RESEARCH ARTICLE

Management, hospital outcome and revascularization trends in non-ST elevation myocardial infarction with high GRACE risk score

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Abstract

Objective: To assess clinical characteristics, management strategies and in-hospital outcome among high-risk patients of non-ST elevation myocardial infarction.

Methods: The retrospective cross-sectional study was conducted at Tabba Heart Institute, Karachi, and comprised data from July 2013 to December 2016 of adult non-ST elevation myocardial infarction patients who had first cardiac event having Global Registry of Acute Coronary Eventsrisk score>140. Subcategories were formed on the basis of score range 140-159, 160-189 and ?190.Stata 12.1 was used for data analysis.

Results: Of the 817 patients, 567(69.4%) were men. Overall, mean age was 66.3±9.3 years. Coronary angiography was performed in 692(84.4%). With higher risk score categories, there was less frequent use of guideline directed medical therapy, coronary angiography and percutaneous or surgical revascularisation ($p<0.05$ each). Overall mortality was 59(7.2%). Mortality rates increased with increase in risk score subcategory ($p<0.05$). Multivariable model identified higher risk score category, no revascularisation and lack of guideline directed medical therapy as significant independent predictors of mortality ($p<0.05$ each).

Conclusion: Mortality increased with higher risk score category. Paradoxically, high-risk patients were less likely to receive guideline directed medical therapy, to undergo coronary angiography and revascularisation, possibly suggesting a risk aversion approach by the treating physicians.

Keywords: Non-ST elevated myocardial infarction, GRACE, Mortality, High risk, Trends. (JPMA 69: 1486; 2019).
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Introduction

Non-ST segment elevation myocardial infarction (NSTEMI) is the most common presentation of acute coronary syndrome (ACS), accounting for almost 60% of such patients.[1] The patho-physiology underlying NSTEMI is more diverse with variable degree of reduction in coronary flow, but usually without complete occlusion. Early invasive management with aggressive medical management has shown a reduction in adverse outcomes in appropriately selected patients with NSTEMI-ACS.[2,3] Over time the incidence of NSTEMI continues to rise, partly due to greater usage of high sensitivity cardiac troponin (hs-cTn) assays to diagnose myocardial necrosis.[1,4]

Patients presenting with NSTEMI are heterogeneous and include a spectrum of risk of adverse events, requiring individualisation of medical management and revascularisation decisions. Therefore early risk stratification in NSTEMI is required for management and is recommended in guidelines.[5] Use of risk scoring systems such as Thrombolysis In Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) have been studied in western as well as Asian population and have shown to be accurate in predicting adverse clinical outcome and identifying patients at high risk for cardiac death.[6-8] GRACE risk score employs a number of patient characteristics such as age, heart rate (HR), systolic blood pressure (SBP), Killip class I to IV (to quantify severity of myocardial infarction in ACS and predict risk of 30-day mortality), cardiac arrest, serum creatinine, ST-segment deviation, and cardiac biomarker status to estimate in-hospital mortality.[9]

Patients with a GRACE risk score >140 have >3% risk of in-hospital mortality compared to <1% in patients who have a low-risk score of <109. Guidelines recommend more aggressive management strategies and greater use of revascularisation in patients who are at higher risk of subsequent events.[10] The results available from the GRACE registry on the contrary report less frequent use of cardiac catheterisation and revascularisation in patients with higher GRACE score, perhaps suggesting a risk aversion approach by the treating physicians.

Data regarding treatment and risk characteristics of higher-risk patients with ACS as well as the adjustment of treatment to individual patients' underlying risk is not available from South Asia. The current study was planned to assess the clinical characteristics, management strategies and in-hospital outcome among NSTMEI

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patients with a GRACE risk score >140.

Patients and Methods

The retrospective cross-sectional study was conducted at Tabba Heart Institute, Karachi, which is a single-specialty cardiac care hospital. After approval from the institutional ethics review committee, data of all consecutive patients admitted with ACS from January 2013 to December 2016 was obtained from the catheterisation laboratory and ACS database maintained according to the standard National Cardiovascular Data Registry and Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry definitions.[11,12] NSTEMI was defined by the presence of following criteria: a) symptoms suggestive of acute coronary ischaemia, b) cardiac biomarkers (troponin T or I) exceeding the diagnostic criteria cut-offs of the institutional laboratory parameters with a clinical presentation consistent with or suggestive of ischaemia, and electrocardiogram (ECG) changes not meeting STEMI criteria. The variables included in GRACE risks score are age, admission HR and SBP, Killip class I to IV on admission (to quantify severity of myocardial infarction in ACS and predict risk of 30-day mortality), cardiac arrest, ST deviation on ECG, elevated troponin and creatinine.[9] GRACE risk score calculator based on the GRACE study nomogram is programmed into the institutional database and automatically provides the score and predicted mortality once all the required variables are entered.[13] As recommended by the non-ST-elevation acute coronary syndromes (NSTEACS) guidelines, the patients in the database were categorised according to their GRACE risk score predicted in-hospital mortality as low (score<109; predicted mortality <1%), intermediate (score 109 to 140, predicted mortality 1-3%) and high (score 140, predicted mortality >3%).[14]

Data of all adult patients with NSTEMI-ACS as their first cardiac event having GRACE risk score 140 was included. In order to determine the quantum of risk gradient, this high-risk population was further categorised into three groups based on the GRACE risk score 140-159, 160-189 and 190.

Detailed demographics, clinical presentation characteristics, in-hospital non-invasive and invasive evaluation, medical management, revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and in-hospital outcome were recorded. Data of patients who did not complete their treatment at the hospital were excluded. Guideline directed medical therapy (GDMT) was defined as combined use of aspirin, thienopyridine, heparin, beta blocker (BB), statin and Angiotensin-converting-enzyme (ACE-I) / Angiotensin II receptor blockers (ARBs).

Stata 12.1 was used for statistical analysis. Patients were categorised according to their initial risk based on their clinical and haemodynamic features, including GRACE and TIMI risk scores. Means and standard deviations (SDs) were calculated for continuous variables and frequencies and percentages were calculated for categorical variables. Chi-square or Fisher exact tests were used for categorical variables according to expected cell counts, and independent sample t-test for continuous variables depending upon variable characteristics. Multivariable logistic regression model with stepwise approach was used to assess predictors of in-hospital mortality. Variables with $p<0.25$ in univariate analysis were considered significant for adjusting into multivariable model and $p<0.05$ were considered significant for the final model, adjusting for GRACE risk score. ACE-I/ARB was excluded from the composite GDMT variable in multivariable adjustment due to lower frequency, and also because it is a guideline recommendation only for patients with at least moderate left ventricular dysfunction (LVD).

Results

Of the 817 patients, 567(69.4%) were men. Overall, mean age was 66.3±9.3 years. Of the total, 448(54.8) patients

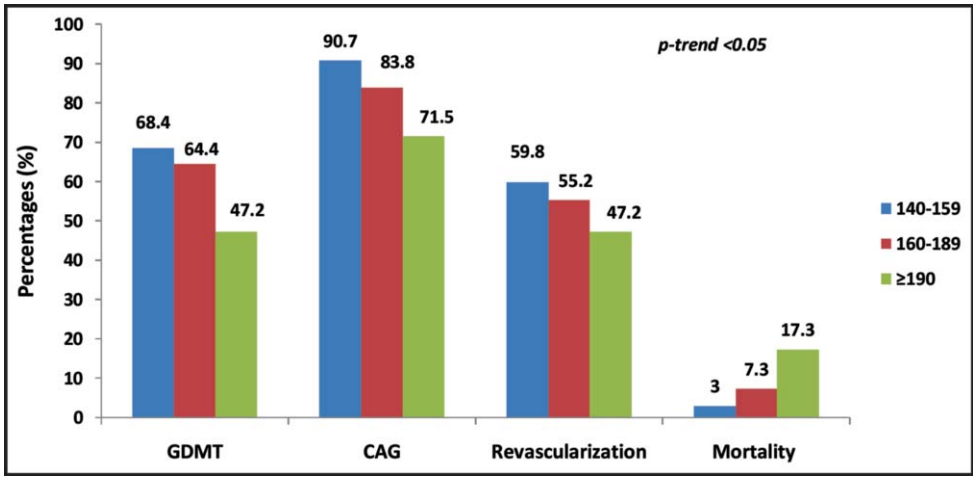

Figure: Trends in guideline directed medical therapy(GDMT), diagnostic coronary angiography (CAG), revascularisation and mortality (n=817). GDMT includes patients received all set of aspirin, thienopyridine, beta-blockers (BB), statins and Angiotensin-converting-enzyme (ACE-I) / Angiotensin II receptor blockers (ARBs).

Table-1: Patient characteristics according to GRACE risk score categories in non ST elevation MI between July 2013 to December 2016 at Tabba Heart Institute (n=817).

Characteristics	Total (n=817)	GRACE Risk Score			p-value
		140-159 (n=358)	160-189 (n=315)	≥190 (n=144)	
Age (years)	66.3±9.3	63.1±8.6	67.5±9.2	71.5±8.4	<0.001
Male gender	567 (69.4)	250 (69.8)	217 (68.9)	100 (69.4)	0.96
Clinical Presentation					
Diabetes mellitus	448 (54.8)	199 (55.6)	170 (53.9)	79 (54.8)	0.92
Dyslipidaemia	183 (22.4)	86 (24.0)	61 (19.3)	36 (25.0)	0.24
Hypertension	574 (70.3)	257 (71.8)	222 (70.5)	95 (65.9)	0.43
Family history of premature CAD	126 (15.4)	62 (17.3)	43 (13.6)	21 (14.6)	0.40
Smoking history	148 (18.1)	73 (20.4)	57 (18.1)	18 (12.5)	0.11
Mean GFR	58.3±28.4	68.6±30.2	53.6±24.0	42.8±22.5	0.001
Severe CKD/on dialysis	122 (14.9)	24 (6.7)	51 (16.2)	47 (32.6)	<0.001
Chronic Lung disease	30 (3.6)	8 (2.2)	10 (3.1)	12 (8.3)	0.008
Prior history of Stroke	37 (4.5)	14 (3.9)	17 (5.4)	6 (4.1)	0.63
Killip Class on Arrival (n=812)					
I	425 (52.4)	265 (75.0)	147 (46.7)	13 (9.0)	<0.001
II	214 (26.4)	60 (17.1)	102 (32.3)	52 (63.1)	
III	140 (17.2)	26 (7.4)	59 (18.7)	55 (38.2)	
IV	33 (4.0)	2 (0.5)	7 (2.3)	24 (16.7)	
Cardiogenic Shock at arrival	33 (4.0)	2 (0.5)	7 (2.3)	24 (16.7)	<0.001
Arrival systolic BP<100 (mm/Hg)	60 (7.3)	8 (2.2)	21 (6.6)	31 (21.5)	<0.001
Heart rate>100 (bpm)	233 (28.5)	72 (20.1)	101 (32.0)	60 (41.6)	<0.001
Cardiac arrest at arrival or stay	35 (4.3)	7 (1.9)	10 (3.2)	18 (12.5)	<0.001
Pre-procedure heart failure	320 (39.2)	84 (23.4)	133 (42.2)	103 (71.5)	<0.001
TIMI risk score ?5	195 (23.8)	59 (16.5)	84 (26.7)	52 (36.1)	<0.001
Mean LVEF	42.2±11.9	44.8±11.2	41.7±11.9	36.5±11.5	<0.001
In-hospital Medication					
Aspirin	804 (98.4)	354 (98.8)	309 (98.1)	141 (97.9)	0.62
Thienopyridine	686 (83.9)	307 (85.7)	275 (87.3)	104 (72.2)	<0.001
Beta Blocker	727 (88.9)	332 (92.7)	281 (89.2)	114 (79.2)	<0.001
ACE/ARBSs	493 (60.3)	243 (67.8)	187 (59.3)	63 (43.7)	<0.001
Statins	772 (94.5)	343 (95.8)	300 (95.2)	129 (89.5)	0.01
LMW/UF Heparin	697 (85.3)	317 (88.5)	264 (83.8)	116 (80.5)	0.04
GP IIb/IIIa	43 (5.2)	17 (4.7)	20 (6.3)	6 (4.1)	0.52

GRACE: Global Registry of Acute Coronary Events
CAD: Coronary artery disease
GFR: Glomerular filtration rate
CKD: Chronic kidney disease
TIMI: Thrombolysis in Myocardial Infarction
LVEF: Left ventricular ejection fraction
ACE: Angiotensin-converting-enzyme
ARB: Angiotensin II receptor blockers
LMW/UF: Low molecular weight / Unfractionated
GP: Glycoprotein.

had diabetes and 574(70.3%) had hypertension. Killip class I was present in 463(52.4%) on arrival, CS was present in 33(4.0%) and 35(4.3%) had a cardiac arrest during their hospital stay. Of the total, 195(23.8%) patients had TIMI risk score ≥5 and 443(54.2%) had moderate or severe renal dysfunction (Table-1).

The optimal medical management included a high usage of aspirin, anticoagulation with heparin or low molecular weight heparin (LMWH), thienopyridine, BB agents and statin drugs. ACE-I or ARB drugs were used in 493 (60.3) patients, and use of Glycoprotein (GP) IIb/IIIa agents was very low (<5%). GDMT was given to 352(43.1%), and to 516(63.1%) patients when excluding ACE/ARB drugs.

Cardiac catheterisation and CAG was performed in 692(84.4%) patients and 47(5.7%) underwent non-invasive stress test. Overall, median left ventricular ejection fraction (LVEF) was 45 (Inter-quartile range [IQR]: 22). Non-obstructive coronary arteries were present in

Table-2: Procedural characteristics according to GRACE risk score categories.

Characteristics	Total (n=817)	GRACE Risk Score			p-value
		140-159 (n=358)	160-189 (n=315)	≥190 (n=144)	
Procedural Characteristics					
Total patients with CAG	692 (84.4)	325(90.7)	264 (83.8)	103(71.5)	<0.001
Coronary disease pattern (n=692)	53 (7.6)	24 (7.4)	26 (9.9)	3 (2.9)	0.07
Non obstructive	266 (38.4)	126(38.8)	91 (34.5)	49 (47.6)	
Left main or 3 vessel	373 (54.0)	175(53.8)	147 (55.6)	51 (49.5)	
1 or 2 Vessel					
Revascularized	456 (55.8)	214 (59.8)	174 (55.2)	68 (47.2)	0.007
PCI	221 (27.1)	105 (29.3)	85 (27.0)	31 (21.5)	
CABG	235 (28.7)	109 (30.5)	89 (28.2)	37 (25.7)	
Median GRACE risk scores	162 (32)	149 (11)	171 (15)	207 (27.5)	<0.001*
Predicted mortality GRACE (%)	7.3	3.9	7.5	≥18	--
Median TIMI risk scores	4 (1)	4(1)	4(2)	4(2)	0.03¶
Predicted mortality TIMI (%)	2.5	2.5	2.5	2.5	--
Observed mortality	59 (7.2)	11 (3.0)	23 (7.3)	25 (17.3)	<0.001

*Kruskal Wallis test p-value
¶Kendal Tau test p-value
GRACE: Global Registry of Acute Coronary Events
CAG: Coronary angiography
PCI: Percutaneous coronary intervention
CABG: Coronary artery bypass graft
TIMI: Thrombolysis in Myocardial Infarction.

Table-3: Multivariable adjusted model for predictors of mortality in NSTEMI patients with GRACE risk score>140 (n=817).

Variables	Univariate				Multivariable			
	OR	p-value	95% CI		OR	p-value	95% CI	
			Lower	Upper			Lower	Upper
GRACE Risk Score (140-159 as reference)								
160-189	2.48	0.01	1.19	5.18	2.25	0.03	1.05	4.67
≥190	6.62	<0.001	3.16	13.87	5.13	<0.001	2.42	10.8
No revascularization	2.08	0.008	1.21	3.58	2.01	0.02	1.12	3.6
Lack of GDMT*	6.69	0.001	2.07	21.6	4.91	0.008	1.5	16.09

Model adjusted for GRACE risk score. Variables part of GRACE risk score were not included in multivariable model i.e. Age, heart rate, systolic blood pressure, serum creatinine, Killip class and cardiac arrest considering multi-collinearity.
*GDMT excludingAngiotensin-converting-enzyme (ACE-I) / Angiotensin II receptor blockers (ARB)
NSTEMI: Non-ST segment elevation myocardial infarction
GRACE: Global Registry of Acute Coronary Events
OR: Odds ratio
CI: Confidence interval
GDMT: Guideline directed medical therapy.

53(7.6%) and left main or triple vessel disease was present in 266(38.4%) patients. Revascularisation was performed in 456(55.8%) patients. Median hospital stay was 3 days (IQR: 5) (Table-2).

During the hospital stay, overall mortality was 59 (7.2%). The deceased patients had significantly worse renal function, more chronic lung disease, higher Killip class, and had more frequent cardiac arrest (p<0.05 each). The deceased patients also had significantly worse haemodynamics i.e. heart rate>100 bmp, SBP<100mm/Hg, more heart failure, lower mean LVEF, and were more likely to have left main or triple vessel coronary artery disease (CAD) (p<0.05 each). Mortality rates tended to increase with increase in the GRACE risk score category (p<0.05).

Multivariable model identified higher GRACE score, no revascularisation, and lack of GDMT as significant independent predictors of mortality, adjusting for GRACE

risk score 140-159 (Table-3).

There was a statistically significant trend towards increasing age with higher GRACE score categories ($p<0.05$). There were also trends towards more adverse baseline clinical characteristics, presentation features, lower left ventricular function (LVF), high-risk coronary anatomy and in-hospital mortality ($p<0.05$ each). Paradoxically, with higher GRACE risk score categories, there was a trend towards less frequent use of GDMT, CAG and percutaneous or surgical revascularisation ($p<0.05$ each) (Figure).

Discussion

The study found that NSTEMI patients admitted with GRACE risk score >140 presented with adverse clinical characteristics and had high in-hospital mortality. Independent predictors of mortality were increasing GRACE score, lack of revascularisation and sub-optimal medical treatment. The results also showed that higher-risk individuals were less likely to receive aggressive medical therapy or undergo diagnostic catheterisation or revascularisation.

Patients who present with NSTEMI have a risk spectrum of immediate and long-term adverse events.[7] Those who are at increased risk have a better outcome with aggressive medical therapy, invasive coronary evaluation and coronary revascularisation.[15] The utilisation of risk scores to identify individuals at risk is recommended by North American and European guidelines.[10,16,17] The findings of the current study further validate the accuracy of the risk estimation by GRACE score in a high-risk South Asian population. The actual mortality of 7.2% is in keeping with the 7.3% mortality predicted by the GRACE score. Within this high-risk subset, the GRACE risk score, in our study, further stratified the patients, with mortality in the third tertile of our study population more than double of the second and more than five-fold of the first tertile. The use of a validated score such as GRACE should allow the treating physicians to identify very high-risk patients early in their care journey and, hence, attempt to prevent adverse cardiac events can be made by provision of care interventions.

Our study also showed that patients identified by high GRACE score had in addition to the individual components of score, multiple advance co-morbidities. Similar to prior studies, our high-risk population had a very high >90% prevalence of obstructive CAD with more than a third having complex, very high-risk coronary anatomy.[18] Additionally, these patients tended to have high likelihood of symptomatic left ventricular (LV) dysfunction with more than a third having ejection fraction <40%. In our study, even in the short term, lack of revascularisation is a predictor of increased mortality. This again lays emphasis on earlier identification of such patients with utilisation of invasive investigation and subsequent appropriate revascularisation.

Clinical trials have shown greater benefit of aggressive medical therapy and revascularisation in high-risk patients and, based on this, all current management guidelines recommend therapy intensity tailored to the patients underlying risk.[19] Clinical practice in real life has shown contrary approach with less use of aggressive treatment in high-risk patients. Results from the GRACE registry and the Myocardial Ischaemia National Audit Project (MINAP) showed declining trend in the use of guideline-based care with increasing GRACE risk score in overall ACS as well as NSTEMI.[20,21] Our findings also showed that even in this high-risk population, there is an inverse relationship between the patients underlying risk and the intensity of treatment. This inverse relationship is present in the declining frequency of individual guideline-recommended medical therapy, diagnostic CAG and overall revascularisation as the patients' underlying risk and mortality goes up. Prior results from the GRACE registry have not shown a reduction in CABG with increasing risk suggesting use of different decision criteria for PCI or CABG, whereas our findings showed this relationship with both modalities of revascularisation.[22] Some studies have suggested the presence of a risk-aversion behaviour by clinicians and that may be one of the underlying reasons for our findings.[23] It is also possible that such patients may have had extensive co-morbidities, making them not suitable for PCI or CABG.

The treating clinicians may not have appreciated the increasingly adverse risk of the patients. The GRACE risk score requires an online calculator or a mobile app whereas the TIMI risk score can be easily calculated at the bedside and is used most of the times for clinical decision-making.[13] In our high-risk study population, the mean TIMI risk score was in the intermediate range and did not vary significantly between the tertile of the high GRACE risk score population. This may have led to an underestimation of the risk. Our findings may suggest lower discriminatory capability of the TIMI risk score in South Asian population. However, a larger study comparing the two scores including all strata of clinical risk would be required before concluding which risk score is better suited for South Asian population.

The independent predictors of early mortality in our findings included increasing GRACE risk scores.[9] This is consistent with other studies in Western and multi-ethnic Asian populations.[24] The other predictors of early

mortality were sub-optimal medical therapy and lack of revascularisation, as reported in literature.[21] Although a favourable impact on outcome with use of optimal medical therapy and revascularisation has been shown before, the surprising finding in the current study is such an early difference in survival.[25] This may be explained by the fact that only high-risk patients with high early event rate were included in the study and the improvement in outcome with optimal therapy and revascularisation in lower risk patient require more time to accrue.

The current study represented significant trends in revascularisation and predictors of mortality in high-risk NSTEMI with respect to local population. This is the first study on high-risk NSTEMI patients stratified by GRACE risk score in South Asian population. Limitations include single-centre retrospective data. The study could be further strengthened by assessing adverse outcomes at follow-up in comparison to low and intermediate GRACE risk score outcomes.

Further studies are required to assess the precision of various ACS risk calculators such as TIMI and GRACE risk scores in predicting adverse cardiac events in South Asian population.

Conclusion

Mortality increased with higher risk GRACE score category. Paradoxically, high-risk patients were less likely to receive GDMT, to undergo CAG and revascularisation, possibly suggesting a risk aversion approach by the treating physicians.

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Conflict of Interest: None.

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