

Original Research Article

Long term prognostic significance of thrombolysis in myocardial infarction risk score after revascularization in non-ST elevation acute coronary syndrome

Pawan Sarda, Gaurav Kumar*, Rohit Mathur, Anil Baroopal, Sanjeev Sanghvi

Department of Cardiology, Dr. SN Medical College, Jodhpur, Rajasthan, India

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***Correspondence:**

Dr. Gaurav Kumar,

E-mail: drgauravdm@icloud.com

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ABSTRACT

Background: Non-ST elevation acute coronary syndrome (NSTEMI-ACS) patients are complex and varied population. Primarily thrombolysis in myocardial infarction (TIMI) risk score was developed to guide therapy and assess the short term (14 days) prognosis of these patients. However, few studies have evaluated the long term prognostic significance of TIMI risk score after revascularization. This study aims at assessing the long term prognostic significance of TIMI risk score, 36 months after revascularization in NSTEMI-ACS.

Methods: This was a retrospective observational cohort study of consecutive NSTEMI-ACS patients (n=150) treated by percutaneous coronary intervention between January 2017 to June 2017 in a tertiary care center. TIMI risk score was calculated for each patient at admission. The primary endpoint was a composite of MACE (death, repeat target-vessel revascularization, and non-fatal recurrent MI) at the end of 36 months of follow up. Clinical secondary endpoints included the individual components of the primary endpoint, death, nonfatal recurrent MI, and repeat target vessel revascularization.

Results: Baseline characteristics for 150 participants were as follows, age 56±9.5 years, 78.7% male, 25% diabetics, 82% hypertensives, and 36% had hypercholesterolemia. The event rates of the primary endpoint and its components after 36 months were 26.6%. Event rates increased significantly as the TIMI risk score increased as determined by regression analysis (p=0.004). The relative risk increased by 66% as the TIMI risk score increased from low risk category (TIMI score 0-2) to high risk (TIMI score 5-6).

Conclusions: TIMI risk score can be used for long term prognostication of NSTEMI-ACS patients after revascularization, and thus can be used by clinicians for therapeutic decision making.

Keywords: Long term prognosis, NSTEMI-ACS, Percutaneous coronary intervention, Risk stratification, TIMI risk score

INTRODUCTION

Acute coronary syndrome refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow. The absence of persistent ST elevation is suggestive of non-ST elevation acute coronary syndromes (NSTEMI-ACS). NSTEMI-ACS can

be further subdivided based on cardiac biomarkers of necrosis. If cardiac biomarkers are elevated and the clinical context is appropriate, the patient is considered to have non-ST elevation myocardial infarction (NSTEMI) otherwise, the patient is deemed to have unstable angina.¹

Patients presenting with NSTEMI-ACS are a heterogeneous group.^{2,3} These patients are at variable risk for adverse

cardiac events and mortality depending upon the presence of various risk factors such as age, diabetes, hypertension, smoking etc.⁴⁻⁸ GRACE and OPERA registries reported that in hospital mortality of NSTEMI-ACS was 4.3% and 5.9%, respectively.^{9,10} In hospital mortality is comparable (4.6% vs. 4.3%), and 1 year mortality is 9.0% in STEMI patients and 11.6% in NSTEMI patients (Log rank $p=0.09$).¹⁰ Further, the clinical performance of a drug-eluting stent with a biodegradable polymer in an unselected patient population (NOBORI-2) study has evidenced that the long-term cardiac mortality and MACE (major adverse cardiac events) following percutaneous coronary intervention (PCI), for NSTEMI were significantly higher against STEMI and stable angina.¹¹ Therefore, risk stratification for this group of patients is both crucial and pragmatic. Identifying high-risk patients, and hence selecting those who would benefit from more aggressive treatment, is essential for the management of NSTEMI-ACS. Several risk scores, such as thrombolysis in myocardial infarction (TIMI), GRACE, and PURSUIT, are employed to categorize patient's risk of adverse events, including death.¹²⁻¹⁴

TIMI is a convenient bed-side clinical score and has been used by clinicians for short term prognosis of NSTEMI-ACS patients. TIMI risk score for NSTEMI-ACS constitutes of seven variables. It is calculated as a simple arithmetic sum of each variable, based on age ≥ 65 years, and clinical data namely: ≥ 3 coronary artery disease (CAD) risk factors (current smoker, hypertension, hypercholesterolemia, diabetes and family history of CAD), use of aspirin in last 7 days, severe angina (\geq episodes in last 24 hours), positive cardiac biomarkers, ECG ST changes ≥ 0.5 mm and known CAD. TIMI 11B trial and a comparison of low molecular weight heparin with unfractionated heparin for unstable coronary artery disease (ESSENCE) trial had initially validated TIMI risk score for short term prognostication of patients with NSTEMI-ACS.¹⁵

However, to the best of the authors' knowledge, the TIMI risk score has not been evaluated for long term prognostication in NSTEMI-ACS patients after revascularization. Poor long-term survival outcomes of NSTEMI-ACS patients even after PCI forms the rationale for the present study, which aims to evaluate the long-term prognostic significance of TIMI risk score in patients after revascularization.

METHODS

Study design

We conducted a retrospective study on 150 consecutive patients who presented with NSTEMI-ACS at a tertiary care centre in Jodhpur, Rajasthan, India. The cohort composed of NSTEMI-ACS patients who had undergone PCI according to current practice guidelines between January 2017 to June 2017. Telephonic and outpatient follow up records were used to ascertain primary and secondary endpoints. Patient characteristics were recorded using the

hospital-based questionnaire. All patients were risk-stratified using the recorded clinical data with TIMI risk score at presentation.

Analysis plan

The baseline characteristics and correlation between adverse events and TIMI risk score for all patients of NSTEMI-ACS treated with PCI were studied. A regression model to evaluate the relationship between TIMI risk score and the primary endpoint was developed. Relative risk with a 95% confidence interval (CI) is reported. Statistical significance was defined as $p < 0.05$ or 95% CI for RR. The predictive discriminatory capacity of the TIMI risk score was expressed as the c-statistic, which represents the area under the ROC (receiver operating characteristic: 0.50 indicating chance discrimination and 1.00 perfect discrimination) curve for predicting long term prognostic significance. All statistical analyses were performed using SPSS 24 statistical software (SPSS Inc. Chicago, IL, USA).

RESULTS

The baseline characteristics are shown in (Table 1). In this study cohort, a total of 40 events occurred, among these, six patients had double events. In the observed time after revascularization, 3 (2%) deaths occurred; repeat TVR done in 11 (7.3%) patients, out of which 2% underwent CABG, and 5.3% PCI, 26 (17%) had recurrent nonfatal MI. The primary endpoint was reached in 26.6% of patients. A statistically significant association exists between TIMI and adverse events calculated through regression curve having a p value of 0.004 (CI=95%). The TIMI risk score varied for the cohort between the values of 0-6. Patients were divided into low risk, moderate risk, and high risk according to their TIMI risk score value of 0-2, 3-4, and ≥ 5 respectively. The relative risk of occurrence of adverse events increases as the TIMI risk score increase from the low risk score (0-2) to high risk score (5 and above). The relative risk increases from 0.288 in the low-risk category to 3.5 in the high-risk category which is 66% higher. (Table 2)

Out of the high-risk patients with TIMI scores of ≥ 5 ($n=15$), 9 patients had triple vessel disease (TVD) whereas 6 had double vessel disease (DVD). For moderate risk ($n=70$), 19 patients had TVD, 26 had DVD and 25 had the single-vessel disease (SVD). Low-risk patients ($n=65$) were associated only with SVD (48 cases) and DVD (17 cases) (Table 3).

Among the seven TIMI variables, ST changes ≥ 0.5 mm and positive cardiac biomarkers are most significantly associated with adverse outcomes having the highest relative risk of 1.692 and 1.444 respectively (Table 4). The area under the curve (AUC) value of 0.755, establishes the TIMI risk score to be a reliable tool for long term risk stratification. ROC for TIMI risk score is statistically significant with a $p=0.005$ for sensitivity and specificity (Figure 1).

Table 1: Baseline characteristics of study patients (n=150).

Characteristic	Total patients N (%)	Characteristic	Total patients N (%)
Age (in years)	56.01±9.51	LMWH	150 (100)
Sex		GP IIb/IIIa inhibitors	58 (38.7)
Male	118 (78.7)	Nitrates	137 (91.1)
Female	32 (21.3)	Beta blockers	129 (86.3)
BMI		Calcium channel blockers	23 (15.2)
>25	32 (21.3)	ACE Inhibitors	130 (86.6)
18-25	108 (72)	Statins	148 (98.6)
<18	10 (6.6)	TIMI score	
eGFR		Low risk , (0-2)	65 (43.3)
>60	145 (96.6)	Moderate risk, (3-4)	70 (46.6)
<60	5 (3.4)	High risk, (5 and above)	15 (10)
Risk factors		Left ventricular ejection fraction	
Diabetes mellitus	38 (25.3)	≥50%	105 (70)
Hypercholesterolemia	54 (36)	40-49%	23 (15.3)
Systemic hypertension	123 (82)	30-39%	15 (10)
Smoking	32 (49)	<30%	7 (4.6)
Previous medications		KILLIP class	
Aspirin	19 (12.6)	Class I	136 (90.6)
Beta blockers	21 (13.9)	Class II, III, IV	14 (9.4)
Calcium channel antagonists	16 (10.6)	Prior events	
ACE inhibitors/ARB	16 (10.6)	PCI	10 (7)
Statins	32 (31.2)	CABG	0 (0)
Clopidogrel	18 (11.9)	Stroke or TIA	4 (2.6)
Nitrates	16 (10.6)	Unstable angina	50 (7.4)
In hospital patient management		NSTEMI	100 (92.6)
Aspirin	150 (100)		

BMI-body mass index; eGFR-estimated glomerular filtration rate; ACE-angiotensin converting enzyme; ARB-angiotensin receptor blocker; LMWH-low molecular weight heparin; GP IIb/IIIa-glycoprotein IIb/IIIa; CABG-coronary bypass grafting; TIA-transient ischemic attack.

Table 2: Relation between TIMI risk score group and composite of death, recurrent myocardial infarction, and repeat revascularization at 36 months.

TIMI risk score group	Mortality	Recurrent MI	TVR with CABG	TVR with PCI	Total Events N (%)	Total cases N (%)	Relative Risk	95%CI
0-2 (low risk)	0	4	1	0	5 (12.5)	65 (43.3)	0.288	0.107-0.676
3-4 (moderate risk)	0	16	2	3	21 (52.5)	70 (46.6)	1.12	0.225-0.969
≥5 (high risk)	3	6	0	5	14 (35)	15 (10)	3.5	1.394-3.905

Table 3: Association of TIMI risk score group with severity of CAD.

TIMI risk score group	SVD	DVD	TVD
Low (0-2)	48	17	0
Moderate (3-4)	25	26	19
High (5 and above)	0	6	9

SVD-single vessel disease; DVD-double vessel disease; TVD-triple vessel disease.

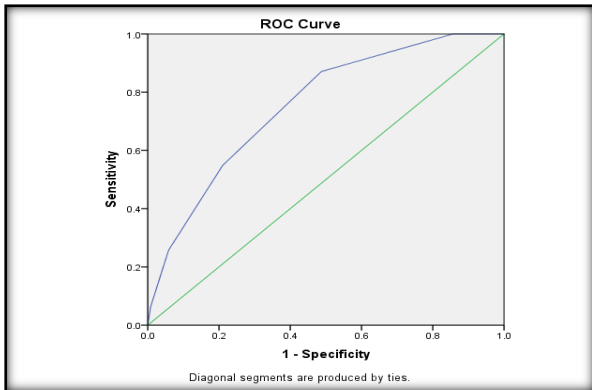


Figure 1: ROC (receiver operating characteristic) curve for determining the sensitivity and specificity of TIMI risk score.

Table 4: Relative risk of composite outcome for each TIMI risk score component.

TIMI Variable	Patient (N)	CV event/ rate, N (%)	Relative Risk	95% CI
Age (≥65 years)	29	15 (51.7)	0.503	0.267-0.949
≥3 CAD factors	38	14 (36.8)	0.537	0.288-1.001
Aspirin	39	20 (51.2)	0.427	0.233-0.782
Angina	57	18 (31.5)	0.654	0.351-1.218
Cardiac biomarker	100	39 (39)	1.444	0.771-2.705
ST changes	92	34 (36.9)	1.692	0.907-3.155
Known CAD	21	18 (85.7)	0.342	0.189-0.620

CI-confidence interval.

DISCUSSION

Guidelines for the treatment of NSTEMI-ACS are based on risk stratification, advocating more expensive and invasive therapies for those at higher absolute risk and therefore those, most likely to benefit.¹⁶ However, contrary to this, a study depicted that cardiac catheterization is not being used optimally in NSTEMI-ACS patients, mainly because clinicians are not risk-stratifying these patients correctly.¹⁷ Even after recommendations from the American Heart Association/ American College of Cardiology and European Society of Cardiology, there is non-concordance among clinicians in risk assessment of patients¹⁸. Risk stratification can play an important role in the optimal management of NSTEMI-ACS patients. Despite the availability of several prognostic risk scores like TIMI, GRACE, and PURSUIT appropriate risk

stratification for long term follow-up have not been studied.¹²⁻¹⁴ The data from the ESSENCE trial and TIMI 11B trial was first used to predict adverse cardiac events in 14 days for patients of NSTEMI-ACS.¹⁵ Another study has also shown a clear correlation between TIMI risk score and duration of event-free survival in unselected patients with possible acute coronary syndrome.¹⁹ Present study validates the use of TIMI risk score for long term prognostication in NSTEMI-ACS patients after revascularization with a statistically significant p value of 0.004.

Studies have supported PCI in helping reduce MACE.²⁰ PCI can lead to an improvement in chest pain and reduction in MACE.²¹ Authors considered mortality, recurrent MI, and repeat TVR after PCI or CABG as MACE in the present study. The rate of occurrence of adverse events in the present study post revascularization with PCI was 26.6% at 36 months. A similar study published from Taiwan reported the occurrence of MACE in 36.7% of patients over a 23 month follow-up.²² However, in that study MACE was defined as all-cause mortality or readmission to hospital for CV related illness including nonfatal MI, heart failure, recurrence of angina pectoris and repeat PCI or CABG. The present study also evidences ECG changes and elevated cardiac biomarkers to be mainly associated with adverse events that are aligned with the study by Chase et al.²³

The C-statistic value in this study is 0.755 (95% CI) which establishes TIMI as a fairly good risk score for long term evaluating the prognosis of NSTEMI-ACS patients. Pedro et al have shown that the TIMI risk score had a C-statistic value of 0.60 (95% CI: 0.56-0.65) for predicting death or MI at one year.²⁴

Limitations

The present study is retrospective, conducted at a single-centre, consisting of a small cohort of patients. Similar studies with large samples can be conducted to further strengthen the findings. Researchers can also look forward to comparing TIMI with other risk stratification scores to establish the best available tool for practitioners.

CONCLUSION

The present study helps to establish the TIMI risk score, as an easy and practical bedside tool that can be used by practitioners for long term risk stratification of patients presenting with NSTEMI-ACS undergoing PCI. As TIMI risk score is already established for in-hospital short term risk stratification, the present study further consolidates its significance because of its ability to predict long term (36 months) prognosis also. This study concludes that even after revascularization, the patients have worse long term prognosis and that can be determined by TIMI risk score calculated at admission. Based on present study results, authors emphasize that all clinical practitioners working at peripheral hospitals where revascularization

facilities are not available must consider bedside TIMI risk score for timely referral of high-risk patients for revascularisation, as this will be detrimental in both short term and long term prognosis. This study will also facilitate them to use more aggressive antithrombin and newer antiplatelet agents with a favourable risk-benefit ratio over long-term follow-up. The study also creates a paradigm for future studies in analyzing more appropriate tools that can be beneficial for all clinical practitioners.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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