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ORIGINAL SCIENTIFIC PAPER

The non-HDL-C/HDL-C ratio is a strong and independent predictor of the no-reflow phenomenon in patients with ST-elevation myocardial infarction

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ABSTRACT

Background: No-reflow (NR) is the inability to achieve adequate myocardial perfusion despite successful restoration of attegrade blood flow in the infarct-related artery after primary percutaneous coronary intervention. The non-HDL-C/HDL-C ratio has been shown to be superior to conventional lipid markers in predicting most cardiovascular diseases. In this study, we wanted to reveal the predictive value of the NR by comparing the Non-HDL-C/HDL-C ratio with traditional and non-traditional lipid markers in patients who underwent primary percutaneous coronary intervention (pPCI) due to ST-elevation myocardial infarction (STEMI).

Methods: A total of 1284 consecutive patients who underwent pPCI for STEMI were included in this study. Traditional lipid profiles were detected and non-traditional lipid indices were calculated. Patients were classified as groups with and without NR and compared in terms of lipid profiles.

Results: No-reflow was seen in 18.8% of the patients. SYNTAX score, maximal stent length, high thrombus burden, atherogenic index of plasma and non-HDL-C/HDL-C ratio were determined as independent predictors for NR ($p < 0.05$, for all). The non-HDL-C/HDL-C ratio predicts the development of NR in STEMI patients with 71% sensitivity and 67% specificity at the best cut-off value. In ROC curve analysis, the non-HDL-C/HDL-C ratio was superior to traditional and non-traditional lipid markers in predicting NR ($p < 0.05$, for all).

Conclusion: The non-HDL-C/HDL-C ratio can be a strong and independent predictor of NR in STEMI patients and and therefore non-HDL-C/HDL-C ratio may be a useful lipid-based biomarker that can be used in clinical practice to improve the accuracy of risk assessment in patients with STEMI.

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Non-HDL-C/HDL-C ratio; ST-elevation myocardial infarction; non-traditional lipids; no-reflow phenomenon

Introduction

ST-segment elevation myocardial infarction (STEMI) is one of the leading cardiovascular mortality and morbidities worldwide. The first treatment option in these patients is primary percutaneous coronary intervention (pPCI), which is performed to restore antegrade flow in the infarct-related artery (IRA) as soon as possible, to improve myocardial microperfusion and to reduce the size of myocardial infarction [1]. However, in 15% to 40% of these patients, despite successful percutaneous coronary intervention to the epicardial culprit coronary artery, adequate angiographic antegrade flow cannot be fully achieved, and the entity called no-reflow phenomenon (NR), which results in inadequate ST-segment resolution on electrocardiography and weak myocardial blush grade (MBG) [2]. To establish the diagnosis of no-reflow, there must be no angiographic evidence of epicardial coronary artery obstruction, conduit vessel spasm, flow-limiting dissection, or obvious *in situ* thrombosis [2]. The no-reflow phenomenon is associated with increased malignant arrhythmia, increased infarct area, congestive heart failure, increased risk of post-procedure reinfarction, and increased in-hospital, short- and long-term cardiovascular mortality [3]. Therefore, knowing the predictors of no-reflow development and taking preventive measures against it may help to increase the surveillance of this patient group in clinical practice. Disorders at the microvasculature level constitute the basic mechanism underlying the no-reflow phenomenon. In this process, ischaemia-reperfusion (IR) damage, endothelial dysfunction, increased proinflammatory processes, distal embolisation, platelet activation and aggregation, high thrombus burden, disruption of

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vasoregulatory mechanisms, activation of the extrinsic coagulation pathway, leukocyte adhesion, microvascular ischaemia and edoema, increased vasoconstrictor mediators and free radical mediated endothelial damage are the main causes that are held responsible for the etiopathogenesis [4].

Dyslipidemia is a well demonstrated major risk factor for cardiovascular diseases (CVD) [5]. Dyslipidemia is characterised by increased plasma concentrations of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) concentrations [5]. In many clinical studies, it has been shown that the predictive and diagnostic values of non-traditional lipid parameters such as non-HDL-C, non-HDL-C/HDL-C ratio (Also known as atherogenic index [AI] or arteriosclerosis index), atherogenic index of plasma (AIP), lipoprotein combined index (LCI), TC/HDL-C and LDL-C/HDL-C, obtained with various combinations of traditional lipid profiles, are superior to conventional lipid parameters alone in various disease groups, especially cardiovascular diseases [6–11].

A relatively new non-traditional lipid ratio, the non-HDL-C/HDL-C ratio, contains information that includes the balance between both atherogenic and anti-atherogenic particles and predicts the association of plasma lipids with cardiovascular events such as coronary artery disease (CAD) better compared to single lipid parameters [8–12]. Non-HDL-C/HDL-C ratio has been shown to be a reliable marker of insulin resistance in patients at high risk of metabolic disease [13]. In this context, the Non-HDL-C/HDL-C ratio is accepted as a reliable atherogenic index marker [14]. Atherogenic index of plasma (AIP), a reliable surrogate marker of insulin resistance, has been reported to be an independent predictor for the development of no-reflow in STEMI patients [15]. Non-HDL-C obtained by subtracting HDL-C from plasma TC, contains atherogenic lipoproteins such as: LDL-C, very low density lipoprotein cholesterol (VLDL-C), medium density lipoprotein cholesterol and lipoprotein(a) [16–18]. Therefore, Non-HDL-C has a higher atherogenic burden than LDL-C, and it has been shown that identifying non-HDL-C as the primary treatment target has better predictive value than LDL-C [18]. Recent studies have shown that non-HDL-C plays a pivotal role in the development and progression of vascular endothelial dysfunction and atherosclerosis [16–18]. Unlike non-HDL-C, HDL-C has positive effects on endothelial functions and atherosclerosis due to its antiatherogenic, antioxidant and anti-inflammatory properties [19]. Also, unlike pro-atherogenic lipoproteins, HDL-C exerts antithrombotic effects by interacting with platelets, coagulation cascade and vascular endothelium [20].

Since non-HDL-C and HDL-C have opposite effects on pathophysiological mechanisms that are important in the pathogenesis of no-reflow, such as endothelial function, platelet aggregation and activation, and oxidant-antioxidant balance, we would like to explore the hypothesis that these two lipid biomarkers combined in a single fraction could better predict no-reflow in STEMI patients [2–4]. The relationship between the non-HDL-C/HDL-C ratio, which has been shown to be strongly associated with some cardiovascular diseases, especially coronary artery disease, and the development of no-reflow has not been demonstrated until now. Due to the close association between no-reflow development and increased adverse cardiovascular events in STEMI patients, we aimed to investigate the relationship between non-HDL-C/HDL-C ratio and no-reflow development in order to better determine risk stratification in STEMI patients.

Methods

Study population and data collection

This retrospectively designed study included 1284 consecutive patients who underwent primary percutaneous coronary intervention (pPCI) within 12 h for STEMI. The diagnosis of STEMI was made according to current guidelines and the medical data of the subjects were obtained from the hospital database. Patients under 18 years of age, patients without accessible serum lipid profile, patients with acute and chronic infections, patients with hematological or autoimmune disorders, those who did not undergo invasive intervention within 12 h of the onset of angina, those who received thrombolytic therapy before the procedure, those with advanced kidney or liver disease, patients with a history of malignancy and using antilipidemic drugs before the procedure were excluded from the study. The present study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Study protocol, laboratory results and measurements

Age, gender, comorbidities and laboratory data of all patients included in the study were recorded. The lipid profile of the patients was recorded from plasma samples obtained after at least 8 h of fasting. Hematological parameters were measured using a haematology

analyser (Beckman Coulter, Avenue Miami, FL, USA) and the lipid panel (TC, HDL-C, and TG) was measured directly by the enzymatic colorimetric method using the commercial Advia 2400 Chemistry system (Siemens Healthcare Diagnostics, Tokyo, Japan) and LDL-C levels were calculated using the Friedewald formula (only for TG < 4.5 mmol/L). Estimated glomerular filtration rate (eGFR) calculated from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation formula. The left ventricular ejection fraction (LVEF) of the patients was calculated using the modified Simpson method. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). The SYNTAX score was calculated using a web calculator (https://www.syntaxscore.org).

Clinical definitions

Diabetes is defined according to the following criteria: (1) fasting plasma glucose (FPG) >126 mg/dL, (2) 2h plasma glucose (PG) >200 mg/dL during oral glucose tolerance test, (3) HbA1c >6.5%, (4) in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random PG >200 mg/dL, or, (5) taking oral antidiabetics or insulin. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or current treatment by any antihypertensive drug. Dyslipidemia was defined as the presence of one of four parameters of the lipid profile measured after at least 8 h of fasting: (1) total cholesterol >200 mg/dl, (2) low-density lipoprotein cholesterol (LDL-C) >130 mg/dl, (3) high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women, and (4) triglycerides >150 mg/dl [21]. Thrombus burden observed before percutaneous coronary intervention was defined as low thrombus burden (LTB) with grade 1–3, and high thrombus burden (HTB) with grade 4–5. Angiographic no-reflow (NR) was defined as Thrombolysis in Myocardial Infarction (TIMI) flow less than grade III in the infarct-related artery without dissection or spasm after successful percutaneous coronary intervention in epicardial coronary arteries [3]. Individuals without clinical signs of heart failure were classified as Killip class I, individuals with rales or crackles in the lungs, an S3 gallop, and elevated jugular venous pressure were classified as Killip class II, individuals with significant acute pulmonary edoema were classified as Killip class III, individuals with evidence of cardiogenic shock or hypotension (measured as systolic blood pressure <90 mmHg), and evidence of low cardiac output (oliguria, cyanosis, or impaired mental status) were classified as Killip class IV. Positive family history of coronary artery disease (CAD) was defined as confirmed evidence of premature CAD in a first degree relative (men <55 and women <65 years of age). At least 50% stenosis in the left main coronary artery (LMCA) and at least 70% stenosis in the other main epicardial coronary arteries was considered as critical stenosis, and the number of vessels with critical stenosis was recorded as the number of stenotic vessels. Multivessel disease is defined as luminal stenosis of at least 70% in at least two major coronary arteries or in one coronary artery in addition to a 50% or greater stenosis of the LMCA.

Calculation of lipid indices

Lipid indices were calculated using atherogenic/anti-atherogenic cholesterol or particle ratios. Non-HDL-C was obtained by subtracting HDL-C from TC. Atherogenic index (Non-HDL-C/HDL-C ratio) was obtained by dividing Non-HDL-C by HDL-C. The atherogenic index of plasma (AIP) was obtained by taking the logarithmic derivative of the ratio of TG to HDL-C Log_{10}(TG/HDL-C). The lipoprotein combined index (LCI) was obtained with the formula: TC x TG x LDL-C/HDL-C. In addition, TC/HDL-C ratio was obtained by dividing TC by HDL-C and LDL-C/HDL-C ratio was obtained by dividing LDL-C by HDL-C.

Periprocedural angiographic evaluation

All patients were diagnosed with STEMI according to current guidelines and pPCI was performed *via* femoral or radial route by experienced invasive cardiologists [22]. All patients were given a loading dose of dual antiplatelet and unfractionated heparin at a dose of 70–100 IU/kg before percutaneous coronary intervention. Thrombolysis in myocardial infarction (TIMI) flow grade classification was used to evaluate the flow after percutaneous coronary intervention in the culprit epicardial coronary artery. [23]. Angiographic NR was defined as TIMI flow grade < III after pPCI in the culprit coronary artery without coronary spasm or dissection [3]. All angiographic images were digitised for quantitative analysis (DICOM viewer, MedCom GmbH, Darmstadt, Germany) and were evaluated by at least two experienced invasive cardiologists who were not aware of the medical data of the patients and the final decision was made. Patients who developed NR were treated using adenosine, glycoprotein IIb/IIIa inhibitors, calcium channel blockers, or a combination of these

drugs, and the option of mechanical thrombectomy was left to the discretion of the operator.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov test was used to check whether the data fit the normal distribution. Normally distributed variables were expressed as mean ± SD and non-normally distributed variables as median (interquartile range [IQR]) and compared with Student's t or Mann-Whitney U tests according to distribution. Categorical values were reported using numbers and percentages. For comparison of categorical variables, the χ2 test or Fisher's exact test was used, as applicable. Pearson correlation coefficient was used to determine the relationship between the non-HDL-C/HDL-C ratio and other non-traditional lipid profiles. Univariate and multivariate regression analyzes were performed to identify independent potential predictors of the no-reflow phenomenon. Baseline variables with statistical significance ($p < 0.05$) determined by univariate analysis were included in the multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cut-off value of the non-HDL-C/HDL-C ratio to predict the no-reflow phenomenon. The optimal cut-off value was calculated from the point of maximum sensitivity and specificity (Youden's index). In addition, comparison of the discrimination capacity of the non-HDL-C/HDL-C ratio and other non-traditional lipid ratios to predict the no-reflow phenomenon was obtained by pairwise comparison of ROC curves with the De-Long method using MedCalc 16 statistical software (MedCalc Software Ltd, Ostend, Belgium). A 2-sided $p < 0.05$ was considered statistically significant.

Results

Of the 1284 subjects who underwent pPCI for STEMI in the study, 71.6% were male, 28.4% were female, and no-reflow phenomenon developed in 242 (18.8%). Basic demographic, medical history, clinical and laboratory data of the study population are indicated in Table 1 according to whether no-reflow has developed or not. While there was no significant difference between the groups in terms of gender, BMI, hypertension, smoking status, previous CAD, family history of CAD and atrial fibrillation, the mean age, incidence of diabetes and dyslipidemia were significantly higher in the no-reflow group than in the no-reflow group. There was no significant difference between the groups in terms of preprocedural medication ($p > 0.05$, for all). The incidence of NYHA III-IV class congestive heart failure and killip class ≥ II was significantly higher in the no-reflow group than in the non-reflow group (11.6% vs 7.5%, $p = 0.038$; 28.5% vs 22.5%, $p = 0.046$; respectively). Fasting plasma glucose, C-reactive protein (CRP), mean platelet volume (MPV), Peak CK-MB and Peak Troponin I levels were significantly higher in the no-reflow group ($p < 0.05$, for all). TC, TG and LDL-C values, which are traditional lipid profile parameters, were higher in the no-reflow group, while HDL-C values were significantly lower ($p < 0.05$, for all). At the same time, the level of non-traditional lipid profiles (Non-HDL-C, LDL-C/HDL-C, TC/HDL-C, LCI, AIP, Non-HDL-C/HDL-C) was significantly higher in the group that developed no-reflow than in the group that did not develop NR ($p < 0.001$, for all) (Figure 1).

The periprocedural and angiographic features of the patients according to the no-reflow status are demonstrated in Table 2. Multi-vessel disease, stenotic vessel count and SYNTAX score, which are indicators of severity and extent of coronary artery disease, were significantly higher in the group that developed no-reflow compared to the group that did not develop ($p = 0.004$, $p = 0.015$, $p = 0.001$; respectively). In addition, no-reflow development was significantly higher in those with high thrombus burden and those with longer maximal stent length ($p < 0.001$, for both). The use of Gp IIb/IIIa inhibitors and the frequency of thrombus aspiration were significantly higher in the no-reflow group, probably because these options are more preferred in patients with high thrombus burden (p=.0.018, $p < 0.001$; respectively). Non-HDL-C/HDL-C ratio showed positive correlation with AIP ($r = 0.491$, $p < 0.001$), LCI ($r = 0.548$, $p < 0.001$), TC/HDL-C ($r = 0.729$, $p < 0.001$) and LDL-C/HDL-C ($r = 0.623$, $p < 0.001$) in correlation analysis (Figure 2). In multivariable regression analysis, SYNTAX score (OR: 1.049, 95%CI: 1.017–1.082, $p = 0.003$), maximal stent length (OR: 1.052, 95%CI: 1.025–1.080, $p < 0.001$), high thrombus burden (OR: 2.025, 95%CI: 1.424–2.880, $p < 0.001$), atherogenic index of plasma (OR: 5.320, 95%CI: 3.293–8.717, $p < 0.001$) and non-HDL-C/HDL-C ratio (OR: 1.628, 95%CI: 1.417–1.870, $p < 0.001$) were determined as independent predictors for the development of no-reflow in STEMI patients who underwent pPCI (Table 3). Although traditional lipid profile parameters (TG, TC, LDL-C and HDL-C) were shown to significantly predict no-reflow development when Receiver Operating Characteristic (ROC) analysis was performed ($p < 0.001$, $p = 0.030$, $p = 0.019$,

Table 1. Distribution of basic demographic, clinical and laboratory data of subjects by status of no-reflow phenomenon in STEMI patients.

Variables	Without no-reflow (NR-) (n = 1042)	With no-reflow (NR+) (n = 242)	*p*
Demographic features and medical history			
Age, years	58.4 ± 12.5	60.5 ± 12.1	0.018
Gender -male, n (%)	751 (72.1)	168 (69.4)	0.410
Body Mass Index, kg/m^2	26.4 ± 1.9	26.6 ± 2.3	0.126
Diabetes Mellitus, n (%)	354 (34.0)	103 (42.6)	0.012
Hypertension, n (%)	661 (63.4)	165 (68.2)	0.165
Dyslipidemia, n (%)	715 (68.6)	202 (83.5)	<0.001
Smoking, n (%)	667 (64.0)	146 (60.3)	0.284
Previous CAD, n (%)	155 (14.9)	45 (18.6)	0.151
Family history of CAD, n (%)	102 (9.8)	26 (10.7)	0.655
Atrial fibrillation, n (%)	34 (3.3)	7 (2.9)	0.768
Hemodynamic characteristics			
SBP, (mmHg)	134 ± 19	136 ± 18	0.151
DBP, (mmHg)	78 ± 13	79 ± 13	0.065
Heart rate, beats/min	87 ± 15	88 ± 15	0.320
LVEF, (%)	49.1 ± 9.5	47.7 ± 11.6	0.054
CHF (NYHA III-IV), n (%)	78 (7.5)	28 (11.6)	0.038
Killip class ≥ II, n (%)	234 (22.5)	69 (28.5)	0.046
Laboratory data			
Fasting plasma glucose, mg/dL	108 (96-134)	120 (99-154)	<0.001
Creatinine, mg/dL	0.80 (0.70-1.00)	0.80 (0.70-1.00)	0.123
Uric acid, mg/dL	5.2 ± 1.5	5.3 ± 1.5	0.290
LDH, U/L	260 (226-310)	260 (234-267)	0.501
Albumin, g/dL	4.2 (3.9-4.5)	4.2 (4.0-4.5)	0.419
CRP, mg/dL	0.78 (0.20-1.80)	0.97 (0.36-1.62)	0.031
e-GFR, mL/min	88.4 ± 19.1	87.9 ± 20.1	0.711
WBC, (x1000/mm^3)	8.6 ± 4.1	8.5 ± 3.5	0.704
Lymphocyte, (x1000/mm^3)	2.0 ± 0.9	1.9 ± 1.0	0.059
Monocyte, (x1000/mm^3)	0.60 (0.49-.86)	0.60 (0.45-0.90)	0.518
Neutrophil, (x1000/mm^3)	7.3 ± 3.7	7.2 ± 3.4	0.859
Hemoglobin, g/dL	13.9 ± 1.8	13.8 ± 1.9	0.269
Hematocrit, %	43.2 ± 5.4	42.9 ± 5.8	0.434
Platelet count, (x1000/mm^3)	267.8 ± 77.0	257.0 ± 80.6	0.054
RDW, %	12.8 ± 1.4	13.2 ± 1.3	0.102
MPV, fL	7.9 (7.1-8.7)	8.0 (7.2-9.1)	0.025
Peak CK-MB, ng/mL	113.3 ± 44.9	120.0 ± 43.2	0.037
Peak Troponin I, ng/ mL	19.3 ± 7.1	20.3 ± 7.3	0.041
Pre-procedure medication			
Antiplatelet, n (%)	203 (19.5)	56 (23.1)	0.201
β-blocker, n (%)	168 (16.1)	37 (15.3)	0.750
ACEI/ARB, n (%)	386 (37.0)	102 (42.1)	0.141
CCB, n (%)	130 (12.5)	36 (14.9)	0.316
Traditional lipid profiles			
TC, mg/dL	173.3 ± 35.6	179.6 ± 35.4	0.013
Triglycerides, mg/dL	146 (103-210)	161 (121-231)	<0.001
HDL-C, mg/dL	37.5 ± 10.1	35.2 ± 10.1	0.001
LDL-C, mg/dL	109.4 ± 35.9	114.7 ± 35.6	0.038
Non-traditional lipid profiles			
Non-HDL-C	146.4 ± 42.4	167.2 ± 40.5	<0.001
LDL-C/HDL-C	3.05 ± 1.15	3.40 ± 1.38	<0.001
TC/HDL-C	4.85 ± 1.34	5.43 ± 1.58	<0.001
LCI ($\times 10^{-3}$)	92.5 ± 67.1	113.2 ± 71.4	<0.001
AIP	0.61 ± 0.26	0.75 ± 0.25	<0.001
AI (Non-HDL-C /HDL-C)	4.00 ± 1.51	5.17 ± 1.82	<0.001

Values are mean ± SD, n (%), or median (interquartile range) unless otherwise stated.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CK-MB, creatine kinase–myocardial band; CRP: C- reactive protein; DBP: diastolic blood pressure; e-GFR: estimated glomerular filtration rate; HDL-C: high -density lipoprotein cholesterol; LDL-C: low -density lipoprotein cholesterol; TC: total cholesterol; LDH, lactate dehydrogenase; LVEF, Left-ventricular ejection fraction; MPV, mean platelet volume; NYHA: New York Heart Association; RDW: red cell distribution width; SBP: systolic blood pressure; WBC: white blood cell; LCI: lipoprotein combined index; AIP: atherogenic index of plasma; AC; AI: atherogenic index.

$p = 0.001$; respectively), their diagnostic performance were not found to be superior to each other (Figure 3). The non-HDL-C/HDL-C ratio (atherogenic index) predicted the development of no-reflow phenomenon in STEMI patients undergoing pPCI, with 71% sensitivity and 67% specificity at the best cut-off value (area under curve [AUC]: 0.699; 95%CI: 0.662–0.737; $p < 0.001$) (Figure 4). In addition, when the performance of non-traditional lipid profiles to predict the no-reflow phenomenon was compared pairwise with ROC analysis, the non-HDL-C/HDL-C ratio was found to be superior to all other non-traditional lipid profiles ($p < 0.05$,

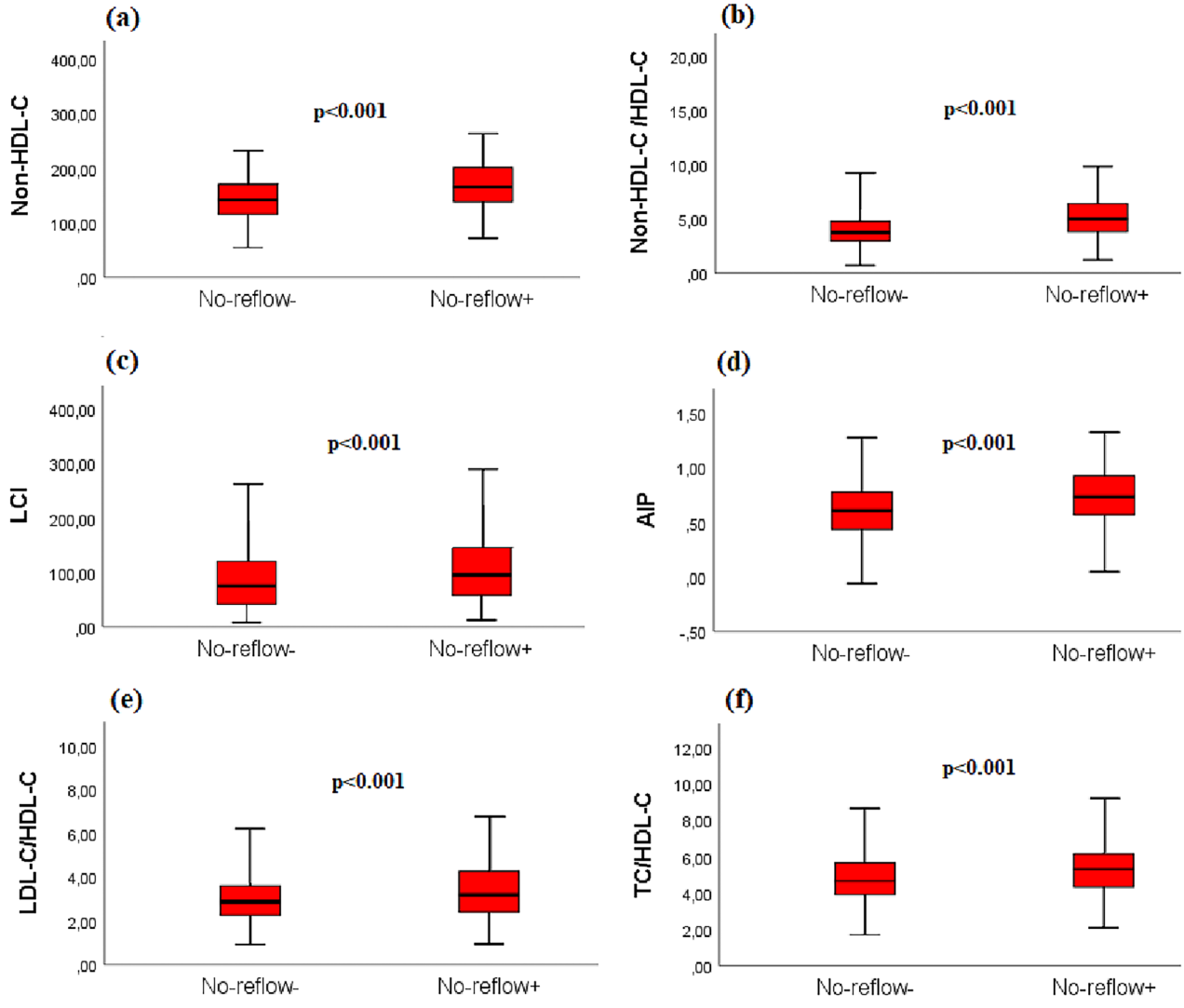


Figure 1. Box-plot chart of the values of non-traditional lipid profiles according to the no-reflow status. AIP, atherogenic index of plasma; HDL-C: high -density lipoprotein cholesterol; LDL-C: low -density lipoprotein cholesterol; LCI: lipoprotein combined index; TC:total cholesterol.

for all comparisons) (Figure 4). Moreover, the diagnostic performance of non-HDL-C/HDL-C ratio for the no-reflow phenomenon was found to be strongly superior to non-HDL-C and HDL-C, which are its components ($p = 0.0095$, $p < 0.001$; respectively).

Discussion

In this study, we determined the non-HDL-C/HDL-C ratio as an independent potential predictor for the development of no reflow in STEMI patients who underwent pPCI. In addition, our study is the first to report comparatively the diagnostic performance of traditional and non-traditional lipid profiles for the development of no-reflow in STEMI patients undergoing pPCI and according to our study results, the non-HDL-C/HDL-C ratio was superior to traditional and non-traditional lipid profiles in predicting no-reflow in STEMI patients.

The no-reflow phenomenon is associated with an increased incidence of adverse cardiovascular events and short- and long-term mortality in STEMI patients, and thus has an important place in the risk strafication of these patients [3,24]. The incidence of no-reflow phenomenon in STEMI patients undergoing pPCI has been reported to range from 15% to 40% [2–4]. In no-reflow pathophysiology, in addition to the effect of prolonged ischaemia, reperfusion injury increases microvascular damage in the perfusion region of the coronary artery associated with infarction, the toxic effect of oxidative stress and energy paradox resulting from ischaemia-reperfusion injury on endothelium and cardiomyocytes, paradoxical micro-vasoconstriction caused by endothelial dysfunction, occlusion of the

Table 2. Periprocedural and angiographic features of the patients according to no-reflow status.

Variables	Without no-reflow (NR-) ($n=1042$)	With no-reflow (NR+) ($n=242$)	p
Door to balloon time, min	56.9 ± 8.0	57.3 ± 9.5	0.474
Multi-vessel disease, n (%)	402 (38.6)	118 (48.8)	0.004
Number of stenotic vessels, n (%)	1.90 ± 0.79	2.04 ± 0.81	0.015
SYNTAX Score	14.2 ± 5.2	15.5 ± 5.1	0.001
Angiographic access route			
Radial access, n (%)	780 (74.9)	178 (73.6)	0.675
Femoral access, n (%)	262 (25.1)	64 (26.4)	
Infarct-related artery			
LAD and/or its branches, n (%)	452 (43.4)	108 (44.6)	0.443
Cx and/or its branches, n (%)	289 (27.7)	74 (30.6)	
RCA and/or its branches, n (%)	265 (25.4)	50 (20.7)	
LMCA, n (%)	13 (1.2)	2 (0.8)	
SVG, n (%)	23 (2.2)	8 (3.3)	
Thrombus burden			
High thrombus burden, n (%)	493 (47.3)	159 (65.7)	<0.001
Low thrombus burden, n (%)	549 (52.7)	83 (34.3)	
Stent type			
DES, n (%)	976 (93.7)	220 (90.9)	0.126
BMS, n (%)	66 (6.3)	22 (9.1)	
Maximal stent diameter, mm	3.23 ± 0.38	3.24 ± 0.39	0.810
Maximal stent length, mm	29.94 ± 6.50	31.92 ± 5.51	<0.001
Procedure type			
Only PTCA, n (%)	35 (3.4)	15 (6.2)	0.111
Direct stenting, n (%)	22 (2.1)	6 (2.5)	
PTCA + stenting, n (%)	985 (94.5)	221 (91.3)	
Occlusion localisation			
Proximal, n (%)	438 (42.0)	98 (40.5)	0.897
Mid, n (%)	390 (37.4)	94 (38.8)	
Distal, n (%)	214 (20.5)	50 (20.7)	
Use of Gp IIb/IIIa inhibitor, n (%)	282 (27.1)	84 (34.7)	0.018
Thrombus aspiration, n (%)	157 (15.1)	69 (28.5)	<0.001
Distal embolisation, n (%)	59 (5.7)	21 (8.7)	0.080

Values are mean ± SD or n (%) unless otherwise stated.
Abbreviations: BMS: bare-metal stent; Cx: circumflex artery; DES: drug-eluting stent; Gp: Glycoprotein; LAD: left anterior descending artery; LMCA: left main coronary artery; PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery; SVG: saphenous vein graft.

microvascular structure by endothelial blebs and packed neutrophils, platelet activation and aggregation, microvascular obstruction as a result of mechanical compression by myocardial edoema, and iatrogenic embolisation of thrombus and/or plaque material during coronary intervention play a fundamental role [4,25]. Although many risk factors have been identified for no-reflow, its etiopathogenesis has not been fully elucidated and although many cardiovascular conditions that have a common pathogenesis with no-reflow development in the medical literature have been shown to be closely related to non-traditional lipid profiles, which are indicators of dyslipidemia, there are not enough reports clarifying the relationship of these parameters with the development of no-reflow [6–18]. The non-HDL-C/HDL-C ratio is a relatively new atherogenic index that combines atherogenic and antiatherogenic lipid particles in a single fraction and has a better predictive value than its constituent components in many cardiovascular conditions, and its relationship with no-reflow phenomenon has not been clearly known until now [8–13].

Dyslipidemia, characterised by an abnormal lipid profile, is one of the major risk factors for atherosclerotic diseases [5]. Recent studies have reported that apolipoprotein B-rich non-HDL-C correlates significantly more with cardiovascular risk than traditional lipid profiles and should be considered a potential therapeutic target [26]. Increasing evidence has shown that non-HDL-C plays a pivotal role in the development and progression of vascular endothelial dysfunction and atherosclerosis, and it is therefore recommended to be routinely measured and included among therapeutic targets by current guidelines [5–7]. It has been shown that the predictive power of non-HDL-C for cardiovascular disease is higher than LDL-C and that non-HDL-C is correlated with vascular endothelial dysfunction and vascular inflammation, which also play a central role in the pathogenesis of the no-reflow phenomenon [4,7,27–29]. Diabetes mellitus is an independent risk factor for the development of no-reflow in STEMI patients, and the development of no-reflow in these patients has been shown to be correlated with inflammatory markers,

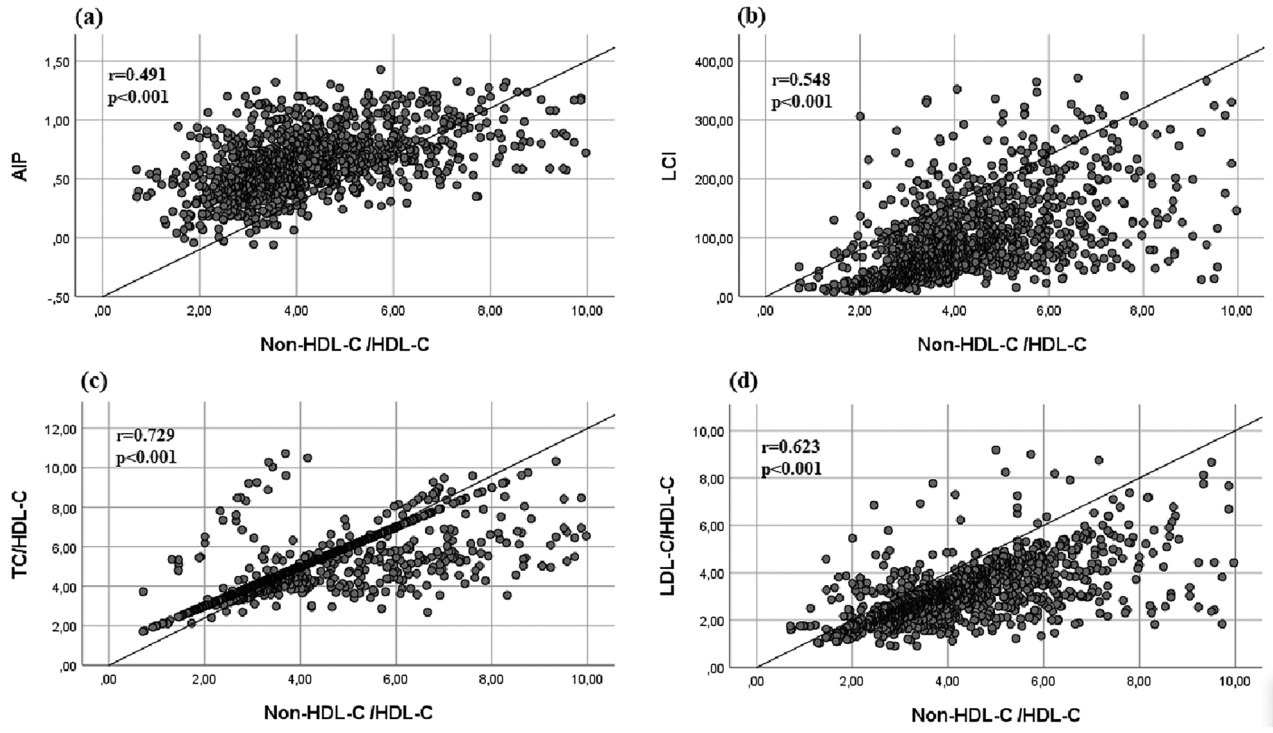


Figure 2. Correlations between non-HDL-C/HDL-C ratio (atherogenic index) and non-traditional lipid profile. AIP: atherogenic index of plasma; HDL-C: high-density lipoprotein cholesterol; LCI: lipoprotein combined index; LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol.

Table 3. Univariable and multivariable regression analysis to identify independent predictors of no-reflow phenomenon.

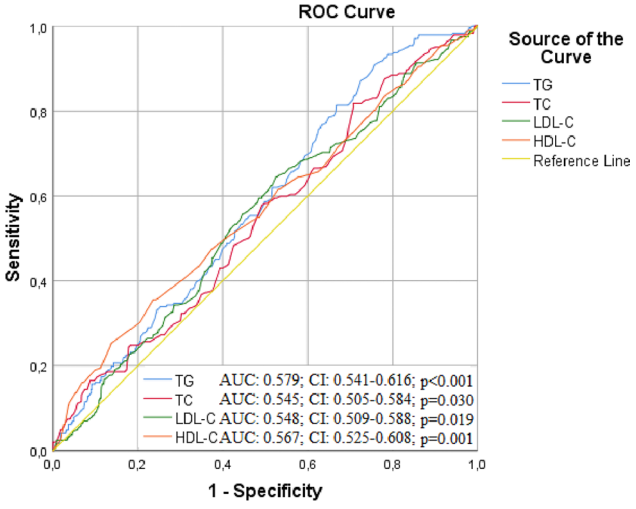
	Univariable analysis		Multivariable analysis Nagelkerke R^2 in final step: 0.605	
	OR (95% CI)	*p*	OR (95% CI)	*P*
Age	1.014 (1.002–1.025)	0.018	1.017 (0.998–1.031)	0.118
Diabetes Mellitus	1.440 (1.083–1.916)	0.012	1.022 (0.711–1.469)	0.907
CHF (NYHA III-IV)	1.617 (1.024–2.553)	0.039	1.152 (0.978–1.971)	0.125
Killip class ≥ II	1.377 (1.005–1.887)	0.046	1.239 (0.845–1.817)	0.272
Fasting plasma glucose	1.004 (1.002–1.007)	0.002	1.005 (0.995–1.008)	0.212
CRP	0.991 (0.904–1.086)	0.842	–	–
MPV	1.105 (1.005–1.215)	0.040	1.053 (0.943–1.176)	0.356
Peak CK-MB	1.003 (1.000–1.006)	0.037	1.003 (0.999–1.007)	0.112
Peak Troponin I	1.020 (1.001–1.039)	0.042	1.032 (0.895–1.055)	0.147
Multi-vessel disease	1.515 (1.144–2.007)	0.004	1.418 (0.592–1.530)	0.311
Number of stenotic vessels	1.243 (1.043–1.481)	0.015	2.328 (0.873–3.182)	0.110
SYNTAX Score	1.046 (1.019–1.073)	0.001	1.049 (1.017–1.082)	**0.003**
Maximal stent length	1.049 (1.027–1.072)	<0.001	1.052 (1.025–1.080)	**<0.001**
High thrombus burden	2.133 (1.593–2.857)	<0.001	2.025 (1.424–2.880)	**<0.001**
Thrombus aspiration	2.248 (1.622-3.117)	<0.001	2.010 (0.998–2.025)	0.221
TC, mg/dL	1.005 (1.001–1.009)	0.013	0.988 (0.976–1.000)	0.057
Triglycerides, mg/dL	1.002 (1.001–1.003)	0.002	0.993 (0.990–1.021)	0.099
HDL-C, mg/dL	0.976 (0.962–0.991)	0.001	1.051 (0.992–1.102)	0.103
LDL-C, mg/dL	1.004 (1.000–1.008)	0.038	1.021 (0.889–1.033)	0.145
Non-HDL-C	1.001 (1.008–1.014)	<0.001	0.999 (0.992–1.006)	0.136
LDL-C/HDL-C	1.246 (1.119–1.387)	<0.001	0.510 (0.335–1.003)	0.085
TC/HDL-C	1.312 (1.193–1.442)	<0.001	1.499 (0.910–2.227)	0.068
LCI	1.004 (1.002–1.006)	<0.001	0.994 (0.988–1.002)	0.059
AIP	7.425 (4.262–12.937)	<0.001	5.320 (3.293–8.717)	**<0.001**
AI (Non-HDL-C /HDL-C)	1.475 (1.355–1.605)	<0.001	1.628 (1.417–1.870)	**<0.001**

Abbreviations: CHF: congestive heart failure; CK-MB: creatine kinase–myocardial band; CRP: C- reactive protein; MPV: mean platelet volume; NYHA: New York Heart Association; HDL-C: high -density lipoprotein cholesterol; LDL-C: low -density lipoprotein cholesterol; TC: total cholesterol; LCI: lipoprotein combined index; AIP: atherogenic index of plasma; AI: atherogenic index; TC: total cholesterol; OR: odds ratio; CI: confidence interval.

and non-HDL-C has been shown to be an early marker of endothelial dysfunction in diabetic patients and correlates with CRP levels [30,31]. Non-HDL-C has been shown to significantly increase the risk of microangiopathy and microvascular dysfunction in patients with type 2 diabetes mellitus (DM) [32]. Another study

suggested that non-HDL-C may be superior to hsCRP in predicting future cardiovascular risk in patients with type 1 DM [33]. A strong correlation was found between the concentrations of non-HDL-C and proinflammatory macrophage phenotypes: CD-14, CD-16 and CD-36 [34]. A study conducted by Karasek et al. found a strong correlation between apolipoprotein B and non-HDL-C and non-HDL-C was shown to be strongly correlated with negative endothelial haemostatic markers such as plasminogen activator inhibitor-1 (PAI-1) and hsCRP [35].

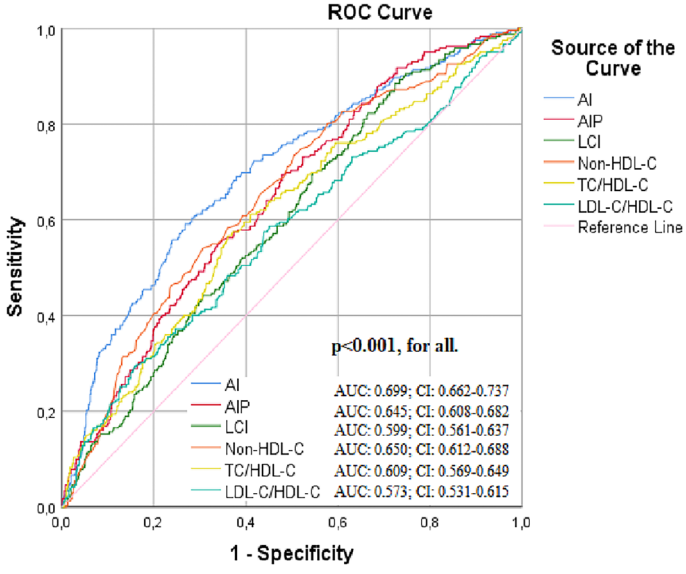
Contrary to the role of non-HDL-C in endothelial and microvascular dysfunction, which is key in the pathogenesis of no-reflow, HDL-C improves endothelial and microvascular functions with antiatherogenic, antithrombotic and anti-inflammatory effects [19,20]. The power of the ratio of non-HDL-C, which is the main atherogenic lipoprotein load in plasma, and antiatherogenic HDL-C particle in a single fraction, was found to be superior to the predictive power of non-HDL-C and HDL-C alone to predict cardiovascular disease development and progression as well demonstrated in many previous studies [8–12]. Zhou et al. have shown that non-HDL-C/HDL-C as a surrogate marker of insulin resistance (IR) can strongly predict patients at high metabolic risk [13]. In another study, it was shown that a high Non-HDL-C/HDL-C ratio also significantly increased the incidence of type 2 DM, which is characterised by insulin resistance and endothelial dysfunction [36,37]. In a study conducted by Byun et al. the non-HDL-C/HDL-C ratio was found to be associated with insulin resistance, especially in female gender [38]. Yang et al. showed in their study that non-HDL-C/HDL-C is closely related to



Pairwise comparison of traditional lipid profiles to predict no-reflow

Compared Variables	ΔAUC	95% CI	*P*
TG *vs* HDL-C	0.0122	-0.0434-0.0679	0.666
TG *vs* LDL-C	0.0304	-0.0210-0.0818	0.246
TG *vs* TC	0.0340	-0.0120-0.0799	0.147
HDL-C *vs* LDL-C	0.0182	-0.0429-0.0792	0.559
HDL-C *vs* TC	0.0217	-0.0452-0.0887	0.525
LDL-C *vs* TC	0.0035	-0.0458-0.0529	0.141

Figure 3. Pairwise comparison of traditional lipid profile with ROC analysis to predict no-reflow.



Pairwise comparison of non-traditional lipid profiles to predict no-reflow

Compared Variables	ΔAUC	95% CI	*P*
AI *vs* AIP	0.0544	0.0135-0.0953	0.0091
AI *vs* Non-HDL-C	0.0496	0.0121-0.0871	0.0095
AI *vs* LCI	0.1013	0.0610-0.140	<0.0001
AI *vs* TC/HDL-C	0.0902	0.0558-0.125	<0.0001
AI *vs* LDL-C/HDL-C	0.1265	0.0868-0.166	<0.0001
AIP *vs* Non-HDL-C	0.0047	-0.0426-0.0522	0.8434
AIP *vs* LCI	0.0462	0.0200-0.0725	0.0006
AIP *vs* TC/HDL-C	0.0358	-0.0040-0.0757	0.0782
AIP *vs* LDL-C/HDL-C	0.0720	0.0246-0.119	0.0029
Non-HDL-C *vs* LCI	0.0510	0.0067-0.0952	0.0238
Non- HDL-C *vs* TC/HDL-C	0.0406	-0.0102-0.0914	0.1171
Non- HDL-C *vs* LDL-C/HDL-C	0.0768	0.0217-0.132	0.0063
LCI *vs* TC/HDL-C	0.0104	-0.0287-0.0494	0.6026
LCI *vs* LDL-C/HDL-C	0.0258	-0.0118-0.0634	0.1784
TC/HDL-C *vs* LDL-C/HDL-C	0.0362	-0.0033-0.0757	0.0728

Figure 4. The non-HDL-C/HDL-C ratio (atherogenic index) predicts the development of no-reflow phenomenon in STEMI patients with 71% sensitivity and 67% specificity at the best cut-off value (3.9). When non-traditional lipid profiles were pairwise compared with ROC analysis to predict the no-reflow phenomenon, the non-HDL-C/HDL-C ratio was superior to all other non-traditional lipid profiles in predicting no-reflow phenomenon. *HDL-C, high* -density lipoprotein cholesterol; LDL-C: low -density lipoprotein cholesterol; TC: total cholesterol; LCI: lipoprotein combined index; AIP: atherogenic index of plasma; AI: atherogenic index; TC:total cholesterol.

microvascular complications in patients with type 2 diabetes mellitus [39]. In this context, it can be interpreted that pathophysiological mechanisms related to insulin resistance such as lipotoxicity, systemic inflammation and oxidative stress may play a role in the endothelial dysfunction and proatherogenic effect of non-HDL-C/HDL-C ratio [40]. Indeed, patients with metabolic syndrome and diabetes mellitus are known to be independent predictors for the development of no-reflow in STEMI patients [30,41].

Non-HDL-C/HDL-C ratio has been shown to play an important role in the risk and progression of CAD [12]. Lipid-rich plaques are a risk factor for the development of no-reflow, and non-HDL-C/HDL-C has been shown to be closely associated with the presence of a detectable lipid-rich core [42,43]. Non-HDL-C/HDL-C ratio has been reported to be an independent predictor for major adverse cardiovascular events as well as severe coronary artery disease [10]. The close relationship of the SYNTAX score, which is a reliable indicator of the extent and severity of coronary artery disease, with non-HDL-C/HDL-C ratio has been reported previously, and the SYNTAX score has been shown to be an independent risk factor for the development of no-reflow in STEMI patients in previous studies, in line with the results of our study [10,44]. The non-HDL-C/HDL-C ratio has been shown to be closely associated with poor coronary colletral circulation in patients with chronic total occlusion, and poor collateral circulation is associated with an increased risk of no-reflow in patients with chronic total occlusion [45,46]. The development of no-reflow in postmenopausal women was associated with worse clinical outcome than in men, and carotid intima media thickness, a marker of atherosclerosis, was closely associated with no-HDL-C/HDL-C in post-menopausal women [9,47,48].

According to these results, it can be said that the non-HDL-C/LDL-C ratio plays a pivotal role in the pathogenesis of no-reflow due to the deterioration of lipid hemostasis, possibly causing endothelial and microvascular dysfunction by leading to insulin resistance and increasing atherosclerotic burden. Süleymanoğlu et al. showed that another non-traditional lipid profile, the atherogenic index of plasma (AIP, Log_{10}[TG/HDL-C]), could be an independent predictor for the development of no-reflow in STEMI patients undergoing pPCI [15]. However, the AIP includes HDL-C as well as the triglyceride (TG) component, and TG measurements are significantly affected by fasting status. Therefore, it restricts the use of AIP in preprocedural risk strafication in these patients in terms of no-reflow development in an emergency situation such as STEMI. It has been shown that the assessment of lipid profile in vascular disease can be reliably reflected by measuring total cholesterol and HDL cholesterol levels, or apolipoproteins, without the need for a fasting interval and without consideration of triglycerides [49]. In this context, it can be said that the non-HDL-C/HDL-C ratio is superior and reliable compared to other traditional and non-traditional lipid profiles in predicting the no-reflow development preprocedureally and taking intensive preventive measures accordingly in STEMI patients.

Our study had some limitations. First, our study was retrospectively designed and conducted with a relatively small study population. Therefore, the causality between non-HDL-C/HDL-C and no-reflow development is not clear. Secondly, only single fasting values were used to calculate lipid indices, which may weaken the correlation between results. Tertiary, only STEMI patients were included in the study and therefore the conclusions of the study cannot be extended to all patients with acute coronary syndrome. Fourth, although multivariable regression analysis is used, residual confounding factors may affect the results. Finally, no-reflow evaluation was obtained visually from angiographic images only, and intravascular ultrasonography and coronary magnetic resonance imaging were not used as more sensitive methods due to the retrospective design.

Conclusions

The results show that the non-HDL-C/HDL-C ratio is an independent and strong predictor of no-reflow development in STEMI patients undergoing pPCI. In addition, the results of the study show that the non-HDL-C/HDL-C ratio is superior to other conventional and non-traditional lipid parameters in predicting the development of no-reflow in STEMI patients.

Authors' contributions

Concept/Design—KT, MK, SA, Mİ, TM; Analysis/Interpretation—KT, MK,SA, MBÇ, AB, RD; Data Collection—KT, MK, SA, Mİ, TM, MBÇ, İHA, AB, RD; Writing—KT,MK, İHA, AB, RD; Critical Revision—KT, MBÇ, İHA, AB, RD; Final Approval—All of the authors; Statistical Analysis—KT, MBÇ,İHA, RD; Overall Responsibility—All of the authors. All authors contributed to the planning, conduct, and reporting of the work. All contributors are responsible for the overall content as guarantors.

Disclosure statement

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Data availability statement

If a reasonable request to the corresponding author might share data of the study.

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