez, J.; Mosqueira, A.; Lüttich, A.; Larrea, J.-A.; et al. Thrombectomy Aspiration Post-Market Study in Acute Stroke with the Q Aspiration Catheter: The TAPAS Study. *J. Neurointerv. Surg.* **2022**, *15*, 674–678. [CrossRef] [PubMed]
18. Kobeissi, H.; Ghozy, S.; Flood, R.; Mortimer, A.; Crossley, R.; Cox, A.; Minks, D.; Wareham, J. Mechanical Thrombectomy with Q Catheter in Stroke Caused by Primary and Secondary Distal and Medium Vessel Occlusions. *Interv. Neuroradiol. J. Peritherapeutic Neuroradiol. Surg. Proced. Relat. Neurosci.* **2023**, 15910199231167916. [CrossRef]
19. Sirakov, S.; Sirakov, A.; Minkin, K.; Karakostov, V.; Raychev, R. Early Clinical Experience with Cascade: A Novel Temporary Neck Bridging Device for Embolization of Intracranial Aneurysms. *J. Neurointerv. Surg.* **2020**, *12*, 303–307. [CrossRef]
20. Tomasello, A.; Hernandez, D.; Gramegna, L.L.; Aixut, S.; Barranco Pons, R.; Jansen, O.; Zawadzki, M.; Lopez-Rueda, A.; Parra-Fariñas, C.; Piñana, C.; et al. Early Experience with a Novel Net Temporary Bridging Device (Cascade) to Assist Endovascular Coil Embolization of Intracranial Aneurysms. *J. Neurosurg.* **2020**, *134*, 591–599. [CrossRef]
21. Bhogal, P.; Wong, K.; Makalanda, H. The Cascade Device—In Vitro Tests to Assess Coil Protrusion into the Parent Vessel. *Interv. Neuroradiol. J. Peritherapeutic Neuroradiol. Surg. Proced. Relat. Neurosci.* **2020**, *26*, 494–500. [CrossRef] [PubMed]
22. Fischer, S.; Weber, A.; Carolus, A.; Drescher, F.; Götz, F.; Weber, W. Coiling of Wide-Necked Carotid Artery Aneurysms Assisted by a Temporary Bridging Device (Comaneci): Preliminary Experience. *J. Neurointerv. Surg.* **2017**, *9*, 1039–1097. [CrossRef] [PubMed]
23. Gupta, R.; Kolodgie, F.D.; Virmani, R.; Eckhouse, R. Comaneci Neck Bridging Device for the Treatment of Cerebral Aneurysms. *J. Neurointerv. Surg.* **2016**, *8*, 181–185. [CrossRef] [PubMed]
24. Bhogal, P.; Simpanen, T.; Wong, K.; Bushi, D.; Sirakov, M.A.; Sirakov, S.; Aggour, M.; Makalanda, L. Use of the Cascade Expandable Net to Treat Cerebral Vasospasm—Initial Clinical Experience from a Single Centre with in Vitro Benchside Tests. *CVIR Endovasc.* **2021**, *4*, 82. [CrossRef] [PubMed]
25. Salem, M.M.; Khalife, J.; Desai, S.; Sharashidze, V.; Badger, C.; Kuhn, A.L.; Monteiro, A.; Salahuddin, H.; Siddiqui, A.H.; Singh, J.; et al. COManeci MechANical Dilation for Vasospasm (COMMAND): Multicenter Experience. *J. Neurointerv. Surg.* **2022**, *15*, 864–870. [CrossRef] [PubMed]
26. Zaidat, O.O.; Castonguay, A.C.; Gupta, R.; Sun, C.-H.J.; Martin, C.; Holloway, W.E.; Mueller-Kronast, N.; English, J.D.; Linfante, I.; Dabus, G.; et al. North American Solitaire Stent Retriever Acute Stroke Registry: Post-Marketing Revascularization and Clinical Outcome Results. *J. Neurointerv. Surg.* **2014**, *6*, 584–588. [CrossRef] [PubMed]
27. Dávalos, A.; Pereira, V.M.; Chapot, R.; Bonafé, A.; Andersson, T.; Gralla, J. Solitaire Group Retrospective Multicenter Study of Solitaire FR for Revascularization in the Treatment of Acute Ischemic Stroke. *Stroke J. Cereb. Circ.* **2012**, *43*, 2699–2705. [CrossRef] [PubMed]
28. Broussalis, E.; Trinka, E.; Hitzl, W.; Wallner, A.; Chroust, V.; Killer-Oberpfalzer, M. Comparison of Stent-Retriever Devices versus the Merci Retriever for Endovascular Treatment of Acute Stroke. *AJNR Am. J. Neuroradiol.* **2013**, *34*, 366–372. [CrossRef]

29. Campbell, B.C.V.; Hill, M.D.; Rubiera, M.; Menon, B.K.; Demchuk, A.; Donnan, G.A.; Roy, D.; Thornton, J.; Dorado, L.; Bonafe, A.; et al. Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials. *Stroke* **2016**, *47*, 798–806. [CrossRef]
30. Binning, M.J.; Bartolini, B.; Baxter, B.; Budzik, R.; English, J.; Gupta, R.; Hedayat, H.; Krajina, A.; Liebeskind, D.; Nogueira, R.G.; et al. Trevo 2000: Results of a Large Real-World Registry for Stent Retriever for Acute Ischemic Stroke. *J. Am. Heart Assoc.* **2018**, *7*, e010867. [CrossRef]
31. Jadhav, A.P.; Desai, S.M.; Budzik, R.F.; Gupta, R.; Baxter, B.; English, J.D.; Bartolini, B.M.; Krajina, A.; Haussen, D.C.; Nogueira, R.G.; et al. First Pass Effect in Patients with Large Vessel Occlusion Strokes Undergoing Neurothrombectomy: Insights from the Trevo Retriever Registry. *J. Neurointerv. Surg.* **2021**, *13*, 619–622. [CrossRef] [PubMed]
32. Protto, S.; Pienimäki, J.-P.; Seppänen, J.; Matkaselkä, I.; Ollikainen, J.; Numminen, H.; Sillanpää, N. TREVO and Capture LP Have Equal Technical Success Rates in Mechanical Thrombectomy of Proximal and Distal Anterior Circulation Occlusions. *J. Neurointerv. Surg.* **2017**, *9*, 644–649. [CrossRef] [PubMed]
33. Li, J.; Tiberi, R.; Bhogal, P.; Buhk, J.-H.; Behme, D.; Tomasello, A.; Ribo, M. Impact of Stent-Retriever Tip Design on Distal Embolization during Mechanical Thrombectomy: A Randomized in Vitro Evaluation. *J. Neurointerv. Surg.* **2023**. [CrossRef]
34. Belachew, N.F.; Dobrocky, T.; Meinel, T.R.; Hakim, A.; Vynckier, J.; Arnold, M.; Seiffge, D.J.; Wiest, R.; Piechowiak, E.I.; Fischer, U.; et al. Risks of Undersizing Stent Retriever Length Relative to Thrombus Length in Patients with Acute Ischemic Stroke. *AJNR Am. J. Neuroradiol.* **2021**, *42*, 2181–2187. [CrossRef] [PubMed]
35. Serna Candel, C.; Aguilar Pérez, M.; Bäzner, H.; Henkes, H.; Hellstern, V. First-Pass Reperfusion by Mechanical Thrombectomy in Acute M1 Occlusion: The Size of Retriever Matters. *Front. Neurol.* **2021**, *12*, 679402. [CrossRef] [PubMed]
36. Haussen, D.C.; Al-Bayati, A.R.; Grossberg, J.A.; Bouslama, M.; Barreira, C.; Bianchi, N.; Frankel, M.R.; Nogueira, R.G. Longer Stent Retrievers Enhance Thrombectomy Performance in Acute Stroke. *J. Neurointerv. Surg.* **2019**, *11*, 6–8. [CrossRef] [PubMed]
37. Zaidat, O.O.; Haussen, D.C.; Hassan, A.E.; Jadhav, A.P.; Mehta, B.P.; Mokin, M.; Mueller-Kronast, N.H.; Froehler, M.T. Impact of Stent Retriever Size on Clinical and Angiographic Outcomes in the STRATIS Stroke Thrombectomy Registry. *Stroke* **2019**, *50*, 441–447. [CrossRef]
38. Wenger, K.; Nagl, F.; Wagner, M.; Berkefeld, J. Improvement of Stent Retriever Design and Efficacy of Mechanical Thrombectomy in a Flow Model. *Cardiovasc. Intervent. Radiol.* **2013**, *36*, 192–197. [CrossRef]
39. Kara, B.; Selcuk, H.H.; Erbahceci Salik, A.; Zalov, H.; Yildiz, O.; Gul, G.; Balkan, B. Single-Center Experience with the Tigertriever Device for the Recanalization of Large Vessel Occlusions in Acute Ischemic Stroke. *J. Neurointerv. Surg.* **2019**, *11*, 455–459. [CrossRef]

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Systematic Review

Current Trends in Gait Rehabilitation for Stroke Survivors: A Scoping Review of Randomized Controlled Trials

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Abstract: Background: Stroke stands as a significant global health concern, constituting a leading cause of disability worldwide. Rehabilitation interventions are crucial in aiding the recovery of stroke patients, contributing to an overall enhancement in their quality of life. This scoping review seeks to identify current trends in gait rehabilitation for stroke survivors. Methods: The review followed the methodological framework suggested by Arksey and O'Malley. Electronic databases, such as CINAHL Complete, MEDLINE Complete, and Nursing & Allied Health Collection, were systematically searched in November 2023. Inclusion criteria comprised papers published in either English or Portuguese from 2013 to 2023. Results: From the initial search, a total of 837 papers were identified; twenty-one papers were incorporated into this review. Thirteen distinct categories of gait rehabilitation interventions were identified, encompassing diverse approaches. These categories comprise conventional rehabilitation exercises, traditional gait training with integrated technology, and gait training supported by modern technologies. Conclusions: Although traditional rehabilitation exercises have historically proven effective in aiding stroke survivors, a recent trend has emerged, emphasizing the development and integration of innovative therapeutic approaches that harness modern technologies.

Keywords: stroke; stroke rehabilitation; rehabilitation; gait; exercise therapy; physical therapy

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1. Introduction

Stroke stands as a substantial global health issue, holding the position of second-leading cause of mortality and the third-leading cause of disability on a worldwide scale.

The burden of stroke is staggering, with six and a half million deaths recorded in 2019, along with over 12.2 million new stroke cases and a prevalence of 101 million stroke survivors [1]. These data emphasize the considerable burden of stroke on public health, encompassing mortality and disability, solidifying its status as one of our era's most prevalent and impactful diseases [2].

Functional changes are frequently observed among stroke survivors [3]. Patients commonly experience cognitive and motor impairments that affect balance, coordination, proprioception, muscle tone, muscle strength, and gait, making them prevalent sequelae of stroke [3,4].

A prior study revealed that up to 83% of stroke survivors experience balance impairment [5]. Motor deficits resulting from a stroke can significantly impact an individual's functional independence. Challenges in balance, coordination, muscle strength, and gait often lead to difficulties in performing basic activities of daily living, such as walking, dressing, and eating. These limitations also impact stroke survivors' abilities to engage in social interactions, pursue leisure activities, and return to work after a stroke [6,7], leaving individuals dependent on others for support and assistance, impeding their sense of autonomy and self-reliance. Moreover, balance impairments significantly contribute to adverse

outcomes following a stroke, including an increased risk of falls [8,9], fall-related injuries such as fractures [10], fear of falling [11], and even mortality [12]. Furthermore, a previous investigation established a correlation between balance deficits in the acute stage of stroke and subsequent cognitive impairment one year post-stroke [13].

The repercussions of a stroke are severe, resulting in various physical, cognitive, and emotional challenges. The impact extends beyond individual health, significantly influencing overall wellbeing and the capacity for an independent and fulfilling life [14,15]. Effectively addressing these challenges through gait rehabilitation enhances their quality of life and facilitates their reintegration into society [16].

Rehabilitation interventions are crucial in assisting stroke survivors in recovering motor function and enhancing their overall quality of life. By improving mobility, motor skills, and functional abilities, stroke survivors can achieve greater independence, leading to a more fulfilling and satisfying life post-stroke [17,18].

The management of stroke demands specialized care from healthcare professionals in both hospital and community settings. Survivors often require comprehensive rehabilitation and support to regain functional abilities and adapt to a new reality [19,20]. Families of stroke survivors also face significant adjustments as they navigate unfamiliar challenges and seek ways to provide necessary care and assistance [21,22].

Gait rehabilitation is crucial in stroke survivors' comprehensive recovery and functional independence [23]. As stroke remains a leading cause of disability worldwide, exploring current trends in gait rehabilitation for this population is of utmost importance.

Developing effective rehabilitation programs after stroke is imperative to address this pressing health issue. By identifying and understanding the impact of rehabilitation interventions on gait recovery, we can enhance the rehabilitation process for stroke survivors, ultimately improving their functional independence and overall quality of life. Therefore, this review seeks to identify current trends in gait rehabilitation for stroke survivors.

2. Methods

The current scoping review adheres to the methodological framework outlined by Arksey and O'Malley [24], which encompasses five distinct stages. Furthermore, to strengthen the scoping study methodology and ensure consistent reporting, we incorporated recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [25].

2.1. Stage 1: Identifying Research Questions

The initial stage involves formulating a precise research question that guides the review. The research question framed for this review was: What are the current trends in gait rehabilitation for stroke survivors?

2.2. Stage 2: Identifying Relevant Studies

On 10 November 2023, the initial search occurred across three databases on the EBSCOhost research platform: CINAHL, MEDLINE, and Nursing & Allied Health Collection.

A search strategy was planned using the Population, Concept, Context (PCC) framework, incorporating the MeSH terms.

The search strategy employed in CINAHL Complete was as follows:

S1: "Stroke"
S2: "Rehabilitation"
S3: "Gait"

Combined search: S1 AND S2 AND S3.

The inclusion/exclusion criteria are outlined in Table 1.

Table 1. Inclusion/exclusion criteria.

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Stroke survivors; Adults $\geq$ 18 years old.	Other health conditions besides stroke; Participants < 18 years old.
Concept	Studies that explore interventions for promoting gait.	Studies that do not explore interventions for promoting gait.
Context	Studies conducted in rehabilitation settings.	Studies conducted in non-rehabilitation settings.
Study design	Randomized controlled trials focusing on interventions that promote gait in stroke survivors.	Other type of studies.

The search was limited to articles published between 2013 and 2023.

Two researchers (J.T. and J.B.F.) independently performed the search, stages 2 to 4.

Given constraints in translation resources, the review excluded papers published in languages other than English or Portuguese.

2.3. Stage 3: Study Selection

All citations were imported into Rayyan—an AI-powered tool for Systematic Literature Reviews, where duplicate citations were identified and eliminated. Subsequently, the citations underwent title and abstract relevance screening. We examined the full text of pertinent papers, including those that met the study criteria for this review.

In cases of uncertainty regarding whether an article fits the review criteria, it proceeded to the subsequent phase. Reviewers held regular meetings throughout the screening to resolve conflicts and address any uncertainties about selecting papers. A third reviewer (S.F.) made the final and conclusive decision if any disagreements occurred.

2.4. Stage 4: Data Charting

A systematic approach was used to retrieve data. Two reviewers, J.T. and J.B.F., extracted data using a customized instrument to collect relevant information addressing the research question. The extracted data encompassed general details (author's name, publication year, title, and country), methodological specifics (study design and aim), and results (interventions employed by health professionals for gait rehabilitation in stroke survivors). Subsequently, all authors thoroughly reviewed and discussed the final data extraction chart.

2.5. Stage 5: Collating, Summarizing, and Reporting the Results

Researchers prepared a PRISMA flow diagram illustrating the study identification, screening, and selection process (Figure 1). To organize and summarize the data, a data-driven thematic analysis was implemented, adhering to the guidelines established by Braun et al. [26]. Two researchers, J.T. and S.F., independently carried out the data review, employing manual coding and analysis to identify recurrent themes in the data.

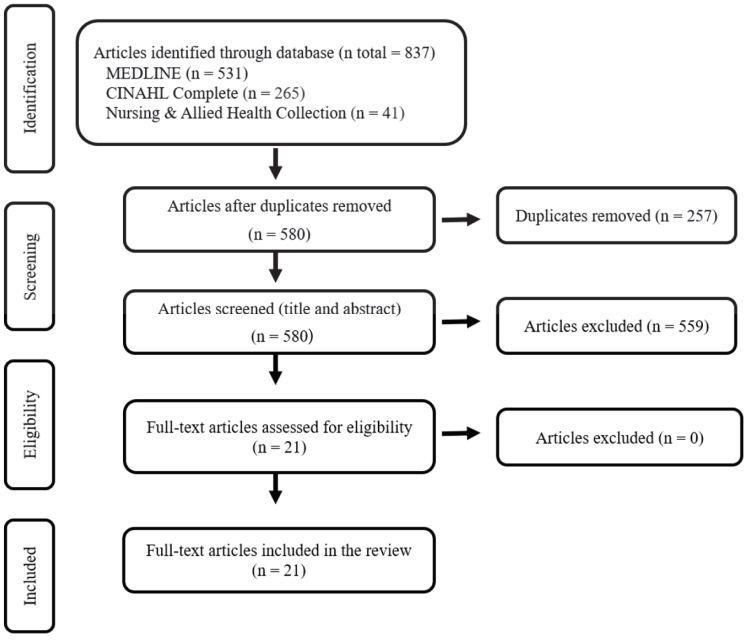

Figure 1. PRISMA flow chart for study selection.

3. Results

The initial search resulted in 837 potentially relevant articles. After removing duplicates and conducting relevance screening based on title and abstract, 517 articles were excluded. Subsequently, 21 articles met the eligibility criteria, full articles were reviewed, and were considered suitable for the review. Figure 1 illustrates the flow chart depicting the screening process.

The 21 included studies spanned the period from 2013 to 2023. Among the 21 studies, 10 were conducted in South Korea [27–36], 1 in North Korea [37], 1 in Poland [38], 1 in Serbia [39], 1 in Pakistan [40], 1 in United States of America [41], 1 in Italy [42], 1 in Turkey [43], 1 in Egypt [44], 1 in The Netherlands [45], 1 in Taiwan [46] and another in China [47] (Table 2).

Data analysis uncovered a range of interventions to enhance gait in stroke survivors. The interventions were classified into 13 groups, and each of these categories is explained below.

Table 2. Data extraction and synthesis.

Author/Year/Country	Study Design/Study Aim	Intervention
Bang and Shin [27] (2016) South Korea	Randomized controlled trial To compare the effects of robot-assisted gait training versus treadmill on spatiotemporal gait parameters, balance, and activities-specific balance confidence with stroke patients.	Robot-assisted gait training
Cha et al. [28] (2014) South Korea	Randomized controlled trial To investigate the effect of intensive gait training with rhythmic auditory stimulation on postural control and gait performance in individuals with chronic hemiparetic stroke.	Rhythmic auditory stimulation

Table 2. *Cont.*

Author/Year/Country	Study Design/Study Aim	Intervention
Choi et al. [29] (2017) South Korea	Randomized controlled trial To investigate the effect of whole-body vibration combined with treadmill training on walking performance in patients with chronic stroke.	Vibration therapy
Druzbicki et al. [38] (2015) Poland	Randomized controlled trial To evaluate the effects of gait training using a treadmill with and without visual biofeedback in patients late after stroke and to compare both training methods.	Visual biofeedback
Dujović et al. [39] (2017) Serbia	Single-blind randomized trial To evaluate the efficacy of an additional novel FES system to conventional therapy in facilitating motor recovery in the lower extremities and improving walking ability after stroke.	Functional electrical stimulation
Ha and Sung [37] (2020) North Korea	Randomized controlled trial To investigate the effect of Fresnel prism glasses on balance and gait in stroke patients with hemiplegia.	Fresnel prism glasses
Hong et al. [30] (2020) South Korea	Randomized controlled trial To determine whether cognitive task training improves walking and balancing abilities for stroke survivors.	Dual-task training
Hwang et al. [31] (2015) South Korea	Randomized controlled trial To investigate the effects of treadmill training with tilt sensor FES on the balance, gait, and muscle architecture of the tibialis anterior in stroke survivors.	Functional electrical stimulation
Iqbal et al. [40] (2020) Pakistan	Randomized controlled trial To compare the effectiveness of dual task-specific training and conventional physical therapy in the ambulation of patients with chronic stroke.	Dual-task training
Kang et al. [32] (2021) South Korea	Randomized controlled trial To investigate the effect of walking training with a weight support feedback cane on chronic stroke patients' lower limb muscle activity and gait ability.	Gait Assistive Devices
Kelley et al. [41] (2013) United States of America	Blinded randomized controlled trial To compare the effectiveness of robotic-assisted body weight-supported treadmill training using the Lokomat® for over-ground gait training in adults with chronic stroke.	Robot-assisted gait training
Kim and Lee [33] (2013) South Korea	Randomized controlled trial To compare the effects of action observation and motor imagery training on recovery from chronic stroke.	Action observation training and motor imagery training
Kim et al. [34] (2017) South Korea	Randomized controlled trial To examine the effect of progressive backward body weight-supported treadmill training on gait in chronic stroke patients with hemiplegic gait.	Backwards walking
Lee et al. [35] (2017) South Korea	Randomized controlled trial To investigate the effects of a wearable tubing assistive walking device on gait parameters (gait speed, cadence, step length, and stride length on affected and less affected sides) in patients with stroke.	Gait Assistive Devices
Moon and Kim [36] (2017) South Korea	Randomized controlled trial To investigate the effects of the newly developed Spine Balance three-dimensional (3D) system on chronic stroke patients' trunk strength and gait abilities.	3D Spine Balance System

Table 2. *Cont.*

Author/Year/Country	Study Design/Study Aim	Intervention
Munari et al. [42] (2020) Italy	Randomized controlled trial To compare the effects of backward treadmill training versus standard forward treadmill training on motor impairment in patients with chronic stroke receiving botulinum toxin type A Therapy.	Backwards walking
Mustafaoglu et al. [43] (2020) Turkey	Randomized controlled trial To investigate the effects of robot-assisted gait training on mobility, activities of daily living, and quality of life in stroke Rehabilitation.	Robot-assisted gait training
Saleh et al. [44] (2019) Egypt	Randomized controlled trial To compare the effect of aquatic versus land motor dual-task training on chronic stroke patients' balance and gait.	Dual-task training
Timmermans et al. [45] (2021) The Netherlands	Randomized controlled trial To compare the efficacy of two walking-adaptability interventions: a novel treadmill-based C-Mill therapy and the standard overground FALLS program.	Augmented reality-based rehabilitation
Yang [46] (2018) Taiwan	Randomized controlled trial To evaluate the effects of applying NMES over ankle dorsiflexion or plantar flexors on ankle control during walking and gait performance in chronic stroke patients.	Functional electrical stimulation
Yu et al. [47] (2020) China	Randomized controlled trial To examine the effects of body weight support Tai Chi training on balance control and walking function in stroke survivors with hemiplegia.	Tai Chi

3.1. Backwards Walking

In the study by Kim et al. [34], participants engaged in a program that combined backward treadmill walking with a gradual reduction in weight support. The systematic reduction in weight support occurred over four weeks, starting with a 40% reduction in the first week and a 10% reduction in subsequent weeks. Participants maintained an average speed ranging from 0.08 to 0.22 m/s, with a 0.1 km/h speed increment introduced at each session. To assist during training, two physical therapists played crucial roles—one positioned behind the subject for weight support and movement guidance and another set by the paretic leg to aid in motor control throughout the gait cycle.

In contrast, the control group underwent conventional forward treadmill training with matched duration and frequency. Results showed that the intervention group exhibited improvements in all dependent variables by week four compared to the control group. In the Munari et al. [42] study, both groups started treadmill training at 60% of their baseline over-ground self-selected speed, determined during gait analysis, with a 1% incline. The findings showed significant improvement in the 10 m Walking Test and stabilometry assessment post-treatment. Remarkably, superior enhancements in both gait and balance were noted following backward treadmill training compared to forward treadmill training.

3.2. Tai Chi

Yu et al. [47] conducted a study in which participants wore a harness connected to an overhead suspension system, supporting a specific percentage of their body weight. The intervention was based on seven steps from the 24-form simplified Tai Chi recommended by the State Sports General Administration of China, encompassing forward steps, backward steps, shuffle steps, empty steps, lunge steps, single-leg support, and turning around. These steps constitute the foundational elements of Tai Chi movements. The training primarily focused on lower limb movements, emphasizing endurance and weight shifts, rather than

upper limb actions. The training program followed a gradual progression corresponding to a 10% reduction in body weight support.

In contrast, the control group underwent conventional rehabilitation training. The findings reveal significant differences between groups in scores related to directional control during the limits-of-stability test. Additionally, the Tai Chi group exhibited superior scores in gait cycle time, step length, step velocity, and range of motion of the joints compared to the control group.

3.3. Dual-Task Training

Saleh et al. [44] investigated the impact of aquatic versus land motor dual-task training. The training involved walking while holding a ball and a cup of water and standing on a balance board with a moving cup in various walking conditions (forward, sideways, and backward). In the water-based exercises, participants performed these tasks in a large swimming pool, while the land group executed the same sequence on solid ground. Both groups showed significant improvements in all outcome variables post-treatment, with the water-based training group demonstrating superior results in overall stability, anteroposterior stability, mediolateral stability, walking speed, step length of affected and non-affected limbs, and time of support on the affected limb compared to the land-based group.

Hong et al. [30] employed dual-task training involving familiar traffic signals. The intervention incorporated scaffolds with marked starting and target points, monitors displaying visual cues for the cognitive task, and elastic bands controlling resistance amounts and difficulties. For the cognitive task training group, the task involved standing and moving the less-affected lower extremity in three hip flexion directions based on red and green cues resembling traffic lights on the monitor. Three traffic signals represented the directions, and colors and locations changed randomly. Cognitive balance training progressed in difficulty: without elastic bands, an elastic band, and a differently colored elastic band for increased resistance. Elastic bands were positioned around the ankle of the less-affected side.

The general task training group performed a similar lower extremity movement without the cognitive task. Significant differences were observed in both groups after the intervention. The cognitive task training group significantly improved all outcome scores after the intervention.

In the study by Iqbal et al. [40], participants in the dual-task training group walked backward, sideways, and forward while holding a 100 g sandbag. Additionally, they performed tasks such as picking up plastic cups in front of their feet. The control group received conventional physiotherapy, encompassing stretching, strengthening exercises, and gait training. Post-treatment assessments revealed a significant enhancement in the 10 m walk, cadence, step length, stride, and cycle time within the dual-task training group.

3.4. Action Observation Training and Motor Imagery Training

Kim and Lee [33] compared the effects of action observation and motor imagery training on stroke survivors. In the action observation training group, participants watched a 20 min task video. This was followed by 10 min of physical training with a therapist based on the video. The video featured adult models performing motions relevant to each participant's hemiplegia. The training program, divided into four stages, focused on trunk stability, mobility, sit-to-stand, weight shifting, and gait improvement. Each stage's video was viewed weekly to reduce individual deviations based on the hemiplegia side. In the motor imagery training group, participants spent 20 min on motor imagery through a computer speaker and 10 min of physical training based on the imagery program. The motor imagery program content mirrored the action observation training program. Participants trained on each stage's content for one week. All participants received neurodevelopmental therapy focusing on trunk and lower extremity movements, sit-to-stand, and gait patterns on level surfaces and stairs. The action observation training group significantly improved

gait speed, cadence, and single limb support compared to the physical training group. However, no significant differences were observed in any of the outcome measures.

3.5. Visual Biofeedback

Druzbicki et al. [38] assessed the impact of gait training using a treadmill, comparing outcomes with and without visual biofeedback. The intervention group utilized a Gait Trainer 2 treadmill featuring real-time visualization of foot placement and the designated foot positioning area. The intervention group engaged in gait training on the treadmill with visual biofeedback, which included step length, foot placement location, and an acoustic signal-confirming task execution accuracy. In contrast, the control group underwent treadmill training without biofeedback. The results indicated that the intervention group yielded superior outcomes, particularly in enhancing the gait cycle, duration of gait phases, and speed of the swing phase. The results indicated that the intervention group achieved superior outcomes, especially in improving the gait cycle, duration of gait phases, and speed of the swing phase.

3.6. Vibration Therapy

Choi et al. [29] explored the impact of whole-body vibration and treadmill training on walking performance using a side-alternating vibrator (Galileo 2000, Novotec, Nettetal, Germany, 2011). Whole-body vibration involved a maximum frequency of 30 Hz and an amplitude of 3 mm, lasting 45 s. Participants stood on the vibration platform with their feet parallel to the axis, lightly holding a support bar. Each session comprised six exercises, each lasting 45 s, including weight shifts, squats, anteroposterior weight shifts, forward lunges, one-leg standing, and deep squats. A 1 min break separated each exercise. The control group performed the identical exercise program minus vibration therapy. The vibration therapy group significantly improved walking speed, cadence, and temporal parameters. In contrast, the control group exhibited improvement solely in walking speed.

3.7. Functional Electrical Stimulation

Hwang et al. [31] used treadmill gait training combined with the WalkAide system, incorporating an inclination sensor for functional electrical stimulation. The WalkAide stimulator, a compact electronic device, was affixed to the common peroneal and anterior tibial nerves, delivering electrical stimulation based on knee flexion angles during walking. The WalkAnalyst program determined the optimal stimulus intensity, followed by treadmill gait training guided by the inclination sensor to facilitate ankle dorsiflexion. The findings suggested that gait training on a treadmill with functional electrical stimulation effectively enhanced balance, gait, and anterior tibial structure.

In the study by Dujović et al. [39], the Functional Electrical Stimulation group, electrical stimulation targeted the tibial nerve in the pre-swing phase and the common peroneal nerve in the swing phase, inducing ankle plantar flexion and dorsiflexion, respectively. The Functional Electrical included a stimulation unit, demultiplexer, clothing with integrated multi-pad electrodes, wireless inertial sensors, and a tablet PC with a dedicated application. The multi-pad electrode garment strategically placed around the knee stimulated the common peroneal and tibial nerves. The stimulator unit delivered a customized pulse train to the multi-pad electrode, with parameters set during calibration (frequency of 40 Hz and pulse width of 400 ms). Results revealed that combining functional electrical stimulation with conventional rehabilitation was more effective in improving walking speed, lower limb mobility, balance, and daily activities compared to conventional rehabilitation alone.

Yang et al. [46] utilized electromyographic-triggered neuromuscular electrical stimulation with two surface electrodes targeting the anterior or medial gastrocnemius of the tibialis. Electrodes were placed at motor points, and the stimulation frequency was set at 50 Hz with a pulse width of 0.2 ms, using a biphasic square wave. Each session lasted 20 min, with a stimulation cycle of 5:15. Participants actively performed dorsiflexion or plantar flexion during sessions based on electromyographic signals of maximal voluntary

contraction. Training intensity ranged from 50 mV to 0 mV to ensure a comfortable full range of motion. After the 20 min stimulation, participants engaged in 15 min of ambulation training with verbal cues emphasizing specific ankle movements. The study concluded that neuromuscular electrical stimulation applied to ankle dorsiflexion and ambulation training effectively strengthened muscles, reduced spasticity, and improved ankle control during push-off and gait performance. Similarly, using neuromuscular electrical stimulation to ankle plantar flexors with ambulation training positively affected gait temporal symmetry in chronic stroke survivors with insufficient ankle control.

3.8. Rhythmic Auditory Stimulation

Cha et al. [28] used rhythmic auditory stimulation in group sessions, incorporating personalized music tapes and a metronome tailored to individual musical preferences. This synchronization aimed to improve rhythmic perception and align with the walking patterns of participants.

The training started with participants becoming familiar with the music's rhythm and coordinating hand and foot movements to the beat. Participants were instructed to walk while synchronizing their movements with the music and metronome to facilitate a seamless transition to coordinated steps. Throughout the sessions, participants engaged in intensive gait exercises enriched by rhythmic auditory stimulation. As the training sessions advanced, the reliance on rhythmic stimulation was systematically reduced, prompting participants to practice intensive gait training independently. The researchers ultimately determined that this all-encompassing approach to intensive gait training, incorporating rhythmic auditory stimulation, significantly enhanced balance and gait performance among stroke survivors.

3.9. Gait Assistive Devices

Kang et al. [32] employed a Weight Support Feedback Cane and a smartphone application that quantitatively measured cane dependence during walking. The Weight Support Feedback Cane facilitated real-time assessment of cane dependence, displaying the information on the cable and the smartphone app. Participants determined a weight-bearing rate based on cane dependence, ranging from 60% to 30%, and made weekly adjustments. An audible signal alerted participants if the loaded weight exceeded the preset rate, continuing until it fell below the limit. Based on the baseline measurement of cane dependence, the weight-bearing rate progressively decreased by 10% weekly, from 60% to 30%. The gait success rate, documented by the smartphone app, influenced the reduction in the weight-bearing rate for the subsequent week.

Results demonstrated that both cane gait training methods (traditional vs. Weight Support Feedback Cane) significantly enhanced lower limb muscle activity and walking ability. The Weight Support Feedback Cane group exhibited more benefits than conventional cane gait training.

Lee et al. [35] explored the impact of a Wearable Tube-Assisted Walking Device on gait parameters in stroke survivors. The device comprises a pelvic belt, an elastic tube, and a conventional elastic orthosis created with an open sock and two strips of elastic material. Elastic tubing was employed to provide elasticity assistance, with patients using tubes half the length of their leg for the test. The application process involves placing the sock on the affected limb, attaching long and short straps on opposite sides, passing over the feet, and securing the pelvic belt. Within this setup, one tube end is affixed to a hole in the conventional elastic orthosis, while the other side is hooked into the pelvic girdle ring. The tubing generates superior traction force, aiding knee flexion during push-off and swing phases of gait by converting stored potential energy into kinetic energy. Results indicated that the Wearable Tube-Assisted Walking Device effectively enhanced gait speed, cadence, and stride length.

3.10. Fresnel Prism Glasses

Ha and Sung [37] explored the efficacy of prismatic Fresnel glasses in balance and gait training for stroke survivors on an electronic treadmill. The Fresnel prism, set at a 15-diopter deflection angle and tailored to individual patients, was applied contralaterally to the hemiplegia. This induced an adaptive effect, translating spatial information into retinal perceptual coordination. Despite no impact on visual perception, the prism significantly enhanced balance and walking ability in stroke patients with hemiplegia and no visual impairment. The use of Fresnel prismatic glasses, even in the absence of visual issues, positively influenced balance and gait training for stroke survivors, underscoring the therapeutic potential of these glasses in improving spatial movement and motor tasks.

3.11. 3D Spine Balance System

Moon and Kim [36] explored the impact of the newly developed three-dimensional (3D) Spine Balance system on stroke survivors. Subjects underwent 30 min of central nervous system development therapy, with the experimental group incorporating additional spinal stability exercises using the Spine Balance 3D system. The Spine Balance 3D system, equipped with diagnostic, exercise, and game modes, was utilized in exercise mode for the study. In this mode, the tilt angle was adjustable from 5° to 60° in eight directions. During training, the system tilted the entire body of subjects while maintaining a straight, neutral position, applying gravity to the torso for stability within the body's line of gravity. The pelvis, sacrum, and femur were secured, and participants crossed their arms over their chests under the inspector's control to prevent torso compensation against gravity. The slope gradually increased, incorporating different tilt angles and torque levels for varied training intensities. Results show that the Spine Balance 3D system enhanced trunk muscle strength and walking ability in chronic stroke patients more effectively than conventional training.

3.12. Augmented Reality-Based Training

Timmermans et al. [45] utilized augmented reality training to enhance walking adaptability. This involved the projection of gait-dependent contextual cues onto the treadmill surface to prompt step adjustments. The training regimen encompassed a variety of exercises, including navigating visual obstacles, adjusting foot positioning in response to regular or irregular sequences of stepping targets (goal-directed stepping), managing gait acceleration and deceleration within a moving projected walking area on the treadmill, tandem walking, and an interactive walking-adaptability game. In contrast, the standard overground program aimed to reduce post-stroke falls by incorporating walking-adaptability exercises. This program included an obstacle course with exercises on obstacle avoidance, foot positioning on uneven surfaces, tandem walking, and slalom walking. The results revealed no significant group differences for the primary outcome measure. Augmented reality training resulted in twice as many steps per session, with equal duration compared to the standard overground program.

3.13. Robot-Assisted Gait Training

Kelley et al. [41] examined the efficacy of robotic-assisted body weight-supported treadmill training utilizing the Lokomat®. In the intervention group, participants were supported by a harness connected to a body weight support system that was adjusted based on individual strength and conditioning levels. The weight was gradually decreased as tolerated. The Lokomat® facilitated sagittal plane assistance for hip and knee joint movements, mimicking a symmetrical reciprocal gait. Participants received visual feedback on their walking pattern through a mirror and a computer display illustrating bilateral hip and knee motions. The walking speed was gradually increased from 0.42 m per second (m/s) to a maximum of 0.89 m/s as tolerated. Guidance force, denoting the assistance provided by the robot-driven gait orthosis for moving the legs through prescribed sagittal plane motions, started at 100% for both legs and was subsequently reduced as participants

demonstrated proficiency in executing the movements. This study detected intragroup variations in the Fugl-Meyer Lower Extremity Motor score and Barthel Index from baseline to post-intervention and baseline to the 3-month follow-up. Nevertheless, no differences were observed between the two groups.

Bang and Shin [27] conducted a comparative analysis to assess the impact of robot-assisted gait training (utilizing Lokomat®) versus treadmill gait training, following a protocol like the Kelley et al. [41] study. The findings demonstrated differences between groups, with the intervention group exhibiting significantly higher gait speed, cadence, step length, and activities-specific balance confidence score than the control group. The robot-assisted gait training group also significantly reduced the double limb support period. Mustafaoglu et al. [43] adopted a protocol similar to previous studies involving the application of Lokomat®. However, they organized participants into three groups: a conventional training group, a robot-assisted gait training group, and a combined training group that received both conventional and robot-assisted gait training. Their findings indicate the mean change in all primary and secondary outcomes, except the Fast 10 m Walk Test. In the subgroup analysis, the combined training group demonstrated significant improvements in the Barthel Index, Stroke-Specific Quality of Life Scale, 6 min Walk Test, and Stair Climbing Test compared to the other two groups.

4. Discussion

The scoping review delves into the evolving landscape of gait training for stroke patients, shedding light on emerging trends extending beyond the conventional rehabilitation exercises traditionally employed in stroke therapy (Figure 2).

Figure 2. Categories of gait rehabilitation interventions.

By synthesizing various studies and identifying patterns and trends in gait rehabilitation, this review provides insights into the rationale behind adopting novel interventions, highlighting their advantages over traditional approaches. Moreover, the review offers a holistic view of the current state of gait training, emphasizing the importance of incorporating innovative strategies to enhance patient outcomes and quality of life.

Furthermore, the review is a practical guide for professionals considering incorporating these interventions into their practice. By identifying and describing interventions, the review enables professionals to make informed decisions about integrating new approaches into their service. This state of play enhances the knowledge base within the field and empowers practitioners to adapt and evolve their treatment protocols to meet stroke survivors' needs better.

While recognizing the well-established effectiveness of conventional rehabilitation exercises for stroke survivors, this review identifies several trends in gait training that surpass traditional approaches: (1) The review highlights a shift towards developing and adopting novel interventions beyond traditional rehabilitation exercises. These interventions include Tai Chi [47], dual-task training [30,40,44], action observation training [33], visual biofeedback [38], vibration therapy [29], and robot-assisted gait training [27,41,43]; (2) There is a trend towards adopting a holistic approach to gait rehabilitation, which involves addressing physical, cognitive, and sensory aspects of gait recovery. Interventions like dual-task [30,40,44] and action observation training [33] incorporate cognitive components, while others, such as vibration therapy [29], target sensory stimulation; (3) There is an emphasis on individualized treatment plans tailored to the specific needs and capabilities of stroke survivors. Interventions like robot-assisted gait training [27,41,43] and wearable assistive devices [32,35] allow customized adjustments and feedback based on individual progress and abilities; and (4) Many emerging interventions leverage technological advancements to enhance gait training outcomes. Examples include wearable sensors, robotic devices, and biofeedback systems to provide real-time feedback and improve patient engagement during rehabilitation.

Several studies have explored a range of gait rehabilitation approaches, including traditional methods with slight modifications such as backward walking through treadmill training with body weight support [34] and straightforward treadmill training [42]. Additionally, the innovative practice of Tai Chi with body weight support has proven beneficial for stroke survivors, leading to significant improvements in directional control and gait patterns [47]. Dual-task training has emerged as a promising avenue, with studies investigating its application through motor tasks in both aquatic and terrestrial environments [44], exclusively in terrestrial settings [30,40]. These varied approaches underscore the importance of introducing exercise variations into traditional practices to optimize rehabilitation outcomes. Action observation and motor imagery training [33] represent another innovative dimension in gait rehabilitation after a stroke. These methods involve integrating conventional exercises with video-based demonstrations and mental visualization, emphasizing the strategic role of instructional materials in optimizing the effectiveness of rehabilitation interventions.

Blending complementary interventions with conventional rehabilitation exercises demonstrates considerable potential for enhancing treatment outcomes in stroke survivors [48].

Integrating complementary interventions alongside conventional rehabilitation exercises holds significant promise for enhancing treatment outcomes in stroke survivors [48]. By incorporating diverse approaches, healthcare professionals aim to tailor rehabilitation experiences for each patient, leading to improved outcomes [49,50]. These novel strategies target the physical aspects of gait and emphasize motivating and engaging patients, enhancing adherence to rehabilitation plans [23,51]. Incorporating interactive therapies can make rehabilitation more enjoyable, potentially improving compliance with prescribed exercises [52,53].

Innovative therapeutic options in stroke rehabilitation, such as augmented reality-based training, robotic-assisted therapy, rhythmic auditory stimulation, and functional electrical stimulation, tap into survivors' various physical and cognitive abilities. This multi-faceted approach to gait training may promote neural plasticity, encouraging the brain to adapt and reorganize in response to the specific demands of each intervention. Promoting neural plasticity is crucial for stroke survivors, as it enhances the brain's ability

to form new connections, compensate for damaged areas, and support functional recovery [54–56]. Therefore, incorporating these innovative therapies represents a promising strategy to optimize rehabilitation outcomes and improve overall functional abilities in survivors. For instance, visual biofeedback [38] in gait rehabilitation demonstrates substantial improvements when combined with treadmill training. Real-time visualization of foot placement and acoustic signals provides an interactive and adaptive training environment. Body vibration Therapy [29] introduces an additional sensory element to treadmill training, offering an innovative approach to optimizing gait performance. Functional electrical stimulation [31,39] incorporates adaptive stimulation, targeting specific nerves during the gait cycle. Intervention based on rhythmic auditory stimulation [28] introduces music as a synchronizing method to improve rhythmic coordination in gait, highlighting the importance of auditory perception in rehabilitation and complementing visual stimuli.

The evolution of rehabilitation highlights a notable shift towards interventions centered exclusively on modern technology, exemplified by innovations such as the weight-bearing feedback cane [32]. This approach underscores the ingenuity in real-time monitoring of weight-bearing during gait, incorporating sound feedback and customizable weight support. Prismatic Fresnel glasses [37] contribute a personalized dimension to visual intervention for hemiplegic patients without visual impairment, offering individually adjusted solutions. The 3D spine balance system [36] utilizes a three-dimensional device for stability exercises, showcasing targeted and specific technological applications for post-stroke patients. Augmented reality-based Rehabilitation [45] represents another stride in leveraging technology, employing interactive projection on the treadmill to generate dynamic and adaptive responses, enhancing the efficiency of gait recovery. Robot-assisted gait training, particularly with Lokomat® [27,41,43], is an innovative and valuable approach, providing specific benefits in personalization, control, and visual feedback. Combining conventional training with Lokomat® training [43] can amplify health gains and improve the quality of life for stroke survivors. This integration showcases the evolving landscape of rehabilitation, emphasizing the strategic incorporation of advanced technologies to enhance the precision and efficacy of interventions.

A notable trend identified in this review is using robotic devices to aid gait training. Robotic equipment offers several advantages, including increased patient independence to engage in more repetitive and customized training sessions. These devices provide precise control and monitoring of movements, allowing therapists to tailor rehabilitation programs to individual needs and track progress effectively [57]. Moreover, incorporating robotic devices has the potential to program rehabilitation exercises for patients to perform multiple daily sessions. This scheduling flexibility provides stroke survivors with increased opportunities for practice and eases the burden on healthcare professionals by reducing the need for constant supervision during each session [58].

The availability of robotic-assisted gait training presents a promising avenue for stroke rehabilitation, as it addresses the demand for intensive, repetitive, and task-specific exercises while optimizing the use of healthcare resources [59–61]. However, despite the promising advantages of robotic-assisted gait training in stroke rehabilitation, these technological devices are not widely utilized in current rehabilitation practices. One significant barrier to their widespread adoption is the substantial financial investment required [62]. Robotic devices often come with high costs that many rehabilitation centers and hospitals may find challenging to afford within their budget constraints.

Furthermore, these devices usually necessitate specialized training and supervision from healthcare professionals, making them challenging to use independently by stroke survivors in their homes [63]. Moreover, the space and setup required for these devices may not be feasible in typical home environments, further hindering their application outside clinical settings [64,65]. As this technology continues to evolve, assessing its effectiveness, cost-effectiveness, and long-term impact on functional outcomes is essential to effectively guide its integration into clinical practice. Long-term follow-up studies and cost-effectiveness analysis are particularly crucial in this regard. By conducting further

research and evaluation, healthcare professionals can better understand the potential benefits and limitations of robotic-assisted gait training, thus optimizing its implementation and maximizing its positive impact on stroke rehabilitation outcomes.

Innovative rehabilitation interventions have the potential to motivate stroke survivors to engage in rehabilitation programs by offering fresh and varied approaches compared to conventional training methods [66,67]. These interventions provide stimulating challenges that encourage active rehabilitation involvement, fostering patient motivation and engagement. Additionally, they offer immediate and visible feedback on patient performance, helping individuals understand their progress and feel motivated to continue with the rehabilitation program.

The integration of complementary interventions alongside conventional exercises further enhances treatment outcomes for stroke survivors. By combining traditional rehabilitation exercises with innovative approaches, patients benefit from a more comprehensive and holistic approach to rehabilitation. These complementary interventions target different aspects of recovery, addressing cognitive, sensory, and motor functions. As a result, stroke survivors experience enhanced engagement, improved functional outcomes, and a higher likelihood of sustained progress throughout their rehabilitation [63,68,69].

Strengths and Limitations

A notable strength of this review lies in its dedicated focus on randomized controlled trials. Our findings offer valuable insights into several approaches for gait rehabilitation, meticulously studied in experimental settings. The comprehensive overview of these interventions fosters a deep understanding of their techniques and methodologies, providing health professionals with the knowledge to replicate them confidently. This emphasis on evidence-based practices enhances the applicability and effectiveness of gait rehabilitation strategies for stroke survivors.

One potential limitation of this review is its inclusion of studies published exclusively in English or Portuguese. This approach introduces language bias and may overlook valuable research in other languages. Consequently, the comprehensiveness of the review could be limited by not considering a broader range of studies from diverse linguistic sources. Furthermore, despite analyzing many results, the restriction of the search to the EBSCO-host research platform is one of the major limitations that may have led to the exclusion of relevant studies from other sources such as Cochrane Central Register of Controlled Trials (CENTRAL) and Embase. Acknowledging these limitations is crucial to ensure transparency and a balanced interpretation of the review's findings.

5. Conclusions

While conventional rehabilitation exercises have long been effective in treating stroke survivors, recent years have seen an increase in the development and integration of new therapeutic approaches involving modern technologies. These complementary interventions improve gait recovery by providing innovative and engaging options for stroke survivors. The complementarity of conventional and technological exercises highlights the importance of an integrated approach in searching for more comprehensive results adapted to each patient's needs.

However, more research is needed to determine these new interventions' effectiveness and long-term benefits, which may guide the future direction of stroke rehabilitation strategies.

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References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet. Neurol.* **2021**, *20*, 795–820. [CrossRef]
2. Donkor, E.S. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res. Treat.* **2018**, *2018*, 3238165. [CrossRef]
3. Gittins, M.; Lugo-Palacios, D.; Vail, A.; Bowen, A.; Paley, L.; Bray, B.; Tyson, S. Stroke impairment categories: A new way to classify the effects of stroke based on stroke-related impairments. *Clin. Rehabil.* **2021**, *35*, 446–458. [CrossRef]
4. Yao, Y.Y.; Wei, Z.J.; Zhang, Y.C.; Li, X.; Gong, L.; Zhou, J.W.; Wang, Y.; Zhang, Y.Y.; Wang, R.P. Functional Disability After Ischemic Stroke: A Community-Based Cross-Sectional Study in Shanghai, China. *Front. Neurol.* **2021**, *12*, 649088. [CrossRef]
5. Tyson, S.F.; Hanley, M.; Chillala, J.; Selley, A.; Tallis, R.C. Balance disability after stroke. *Phys. Ther.* **2006**, *86*, 30–38. [CrossRef]
6. Kim, Y.W. Update on Stroke Rehabilitation in Motor Impairment. *Brain NeuroRehabil.* **2022**, *15*, e12. [CrossRef] [PubMed]
7. Norlander, A.; Iwarsson, S.; Jönsson, A.C.; Lindgren, A.; Månsson Lexell, E. Living and ageing with stroke: An exploration of conditions influencing participation in social and leisure activities over 15 years. *Brain Inj.* **2018**, *32*, 858–866. [CrossRef] [PubMed]
8. Bower, K.; Thilarajah, S.; Pua, Y.H.; Williams, G.; Tan, D.; Mentiplay, B.; Denehy, L.; Clark, R. Dynamic balance and instrumented gait variables are independent predictors of falls following stroke. *J. Neuroeng. Rehabil.* **2019**, *16*, 3. [CrossRef] [PubMed]
9. Goljar, N.; Globokar, D.; Puzić, N.; Kopitar, N.; Vrabič, M.; Ivanovski, M.; Vidmar, G. Effectiveness of a fall-risk reduction programme for inpatient rehabilitation after stroke. *Disabil. Rehabil.* **2016**, *38*, 1811–1819. [CrossRef]
10. Goto, Y.; Otaka, Y.; Suzuki, K.; Inoue, S.; Kondo, K.; Shimizu, E. Incidence and circumstances of falls among community-dwelling ambulatory stroke survivors: A prospective study. *Geriatr. Gerontol. Int.* **2019**, *19*, 240–244. [CrossRef]
11. Schinkel-Ivy, A.; Inness, E.L.; Mansfield, A. Relationships between fear of falling, balance confidence, and control of balance, gait, and reactive stepping in individuals with sub-acute stroke. *Gait Posture* **2016**, *43*, 154–159. [CrossRef] [PubMed]
12. Ramnemark, A.; Nilsson, M.; Borssén, B.; Gustafson, Y. Stroke, a major and increasing risk factor for femoral neck fracture. *Stroke* **2000**, *31*, 1572–1577. [CrossRef] [PubMed]
13. Ursin, M.H.; Bergland, A.; Fure, B.; Tørstad, A.; Tveit, A.; Ihle-Hansen, H. Balance and Mobility as Predictors of Post-Stroke Cognitive Impairment. *Dement. Geriatr. Cogn. Disord. Extra* **2015**, *5*, 203–211. [CrossRef] [PubMed]
14. Hartley, T.; Burger, M.; Inglis-Jassiem, G. Post stroke health-related quality of life, stroke severity and function: A longitudinal cohort study. *Afr. J. Disabil.* **2022**, *11*, 947. [CrossRef] [PubMed]
15. Poomalai, G.; Prabhakar, S.; Sirala Jagadesh, N. Functional Ability and Health Problems of Stroke Survivors: An Explorative Study. *Cureus* **2023**, *15*, e33375. [CrossRef] [PubMed]
16. Olawale, O.A.; Usman, J.S.; Oke, K.I.; Osundiya, O.C. Evaluation of Predictive Factors Influencing Community Reintegration in Adult Patients with Stroke. *J. Neurosci. Rural Pract.* **2018**, *9*, 6–10. [CrossRef] [PubMed]
17. Lin, S.H.; Dionne, T.P. Interventions to Improve Movement and Functional Outcomes in Adult Stroke Rehabilitation: Review and Evidence Summary. *J. Particip. Med.* **2018**, *10*, e3. [CrossRef]
18. Vincent-Onabajo, G.; Shaphant, N.D. Relationship between functional independence and psychosocial quality of life of stroke survivors undergoing outpatient rehabilitation in Maiduguri, Nigeria. *J. Patient-Rep. Outcomes* **2019**, *3*, 18. [CrossRef]
19. Lip, G.Y.H.; Lane, D.A.; Lenarczyk, R.; Boriani, G.; Doehner, W.; Benjamin, L.A.; Fisher, M.; Lowe, D.; Sacco, R.L.; Schnabel, R.; et al. Integrated care for optimizing the management of stroke and associated heart disease: A position paper of the European Society of Cardiology Council on Stroke. *Eur. Heart J.* **2022**, *43*, 2442–2460. [CrossRef]
20. Kernan, W.N.; Viera, A.J.; Billinger, S.A.; Bravata, D.M.; Stark, S.L.; Kasner, S.E.; Kuritzky, L.; Towfighi, A.; American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; et al. Primary Care of Adult Patients After Stroke: A Scientific Statement from the American Heart Association/American Stroke Association. *Stroke* **2021**, *52*, e558–e571. [CrossRef]
21. Kalavina, R.; Chisati, E.; Mlenzana, N.; Wazakili, M. The challenges and experiences of stroke patients and their spouses in Blantyre, Malawi. *Malawi Med. J. J. Med. Assoc. Malawi* **2019**, *31*, 112–117. [CrossRef]
22. Lu, Q.; Mårtensson, J.; Zhao, Y.; Johansson, L. Needs of family members caring for stroke survivors in china: A deductive qualitative content analysis study by using the caregiver task inventory-25. *BMC Geriatr.* **2022**, *22*, 96. [CrossRef] [PubMed]
23. Tavares, E.; Coelho, J.; Rogado, P.; Correia, R.; Castro, C.; Fernandes, J.B. Barriers to Gait Training among Stroke Survivors: An Integrative Review. *J. Funct. Morphol. Kinesiol.* **2022**, *7*, 85. [CrossRef] [PubMed]
24. Arksey, H.; O'Malley, L. Scoping Studies: Towards a Methodological Framework. *Int. J. Soc. Res.* **2005**, *8*, 19–32. [CrossRef]

25. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.J.; Horsley, T.; Weeks, L.; et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [CrossRef] [PubMed]
26. Braun, V.; Clarke, V.; Hayfield, N.; Terry, G. *Handbook of Research Methods in Health Social Sciences*; Springer: Berlin/Heidelberg, Germany, 2019.
27. Bang, D.-H.; Shin, W.-S. Effects of robot-assisted gait training on spatiotemporal gait parameters and balance in patients with chronic stroke: A randomized controlled pilot trial. *NeuroRehabilitation* **2016**, *38*, 343–349. [CrossRef] [PubMed]
28. Cha, Y.; Kim, Y.; Hwang, S.; Chung, Y. Intensive gait training with rhythmic auditory stimulation in individuals with chronic hemiparetic stroke: A pilot randomized controlled study. *NeuroRehabilitation* **2014**, *35*, 681–688. [CrossRef]
29. Choi, W.; Han, D.; Kim, J.; Lee, S. Whole-Body Vibration Combined with Treadmill Training Improves Walking Performance in Post-Stroke Patients: A Randomized Controlled Trial. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2017**, *23*, 4918–4925. [CrossRef]
30. Hong, S.-Y.; Moon, Y.; Choi, J.-D. Effects of Cognitive Task Training on Dynamic Balance and Gait of Patients with Stroke: A Preliminary Randomized Controlled Study. *Med. Sci. Monit. Basic Res.* **2020**, *26*, e925264. [CrossRef]
31. Hwang, D.-Y.; Lee, H.-J.; Lee, G.-C.; Lee, S.-M. Treadmill training with tilt sensor functional electrical stimulation for improving balance, gait, and muscle architecture of tibialis anterior of survivors with chronic stroke: A randomized controlled trial. *Technol. Health Care Off. J. Eur. Soc. Eng. Med.* **2015**, *23*, 443–452. [CrossRef]
32. Kang, Y.S.; Oh, G.B.; Cho, K.H. Walking Training with a Weight Support Feedback Cane Improves Lower Limb Muscle Activity and Gait Ability in Patients with Chronic Stroke: A Randomized Controlled Trial. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2021**, *27*, e931565. [CrossRef]
33. Kim, J.-H.; Lee, B.-H. Action observation training for functional activities after stroke: A pilot randomized controlled trial. *NeuroRehabilitation* **2013**, *33*, 565–574. [CrossRef]
34. Kim, K.H.; Lee, K.B.; Bae, Y.-H.; Fong, S.S.M.; Lee, S.M. Effects of progressive backward body weight suppoted treadmill training on gait ability in chronic stroke patients: A randomized controlled trial. *Technol. Health Care Off. J. Eur. Soc. Eng. Med.* **2017**, *25*, 867–876. [CrossRef] [PubMed]
35. Lee, S.-M.; Cynn, H.-S.; Yi, C.-H.; Yoon, T.-L.; Lee, J.-H. Wearable tubing assistive walking device immediately enhances gait parameters in subjects with stroke: A randomized controlled study. *NeuroRehabilitation* **2017**, *40*, 99–107. [CrossRef] [PubMed]
36. Moon, S.-J.; Kim, T.-H. Effect of three-dimensional spine stabilization exercise on trunk muscle strength and gait ability in chronic stroke patients: A randomized controlled trial. *NeuroRehabilitation* **2017**, *41*, 151–159. [CrossRef] [PubMed]
37. Ha, S.-Y.; Sung, Y.-H. Effects of Fresnel prism glasses on balance and gait in stroke patients with hemiplegia: A randomized controlled trial pilot study. *Technol. Health Care Off. J. Eur. Soc. Eng. Med.* **2020**, *28*, 625–633. [CrossRef] [PubMed]
38. Druzbicki, M.; Guzik, A.; Przysada, G.; Kwolek, A.; Brzozowska-Magon, A. Efficacy of Gait Training Using a Treadmill with and without Visual Biofeedback in Patients After Stroke: A Randomized Study. *J. Rehabil. Med.* **2015**, *47*, 419–425. [CrossRef] [PubMed]
39. Dujović, S.D.; Malešević, J.; Maleševićc, N.; Vidaković, A.S.; Bijelić, G.; Keller, T.; Konstantinović, L. Novel multi-pad functional electrical stimulation in stroke patients: A single-blind randomized study. *NeuroRehabilitation* **2017**, *41*, 791–800. [CrossRef] [PubMed]
40. Iqbal, M.; Arsh, A.; Hammad, S.M.; Haq, I.U.; Darain, H. Comparison of dual task specific training and conventional physical therapy in ambulation of hemiplegic stroke patients: A randomized controlled trial. *J. Pak. Med. Assoc.* **2020**, *70*, 7–10. [CrossRef]
41. Kelley, C.P.; Childress, J.; Boake, C.; Noser, E.A. Over-ground and robotic-assisted locomotor training in adults with chronic stroke: A blinded randomized clinical trial. *Disabil. Rehabil. Assist. Technol.* **2013**, *8*, 161–168. [CrossRef]
42. Munari, D.; Serina, A.; Disarò, J.; Modenese, A.; Filippetti, M.; Gandolfi, M.; Smania, N.; Picelli, A. Combined effects of backward treadmill training and botulinum toxin type A therapy on gait and balance in patients with chronic stroke: A pilot, single-blind, randomized controlled trial. *NeuroRehabilitation* **2020**, *46*, 519–528. [CrossRef] [PubMed]
43. Mustafaoglu, R.; Erhan, B.; Yeldan, I.; Gunduz, B.; Tarakci, E. Does robot-assisted gait training improve mobility, activities of daily living and quality of life in stroke? A single-blinded, randomized controlled trial. *Acta Neurol. Belg.* **2020**, *120*, 335–344. [CrossRef] [PubMed]
44. Saleh, M.S.M.; Rehab, N.I.; Aly, S.M.A. Effect of aquatic versus land motor dual task training on balance and gait of patients with chronic stroke: A randomized controlled trial. *NeuroRehabilitation* **2019**, *44*, 485–492. [CrossRef] [PubMed]
45. Timmermans, C.; Roerdink, M.; Meskers, C.G.M.; Beek, P.J.; Janssen, T.W.J. Walking-adaptability therapy after stroke: Results of a randomized controlled trial. *Trials* **2021**, *22*, 923. [CrossRef] [PubMed]
46. Yang, Y.-R.; Mi, P.-L.; Huang, S.-F.; Chiu, S.-L.; Liu, Y.-C.; Wang, R.-Y. Effects of neuromuscular electrical stimulation on gait performance in chronic stroke with inadequate ankle control—A randomized controlled trial. *PLoS ONE* **2018**, *13*, e0208609. [CrossRef] [PubMed]
47. Yu, X.-M.; Jin, X.-M.; Lu, Y.; Gao, Y.; Xu, H.-C.; Xue, X.; Fang, L.; Hu, J. Effects of Body Weight Support-Tai Chi Footwork Training on Balance Control and Walking Function in Stroke Survivors with Hemiplegia: A Pilot Randomized Controlled Trial. *Evid.-Based Complement. Altern. Med. ECAM* **2020**, *2020*, 9218078. [CrossRef] [PubMed]
48. Lin, D.J.; Finklestein, S.P.; Cramer, S.C. New Directions in Treatments Targeting Stroke Recovery. *Stroke* **2018**, *49*, 3107–3114. [CrossRef] [PubMed]

49. Domingos, J.; Dean, J.; Cruickshank, T.M.; Śmiłowska, K.; Fernandes, J.B.; Godinho, C. A Novel Boot Camp Program to Help Guide Personalized Exercise in People with Parkinson Disease. *J. Pers. Med.* **2021**, *11*, 938. [CrossRef]
50. Fernandes, J.B.; Teixeira, F.; Godinho, C. Personalized Care and Treatment Compliance in Chronic Conditions. *J. Pers. Med.* **2022**, *12*, 737. [CrossRef]
51. Fernandes, J.B.; Domingos, J.; Família, C.; Veríssimo, J.; Castanheira, P.; Menezes, C.; Vicente, C.; Santos, C.; Marvão, E.; Coelho, J.; et al. Adapted Portuguese folk dance intervention for subacute rehabilitation post-stroke: Study protocol. *Front. Public Health* **2023**, *11*, 1200093. [CrossRef]
52. Fernandes, J.B.; Fernandes, S.B.; Almeida, A.S.; Vareta, D.A.; Miller, C.A. Older Adults' Perceived Barriers to Participation in a Falls Prevention Strategy. *J. Pers. Med.* **2021**, *11*, 450. [CrossRef]
53. Laver, K.E.; Lange, B.; George, S.; Deutsch, J.E.; Saposnik, G.; Crotty, M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst. Rev.* **2017**, *11*, CD008349. [CrossRef] [PubMed]
54. Bryck, R.L.; Fisher, P.A. Training the brain: Practical applications of neural plasticity from the intersection of cognitive neuroscience, developmental psychology, and prevention science. *Am. Psychol.* **2012**, *67*, 87–100. [CrossRef] [PubMed]
55. Dhami, P.; Moreno, S.; DeSouza, J.F. New framework for rehabilitation—Fusion of cognitive and physical rehabilitation: The hope for dancing. *Front. Psychol.* **2015**, *5*, 1478. [CrossRef] [PubMed]
56. Milewska-Jędrzejczak, M.; Głąbiński, A. The Influence of Conventional and Innovative Rehabilitation Methods on Brain Plasticity Induction in Patients with Multiple Sclerosis. *J. Clin. Med.* **2023**, *12*, 1880. [CrossRef] [PubMed]
57. Calafiore, D.; Negrini, F.; Tottoli, N.; Ferraro, F.; Ozyemisci-Taskiran, O.; de Sire, A. Efficacy of robotic exoskeleton for gait rehabilitation in patients with subacute stroke: A systematic review. *Eur. J. Phys. Rehabil. Med.* **2022**, *58*, 1–8. [CrossRef]
58. Poli, P.; Morone, G.; Rosati, G.; Masiero, S. Robotic technologies and rehabilitation: New tools for stroke patients' therapy. *BioMed Res. Int.* **2013**, *2013*, 153872. [CrossRef]
59. Aprile, I.; Conte, C.; Cruciani, A.; Pecchioli, C.; Castelli, L.; Insalaco, S.; Germanotta, M.; Iacovelli, C. Efficacy of Robot-Assisted Gait Training Combined with Robotic Balance Training in Subacute Stroke Patients: A Randomized Clinical Trial. *J. Clin. Med.* **2022**, *11*, 5162. [CrossRef]
60. Chen, B.; Ma, H.; Qin, L.Y.; Gao, F.; Chan, K.M.; Law, S.W.; Qin, L.; Liao, W.H. Recent developments and challenges of lower extremity exoskeletons. *J. Orthop. Transl.* **2015**, *5*, 26–37. [CrossRef]
61. Morone, G.; Bragoni, M.; Iosa, M.; De Angelis, D.; Venturiero, V.; Coiro, P.; Pratesi, L.; Paolucci, S. Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. *Neurorehabil. Neural Repair* **2011**, *25*, 636–644. [CrossRef]
62. Duret, C.; Grosmaire, A.G.; Krebs, H.I. Robot-Assisted Therapy in Upper Extremity Hemiparesis: Overview of an Evidence-Based Approach. *Front. Neurol.* **2019**, *10*, 412. [CrossRef]
63. Saraiva, J.; Rosa, G.; Fernandes, S.; Fernandes, J.B. Current Trends in Balance Rehabilitation for Stroke Survivors: A Scoping Review of Experimental Studies. *Int. J. Environ. Res. Public Health* **2023**, *20*, 6829. [CrossRef]
64. Christoforou, E.G.; Avgousti, S.; Ramdani, N.; Novales, C.; Panayides, A.S. The Upcoming Role for Nursing and Assistive Robotics: Opportunities and Challenges Ahead. *Front. Digit. Health* **2020**, *2*, 585656. [CrossRef] [PubMed]
65. Li, L.; Tyson, S.; Weightman, A. Professionals' Views and Experiences of Using Rehabilitation Robotics with Stroke Survivors: A Mixed Methods Survey. *Front. Med. Technol.* **2021**, *3*, 780090. [CrossRef] [PubMed]
66. Verrienti, G.; Raccagni, C.; Lombardozzi, G.; De Bartolo, D.; Iosa, M. Motivation as a Measurable Outcome in Stroke Rehabilitation: A Systematic Review of the Literature. *Int. J. Environ. Res. Public Health* **2023**, *20*, 4187. [CrossRef] [PubMed]
67. Fernandes, J.B.; Ferreira, N.; Domingos, J.; Ferreira, R.; Amador, C.; Pardal, N.; Castro, C.; Simões, A.; Fernandes, S.; Bernardes, C.; et al. Health Professionals' Motivational Strategies to Enhance Adherence in the Rehabilitation of People with Lower Limb Fractures: Scoping Review. *Int. J. Environ. Res. Public Health* **2023**, *20*, 7050. [CrossRef] [PubMed]
68. Shahid, J.; Kashif, A.; Shahid, M.K. A Comprehensive Review of Physical Therapy Interventions for Stroke Rehabilitation: Impairment-Based Approaches and Functional Goals. *Brain Sci.* **2023**, *13*, 717. [CrossRef]
69. Amin, F.; Waris, A.; Iqbal, J.; Gilani, S.; Rehman, M.; Mushtaq, S.; Khan, N.; Khan, M.; Jameel, M.; Tamam, N. Maximizing stroke recovery with advanced technologies: A comprehensive assessment of robot-assisted, EMG-Controlled robotics, virtual reality, and mirror therapy interventions. *Results Eng.* **2024**, *21*, 101725. [CrossRef]

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Value of Automatically Derived Full Thrombus Characteristics: An Explorative Study of Their Associations with Outcomes in Ischemic Stroke Patients

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Abstract: (1) **Background**: For acute ischemic strokes caused by large vessel occlusion, manually assessed thrombus volume and perviousness have been associated with treatment outcomes. However, the manual assessment of these characteristics is time-consuming and subject to inter-observer bias. Alternatively, a recently introduced fully automated deep learning-based algorithm can be used to consistently estimate full thrombus characteristics. Here, we exploratively assess the value of these novel biomarkers in terms of their association with stroke outcomes. (2) **Methods**: We studied two applications of automated full thrombus characterization as follows: one in a randomized trial, MR CLEAN-NO IV (n = 314), and another in a Dutch nationwide registry, MR CLEAN Registry (n = 1839). We used an automatic pipeline to determine the thrombus volume, perviousness, density, and heterogeneity. We assessed their relationship with the functional outcome defined as the modified Rankin Scale (mRS) at 90 days and two technical success measures as follows: successful final reperfusion, which is defined as an eTICI score of 2b-3, and successful first-pass reperfusion (FPS). (3) **Results**: Higher perviousness was significantly related to a better mRS in both MR CLEAN-NO IV and the MR CLEAN Registry. A lower thrombus volume and lower heterogeneity were only significantly related to better mRS scores in the MR CLEAN Registry. Only lower thrombus heterogeneity was significantly related to technical success; it was significantly related to a higher chance of FPS in the MR CLEAN-NO IV trial (OR = 0.55, 95% CI: 0.31–0.98) and successful reperfusion in the MR CLEAN Registry (OR = 0.88, 95% CI: 0.78–0.99). (4) **Conclusions**: Thrombus characteristics derived from automatic entire thrombus segmentations are significantly related to stroke outcomes.

Keywords: ischemic stroke; thrombus; artificial intelligence; imaging biomarkers; computed tomography scan

1. Introduction

The effectiveness of endovascular treatment (EVT) was shown for patients with large vessel occlusion (LVO) strokes in 2015 [1,2], making EVT the standard treatment for LVO patients arriving at the hospital within 6 h after the stroke onset. However, new trials have shown that a wider group of patients can benefit from this treatment [3,4]. With the increasing demand, identifying factors that can predict the outcome of EVT is of higher interest.

Collecting extensive clinical information from ischemic stroke patients who present themselves to the hospital in the acute phase is difficult and sometimes unfeasible. Imaging characteristics, on the other hand, are more rapidly and consistently available and contain pertinent information about the patient's present condition. In LVO stroke patients, certain radiological imaging characteristics of the thrombus on CT scans, such as length, volume, perviousness, and density, have been shown to be related to various outcome measures of stroke treatment [5–10]. However, thrombus location is the only thrombus imaging characteristic that is currently taken into account during the triage of ischemic stroke patients [11]. One reason for focusing only on this imaging characteristic and disregarding the others, apart from its established association with the outcome, is the fact that the thrombus location can be estimated without any need for annotation.

Quantifying most thrombus imaging characteristics requires annotating the thrombus. Thrombus annotations are commonly performed manually [12]. One disadvantage of manual annotations is that they are time consuming and therefore cannot be used in the clinical setting of stroke treatment. Another disadvantage of manual annotations is that they are subject to inter-observer variation [13].

Unlike manual methods, automatic methods can be used to create full thrombus annotations for a large dataset with minimal effort [14,15]. Additionally, provided the same model is used for segmentation, there will be no inter-observer variability in the automatic annotations. Therefore, they can potentially pave the way for involving thrombus characteristics in making treatment decisions in the clinic. Previously, we developed an automatic thrombus segmentation algorithm that had a good agreement with manual annotations [16]. However, the value of the automatic segmentations for extracting thrombus characteristics has not yet been established.

In this exploratory imaging biometrics study, we investigate the association of full thrombus characteristics calculated from the automatic segmentations with the functional outcome and technical success of endovascular treatment (EVT). Automated thrombus analysis is particularly valuable in large datasets such as registries and trials. However, differences in trial and registry populations (caused by strict inclusion criteria of trials) can affect the observed significant associations [17]. Furthermore, combining these populations may influence relationships between thrombus imaging and outcomes. Therefore, we study the value of fully automatically generated thrombus characteristics in the two distinct populations of LVO stroke patients treated with EVT.

2. Materials and Methods

2.1. Patient Selection

We included patients from two populations as follows: the Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry and from the MR CLEAN-NO IV trial. Studying these two populations allows us to evaluate the value of automated segmentations in two potentially relevant applications of automated thrombus segmentations as follows: large clinical trials and large registries.

The MR CLEAN Registry [18] was a prospective observational study that followed the completion of the MR CLEAN trial [1], which was the first trial demonstrating the benefit of endovascular treatment in LVO stroke patients. The registry enrolled all the patients who underwent EVT in the Netherlands between March 2014 and January 2019, with eligible patients receiving intravenous thrombolysis (IVT) before EVT.

MR CLEAN-NO IV [19] was a prospective trial where patients with LVO were randomized between treatment with IVT prior to EVT or EVT alone. This trial included patients from twenty centers in the Netherlands, France, and Belgium between 2018 and 2020. Only patients who were directly presented to an EVT-capable center within 4.5 h after the stroke onset were included. The baseline scans included in the NO IV trial were all acquired before IVT administration.

The patient selection procedure is schematically depicted in Figure 1. For each patient, the highest quality non-contrast CT (NCCT) and CT angiography (CTA) imaging available was used for further processing. Exclusion based on low scan quality includes a CTA slice thickness > 2 mm, NCCT slice thickness > 5 mm, number of slices < 8, the scan having incomplete brain coverage, the scan being made with sharp convolutional reconstruction kernels, or the scan having movement artefacts.

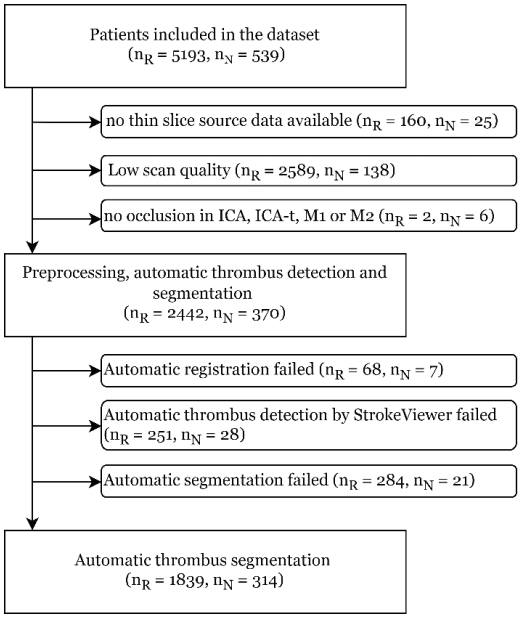

Figure 1. Flow chart of patient selection. n_R refers to the number of patients in the Registry dataset, and n_N refers to the number of patients in the NO IV dataset.

2.2. Automatic Thrombus Segmentation

We used a previously validated automatic thrombus segmentation algorithm [16]. The entire pipeline is automatic, and we used the output of the thrombus segmentation algorithm without any manual adjustments. The first step of the algorithm is to localize the thrombus with an off-the-shelf software, StrokeViewer LVO version 3.2.13 (Nicolab, Amsterdam, The Netherlands; www.nicolab.com/strokeviewer-home (accessed on 21 February 2024)). Subsequently, a neural network is used to segment the thrombus based on both the NCCT and CTA scans. The result is a 3D segmentation of the thrombus.

2.3. Thrombus Imaging Characteristics

We assessed the thrombus volume, perviousness, density, and heterogeneity. Thrombus perviousness quantifies thrombus permeability by comparing the average thrombus attenuation in the CTA and NCCT scans. This difference is named the Thrombus Attenuation Increase (TAI) [6]. Santos et al. (2021) proposed a method to calculate the TAI over the entire thrombus by comparing the intensity histograms of CTA and NCCT. This includes differences between the first (TAI_{Q1}), second (TAI_{Q2}), or third (TAI_{Q3}) histogram quartiles, or the lag that results in the maximum cross correlation value between the two histograms (TAI_{MCC}). Additionally, we included the median intensity of the thrombus in CTA as a measure of contrast penetration irrespective of thrombus density. Definitions of perviousness, density, and heterogeneity are depicted in Figure 2.

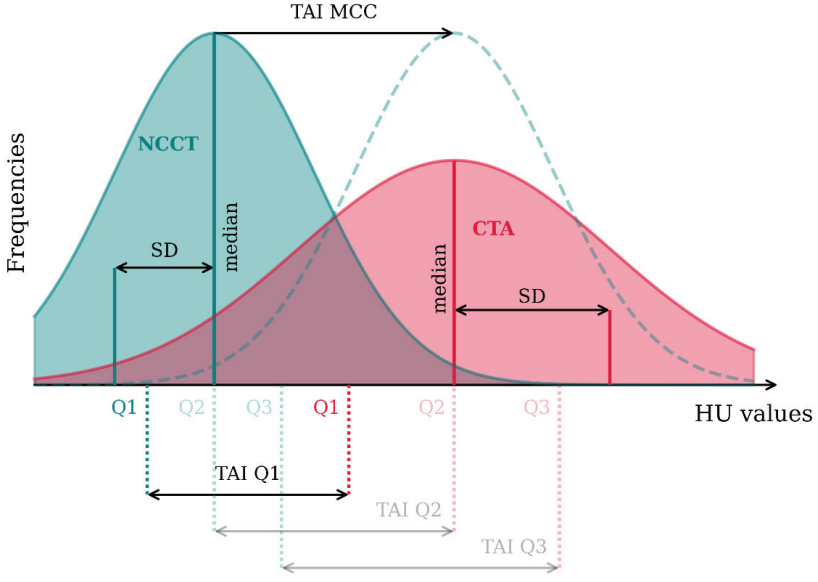

Figure 2. A representation of the thrombus characteristics that are calculated from the histogram of Hounsfield Unit (HU) intensity values of the thrombus in NCCT (green) and CTA (red). Three TAI (Thrombus Attenuation Increase) values are calculated from the difference between the first, second, and third quartiles (Q1, Q2, and Q3) of the two histograms. TAI_{MCC} (maximum cross correlation) is a measure of how much the NCCT histogram should be moved to achieve the maximum cross correlation with the CTA histogram. The distribution showed with a green, dashed line is the shifted NCCT histogram. Heterogeneity is defined as the CTA and NCCT SD (Standard Deviation). Density is shown as the CTA and NCCT median. In this figure, we have assumed the two histograms are normal distributions. In case of a non-normal distribution, median values do not overlap with the second quartile, and TAI_{MCC} is not necessarily the exact distance between the two medians.

Thrombus density is the median density of the thrombus in NCCT (measured in HU values). We defined thrombus heterogeneity as the spread of density values in the thrombus and approximated it using the Standard Deviation (SD) of its histogram in both CTA and NCCT.

2.4. Outcome Measures

The association of the thrombus characteristics with the three outcome measures were assessed as follows: (1) the functional outcome measured on the modified Rankin Scale (mRS) after 90 days, (2) the successful final reperfusion defined as an expanded

Thrombolysis in Cerebral Infarction (eTICI) score of 2b-3, and (3) the first-pass reperfusion success (FPS).

Ordinal mRS values were inverted as per previous MR CLEAN Registry studies [18], so odds ratios below one indicate a worse functional outcome. Successful reperfusion is defined as an eTICI score of 2b, 2c, or 3, indicating more than 50% reperfusion of the affected territory. FPS is defined as successful reperfusion after the first thrombectomy attempt.

2.5. Statistical Analysis

We report the baseline characteristics of the Registry and NO IV populations. Numerical variables were summarized using median and interquartile ranges, while categorical variables were presented as counts and percentages. The pre-stroke mRS and the Alberta Stroke Program Early CT Score (ASPECTS) were summarized by grouping some of their levels together. For the pre-stroke mRS, patients with an mRS of 2 or higher are grouped together. For the ASPECTS, three bins are made by grouping patients with an ASPECTS of 0 to 4, 5 to 7, and 8 to 10. In order to compare the two populations, Mann–Whitney U tests and Chi-square tests were used for numerical variables and categorical variables, respectively. Thrombus characteristics were summarized using the median and interquartile range and compared between populations using the Mann–Whitney U test. A p-value of <0.05 was considered to be significant.

We used logistic regression to investigate the associations between the thrombus characteristics and the outcome measures in both populations. Uni-variable ordinal and binary logistic regressions were used to study the relationship between the thrombus characteristics and the mRS, as well as the two technical success measures, respectively. Odds ratios (ORs) and 95% confidence intervals were reported to describe the effect of each thrombus characteristic on the outcome.

All statistical analyses were carried out using R (R version 4.0.5 (31 March 2021)). The missing values in the clinical data were imputed using multiple data imputation with additive regression, bootstrapping, and predictive mean matching using the Hmisc package (Frank E, 2021) with 5 imputations per missing value. Age, occlusion location, baseline NIHSS, administration of IVT, diabetes, onset-to-arterial puncture time, administration of the antiplatelet, atrial fibrillation, atherosclerosis, and collateral scores were used to inform the imputation. A sensitivity analysis was carried out for data imputation by undertaking a complete case analysis in which the cases with missing values were omitted and comparing the results with the imputed analysis (Appendix B).

We also performed multi-variable logistic regression analysis to investigate the effect of each thrombus characteristic on the selected outcome measures while making adjustments for the effect of the potential confounders (details are mentioned in Appendix A).

The consistency of the thrombus characteristics calculated from the automatic and manual segmentations was tested over a subset of the NO IV dataset in Appendix C.

3. Results

3.1. Population Characteristics

Table 1 summarizes the baseline characteristics of the two populations, showing significant differences between them. The median onset-to-groin time is more than twice as long in the Registry population compared with that of the NO-IV population. The percentage of patients who received IVT is considerably higher in the Registry population. Additionally, pre-stroke mRS scores ≥ 2 are more common for Registry patients. The collateral scores are better in the NO-IV population, and there are more M2 occlusions present in the Registry population than in the NO-IV one. The median age is higher in the Registry population, and there are more patients present with atherosclerosis in the NO-IV population. The time between the NCCT and CTA scans is longer in the Registry population.

Table 1. Descriptive characteristics of the included populations. Median and interquartile ranges (IQRs) are used to describe the continuous variables. Frequencies and percentages are reported for the categorical variables. In cases where data were missing, the number of available data is shown as "(n = x)". "**†**" indicates a significant difference between the two populations. NIHSS: National Institutes of Health Stroke Scale; NCCT: Non-contrast Computed Tomography; CTA: Computed Tomography Angiography; mRS: Modified Rankin Scale; ASPECTS: Alberta Stroke Program Early CT Score; ICA: Internal Carotid Artery; ICA-t: ICA terminus; IVT: Intravenous Thrombolysis; eTICI: expanded Treatment in Cerebral Infarction

	MR CLEAN Registry (n = 1839)	**MR CLEAN-NO IV (n = 314)**	***p*-Value**
Age, median (year, IQR)	72 (63–81)	70 (63–78)	0.03 †
Sex (men), n (%)	1007 (54.8%)	191 (60.8%)	0.05
Baseline NIHSS, median (IQR)	16 (11–20); (n = 1822)	17 (11–20)	0.09
Onset-to-arterial puncture time, median (IQR)	190 (138–269); (n = 1789)	92 (68–141)	<0.0001 †
Atherosclerosis (yes), n (%)	216 (11.7%)	49 (16.2%); (n = 303)	0.04 †
Diabetes (yes), n (%)	286 (15.7%); (n = 1825)	46 (14.6%)	0.71
Hypertension, n (%)	912 (50.6%); (n = 1801)	152 (48.6%)	0.54
Time between NCCT and CTA (minute), median (IQR)	13.4 (7.7–34.7); (n = 1609)	9.3 (6.8–13.4); (n = 197)	<0.0001 †
Pre-stroke mRS	(n = 1786)	(n = 313)	0.003 †
0	1166 (65.3%)	215 (68.7%)	
1	261 (14.6%)	59 (18.8%)	
≥2	359 (20.1%)	39 (12.5%)	
ASPECTS	(n = 1829)		0.21
0–4	79 (4.3%)	11 (3.5%)	
5–7	360 (19.7%)	50 (15.9%)	
8–10	1390 (76%)	253 (80.6%)	
Collateral score	(n = 1802)	(n = 311)	0.004 †
Score 0 (absent collaterals)	96 (5.3%)	21 (6.8%)	
Score 1 (filling = 50% of occluded area)	712 (39.5%)	90 (28.9%)	
Score 2 (>50% but less than <100%)	701 (38.9%)	137 (44.1%)	
3 (100% of the occluded area)	293 (16.3%)	63 (20.3%)	
Thrombus location	(n = 1825)		0.002 †
ICA	72 (3.9%)	1 (3%)	
ICA-t	380 (20.8%)	78 (24.8%)	
M1	1115 (61.1%)	200 (63.7%)	
M2	258 (14.1%)	35 (11.1%)	
Antiplatelet use (yes), n (%)	549 (30.2%); (n = 1819)	104 (33.1%)	0.33
IVT (yes), n (%)	1251 (68.4%); (n = 1830)	166 (52.9%)	<0.0001 †
First-pass success (yes), n(%)	467 (34%); (n = 1373)	143 (51.8%); (n = 276)	<0.0001 †
eTICI 2b/2c/3	1156 (65.8%); (n = 1757)	227 (79.1%); (n = 287)	<0.0001 †
mRS 90 days	(n = 1673)		<0.0001 †
0	129 (7.7%)	11 (3.5%)	
1	294 (17.6%)	36 (11.5%)	
2	296 (17.7%)	110 (35.0%)	

Table 1. *Cont.*

	MR CLEAN Registry (n = 1839)	MR CLEAN-NO IV (n = 314)	*p*-Value
3	219 (13.1%)	35 (11.1%)	<0.0001 †
4	188 (11.2%)	29 (9.2%)	
5	90 (5.4%)	31 (9.9%)	
6	457(27.3%)	62 (19.7%)	

First-pass success and successful reperfusion rates are higher in the NO-IV population. The mRS after a 90 day distribution is also significantly different between the two populations, where the percentage of patients with an mRS between 0 and 2 is 50% in the NO-IV population and 43% in the Registry one.

There are no missing data points for the mRS in the NO-IV population, but 9% of the data are missing for this outcome measure in the Registry one. The FPS data were missing for 25% in the Registry population and 12% in the NO-IV one. The missing data percentages for successful reperfusion were 4% for the Registry population and 9% for the NO-IV one.

The distributions of the thrombus characteristics in both the populations are presented in Table 2. Apart from the volume, the distribution of all the thrombus characteristics differed between the two population. Thrombi were more pervious and heterogeneous in the NO IV population than in the Registry one.

Table 2. Comparing the thrombus characteristics between the two populations. Median and interquartile ranges (IQRs) are used to describe the variables. "†" indicates a significant difference between the two populations. TAI: Thrombus Attenuation Increase; SD: Standard Deviation; HU: Hounsfield Unit; NCCT: Non-contrast Computed Tomography; CTA: Computed Tomography Angiography; MCC: Maximum Cross Correlation

		MR CLEAN Registry (n = 1839)	MR CLEAN-NO IV (n = 314)	*p*-Value
Volume (mm^3), median (IQR)		128 (49–261)	132 (53–271)	0.46
Density (HU)	NCCT median median (IQR)	47.6 (44.8–50.8)	49.2 (45.8–53.1)	<0.0001 †
Perviousness (HU)	TAI_{Q1} median (IQR)	0.51 (−5.0–6.5)	3.5 (−2.8–8.1)	<0.0001 †
	TAI_{Q2} median (IQR)	5.8 (−0.3–13.0)	9.6 (2.9–16.0)	<0.0001 †
	TAI_{Q3} median (IQR)	11.9 (3.9–22.0)	15.7 (8.6–25.0)	<0.0001 †
	TAI_{MCC} median (IQR)	4.3 (−1.6–10.9)	7.3 (0.0–12.7)	<0.0001 †
	CTA median median (IQR)	54.0 (47.0–61.7)	58.0 (53.0–65.7)	<0.0001 †
Heterogeneity (HU)	CTA SD median (IQR)	21.2 (15.7–18.1)	24.0 (18.3–31.3)	<0.0001 †
	NCCT SD (HU)	8.6 (6.7–10.6)	9.1 (7.1–11.1)	0.01 †

3.2. Associations with the Outcome

In Table 3, the univariate associations between the thrombus characteristics and the outcome measures are presented. For multiple thrombus characteristics, a statistically significant association with the outcome is observed.

Table 3. Odds ratios relating the thrombus characteristics to the outcome measures in the univariate analysis. Numbers in the parenthesis show a 95% CI. Functional outcome: the reversed mRS (OR < 1 indicates a worse outcome); FPS: first-pass success, eTICI 2b-3 with a single thrombectomy device pass; eTICI2b+: successful reperfusion, eTICI $\geq$ 2b at the end of the procedure; HUs: Hounsfield Units; TAI: Thrombus Attenuation Increase; SD: Standard Deviation; OR: odds ratio; CI: confidence interval; NCCT: Non-contrast Computed Tomography; CTA: Computed Tomography Angiography; MCC: Maximum Cross Correlation and "**ǂ**" and the bold text indicate a statistically significant relationship.

		VOLUME	DENSITY	PERVIOUSNESS					HETEROGENEITY	
		Volume (per 0.1 mL)	*NCCT median* (per 10 HU)	TAI_{Q1} (per 10 HU)	TAI_{Q2} (per 10 HU)	TAI_{Q3} (per 10 HU)	TAI_{MCC} (per 10 HU)	*CTA median* (per 10 HU)	*CTA SD* (per 10 HU)	*NCCT SD* (per 10 HU)
Functional Outcome	Registry	**0.91 ǂ** (0.87–0.95)	0.98 (0.87–1.09)	**1.14 ǂ** (1.07–1.21)	**1.10 ǂ** (1.04–1.15)	**1.05 ǂ** (1.02–1.09)	**1.11 ǂ** (1.05–1.17)	**1.09 ǂ** (1.03–1.15)	**0.93 ǂ** (0.87–0.99)	**0.87 ǂ** (0.77–0.98)
	NO IV	0.91 (0.81–1.02)	1.15 (0.81–1.62)	**1.20 ǂ** (1.01–1.44)	**1.22 ǂ** (1.04–1.42)	**1.16 ǂ** (1.02–1.30)	**1.17 ǂ** (0.01–1.35)	**1.23 ǂ** (1.06–1.44)	1.14 (0.94–1.40)	0.76 (0.53–1.09)
FPS	Registry	0.94 (0.88–1.00)	0.93 (0.80–1.08)	1.07 (0.97–1.18)	1.04 (0.96–1.12)	1.03 (0.98–1.08)	1.05 (0.97–1.14)	1.02 (0.96–1.10)	1.01 (0.92–1.12)	0.97 (0.84–1.13)
	NO IV	0.92 (0.79–1.06)	0.70 (0.44–1.12)	1.01 (0.82–1.25)	1.07 (0.89–1.29)	1.11 (0.95–1.29)	1.05 (0.87–1.27)	1.00 (0.84–1.20)	1.06 (0.84–1.34)	**0.55 ǂ** (0.31–0.98)
eTICI2b+	Registry	1.01 (0.95–1.06)	0.93 (0.82–1.05)	0.96 (0.89–1.03)	0.97 (0.91–1.03)	0.98 (0.94–1.03)	0.98 (0.92–1.05)	0.95 (0.90–1.01)	0.96 (0.89–1.04)	**0.88 ǂ** (0.78–0.99)
	NO IV	0.99 (0.84–1.17)	1.20 (0.72–2.00)	0.94 (0.70–1.26)	0.94 (0.75–1.17)	0.98 (0.83–1.16)	1.00 (0.81–1.23)	0.97 (0.77–1.22)	1.03 (0.76–1.38)	0.75 (0.47–1.21)

In the Registry population, a lower volume, higher perviousness, and lower heterogeneity were significantly associated with a more favorable functional outcome. Perviousness was also significantly associated with the mRS in the NO IV population. However, volume and heterogeneity were neither statistically nor significantly related to the mRS in the NO IV population.

Only thrombus heterogeneity in NCCT was significantly related to FPS in the NO IV population, but none of the thrombus characteristics were significantly related to FPS in the Registry population. The effect of thrombus heterogeneity on FPS is large in the NO IV population where for every increase in heterogeneity (SD of NCCT) by 10 HUs, the chance of achieving first-pass success is reduced by 45%.

Thrombus heterogeneity in NCCT was the only thrombus characteristic that was significantly related to successful reperfusion in the Registry population where there is a higher chance to achieve successful reperfusion for less heterogeneous (more homogenous) thrombi. None of the thrombus characteristics were significantly associated with successful reperfusion in the NO IV population.

4. Discussion

In our study, fully automatically calculated thrombus characteristics were significantly associated with functional and procedural reperfusion outcomes in patients with acute ischemic strokes who were treated with EVT. Despite the differences between the two populations, perviousness was positively associated with a better functional outcome in both the Registry and NO IV trial, indicating a robust link between this biomarker and the functional outcome. The thrombus volume and heterogeneity were significantly associated with a worse functional outcome in the Registry population but not in the NO IV one. While the relationship between the volume and 90-day mRS is not significant in the NO IV population, we want to point out that the effect size in both populations is the same. Therefore, a potential cause for this difference in significance may be the smaller size of the NO IV population.

In this study, heterogeneity was the only thrombus characteristic significantly associated with reperfusion success; it was significantly associated with a lower chance of FPS in the NO IV population and with a lower chance of final successful reperfusion in the Registry population. Furthermore, heterogeneity in NCCT and perviousness estimated as the median density in CTA remained statistically and significantly associated with successful reperfusion even after adjusting for confounders. However, it is important to acknowledge a discrepancy between the two populations regarding the significant associations observed between heterogeneity and the outcome. Therefore, additional investigations are required to discern the patient groups for which heterogeneity can be a valuable biomarker. Furthermore, in this study we used a basic and intuitive definition for heterogeneity, while more complex formulations may be more descriptive of this biomarker [20,21].

We found a significant association between the thrombus volume and functional outcome in the Registry population. This association was also reported by Baek et al. (2017) [22] and van Voorst et al. (2023) [9], but it was not found by Borst et al. (2017) [23]. Unlike Baek et al. (2017) [22], we did not find a significant association between the thrombus volume and successful reperfusion.

We did not find a significant association between the density and any of the outcome measures. Similar results were found by Dutra et al. (2019) [5] for a 90-day mRS, by Baek et al. (2017) [22] for FPS, as well as by Jagani et al. (2017) [24] for successful reperfusion. Most of the studies that did find a relation between the thrombus density and outcome were focusing on IVT treatment only [25,26], thereby indicating that unlike IVT, thrombus density does not have an important role in EVT treatment.

Perviousness was the only thrombus characteristic significantly related to the 90-day mRS in both populations. The same relationship was observed on part I of the MR CLEAN Registry [5] and MR CLEAN trial populations for both sample-based [6] and entire thrombus [27] perviousness. Although Kappelhof et al. (2021) [28] did not find a significant association between perviousness and the mRS in patients who were treated with EVT in the pooled data of seven trials, they did find a positive association in patients treated with IVT. Similarly to previous studies, we did not find a significant association between perviousness and FPS [29] or successful reperfusion [28].

Our study provides the grounds to better understand the relationship between automatic thrombus characteristics and the outcome. Having a robust and reproducible measure of full thrombus analysis, such as that presented in our study, could aid in the understanding of the contradictory findings in previous studies. Despite omitting the inter-observer bias through the automatic annotations, we found that the significant associations between thrombus characteristics and outcomes differed between the MR CLEAN Registry and MR CLEAN-NO IV populations. These differences in significant associations could be caused by the restricted size of the populations. However, with the largest study size up to date, we do not think that this is the main cause of this difference. It is likely that the dissimilarities between the two populations contributes to the differences in the found associations. In future research, these population dissimilarities could be further explored to explain the causes of the observed associations based on the findings of this study. This is a necessary next step before creating a prognostics model to be used in the clinic. However, studying causality is outside of the scope of this paper.

The use of the automatic segmentations also allowed for the inclusion of a high number of patients in this study where we report on the largest patient population analyzed to date. Furthermore, the data used in this study were international and multi-centered, improving the generalizability of our results. However, it has to be noted that almost half of the patients had to be excluded because of low image quality. This was mostly due to a requirement for thin-slice images. Many centers do not save the thin-slice scans to avoid high storage costs. However, if the thrombus segmentation algorithm is integrated in the clinical workflow, it is possible to apply the algorithm on the thin-slice images before deleting them, thereby significantly decreasing the number of omitted scans.

Another strength of this study is that the analysis was not limited to one population. The data of patients who were enrolled in the MR CLEAN-NO IV trial were prospectively collected, and most patients had high-quality scans available, while the Registry dataset contained more patients with comorbidities, low-quality scans, and missing data compared with the MR CLEAN-NO IV population. Additionally, the quality of EVT treatment may have improved over the course of collecting the Registry data and beyond its completion. On the other hand, the Registry provides a realistic representation of the LVO patients who are eligible for EVT in the Netherlands. The trial data, with its carefully selected patients, closely resemble the populations commonly used to study the relationship between biomarkers and the outcome. On the other hand, the Registry data, containing more patients and being more reflective of real-world scenarios, offer insights into a broader patient cohort. We chose to analyze these populations separately to capture their unique attributes and strengths. Additionally, due to the smaller size of the MR CLEAN-NO IV population, we opted to not merge it with the Registry dataset to preserve its valuable information.

A limitation of our study is that of the high number of analyses conducted, thereby increasing the risk of accidental findings. Since we followed an exploratory analysis approach, we did not make corrections for multiple testing. However, it has to be noted that even though we looked at multiple definitions for some characteristics, we have only addressed four thrombus characteristics and three outcome measures.

In this analysis, thrombi were fully automatically segmented without manual adjustments, potentially leading to suboptimal segmentations in certain cases, such as occlusions in the proximal ICA or M2. Pseudo-occlusions were not explicitly inspected. However, the high number of patients included in this study is expected to account for the potential bias caused by these outliers. Additionally, we made use of both NCCT and CTA to better utilize the different information that each modality provides. However, this means that the segmentation method is only applicable in cases where both NCCT and CTA are available.

Finding causality and studying the confounding factors were not the focus of this study. In some of the adjusted analyses, associations were no longer statistically significant, indicating collinearity between parameters. It is shown that thrombus characteristics can be significantly associated with other factors such as etiology [30] and the collateral score [31]. However, an extensive evaluation of these collinearities is beyond the scope of our exploratory biomarker study. Additionally, it is relevant to know the relationship between the thrombus characteristics and outcome regardless of the confounding factors because imaging characteristics can be easily calculated from CT scans while confounding factors may not be known or easily calculable.

Finally, data were not available for all the outcome measures over the entire study population. We have used imputation for the bias that is caused by the possible non-random absence of data. However, since imputed values can only be based on non-missing data, they are not free of bias. This is especially the case for FPS in the Registry where the percentage of missing data were high. We conducted a complete case analysis in Appendix B to assess the potential bias.

5. Conclusions

Fully automatically computed thrombus characteristics from the entire thrombus are significantly associated with the functional outcome and technical success in EVT-treated anterior circulation acute ischemic strokes. We observed different, significant associations in the Registry and NO IV trial populations, thereby suggesting that these relations are population-specific. Nonetheless, we found that a lower thrombus volume, higher perviousness, and lower heterogeneity were significantly associated with a better functional outcome, while lower heterogeneity was correlated with improved reperfusion. These findings support the use of automatically assessed radiological thrombus characteristics in stroke research and clinical practice.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Central Medical Ethics Committee and the Research Board of the Erasmus MC University Medical Center, Rotterdam, The Netherlands (MEC-2014-235 and MEC-2017-368).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data for this study are available upon reasonable request.

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Conflicts of Interest: HM is a cofounder and shareholder of Nicolab and Trianect.

Appendix A

The odds ratios relating thrombus characteristics to the outcome after adjusting for confounders can be seen in Table A1. We made adjustments for age, occlusion location, the baseline National Institutes of Health Stroke Scale (NIHSS), IVT, diabetes, onset-to-arterial puncture time, antiplatelet, atrial fibrillation, atherosclerosis, and collateral scores.

None of the thrombus characteristics are independently related to the functional outcome and FPS in either population. However, perviousness formulated as the CTA median intensity and heterogeneity in NCCT are significantly related to successful reperfusion in the Registry population.

Table A1. Odds ratios for the multi-variable (adjusted) analysis. Numbers in the parenthesis show a 95% CI. Functional outcome: reversed mRS (OR < 1 indicates a worse outcome); FPS: first-pass success; eTICI2b+: successful reperfusion; HUs: Hounsfield Units; TAI: Thrombus Attenuation Increase; SD: Standard Deviation; OR: odds ratio; CI: confidence interval; NCCT: Non-contrast Computed Tomography; CTA: Computed Tomography Angiography; MCC: Maximum Cross Correlation and "**†**" and the bold text indicate a statistically significant relationship.

		VOLUME	**DENSITY**	**PERVIOUSNESS**					**HETEROGENEITY**	
		Volume **(per 0.1 mL)**	***NCCT Median*** **(per 10 HU)**	***TAI_{Q1}*** **(per 10 HU)**	***TAI_{Q2}*** **(per 10 HU)**	***TAI_{Q3}*** **(per 10 HU)**	***TAI_{MCC}*** **(per 10 HU)**	***CTA Median*** **(per 10 HU)**	***CTA SD*** **(per 10 HU)**	***NCCT SD*** **(per 10 HU)**
Functional Outcome	Registry	0.98 (0.93–1.03)	0.94 (0.83–1.05)	1.03 (0.97–1.10)	1.02 (0.96–1.07)	1.01 (0.97–1.04)	1.03 (0.97–1.09)	1.00 (0.95–1.06)	0.95 (0.89–1.02)	0.92 (0.83–1.03)
	NO IV	1.02 (0.90–1.17)	0.84 (0.58–1.22)	1.18 (0.97–1.43)	1.16 (0.98–1.38)	1.09 (0.96–1.25)	1.13 (0.97–1.32)	1.12 (0.95–1.32)	1.16 (0.94–1.43)	0.83 (0.56–1.23)

Table A1. *Cont.*

		VOLUME	DENSITY	PERVIOUSNESS						HETEROGENEITY
		Volume (per 0.1 mL)	*NCCT Median* (per 10 HU)	TAI_{Q1} (per 10 HU)	TAI_{Q2} (per 10 HU)	TAI_{Q3} (per 10 HU)	TAI_{MCC} (per 10 HU)	*CTA Median* (per 10 HU)	*CTA SD* (per 10 HU)	*NCCT SD* (per 10 HU)
FPS	Registry	0.97 (0.90–1.04)	0.97 (0.83–1.12)	1.05 (0.95–1.17)	1.03 (0.95–1.10)	1.02 (0.97–1.07)	1.04 (0.96–1.13)	1.02 (0.95–1.10)	1.01 (0.91–1.12)	0.99 (0.85–1.14)
	NO IV	0.95 (0.80–1.12)	0.69 (0.41–1.15)	1.02 (0.81–1.27)	1.05 (0.86–1.28)	1.09 (0.93–1.29)	1.03 (0.84–1.26)	0.99 (0.81–1.20)	1.06 (0.83–1.35)	0.58 (0.32–1.02)
eTICI2b+	Registry	1.01 (0.95–1.07)	0.91 (0.80–1.04)	0.94 (0.87–1.01)	0.96 (0.90–1.02)	0.98 (0.93–1.02)	0.97 (0.90–1.04)	**0.94** ✝ (0.88–1.00)	0.96 (0.89–1.04)	**0.87** ✝ (0.78–0.99)
	NO IV	0.97 (0.79–1.19)	1.07 (0.63–1.82)	0.94 (0.68–1.29)	0.93 (0.72–1.21)	0.96 (0.79–1.15)	1.00 (0.80–1.26)	0.95 (0.75–1.22)	1.04 (0.76–1.43)	0.83 (0.50–1.36)

Appendix B

For each outcome measure, a complete case analysis was performed where the cases with missing data were excluded and the uni-variable logistic regression was performed without data imputation. The results are reported in Table A2. One notable difference is that even though the effects are not different, the volume and perviousness formulated as TAI_{Q1} and TAI_{MCC} are correlated with FPS in the Registry population in the complete case analysis. Additionally, the direction of the effect of the volume on successful reperfusion is reversed between the imputed and complete case analysis for the NO IV population.

Table A2. Odds ratios of the complete case uni-variable analysis for both the Registry and NO IV populations. Numbers in the parenthesis show a 95% CI. Functional outcome: reversed mRS (OR < 1 indicates a worse outcome); FPS: first-pass success; eTICI2b+ =: successful reperfusion; HUs: Hounsfield Units; TAI: Thrombus Attenuation Increase; SD: Standard Deviation; OR: odds ratio; CI: confidence interval; NCCT: Non-contrast Computed Tomography; CTA: Computed Tomography Angiography; MCC: Maximum Cross Correlation and "✝" and the bold text indicate a statistically significant relationship.

		VOLUME	DENSITY	PERVIOUSNESS						HETEROGENEITY
		Volume (per 0.1 mL)	*NCCT Median* (per 10 HU)	TAI_{Q1} (per 10 HU)	TAI_{Q2} (per 10 HU)	TAI_{Q3} (per 10 HU)	TAI_{MCC} (per 10 HU)	*CTA Median* (per 10 HU)	*CTA SD* (per 10 HU)	*NCCT SD* (per 10 HU)
Functional Outcome	Registry	**0.90** ✝ (0.86–0.95)	0.96 (0.86–1.07)	**1.14** ✝ (1.07–1.22)	**1.10** ✝ (1.04–1.16)	**1.06** ✝ (1.02–1.10)	**1.11** ✝ (1.05–1.18)	**1.09** ✝ (1.04–1.15)	**0.93** ✝ (0.86–0.99)	**0.85** ✝ (0.75–0.96)
	NO IV	0.91 (0.81–1.02)	1.15 (0.82–1.62)	**1.20** ✝ (1.01–1.44)	**1.22** ✝ (1.04–1.42)	**1.16** ✝ (1.02–1.30)	**1.17** ✝ (1.01–1.35)	**1.23** ✝ (1.06–1.44)	1.14 (0.94–1.40)	0.76 (0.53–1.09)
FPS	Registry	**0.93** ✝ (0.87–0.99)	0.96 (0.83–1.12)	**1.11** ✝ (1.00–1.22)	1.06 (0.98–1.15)	1.02 (0.97–1.08)	**1.09** ✝ (1.00–1.19)	1.05 (0.97–1.14)	1.03 (0.94–1.13)	0.96 (0.84–1.11)
	NO IV	0.91 (0.79–1.04)	0.68 (0.44–1.04)	1.02 (0.82–1.27)	1.09 (0.90–1.32)	1.13 (0.97–1.32)	1.09 (0.90–1.31)	1.01 (0.84–1.21)	1.03 (0.81–1.31)	**0.54** ✝ (0.30–0.97)
eTICI2b+	Registry	1.01 (0.95–1.06)	0.93 (0.82–1.06)	0.96 (0.89–1.03)	0.96 (0.91–1.03)	0.98 (0.94–1.03)	0.98 (0.92–1.05)	0.95 (0.89–1.01)	0.96 (0.88–1.04)	**0.87** ✝ (0.77–0.98)
	NO IV	1.05 (0.88–1.24)	1.15 (0.69–1.90)	0.93 (0.72–1.21)	0.95 (0.76–1.19)	0.97 (0.82–1.16)	0.99 (0.79–1.23)	0.98 (0.79–1.22)	1.01 (0.76–1.36)	0.76 (0.47–1.24)

Appendix C

In order to test the consistency between the manually and automatically calculated thrombus characteristics, a set of randomly chosen cases from MR CLEAN-NO IV was both manually and automatically segmented. Initially, the same subset of 100 patients included in the test set of [16] was used, and subsequently 2 patients were excluded because the automatic method did not produce a segmentation. Thrombus characteristics were calculated for both the manual and automatic segmentations and two-way mixed effects, and the single rater intra-class correlation coefficient (ICC) was calculated between them for each of the thrombus characteristics. The results are reported in Table A3. According to the guidelines provided by [32], to interpret the ICC, the automatically calculated TAI_{Q1}, TAI_{Q2}, TAI_{MCC}, CTA median, and NCCT SD have an excellent agreement; the volume, NCCT median, and TAI_{Q3} have a good agreement; and the CTA SD has a fair agreement with the manually calculated characteristics.

Table A3. Intra-class correlation coefficient (ICC) between the thrombus characteristics calculated from the automatic and manual segmentations on a subset of the MR CLEAN-NO IV population.

	VOLUME	DENSITY	PERVIOUSNESS					HETEROGENEITY	
	Volume	*NCCT Median*	TAI_{Q1}	TAI_{Q2}	TAI_{Q3}	TAI_{MCC}	*CTA Median*	*CTA SD*	*NCCT SD*
ICC	0.60	0.62	0.88	0.81	0.63	0.85	0.84	0.43	0.87

References

1. Berkhemer, O.A.; Fransen, P.S.S.; Beumer, D.; van den Berg, L.A.; Lingsma, H.F.; Yoo, A.J.; Schonewille, W.J.; Vos, J.A.; Nederkoorn, P.J.; Wermer, M.J.H.; et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N. Engl. J. Med.* **2015**, *372*, 11–20. [CrossRef] [PubMed]
2. Campbell, B.C.V.; Mitchell, P.J.; Kleinig, T.J.; Dewey, H.M.; Churilov, L.; Yassi, N.; Yan, B.; Dowling, R.J.; Parsons, M.W.; Oxley, T.J.; et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. *N. Engl. J. Med.* **2015**, *372*, 1009–1018. [CrossRef]
3. Nogueira, R.G.; Jadhav, A.P.; Haussen, D.C.; Bonafe, A.; Budzik, R.F.; Bhuva, P.; Yavagal, D.R.; Ribo, M.; Cognard, C.; Hanel, R.A.; et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N. Engl. J. Med.* **2018**, *378*, 11–21. [CrossRef] [PubMed]
4. Albers, G.W.; Marks, M.P.; Kemp, S.; Christensen, S.; Tsai, J.P.; Ortega-Gutierrez, S.; McTaggart, R.A.; Torbey, M.T.; Kim-Tenser, M.; Leslie-Mazwi, T.; et al. Thrombectomy for Stroke at 6 to 16 h with Selection by Perfusion Imaging. *N. Engl. J. Med.* **2018**, *378*, 708–718. [CrossRef] [PubMed]
5. Dutra, B.G.; Tolhuisen, M.L.; Alves, H.C.B.R.; Treurniet, K.M.; Kappelhof, M.; Yoo, A.J.; Jansen, I.G.H.; Dippel, D.W.J.; Van Zwam, W.H.; Van Oostenbrugge, R.J.; et al. Thrombus Imaging Characteristics and Outcomes in Acute Ischemic Stroke Patients Undergoing Endovascular Treatment. *Stroke* **2019**, *50*, 2057–2064. [CrossRef] [PubMed]
6. Santos, E.M.M.; Marquering, H.A.; Den Blanken, M.D.; Berkhemer, O.A.; Boers, A.M.M.; Yoo, A.J.; Beenen, L.F.; Treurniet, K.M.; Wismans, C.; Van Noort, K.; et al. Thrombus Permeability Is Associated with Improved Functional Outcome and Recanalization in Patients with Ischemic Stroke. *Stroke* **2016**, *47*, 732–741. [CrossRef] [PubMed]
7. Yoo, J.; Baek, J.H.; Park, H.; Song, D.; Kim, K.; Hwang, I.G.; Kim, Y.D.; Kim, S.H.; Lee, H.S.; Ahn, S.H.; et al. Thrombus volume as a predictor of nonrecanalization after intravenous thrombolysis in acute stroke. *Stroke* **2018**, *49*, 2108–2115. [CrossRef]
8. Riedel, C.H.; Zimmermann, P.; Jensen-Kondering, U.; Stingele, R.; Deuschl, G.; Jansen, O. The importance of size: Successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* **2011**, *42*, 1775–1777. [CrossRef]
9. van Voorst, H.; Bruggeman, A.A.E.; Andriessen, J.; Hoving, J.W.; Konduri, P.R.; Yang, W.; Kappelhof, M.; Arrarte Terreros, N.; Roos, Y.B.W.E.M.; van Zwam, W.H.; et al. Prognostic Value of Thrombus Volume and Interaction With First-Line Endovascular Treatment Device Choice. *Stroke* **2023**, *54*, 1056–1065. [CrossRef]
10. Bala, F.; Cimflova, P.; Singh, N.; Zhang, J.; Kappelhof, M.; Kim, B.J.; Najm, M.; Golan, R.; Elebute, I.; Benali, F.; et al. Impact of vessel tortuosity and radiological thrombus characteristics on the choice of first-line thrombectomy strategy: Results from the ESCAPE-NA1 trial. *Eur. Stroke J.* **2023**, *8*, 675–683. [CrossRef]
11. Warner, J.J.; Harrington, R.A.; Sacco, R.L.; Elkind, M.S.V. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke. *Stroke* **2019**, *50*, 3331–3332. [CrossRef]
12. Hofmeister, J.; Bernava, G.; Rosi, A.; Vargas, M.I.; Carrera, E.; Montet, X.; Burgermeister, S.; Poletti, P.A.; Platon, A.; Lovblad, K.O.; et al. Clot-Based Radiomics Predict a Mechanical Thrombectomy Strategy for Successful Recanalization in Acute Ischemic Stroke. *Stroke* **2020**, *51*, 2488–2494. [CrossRef]
13. Santos, E.M.M.; Yoo, A.J.; Beenen, L.F.; Berkhemer, O.A.; den Blanken, M.D.; Wismans, C.; Niessen, W.J.; Majoie, C.B.; Marquering, H.A. Observer variability of absolute and relative thrombus density measurements in patients with acute ischemic stroke. *Neuroradiology* **2016**, *58*, 133–139. [CrossRef]
14. Zhu, K.; Bala, F.; Zhang, J.; Benali, F.; Cimflova, P.; Kim, B.J.; McDonough, R.; Singh, N.; Hill, M.D.; Goyal, M.; et al. Automated Segmentation of Intracranial Thrombus on NCCT and CTA in Patients with Acute Ischemic Stroke Using a Coarse-to-Fine Deep Learning Model. *Am. J. Neuroradiol.* **2023**, *44*, 641–648. [CrossRef]
15. Dumitriu LaGrange, D.; Hofmeister, J.; Rosi, A.; Vargas, M.I.; Wanke, I.; Machi, P.; Lövblad, K.-O. Predictive value of clot imaging in acute ischemic stroke: A systematic review of artificial intelligence and conventional studies. *Neurosci. Inform.* **2023**, *3*, 100114. [CrossRef]
16. Mojtahedi, M.; Kappelhof, M.; Ponomareva, E.; Tolhuisen, M.; Jansen, I.; Bruggeman, A.A.E.; Dutra, B.G.; Yo, L.; Lecouffe, N.; Hoving, J.W.; et al. Fully Automated Thrombus Segmentation on CT Images of Patients with Acute Ischemic Stroke. *Diagnostics* **2022**, *12*, 698. [CrossRef]

17. Gliklich, R.E.; Leavy, M.B.; Dreyer, N.A. (Eds.) Chapter 3, Registry Design. In *Registries for Evaluating Patient Outcomes: A User's Guide*, 4th ed.; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2020. Available online: https://www.ncbi.nlm.nih.gov/books/NBK562568/ (accessed on 21 February 2024).
18. Jansen, I.G.H.; Mulder, M.J.H.L.; Goldhoorn, R.J.B. Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (MR CLEAN Registry). *BMJ* **2018**, *360*, K949. [CrossRef] [PubMed]
19. LeCouffe, N.E.; Kappelhof, M.; Treurniet, K.M.; Rinkel, L.A.; Bruggeman, A.E.; Berkhemer, O.A.; Wolff, L.; van Voorst, H.; Tolhuisen, M.L.; Dippel, D.W.J.; et al. A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke. *N. Engl. J. Med.* **2021**, *385*, 1833–1844. [CrossRef] [PubMed]
20. Dumitriu LaGrange, D.; Reymond, P.; Brina, O.; Zboray, R.; Neels, A.; Wanke, I.; Lövblad, K.O. Spatial heterogeneity of occlusive thrombus in acute ischemic stroke: A systematic review. *J. Neuroradiol.* **2023**, *50*, 352–360. [CrossRef] [PubMed]
21. Qiu, W.; Kuang, H.; Nair, J.; Assis, Z.; Najm, M.; McDougall, C.; McDougall, B.; Chung, K.; Wilson, A.T.; Goyal, M.; et al. Radiomics-Based Intracranial Thrombus Features on CT and CTA Predict Recanalization with Intravenous Alteplase in Patients with Acute Ischemic Stroke. *Am. J. Neuroradiol.* **2019**, *40*, 39–44. [CrossRef]
22. Baek, J.H.; Yoo, J.; Song, D.; Kim, Y.D.; Nam, H.S.; Kim, B.M.; Kim, D.J.; Lee, H.S.; Heo, J.H. Predictive value of thrombus volume for recanalization in stent retriever thrombectomy. *Sci. Rep.* **2017**, *7*, 15938. [CrossRef]
23. Borst, J.; Berkhemer, O.A.; Santos, E.M.M.; Yoo, A.J.; Den Blanken, M.; Roos, Y.B.W.E.M.; Van Bavel, E.; Van Zwam, W.H.; Van Oostenbrugge, R.J.; Lingsma, H.F.; et al. Value of thrombus CT Characteristics in Patients with Acute Ischemic Stroke. *Am. J. Neuroradiol.* **2017**, *38*, 1758–1764. [CrossRef]
24. Jagani, M.; Kallmes, D.F.; Brinjikji, W. Correlation between clot density and recanalization success or stroke etiology in acute ischemic stroke patients. *Interv. Neuroradiol.* **2017**, *23*, 274–278. [CrossRef]
25. Liu, Y.; Brinjikji, W.; Abbasi, M.; Dai, D.; Arturo Larco, J.L.; Irfan Madhani, S.; Shahid, A.H.; Madalina Mereuta, O.; Nogueira, R.G.; Kvamme, P.; et al. Quantification of clot spatial heterogeneity and its impact on thrombectomy. *J. Neurointerv. Surg.* 2021; *ahead of print*. [CrossRef]
26. Moftakhar, P.; English, J.D.; Cooke, D.L.; Kim, W.T.; Stout, C.; Smith, W.S.; Dowd, C.F.; Higashida, R.T.; Halbach, V.V.; Hetts, S.W. Density of thrombus on admission CT predicts revascularization efficacy in large vessel occlusion acute ischemic stroke. *Stroke* **2013**, *44*, 243–245. [CrossRef]
27. Santos, E.M.M.; Arrarte Terreros, N.; Kappelhof, M.; Borst, J.; Boers, A.M.M.; Lingsma, H.F.; Berkhemer, O.A.; Dippel, D.W.J.; Majoie, C.B.; Marquering, H.A.; et al. Associations of thrombus perviousness derived from entire thrombus segmentation with functional outcome in patients with acute ischemic stroke. *J. Biomech.* **2021**, *128*, 110700. [CrossRef]
28. Kappelhof, M.; Tolhuisen, M.L.; Treurniet, K.M.; Dutra, B.G.; Alves, H.; Zhang, G.; Brown, S.; Muir, K.W.; Dávalos, A.; Roos, Y.B.W.E.M.; et al. Endovascular Treatment Effect Diminishes With Increasing Thrombus Perviousness. *Stroke* **2021**, *52*, 3633–3641. [CrossRef] [PubMed]
29. Byun, J.-S.; Nicholson, P.; Hilditch, C.A.; Chun, A.; Tsang, O.; Pereira, M.; Krings, T.; Fang, Y.; Brinjikji, W. Thrombus perviousness is not associated with first-pass revascularization using stent retrievers. *Interv. Neuroradiol.* **2018**, *25*, 285–290. [CrossRef] [PubMed]
30. Boodt, N.; Compagne, K.C.J.; Dutra, B.G.; Samuels, N.; Tolhuisen, M.L.; Alves, H.C.B.R.; Kappelhof, M.; Lycklama à Nijeholt, G.J.; Marquering, H.A.; Majoie, C.B.L.M.; et al. Stroke Etiology and Thrombus Computed Tomography Characteristics in Patients with Acute Ischemic Stroke: A MR CLEAN Registry Substudy. *Stroke* **2020**, *51*, 1727–1735. [CrossRef] [PubMed]
31. Alves, H.C.; Treurniet, K.M.; Dutra, B.G.; Jansen, I.G.H.; Boers, A.M.M.; Santos, E.M.M.; Berkhemer, O.A.; Dippel, D.W.J.; Van Der Lugt, A.; Van Zwam, W.H.; et al. Associations between collateral status and thrombus characteristics and their impact in anterior circulation stroke. *Stroke* **2018**, *49*, 391–396. [CrossRef] [PubMed]
32. Cicchetti, D.V. Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. *Psychol. Assess.* **1994**, *6*, 284. [CrossRef]

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Peripheral Artery Disease among a High-Risk Asian Population with Ischaemic Stroke, Cardiovascular Disease, or Diabetes Mellitus

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Abstract: Background: Peripheral artery disease (PAD) affects more than 100 million people globally. Most PAD studies have been performed among predominantly White populations—less is known about other ethnicities. The aim of this cross-sectional study was to determine the prevalence and risk factors of PAD in a high-risk Asian population with ischaemic stroke (IS), myocardial infarction, unstable angina (CVD), or diabetes mellitus (DM). **Methods:** Patients admitted for IS, CVD, or DM were recruited. Data were collected on age, sex, body mass index (BMI), index condition (CVD, IS, DM), history of hypertension, DM, hypercholesterolaemia, cigarette smoking, and claudication. The Edinburgh Claudication Questionnaire was administered, the ankle brachial index (ABI) was determined, and PAD was diagnosed if ABI was $\leq$0.9. **Results:** Of the 450 subjects recruited, 150 were placed in each index disease group, the mean age was 61.9 $\pm$ 10.32 years, 43.1% were female, and the mean BMI was 23.9 $\pm$ 4.3. Hypertension was reported in 59.3%, DM in 63.6%, hypercholesterolaemia in 39.6%, and smoking in 42.9% of patients. The prevalence of PAD was 27.1%, 22.0% in IS, 29.3% in CAD, and 30.0% in DM. PAD was associated with increasing age (adjusted odds ratio (aOR) 1.04/year, 95% confidence interval [CI] 1.01–1.06; $p < 0.001$), reduced BMI (aOR 0.94, 95% CI 0.89–0.99; $p = 0.026$), DM (aOR 1.59, 95% CI 1.20–3.18; $p = 0.007$), and hypercholesterolaemia (aOR 1.82, 95% CI 1.17–2.28; $p = 0.007$). It was more frequent in non-lacunar versus lacunar acute IS, non-ST segment elevation versus ST-segment elevation acute myocardial infarction, and insulin-treated versus non-insulin-treated DM. **Conclusions:** Our study showed a high prevalence of PAD among high-risk Asian patients. This was associated with increasing age, DM, and hypercholesterolaemia and inversely associated with BMI. Different rates were found in sub-groups of IS, CVD, and DM. Systematic approaches were used to identify these high-risk individuals and to improve their outcomes.

Keywords: peripheral artery disease; ischaemic stroke; cardiovascular disease; diabetes mellitus

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1. Introduction

Peripheral arterial disease (PAD) is atherosclerosis leading to the narrowing of the major arteries distal to the aortic arch [1]. In 2019, an estimated 113,443,016 individuals worldwide suffered from PAD, which is a 72% increase from 1990 [2]. The age-standardised prevalence per 100,000 in 2019 was 1402 per 100,000, while the age-standardised disability-adjusted life years lost (DALYs) attributable to PAD was 19.5 per 100,000, representing a 37% increase over 1990. The global burden due to PAD is expected to keep rising. A sex difference has also been noted, with prevalence and disability being higher in females, while mortality and years of life lost are greater among males. On a global basis, the number of people with PAD is highest in the Western Pacific region, intermediate in the Americas, Southeast Asia and Europe, and lowest in the Eastern Mediterranean region

and Africa [3]. PAD prevalence is higher in the European Union than in other European countries [4] and in Black individuals compared to other ethnicities in the United States [5]. The burden of disease increases with the increasing sociodemographic index (SDI), with lower SDI regions undergoing a rapid growth of PAD-related burden compared to higher SDI regions [6]. These variations may be related to differences in the awareness, detection and control of vascular risk factors, accessibility to healthcare and differences in SD. But ethnicity may also have a role.

There are a number of well-recognised risk factors for PAD. These include advancing age (odds ratio OR 1.55 per 10-year increase, 95% confidence interval 95% CI 1.38–1.75), sex (OR 0.74, 95% CI 0.6–0.91 in males) diabetes mellitus (DM, OR 1.89, 95% CI 1.68–2.13), smoking (former smoking OR 1.70, 95% CI 1.39–2.09, current smoking OR 2.82, 95% CI 2.00–3.98), hypertension (OR 1.67, 95% CI 1.50–1.86), obesity (BMI > 30 kg/m^2, OR 1.55, 95% CI 1.23–1.96) and hypercholesterolaemia (OR 1.34, 95% CI 1.17–1.53); it is also associated with stroke (OR 2.35, 95% CI 1.74–3.16) and coronary heart disease (OR 1.72, 95% CI 1.48–1.99) [3]. With the demographic trend of continued ageing in the world population and the projected rise in vascular risk factors, a greater burden of PAD can be expected in the foreseeable future.

The clinical spectrum of those with PAD ranges from being asymptomatic to claudication to critical limb ischaemia [7]. Effective therapies to reduce progression and/or limb loss include the cessation of smoking, exercise programs for claudication, lipid-lowering therapy, anti-thrombotic therapy with a single antiplatelet agent or combination aspirin with rivaroxaban, treatment of hypertension with an angiotensin-converting enzyme or angiotensin receptor blocker, grafts and endovascular techniques [8–10].

In addition to limb loss, PAD is associated with poorer prognosis, reduced quality of life and increased mortality [11]. It may also be a marker for atherosclerotic outcomes in other vascular beds [12]. Evidence of coexisting PAD is of prognostic value. In the international REACH registry, which enrolled patients from 44 countries (including Singapore) with established CVD, CeVD, PAD or with at least three atherothrombotic risk factors, the 3-year rate of myocardial infarction, stroke, vascular death or rehospitalisation for patients with symptomatic vascular disease in one vascular bed was 25.5% versus 40.5% among those with disease in multiple vascular beds, ($p < 0.001$) [13].

While claudication is a classical symptom of PAD, a careful history and physical examination are needed to rule out other causes of lower limb pain, including musculoskeletal and neurogenic causes [14]. The Edinburgh Claudication Questionnaire, an improved version of the World Health Organization (WHO)/Rose questionnaire, is a validated screening tool for PAD [15]. The ankle brachial index (ABI) is an inexpensive, non-invasive test where the ratio of the highest systolic blood pressure at the ankle to that of the brachial artery ≤ 0.9 is suggestive of PAD, with high sensitivity and specificity [16,17].

Most of the studies on PAD have been performed among white people—much less is known about the characteristics of this disease in other ethnicities [18]. Differing patterns of disease have been observed between Caucasians (more abdominal aortic aneurysms) and Black individuals and Asians (more distal arterial disease) [19]. Overall, the prevalence of PAD is higher in Black individuals [20] and lower in South Asians [21]. More data on Asian populations are needed.

There is an increased risk of PAD among those with stroke, CVD, or the aforementioned DM [3]. In a Malaysian study of 301 patients aged 32–90 years with established CVD, ischaemic stroke (IS) or DM, the overall prevalence of PAD was 23%, and it was 33%, 28% and 24% among patients with pre-existing CVD, IS and DM, respectively [22]. However, that study had small patient numbers and did not explore the risk ratios of PAD associated with the individual risk factors, nor among the subtypes of the disease groups investigated, to determine who was at particularly high risk of having PAD.

The aim of this study was to determine the prevalence of PAD in a high-risk Asian population with IS, CVD or DM, the risk of its associated factors and investigate PAD within each of the three included disease groups.

2. Materials and Methods

The study was performed in Tan Tock Seng Hospital (TTSH), a public hospital located in central Singapore, serving the surrounding population of 1.4 million people.

Consecutive patients admitted to the Departments of Neurology for IS, Cardiology for myocardial infarction or unstable angina (CVD), or General Medicine with DM between 1 April and 30 September 2000 were approached to participate. Inclusion criteria included the following: diagnosis with IS, CVD or DM; informed consent obtainable from patients or their legally acceptable representative. Exclusion criteria were those who were aged less than 40 years, drowsy or aphasic throughout their hospital stay, or had amputations of both upper limbs or both lower limbs. Recruitment among the 3 disease groups was concurrent.

After obtaining informed consent from eligible subjects in the language they were conversant in, the trained study nurse administered a standardised questionnaire. Data were collected on subject demographics, age, sex, and index condition (IS, CVD, DM). Hypertension was diagnosed if there was a history of hypertension or if the patient had been prescribed medications for hypertension. DM was diagnosed if there was a history of DM or if the patient had been prescribed medications for DM. Hypercholesterolaemia was diagnosed if there was a history of hypercholesterolaemia or if the patient had been prescribed medications for hypercholesterolaemia. Cigarette smoking was diagnosed if the patient was a current or former smoker. Claudication was diagnosed if there was a history of calf pain on either side when walking, which was relieved by rest). The body mass index (BMI = weight/height^2) was calculated. Subjects were then asked to fill in the Edinburgh Claudication Questionnaire. Finally, the ABI was determined in the right and left leg with the subject lying at rest—the highest systolic blood pressure (SBP) in the dorsalis pedis or posterior tibial artery of that lower limb was determined using the Doppler probe and was divided by the highest SBP after measuring in both brachial arteries using the standard auscultatory technique. PAD was diagnosed if ABI was $\leq$0.9 in either limb. There are recommendations to use ABI > 1.4 [23,24] or the toe-brachial index, especially among those with diabetes mellitus [17,25], to diagnose PAD. However, these parameters and indices were not used in the analysis of this study so as to allow comparisons of our findings with other studies discussed in this paper, as they largely used ABI < 0.9 to diagnose PAD. The research staff performing the ABI measurement were blinded to the other study information.

Data were analysed using the Statistical Package for Social Sciences (SPSS) v25 (New York, NY, USA). Mean and standard deviations were calculated for normally distributed continuous variables, median and interquartile ranges for non-normally distributed continuous variables, and proportions for categorical variables. Significant differences in baseline characteristics were evaluated among those with and without PAD by univariable analysis, using the unpaired t-test for continuous variables and chi-square for categorical variables. Finally, multivariable analysis using logistic regression was performed using variables that were significantly associated with the univariable analysis for PAD. Statistical significance was taken at the $p = 0.05$ level.

Using the estimate of a prevalence of PAD of 25% found in the Malaysian study [22] and the range of 24–26% for a 95% CI, the sample size would be 451 subjects. Thus, the target was to recruit 450 subjects, 150 in each of the 3 groups of IS, CVD and DM.

3. Results

The mean age of study subjects was 62 years, with fewer females than males and the described risk vascular factors (Table 1). The overall prevalence of PAD was 27.1%, higher than the symptoms of claudication or by the Edinburgh Questionnaire. By index disease, females outnumbered males only among those with DM, and hypercholesterolaemia and smoking were most frequent among those with CVD. Previous myocardial infarction was the least frequent among IS, while a previous stroke was the least common among those with CVD. While not statistically significant, PAD, as assessed by the symptoms of

claudication, the Edinburgh Questionnaire and ABI, is highest among those with DM. Age and the number of years with DM were similar across all three index diseases.

Table 1. Characteristics of study subjects overall and by index disease.

Characteristic	Overall (n = 450)	Ischaemic Stroke (n = 150)	Cardiovascular Disease (n = 150)	Diabetes Mellitus (n = 150)	*p*-Value
Age, years mean ± SD	61.9 ± 10.3	62.7 ± 10.2	61.2 ± 11.3	61.7 ± 9.5	0.438
Female %	43.1	44.7	30.7	54.0	<0.001
BMI	23.9 ± 4.3	24.1 ± 4.1	24.0 ± 4.2	23.8 ± 4.5	0.76
Hypertension %	59.3	63.3	56.7	58.0	0.46
Diabetes mellitus %	63.6	43.3	47.3	100.0	<0.001
Number of years of diabetes mellitus if diabetic; years mean ± SD	10.5 ± 9.1	9.8 ± 7.5	10.9 ± 8.4	10.7 ± 10.0	0.76
Hypercholesterolaemia %	39.6	30.0	52.0	36.7	<0.001
Smoker %	42.9	38.0	54.0	36.7	<0.001
Previous stroke %	14.9	18.7	7.3	18.7	0.006
Previous myocardial infarction %	11.3	3.3	18.0	12.7	0.001
Intermittent claudication %	18.4	16.0	15.3	24.0	0.098
PAD by Edinburgh Questionnaire %	11.1	12.0	8.7	12.7	0.26
PAD by ABI %	27.1	22.0	29.3	30.0	0.224

Legend—SD, standard deviation; ABI, ankle brachial index.

Within the index diseases, the frequency of PAD varied among the subtypes (Table 2). Among IS, PAD by ABI was found in 16.5% of lacunar infarction and 32.1% of non-lacunar infarction ($p = 0.03$). For CVD, PAD by ABI was found in 25.4% of unstable angina, 28.2% of ST segment elevation acute myocardial infarction, and 34.6% of non-ST-segment elevation myocardial infarction ($p = 0.56$). Among DM patients, PAD by ABI was found in 28.9% of non-insulin-treated diabetics and 60.0% of insulin-treated diabetics ($p = 0.14$).

Table 2. Peripheral disease in index disease subtypes.

Disease	Subtype	PAD Present (n)	PAD Absent (n)	*p*
Ischaemic stroke	Lacunar	16	81	0.03
	Non-lacunar	17	13	
Cardiovascular disease	Unstable angina	15	44	0.56
	ST elevation myocardial infarction	11	28	
	Non-ST elevation myocardial infarction	18	34	
Diabetes mellitus	Insulin-dependant	3	2	0.14
	Non-insulin dependant	42	103	

PAD occurred more frequently among older ages, females, and those with DM or hypercholesterolaemia; it was also associated with lower BMI (Table 3). However, the effect of sex was lost in multivariable analysis. The odds increased by 4% per year, and increasing

age was nearly doubled by the presence of DM or hypercholesterolaemia and lowered by 6% for each increased unit of BMI. There was no significant effect on smoking status or index disease.

Table 3. Factors associated with peripheral artery disease, univariable, and multivariable analyses.

Characteristic	PAD Present (n = 122)	PAD Absent (n = 328)	*p*-Value	OR	95% CI	*p*-Value
Age, years mean ± SD	65.1 ± 10.1	60.65 ± 10.2	0.001	1.04/year	1.01–1.06	<0.001
Female %	52.5	39.6	0.015	1.50	0.96–2.33	0.07
BMI	23.1 ± 4.5	24.3 ± 4.1	0.014	0.94	0.89–0.99	0.026
Hypertension %	61.5	58.5	0.57			
Diabetes mellitus %	75.4	59.1	0.001	1.95	1.20–3.18	0.007
Number of years of diabetes mellitus if diabetic; years mean ± SD	11.8 ± 9.2	9.9 ± 8.9	0.094			
Hypercholesterolemia %	50.0	35.7	0.006	1.82	1.17–2.82	0.007
Smoker %	41.0	43.6	0.62			
Index disease Ischaemic stroke Cardiovascular disease Diabetes mellitus	 27.0 36.1 36.9	 35.7 32.3 32.0	0.224			
Intermittent claudication %	30.3	14.0	<0.001			
PAD by Edinburgh Questionnaire %	19.7	7.9	<0.001			

Legend—PAD, peripheral vascular disease; OR, odds ratio; SD, standard deviation.

4. Discussion

Our study found that PAD was present in 27% of a high-risk Asian population with ischaemic stroke, cardiovascular disease, and diabetes mellitus. PAD was detected more frequently by ABI than symptoms of claudication or the Edinburgh questionnaire. Upon multivariable analysis, PAD was most strongly associated with increasing age, diabetes mellitus and hypercholesterolaemia and reduced with higher BMI.

The prevalence of PAD of 27.1% was comparable to the 25% found in the Malaysian study among similarly high-risk patients [22]. They found PAD in 23–28% of patients with IS, 33% of patients with pre-existent CVD, and 24% with DM; the corresponding frequencies in our study were 22.0%, 29.3%, and 30.0%, respectively. This is understandable as Malaysia and Singapore are neighbouring countries with Chinese, Malays and Indians as the main ethnic groups.

PAD was detected in 22% of our IS patients. Among 1293 Korean patients with acute IS or a transient ischaemic attack (TIA), an ABI of $\leq$0.9 was found in 13.0% [26]. In a Pakistani study of 327 IS patients, the mean age was 57.6 ± 12.8 years, and PAD was identified in 18.3% of patients with ABI [27]. In Thailand, an ABI $\leq$ 0.9 was observed in 18.1% of 747 IS or TIA patients [28].

We identified PAD in 29.3% of our patients with CVD. Among 711 Korean patients, the mean age was 63.4 ± 11.0 years after undergoing percutaneous coronary intervention for CVD, and the prevalence of PAD was considerably lower, at 12.8% [29]. Approximately 38.4% of 117 Thai patients, with a mean age of 65 years, undergoing coronary angiography had PAD [30], while 19.1% of patients with coronary artery disease had PAD in another Singapore study [31].

PAD was diagnosed in 33% of our DM patients. In a multi-centre study of 6625 patients with DMs in Korea, China, Taiwan, Hong Kong, Indonesia, Thailand and the

Philippines, the mean age was 63.7 ± 8.2 years, and the frequency of PAD was 17.7% using ABI ≤ 0.9 [32]. In a study of 3906 diabetics in Japan, the mean age was 60.8 years, and the frequency of PAD was 7.6% using a device "form PWV/ABI" [33]. In a Singapore study, 521 diabetics had a prevalence of PAD, defined as a resting ABI of <0.9 on either leg and/or a history of gangrene or non-traumatic amputation in 15.2% (95% CI, 12.3–18.5) [34]. As these studies are based on different disease populations, differing ages, and different diagnostic techniques to detect PAD, the prevalence of PAD among these studies is not directly comparable. Still, the prevalence of PAD in our study appears higher than in most Asian studies and is closest to that found in Malaysia.

Our study found that among ISs, PAD via the ABI was found in 32.1% of patients experiencing non-lacunar infarction and 16.5% with lacunar infarction. In a study in China, 31.51% of patients with stroke from large artery atherosclerosis had PAD (ABI < 0.9), compared with 19.75% with small artery disease ($p = 0.045$) [35]. In a Korean study on IS, the prevalence of abnormal ABI was 18.4% in large artery atherosclerosis and 7% in small artery disease ($p < 0.001$) [26]. In the previously mentioned Thai study, abnormal ABI was more frequent among those with large artery disease (20.4%, $p < 0.001$) [28]

In our study, for CVD, PAD by ABI was found in 25.4% of unstable angina, 28.2% of ST-segment elevation acute myocardial infarction, and 34.6% of non-ST-segment- elevation myocardial infarction patients. In a French study, previous non-Q-wave myocardial infarction was associated with PAD (OR 1.50; 95% CI, 1.08 to 2.08; $p = 0.02$) [36].

Our study found strong associations between PAD and increasing age, DM and hypercholesterolaemia. This is consistent with the meta-analysis showing risk factors for PAD, including advancing age (OR per 10-year increase 1.55, 95% CI 1.38–1.75), DM (OR 1.89, 95% CI 1.68–2.13), and hypercholesterolaemia (OR 1.34, 95% CI 1.17–1.53); it also showed strong associations with smoking and hypertension [3]. While this study showed a non-significant trend among smokers, no association was found with hypertension—the reasons for these observations are unclear and would require further investigation.

Of interest was our finding of an inverse association between PAD and BMI, consistent with the so-called 'obesity paradox', where PAD is less frequent among those with obesity. A recent review of studies on obesity and PAD had mixed findings [37]. Some studies found positive associations of PAD with a high BMI or upper body obesity or only among women; others showed that a high BMI or being overweight was a protective factor against PAD. In a study in China on 11,477 community-dwelling adults aged 40 years and above, for each standard deviation increase in the weighted BMI genetic risk score, the odds ratio (OR) for PAD was 1.17 (95% CI 1.07–1.27; $p = 0.0004$) [38]. However, a Thai study found that being overweight (body mass index [BMI] > 25 kg/m^2, had a reduced risk of PAD (OR = 0.54, $p < 0.05$) [39].

Different studies have used differing criteria for the diagnosis of PAD. Clinically, while a single question on calf pain when walking can be asked, it is preferable that a validated questionnaire, such as the WHO/Rose or Edinburgh Claudication Questionnaire, be used. As an improved version of the World Health Organization (WHO)/Rose questionnaire, it is a validated screening tool for PAD with a sensitivity of 91.3% (95% CI, 88.1–94.5%) and specificity of 99.3% (95% CI, 98.9–100%) [15]. Where feasible, an objective assessment by the ABI would allow accurate documentation and the assessment of severity. The ABI is an inexpensive, non-invasive test, where the ratio of the highest systolic blood pressure at the ankle to that of the brachial artery ≤0.9 is suggestive of PAD, with a sensitivity of 61% (95% CI 55–69%), and specificity of 92% (95% CI, 89–95%) [16,17]. We note that among those diagnosed as having PAD on ABI, only 30.3% were positive on the question of intermittent claudication, and 19.7% by the questionnaire; among those without PAD, the proportions were 14.0% and 7.9%, respectively. In the Malaysian study, only 27% of those diagnosed as having PAD by ABI had symptoms [22]. This may be reflective of the subjective nature of questions and questionnaires, which are affected by interpretation by the patient—this further supports the use of an objective assessment using the ABI measurement to diagnose PAD.

In our study, the prevalence of PAD was highest using the ABI in all three disease groups. In view of the high prevalence, the consequences if left untreated and the availability of evidence-based interventions, detecting PAD by ABI should be part of the routine assessment of patients at risk of PAD.

The detection of PAD is important, not only for its presence. It may also be a marker for atherosclerotic outcomes in other vascular beds. Among those with established cerebro- (CeVD) or cardiovascular (CVD) disease, having PAD on top of this increases the risk of major cardiac events; in the EUCLID trial, compared to those with isolated PAD, the adjusted hazard ratios (aHR) were 1.34 (95% CI, 1.15–1.57) for PAD + CeVD, 1.65 (95% CI, 1.43–1.91) for PAD + CVD, and 1.99 (95% CI, 1.69–2.34) for PAD + CeVD + CVD [12].

With the rising numbers and ageing of world populations, the burden of PAD is likely to keep increasing. This can be counter-balanced by increasing efforts to effectively detect and optimally treat vascular risk factors—this will also help reduce the burden of other vascular diseases, such as stroke and CAD. Screening for PAD by asking the patient to fill in the Edinburgh questionnaire while sitting in the clinic waiting room, or even better, by trained healthcare professionals performing ABI at regular intervals among those at risk of PAD, should become part of the routine evaluation of our patients in primary care. A system should be in place to allow seamless referral for those suspected to have PAD to accessible specialists and teams interested and trained in the management of PAD. Public awareness of PAD can be raised by health education campaigns.

Our study has some limitations. Although it was a single-centre study, and several other studies corroborated our findings, the sample size was modest—stronger associations may have been found with a larger study population. The study was performed on hospitalised patients, and the findings may not be generalisable to the community. ABI < 0.9 was used to diagnose PAD; however, an ABI > 1.4, or the toe-brachial index, especially among those with diabetes mellitus, have been proposed. Thus, the prevalence of PAD may have been underestimated in this study. Still, this study has some strengths—the overall sample size was not small, the study population was well-defined, a standardised questionnaire and well-recognised assessment tools were used (Edinburgh Questionnaire, ABI), and the study findings were consistent with the published literature. It also provides hard-to-find data on Asian patients. Overall, our study techniques were robust and provided important information for PAD among Asian patients with IS, CVD or DM.

5. Conclusions

This study detected PAD by ABI in a quarter of high-risk patients with IS, CVD, or DM. Consistent with the published literature, PAD was associated with increasing age, diabetes mellitus and hypercholesterolemia. Different rates were found within sub-groups and IS, CVD and DM. More such studies on PAD among Asian patients are needed to help fashion PAD management guidelines developed for the Asia–Pacific region [40]. On a practical basis, screening for PAD by ABI should be routinely performed among patients with ischaemic stroke, cardiovascular disease or diabetes mellitus.

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References

1. Hennion, D.R.; Siano, K.A. Diagnosis and treatment of peripheral arterial disease. *Am. Fam. Physician* **2013**, *88*, 306–310. [PubMed]
2. Eid, M.A.; Mehta, K.; Barnes, J.A.; Wanken, Z.; Columbo, J.A.; Stone, D.H.; Goodney, P.; Smith, M.M. The global burden of peripheral artery disease. *J. Vasc. Surg.* **2023**, *77*, 1119–1126.e1. [CrossRef] [PubMed]
3. Song, P.; Rudan, D.; Zhu, Y.; Fowkes, F.J.I.; Rahimi, K.; Fowkes, F.G.R.; Rudan, I. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: An updated systematic review and analysis. *Lancet Glob. Health* **2019**, *7*, e1020–e1030. [CrossRef] [PubMed]
4. Olinic, D.M.; Spinu, M.; Olinic, M.; Homorodean, C.; Tataru, D.A.; Liew, A.; Schernthaner, G.H.; Stanek, A.; Fowkes, G.; Catalano, M. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. *Int. Angiol.* **2018**, *37*, 327–334. [CrossRef] [PubMed]
5. Selvin, E.; Erlinger, T.P. Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* **2004**, *110*, 738–743. [CrossRef] [PubMed]
6. You, Y.; Wang, Z.; Yin, Z.; Bao, Q.; Lei, S.; Yu, J.; Xie, X. Global disease burden and its attributable risk factors of peripheral arterial disease. *Sci. Rep.* **2023**, *13*, 19898. [CrossRef] [PubMed]
7. Ouriel, K. Peripheral arterial disease. *Lancet* **2001**, *358*, 1257–1264. [CrossRef] [PubMed]
8. Abramson, B.L.; Al-Omran, M.; Anand, S.S.; Albalawi, Z.; Coutinho, T.; de Mestral, C.; Dubois, L.; Gill, H.L.; Greco, E.; Guzman, R.; et al. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. *Can. J. Cardiol.* **2022**, *38*, 560–587. [CrossRef] [PubMed]
9. Aboyans, V.; Ricco, J.B.; Bartelink, M.E.L.; Björck, M.; Brodmann, M.; Cohnert, T.; Collet, J.P.; Czerny, M.; De Carlo, M.; Debus, S.; et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: The European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur. Heart J.* **2018**, *39*, 763–816. [CrossRef] [PubMed]
10. Gerhard-Herman, M.D.; Gornik, H.L.; Barrett, C.; Barshes, N.R.; Corriere, M.A.; Drachman, D.E.; Fleisher, L.A.; Fowkes, F.G.R.; Hamburg, N.M.; Kinlay, S.; et al. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2017**, *69*, e71–e126. [CrossRef] [PubMed]
11. Bauersachs, R.; Debus, S.; Nehler, M.; Huelsebeck, M.; Balradj, J.; Bowrin, K.; Briere, J.-B. A Targeted Literature Review of the Disease Burden in Patients With Symptomatic Peripheral Artery Disease. *Angiology* **2020**, *71*, 303–314. [CrossRef] [PubMed]
12. Gutierrez, J.A.; Mulder, H.; Jones, W.S.; Rockhold, F.W.; Baumgartner, I.; Berger, J.S.; Blomster, J.I.; Fowkes, F.G.R.; Held, P.; Katona, B.G.; et al. Polyvascular Disease and Risk of Major Adverse Cardiovascular Events in Peripheral Artery Disease: A Secondary Analysis of the EUCLID Trial. *JAMA Netw. Open* **2018**, *1*, e185239. [CrossRef] [PubMed] [PubMed Central]
13. Alberts, M.J.; Bhatt, D.L.; Mas, J.-L.; Ohman, E.M.; Hirsch, A.T.; Röther, J.; Salette, G.; Goto, S.; Smith, S.C.; Liau, C.-S.; et al. REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur. Heart J.* **2009**, *30*, 2318–2326. [CrossRef] [PubMed] [PubMed Central]
14. Kullo, I.J.; Rooke, T.W. Peripheral Artery Disease. *N. Engl. J. Med.* **2016**, *374*, 861–871. [CrossRef] [PubMed]
15. Leng, G.C.; Fowkes, F.G. The Edinburgh Claudication Questionnaire: An improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J. Clin. Epidemiol.* **1992**, *45*, 1101–1109. [CrossRef] [PubMed]
16. Aboyans, V.; Criqui, M.H.; Abraham, P.; Allison, M.A.; Creager, M.A.; Diehm, C.; Fowkes, F.G.; Hiatt, W.R.; Jönsson, B.; Lacroix, P.; et al. Measurement and interpretation of the ankle-brachial index: A scientific statement from the American Heart Association. *Circulation* **2012**, *126*, 2890–2909. [CrossRef]
17. Herraiz-Adillo, Á.; Cavero-Redondo, I.; Álvarez-Bueno, C.; Pozuelo-Carrascosa, D.P.; Solera-Martínez, M. The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: A systematic review and meta-analysis. *Atherosclerosis* **2020**, *315*, 81–92. [CrossRef] [PubMed]
18. Bennett, P.C.; Silverman, S.; Gill, P.S.; Lip, G.Y. Ethnicity and peripheral artery disease. *QJM* **2009**, *102*, 3–16. [CrossRef] [PubMed]
19. Hobbs, S.D.; Wilmink, A.B.; Bradbury, A.W. Ethnicity and peripheral arterial disease. *Eur. J. Vasc. Endovasc. Surg.* **2003**, *25*, 505–512. [CrossRef] [PubMed]
20. Vitalis, A.; Lip, G.Y.; Kay, M.; Vohra, R.K.; Shantsila, A. Ethnic differences in the prevalence of peripheral arterial disease: A systematic review and meta-analysis. *Expert Rev. Cardiovasc. Ther.* **2017**, *15*, 327–338. [CrossRef] [PubMed]
21. Sebastianski, M.; Makowsky, M.J.; Dorgan, M.; Tsuyuki, R.T. Paradoxically lower prevalence of peripheral arterial disease in South Asians: A systematic review and meta-analysis. *Heart* **2014**, *100*, 100–105. [CrossRef] [PubMed]
22. Amudha, K.; Chee, K.H.; Tan, K.S.; Tan, C.T.; Lang, C.C. Prevalence of peripheral artery disease in urban high-risk Malaysian patients. *Int. J. Clin. Pract.* **2003**, *57*, 369–372. [CrossRef] [PubMed]
23. Golledge, J.; Moxon, J.V.; Rowbotham, S.; Pinchbeck, J.; Quigley, F.; Jenkins, J. High ankle brachial index predicts high risk of cardiovascular events among people with peripheral artery disease. *PLoS ONE* **2020**, *15*, e0242228. [CrossRef] [PubMed]

24. Yang, Y.; Liu, L.; Sun, H.; Nie, F.; Hu, X. Relation between high Ankle-Brachial Index and cardiovascular outcomes in the general population and cardiovascular disease: A meta-analysis. *Int. Angiol.* **2020**, *39*, 131–138. [CrossRef] [PubMed]
25. Singhania, P.; Das, T.C.; Bose, C.; Mondal, A.; Bhattacharjee, R.; Singh, A.; Mukhopadhyay, S.; Chowdhury, S. Toe brachial index and not ankle brachial index is appropriate in initial evaluation of peripheral arterial disease in type 2 diabetes. *Diabetol. Metab. Syndr.* **2024**, *16*, 52. [CrossRef] [PubMed]
26. Chung, P.-W.; Kim, D.-H.; Kim, H.Y.; Park, K.-Y.; Park, T.H.; Hong, J.M.; Kim, G.-M.; Bang, O.Y.; Oh, K.; Lee, S.J. Differences of ankle-brachial index according to ischemic stroke subtypes: The peripheral artery disease in Korean patients with ischemic stroke (PIPE) study. *Eur. Neurol.* **2013**, *69*, 179–184. [CrossRef] [PubMed]
27. Rahman, A.S.; Akhtar, S.W.; Jamal, Q.; Sultana, N.; Siddiqui, M.A.; Hassan, Z. Ischaemic stroke and peripheral artery disease. *J. Pak. Med. Assoc.* **2017**, *67*, 1138–1144. [PubMed]
28. Ratanakorn, D.; Keandoungchun, J.; Tegeler, C.H. Prevalence and association between risk factors, stroke subtypes, and abnormal ankle brachial index in acute ischemic stroke. *J. Stroke Cerebrovasc. Dis.* **2012**, *21*, 498–503. [CrossRef] [PubMed]
29. Kim, E.K.; Song, P.S.; Yang, J.H.; Bin Song, Y.; Hahn, J.-Y.; Choi, J.-H.; Gwon, H.-C.; Lee, S.H.; Hong, K.P.; Park, J.E.; et al. Peripheral artery disease in korean patients undergoing percutaneous coronary intervention: Prevalence and association with coronary artery disease severity. *J. Korean Med. Sci.* **2013**, *28*, 87–92. [CrossRef] [PubMed] [PubMed Central]
30. Dharmasaroja, P.A.; Piyayotai, D.; Hutayanon, P.; Buakhamsri, A.; Intharakham, K. Extracranial carotid stenosis and peripheral arterial disease in Thai patients with coronary artery disease. *Angiology* **2010**, *61*, 29–32. [CrossRef] [PubMed]
31. Sim, E.K.; Koo, G.; Adebo, O.A.; Lim, M.C.; Choo, M.H.; Lee, C.N. Prevalence of peripheral artery disease in patients with coronary artery disease. *Ann. Acad. Med. Singap.* **1993**, *22*, 898–900. [PubMed]
32. Rhee, S.Y.; Guan, H.; Liu, Z.M.; Cheng, S.W.-K.; Waspadji, S.; Palmes, P.; Tai, T.Y.; Suwanwalaikorn, S.; Kim, Y.S. PAD-SEARCH Study Group. Multi-country study on the prevalence and clinical features of peripheral arterial disease in Asian type 2 diabetes patients at high risk of atherosclerosis. *Diabetes Res. Clin. Pract.* **2007**, *76*, 82–92. [CrossRef] [PubMed]
33. Maeda, Y.; Inoguchi, T.; Tsubouchi, H.; Sawada, F.; Sasaki, S.; Fujii, M.; Saito, R.; Yanase, T.; Shimabukuro, M.; Nawata, H.; et al. High prevalence of peripheral arterial disease diagnosed by low ankle-brachial index in Japanese patients with diabetes: The Kyushu Prevention Study for Atherosclerosis. *Diabetes Res. Clin. Pract.* **2008**, *82*, 378–382. [CrossRef] [PubMed]
34. Lekshmi Narayanan, R.M.; Koh, W.P.; Phang, J.; Subramaniam, T. Peripheral arterial disease in community-based patients with diabetes in Singapore: Results from a Primary Healthcare Study. *Ann. Acad. Med. Singap.* **2010**, *39*, 525–527. [CrossRef] [PubMed]
35. Li, Z.; Liu, J. Coexistence of low ankle-brachial index and intra-cranial atherosclerosis? *Int. Angiol.* **2014**, *33*, 461–465. [PubMed]
36. Mourad, J.-J.; Cacoub, P.; Collet, J.-P.; Becker, F.; Pinel, J.-F.; Huet, D.; Sevestre-Pietri, M.-A.; Priollet, P. ELLIPSE scientific committee and study investigators. Screening of unrecognized peripheral arterial disease (PAD) using ankle-brachial index in high cardiovascular risk patients free from symptomatic PAD. *J. Vasc. Surg.* **2009**, *50*, 572–580. [CrossRef] [PubMed]
37. Lempesis, I.G.; Varrias, D.; Sagris, M.; Attaran, R.R.; Altin, E.S.; Bakoyiannis, C.; Palaiodimos, L.; Dalamaga, M.; Kokkinidis, D.G. Obesity and Peripheral Artery Disease: Current Evidence and Controversies. *Curr. Obes. Rep.* **2023**, *12*, 264–279. [CrossRef] [PubMed] [PubMed Central]
38. Huang, Y.; Xu, M.; Xie, L.; Wang, T.; Huang, X.; Lv, X.; Chen, Y.; Ding, L.; Lin, L.; Wang, W.; et al. Obesity and peripheral arterial disease: A Mendelian Randomization analysis. *Atherosclerosis* **2016**, *247*, 218–224. [CrossRef] [PubMed]
39. Sritara, P.; Sritara, C.; Woodward, M.; Wangsuphachart, S.; Barzi, F.; Hengprasith, B.; Yipintsoi, T. Prevalence and risk factors of peripheral arterial disease in a selected Thai population. *Angiology* **2007**, *58*, 572–578. [CrossRef] [PubMed]
40. Abola, M.T.B.; Golledge, J.; Miyata, T.; Rha, S.-W.; Yan, B.P.; Dy, T.C.; Ganzon, M.S.V.; Handa, P.K.; Harris, S.; Zhisheng, J.; et al. Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease: A Report from the Asian Pacific Society of Atherosclerosis and Vascular Disease Asia-Pacific Peripheral Artery Disease Consensus Statement Project Committee. *J. Atheroscler. Thromb.* **2020**, *27*, 809–907. [CrossRef]

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Review

The Changing Landscape of Intravenous Thrombolysis for Acute Ischaemic Stroke

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Abstract: Intravenous thrombolysis remains the most accessible and effective reperfusion therapy available to patients with acute ischaemic stroke. Treatment with intravenous thrombolysis improves the odds of favourable functional outcome with the unacceptably low risk of haemorrhagic complications. Even in the current era of endovascular thrombectomy, intravenous thrombolysis remains the backbone of acute stroke treatment due to its accessibility and relative ease of administration. Since intravenous alteplase was first approved for acute ischaemic stroke in the mid 1990s, there have been significant advances in expanding the indication and time window for treatment, in addition to transitioning towards tenecteplase use for stroke thrombolysis. In this review, we will provide a narrative on the use of thrombolysis in acute ischaemic stroke including an up-to-date discussion on recent advances in thrombolytic therapy.

Keywords: thrombolysis; stroke; tenecteplase; alteplase; outcome

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1. Introduction

Intravenous thrombolysis remains the most accessible reperfusion therapy for acute ischaemic stroke despite recent advances in endovascular thrombectomy (EVT). However, as EVT can only be offered to the 30–40% of stroke patients with large vessel occlusion, systemic thrombolysis remains a vital first line treatment.

Intravenous alteplase, a recombinant tissue-type plasminogen activator (r-tPA), has been the standard thrombolytic agent for three decades since it was first proven to be effective in the mid-1990s. It is administered in a split dose fashion with a 10% bolus of total dose (0.9 mg/kg) followed by an hour-long infusion of the remaining dosage. Since the initial landmark NINDS (National Institute of Neurological Disorders and Stroke) trial with a 3 h time window [1], there has been a progressive expansion of the window of eligibility, transitioning from a time-based selection approach to a tissue-based approach using advanced imaging [2].

Tenecteplase, a genetic mutant of alteplase, has been long used for ST segment myocardial infarction [3]. Tenecteplase has a longer half-life than alteplase and is pragmatically advantageous due to single bolus administration. Tenecteplase at 0.25 mg/kg has been shown to improve early recanalization compared with alteplase in the setting of large vessel occlusion undergoing EVT, and several large clinical trials have demonstrated non-inferiority to alteplase when used within the standard 4.5 h time window [4–8]. Using advanced imaging selection, tenecteplase can also be administered to select patients with large vessel occlusion up to 24 h from stroke onset [9]. Although European Stroke Organisation and Stroke Foundation of Canada guidelines endorse the use of tenecteplase in acute ischaemic stroke [10,11], its use remains off-label in most parts of the world.

We aim to provide a narrative review of the role of thrombolysis in acute ischaemic stroke and to provide an up-to-date summary of the recently completed clinical trials supporting the changing of the guard to tenecteplase.

2. Time Window for Thrombolysis—From Time Clock to Tissue Clock

Intravenous thrombolysis within 4.5 h of symptom onset is considered the routine time window without the need for advanced imaging selection with either computed tomography (CT) perfusion or magnetic resonance imaging (MRI). However, this restrictive time-based criteria excludes a significant proportion of patients due to unwitnessed onset or uncertain onset due to aphasia or waking with symptoms and those presenting beyond 4.5 h. Because of this, it would preclude patients living at distance from a thrombolysis-capable stroke centre due to transport delays.

Several randomised clinical trials have assessed the benefit of an imaging-based selection approach to manage these patients with intravenous thrombolysis. The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial [3] used the concept of DWI-FLAIR mismatch (Figure 1) and randomised patients with wake-up stroke or stroke of unknown onset time to either placebo or intravenous alteplase on the premise that the stroke onset was recent given lack of corresponding FLAIR changes. The trial included 503 patients, with 254 randomised to alteplase and 249 to placebo. Despite not reaching its pre-specified target of 800 due to cessation of funding, alteplase treatment was significantly associated with favourable functional outcomes (mRS of 0–1) at 90 days compared to the placebo group (53.3% vs. 41.8%, adjusted OR1.61; 95% CI 1.09 to 2.36, $p = 0.02$.). Although there was a numerically higher number of symptomatic intracranial haemorrhages in the alteplase group, this was not statistically significant (2.0% vs. 0.4%, aOR 4.95; 95% CI 0.57 to 42.87, $p = 0.15$). Similar trends were seen for rates of death at 90 days (aOR 3.38; 95% CI 0.92–12.52, $p = 0.07$).

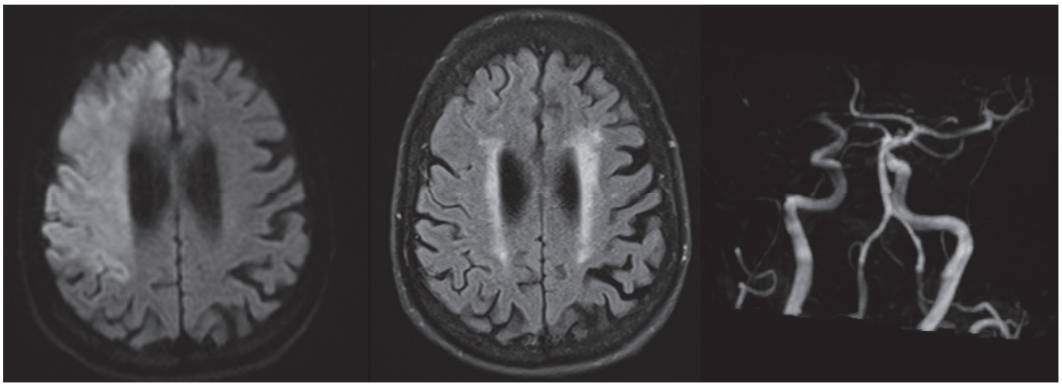

Figure 1. Example of MRI DWI-FLAIR mismatch in a patient with occlusion of right terminal internal carotid artery.

However, the major limitation of using an MRI imaging approach is that MRI may not be accessible particularly in middle- and lower-income countries. Ma et al. [4] reported the results of the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial, which was a placebo-controlled trial randomising patients to treatment within 9 h (9 h in this study refers to within 9 h of the midpoint between falling asleep and waking with stroke symptoms) of last known well or wake-up stroke. Most patients in this trial were screened by CT perfusion imaging and were eligible if they had a perfusion mismatch. The study was terminated early due to the publication of the WAKE-UP trial and enrolled 225 patients out of the planned 310 patients. Patients allocated to intravenous thrombolysis were more likely to achieve functional independence at 90 days (35.4% vs. 29.5%, adjust risk ratio 1.44, 95% CI 1.01–2.06, $p = 0.04$). There was a trend towards increased risk of symptomatic haemorrhage (6.2% vs. 0.9%, $p = 0.05$).

A systematic review and individual patient data meta-analysis by Campbell et al. [5] with data from three clinical trials utilising perfusion imaging selection to treat patient

beyond 4.5 h (EXTEND, ECASS4: ExTEND (European Cooperative Acute Stroke Study—4: Extending the time for thrombolysis in emergency neurological deficits) [6] and EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) [7]) included 414 patients and showed that alteplase treatment was associated with a higher rate of excellent functional outcome (mRS 0–1) at 3 months (36% vs. 29%, OR 1.86; 95% CI 1.15 to 2.99, $p = 0.01$). Rates of symptomatic intracranial haemorrhage were comparable (~5%) to the 3–4.5 h time window for alteplase in the ECASS III trial [12].

The major limitation of the extended time window trials was that most patients were recruited prior to the era of thrombectomy, and patients with LVO (~31% in WAKE-UP and 61% in the meta-analysis by Campbell et al. [13]) in the extended time window would likely have been eligible for endovascular thrombectomy with the current approach.

Two further clinical trials assessing the effect of 0.25 mg/kg tenecteplase thrombolysis between 4.5 and 24 h in patients with confirmed anterior circulation LVO have been published.

Both the Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase (TIMELESS) trial and the Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events–III (TRACE-III) trial randomised patients with proven LVO with perfusion mismatch to either tenecteplase or best medical therapy [9,14]. The major difference between TIMELESS and TRACE III was that EVT patients were included in TIMELESS while TRACE III only enrolled patients without access to EVT.

TIMELESS [14] randomised 458 patients to tenecteplase therapy or placebo, and EVT was performed in 77.3% of the entire cohort. The primary endpoint was ordinal score on the modified Rankin Scale, and there was no difference between the two arms, with a median score of 3 in each arm ($p = 0.45$). There were also no differences in functional outcome as a dichomtized outcome (90-day modified Rankin 0–2, 46% vs. 42.4%) or on the ordinal scale. However, in the subgroup analysis, tenecteplase resulted in improved functional outcomes for patients with M1 occlusion in the primary outcome with adjust common OR on modified Rankin scale score of 1.59 (95% CI 1.00–2.52) and with more achieving 90-day independence 45.9% vs. 31.4% (aOR, 2.03; 95% CI, 1.14 to 3.66). The rate of symptomatic intracranial haemorrhage was 3.2%.

TRACE-III [9] was conducted in China and included only Chinese patients, with the primary outcome being excellent functional outcome (mRS 0–1) at 90 days. The trial included 516 patients, with 264 randomised to tenecteplase and 252 to standard medical therapy. Primary outcome was achieved in 33% of tenecteplase patients compared with 24.2% in the non-thrombolytic arm (relative risk 1.37 (95% CI 1.04–1.81), $p = 0.03$.). Tenecteplase treatment also resulted in increased rates of reperfusion at 24 h (20.1% vs. 11.8%). The rate of symptomatic intracranial haemorrhage was 3% in the tenecteplase arm, consistent with rates of symptomatic intracranial haemorrhage from other tenecteplase trials.

There is, therefore, a large body of evidence that selection for intravenous thrombolysis can be selected using a tissue clock paradigm rather than a pre-defined rigid time criteria. However, perfusion imaging is not sensitive for lacunar infarcts or brainstem infarcts, and imaging-based approaches for extended-window thrombolysis may only be applicable using MRI.

There is emerging evidence of the use of tenecteplase in the extended time window beyond 4.5 h, but the evidence of clinical benefit is limited to two clinical trials in patients with proximal LVO. The results of TRACE III suggest tenecteplase is reasonable in patients with LVO and perfusion mismatch but without access to thrombectomy, but there is currently no firmevidence to support routine use of tenecteplase beyond the standard 4.5 h time window, either as stand-alone treatment or as bridging treatment prior to thrombectomy.

3. Clinical Trials of Tenecteplase

Tenecteplase has been long perceived as a potential thrombolytic agent to replace alteplase. Tenecteplase has several practical and pharmacological advantages to alteplase; it can be administered as a single bolus and has 15-times-higher specificity to fibrin, de-

creased binding affinity to plasminogen activator inhibitor 1 (PAI−1), and a longer half-life than alteplase. In addition to TIMELESS and TRACE III, there have been a number of randomised clinical trials assessing tenecteplase stroke thrombolysis, and the table below summarises the main studies over the last 8 years. The early clinical trials of tenecteplase used different dosing regimens, from 0.1 mg/kg to 0.5 mg/kg. However, 0.5 mg/kg was associated with significant haemorrhagic risk [15] and this dosing has not been further tested in clinical trials. A summary of clinical trial data is provided in Table 1. The following passages will focus on the more recent clinical trials.

Table 1. Recent studies investigating the use of tenecteplase in acute stroke management.

Author	Year	Design/Trial Name	Participants	Tenecteplase dose	Comparison	Primary Outcome	Notes
Logallo et al. [16]	2017	Randomised, open-label, blinded, superiority trial. NOR-TEST.	1100, across 13 stroke units in Norway	0.4 mg/kg	Alteplase 0.9 mg/kg	mRS 0–3 at 3 months. OR 1.08 (CI 0.84–1.38) $p = 0.52$	Within 4.5 h of symptom onset of awakening with symptoms. Included bridging to thrombectomy. Median NIHSS 4 (IQR 2–8). Secondary and safety outcomes: -Death at day 90 ($p = 0.68$) -Serious adverse effects by day 90 ($p = 0.74$)
Campbell et al. [4]	2018	Randomised, open-label, blinded, non-inferiority followed by superiority trial. EXTEND-IA TNK part 1.	202, across 13 centres in Australia and New Zealand	0.25 mg/kg	Alteplase 0.9 mg/kg	Reperfusion of >50% ischaemic territory, or absence of retrievable clot. Non inferiority: -Incidence difference 12 percentage point (CI 2–21) -$p = 0.002$) Superiority: -Adjusted OR 2.6 (1.1–5.9) -$p = 0.02$.	Within 4.5 h of symptom onset. Included bridging to thrombectomy. Large vessel occlusions (ICA, M1, M2, basilar). Median NIHSS 17 (IQR 12–22) both groups. Secondary and safety outcomes: -mRS ordinal at 90 days (TNK 2 vs. 3 $p = 0.04$) -Functional independence ($p = 0.06$) -Early neuro improvement ($p = 0.70$) -Safety death ($p = 0.08$) -sICH ($p = 0.99$)
Campbell et al. [17]	2020	Randomised, open-label, blinded. EXTEND-IA TNK part 2.	300, across 27 hospitals in Australia and New Zealand	0.4 mg/kg	0.25 mg/kg tenecteplase	Reperfusion of >50% ischaemic territory. Risk difference 0.0% (CI −8.9%–8.9%) $p = 0.89$.	Within 4.5 h of symptom onset, before planned thrombectomy. Large vessel occlusions (ICA, M1, M2, basilar). Median NIHSS 17 (0.4 mg/kg) and 16 (0.25 mg/kg). Secondary and safety outcomes: -mRS 90 days ($p = 0.73$) -Freedom from disability ($p = 0.69$) -sICH 36 h ($p = 0.12$) -All-cause death ($p = 0.35$)
Bivard et al. [18]	2022	Randomised, open-label, blinded (masked), superiority. TASTE-A.	104 across 5 tertiary Melbourne hospitals	0.25 mg/kg	Alteplase 0.9 mg/kg	Volume of perfusion lesion on arrival to hospital on CTP. Adjusted incidence rate ratio 0.55 (CI 0.37–0.81) $p = 0.003$	Within 4.5 h of symptom onset. Median NIHSS 8 both groups (IQR 5–14 and 5–17). Secondary and safety outcomes: -mRS 5–6 at 90 days ($p = 0.93$) -sICH 36 h (none occurred) -Death 90 days ($p = 0.88$)
Kvistad et al. [5]	2022	Randomised, open-label, blinded, non-inferiority (3% margin). NOR-TEST 2, part A.	204 patients across 11 hospitals in Norway	0.4 mg/kg	Alteplase 0.9 mg/kg	mRS 0–1 at 3 months. OR 0.45 (CI 0.25–0.8). $p = 0.0064$	Within 4.5 h of symptom onset. Stopped early due to higher sICH rates in TNK group. Moderate or severe strokes, NIHSS 6 or more. Secondary and safety outcomes: -Any ICH (more TNK $p = 0.0031$) -sICH (more TNK $p = 0.061$) -Mortality (more TNK $p = 0.013$)

Table 1. *Cont.*

Author	Year	Design/Trial Name	Participants	Tenecteplase dose	Comparison	Primary Outcome	Notes
Menon et al. [6]	2022	Randomised, open-label, blinded, non-inferiority 5% margin (secondary superiority). AcT.	1577 patients across 22 primary and comprehensive stroke centres in Canada	0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0–1 at 90–120 days. Risk difference 2.15 (CI −2.6–6.9). Meeting non-inferiority threshold.	Within 4.5 h of symptom onset. Included bridging to thrombectomy. TNK trend to better, not superior, on secondary analysis. Median NIHSS 9 (TNK) 10 (alteplase). Secondary and safety outcomes): -sICH (no difference) -death (no difference)
Roaldsen et al. [19]	2023	Randomised, control, open-label, blinded endpoint. TWIST.	578 patients across 77 hospitals in 10 countries.	0.25 mg/kg	No thrombolysis	mRS at 90 days (ordinal logistic regression with ITT). OR 1.18 (CI 0.88–1.58). $p = 0.27$.	Within 4.5 h of awakening with symptoms. Wake-up stroke NIHSS > 2 or aphasia. Selection with non-contrast CT. Median ASPECT 10. >50% NIHSS < 8 (see table). Secondary and safety outcomes: -Mortality ($p = 0.37$) -sICH ($p = 0.28$) -Any intracranial haem ($p = 0.64$)
Wang et al. [7]	2023	Randomised, open-label, blinded endpoint, non-inferiority 3.74%. TRACE−2.	1430 patients across 53 centres in China	0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0–1 at 90 days. RR 1.07 (CI 0.98–1.16). TNK non-inferior.	Within 4.5 h of last known well. Excluded if thrombectomy candidate (ineligible or refused). NIHSS 5–25. >50% NIHSS < 8. Secondary and safety outcomes: -sICH ($p = 0.74$) -Mortality (0.22)
Albers et al. [14]	2024	Randomised placebo control, double-blind. TIMELESS.	458 patients across from 112 centres across USA and Canada.	0.25 mg/kg	Placebo	mRS at 90 days. Adjusted common odds ratio 1.13 (CI 0.82–1.57). $p = 0.45$.	4.5–24 h since last known well. Bridging to thrombectomy included (77.3% of patients). MCA M1 or M2 or ICA ~only. Median NIHSS 12 both groups. Secondary and safety outcomes: -Functional independence (no difference) -sICH (no difference) -Death (no difference) -Sub-group analysis (not powered) favoured TNK in M1 occlusion.
Coutts et al. [20]	2024	Randomised, open-label control trial, TEMPO−2	886 patients across 48 hospitals in Australia, Austria, Brazil, Canada, Finland, Ireland, New Zealand, Singapore, Spain, and UK.	0.25 mg/kg	Non-thrombolytic standard of care.	Return to baseline function (mRS) RR 0.96 (CI 0.88–1.04) $p = 0.29$	Within 12 h of stroke onset. Stopped early for futility (no benefit and possible harm). Minor stroke NIHSS 0–5 with vessel occlusion or perfusion deficit on imaging. Secondary and safety outcomes: -sICH—higher in TNK: RR 4.2 (0.9–19.7, $p = 0.059$) -Death—higher in TNK: adjusted HR 3.8 (CI 1.4–10.2, $p = 0.0085$)
Xiong et al. [9]	2024	Randomised blinded end-point evaluation control, open-label trial TRACE-III	516 patients across 58 centres in China.	0.25 mg/kg	Standard medical treatment.	Absence of disability (mRS 0–1) at 90 days Relative rate (?OR) 1.37 (CI 1.04–1.81) $p = 0.03$	4.5–24 h from last known well. Large vessel occlusion (ICA or MCA branches M1 or M2). Excluded if planned for thrombectomy, but <2% (similar in each group) had rescue thrombectomy. Median NIHSS 11 in TNK and 10 in controls groups. Secondary and safety outcomes: -sICH higher in TNK group. -Death (similar between groups)

Table 1. *Cont.*

Author	Year	Design/Trial Name	Participants	Tenecteplase dose	Comparison	Primary Outcome	Notes
Parsons et al. [21]	2024	Randomised, open-label, blinded endpoint, non-inferiority 3%. TASTE	601 patients (of planned 830 patients) across 35 hospitals in 8 countries.	0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0–1 at 3 months. Standardised RD 0.03 (non-inferiority criteria less than −0.03)	Within 4.5 h of symptom onset. Stopped early due to results of previous tenecteplase trials. Non-inferiority demonstrated on per-protocol analysis. Safety Secondary and safety outcomes: -sICH -All cause mortality
Muir et al. [22]	Yet to be published. Preprint in the Lancet	Randomised, non-inferior and superiority. ATTEST−2.	1858 patients across 40 hospitals in the UK.	0.25 mg/kg	Alteplase 0.9 mg/kg	Adjusted common OR 1.07 (CI 0.90–1.27) meeting non-inferiority, but not superior.	Not published yet but presented at World Stroke Conference 2023. Within 4.5 h of symptom onset. Secondary and safety outcomes: -mRS 0–1 -mRS overall -Safety (no difference)

CI, 95% confidence interval; ICH, intracerebral haemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RD, risk difference; RR, relative risk; TNK, Tenecteplase; sICH, symptomatic intracerebral haemorrhage.

The first positive trial was the Australian Tenecteplase Trial, which randomised patients to one standard-dose alteplase (n = 25) and two tenecteplase dosing arms at 0.1 mg/kg and 0.25 mg/kg (n = 25 in each group) in patients with target CT perfusion mismatch within 6 h of symptom onset [23]. The pooled tenecteplase arms had high rates of reperfusion and clinical improvement at 24 h when compared to alteplase, and the 0.25 mg/kg tenecteplase dose was superior to the lower dose and to alteplase on all efficacy outcomes. This trial marked a significant milestone as it suggested the efficacy of 0.25 mg/kg tenecteplase in recanalizing vascular occlusions.

The Norwegian Tenecteplase Stroke Trial (NOR-TEST) trial was the first phase III tenecteplase stroke thrombolysis trial to be completed. It assessed the efficacy and safety of 0.4 mg/kg tenecteplase compared to the standard dosing of alteplase (0.9 mg/kg) in patients presenting with acute ischaemic stroke [16]. The trial randomised 1100 patients, with 549 to tenecteplase and 555 to alteplase. NOR-TEST, however, failed to show the superiority of 0.4 mg/kg tenecteplase when compared to alteplase for achieving 90-day independence, (64% vs. 63%, odds ratio 1.08, 95% CI 0.84–1·38; $p = 0.52$,), and there was no increase in symptomatic haemorrhage (3% vs. 2%, $p = 0.49$). However, this trial included patients with minor symptoms (median NIHSS 4), and nearly a fifth of the enrolled patients had a stroke mimic diagnosis. A subsequent trial, the NOR-TEST 2A trial, compared 0.4 mg/kg tenecteplase to alteplase and randomised 216 patients before the trial was stopped early due to signs of harm. Treatment with 0.4 mg/kg tenecteplase resulted in increased intracranial haemorrhage (21/100, 21%) when compared to alteplase (7/104, 6.7%), unadjusted OR 3·68 [95% CI 1.49–9.11]; $p = 0.0031$) and higher mortality (15/96, 15.6% vs. 5/101, 5.0%, unadjusted OR 3.56 [95% CI 1.24–10.21]; $p = 0.013$) [5].

The efficacy of tenecteplase in achieving recanalization in the LVO population when given within 4.5 h was examined in the two The Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trials [4,17]. In EXTEND-IA TNK part one (n = 202, 101 patients in each thrombolytic arm), tenecteplase 0.25 mg/kg treatment led to 22% early reperfusion of >50% of affected territory or absence of retrievable thrombus when compared to 10% achieved in alteplase (OR 2.6, 95%CI 1.1–5.9, $p = 0.02$). In EXTEND-IA TNK part two, which randomised 300 patients with LVO referred for EVT to either 0.25 mg/kg or 0.4 mg/kg tenecteplase, reported similar rates of early reperfusion in each dosing arm (19% each) aRR, 1.03 (0.66 to 1.61) $p = 0.89$). There were no differences seen in functional outcomes at 90 days (median mRS 2 vs. 2, aOR 0.96 (0.74 to 1.24) $p = 0.73$) and the safety profiles were similar, but the 0.4 mg/kg dose had statistically non-significantly higher rates of symptomatic intracranial haemorrhage (4.7% vs. 1.3%) than the 0.25 mg/kg arm.

The Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT) trial in Canada was the first large phase III clinical trial to show non-inferiority of 0.25 mg/kg tenecteplase when compared to alteplase within the 4.5 h time window [6]. AcT included 1600 patients including 816 randomised to tenecteplase and 784 to alteplase. The primary outcome was 90–120 excellent outcome defined as modified Rankin 0–1. Tenecteplase treatment resulted in similar rates of excellent functional outcomes when compared to alteplase (36·9% vs. 34·8%, risk different 2.1%, 95% CI −2.6–6.9), which met the prespecified non-inferiority threshold. Tenecteplase also had comparable rates of symptomatic intracranial haemorrhage (3.4% vs. 3.2%) and 90-day mortality (15.3% vs. 15.4%) when compared to alteplase.

The Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-II (TRACE−2) trial randomised 1430 thrombectomy-ineligible patients to either 0.25 mg/kg tenecteplase (n = 716) or 0.9 mg/kg alteplase (n = 714) with the primary endpoint of 90-day excellent outcome (modified Rankin Scale 0–1). Tenecteplase was non-inferior to alteplase, with primary outcome occurring in 62% tenecteplase vs. 58% alteplase patients (risk ratio 1.07, 95% CI 0.98–1.16). Comparable rates of symptomatic intracranial haemorrhage at 36 h (2% in each arm) and 90-day mortality (7% vs. 5%) were noted [7]. It should be noted that in TRACE−2, a Chinese version (CSPC Recomgen Pharmaceutical (Guangzhou, China) Co., Ltd. (formally Guangzhou Recomgen Biotech Co., Ltd.) of tenecteplase (rhTNK-tPA) was used, although it was noted to have similar pharmacological properties to industry-standard tenecteplase (Boehringer Ingelheim, Germany/Genentech, USA).

The tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4.5 h of onset of ischaemic stroke (TASTE) trial was the only phase III clinical trial to have utilised perfusion imaging selection and randomised 680 patients to either 0.25 mg/kg tenecteplase (n = 339) or standard-dose alteplase (n = 341). It was a non-inferiority trial and was stopped early due to the release of results of other large clinical trials demonstrating non-inferiority. The primary endpoint of 90-day functional independence was achieved in 57% of tenecteplase patients compared with 55.3% in alteplase. The non-inferiority margin of 0.03 was narrowly missed in the intention to treat the population (standardised risk difference, SRD = 0·03[95%CI: −0.033, 0.10], one-tailed pnon-inferiority = 0·031) but the non-inferiority margin was crossed in the per-protocol population. The symptomatic intracranial haemorrhage rate of 3% in the tenecteplase patients were consistent with that reported in other tenecteplase trials utilising 0.25 mg/kg [21].

Importantly, an updated study level meta-analysis published in the TASTE trial manuscript showed that tenecteplase was superior to alteplase, with a number needed to treat of 25 to achieve an additional functional independence outcome. The results of TASTE, the recent tenecteplase trials, and the updated meta-analysis have provided substantial evidence that 0.25 mg tenecteplase is the current optimal treatment for stroke thrombolysis in the standard time window.

4. Mild Ischaemic Stroke

Mild AIS treatment, typically defined as an NIHSS of 5 or less, remains an area of controversy as the clinician needs to balance between the risk of haemorrhagic complications and potential benefits of treatment, given that patient recovery is expected as part of natural history. Three randomised clinical trial have been completed.

Two clinical trials have failed to demonstrate the benefits of alteplase in minor ischaemic strokes. In a randomised, double-blind, double-placebo controlled trial, the PRISMS trial, intravenous alteplase was compared to oral aspirin in patients with minor, non-disabling strokes (NIHSS < 5) presenting within 3 h of symptom onset. The trial was stopped early owing to slow recruitment and included 313 patients in its final analysis, with 156 patients in the alteplase group and 157 in the aspirin group. The primary outcome of favourable outcomes (defined as mRS < 2) at 90 days did not differ between the two study groups (alteplase 78.2%, 122/156; aspirin 81.5%, 128/157) [24]. Symptomatic intracranial

haemorrhage occurred in 3.2% of alteplase patients while aspirin-treated patients had symptomatic intracranial haemorrhage.

Following the PRISMS trial, Chen et al. subsequently evaluated alteplase vs. dual antiplatelet therapy (DAPT) in the ARAMIS trial. Patients from 38 Chinese hospitals with acute, minor, non-disabling strokes (NIHSS $\leq$ 5) presenting with 4.5 h of symptom-onset were randomised to DAPT (aspirin and clopidogrel) vs. intravenous alteplase. The trial included 719 patients with 369 patients assigned to DAPT and 350 to alteplase. The primary outcome of favourable neurological outcome (mRS < 2) at 90 days was achieved in 93.8% of the DAPT group and 91.4% of the alteplase group (indicating the non-inferiority of DAPT with a risk difference of 2.3%, 95% CI −1.5% to 6.2%) [25]. Symptomatic intracranial haemorrhage rate was low in both groups (0.3% DAPT group and 0.9% alteplase group). The results of PRISMS and ARAMIS indicate that intravenous alteplase was not more effective in achieving excellent functional outcome with compared with antiplatelet treatment.

A multicentre, prospective, randomised, open-label, blinded-endpoint, controlled trial of thrombolysis with tenecteplase versus standard of care in the prevention of disability at 3 months in minor ischaemic stroke with proven acute symptomatic occlusion (TEMPO−2) trial has recently been published [20]. This trial randomised patients with mild ischaemic stroke (NIHSS $\leq$ 5) with either intracranial arterial occlusion or focal perfusion abnormality to receive tenecteplase 0.25 mg/kg or best medical therapy within 12 h of stroke onset. The trial was stopped early for futility after 886 patients were included (tenecteplase 369, non-thrombolytic treatment 454). The primary outcome was a return to baseline functioning on a premorbid modified Rankin scale, and there was no difference between the tenecteplase and non-thrombolytic arms (71.5% vs. 74.8%, RR 0.96, 95% CI 0.88–1.04, p = 0.2882).

In the subset of patients with proven vascular or large vessel occlusion, tenecteplase treatment resulted in significantly higher rates of recanalization on repeat imaging between 4 to 8 h after randomisation (any vessel occlusion (TNK = 256, control = 259) 48% vs. 22%, p < 0.0001; large vessel occlusion (TNK = 46, control = 40), 48% vs. 13%, p = 0.0005) [20]. However, subgroup analysis in these populations did not demonstrate improvements in outcomes with tenecteplase, which is an unexpected finding. The reason for this is unclear, and further post hoc analyses will likely provide insights into these findings.

In a recent large systematic review and meta-analysis comparing the effect of thrombolysis with alteplase and best medical therapy in mild ischaemic stroke (NIHSS $\leq$5), just over 13,000 patients were included [26]. The study involved patients from 20 studies, including three randomised clinical trials, with 4972 patients receiving thrombolysis compared with 8425 patients receiving best medical therapy. There were no differences between thrombolysis and best medical treatment in terms of improved functional outcome, reduced mortality, or rates of recurrent stroke. However, thrombolysis was associated with a nearly two-fold increase in early neurological deterioration (OR, 1.81 [95% CI, 1.17–2.80]) and symptomatic intracerebral haemorrhage (OR, 7.48 [95% CI, 3.55–15.76]).

Along the same lines, a large observational registry by Seners et al. assessed the impact of added EVT on outcomes after thrombolysis with alteplase in patients with mild ischaemic stroke (NIHSS $\leq$5) with proven proximal occlusion of the M1 or M2 segments [27]. Added EVT after alteplase was associated with increased odds of an excellent outcome in confirmed proximal (OR = 3.26; 95% CI = 1.67–6.35; p = 0.0006) or distal (OR = 1.69; 95% CI = 1.01–2.82; p = 0.04) M1 occlusion but was associated with lower odds of a good outcome in patients with M2 occlusion (OR = 0.53; 95% CI = 0.38–0.75; p = 0.0003) and increased rates of symptomatic haemorrhage (OR = 4.40; 95% CI = 2.20–8.83; p < 0.0001).

These studies, along with the recently published TEMPO−2 trial, suggest that intravenous thrombolysis should not be routinely administered to patients with truly non-disabling mild ischaemic stroke. Specific patient characteristics may potentially influence this decision, such as the presence and location of LVO and whether EVT is being considered. However, the authors recommend that the decision-making process for providing thrombolysis to patients with a low NIHSS should be individualised, and that clinicians

should consider refraining from treating patients with truly non-disabling stroke, such as minor sensory symptoms or mild non-disabling facial weakness.

5. Non-Advanced Imaging for Wake-Up Stroke

Whether non-advanced imaging can be used to select patients for thrombolysis has been tested in the Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST) trial [19]. TWIST randomised 578 patients within 4.5 h of waking or found with stroke symptoms using non-contrast CT scan to either 0.25 mg/kg tenecteplase (n = 288) or best medical therapy (n = 246), with inclusion of patients with vessel occlusion proceeding to thrombectomy in either study group. The primary end point was ordinal shift on the 90-day modified Rankin scale, which was negative (adjusted OR 1.18 955 CI 0.88–1.58, $p = 0.27$). There were no safety concerns with no difference in mortality (10% vs. 9%) or symptomatic intracranial haemorrhage (2% vs. 1%). Although the primary results were negative, the treatment effect was likely reduced by more control patients (14%) proceeding to thrombectomy than tenecteplase (6%) patients. It also provided important safety data with comparable rates of symptomatic haemorrhage compared to clinical trials utilising advanced imaging for patient selection.

6. Thrombolysis Prior to Endovascular Thrombectomy

Demonstrating a benefit for pre-thrombectomy thrombolysis has been debated [28]. Whether intravenous thrombolysis (with tPA or TNK) offered any additional benefit over and above that of endovascular thrombectomy was examined in several clinical trials, without a definitive answer. Dissolution of a thrombo-embolus (by thrombolysis) may make for an easier subsequent clearing of the LVO by thrombectomy. However, it is not without cost (time, financial, and potential adverse effects).

A meta-analysis of six randomised trials has recently evaluated this question. The analysis only included patients presenting with an anterior circulation LVO to a thrombectomy-capable centre. Additional benefit from intravenous thrombolysis (defined as a favourable shift in mRS at 90 days) was only seen in patients who received it within 2 h 20 min from symptom onset. After that, thrombolysis did not afford added benefit over and above that of endovascular thrombectomy [29].

7. Guideline Recommendations for Tenecteplase

The European Stroke Organisation and the Heart and Stroke Foundation of Canada guidelines have updated their recommendations for tenecteplase. Both best practice guidelines have issued strong recommendations for 0.25 mg/kg tenecteplase as an alternative to alteplase for thrombolysis-eligible patients within 4.5 h from stroke onset [10,30], while the guidelines from the American Heart Association/American Stroke Association have yet to update the previous guidelines issued in 2019 [31].

8. Transitioning to Tenecteplase—Real World Application

The results of clinical trials have shown that 0.25 mg/kg tenecteplase is the standard dose for stroke thrombolysis, and given its pragmatic advantages, it is likely that tenecteplase will be used instead of alteplase for stroke thrombolysis. However, tenecteplase has already been used as a routine thrombolytic medication in several centres in New Zealand, the United States, and Europe prior to the completion of large clinical trials.

In New Zealand, tenecteplase transition occurred early in two comprehensive stroke centres in Christchurch and Wellington and associated rural stroke networks, driven by the lack of consistent access to EVT and demonstration in EXTEND-IA TNK trials of the superiority of tenecteplase in LVO [4,17]. The experience of routine use of tenecteplase has been reported in these networks with contemporaneous alteplase comparators. Both studies reported the same rates of symptomatic intracranial haemorrhage (sICH) of 1.8% in tenecteplase patients, which were lower than in alteplase patients (2.4% in Christchurch

and 3.4% in Wellington) [32]. Additionally, in the Wellington study, the door-to-needle time was 10 min shorter in tenecteplase patients.

In France, the TETRIS study group (2021) published a retrospective cohort of 588 large vessel occlusion (LVO) stroke patients treated with tenecteplase prior to EVT [33]. They found a comparable sICH rate of 2.5%. Functional independence at 90 days (mRS $\leq$ 2) was 47.2%, comparable to outcomes after thrombectomy with alteplase. Tenecteplase also resulted in vessel recanalization in 20.5%, consistent with reported rates from the EXTEND-IA TNK trial.

In the United States, the Ascension Network in Texas were the first network to complete the change, and their results were in line with experience from New Zealand, with comparable safety data and a reduction in door-to-needle time [34]

The largest real-world experience has been reported by The Comparative Effectiveness of Routine Tenecteplase vs. Alteplase in Acute Ischemic Stroke (CERTAIN) collaboration, an academic collaboration from 25 stroke networks with >100 thrombolysis-capable hospitals throughout New Zealand, Australia, and the United States. An analysis of symptomatic intracranial haemorrhage risk between thrombolytic agents included 9238 patients (1925 tenecteplase and 7313 alteplase patients). The tenecteplase-treated group had significantly lower symptomatic haemorrhage risk (1.8% with tenecteplase- vs. 3.6% with alteplase-treated patients, p value < 0.001), despite tenecteplase patients having higher risk features for haemorrhage including older age (73 vs. 70), more male sex (54% vs. 51%), higher NIHSS (9 vs. 7), and higher rates of LVO (48% vs. 25%). The lower risk of symptomatic haemorrhage was consistent throughout subgroups with or without EVT [35].

Tenecteplase may also offer a financial benefit when compared to alteplase. A retrospective medical record review across six hospitals over a 4-month period in 2022 in the United States showed a direct cost saving for the health system of $209,476.80 when treating 129 acute ischaemic stroke patients with tenecteplase compared to alteplase (102 patients with alteplase and 117 patients with tenecteplase) [36].

9. Pragmatic Consideration for Transitioning to Tenecteplase Thrombolysis

It is anticipated that tenecteplase will progressively transition into routine stroke thrombolysis on a global scale. However, the current tenecteplase vials are available in 40 mg or 50 mg doses with markers designed for cardiac thrombolysis (0.5 mg/kg). Early adopters from New Zealand and the United States have outlined the transition processes, emphasising the need for various clinical stakeholders, including emergency department staff, nursing staff, and general medical personnel managing acute stroke, to be informed of protocol changes [32,34,37]. To prevent potential dosing errors, the authors recommend the use of tenecteplase dosing charts similar to the existing weight-based dosing for alteplase and to clearly indicate that the current dosing markers on the 40 or 50 mg vials are not intended for stroke use to prevent administration of the cardiac dose of tenecteplase. Upon transitioning, it is crucial to remove all alteplase vials from existing drug stocks to mitigate the risk of administering the incorrect thrombolytic agent. It is expected that the production of stroke-appropriate dosing vials will commence alongside the rollout of tenecteplase for stroke care, which will further minimise the potential for dosing errors. Until then, the above strategies will help prevent avoidable errors.

10. Tenecteplase Transition to Low Resource Health Settings

A significant proportion of tenecteplase trials have enrolled patients within the standard thrombolysis time window (<4.5 h from last known well or onset time), while other trials have included extended time window studies requiring advanced imaging, such as perfusion imaging. To date, no tenecteplase trials have used MRI perfusion mismatch to guide patient selection. Access to advanced imaging may not be available across all healthcare settings due to resource limitations, but this does not affect patient selection for tenecteplase thrombolysis within the standard time window. The only tenecteplase trial to have used non-advanced imaging was TWIST, which randomised patients with mild to

moderate ischaemic stroke to tenecteplase within 4.5 h of waking up with stroke symptoms based on non-contrast CT selection. Although the trial yielded negative results, the rate of symptomatic intracerebral haemorrhage in the tenecteplase arm was 2%, consistent with rates reported in other tenecteplase clinical trials.

The ongoing EXIST-BT2 clinical trial is randomising 1250 Chinese patients to either tenecteplase or medical management in the 4.5 to 6 h time window using non-advanced imaging selection [38]. Until further evidence is available, the authors believe it is reasonable to consider individualised decision-making to offer tenecteplase thrombolysis for patients with mild to moderate stroke within 4.5 h of waking, provided they have a favourable non-contrast CT scan.

11. Conclusions and Future Directions

The landscape of intravenous thrombolysis in acute ischaemic stroke has undergone significant revolutionary changes over recent years. The window of eligibility has continued to expand with the use of advanced imaging, transitioning into an era utilising the tissue clock instead of a rigid time clock for patient selection. More recent trials have proven that 0.25 mg/kg tenecteplase is non-inferior to alteplase and is superior to alteplase at achieving vascular recanalization. The recent trial data will result in a global changing of the guard to tenecteplase.

Despite the advantages, there remains a number of unaddressed questions in tenecteplase thrombolysis including extrapolating results from alteplase such as utilising MRI DWI-FLAIR mismatch for selection of patients with unknown onset time. In low-income regions of the world, where access to advanced imaging is limited, could basic imaging modalities such as non-contrast CT be sufficient for patient selection? Finally, given the improving work flow in reducing time metrics for patients proceeding to thrombectomy, does bridging therapy with tenecteplase improve patient outcome? These questions are likely to be addressed with further real world data and results of ongoing clinical trials to optimise patient management and outcome with thrombolysis for acute ischaemic stroke.

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References

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke. *N. Engl. J. Med.* **1995**, *333*, 1581–1588. [CrossRef] [PubMed]
2. Demeestere, J.; Wouters, A.; Christensen, S.; Lemmens, R.; Lansberg, M.G. Review of Perfusion Imaging in Acute Ischemic Stroke. *Stroke* **2020**, *51*, 1017–1024. [CrossRef] [PubMed]
3. de Werf, F.V. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* **1999**, *354*, 716–722. [CrossRef] [PubMed]
4. Campbell, B.C.V.; Mitchell, P.J.; Churilov, L.; Yassi, N.; Kleinig, T.J.; Dowling, R.J.; Yan, B.; Bush, S.J.; Dewey, H.M.; Thijs, V.; et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *N. Engl. J. Med.* **2018**, *378*, 1573–1582. [CrossRef] [PubMed]
5. Kvistad, C.E.; Næss, H.; Helleberg, B.H.; Idicula, T.; Hagberg, G.; Nordby, L.M.; Jenssen, K.N.; Tobro, H.; Rörholt, D.M.; Kaur, K.; et al. Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): A phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *Lancet Neurol.* **2022**, *21*, 511–519. [CrossRef] [PubMed]
6. Menon, B.K.; Buck, B.H.; Singh, N.; Deschaintre, Y.; Almekhlafi, M.A.; Coutts, S.B.; Thirunavukkarasu, S.; Khosravani, H.; Appireddy, R.; Moreau, F.; et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): A pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet* **2022**, *400*, 161–169. [CrossRef] [PubMed]
7. Wang, Y.; Li, S.; Pan, Y.; Li, H.; Parsons, M.W.; Campbell, B.C.V.; Schwamm, L.H.; Fisher, M.; Che, F.; Dai, H.; et al. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): A phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. *Lancet* **2023**, *401*, 645–654. [CrossRef] [PubMed]

8. Bivard, A.; Garcia-Esperon, C.; Churilov, L.; Spratt, N.; Russell, M.; Campbell, B.C.; Choi, P.; Kleinig, T.; Ma, H.; Markus, H.; et al. Tenecteplase versus alteplase for stroke thrombolysis evaluation (TASTE): A multicentre, prospective, randomized, open-label, blinded-endpoint, controlled phase III non-inferiority trial protocol. *Int. J. Stroke* **2023**, *18*, 751–756. [CrossRef] [PubMed]
9. Xiong, Y.; Campbell, B.C.V.; Schwamm, L.H.; Meng, X.; Jin, A.; Parsons, M.W.; Fisher, M.; Jiang, Y.; Che, F.; Wang, L.; et al. Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy. *N. Engl. J. Med.* **2024**, *391*, 203–212. [CrossRef]
10. Alamowitch, S.; Turc, G.; Palaiodimou, L.; Bivard, A.; Cameron, A.; De Marchis, G.M.; Fromm, A.; Kõrv, J.; Roaldsen, M.B.; Katsanos, A.H.; et al. European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke. *Eur. Stroke J.* **2023**, *8*, 8–54. [CrossRef]
11. Canadian Stroke Best Practices. Acute Stroke Management. Available online: https://www.strokebestpractices.ca/en/recommendations/acute-stroke-management/ (accessed on 22 September 2024).
12. Hacke, W.; Guidetti, D.; Machnig, T.; Toni, D. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *N. Engl. J. Med.* **2008**, *359*, 1317–1329. [CrossRef] [PubMed]
13. Campbell, B.C.V.; Ma, H.; Ringleb, P.A.; Parsons, M.W.; Churilov, L.; Bendszus, M.; Levi, C.R.; Hsu, C.; Kleinig, T.J.; Fatar, M.; et al. Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: A systematic review and meta-analysis of individual patient data. *Lancet* **2019**, *394*, 139–147. [CrossRef] [PubMed]
14. Albers, G.W.; Jumaa, M.; Purdon, B.; Zaidi, S.F.; Streib, C.; Shuaib, A.; Sangha, N.; Kim, M.; Froehler, M.T.; Schwartz, N.E.; et al. Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection. *N. Engl. J. Med.* **2024**, *390*, 701–711. [CrossRef] [PubMed]
15. Haley, E.C.; Lyden, P.D.; Johnston, K.C.; Hemmen, T.M. The TNK in Stroke Investigators A Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke. *Stroke* **2005**, *36*, 607–612. [CrossRef] [PubMed]
16. Logallo, N.; Novotny, V.; Assmus, J.; Kvistad, C.E.; Alteheld, L.; Rønning, O.M.; Thommessen, B.; Amthor, K.-F.; Ihle-Hansen, H.; Kurz, M.; et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol.* **2017**, *16*, 781–788. [CrossRef]
17. Campbell, B.C.V.; Mitchell, P.J.; Churilov, L.; Yassi, N.; Kleinig, T.J.; Dowling, R.J.; Yan, B.; Bush, S.J.; Thijs, V.; Scroop, R.; et al. Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients with Large Vessel Occlusion Ischemic Stroke: The EXTEND-IA TNK Part 2 Randomized Clinical Trial. *JAMA* **2020**, *323*, 1257–1265. [CrossRef] [PubMed]
18. Bivard, A.; Zhao, H.; Churilov, L.; Campbell, B.C.V.; Coote, S.; Yassi, N.; Yan, B.; Valente, M.; Sharobeam, A.; Balabanski, A.H.; et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): A phase 2, randomised, open-label trial. *Lancet Neurol.* **2022**, *21*, 520–527. [CrossRef] [PubMed]
19. Roaldsen, M.B.; Eltoft, A.; Wilsgaard, T.; Christensen, H.; Engelter, S.T.; Indredavik, B.; Jatužis, D.; Karelis, G.; Kõrv, J.; Lundström, E.; et al. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): A multicentre, open-label, randomised controlled trial. *Lancet Neurol.* **2023**, *22*, 117–126. [CrossRef]
20. Coutts, S.B.; Ankolekar, S.; Appireddy, R.; Arenillas, J.F.; Assis, Z.; Bailey, P.; Barber, P.A.; Bazan, R.; Buck, B.H.; Butcher, K.S.; et al. Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): A randomised, open label, phase 3 superiority trial. *Lancet* **2024**, *403*, 2597–2605. [CrossRef]
21. Parsons, M.W.; Yogendrakumar, V.; Churilov, L.; Garcia-Esperon, C.; Campbell, B.C.; Russell, M.L.; Sharma, G.; Chen, C.; Lin, L.; Chew, B.L.; et al. Tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4· 5 h of onset of ischaemic stroke (TASTE): A multicentre, randomised, controlled, phase 3 non-inferiority trial. *Lancet Neurol.* **2024**, *23*, 775–786. [CrossRef]
22. Muir, K.; Ford, G.; Ford, I.; Wardlaw, J.; McConnachie, A.; Greenlaw, N.; Mair, G.; Sprigg, N.; Price, C.I.; Macleod, M.J.; et al. Randomised Trial of Tenectplase Versus Alteplase for Acute Stroke within 4.5h of Onset: The Second Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2). 2024. Available online: https://www.ssrn.com/abstract=4831843 (accessed on 8 September 2024).
23. Parsons, M.; Spratt, N.; Bivard, A.; Campbell, B.; Chung, K.; Miteff, F.; O'Brien, B.; Bladin, C.; McElduff, P.; Allen, C.; et al. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke. *N. Engl. J. Med.* **2012**, *366*, 1099–1107. [CrossRef] [PubMed]
24. Khatri, P.; Kleindorfer, D.O.; Devlin, T.; Sawyer, R.N.; Starr, M.; Mejilla, J.; Broderick, J.; Chatterjee, A.; Jauch, E.C.; Levine, S.R.; et al. Effect of Alteplase vs Aspirin on Functional Outcome for Patients with Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial. *JAMA* **2018**, *320*, 156. [CrossRef] [PubMed]
25. Chen, H.-S.; Cui, Y.; Zhou, Z.-H.; Zhang, H.; Wang, L.-X.; Wang, W.-Z.; Shen, L.-Y.; Guo, L.-Y.; Wang, E.-Q.; Wang, R.-X.; et al. Dual Antiplatelet Therapy vs Alteplase for Patients with Minor Nondisabling Acute Ischemic Stroke: The ARAMIS Randomized Clinical Trial. *JAMA* **2023**, *329*, 2135. [CrossRef] [PubMed]
26. Zhang, Y.; Lv, T.; Nguyen, T.N.; Wu, S.; Li, Z.; Bai, X.; Chen, D.; Zhao, C.; Lin, W.; Chen, S.; et al. Intravenous Alteplase Versus Best Medical Therapy for Patients with Minor Stroke: A Systematic Review and Meta-Analysis. *Stroke* **2024**, *55*, 883–892. [CrossRef] [PubMed]
27. Seners, P.; Perrin, C.; Lapergue, B.; Henon, H.; Debiais, S.; Sablot, D.; Girard Buttaz, I.; Tamazyan, R.; Preterre, C.; Laksiri, N.; et al. Bridging Therapy or IV Thrombolysis in Minor Stroke with Large Vessel Occlusion. *Ann. Neurol.* **2020**, *88*, 160–169. [CrossRef]
28. Derdeyn, C. Advances in Thrombectomy for Acute Ischemic Stroke. *JAMA Surg.* **2024**, *159*, 604. [CrossRef] [PubMed]

29. Kaesmacher, J.; Cavalcante, F.; Kappelhof, M.; Treurniet, K.M.; Rinkel, L.; Liu, J.; Yan, B.; Zi, W.; Kimura, K.; Eker, O.F.; et al. Time to Treatment with Intravenous Thrombolysis Before Thrombectomy and Functional Outcomes in Acute Ischemic Stroke: A Meta-Analysis. *JAMA* **2024**, *331*, 764–777. [CrossRef]
30. *Canadian Stroke Best Practices. 5. Acute Ischemic Stroke Treatment.* 2024. Available online: https://www.strokebestpractices.ca/en/recommendations/acute-stroke-management/acute-ischemic-stroke-treatment/ (accessed on 7 August 2024).
31. Stroke. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Available online: https://www.ahajournals.org/doi/10.1161/STR.0000000000000211 (accessed on 7 August 2024).
32. Mahawish, K.; Gommans, J.; Kleinig, T.; Lallu, B.; Tyson, A.; Ranta, A. Switching to Tenecteplase for Stroke Thrombolysis: Real-World Experience and Outcomes in a Regional Stroke Network. *Stroke* **2021**, *52*, e590–e593. [CrossRef] [PubMed]
33. Gerschenfeld, G.; Smadja, D.; Turc, G.; Olindo, S.; Laborne, F.-X.; Yger, M.; Caroff, J.; Gonçalves, B.; Seners, P.; Cantier, M.; et al. Functional Outcome, Recanalization, and Hemorrhage Rates After Large Vessel Occlusion Stroke Treated with Tenecteplase Before Thrombectomy. *Neurology* **2021**, *97*, E2173–E2184. [CrossRef]
34. Warach, S.J.; Dula, A.N.; Milling, T.J.; Miller, S.; Allen, L.; Zuck, N.D.; Miller, C.; Jesser, C.A.; Misra, L.R.; Miley, J.T.; et al. Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice. *Stroke* **2022**, *53*, 3583–3593. [CrossRef] [PubMed]
35. Warach, S.J.; Ranta, A.; Kim, J.; Song, S.S.; Wallace, A.; Beharry, J.; Gibson, D.; Cadilhac, D.A.; Bladin, C.F.; Kleinig, T.J.; et al. Symptomatic Intracranial Hemorrhage with Tenecteplase vs Alteplase in Patients with Acute Ischemic Stroke: The Comparative Effectiveness of Routine Tenecteplase vs Alteplase in Acute Ischemic Stroke (CERTAIN) Collaboration. *JAMA Neurol.* **2023**, *80*, 732–738. [CrossRef] [PubMed]
36. Pace, A.; Wai, M.; Frye, E. Implementation of a Tenecteplase Protocol for Treatment of Acute Ischemic Stroke in a Health System. *Innov. Pharm.* **2024**, *15*. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11107964/ (accessed on 1 September 2024).
37. Zhong, C.S.; Beharry, J.; Salazar, D.; Smith, K.; Withington, S.; Campbell, B.C.V.; Wilson, D.; Le Heron, C.; Mason, D.; Duncan, R.; et al. Routine Use of Tenecteplase for Thrombolysis in Acute Ischemic Stroke. *Stroke* **2021**, *52*, 1087–1090. [CrossRef] [PubMed]
38. Wang, Y.-H.; Guo, Z.-N.; Chen, M.-R.; Yao, Z.-G.; Nguyen, T.N.; Saver, J.L.; Yang, Y.; Chen, H.-S. Intravenous tenecteplase for acute ischemic stroke between 4.5 and 6 h of onset (EXIT-BT2): Rationale and Design. *Eur. Stroke J.* **2024**. *first published online*. [CrossRef]

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