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The relationship between homocysteine and no-reflow phenomenon in patients undergoing primary percutaneous coronary intervention

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ABSTRACT

Aims: The current study aimed to investigate the relationship between homocysteine and no-reflow phenomenon in patients undergoing primary percutaneous coronary intervention (pPCI).

Methods: Patients with ST-elevation myocardial infarctions (STEMI) who underwent pPCI in our center between May 01, 2022, and 20 August 2023 were included in this cross-sectional observational study. Patients were classified into two groups according to the occurrence of no-reflow during pPCI. Findings were compared between the two groups.

Results: A total of 332 patients [male, 75 (%82.8)] with STEMI undergoing pPCI, were included. Among them, 35 (10.5%) patients developed no-reflow. Homocysteine level was significantly higher in the no-reflow(+) group than the no-reflow(-) group [median (IQR), 19.02 (16.11-22.23 vs. 12.45 (10.99-14.93), p=0.019]. According to the multivariate analysis, homocysteine level, TIMI risk score, and postdilatation were independent predictors of no-reflow occurrence [Odds Ratio (95% CI), 1.127 (1.042-1.218), p=0.003, 1.385 (1.157-1.659), p<0.001, and 2.396 (1.092-5.257), p=0.029, respectively]. Considering the ROC curve analysis for homocysteine predicting no-reflow, the area under the curve (AUC) was 0.714 with an optimal cut-off value of 14.1 (sensitivity of 71%, specificity 62%).

Conclusion: Higher admission homocysteine levels were associated with no-reflow development in STEMI patients during pPCI. Higher levels of homocysteine may identify a subset of patients at a higher risk of no-reflow development during pPCI.

Keywords: No-reflow, homocysteine, STEMI, PCI

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the most effective and gold-standard treatment for ST-elevation myocardial infarction (STEMI).[1] In addition to ensuring quick antegrade blood flow, it also lowers myocardial necrosis and raises survival rates.[2] However, this advantageous effect may remain incapable when a patient develops a no-reflow phenomenon.[3] No-reflow phenomenon, shortly no-reflow, is a post-PCI complication characterized by insufficient myocardial perfusion in the coronary arteries without any angiographic indications of dissection, obstruction, or spasm in the epicardial vessels.[4] This phenomenon is related to the functional and structural change of the coronary microcirculation and, as a result, cardiovascular mortality.[5] The pathophysiological etiology is thought to be associated with distal atherothrombotic embolization, ischemic damage, reperfusion injury, microcirculation abnormality, inflammatory response, individual susceptibility, and endothelial dysfunction.[5,6]

Homocysteine, a sulfur-containing amino acid, is produced as a result of the catabolism of methionine.[7] This molecule can cause endothelial dysfunction and oxidative stress by producing free radicals.[7,8] Both oxidative stress and endothelial dysfunction increase cardiovascular risk.[8,9] A vast number of studies investigated the relationship between homocysteine and cardiovascular diseases.[6,8-11] Higher homocysteine levels were associated with poor cardiovascular outcomes, in these researches. However, the impact of homocysteine on no-reflow has not been examined well. The relationship between homocysteine and the no-reflow phenomenon after pPCI

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has remained unclear. The current study aimed to address this gap, examining the relationship between homocysteine and no-reflow phenomenon in STEMI patients during pPCI.

METHODS

Patients

Patients with STEMI who underwent pPCI in our center between May 01, 2022, and 20 August 2023 were included in this cross-sectional observational study. Diagnosis and treatment of STEMI were based on guideline recommendations.[12] The research excluded individuals with acute infections, malignancies, coagulopathy, and patients receiving anticoagulant therapy. Our endpoint was the development of no-reflow during pPCI. Patients were classified into two groups according to the occurrence of no-reflow during pPCI. Findings were compared between the two groups.

Ethics

The protocol of the study was approved by the ethics committee of Kafkas University (Date: 27.04.2022, Decision No: 80576354-050-99/128) according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Blood Sample

Routine complete blood cell count and blood biochemical measurements were performed on a blood sample obtained on admission. Plasma total homocysteine at admission was measured using a colorimetric assay test kit from Elabscience Biotechnology, Wuhan, China. The measurement protocol was obtained from Elabscience and the results were determined using a spectrophotometer (Epoch, Biotech, USA).

Coronary Angiography

The percutaneous trans-femoral (Judkins) approach was followed in the performance of both coronary angiography and pPCI. All patients received anticoagulation therapy with unfractionated heparin of 70–100 units/kg (maximal dose 10.000 units) and antiplatelet therapy with acetylsalicylic acid (300 mg). Also, a loading dose of clopidogrel (300–600 mg) or (ticagrelor 180 mg) was given before the pPCI. Intravenous nitroglycerine and Glycoprotein IIb/IIIa inhibitors were introduced if necessary. Coronary blood flow was defined per TIMI flow classification which classifies coronary flow as follows: TIMI grade 0, no perfusion (no antegrade flow beyond the point of occlusion); TIMI grade 1, penetration without perfusion (the contrast material passes beyond the area of obstruction, but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run); TIMI grade 2, perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery; TIMI grade 3, full perfusion of the infarct vessel with normal flow.[13,14] On this base, patients with TIMI flow below grade 3 was defined as no-reflow in the current study. Thrombus burden was assessed according to the TIMI thrombus grading scale that ranged from grade 0 (no thrombus) to grade 5 (very large thrombus causing vessel occlusion).[14]

Syntax II score was calculated using six clinical variables including age, gender, left ventricular ejection fraction (LVEF), chronic obstructive pulmonary disease, peripheral arterial disease, and creatinine clearance, as well as two anatomical variables including Syntax score and the existence of left main coronary artery disease.[15] The Thrombolysis in Myocardial Infarction (TIMI) risk score was calculated in conformity with Marrow et al.[16] Cockroft–Gault formula was performed for the calculation of glomerular filtration rate (eGFR).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 20.0 was used for the statistical analyses. Continuous variables are expressed as mean ± standard deviation (SD), minimum and maximum values. Variables that did not show normal distribution were presented as median [interquartile range (IQR)], mean, minimum, and maximum values. Frequencies and percentages were used to represent the categorical variables. The Kolmogorov-Smirnov test was used to test the normality distribution of continuous variables. While the chi-square or Fisher exact test was utilized for the comparison of the categorical data, the Student t-test or Mann–Whitney U test was used to compare continuous variables between the two groups. The Pearson correlation test was employed to assess the association between age and homocysteine levels. A univariate regression analysis was performed including factors potentially related to no-reflow as shown in **Table 1**. Also, a multivariate logistic regression analysis (forward likelihood ratio method) with a significance level of 0.05 was used to determine the independent determinants of no-reflow. Using a receiver operating characteristic (ROC) curve analysis, an optimal homocysteine value for predicting no-reflow was found. For statistical significance, a two-sided p-value of less than 0.05 was established as the cut-off point.

RESULTS

A total of 332 patients [male, 75 (%82.8)] with STEMI undergoing pPCI, were included. Among them, 35 (10.5%) patients developed no-reflow. **Table 2** shows the comparison of demographics, lesion features, and procedural aspects, based on the presence of no-reflow. The no-reflow (+) group was older (mean+SD, 61.7±12.4 vs. 55.9±10.7, p=0.003) and had significantly higher

Table 1. Univariate and multivariate regression analysis for predicting no-reflow

	Univariate		Multivariate	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Homocysteine	1.151 (1.069-1.239)	<0.001	1.127 (1.042-1.218)	0.003
Pain-to-ballon time	1.004 (1.002-1.007)	0.001	-	-
TIMI risk score	1.361 (1.150-1.611)	<0.001	1.385 (1.157-1.659)	<0.001
Postdilatation	2.280 (1.123-4.629)	0.023	2.396 (1.092-5.257)	0.029
Age	1.048 (1.016-1.082)	0.004	-	-
Syntax II score	1.155 (0.987-1.351)	0.072	-	-

CI, confidence interval; OR, odds ratio; TIMI, thrombolysis in myocardial infarction

Table 2. Comparison of demographics, lesion features, and procedural aspects, based on the presence of no-reflow

	Total (n=332)	**No-reflow (+) (n=35)**	**No-reflow (-) (n=297)**	**P-value**
Male, n(%)	275 (82.8)	25 (71.4)	250 (84.2)	0.059
Age (years), mean±SD (min-max)	56.5±11 (27-90)	61.7±12.4(41-90)	55.9±10.7(27-86)	0.003
SBP (mmHg), median (IQR), mean (min-max)	135 (120-147) 136 (66-245)	140 (128-177) 146 (69-240)	133 (120-143) 135 (66-245)	0.027
DBP (mmHg), mean±SD (min-max)	80±18 (32-145)	85±23 (32-130)	80±18 (35-145)	0.120
Heart rate (beat/minute), mean±SD (min-max)	78±16 (27-132)	81±18 (37-114)	78±16 (27-132)	0.255
Syntax II score, median (IQR), mean (min-max)	31.3 (25.4-39.0) 33.4(15.5-73.3)	43.5 (31.5-52.8) 42.9 (26.1-71)	30.4 (24.7-37.6) 32.3 (15.5-73.3)	0.036
TIMI risk score, median (IQR), mean (min-max)	2 (1-4) 2.57 (0-10)	4 (2-5) 3.66 (1-7)	2 (1-3) 2.44(0-10)	<0.001
TIMI thrombus grade, mean±SD (min-max)	4.90±0.44 (2-5)	4.97±0.16 (4-5)	4.89±0.47 (2-5)	0.304
Killip class, mean±SD (min-max)	1.25±0.55 (1-4)	1.57±0.74 (1-3)	1.21±0.52 (1-4)	<0.001
Procedural features				
Predilatation, n(%)	303 (91)	34 (97)	269 (90)	0.193
Stent length (mm), median (IQR), mean (min-max)	20 (16-28) 23 (10-95)	25 (19-35.5) 28 (10-95)	20 (16-28) 23 (10-78)	0.037
Stent diameter (mm), median (IQR), mean (min-max)	3 (3-3.25) 3.08 (2.5-4)	3 (3-3.5) 3.16 (2.5-4)	3 (3-3.25) 3.07 (2.5-4)	0.185
Postdilataion, n (%)	104 (31,3)	17 (48,6)	87 (29.3)	0.020
Door-to-balloon time (minute), median (IQR), mean (min-max)	30 (25-35) 31 (18-213)	32 (28-35) 32 (20-48)	30 (25-35) 31 (18-213)	0.207
Pain-to-balloon time (minute), median (IQR), mean (min-max)	150 (80-240) 176 (25-590)	230 (155-297) 241 (50-590)	150 (80-230) 168 (25-590)	<0.001
Maximum balloon inflation pressure (atmosphere), median (IQR), mean (min-max)	14 (14-16) 14.8 (10-22)	15 (14-16) 15.4 (10-22)	14 (14-16) 14.7 (10-22)	0.115
Visible distal embolization, n(%)	14 (4.2)	7 (20)	7 (2.4)	<0.001
lesion location (proximal), n(%)	236 (71.1)	31 (88.6)	205 (69)	0.016
Infarc related artery ectasia, n(%)	14 (4.2)	1 (2.9)	13 (4.4)	0.672
Multivessel disease, n(%)	226 (68)	21 (60)	205 (69)	0.279
Comorbities				
Hypertension, n (%)	151 (45.5)	22 (62.9)	129 (43.4)	0.029
Diabetes, n (%)	77 (23.2)	12 (34.3)	65 (21.9)	0.100
Smoking, n (%)	188 (56.6)	15 (42.9)	173 (58.2)	0.082
COPD, n (%)	19 (5.7)	1 (2.6)	18 (6.1)	0.440
Dyslipidemia, n (%)	138 (41.6)	10 (28.6)	128 (43.1)	0.099
Coronary artery disease (n)	3	0	3	
Family history, n(%)	66 (19.9)	7 (20)	59 (19.9)	0.985
Chronic renal disease, n(%)	9 (2.7)	3 (8.6)	6 (2)	0.024

COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction; TIMI, thrombolysis in myocardial infarction

systolic blood pressure, Syntax II risk score, and TIMI risk score compared to the no-reflow (-) group [median (IQR), 140 (128-177) vs. 133 (120-143), p=0.027, 43.5 (31.5-52.8) vs. 30.4 (24.7-37.6), p=0.036 and 4 (2-5) vs. 2 (1-3), p<0.001, respectively]. killips class was also significantly higher in the no-reflow (+) group (mean±SD, 1.57±0.74 vs. 1.21±0.52, p<0.001). For comorbidities, hypertension and chronic renal disease were more frequent in patients with no-reflow [n (%), 22 (62.9) vs. 129 (43.4), p=0.029 and 3 (8.6) vs. 6(2), p=0.024, respectively]. Regarding lesion and procedural features, in the no-reflow(+) group stent length and pain-to-balloon time were significantly longer than in the no-reflow(-) group [median (IQR), 25 mm (19-35.5 mm) vs 20 mm (16-28 mm), p=0.037 and 230 minutes (155- 297) vs. 150 minutes (80-230), p<0.001, respectively]. Also, proportions of postdilatation, distal embolization, and stent implantation to the proximal of the artery rather than mid or distal were significantly higher in the no-reflow (+) group [n (%), 17 (48.6) vs. 87 (29.3), p=0.020, 7 (20) vs. 7 (2.4), p<0.001 and 31 (88.6) vs. 205 (69), p=0.016, respectively].

A comparison of laboratory findings is presented in **Table 3**. Homocysteine level was significantly higher in the no-reflow (+) group than the no-reflow (-) group [median (IQR), 19.02 (16.11-22.23) vs. 12.45 (10.99-14.93), p=0.019]. Levels of Troponin, CK-MD, CK, MPV, and glucose were also significantly higher in the no-reflow (+) group. [median (IQR), 9.8 (3.6-13.8) vs. 2.3 (0.8-5.3), p<0.001, 54 (38-62) vs. 34 (24-45), p<0.001, 564 (292-854) vs. 332 (195-568), p=0.005, 9.4 (8.75-10.55) vs. 9 (8.2-9.8), p=0.034 151 and (121-207) vs. 128 (108-167), p=0.009, respectively]. As well as, neutrophil and uric acid levels showed significantly higher means in the same group (mean+SD, 11.75±3.85 vs. 10.26±2.87, p=0.006 and 5.75±1.91 vs. 5.12±1.42, p=0.023, respectively).

Table 3. Comparison of laboratory findings based on the presence of no-reflow

	Total (n=332)	No-reflow (+) (n=35)	No-reflow (-) (n=297)	P-value
Laboratory				
Homocysteine (µmol/L), median (IQR), mean (min-max)	12.56 (11.04-16.30) 13.72 (1.92-42.8)	19.02 (16.11-22.23) 16.84 (8.69-42.8)	12.45 (10.99-14.93) 13.35 (1.92-34.69)	0.019
Hemoglobin (g/dl),mean±SD (min-max)	13.92±1.67 (8.5-19)	13.49±1.60 (9.6-17)	13.9±1.67 (8.5-19)	0.104
WBC (×10³/µL), median (IQR), mean (min-max)	12.83 (11.14-14.59) 13.2 (6.2-25)	14 (11.45-17.45) 14.4 (8.2-25)	12.7 (11.1-14.4) 13.0 (6.2-25)	0.056
Neutrophil (×10³/µL), mean±SD (min-max)	10.42±3.01 (4-21.9)	11.75±3.85 (5.2-21.9)	10.26±2.87 (4-21.3)	0.006
Lymphocyte(×10³/µL), median (IQR), mean (min-max)	1.8 (1.3-2.5), 1.95 (0.4-6.11)	1.6 (1.2-2.2), 1.86 (0.5-4.7)	1.8 (1.3-2.5), 1.96 (0.4-6.11)	0.381
Platelet (×10³/µL), mean±SD (min-max)	262±63 (105-494)	257±82 (105-465)	262±60 (119-494)	0.645
PDW (fL), mean±SD (min-max)	16.07±1.32 (10-18.1)	16.08±1.32 (12.8-18)	16.06±1.32 (10-18.1)	0.953
MPV (fL), median (IQR), mean (min-max)	9 (8.2-9.8), 9.1(6.5-14.3)	9.4 (8.75-10.55), 9 (7.1-13)	9 (8.2-9.8), 9(6.5-14.3)	0.034
Troponin I (ng/ml), median (IQR), mean (min-max)	2.67 (0.81-5.82), 5.48 (0.001-64)	9.8 (3.6-13.8), 10.82(0.5-57)	2.3 (0.8-5.3), 4.84 (0.001-64)	<0.001
CK-MB (ng/ml), median (IQR)], mean (min-max)	35.5 (25-47), 40.7 (7-259)	54 (38-62), 57 (10-211)	34 (24-45), 38.8 (7-259)	<0.001
CK (ng/ml), median (IQR), mean (min-max)	349 (206-643), 448 (26-2876)	564 (292-854), 653 (39-2876)	332 (195-568), 423 (26-1675)	0.005
Creatinine (mg/dl), median (IQR), mean (min-max)	0.90 (0.79-1.03), 0.93 (0.48-2.3)	0.85 (0.80-1.10), 0.96 (0.58-1.9)	0.90 (0.79-1.03), 0.93 (0.48-2.3)	0.955
eGFR, median (IQR), mean (min-max)	85 (70-100), 85 (25-160)	75 (67-99), 79 (34-135)	86 (71-100), 86 (25-160)	0.099
Glucose (mg/dl), median (IQR), mean (min-max)	130 (109-172), 151 (44-493)	151 (121-207), 149 (67-335)	128 (108-167), 149 (44-493)	0.009
Total protein (g/dl), mean±SD (min-max)	6.63±0.67 (4.7-9.3)	6.63±0.65 (5.2-7.7)	6.63±0.67 (4.7-9.3)	0.984
Albumin (g/dl), median (IQR), mean (min-max)	3.8 (3.5-4.08), 3.81 (2.4-6.2)	3.7 (3.3-4.04), 3.71 (2.5-5.17)	3.8 (3.5-4.08), 3.83 (2.4-6.2)	0.289
Uric acid (mg/dl), mean±SD (min-max)	5.19±1.50 (1.7-11.9)	5.75±1.91 (3-11.7)	5.12±1.42 (1.7-11.9)	0.023
Total cholesterol (mg/dl), median (IQR), mean (min-max)	183 (156-210), 186 (87-386)	176 (143-191), 176 (94-321)	183 (159-211), 187 (87-386)	0.126
LDL (mg/dl), mean±SD (min-max)	119±38 (34-246)	112±41 (45-207)	120±37 (34-246)	0.296
HDL (mg/dl), mean±SD (min-max)	39.8±12.0 (18-83)	41.7±12.9 (20-73)	39.5±11.9 (18-83)	0.348
Triglycerides (mg/dl), median (IQR), mean (min-max)	121 (86-166), 136 (27-936)	112 (80-147), 112 (39-213)	124 (87-167), 139 (27-936)	0.123

CK, creatine kinase; CK-MB, creatine kinase MB; eGFR, estimated glomerular filtration rate; fL, femtolitre; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high density lipoprotein; MPV, mean platelet volume; SD, standard deviation; PDW, platelet distribution width; WBC, white blood count;

According to the multivariate analysis, homocysteine, TIMI risk score, and postdilatation were independent predictors of no-reflow occurrence [Odds Ratio (95% CI), 1.127 (1.042-1.218), p=0.003, 1.385 (1.157-1.659), p<0.001, and 2.396 (1.092-5.257), p=0.029, respectively] (**Table 1**). Considering the ROC curve analysis for homocysteine predicting no-reflow, the area under the curve (AUC) was 0.714 with an optimal cut-off value of 14.1 (sensitivity of 71%, specificity 62%) (**Figure**). Last but not least, homocysteine level was significantly correlated with age (R2=0.001, p=0.038).

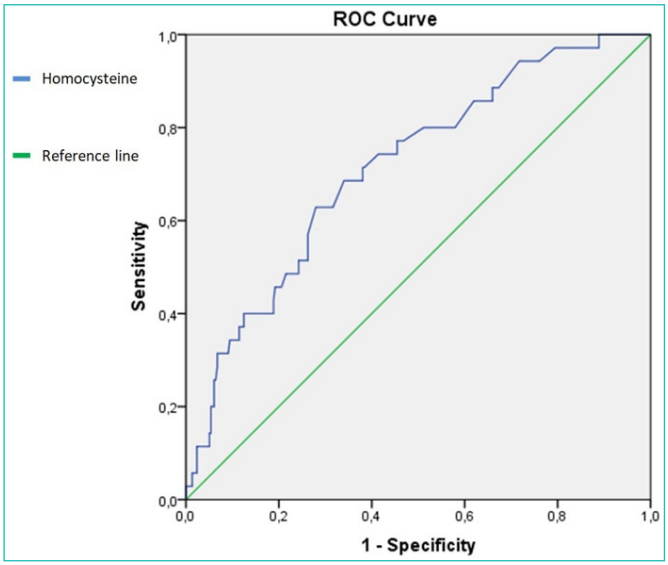

Figure. Diagnostic accuracy of homocysteine value on no-reflow development during pPCI by ROC curve.

pPCI, primary percutaneous intervention; ROC, receiver operating characteristic curve

DISCUSSION

In this study, we focused on the potential relationship between homocysteine and no-reflow development in patients undergoing pPCI. Our results demonstrated a significant relation between serum homocysteine level and the occurrence of no-reflow in this population. Patients with higher levels of homocysteine developed more frequent no-reflow. Furthermore, homocysteine along with the TIMI risk score and postdilatation was an independent predictor of no-reflow in the current work. Besides, no-reflow was significantly associated with age, higher values of systolic blood pressure, Syntax II risk score, TIMI risk score, Killips class, neutrophil, MPV, troponin I, CK-MD, CK, glucose, uric acid, longer stent length and pain-to-balloon time.

No-reflow is linked to a higher risk of rehospitalization, negative ventricular remodeling, malignant arrhythmias, heart failure, and mortality.[17] Endothelial cell dysfunction and microvascular damage are well-established mechanisms of no-reflow.[18,19]

In the meantime, the relationship of homocysteine with endothelial cell dysfunction and microvascular damage has been demonstrated in many studies.[20,21] Homocysteine may trigger microcirculation dysfunction and endothelial cell injury through several mechanisms. Elevated homocysteine can contribute to significant oxidative stress and the production of oxygen radicals.[22] By inhibiting nitric oxide synthase, oxygen free radicals can decrease the synthesis of nitric oxide (NO), which can seriously harm vascular endothelial cells.[23] Higher homocysteine values might also cause thrombin regulatory protein activity by increasing low-density lipoprotein's natural oxidation, further damaging endothelial cells.[24] Moreover, elevated levels of homocysteine have the potential to cause the production of cyclins D and A, hence inducing vascular smooth muscle proliferation and enhancing vascular resistance.[25] The expression of thrombomodulin, von Willebrand factor, and cell adhesion molecules may also be promoted by high homocysteine values. Consequently, they may raise vascular resistance by damaging vascular endothelial cells while stimulating the proliferation of smooth muscle cells.[23] Our findings support the role of homocysteine in the pathogenesis of no-reflow in patients with coronary STEMI undergoing pPCI. Li et al.[26] also showed a close relationship between elevated Hcy levels and no-reflow. They included 54 patients with no-reflow who underwent non-emergency coronary angiography. The patients were compared with 101 control group with normal coronary angiography. However, our study population included patients with STEMI who underwent pPCI. In other words, the comparison was made based on no-reflow development in a homogeneous population in our study. Moreover, we found homocysteine as an independent predictor of no-reflow occurrence.

In a similar line to a past study, our findings demonstrated a significant relationship between TIMI risk score and no-reflow.[27] Of note, we found the TIMI risk score as an independent predictor of no-reflow. TIMI risk score includes clinical variables like age, diabetes mellitus/hypertension/angina, blood pressure, heart rate, Killip class, weight, anterior ST-elevation or left bundle branch block, and time to treatment.[28] Among these, age and hypertension were also associated with no-reflow in the present study. Along the lines of previous reports, distal embolization,[29] ischemia time,[30] stent length,[31] and postdilatation[31] were also associated with no-reflow in the current work.

Early estimation of no-reflow risk factors may have an impact on the prevention of this phenomenon. According to the present findings, higher levels of homocysteine may identify a subset of patients at a higher risk of no-reflow development during pPCI. Therefore, It should be kept in

mind that STEMI patients with higher homocysteine levels may be more susceptible to no-reflow during pPCI. Further studies are necessary to confirm the present findings and elucidate the mechanisms behind these findings.

Limitations

There are some important limitations in the current study. This is an observational single-center study. Therefore, it is not appropriate to apply these results to other populations. The sample size included in the study is quite small.

CONCLUSION

Higher homocysteine levels, higher TIMI risk scores, and postdilatation were associated with no-reflow development during pPCI. Higher levels of homocysteine may identify a subset of patients at a higher risk of no-reflow development during pPCI. More prospective multicenter studies involving a wider population are required to review the significance of the current findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committe of Kafkas University (Date: 27.04.2022, Decision No: 80576354-050-99/128).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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