Received: 13 October 2022 | Accepted: 1 December 2022

DOI: 10.1111/ene.15658

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Clinical outcomes of delayed mechanical thrombectomy: Descriptive analysis and development of a screening tool

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Abstract

Background and purpose: Limited data guide the selection of patients with large vessel occlusion ischaemic stroke who may benefit from referral to a distant tertiary centre for mechanical thrombectomy (MT). We aimed to characterize this population, describe clinical outcomes and develop a screening system to identify patients most likely to benfit from delayed mechanical thrombectomy (MT).

Methods: We undertook a retrospective cohort analysis enrolling patients transferred from regional sites to one of two MT comprehensive stroke units with a time from non-contrast computed tomography (NCCT) of the brain to reperfusion of 4 h or more. We describe Alberta Stroke Programme Early Computed Tomography Score (ASPECTS), National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) in our patients and compare these patients to those in extended-time-window trials. Lastly, we developed and validated a scoring model to help clinicians identify appropriate patients based on variables associated with poor outcomes.

Results: We included 563 patients, 46% of whom received thrombolysis; the median (interquartile range [IQR]) ASPECTS was 8 (7–10) and the median (IQR) NIHSS score was 16 (11–20). The median (IQR) symptom to mechanical reperfusion time was 390 (300–580) min. Eight patients (1%) had a symptomatic haemorrhage. We achieved good clinical outcome (defined as mRS score ≤2) in 299 patients (54%). Age, diabetes, NIHSS score and ASPECTS were used to create a weighted scoring system with a validated area under the curve of 0.83 (95% confidence interval 0.74–0.92).

Conclusion: Our study shows, in highly selected patients, that delayed MT many hours after baseline NCCT is associated with good clinical outcomes. However, older patients with diabetes, high NIHSS score and low ASPECTS may not benefit from transfer to a hub centre many hours away for MT in this model of care.

KEYWORDS
brain ischaemia, rural, stroke*/therapy, thrombectomy, treatment outcome

INTRODUCTION

New Zealand is sparsely populated over a large geographical area, with three cities (Auckland, Wellington, and Christchurch) comprising 52% of the population (Figure 1). This geography necessitates a hub-and-spoke model of stroke care, with mechanical thrombectomy (MT) only provided in these three centres [1, 2]. Patients who present to remote centres with large vessel occlusion stroke and favourable imaging are transferred to these MT centres by helicopter or aeroplane. Imaging is not repeated so as not to delay reperfusion, except in cases of significant clinical deterioration or a substantial time delay over and above what is normally expected. This transfer process leads to delays to MT and worse functional outcomes than in patients who present directly to an MT centre [3, 4], and is resource intensive, often leaving rescue vehicles unavailable for other problems that arise within an entire region.

Studies have demonstrated clinical benefit of MT in an extended time window up to 24 h from symptom onset [5]. However, all patients in these trials had perfusion imaging immediately prior to MT. Limited data are guiding the selection of patients referred from a distant centre for MT. We aimed to characterize this population, describe clinical outcomes and compare the results with those of the extended-time-window trials. Finally, to help refine patient selection for future management, we developed a scoring system to predict those who are most likely to benefit from transfer and delayed MT.

METHODS

Case ascertainment

We retrospectively identified all consecutive patients transferred to Christchurch and Auckland hospitals for MT between July 2018 and June 2021 from the regional catchment areas with transfer times (from diagnosis on computed tomography [CT] to mechanical reperfusion) of 4 h or more. Inclusion criteria included pre-morbid functional independence (modified Rankin Scale [mRS] score ≤2) and favourable baseline imaging (non-contrast CT scan [NCCT], and CT perfusion imaging where available). Posterior circulation strokes were excluded. We collected baseline demographics and risk factors (Table 1). Baseline imaging and reperfusion indices (Expanded Thrombolysis In Cerebral Infarction [eTICI] scores) were collected locally. Alberta Stroke Programme Early CT Score (ASPECTS) was assessed locally and prior to study conception. The primary outcome was 3-month mRS score, which was collected locally and prior to study conception. Table 1 provides a descriptive analysis of our cohort.

Model development

We derived the screening score from the Auckland dataset. We defined good outcome as mRS score ≤2. We selected a prespecified list

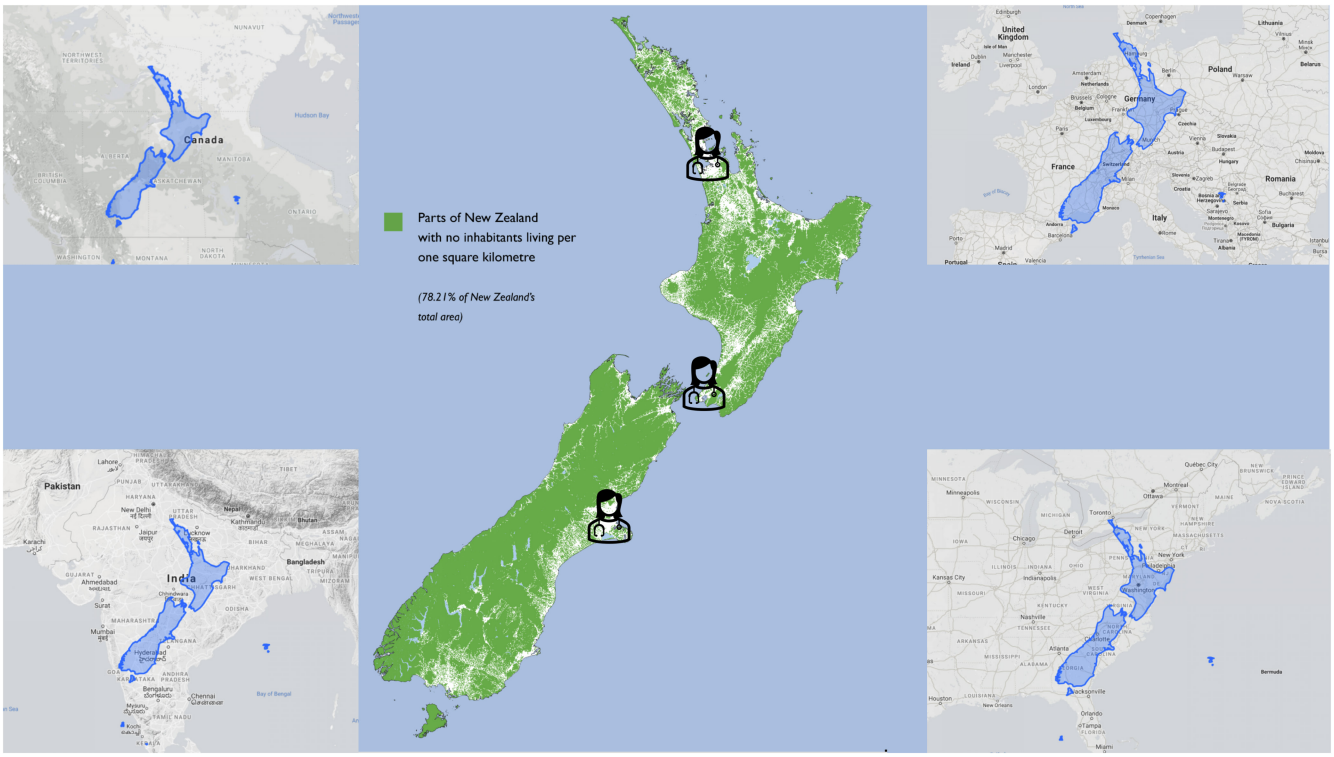

FIGURE 1 Areas in green indicate no inhabitants per 1 square kilometre. The locations of the endovascular centres are marked. In each corner of the figure, New Zealand has been overlayed on other parts of the world to give a true representation of New Zealand's land mass. Modified with permission. Map of New Zealand showing the population density and it's landmass relative to other locations. The locations of the endovascular units are marked.

TABLE 1 Baseline characteristics, imaging and outcomes

		All ($n = 563$)	Auckland ($n = 488$)	Christchurch ($n = 75$)
Age, median (IQR) years		70 (79–79)	70 (59–78)	74 (62–81)
Sex: male, *n* (%)		284 (50)	242 (50)	42 (56)
Hypertension, *n* (%)		357 (64)	308 (63)	49 (66)
Hyperlipidaemia, *n* (%)		243 (43)	216 (44)	27 (36)
Atrial fibrillation, *n* (%)		285 (51)	249 (51)	36 (48)
Diabetes, *n* (%)		95 (16)	85 (17)	10 (14)
Current smoker, *n* (%)		148 (26)	146 (30)	2 (3)
Ischaemic heart disease, *n* (%)		116 (21)	100 (20)	16 (22)
Congestive heart failure, *n* (%)		103 (18)	95 (19)	8 (11)
Previous stroke, *n* (%)		74 (13)	64 (13)	10 (14)
Warfarin at time of stroke, *n* (%)		48 (9)	45 (9)	3 (4)
DOAC at time of stroke, *n* (%)		88 (16)	82 (17)	6 (8)
Antiplatelets at time of stroke, *n* (%)		130 (23)	103 (21)	27 (36)
Received thrombolysis, *n* (%)		261 (46)	214 (44)	47 (63)
Wake-up stroke, *n* (%)		16 (21 [Christchurch only])	N/A	16 (21)
Arrived at MT centre after hours, *n* (%)		257 (47)	226 (46)	38 (51)
Onset to needle time if thrombolysed ($n = 257$), median (IQR) min		150 (121–190)	150 (125–195)	142 (110–185)
Vessel affected	Left MCA, *n* (%)	381 (68)	338 (69)	42 (57)
	Right, MCA *n* (%)	98 (17)	82 (17)	16 (21)
ASPECTS: median (IQR) ($n = 562$)		8 (7–10)	8 (7–10)	9 (7–10)
Core infarct volume, median (IQR), Christchurch only, $n = 41$		17 (5–33)	N/A	17 (5–33)
Penumbra volume, median (IQR), Christchurch only, $n = 41$		89 (51–125)	N/A	89 (51–125)
MT (final eTICI score)	0	32 (6)	27 (6)	5 (7)
	1	1 (1)	4 (1)	1 (1)
	2a	37 (7)	31 (6)	6(8)
	2b	102 (18)	77 (16)	25 (33)
	2c	94 (17)	92 (19)	2 (3)
	3	293 (52)	257 (53)	36 (48)
MT eTICI 2b or better, *n* (%)		489 (87)	426 (87)	63 (84)
Symptom to reperfusion time, median (IQR) min		390 (300–580)	370 (291–570)	458 (404–671)
Symptom to reperfusion time excl. wake-up (Christchurch only), median (IQR) min		436 (389–494) $n = 59$	N/A	436 (389–494) $n = 59$
Reperfused in under 6 h, *n* (%)		232 (41)	221 (45)	11 (15)
Baseline NIHSS score, median (IQR)		16 (11–20)	16 (11–20)	16 (9–22)
Day-1 NIHSS score, median (IQR)		8 (3–15)	7 (3–15)	11 (4–20)
Symptomatic ICH, *n* (%)		8 (1)	8 (1)	0 (0)
HI1, *n* (%)		18 (3)	11(2)	7 (9)
HI2, *n* (%)		11 (2)	6 (1)	5 (7)
PH1, *n* (%)		14 (2)	13 (3)	1 (1)
PH2, *n* (%)		18 (3)	18 (4)	0 (0)
Pre-stroke mRS score, median (IQR)		0 (0–0)	0 (0–0)	0 (0–0)
3 month mRS score ($n = 558$), median (IQR)		2 (1–4)	2 (1–4)	2 (1–4)

Abbreviations: ASPECTS, Alberta Stroke Programme Early Computed Tomography Score; DOAC, direct oral anticoagulant; eTICI, Expanded Thrombolysis in Cerebral Infarction; HI, haemorrhagic infarction; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institute of Health Stroke Scale; PH, parenchymal haemorrhage.

of variables as part of the data capture sheet based on factors known to be associated with stroke and clinical outcome. We only included variables for potential selection into the model if they were available at the spoke sites (i.e., variables such as final eTICI score or symptomatic intracerebral haemorrhage were not entered into the model). We used leave-one-out information criteria to find the model which had the best out-of-sample pointwise predictive accuracy [6]. We then created a weighted scoring system by multiplying all regression β-coefficients by 100 to ensure all coefficients were integers. The model was then simplified by quantizing the scores into five equal sets. We then calculated the area under the curve (AUC) and compared this to the AUC of the model with all the variables.

Model validation

After developing the model using data from the Auckland dataset, we validated it using the Christchurch dataset. Using the rounded weights in the risk function, we estimated the participant-specific probabilities of a good clinical outcome. We checked the fit of the model by (i) comparing observed versus predicted rates of good outcomes and (ii) checking the discrimination by analysing the AUC. We then used the receiver-operating characteristic curve to select a cut-off point to help maximize sensitivity without an increase in excessive false positives.

We did not undertake a sample size calculation but rather a post hoc analysis investigating whether our derivation and validation cohort were sufficient to evaluate our model's performance. We followed the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) checklist for model prediction and validation studies. We undertook statistical analysis using R 4.1.2 [7] and brms 2.16.3 [8].

This study had approval from the New Zealand Health and Disability Ethics Committee. All data were collected as part of routine care, and additional patient consent was not required, as per legislation.

RESULTS

A total of 563 patients were transferred to our hub centres for MT (488 to Auckland and 75 to Christchurch). The median (interquartile range [IQR]) age was 70 (59–79) years and 284 of the patients (50%) were male. Vascular risk factors present in the group included: hypertension, 357 (64%); hyperlipidaemia, 243 (43%); atrial fibrillation, 285 (51%); diabetes, 95 (16%); ischaemic heart disease, 116 (21%); previous stroke, 74 (13%); and current smoking, 148 (26%). In all, 48 (9%) and 88 patients (16%) were taking warfarin and a direct oral anticoagulant, respectively. Patients from the two centres were similar in terms of demographics and risk factor profiles, apart from a greater prevalence of smoking and use of anticoagulant therapy in Auckland patients (Table 1). No patients underwent repeat imaging at the hub site prior to MT.

Sixty-eight percent of patients had an M1 middle cerebral artery (MCA) occlusion, 17% an M2 MCA occlusion, and 14% a tandem internal carotid artery and MCA occlusion. The median (IQR) National Institute of Health Stroke Scale (NIHSS) score was 16 (11–20) and the median (IQR) ASPECTS was 8 (7–10) A total of 261 patients (46%) received thrombolysis, with a median (IQR) onset to needle time of 150 (121–190) min, and 257 patients (47%) arrived at the MT centre after office hours (defined as Monday–Friday 08:00–16:00 h).

Four hundred and eighty-nine patients (87%) achieved a post-MT score of TICI2b or above. The median (IQR) symptom to reperfusion time across both sites was 390 min/6.5 h (300–580 min/5 h–9.6 h). However, this varied between sites, with more prolonged times in Christchurch compared with Auckland (458 min, IQR 404–671 vs. 370, IQR 291–570; $p < 0.001$). Eight patients (1%) had a symptomatic haemorrhage. The median (IQR) 90-day mRS score was 2 (1–4). Good clinical outcome was achieved in 299 patients (54%) and was similar for the two sites. When including only patients with symptom to reperfusion times ≥12 h, 48/103 (47%) achieved a good outcome (median [IQR] symptom to reperfusion time 15 [13.75–19] h).

Univariable predictors of good clinical outcomes (mRS score ≤2) were age, hypertension, diabetes, ASPECTS and NIHSS score (apart from ASPECTS all inversely related). Time from CT to reperfusion, different antithrombotics and history of atrial fibrillation or previous stroke had little effect on outcome (Table 2).

Model development

Our primary outcome (3-month mRS score) was available in 483 of 488 patients (99%). We removed the five patients without these data from the model development. Age, history of hypertension, diabetes, hyperlipidaemia, heart failure, ischaemic heart disease, current smoking, atrial fibrillation, previous stroke, NIHSS score, ASPECTS, anticoagulation, antiplatelet and time to reperfusion were considered in model comparison (Table 2). This model produced an AUC of 0.75 (0.71–0.79). Using leave-one-out information criteria, the model with the best out-of-sample predictive accuracy included the variables age, ASPECTS, diabetes, and NIHSS score. The odds ratios (and β-coefficients) are shown in Table 3. The AUC for this model was 0.74 (0.69–0.78).

Model validation

Complete data were available in 73 of 75 patients in the validation cohort. We quantized the scores to create five equal datasets and simplified the model further. The predicted scores in the test set performed better than expected based on what was observed in the training set (Table 4). The AUC was 0.84 (95% CI 0.75–0.93; Figure 2). The simplified discrete model's AUC was 0.83 (95% CI 0.74–0.92).

There was no single cut-off point that separated patients with good outcomes from those without. Nevertheless, a cut-off quantized score of 4 would correctly identify almost all patients with a good outcome (38/39; 97%), with an acceptable false-positive rate (20/34; 59%). This cut-off point corresponds to a score of −62. More simply, among patients without diabetes, with an ASPECTS of 10, and a baseline NIHSS score of 20, patients should be no older than 94.5 years old. For every ASPECTS point decrease, the age cut-off drops by approximately 5 years. For example, if the ASPECTS is 4, the age cut-off would be 66 years. In patients with diabetes, this changes dramatically. In patients with diabetes, those with an ASPECTS of 10 should be no older than 65 years.

TABLE 2 Univariable predictors of an independent outcome (modified Rankin Scale score ≤2) at 3 months

Variable	OR (95% CI)
Age (every year)	0.96 (0.95–0.98)
Hypertension	0.62 (0.39–0.99)
Hypercholesterolaemia	1.48 (0.91–2.42)
Diabetes	0.31 (0.17–0.55)
Atrial fibrillation	0.98 (0.63–1.51)
Current smoker	1.11 (0.69–1.74)
Previous stroke	0.81 (0.43–1.54)
DOAC	0.84 (0.44–1.59)
Warfarin	1.96 (0.82–4.97)
Antiplatelet	0.85 (0.49–1.48)
Ischaemic heart disease	0.82 (0.47–1.44)
Congestive heart failure	1.04 (0.59–1.86)
Time to reperfusion	1.00 (1.00–1.00)
ASPECTS score (per point lost)	0.82 (0.74–0.90)
Baseline NIHSS (per point increase)	0.90 (0.97–0.94)

Abbreviations: ASPECTS, Alberta Stroke Programme Early Computed Tomography Score; CI, confidence interval; DOAC, direct oral anticoagulant; NIHSS, National Institute of Health Stroke Score; OR, odds ratio.

TABLE 4 Yield of independence at outcome from the optimized model compared to the actual yield at each quantized score.

Quantized score [raw score]	*N* (73)	Observed good outcome	Predicted good outcome
1 [x > 103]	14	14/14 (100%)	81%
2 [62 < x < = 103]	14	10/14 (71%)	67%
3 [7 < x < = 62]	15	6/15 (40%)	58%
4 [−62 < x < = 7]	15	8/15 (53%)	40%
5 [x < = −62]	15	1/15 (7%)	24%

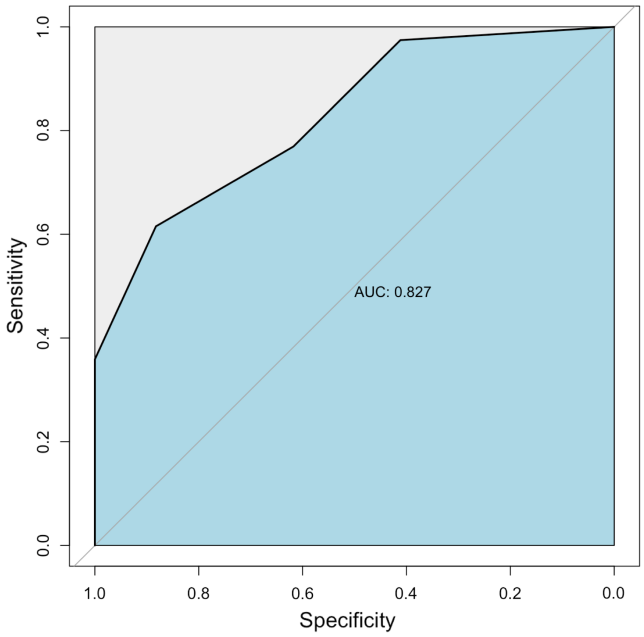

FIGURE 2 Receiver-operating characteristic curve for Christchurch test data binned score. AUC, area under the curve

TABLE 3 Multivariable predictors of independent outcome (modified Rankin Scale score ≤2) at 3 months

Variable	OR	Beta coefficient	Score
Intercept		3.06 (1.68 to 4.55)	306
Age (per year)	0.96 (0.94–0.97)	−0.04 (−0.06 to −0.03)	−4
ASPECTS (Per point lost)	0.83 (0.73–0.94)	−0.24 (−0.06 to −0.32)	−24
Diabetes (Yes, No)	0.30 (0.17–0.52)	−1.20 (−1.76 to −0.66)	−120
NIHSS (per point increase)	0.92 (0.88–0.94)	−0.09 (−0.13 to −0.06)	−9

Abbreviations: ASPECTS, Alberta Stroke Programme Early Computed Tomography Score; NIHSS, National Institute of Health Stroke Score; OR, odds ratio.

DISCUSSION

Although the benefit of extended-time-window MT has been clearly demonstrated, it remains unclear whether this benefit extends to people who are initially assessed for their stroke at a regional centre and require subsequent transfer for an interventional procedure. We show that outcomes in highly selected patients with ischaemic stroke and significant time delays from CT to MT are similar to patients enrolled in extended-window trials. This is without the need for repeat imaging at the site of MT. Our rates of functional independence (54%) were similar to those in the DAWN trial [9] (49%) and DEFUSE 3 trial [10] (44%). We show a hub-and-spoke model of stroke care with MT centres many hours away from spoke centres is a viable model of care using NCCT. We also show a combination of age, ASPECTS, NIHSS score, and history of diabetes can help refine patient selection for appropriate transfer to MT centres.

Our findings support a recent study showing that MT is an effective treatment in the extended time frame [5] and NCCT can be safely used to select appropriate patients [11]. Furthermore, they support recent studies showing that hub-and-spoke stroke network infrastructures enable access to successful MT in patients with stroke living remotely [12, 13]. In keeping with other hub-and-spoke stroke transfer studies, we found NIHSS score, ASPECTS and age to be important determinants of outcome [12, 13]. Although the median time to MT in the extended-time-window trials was longer than ours (approximately 12 h vs. 6.5 h), outcomes in our cohort, restricting symptom-to-reperfusion times to ≥12 h, were similar.

In contrast to an individual patient meta-analysis of extended-time-window patients [5], we would suggest patients with large infarcts, advancing age or diabetes could be excluded from receiving MT in our model of care. There are some important differences which form the basis of this differing opinion. Most patients in these trials were enrolled using advanced perfusion (CT or MRI), and there were only very few with ASPECTS <6. Most importantly, MT was undertaken acutely (usually <2 h) after baseline imaging, in contrast to our study where the median time from baseline CT to MT was 6.5 h. Infarct changes seen on NCCT likely reflect core infarct and therefore such patients are less likely to benefit from reperfusion, especially if that reperfusion is several hours away. The effect size of diabetes was surprising and not seen in other extended-time-window trials [5] nor in other hub-and-spoke studies and may indicate poor collaterals, which then fail during the delay taken to achieve reperfusion. The lack of association between stroke onset to reperfusion time and outcome is surprising and contrasts with other inter-hospital stroke transfer studies [3]. However, these other studies compared outcomes with those of patients not requiring transfer. Infarct growth is logarithmic, with most occurring in the first 6 h [14]. Our patients' median time to reperfusion was 6.5 h, which likely explains the loss of signal here.

Strengths of our study include the fact that all consecutive transfer patients were enrolled, ASPECTS was assessed prior to study conception, thereby limiting bias, and follow-up mRS score was available in 99% of patients. Lastly, our study captures a large proportion of the New Zealand population and is closely generalizable to a national cohort. Our study also has some limitations. The patients were already highly selected so are not generalizable to a routine large artery occlusion population. Furthermore, information on the number of patients at spoke sites with large vessel occlusions not transferred for MT was not available. Lastly, our validation cohort was small, which limited the ability to fully evaluate our risk model.

In conclusion, our study shows, in highly selected patients, that delayed MT many hours after baseline NCCT is associated with good clinical outcomes. This shows a hub-and-spoke model for stroke thrombectomy is appropriate in regions with sparse populations over vast geographical distances. Older patients with diabetes, low ASPECTSs, and high baseline NIHSS scores may not benefit from transfer to a distant centre for MT in this model of care.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Berry-Noronha A, Myall D, Hong JB, et al. Clinical outcomes of delayed mechanical thrombectomy: Descriptive analysis and development of a screening tool. *Eur J Neurol*. 2022;00:1-7. doi:10.1111/ene.15658