ORIGINAL RESEARCH

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Predictors of No-reflow Phenomenon Development in Patients Presenting with ST Segment Elevated Myocardial Infarction and Treated with Primary Percutaneous Coronary Intervention

Birincil Perkütan Koroner Girişim Uygulanan ST Segment Yükselmeli Miyokart İnfarktüsü Hastalarında Akımsızlık Fenomeni Gelişimi Öngördürücüleri

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Abstract

Objective: No-reflow phenomenon is one of well-known complications of percutaneous coronary intervention (PCI). The rate of no-reflow phenomenon was reported between 2-44% differing on the accompanying situations and more frequent in acute myocardial infarction. Predictive factors for no-reflow phenomenon have not been clearly defined. We aimed to define predictive factors for no-reflow development in patients who presented with ST-segment elevation MI (STEMI) and treated with primary (PPCI).

Method: Patients who underwent PPCI between 2017 and 2021 in our clinic were included retrospectively. Demographic, clinical and laboratory findings were recorded. Two groups generated according to no-reflow development: no-reflow (+) and (-).

Results: Six hundred eighty-nine patients were included. Mean age was 55.9±8.7 years and 71.8% were male. 107 patients (15.5%) were formed no-reflow (+) group and 582 patients were formed no-reflow (-) group. Left ventricular ejection fraction, troponin, fasting blood glucose, TIMI thrombus grade and TIMI thrombus category were determined as independent predictors of no-reflow development.

Conclusion: Considering the relationship between no-reflow development and adverse outcomes such as in-hospital adverse cardiac events, left ventricular remodeling, malignant ventricular arrhythmia, or

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Amaç: Koroner anjiyografide (KAG) mekanik tıkanıklık olmamasına ve sorumlu koroner arterde yeterli açıklık sağlanmasına rağmen ilgili myokard segmentinde perfüzyonun sağlanamamasına no-reflow (akımsızlık) fenomeni denir. No-reflow fenomeninin akut myokard infarktüsü (MI) hastalarında daha sık olduğu ve tekrarlayan MI, hastane içi istenmeyen kardiyak olaylar, sol ventrikül yeniden yapılanması, malign ventriküler aritmi ve uzun dönemde kalp yetersizliği gelişimi ile ilişkili olduğu son yapılan çalışmalarda gösterilmiştir. No-reflow fenomenini öngördürücü faktörler net olarak tanımlanamamıştır. Biz bu çalışmamızda, kliniğimize ST segment yükselmeli MI (STSYMI) ile başvuran hastalarda no-reflow gelişimi ile ilgili öngördürücü faktörleri tanımlamayı amaçladık.

Yöntem: Kliniğimize 2017-2021 tarihleri arasında STYMI tanısı ile primer perkütan koroner girişim (PPKG) uygulanan hastalar geriye dönük dahil edildi. Demografik, klinik ve laboratuvar bulguları hastane veri tabanı taranarak elde edildi. KAG'de sorumlu epikardiyal koroner arterde yeterli açıklık sağlanmasına ve spazm, diseksiyon olmamasına rağmen TIMI ≤2 akım olan hastalar no-reflow gelişen gruba dahil edildi. No-reflow fenomeni gelişimini öngördürebilecek demografik, klinik, laboratuvar ve anjiyografik parametrelerin tanımlanması planlandı.

Bulgular: Çalışmamıza toplam 689 hasta dahil edildi. Yaş ortalaması 55,9±8,7 olup hastaların %71,8'i erkekti. No-reflow gelişimine göre 2

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Abstract

heart failure, it may help to identify the factors that predict the risk of no-reflow and take preventive measures to improve the long-term outcome.

Keywords: No-reflow, ST elevation myocardial infarction, TIMI thrombus grade

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grup oluşturulduğunda 107 hastada (%15,5) no-reflow geliştiği gözlendi. Lojistik regresyon analizinde sol ventrikül ejeksiyon fraksiyonu, troponin, açlık kan şekeri, TIMI trombüs yükü ve TIMI trombüs yükünün derecesi no-reflow gelişiminin bağımsız öngördürücüleri olarak saptandı.

Sonuç: Hastane içi istenmeyen kardiyak olaylar, sol ventrikül yeniden şekillenmesi, malign ventriküler aritmi ve kalp yetmezliği sıklığının no-reflow fenomeni gelişen hastalarda fazla olduğu göz önünde bulundurulduğunda, no-reflow riskinin öngördürücü faktörlerinin belirlenmesi uzun vadeli sonucu iyileştirmek için önleyici tedbirler alınmasına yardımcı olabilir.

Anahtar kelimeler: No-reflow, ST segment yükselmeli miyokard infarktüsü, TIMI trombüs derecesi

Introduction

Percutaneous coronary intervention (PCI) is a widely used treatment regimen in cardiology era and is the main treatment for patients with presenting with ST segment elevation myocardial infarction (STEMI) (1,2). No-reflow phenomenon is an extreme form of coronary slow flow (3) and one of the well-known complications of PCI (4,5). Inadequate myocardial perfusion despite lack of angiographic epicardial vessel dissection, obstruction or spasm is called the "no-reflow" phenomenon (6). The rate of no-reflow phenomenon was reported between 2-44% differing on the accompanying situations (4,7). It is known to be more frequent in patients presenting with acute myocardial infarction (8,9). Considering the relation between short and long-term adverse cardiovascular events (10), defining related risk factors and patients under risk may help to take precautions to decrease the no-reflow development and improve outcomes.

In this study, we aimed to define the predictive factors for the development of no-reflow in patients presenting with STEMI and treated with primary PCI (PPCI).

Materials and Methods

All STEMI patients who underwent PPCI between 2017-2021 in our center were included in this retrospective single center study. Local hospital electronic database and patients' files were screened to for demographic, clinical and laboratory data. ST elevation myocardial infarction diagnosis was based on recent guidelines (1). Patients who did not undergo stent implantation due to unsuitable anatomy or decided to be treated by emergent surgery were excluded. Additionally, patients presenting after 12 hours from the symptom onset, underwent rescue PCI and those with spontaneous or procedure related coronary dissection were excluded. Coronary flow was defined according to Thrombolysis in Myocardial Infarction (TIMI) score and no-reflow was defined as TIMI flow grade ≤2 (11).

Congestive heart failure (CHF) (12), hypertension (HT) (13), stroke (14), transient ischemic attack (TIA) (15), diabetes mellitus (DM) (16) was defined according to recent guidelines. Simpson's method was applied to measure left ventricular ejection fraction (EF) by transthoracic echocardiography (Vivid S70; GE Medical System, Herten, Norway).

Coronary angiography views were reviewed to define culprit vessel and lesion localization, TIMI flow and thrombus grades on admission. Thrombus burden was classified based on TIMI thrombus grade (TTG); values >3 indicating high and ≤3 indicating low TTG (17). Coronary artery stenosis was defined at least 70% decrease in the internal diameter of the left anterior descending or circumflex or right coronary artery and their major branches or a 50% decrease in internal diameter of left main coronary artery (18). Stent type (bare metal or drug eluting), stent size (length, diameter), the type and dose of anticoagulant, antiaggregant agents were documented. Two groups were created according to no-reflow development as no-reflow (+) and (-) group. No-reflow phenomena development is accepted as the primary endpoint of the study. Human Studies and Research Committee of our institution approved the study and patient consent was waived accordingly. (Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital date: 16/11/2022; decision number: 2022/11/07/028). Patient consent was waived due to retrospective design of the study.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA). Categorical data are stated as number (n) and percentages (%) and continuous variables are stated as mean ± standard deviation. Differences in categorical variables were analyzed with chi-square test. Student's t-test or Mann-Whitney U test was used to compare unpaired samples. Independent variables of no-reflow development were identified by using univariate and multivariate logistic regression analyses. In order to find a cut-off value for the laboratory parameters receiver operating characteristic (ROC) curves were acquired and the ideal values with the greatest total sensitivity and specificity in the prediction of no-reflow were selected. Groups were compared for all parameters with regards to no-reflow occurrence. A 2-sided p<0.05 was assumed as statistically significant.

Results

Seven hundred and fifty-seven patients were evaluated. After exclusion of patients as defined in methodology and those with lack of data, finally 689 patients were included in this retrospective study (Figure 1). The mean age was 55.9±8.7 and 70.1% were male. When patients were grouped according to no-reflow development as no-reflow (+) an (-); 107 (15.5%) patients formed the no-reflow (+) whereas 582 (84.5%) patients formed no-reflow (-) group. Both groups were similar in terms of age, gender, body mass index, incidence of hyperlipidemia, history of myocardial infarction and coronary artery bypass surgery. However, smoking status (62.6% vs. 55.7%; p=0.036), incidence of HT (57.1% vs. 38.8%: p=0.001) and DM (46.7% vs. 31.6%; p=0.002), patients with a history of stroke (11.2% vs. 2.4%; p<0.0001), and CHF (20.6% vs. 10.9%; p=0.006) were significantly higher in no-reflow (+) group. In terms of laboratory markers; NT pro-BNP [1350 (62-3500) vs.1056 (50-35000); p=0.012], troponin (114.2±26.4 vs. 56.6±11.6; p<0.0001), fasting blood glucose (166.3±68.3 vs. 131.3±38.7; p<0.0001) were significantly higher and albumin (3.9±0.6 vs. 4.2±0.6; p=0.043), left ventricular EF (51.2±11.3 vs. 56.1±9.5; p<0.0001) levels were significantly lower in no-reflow (+) group. Furthermore, when angiographic findings were evaluated stent length (33.5±6.3 vs. 23.3±5.2; p<0.0001), TTG [2.9 (0-5) vs. 1.6 (0-5); p<0.0001)], volume of contrast media (166±22 vs. 101±15; p<0.0001) and GENSINI score (21.8±9.2 vs. 19.9±8.5; p=0.032) were significantly higher in no-reflow (+) group. Moreover 30-day cardiovascular mortality (13.1% vs. 3.6%; p<0.0001) was significantly higher in no-reflow (+) group (Table 1).

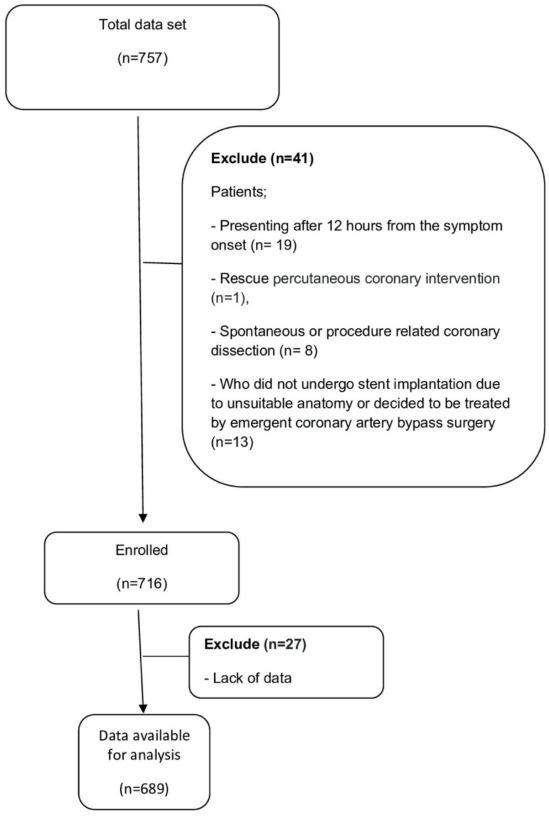

Figure 1. Selection of the study population

To further evaluate individual risk factors for no-reflow development, univariate logistic regression analysis was performed for smoking, DM, HT, history of stroke, and CHF, volume of contrast media used, left ventricular EF, NT pro-BNP, troponin, fasting blood glucose, albumin, GENSINI score, TTG, TTG class and stent length, respectively. By univariate logistic regression analysis, smoking, presence of DM, HT, history of stroke, left ventricular EF, troponin, fasting blood glucose, GENSINI score, TTG and TTG class were correlated with no-reflow development. These variables were assessed in the multivariate logistic regression model. Left ventricular EF [p=0.046, β: 0.952, OR (95% CI): 0.907-0.999], troponin [p<0.0001, β: 1.177, OR (95% CI): 1.131-1.226], fasting blood glucose [p=0.032, β: 1.010, OR (95% CI): 1.001-1.018], TTG [p=0.035, β: 1.834, OR (95% CI): 1.043-3.226] and TTG class [p=0.016, β: 2.788, OR (95% CI): 1.162-5.762] were revealed as independent risk factors associated with no-reflow development by multivariate logistic regression analyses (Table 2). ROC curve analysis was performed to identify the optimal cut-off value and area under the curve (AUC) for troponin, glucose and TTG. ROC curve for accuracy of troponin,

Table 1. Clinical, demographic, laboratory and angiographic data

Variables	All n=689	Group 1 No-reflow (+) n=107	Group 2 No-reflow (-) n=582	p
Clinical Characteristics and Comorbidities				
Age (years)	55.9±8.7	56.7±8.8	55.7±8.6	0.308
Male, n (%)	495 (71.8)	75 (70.1)	420 (72.2)	0.661
Body mass index, (kg/m²)	27.4±4.4	27.9±5.1	27.4±4.3	0.723
Smoking, n (%)	391 (56.7)	67 (62.6)	324 (55.7)	**0.036**
Hypertension, n (%)	287 (41.7)	61 (57.1)	226 (38.8)	**0.001**
Hyperlipidemia, n (%)	249 (36.1)	44 (41.1)	205 (35.2)	0.243
Diabetes mellitus, n (%)	234 (34.0)	50 (46.7)	184 (31.6)	0.002
Previous myocardial infarction, n (%)	117 (16.9)	18 (16.8)	99 (17.1)	0.428
Previous CABG, n (%)	77 (11.2)	12 (11.2)	65 (11.1)	0.546
Previous stroke, n (%)	26 (3.8)	12 (11.2)	14 (2.4)	**<0.0001**
Previous CHF, n (%)	86 (12.5)	20 (20.6)	64 (10.9)	**0.006**
Left ventricular ejection fraction, %	55.3±9.9	51.2±11.3	56.1±9.5	**<0.0001**
Laboratory Parameters				
Urea, mg/dL	34.1±13.5	34.4±13.5	33.9±13.5	0.831
Creatinine, mg/dL	0.9±0.6	0.9±0.2	0.9±0.5	0.979
Hemoglobin, g/dL	14.1±1.7	14.2±1.7	14.1±1.6	0.709
Hematocrit, (%)	42.3±5.2	42.8±5.1	42.2±5.3	0.352
WBC x10³/μL	9.7±4.3	9.7±5.2	8.9±4.6	0.289
Platelet counts 10³/μL	236.6±67.6	245.1±63.6	234.9±68.3	0.246
Albumin, g/dL	4.0±0.4	3.9±0.6	4.2±0.6	**0.043**
CRP, mg/L	0.9 (0.1-9.4)	1.2 (0.16-5.08)	1.6 (0.1-9.4)	0.783
NT pro-BNP, pg/mL	737 (50-35000)	1350 (62-3500)	1056 (50-35000)	**0.012**
Troponin, ng/mL	65.5±25.6	114.2±26.4	56.6±11.6	**<0.0001**
Fasting blood glucose, mg/dL	136.7±46.3	166.3±68.3	131.3±38.7	**<0.0001**
Total cholesterol, mg/dL	181.6±41.5	182.5±38.9	176.7±53.3	0.344
Triglycerides, mg/dL	159.7±63.2	167.7±61.4	158.2±63.5	0.306
LDL cholesterol, mg/dL	123.2±34.8	123.9±34.7	119.5±35.5	0.386
HDL cholesterol, mg/dL	38.5±10.3	38.1±14.8	40.2±9.1	0.172
Angiographic findings				
Stent length, mm	26.2±5.4	33.5±6.3	23.3±5.2	**<0.0001**
Stent diameter, mm	2.9±0.4	2.9±0.5	2.9±0.4	0.947
TTG	1 (0-5)	2.9 (0-5)	1.6 (0-5)	**<0.0001**
TTG category, n (%)				
≤3	500 (72.6)	62 (57.9)	438 (75.3)	
>3	189 (27.4)	45 (42.1)	144 (24.7)	**<0.0001**
Volume of contrast media, (mL)	137±51	166±22	101±15	**<0.0001**
GENSINI score	20.2±2.1	21.8±9.2	19.9±8.5	**0.032**
Mortality, n (%)	35 (5.1)	14 (13.1)	21 (3.6)	**<0.0001**

CABG: Coronary artery bypass graft, CHF: Congestive heart failure, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, NT-proBNP: N terminal peptide brain natriuretic peptide, TTG: TIMI thrombus grade, WBC: White blood cell

glucose and TTG for predicting no-reflow development in STEMI patients is shown in Figure 2. The AUC for troponin was 0.984 (95% CI: 0.976-0.993). A cut-off value of 77.5 for troponin was associated with 92.5% sensitivity and 91.8% specificity in prediction of no-reflow development. Additionally, the AUC for glucose was 0.659 (95% CI: 0.596-0.721) and a cut-off value of 139.5 for glucose was associated with 66.4% sensitivity and 62.7% specificity in prediction of no-reflow development. Moreover, AUC for TTG was 0.680 (95% CI: 0.633-0.727) and a cut-off value of 3.0 for TTG was associated with 68.2% sensitivity and 66.7% specificity in prediction of no-reflow development.

Discussion

In this study we sought to assess predictive factors for no-reflow development in patients presenting with STEMI and treated with PPCI. Consequently, reduced left ventricular EF, higher troponin and fasting blood glucose levels on admission, TTG and TTG class were revealed as independent risk factors associated with no-reflow

Table 2. Univariate and multivariate logistic regression analysis for predictors of no-reflow development

	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
Smoking	0.080	0.004-0.115	**0.028**	0.580	0.206-1.629	0.301
Diabetes mellitus	0.116	0.031-0.145	**0.002**	0.715	0.239-2.141	0.548
Hypertension	0.134	0.044-0.153	**<0.0001**	1.020	0.360-2.886	0.971
Previous CHF	0.715	0.033-1.196	0.132			
Previous stroke	0.318	0.178-0.459	**<0.0001**	0.339	0.019-6.165	0.465
Left ventricular ejection fraction	0.516	0.365-0.667	**<0.0001**	0.952	0.907-0.999	**0.046**
NT pro-BNP	0.456	0.239-1.098	0.078			
Troponin	0.600	0.557-0.643	**<0.0001**	1.177	1.131-1.226	**<0.0001**
Fasting blood glucose	0.138	0.056-0.219	**0.001**	1.010	1.001-1.018	**0.032**
Albumin	0.924	0.808-1.109	0.749			
GENSINI score	1.026	1.002-1.050	**0.033**	0.978	0.902-1062	0.601
TTG	1.322	1.199-1.459	**<0.0001**	1.834	1.043-3.226	**0.035**
TTG class	0.453	0.295-0.695	**<0.0001**	2.788	1.162-5.762	**0.016**
Volume of contrast media	0.981	0.556-1.731	0.947			
Stent length	1.008	0.970-1.046	0.699			

CHF: Congestive heart failure, NT-proBNP: N terminal peptide brain natriuretic peptide, TTG: TIMI thrombus grade, CI: Confidence interval, OR: Odds ratio

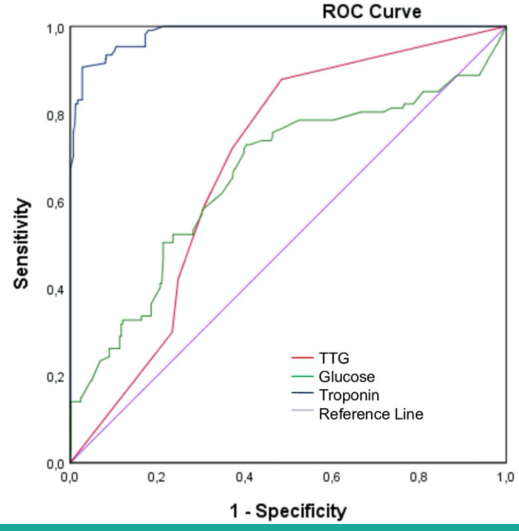

Figure 2. ROC curve for accuracy of troponin, glucose and TIMI thrombus grade for predicting no-reflow development in patients presenting with ST segment elevated myocardial infarction and treated with primary percutaneous coronary intervention

ROC: Receiver operating characteristic, TIMI: Thrombolysis in myocardial infarction

development. Therefore TTG ≥3, increased troponin and fasting blood glucose levels on admission can be used in conjunction with reduced left ventricular EF in order to stratify patients under risk of no-reflow development with a diagnosis of STEMI and treated with PPCI.

Previous studies have stated that lack of reflow may be associated with some clinical determinants. A relationship between delayed reperfusion and no-reflow phenomenon has been demonstrated (19,20). In our study, troponin values were higher in patients with no-reflow compared to those with normal flow, which may be related to prolonged symptoms and time to reperfusion. Also, recent studies have shown a higher incidence of no-reflow in patients with reduced left ventricular EF (19,21). Reduced microvascular perfusion in conjunction with reduced EF may one of the underlying pathophysiological mechanisms. In addition, increased left ventricular end-diastolic pressure and impaired coronary perfusion may trigger no-reflow development (8,22,23). In our study, we revealed decreased left ventricular EF as an independent predictor of no-reflow development. However, the relation between hyperglycemia and no-reflow has been shown and it was thought to be linked with microvascular dysfunction. This leads to larger infarct size and worse functional recovery (24,25). In the present study, high fasting blood glucose levels on admission was detected as an independent predictor of no-reflow development.

Implanted stent length and diameter were reported as predictors of no-reflow development previously (26). Although, there were no difference regarding stent diameter, stent length was higher in no-reflow (+) group in our study. However, stent length was not found as an independent predictor for no-reflow development in further analysis.

Various clinical, laboratory and angiographic parameters were defined as predictors for no-reflow development previously. Age, male gender, smoking, DM, HT and the Killip class were reported to be related with increased risk of no-reflow development in a metanalysis (27). One of the underlying mechanisms is thought to be endothelial dysfunction, and it has been shown that advanced age, DM, HT and male gender are also associated with endothelial dysfunction (28-31). Impaired coronary flow reserve and increased vulnerability of the myocardium might be the other underlying mechanisms in conjunction with endothelial dysfunction. Moreover, preexisting microvascular dysfunction which was thought to be associated with these risk factors might be the facilitating mechanism (32). According to our results, groups were familiar regarding age and sex; whereas DM, HT and smoking were found to be higher in no-reflow (+) group, however those were not found independent predictors of no-reflow development. High serum glucose levels on admission, TTG and TTG class were independent predictors associated with no-reflow development according to our results.

Distal embolization of plaque and/or thrombus may result with no-reflow. Plaque volume was evaluated with intravascular ultrasound after primary PCI and decrease in plaque volume was observed more obvious those with inadequate flow (33). Considering the high prevalence of thrombus burden in STEMI patients, distal embolization is one of the possible mechanisms. However, we did not perform intravascular imaging. Additionally, increased alpha adrenergic tone, thromboxane A2 and serotonin levels may end up with exaggerated vasoconstriction and no-reflow. These pathophysiological mechanisms should not be ignored, but in this article, we aimed to define clinical risk factors and raise clinical suspicion.

Single-center and retrospective design with a relatively small patient population were the main limitations of the study. The time interval from symptom onset to CAG of each patient and no-reflow may be reasons for increased mortality in STEMI patients. Our results were based on CAG findings; however, advanced imaging options (intravenous ultrasound and optical coherence tomography) may provide crucial information such as thrombus and plaque burden and erosions which may augment no-reflow phenomena development. Definitely, larger and prospectively designed further studies are needed to demonstrate the relationship between predictive factors for the development of no-reflow in patients presenting with STEMI. Our study showed that no-reflow during PPCI is associated with 30-day mortality.

Conclusion

TIMI thrombus grade ≥3, higher levels of troponin and fasting blood glucose on admission can be used in conjunction with reduced left ventricular ejection fraction in order to stratify patients for high risk of no-reflow development presenting with STEMI and treated with PPCI. The incidence of in-hospital adverse cardiac events, left ventricular remodeling, malignant ventricular arrhythmia, and long-term development of heart failure, were increased in patients with no-reflow phenomenon. Thus, identifying predictive factors for no-reflow development may help to take precautions to decrease the no-reflow incidence and improve long-term results. Prospective studies, evaluating

the effect of protective measures and strengthen with the intravascular imaging modalities to define the underlying mechanism in patient basis would give more reliable evidence.

Ethics

Ethics Committee Approval: Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital date: 16/11/2022; decision number: 2022/11/07/028.

Informed Consent: Informed consent waived due to retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.D., S.Ö., İ.Ş., E.O., Design: E.D., S.Ö., İ.Ş., E.O., Data Collection or Processing: E.D., S.Ö., Analysis or Interpretation: E.D., S.Ö., Drafting Manuscript: E.D., S.Ö., Critical Revision of Manuscript: E.D., S.Ö., İ.Ş., E.O., Final Approval and Accountability: E.D., S.Ö., İ.Ş., E.O., Technical of Material Support: İ.Ş., E.O., Writing: E.D., S.Ö., İ.Ş., E.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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