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# The Burden of Short-term Major Adverse Cardiac Events and its Determinants after Emergency Percutaneous Coronary Revascularization: A Prospective Follow-up Study

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## Abstract

**Objectives:** Primary percutaneous coronary intervention (PCI) remains recommended reperfusion therapy for patients with acute ST-elevation myocardial infarction. This study aimed to evaluate the short-term major adverse cardiac events (MACE) and their determinants among patients who underwent primary PCI at a tertiary care cardiac center of Karachi, Pakistan.

**Methods:** A cohort of patients who underwent primary PCI were followed for the MACE. Multivariable Cox-regression analysis was performed with backward conditional variable selection and hazard ratio (HR) along with 95% confidence interval (CI) were obtained.

**Results:** A total of 1150 patients were included, of which follow-up was successful in 95.8% (1102) and median follow-up duration was 6.1 [6.9–5.1] months. MACE were observed in 210 (19.1%) patients with 14.2% (157) all-cause mortality, 5.4% (60) cardiac mortality, 0.7% (8) stroke, 3.6% (40) re-hospitalization due to heart failure, and 6.1% (67) myocardial infarction requiring revascularization. Independent predictors of short-term MACE were found to be admission glucose  $\geq 200$  mg/dL (1.66 [1.25–2.21]), serum creatinine  $\geq 1.5$  mg/dL (1.52 [1.02–2.27]), intubation (2.81 [1.98–4.00]), history of PCI (2.06 [1.45–2.93]), history of cerebrovascular accident (2.64 [1.34–5.2]), left ventricular end-diastolic pressure  $\geq 20$  mmHg (1.81 [1.3–2.51]), triple vessel diseases (1.43 [1.08–1.9]), culprit left main or proximal left anterior descending artery (1.77 [1.32–2.35]), pre-dilatation (2.14 [1.2–3.82]), and thrombus grade  $\geq 4$  (2.21 [1.51–3.24]).

**Conclusions:** A significant number of individuals undergone primary PCI are still vulnerable to subsequent short-term MACE, hence, systematic follow-up and early risk stratification should be considered as an integral part of STEMI management protocol specially for patients with high-risk features as highlighted herein.

**Keywords:** Myocardial infarction, ST Elevation myocardial infarction, Percutaneous coronary intervention, Death, Sudden, Cardiac

## 1. Introduction

In the west, atherosclerotic cardiovascular disease is still the major factor of disability and mortality [1]. ST-segment elevation myocardial infarction (STEMI) presents an intense manifestation of the

coronary arteries involvement associated with adverse prognosis such as acute pump failure, lethal arrhythmias, left ventricular (LV) dysfunction, and myocardial rupture in short-term as well as long-term basis [2]. Emergency percutaneous coronary revascularization (PPCI) is widely acknowledged as the foremost successful treatment for reinstating

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vessel patency, saving compromised myocardium, and maintaining heart function [2]. Owing to unfavorable LV restoration, culprit lesion restenosis, de novo coronary stenosis and myocardial stunning, a significant number of individuals are still vulnerable to initial mechanical/electrical complications and late major adverse cardiovascular events (MACE) [3], making the identification of highly vulnerable patient subsets a critical issue in improving overall outcome of disease.

Even after the successful PCI and optimal treatments that include dual antiplatelet therapy (DAPT), as high as 15% of individuals with STEMI experiences MACE primarily because of thrombotic impediments [4]. The clinical practice guidelines have vividly outlined the management and treatment protocols, however, recommendations regarding assessment of the short-or long-term risk of MACE are not very clear. Fewer techniques can be applied to estimate the occurrence of MACE among individuals with STEMI after primary PCI to guide communication between clinician and patient to mitigate the risk of post-discharge adverse events [5].

Various risk and prognosis evaluation models for cardiovascular disease have been developed in various sub-groups for the guided management of patients [6,7], guideline-recommended and most commonly used models for the prediction of short and medium-term cardiovascular outcomes for individuals with the acute coronary syndrome (ACS) are the GRACE score and Thrombolysis in Myocardial Infarction (TIMI) risk score [8]. In addition to these two, the CADILLAC risk score is applied for predicting one month and one year death in patients with acute myocardial infarction (AMI) after PCI [6]. Unfortunately, there is no clear clinical risk stratification for prolonged MACE in individuals with ACS after PCI. The extent of the infarcted and remnant viable myocardium is the most important prognostic factor for individuals with STEMI. As soon as the culprit vessel is effectively opened by primary PCI and the ischemic region is restricted, a variety of additional parameters can come into play in predicting the medium- and long-term outcomes of these individuals.

Precision medicine requires that the management, procedures, and treatments be tailored to every patient's expected risk. Recently a growing number of researches have centered on laboratory testing-based parameters for risk prediction. However, such data is skewed to certain geographies, and data from low- and middle-income countries, such as Pakistan, are very limited. Therefore, the objective of this study was to assess the short-term MACE and their determinants among patients who have

#### List of abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
CHF	congestive heart failure
CI	confidence interval
CS	cardiogenic shock
CVA	cerebrovascular accident
DAPT	dual antiplatelet therapy
eGFR	estimated glomerular filtration rate
GRACE	Global registry of acute coronary events
HR	hazard ratio
IQR	interquartile range
LV	left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
OPD	outpatient department
PCI	percutaneous coronary intervention
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
TB	thrombus burden
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction

undergone primary PCI at a tertiary care cardiac center of Karachi, Pakistan.

## 2. Material and methods

This study was conducted at the largest public sector tertiary care cardiac center of Karachi, Pakistan between August 2020 and July 2021. The study was approved by the ethical review board of the institution (ERC-30/2020) informed consent was obtained from all the recruited patients or their legal caretakers for the procedure, inclusion in this study, post-discharge follow-up, and publication of research findings. In this study, a prospectively recruited cohort of patients were followed for the incidence of short-term MACE after primary PCI. Inclusion criteria for the study were consecutive individuals presented with chest pain at the emergency department of the public sector tertiary care cardiac center of Karachi, Pakistan, diagnosed with STEMI, and undergone primary PCI within a recommended window period of 12 h with an exception for patients in cardiogenic shock at presentation. Major exclusion criteria included unsuccessful procedure, the requirement for multi-vessel PCI during the index procedure, and the presence of serious illness with a life expectancy of less than one year. As per the clinical practice guidelines and routine institution policy, culprit artery was treated in the index procedure unless hemodynamics and clinical status of patient were compelling enough for multi-vessel PCI. Therefore,

due to expected higher MACE, patients needing multi-vessel PCI during the index procedure were excluded.

Data for this study were collected on a predefined structured proforma consisting of demographic characteristics, clinical characteristics, laboratory investigations, angiographic findings, procedure-related details, post procedure in-hospital outcomes, and short-term MACE. MACE was defined as the occurrence of either all-cause mortality, cardiovascular mortality, myocardial infarction (with or without revascularization), unplanned hospitalization due to heart failure, or occurrence of stroke/cerebrovascular events during the follow-up period. Due to COVID-19 restrictions, most of the follow-up data were obtained through telephonic contact on the registered number of the patient or her/his emergency contact/legal caretaker. Follow-up was planned after 6-months of the index hospitalization. Protocol for the lost to follow-up was non-responders to the three contact attempts on three separate days at the registered contact number of the patient as well as her/his emergency contact/legal caretaker during the 9:00 am to 5:00 pm window. Alongside telephonic follow-up, the scheduled outpatient department (OPD) visits of the patients were also recorded, and at the end of the study period most recent status of the patient was taken as the outcome. Pharmacological management, in-hospital as well as at the time of discharge, were as per the guideline recommendations. Each patient received initial doses of aspirin, clopidogrel, unfractionated heparin, and bolus dose of glycoprotein inhibitors (IIb/IIIa), and DAPT as a maintenance therapy continued for at least 1 year, the dosage of all the medications were as per the guidelines recommendations. Due to cost-effectiveness, use of Ticagrelor was limited to patients with diabetes, high-risk anatomy, or stent thrombosis.

Sample size for the study was calculated using WHO sample size calculator version 2.0 against the primary outcome of incidence of MACE after primary PCI. A study conducted by Cai A et al. [9], reported MACE in 21.7% of the patients at  $0.8 \pm 0.3$  year follow-up after PCI (urgent or elective). Hence taking expected MACE rate of 21.7%, with confidence level of 95%, and an absolute precision level (margin of error) of 2.5%, a sample size of 1045 was calculated for the study. Adjusting for the expected loss to follow-up rate of 10%, a total of 1150 patients were recruited in this study. Collected data were analyzed with the help of IBM SPSS version 21.0. Patients were stratified into two groups based on the occurrence of short-term MACE. Demographic characteristics, clinical characteristics, laboratory

investigations, angiographic findings, and procedure-related details were compared between the two groups. Continuous response variables were expressed as mean  $\pm$  standard deviation (SD) or median [interquartile range (IQR)] and independent-sample t-test/Mann–Whitney U test was applied to compare between the two groups. Frequency (%) was computed for categorical response variables and distribution of variables with two levels was compared between the two groups with the help of the Chi-square test or Fisher's Exact test if the expected cell count were less than five. Similarly, the distribution of variables with more than two levels were compared between the two groups with the help of the Chi-square test or Likelihood Ratio test if the expected cell count were less than five. Univariate and multivariable Cox regression analysis was performed with backward conditional variable selection and hazard ratio (OR) along with 95% confidence interval (CI) were obtained. Variables with a p-value of  $<0.10$  in the univariate analysis were taken as regressors in the multivariable Cox regression analysis and p-value  $\leq 0.05$  was taken criteria for statistical significance.

### 3. Results

A total of 1150 patients were recruited for this study out of which 48 (4.2%) patients lost to follow-up, hence, 1102 patients with a successful median follow-up of 6.1 [6.9–5.1] months were included in the analysis for the study. Male patients were 79.6% (877) of the total sample and the mean age was  $55.66 \pm 11.48$  years with 25% (275) of the patients being  $\geq 65$  years of age. During the follow-up duration, MACE was observed in 210 (19.1%) patients. The occurrence of MACE was observed to be associated with older age with a mean age of  $58.43 \pm 11.01$  vs.  $55 \pm 11.5$ ;  $p < 0.001$  for patients with and without MACE respectively. At presentation hypotension (SBP  $< 90$  mmHg), tachycardia ( $\geq 100$  bpm), impaired random blood glucose level ( $\geq 200$  mg/dL), serum creatinine  $\geq 1.5$  mg/dL, and higher Killip class were found to be associated with the occurrence of short-term MACE (Table 1). Similarly, patients with arrhythmias on presentation, in cardiac arrest, or intubated had significantly higher distribution among patients with short-term MACE. Type of MI and presence of certain co-morbid conditions such as hypertension, diabetes, prior PCI, history of cerebrovascular accident (CVA)/transient ischemic attack (TIA), or chronic kidney disease were also found to be associated with increased incidence of short-term MACE.

Table 1. Association of short-term major adverse cardiovascular events (MACE) with various demographic characteristics and clinical factors.

Characteristics	Total	MACE		P-value
		No	Yes	
<b>Total (N)</b>	<b>1102</b>	<b>892 (80.9%)</b>	<b>210 (19.1%)</b>	<b>-</b>
<b>Gender</b>				
Female	20.4% (225)	19.4% (173)	24.8% (52)	0.083
Male	79.6% (877)	80.6% (719)	75.2% (158)	
<b>Age (years)</b>	<b>55.66 ± 11.48</b>	<b>55 ± 11.5</b>	<b>58.43 ± 11.01</b>	<b>&lt;0.001</b>
<45 years	14.5% (160)	15.8% (141)	9% (19)	0.008
45–64 years	60.5% (667)	60.8% (542)	59.5% (125)	
≥65 years	25% (275)	23.4% (209)	31.4% (66)	
<b>Total Ischemic Time (hours)</b>	<b>350 [500–240]</b>	<b>340 [480–230.5]</b>	<b>372.5 [580–240]</b>	<b>0.075</b>
≤120 min	4.1% (45)	4.3% (38)	3.3% (7)	0.154
121–360 min	48.6% (536)	49.3% (440)	45.7% (96)	
361–720 min	36.8% (405)	36.9% (329)	36.2% (76)	
>720 min	10.5% (116)	9.5% (85)	14.8% (31)	
<b>Systolic blood pressure (mmHg)</b>	<b>130.9 ± 25.1</b>	<b>132.5 ± 24.1</b>	<b>123.8 ± 27.9</b>	<b>&lt;0.001</b>
>90 mmHg	94.1% (1037)	96.4% (860)	84.3% (177)	<0.001
≤90 mmHg	5.9% (65)	3.6% (32)	15.7% (33)	
<b>Heart Rate (bpm)</b>	<b>84.9 ± 20.1</b>	<b>84 ± 19</b>	<b>88.8 ± 24</b>	<b>0.007</b>
<100 bpm	77.8% (857)	80.4% (717)	66.7% (140)	<0.001
≥100 bpm	22.2% (245)	19.6% (175)	33.3% (70)	
<b>Random glucose level (mg/dL)</b>	<b>157 [209–130]</b>	<b>150.5 [200–127.5]</b>	<b>188 [250–140]</b>	<b>&lt;0.001</b>
<200 mg/dL	71.2% (785)	74.7% (666)	56.7% (119)	<0.001
≥200 mg/dL	28.8% (317)	25.3% (226)	43.3% (91)	
<b>Hemoglobin level (mg/dL)</b>	<b>13.68 ± 1.93</b>	<b>13.71 ± 1.91</b>	<b>13.55 ± 2.03</b>	<b>0.279</b>
>12.5 mg/dL	71.9% (792)	73% (651)	67.1% (141)	0.090
≤12.5 mg/dL	28.1% (310)	27% (241)	32.9% (69)	
<b>Neutrophil count (cells/μL)</b>	<b>9.81 ± 3.82</b>	<b>9.69 ± 3.76</b>	<b>10.31 ± 4.07</b>	<b>0.046</b>
<9.5 cells/μL	53.5% (590)	54.9% (490)	47.6% (100)	0.056
≥9.5 cells/μL	46.5% (512)	45.1% (402)	52.4% (110)	
<b>Platelet count (cells/μL)</b>	<b>235 [281–192]</b>	<b>236 [279.5–191.5]</b>	<b>229.5 [287–192]</b>	<b>0.824</b>
<400 cells/μL	97.5% (1075)	98.1% (875)	95.2% (200)	0.016
≥400 cells/μL	2.5% (27)	1.9% (17)	4.8% (10)	
<b>Serum creatinine (mg/dL)</b>	<b>1.03 ± 0.47</b>	<b>1.02 ± 0.48</b>	<b>1.09 ± 0.43</b>	<b>0.037</b>
<1.5 mg/dL	91.7% (1011)	93% (830)	86.2% (181)	0.001
≥1.5 mg/dL	8.3% (91)	7% (62)	13.8% (29)	
<b>Killip Class</b>				
I	76.4% (842)	82.6% (737)	50% (105)	<0.001
II	12.3% (135)	10.1% (90)	21.4% (45)	
III	6.9% (76)	4.7% (42)	16.2% (34)	
IV	4.4% (49)	2.6% (23)	12.4% (26)	
<b>Type of myocardial infarction (MI)</b>				
Anterior	54.4% (599)	52.4% (467)	62.9% (132)	0.003**
Inferior	19.5% (215)	21.5% (192)	11% (23)	
Inferior with RV	17.1% (188)	16.7% (149)	18.6% (39)	
Inferio-posterior	5.6% (62)	5.9% (53)	4.3% (9)	
Lateral	1.8% (20)	2% (18)	1% (2)	
Posterior	1.6% (18)	1.5% (13)	2.4% (5)	
<b>Intubated</b>	<b>13.3% (147)</b>	<b>8.3% (74)</b>	<b>34.8% (73)</b>	<b>&lt;0.001</b>
<b>Arrhythmias on presentation</b>	<b>12.4% (137)</b>	<b>9.2% (82)</b>	<b>26.2% (55)</b>	<b>&lt;0.001</b>
<b>Cardiac arrest</b>	<b>6.2% (68)</b>	<b>3.8% (34)</b>	<b>16.2% (34)</b>	<b>&lt;0.001</b>
<b>Co-morbid conditions</b>				
Hypertension	58.2% (641)	55.8% (498)	68.1% (143)	0.001
Smoking	31.3% (345)	32.5% (290)	26.2% (55)	0.076
Diabetes mellitus	39.8% (439)	36.4% (325)	54.3% (114)	<0.001
Prior PCI	6.9% (76)	3.9% (35)	19.5% (41)	<0.001
History of CVA/TIA	2% (22)	1.5% (13)	4.3% (9)	0.023
Chronic kidney disease	3.8% (42)	3.3% (29)	6.2% (13)	0.045

MACE = major adverse cardiovascular events, RV = right ventricular, PCI = percutaneous coronary intervention, CVA = cerebrovascular accident, TIA = transient ischemic attack.

\*\*Likelihood Ratio test, Fisher's Exact test.

The occurrence of MACE was observed to be associated with elevated left ventricular end-diastolic pressure (LVEDP  $\geq 20$  mmHg), mean LVEDP ( $23.0 \pm 8.0$  vs.  $17.7 \pm 5.8$  mmHg;  $p < 0.001$ ) was found to be significantly higher among patients with short-term MACE. Patients with elevated LVEDP ( $\geq 20$  mmHg) were found to be at increased risk of MACE with risk ratio of 4.07 [2.94–5.63] and MACE rate of 31.1% (147/472) among patients with elevated LVEDP as against 10.0% (63/630) among patients with LVEDP  $< 20$  mmHg. Similarly, reduced left ventricular ejection fraction (LVEF  $\leq 30\%$ ) was found to be more prevalent in patients with short-term MACE, 40% vs. 13.2%, as compared to the patients without short-term MACE respectively. Intra-aortic balloon pump placement and use of pre-balloon were also found to be associated with increased

incidence of MACE. Among other angiographic findings, distribution of the number of vessels involved, infarct-related artery, thrombus grade, pre-and post-procedure thrombolysis in myocardial infarction (TIMI) flow grade was found to have a significant association with the incidence of short-term MACE (Table 2).

The occurrence of short-term MACE was found to be strongly associated with the incidence of in-hospital post-procedure complications such as slow flow/no-reflow, arrhythmias, cardiogenic shock, stent thrombosis, contrast-induced nephropathy, or CVA/TIA (Table 2). Median follow-up duration after primary PCI was 6.1 [6.9–5.1] months, during this duration cumulative MACE was observed in 19.1% (210) with all-cause mortality in 14.2% (157), cardiac mortality in 5.4% (60). Myocardial infarction was

Table 2. Association of short-term major adverse cardiovascular events (MACE) with various angiographic findings, procedural characteristics, and in-hospital outcomes.

Characteristics	Total	MACE		P-value
		No	Yes	
<b>Total (N)</b>	<b>1102</b>	<b>892 (80.9%)</b>	<b>210 (19.1%)</b>	<b>-</b>
<b>Access for procedure</b>				
Radial	73% (804)	78.1% (697)	51% (107)	$< 0.001^{**}$
Femoral	25.9% (285)	20.4% (182)	49% (103)	
Switchover	1.2% (13)	1.5% (13)	0% (0)	
<b>LVEDP (mmHg)</b>	$18.7 \pm 6.6$	$17.7 \pm 5.8$	$23 \pm 8$	$< 0.001$
$< 20$ mmHg	57.2% (630)	63.6% (567)	30% (63)	$< 0.001$
$\geq 20$ mmHg	42.8% (472)	36.4% (325)	70% (147)	
<b>LVEF (%)</b>	$40.7 \pm 9.1$	$42 \pm 8.5$	$35.1 \pm 9.2$	$< 0.001$
$\leq 30\%$	18.3% (202)	13.2% (118)	40% (84)	$< 0.001$
30–44%	36.3% (400)	36% (321)	37.6% (79)	
$\geq 45\%$	45.4% (500)	50.8% (453)	22.4% (47)	
<b>IABP used</b>	4.7% (52)	2.4% (21)	14.8% (31)	$< 0.001$
<b>Number of vessels involved</b>				
Single vessel disease	36.7% (404)	38.6% (344)	28.6% (60)	0.001
Two vessel disease	32.8% (361)	33.2% (296)	31% (65)	
Three vessel disease	30.6% (337)	28.3% (252)	40.5% (85)	
<b>Recanalized vessel</b>	5.7% (63)	6.2% (55)	3.8% (8)	0.186
<b>Culprit coronary artery</b>				
Left main	1.6% (18)	0.8% (7)	5.2% (11)	$< 0.001^{**}$
LAD: Proximal	35.2% (388)	32.3% (288)	47.6% (100)	
LAD: Non-Proximal	17.8% (196)	19.6% (175)	10% (21)	
Circumflex	11.1% (122)	11.7% (104)	8.6% (18)	
Right coronary artery	33.1% (365)	34.4% (307)	27.6% (58)	
Diagonal	0.9% (10)	0.9% (8)	1% (2)	
Ramus	0.3% (3)	0.3% (3)	0% (0)	
<b>Pre-procedure TIMI flow</b>				
0	54.3% (598)	49.8% (444)	73.3% (154)	$< 0.001$
I	18.7% (206)	19.6% (175)	14.8% (31)	
II	17.1% (188)	18.8% (168)	9.5% (20)	
III	10% (110)	11.8% (105)	2.4% (5)	
<b>Thrombus Grade</b>				
G1	4.6% (51)	5.3% (47)	1.9% (4)	$< 0.001$
G2	5.4% (59)	6.5% (58)	0.5% (1)	
G3	24.9% (274)	27.6% (246)	13.3% (28)	
G4	11.5% (127)	11.5% (103)	11.4% (24)	
G5	53.6% (591)	49.1% (438)	72.9% (153)	

(continued on next page)

Table 2. (continued)

Characteristics	Total	MACE		P-value
		No	Yes	
<b>Pre-balloon used</b>				
Not done	56.1% (618)	58.6% (523)	45.2% (95)	<0.001
Dottering	41.2% (454)	39.5% (352)	48.6% (102)	
Balloon done	2.7% (30)	1.9% (17)	6.2% (13)	
<b>Mean vessel diameter</b>				
≤3.5 mm	3.5 ± 0.3	3.5 ± 0.3	3.5 ± 0.3	0.636
>3.5 mm	31.7% (349)	31.8% (284)	31% (65)	0.804
<b>Total lesion length</b>				
≥35 mm	27.6 ± 11.7	27.5 ± 11.4	28.1 ± 12.8	0.464
<35 mm	81.1% (894)	81.5% (727)	79.5% (167)	0.510
<b>Post-procedure TIMI flow</b>				
0	18.9% (208)	18.5% (165)	20.5% (43)	
I	0.8% (9)	0.4% (4)	2.4% (5)	<0.001**
II	2.3% (25)	1.2% (11)	6.7% (14)	
III	7.7% (85)	5.4% (48)	17.6% (37)	
<b>Peri-procedure complications and in-hospital outcomes</b>				
Slow flow/no-reflow	89.2% (983)	92.9% (829)	73.3% (154)	
Access site complications	24.1% (266)	19.1% (170)	45.7% (96)	<0.001
Bleeding	0.5% (6)	0.7% (6)	0% (0)	0.602^
Arrhythmias	0.9% (10)	0.4% (4)	2.9% (6)	0.005^
Cardiogenic shock	4.3% (47)	1.9% (17)	14.3% (30)	<0.001
Stent Thrombosis	3.6% (40)	1.6% (14)	12.4% (26)	<0.001
CIN	2.2% (24)	0.1% (1)	11% (23)	<0.001^
CVA/TIA	9.5% (105)	7.7% (69)	17.1% (36)	<0.001
In-hospital death	0.4% (4)	0% (0)	1.9% (4)	<0.001^
	4.4% (49)	0% (0)	23.3% (49)	<0.001^

MACE = major adverse cardiovascular events, LVEDP = left ventricular end-diastolic pressure, LVEF = left ventricular ejection fraction, IABP = intra-aortic balloon pump, LAD = left anterior descending artery, TIMI = thrombolysis in myocardial infarction, CIN = contrast induce nephropathy, CVA = cerebrovascular accident, TIA = transient ischemic attack.

\*\*Likelihood Ratio test, ^Fisher's Exact test.

observed in 6.1% (67) of which 3.4% (37) required repeat revascularization, hospitalization due to HF in 3.6% (40), and occurrence of stroke/CVA in eight patients (0.7%). A majority, 89.7% (989), of the patient self-reported being adherent to the prescribed medications.

On the multivariable Cox-regression analysis, impaired random blood glucose level (≥200 mg/dL), serum creatinine ≥1.5 mg/dL, intubation status, history of PCI, history of CVA/TIA, elevated LVEDP (≥20 mmHg), three-vessel involved diseases, culprit left main or proximal left anterior descending artery, high thrombus grade (≥4), and pre-ballooning were found to be the independent factors associated with increased risk of short-term MACE (Table 3).

#### 4. Discussion

Owing to the primary PCI, a significant improvement in the short- and long-term survival of STEMI patients has been witnessed in recent years, however, a considerable number of patients also experience short- and long-term MACE events after successful primary PCI. Considering the importance of knowing the factors associated with increased risk

of adverse outcomes for the timely risk stratification, in this study we have evaluated the incidence of short-term MACE and its determinants in a prospectively recruited cohort of patients undergoing primary PCI at a tertiary care cardiac center of a developing country. We observed the incidence rate of MACE as 19.1% during the median follow-up duration of 6.1 [6.9–5.1] months after primary PCI. Increased risk of short-term MACE was found to be associated with admission random blood glucose of ≥200 mg/dL and serum creatinine of ≥1.5 mg/dL. It was also found to be higher among intubated patients and patients with a history of PCI, stroke, or cerebrovascular accident. Angiographic evidence of elevated LVEDP (≥20 mmHg), three-vessel involved diseases, culprit left main or proximal left anterior descending artery, and high thrombus grade (≥4) were also observed to be significant determinants of short-term MACE after primary PCI. Patients who had undergone pre-ballooning were also found to have an increased risk of short-term MACE.

The reported short-term MACE rate of 19.1% in this study is within the range of previously reported rate ranging from 2.78% to as high as 47.6%. The varying rates of MACE in various studies is majorly

Table 3. Univariate and multivariable Cox-regression analysis for short-term major adverse cardiovascular events after primary percutaneous coronary intervention.

Factors	Univariate		Multivariable	
	HR [95% CI]	P-value	HR [95% CI]	P-value
Female	1.22 [0.89–1.66]	0.223	–	–
Age $\geq$ 65 years	1.4 [1.04–1.87]	0.024*	–	–
Total ischemic time $\geq$ 9 h	1.48 [1.1–1.99]	0.01*	–	–
Systolic blood pressure $\leq$ 90 mmHg	4.01 [2.76–5.82]	<0.001*	–	–
Heart rate $\geq$ 100 bpm	1.98 [1.49–2.65]	<0.001*	–	–
RBS $\geq$ 200 mg/dL	1.9 [1.45–2.5]	<0.001*	1.66 [1.25–2.21]	<0.001*
Hemoglobin $\leq$ 12.5 mg/dL	1.32 [0.99–1.77]	0.057	–	–
Neutrophil count <9.5 cells/ $\mu$ L	1.43 [1.09–1.87]	0.011*	–	–
Platelets $\geq$ 400 cells/ $\mu$ L	1.74 [0.92–3.29]	0.087	–	–
Creatinine $\geq$ 1.5 mg/dL	1.98 [1.34–2.93]	<0.001*	1.52 [1.02–2.27]	0.041*
Killip class IV	4.2 [2.78–6.35]	<0.001*	–	–
Intubated	5.45 [4.08–7.27]	<0.001*	2.81 [1.98–4]	<0.001*
Arrhythmias on presentation	3.27 [2.4–4.46]	<0.001*	1.36 [0.95–1.96]	0.092
Cardiac arrest	3.86 [2.67–5.58]	<0.001*	–	–
Hypertension	1.46 [1.09–1.95]	0.011*	–	–
Smoking	0.85 [0.63–1.16]	0.314	–	–
Diabetes mellitus	1.71 [1.3–2.25]	<0.001*	–	–
Prior PCI	2.61 [1.85–3.68]	<0.001*	2.06 [1.45–2.93]	<0.001*
History of CVA/TIA	1.95 [1–3.8]	0.051	2.64 [1.34–5.2]	0.005*
CKD	1.87 [1.06–3.27]	0.03*	–	–
LVEDP $\geq$ 20 mmHg	3.34 [2.49–4.49]	<0.001*	1.81 [1.3–2.51]	<0.001*
LVEF $\leq$ 35%	2.89 [2.18–3.81]	<0.001*	–	–
IABP used	5.01 [3.41–7.36]	<0.001*	–	–
Three vessel disease	1.61 [1.22–2.12]	<0.001*	1.43 [1.08–1.9]	0.014*
LM or proximal LAD	1.85 [1.41–2.42]	<0.001*	1.77 [1.32–2.35]	<0.001*
Thrombus grade $\geq$ 4	2.9 [2–4.21]	<0.001*	2.21 [1.51–3.24]	<0.001*
Pre TIMI flow grade 0	2.26 [1.66–3.07]	<0.001*	–	–
Pre-balloon done	1.6 [0.91–2.82]	0.104	2.14 [1.2–3.82]	0.01*
Vessel diameter $\leq$ 3.5 mm	1.06 [0.79–1.43]	0.678	–	–
Lesion Length $\geq$ 35 mm	1.11 [0.8–1.56]	0.528	–	–

HR = hazard ratio, CI = confidence interval, RBS = random blood sugar, PCI = percutaneous coronary intervention, CVA = cerebrovascular accident, TIA = transient ischemic attack, CKD = chronic kidney disease, LVEDP = left ventricular end-diastolic pressure, LVEF = left ventricular ejection fraction, IABP = intra-aortic balloon pump, LM = left main, LAD = left anterior descending artery, TIMI = thrombolysis in myocardial infarction.

\*significant at 5%.

dependent on the length of follow-up and type of patients. For instance MACE was reported to be 21.7% after  $0.8 \pm 0.3$  year follow-up after PCI (urgent or elective) [9], among patients with ACS it was reported to be 47.6% after median follow-up duration of 23 [5 to 55] months [10], 2.78%–3.43% of the patients were reported to develop MACE after 30-days of PCI (elective or urgent) [11], ischemic events after three years of PCI were observed to be 19.3%–41.0% depending on anemic status [12], among patients with STEMI MACE after  $19 \pm 5$  months was reported to be 12.8%–16.2% depending on the presence of high thrombus burden (TB) at the time of procedure [13], MACE rate among STEMI patients after follow-up of  $18.2 \pm 7.8$  months was 12.8%–15% incremental in relation to the thrombus grade [14], similarly, depending on the LVEDP at the time of procedure MACE after 30-days were reported to be 3.7%–6.3% and 17.3%–20.1% after two years of

primary PCI [15]. In addition to the length of follow-up and type of patients, the varying rates of MACE also stem from the differences in definition of MACE itself across various observational studies. Hence, head to head comparison of MACE in our population with that reported from other regions is not fruitful.

A study of similar nature in the Chinese population by Tsai IT et al. [10] reported, in addition to the clinical characteristics, various angiographic findings were also found to be associated with an increased risk of MACE. The likelihood of a MACE among ACS patients with elective PCI was increased by three-vessel disease, stent placement, hypertension, and estimated glomerular filtration rate (eGFR) or uric acid. Apart from the major predictors of MACE in CAD patients, factors like age [16], female gender, hypertension, number of stents placed [11], chronic heart failure [11], eGFR [17],

anaemia [12], HDL-cholesterol [18], and hs-CRP [19], the progression of MACE in our sample was additionally identified by the factors such as status of pre-or post-procedure intubation, prior PCI, history of CVA/TIA, LVEDP  $\geq 20$  mmHg, triple vessel diseases, LM or proximal LAD as a culprit, high thrombus burden (grade  $\geq 4$ ), and patients in whom pre-balloon was done.

In our sample, a high thrombus burden was observed to be an important determinant of an increased likelihood of short-term MACE. A study conducted by Martí et al. [13] evaluated the clinical impact of TG in a systematic primary PCI and found that in the acute phase greater infarct size and increased incidence of angiographic complications are linked to higher thrombus burden. In our study, we have observed that a high thrombus burden (thrombus grade  $\geq 4$ ) is linked to an elevated risk of incidence of short-term MACE with adjusted HR of 2.21 [95% CI: 1.51–3.24]. Our study findings were consistent with results of other researches presenting that angiographic evidence of coronary thrombi as a proven indicator of poor hospital course and adverse cardiac events [14]. In reality, distal embolization of thrombotic constituents or primary PCI-induced or spontaneous occlusion of epicardial vessels might compromise not only coronary but also myocardial perfusion [20].

Left main involvement or 3 vessel disease are considered to be the severe coronary anatomies associated with poor prognosis and increased risk of MACE [21], so as the involvement of proximal LAD. Involvement of proximal LAD is more common in STEMI setting and it is considered to be of greater severity and can lead to poor prognosis [22]. Consistent with these findings culprit LM or proximal LAD and three-vessel disease were found to be independent predictors of short-term MACE after primary PCI with adjusted HR of 1.77 [95% CI: 1.32–2.35] and 1.43 [95% CI: 1.08–1.9] respectively.

Elevated LVEDP is another important prognostic marker that is believed to have associated with a higher probability of deaths and cardiac failure after acute MI [23]. LVEDP is a biologically integrated measure of total ventricular function and higher LVEDP may deteriorate the detrimental period of LV remodeling with infarct enlargement and increasing cardiac dysfunction. It is related to the degree of myocardial ischemia, a decreased myocardial salvage, and reported as an independent predictor of adverse outcomes after primary PCI, despite baseline LVEF adjustment, individuals with LVEDP more than or equal to 24 mmHg are reported to be at higher risk of early and late mortality [15]. In our study LVEDP  $\geq 20$  mmHg was found to

be another independent predictor with adjusted HR of 1.81 [95% CI: 1.3–2.51].

A study conducted by Radovanovic D et al. [24] observed that in patients with STEMI, a history of previous MI is a strong predictor of in-hospital mortality with an odds ratio of 1.27 [95% CI: 1.05–1.53]. Align with these observations, in our study prior PCI was also found to be associated with increased incidence of short-term MACE with adjusted HR of 2.06 [95% CI: 1.45–2.93]. Patients with a second MI were shown to call health care providers faster, more likely to have dyspnea, less typical symptoms, and have smaller infarct size, but are observed to be less likely to get evidence-based treatment, eventually resulting in an increased risk of both in-hospital and 1-year adverse cardiac outcomes [24].

Our observation of hyperglycemia (RBS  $\geq 200$  mg/dL) being an independent predictor of short-term MACE is aligned with the existing literature regarding stress hyperglycemia. In patients with acute myocardial infarction stress hyperglycemia is correlated with an elevated risk of in-hospital deaths in both diabetic and non-diabetic patients, as well as a high risk of congestive heart failure (CHF) or cardiogenic shock (CS) in non-diabetic individuals [25]. A systematic review by Capes SE et al. [26] reported that patients without diabetes with glucose values greater than or equal to 6.1–8.0 mmol/L were at a 3.9-fold (95% CI: 2.9 to 5.4) increased risk of mortality compared to those with lesser glucose concentrations. In the context of STEMI, hyperglycemia might be transitory and stress-induced, instead of the reflection of patient's underlying glucose metabolic condition [27]. Nevertheless, in our study elevated glucose level ( $\geq 200$  mg/dL) regardless of diabetes status at admission was found to be associated with a higher risk of short-term MACE post-primary PCI with HR of 1.66 [95% CI: 1.25–2.21].

Impaired creatinine on admission regardless of chronic kidney diseases was found to be another significant determinant, elevated serum creatinine at arrival ( $\geq 1.5$  mg/dL) was observed to be an independent predictor with adjusted HR of 1.52 [95% CI: 1.02–2.27]. Various other studies have also witnessed the prognostic role of serum creatinine, such as a study conducted by Arnold SV et al. [28] reported higher serum creatinine as an important predictor of long-term mortality after AMI with a hazard ratio of 1.27 [95% CI: 1.18 to 1.36] for per 50% rise. Another study observed that slightly raised admission serum creatinine levels are associated to an increased mortality rate after one year of AMI [29]. Various other studies reported elevated

creatinine and/or impaired creatinine clearance (Cr Cl) on presentation as a strong and independent predictor of subsequent mortality after AMI, independent of other conventional risk factors [30].

A recent study by D'Ascenzo F et al. [31] developed and validated the PRAISE score based on machine learning algorithms. It showed great potential and predictive power for all-cause death (0.92 [95% CI: 0.90–0.93]), myocardial infarction (0.81 [95% CI: 0.76–0.85]), major bleeding (0.86 [95% CI: 0.82–0.89]) at one year of ACS event. Incorporation of significant clinical determinants can help further improving the accuracy of machine learning algorithms for adverse events following acute cardiac event.

Even though, to the best of our knowledge this is the largest data reported for our population but the main limitations remained observational nature of study and single center experience. Additionally, data regarding post-procedural revascularizations (non-culprit vessel intervention or needing coronary artery bypass grafting) concerning stable or unstable residual angina apart from culprit artery were not captured which can have a certain role in determining follow-up MACE. For better understanding of MACE in regional and global spectrum, studies with uniform definitions and follow-up intervals are warranted.

## 5. Conclusions

A significant number of patients were found to experience short-term MACE after primary PCI. Several determinants for the short-term MACE were identified among which independent predictors of MACE were admission blood glucose  $\geq 200$  mg/dL, serum creatinine  $\geq 1.5$  mg/dL, intubation, history of PCI, history of cerebrovascular accident, left ventricular end-diastolic pressure  $\geq 20$  mmHg, triple vessel diseases, culprit left main or proximal left anterior descending artery, and high thrombus grade ( $\geq 4$ ). Cardiologists can make use of these important clinical and angiographic determinants for beforehand risk assessment of MACE to optimize management and monitoring strategy tailored to the patients' expected risk of MACE.

## Author contribution

Conception and design of Study: RK, JAS; Literature review: RK, BAS, AA, NK, TS; Acquisition of data: RK, BAS, MK, NK, NQ, MK; Analysis and interpretation of data: RK, MK, NK, JAS, TS, NQ; Research investigation and analysis: RK, JAS, BAS, AA, MK, NK, JAS, TS; Data collection: BAS, AA, NK, TS, NQ, MK; Revising and editing the manuscript

critically for important intellectual contents: RK, JAS, AA, JAS; Data preparation and presentation: RK, JAS; Supervision of the research: JAS, AA; Research coordination and management: RK, NQ, MK; Funding for the research: RK, JAS.

## Disclaimer

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## Conflict of interest

None to declare.

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