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ORIGINAL RESEARCH

Predictive values of D-dimer assay, GRACE scores and TIMI scores for adverse outcome in patients with non-ST-segment elevation myocardial infarction

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Purpose: To determine the predictive values of D-dimer assay, Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores for adverse outcome in patients with non-ST-segment elevation myocardial infarction (NSTEMI).

Patients and methods: A total of 234 patients (mean age: 57.2±11.7 years, 75.2% were males) hospitalized with NSTEMI were included. Data on D-dimer assay, GRACE and TIMI risk scores were recorded. Logistic regression analysis was conducted to determine the risk factors predicting increased mortality.

Results: Median D-dimer levels were 349.5 (48.0–7,210.0) ng/mL, the average TIMI score was 3.2±1.2 and the GRACE score was 90.4±27.6 with high GRACE scores (>118) in 17.5% of patients. The GRACE score was correlated positively with both the D-dimer assay (r=0.215, P=0.01) and TIMI scores (r=0.504, P=0.000). Multivariate logistic regression analysis revealed that higher creatinine levels (odds ratio =18.465, 95% confidence interval: 1.059–322.084, P=0.046) constituted the only significant predictor of increased mortality risk with no predictive values for age, D-dimer assay, ejection fraction, glucose, hemoglobin A1c, sodium, albumin or total cholesterol levels for mortality.

Conclusion: Serum creatinine levels constituted the sole independent determinant of mortality risk, with no significant values for D-dimer assay, GRACE or TIMI scores for predicting the risk of mortality in NSTEMI patients.

Keywords: acute coronary syndrome, non-ST-segment elevation myocardial infarction, GRACE score, D-dimer assay, TIMI score

Introduction

Acute coronary syndrome (ACS) is characterized by a spectrum of distinct clinical entities with a common etiology that ranges from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction depending on the severity.[1,2] Despite advances in coronary intervention techniques and equipment, ACS has still been associated with high morbidity and mortality rates.[3] This necessitates the use of guideline-recommended clinical risk score calculations for identifying life-threatening adverse cardiac outcomes, particularly in NSTEMI and UA patients, and for determining appropriate treatment and follow-up strategies.[4–6]

The term "NSTEMI patients" refers to a heterogeneous population of ACS with varying short- and long-term mortality and recurrent adverse cardiac events,

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emphasizing the crucial role of early risk stratification in these patients.[6–8]

Thrombolysis in Myocardial Infarction (TIMI)[9] risk scores and Global Registry of Acute Coronary Events (GRACE)[10] risk scores are amongst the most commonly used risk scores used to enable early risk stratification upon a patient's admission to a hospital. They are derived from databases from the comprehensive clinical trials involving NSTE-ACS or the entire spectrum of ACS, respectively.[6,8–10] The GRACE risk score is the most extensively validated and studied score that is indicated for predicting the risk of ischemic events and that is associated with prognosis in ACS.[8,11]

Owing to the acute thrombotic occlusion of coronary arteries in the etiology of ACS, and thus ongoing thrombosis in the coronary vessels that consumes platelets and clotting factors,[1,4,12,13] D-dimer level, a marker of cross-linked fibrin turnover, has been associated with ischemic heart diseases, with increased levels shown in patients with ACS.[13,14]

This cross-sectional study was aimed at determining the predictive values of D-dimer assay, GRACE and TIMI scores for adverse outcome in patients with NSTEMI.

Patients and methods

Study population

A total of 234 patients (mean [standard deviation; SD] age: 57.2 [11.7] years, 75.2% were males) hospitalized with the diagnosis of NSTEMI upon their admission to emergency service with chest pain were included in this cross-sectional prospective study conducted at Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital between June 2014 and December 2014. Patients who had acute aortic dissection, known malignancy, venous thromboembolism, pulmonary embolism and chronic kidney failure and who were on erythropoietin therapy were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Research Ethics Committee (date of approval: 06/01/2011; protocol number: 46).

Assessments

Data on demographics (age, sex), smoking status, diabetes history, previous cardiac interventions, current infarct type and treatment approach (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], medical treatment), the use of acetylsalicylic acid in the last week, pain in the last 24 h, vital signs (heart rate [beats per minute, or bpm], diastolic and systolic blood pressure [BP]), routine blood biochemistry and hemogram analysis, and D-dimer assay, GRACE and TIMI risk scores were recorded for each patient at the time of hospitalization. Patients were diagnosed with hypertension, with systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg, or they were under treatment with antihypertensive medications. Diabetes was defined as a state with a fasting plasma sugar level ≥126 mg/dL, a random glucose level ≥200 mg/dL or the ongoing treatment of diabetes.[15,16] Cardiac death was evaluated during 14-month follow-up. The relation of D-dimer levels with GRACE and TIMI risk scores was analyzed. Demographic and laboratory parameters were evaluated with respect to GRACE scores (high vs low) and outcome (survivors vs non-survivors). Logistic regression analysis was conducted to determine the risk factors predicting high GRACE scores and mortality.

Diagnosis of acute NSTEMI

NSTEMI was defined by electrocardiographic prominent T-wave inversion and/or the positive biomarkers of necrosis (eg, troponin, CK-MB) in the absence of ST-segment elevation and in an appropriate clinical setting (an anginal equivalent or chest discomfort).[17]

Calculation of GRACE risk score

The GRACE risk score was calculated based on age, heart rate, systolic BP, baseline creatinine level, history of congestive heart failure, in-hospital PCI, history of MI, ST-segment depression on admission electrocardiography (ECG) and elevated cardiac enzyme or marker levels.[10,18] Plasma 99th percentile reference limits for T troponin (ng/mL) were used in consideration of the elevated cardiac marker. ST-segment depression was defined as decreased ST segment: 0.5 mV below the isoelectric line in any ECG lead. To examine the adverse outcome for different ranges of the GRACE score, patients were divided into two subgroups: one for low GRACE risk score (≤118) and the other for high GRACE risk score (>118).

Calculation of TIMI score

The TIMI risk score was calculated based on seven independent risk factors for UA/NSTEMI, including age >65 years, ≥3 coronary artery disease (CAD) risk factors, documented CAD at catheterization (>50% stenosis), ST-segment deviation >0.5 mm, ≥2 angina episodes in

the prior 24 h, aspirin within the prior week and elevated cardiac biomarkers.[9]

D-dimer assay

Serum D-dimer levels were measured via particle-enhanced immunoturbidimetric methods using commercial kits (Roche Diagnostics, Mannheim, Germany) with the aid of a Roche Cobas 6000 c501 analyzer (Roche Diagnostics) based on a reference range of <500 ng/mL.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). A chi-square test was used for the comparison of categorical variables, whereas numeric variables were analyzed using the independent samples *t*-test. Correlation analysis was performed via Pearson's correlation analysis. Logistic regression analysis was performed for the determinants of risk for a high GRACE score and mortality using the enter method. Data were expressed as "mean (SD)", minimum–maximum and n (%), where appropriate. $P<0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics and laboratory findings

Active smoking was noted in 46.2% of patients, and diabetes mellitus was evident in 47.9%. The majority (80.3%) of patients had no history of previous cardiac intervention, whereas multi-vessel disease was evident during hospitalization in 57.7% of patients and was treated with PCI (44.4%), CABG (20.1%) and medical group (35.5%). After 14-month of follow-up, mortality occurred in 11 (4.7%) patients (Table 1).

The data on routine blood biochemistry findings are summarized in Table 1. Median D-dimer levels were 349.5 (48.0–7,210.0) ng/mL, the average TIMI score was 3.2 (1.2) and the GRACE score was 90.4 (27.6) with the

Table 1 Demographic and clinical characteristics and laboratory findings

Demographic and clinical characteristics	Result	Laboratory findings, mean (SD)	Result
Age (years), mean (SD)	57.2 (11.7)	Glucose (mg/dL)	149.2 (87.3)
Sex, n (%)		HbA1c (%)	6.6 (1.7)
Female	58 (24.8)	Sodium (mmol/L)	138.6 (3.5)
Male	176 (75.2)	Potassium (mmol/L)	4.5 (0.5)
Smoking status, n (%)		Albumin (g/dL)	4.2 (0.4)
Non-smoker	65 (27.8)	Creatinine (mg/dL)	0.9 (0.3)
Active smoker	108 (46.2)	GGT (U/L)	34.8 (36.2)
Ex-smoker	61 (26.1)	AST (U/L)	35.4 (37.9)
Diabetes mellitus, n (%)	112 (47.9)	ALT (U/L)	25.2 (26.5)
Previous cardiac intervention, n (%)		Uric acid (mg/dL)	5.6 (1.6)
None	188 (80.3)	HDL cholesterol (mg/dL)	41.0 (14.2)
CABG	20 (0.085)	Total cholesterol (mg/dL)	199.3 (47.9)
PCI or >50% plaque	26 (11.1)	Triglyceride (mg/dL)	217.1 (170.6)
Infarct type, n (%)		Hemoglobin (g/dL)	14.2 (2.0)
None or <50% coronary lesion	26 (11.1)	Hematocrit (%)	43.0 (5.6)
LAD or diagonal artery	45 (19.2)	WBC count ($10^3/mm^3$)	9.7 (2.8)
Circumflex or obtuse marginal artery	14 (6.0)	Platelet count ($10^3/mm^3$)	250.7 (86.5)
Right coronary artery	14 (6.0)	**GRACE score**	
Multi-vessel disease	135 (57.7)	Mean (SD)	90.4 (27.6)
Treatment approach, n (%)			
PCI	104 (44.4)	High (>118), n (%)	41 (17.5)
CABG	47 (20.1)	Low, n (%)	193 (82.5)
Medical treatment	83 (35.5)	**TIMI score**	3.2 (1.2; 1.0–7.0)
Duration of follow-up, mean (SD)	14.8 (2.0)	**D-dimer (ng/mL)**	
Outcome, n (%)		Mean (SD)	677.6 (1,039.7)
Alive	223 (95.3)	Median (min–max)	349.5 (48.0–7,210.0)
Deceased	11 (4.7)		
In-hospital	1 (0.4)		
Post-discharge	10 (4.3)		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; GGT, gamma-glutamyl transferase; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending coronary artery; min, minimum; max, maximum; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

identification of high GRACE scores (>118) in 17.5% of patients (Table 1).

Correlation among D-dimer assay, GRACE and TIMI scores

The GRACE score was correlated positively with both D-dimer assay (r=0.215, P=0.01) and TIMI scores (r=0.504, P=0.000). D-dimer assay and TIMI scores were also positively correlated (r=0.253, P=0.000) (Table 2).

Demographic and laboratory parameters in patients with high vs low GRACE scores

More high than low GRACE scores were associated with older age (72.2 [6.5] years vs 54.1 [10.0] years, P=0.000), a higher percentage of non-smokers (43.9% vs 24.4%, P=0.038), a higher mean D-dimer assay (1,157.7 [1,537.7] ng/mL vs 572.4 [865.3] ng/mL, P=0.001), higher TIMI scores (4.1 [1.2] vs 2.9 [1.1], P<0.001) and higher levels for heart rate (86.5 [23.9] bpm vs 75.5 [16.3] bpm, P=0.000) and creatinine levels (1.0 [0.3] mg/dL vs 0.9 [0.2] mg/dL, P=0.002), as opposed to a lower diastolic BP (74.7 [14.5] mmHg vs 81.4 [14.2] mmHg, P=0.011) as well as lower albumin (3.9 [0.4] g/dL vs 4.3 [0.3] g/dL, P=0.000), triglyceride (147.7 [115.3] mg/dL vs 232.0 [177.0] mg/dL, P=0.033) and hematocrit levels (39.1 [5.6]% vs 43.9 [5.2]%, P=0.000) (Table 3).

Demographic and laboratory parameters in survivors vs non-survivors

After an average of 15.4 and 14.8 months of follow-up, respectively, more non-survivors than survivors had older age (64.3 [8.5] years vs 56.9 [11.8] years, P=0.041) and higher levels recorded for D-dimer assay (1,568.1 [1,489.0] ng/mL vs 632.5 [995.4] ng/mL, P=0.003), glucose (242.5 [249.1] mg/dL vs 144.6 [68.9] mg/dL, P=0.000), hemoglobin A1c (HbA1c) (8.1 [3.9]% vs 6.6 [1.6]%, P=0.006) and creatinine (1.2 [0.3] mg/dL vs 0.9 [0.3] mg/dL, P=0.000), whereas they had lower levels recorded for the ejection fraction (44.5 [13.6]% vs 53.5 [10.0]%, P=0.007), albumin

Table 2 Correlation between D-dimer, GRACE and TIMI scores

	GRACE score	D-dimer	TIMI score
GRACE score			
r	1	0.215	0.504
p	–	0.001	<0.001
n	234	228	234
D-dimer			
r	0.215	1	0.253
p	0.001	–	<0.001
n	228	228	228
TIMI score			
r	0.504	0.253	1
p	<0.001	<0.001	–
n	234	228	234

Notes: *r*, correlation coefficient; *p*, Pearson's correlation analysis.
Abbreviations: GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis in Myocardial Infarction.

Table 3 Demographic and laboratory parameters in patients with high vs low GRACE scores

Parameters	GRACE score		
	Low (n=193)	High (n=41)	*P*-value*
Sex	n (%)	n (%)	
Female	44 (22.8)	14 (34.2)	0.126
Male	149 (77.2)	27 (65.8)	
Smoking status			
Non-smoker	47 (24.4)	18 (43.9)	0.038#
Active smoker	94 (48.7)	14 (34.1)	
Ex-smoker	52 (26.9)	9 (22.0)	
Diabetes mellitus	90 (46.6)	22 (53.7)	0.413
Previous CABG/PCI	14 (7.3)	7 (17.1)	0.07
Current treatment			
CABG	35 (18.1)	12 (29.3)	0.193
PCI	12 (6.2)	14 (34.1)	
Medical treatment	98 (50.8)	15 (36.6)	
	Mean (SD)	**Mean (SD)**	
Age (years)	54.1 (10.0)	72.2 (6.5)	<0.001
Cardiovascular parameters			
D-dimer (ng/mL)	572.4 (865.3)	1,157.7 (1,537.7)	0.001
TIMI score	2.9 (1.1)	4.1 (1.2)	<0.001
SBP (mmHg)	140.4 (23.8)	134.8 (20.2)	0.159
DBP (mmHg)	81.4 (14.2)	74.7 (14.5)	0.011
Heart rate (bpm)	75.5 (16.3)	86.5 (23.9)	<0.001
Complete blood count			
Hemoglobin (g/dL)	14.4 (1.9)	12.7 (2.0)	0.988
Hematocrit (%)	43.9 (5.2)	39.1 (5.6)	<0.001
WBC count (10^3/mm^3)	9.8 (2.8)	9.6 (3.2)	0.733
Platelet count (10^3/mm^3)	248.4 (80.5)	261.8 (110.9)	0.368
Blood biochemistry			
Glucose (mg/dL)	149.9 (89.2)	146.3 (78.6)	0.816
HbA1c (%)	6.6 (1.8)	6.7 (1.5)	0.863
Sodium (mmol/L)	138.7 (3.4)	138.2 (4.1)	0.122
Potassium (mmol/L)	4.4 (0.5)	4.6 (0.5)	0.330
Albumin (g/dL)	4.3 (0.3)	3.9 (0.4)	<0.001
Creatinine (mg/dL)	0.9 (0.2)	1.0 (0.3)	0.002
GGT (U/L)	34.9 (34.0)	34.0 (45.4)	0.875
AST (U/L)	36.4 (40.8)	30.9 (19.3)	0.404
ALT (U/L)	26.7 (28.7)	17.8 (9.6)	0.051
Uric acid (mg/dL)	5.5 (1.5)	6.0 (1.9)	0.079
HDL cholesterol (mg/dL)	40.5 (14.1)	43.7 (14.5)	0.191
LDL cholesterol	123.7 (43.3)	107.0 (33.8)	0.241
Total cholesterol (mg/dL)	203.9 (48.3)	178.1 (40.0)	0.427
Triglyceride (mg/dL)	232.0 (177.0)	147.7 (115.3)	0.033

Notes: *Independent samples *t*-test; #χ^2 test.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

(3.8 [0.5] g/dL vs 4.2 [0.4] g/dL, *P*=0.001) and total cholesterol (161.1 [39.9] mg/dL vs 201.1 [47.6] mg/dL, *P*=0.010). No difference was noted between survivors and non-survivors with respect to GRACE and TIMI scores (Table 4).

Table 4 Demographic and laboratory parameters in survivors vs non-survivors

Parameters	Outcome		
	Survived (n=223)	Died (n=11)	*P*-value*
Sex	**n (%)**	**n (%)**	
Female	56 (25.0)	2 (18.0)	0.603
Male	167 (75.0)	9 (81.0)	
Smoking status			
Non-smoker	61 (27.0)	4 (36.0)	0.654
Active smoker	105 (47.0)	3 (28.0)	
Ex-smoker	57 (26.0)	4 (36.0)	
Diabetes mellitus	106 (47.5)	6 (60.0)	0.468
Previous CABG	19 (8.5)	2 (18.1)	0.261
Current treatment			
CABG	43 (19.3)	4 (36.4)	0.348
PCI	101 (45.3)	3 (27.2)	
Medical treatment	89 (35.4)	4 (36.4)	
	Mean (SD)	**Mean (SD)**	***P*-value#**
Age (years)	56.9 (11.8)	64.3 (8.5)	0.041
Follow-up duration (months)	14.8 (2.0)	15.4 (1.2)	0.342
Cardiovascular parameters			
D-dimer (ng/mL)	632.5 (995.4)	1,568.1 (1,489.0)	0.003
GRACE score	89.3 (27.4)	113.3 (23.1)	0.597
TIMI score	3.1 (1.2)	4.6 (1.4)	0.359
Ejection fraction (%)	53.5 (10.0)	44.5 (13.6)	0.007
SBP (mmHg)	139.8 (23.5)	139.0 (29.2)	0.925
DBP (mmHg)	80.3 (14.5)	80.5 (13.8)	0.972
Heart rate (bpm)	79.5 (14.9)	80.0 (7.8)	0.927
Complete blood count			
Hemoglobin (g/dL)	14.2 (2.0)	12.9 (1.3)	0.094
Hematocrit (%)	43.2 (5.6)	40.1 (4.0)	0.074
WBC count (10^3/mm^3)	9.7 (2.8)	9.5 (3.9)	0.830
Platelet count (10^3/mm^3)	250.7 (83.7)	252.2 (137.2)	0.955
Blood biochemistry			
Glucose (mg/dL)	144.6 (68.9)	242.5 (249.1)	<0.001
HbA1c (%)	6.6 (1.6)	8.1 (3.9)	0.006
Sodium (mmol/L)	138.7 (3.3)	136.0 (7.0)	0.012
Potassium (mmol/L)	4.4 (0.5)	4.7 (0.5)	0.094
Albumin (g/dL)	4.2 (0.4)	3.8 (0.5)	0.001
Creatinine (mg/dL)	0.9 (0.3)	1.2 (0.3)	<0.001
GGT (U/L)	34.1 (34.0)	47.6 (66.9)	0.227
AST (U/L)	35.5 (38.6)	33.6 (20.5)	0.875
ALT (U/L)	25.2 (26.9)	24.5 (17.2)	0.929
Uric acid (mg/dL)	5.6 (1.5)	6.4 (2.4)	0.086
HDL cholesterol (mg/dL)	41.0 (14.1)	41.8 (16.7)	0.861
Total cholesterol (mg/dL)	201.1 (47.6)	161.1 (39.9)	0.010
Triglyceride (mg/dL)	219.7 (169.6)	160.0 (192.9)	0.280

Notes: *χ^2 test; #independent samples *t*-test.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

Table 5 Logistic regression analysis for risk factors predicting mortality

Parameters	Odds ratio	95% confidence interval	*P*-value
Age	1.025	0.930; 1.130	0.617
D-dimer	1.000	0.999; 1.000	0.701
Creatinine	18.465	1.059; 322.084	0.046
Ejection fraction	0.952	0.886; 1.023	0.177
Glucose	1.004	0.995; 1.013	0.407
Hemoglobin A1c	1.074	0.661; 1.747	0.772
Sodium	0.940	0.749; 1.180	0.596
Albumin	0.242	0.024; 2.392	0.225
Total cholesterol	0.980	0.956; 1.004	0.100

Logistic regression analysis for risk factors predicting mortality

Multivariate logistic regression analysis revealed that higher creatinine levels (odds ratio =18.465, 95% confidence interval [CI]: 1.059–322.084, *P*=0.046) constituted the only significant predictor of increased mortality risk with no predictive values for age, D-dimer assay, ejection fraction, glucose, HbA1c, sodium, albumin or total cholesterol levels for mortality (Table 5).

In a receiver operating characteristic (ROC) curve analysis, the area under the ROC curve for D-dimer assay to discriminate non-survivors from survivors in NSTEMI was 0.77 (95% CI: 0.66–0.88, *P*=0.002), and the optimal cutoff value was 648 ng/mL. Sensitivity and specificity with a cutoff value of 648 ng/mL were 64% and 79%, respectively (Figure 1).

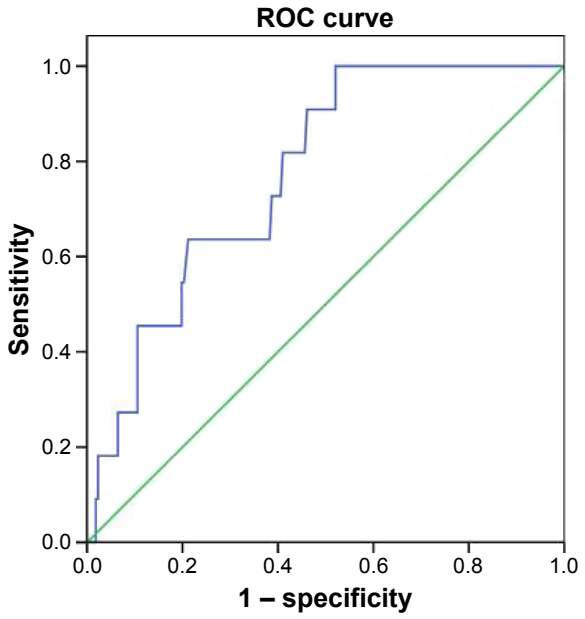

Figure 1 Receiver operating characteristic (ROC) curve analysis for area under ROC curve and optimal cutoff value of D-dimer to discriminate non-survivors from survivors in non-ST-segment elevation myocardial infarction.
Note: Diagonal segments are produced by ties.

Discussion

Our findings in a cohort of NSTEMI patients composed predominantly of males and patients with no history of previous coronary intervention revealed the diagnosis of multi-vessel disease (57.7%), the implementation of PCI/CABG (60.0%) during hospitalization in most of the patients and a mortality rate of 4.7% within an average of 14.8 months post-discharge. Older age, higher D-dimer assay and creatinine levels, and lower albumin levels were associated with both higher GRACE scores and mortality risk in the univariate analysis, whereas, except for the creatinine levels that predicted increased mortality per se, none of them was found to be a significant determinant of mortality risk in the multivariate analysis.

Amongst the variables associated with non-survivors in the univariate analysis (older age, higher levels for D-dimer assay, glucose, HbA1c and creatinine, and lower levels for the ejection fraction, albumin and total cholesterol), only higher creatinine levels predicted the increased risk for mortality in our cohort. This seems consistent with data on the prognostic importance of an elevated initial serum creatinine upon admission and the independent predictive values of renal impairment for higher in-hospital and short-term mortality among ACS patients, regardless of the subset, that were reported in past studies.[19–22]

Older age, poor glycemic control, a low ejection fraction and hypoalbuminemia along with high serum creatinine were found to be more common among non-survivors than survivors based on univariate analysis in our cohort. This seems consistent with data from past studies indicating a higher likelihood of renal impairment among older patients with comorbid hypertension, diabetes mellitus and cardiac failure, along with a stronger predictive value of even mild renal impairment for mortality and adverse cardiovascular outcome in ACS patients with left ventricular impairment.[20–23]

The predictive value of the GRACE risk score has been validated in NSTEMI by several long-term studies,[6,8,20,23,24] although it has also been shown that the GRACE risk score accurately discriminates survivors from non-survivors over the longer term in all subsets of ACS patients.[6,18,20,25,26] However, although high D-dimer levels, older age, high creatinine levels and low albumin levels were commonly noted in patients with high GRACE scores, as well as among non-survivors, no significant difference was noted between non-survivors and survivors with respect to GRACE scores in our cohort.

More females than males were reported to have a higher likelihood of presenting with atypical symptoms and more unfavorable baseline characteristics, such as higher GRACE scores, older age, a lower ejection fraction, a higher rate of heart failure, hypertension, diabetes and renal dysfunction upon admission, as associated with worse prognosis of ACS and a higher mortality rate among females.[27–29] Hence, it is worth noting that, despite male predominance, no sex influence was noted on GRACE scores or mortality risk in our cohort.

D-dimer levels, which were positively correlated with both GRACE and TIMI scores, were significantly higher in patients with high GRACE scores and in non-survivors, along with the optimal cutoff value of 648 ng/mL identified for discriminating non-survivors from survivors in our cohort. Accordingly, the significantly higher levels of D-dimer reported in ACS patients than in the controls have been indicated to reflect the pro-coagulant state associated independently with recurrent coronary events in past studies.[13,14,30] Thus, although our findings on univariate analysis support the potential role of D-dimer assay in diagnosis, risk stratification and all-cause mortality risk prediction among ACS patients,[14,31,32] multivariate analysis revealed no predictive value of D-dimer assay either for a high GRACE score or mortality risk in our cohort of NSTEMI patients.

The TIMI scores were correlated positively with both D-dimer levels and GRACE scores, whereas they did not differ between non-survivors and survivors and had no predictive value for higher GRACE scores or increased mortality risk. This seems consistent with the association of TIMI scores with the lowest discriminatory accuracy to predict death as compared with the GRACE and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin therapy (PURSUIT) scores reported on a consecutive NSTE-ACS cohort.[8]

A lower ejection fraction in non-survivors than in survivors in our cohort supports the likelihood of future complications due to a high risk of cardiac events, including not only recurrent myocardial ischemic events but also heart failure and arrhythmias among patients with NSTEMI.[6]

Higher rates for CABG/PCI among patients with high GRACE scores in our cohort seem notable considering that patients with PCI who present with NSTEMI have very high GRACE scores and represent a very high-risk patient population regarding mortality.[5] The exclusion or underpresentation of NSTEMI patients with prior coronary intervention in clinical trials has prevented the determination of best management strategy in these patients.[5] It should be noted that only one fifth of our cohort was composed of NSTEMI patients with prior coronary intervention.[5]

The main limitation of our study was its small sample size, which precludes us from reaching a more definitive conclusion regarding the predictive values of D-dimer assay,

GRACE and TIMI scores for adverse outcome in patients with NSTEMI and making a significant contribution to the refining of risk scores. The restriction of outcome to mortality is another limitation, which also results from small sample size. Since there was no myocardial infarction or coronary revascularization recorded in our cohort during study period, we could not assess the overall major adverse cardiac events risk, but could assess only mortality risk associated with elevated D-dimer for NSTEMI patients. The use of major adverse cardiac events as the outcome for D-dimer may have provided more opportunity to assess the risk associated with elevated D-dimer for NSTEMI patients. Still, evidence from this study may contribute to meta-analysis and systematic reviews, and it may form a basis for further larger-scale studies on the validity of the GRACE risk scale and risk stratification score for predicting the risk of mortality among patients with NSTEMI.

Conclusion

In conclusion, our findings in a cohort of NSTEMI patients revealed a positive correlation among TIMI scores, GRACE scores and D-dimer levels. Although higher D-dimer levels were noted in non-survivors than in survivors, and although both D-dimer levels and TIMI scores were higher in patients with high GRACE scores, serum creatinine levels constituted the sole independent determinant of mortality risk, with no significant values of D-dimer levels or of GRACE or TIMI scores to predict the risk of mortality in NSTEMI patients. Larger-scale multicenter investigations with long-term follow-up are required to address the validity of the GRACE risk scale as well as to determine the ideal risk stratification score for predicting the risk of mortality upon admission among patients with NSTE-ACS.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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