BRIEF REPORT

Application of the TIMI Risk Score for ST-Elevation MI in the National Registry of Myocardial Infarction 3

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Context The Thrombolysis in Myocardial Infarction (TIMI) risk score for ST-elevation myocardial infarction (STEMI) is a simple integer score for bedside risk assessment of patients with STEMI. Developed and validated in multiple clinical trials of fibrinolysis, the risk score has not been validated in a community-based population.

Objective To validate the TIMI risk score in a population of STEMI patients reflective of contemporary practice.

Design, Setting, and Participants The risk score was evaluated among 84 029 patients with STEMI from the National Registry of Myocardial Infarction 3 (NRMI 3), which collected data on consecutive patients with myocardial infarction (MI) from 1529 US hospitals between April 1998 and June 2000.

Main Outcome Measures Ability of the TIMI risk score to correctly predict risk of death in terms of model discrimination (*c* statistic) and calibration (agreement of predicted and observed death rates).

Results Patients in NRMI 3 tended to be older, to be more often female, and to have a history of coronary disease more often than those in the derivation set. Forty-eight percent received reperfusion therapy. The TIMI risk score revealed a significant graded increase in mortality with rising score (range, 1.1%-30.0%; $P<.001$ for trend). The risk score showed strong prognostic capacity overall ($c=0.74$ vs 0.78 in derivation set) and among patients receiving acute reperfusion therapy ($c=0.79$). Predictive behavior of the risk score was similar between fibrinolytic-treated patients (n=23 960; $c=0.79$) and primary percutaneous coronary intervention patients (n=15 348; $c=0.80$). In contrast, among patients not receiving reperfusion therapy, the risk score underestimated death rates and offered lower discriminatory capacity ($c=0.65$).

Conclusions Sufficiently simple to be practical at the bedside and effective for risk assessment across a spectrum of patients, the TIMI risk score may be useful in triage and treatment of patients with STEMI who are treated with reperfusion therapy.

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EFFECTIVE RISK STRATIFICATION IS integral to management of acute coronary syndromes.[1] Even among patients with ST-elevation myocardial infarction (STEMI), for whom initial therapeutic options are well-defined, patient risk characteristics impact short- and long-term medical decision making.[2-4] Early risk assessment guides triage to alternative levels of hospital care, decisions regarding therapeutic interventions, and application of clinical pathways that direct patient care and use of clinical resources. Despite well-characterized risk predictors,[5-7] reliable quantitative estimation of risk is challenging, as patients present with complex risk profiles requiring integration of numerous elements of qualitative and quantitative data. Thus, practical tools that enhance clinicians' ability to rapidly and accurately assess risk are of substantial interest.

The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI is a simple integer score that can be used at the bedside for risk stratification of patients at presentation with ST-elevation acute coronary syndromes.[8] Derived from 14 114 patients enrolled in the InTIME II (Intravenous nPA for Treatment of Infarcting Myocardium Early) trial, the TIMI risk score is a ro-

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bust clinical tool for mortality risk prediction in fibrinolytic-eligible patients with STEMI.[8] Although it is documented to perform well among patients receiving fibrinolytics in clinical trials,[8] the TIMI risk score has not been validated in a general population of patients with STEMI, including those treated with primary coronary revascularization or not receiving any form of acute reperfusion therapy. Since prospective validation in a data set reflective of contemporary practice is important prior to widespread application of any prediction rule, we evaluated the prognostic performance of the TIMI risk score in a heterogeneous population treated in US hospitals for acute myocardial infarction (MI) and entered into the National Registry of Myocardial Infarction 3 (NRMI 3).

METHODS

The third NRMI is a prospective, observational database of demographics, practice patterns, and health outcomes among patients with acute MI.[9] Data were collected on consecutive patients with MI from 1529 hospitals between April 1998 and June 2000. All treatment decisions were made at the discretion of the treating physicians. The present analysis included patients with ST elevation or presumed new left bundle-branch block who completed their stay at the admitting hospital and were not in cardiogenic shock at the initial evaluation.

The TIMI risk score for STEMI is a weighted integer score based on 8 clinical risk indicators that can be easily ascertained at presentation (TABLE 1).[8] For each patient, the score is calculated as the arithmetic sum of the points for each risk feature present (range, 0-14). The TIMI risk score was developed using multivariable methods among patients from the InTIME II trial, a phase 3 trial of lanoteplase vs alteplase reperfusion therapy.[8] The risk score was derived based on mortality through 30 days after presentation but showed stable prognostic performance across multiple time points, including time to discharge (c=0.78).[8]

Evaluation of the TIMI risk score was based on NRMI 3 patients with complete baseline data (89%). The prognostic discriminatory capacity of the TIMI risk score was expressed as the c statistic, representing the area under the receiver operating characteristic curve for prediction of in-hospital death.[10] Differences in event rates with increasing risk scores were assessed using the χ^2 test for trend. Model calibration was assessed by construction of plots of predicted vs actual death rates across the entire spectrum of predicted risk. Testing for differences in mortality gradients among groups with different treatment modes was performed using logistic regression analysis with interaction terms. The prognostic contributions of variables not included in the risk score were assessed by stepwise logistic regression. Patients who did not receive any reperfu-

Table 1. Elements of the TIMI Risk Score*

Clinical Risk Indicators	Points
Historical	
Age, y	
≥75	3
65-74	2
History of diabetes, hypertension, or angina	1
Examination	
Systolic blood pressure <100 mm Hg	3
Heart rate >100/min	2
Killip class II-IV	2
Weight <67 kg	1
Presentation	
Anterior ST elevation or left bundle-branch block	1
Time to reperfusion therapy >4 h	1
Total possible points	14

*TIMI indicates Thrombolysis in Myocardial Infarction.

Table 2. Baseline Characteristics of the NRMI 3 Validation and InTIME II Derivation Sets*

Characteristics	NRMI 3 Validation Set: All Patients (n = 84 029)	NRMI 3 Validation Set: Reperfusion Therapy (n = 40 214)	NRMI 3 Validation Set: No Reperfusion Therapy (n = 43 815)	InTIME II Derivation Set (n = 14 114)
Demographics				
Age, y				
Mean (SD)	69 (14)	63 (13)	74 (13)	61 (12)
>75, %	38.3	21.1	54.1	13.4
Female, %	40.5	31.4	48.8	24.8
Weight, kg				
Mean (SD)	79 (20)	83 (19)	75 (20)	78 (14)
<67, %	28.0	18.4	36.9	20.0
Risk factors, %				
Current smoker	27.2	37.7	17.6	45.0
Diabetes	27.2	19.6	34.2	14.1
History of hypertension	54.0	47.7	59.8	30.4
Cardiovascular history, %				
Prior myocardial infarction	23.3	17.5	28.5	16.0
Prior angina	11.5	8.8	13.9	21.6
Prior PCI	9.5	11.1	8.0	4.4
Prior CABG	10.8	7.1	14.2	2.7
Presenting characteristics				
Infarct location, %				
Anterior or LBBB	48.6	36.8	59.4	42.7
Inferior	44.5	59.7	30.5	57.3
Killip class II-IV, %	25.1	10.9	38.2	12.2
Heart rate, beats/min				
Mean (SD)	86 (24)	78 (20)	93 (25)	76 (18)
>100, %	23.8	12.1	34.5	7.6
Systolic blood pressure, mm Hg				
Mean (SD)	141 (32)	140 (31)	141 (33)	139 (22)
<100, %	8.7	8.3	9.1	2.5
Treatment				
Time to reperfusion therapy >4 h, %	. . .	30.4	. . .	24.4
TIMI risk score, median (interquartile range)	4 (2-6)	3 (1-5)	5 (4-7)	3 (1-4)

*NRMI 3 indicates National Registry of Myocardial Infarction 3; InTIME II, Intravenous nPA for Treatment of Infarcting Myocardium Early; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LBBB, left bundle-branch block; ellipses, data not applicable; and TIMI, Thrombolysis in Myocardial Infarction.

sion therapy were not assessed for the predictor variable of time to reperfusion therapy. Two-tailed P values $<.05$ were considered significant. Analyses were performed using SAS, version 8.0 (SAS Institute Inc, Cary, NC).

RESULTS

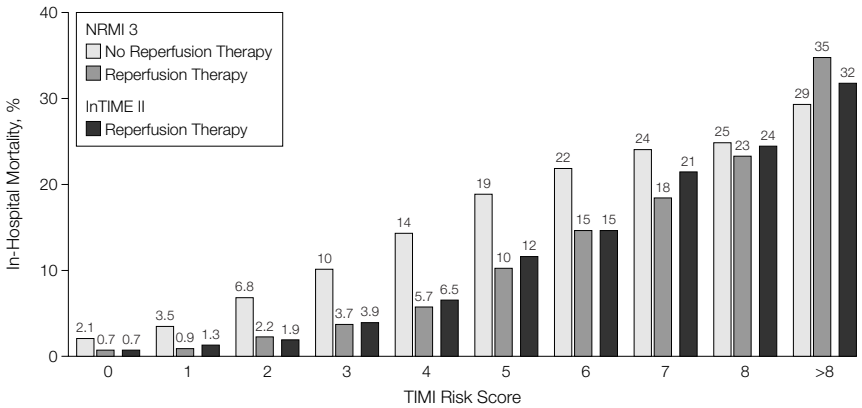
The analysis included 84029 patients with STEMI. Baseline characteristics are summarized in TABLE 2. Patients from NRMI 3 tended to be older; were more often female; and tended to have more heart failure, previous MIs, and prior coronary revascularization procedures than patients in the derivation set.[8] Among the NRMI 3 validation set, 40214 patients (48%) were treated with pharmacological or mechanical reperfusion therapy. Those who underwent primary percutaneous coronary intervention (n=15348) represented 38% of patients who received reperfusion therapy. Patients treated without reperfusion therapy had more frequent high-risk features and a higher median TIMI risk score (Table 2).

In-hospital mortality was 12.6% (n=10612). Application of the TIMI risk score in the overall population from NRMI 3 revealed a significant, nearly 30-fold graded increase in risk between patients with a score of 0 and those with a score of 8 or higher (range, 1.1%-30.0%; $P<.001$ for trend). Assessed by the area under the receiver operating characteristic curve, the risk score showed a strong prognostic capacity ($c=0.74$) that was comparable with the risk score performance in the InTIME II trial ($c=0.78$).[8]

Stratification of the population into those who were treated with vs without reperfusion therapy revealed substantial differences in risk score discriminatory performance as well as in calibration. The prognostic capacity of the TIMI risk score among patients treated with acute reperfusion therapy ($c=0.79$) was unchanged compared with InTIME II and was similar between patients treated with fibrinolytics and those who underwent primary percutaneous coronary interventions ($c=0.79$ vs 0.80), with no significant difference in the slope of the risk gradient between the 2 groups ($P=.09$ for interaction).

The FIGURE shows the behavior of the TIMI risk score in terms of predicting death across the spectrum of expected risk. The observed mortality rates for patients in NRMI 3 receiving reperfusion therapy were strongly concordant with risk estimates derived from InTIME II ($r=0.99$; Figure), indicating good model calibration. Among patients treated without reperfusion

Figure. Prediction of In-Hospital Mortality With TIMI Risk Score for STEMI



Total No. of Patients

No Reperfusion Therapy, NRMI 3									
1258	2945	2479	3590	5771	6000	5881	5295	4453	6143
Reperfusion Therapy, NRMI 3									
4039	7630	6223	5739	5750	4261	2781	1765	1011	1015
Reperfusion Therapy, InTIME II									
1705	3029	2287	2252	1983	1313	824	367	209	145

STEMI indicates ST-elevation myocardial infarction; NRMI 3, the National Registry of Myocardial Infarction 3. Data for the Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME II) trial are from Morrow.[8]

Table 3. Adjusted Mortality Risk Relationships in NRMI 3 vs InTIME II*

Risk Characteristics	NRMI 3		InTIME II, OR (95% CI)	Points in TIMI Risk Score
	Reperfusion Therapy, OR (95% CI)	No Reperfusion Therapy, OR (95% CI)		
Age ≥75 y	3.3 (3.0-3.7)	1.6 (1.5-1.7)	2.7 (2.2-3.2)	3
Killip class II-IV	2.4 (2.2-2.7)	1.5 (1.4-1.6)	2.3 (1.9-2.7)	2
Heart rate >100/min	2.2 (2.0-2.4)	1.2 (1.2-1.3)	2.3 (1.9-2.8)	2
Anterior MI or LBBB	1.7 (1.6-1.8)	0.93 (0.9-1.0)	1.6 (1.4-1.9)	1
SBP <100 mm Hg	3.2 (2.8-3.5)	4.3 (4.0-4.6)	2.7 (1.9-3.8)	3
Time to reperfusion therapy >4 h	1.0 (0.9-1.1)	. . .	1.4 (1.2-1.6)	1
Weight <67 kg	1.4 (1.2-1.5)	1.2 (1.2-1.3)	1.4 (1.2-1.7)	1
History of angina, hypertension, or diabetes	1.1 (1.0-1.2)	0.94 (0.9-1.0)	1.4 (1.2-1.6)	1
Nonsmoker	1.6 (1.5-1.8)	1.5 (1.3-1.6)	1.3 (1.1-1.5)	
Prior MI	†	0.9 (0.8-1.0)	1.3 (1.1-1.6)	
Peripheral vascular disease	NA	NA	1.5 (1.1-1.9)	
Antiarrhythmic medication	NA	NA	1.8 (1.1-2.8)	
Lipid-lowering medication	NA	NA	0.7 (0.5-1.0)	
Female	1.4 (1.3-1.6)	†	1.2 (1.0-1.5)	

*Comparison of the full Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME II) multivariable model between data sets should be viewed with caution because of missing covariates in the National Registry of Myocardial Infarction 3 (NRMI 3). OR indicates odds ratio; CI, confidence interval; MI, myocardial infarction; LBBB, left bundle-branch block; SBP, systolic blood pressure; ellipses, data not applicable; and NA, data not available in NRMI 3.
†Variable did not enter into model.

therapy, a significant graded relationship between the TIMI risk score and mortality was also evident ($P<.001$ for trend; Figure). Of note, however, the slope of the risk gradient in this group was less steep owing to a pattern of higher mortality among patients with risk scores in the low and middle range ($P<.001$ for interaction; $c=0.65$). As such, the quantitative mortality estimates from InTIME II underestimated the risk for patients treated without reperfusion therapy except those with the highest predicted death rates.

Exploratory analysis was performed to identify additional important predictors in patients treated without reperfusion therapy. Among the variables considered, bleeding risk (active internal bleeding or recent surgery/trauma), uncertainty regarding diagnosis, major organ failure, and chronic renal failure added significantly to the multivariable model including each of the risk score predictors ($c=0.746$; $P<.001$). While history of smoking and prior stroke added further to the model, the improvement in discriminatory capacity was small ($c=0.750$).

COMMENT

Results from risk prediction tools developed in carefully selected patients enrolled in clinical trials may not be generalizable to heterogeneous, "real-world" patient populations. This analysis demonstrates the robust prognostic performance of the TIMI risk score in a general population of patients with ST-elevation acute coronary syndromes treated with acute reperfusion therapy in a diverse group of US hospitals. The strong predictive capacity of the risk score was evident among patients treated with either pharmacological or mechanical reperfusion therapy. These observations establish the prognostic efficacy of the TIMI risk score in a large group of patients representative of contemporary clinical practice.

Patients who were not administered reperfusion therapy showed a pattern of higher mortality risk. Although the difference in outcomes may be due in part to the established benefits of reperfusion therapy, we identified several high-risk features not included in the TIMI risk score that are likely related to the decision not to administer reperfusion therapy, and offer additional predictive information. While the quantitative mortality estimates from InTIME II do not apply to these patients, the TIMI risk score may aid in their categorization into groups of low, moderate, and high relative risk. Limited information is available regarding the performance of other validated models stratified by use of reperfusion therapy. Our data suggest that future work should include evaluation of existing and new models in these important subgroups of the overall population with acute MI (TABLE 3).

The TIMI risk score was developed with the objective of creating a risk assessment tool that is both effective and convenient for use at patient presentation. With just a few important clinical factors, the risk score captures the majority of prognostic information available from more complex models among patients treated with reperfusion therapy.[8] The discriminatory capacity of the model could be increased by inclusion of additional variables or more complex modeling, but at the cost of hindering practical application. Other well-validated models have been derived for the purpose of risk-adjusted analysis of hospital outcomes to direct quality improvement efforts.[7,11] Such models have incorporated data acquired during hospitalization to provide high-discriminatory capacity with respect to long-term outcomes. In contrast, the TIMI risk score is based on clinical information that is available at the time of hospital arrival and, thus, is suitable for early risk stratification at the bedside without the need for a computer. The impact of differences in treatment, along with noninvasive and invasive data accrued during the course of hospitalization, should be considered by clinicians in a continuous process of updating the initial assessment of risk offered by the TIMI risk score.

Sufficiently simple to be practical at the bedside and effective for risk assessment across a heterogeneous spectrum of patients, the TIMI risk score may be clinically useful in the triage and treatment of patients with STEMI who undergo acute reperfusion therapy.

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Drafting of the manuscript: Morrow.
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