BMJ Neurology Open

Predictions for functional outcome and mortality in acute ischaemic stroke following successful endovascular thrombectomy

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To cite: Zeng M, Smith L, Bird A, *et al*. Predictions for functional outcome and mortality in acute ischaemic stroke following successful endovascular thrombectomy. *BMJ Neurology Open* 2024;**6**:e000707. doi:10.1136/bmjno-2024-000707

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjno-2024-000707).

Received 07 March 2024
Accepted 10 June 2024

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ABSTRACT

Background Accurate outcome predictions for patients who had ischaemic stroke with successful reperfusion after endovascular thrombectomy (EVT) may improve patient treatment and care. Our study developed prediction models for key clinical outcomes in patients with successful reperfusion following EVT in an Australian population.

Methods The study included all patients who had ischaemic stroke with occlusion in the proximal anterior cerebral circulation and successful reperfusion post-EVT over a 7-year period. Multivariable logistic regression and Cox regression models, incorporating bootstrap and multiple imputation techniques, were used to identify predictors and develop models for key clinical outcomes: 3-month poor functional status; 30-day, 1-year and 3-year mortality; survival time.

Results A total of 978 patients were included in the analyses. Predictors associated with one or more poor outcomes include: older age (ORs for every 5-year increase: 1.22–1.40), higher premorbid functional modified Rankin Scale (ORs: 1.31–1.75), higher baseline National Institutes of Health Stroke Scale (ORs: 1.05–1.07) score, higher blood glucose (ORs: 1.08–1.19), larger core volume (ORs for every 10 mL increase: 1.10–1.22), pre-EVT thrombolytic therapy (ORs: 0.44–0.56), history of heart failure (outcome: 30-day mortality, OR=1.87), interhospital transfer (ORs: 1.42 to 1.53), non-rural/regional stroke onset (outcome: functional dependency, OR=0.64), longer onset-to-groin puncture time (outcome: 3-year mortality, OR=1.08) and atherosclerosis-caused stroke (outcome: functional dependency, OR=1.68). The models using these predictors demonstrated moderate predictive abilities (area under the receiver operating characteristic curve range: 0.752–0.796).

Conclusion Our models using real-world predictors assessed at hospital admission showed satisfactory performance in predicting poor functional outcomes and short-term and long-term mortality for patients with successful reperfusion following EVT. These can be used to inform EVT treatment provision and consent.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous prognostic studies have focused on 3-month functional outcomes and few investigations on other outcomes. Some inconsistencies in identified predictors have meant that clinical impact has been limited.

WHAT THIS STUDY ADDS

⇒ This study contributes new knowledge by investigating comprehensive real-world predictors assessed at hospital admission and developing models for key clinical outcomes, including 3-month poor functional status, 30-day, 1-year and 3-year mortality, and survival time. The models developed demonstrated satisfactory performance. Risk of bias was minimised by collecting all incident cases that fulfil the inclusion criteria over a 7-year period, ensuring complete population ascertainment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The identified predictors and models developed have the potential to inform treatment decisions, patient consent and enable further validations.

INTRODUCTION

Patients with acute ischaemic stroke caused by large vessel occlusion (LVO) are at high risk of subsequent disability and mortality.[1] Currently, endovascular thrombectomy (EVT) is the standard treatment for selected patients with LVO who present within a window of time that may enable meaningful intervention.[2] However, despite successful reperfusion after EVT, around 50% of treated patients still experience long-term functional dependency.[2] This indicates that successful reperfusion after EVT does not necessarily translate into favourable clinical outcomes. Therefore, early identification of patients likely to have poor outcomes could enable better patient-centred decisions and tailored post-EVT care plans, ultimately helping improve clinical outcomes and resource allocation in acute stroke management.

Prediction in patients with successful reperfusion is a relatively unexplored area with several major gaps of knowledge. First, a 3-month functional outcome has been used as the endpoint in most prior studies.[3 4] However, this may not adequately capture the full trajectory of recovery or the ultimate status of patients with LVO after successful reperfusion, necessitating the analysis of other outcomes, such as mortality over a shorter or a longer term. Second, predictors identified previously have been inconsistent across studies.[3 4] Due to heterogeneity in patient characteristics, differences in local healthcare resources and continuous advancements in EVT techniques and devices, it is crucial to advance the exploration and validation on up-to-date and local specific patient data regarding prognostic prediction in LVO stroke.

Using a real-world population-based dataset collected over 7 years with complete population ascertainment from two Australian jurisdictions, this study aimed to identify predictors and develop models for key clinical outcomes in all patients with anterior circulation LVO stroke with successful reperfusion following EVT. These outcomes include 3-month functional outcomes, 30-day, 1-year and 3-year mortality, as well as the survival time over 7 years.

METHODS

Study population

The study population included all consecutive patients with anterior circulation LVO stroke admitted to the Royal Adelaide Hospital and treated with EVT between 1 December 2016 and 31 October 2023. This public tertiary referral centre located in South Australia (SA) is the sole provider of EVT services for patients who had stroke from SA and the Northern Territory. Patients were included in the main analysis if they: (1) had confirmed LVO by neuroimaging in the proximal anterior cerebral circulation, including intracranial internal carotid artery, middle cerebral artery M1 or M2 segments, (2) were treated with EVT within 24 hours after the stroke onset, (3) had successful reperfusion (thrombolysis in cerebral infarction (TICI) grade of 2b-3) immediately after EVT and (4) were aged ≥18 years. Patients with basilar artery occlusion were excluded due to greater heterogeneity and evolving treatment evidence/techniques during the study period. For the analysis of 1-year and 3-year mortality, patients with less than one or three follow-up years, respectively, were excluded to ensure outcomes were ascertainable for all subjects within the timeframe.

Data and assessment

Variables used for prediction in data analyses included:

1. demographic characteristics: age, sex, geographical site of stroke onset (urban or rural/regional area) and socio-economic status;
2. physical and pathological tests at admission: premorbid functional status (assessed by modified Rankin Scale (mRS)), National Institutes of Health Stroke Scale (NIHSS) score, systolic and diastolic blood pressure levels and blood glucose level;
3. neuroimaging features at admission: CT perfusion (CTP)-defined core volume and perfusion lesion, and occlusion sites;
4. clinical history and stroke risk factors: pre-existing antiplatelet therapy, pre-existing anticoagulant therapy, prior stroke, prior transient ischaemic attack, hypertension, obesity, diabetes, dyslipidaemia, ischaemic heart disease, heart failure, current or prior atrial fibrillation, chronic obstructive pulmonary disease, ever smoked, and cause of stroke; and
5. treatment-relevant details: pre-EVT thrombolytic therapy, onset-to-groin puncture time and method of arrival.

The outcome variables were very poor functional outcome (mRS ≥5), non-independent mobility (mRS ≥4), functional dependency (mRS ≥3), 30-day, 1-year and 3-year mortality, as well as the survival rate over 7 years.

Stroke onset location postcodes were categorised as urban or rural/regional based on the greater capital city using Australian Bureau of Statistics (ABS) classifications.[5] The residential address postcode was used to determine socioeconomic status through the decile Index of Relative Socioeconomic Advantage and Disadvantage from ABS.[6] Pre-existing therapy, including aspirin, clopidogrel, dipyridamole and ticagrelor, were recoded as pre-existing antiplatelet therapy, and apixaban, enoxaparin, warfarin, rivaroxaban and dabigatran were recorded as pre-existing anticoagulant therapy.

CTP raw data were preprocessed using MIStar (Apollo Medical Imaging Technology, Melbourne, Australia) and/or RAPID V.4 (iSchemaView, Menlo Park, California, USA). The software-generated CTP defined core volume and perfusion lesion volume maps using deconvolution models.[7 8] Core volume was defined as the volume with relative cerebral blood flow <30% of the contralateral hemisphere in both software packages, and perfusion lesion volume, was defined as the volume with delay time >3 s in MIStar[7] and the time-to-peak concentration (Tmax) >6 s in RAPID.[8] These automatic imaging-derived volumes were qualitatively validated by a consultant vascular neurologist (TK). MIStar core volumes were preferentially used, except when the artefact prevented interpretation, where RAPID volumes were employed. Occlusion sites were identified using CT angiography by two vascular neurologists. The TICI grade was independently determined by a consultant neurologist and a consultant neuro-interventionalist (TK and RS) based on the modified TICI score and/or the expanded TICI score using digital subtraction angiography.[9] Functional outcomes scored by mRS were assessed during follow-up clinical consultations or via interviews by trained nurses and/or neurologists. Other clinical variables were recorded and validated as part of the routine admission procedure for a patient with stroke prior to this project.

Statistical analyses

Continuous variables were described using means and SD if they followed a normal distribution, and as medians and IQRs if they were non-normal. To avoid violating criteria regarding event per predictor (<10),[10] bivariate regression analyses were performed for initial predictor screening. Meaningful predictors derived from bivariate analyses were then used as potential covariates in multivariable regression models. Logistic regression was used for binary outcomes including 3-month functional outcomes and mortality and Cox regression was used for the survival rate, with the timeframe from the date of hospital admission to the date of death or the censor date, whichever came first. According to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines recommendation,[11] Akaike Information Criterion (AIC) (equivalent to p<0.157 for one free parameter; p<0.135 for two free parameters; and p<0.112 for three free parameters)[12] was used to select predictors. The final model selection used bootstrap backward selection (AIC level) with 200 bootstrap samples and 20 multiple imputations to address missing data. Final models were built using predictors that were selected in over 70% bootstraps (>140),[13] and model coefficients and p values were derived from pooled results of multiple imputed data. Bootstrap-corrected areas under the receiver operating characteristic curve (AUC) and 95% CIs were calculated to determine the predictive performance, with bootstrap-corrected sensitivity and specificity calculated using a threshold selected based on the point closest to the top-left corner of the receiver operating characteristic curve.[14] Model thresholds with a sensitivity of 80% were also estimated. Sensitivity analyses were conducted by replicating all analyses in a larger sample additionally including patients with LVO with unsuccessful reperfusion. All statistical analyses were performed using R V.4.2.2.

RESULTS

Baseline characteristics

The baseline characteristics of the study sample are summarised in table 1. A total of 978 patients achieved successful reperfusion. The median age was 74.0 years, and 467 (47.8%) patients were female. A total of 183 (18.7%) patients were from rural/regional areas. At admission, most patients were physically independent (n=909, 92.9%). The median NIHSS score was 14.0 (IQR: 8.0–20.0). The median volumes of core infarct and perfusion lesion were 14.0 mL (IQR: 5.0–35.0 mL) and 106.5 mL (IQR: 66.3–152.0 mL), respectively. In total, 600 (61.3%) patients received EVT alone, and 378 (38.7%) received pre-EVT thrombolytic therapy.

For functional outcomes, 385 (43.5%) patients had mRS ≥3 at 90 days, 262 (29.6%) had mRS ≥4 and 190 (21.5%) had mRS ≥5. In terms of mortality, 122 (12.5%) patients had died within 30 days, 182 (21.5%) had died within 1 year and 240 (38.4%) had died within at 3 years.

Table 1 Baseline characteristics of patients with large vessel ischaemic stroke with successful reperfusion (N=978)

Variables	Summary statistics
Age (years), median (IQR)	74.0 (63.0–82.0)
Female sex, n (%)	467 (47.8)
Rural/regional stroke onset, n (%)	183 (18.7)
Index of relative socioeconomic advantage and disadvantage, median (IQR)	5.0 (2.0–8.0)
Premorbidly independent (mRS ≤2), n (%)	909 (92.9)
Baseline NIHSS, median (IQR)	14.0 (8.0–20.0)
Baseline blood glucose (mmol/L), median (IQR)	6.6 (5.7–8.1)
Baseline SBP (mm Hg), mean (SD)	145.7 (24.5)
Baseline DBP (mm Hg), mean (SD)	81.3 (16.3)
Core volume at admission (mL), median (IQR)	14.0 (5.0–35.0)
Perfusion lesion volume at admission (mL), median (IQR)	106.5 (66.3–152.0)
ICA occlusion, n (%)	200 (20.4)
M1 MCA occlusion, n (%)	688 (70.3)
M2 MCA occlusion, n (%)	351 (35.9)
Current or prior atrial fibrillation, n (%)	443 (45.3)
Prior stroke, n (%)	118 (12.1)
Prior transient ischaemic attack, n (%)	62 (6.3)
Hypertension, n (%)	607 (62.1)
Obesity, n (%)	106 (10.8)
Diabetes, n (%)	224 (22.9)
Dyslipidaemia, n (%)	409 (41.8)
Ischaemic heart disease, n (%)	191 (19.5)
History of heart failure, n (%)	93 (9.5)
Chronic obstructive pulmonary disease, n (%)	65 (6.6)
Ever smoked, n (%)	295 (30.2)
Cause of stroke, n (%)	
Cardioembolic	475 (48.6)
Atherosclerosis	188 (19.2)
Undetermined	315 (32.2)
Pre-EVT thrombolytic therapy, n (%)	378 (38.7)
Pre-existing antiplatelet therapy, n (%)	186 (19.0)
Pre-existing anticoagulant therapy, n (%)	221 (22.6)
Onset-to-groin puncture time (hours), median (IQR)	3.6 (2.8–6.4)
Method of arrival, n (%)	
Ambulance or road retrieval	573 (58.6)
Driven by companion or walk-in	23 (2.4)

Continued

Table 1 Continued

Variables	Summary statistics
Interhospital transfer	321 (32.8)
Aero-retrieval	61 (6.2)
Functional outcome at 3 months (N=885)	
Very poor functional outcome (mRS ≥5), n (%)	190 (21.5)
Non-independent mobility (mRS ≥4), n (%)	262 (29.6)
Functional dependency (mRS ≥3), n (%)	385 (43.5)
Mortality (30 days, N=978; 1 year, N=846; 3 years, N=625)	
30 days, n (%)	122 (12.5)
1 year, n (%)	182 (21.5)
3 years, n (%)	240 (38.4)

DBP, diastolic blood pressure; EVT, endovascular thrombectomy; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Predictors and model performance

Predictors of poor functional outcomes defined using different thresholds are shown in table 2. Five predictors were consistently associated with poor functional outcomes regardless of the thresholds: older age, higher premorbid mRS, higher NIHSS score, higher blood glucose, larger CTP-defined core volume. Receiving thrombolysis before thrombectomy is consistently associated with a reduced risk of poor functional outcomes. Interhospital transfer was associated with an increased risk of non-independent mobility (mRS ≥4) and functional dependency (mRS ≥3). Rural/regional stroke onset and atherosclerosis-caused stroke patients were more likely to have functional dependency (mRS ≥3).

Four predictors showed associations consistently with short-term and long-term mortality from logistic regression models (table 3): older age, higher premorbid mRS, higher blood glucose and larger core volume. Pre-EVT thrombolytic therapy is consistently associated with a reduced risk of mortality. History of heart failure was associated with a higher risk of 30-day mortality, and longer onset-to-groin puncture time was associated with a higher risk of 3-year mortality. The predictors mentioned above remained statistically significant with consistent directions of effect in the analysis of survival rate using Cox regression (online supplemental table S1). The Kaplan-Meier curve for survival rates of patients showed that out of 266 patients who die over a 7-year period, 182 (68.4%) deceased within the first year (online supplemental figure S1A).

Table 2 ORs for functional outcomes at 3 months from multivariable logistic regression

Predictive variables	ORs (95% CIs)	P value
Very poor functional outcome (mRS ≥5)		
Age (every 5-year increase)	1.22 (1.16, 1.34)	<0.001
Premorbid mRS score	1.67 (1.41, 1.98)	<0.001
Baseline NIHSS	1.05 (1.02, 1.07)	0.003
Baseline blood glucose (per 1 mmol/L glucose)	1.15 (1.09, 1.21)	<0.001
Core volume (10 mL increase)	1.22 (1.10, 1.22)	<0.001
Pre-EVT thrombolytic therapy	0.44 (0.30, 0.64)	<0.001
Non-independent mobility (mRS ≥4)		
Age (5-year increase)	1.22 (1.10, 1.28)	<0.001
Premorbid mRS score	1.75 (1.48, 2.08)	<0.001
Baseline NIHSS	1.07 (1.04, 1.09)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.19 (1.12, 1.26)	<0.001
Core volume (10 mL increase)	1.10 (1.10, 1.22)	<0.001
Pre-EVT thrombolytic therapy	0.48 (0.34, 0.67)	<0.001
Method of arrival, n (%)		
Ambulance or road retrieval	Reference	
Driven by companion or walk-in	0.35 (0.05, 1.45)	0.216
Interhospital transfer	1.42 (1.00, 2.02)	0.025
Aero-retrieval	1.37 (0.69, 2.63)	0.468
Functional dependency (mRS ≥3)		
Age (5-year increase)	1.22 (1.16, 1.34)	<0.001
Premorbid mRS score	1.51 (1.28, 1.80)	<0.001
Baseline NIHSS	1.06 (1.04, 1.09)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.16 (1.10, 1.23)	<0.001
Core volume (10 mL increase)	1.10 (1.10, 1.22)	<0.001
Pre-EVT thrombolytic therapy	0.48 (0.35, 0.65)	<0.001
Non-rural/regional stroke onset	0.64 (0.41, 0.98)	0.013
Method of arrival, n (%)		
Ambulance or road retrieval	Reference	
Driven by companion or walk-in	0.34 (0.07, 1.15)	0.305
Interhospital transfer	1.53 (1.10, 2.14)	0.077
Aero-retrieval	1.21 (0.60, 2.45)	0.661
Cause of stroke		

Continued

Table 2 Continued

Predictive variables	ORs (95% CIs)	P value
Cardioembolic	Reference	
Atherosclerosis	1.68 (1.13, 2.52)	0.031
Undetermined	0.97 (0.68, 1.37)	0.907

EVT, endovascular thrombectomy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

The bootstrap-corrected AUCs, sensitivity and specificity (table 4) of the fitted multivariable models demonstrated moderate predictive values (AUCs: 0.752–0.796; sensitivity: 0.641–0.729; specificity: 0.691–0.777). The pool model equations with specification and examples are described in online supplemental table S2.

Table 3 ORs for mortality (30 days, 1 year and 3 years) from multivariable logistic regression

Predictive variables	Odds ratios (95% CIs)	P value
Mortality at 30 days		
Age (5-year increase)	1.22 (1.16, 1.34)	<0.001
Premorbid mRS score	1.31 (1.07, 1.58)	0.006
Baseline blood glucose (per 1 mmol/L glucose)	1.11 (1.05, 1.17)	<0.001
Core volume (10 mL increase)	1.22 (1.10, 1.34)	<0.001
History of heart failure	1.87 (1.02, 3.31)	0.044
Pre-EVT thrombolytic therapy	0.56 (0.35, 0.87)	0.011
Mortality at 1 year		
Age (5 year increase)	1.34 (1.28, 1.47)	<0.001
Premorbid mRS score	1.48 (1.24, 1.75)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.08 (1.03, 1.14)	0.004
Core volume (10 mL increase)	1.22 (1.10, 1.22)	<0.001
Pre-EVT thrombolytic therapy	0.51 (0.34, 0.75)	0.001
Mortality at 3 years		
Age (5-year increase)	1.40 (1.28, 1.54)	<0.001
Premorbid mRS score	1.62 (1.32, 2.00)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.18 (1.11, 1.27)	<0.001
Core volume (10 mL increase)	1.22 (1.10, 1.34)	<0.001
Pre-EVT thrombolytic therapy	0.47 (0.31, 0.70)	0.001
Onset-to-groin puncture time (1-hour increase)	1.08 (1.02, 1.14)	0.012

EVT, endovascular thrombectomy; mRS, modified Rankin scale.

The sensitivity analyses did not show any material change from the main analyses (online supplemental tables S3–S7 and figure S1B).

DISCUSSION

This is the first study investigating LVO prognosis in successful reperfusion that has investigated multiple clinical outcomes beyond the traditional focus on functional status. In our clinical cohort of 978 patients with LVO with successful reperfusion, we identified a broad range of predictors obtained at hospital admission, for 3-month poor functional outcomes and mortality. These include older age, higher premorbid functional mRS, higher baseline NIHSS, higher blood glucose, larger core volume, no pre-EVT thrombolytic therapy, history of heart failure, hospital transfer, rural/regional stroke onset, atherosclerosis-caused stroke and longer onset-to-groin puncture time. Remarkably, several factors, such as age, premorbid functional mRS, blood glucose and core volume, were predictive for both functional outcomes and mortality. The overlap in these predictors highlights their critical role in stroke prognosis across different stages of the disease course. However, a few predictors were specific to individual outcomes (e.g., history of heart failure for mortality and interhospital transfer for functional outcomes), indicating that there is still a unique aspect of each outcome that is necessary for exploration.

The prediction models developed using these variables demonstrated AUCs ranging from 0.768 to 0.784 for functional outcomes, and 0.752 to 0.796 for mortality. An AUC between 0.7 and 0.8 is generally considered acceptable performance for clinical prediction models.[15] Therefore, our models showed satisfactory predictive performance in differentiating between LVO patients with varying outcomes. This has important implications for clinical decision-making, as effective risk stratification at hospital admission enables clinicians to identify patients with greatest risk of poor outcomes even after successful EVT reperfusion. In clinical practice, these models are recommended to guide the need for additional care for patients and patient consent, rather than to withhold EVT treatment. As such, high-risk patients could receive extra ancillary investigative treatments and/or adjunct treatments, and may be considered for trialling new therapies. We selected the model thresholds with a sensitivity of 80%, allowing the identification of 80% of patients with poor outcomes postreperfusion, while this also means a small amount of patients at high risk (20%) might be missed for such additional care. Additionally, a high sensitivity also increases the false positive rate, which ranges from 32.0% to 43.0% in our models. Although this may lead to some waste of healthcare resources, it would be counterbalanced by the administration of postoperative care to those patients at risk of poor outcomes. When obtaining consent, the above uncertainty should be communicated clearly to patients and family members, ensuring informed decisions are made with a full understanding of

Table 4 Model performance of outcomes

Outcome	Corrected AUC (95% CI)	Corrected SEN (95% CI)	Corrected SPE (95% CI)
Very poor functional outcome (mRS ≥5)	0.784 (0.751, 0.817)	0.662 (0.605, 0.720)	0.777 (0.725, 0.828)
Non-independent mobility (mRS ≥4)	0.782 (0.752, 0.813)	0.729 (0.679, 0.779)	0.691 (0.638, 0.745)
Functional dependency (mRS ≥3)	0.768 (0.738, 0.799)	0.697 (0.645, 0.749)	0.702 (0.646, 0.759)
Mortality at 30 days	0.752 (0.702, 0.802)	0.641 (0.559, 0.724)	0.736 (0.663, 0.809)
Mortality at 1 year	0.767 (0.728, 0.806)	0.689 (0.616, 0.762)	0.693 (0.625, 0.760)
Mortality at 3 years	0.796 (0.763, 0.829)	0.716 (0.657, 0.775)	0.734 (0.673, 0.795)

Thresholds for sensitivity and specificity shown in the table were selected based on point closest to the top-left corner of the receiver operating characteristic curve in each bootstrap sampling.
AUC, areas under the receiver operating characteristic curve; mRS, modified Rankin scale; SEN, sensitivity; SPE, specificity.

potential benefits and risks and appropriate expectations are set without overpromising.

The majority of existing prognostic prediction models for LVO stroke broadly encompass EVT-treated patients, regardless of the reperfusion outcomes.[15] Considering reperfusion status in prognostic models is crucial because EVT can significantly affect patient recovery and mortality. By accounting for reperfusion outcomes, our models can provide more specific risk assessments and identify patients with suboptimal clinical outcomes despite technically successful interventions. This also helps ensure that patient and family expectations are properly set based on the possibility of successful reperfusion. Additionally, the development of prediction models specifically for patients with successful reperfusion has been limited and most previous studies have used 90-day mRS as the endpoint.[3] Our study fills an important gap by incorporating short-term and long-term mortality data and explores the factors associated with more severe outcomes.[16]

Our models also innovate by maximising their applicability and ease of implementation in emergency scenarios where time is a paramount factor, through the use of variables that are all immediately and routinely accessible at hospital admission. The rate of futile reperfusion observed here (43.5%) aligns with previous observations in other jurisdictions (32.4%–69.6%),[17] possibly suggesting comparable patient characteristics and healthcare resources. Nonetheless, further preclinical assessment of the models across diverse clinical settings are needed. By providing equations, we offer a quantitative tool that can help stratify patients by risk and guide more effective consent and treatment. This also ensures the transparency and straightforwardness of the rationale and mechanisms behind these models, allowing other research groups from various regions to conduct observational trials to further evaluate properties and potential clinical utility of models. This also enables researchers to identify potential limitations of the models and allows improvement of the models in the reliability and utility before the implementation in real-world clinical settings.

There are several modifiable predictors identified in this study that can inform treatment provision. For example, history of heart failure was associated with 87% increase in mortality risk. Every 1 mmol/L increase in blood glucose at admission showed an association with an 15% increased risk for poor functional outcomes. Heart failure, indicative of pre-existing cardiovascular compromise, worsens stroke prognosis via inflammatory response, pulmonary oedema, hypoxia and cardiac arrhythmia.[18] Similarly, hyperglycaemia has been associated with increased proinflammatory states, exacerbating cerebral impairment and hindering neurovascular repair.[19] These findings highlight the detrimental effects of compromised cardiac function and glucose metabolism for stroke recovery, suggesting the need for personalised treatment and care in terms of cardiometabolic health.

We also identified several predictors specifically in terms of stroke triage. For example, thrombolysis before thrombectomy was associated with at least 44% decreased risk in poor outcomes. This is possibly because of the initial dissolution of the clot, which complements subsequent mechanical thrombectomy and suggests the need to consider thrombolytic therapy before mechanical thrombectomy if time permits. Also, a swift triage plays a pivotal role for recovery. Delayed treatment can result in ischaemic core expansion and our study showed that every 10 mL increase in core volume is associated with at least 10% increased risk of poor outcomes. Additionally, every 1 hour increase in onset-to-groin puncture time was observed to be associated to an increase of 8% in the risk of 3-year mortality. This highlights 'time is brain' concept[20] and reinforces the importance of immediate medical response to stroke symptoms and the need for swift diagnosis and treatments. The associations of rural/regional stroke onset and interhospital transfer with poor prognosis might partially reflect this concept as the associations remained significant after adjusting for the

onset-to-groin puncture time and socioeconomic status. Other elements may also play an important role in the poorer outcomes observed in these patients, such as suboptimal management of major risk factors in rural/regional[21] and inadequate provision for haemodynamic or respiratory complications in transit.[22] Therefore, enhancing healthcare infrastructure, including targeted public health promotion in remote regions and better emergency medical services during the transit are needed.

Despite inconsistency regarding the association of atherosclerotic LVO with poor prognosis in prior studies,[23–26] we add to the current evidence with the findings that atherosclerosis-caused LVO was at 68% higher risk of functional dependency compared with cardioembolic LVO. Prior inconsistency in findings was likely due to variability in diagnostic accuracy (eg, accuracy of intracranial atherosclerosis diagnosis), peri-EVT or post-EVT antithrombotic use, and thrombectomy techniques.[27] Notably, a recent study showed no difference in prognostic outcomes between patients with atherosclerotic and non-atherosclerotic aetiologies, when current thrombectomy techniques (A Direct Aspiration First Pass Technique [ADAPT]) were used.[27] Although our data are not definitive in terms of guiding treatment decisions, our findings highlight the necessity of high-quality randomised trial data to guide periprocedural and post-procedural treatments in these patients.

We found older age, higher premorbid mRS and higher baseline NIHSS score to be associated consistently with poor outcomes in this study. Although these predictors are non-modifiable, they provide critical information for risk stratification and tailor treatment at hospital admission. For example, we can better manage age-related factors, such as severe comorbidities, fragility and poor nutrition, at an early stage to improve patient outcomes. Premorbid mRS score and baseline NIHSS by providing quantifiable information could help inform rapid and comprehensive assessment on presentation to help risk stratification.

A strength of the current study is the high-quality data of EVT-treated patients with LVO collected from two Australian jurisdictions with complete population ascertainment. Our study design ensured adequate power for the statistical analyses and minimised random errors and selection bias. The breadth of the data enabled a comprehensive investigation into prognostic factors of LVO in an emergency setting across various clinical contexts. Another strength was the enrichment of the clinical outcomes investigated. This not only validated prior findings regarding 3-month functional outcomes, but also significantly extended previous literature with novel analysis on mortality over a long period of follow-up. In addition, model performance was robustly estimated and corrected using bootstrap techniques with multiple imputation for handling missing data.

Several study limitations need to be acknowledged. First, the evolving patient characteristics over time, including an increasing inclusion of patients with M2 MCA occlusion, advanced cancer or diagnosis of dementia, and the establishment of a comprehensive tele-stroke network in 2018,[28] may have introduced confounding that is unaccounted for in the current study. Second, evidence for treatment expansion, such as in basilar occlusion and large core trials, occurred during the timeframe of our study, and the present findings might not fully capture the latest knowledge on this topic.

CONCLUSIONS

We identified a broad range of predictors routinely obtained at hospital admission that were associated with poor short-term functional outcomes and long-term mortality, based on a 7-year consecutive clinical cohort. These include older age, higher premorbid functional mRS, higher baseline NIHSS, higher blood glucose, larger core volume, no pre-EVT thrombolytic therapy, history of heart failure, hospital transfer, rural/regional stroke onset, atherosclerosis-caused stroke and longer groin-to-puncture time. The models developed using these predictors demonstrated satisfactory predictive ability. Rather than being used to exclude patients from EVT treatment, the predictors identified and models developed could be potentially used to inform treatment decision, patient consent, and future validations.

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Contributors MZ, as the guarantor for the overall content, contributed to study conception, study design, collection and analysis of data, and draft writing. LJP contributed to the study conception, study design, data collection, data analysis and critical revision of the manuscript. RS, TK, JJ and MJ contributed to the study design, data collection, data analysis and critical revision of the manuscript. AB, LS, VQ-NT, SB and JH contributed to the study design and critical revision of the manuscript. We thank Dr Meegan Gun and Mr Roy Drew for assisting with the data collection.

Funding MZ is supported by an Australian Government Research Training Program Scholarship by the University of Adelaide. AB and LS are supported by GlaxoSmithKline industry PhD and Australian Government Research Training Program scholarships by the University of Adelaide. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Approval was granted by Central Adelaide Local Health Network Human Research Ethics Committee (ID15445).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the authors upon reasonable request.

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Table S1: Hazard ratios for survival from Cox regression

Predictive variables	Hazard ratios (95% CIs)	P-value
Age (5-year increase)	1.34 (1.22, 1.40)	<0.001
Premorbid mRS score	1.25 (1.11, 1.40)	<0.001
Baseline NIHSS	1.02 (1.00, 1.04)	0.062
Baseline blood glucose (per 1 mmol/L glucose)	1.03 (1.01, 1.05)	<0.001
Core volume (10 mL increase)	1.10 (1.10, 1.10)	<0.001
History of heart failure	1.51 (1.08, 2.12)	0.018
Thrombolysis before thrombectomy	0.64 (0.49, 0.84)	0.001

Abbreviations: CI, confidence interval; mRS, modified Rankin scale; NIHSS, national institutes of health stroke scale.

Table S2. Using models to predict outcomes investigated.

1. The estimated risk of logistic regression model is formally calculated as formula below:

$$P = \frac{1}{1 + e^{-(x)}}$$

Very poor functional outcome (mRS≥5):
x = –2.75 + 0.04*(age in years–72) + 0.51*(premorbid mRS score) + 0.05*(baseline NIHSS) + 0.14*(baseline blood glucose in mmol/L–7.5) + 0.02*(core volume in ml) – 0.82*(if pre-EVT thrombolytic therapy)
Quantile-based cutoff: low risk, <0.10; moderate risk, 0.10-0.22; high risk, ≥0.23

Non-independent mobility (mRS≥4):
x = –2.46 + 0.04*(age in years–72) + 0.56*(premorbid mRS score) + 0.06*(baseline NIHSS) + 0.17*(baseline blood glucose in mmol/L–7.5) + 0.01*(core volume in ml) – 0.74*(if pre-EVT thrombolytic therapy) – 1.05*(if driven by companion or walk-in) + 0.35*(if interhospital transfer) + 0.31*(if aero-retrieval)
Quantile-based cutoff: low risk, <0.15; moderate risk, 0.15-0.33; high risk, ≥0.34

Functional dependency (mRS≥3):
x = –1.39 + 0.04*(age in years–72) + 0.41*(premorbid mRS score) + 0.06*(baseline NIHSS) + 0.15*(baseline blood glucose in mmol/L–7.5) + 0.01*(core volume in ml) – 0.74*(if pre-EVT thrombolytic therapy) – 0.45*(if non-rural/regional stroke onset) – 1.08*(if driven by companion or walk-in) + 0.43*(if interhospital transfer) + 0.19*(if aero-retrieval) + 0.52*(if atherosclerosis) – 0.03*(if undetermined)
Quantile-based cutoff: low risk, <0.28; moderate risk, 0.28-0.53; high risk, ≥0.54

Mortality within 30 days:
x = –2.77 + 0.05*(age in years–72) + 0.27*(premorbid mRS score) + 0.10*(baseline blood glucose in mmol/L–7.5) + 0.02*(core volume in ml) + 0.62*(if heart failure) – 0.58*(if pre-EVT thrombolytic therapy)
Quantile-based cutoff: low risk, <0.06; moderate risk, 0.06-0.11; high risk, ≥0.12

Mortality within 1 year:
x = –1.98 + 0.06*(age in years–72) + 0.39*(premorbid mRS score) + 0.08*(baseline blood glucose in mmol/L–7.5) + 0.02*(core volume in ml)– 0.68*(if pre-EVT thrombolytic therapy)
Quantile-based cutoff: low risk, <0.10; moderate risk, 0.10-0.23; high risk, ≥0.24

Mortality within 3 years:
x = –1.53 + 0.07*(age in years–72) + 0.48*(premorbid mRS score) + 0.17*(baseline blood glucose in mmol/L–7.5) + 0.02*(core volume in ml) – 0.77*(if pre-EVT thrombolytic therapy) + 0.08*(onset-to-groin puncture time)
Quantile-based cutoff: low risk, <0.20; moderate risk, 0.20-0.48; high risk, ≥0.49

Example
Assume a male patient with predictive variables as a reference: aged 72 years from with Modified Rankin mRS 1, baseline NIHSS 14, baseline blood glucose 7.5 mmol/L, core volume 14.0 ml, no past heart failure, rural/regional stroke onset, ambulance retrieval, stroke caused by cardioembolic, and onset-to-groin puncture time in 3.6 hours, while without pre-EVT thrombolytic therapy.
The patient's predictive classifications would be:

- **Very poor functional outcome** = at moderate risk (predictive risk score 0.22)
- **Non-independent mobility** = at high risk (predictive risk score 0.40)
- **Functional dependency** = at moderate risk (predictive risk score 0.50)
- **Mortality within 30 days**= at moderate risk (predictive risk score 0.10).
- **Mortality within 1 year** = at moderate risk (predictive risk score 0.21).
- **Mortality within 3 years** = at moderate risk (predictive risk score 0.38).

The false positive rates for the above outcomes would be in the range of 32.0% to 43.0% with the model thresholds set as a sensitivity of 80%.

Note. a. The quantile-based cutoffs for classifications are selected based on 33rd (lower threshold) and 66th (upper threshold) percentiles of the distribution of risk scores and patient's risk is classified as low (below the 33rd percentile), moderate (between the 33rd and 66th percentiles), or high (above the 66th percentile) categories. b. Age and baseline blood glucose levels were adjusted by subtracting the mean.

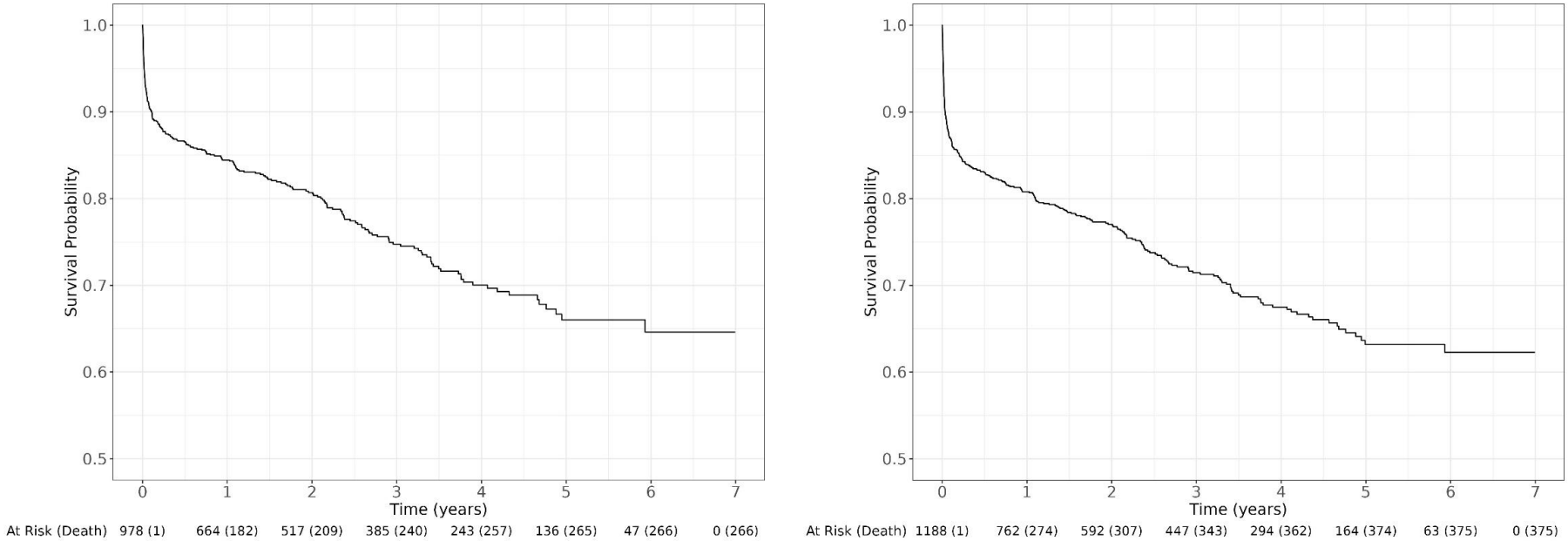

Figure S1. Kaplan-Meier Curve for survival rates: A. large vessel ischemic stroke patients with successful reperfusion after endovascular thrombectomy. B. large vessel ischemic stroke patients after endovascular thrombectomy.

Table S3: Baseline characteristics of large vessel ischemic stroke patients (N=1188)

Variables	Summary statistics
Age (years), median (IQR)	75.0 (64.0-82.3)
Female sex, n (%)	573 (48.2)
Rural/regional stroke onset, n (%)	223 (18.8)
Index of relative socio-economic advantage and disadvantage, median (IQR)	5.0 (2.0-8.0)
Pre-morbidly independent (mRS≤2), n (%)	1096 (92.3)
Baseline NIHSS, median (IQR)	14.0 (8.0-20.0)
Baseline blood glucose (mmol/L), median (IQR)	6.6 (5.7-8.2)
Baseline SBP (mm Hg), mean (SD)	146.1 (25.0)
Baseline DBP (mm Hg), mean (SD)	81.3 (16.2)
Core volume at admission (mL), median (IQR)	14.5 (5.0-35.0)
Perfusion lesion volume at admission (mL), median (IQR)	106.0 (67.0-154.0)
ICA occlusion, n (%)	250 (21.0)
M1 MCA occlusion, n (%)	826 (69.5)
M2 MCA occlusion, n (%)	431 (36.3)
Current or prior atrial fibrillation, n (%)	534 (44.9)
Prior stroke, n (%)	153 (12.9)
Prior transient ischemic attack, n (%)	72 (6.1)
Hypertension, n (%)	747 (62.9)
Obesity, n (%)	133 (11.2)
Diabetes, n (%)	283 (23.8)
Dyslipidaemia, n (%)	504 (42.4)
Ischemic heart disease, n (%)	244 (20.5)
History of heart failure, n (%)	120 (10.1)
Chronic obstructive pulmonary disease, n (%)	88 (7.4)
Smoking, n (%)	358 (30.1)
Cause of stroke, n (%)	
Cardioembolic	567 (47.7)
Atherosclerosis	230 (19.4)
Undetermined	391 (32.9)
Pre-EVT thrombolytic therapy, n (%)	439 (37.7)
Pre-existing antiplatelet therapy, n (%)	240 (20.2)
Pre-existing anticoagulant therapy, n (%)	263 (22.1)
Onset-to-groin puncture time (hours), median (IQR)	3.6 (2.8-6.4)
Method of arrival, n (%)	
Ambulance or road retrieval	690 (58.1)
Driven by companion or walk-in	26 (2.2)
Interhospital transfer	400 (33.7)
Aero-retrieval	72 (6.1)
Functional outcome at 3 months (N=1088)	
Very poor functional outcome (mRS≥5), n (%)	289 (26.6)
Non-independent mobility (mRS≥4), n (%)	387 (35.6)
Functional dependency (mRS≥3), n (%)	541 (49.7)
Mortality (30 days, N=1188; 1 year, N=1036; 3 years, N=790)	
30 days, n (%)	198 (16.7)
1 year, n (%)	274 (26.4)
3 years, n (%)	343 (43.4)

Abbreviations: SD, standard deviation; mRS, modified Rankin scale; NIHSS, national institutes of health stroke scale; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICA, internal carotid artery; MCA, middle cerebral artery.

Table S4: Odds ratios for functional outcomes at 3 months from multivariable logistic regression on all patients: sensitivity analysis

Predictive variables	Odds ratios (95% CIs)	P-value
Very poor functional outcome (mRS≥5)		
Age (5-year increase)	1.28 (1.22, 1.40)	<0.001
Premorbid mRS score	1.49 (1.29, 1.72)	<0.001
Baseline NIHSS	1.06 (1.04, 1.08)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.13 (1.07, 1.18)	<0.001
Core volume (every 10 mL increase)	1.22 (1.10, 1.22)	<0.001
Thrombolysis before thrombectomy	0.41 (0.30, 0.57)	<0.001
Non-independent mobility (mRS≥4)		
Age (5-year increase)	1.28 (1.16, 1.34)	<0.001
Premorbid mRS score	1.59 (1.38, 1.85)	<0.001
Baseline NIHSS	1.07 (1.05, 1.09)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.18 (1.12, 1.24)	<0.001
Core volume (every 10 mL increase)	1.22 (1.10, 1.22)	<0.001
Thrombolysis before thrombectomy	0.42 (0.31, 0.57)	<0.001
Method of arrival, n (%)		
Ambulance or road retrieval	Reference	
Driven by companion or walk-in	0.52 (0.11, 1.78)	0.347
Interhospital transfer	1.42 (1.04, 1.93)	0.026
Aero-retrieval	1.29 (0.70, 2.32)	0.410
Functional dependency (mRS≥3)		
Age (5-year increase)	1.28 (1.22, 1.34)	<0.001
Premorbid mRS score	1.60 (1.37, 1.88)	<0.001
Baseline NIHSS	1.07 (1.05, 1.10)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.13 (1.08, 1.19)	<0.001
Core volume (every 10 mL increase)	1.10 (1.10, 1.22)	<0.001
Thrombolysis before thrombectomy	0.47 (0.36, 0.63)	<0.001
Non-rural/regional stroke onset	0.52 (0.37, 0.73)	0.001
Cause of stroke		
Cardioembolic	Reference	
Atherosclerosis	1.47 (1.03, 2.12)	0.004
Undetermined	1.11 (0.82, 1.52)	0.297

Abbreviations: CI, confidence interval; mRS, modified Rankin scale; NIHSS, national institutes of health stroke scale.

Table S5: Odds ratios for mortality (30 days, 1 year and 3 years) from multivariable logistic regression on all patients: sensitivity analysis

Predictive variables	Odds ratios (95% CIs)	P-value
Mortality within 30 days		
Age (5-year increase)	1.28 (1.16, 1.40)	<0.001
Premorbid mRS score	1.23 (1.05, 1.44)	0.016
Baseline NIHSS	1.05 (1.02, 1.07)	<0.001
Diastolic blood pressure (per 1 mmHg)	1.01 (1.00, 1.02)	0.023
Baseline blood glucose (per 1 mmol/L glucose)	1.09 (1.04, 1.14)	0.001
Core volume (10 mL increase)	1.22 (1.10, 1.22)	<0.001
Thrombolysis before thrombectomy	0.53 (0.36, 0.76)	0.001
Mortality within 1 year		
Age (5-year increase)	1.34 (1.28, 1.47)	<0.001
Premorbid mRS score	1.40 (1.21, 1.64)	<0.001
Baseline NIHSS	1.04 (1.02, 1.06)	0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.08 (1.03, 1.13)	0.003
Core volume (10 mL increase)	1.22 (1.10, 1.22)	<0.001
Thrombolysis before thrombectomy	0.46 (0.33, 0.64)	<0.001
Mortality within 3 years		
Age (5-year increase)	1.40 (1.28, 1.54)	<0.001
Premorbid mRS score	1.66 (1.39, 2.00)	<0.001
Baseline blood glucose (per 1 mmol/L glucose)	1.14 (1.08, 1.21)	<0.001
Core volume (10 mL increase)	1.22 (1.22, 1.34)	<0.001
Thrombolysis before thrombectomy	0.42 (0.29, 0.61)	<0.001
Onset-to-groin puncture time (1-hour increase)	1.06 (1.01, 1.11)	0.027

Abbreviations: CI, confidence interval; mRS, modified Rankin scale.

Table S6: Hazard ratios for survival from Cox regression on all patients: sensitivity analysis

Predictive variables	Hazard ratios (95% CIs)	P-value
Age (5-year increase)	1.28 (1.22, 1.34)	<0.001
Premorbid mRS score	1.20 (1.10, 1.32)	<0.001
Baseline NIHSS	1.03 (1.01, 1.05)	<0.001
Core volume (10 mL increase)	1.10 (1.10, 1.10)	<0.001
Diabetes mellitus	1.57 (1.26, 1.97)	<0.001
Thrombolysis before thrombectomy	0.65 (0.52, 0.81)	<0.001

Abbreviations: CI, confidence interval; mRS, modified Rankin scale; NIHSS, national institutes of health stroke scale.

Table S7: Model performance of outcomes on all patients: sensitivity analysis

Outcome	Corrected AUC (95% CI)	Corrected SEN (95% CI)	Corrected SPE (95% CI)
Very poor functional outcome (mRS≥5)	0.779 (0.749, 0.809)	0.660 (0.607, 0.712)	0.767 (0.721, 0.813)
Non-independent mobility (mRS≥4)	0.784 (0.757, 0.811)	0.697 (0.649, 0.744)	0.722 (0.671, 0.773)
Functional dependency (mRS≥3)	0.778 (0.751, 0.805)	0.692 (0.648, 0.737)	0.712 (0.663, 0.760)
Mortality within 30 days	0.754 (0.717, 0.790)	0.701 (0.635, 0.768)	0.691 (0.629, 0.753)
Mortality within 1 year	0.776 (0.748, 0.805)	0.689 (0.630, 0.749)	0.717 (0.659, 0.775)
Mortality within 3 years	0.793 (0.764, 0.822)	0.710 (0.652, 0.767)	0.729 (0.666, 0.792)

Abbreviation: AUC, areas under the receiver operating characteristic curve; CI, confidence interval; SEN, sensitivity; SPE, specificity; mRS, modified Rankin scale.

Note: Thresholds for sensitivity and specificity shown in the table were selected based on point closest to the top-left corner of the receiver operating characteristic curve in each bootstrap sampling.