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ORIGINAL ARTICLE

Predictors of 6-month Mortality in Patients with Non-ST Elevation Acute Coronary Syndrome: A Study in Pakistani Population

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Abstract

Objectives: **For Southern Asian countries like Pakistan, there is inadequate evidence of risk factors associated with mortality in patients suffering from acute coronary syndrome (ACS), especially non-ST elevation ACS (NSTE-ACS) cases. Therefore, aim of this study was to evaluate predictors of 6-months mortality of patients presenting with NSTE-ACS.**

Methods: **For this prospective observational study we recruited adult patients diagnosed with NSTE-ACS at a tertiary cardiac center. All he patients were followed-up after six months and survival status was recorded. Logistic regression analysis was performed for six-month mortality and odds ratio (OR) and 95% confidence interval (CI) were reported.**

Results: **Six-month follow-up was successful for 280 patients. On univariate analysis age >65 years, increased heart rate, cardiac arrest at presentation, Killip class II-IV at presentation, and diabetes were found to be associated with increased risk of 6-months mortality with OR [95% CI] of 4.27 [1.9−9.58], 1.25 [1.1−1.41], 139.44 [16.9−1150.78], 68.45 [7.88−594.41], and 2.35 [1.06−5.22] respectively. On multivariable analysis Killip class II-IV at presentation, thrombolysis in myocardial infarction (TIMI) score of >4, and global registry of acute coronary events (GRACE) score ≥150 were found to be independent predictors of mortality after six months of NSTE-ACS with adjusted OR of 32.93 [2.65−408.8], 3.42 [1.35−8.66], and 8.43 [3.33−21.38] respectively.**

Conclusions: **For patients with NSTE-ACS, our study showed seven clinical parameters to be associated with an increased risk of 6-month mortality. These included increasing age, increased heart rate, cardiac arrest at presentation, Killip class II-IV, diabetes, TIMI score of >4 and GRACE score of >150. Thereby aiding clinicians to apply strategic and precise interventions in monitoring these patients accordingly.**

Keywords: Acute coronary syndrome, Non-ST elevation ACS, Predictors, 6-month mortality

1. Introduction

Acute myocardial infarction (AMI) which includes ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), remains one of the world's leading causes of death, although significant changes and developments in cardiac treatment and its control have been made [1]. More than 8 million individuals die from AMI every year, according to the World Health Organization [2]. In general,

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mortality rates range dramatically from 5 to 30% based on the patient's characteristics, the severity of ischemic disease, the country's healthcare system, among other factors. Patients presenting with STEMI have higher in-hospital mortality [3], but at 6 months the mortality rate of STEMI and NSTEMI are almost similar [4]. In Southern Asian countries, where resources are limited, there is inadequate evidence of risk factors associated with mortality in patients suffering from ACS, especially NSTEMI cases. This applies in particular to Pakistan with a population of 212.2 million and a weak health infrastructure [5] which leads to inadequate documentation of cardiovascular diseases and its mortality.

Previously many studies have been conducted to investigate the predictors of mortality of patients presenting with AMI [6–11]. However, these studies were taken place in western populations with presumably ideal treatment and disease control. Several studies have showcased various clinical characteristics of the AMI patients with their comorbidities as predictors of cardiovascular mortality [7,8,11–14]. There is significant evidence to believe that in the South Asian countries like Pakistan, conventional risk factors that are well known in high-income countries play a similar role in cardiovascular diseases (CVD) mortality. However, greater mortality rate in these regions can be justified by varying risk factors including different genetics, lifestyle and healthcare service and other additional factors. Despite greater CVD burden on lower middle income countries like Pakistan [15], limited data exists regarding predictors of mortality of NSTEMI. We therefore evaluated predictors of 6-months mortality of patients presenting with NSTEMI at the largest cardiac care center of the country, in effort to explore the factors which have a major effect on mortality of NSTEMI patients in this study.

2. Methods

For this prospective observational study we recruited 300 adult patients, between 18 and 80 years of age, diagnosed as non-ST elevation acute coronary syndrome (NSTE-ACS) at emergency department of a tertiary care cardiac hospital of Karachi, Pakistan between October 2019 and March 2020. Study was approved by the ethical review committee of the institution (ERC-43/2019). Patients with history of cardiac related intervention or surgery or patients who refused to give consent for participation and follow-up were excluded.

List of Abbreviations

CVD	cardiovascular diseases
ACS	acute coronary syndrome
AMI	acute myocardial infarction
NSTE-ACS	non-ST elevation acute coronary syndrome
STEMI	ST elevation myocardial infarction
GRACE	global registry of acute coronary events
TIMI	thrombolysis in myocardial infarction
CI	confidence interval
SD	standard deviation
OR	odds ratio

Diagnosis of NSTE-ACS was made based on history of typical chest pain, electrocardiogram (ECG) changes, and rise of high-sensitivity troponin I as per the guidelines. Patients' clinical status at presentation, demographic data, risk profile, and risk stratification scores such as TIMI and GRACE 2.0 scores were obtained. All the patients were managed as per the clinical practice guidelines and institutional protocols by consultant cardiologists. All he patients were followed-up after six months and survival status was recorded. Cases lost during follow-up were excluded from the final analysis.

Collected data were analyzed using IBM SPSS (version 21). Patients' baseline characteristics such as demographics, risk factors, hemodynamic parameters, functional class, and risk scores were expressed as mean ± standard deviation (SD) or frequency percentages (%) appropriately and compared by the six-month survival status with the help of t-test or Chi-square test. Univariate logistic regression analysis was performed with six-month mortality as dependent and patients' baseline characteristics as independent variables. After removing clinically and statistically redundant variables in the presence of GRACE and TIMI score, the explanatory variables for the multivariable logistic regression analysis were KILLIP class II-IV, TIMI score of 4 or higher, and GRACE 2.0 score of 150 or higher to determine the predictors of short-term (six-month) mortality. Results of the univariate and multivariate logistic regression analysis are reported odds ratio (OR) along with its 95% confidence interval. Statistical criteria for significance was p-value of 0.05 or lesser.

3. Results

A total of 300 NSTE-ACS were recruited for this study, 6-months follow-up was successful for 280 patients with lose to follow-up rate of 6.7%. Baseline

Table 1. Baseline demographic and clinical characteristics stratified by the survival status after six months of NSTE-ACS.

Characteristics	Total	Outcome after 6 months		p-value
		Survived	Expired	
Total (N)	**280**	**252**	**28**	**-**
Gender				
Male	76.8% (215)	77.4% (195)	71.4% (20)	0.479
Female	23.2% (65)	22.6% (57)	28.6% (8)	
Age (years)	58.19 ± 10.68	57.42 ± 10.05	65.11 ± 13.58	<0.001*
≤50 years	26.8% (75)	27.4% (69)	21.4% (6)	0.001*
51–65 years	51.1% (143)	53.6% (135)	28.6% (8)	
>65 years	22.1% (62)	19% (48)	50% (14)	
KILLIP class at presentation				
I	84.6% (237)	90.9% (229)	28.6% (8)	<0.001*
II	12.9% (36)	8.7% (22)	50% (14)	
III	1.8% (5)	0% (0)	17.9% (5)	
IV	0.7% (2)	0.4% (1)	3.6% (1)	
Risk factors				
Diabetes	41.8% (117)	39.7% (100)	60.7% (17)	0.032*
Hypertension	84.6% (237)	84.1% (212)	89.3% (25)	0.473
Smoking	27.1% (76)	27.8% (70)	21.4% (6)	0.474
Family history of CAD	11.1% (31)	10.7% (27)	14.3% (4)	0.568
Dyslipidemia	14.6% (41)	14.3% (36)	17.9% (5)	0.612
Obesity	7.9% (22)	7.1% (18)	14.3% (4)	0.183
Sedentary lifestyle	30.7% (86)	30.2% (76)	35.7% (10)	0.545
Cardiac arrest	3.9% (11)	0.4% (1)	35.7% (10)	<0.001*
Heart Rate (bpm)	77.49 ± 13.98	76.45 ± 13.01	86.89 ± 18.54	<0.001*
SBP (mmHg)	121.04 ± 16.77	121.16 ± 16.45	119.89 ± 19.69	0.705
Serum creatinine (ng/dL)	1.48 ± 6.98	1.49 ± 7.36	1.43 ± 0.67	0.970
Troponin I (ng/dL)	6.74 ± 17.21	6.63 ± 17.81	7.77 ± 10.62	0.740
Electrocardiography (ECG) at presentation				
T-wave Inversion	32.1% (90)	32.9% (83)	25% (7)	0.394
ST-segment depression	43.2% (121)	43.3% (109)	42.9% (12)	0.968
Wellens Sign	2.5% (7)	2.4% (6)	3.6% (1)	0.702
Nonspecific changes	14.6% (41)	13.5% (34)	25% (7)	0.102
Ejection Fraction (%) on echocardiography				
≤30%	22.9% (64)	19.8% (50)	50% (14)	<0.001*
30–45%	35.4% (99)	34.9% (88)	39.3% (11)	0.647
>45%	41.8% (117)	45.2% (114)	10.7% (3)	<0.001*
TIMI Score	3.17 ± 0.86	3.1 ± 0.84	3.86 ± 0.76	<0.001*
TIMI Score ≥4	34.6% (97)	31.3% (79)	64.3% (18)	<0.001*
GRACE 2.0 Score	120.64 ± 33.1	116.68 ± 30.16	156.29 ± 37.38	<0.001*
GRACE Score ≥150	18.9% (53)	14.3% (36)	60.7% (17)	<0.001*

CAD = coronary artery diseases, SBP = Systolic blood pressure, GRACE = Global Registry for Acute Coronary Events, TIMI = thrombolysis in myocardial infarction.
* Significant at 5%.

demographic and clinical characteristics stratified by the survival status after six months of NSTE-ACS are presented in Table 1. Overall mortality rate after six months of NSTE-ACS was 10.0% (28/280). Mean age of the expired patients was significantly higher than that that of survived patients, 65.11 ± 13.58 vs. 57.42 ± 10.05 years; $p < 0.001$. Mortality rate was significantly higher among patients above 65 years of age, 22.6% (14/62) vs. 6.4% (14/218); $p < 0.001$, as compared to patient group between 18 and 65 years of age. Killip class at presentation was found to be associated with 6-months mortality with mortality rate of 3.4% (8/237) vs. 46.5% (20/43); $p < 0.001$ in patients with Killip class I and II to IV respectively. Similarly, patients in cardiac arrest and patients with diabetes were found to have significantly higher mortality rate with mortality rates of 14.5% (17/117) vs. 6.7% (11/163); $p = 0.032$ for diabetic and non-diabetic patients and 90.9% (10/11) vs. 6.7% (18/269); $p < 0.001$ for patients with and without cardiac arrest respectively.

Left heart catheterization (LHC) findings and management strategy stratified by the survival status after six months of NSTE-ACS are presented in Table 2. LHC was performed in 99 (35.4%) patients and subsequently percutaneous coronary interventions (PCI) was performed in only 38 (13.6%) patients while remaining 86.4% of the patients received medical treatment. Among patients who undergone LHC, diseased left main (LM) and

Table 2. Left heart catheterization findings and management strategy stratified by the survival status after six months of NSTE-ACS.

Characteristics	Total	Outcome after 6 months		p-value
		Survived	Expired	
Total (N)	**280**	**252**	**28**	-
Left heart catheterization done	35.4% (99)	35.3% (89)	35.7% (10)	0.967
Number of diseases vessels				
Normal	2% (2)	2.2% (2)	0% (0)	0.336
Single vessel (SVD)	26.3% (26)	27% (24)	20% (2)	
Two vessel (2VD)	16.2% (16)	18% (16)	0% (0)	
Three vessel (3VD)	55.6% (55)	52.8% (47)	80% (8)	
Involved vessel				
Left main	11.1% (11)	9% (8)	30% (3)	0.045*
Left anterior descending artery (LAD)	86.9% (86)	85.4% (76)	100% (10)	0.195
Right coronary artery (RCA)	66.7% (66)	67.4% (60)	60% (6)	0.637
Left circumflex (LCx)	68.7% (68)	67.4% (60)	80% (8)	0.416
Obtuse marginal (OM)	4% (4)	2.2% (2)	20% (2)	0.007*
None	2% (2)	2.2% (2)	0% (0)	0.632
Management Strategy				
Medical treatment	86.4% (242)	85.3% (215)	96.4% (27)	0.103
PCI done	13.6% (38)	14.7% (37)	3.6% (1)	
Access site				
Radial	86.8% (33)	89.2% (33)	0% (0)	0.009*
Femoral	13.2% (5)	10.8% (4)	100% (1)	
PCI vessel				
LAD	57.9% (22)	59.5% (22)	0% (0)	–
LCx	7.9% (3)	8.1% (3)	0% (0)	
LM to LAD	2.6% (1)	2.7% (1)	0% (0)	
LCx and RCA	2.6% (1)	2.7% (1)	0% (0)	
RCA	26.3% (10)	27% (10)	0% (0)	
SVG-OM and LCx	2.6% (1)	0% (0)	100% (1)	

PCI = percutaneous coronary interventions, SVG = saphenous vein graft.
* Significant at 5%.

obtuse marginal (OM) were more common in expired cohort as compared to survived cohort. Six-month mortality rate was relatively higher for medically treated patients as compared to the patients who underwent PCI (11.2% (27/242) vs. 2.6% (1/38); p = 0.103).

Odds ratios (OR) of mortality after six months of NSTE-ACS by various clinical characteristics in multivariate and univariate logistic regression

Table 3. Odds ratios (OR) of multivariate and univariate logistic regression analysis for mortality after six months of NSTE-ACS.

Parameters	Univariate		Multivariate	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Female	1.37 [0.57–3.27]	0.481	–	–
>65 years	4.27 [1.9–9.58]	<0.001*	–	–
Heart Rate (per 5 bpm)	1.25 [1.1–1.41]	<0.001*	–	–
Serum creatinine (ng/dL)	1 [0.94–1.06]	0.971	–	–
Troponin I (ng/dL)	1 [0.99–1.02]	0.743	–	–
Cardiac arrest	139.44 [16.9–1150.78]	<0.001*	32.93 [2.65–408.8]	0.007*
KILLIP class II-IV	68.45 [7.88–594.41]	<0.001*	–	–
Diabetes	2.35 [1.06–5.22]	0.036*	–	–
Hypertension	1.57 [0.45–5.46]	0.476	–	–
Family history of CAD	1.39 [0.45–4.3]	0.569	–	–
Dyslipidemia	1.3 [0.47–3.65]	0.613	–	–
Smoking	0.71 [0.28–1.82]	0.475	–	–
Obesity	2.17 [0.68–6.93]	0.192	–	–
PCI done	0.22 [0.03–1.63]	0.137	–	–
TIMI Score ≥4	3.94 [1.74–8.93]	0.001*	3.42 [1.35–8.66]	0.009*
GRACE 2.0 Score ≥150	9.27 [4.02–21.4]	<0.001*	8.43 [3.33–21.38]	<0.001*

OR = odds ratio, CI = confidence interval, CAD = coronary artery diseases, GRACE = Global Registry for Acute Coronary Events, TIMI = thrombolysis in myocardial infarction.
* Significant at 5%.

analysis are presented in Table 3. On univariate analysis age above 65 years, increased heart rate, cardiac arrest at presentation, Killip class II-IV at presentation, and diabetes were found to be associated with increased risk of 6-months mortality with OR [95% CI] of 4.27 [1.9–9.58], 1.25 [1.1–1.41], 139.44 [16.9–1150.78], 68.45 [7.88–594.41], and 2.35 [1.06–5.22] respectively. Risk stratification based on TIMI score with cutoff of ≥4 had OR of 3.94 [1.74–8.93] with mortality rate of 18.6% (18/97) vs. 5.5% (10/183); $p < 0.001$ for patients with TIMI score ≥4 and < 4 respectively. Similarly, risk stratification based on GRACE score with cutoff of ≥150 had OR of 9.27 [4.02–21.4] with mortality rate of 32.1% (17/53) vs. 4.8% (11/227); $p < 0.001$ for patients with GRACE 2.0 score ≥150 and < 150 respectively. On multivariable analysis KILLIP class II-IV, TIMI Score ≥4 and GRACE 2.0 score ≥150 were found to be independent predictors of mortality after six months of NSTE-ACS with adjusted OR of 32.93 [2.65–408.8], 3.42 [1.35–8.66], and 8.43 [3.33–21.38] respectively.

4. Discussion

This study is the first to investigate the predictors of 6-months mortality in a relatively large number of NSTE-ACS patients hospitalized in tertiary cardiac care center in Pakistan. The observed predictors in this study were similar to the ones found in the large acute myocardial infarction registries of western regions like USA and Europe. Here we observed several baseline characteristics such as age, KILLIP class, diabetes, cardiac arrest, heart rate, TIMI score and GRACE 2.0 score to be significant ($p \leq 0.05$) predictors of 6-months mortality of patients presenting with NSTEMI.

In our study, mortality rate for the patients with NSTE-ACS at 6-month was observed to be 10.0%, data on post discharge outcome of these patients is scarce, especially for South Asian Region. A study based on Korea Acute Myocardial Infarction Registry by Kim HK et al. [16] reported one year mortality rate of 14.3% after NSTEMI. A study conducted by Chehab O et al. [17] in Beirut, Lebanon, reported in-hospital mortality rate of 7.6% for NSTEMI patients.

In several AMI trials, elderly age has been a constant mortality predictor. In a study by Goldberg et al. found that the probability of mortality was more than 10-fold greater proportionally with patients over 85 years of age than with patients aged between 55 and 64 [18]. Similar results can be found in studies by Chehab, Omar et al. [17] and Rosengren et al. [19]. These findings are in consistent with the result of our study, where age more than 65 years old proves to be a significant mortality predictor. One possible explanation for this is that elderly people are expected to have more severe heart disease, but they are less likely to undergo the same intense care in revascularization and anti-ischemic therapy procedures than younger patients [19–22].

In terms of multivariate analysis, cardiac arrest at presentation and GRACE risk score above 150 were found to be strong independent predictors of mortality of NSTE-ACS. The recommendations of the European Society of Cardiology (ESC) have emphasized the importance of cardiac arrest in the treatment of patients with AMI due to their high risk association [23] This finding is in consistent with a study by Chen, Ying-Hwa et al., which concluded both risk score models (TIMI and GRACE) having high discriminatory accuracy in predicting both short and long-term mortality for ACS, including NSTEMI group of patients [24].

Moreover, our analysis demonstrates KILLIP class II-IV, and prior history of diabetes as the only risk factor, to be significant predictors of mortality for 6-months of NSTEMI. This result can be compared with a study by Kim, Hyun Kuk et al. [16]. For more than 50 years, Killip class was known as a significant mortality predictor [25]. Diabetes accounts for 1.6 million deaths annually worldwide [26], where diabetes being one of the most prevalent non-communicable diseases in Pakistan, with up to 11.7% of the adult population living with it [27].

There are certain limitations in the study which we cannot overlook upon. Firstly, this is a single center study conducted at a tertiary care cardiac center of Pakistan, therefore its results cannot be generalized to the whole region. To accurately evaluate the predictors of mortality for NSTEMI patients, data should be collected from multiple settings from different regions. Secondly, being a prospective study, there were few losses of follow up data which could result in biasness. Thirdly, we did not consider therapeutic interventions or prescribed medications in our parameters, which may have certain impact on the mortality rate for patients in our setting. Additional studies must be carried out to remove these limitations and gain further insight to the predictors of mortality of NSTEMI patients.

5. Conclusion

In conclusion, our study demonstrates various clinical parameters as predictors of 6-months mortality for patients presenting with NSTE-ACS. These included age, KILLIP class, diabetes, cardiac arrest,

heart rate, TIMI score and GRACE score. With prior knowledge of the significance of mortality predictors, this may prove to be a life-saving tool in cardiac care settings, where it would aid clinicians to reduce the mortality rate in patients presenting with NSTEMI.

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Conflict of interest

None to declare.

Authors' contribution

Dileep Kumar: Conception, Literature review, Methodology, Software analysis, Investigation, Writer-original draft, Writing- review & editing, Visualization, Project administration, Fundings.

Tahir Saghir: Conception, Investigation, Writing-review & editing, Supervision, Fundings.

Rajesh Kumar: Literature review, Methodology, Investigation, Data collection.

Jawaid Akbar Sial: Literature review, Investigation, Data collection, Writer-original draft, Writing-review & editing, Supervision.

Kamran Ahmed Khan: Methodology, Software analysis, Investigation, Writer-original draft.

Jehangir Ali Shah: Literature review, Methodology, Investigation, Data collection, Writer-original draft.

Musa Karim: Software analysis, Investigation, Writer-original draft, Writing- review & editing, Visualization.

Abdul Mueed: Literature review, Software analysis, Investigation, Data collection, Writer-original draft.

Reeta Bai: Methodology, Software analysis, Data collection, Project administration.

Hitesh Kumar: Methodology, Data collection, Project administration.

Sajjad Ali: Methodology, Data collection, Project administration.

Rekha Kumari: Methodology, Software analysis, Investigation, Data collection, Project administration.

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