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Clinician-Selected Alteplase Dosing in Acute Ischemic Stroke: Treatment Patterns and Adjusted Outcomes in a Taiwanese Registry

Chin-Yuan Huang[1,2] | Sheng-Ta Tsai[3,4,5] | Hong-Mo Shih[2,3,6] | Yen-Wei Chiu[1,2] | Chen-An Wang[7] | Shin-Kuang Jiang[4,8] | Chia-Wei Lin[1,9]

[1]Department of Emergency Medicine, China Medical University Hospital, Taichung, Taiwan | [2]Department of Public Health, China Medical University, Taichung, Taiwan | [3]School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan | [4]Department of Neurology, China Medical University Hospital, Taichung, Taiwan | [5]Neuroscience and Brain Disease Center, College of Medicine, China Medical University, Taichung, Taiwan | [6]Department of Emergency Medicine, Taichung City Municipal Geriatric Rehabilitation General Hospital, Taichung, Taiwan | [7]Department of Emergency Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan | [8]Department of Neurology, Taichung City Municipal Geriatric Rehabilitation General Hospital, Taichung, Taiwan | [9]Stroke Center, China Medical University Hospital, Taichung, Taiwan

Correspondence: Chia-Wei Lin (016690@tool.caaumed.org.tw)

Received: 20 July 2026 | **Revised:** 30 September 2026 | **Accepted:** 9 November 2026

Keywords: acute ischemic stroke | alteplase | dose selection | functional outcome

ABSTRACT

Purpose: Clinicians sometimes administer alteplase doses below the guideline-recommended regimen in routine stroke care, yet the patient characteristics underlying these decisions and their relationship with outcomes remain incompletely understood. This study aimed to identify factors associated with clinician-selected alteplase dosing and to examine the relationship between dose category and clinical outcomes.

Method: We retrospectively studied 418 Taiwanese patients with acute ischemic stroke who received intravenous alteplase without endovascular thrombectomy between January 2017 and June 2022. Administered doses were categorized as low (0.46–0.64 mg/kg), medium (0.67–0.84 mg/kg), or standard (0.85–0.94 mg/kg). Multinomial logistic regression identified factors associated with clinician-selected dose, and logistic regression evaluated good 90-day functional outcome, defined as a modified Rankin Scale score of 0–2.

Finding: Older age was independently associated with low-dose rather than standard-dose treatment (adjusted odds ratio [aOR] per year, 1.07; 95% confidence interval [CI], 1.04–1.09). Diabetes mellitus was associated with both medium-dose (aOR, 1.84; 95% CI, 1.02–3.29) and low-dose treatment (aOR, 2.71; 95% CI, 1.60–4.60). Good 90-day outcome occurred in 44.0%, 53.6%, and 67.9% of the low-, medium-, and standard-dose groups, respectively. However, dose category was not independently associated with good outcome after adjustment for baseline characteristics and prestroke antithrombotic therapy. Hemorrhagic outcome estimates were imprecise because symptomatic intracranial hemorrhage events were uncommon.

Conclusion: Real-world alteplase dosing primarily reflected baseline patient risk profiles and treatment-selection patterns. Crude differences in 90-day functional outcome between dose groups were attenuated after adjustment and should therefore be interpreted as treatment-selection associations rather than causal treatment effects.

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1 | Introduction

Stroke remains a leading cause of death and disability worldwide (Feigin et al. 2025; Fan et al. 2023). Intravenous alteplase is an established reperfusion treatment for eligible patients with acute ischemic stroke presenting within the therapeutic time window (Powers et al. 2019; Hacke et al. 2008). Although the guideline-recommended regimen is 0.9 mg/kg in most countries, the dose actually administered in routine care may be individualized when clinicians perceive a heightened risk of hemorrhage, frailty, or treatment-related complications. These decisions are made under substantial time pressure and may reflect patient characteristics that are not fully captured by formal eligibility criteria.

The optimal alteplase dose in Asian populations has remained controversial. Comparative studies and meta-analyses have reported heterogeneous results regarding functional recovery and hemorrhagic complications with reduced-dose versus standard-dose alteplase (Liao et al. 2014; Kim et al. 2015; Dong et al. 2016; Liu et al. 2018). Observational data also suggest variation in hemorrhagic risk after thrombolysis across patient populations (Mehta et al. 2014; Menon et al. 2012). Japan adopted a 0.6-mg/kg regimen on the basis of domestic clinical evidence, whereas 0.9 mg/kg remains the internationally recommended standard (Powers et al. 2019; Yamaguchi et al. 2006). The ENCHANTED trial did not establish noninferiority of low-dose alteplase for death or disability, although it reported fewer symptomatic intracranial hemorrhages (sICH) with the lower dose (Anderson et al. 2016). Observational studies have likewise produced inconsistent findings (Liao et al. 2014; Kim et al. 2015; Chao et al. 2014; Chen et al. 2022; Li et al. 2026; Wang and Ji 2023; Zhao et al. 2018; Rahimi et al. 2025), in part because patients selected for lower doses often differ substantially from those receiving standard treatment.

An additional challenge is that real-world practice does not always follow a simple low-versus-standard dichotomy. Some patients receive intermediate doses that are neither guideline-defined nor well represented in randomized trials. The clinical characteristics associated with this treatment pattern remain poorly described, and crude outcome comparisons may be strongly influenced by confounding by indication. We therefore examined clinician-selected alteplase dosing in a Taiwanese stroke registry. The primary objective was to identify baseline clinical characteristics associated with low-, medium-, or standard-dose treatment. Secondary objectives were to describe hemorrhagic and early neurologic outcomes and to determine whether dose category was independently associated with good 90-day functional outcome after adjustment for baseline risk profiles and prestroke antithrombotic therapy.

2 | Methods

2.1 | Study Design and Participants

We conducted a retrospective single-center cohort study at China Medical University Hospital, a tertiary referral center in Taiwan. Consecutive Taiwanese patients with acute ischemic stroke who received intravenous alteplase between January 2017 and June 2022 were screened. The study was approved by the Research Ethics Committee of China Medical University Hospital (CMUH111-REC1-199, continuing review), which waived the requirement for written informed consent because of the retrospective design and use of deidentified data.

Patients treated with intravenous alteplase monotherapy were eligible. Patients who underwent combined endovascular therapy, were non-Taiwanese, had incomplete key clinical or outcome data, or received doses outside the prespecified dose categories were excluded. The final analytic cohort comprised 418 patients (Figure 1). Study size was determined by all eligible registry patients during the study period; no a priori sample-size calculation was performed.

Of the included patients, 130 (31.1%) were transferred from outside hospitals and 288 (68.9%) were direct arrivals. For transferred patients, pretreatment neurologic severity, alteplase dose, treatment time, and relevant clinical characteristics were obtained from referral records and verified against the receiving-hospital electronic medical record when available. The exposure of interest was the dose actually administered, regardless of whether the dosing decision was made at the referring hospital or the study hospital. Door-to-needle time was not compared by transfer status because alteplase had already been initiated at the referring hospital for transferred patients, making a single receiving-hospital door-to-needle metric not directly comparable with that of direct arrivals.

2.2 | Clinical Variables and Outcomes

Demographic and clinical variables were extracted from electronic medical records. Recorded variables included age, sex, body mass index (BMI), admission systolic and diastolic blood pressure, onset-to-alteplase time, and comorbid hypertension, diabetes mellitus (DM), prior stroke, uremia, dyslipidemia, coronary artery disease, valvular heart disease (VHD), atrial fibrillation (AF), heart failure (HF), and malignancy. Comorbidities were ascertained from documented medical history, admission records, diagnostic testing during hospitalization, and follow-up records when applicable.

Prestroke antithrombotic therapy was reviewed from electronic medical records and referral documents. Antiplatelet therapy included aspirin, clopidogrel, cilostazol, or dual antiplatelet therapy; oral anticoagulant therapy included warfarin and direct oral anticoagulants. Alteplase was administered to warfarin-treated patients only when the international normalized ratio was below the accepted eligibility threshold. For patients with dabigatran exposure, idarucizumab reversal was given before alteplase when clinically indicated. No patient with factor Xa inhibitor exposure had documented regular intake within 48 h before alteplase administration.

Baseline National Institutes of Health Stroke Scale (NIHSS) score was defined as the score closest to alteplase administration before treatment. For transferred patients, a referring-hospital NIHSS score was used when it reflected pretreatment neurologic status. NIHSS was recorded again at approximately 24 h. Baseline severity was categorized as mild (1–4), moderate (5–15), moderate to severe (16–20), or severe (>20). The 24-h NIHSS change was

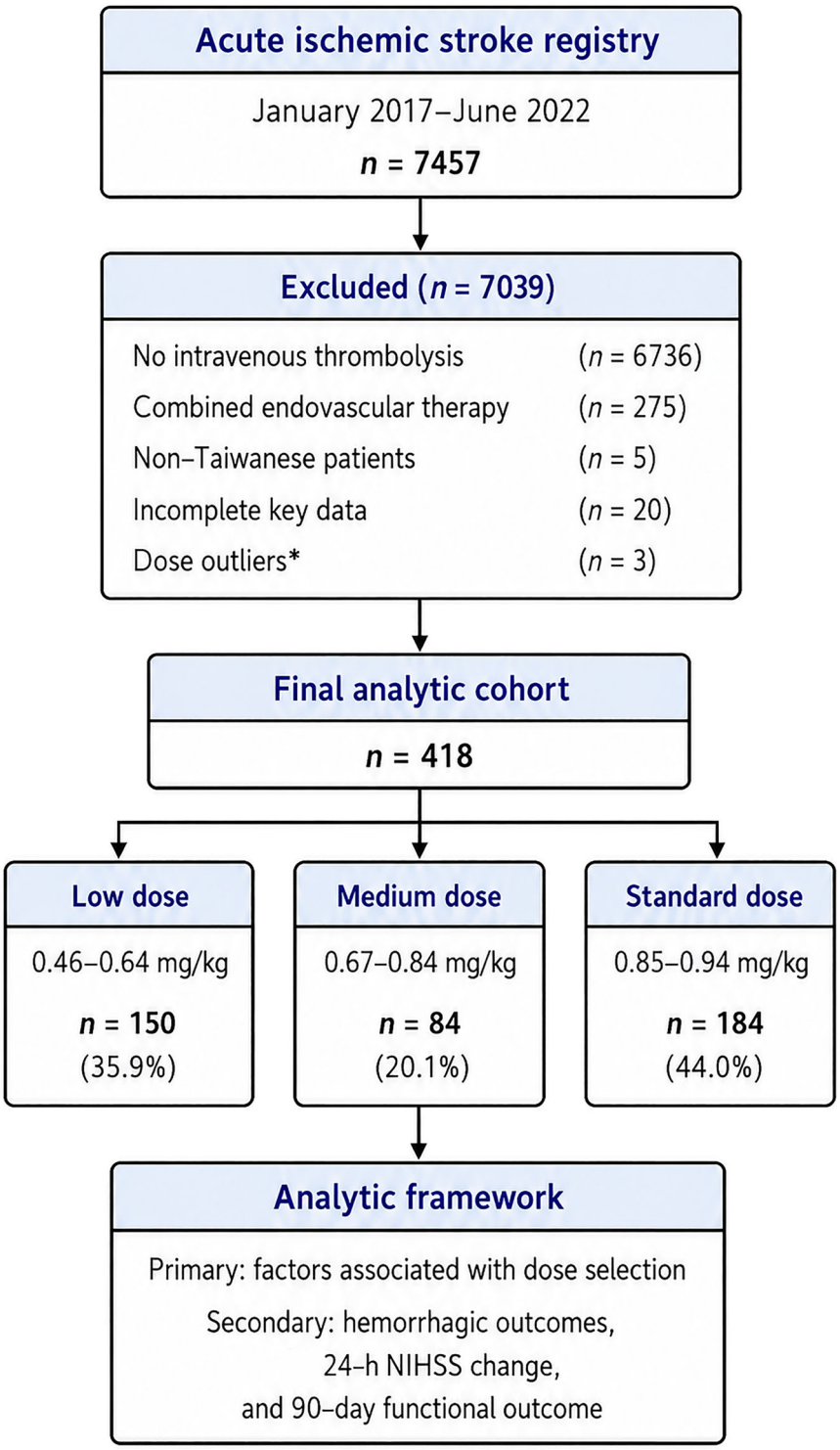


FIGURE 1 | Study design and patient selection. The flowchart summarizes the registry cohort, exclusion criteria, final analytic cohort, dose categories, and analytic framework.

analyzed descriptively because baseline severity differed across dose groups.

Hemorrhagic outcomes were hemorrhagic transformation (HT) and sICH. sICH was defined as intracranial hemorrhage within 36 h of alteplase accompanied by an NIHSS increase of at least 4 points or death, with the hemorrhage judged to be the likely cause of deterioration. Functional outcome was measured with the modified Rankin Scale (mRS) at 90 days. Dedicated stroke-team quality-control assistants routinely conducted structured telephone follow-up at approximately 30, 90, and 180 days. Assessors were not formally blinded by protocol, but alteplase dose information was not routinely reviewed or used during assessment. Good functional outcome was defined as mRS 0–2. Prestroke mRS was not consistently documented, and return to prestroke functional status could not be reliably assessed. Complete 90-day mRS data were available for all 418 patients in the analytic cohort; missing outcome data were not imputed.

2.3 | Alteplase Dose Classification

Administered alteplase dose was categorized as low (0.46–0.64 mg/kg), medium (0.67–0.84 mg/kg), or standard (0.85–0.94 mg/kg). The standard category represented a practical observed range around the guideline-recommended 0.90-mg/kg regimen, allowing for real-world variation in weight ascertainment and dose preparation. No patient received exactly 0.95 mg/kg; therefore, the upper-bound convention did not affect patient classification. No patient received 0.65–0.66 mg/kg, supporting boundaries at 0.64 and 0.67 mg/kg. The medium-dose category represented an empirically observed intermediate treatment pattern and was not intended to represent a guideline-defined regimen.

For patients treated at the study hospital, body weight used for alteplase dosing was routinely measured using a weighing bed. For patients treated before interhospital transfer, body weight and treatment information were obtained from referral records; whether body weight had been directly measured or estimated at the referring hospital could not be consistently determined retrospectively.

2.4 | Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as number (percentage). Between-group comparisons used one-way analysis of variance for normally distributed continuous variables, the Kruskal–Wallis test for skewed continuous variables, and the chi-square or Fisher exact test for categorical variables, as appropriate.

Multinomial logistic regression was used to identify clinical factors associated with alteplase dose category, with standard dose as the reference. Odds ratios (ORs) were estimated for medium versus standard and low versus standard dose. Unadjusted, age- and sex-adjusted, and multivariable models were constructed. Age, sex, and baseline NIHSS severity were prespecified core adjustment variables. Additional covariates were selected on the basis of clinical relevance and observed baseline differences and included BMI, DM, AF, uremia, VHD, HF, and malignancy. Sparse estimates, particularly for VHD, were interpreted as exploratory.

Two sensitivity analyses assessed robustness of the dose-selection model. First, the low- and medium-dose groups were combined as a nonstandard-dose group and compared with the standard-dose group using binary logistic regression with the same adjustment covariates. Second, prestroke antiplatelet and anticoagulant therapy were added to the multinomial model.

For 90-day outcome, logistic regression modeled good functional outcome (mRS 0–2), with standard dose as the reference. Models were unadjusted; adjusted for age, sex, and baseline NIHSS score; and fully adjusted for age, sex, BMI, baseline NIHSS score, DM, AF, prior stroke, HF, VHD, onset-to-alteplase time, prestroke antiplatelet therapy, and prestroke anticoagulant therapy. For HT and sICH, pairwise ORs with 95% CIs were calculated relative to standard dose; Fisher exact tests were used because sICH events were few.

A post-hoc analysis compared transferred and direct-arrival patients with respect to onset-to-alteplase time, administered dose, and dose-category distribution. Continuous variables were compared using the Mann–Whitney U test and categorical variables using the chi-square or Fisher exact test, as appropriate. Among medium-dose patients, receipt of exactly 50 mg of alteplase was summarized descriptively overall and by transfer status. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

During manuscript preparation, the authors used OpenAI ChatGPT and OpenAI image-generation tools for English-language editing, organization of manuscript content, formatting, and the visual layout of the figures and graphical abstract. These tools were not used for study design, patient selection, data collection, statistical analysis, generation or alteration of research data, or determination of the study conclusions. All AI-assisted text, numerical labels, references, figures, and graphical abstract elements were reviewed and revised by the authors and verified against the original data tables and statistical outputs. The authors take full responsibility for the accuracy and integrity of the final manuscript.

3 | Results

3.1 | Study Population

During the study period, 7457 patients with acute ischemic stroke were identified from the institutional stroke registry. After application of the predefined inclusion and exclusion criteria, 418 patients who received intravenous alteplase monotherapy were included in the final analysis (Figure 1). Of these, 150 (35.9%) received low-dose alteplase, 84 (20.1%) received medium-dose alteplase, and 184 (44.0%) received standard-dose alteplase. Overall, 130 patients (31.1%) were interhospital transfers and 288 (68.9%) were direct arrivals.

3.2 | Baseline Characteristics

Baseline characteristics are summarized in Table 1. Patients receiving lower alteplase doses were generally older and had a greater burden of vascular comorbidities than those receiving standard-dose treatment. Median age increased from 64.5 years in the standard-dose group to 71 years in the medium-dose group and 78 years in the low-dose group ($p < 0.001$). DM, uremia, AF, and HF also differed across groups. Although uremia and VHD had identical marginal distributions across the three dose groups, they represented distinct patient-level variables; only one patient had both conditions.

Mean baseline NIHSS scores were 10.61 ± 6.38, 12.43 ± 6.51, and 13.23 ± 6.79 in the standard-, medium-, and low-dose groups, respectively ($p = 0.001$). Prestroke antiplatelet and oral anticoagulant use also differed across dose groups (Table S1).

3.3 | Clinical Factors Associated With Clinician-Selected Alteplase Dose

Multivariable multinomial logistic regression demonstrated that older age and DM were the most consistent clinical characteristics associated with clinician-selected nonstandard alteplase dosing (Table 2 and Figure 2). Compared with standard-dose treatment, each additional year of age was independently associated with a greater likelihood of receiving low-dose alteplase (aOR, 1.07; 95% CI, 1.04–1.09; $p < 0.001$). DM was independently associated with both medium-dose (aOR, 1.84; 95% CI, 1.02–3.29; $p = 0.042$) and low-dose treatment (aOR, 2.71; 95% CI, 1.60–4.60; $p < 0.001$).

VHD was associated with low-dose treatment in the primary model (aOR, 6.72; 95% CI, 1.29–35.08; $p = 0.024$), but the estimate was based on only 12 patients and was therefore considered exploratory. After additional adjustment for prestroke antiplatelet and anticoagulant therapy, DM remained associated with low-dose treatment (aOR, 2.89; 95% CI, 1.65–5.06; $p < 0.001$), whereas the VHD estimate remained imprecise (Table S2). In this sensitivity model, HF was inversely associated with medium-dose treatment (aOR, 0.13; 95% CI, 0.03–0.58; $p = 0.008$), whereas prestroke anticoagulant therapy was positively associated with medium-dose treatment (aOR, 9.21; 95% CI, 1.56–54.47; $p = 0.014$). Given the small numbers of affected or exposed patients and the wide confidence intervals, these findings were considered exploratory. In the binary sensitivity analysis comparing nonstandard with standard dosing, older age (aOR, 1.04; 95% CI, 1.03–1.06; $p < 0.001$) and DM (aOR, 2.24; 95% CI, 1.40–3.57; $p < 0.001$) remained independently associated with nonstandard dosing (Table S3).

In a post-hoc analysis by transfer status, median onset-to-alteplase time did not differ significantly between transferred and direct-arrival patients (118 [IQR 90–158] vs. 126.5 [96–165] min; $p = 0.089$). The overall three-category dose distribution differed between groups ($p < 0.001$): transferred patients more frequently received medium-dose alteplase (30.8% vs. 15.3%), whereas low-dose treatment was less frequent among transferred than direct-arrival patients (23.1% vs. 41.7%). The proportion receiving standard-dose alteplase was similar (46.2% vs. 43.1%; $p = 0.628$). When the low- and medium-dose categories were combined, the overall frequency of nonstandard dosing was also similar (53.8% vs. 56.9%; $p = 0.628$), although median administered dose was modestly higher among transferred patients (0.80 [0.69–0.90] vs. 0.70 [0.60–0.90] mg/kg; $p = 0.030$). Among the 84 medium-dose patients, 43 (51.2%) received exactly 50 mg of alteplase; the corresponding proportions were 55.0% among transferred medium-dose patients and 47.7% among direct-arrival medium-dose patients. Detailed results of the post-hoc analysis according to transfer status are provided in Table S4.

3.4 | Hemorrhagic and Functional Outcomes

Hemorrhagic outcomes are summarized in Table 3. HT occurred in 24.0%, 28.6%, and 26.6% of the low-, medium-, and standard-dose groups, respectively. Compared with standard dose, the ORs for HT were 0.87 (95% CI, 0.53–1.43; $p = 0.615$) for low dose and 1.10 (95% CI, 0.62–1.96; $p = 0.768$) for medium dose. sICH occurred in 4.0%, 7.1%, and 6.0% of the groups, respectively. The corresponding ORs were 0.66 (95% CI, 0.24–1.82; $p = 0.463$) for low dose and 1.21 (95% CI, 0.43–3.39; $p = 0.788$) for medium dose. Only 23 sICH events occurred overall (6 in the low-dose group, 6 in the medium-dose group, and 11 in the standard-dose group). Accordingly, the study was not powered to establish either superiority or non-inferiority for hemorrhagic safety outcomes, and the absence of statistically significant differences should not be interpreted as evidence of equivalent safety.

Median 24-hour NIHSS change was 3 (1–6.75) in the low-dose group, 3 (0–7) in the medium-dose group, and 3 (1–7) in the standard-dose group ($p = 0.708$). Because this was an unadjusted comparison and baseline severity differed across groups, it should be interpreted descriptively rather than as evidence of equivalent early neurologic response.

Crude functional outcomes appeared more favorable among patients receiving standard-dose alteplase. Good functional outcome (mRS 0–2) at 90 days occurred in 67.9% of the standard-dose group, compared with 53.6% and 44.0% of the medium- and low-dose groups, respectively ($p < 0.001$). However, these apparent differences were attenuated after multivariable adjustment for baseline characteristics and prestroke antithrombotic therapy (Figure 3 and Table 4). In the fully adjusted model, neither medium-dose (aOR, 0.96; 95% CI, 0.51–1.83; $p = 0.911$) nor low-dose alteplase (aOR, 1.02; 95% CI, 0.57–1.83; $p = 0.938$) was independently associated with good 90-day functional outcome.

4 | Discussion

4.1 | Principal Findings

This study investigated clinician-selected alteplase dosing in routine clinical practice rather than comparing randomized or predefined treatment regimens. Older age and DM were the most reproducible characteristics associated with clinician-selected nonstandard dosing. Although patients receiving lower doses had less favorable crude functional outcomes, dose category was not independently associated with good 90-day outcome after adjustment for baseline characteristics and prestroke antithrombotic therapy. Hemorrhagic estimates were imprecise because

TABLE 1 | Baseline characteristics according to administered alteplase dose category.

Variable	Low dose ($n = 150$)	Medium dose ($n = 84$)	Standard dose ($n = 184$)	p-value
Demographic and continuous clinical characteristics				
Age, y, median (IQR)	78 (66.3–86)	71 (61–79)	64.5 (55–73)	< 0.001
BMI, median (IQR)	24.4 (21.4–26.8)	24.0 (22.6–27.3)	25.3 (23.0–27.8)	0.010
SBP, mm Hg, median (IQR)	155 (133–174)	162 (144–181)	158 (135–176)	0.207
DBP, mm Hg, median (IQR)	90 (78.3–101)	97 (82.8–108)	90.5 (80–102)	0.080
Onset-to-alteplase time, min, median (IQR)	133 (100–164)	120 (91–163)	116 (93–160)	0.304
Baseline NIHSS, mean ± SD	13.23 ± 6.79	12.43 ± 6.51	10.61 ± 6.38	0.001
Sex and medical history				
Sex				0.001
Male	85 (56.7%)	49 (58.3%)	137 (74.5%)	
Female	65 (43.3%)	35 (41.7%)	47 (25.5%)	
Hypertension	132 (88.0%)	74 (88.1%)	148 (80.4%)	0.101
DM	69 (46.0%)	31 (36.9%)	51 (27.7%)	0.002
Prior stroke	46 (30.7%)	22 (26.2%)	22 (12.0%)	< 0.001
Uremia	9 (6.0%)	1 (1.2%)	2 (1.1%)	0.025
Dyslipidemia	118 (78.7%)	57 (67.9%)	136 (73.9%)	0.188
CAD	19 (12.7%)	4 (4.8%)	12 (6.5%)	0.054
VHD	9 (6.0%)	1 (1.2%)	2 (1.1%)	0.025
AF	56 (37.3%)	38 (45.2%)	52 (28.3%)	0.019
HF	27 (18.0%)	5 (6.0%)	16 (8.7%)	0.008
Malignancy	11 (7.3%)	1 (1.2%)	6 (3.3%)	0.077
Baseline stroke severity				
Baseline NIHSS severity				0.002
Mild (1–4)	10 (6.7%)	6 (7.1%)	29 (15.8%)	
Moderate (5–15)	79 (52.7%)	52 (61.9%)	117 (63.6%)	
Moderate to severe (16–20)	36 (24.0%)	15 (17.9%)	19 (10.3%)	
Severe (> 20)	25 (16.7%)	11 (13.1%)	19 (10.3%)	

Note: Data are *n* (%) unless otherwise indicated. VHD and uremia had identical marginal distributions across dose groups but represented distinct patient-level variables; only one patient had both conditions.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation; VHD, valvular heart disease.

TABLE 2 | Factors associated with clinician-selected alteplase dose category.

Variable	Unadjusted OR (95% CI); *p*	Age- and sex-adjusted OR (95% CI); *p*	Multivariable OR (95% CI); *p*
Panel A. Medium dose versus standard dose			
Age	1.03 (1.01–1.05); 0.002	—	1.02 (0.99–1.04); 0.095
BMI	0.96 (0.90–1.02); 0.178	0.99 (0.92–1.06); 0.777	0.97 (0.91–1.05); 0.485
Male sex	0.48 (0.28–0.83); 0.008	—	0.59 (0.33–1.09); 0.094
DM	1.53 (0.88–2.64); 0.131	1.63 (0.93–2.87); 0.086	1.84 (1.02–3.29); 0.042
AF	2.10 (1.23–3.59); 0.007	1.55 (0.87–2.76); 0.139	1.65 (0.91–3.01); 0.102
Uremia	1.10 (0.10–12.26); 0.940	0.77 (0.07–8.83); 0.834	0.74 (0.06–8.53); 0.808
VHD	1.10 (0.09–12.26); 0.940	0.88 (0.08–10.06); 0.918	1.14 (0.10–13.61); 0.917
HF	0.66 (0.24–1.88); 0.441	0.53 (0.18–1.55); 0.248	0.37 (0.12–1.11); 0.075
Malignancy	0.36 (0.04–3.02); 0.344	0.33 (0.04–2.83); 0.312	0.34 (0.04–2.92); 0.323
Panel B. Low dose versus standard dose			
Age	1.07 (1.05–1.09); < 0.001	—	1.07 (1.04–1.09); < 0.001
BMI	0.92 (0.87–0.97); 0.003	0.99 (0.92–1.05); 0.645	0.96 (0.90–1.03); 0.272
Male sex	0.45 (0.28–0.71); < 0.001	—	0.77 (0.44–1.34); 0.358
DM	2.22 (1.41–3.50); < 0.001	2.54 (1.54–4.17); < 0.001	2.71 (1.60–4.60); < 0.001
AF	1.51 (0.95–2.40); 0.079	0.79 (0.47–1.34); 0.390	0.81 (0.46–1.42); 0.458
Uremia	5.81 (1.24–27.31); 0.026	4.14 (0.83–20.55); 0.082	2.83 (0.56–14.47); 0.210
VHD	5.81 (1.23–27.31); 0.026	5.42 (1.08–27.28); 0.040	6.72 (1.29–35.08); 0.024
HF	2.31 (1.19–4.46); 0.013	1.60 (0.77–3.33); 0.207	1.14 (0.53–2.48); 0.734
Malignancy	2.35 (0.85–6.51); 0.101	1.75 (0.57–5.39); 0.327	2.14 (0.71–6.49); 0.177

Note: ORs represent the odds of receiving the indicated alteplase dose category rather than standard-dose alteplase. Age- and sex-adjusted models included age and sex as covariates for all other predictors; separate estimates for age and sex were not displayed in this column, as indicated by an em dash. The multivariable model adjusted for age, sex, BMI, DM, AF, uremia, VHD, HF, malignancy, and baseline NIHSS severity group. Age, sex, and baseline NIHSS severity were prespecified core adjustment variables. Baseline NIHSS severity was included in the model but is not displayed as a separate row. Estimates for sparse comorbidities, particularly VHD, should be interpreted as exploratory.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HF, heart failure; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; VHD, valvular heart disease.

TABLE 3 | Hemorrhagic outcomes according to administered alteplase dose category.

Outcome	Dose category	Events/total (%)	OR vs. standard	95% CI	*p*-value
HT	Low	36/150 (24.0%)	0.87	0.53–1.43	0.615
HT	Medium	24/84 (28.6%)	1.10	0.62–1.96	0.768
HT	Standard	49/184 (26.6%)	Reference	—	—
sICH	Low	6/150 (4.0%)	0.66	0.24–1.82	0.463
sICH	Medium	6/84 (7.1%)	1.21	0.43–3.39	0.788
sICH	Standard	11/184 (6.0%)	Reference	—	—

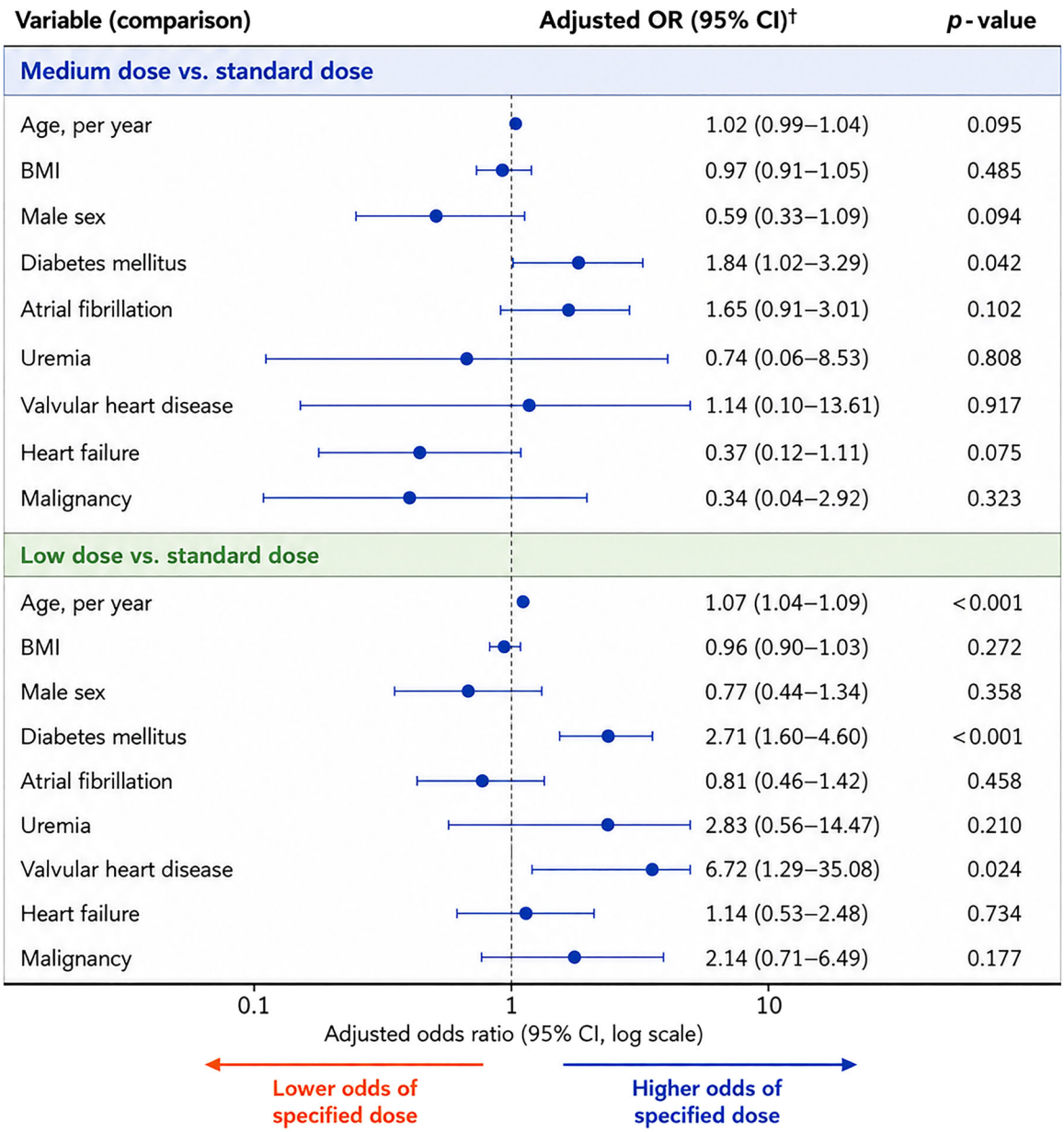
Note: Odds ratios were calculated with standard-dose alteplase as the reference. *p*-values are from pairwise Fisher exact tests. The small number of symptomatic intracranial hemorrhage events resulted in wide confidence intervals and limited precision.

Abbreviations: CI, confidence interval; HT, hemorrhagic transformation; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

sICH events were uncommon and should not be interpreted as evidence of equivalent safety. Collectively, these findings suggest that real-world alteplase dosing reflects baseline patient risk profiles and treatment-selection behavior rather than the intrinsic effectiveness of the administered dose.

4.2 | Clinical Decision-Making in Alteplase Dose Selection

Older age and DM were the two most reproducible factors associated with clinician-selected dose reduction. Both may



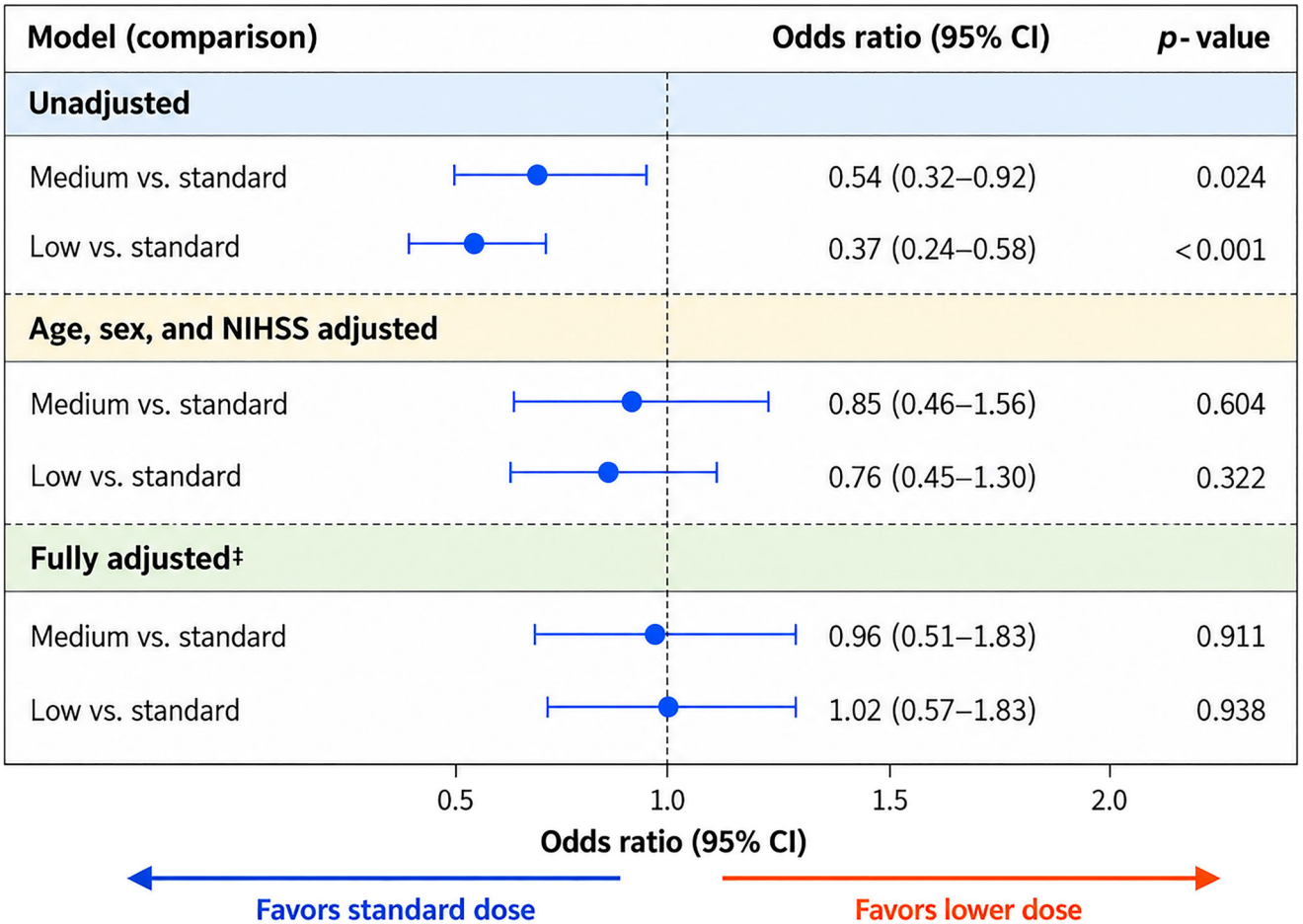
† Model adjusted for age, sex, BMI, diabetes mellitus, atrial fibrillation, uremia, valvular heart disease, heart failure, malignancy, and baseline NIHSS severity group. Standard dose (0.85–0.94 mg/kg) is the reference category. Baseline NIHSS severity group is included in the model but not displayed.

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale.

FIGURE 2 | Clinical factors associated with clinician-selected alteplase dose. Adjusted ORs and 95% CIs are shown for medium versus standard and low versus standard dose. The vertical line indicates an OR of 1. VHD estimates are exploratory because the number of affected patients was small.

influence physicians' perceptions of frailty, vascular injury, and hemorrhagic risk, even when patients meet formal thrombolysis eligibility criteria (Powers et al. 2019; Mehta et al. 2014; Menon et al. 2012). These associations should not be interpreted as proof that either characteristic directly caused the dosing decision, particularly because some comorbidities may have been documented during hospitalization rather than known with certainty at the moment of treatment. Nevertheless, their consistency across primary and sensitivity analyses supports the interpretation that clinicians tended to select lower doses for patients with less favorable baseline risk profiles.

The intermediate-dose group is also clinically informative. It represented an empirically observed practice pattern rather than a guideline-endorsed regimen. Most previous studies have compared approximately 0.6 mg/kg with 0.9 mg/kg alteplase (Liao et al. 2014; Kim et al. 2015; Dong et al. 2016; Liu et al. 2018; Yamaguchi et al. 2006; Chao et al. 2014; Anderson et al.



Good functional outcome was defined as a modified Rankin Scale score of 0–2 at 90 days.

† Reference group: standard dose (0.85–0.94 mg/kg).

‡ Model adjusted for age, sex, BMI, baseline NIHSS, diabetes mellitus, atrial fibrillation, prior stroke, heart failure, valvular heart disease, onset-to-alteplase time, prestroke antiplatelet therapy, and prestroke anticoagulant therapy.

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

FIGURE 3 | Association between alteplase dose and good 90-day functional outcome. Good outcome was defined as mRS 0–2 at 90 days. The fully adjusted model included age, sex, BMI, baseline NIHSS, DM, AF, prior stroke, HF, VHD, onset-to-alteplase time, and prestroke antiplatelet and anticoagulant therapy.

2016; Chen et al. 2022; Li et al. 2026; Wang and Ji 2023; Zhao et al. 2018; Rahimi et al. 2025). A binary low-versus-standard framework would therefore have obscured a substantial group of patients whose administered doses fell between these conventional regimens.

Approximately half of the medium-dose patients received exactly 50 mg of alteplase, suggesting that single-vial administration may have contributed to the intermediate-dose pattern. However, because this did not account for all medium-dose cases and weight ascertainment at referring hospitals could not always be verified, the medium-dose category should not be interpreted as representing a single standardized dosing strategy. Transfer status appeared to influence the distribution between low- and medium-dose treatment, but not the overall frequency of nonstandard versus standard dosing.

4.3 | Interpretation of Dose–Outcome Associations

Prior randomized and observational studies of reduced-dose alteplase have reported heterogeneous results (Liao et al. 2014; Kim et al. 2015; Dong et al. 2016; Liu et al. 2018; Yamaguchi et al. 2006; Chao et al. 2014; Anderson et al. 2016; Chen et al. 2022; Li et al. 2026; Wang and Ji 2023; Zhao et al. 2018; Rahimi et al. 2025). In ENCHANTED, low-dose alteplase reduced sICH but did not meet the prespecified criterion for noninferiority with respect to death or disability (Anderson et al. 2016). Observational studies have variously reported comparable outcomes, lower hemorrhagic risk with reduced dosing, or better functional recovery with standard dosing (Liao et al. 2014; Kim et al. 2015; Chao et al. 2014; Chen et al. 2022; Li et al. 2026; Wang and Ji 2023; Zhao et al. 2018; Rahimi et al. 2025). These differences may partly

TABLE 4 | Early neurologic change and 90-day functional outcome.

Panel A. Descriptive outcomes				
Dose category	**NIHSS change, median (IQR)**	***p*-value**	**Good 90-day mRS, n (%)**	***p*-value**
Low	3 (1–6.75)	0.708	66 (44.0%)	< 0.001
Medium	3 (0–7)		45 (53.6%)	
Standard	3 (1–7)		125 (67.9%)	

Panel B. Logistic regression for good 90-day functional outcome				
Model	**Comparison**	**OR**	**95% CI**	***p*-value**
Unadjusted	Medium vs. standard	0.54	0.32–0.92	0.024
Unadjusted	Low vs. standard	0.37	0.24–0.58	< 0.001
Age-, sex-, NIHSS-adjusted	Medium vs. standard	0.85	0.46–1.56	0.604
Age-, sex-, NIHSS-adjusted	Low vs. standard	0.76	0.45–1.30	0.322
Multivariable adjusted	Medium vs. standard	0.96	0.51–1.83	0.911
Multivariable adjusted	Low vs. standard	1.02	0.57–1.83	0.938

Note: NIHSS change was calculated as baseline NIHSS minus 24-h NIHSS; positive values indicate neurologic improvement. Good functional outcome was defined as a mRS score of 0–2 at 90 days. For Panel B, ORs represent the odds of good functional outcome, with standard dose as the reference. The age-, sex-, and NIHSS-adjusted model included age, sex, and baseline NIHSS score. The multivariable model additionally adjusted for BMI, DM, AF, prior stroke, HF, VHD, onset-to-alteplase time, prestroke antiplatelet therapy, and prestroke anticoagulant therapy.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HF, heart failure; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; VHD, valvular heart disease.

reflect variation in study populations, dose definitions, outcome ascertainment, and treatment selection.

In our cohort, patients receiving lower doses were older, had greater baseline stroke severity, and carried a greater burden of vascular comorbidity. Their less favorable crude 90-day outcomes are therefore consistent with confounding by indication: clinicians preferentially selected lower doses for patients who already had less favorable prognostic profiles. Once these measured differences were considered, the association between dose category and good 90-day outcome was no longer evident. This finding does not demonstrate therapeutic equivalence, because residual confounding and limited statistical precision remain possible. Rather, it shows why nonrandomized dose–outcome comparisons should not be interpreted as causal treatment effects without careful adjustment.

Because prestroke mRS was not consistently documented, residual confounding by baseline disability and frailty cannot be excluded. If preexisting disability or frailty was more prevalent among patients selected for lower alteplase doses, omission of this factor would be expected to bias the adjusted ORs for good 90-day functional outcome downward for the lower-dose groups, because baseline frailty could both increase the likelihood of dose reduction and independently reduce the probability of achieving mRS 0–2 at 90 days. Moreover, patients with prestroke mRS > 2 could not meet the study definition of good outcome even if they returned to their prestroke functional level. This does not imply that lower-dose alteplase is beneficial; rather, it further limits causal interpretation of the adjusted dose–outcome associations.

The hemorrhagic findings require the same caution. The small number of sICH events produced wide CIs, and the study was not designed or powered to establish either superiority or non-inferiority for hemorrhagic safety outcomes. Accordingly, absence of statistical significance cannot be interpreted as evidence of equivalent safety. Similarly, the unadjusted 24-h NIHSS change was descriptive and should not be interpreted as demonstrating comparable early treatment response, because baseline stroke severity differed across groups.

4.4 | Clinical and Research Implications

These findings highlight a gap between guideline-defined dosing and treatment delivered in routine practice. Variation in administered dose appears to reflect individualized physician judgment rather than a standardized dose-reduction algorithm. The results do not support recommending patient-specific dose reduction on the basis of age, DM, or the other variables examined. Instead, they underscore the need to document why a nonstandard dose is chosen and to distinguish analyses of treatment selection from analyses of comparative effectiveness.

Future multicenter prospective studies should record the information available to clinicians at the time of thrombolysis, including estimated versus measured body weight, perceived bleeding risk, frailty, prestroke function, patient or family preference, and the clinician responsible for dose selection. Such studies would be better positioned to determine whether individualized dose modification changes clinical benefit or harm.

4.5 | Strengths and Limitations

This study analyzed actual administered alteplase doses in a clinically characterized Taiwanese cohort, distinguished an intermediate real-world dosing pattern, and included sensitivity analyses addressing prestroke antithrombotic therapy and nonstandard dosing. Several limitations should be acknowledged. First, the retrospective single-center design limits causal inference and generalizability. Second, dose categories were empirically defined from the observed distribution, and the medium-dose category is not guideline-defined; approximately half of medium-dose patients received exactly 50 mg, suggesting that vial size may have contributed to this treatment pattern. Third, although body weight was routinely measured with a weighing bed for patients treated at the study hospital, weight ascertainment at referring hospitals could not be consistently verified, and the analysis could not capture all reasons for dose selection, including clinician preference or patient and family preference. Fourth, some cardiovascular comorbidities may have been identified during hospitalization or follow-up rather than known at the moment of alteplase administration; these variables should therefore be viewed as correlates of dosing patterns rather than confirmed determinants of the acute decision. Fifth, prestroke mRS was not consistently available, leaving residual confounding by premorbid disability or frailty, and the 90-day mRS assessment was not formally blinded by protocol. Finally, complete-case analysis may introduce selection bias, and the study had limited precision for uncommon hemorrhagic outcomes and sparse comorbidities such as VHD; in particular, it was underpowered to establish superiority or non-inferiority for sICH.

5 | Conclusion

Older age and DM were the most consistent clinical characteristics associated with clinician-selected lower or nonstandard alteplase dosing. Crude differences in 90-day functional outcome were attenuated after multivariable adjustment, indicating that nonrandomized comparisons among dose groups are strongly shaped by treatment selection and baseline risk. These findings do not establish the comparative efficacy or safety of individualized dose reduction and do not support a patient-specific dose-reduction algorithm. Prospective multicenter studies are needed to determine whether nonstandard alteplase dosing alters clinical benefit or harm.

Author Contributions

Chin-Yuan Huang: Writing – original draft, investigation, data curation. **Sheng-Ta Tsai**: writing – original draft, writing – review and editing, methodology, validation. **Hong-Mo Shih**: conceptualization, supervision, formal analysis. **Yen-Wei Chiu**: resources, visualization, software. **Chen-An Wang**: writing – original draft. **Shin-Kuang Jiang**: investigation, writing – original draft. **Chia-Wei Lin**: writing – review and editing, resources, supervision, project administration, data curation, methodology, conceptualization. All authors approved the final version to be published.

Acknowledgments

The authors have nothing to report.

Funding

This work was supported in part by China Medical University Hospital, Taiwan (Grant No. DMR-115-072).

Ethics Statement

The study was approved by the Research Ethics Committee of China Medical University Hospital (CMUH111-REC1-199, continuing review). The requirement for written informed consent was waived because of the retrospective design and use of deidentified data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The deidentified patient-level data are not publicly available because of patient privacy, institutional review board conditions, and institutional data-governance requirements. Data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1002/brb3.71950.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Material: brb371950-sup-0001-SuppMat.docx