Clinical Interventions in Aging

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Premorbid Frailty Status and Functional Independence in Acute Ischemic Stroke Patients Following Endovascular Treatment in the Late Window

Liping Huang[1,*], Chen Gong[1,*], Zhongming Qiu[2,*], Shuyu Jiang[1,*], Min Song[1,*], Zhiyuan Wang[1], Yankun Chen[1], Tao Xu[1], Pan Hu[1], Shengli Chen[3], Yangmei Chen[1,4], Thanh N Nguyen[5], Chang Liu[1]

[1]Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China; [2]Department of Neurology, Xinqiao Hospital and The Second Affiliated Hospital, Army Medical University (Third Military Medical University), Chongqing, People's Republic of China; [3]Department of Neurology, Chongqing University Three Gorges Hospital, Chongqing, Wanzhou, People's Republic of China; [4]Key Laboratory of Major Brain Disease and Aging Research (Ministry of Education), Chongqing Medical University, Chongqing, People's Republic of China; [5]Department of Neurology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA

*These authors contributed equally to this work

Correspondence: Chang Liu, Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China, Tel +8615696811121, Email liuchanghy@hospital.cqmu.edu.cn; Thanh N Nguyen, Department of Neurology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, USA, Email Thanh.Nguyen@bmc.org

Purpose: Although the predictive role of cerebral tissue impairment has been extensively investigated in acute ischemic stroke (AIS) patients undergoing endovascular treatment (EVT) in the late window, the impact of peripheral organs on clinical outcomes in these patients remains largely unknown. Therefore, we aimed to explore whether frailty, a reflection of the patient's physical status based on peripheral organ health at admission, could be associated with outcomes among AIS patients treated by EVT in the late window of 6–24 hours from stroke onset.

Patients and Methods: This was a post-hoc analysis of our RESCUE-BT trial, with findings validated in an external cohort. The 5-factor modified frailty index (mFI-5), a scale of five factors that could reflect premorbid physical conditions, was applied to estimate frailty status. The primary outcome was functional independence, defined as a 90-day modified Rankin Scale (mRS) score of 0–2.

Results: There were 755 patients included in this study. After identifying the cut-off value of mFI-5 by the marginal effects approach, patients were divided into the frail group (mFI-5≥2) and the non-frail group (mFI-5<2). In multivariable analysis, frailty significantly reduced the likelihood of functional independence (aOR 0.37, 95% CI 0.21–0.65, P<0.001). Similar results were detected in the novel cohort constructed with propensity score matching (aOR 0.44, 95% CI 0.22–0.85, P=0.015) and in the external validation cohort (aOR 0.38, 95% CI 0.16–0.89, P=0.028). Moreover, frailty significantly improved the predictive performance of traditional predictors with an AUC of 0.77 (P=0.036 by DeLong's test).

Conclusion: This study demonstrated that frailty according to the mFI-5 index was inversely associated with functional independence among AIS patients receiving EVT in the late window.

Keywords: ischemic stroke, endovascular treatment, late window, frailty, mFI-5

Introduction

Randomized clinical trials have demonstrated that endovascular treatment (EVT) is the first-line therapeutic strategy for acute ischemic stroke (AIS) caused by large vessel occlusion (LVO).[1,2] However, even if treated by EVT, less than 40% of AIS patients in the late time window (6 to 24 hours from the last known well) achieved functional independence.[3,4] Specifically, as reported in a nationally representative study in 2020, the estimated prevalence and mortality rate of stroke in China were 2.6% and 3.43‰, respectively.[5] Over the past two decades, the absolute number of stroke incidents and

Received: 4 November 2024
Accepted: 16 April 2025
Published: 1 May 2025

mortality has increased by 70% and 43%,[6] underscoring the necessity of novel prognostic markers to improve clinical decision-making and periprocedural management strategies. Although the predictive roles of cerebral tissue impairment have been extensively investigated in AIS patients undergoing EVT in the late window, the impacts of peripheral organs on outcomes in these patients remain largely unknown.

Frailty is a syndrome characterized by increased vulnerability to stressors caused by a cumulative decline across multiple physiological systems.[7] In several clinical settings, including neurosurgery and brain tumor resection, frailty has been reported to increase the incidence of mortality and complications.[8] Stroke, a prototypical stressor event, is often associated with multiple comorbidities, such as hypertension and diabetes.[9] However, frailty was rarely evaluated in recent practice guidelines on stroke and was not yet routinely measured in stroke patients.[10] Recent pilot studies recruiting AIS patients within 6 hours of stroke onset reported that frailty status was associated with mortality and poor functional outcomes in stroke patients.[11] Due to differences in clinical features and outcomes between AIS in the early and late time window,[4,12] the impact of frailty on AIS patients undergoing EVT in the late window remains unclear.

Among existing frailty assessment tools, the five-item modified frailty index (mFI-5) from the American College of Surgeons National Surgical Quality Improvement Program is widely recommended and applied in various emergency conditions.[13–15] The mFI-5, consisting of five easily accessible parameters, enables a rapid and objective frailty assessment by integrating key dysfunctions from multiple peripheral organs[13] which is aligned with the need to conserve time and resources in the emergency procedure.[16] In contrast, tools like the 33-item cumulative deficit frailty index and the Hospital Frailty Risk Score require extensive clinical data and complex calculations, making them impractical for rapid evaluations in emergencies.[17] Additionally, previous literature has shown that mFI-5 demonstrates comparable predictive value to other assessment tools across multiple clinical scenarios.[18,19] Therefore, based on our national multicenter trial of RESCUE-BT, the current study aimed to investigate the impacts of frailty evaluated by the mFI-5 on clinical outcomes in AIS patients undergoing EVT in the late window and to validate these findings in an external cohort.

Materials and Methods

Study Design and Participants

The RESCUE-BT was a prospective, double-blind, randomized clinical trial of intravenous tirofiban plus EVT versus placebo plus EVT for patients presenting with an occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) within 24 hours of symptom onset. The trial protocol and patient eligibility criteria have been reported.[20] The study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn, ChiCTR-INR-17014167). This study was conducted in compliance with the Declaration of Helsinki. All recruited patients or legal representatives signed a written informed consent before randomization. Among 948 patients randomized in the RESCUE-BT trial, patients meeting time from stroke onset to groin puncture greater than 360 minutes and with pre-stroke modified Rankin Scale (mRS) score 0–2 were included in the current cohort.

For the external validation cohort, we included 223 acute ischemic stroke (AIS) patients with large vessel occlusion (LVO), who met the above inclusion criteria, from the Second Affiliated Hospital of Chongqing Medical University and the Chongqing University Three Gorges Hospital between January 2019 and September 2023. The study protocol was approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (NO.2023–43).

Assessment of Frailty

Frailty was evaluated by the mFI-5 index, as described by the American College of Surgeons National Surgical Quality Improvement Programs database.[14] This index integrated functional status and complications, with scores ranging from 0 to 5. Patients were assigned one point for each of the following: non-independent functional status before stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and hypertension requiring medication. Frailty was defined as mFI-5 scores ≥2.[21]

Data Collection and Assessment

We retrospectively collected baseline characteristics, including patient age, sex, diabetes mellitus, hypertension, atrial fibrillation, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), pre-stroke mRS score, occlusion site, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, National Institutes of Health Stroke Scale (NIHSS) score, and Alberta Stroke Program Early CT Score (ASPECTS). The time from stroke onset to puncture (OTP) and time from stroke onset to recanalization (OTR) were also recorded. The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral vessel grading system was used to assess collateral status. The quality of reperfusion was evaluated using the extended Thrombolysis in Cerebral Infarction (eTICI) score at final angiography.

Outcomes

The primary outcome was functional independence at 90 days, defined as an mRS score of 0–2. For the derivation set from the RESCUE-BT trial, the mRS assessment was independently evaluated by two mRS-certified neurologists. Their evaluations were based on structured video or voice recordings. In cases of disagreement, a third neurologist adjudicated the final score.[20] For the external validation cohort, the same procedure was followed, with adjudication by two certified neurologists (L.H. and C.G), and disagreements resolved by a third neurologist (C.L). All neuroradiologists were blinded to treatment allocation during mRS data analysis. The secondary outcome included the mRS score at 90 days, ranging from 0 (asymptomatic) to 6 (death), and the change in NIHSS score from baseline to 24 hours or 5–7 days post-recanalization. Safety outcomes included 90-day mortality, the incidence of any intracranial hemorrhage (ICH), and symptomatic ICH (sICH) within 48 hours after EVT. Any ICH and sICH were assessed using follow-up CT or MRI. The sICH was diagnosed according to the Heidelberg Bleeding Classification.[22]

Statistical Analysis

Among patients in this study, the relationship between frailty and functional independence was evaluated using marginal effects from the sjPlot package (https://CRAN.R-project.org/package=sjPlot). After identifying the threshold of mFI-5 as 2, patients were classified into the frail group (mFI-5 of 2–5) and the non-frail group (mFI-5 of 0–1). The normality of data distribution was assessed using the Kolmogorov–Smirnov test (S-*K* test). Chi-squared or Fisher exact tests were used for categorical variables. Based on the distribution of normality, continuous variables were compared using the Student's *t*-test ($P \geq 0.050$ in the S-*K* test) or the Mann–Whitney *U*-test ($P<0.050$ in the S-*K* test) to compare baseline characteristics, imaging data, and treatment characteristics between the two groups. Significant factors ($P<0.100$) and variables previously associated with functional outcomes were selected via univariable analysis and subsequently included in the multivariable logistic regression model. The results were reported as odds ratios (OR) and 95% confidence intervals (CI). In the external validation cohort, logistic analysis was applied to verify the impact of frailty status in predicting outcomes.

For sensitivity purposes, we assessed the heterogeneity of the effect of frailty within subgroups based on patient age, baseline NIHSS score, ASITN/SIR, baseline ASPECTS, OTR, and eTICI score. Given the potential influence of frailty on successful recanalization (eTICI≥2b), multiple logistic regression models were employed to evaluate efficacy and safety outcomes among patients with successful recanalization. Moreover, we used the nearest-neighbor matching algorithm to perform 1:2 propensity score matching. In the analysis, we took the above confounding variables as covariates. Additionally, receiver operating characteristic (ROC) curves were used to examine the relationships between frailty status and functional independence, with DeLong's test applied to test for significant differences between c-statistics. All tests were two-sided, and $P<0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 26.0; IBM SPSS Statistics) and R software (version 4.2.2).

Data Availability Statement

Datasets acquired and analyzed during the study are available from the corresponding author on request.

Results

Patient Characteristics

Among the 948 patients randomized in the RESCUE-BT trial, 532 AIS patients receiving EVT in the 6-to-24-hour window were enrolled in this study (Supplementary Figure S1A). Based on the same inclusion and exclusion criteria, we included 223 AIS patients in an external validation cohort from two medical centers in Chongqing (Supplementary Figure S1B). The median age was 66 years, and 64.3% were men (Supplementary Table S1). Other baseline characteristics between the groups were shown in Supplementary Table S1. A total of 247 (46.4%) patients achieved functional independence (90-day mRS≤2).

Based on the margin effects of logistic regression analysis, Figure 1A illustrated the probability of achieving functional independence (mRS≤2) versus poor outcome (mRS≥3) at 90 days with higher mFI-5. The probability distributions of functional independence and poor outcome intersected between mFI-5 scores of 0 and 1, suggesting that a higher mFI-5 of 1 (dotted line) might be an appropriate threshold value to discriminate between functional independence and poor outcomes. To further validate this finding, we analyzed the association between mFI-5 and favorable functional outcomes among patients stratified by mFI-5 scores of 1 or ≥2. Logistic regression analysis showed patients with mFI-5≥2 had significantly lower odds of functional independence (adjusted OR (aOR) 0.31, 95% CI 0.17–0.56, P<0.001) (Figure 1B) and favorable outcome (aOR 0.28, 95% CI 0.15–0.51, P<0.001) (Figure 1C). These above analyses might demonstrate that the optimal threshold for determining frailty should be an mFI-5 score of 2.

With the cut-off value of mFI-5, 443 patients were assigned to the non-frail group and 89 to the frail group. Compared with the non-frail group, the proportion of females (46.1% vs 33.6%, P=0.025) was significantly higher in the frail group. There were 235 (53.0%) patients with mFI-5 of 1 in the non-frailty group, and 86 (96.6%) patients with mFI-5 of 2 in the frailty group. Other baseline characteristics were well-balanced between the groups (P>0.05) (Table 1).

The Impact of Frailty on Clinical Outcomes

The median [IQR] mRS at 90 days was 4 [2–5] in the frail group and 3 [1–4] in the non-frail group (aOR 2.48, 95% CI 1.62–3.81, P <0.001) (Table 2). The frail group had a significantly lower frequency of functional independence than the non-frail group (29.2% vs 49.9%, aOR 0.37, 95% CI 0.21–0.65, P<0.001) (Table 2 and Figure 2). After adjusting for center stratification, frailty remained independently associated with lower functional independence (29.2% vs 49.9%, aOR 0.31, 95% CI 0.17–0.58, P<0.001) (Supplementary Table S2). Frailty was also negatively correlated with the NIHSS score change at 24 hours (aOR 2.19, 95% CI 1.45–3.30, P<0.001) and 5–7 days after recanalization (aOR 2.03, 95% CI 1.35–3.06, P<0.001).

However, there was no correlation between frailty and sICH (aOR 1.19, 95% CI 0.53–2.71, P=0.663) (Table 2). Similarly, the incidence of HI1, HI2, PH1, and PH2 hemorrhagic subtypes did not significantly differ between frail and non-frail patients (P>0.05) (Supplementary Table S3). Regarding non-hemorrhagic complications, frail patients had a significantly higher likelihood of developing pneumonia after EVT (65.2% vs 51.7%, aOR 1.77, 95% CI 1.07–2.94, P=0.025) (Supplementary Table S4).

The Association Between Frailty and Traditional Risk Factors

In multivariable logistic regression analysis, frailty (aOR 0.37, 95% CI 0.21–0.65, P<0.001), age (aOR 0.96, 95% CI 0.94–0.98, P<0.001), baseline NIHSS score (aOR 0.90, 95% CI 0.86–0.94, P<0.001), baseline ASPECTS (aOR 1.21, 95% CI 1.06–1.36, P=0.003) and eTICI score (aOR 1.55, 95% CI 1.31–1.83, P<0.001) were associated with functional independence (Supplementary Table S5).

Receiver operating characteristic (ROC) curve analysis demonstrated that adding frailty into the conventional predictive model significantly improved its performance in predicting 90-day functional independence (P=0.036, by DeLong's test) (Figure 3).

Subgroup and Sensitivity Analysis

We did not detect any evidence of heterogeneity in the efficacy of frailty status among prespecified subgroups (defined according to age, baseline NIHSS, ASITN/SIR grades, baseline ASPECTS, OTR and eTICI, P for interaction > 0.05) (Figure 4).

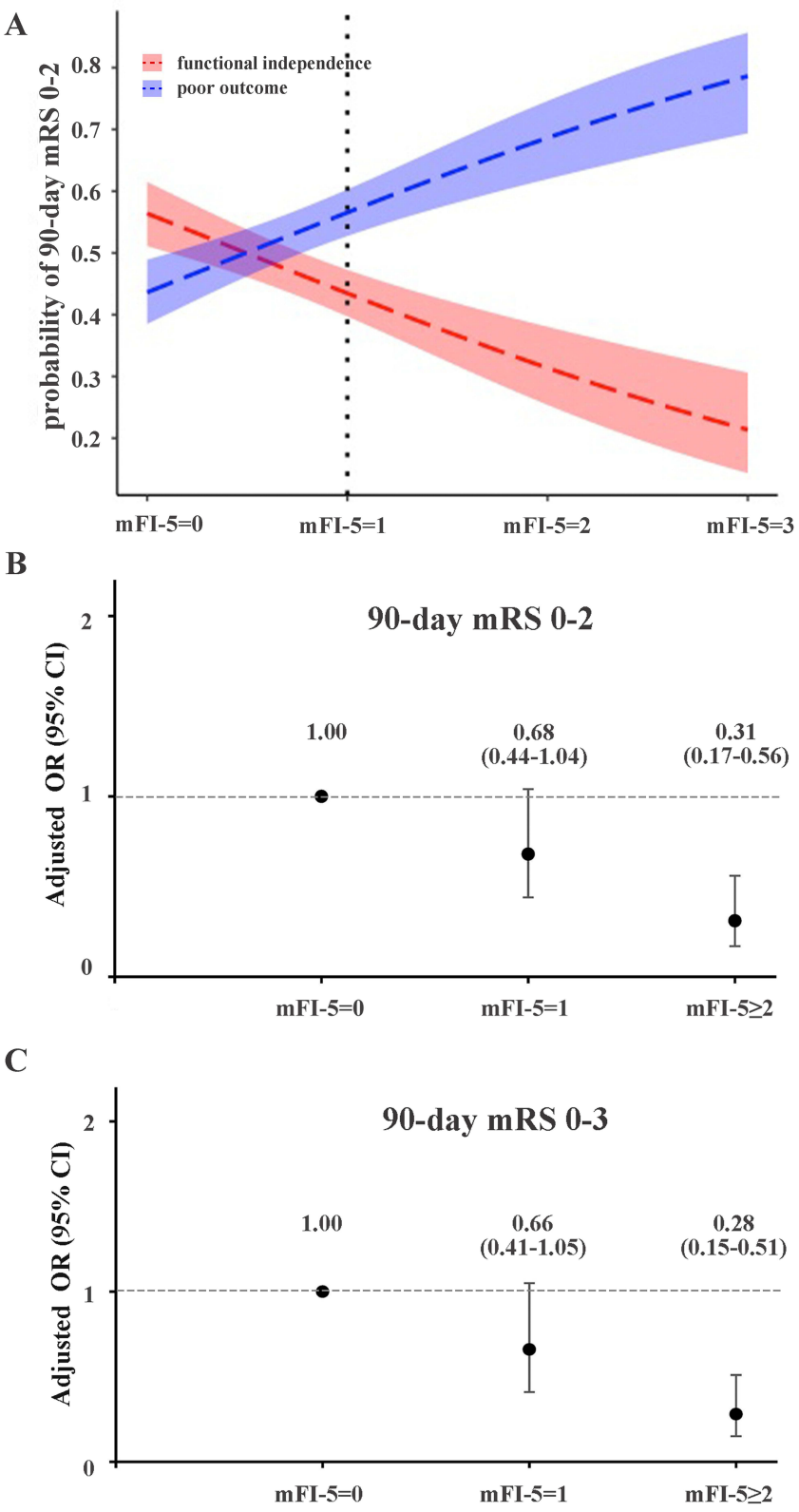

Figure 1 Marginal effects to exhibit the relationship between mFI-5 and 90-day functional Independence. Patients with mFI-5 scores greater than 1 exhibited an increased likelihood of poor outcomes (**A**). Those with mFI-5≥2 had significantly lower rates of functional independence (mRS 0–2) (**B**) and favorable outcome (mRS 0–3) (**C**).
Notes: The regression for marginal effects was adjusted by age, sex, atrial fibrillation, pre-stroke mRS score, baseline NIHSS score, baseline ASPECTS, ASITN/SIR grade, eTICI grade, occlusion site, and OTR. Adjusted ORs with 95% CIs are reported, with a mFI-5 score of 0 as the reference category.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score, occlusion site; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology, eTICI, extended thrombolysis in cerebral infarction; OTR, time from stroke onset to recanalization.

https://doi.org/10.2147/CIA.S504456

https://doi.org/10.2147/CIA.S504456

Table 1 Baseline Characteristics According to Groups of Non-Frail/Frail

Characteristics	Enrolled Patients				Propensity Score Matching			
	All (n=532)	Non-Frail (n=443)	Frail (n=89)	Pvalue	All (n=239)	Non-Frail (n=156)	Frail (n=83)	P value
Age, median (IQR)	66 (55–74)	65 (55–74)	68 (61–72)	0.081	68 (59–74)	68 (59–75)	68 (61–73)	0.844
Male sex, n (%)	342 (64.3)	294 (66.4)	48 (53.9)	0.025	137 (57.3)	92 (59.0)	45 (54.2)	0.479
Atrial fibrillation, n (%)	130 (24.4)	109 (24.6)	21 (23.6)	0.840	57 (23.8)	37 (23.7)	20 (24.1)	0.948
Hypertension, n (%)	284 (53.4)	198 (44.7)	86 (96.6)	<0.001	150 (62.8)	70 (44.9)	80 (96.4)	<0.001
Diabetes mellitus, n (%)	107 (20.1)	28 (6.3)	79 (88.8)	<0.001	87 (36.4)	13 (8.3)	74 (89.2)	<0.001
Congestive heart failure, n (%)	19 (3.6)	7 (1.6)	12 (13.5)	<0.001	15 (6.3)	3 (1.9)	12 (14.5)	<0.001
Chronic obstructive pulmonary disease, n (%)	6 (1.1)	2 (0.5)	4 (4.5)	0.006	4 (1.7)	1 (0.6)	3 (3.6)	0.239
Pre-stroke mRS score, n (%)				0.001				0.331
0	494 (92.9)	419 (94.6)	75 (84.3)		215 (90.0)	143 (91.7)	72 (86.7)	
1	27 (5.1)	15 (3.4)	12 (13.5)		20 (8.4)	10 (6.4)	10 (12.0)	
2	11 (2.1)	9 (2.0)	2 (2.2)		4 (1.7)	3 (1.9)	1 (1.2)	
mFI-5, n (%)				<0.001				<0.001
0	208 (39.1)	208 (47.0)	0 (0.0)		69 (28.9)	69 (44.2)	0 (0.0)	
1	235 (44.2)	235 (53.0)	0 (0.0)		87 (36.4)	87 (55.8)	0 (0.0)	
2	86 (16.2)	0 (0.0)	86 (96.6)		80 (33.5)	0 (0.0)	80 (96.4)	
3	3 (0.6)	0 (0.0)	3 (3.4)		3 (1.3)	0 (0.0)	3 (3.6)	
TOAST, n (%)				0.203				0.244
Large artery atherosclerosis	294 (55.3)	237 (53.5)	57 (64.0)		138 (57.7)	85 (54.5)	53 (63.9)	
Cardiogenic embolism	169 (31.8)	143 (32.3)	26 (29.2)		70 (29.3)	46 (29.5)	24 (28.9)	
Unknown	21 (3.9)	19 (4.3)	2 (2.2)		8 (3.3)	6 (3.8)	2 (2.4)	
Other	48 (9.0)	44 (9.9)	4 (4.5)		23 (9.6)	19 (12.2)	4 (4.8)	
Occlusion site, n (%)				0.054				0.860
ICA	88 (16.5)	67 (15.1)	21 (23.6)		43 (18.0)	27 (17.3)	16 (19.3)	
MCA-M1	364 (68.4)	304 (68.6)	60 (67.4)		175 (73.2)	116 (74.4)	59 (71.1)	
MCA-M2	80 (15.0)	72 (16.3)	8 (9.0)		21 (8.8)	13 (8.3)	8 (9.6)	
Clinical examination at arrival								
Baseline NIHSS score, median (IQR)	15 (11–19)	14 (11–19)	15 (11–19)	0.443	16 (12–19)	16 (12–19)	15 (12–19)	0.847
Baseline ASPECTS score, median (IQR)	7 (7–9)	7 (7–9)	8 (7–9)	0.221	8 (7–9)	8 (7–9)	8 (7–9)	0.896
ASITN/SIR score, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.089	2 (2–3)	2 (2–3)	2 (2–3)	0.538
eTICI score, median (IQR)	3 (2b-3)	3 (2b-3)	3 (2b-3)	0.592	2c (2b-3)	2c (2b-3)	3 (2b-3)	0.480
eTICI 2b-3, n (%)	482 (90.6)	401 (90.5)	81 (91.0)	0.885	214 (89.5)	139 (89.1)	75 (90.4)	0.762
Time from stroke onset, median (IQR), min								
To recanalization	678.5 (543.0–869.2)	680.0 (545.0–870.0)	655.0 (536.5–860.0)	0.649	680.0 (561.0–860.0)	706.5 (567.5–858.0)	655.0 (538.0–860.0)	0.590
To puncture	589.5 (460.0–788.7)	590.0 (460.0–785.0)	580.0 (470.0–794.0)	0.801	588.0 (464.0–773.0)	595.0 (460.0–768.5)	580.0 (472.0–793.0)	0.924

Notes: Frail modified by mFI index (include–functional status, diabetes mellitus, chronic obstructive pulmonary disease (COPD),congestive heart failure (CHF), and hypertension requiring medication).

Abbreviations: IQR interquartile range; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; Etici, extended thrombolysis in cerebral infarction; OTR, the time from stroke onset to recanalization; OTP, the time from stroke onset to puncture.

Table 2 Clinical Outcomes According to Groups of No-Frail/Frail

Clinical Outcomes	Enrolled Patients			P value	Adjusted OR (95% CI)	P value[c]	Propensity Score Matching			P value	Adjusted OR (95% CI)	P value[c]
	All (n=532)	Non-Frail (n=443)	Frail (n=89)				All (n=239)	Non-Frail (n=156)	Frail (n=83)			
Primary outcome												
90-day mRS 0–2, n (%)	247 (46.4)	221 (49.9)	26 (29.2)	<0.001	0.37 (0.21–0.65)	<0.001	89 (37.2)	65 (41.7)	24 (28.9)	0.052	0.44 (0.22–0.85)	0.015
Second outcome												
90-day mRS, median (IQR)	3 (1–4)	3 (1–4)	4 (2–5)	<0.001	2.48 (1.62–3.81)	<0.001	3 (1–5)	3 (1–4)	4 (2–6)	0.004	2.58 (1.57–4.24)	<0.001
90-day mRS 0–1, n (%)	177 (33.3)	162 (36.6)	15 (16.9)	<0.001	0.35 (0.18–0.67)	0.002	66 (27.6)	52 (33.3)	14 (16.9)	0.007	0.29 (0.13–0.63)	0.002
90-day mRS 0–3, n (%)	332 (62.4)	293 (66.1)	39 (43.8)	<0.001	0.34 (0.20–0.60)	<0.001	129 (54.0)	94 (60.3)	35 (42.2)	0.008	0.29 (0.14–0.59)	0.001
NIHSS score change from baseline, median (IQR)												
24 h after randomization	−1 (−5 to 1)	−2 (−6 to 1)	0 (−3 to 8)	0.003	2.19 (1.45–3.30)	<0.001	−1 (−5 to 3)	−2 (−5 to 2)	0 (−4 to 9)	0.047	1.82 (1.14–2.92)	0.012
5–7 d after randomization or at early discharge	−4 (−9 to 0)	−5 (−9 to 0)	−2 (−7 to 8)	0.009	2.03 (1.35–3.06)	<0.001	−3 (−9 to 4)	−4 (−9 to 4)	−2 (−7 to 8)	0.101	1.69 (1.06–2.70)	0.027
Safety outcome												
Any ICH within 48h[a], n (%)	174 (32.9)	145 (33.0)	29 (32.6)	0.946	0.87 (0.52–1.48)	0.630	84 (35.3)	58 (37.4)	26 (31.3)	0.348	0.72 (0.39–1.33)	0.303
sICH within 48h[b], n (%)	44 (8.3)	35 (8.0)	9 (10.1)	0.501	1.19 (0.53–2.71)	0.663	27 (11.3)	18 (11.6)	9 (10.8)	0.858	0.86 (0.34–2.18)	0.754
90-day Mortality, n (%)	91 (17.1)	69 (15.6)	22 (24.7)	0.037	1.73 (0.95–3.15)	0.073	51 (21.3)	30 (19.2)	21 (25.3)	0.275	1.55 (0.77–3.10)	0.217

Notes: *Frail* modified by mFI index (include–functional status, diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and hypertension requiring medication). [a]Missing data in 3 patients in all enrolled patients and 1 in propensity score matching patients. [b]Missing data in 3 patients in all enrolled patients and 1 in propensity score matching patients. [c]Values were adjusted for age, sex, atrial fibrillation, pre-stroke mRS score.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score, occlusion site; ASITN/SIR the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; eTICI, extended thrombolysis in cerebral infarction, and OTR, time from stroke onset to recanalization; mRS modified Rankin Scale; IQR, interquartile range, ICH intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; OR, odd ratio, CI confidence interval.

https://doi.org/10.2147/CIA.S504456

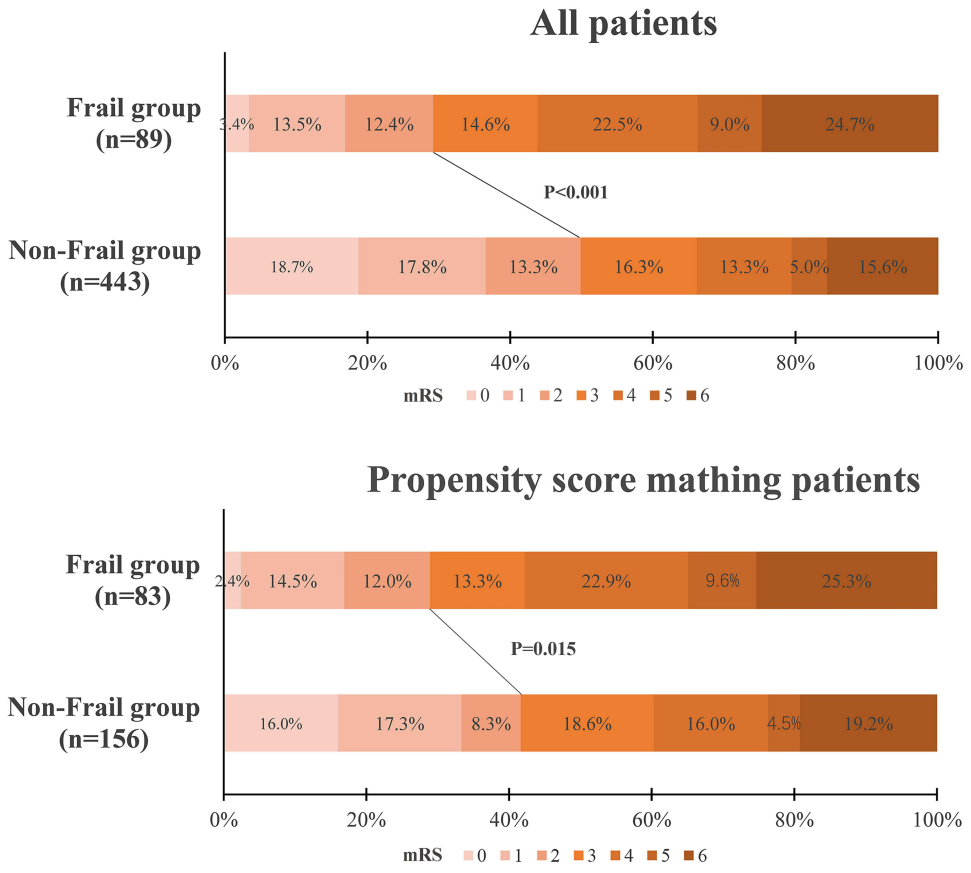

Figure 2 Distribution of the modified Rankin Scale (mRS) scores at 90 days in the frail and the non-frail groups.

Baseline characteristics were well balanced between the frail and non-frail groups after 1:2 propensity score matching (PSM) (Table 1). In PSM analysis, frail patients still demonstrated a significantly lower proportion of 90-day functional independence compared to non-frail patients (28.9% vs 41.7%, aOR 0.44, 95% CI 0.22–0.85, P = 0.015) (Table 2).

The Impact of Frailty on Patients with Successful Recanalization

Among 482 AIS patients with successful recanalization (eTICI≥2b), frailty was inversely associated with functional independence (aOR 0.39, 95% CI 0.22–0.69, P=0.001). The median [IQR] mRS at 90 days in the frail group was 4 [2–5], significantly higher than 2 [1–4] in the non-frail group (aOR 2.41, 95% CI 1.54–3.76, P<0.001) (Table 3).

Validation in the External Cohort

The baseline characteristics of the external validation cohort were presented in Supplementary Table S6. The median (IQR) mRS at 90 days was significantly higher in the frail group than in the non-frail group (3 [2–5] vs 2 [1–4], aOR 2.05, 95% CI 1.08–3.88, P=0.027). Additionally, frail patients had significantly lower rates of functional independence (aOR 0.38, 95% CI 0.16–0.89, P=0.028) (Table 4).

Discussion

To our knowledge, this multicenter cohort study is the first to explore the association between premorbid frailty status and functional independence among AIS patients treated with EVT in the late window. Our findings suggest that: 1) frailty, as assessed by the mFI-5 index, was inversely associated with 90-day functional independence in patients undergoing EVT in the extended window (6–24 hours from stroke onset). 2) the negative impact of frailty on clinical outcomes persisted in an external cohort and was not modified by traditional risk factors. 3) these comorbidities

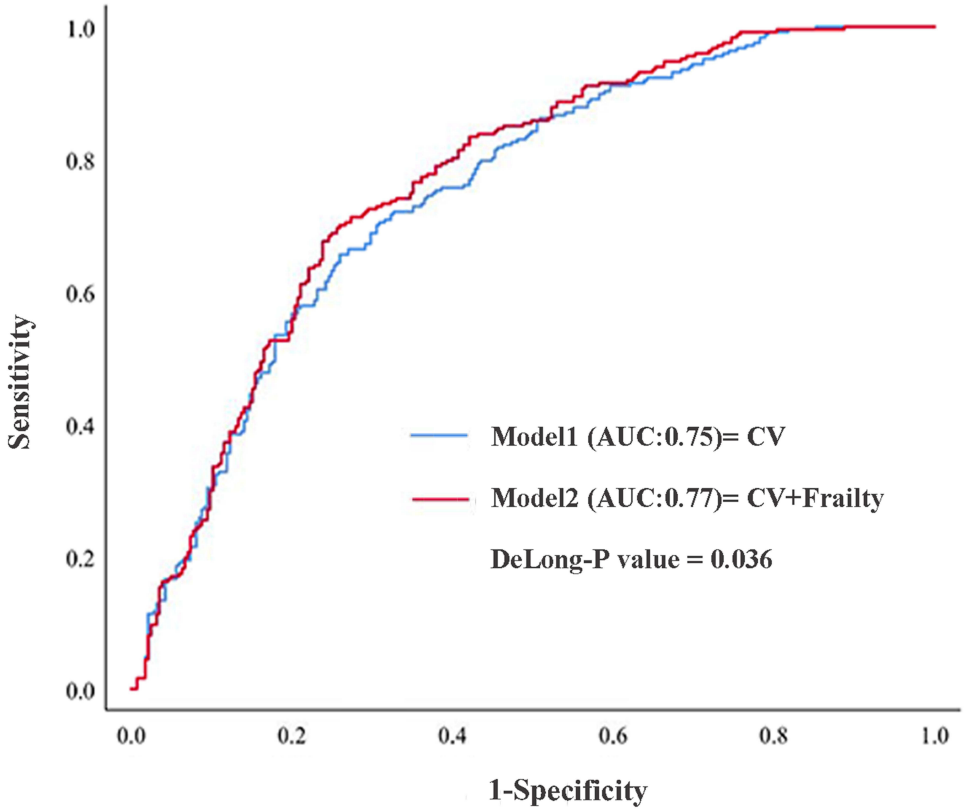

Figure 3 Receiver operating characteristic (ROC) curve analysis for predicting 90-day functional Independence.
Notes: Model 1 represented the baseline conventional model, which included age, sex, atrial fibrillation, pre-stroke mRS score, baseline NIHSS score, baseline ASPECTS, ASITN/SIR grade, eTICI grade, occlusion site, and OTR. Model 2 incorporated frailty into the conventional model. Model 2(AUC:0.77) exhibited higher predictive performance than model 1(AUC:0.75) for predicting functional independence (mRS 0–2) (ΔAUC = 0.02, p =0.036, by DeLong's test).
Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; eTICI, extended thrombolysis in cerebral infarction; OTR time from stroke onset to recanalization.

encompassed by mFI-5 might have a cumulative effect on clinical outcomes. 4) adding frailty status to the baseline traditional variable model significantly enhanced the prediction of 90-day functional independence.

The notion of frailty and comorbidities in patients with cerebrovascular disorders has attracted increasing attention.[23] Several reports identified a significant association between frailty and adverse events after cerebrovascular intervention.[11,17] Unlike previous studies, our analysis focused on AIS patients receiving EVT in the late window and demonstrated the predictive value of frailty in this specific population. Notably, our post-hoc analysis of the RESCUE-BT trial revealed that nearly 70% of frail patients undergoing EVT during the late window failed to achieve functional independence. This elevated failure rate might be attributed to two key factors: First, patients in the late window had a longer onset-to-recanalization (OTR) time, resulting in more severe brain tissue damage and a higher risk of reperfusion injury after revascularization.[24] Second, frail patients have increased vulnerability and reduced brain tissue tolerance.[25] Therefore, prolonged OTR time might exacerbate their low tolerance to reperfusion stressors and increase the incidence of poor prognosis. In addition, our sensitivity analyses demonstrated frailty was significantly associated with poor outcomes even after successful recanalization, underscoring prior brain injury and brain tissue fragility. Lastly, patients with higher frailty scores often have greater pre-stroke disability or higher pre-stroke mRS, suggesting that functional independence may not be a realistic endpoint. Instead, a more appropriate treatment goal for these patients could be returning to their baseline pre-stroke mRS.

The components of mFI-5 include hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF), which are factors that can impact the outcomes of patients with AIS. First, in addition to promoting atherosclerosis and carotid artery stenosis, hypertension was an independent determinant of adverse

https://doi.org/10.2147/CIA.S504456

Subgroup	Number of patients	aOR	95%CI		aOR（95%CI）forest plot	P value	P value for interaction
Over all	532	0.37	0.21	0.65		<0.001	
Age							0.520
< 66	264	0.35	0.15	0.84		0.019	
≥ 66	268	0.34	0.15	0.74		0.007	
Baseline NIHSS							0.380
< 15	260	0.44	0.20	0.96		0.039	
≥ 15	272	0.25	0.10	0.60		0.002	
ASITN/SIR							0.167
< 2	120	0.15	0.02	0.98		0.048	
≥ 2	412	0.44	0.24	0.80		0.008	
Baseline ASPECTS							0.374
≤ 7	266	0.34	0.13	0.88		0.027	
> 7	266	0.36	0.17	0.75		0.007	
OTR							0.129
< 678	264	0.43	0.19	0.93		0.034	
≥ 678	268	0.30	0.13	0.72		0.007	
eTICI							0.067
0-2a	50					NA	
2b-3	482	0.39	0.22	0.69		0.001	

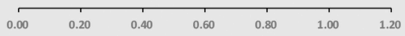

Figure 4 Subgroup analysis of functional Independence (mRS 0–2) at 90 days based on frailty status.
Notes: The forest plot illustrated the odds ratios (ORs) for functional independence at 90 days in the prespecified subgroups. The thresholds for age, baseline.
Abbreviations: NIHSS, score, ASPECTS, ASITN/SIR, and OTR were chosen at the median.; TICI was categorizeSd according to clinical characteristics. Adjusted variables included age, sex, atrial fibrillation, pre-stroke mRS score, baseline NIHSS score, baseline ASPECTS, ASITN/SIR grade, eTICI grade, occlusion site, and OTR.; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score, occlusion site; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; eTICI, extended thrombolysis in cerebral infarction; OTR, time from stroke onset to recanalization.

outcomes after EVT in AIS.[26] Second, diabetes mellitus was associated with less salvageable tissue at admission and worse infarct progression, significantly affecting the 90-day clinical outcomes after EVT.[27] Third, COPD might act as a surrogate for a clinically significant smoking burden.[28] A case-control study demonstrated a strong dose-response relationship between daily smoking and ischemic stroke, regardless of gender.[29] Fourth, a fall in arterial blood pressure due to low cardiac output in AIS with CHF could lead to impaired autoregulation of cerebral blood flow, making patients more susceptible to ischemic injury.[30] Thus, mFI-5 represents well-known vascular risk factors, which are of relevance to cerebrovascular pathology. In clinical practice, multiple comorbidities are widely observed among AIS patients.[9] However, few studies have reported their combined impact on prognosis. In this study, we observed that patients with frailty based on the cumulative effect of comorbidities, showed worse outcomes.[21]

The findings of this study expand the applicability of mFI-5 to AIS patients in the late time window. Current guidelines for AIS patients to receive EVT are written by the patient's age, occlusion site, NIHSS score, and ASPECTS at admission.[31,32] However, these factors focus mainly on the baseline stroke severity and degree of cerebral tissue damage while neglecting the premorbid general physical status. Frailty characterizes the patients' systemic comorbidities before stroke. In clinical practice, mFI might serve as a valuable risk-stratification tool to identify frail patients with lower potential for recovery, thereby optimizing periprocedural management strategies such as tailoring rehabilitation intensity and strengthening the monitoring.[33,34] Therefore, while frailty may attenuate the absolute benefit of EVT, existing evidence suggests that the rate of favorable outcomes among AIS patients in the late window could be improved by EVT, which remains a recommended treatment option at present.[2]

Several limitations should be noticed when interpreting our findings. Firstly, this study was a post-hoc analysis of the RESCUE-BT trial, carrying a risk of type I error. To minimize the effects on the results of this study, we conducted a multicenter external cohort to confirm our results. Secondly, as the RESCUE-BT trial excluded patients who had undergone pre-operative thrombolysis and patients in the late time window were not recommended for thrombolysis, we were unable to assess the impact of frailty on the outcomes of patients receiving bridging therapy. Thirdly, the small number of people with mini-stroke subgroup (NIHSS ≤ 5 at admission) limited the statistical power to determine the effects of frailty.[35] Future prospective studies with larger cohorts are required to assess the role of frailty in patients

Table 3 Clinical Outcomes According to Groups of No-Frail/Frail in Patients with Successful Recanalization

Clinical Outcomes	Enrolled Patients			P value	Adjusted OR[a] (95% CI)	P value[a]
	All (n=482)	Non-Frail (n=401)	Frail (n=81)			
Primary outcome						
90-day mRS 0–2, n (%)	240 (49.8)	214 (53.4)	26 (32.1)	<0.001	0.39 (0.22–0.69)	0.001
Second outcome						
90-day mRS, median (IQR)	3 (1–4)	2 (1–4)	4 (2–5)	<0.001	2.41 (1.54–3.76)	<0.001
90-day mRS 0–1, n (%)	173 (35.9)	158 (39.4)	15 (18.5)	<0.001	0.36 (0.19–0.71)	0.003
90-day mRS 0–3, n (%)	317 (65.8)	278 (69.3)	39 (48.1)	<0.001	0.38 (0.21–0.67)	<0.001
NIHSS score change from baseline, median (IQR)						
24 h after randomization	−2 (−6 to 1)	−2 (−6 to 1)	−1 (−4 to 6)	0.003	2.17 (1.41–3.35)	<0.001
5–7 d after randomization or at early discharge	−5 (−9 to 0)	−5 (−10 to −1)	−3 (−8 to 3)	0.016	1.97 (1.28–3.03)	0.002
Safety outcome						
Any ICH within 48h, n (%)	150 (31.1)	124 (30.9)	26 (32.1)	0.835	0.93 (0.53–1.62)	0.808
sICH within 48h, n (%)	36 (7.5)	29 (7.2)	7 (8.6)	0.660	1.12 (0.45–2.80)	0.804
90-day Mortality, n (%)	74 (15.4)	56 (14.0)	18 (22.2)	0.060	1.62 (0.84–3.09)	0.145

Notes: Frail modified by mFI index. [a]Values were adjusted for age, sex, atrial fibrillation, pre-stroke mRS score.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score, occlusion site; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; eTICI, extended thrombolysis in cerebral infarction; OTR, time from stroke onset to recanalization; mRS, modified Rankin Scale; IQR, interquartile range; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; OR, odd ratio; CI, confidence interval.

Table 4 Clinical Outcomes According to Groups of No-Frail/Frail in the External Validation Cohort

Clinical Outcomes	Enrolled Patients			P value	Adjusted OR[a] (95% CI)	P value[a]
	All (n=223)	Non-Frail (n=181)	Frail (n=42)			
Primary outcome						
90-day mRS 0–2, n (%)	111 (49.8)	95 (52.5)	16 (38.1)	0.093	0.38 (0.16–0.89)	0.028
Second outcome						
90-day mRS, median (IQR)	3 (1–4)	2 (1–4)	3 (2–5)	0.073	2.05 (1.08–3.88)	0.027
90-day mRS 0–1, n (%)	72 (32.3)	63 (34.8)	9 (21.4)	0.095	0.37 (0.14–0.96)	0.041
90-day mRS 0–3, n (%)	149 (66.8)	126 (69.6)	23 (54.8)	0.066	0.40 (0.17–0.92)	0.033
NIHSS score change from baseline, median (IQR)						
24 h after randomization	0 (−3 to 1)	0 (−3 to 1)	0 (−2 to 4)	0.055	1.77 (0.95–3.30)	0.068
5–7 d after randomization or at early discharge	−3 (−8 to 0)	−3 (−8 to 0)	−2 (−6 to 2)	0.122	1.69 (0.91–3.12)	0.093
Safety outcome						
Any ICH within 48h, n (%)	49 (22.0)	43 (23.8)	6 (14.3)	0.182	0.54 (0.19–1.47)	0.228
sICH within 48h, n (%)	15 (6.7)	12 (6.6)	3 (7.1)	1.000	1.45 (0.31–6.72)	0.634
90-day Mortality, n (%)	40 (17.9)	31 (17.1)	9 (21.4)	0.513	1.40 (0.55–3.56)	0.474

Notes: Frail modified by mFI index. [a]Values were adjusted for age, sex, atrial fibrillation, pre-stroke mRS score.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score, occlusion site; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; eTICI, extended thrombolysis in cerebral infarction; OTR, time from stroke onset to recanalization; mRS, modified Rankin Scale; IQR, interquartile range; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; OR, odd ratio; CI, confidence interval.

suffering mini-strokes or undergoing bridging therapy. Lastly, medical history and prior treatments were recorded from physician notes, which often included patient-reported information, introducing a potential recall bias. Future studies should investigate the role of frailty in identifying patients in decision-making for EVT and predicting outcomes by enrolling patients who receive EVT and those who do not.

Conclusion

This multicenter cohort study demonstrated that pre-stroke frailty, as assessed by the mFI-5 index, was independently associated with poor prognosis in AIS patients undergoing EVT in the late window. As a complementary prognostic marker to existing traditional indicators, frailty assessment may aid in refining risk stratification and optimizing perioperative patient management.

Ethical Approval

The present study was the post-hoc analysis of the RESCUE-BT trial, which was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn, ChiCTR-INR-17014167). The study was approved by the research board at each participating center and informed consents were obtained from all patients or their authorized representatives. For the external validation cohort, the study protocol was approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (NO.2023-43).

Funding

This study has received funding from the National Natural Science Foundation of China (No. 82001264), China Postdoctoral Science Foundation (No. 2023M740444), and Chongqing Technology Innovation and Application Development Project (No. CSTB2022TIAD-KPX0160).

Disclosure

Dr Thanh N Nguyen is an associate editor for Stroke; advisory board for Brainomix, Aruna Bio; and speaker for Genentech and Kaneka, outside the submitted work. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

References

1. Nguyen TN, Abdalkader M, Fischer U, et al. Endovascular management of acute stroke. *The Lancet*. 2024;404(10459):1265–1278. doi:10.1016/S0140-6736(24)01410-7
2. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11–21. doi:10.1056/NEJMoa1706442
3. Seker F, Qureshi MM, Möhlenbruch MA, et al. Reperfusion without functional independence in late presentation of stroke with large vessel occlusion. *Stroke*. 2022;53(12):3594–3604. doi:10.1161/STROKEAHA.122.039476
4. Asdaghi N, Wang K, Gardener H, et al. Impact of time to treatment on endovascular thrombectomy outcomes in the early versus late treatment time windows. *Stroke*. 2023;54(3):733–742. doi:10.1161/STROKEAHA.122.040352
5. Tu WJ, Zhao Z, Yin P, et al. Estimated Burden of Stroke in China in 2020. *JAMA Netw Open*. 2023;6(3):e231455. doi:10.1001/jamanetworkopen.2023.1455
6. Feigin VL, Stark BA, Johnson CO. 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(10):795–820. doi:10.1016/S1474-4422(21)00252-0
7. Morley J, Vellas B, Kan GA, et al. Frailty consensus: a call to action. *Journal of the American Medical Directors Association*. 2013;14(6):392–397. doi:10.1016/j.jamda.2013.03.022
8. Hewitt J, Carter B, McCarthy K. Frailty predicts mortality in all emergency surgical admissions regardless of age. *An Observational Study. Age and Ageing*. 2019;48(3).
9. Evans NR, Todd OM, Minhas JS, et al. Frailty and cerebrovascular disease: concepts and clinical implications for stroke medicine. *International Journal of Stroke*. 2021;17(3):251–259. doi:10.1177/17474930211034331
10. Turc G, Bhogal P, Fischer U, et al. European stroke organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. *Journal of Neurointerventional Surgery*. 2019;11:535–538. doi:10.1136/neurintsurg-2018-014568
11. Tan BYQ, Jsy H, Leow AS, et al. Effect of frailty on outcomes of endovascular treatment for acute ischaemic stroke in older patients. *Age and Ageing*. 2022;51(4). doi:10.1093/ageing/afac096
12. Dhillon PS, Butt W, Podlasek A, et al. Perfusion imaging for endovascular thrombectomy in acute ischemic stroke is associated with improved functional outcomes in the early and late time windows. *Stroke*. 2022;53(9):2770–2778. doi:10.1161/STROKEAHA.121.038010
13. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-factor modified frailty index using American College of Surgeons NSQIP data. *Elsevier*. 2017;226(2).173–81
14. Simon HL, Reif de Paula T, da Luz MM P, Nemeth SK, Moug SJ, Keller DS. Frailty in older patients undergoing emergency colorectal surgery: USA national surgical quality improvement program analysis. *Br J Surg*. 2020;107(10):1363–1371. doi:10.1002/bjs.11770
15. Agathis AZ, Bangla VG, Divino CM. Assessing the mFI-5 frailty score and functional status in geriatric patients undergoing inguinal hernia repairs. *Hernia*. 2024;28(1):135–145. doi:10.1007/s10029-023-02905-w

16. Arnim CAFV, Msarwa S, Reiter S, Eli I, Winocur E, Sarig R. Analysis of frailty in geriatric patients as a prognostic factor in endovascular treated patients with large vessel occlusion strokes. *Journal of Clinical Medicine*. 2021;11:10. doi:10.3390/jcm11010010
17. Nevan J, Timothy A, Karen MG, et al. Frailty and stroke thrombectomy outcomes—an observational cohort study. *Age and Ageing*. 2022:afab260
18. Khalafallah AM, Huq S, Jimenez AE, Brem H, Mukherjee D. The 5-factor modified frailty index: an effective predictor of mortality in brain tumor patients. *J Neurosurg*. 2021;135(1):78–86. doi:10.3171/2020.5.JNS20766
19. Mouchtouris N, Luck T, Locke K, et al. Comparison of 5-Item and 11-item modified frailty index as predictors of functional independence in patients with spinal cord injury. *Global Spine J*. 2025;15(2):782–789. doi:10.1177/21925682231211279
20. Shuai J, Gong Z, Huang L. Effect of intravenous tirofiban vs placebo before endovascular thrombectomy on functional outcomes in Large vessel occlusion stroke: the RESCUE BT randomized clinical trial. *JAMA*. 2022;328(6):543–553. doi:10.1001/jama.2022.12584
21. Mcgovern J, Grayston A, Coates D, et al. The relationship between the modified frailty index score (mFI-5), malnutrition, body composition, systemic inflammation and short-term clinical outcomes in patients undergoing surgery for colorectal cancer. *BMC Geriatrics*. 2023;23. doi:10.1186/s12877-022-03703-2
22. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46(10):2981–2986. doi:10.1161/STROKEAHA.115.010049
23. Liu C, Li F, Chen L, et al. Effects of tirofiban on large vessel occlusion stroke are modified by etiology and renal function. *Annals of Clinical and Translational Neurology*. 2023;11(3):618–628. doi:10.1002/acn3.51982
24. Kim JT, Goyal M, Levy EI, Liebeskind D, Saver JL. Onset to reperfusion time as a determinant of outcomes across a wide range of ASPECTS in endovascular thrombectomy: pooled analysis of the SWIFT, SWIFT PRIME, and STAR studies. *Journal of Neurointerventional Surgery*. 2019;12(3):240–5
25. Stolarski A, Whang E, Kristo G. Association of preoperative patient frailty and operative stress with postoperative mortality. *JAMA Surgery*. 2020;155(1):901–908. doi:10.1001/jamasurg.2020.1686
26. Webb AJS, Werring DJ. New insights into cerebrovascular pathophysiology and hypertension. *Stroke*. 2022;53(4):1054–1064. doi:10.1161/STROKEAHA.121.035850
27. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. *The American Journal of the Medical Sciences*. 2016;351(4):380–386. doi:10.1016/j.amjms.2016.01.011
28. Portegies MLP, Lahousse L, Joos GF, et al. Chronic obstructive pulmonary disease and the risk of stroke: the Rotterdam study. *American Journal of Respiratory & Critical Care Medicine*. 2016;193:251–258. doi:10.1164/rccm.201505-0962OC
29. Markidan J, Cole JW, Cronin CA, et al. Smoking and risk of ischemic stroke in young men. *Stroke a Journal of Cerebral Circulation*. 2018;49:1276–1278. doi:10.1161/STROKEAHA.117.018859
30. Kang S-H, Kim J, Park JJ. Risk of stroke in congestive heart failure with and without atrial fibrillation. *International Journal of Cardiology*. 2017;248:182–7
31. Warner JJ, Harrington RA, Sacco RL, Elkind MSV. 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(12):3331–3332. doi:10.1161/STROKEAHA.119.027708
32. Zeinhom MG, Ahmed SR, Kohail AM, et al. A multicenter trial on the predictors of different subtypes of hemorrhagic infarction after thrombolysis. *Sci Rep*. 2024;14(1):29822. doi:10.1038/s41598-024-76189-0
33. Kim DH, Rockwood K. Frailty in older adults. *N Engl J Med*. 2024;391(6):538–548. doi:10.1056/NEJMra2301292
34. Zeinhom MG, Khalil MFE, Kamel IFM, et al. Predictors of the unfavorable outcomes in acute ischemic stroke patients treated with alteplase, a multi-center randomized trial. *Sci Rep*. 2024;14(1):5960. doi:10.1038/s41598-024-56067-5
35. Tu WJ, Xu Y, Liu Y, Du J, Zhao J. Endovascular thrombectomy or bridging therapy in minor ischemic stroke with large vessel occlusion. *Thromb Res*. 2022;219:150–154. doi:10.1016/j.thromres.2022.09.020