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Pretreatment CHA_2DS_2-VASc-HS Score for Predicting Failed Thrombolysis in ST-Elevation Myocardial Infarction: A Cross-Sectional Diagnostic Accuracy Study in Bangladesh

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Abstract

Background

Fibrinolysis remains the principal reperfusion strategy for ST-elevation myocardial infarction (STEMI) in Bangladesh and in most low- and middle-income settings, yet it fails in a substantial minority of patients, and failure is currently recognized only 90 minutes after treatment has begun. We assessed the diagnostic accuracy of the CHA_2DS_2-VASc-HS score, recorded before thrombolysis from the history, previous medical records, and physical examination, for failed thrombolysis.

Methodology

In this cross-sectional diagnostic accuracy study, 166 of 219 patients (75.8%) with STEMI treated with streptokinase at a tertiary cardiac center in Dhaka between February 2023 and January 2024 were enrolled by consecutive sampling and underwent CHA_2DS_2-VASc-HS scoring on admission, before the infusion was started. The outcome of thrombolysis was classified as successful or failed 90 minutes after the start of the infusion using a composite of clinical and electrocardiographic criteria, and all analyzed patients underwent coronary angiography within 48 hours of symptom onset. Discrimination was assessed by receiver operating characteristic analysis, an exploratory optimal cutoff by the Youden index with bootstrap internal validation, and factors independently associated with failure by multivariable logistic regression. The score was also compared with the $CHADS_2$ and CHA_2DS_2-VASc scores.

Results

Thrombolysis failed in 91 patients (54.8%). The mean CHA_2DS_2-VASc-HS score was 4.54 ± 1.07 in the failed group and 2.52 ± 0.94 in the successful group (t = 12.98, P < 0.001). The area under the receiver operating characteristic curve was 0.933 (95% confidence interval (CI), 0.894-0.971), greater than those of the $CHADS_2$ score (0.845) and the CHA_2DS_2-VASc score (0.831) (P < 0.001 for both). A cutoff of ⩾4 gave the highest Youden index (0.819), with a sensitivity of 91.2% (95% CI, 83.6%-95.5%), specificity of 90.7% (95% CI, 82.0%-95.4%), and overall accuracy of 91.0%, with negligible optimism on bootstrap validation that repeated the cutoff selection. Results were similar when ST-segment resolution alone was used as the reference standard (area under the curve, 0.948). A conservative version of the score that excluded any diabetes or hyperlipidemia classification compatible with admission laboratory values had an area under the curve of 0.863. The score correlated inversely with angiographic TIMI flow grade (ρ = −0.70, P < 0.001).

Conclusions

In this single-center cohort of South Asian patients treated with streptokinase, a pretreatment CHA_2DS_2-VASc-HS score of 4 or more was strongly associated with failed thrombolysis and discriminated failure with high accuracy using information recorded at presentation, although admission laboratory values may have informed two of its components in some patients. The threshold is exploratory and requires external validation. Whether it can help to prioritize limited transfer capacity is a hypothesis that requires prospective evaluation.

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Keywords: bangladesh, cha2ds2-vasc-hs score, failed reperfusion, rescue percutaneous coronary intervention, risk stratification, st-elevation myocardial infarction, streptokinase, thrombolytic therapy

Introduction

Ischemic heart disease is still the largest single contributor to premature mortality worldwide, and modeling of Global Burden of Disease data indicates that its absolute toll will keep climbing until at least 2050, with almost all of that increment falling on low- and middle-income countries [1,2]. Bangladesh sits inside that shift. Ischemic heart disease is now the leading cause of death and of disability-adjusted life-years lost in the country, and the epidemic is expanding faster than the interventional capacity built to answer it [3].

That mismatch dictates how ST-elevation myocardial infarction (STEMI) is actually treated here. Contemporary European and North American guidelines place primary percutaneous coronary intervention (PCI) first whenever a wire can cross the culprit lesion within 120 minutes of diagnosis [4,5]. In Bangladesh, the small number of catheterization laboratories is concentrated in a few tertiary hospitals in Dhaka and two or three divisional cities, so most patients reach a non-PCI-capable facility first and the 120-minute window has usually closed before a transfer can even be arranged. Fibrinolysis, in the great majority of cases with streptokinase, the only agent most public hospitals can afford, therefore remains the default reperfusion strategy, a pattern repeated across low- and middle-income health systems [6].

Fibrinolysis, however, restores normal epicardial flow in only a proportion of occluded arteries, and failure is both common and consequential. Roughly a third to a half of treated patients do not reperfuse, and they sustain larger infarcts, poorer left ventricular function, more heart failure, and higher mortality than patients in whom the artery opens [7,8]. The established remedy is rescue PCI, and its benefit is steeply time-dependent [9]. Current European and North American guidelines recommend transfer of every patient to a PCI-capable center immediately after fibrinolysis, with rescue PCI when reperfusion fails and routine angiography within 2 to 24 hours when it succeeds [4,5]. Where transfer capacity is limited, however, this is not always achievable, and in practice the urgency of transfer is often decided by the outcome of fibrinolysis. Failure is recognized retrospectively, from ST-segment resolution on an electrocardiogram recorded 90 minutes after the infusion has begun. Where the referral center may be three or four hours away by road, waiting ninety minutes before deciding that rescue PCI is needed adds to the delay that rescue PCI is meant to shorten. A clinician at the bedside before the infusion starts has no validated instrument with which to estimate whether fibrinolysis is likely to fail in a particular patient.

Established risk scores do not fill that gap. The TIMI risk score for STEMI [10] can be calculated at the bedside from age, a history of diabetes, hypertension or angina, systolic blood pressure, heart rate, Killip class, body weight, anterior ST elevation or left bundle branch block, and time to treatment, whereas the GRACE score [11] also requires serum creatinine and cardiac biomarker status. Both, however, were derived to predict death rather than reperfusion failure, and neither was designed to identify the patient in whom fibrinolysis will not open the infarct-related artery. The CHA2DS2-VASc-HS score is a plausible alternative. Cetin and colleagues modified the familiar CHA2DS2-VASc score by reversing its sex weighting and adding hyperlipidemia and smoking, and showed that the resulting score tracked the angiographic severity of coronary artery disease [12]. Although the parent CHA2DS2-VASc score was developed to estimate the risk of stroke in atrial fibrillation, its components, namely heart failure, hypertension, age, diabetes, vascular disease and previous thromboembolism, are also markers of atherosclerotic burden, endothelial dysfunction, impaired fibrinolysis and microvascular disease, and the HS modification was designed specifically for patients with coronary artery disease [12]. The CHA2DS2-VASc-HS score is designed to be assembled from history and bedside examination and can be completed in under a minute, although the definitions of some of its components, such as diabetes and hyperlipidemia, also allow laboratory criteria. Related scores have since been examined in acute coronary syndromes, but most of this evidence concerns scores other than CHA2DS2-VASc-HS itself. The CHA2DS2-VASc-HSF score, which adds family history to the HS modification, has been linked to no-reflow after primary PCI [13], the parent CHA2DS2-VASc score to acute stent thrombosis [14], the CHA2DS2-VASc-HSF score to the angiographic severity of coronary disease, including in acute coronary syndromes [15-17], and the CHA2DS2-VASc score to spontaneous reperfusion in STEMI [18]. Direct evidence for the CHA2DS2-VASc-HS score in acute coronary syndromes therefore remains limited.

Its behavior before fibrinolysis, by contrast, rests on very little evidence, essentially a single dedicated study in a Turkish cohort [19]. No external validation exists in a South Asian population, even though South Asians develop coronary disease a decade earlier with a distinctive risk-factor profile, and even though this is exactly the population still treated with fibrinolysis first. We therefore assessed the diagnostic accuracy of the existing CHA2DS2-VASc-HS score, calculated before treatment, for failed thrombolysis in Bangladeshi patients with STEMI treated with streptokinase. As a secondary and exploratory aim, we examined which threshold best separated failed from successful thrombolysis in this cohort, recognizing that a threshold selected in this way requires validation in independent patients before it can inform decisions about transfer.

Materials And Methods

Study design and setting

This was a cross-sectional analytical study of diagnostic accuracy conducted in the Department of Cardiology, National Heart Foundation Hospital and Research Institute (NHFH&RI), Mirpur, Dhaka, Bangladesh, from February 2023 to January 2024. NHFH&RI is a tertiary referral cardiac center with a 24-hour catheterization laboratory that receives patients both directly and by referral from non-PCI-capable hospitals. Data were recorded prospectively on a predesigned data collection sheet at the time of admission and during the index hospitalization, and omissions were corrected by retaking the history or reexamining the patient. Primary PCI was not performed in the patients included in this study, and the reasons for choosing fibrinolysis in individual patients were not recorded on the study form. In Bangladesh, most of the cost of primary PCI is borne by patients, and fibrinolysis with streptokinase remains in common use even in hospitals that have a catheterization laboratory. The report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for observational studies [20].

Participants

During the study period, 219 patients with STEMI received streptokinase. Of these, 166 (75.8%) underwent coronary angiography during the index admission, met the eligibility criteria, and were enrolled by consecutive sampling for analysis. STEMI was diagnosed according to the prevailing European Society of Cardiology criteria: new ST-segment elevation at the J point in at least two contiguous leads, of ⩾ 2.5 mm in men younger than 40 years, ⩾ 2 mm in men aged 40 years or older, or ⩾ 1.5 mm in women in leads V2-V3, and/or ⩾ 1 mm in the other leads, in the absence of left ventricular hypertrophy or left bundle branch block [4].

Patients were excluded if they were not candidates for thrombolysis, received tenecteplase, underwent primary percutaneous coronary intervention, had known severe renal or hepatic disease, active infectious or inflammatory disease, previous or current malignancy or a known hematological disorder, or declined consent. A minimum sample size of 137 was calculated for a diagnostic accuracy study using the reported sensitivity and specificity of a high CHA2DS2-VASc-HS score for failed reperfusion, an assumed prevalence of failure of 40%, 95% confidence, and a desired precision of 0.1; 166 eligible patients were enrolled during the study period, and all were included in the analysis. The flow of participants is shown in Figure *1*. The 53 patients (24.2%) who were not analyzed either did not undergo coronary angiography during the index admission or met one or more of the exclusion criteria listed above, and the individual reasons were not recorded separately. Because correlation of the outcome of thrombolysis with angiographic TIMI flow grade was a specific objective of the study, coronary angiography during the index admission was an inclusion criterion, and study data were collected only for enrolled patients, so patients without angiography could not be added to the analysis of the clinical and electrocardiographic outcome. All patients received streptokinase at NHFH&RI, where the score was calculated on admission, so no patient had received fibrinolysis before scoring.

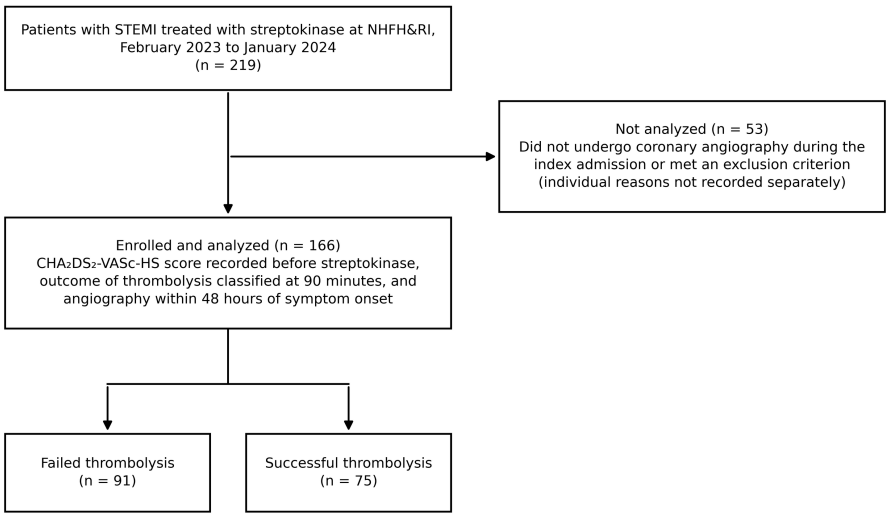


FIGURE 1: Flow of participants through the study.

STEMI, ST-elevation myocardial infarction; NHFH&RI, National Heart Foundation Hospital and Research Institute

Index test: the CHA_2DS_2-VASc-HS score

The CHA_2DS_2-VASc-HS score was calculated for every patient in the emergency room before the streptokinase infusion was connected by a clinician who was necessarily aware of the patient's history but could not know the outcome of thrombolysis, which is determined only 90 minutes later. One point each was assigned for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65-74 years, male sex, hyperlipidemia, and current smoking, and two points each for age ⩾75 years and previous stroke, transient ischemic attack, or thromboembolism, giving a possible range of 0 to 11 [12]. The components were recorded from the history obtained from the patient or accompanying relatives, previous medical records, current treatment, and the bedside examination, and the score was calculated clinically before the infusion was started. Because the definitions of diabetes mellitus and hyperlipidemia given below also include laboratory criteria, admission laboratory values may have contributed to the classification of these two components in patients without a previously known diagnosis. The study form recorded whether each component was present, but it did not record whether a diagnosis of diabetes mellitus or hyperlipidemia had been documented before admission or was first assigned during the admission, nor did it record the time at which admission laboratory results were reported. We therefore cannot establish for every patient that these two components were based only on information available before the streptokinase infusion was started. All other components were based on the history, previous medical records, current treatment, and bedside examination. The extent of this uncertainty was examined in the sensitivity analyses described below. Omissions were corrected by retaking the history, so that no component was missing. For the analysis, the total score of every patient was computed from the recorded components according to the weights above.

Congestive heart failure was defined as clinical heart failure on admission, operationalized as Killip class II or above [21]. This definition was chosen because left ventricular ejection fraction was not known before thrombolysis, so a definition based on echocardiography, such as the ejection fraction below 40% used by Kilic and colleagues [19], could not have been applied at the time of scoring. The component therefore reflects acute clinical severity at presentation rather than chronic heart failure. Hypertension was defined as a systolic blood pressure ⩾140 mmHg and/or a diastolic blood pressure ⩾90 mmHg on repeated office measurements before the index event, or the use of antihypertensive medication. Diabetes mellitus was defined by American Diabetes Association criteria [22] or the use of glucose-lowering therapy. Hyperlipidemia was defined as a low-density lipoprotein cholesterol concentration ⩾160 mg/dL or the use of lipid-lowering medication. Smoking was defined as more than 10 cigarettes daily for at least one year without a quit attempt. Vascular disease comprised previous myocardial infarction, angiographically significant coronary artery disease documented before the index event, peripheral arterial disease, or aortic plaque. The angiogram of the index admission was not used for this component, as reflected in its prevalence of 10.2% in a cohort in which every patient had an infarct-related artery on angiography.

Reference standard: outcome of thrombolysis

All patients received intravenous streptokinase 1.5 million units over one hour. All patients also received dual antiplatelet therapy with aspirin and clopidogrel, a statin, and low-molecular-weight heparin according to the institutional protocol, but the timing and doses of these drugs were not recorded on the study form. A 12-lead electrocardiogram (10 mm/mV, 25 mm/s) was recorded on admission and again 90 minutes after the start of the infusion. Thrombolysis was classified as successful when at least two of three criteria were met, namely, reduction of chest pain, resolution of ST-segment elevation by more than 50% in the lead showing maximal elevation, and the appearance of reperfusion arrhythmia. Patients not meeting these criteria were classified as having failed thrombolysis. This two-of-three rule was the composite definition specified in the study protocol, and it differs from definitions based on ST-segment resolution alone. Resolution of ST-segment elevation by less than 50% at 60-90 minutes is the electrocardiographic criterion for failed fibrinolysis in current guidelines [4], and the accuracy of ST-segment resolution and symptom resolution as markers of reperfusion has been assessed against angiography [23]. Reduction of chest pain was based on the patient's report at 90 minutes compared with before the infusion. Reperfusion arrhythmia comprised premature ventricular contractions, accelerated idioventricular rhythm, or nonsustained ventricular tachycardia occurring after the start of the infusion. Reperfusion arrhythmia was recorded as present or absent, and its time of onset relative to the 90-minute assessment was not recorded on the study form. Electrocardiograms were reported, and the outcome of thrombolysis was classified by cardiologists who did not participate in the calculation of the score, but formal blinding of these assessors to the score was not documented.

Coronary angiography

Coronary angiography was performed during the index hospitalization, within 48 hours of the onset of chest pain. TIMI flow grade was taken from the diagnostic coronary angiogram. The exact interval from the start of streptokinase to angiography, and the number and timing of rescue PCI procedures, were not recorded on the study form. Flow in the infarct-related artery was graded by the TIMI classification: grade 0, no antegrade flow beyond the point of occlusion; grade 1, faint antegrade flow with incomplete filling of the distal bed; grade 2, complete but delayed filling of the distal bed; and grade 3, prompt and complete filling [24]. Angiograms were assessed by experienced interventional cardiologists, with a third operator adjudicating disagreement by consensus. Formal blinding of the angiogram readers to the score and to the clinical classification of reperfusion was not documented. Because angiography was performed some hours after the 90-minute assessment, flow grade at angiography may also reflect delayed reperfusion, reocclusion,

or intervening treatment, and it was therefore treated as supportive information rather than as confirmation of reperfusion status at 90 minutes.

Other measurements

Demographic data, cardiovascular risk factors, the interval between the onset of chest pain and the start of thrombolysis (pain-to-needle time), Killip class, blood pressure, body mass index, and infarct location were recorded on a predesigned data collection sheet. Venous blood was drawn on admission for glycated hemoglobin, serum creatinine, troponin I, a fasting lipid profile, and N-terminal pro-B-type natriuretic peptide. Transthoracic echocardiography was performed during the index admission, and left ventricular ejection fraction was measured by the modified Simpson method.

Statistical analysis

SPSS software (Version 22.0, IBM Corp., Armonk, NY) was used for the analysis. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared using the Welch t-test or Mann-Whitney U test. Frequencies and percentages were used to describe categorical variables, which were compared using the chi-square or Fisher's exact test. Logistic regression was performed using three models: Model 1 (pain-to-needle time, anterior infarct location, body mass index, and serum creatinine), Model 2 (Model 1 plus the CHA_2DS_2-VASc-HS score), and Model 3 (the score with the two covariates that remained significant in Model 1). Discrimination was assessed by receiver operating characteristic analysis. The exploratory cutoff was identified using the Youden index and validated with 2,000 bootstrap samples (Python 3.10, Python Software Foundation (PSF), Wilmington, DE). Comparisons with the $CHADS_2$ and CHA_2DS_2-VASc scores were performed using the DeLong method. Sensitivity analyses used ST-segment resolution alone as the reference standard, the score without hyperlipidemia with and without diabetes, a conservative version excluding laboratory-compatible diabetes and hyperlipidemia classifications, and reclassification of up to three failed patients. Spearman correlation was used to assess the relationship between the score and TIMI flow grade. Missing values were not imputed. Statistical significance was set at $P < 0.05$.

Ethical consideration

The study protocol was approved by the Ethical Review Committee of the National Heart Foundation Hospital and Research Institute (approval no. NHFH&RI/4-14/7/AD/432). Written informed consent was obtained from every participant or, when the clinical condition precluded this, from an accompanying relative. Enrollment did not alter treatment, and no patient experienced any delay in thrombolysis as a result of participation.

Results

Among the 166 patients included in the analysis, thrombolysis failed in 91 patients (54.8%) and succeeded in 75 (45.2%). The baseline demographic and clinical characteristics of the two groups are summarized in Table *1*. The mean age of the cohort was 54.64 ± 11.21 years, 136 patients (81.9%) were men, and 41 (24.7%) were aged 65 years or older. Hypertension was the most common risk factor (105 patients, 63.3%), followed by diabetes mellitus (97, 58.4%), current smoking (66, 39.8%), a family history of premature coronary artery disease (58, 34.9%), and hyperlipidemia (54, 32.5%). On arrival, 95 patients (57.2%) were in Killip class I, and 46 (27.7%) were in Killip class III or IV. The mean pain-to-needle time was 5.88 ± 2.90 hours, and 82 patients (49.4%) had an anterior infarct.

Variable	Failed thrombolysis (*n* = 91)	Successful thrombolysis (*n* = 75)	Test statistic	*P*-value
Age (years), mean ± SD	57.09 ± 11.77	51.67 ± 9.77	$t = 3.24$	0.001
Age ≥ 65 years, *n* (%)	32 (35.2)	9 (12.0)	$\chi^2 = 10.65$	0.001[a]
Male sex, *n* (%)	77 (84.6)	59 (78.7)	$\chi^2 = 0.62$	0.430[a]
Body mass index (kg/m²), mean ± SD	27.84 ± 5.30	24.30 ± 2.46	$t = 5.67$	<0.001
Diabetes mellitus, *n* (%)	65 (71.4)	32 (42.7)	$\chi^2 = 12.84$	<0.001[a]
Hypertension, *n* (%)	75 (82.4)	30 (40.0)	$\chi^2 = 30.03$	<0.001[a]
Hyperlipidemia, *n* (%)	41 (45.1)	13 (17.3)	$\chi^2 = 13.16$	<0.001[a]
Current smoking, *n* (%)	40 (44.0)	26 (34.7)	$\chi^2 = 1.12$	0.290[a]
Family history of premature CAD, *n* (%)	32 (35.2)	26 (34.7)	$\chi^2 = 0.00$	1.000[a]
Vascular disease, *n* (%)	13 (14.3)	4 (5.3)	$\chi^2 = 2.68$	0.102[a]
Previous stroke/TIA, *n* (%)	4 (4.4)	1 (1.3)	NA	0.379[b]
Congestive heart failure (Killip ≥ II), *n* (%)	57 (62.6)	14 (18.7)	$\chi^2 = 30.70$	<0.001[a]
Pain-to-needle time (h), mean ± SD	6.70 ± 2.97	4.90 ± 2.48	$t = 4.26$	<0.001
Systolic blood pressure (mmHg), mean ± SD	108.23 ± 21.96	107.15 ± 19.92	$t = 0.33$	0.741
Diastolic blood pressure (mmHg), mean ± SD	87.06 ± 25.12	79.86 ± 16.92	$t = 2.18$	0.031
Killip class I, *n* (%)	34 (37.4)	61 (81.3)	NA	<0.001[b]
Killip class II, *n* (%)	16 (17.6)	9 (12.0)		
Killip class III, *n* (%)	38 (41.8)	4 (5.3)		
Killip class IV, *n* (%)	3 (3.3)	1 (1.3)		
Anterior infarct location, *n* (%)	54 (59.3)	28 (37.3)	$\chi^2 = 7.11$	0.008[a]
Pathological Q wave on admission ECG, *n* (%)	22 (24.2)	5 (6.7)	$\chi^2 = 8.01$	0.005[a]

TABLE 1: Baseline demographic and clinical characteristics of the study population according to the outcome of thrombolysis (N = 166).

Continuous variables were compared using the independent-samples t-test (t statistic).

[a]Chi-square test with Yates continuity correction (χ^2 statistic).

[b]Fisher's exact test. Blood pressure was not recorded in two patients, one in each group.

CAD, coronary artery disease; TIA, transient ischemic attack; ECG, electrocardiogram; SD, standard deviation; NA, not applicable because the Fisher exact test does not yield a test statistic

Compared with patients whose thrombolysis succeeded, those in whom it failed were older (57.09 ± 11.77 vs. 51.67 ± 9.77 years, $t = 3.24$, $P = 0.001$), more often aged 65 years or older (35.2% vs. 12.0%, $\chi^2 = 10.65$, $P = 0.001$), had a higher body mass index (27.84 ± 5.30 vs. 24.30 ± 2.46 kg/m², $t = 5.67$, $P < 0.001$), and presented later after symptom onset (6.70 ± 2.97 vs. 4.90 ± 2.48 hours, $t = 4.26$, $P < 0.001$). Diabetes mellitus (71.4% vs. 42.7%), hypertension (82.4% vs. 40.0%), hyperlipidemia (45.1% vs. 17.3%), and Killip class II or above (62.6% vs. 18.7%) were all more frequent in the failed group ($\chi^2 = 12.84$, 30.03, 13.16, and 30.70, respectively; $P < 0.001$ for each). Anterior infarct location (59.3% vs. 37.3%, $\chi^2 = 7.11$, $P = 0.008$) and a pathological Q wave on the admission electrocardiogram (24.2% vs. 6.7%, $\chi^2 = 8.01$, $P = 0.005$) were also more common among

patients whose thrombolysis failed, and their diastolic blood pressure was modestly higher (87.06 ± 25.12 vs. 79.86 ± 16.92 mmHg, $t = 2.18$, $P = 0.031$). Male sex, current smoking, family history of premature coronary artery disease, vascular disease, previous stroke or transient ischemic attack, and systolic blood pressure did not differ significantly between the groups.

The laboratory, electrocardiographic, and echocardiographic findings are presented in Table 2. Serum creatinine was higher in the failed group than in the successful group (1.49 ± 0.86 vs. 1.26 ± 0.36 mg/dL, $t = 2.31$, $P = 0.022$), and NT-proBNP was nearly three times as high, with a median of 2100 pg/mL (interquartile range, 1,382-2,825) vs. 720 pg/mL (interquartile range, 379-998) ($U = 5,446$, $P < 0.001$). Left ventricular ejection fraction was about five percentage points lower in patients whose thrombolysis failed (39.32 ± 6.18% vs. 44.28 ± 5.19%, $t = -5.62$, $P < 0.001$). Glycated hemoglobin, troponin I, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides did not differ significantly between the groups. Regional wall motion abnormality was present in every patient and therefore could not discriminate between them. ST-segment resolution of more than 50% at 90 minutes was recorded in 74 patients (44.6%) and, as expected from its role in the reference standard, was almost entirely confined to the successful group (97.3% vs. 1.1%, $\chi^2 = 150.25$, $P < 0.001$). Reduction of chest pain after streptokinase, by contrast, occurred in 162 patients (97.6%), did not differ between the groups (98.7% vs. 96.7%, $P = 0.628$), and therefore carried no discriminatory value in this cohort. A reperfusion arrhythmia was recorded in 30 patients (18.1%), including 3 (3.3%) in the failed group and 27 (36.0%) in the successful group ($P < 0.001$) (Table 2).

Variable	Failed thrombolysis (*n* = 91)	Successful thrombolysis (*n* = 75)	Test statistic	*P*-value
HbA1c (%)	7.66 ± 2.14	7.11 ± 1.98	$t = 1.72$	0.087
Serum creatinine (mg/dL)	1.49 ± 0.86	1.26 ± 0.36	$t = 2.31$	0.022
Troponin I (ng/mL)	42.17 ± 22.35	41.38 ± 25.72	$t = 0.21$	0.836
Total cholesterol (mg/dL)	198.57 ± 55.17	196.35 ± 44.67	$t = 0.29$	0.774
LDL cholesterol (mg/dL)	126.15 ± 42.35	122.27 ± 33.55	$t = 0.66$	0.510
HDL cholesterol (mg/dL)	40.23 ± 9.66	45.19 ± 39.32	$t = −1.07$	0.290
Triglyceride (mg/dL)	197.62 ± 154.47	177.61 ± 140.98	$t = 0.87$	0.385
Left ventricular ejection fraction (%)	39.32 ± 6.18	44.28 ± 5.19	$t = −5.62$	<0.001
NT-proBNP (pg/mL), median (IQR)	2,100 (1,382-2,825)	720 (379-998)	$U = 5446$	<0.001[c]
ST-segment resolution > 50% at 90 min, *n* (%)	1 (1.1)	73 (97.3)	$\chi^2 = 150.25$	<0.001[a]
Reduction of chest pain after streptokinase, *n* (%)	88 (96.7)	74 (98.7)	NA	0.628[b]
Reperfusion arrhythmia, *n* (%)	3 (3.3)	27 (36.0)	NA	<0.001[b]

TABLE 2: Laboratory, electrocardiographic, and echocardiographic findings according to the outcome of thrombolysis (N = 166).

Values are mean ± SD unless stated otherwise. Reperfusion arrhythmia comprised premature ventricular contractions, accelerated idioventricular rhythm, or nonsustained ventricular tachycardia. Reperfusion arrhythmia was recorded as present or absent, and its time of onset relative to the 90-minute assessment was not recorded.

[a]Chi-square test with Yates continuity correction (χ^2 statistic).

[b]Fisher's exact test.

[c]Mann-Whitney U test; remaining comparisons by independent-samples t-test.

HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; IQR, interquartile range; NA, not applicable because the Fisher's exact test does not yield a test statistic; t, t statistic; U, Mann-Whitney U statistic

At the patient level, all 72 patients (43.4%) with both reduction of chest pain and ST-segment resolution were in the successful group, whereas 88 of the 90 patients (97.8%) with reduction of chest pain alone, one of

the two patients (50.0%) with ST-segment resolution alone, and both patients (100%) with neither finding were in the failed group. Because the time of onset of arrhythmia was not recorded, between one and three of the arrhythmias in the failed group may have occurred after the 90-minute assessment or may reflect misclassification; this was examined in a sensitivity analysis. Because nearly all patients reported a reduction in chest pain, the classification of thrombolysis was determined largely by ST-segment resolution.

The distribution of the CHA_2DS_2-VASc-HS score and its individual components according to the outcome of thrombolysis is shown in Table 3. The total score was computed from the recorded components for every patient. The mean score for the whole cohort was 3.63 ± 1.42. It was 4.54 ± 1.07 in patients whose thrombolysis failed and 2.52 ± 0.94 in those in whom it succeeded, a difference of 2.02 points (t = 12.98, P < 0.001). Among the components, congestive heart failure (62.6% vs. 18.7%), hypertension (82.4% vs. 40.0%), diabetes mellitus (71.4% vs. 42.7%), and hyperlipidemia (45.1% vs. 17.3%) were each significantly more frequent in the failed group (χ^2 = 30.70, 30.03, 12.84, and 13.16, respectively; P < 0.001 for each), as was age 65-74 years (29.7% vs. 12.0%, χ^2 = 6.55, P = 0.010). Age 75 years or older was recorded only in the failed group (5 patients, 5.5%), although the difference did not reach statistical significance (P = 0.065). Male sex, smoking, vascular disease, and previous stroke, transient ischemic attack, or thromboembolism were not significantly associated with the outcome.

Component/score	Failed thrombolysis (*n* = 91)	Successful thrombolysis (*n* = 75)	Test statistic	*P*-value
Congestive heart failure (C)	57 (62.6)	14 (18.7)	χ^2 = 30.70	<0.001[a]
Hypertension (H)	75 (82.4)	30 (40.0)	χ^2 = 30.03	<0.001[a]
Age ≥ 75 years (A_2)	5 (5.5)	0 (0.0)	NA	0.065[b]
Diabetes mellitus (D)	65 (71.4)	32 (42.7)	χ^2 = 12.84	<0.001[a]
Previous stroke/TIA/thromboembolism (S_2)	4 (4.4)	1 (1.3)	NA	0.379[b]
Vascular disease (V)	13 (14.3)	4 (5.3)	χ^2 = 2.68	0.102[a]
Age 65-74 years (A)	27 (29.7)	9 (12.0)	χ^2 = 6.55	0.010[a]
Male sex (Sc)	77 (84.6)	59 (78.7)	χ^2 = 0.62	0.430[a]
Hyperlipidemia (H)	41 (45.1)	13 (17.3)	χ^2 = 13.16	<0.001[a]
Smoking (S)	40 (44.0)	26 (34.7)	χ^2 = 1.12	0.290[a]
Total score, mean ± SD	4.54 ± 1.07	2.52 ± 0.94	t = 12.98	<0.001

TABLE 3: Distribution of CHA2DS2-VASc-HS score components and total score according to the outcome of thrombolysis (N = 166).

Values are *n* (%) unless stated otherwise. NA, not applicable because the Fisher's exact test does not yield a test statistic. Congestive heart failure was defined as Killip class II or above on admission.

[a]Chi-square test with Yates continuity correction (χ^2 statistic).

[b]Fisher's exact test; total score compared by independent-samples t-test (t statistic).

TIA, transient ischemic attack

Receiver operating characteristic analysis showed that the pretreatment CHA_2DS_2-VASc-HS score discriminated failed from successful thrombolysis, with an area under the curve of 0.933 (95% CI, 0.894-0.971; P < 0.001) (Figure 2). The point of best balance between sensitivity and specificity was at a score of 4, where sensitivity was 91.2% and the false-positive rate was 9.3%.

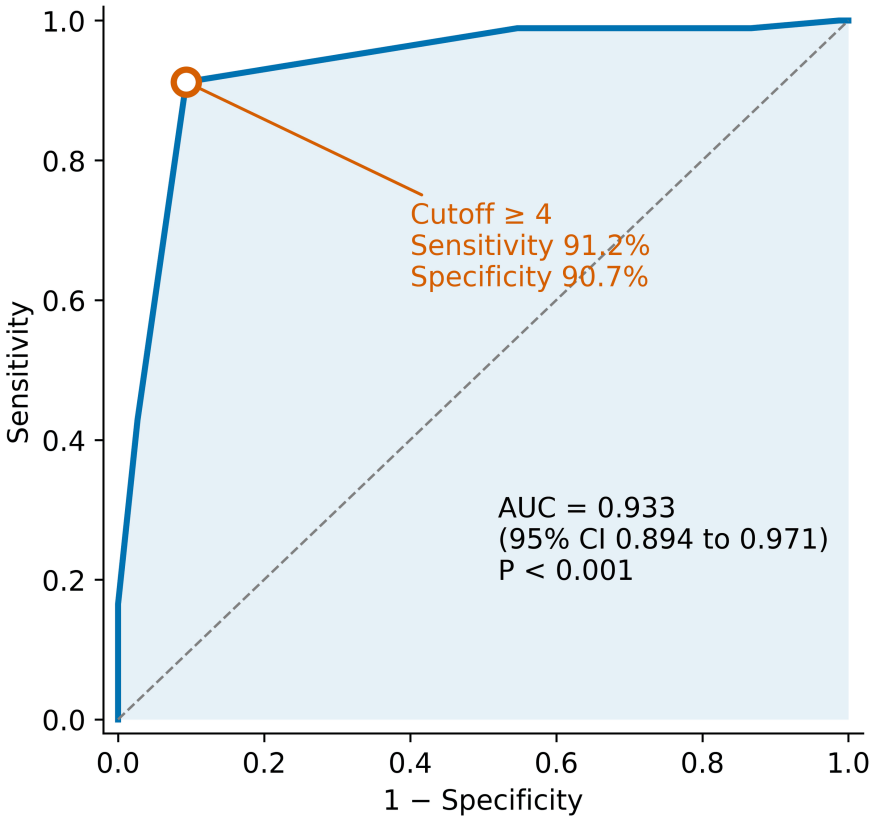


FIGURE 2: Receiver operating characteristic curve for the pretreatment CHA2DS2-VASc-HS score in predicting failed thrombolysis (N = 166).

The circle marks the cutoff of ≥4 identified by the Youden index.

The diagnostic performance of the score at successive cutoff values is shown in Table 4. Lower thresholds favored sensitivity at the expense of specificity, so that a cutoff of ⩾3 identified 90 of the 91 patients whose thrombolysis failed (sensitivity, 98.9%) but was only 45.3% specific. Higher thresholds did the reverse, and a cutoff of ⩾5 was 97.3% specific but only 42.9% sensitive. The threshold of ⩾4 maximized the Youden index at 0.819, with a sensitivity of 91.2% (95% CI, 83.6%-95.5%), a specificity of 90.7% (95% CI, 82.0%-95.4%), a positive predictive value of 92.2% (95% CI, 84.8%-96.2%), a negative predictive value of 89.5% (95% CI, 80.6%-94.6%), and an overall accuracy of 91.0% (95% CI, 85.6%-94.4%). The corresponding positive and negative likelihood ratios were 9.8 and 0.10. At this threshold, 151 of the 166 patients (91.0%) were classified correctly. Seven of the 90 patients (7.8%) with a score of 4 or more reperfused, and eight of the 76 patients (10.5%) with a score below 4 did not. In bootstrap internal validation, in which the cutoff was selected afresh in each of 2,000 bootstrap samples, a cutoff of ⩾4 was selected in every sample, and the optimism-corrected sensitivity (91.3%), specificity (90.6%), and accuracy (91.0%) were virtually identical to the apparent estimates.

Cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, %	Youden index
≥2	98.9 (94.0-99.8)	13.3 (7.4-22.8)	58.1 (50.2-65.5)	90.9 (62.3-98.4)	60.2	0.122
≥3	98.9 (94.0-99.8)	45.3 (34.6-56.6)	68.7 (60.3-76.0)	97.1 (85.5-99.5)	74.7	0.442
≥4	91.2 (83.6-95.5)	90.7 (82.0-95.4)	92.2 (84.8-96.2)	89.5 (80.6-94.6)	91.0	0.819
≥5	42.9 (33.2-53.1)	97.3 (90.8-99.3)	95.1 (83.9-98.7)	58.4 (49.6-66.7)	67.5	0.402
≥6	16.5 (10.3-25.4)	100.0 (95.1-100.0)	100.0 (79.6-100.0)	49.7 (41.8-57.6)	54.2	0.165

TABLE 4: Diagnostic performance of the CHA2DS2-VASc-HS score for failed thrombolysis at successive cutoff values (N = 166).

The cutoff of ≥4 yielded the maximum Youden index.

CI, confidence interval (Wilson score method); PPV, positive predictive value; NPV, negative predictive value

The proportion of patients with failed thrombolysis at each value of the score is shown in Figure 3. Failure occurred in 1 of the 35 patients (2.9%) with a score of 0 to 2 and in 7 of the 41 patients (17.1%) with a score of 3. Above the cutoff, the proportion rose abruptly, with failure in 44 of 49 patients (89.8%) with a score of 4, in 24 of 26 patients (92.3%) with a score of 5, and in all 15 patients (100%) with a score of 6 or more. Overall, 83 of the 90 patients (92.2%) with a score of 4 or more failed to reperfuse, compared with 8 of the 76 patients (10.5%) with a score below 4.

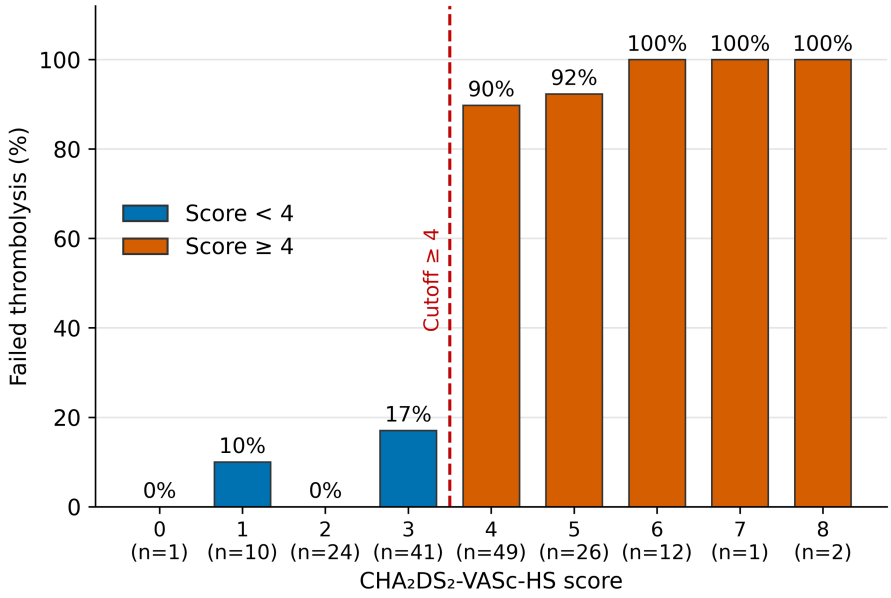


FIGURE 3: Proportion of patients with failed thrombolysis at each value of the CHA2DS2-VASc-HS score.

The dashed line marks the cutoff of ≥4.

The results of univariable and multivariable logistic regression for failed thrombolysis are presented in Table 5. In univariable analysis, pain-to-needle time (odds ratio, 1.26 per hour; 95% CI, 1.12-1.42; Wald $\chi^2 = 14.82$), body mass index (odds ratio, 1.47 per kg/m^2; 95% CI, 1.28-1.70; Wald $\chi^2 = 28.17$), age (odds ratio, 1.05 per year; 95% CI, 1.02-1.08; Wald $\chi^2 = 9.22$), anterior infarct location (odds ratio, 2.45; 95% CI, 1.31-4.59; Wald $\chi^2 = 7.83$), pathological Q wave (odds ratio, 4.46; 95% CI, 1.60-12.46; Wald $\chi^2 = 8.16$), and serum creatinine (odds ratio, 2.53 per mg/dL; 95% CI, 1.01-6.36; Wald $\chi^2 = 3.93$) were each significantly associated with failed thrombolysis, whereas male sex was not (Wald $\chi^2 = 0.98$, $P = 0.323$). The multivariable model (Model 1) included pain-to-needle time, anterior infarct location, body mass index, and serum creatinine, none of which is a component of the CHA_2DS_2-VASc-HS score. In this model, a longer pain-to-needle time (adjusted

odds ratio, 1.27 per hour; 95% CI, 1.10-1.46; Wald χ^2 = 10.62, P = 0.001) and a higher body mass index (adjusted odds ratio, 1.42 per kg/m²; 95% CI, 1.23-1.64; Wald χ^2 = 23.02, P < 0.001) remained associated with failed thrombolysis after adjustment for the other variables in the model, whereas anterior infarct location (adjusted odds ratio, 1.80; 95% CI, 0.85-3.81; Wald χ^2 = 2.40, P = 0.121) and serum creatinine (adjusted odds ratio, 2.25; 95% CI, 0.87-5.82; Wald χ^2 = 2.80, P = 0.094) did not. The Nagelkerke pseudo R^2 of the model was 0.412, and the overall model was statistically significant (likelihood ratio χ^2 = 61.19, df = 4, P < 0.001). When the CHA_2DS_2-VASc-HS score was added to all four covariates (Model 2), its adjusted odds ratio was 10.11 per point (95% CI, 4.51-22.67, P < 0.001), pain-to-needle time (1.35 per hour; 95% CI, 1.07-1.72) and body mass index (1.42 per kg/m²; 95% CI, 1.13-1.80) remained associated, and anterior infarct location and serum creatinine did not (P = 0.481 and P = 0.170; Nagelkerke pseudo R^2 = 0.786). In the more parsimonious Model 3, which contained the score, pain-to-needle time, and body mass index, the corresponding adjusted odds ratios were 9.76 per point (95% CI, 4.47-21.32, P < 0.001), 1.29 per hour (95% CI, 1.03-1.62, P = 0.025), and 1.40 per kg/m² (95% CI, 1.12-1.75, P = 0.003) (Nagelkerke pseudo R^2 = 0.772). The area under the curve was 0.682 (95% CI, 0.602-0.763) for pain-to-needle time and 0.792 (95% CI, 0.725-0.860) for body mass index, and both were lower than that of the score (P < 0.001 for each).

Variable	Unadjusted OR (95% CI)	Wald χ^2	*P*-value	Adjusted OR (95% CI)	Wald χ^2	*P*-value
Pain-to-needle time (per hour)	1.26 (1.12-1.42)	14.82	<0.001	1.27 (1.10-1.46)	10.62	0.001
Anterior infarct location	2.45 (1.31-4.59)	7.83	0.005	1.80 (0.85-3.81)	2.40	0.121
Body mass index (per kg/m²)	1.47 (1.28-1.70)	28.17	<0.001	1.42 (1.23-1.64)	23.02	<0.001
Serum creatinine (per mg/dL)	2.53 (1.01-6.36)	3.93	0.048	2.25 (0.87-5.82)	2.80	0.094
Pathological Q wave	4.46 (1.60-12.46)	8.16	0.004	-	-	-
Age (per year)	1.05 (1.02-1.08)	9.22	0.002	-	-	-
Male sex	1.49 (0.67-3.30)	0.98	0.323	-	-	-

TABLE 5: Univariable and multivariable logistic regression analysis for failed thrombolysis (N = 166).

Wald χ^2 values have 1 degree of freedom. The adjusted ORs are from Model 1, which included pain-to-needle time, anterior infarct location, body mass index, and serum creatinine (Nagelkerke-type pseudo R^2 = 0.412; likelihood ratio χ^2 = 61.19, df = 4, P < 0.001). The CHA_2DS_2-VASc-HS score and its individual components were not entered in Model 1. The results of Model 2, in which the score was added to all four covariates, and Model 3, in which the score was added to pain-to-needle time and body mass index only, are reported in the text.

OR, odds ratio; CI, confidence interval

The angiographic TIMI flow grade in the infarct-related artery according to the outcome of thrombolysis and the score category is shown in Table *6*. Coronary angiography demonstrated TIMI 0 or 1 flow in 89 patients (53.6%), TIMI 2 flow in 23 (13.9%), and TIMI 3 flow in 54 (32.5%). Flow grade was strongly related to the outcome of thrombolysis (χ^2 = 151.57, df = 3, P < 0.001). Of the 91 patients whose thrombolysis failed, 88 (96.7%) had TIMI 0 or 1 flow and none had TIMI 3 flow, whereas 54 of the 75 patients (72.0%) with successful thrombolysis had TIMI 3 flow and only one (1.3%) had TIMI 0 or 1 flow. The score category showed a similar pattern. Among the 90 patients with a score of 4 or more, 82 (91.1%) had TIMI 0 or 1 flow and 5 (5.6%) had TIMI 3 flow, compared with 7 (9.2%) and 49 (64.5%), respectively, of the 76 patients with a score below 4 (χ^2 = 111.24, df = 3, P < 0.001).

TIMI flow grade	Total (*N* = 166)	Failed (*n* = 91)	Successful (*n* = 75)	χ² value	*P*-value	Score ≥ 4 (*n* = 90)	Score < 4 (*n* = 76)
TIMI 0	28 (16.9)	27 (29.7)	1 (1.3)	151.57	<0.001[a]	26 (28.9)	2 (2.6)
TIMI 1	61 (36.7)	61 (67.0)	0 (0.0)			56 (62.2)	5 (6.6)
TIMI 2	23 (13.9)	3 (3.3)	20 (26.7)			3 (3.3)	20 (26.3)
TIMI 3	54 (32.5)	0 (0.0)	54 (72.0)			5 (5.6)	49 (64.5)

TABLE 6: Angiographic TIMI flow grade in the infarct-related artery according to the outcome of thrombolysis and CHA2DS2-VASc-HS score category (N = 166).

Values are *n* (%).

[a]Chi-square test (χ² statistic with 3 degrees of freedom). The comparison of TIMI flow grade between score categories was also significant (χ² = 111.24, df = 3, *P* < 0.001).

TIMI, Thrombolysis in Myocardial Infarction

The relationship between the score and angiographic flow is illustrated in Figure 4. The CHA2DS2-VASc-HS score was inversely correlated with TIMI flow grade (Spearman ρ = −0.70, *P* < 0.001). Patients with TIMI 0 and TIMI 1 flow had mean scores of 4.57 ± 0.96 and 4.54 ± 1.12, respectively, with a median of 4 in both groups, whereas those with TIMI 2 and TIMI 3 flow had mean scores of 2.74 ± 1.01 and 2.48 ± 0.95, with a median of 3 in both groups. The interquartile ranges of the impaired-flow groups (TIMI 0 and 1) did not overlap with those of the restored-flow groups (TIMI 2 and 3), so that a higher pretreatment score was consistently associated with poorer flow in the infarct-related artery at the time of angiography.

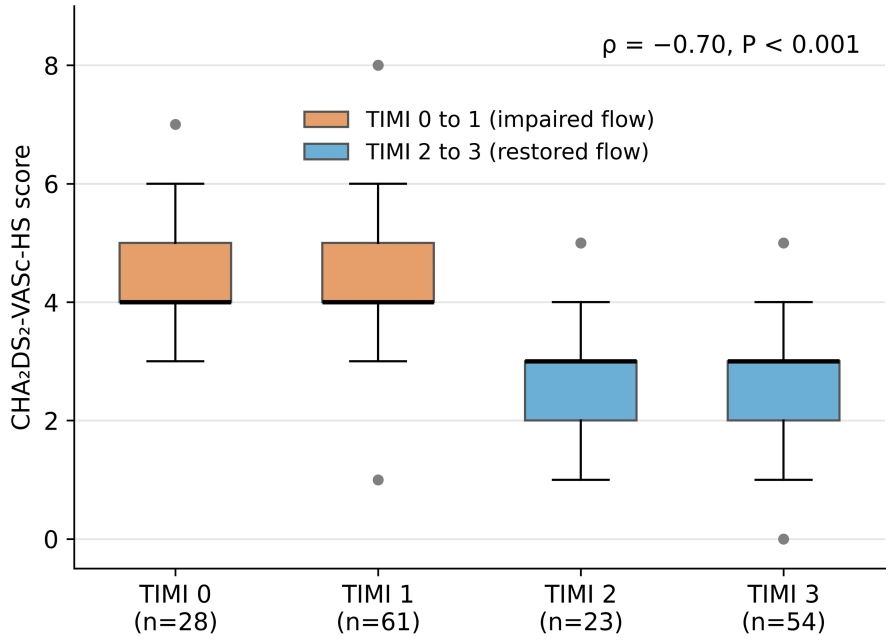


FIGURE 4: CHA2DS2-VASc-HS score according to angiographic TIMI flow grade in the infarct-related artery.

Boxes show the median and interquartile range; whiskers extend to 1.5 times the interquartile range.

TIMI, Thrombolysis In Myocardial Infarction

The discrimination of the CHA_2DS_2-VASc-HS score is compared with that of the $CHADS_2$ and CHA_2DS_2-VASc scores, and with the results of the sensitivity analyses, in Table 7. The $CHADS_2$ score discriminated

failed thrombolysis with an area under the curve of 0.845 (95% CI, 0.786-0.904), and its best cutoff of ⩾2 gave a sensitivity of 85.7% and a specificity of 69.3%. The CHA_2DS_2-VASc score had an area under the curve of 0.831 (95% CI, 0.770-0.893). The area under the curve of the CHA_2DS_2-VASc-HS score was significantly greater than that of the $CHADS_2$ score (difference, 0.088; $P < 0.001$) and that of the CHA_2DS_2-VASc score (difference, 0.101; $P < 0.001$). When the electrocardiographic criterion alone was used as the reference standard, three patients (1.8%) changed category (one failed patient with ST-segment resolution and two successful patients without it), and 92 patients (55.4%) were classified as having failed thrombolysis. The area under the curve was then 0.948 (95% CI, 0.915-0.982), the cutoff of ⩾4 again gave the highest Youden index, and sensitivity and specificity were 92.4% and 93.2%, respectively. This analysis does not depend on reperfusion arrhythmia. When up to three patients with failed thrombolysis were reclassified as successful, the area under the curve ranged from 0.895 to 0.949, and the cutoff of ⩾4 remained optimal, with a sensitivity of 90.9%-94.3% and a specificity of 87.2%-91.0%. When hyperlipidemia was removed from the score, the area under the curve was 0.900 (95% CI, 0.853-0.948), and when both hyperlipidemia and diabetes mellitus were removed, it was 0.853 (95% CI, 0.796-0.911). The classification of diabetes mellitus or hyperlipidemia was compatible with the admission laboratory values in 102 patients (61.4%). When all of these classifications were removed in the conservative history-only version, the area under the curve was 0.863 (95% CI, 0.807-0.918), lower than that of the full score ($P < 0.001$), and the best cutoff of ⩾3 gave a sensitivity of 84.6% and a specificity of 73.3%.

Score or analysis	Reference standard	AUC (95% CI)	Best cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	*P*-value*
CHA_2DS_2-VASc-HS	Composite	0.933 (0.894-0.971)	≥ 4	91.2 (83.6-95.5)	90.7 (82.0-95.4)	Reference
$CHADS_2$	Composite	0.845 (0.786-0.904)	≥ 2	85.7 (77.1-91.5)	69.3 (58.2-78.6)	<0.001
CHA_2DS_2-VASc	Composite	0.831 (0.770-0.893)	≥ 3	67.0 (56.9-75.8)	86.7 (77.2-92.6)	<0.001
CHA_2DS_2-VASc-HS without hyperlipidemia	Composite	0.900 (0.853-0.948)	≥ 4	72.5 (62.6-80.6)	93.3 (85.3-97.1)	0.016
CHA_2DS_2-VASc-HS without hyperlipidemia and diabetes	Composite	0.853 (0.796-0.911)	≥ 3	80.2 (70.9-87.1)	78.7 (68.1-86.4)	<0.001
CHA_2DS_2-VASc-HS, conservative history only version	Composite	0.863 (0.807-0.918)	≥ 3	84.6 (75.8-90.6)	73.3 (62.4-82.0)	<0.001
CHA_2DS_2-VASc-HS	ST-segment resolution alone	0.948 (0.915-0.982)	≥ 4	92.4 (85.1-96.3)	93.2 (85.1-97.1)	NA

TABLE 7: Discrimination of the CHA2DS2-VASc-HS score compared with the CHADS2 and CHA2DS2-VASc scores, and sensitivity analyses (N = 166).

The composite reference standard required at least two of the following three criteria: reduction of chest pain, ST-segment resolution >50%, and reperfusion arrhythmia at 90 minutes. Confidence intervals for the area under the curve were calculated using the Hanley and McNeil method, and those for sensitivity and specificity using the Wilson score method. The best cutoff was the value with the highest Youden index. The conservative history-only version counted diabetes mellitus only when the admission HbA1c was below 6.5% and hyperlipidemia only when the admission low-density lipoprotein cholesterol was below 160 mg/dL.

*Comparison of the area under the curve with that of the CHA2DS2-VASc-HS score against the same reference standard (DeLong test).

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NA, not applicable because the reference standard differs

Discussion

In this consecutive series of 166 Bangladeshi patients thrombolyzed with streptokinase for STEMI, a score recorded at presentation from the history, previous medical records, and bedside examination separated those who reperfused from those who did not with an accuracy that we did not anticipate. The CHA2DS2-VASc-HS score was about two points higher in the failed group, discriminated with an area under the curve of 0.933, and at a threshold of four correctly classified 151 of 166 patients (91.0%). Because the score is intended to be completed before the infusion is connected, this information could be available 90 minutes earlier than the electrocardiographic assessment. However, the threshold was selected in this cohort; its performance in independent patients remains to be established, and admission laboratory values may have

informed two of its components in some patients, as discussed below.

In the largest previous study to test this score against fibrinolytic failure, Alıcı et al. identified a lower optimal cutoff of 3 and reported more modest discrimination, with an area under the curve of 0.764 [18]. Several differences between the two studies may contribute to this gap. Streptokinase, a non-fibrin-specific agent with lower patency rates than tenecteplase, was given to every patient, so the biological signal separating responders from nonresponders may be wider. Presentation was also late, at a median pain-to-needle interval of six hours, and the accumulated risk burden the score measures is most damaging when the artery has been occluded longest. The component definitions also differed. Kilic et al. defined heart failure as an ejection fraction below 40%, whereas we used Killip class II or above at admission, which captures acute clinical severity during the index infarction and was the only measure of heart failure available before thrombolysis. The definitions of hyperlipidemia and smoking also differed between the studies [19]. Because Killip class is itself a strong correlate of infarct size and adverse outcome, its inclusion may have contributed to the higher area under the curve in our cohort, together with differences in case mix, so that the two estimates are not directly comparable. Our findings sit alongside work showing that the related CHA2DS2-VASc-HSF score predicts no-reflow after primary PCI, grades coronary disease severity, and forecasts slow flow during rotational atherectomy [13,15,16,25], and alongside Bangladeshi data linking the score to adverse in-hospital outcomes after non-ST-elevation infarction [26].

The $CHADS_2$ score, which contains five of the same items, also discriminated failed thrombolysis in our cohort, which is consistent with the greater prevalence of older age, heart failure, hypertension, and diabetes among patients whose thrombolysis failed. Its simplicity makes it attractive as a screening tool in resource-limited settings such as Bangladesh. However, its area under the curve was significantly lower than that of the CHA_2DS_2-VASc-HS score, and at its best cutoff it misclassified almost one third of the patients whose thrombolysis succeeded. The additional items of the CHA_2DS_2-VASc-HS score, namely, hyperlipidemia, smoking, male sex, age 65 to 74 years, and vascular disease, are equally available at the bedside, so the gain in discrimination comes at little practical cost. Both scores nevertheless require validation in independent cohorts before either can be recommended for clinical use.

Why a tally of clinical comorbidities should forecast the fate of pharmacological clot lysis deserves comment, because the components are not arbitrary. Each may plausibly oppose reperfusion. Diabetes produces a hypofibrinolytic state through elevated plasminogen activator inhibitor-1 and a densely packed, lysis-resistant fibrin network [27]. It was present in 71.4% of failures here. Hypertension remodels the coronary microcirculation, so that even a recanalized epicardial artery may not perfuse the myocardium [28]. Hyperlipidemia enlarges thrombus burden, smoking and age compound endothelial dysfunction, and clinical heart failure at presentation signals a ventricle with little reserve. We therefore hypothesize that the score acts in part as a bedside summary of microvascular vulnerability, a view that accords with contemporary accounts of microvascular obstruction as a major barrier to myocardial reperfusion [29]. This interpretation remains a hypothesis, because the study did not measure microvascular function or obstruction. Angiographic TIMI flow grade describes epicardial patency rather than myocardial tissue reperfusion, so the inverse correlation between the score and TIMI flow supports an association with epicardial patency at the time of angiography but cannot establish a microvascular mechanism.

Two further observations are consistent with that reading. Patients whose thrombolysis failed had markedly lower ejection fractions and NT-proBNP concentrations roughly three times higher than those in whom it succeeded, a marker that tracks infarct size and prognosis after myocardial infarction [30]. Because failure was concentrated among patients scoring four or more, a high score may identify a ventricle already under strain rather than merely an elderly comorbid patient, although these measurements were obtained after treatment and may also reflect the consequences of failed reperfusion. After adjustment for the other variables in the multivariable model, a longer pain-to-needle time and a higher body mass index remained associated with failed thrombolysis, and both associations persisted when the score was added, whether to all four covariates or to these two variables alone, which is consistent with a longer ischemic burden and a more adverse metabolic profile. Neither variable, however, discriminated as well as the score, with areas under the curve of 0.682 and 0.792, respectively.

The potential clinical relevance of these findings lies in settings where fibrinolysis is given first and the catheterization laboratory is far away. Current guidelines recommend that every patient be transferred to a PCI-capable center immediately after fibrinolysis, with rescue PCI when reperfusion fails and routine early angiography when it succeeds [4,5], and our findings do not alter that recommendation. Transfer and the indication for rescue PCI are distinct decisions, and the score was evaluated only against the outcome of thrombolysis. Where transfer capacity is limited and not every patient can be moved at once, a high pretreatment score might help to decide which patients should be transferred first, so that preparation for possible rescue PCI can begin while the infusion is running rather than after the 90-minute electrocardiogram. This possible role is a hypothesis that requires prospective clinical evaluation. Eight of the 76 patients (10.5%) scoring below the threshold still had failed thrombolysis, and the safety of delaying or withholding transfer on the basis of a low score was not evaluated, so a low score should not be used to withhold transfer or the standard 90-minute assessment of reperfusion.

The principal strengths of this study are the consecutive enrollment of a well-defined clinical population, the calculation of the index test before the reference standard could be known, and the availability of coronary angiography in every analyzed patient, which provided supportive anatomical information, although flow at angiography performed hours later does not directly represent reperfusion status at 90 minutes. Several limitations should be acknowledged. First, this was a single-center study, so selection bias cannot be excluded, and the findings may not generalize to district hospitals, where the case mix is likely to differ. The sample, although larger than the calculated minimum, was modest, and larger studies are needed to confirm the findings. Second, the requirement for coronary angiography during the index admission necessarily excluded patients who died early or were too unstable for transfer to the catheterization laboratory, which may have removed the highest-risk patients from the cohort. Of the 219 patients who received streptokinase, 53 (24.2%) were not analyzed. If these patients differed in their score or in their likelihood of failed thrombolysis, which is plausible for those who died early or were unstable, the accuracy estimated in the analyzed cohort may differ from that in all patients treated with streptokinase, and spectrum bias cannot be excluded. Third, all patients received streptokinase, and the diagnostic performance reported here should not be extrapolated to fibrin-specific agents such as tenecteplase without further study. Fourth, the reference standard is a composite that includes a subjective assessment of chest pain and differs from definitions based on ST-segment resolution alone, although the results were similar when the electrocardiographic criterion alone was used. In addition, the time of onset of reperfusion arrhythmia was not recorded, although reclassifying the patients who could be affected did not materially change the results. Fifth, although the score itself was applied rather than developed in this cohort, the threshold of four was selected and evaluated in the same sample. Bootstrap internal validation suggested little optimism, but the reported sensitivity and specificity remain apparent estimates, and external validation in an independent population is required before the threshold can be used in practice. Sixth, the definitions of diabetes mellitus and hyperlipidemia included laboratory criteria, and the study form did not record whether these diagnoses predated admission or when laboratory results became available, so the full score could not be recalculated with certainty from pretreatment information alone. In a conservative analysis, discrimination was lower (area under the curve, 0.863 vs. 0.933), so the reported accuracy may overstate that of a score calculated strictly from history and examination. Seventh, the individual reasons for exclusion, the timing and doses of antithrombotic drugs, the interval from streptokinase to angiography, and the timing of rescue PCI were not recorded on the study form, and formal blinding of the outcome and angiogram assessors to the score was not documented. Finally, the study reports reperfusion status rather than clinical endpoints; follow-up beyond the index admission was not undertaken, and the study did not evaluate whether decisions based on the score improve outcomes.

Conclusions

The present study showed that a higher CHA_2DS_2-VASc-HS score, calculated before the start of streptokinase, was strongly associated with failed thrombolysis in Bangladeshi patients with STEMI, and an exploratory threshold of four or more identified failure with 91.2% sensitivity and 90.7% specificity. In addition, a higher score was related to poorer angiographic flow in the infarct-related artery, and the score discriminated failure better than the $CHADS_2$ and CHA_2DS_2-VASc scores. Because admission laboratory values may have informed the diabetes and hyperlipidemia components in some patients, the accuracy of the score when calculated strictly without laboratory results should be confirmed, and a low score should not be used to withhold or delay the transfer recommended by current guidelines. Further studies, especially prospective multicenter research with clinical endpoints, are suggested to validate the threshold externally and to establish whether using the score to prioritize limited transfer capacity improves outcomes in health systems that continue to depend on fibrinolysis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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