Incidence and predictors of poor functional outcome despite complete recanalisation following endovascular thrombectomy for acute ischaemic stroke

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Incidence and predictors of poor functional outcome despite complete recanalisation following endovascular thrombectomy for acute ischaemic stroke

Permesh Singh Dhillon,[a,b,f] Waleed Butt,[c] Omar Marei,[a,f] Anna Podlasek,[d] Norman McConachie,[a] Robert Lenthall,[a] Sujit Nair,[a] Luqman Malik,[a] Pervinder Bhogal,[e] Hegoda Levansri Dilrukshan Makalanda,[e] Robert A Dineen,[b,f] and Timothy J England,[g,h]

Background: Numerous ischaemic stroke patients experience poor functional outcome despite successful recanalisation following endovascular thrombectomy (EVT). We aimed to identify the incidence and predictors of futile complete recanalisation (FCR) in a national stroke registry. *Methods:* Patients who achieved complete recanalisation (mTICI 3) following EVT, between October 2015 and March 2020, were included from a United Kingdom national stroke registry. Modified Rankin Scale of 4-6 at discharge was defined as a 'poor/futile outcome'. Backward stepwise multivariable logistic regression analysis was performed with FCR as the dependent variable, incorporating all baseline characteristics, procedural time metrics and post-procedural events. *Results:* We included 2132 of 4383 patients (48.8%) with complete recanalisation post-EVT, of which 948 patients (44.4%) developed FCR. Following multivariable regression analysis adjusted for potential confounders, patients with FCR were associated with multiple baseline patient, imaging and procedural factors: age (p=0.0001), admission NIHSS scores (p=0.0001), pre-stroke disability (p=0.007), onset-to-puncture (p=0.0001) and procedural times (p=0.0001), presence of diabetes (p=0.005), and use of general anaesthesia (p=0.0001). Although not predictive of outcome, post-procedural events including development of any intracranial haemorrhage (ICH) (p=0.0001), symptomatic ICH (sICH) (p=0.0001) and early neurological deterioration (END) (p=0.007) were associated with FCR. *Conclusion:* Nearly half of patients in this national registry experienced FCR following EVT. Significant predictors of FCR included increasing age, admission NIHSS scores, pre-stroke disability, onset-to-puncture and procedural times, presence of diabetes, atrial fibrillation, and use of general anaesthesia. Post procedural development of any ICH, sICH, and END were associated with FCR.

Keywords: Endovascular thrombectomy—Symptomatic intracranial hemorrhage—Early neurological deterioration—Computed tomography—Stroke

From the [a]Interventional Neuroradiology, Nottingham University Hospitals NHS Trust, UK; [b]NIHR Nottingham Biomedical Research Centre, Nottingham, UK; [c]Interventional Neuroradiology, University Hospitals Birmingham NHS Trust, UK; [d]Tayside Innovation Medtech Ecosystem (TIME), University of Dundee, UK; [e]Interventional Neuroradiology, Barts Health NHS Trust, London, UK; [f]Radiological Sciences, Mental Health & Clinical Neuroscience, School of Medicine, University of Nottingham, UK; [g]Stroke Trials Unit, Mental Health & Clinical Neuroscience, School of Medicine, University of Nottingham, UK; and [h]Stroke, University Hospitals of Derby and Burton NHS Foundation Trust, UK.

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Corresponding author. E-mail: permesh.dhillon@nottingham.ac.uk.

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Introduction

A large proportion of patients experience a poor functional outcome despite very high rates of successful recanalisation following endovascular thrombectomy (EVT) for large vessel occlusion (LVO) in acute ischaemic stroke (AIS).[1,2] Multiple baseline clinical and imaging characteristics, procedural time metrics, and post-procedural events have been associated with futile recanalisation, which is commonly defined as modified Rankin Scale (mRS) 3-6 at 90 days despite successful recanalisation of modified thrombolysis in cerebral infarction ((mTICI) 2B-3).[1,2] Knowledge of these factors is important in determining modifiable risk factors for potential target therapies and for optimising patient selection and care.

Despite a significantly higher likelihood of achieving good functional outcome (mRS0-2 at 90 days) following complete recanalisation (mTICI 3) compared to partial recanalisation (mTICI 2b)[3], most studies have only reported predictors of futile recanalisation based on the mTICI≥2b recanalisation rates.[1,2] Furthermore, the definition of futile recanalisation itself remains debatable and is subject to interpretation, as some may consider moderate disability with minimal assistance required (mRS 3) as a 'non-futile' outcome following recovery from an LVO.[4] Herein, we aim to identify the incidence and predictors of futile complete recanalisation (FCR) (mRS 4-6 at hospital discharge or worsening of the pre-stroke disability of mRS 4-5 despite achieving mTICI 3 recanalisation) in a national stroke registry.

Methods

Ethics

The Sentinel Stroke National Audit Programme (SSNAP) registry has permission to collect patient data without explicit patient consent, granted by the Confidentiality Advisory Group of the National Health Service Health Research Authority under Section 251. Pseudonymised/de-identified data use was approved by the Healthcare Quality Improvement Partnership (HQIP) Data Access Request Group. Additional ethical approval was not sought or required for this study. Data access requests should be directed to SSNAP as the data provider and the HQIP as the data controller.

Data source and study design

We performed a cohort study using prospectively collected data from patients enrolled in the SSNAP registry according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. SSNAP is a national stroke registry that includes all hospitals admitting patients with acute stroke in England and Wales (covering 92% of the population of the United Kingdom, UK).[5] Overall, case ascertainment in SSNAP is estimated to be over 90% of all acute stroke admissions. Patient data, which include demographic and clinical characteristics, treatments, and outcomes, are submitted prospectively by clinical teams using a secure web-based case report form with real-time data validation checks to ensure data quality, from the time of admission up to 6 months after stroke.[6]

Pseudonymised individual level data of adult patients (≥18 years) presenting with AIS who achieved complete recanalisation (mTICI 3) following EVT between 1st October 2015 and 31st March 2020 in England and Wales were included. FCR was considered as mRS 4-6 at hospital discharge or worsening of the pre-stroke disability of mRS 4-5 despite achieving mTICI 3 recanalisation. Patients were dichotomised according to FCR vs non-FCR. Patients with missing discharge mRS and those who achieved mTICI≤2b post-EVT were excluded. The selection of EVT-eligible patients was at the discretion of the practitioners based on each institution's protocol. Data on parenchymal imaging findings and clot location were not available in the registry. No specific limits were applied to the clinical inclusion criteria, including age, pre-stroke disability and baseline stroke severity National Institutes of Health Stroke Scale (NIHSS).

Outcome measures

Functional outcome was assessed with the mRS by a member of the Stroke team/physician, ranging from 0 (no symptoms) to 5 (severe disability/bedridden) and 6 (death). FCR was considered as mRS 4-6 at hospital discharge or worsening of the pre-stroke disability of mRS 4-5 despite achieving mTICI 3 recanalisation. Post-procedural outcomes included early neurological deterioration (END) (24-hour NIHSS increase ≥4 from baseline), any type of intracranial haemorrhage (ICH), and symptomatic ICH (sICH) defined according to the European Collaborative Acute Stroke Study (ECASS) II[7] as any ICH with an increase of the NIHSS score of ≥4 within 24 hours or death). Baseline characteristics and workflow time metrics were described. The mRS was assessed by a member of the Stroke team/physician at discharge and during a routinely scheduled clinical visit at 6 months, or by a specialist nurse during a follow-up telephone interview if the patient was unable to attend. The NIHSS was assessed by a member of the Stroke team/physician or by a specialist nurse at admission and at 24 hours post admission. It would be expected that the Stroke physicians and specialist nurses who specialise in assessing the mRS and NIHSS on a routine clinical basis for all stroke admissions, would have undergone appropriate training and credentialing.

Statistical analysis

Study characteristics were summarised by FCR vs non-FCR using descriptive statistics and univariate analysis. Continuous variables were expressed as means and standard deviation (SD) and categorical variables were expressed as frequencies or percentages. Comparisons of

baseline variables were made using the Chi-square, or Student's t-test, wherever applicable. Backward stepwise multivariable logistic regression analysis was then performed, incorporating all available baseline characteristics, procedural time metrics and post-procedural events. Outcomes were expressed as an odds ratio (OR) with a 95% confidence interval (CI). Apart from the excluded missing data for the mRS at discharge, the remaining missing data included the status of END and intracranial haemorrhage post EVT, proportions of which are included in Table 1. Two-tailed p-value of <0.05 was considered statistically significant. All analyses were conducted using StataSE 17.1.

Results

Characteristics of study population

A total of 4383 patients admitted to 123 hospitals, of which 25 were EVT-capable neuroscience centres, underwent EVT for LVO during the study period. The number of EVT cases performed per year steadily increased from 602 (2016/2017) to 1607 (2019/2020), equating to just under 2% of all acute stroke admissions per year, due to the limitations in 24/7 EVT service availability.[8] Of the 4383 patients who underwent EVT, 2132 patients (48.8%) who achieved complete recanalisation post-EVT were included (Fig. 1). Overall, 55.9% of these patients were male, the mean NIHSS on admission was 16, 59.9% received intravenous thrombolysis prior to EVT and 23.2% were selected for EVT using perfusion imaging. The rate of FCR was 44.4% (948/2132). Baseline characteristics and univariate comparisons of patients with and without FCR are presented in Table 1.

Outcomes

Following multivariable regression analysis adjusted for all available potential confounders, patients with FCR

Table 1. *Table of characteristics of patients who achieved complete recanalisation (modified thrombolysis in cerebral infarction ((mTICI) 3), dichotomised to futile complete recanalisation (FCR; modified Rankin Scale 4-6 despite complete recanalisation) and non-FCR.*

Feature	Overall, n (%) or mean±SD	FCR, n (%) or mean±SD	Non-FCR, n (%) or mean±SD	P value
	Socio-demographics			
Sample size	2132	948	1184	
Sex (male)	1192 (55.9)	527 (55.6)	665 (56.2)	0.79
Age: <60 years	556 (26.1)	191 (20.2)	365 (30.8)	<**0.001**
60-69	438 (20.5)	183 (19.3)	255 (21.5)	
70-79	645 (30.2)	298 (31.4)	347 (29.3)	
80-89	440 (20.6)	238 (25.1)	202 (17.1)	
>90	53 (2.5)	38 (4.0)	15 (1.3)	
	Baseline characteristics			
NIHSS on admission	16.4±6.8	18.1±6.7	15.0±6.6	<**0.001**
Pre-stroke disability (mRS≤2)	2037 (95.5)	892 (94.1)	1145 (96.7)	**0.003**
Intravenous Thrombolysis	1277 (59.9)	505 (53.3)	772 (65.2)	<**0.001**
Contact Aspiration (CA)	733 (34.3)	328 (37.1)	405 (37.3)	0.84
Stent Retriever (SR)	371 (17.4)	139 (15.7)	232 (21.4)	**0.001**
Combined CA & SR	865 (40.5)	416 (47.1)	449 (41.3)	**0.01**
Balloon Guide Catheter	467 (21.9)	218 (23.0)	249 (21.0)	0.28
General Anaesthesia	1138 (53.4)	575 (60.7)	563 (47.5)	<**0.001**
	Co-morbidities			
Hypertension	1009 (47.3)	482 (50.8)	527 (44.5)	**0.004**
Diabetes Mellitus	301 (14.1)	164 (17.3)	137 (11.6)	<**0.001**
Atrial fibrillation	472 (22.1)	249 (26.3)	223 (18.8)	<**0.001**
Prior Stroke/TIA	341 (16.0)	162 (17.1)	179 (15.1)	0.22
Congestive heart failure	110 (5.2)	55 (5.8)	55 (4.6)	0.23
	Time Metrics (mins)			
Onset to Groin Puncture	367.5±343.4	403.8±352.4	338.5±333.3	<**0.001**
Groin Puncture to End of Procedure	47.8±33.1	53.7±36.2	43.1±29.6	<**0.001**
	Post Procedural Factors			
END	151/2049 (7.4)	126/909 (13.9)	25/1140 (2.2)	<**0.001**
Any ICH	214/1535 (13.9)	147/708 (20.8)	67/827 (8.1)	<**0.001**
sICH	32/1447 (2.2)	28/637 (4.4)	4/810 (0.5)	<**0.001**

n=number of patients, SD=standard deviation, mRS=modified Rankin scale, TIA=transient ischaemic attack, NIHSS=National Institutes Stroke Severity, sICH=symptomatic intracranial haemorrhage, END=Early neurological deterioration (NIHSS worsening ≥4)

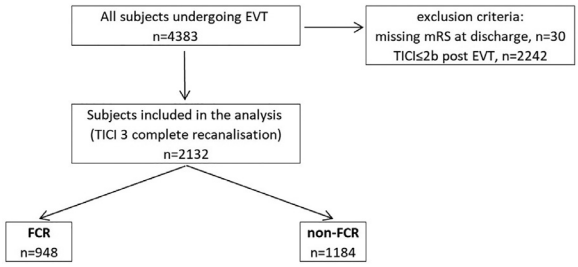

Fig. 1. *Flow chart of the patient inclusion, exclusion and outcome data for patients who achieved complete vessel recanalisation (modified thrombolysis in cerebral infarction mTICI 3) following endovascular thrombectomy.*

were associated with multiple baseline patient, imaging and procedural factors: age (p=0.0001), admission NIHSS scores (p=0.0001), pre-stroke disability (p=0.007), onset-to-puncture (p=0.0001) and procedural times (p=0.0001), presence of diabetes (p=0.005), and use of general anaesthesia (p=0.0001). Although not predictive of outcome, post procedural events including development of any ICH (p=0.0001), sICH (p=0.0001) and END (p=0.007) were associated with FCR (Fig. 2, Table 2). The EVT technique use of stentretriever only (p=0.07), contact aspiration only (p=0.94), or combined stentretriever and contact aspiration (p=0.61), as well as concomitant balloon guide catheter use (p=0.12) during EVT were not associated with FCR. The remaining outcomes are detailed in Table 2.

Discussion

In this national stroke registry, nearly half (44.4%) of patients experienced FCR following EVT for AIS. Increasing age, admission NIHSS scores, pre-stroke disability, onset-to-puncture and procedural times, presence of diabetes, and use of general anaesthesia, were significant predictors of FCR. Post procedural development of any ICH, sICH, and END were significantly associated with FCR.

Overall, our findings are consistent with previous studies of modest sample sizes that reported similar rates and risk factors of futile recanalisation, despite confining our analysis to patients who achieved complete recanalisation (mTICI 3) (a significantly stronger predictor of good functional outcome compared to partial mTICI 2b recanalisation), and a more stringent definition of a futile outcome (mRS 4-6) following EVT.[1,2,9-12] This suggests that various pre- and post-procedural factors other than complete vessel recanalisation play a significant role in the functional outcome. Certain factors such as increasing age, pre-stroke disability and co-morbidities are non-modifiable,

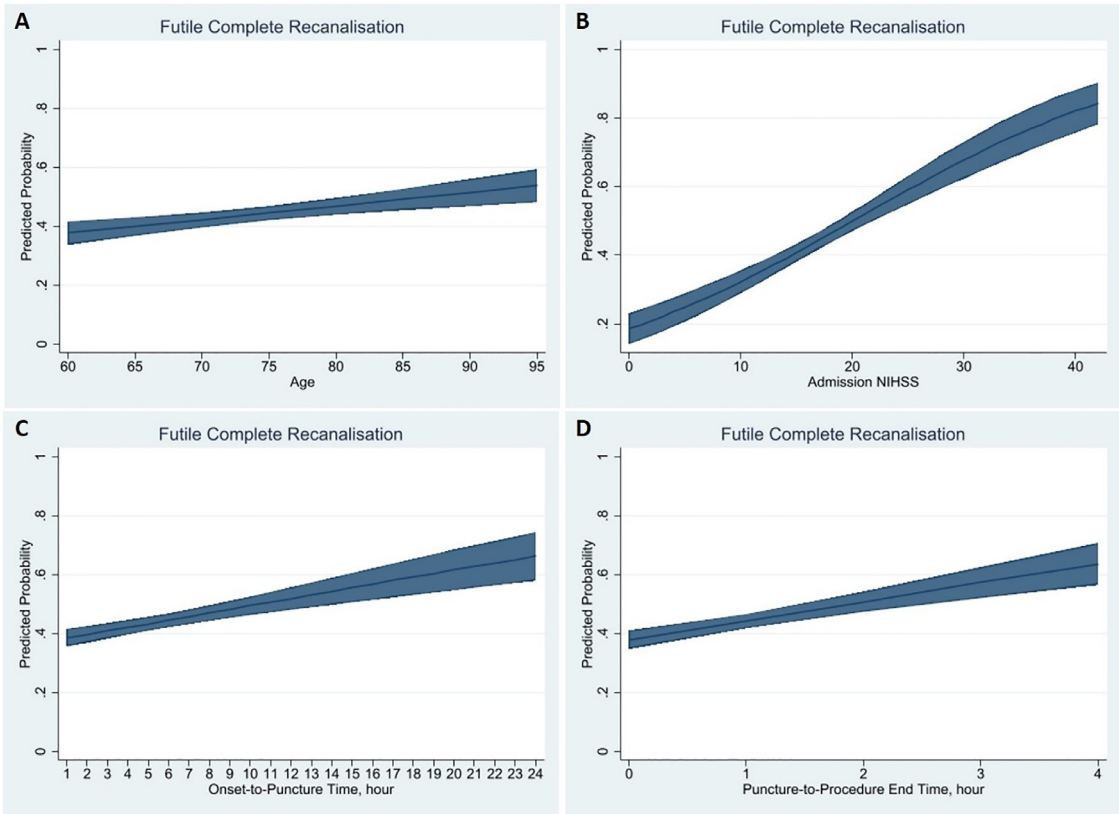

Fig. 2. *Associations between futile complete recanalisation (modified Rankin Scale 4-6 at discharge despite complete mTICI3 recanalisation) and: a) age, b) admission NIHSS, c) stroke onset-to-arterial puncture time, and d) arterial puncture-to-recanalisation time. Multivariable logistic regression analysis was performed adjusted for all independent variables. The central line indicates the predicted outcomes for a hypothetical patient with mean values for the adjusted data variables and the blue shading represents the 95% confidence intervals.*

Table 2. *Multivariable logistic regression analysis for the data variables associated with futile complete recanalisation (modified Rankin Scale 4-6 despite complete TICI3 recanalisation).*

Independent variables	Adjusted OR (95% CI)	P value
Age	1.13 (1.07 - 1.21)	**0.0001***
Sex, male	1.12 (0.88 – 1.43)	0.32
Hypertension	0.89 (0.69 – 1.15)	0.39
Diabetes mellitus	1.62 (1.15 – 2.27)	**0.005***
Atrial fibrillation	1.29 (0.95 – 1.76)	0.09
Heart failure	0.77 (0.45 – 1.31)	0.34
Previous Stroke/TIA	0.99 (0.71 – 1.37)	0.97
Pre-Stroke disability (mRS)	1.22 (1.05 – 1.41)	**0.007***
Admission NIHSS	1.08 (1.06 – 1.10)	**0.0001***
Intravenous thrombolysis	0.81 (0.62 – 1.07)	0.14
General anaesthesia	1.71 (1.34 – 2.19)	**0.0001***
SR technique only	0.63 (0.36 – 1.04)	0.07
CA technique only	0.98 (0.60 – 1.58)	0.94
Combined SR & CA	0.88 (0.54 – 1.42)	0.61
BGC	1.23 (0.94 – 1.63)	0.12
END	4.85 (1.54 – 15.29)	**0.007***
Any ICH	2.77 (1.94 – 3.96)	**0.0001***
sICH	9.26 (3.23 – 26.55)	**0.0001***
Onset-to-Puncture Time, hour	1.06 (1.03 – 1.08)	**0.0001***
Puncture-to-Recanalisation, hour	1.37 (1.21 – 1.55)	**0.0001***

OR=odds ratio, CI=confidence interval, mRS=modified Rankin scale, sICH=symptomatic intracranial haemorrhage, TICI=thrombolysis in cerebral infarction, NIHSS=national institutes of health stroke scale, END=Early neurological deterioration (NIHSS worsening ≥4). *=statistically significant, SR=stent-retriever, CA=contact-aspiration, TIA=transient ischaemic attack, BGC=balloon guide catheter.

and are associated with diminished brain reserve and frailty, thereby limiting the degree of functional recovery.[13] It is possible that patients with diabetes mellitus may be associated with microvascular dysfunction, which has been shown to be associated with poorer outcome.[14] However, it is important to note that patients with such characteristics should not be excluded from EVT treatment. Instead, further prognostication studies are warranted to aid in the risk stratification and optimisation of patient selection in an increasingly frail ageing population. Continued efforts should also be made to reduce the procedural and stroke onset-to-arterial puncture times, including mitigation of potential imaging and transportation delays, as well as the development of adjuvant therapies (e.g. neuroprotectants) to potentially slow any infarct growth prior to vessel recanalization. Post-procedural events such as sICH and END remain associative, rather than predictive of FCR, and as such may not reliably inform the pre-selection of patients for EVT treatment.

The strengths of this study include the large sample size and high quality data within the SSNAP database from standardised case definitions, internal validation and audit trails. There are several limitations. First, due to the observational design, selection bias, inherent confounders and the lack of consecutive case ascertainment (although reported to be over 90% in the registry) may have influenced the results. Second, variables such as ASPECTS, collateral status or clot location were not available in this registry, precluding further comparison. Hence, further patient and imaging related factors, including other confounders that may influence the functional outcome such as the peri-procedural blood pressure, pre-morbid medications, smoking status, underlying cause of the stroke (embolic vs atherosclerosis) or the number of EVT attempts could not be studied. However, many potential clinically relevant predictors were detected in our study due to the large sample size. Third, the definition of a 'futile' outcome following EVT remains debatable and is subject to interpretation, with its variability precluding direct comparisons with other studies. It is possible that patients with moderate disability may still have a good quality of life, and hence mRS 4-6 was utilised as a measure of poor/futile outcome. Fourth, variations in the sensitivity of imaging detection of intracranial haemorrhage and the definitions or classifications of sICH and END across studies precludes direct comparisons. Furthermore, although routinely performed in clinical practice in the United Kingdom, it was not possible to ascertain if all patients underwent CT Head imaging 24 hours post EVT in this registry. Fifth, the mTICI score of 2c was not recorded in this registry. Hence, patients with near-complete recanalisation may have been included in the cohort of patients who achieved an mTICI 3 score (complete recanalisation). Sixth, the primary outcome measure of mRS at discharge was used instead of mRS at 90 days or 6 months due to the poor 6-month follow-up available (approximately 30% of the entire cohort), and that the mRS data at 90 days were not collected in this registry. Nevertheless, mRS at discharge has been shown to have a high correlation with disability at 3 months.[15] Last, the angiographic measures (mTICI) were assessed at a local level rather than evaluated by a central core laboratory, which may have overestimated the recanalisation scores.

Conclusion

A large proportion of patients in this national registry experienced FCR following EVT. Significant predictors of FCR included increasing age, admission NIHSS scores, pre-stroke disability, onset-to-puncture and procedural times, presence of diabetes, and use of general anaesthesia. Development of any ICH, sICH, and END post procedurally were associated with FCR. Continued efforts to improve the time-to-treatment/recanalisation and development of adjuvant therapies (e.g. neuroprotectants) whilst enhancing patient selection for EVT treatment should be considered.

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Contributorship statement

Conception and design: PSD, WB. Acquisition of the data: PSD. Analysis and interpretation of the data: PSD, WB. Critical revision of the manuscript: PSD, WB, AP, NM, RL, SN, LM, PB, HLDM, RAD, TJE. Study supervision: RAD, TJE. Guarantor of this work: PSD. All authors approved the final version of the manuscript.

Declaration of Competing Interest

None declared.

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