



Original Article

Novel predictors and adverse long-term outcomes of No-reflow phenomenon in patients with acute ST elevation myocardial infarction undergoing primary percutaneous coronary intervention



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ABSTRACT

Objectives: The no-reflow phenomenon occurs in 25% of patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), and may be associated with adverse outcomes. The aim of our study was to detect novel predictors of no-reflow phenomenon and the resulting adverse long term outcomes.

Methods: We enrolled 400 STEMI patients undergoing primary PCI; 228 patients had TIMI flow 3 after PCI (57%) and the remaining 172 patients had TIMI flow <3 (43%). Fibrinogen to albumin ratio (FAR), high sensitive C-reactive protein to albumin ratio (CAR), and atherogenic index of plasma (AIP) were calculated. Long term mortality and morbidity during 6 months follow up were recorded. These data were compared among both groups.

Results: In multivariate regression analysis, old age (OR = 1.115, 95% CI: 1.032–1.205, P = 0.006), higher troponin level >5.6 ng/mL (OR = 1.040, 95% CI: 1.001–1.080, P = 0.04), diabetes mellitus (OR = 4.401, 95% CI: 1.081–17.923, P = 0.04) and heavy thrombus burden (OR = 16.915, 95% CI: 5.055–56.602, P < 0.001) could be considered as predictors for the development of no-reflow. Interestingly, CAR >0.21, FAR >11.56, and AIP >0.52 could be considered as novel powerful independent predictors (OR = 3.357, 95% CI: 2.288–4.927, P < 0.001, OR = 4.187, 95% CI: 2.761–6.349, P < 0.001, OR = 16.794, 95% CI: 1.018–277.01, P = 0.04, respectively). Higher long term mortality (P < 0.001) and heart failure (P < 0.001) was also strongly related to incidence of no-reflow.

Conclusion: No-reflow could be attributed to novel predictors as CAR, FAR, and AIP. This phenomenon was associated with long term adverse events as higher mortality and pump failure.

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1. Introduction

Acute treatment of ST elevation myocardial infarction (STEMI) is restoration of myocardial perfusion by recanalization of the occluded vessel. Early recanalization is associated with better outcome. Therefore, primary percutaneous coronary intervention (PCI) has become the treatment of choice for acute STEMI.¹

The no-reflow phenomenon is defined as inadequate myocardial perfusion passing through a given segment of coronary circulation with no angiographic evidence of mechanical vessel obstruction. No-reflow occurs in 25% of STEMI patients undergoing primary PCI.² Microvascular obstruction due to thrombosis, distal

embolization, and microvascular spasm are the suggested mechanisms for no-reflow.³ No-reflow is associated with larger infarct size, lower left ventricular ejection fraction (LVEF), adverse left ventricular remodelling in the late phase of myocardial infarction (MI), and increased risk of heart failure, risk of cardiac rupture, and risk of death.⁴ Both short term and long term prognoses of no-reflow are poor in humans. Malignant arrhythmias, pump failure, cardiac rupture and re-infarction are potential complications of no-reflow during the immediate in-hospital course.⁵

The inflammatory biomarkers; as high sensitive C-reactive protein (hs-CRP), fibrinogen, and albumin levels; have a positive correlation with no-reflow and platelets aggregation in STEMI patients who underwent primary PCI.⁶ Furthermore, atherogenic index of plasma (AIP) has been reported to be a strong independent predictor of all-cause mortality in acute coronary syndromes (ACS) after coronary revascularization.⁷ Thus, the aim of this study was to

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detect novel predictors of no-reflow as CRP to albumin ratio (CAR), fibrinogen to albumin ratio (FAR) and AIP. Also, the long term adverse events (mortality, malignant arrhythmias, heart failure, and recurrent myocardial infarction) associated with no-reflow phenomenon were investigated in this study.

2. Methods

2.1. Study population

Between 2017 and 2019, a total of 400 patients with acute STEMI who underwent primary PCI at our institution were considered for inclusion in this cross-sectional observational study. Acute STEMI was defined, according to the “Fourth Universal Definition of Myocardial Infarction.”⁸ The exclusion criteria were: patients with atrial fibrillation, thrombolytic therapy or glycoprotein inhibitors (GPI) prior to PCI, unsuitable lesion for PCI, coronary spasm and prior or emergent coronary artery bypass grafting (CABG). Ethical approval was obtained from the Ethics and Research Committee of our institution. All patients gave written informed consent prior to enrolment in the study. The research was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were classified into two main groups: Group I with normal coronary blood flow post PCI (TIMI = 3, n = 228), and Group II with no or slow coronary blood reflow post PCI (TIMI < 3, n = 172).

2.2. Clinical data collection

The traditional risk factors were collected⁹ with calculation of the following parameters: time-to-door, door-to-balloon time, and time-to-reperfusion.¹⁰ The CHA₂DS₂VASc score was also calculated.¹¹ Though patients with atrial fibrillation were excluded from this study, we did the scoring in all patients.¹² In the long term follow up, mortality and other adverse outcomes as malignant arrhythmias, heart failure, and recurrent myocardial infarction (MI) were recorded within 6 months.

2.3. Laboratory analysis and echocardiography

Venous blood samples were obtained from peripheral veins after the provision of emergency service. Novel parameters were measured as AIP was also calculated using the formula $\log(TG/HDL-C)$.¹³ Transthoracic echocardiography (TTE) was done to assess left ventricular functions.

2.4. Coronary angiography protocol

Coronary angiography and revascularization options were related to the standard guidelines and the discretion of the treating physician.¹⁴ In heavy thrombus burden lesion, thrombus aspiration was performed manually using aspiration catheters. Intravenous anti-platelet drug that was used in the setting of primary PCI is GPIIb/IIIa Tirofiban (0.4 mic/kg/min for 30 min, then 0.1 mic/kg/min for 18 h post PCI). Bare metal stents (BMS) were preferred over drug eluting stents (DES) in 170 patients (42.5%) due to financial issues (64 patients, 37.7%) in addition to concerns of a high bleeding risk (n = 34, 20%), poor compliance (n = 39, 22.9%) or the need for urgent/semi-urgent surgery (n = 33, 19.4%).

2.5. Angiographic analysis

Angiographic analysis was done by two independent expert operators. Infarct related artery (IRA) was identified and its severity was considered as: total and subtotal. Thrombolysis in Myocardial Infarction (TIMI) flow grading system is used to evaluate

myocardial perfusion in IRA before and after PCI.¹⁵ Angiographic analysis was done according to standard guidelines.¹⁶

3. Statistical analyses

Data distribution was assessed according to the Kolmogorov–Smirnov test. Categorical data were compared using the chi-square test or Fisher exact test. Continuous variables were compared using an unpaired Student's *t*-test or Mann–Whitney *U*-test. Data were expressed as mean \pm standard deviation. The no-reflow independent predictions were found using the multivariate model, which contained all significantly associated variables based on the *P*-value of the univariate conditional regression analyses (*P* < 0.05). Receiver operating characteristic curve (ROC) was generated to determine different cut off values. The Kaplan Meier method was used to create long term survival curves. All tests were two-sided, and a *p*-value of < 0.05 represented statistically significant differences. All analyses were performed using SPSS version 20 (SPSS Inc., USA).

4. Results

A total of 400 consecutive STEMI patients who presented to the emergency department and underwent primary PCI was included in this study. Out of the 400 patients, 228 patients had TIMI flow 3 after PCI (57%) and the remaining 172 patients had TIMI flow < 3 (43%); 28 patients with TIMI flow 0 (7%), 40 patients with TIMI flow 1 (10%), and 104 patients with TIMI flow 2 (26%).

4.1. Demographic characteristics

The study population included 284 males (71%) and 116 females (29%). In normal flow group, 68.4% of the patients were males compared to 74.4% in the no-reflow group (*P* = 0.19). The mean age of the no-reflow group was significantly higher than that of the normal flow one (65.21 \pm 11.89 vs. 56.61 \pm 10.39 years, *P* < 0.001). Baseline demographic characteristics are shown in (Table 1).

4.2. Clinical characteristics

Clinical parameters that were significantly higher in the no-reflow group were: symptoms-to-door (*P* < 0.001), time to reperfusion (*P* < 0.001), systolic and diastolic blood pressure (SBP and DBP) (*P* < 0.001 for each), and KILLIP classification (*P* < 0.001). LVEF was significantly lower in no-reflow group compared to normal flow group (*P* < 0.001). Baseline clinical characteristics are shown in (Table 1).

4.3. Laboratory characteristics

Baseline laboratory characteristics are shown in (Table 1). There was a highly significant increase in the values of CK-MB level (*P* < 0.001) and troponin I level (*P* < 0.001) in the no-reflow group, compared to normal flow group. Inflammatory parameters were more frequent in no-reflow group, where both leukocytes and neutrophil counts (*P* < 0.001), hs-CRP (*P* < 0.001) and fibrinogen levels were significantly higher (*P* < 0.001), compared to normal flow group.

Interestingly, in this study, the following novel parameters were significantly higher in no-reflow group: CAR (*P* < 0.001), FAR (*P* < 0.001), and AIP (*P* < 0.001), compared to normal flow group.

Table 1
Demographic, clinical and laboratory characteristics of the studied groups.

	Normal flow (TIMI = 3) (n = 228)	No reflow (TIMI <3) (n = 172)	P-value
Demographic characteristics			
Male sex, n(%)	156 (68.4%)	128 (74.4%)	0.19
Age (years)	56.61 ± 10.39	65.21 ± 11.89	<0.001**
BMI (kg/m ²)	26.58 ± 3.94	28 ± 5.43	0.004*
Cardiovascular risk factors			
Diabetes Mellitus	104 (45.6%)	120 (69.8%)	<0.001**
Hypertension	100 (43.9%)	120(69.8%)	<0.001**
Family history of CADs	24 (10.5%)	16 (9.4%)	0.72
Smoker	140 (61.4%)	104 (60.5%)	0.85
Dyslipidemia	64 (28.1%)	52 (30.2%)	0.64
CHA2DS2VASc score	1.74 ± 1.19	2.77 ± 1.48	<0.001**
Clinical characteristics			
Symptoms to door (hours)	7.81 ± 5.66	11.63 ± 5.42	<0.001**
Door to balloon (hours)	1.3 ± 0.41	1.4 ± 0.68	0.09
Time to reperfusion (hours)	9.11 ± 5.66	13.02 ± 5.4	<0.001**
Blood pressure (mmHg)			
SBP	124.77 ± 30.87	140.72 ± 29.11	<0.001**
DBP	68.16 ± 14.93	78.37 ± 19.35	<0.001**
KILLIP class ≥ II	40 (17.5%)	68 (39.5%)	<0.001**
ECG			
Inferior MI	108 (47.4%)	80 (46.5%)	0.87
Anterior MI	120 (52.6%)	92 (53.5%)	
LVEF (%)	46.37 ± 10.65	42.26 ± 9.19	<0.001**
LV diastolic dysfunction			
Grade 1	120 (52.6%)	68 (39.5%)	0.02*
Grade 2	80 (35.1%)	84 (48.8%)	
Grade 3	28 (12.3%)	20 (11.6%)	
Laboratory characteristics			
CK-MB (U/L)	194.29 ± 145.75	255.07 ± 172.25	<0.001**
Troponin (ng/ml)	13.4 ± 16.12	22.28 ± 16.54	<0.001**
Creatinine (mg/dl)	0.98 ± 0.37	1.09 ± 0.57	0.03*
GFR (%)			
Pre PCI	93.53 ± 36.68	96 ± 49.09	0.58
Post PCI	95.93 ± 44.17	95.61 ± 49.64	0.95
TGs (mg/ml)	135.91 ± 48.92	179.33 ± 58.42	<0.001**
LDL (mg/dl)	123.56 ± 24.21	125.83 ± 23.27	0.35
HDL (mg/dl)	38.36 ± 7.69	39.74 ± 7.59	0.08
Hemoglobin (gm/dl)	13.59 ± 1.91	13.97 ± 2.08	0.06
Leukocytes (×10 ³ /μL)	9.72 ± 1.59	12.14 ± 1.99	<0.001**
Platelet count (×10 ³ /μL)	237.6 ± 75.08	212.72 ± 67.422	0.001*
Neutrophils (×10 ³ /μL)	7.47 ± 9.76	9.76 ± 3.17	<0.001**
Lymphocytes (×10 ³ /μL)	1.76 ± 0.88	1.38 ± 0.68	0.03*
Serum albumin (g/L)	36.37 ± 3.5	35.39 ± 3.37	0.005*
hs-CRP (mg/dL)	7.34 ± 1.89	9.14 ± 2.03	<0.001**
Fibrinogen (mg/dL)	359.98 ± 42.24	457.62 ± 36.19	<0.001**
CAR	0.2 ± 0.05	0.25 ± 0.07	<0.001**
FAR	9.95 ± 1.27	13.02 ± 0.55	<0.001**
AIP	0.53 ± 0.18	0.64 ± 0.14	<0.001**

AIP: atherogenic index of plasma; BMI: body mass index; CADs: coronary artery diseases; CAR: C-reactive protein to albumin ratio; CK-MB: creatinine kinase-MB; DBP: diastolic blood pressure; ECG: electrocardiogram; FAR: fibrinogen to albumin ratio; GFR: glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; SBP: systolic blood pressure; TGs: triglycerides; TIMI: thrombolysis in myocardial infarction.

*Statistically significant difference between two groups (p < 0.05).

**Highly statistically significant difference between two groups (p < 0.001).

4.4. Angiographic and procedural characteristics

It was noted that, compared to normal flow group, the percentage of the totally occluded arteries, long and proximal lesions were significantly higher in the no-reflow group (P < 0.001, P = 0.001, P = 0.004, respectively). Moreover, heavy thrombus burden was more frequent in no-reflow group (P < 0.001). Also, compared to normal flow group, thrombus aspiration was needed in 81.4% of patients in no-reflow group (P < 0.001), with the use of GPI in 65.1% patients (P < 0.001). The amount of contrast used during PCI was significantly more in the no-reflow group (P < 0.001). Myocardial Blush Grade (MBG) after the procedure could be correlated to post-PCI TIMI flow (P < 0.001). Of note, the deployed stents were significantly longer in no-reflow group compared to normal flow group (30.18 ± 11.48 vs. 25.7 ± 10.04 mm,

P < 0.001). However, there was no significant difference between both groups regarding the site of vascular access (P = 0.89), the need of balloon pre-dilatation (P = 0.15), and the number (P = 0.07) and diameter of used stents (P = 0.6) (Table 2).

4.5. Long term outcomes

Kaplan–Meier curves between patients with no-reflow and those with normal flow for 6 months mortality revealed worse outcomes with higher mortality in no-reflow group (P < 0.001) (Fig. 1). Among other long term outcome parameters that were recorded in both groups within 6 months follow up, pump failure was found to be significantly higher in the no-reflow group than the normal flow group (37.2% vs. 17.5%, P < 0.001). However, there was no significant difference between both groups regarding other

Table 2
Angiographic and procedural characteristics of the studied groups.

	Normal flow (TIMI = 3) (n = 228)	No reflow (TIMI <3) (n = 172)	P-value
Angiographic characteristics			
Culprit artery			0.71
LAD	124 (54.4%)	92 (53.5%)	
LCX	26 (11.4%)	16 (9.3%)	
RCA	78 (34.2%)	64 (37.2%)	
Type of occlusion			<0.001**
Total	172 (75.4%)	156 (90.7%)	
Subtotal	56 (24.6%)	16 (9.3%)	
Site of occlusion			0.004*
Proximal	108 (47.4%)	100 (58.1%)	
Distal	120 (52.6%)	68 (39.5%)	
Mid segment	0 (0%)	4 (2.3%)	
Lesion length (mm)	23.12 ± 9.21	27.83 ± 10.27	0.001*
Number of vessels			0.56
1	124 (54.4%)	96 (55.8%)	
2	52 (22.8%)	32 (18.6%)	
3	52 (22.8%)	44 (25.6%)	
Thrombus burden (heavy)	80 (35.1%)	140 (81.4%)	<0.001**
Procedural Characteristics			
Vascular access			
Radial	36 (15.8%)	28 (16.3%)	0.89
Femoral	192 (84.2%)	144 (83.7%)	
Balloon pre-dilatation	116 (50.9%)	100 (58.1%)	0.15
Stent Type			
DES	116 (50.9%)	114 (66.3%)	0.002*
BMS	112 (49.1%)	58 (33.7%)	
Number			
1	168 (73.3%)	122 (70.9%)	0.07
2	60 (26.3%)	46 (26.7%)	
3	0 (0%)	4 (2.3%)	
Diameter (mm)	3.15 ± 0.43	3.12 ± 0.55	0.6
Length (mm)	25.7 ± 10.04	30.18 ± 11.48	<0.001**
Thrombus aspiration	80 (35.1%)	140 (81.4%)	<0.001**
GPI	60 (26.3%)	112 (65.1%)	<0.001**
Amount of contrast (ml)	199.12 ± 68.47	228.02 ± 89.27	<0.001**
MBG (Post -PCI)			
0	0 (0%)	52 (30.2%)	<0.001**
1	0 (0%)	68 (39.5%)	
2	96 (42.1%)	52 (30.2%)	
3	132 (57.9%)	0 (0%)	

BMS: bare-metal stent; DES: drug-eluting stent; GPI: glycoprotein inhibitor; LAD: left anterior descending artery; LCX: left circumflex artery; MBG: myocardial blush grade; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIMI: thrombolysis in myocardial infarction.

*Statistically significant difference between two groups (p < 0.05).

**Highly statistically significant difference between two groups (p < 0.001).

adverse outcomes as recurrent MI and malignant arrhythmia (Table 3).

4.6. Independent predictors of no-reflow phenomenon

Independent predictors of no-reflow phenomenon were summarized in (Table 4). In univariate logistic regression analysis, there were significant relations of age, symptom-to-door, time-to-reperfusion, KILLIP class ≥ II, CHA₂DS₂VASc score, CK-MB, troponin I level, heavy thrombus burden, hypertension, diabetes mellitus, total occlusion, CAR, FAR, and AIP with incidence of no-reflow phenomenon (P < 0.001). In multivariate logistic regression analysis, it was found that age (P < 0.006), diabetes mellitus (P < 0.04), troponin I level (P < 0.04), heavy thrombus burden (P < 0.001), CAR (P < 0.001), FAR (P < 0.001), and AIP (P = 0.04) were independent predictors of no-reflow phenomenon.

ROC statistical analyses showed that age >56 years (sensitivity 72.1%, specificity 56.1%), troponin I > 5 ng/mL (sensitivity 76.7%, specificity 50.9%), CAR > 0.21 (sensitivity 74.4%, specificity 55.3%), FAR > 11.56 (sensitivity 87.2%, specificity 89.5%), and AIP > 0.52 (sensitivity 75.6%, specificity 50%) were the best cut-off values for predicting no-reflow phenomenon (Fig. 2).

5. Discussion

The main findings of this study are summarized as follows: 1) Old age, history of diabetes mellitus, high troponin levels, and heavy thrombus burden, all were found to be independent predictors of incidence of no-reflow in STEMI patients treated with primary PCI.; 2) CAR, FAR, and AIP could be considered as novel predictors for the development of no-reflow phenomenon; 3) Adverse long term outcomes as higher mortality and pump failure were more frequent in patients with no-reflow.

Previous studies documented that increased incidence of no-reflow phenomenon was related to higher CHA₂DS₂VASc score¹¹ in addition to other individual traditional risk factors as old age, hypertension, higher KILLIP class,¹⁷ higher BMI,^{18,19} diabetes mellitus.²⁰ The present study confirmed these findings, and this may be attributed to neuro-hormonal activation¹⁷ and the fact that hypertension may induce interstitial fibrosis and remodelling of the small intra-myocardial vessels,¹⁷ in addition to coronary microvascular dysfunction induced by diabetes mellitus.²⁰

It was previously stated that no-reflow may be related to some clinical predictors.²¹ In this study, patients with no-reflow had higher troponin I and creatine kinase-MB (CK-MB) (P < 0.001) with more prolonged symptoms to door and time to reperfusion

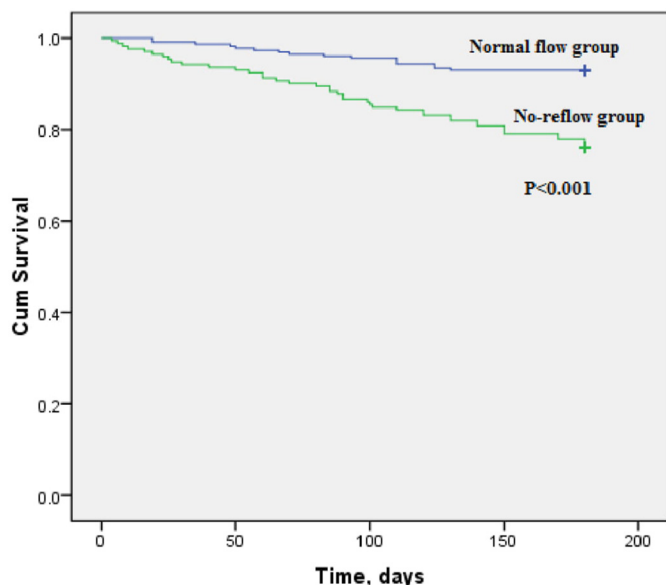


Fig. 1. Kaplan–Meier curve between normal flow group and no-reflow group for 6-months mortality. There is a highly significant difference between both group ($P < 0.001$) regarding 6-months mortality rate.

($P < 0.001$) times, compared to those with normal flow. Also, the incidence of no-reflow was associated with decreased LVEF on admission ($P < 0.001$) with no significant superiority of anterior MI over inferior MI regarding the incidence of no-reflow ($P = 0.87$). These data are concordant with Mazhar et al,² Sabin et al,³ and Fajar et al.¹⁷ However, Ipek et al¹¹ and Tanaka et al²² found no significant difference in incidence of no-reflow in relation to time-to reperfusion.

Regarding the angiographic predictors, total and proximal occlusions were associated with increased incidence of no-reflow.²³ This study confirmed this hazardous correlation which may result in larger areas of myocardial infarction with more significant hemodynamic instability.²⁰ In addition, no-reflow in this study was associated with lower MBG, Longer lesion, thrombus aspiration, lower pre-procedural TIMI flow and more amount of used contrast ($P < 0.001$). This is concordant with Sabin et al,³ Jeong et al,²⁴ and the data obtained from the meta-analysis conducted by Fajar et al.¹⁷

This study confirmed also the role of inflammatory parameters in no-reflow development with significantly higher leukocyte and neutrophil counts ($P < 0.001$) and lower lymphocyte count ($P < 0.001$), compared to normal reflow group. This finding is supported by the retrospective study of Kosuge et al²⁵ and Takahashi et al²⁶ who stated that a higher leucocytic count was an independent predictor of no reflow in patients with a first anterior AMI. The underlying mechanism is complex. Ischemic injury

damages mycardiocytes with subsequent neutrophil plugging and release of oxygen-free radicals leading to endothelial injury.^{20,27}

The effect of inflammatory biomarkers; as hs-CRP, fibrinogen, and albumin levels; on no-reflow development has been more clearly investigated in this study. Serum albumin is the major serum protein that participates in inflammatory response. Fibrinogen is also a biomarker of chronic inflammation, which is known to be a precursor to fibrin and accelerates platelet aggregation. CRP is one of the most commonly used biomarkers with a positive correlation with no-reflow in STEMI patients who underwent primary PCI.⁶

The present study confirmed this link between these inflammatory mediators and no-reflow development. It was noted that CRP and fibrinogen levels were significantly higher ($P < 0.001$), and the albumin level was significantly lower ($P = 0.005$) in no-reflow group than in normal flow group.

Previous studies have demonstrated that AIP is strongly associated with CAD. Furthermore, AIP has been reported to be a strong independent predictor of all-cause mortality in ACS after coronary revascularization.⁷ In concordance with these studies, our study revealed that AIP was significantly higher in no-reflow group than normal flow group ($P < 0.001$).

Of note, multivariate regression analysis in our study stated that CAR, FAR, AIP could be considered as novel powerful independent predictors for the development of no-reflow phenomenon (OR = 3.357, 95% CI: 2.288–4.927, $P < 0.001$, OR = 4.187, 95% CI: 2.761–6.349, $P < 0.001$, OR = 16.794, 95% CI: 1.018–277.01, $P = 0.04$, respectively). The best cut-off values were >0.21 for CAR (sensitivity 76.7%, specificity 50.9%), >11.56 for FAR (sensitivity 87.2%, specificity 89.5%), and >0.52 for AIP (sensitivity 75.6%, specificity 50%).

The exact underlying pathophysiology between these novel predictors and no-reflow phenomenon remained controversial. Serum albumin is an important inhibitor of platelet activation and aggregation and is an important mediator of platelet induction.²⁸ Raised CAR can be linked to the diminished coronary microvascular reactions to both independent vasodilators and endothelium-dependent stimuli.²⁹ The underlying mechanism between higher levels of FAR and no-reflow development could be attributed to the fact that low albumin levels promotes fibrinolysis, thereby inhibiting the physiological fibrinolytic system and reducing the spontaneous dissolution of the thrombus.³⁰ The association of AIP with no-reflow may be a consequence of that inflammatory process, where the remnant particles formed by lipolysis of TG-rich lipoproteins may participate in vascular wall inflammation.³¹

Other independent predictors for incidence of no-reflow phenomenon were old age (OR = 1.115, 95% CI: 1.032–1.205, $P = 0.006$) with cut off value > 56 years (sensitivity 72.1%, specificity 56.1%), higher troponin level (OR = 1.040, 95% CI: 1.001–1.080, $P = 0.04$) with cut-off value > 5.6 ng/mL (sensitivity 76.7%, specificity 50.9%), and heavy thrombus burden (OR = 16.915, 95% CI: 5.055–56.602, $P < 0.001$). Also, diabetes mellitus was considered as important

Table 3
Long term outcomes of the studied groups.

	Normal flow (TIMI = 3) (n = 228)	No reflow (TIMI <3) (n = 172)	P-value
Mortality	16 (7%)	41 (23.8%)	<0.001**
Heart failure	40 (17.5%)	64 (37.2%)	<0.001**
Recurrent MI	16 (7%)	9 (5.2%)	0.5
Malignant arrhythmia	48 (21.1%)	24 (14%)	0.07

MI: myocardial infarction; TIMI: thrombolysis in myocardial infarction; VF: ventricular fibrillation; VT: ventricular tachyarrhythmia.

*Statistically significant difference between two groups ($p < 0.05$).

**Highly statistically significant difference between two groups ($p < 0.001$).

Table 4
Univariate and multivariate regression analysis for the parameters affecting no reflow cases (TIMI <3).

	Univariate		Multivariate	
	P-value	OR (95% C.I)	P-value	OR (95% C.I)
Age (years)	<0.001**	1.072* (1.050–1.093)	0.006*	1.115* (1.032–1.205)
Diabetes mellitus	<0.001**	2.751* (1.813–4.175)	0.04*	4.401* (1.081–17.923)
Hypertension	<0.001**	2.954* (1.946–4.484)	0.16	2.518 (0.701–9.045)
CHA2DS2VASc score	<0.001**	1.759* (1.496–2.067)	0.06	0.460 (0.205–1.030)
Symptoms-to-door	<0.001**	1.129* (1.085–1.174)	0.16	0.335 (0.073–1.543)
Time to reperfusion	<0.001**	1.132* (1.088–1.177)	0.12	3.412 (0.739–15.756)
KILLIP class (class I vs.class ≥ II)	<0.001**	3.073* (1.944–4.859)	0.79	0.845 (0.245–2.908)
CK-MB	<0.001**	1.002* (1.001–1.004)	0.25	0.998 (0.994–1.002)
Troponin (ng/ml)	<0.001**	1.033* (1.020–1.046)	0.04*	1.040* (1.001–1.080)
CAR	<0.001**	6.094* (4.284–8.668)	< 0.001**	3.357* (2.288–4.927)
FAR	<0.001**	5.099* (3.761–6.912)	< 0.001**	4.187* (2.761–6.349)
AIP	<0.001**	97.070* (23.312–404.196)	0.04*	16.794* (1.018–277.01)
Type of occlusion (total vs. subtotal occlusion)	<0.001**	3.174* (1.749–5.763)	0.66	0.722 (0.170–3.060)
Thrombus burden (heavy)	<0.001**	8.094* (5.056–12.958)	<0.001**	16.915* (5.055–56.602)

AIP: atherogenic index of plasma; CAR: C-reactive protein to albumin ratio; C.I: confidence interval; CK-MB: creatinine kinase-MB; FAR: fibrinogen to albumin ratio; OR: odds ratio.

*Statistically significant difference between two groups (p < 0.05).

**Highly statistically significant difference between two groups (p < 0.001).

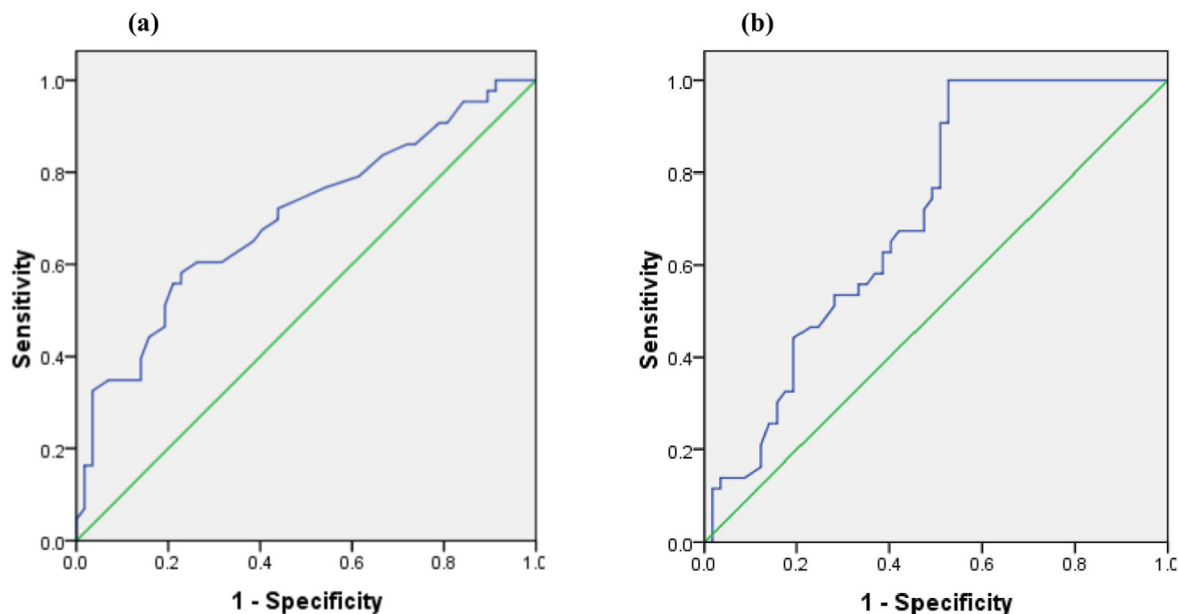


Fig. 2. Receiver operating characteristic (ROC) curve (a) the cut-off age value on the ROC curve was >56 years old with sensitivity of 72.1% and specificity of 56.1%, (b) the cut-off serum troponin value on the ROC curve was >5 ng/mL with sensitivity of 76.7% and specificity of 50.9%, (c) the cut-off CAR value on the ROC curve was >0.21 with sensitivity 74.4% and specificity 55.3%, (d) the cut-off FAR value on the ROC curve was >11.56 with sensitivity 87.2%, specificity 89.5%, and (e) the cut-off AIP value on the ROC curve was >0.52 with sensitivity 75.6%, specificity 50%.

independent clinical predictors of no-reflow phenomenon (OR = 4.401, 95% CI: 1.081–17.923, P = 0.04), and this may be attributed to the effects of diabetes mellitus on both micro-vasculature and macro-vasculature.²⁰

Regarding long term outcome of no-reflow phenomenon in our study, Kaplan–Meier curve revealed a significant difference between no-reflow and normal groups for 6 months mortality (P < 0.001). Also, incidence of pump failure (P < 0.001) was strongly related to incidence of no-reflow. This data is concordant with that

obtained from Uyarel et al³² and Acet et al.³³ However, there were no significant differences regarding recurrent MI and malignant arrhythmias between both groups.

6. Limitations

The present study has some limitations. First, this study included relatively small numbers of patients as the results were obtained from only one centre. Therefore, a larger study population

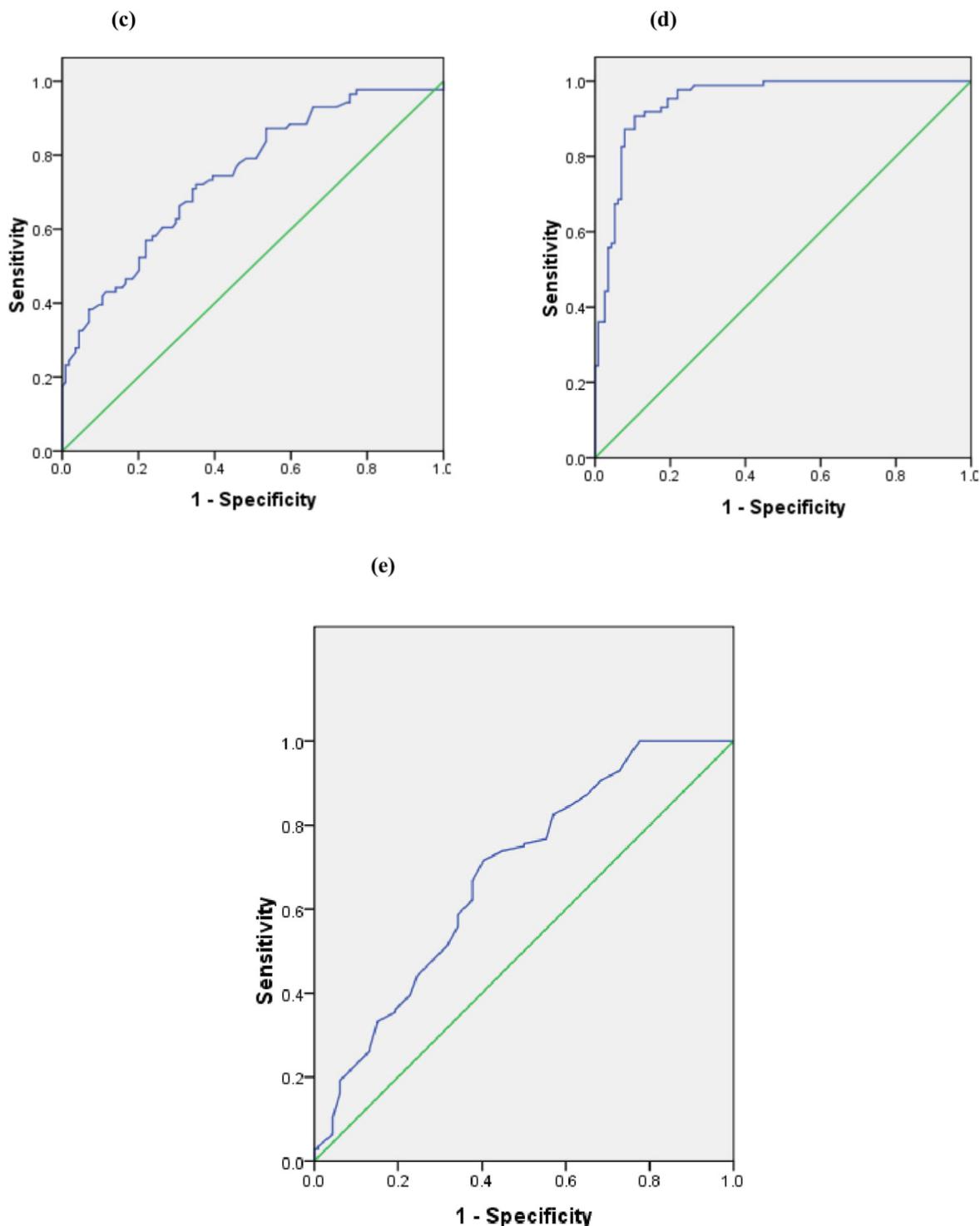


Fig. 2. (continued).

with no-reflow phenomenon is needed in future studies. Second, the present study was a cross-sectional observational one. However, data processing, and statistical analyses were conducted by independent research personnel. Finally, duration of follow-up was relatively short. So, further studies with longer follow-up periods are needed.

7. Conclusions

The no-reflow phenomenon may be related to variable clinical, angiographic and inflammatory predictors, with subsequent development of adverse long term outcomes as high mortality and pump failure. This study confirmed the valuable role of CAR, FAR, and AIP as novel predictors for the development of no-reflow phenomenon.

What is already known?

- No-reflow occurs in 25% of STEMI patients undergoing primary angioplasty.
- Micro-vascular obstruction due to thrombosis, distal embolization, and microvascular spasm are the suggested mechanisms for no-reflow.
- Prediction of patients at risk for no-reflow before primary angioplasty may be beneficial from the perspective of prevention.

What this study adds?

- This study confirmed the valuable role of some novel predictors; as CAR, FAR and AIP, for the development of no-reflow phenomenon with subsequent development of adverse long term outcomes as high mortality and pump failure.

Authorship

All authors have made substantial contributions to all of the following: (1) the conception and study design, data acquisition, and data analysis and interpretation, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

There is no conflict of interests.

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