Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1410973

Anatolian Curr Med J. 2024;6(2):108-115

A biomarker for estimating no-reflow phenomenon in PCI-treated non-ST-segment elevation myocardial infarction patients: serum Cystatin C

Ömer Genç[1], Abdullah Yıldırım[2], Aslan Erdoğan[1]

[1]Department of Cardiology, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkiye
[2]Department of Cardiology, Adana City Hospital, Adana, Turkiye

Cite this article as: Genç Ö, Yıldırım A, Erdoğan A. A biomarker for estimating no-reflow phenomenon in PCI-treated non-ST-segment elevation myocardial infarction patients: serum Cystatin C. *Anatolian Curr Med J.* 2024;6(2):108-115.

Received: 29.12.2023 ◆ **Accepted**: 18.01.2024 ◆ **Published**: 08.03.2024

ABSTRACT

Aims: Cystatin C (Cys-C) is a biochemical marker associated not only with renal function but also with inflammatory processes. We aimed to investigate the relationship between the post-percutaneous coronary intervention (PCI) no-reflow phenomenon (NRP) and Cys-C in patients with non-ST-segment elevation acute coronary syndrome (NST-ACS).

Methods: This retrospective, single-center observational study consecutively enrolled patients who were hospitalized with a diagnosis of NST-ACS and underwent PCI between October 2021 and February 2022. Baseline characteristics, medications, admission laboratory parameters, and angiographic features were recorded. Logistic regression and sensitivity analyses were performed to identify parameters associated with NRP.

Results: Out of 199 patients (mean age: 62.0±10.3, 59.8% male), 36 (18.1%) developed NRP. Patients who developed NRP had a lower ejection fraction (49.7±10.3% vs. 53.5±7.1%, p=0.046) and were less likely to be male (36.1% vs. 65.0%, p=0.001). Additionally, individuals with NRP exhibited higher blood urea and C-reactive protein levels than those without NRP (p<0.05 for both). Similarly, serum Cys-C levels were elevated in the former group (1.44±0.57 vs. 1.07±0.40 mg/L, p=0.001). Multivariable logistic regression analysis demonstrated that Cys-C [odds ratio (OR)=4.793, p=0.014] and culprit lesion [OR=8.112, p=0.043 for LCx, OR=27.025, p=0.001 for RCA] were independently associated with NRP. Receiver operating characteristic curve analysis showed a cut-off point >1.1 mg/L for Cys-C determined NRP with 72.2% sensitivity and 66.9% specificity (area under the curve=0.711, p<0.001).

Conclusion: We have demonstrated a potential association between the serum Cys-C level at admission and the occurrence of NRP among NST-ACS patients undergoing PCI.

Keywords: Cystatin C, no-reflow phenomenon, non-ST-segment elevation acute coronary syndrome, percutaneous coronary intervention

INTRODUCTION

Despite the widespread use of percutaneous coronary intervention (PCI) and improvements in in-hospital care policies, as well as evidence-based antiplatelet regimens in recent years, acute coronary syndrome (ACS) remains a significant cause of morbidity and mortality worldwide.[1] While the term ACS has been classified into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NST-ACS) based on electrocardiographic features due to its diverse range of pathophysiological foundations, there is a demand for additional early risk stratification strategies to predict prognosis in both subgroups.[2] Hence, traditional scores such as Thrombolysis In Myocardial Infarction (TIMI) and The Global Registry of Acute Coronary Events (GRACE) risk scores, as endorsed by the European Society of Cardiology, along with electrocardiographic findings, clinical variables such as high-sensitivity cardiac troponin I, and more recently, biochemical markers indicating inflammation, have been employed to ascertain the optimal timing for implementing an invasive strategy in patients with NST-ACS.[3-5]

The no-reflow phenomenon (NRP) is a complex condition characterized by inadequate distal flow in the epicardial coronary artery during the procedure, despite the absence of angiographic evidence of mechanical obstruction, dissection, or spasm.[6] The incidence of NRP varies between 2.0% and 18.8% in

Corresponding Author: Ömer GENÇ, dr.genc@hotmail.com

patients undergoing primary or elective PCI, as reported in various studies and meta-analyses.[7,8] While the pathophysiology remains unclear, distal embolization, high thrombus burden, ischemic injury, and reperfusion injury are commonly implicated factors in ACS. The cause is typically multifactorial and individual.[9-11] The occurrence of NRP after PCI is closely linked to major adverse cardiovascular events, including heart failure (HF), stroke, myocardial injury, ventricular arrhythmias, and in-hospital mortality when compared to cases with normal coronary flow.[12,13]

In contemporary research, low molecular-mass plasma proteins have emerged as crucial contributors to both physiological and pathological conditions. Cys-C, a member of the type 2 cystatin superfamily, serves as an endogenous inhibitor of cysteine proteinases. The kidney acts as the primary catabolic pathway for Cys-C, which is found in nearly all body fluids. This proteinase undergoes nearly complete elimination from circulation through glomerular ultrafiltration, with minimal peritubular reuptake.[14] Consequently, it stands out as a superior marker for estimated glomerular filtration rate (e-GFR) compared to creatinine.[15] The advent of fast, accurate, and widely available immunoassay methods now enables the routine use of Cys-C as a marker for various clinical conditions beyond renal function. Further substantiating this, certain studies have indicated the utility of Cys-C in post-PCI risk stratification and the prediction of adverse cardiac events in ACS.[16,17] In our study, the primary objective was to clarify the role of Cys-C in determining NRP in patients presenting with NST-ACS and undergoing PCI.

METHODS

Ethical Statement

The design of the present study received approval from the Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2023, Decision No: 3051), and the research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Design and Population

We included a total of 199 consecutive patients who were admitted to Adana City Training and Research Hospital between October 2021 and February 2022 with symptoms related to ischemia in this single-center, retrospectively designed study. These patients were diagnosed with NST-ACS and subsequently underwent PCI. Diagnosis and treatment protocols followed the current guidelines of the European Society of Cardiology.[18] Various parameters, including epidemiological, demographic, clinical, laboratory, echocardiographic, and procedural data, were systematically recorded. Patients meeting any of the following criteria were excluded from the study: age <18 years, chronic lung and liver disease, hereditary coagulation disorders, history of malignancy, previous fibrinolytic therapy, active infection, autoimmune connective tissue disease, medical decision after coronary angiography or inability to undergo PCI, e-GFR <60 mL/min/1.73 m², and cases with missing files and records (**Figure 1**). Echocardiographic examinations were conducted during hospitalization by independent cardiologists who were blinded to the study data, following the guidelines of the European Association of Cardiovascular Imaging.[19]

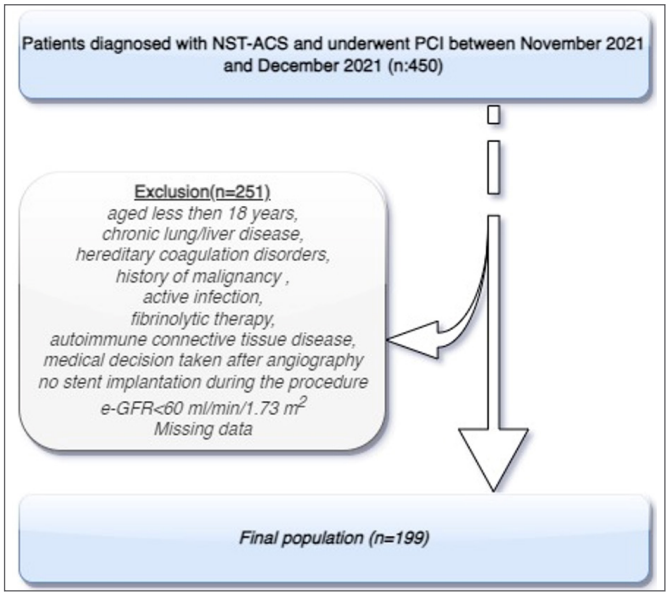

Figure 1. Flow chart

The medical histories of patients were retrieved from both the hospital records and the national health registry systems. Hypertension was defined as a systolic blood pressure greater than 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg, or the use of antihypertensive medication. In addition to the presence of signs and symptoms, diabetes mellitus (DM) was diagnosed in individuals who met at least one of the following criteria: fasting blood glucose of ≥126 mg/dl, 2-hour post-load plasma glucose of ≥200 mg/dl, HbA1c ≥6.5%, or random blood glucose of ≥200 mg/dl.

Laboratory Analysis

The blood samples were collected in EDTA tubes at the emergency triage unit upon the patient's admission. Biochemical samples were promptly analyzed using a fully automated systems analyzer (Roche Diagnostics, Indianapolis, USA) without delay. Plasma high-sensitivity cardiac troponin I was examined using Beckman Coulter automatic analyser (Beckman

Coulter, Brea, CA). Cys-C samples were obtained from the antecubital vein within the first 6 hours of hospital admission and before the PCI procedure. These samples were analyzed using fully Siemens nephelometric analyzer (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The range of the kit used for analysis is 0.56-0.99 mg/L.

Coronary Angiography

Coronary angiographies for all patients were conducted using SIEMENS AXIOM Artis zee 2011 equipment (Siemens Healthcare, Erlangen, Germany) through the femoral or radial route with a 6-7 French catheter, adhering to current recommendations. Prior to the procedure, all patients received an intravenous bolus of unfractionated heparin at a dose of 70-100 IU/kg. Throughout the procedure, pre- and post-dilatation, the use of glycoprotein IIb/IIIa inhibitors, and thrombus aspiration were carried out at the discretion of the operator. The stents implanted were new-generation drug-eluting stents, with their diameter and length left to the operator's choice. Loading and maintenance doses of oral P2Y12 inhibitors after the procedure [prasugrel (60 mg loading-10 mg daily maintenance), ticagrelor (180 mg loading-180 mg daily maintenance), and clopidogrel (600 mg loading-75 mg daily maintenance)] were administered in accordance with current guidelines. Acetylsalicylic acid loading (300 mg) took place before the procedure, and a low dose (81-100 mg) was maintained post-procedure. Subsequently, angiographic images were independently evaluated by two cardiologists. The flow status in the infarct-related artery after PCI was assessed using the TIMI flow grading system.[20] The NRP was defined as a TIMI score ≤2 without significant residual obstruction and/or flow-limiting conditions, while normal flow was designated as a TIMI score of 3.[21]

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20; Armonk, NY: IBM Corp., SPSS Inc., Chicago, Illinois, USA). Continuous variables were assessed for distribution, and normality was determined using histogram graphs, skewness, and kurtosis measures, and the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean ± standard deviation, while non-normally distributed variables were reported as median (interquartile range: 25th-75th percentile). Categorical variables were expressed as frequency and percentage. The χ^2 (Chi-square) test was employed for comparing categorical parameters between groups. For normally distributed groups, the independent two-sample t-test was used, whereas the Mann-Whitney U test was applied for the comparison of non-normally distributed numerical parameters when comparing two groups. Variables with a significant p-value of <0.05 in hypothesis testing were subjected to univariable logistic regression analysis. Multivariable analysis for regression was then conducted with parameters having p<0.05 in univariable logistic regression analysis. Receiver Operating Characteristic (ROC) analysis was performed to assess the discriminative ability of Cys-C in determining NRP. The cut-off point for Cys-C was established based on the Youden index. Statistical significance was defined as p<0.05.

RESULTS

The mean age of the 199 NST-ACS patients included in the study was 62.0±10.3 years, and 59.8% were male. NRP developed in 36 (18.1%) patients who underwent PCI. Patients who developed NRP had a lower left ventricular ejection fraction (EF) (49.7±10.3% vs. 53.5±7.1%, p=0.046) and were less likely to be male (36.1% vs. 65.0%, p=0.001). Risk factors were similar between the groups with and without post-PCI NRP. Similarly, medications used at admission were also comparable. When laboratory parameters were evaluated, urea (43.5±16.9 vs. 35.2±13.6 mg/dl, p=0.008) and C-reactive protein (CRP) (7.1 vs. 3.8 mg/dl, p=0.002) were higher in the NRP group. Additionally, Cys-C was higher in those with NRP than those without NRP (1.44±0.57 vs. 1.07±0.40 mg/L, p=0.001) (**Figure 2**). Angiographic characteristics were similar between the two groups except for the culprit lesion. Detailed baseline characteristics, risk factors, medications, and angiographic features of the study population are shown in **Table 1**.

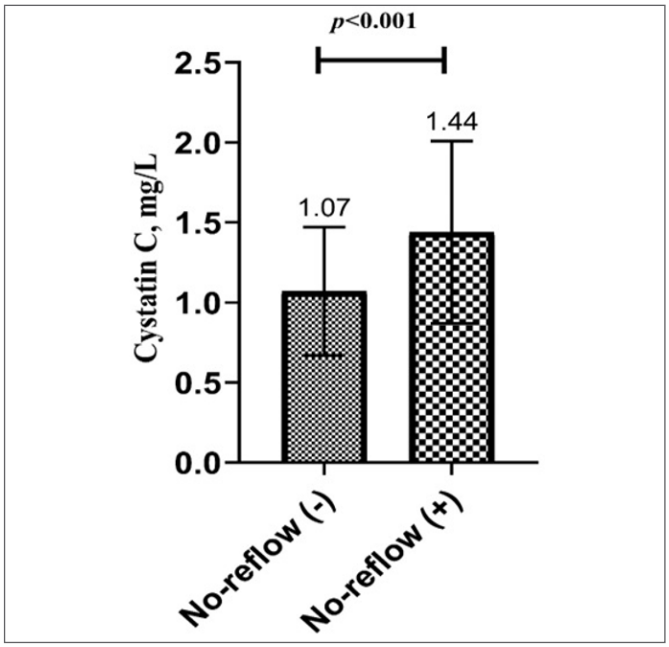

Figure 2. Categorizing mean serum Cystatin C levels based on coronary no-reflow status.

Table 1. Baseline features, risk factors, medications, and angiographic data for the study population

Variables	All (n=199, 100%)	No-reflow phenomenon		p*
		No (n=163, 81.9%)	Yes (n=36, 18.1%)	
Baseline Characteristics and Risk Factors				
Age (years)	62.0±10.3	61.6±10.2	63.8±10.6	0.243
Male gender, n (%)	119 (59.8)	106 (65.0)	13 (36.1)	0.001
Ejection fraction, %	52.8±7.9	53.5±7.1	49.7±10.3	0.046
Diabetes mellitus, n (%)	93 (46.7)	77 (47.2)	16 (44.4)	0.761
Hypertension, n (%)	62 (31.2)	49 (30.1)	13 (36.1)	0.478
Hyperlipidemia, n (%)	43 (21.6)	36 (22.1)	7 (19.4)	0.727
Family history of CVD, n (%)	18 (9.0)	17 (10.4)	1 (2.8)	0.206
Current smoker, n (%)	36 (18.1)	32 (19.6)	4 (11.1)	0.229
Medications taken by patients upon admission, n (%)				
ACEi /ARB	31 (15.6)	27 (16.6)	4 (11.1)	0.414
Beta-blockers	20 (10.1)	19 (11.7)	1 (2.8)	0.134
Calcium channel blockers	7 (3.5)	6 (3.7)	1 (2.8)	0.629
Diuretics	5 (2.5)	4 (2.5)	1 (2.8)	0.635
Statins	7 (3.5)	7 (4.3)	0 (0)	0.355
Laboratory findings				
WBC, 10^3/µl	8.4±2.5	8.3±2.5	8.4±2.5	0.988
Hemoglobin, mg/dl	13.2±2.0	13.4±1.9	12.4±2.6	0.032
Platelet count, 10^3/µl	238±73	237±71	243±83	0.662
Urea, g/dl	36.7±14.6	35.2±13.6	43.5±16.9	0.008
Creatinine, mg/dl	0.83±0.21	0.82±0.20	0.87±0.23	0.213
LDL-C, mg/dl	125±47	127±49	117±37	0.236
HDL-C, mg/dl	44±12	44±11	44±17	0.991
Total cholesterol, mg/dl	193±65	195±67	182±56	0.278
Triglycerides, mg/dl	149 (110-208)	153 (112-223)	134 (95-168)	0.056
C-reactive protein, mg/dl	4.3 (2.0-9.8)	3.8 (1.8-8.3)	7.1 (3.2-30.9)	0.002
BNP, pg/ml	1153 (282-3576)	1075 (225-3306)	1668 (437-6280)	0.041
hs-cTnI, pg/ml	3800 (717-6850)	3666 (658-6850)	4400 (1175-7164)	0.411
Angiographic features				
Culprit lesion, n (%)				<0.001
LAD	69 (34.7)	67 (41.1)	2 (5.6)	
LCx	32 (16.1)	27 (16.6)	5 (13.9)	
RCA	98 (49.2)	69 (42.3)	29 (29.6)	
Stent diameter, mm	3.0 (2.25-3.0)	3.0 (2.25-3.5)	2.5 (2.25-3.0)	0.375
Stent length, mm	27 (8-36)	21 (12-54)	28 (12-36)	0.528
Pre-dilatation, n (%)	126 (63.3)	101 (62.0)	25 (69.4)	0.399
Post-dilatation, n (%)	67 (33.7)	55 (33.7)	12 (33.3)	0.963
Thrombus aspiration, n (%)	18 (9.0)	16 (9.8)	2 (5.6)	0.537
Gp IIb/IIIa receptor inhibitors, n (%)	21 (10.6)	18 (11.0)	3 (8.3)	0.632

Values are n (%), median (interquartile range [IQR]), or mean± standard deviation. P value was calculated using an independent samples t-test or the Mann-Whitney U-test for continuous variables and a chi-squared test or the Fisher's exact test for categorical variables, as appropriate. Abbreviations: ACEi, Angiotensin-Converting enzyme inhibitors; ARB, angiotensin receptor blockers; BNP, Brain natriuretic peptide; CVD, cardiovascular disease; Gp, Glycoprotein; hs-cTnI, high-sensitivity cardiac troponin I; HDL-C, High-density lipoprotein cholesterol; LAD, left anterior descending; LCx, left circumflex; LDL-C, low-density lipoprotein cholesterol; RCA, right coronary artery; WBC, white blood cell. *p<0.05 was considered significant.

The univariable logistic regression analysis revealed that sex [Odds Ratio (OR)=0.304, 95% Confidence Interval (CI):0.143-0.645, p=0.002, for male], left ventricular EF [OR=0.946, 95% CI:0.906-0.988, p=0.012], urea [OR=1.035, 95% CI:1.011-1.059, p=0.003], CRP [OR=1.018, 95% CI:1.003-1.034, p=0.019], brain natriuretic peptide [OR=1.010, 95% CI:1.003-1.017, p=0.007], Cys-C [OR=4.483, 95% CI:2.097-9.581, p<0.001], and culprit lesion [OR=6.204, 95% CI:1.134-33.945, p=0.035 for LCx, OR=14.080, 95% CI:3.231-61.346, p<0.001 for RCA] are associated with NRP. When these parameters were entered into multivariable logistic regression analysis, serum Cys-C [OR=4.793, 95% CI:1.371-16.763, p=0.014] and culprit lesion [OR=8.112, 95% CI:1.067-61.685, p=0.043 for LCx, OR=27.025, 95% CI:4.174-174.967, p=0.001 for RCA] were independent predictors of NRP (**Table 2**). ROC curve analysis showed that a cut-off point >1.1 mg/L for Cys-C determined NRP with 72.2% sensitivity and 66.9% specificity (Area Under the Curve=0.711, 95% CI:0.613-0.809, p<0.001) (**Figure 3**).

Table 2. Univariable and multivariable logistic regression analyses of no-reflow phenomenon

Variable	Univariable			Multivariable+		
	OR	95% CI	p*	OR	95% CI	p*
Gender, male	0.304	0.143-0.645	0.002	0.471	0.199-1.114	0.087
Ejection fraction	0.946	0.906-0.988	0.012	1.010	0.945-1.080	0.771
Urea	1.035	1.011-1.059	0.003	0.999	0.964-1.035	0.956
C-reactive protein	1.018	1.003-1.034	0.019	1.001	0.985-1.018	0.880
BNP	1.010	1.003-1.017	0.007	1.008	0.998-1.019	0.133
Cystatin C	4.483	2.097-9.581	<0.001	4.793	1.371-16.763	0.014
Culprit lesion			0.001			0.001
LAD	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	-
LCx	6.204	1.134-33.945	0.035	8.112	1.067-61.685	0.043
RCA	14.080	3.231-61.346	<0.001	27.025	4.174-174.967	0.001

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; LAD, left anterior descending; LCx, left circumflex; OR, odds ratio; RCA, right coronary artery. +Model performance parameters: Omnibus tests of model coefficients p<0.001, Model chi-square=51.2, -2 Log likelihood=136.9, Hosmer-Lemeshow test p=0.968. *p<0.05 was considered significant.

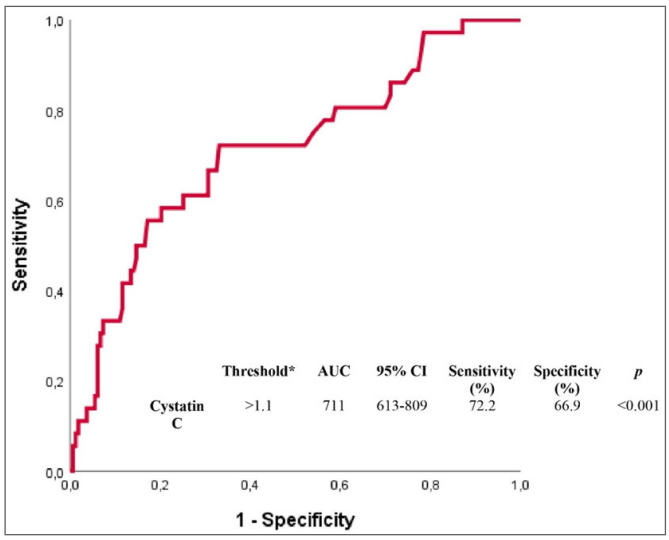

Figure 3. Receiver operating characteristic curve analysis for Cystatin C in the detection of the no-reflow phenomenon among NST-ACS patients undergoing PCI. Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval. * The cut-off point was established based on the Youden index.

DISCUSSION

Our study, investigating the role of Cys-C in detecting NRP, can be summarized with the following key findings: (i) NRP was detected in 36 out of 199 NST-ACS patients undergoing PCI, constituting 18.1% of the cohort. (ii) Cys-C and the culprit lesion were found to be associated with NRP. (iii) A cut-off point >1.1 mg/L for Cys-C determined NRP with 72.2% sensitivity and 66.9% specificity.

In current guidelines, the recommended treatment option for NST-ACS patients involves triage based on risk stratification, with revascularization of eligible patients through PCI.[22] A successful invasive strategy typically results in the improvement of coronary microcirculation within 24 hours post-PCI. However, NRP, a significant complication associated with PCI of the infarct-related artery, can lead to microcirculatory disturbances, suboptimal ventricular remodeling, enlargement of the infarct, early signs of HF, and impaired cardiac function due to inadequate blood flow.[23] Despite advancements in PCI techniques, the utilization of new-generation stents, improved intracoronary imaging modalities, and the implementation of new-generation antiplatelet therapy regimens, the incidence of NRP remains high. In our study, we observed an NRP incidence of 18.1%, consistent with a wide range of 5-60% reported in other studies.[24,25] This variability may be partly attributed to clinicopathological conditions such as demographic factors (e.g., gender), medical history (hypertension, diabetes, and hypercholesterolemia), clinical presentation (long total ischemic time, presentation with shock), laboratory parameters (poor renal function, increased inflammatory markers), and per-procedural factors (high thrombus burden).[23,26-28] NRP is more frequently observed, particularly in degenerated saphenous veins and following rotational atherectomy. Despite the availability of alternative treatments such as intracoronary vasodilators, glycoprotein IIb/IIIa platelet receptor antagonists, and intracoronary epinephrine, there is no universally accepted standard treatment.[23,29] Therefore, identifying factors related to NRP may represent the most effective approach for preventing adverse outcomes.30

Cystatin C, a cysteine protease inhibitor, has been previously investigated in patients presenting with ACS. Previous studies and meta-analyses have reported that Cys-C plays a prognostic role, is a predictor of mortality, and is useful in risk stratification. However, data regarding its association with PCI-related adverse events is limited. Cheng et al.[30] identified an independent association between admission Cys-C levels and NRP among STEMI patients treated with primary PCI. Another study found an independent association between Cys-C and NRP in 68 STEMI patients.[31] In our study, we observed similar results in patients with NST-ACS. Several mechanisms may elucidate the potential role of Cys-C in patients with ACS and its association with NRP. The first and most well-established mechanism is the robust correlation

between Cys-C and renal function. In a study involving 726 NST-ACS patients, Jernberg et al.[2] demonstrated that Cys-C was an independent predictor of mortality and adverse outcomes. Upon categorizing patients based on serum Cys-C levels, they observed a 12-fold higher mortality rate in the 4th quartile compared to the 1st quartile. This association was attributed to Cys-C being a more reliable indicator of renal function and the robust connection between renal function and mortality in NST-ACS patients. The well-established association between renal function and mortality has been attributed to various mechanisms, including atherosclerosis and vascular damage.[32] Renal dysfunction can accelerate atherosclerosis by inducing alterations in pathways such as glucose metabolism, blood pressure, lipids, lipoproteins, homocysteine, and inflammatory processes.[33]

Although our study did not include a mortality analysis, it affirmed the association between NRP and Cys-C, a significant indicator of adverse events. The role of Cys-C in interpreting our findings is crucial due to the established link between poor prognosis and renal function in ACS patients. However, it's noteworthy that our study comprised patients with creatinine-based e-GFR >60 ml/min/1.73 m², which might be a limitation in predicting renal failure. Hence, a more accurate e-GFR estimation would enhance the predictive ability of outcomes in NST-ACS patients. Nonetheless, the association of elevated Cys-C with NRP may not be entirely attributable to renal dysfunction; it could also be explained by the association between Cys-C and HF. For instance, in a large cohort study involving 5956 ACS patients, Lou et al.[34] observed correlations between Cys-C and brain natriuretic peptide, left ventricular EF, and ventricular diameters. Furthermore, a close association was identified between Cys-C and adverse cardiovascular events as well as all-cause mortality in ACS. This association may suggest that Cys-C could serve as a biomarker reflecting systemic dysregulation and pathophysiological pathways in early HF. In a separate study, Suthahar et al.[35] demonstrated the association between Cys-C and HF in both sexes. It has been observed that the incidence of NRP after PCI may be higher in patients with a prolonged duration of ischemia, a large area of myocardial involvement, a diagnosis of HF, or a history of myocardial infarction. Pantea-Roşan et al.[36] found that NRP was associated with lower EF and short-term complications in 942 STEMI patients. In a meta-analysis of 27 studies, NRP was linked to Killip class ≥2, elevated creatinine, and lower EF.[8]

Another potentially significant role of Cys-C is its potential contribution to the link between inflammatory mechanisms and NRP. In a large cohort study, Grubb et al.[37] reported that elevated serum Cys-C and CRP levels were associated with increased cardiovascular events and death in elderly patients. Urbonaviciene et al.[38] identified a significant correlation between Cys-C and high-sensitivity CRP. These studies suggest that Cys-C may serve as a marker of inflammation. Consequently, inflammation-related atherosclerotic changes, Cys-C, and cardiovascular diseases may be implicated in the mechanisms associated with NRP. However, there are also studies with conflicting results on this issue. Some argue that the relationship between Cys-C and CRP may reflect the early stages of chronic kidney disease rather than the inflammatory process.[39] Grubb et al.[37] demonstrated that Cys-C was not associated with CRP when adjusted for renal function. Niccoli et al.[40] proposed that Cys-C is linked to atherosclerotic burden in a CRP-independent manner. In this context, we recognize that Cys-C is a better indicator of renal function. In summary, the role of Cys-C in predicting cardiovascular events may be more relevant to renal function.

Limitations

This study has certain important limitations. Foremost among these is its nature as a single-center retrospective investigation, including a limited patient cohort, which may potentially constrain the generalizability of our findings. Additionally, the study lacks control for temporal changes in Cys-C levels and does not delve into the prognostic implications of these observed outcomes. Lastly, due to its retrospective design, various confounding factors associated with NRP could not be comprehensively addressed in the analysis. To enhance the robustness of our conclusions, it is imperative to conduct prospective, large-scale studies that systematically explore the prognostic implications of NRP in NST-ACS patients with a focus on Cys-C levels. These future investigations may facilitate a more comprehensive understanding of the prognostic impact of NRP in the context of Cys-C and enable more nuanced and widely applicable insights into its clinical significance.

CONCLUSION

This study has revealed the role of Cys-C in determining NRP among NST-ACS patients undergoing PCI. The clarification of these processes contributes to a comprehensive understanding of the nature of NRP and, consequently, may aid in its prevention and improved treatment. Enhancing the identification and treatment of no-reflow to ensure adequate blood flow in infarct-related arteries could yield significant benefits, including the reduction of infarct area expansion, subsequent ventricular remodeling, and ultimately a decrease in the rates of congestive HF and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the University of Health Sciences, Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2023, Decision No: 3051).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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 of 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.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095-2128.
2. Jernberg T, Lindahl B, James S, Larsson A, Hansson L-O, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circ.* 2004;110(16):2342-2348.
3. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circ.* 2003;108(3):275-281.
4. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-842.
5. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091.
6. Stouffer GA, Lenihan D, Lerakis S, et al. Incidence and management of "no-reflow" following percutaneous coronary interventions. *Am J Med Sci*. 2005;329(2):78-85.
7. Harbalıoğlu H, Genç Ö, Alıcı G, Quisi A, Yıldırım A. Impact of HAT2CH2 Score on the development of no-reflow phenomenon in patients with ST-segment elevation myocardial infarction. *Angiol.* 2024;75(1):44-53.
8. Fajar JK, Heriansyah T, Rohman MS. The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: a meta-analysis. *Indian Heart J.* 2018;70(Suppl 3):S406-S418.
9. Dong-bao L, Qi H, Zhi L, Shan W, Wei-ying J. Predictors and long-term prognosis of angiographic slow/no-reflow phenomenon during emergency percutaneous coronary intervention for ST-elevated acute myocardial infarction. *Clin Cardiol.* 2010;33(12):E7-E12.
10. Wong DT, Puri R, Richardson JD, Worthley MI, Worthley SG. Myocardial 'no-reflow'—diagnosis, pathophysiology and treatment. *Int J Cardiol.* 2013;167(5):1798-1806.
11. Zhou H, He X-y, Zhuang S-w, et al. Clinical and procedural predictors of no-reflow in patients with acute myocardial infarction after primary percutaneous coronary intervention. *World J Emerg Med.* 2014;5(2):96.
12. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol.* 2010;55(21):2383-2389.
13. Mehta RH, Harjai KJ, Boura J, et al. Prognostic significance of transient no-reflow during primary percutaneous coronary intervention for ST-elevation acute myocardial infarction. *Am J Cardiol.* 2003;92(12):1445-1447.
14. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. *Crit Rev Clin Lab Sci.* 2004;41(5-6):467-550.
15. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem.* 2002;48(5):699-707.
16. Correa S, Morrow DA, Braunwald E, et al. Cystatin C for risk stratification in patients after an acute coronary syndrome. *J Am Heart Assoc.* 2018;7(20):e009077.
17. Åkerblom A, Wallentin L, Siegbahn A, et al. Cystatin C and estimated glomerular filtration rate as predictors for adverse outcome in patients with ST-elevation and non-ST-elevation acute coronary syndromes: results from the platelet inhibition and patient outcomes study. *Clin Chem.* 2012;58(1):190-199.
18. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2018; 40(2):87-165.
19. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging.* 2017;18(3):254-275.
20. Gibson CM, Schömig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. *Circ.* 2004;109(25):3096-3105.
21. Kirma C, Izgi A, Dundar C, et al. Clinical and procedural predictors of no-reflow phenomenon after primary percutaneous coronary interventions experience at a single center. *Circ J.* 2008;72(5):716-721.
22. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J.* 2023;44(38):3720-3826.
23. Rezkalla SH, Stankowski RV, Hanna J, Kloner RA. Management of no-reflow phenomenon in the catheterization laboratory. *JACC: Cardiovasc Intervent.* 2017;10(3):215-223.
24. Bouleti C, Mewton N, Germain S. The no-reflow phenomenon: state of the art. *Arch Cardiovasc Dis.* 2015;108(12):661-674.
25. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no reflow. *Int J Cardiol.* 2015;187:273-280.
26. Kurtul A, Murat SN, Yarlioglues M, Duran M, Celik IE, Kilic A. Mild to moderate renal impairment is associated with no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. *Angiol.* 2015;66(7):644-651.
27. Pantsios C, Kapelios C, Vakrou S, et al. Effect of elevated reperfusion pressure on "no reflow" area and infarct size in a porcine model of ischemia-reperfusion. *J Cardiovasc Pharmacol Ther.* 2016;21(4):405-411.
28. Ipek G, Onuk T, Karatas MB, et al. CHA2DS2-VASc score is a predictor of no-reflow in patients with st-segment elevation myocardial infarction who underwent primary percutaneous intervention. *Angiol.* 2016;67(9):840-845.

29. Harding SA. The role of vasodilators in the prevention and treatment of no-reflow following percutaneous coronary intervention. *Heart.* 2006;92(9):1191-1193.
30. Cheng C, Liu XB, Bi SJ, Lu QH, Zhang J. Serum cystatin C levels relate to no-reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction. *PLoS One.* 2019;14(8):e0220654.
31. Rofyda OF, Hussein SE, Rasha AT, et al. The relationship between the levels of serum cystatin C and the occurrence of the no-reflow phenomenon during primary percutaneous coronary interventions. *Med J Cairo Univ.* 2023;91(06):897-908.
32. Cerne D, Kaplan-Pavlovcic S, Kranjec I, Jurgens G. Mildly elevated serum creatinine concentration correlates with the extent of coronary atherosclerosis. *Ren Fail.* 2000;22(6):799-808.
33. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet.* 2000;356(9224):147-152.
34. Lou B, Luo Y, Zhang H, et al. Association between cystatin C and Cardiac function in acute myocardial infarction patients: a real-world analysis. *Dis Markers.* 2022;2022:7267937.
35. Suthahar N, Lau ES, Blaha MJ, et al. Sex-specific associations of cardiovascular risk factors and biomarkers with incident heart failure. *J Am Coll Cardiol.* 2020;76(12):1455-1465.
36. Pantea-Roșan LR, Pantea VA, Bungau S, et al. No-reflow after PPCI—a predictor of short-term outcomes in STEMI patients. *J Clin Med.* 2020;9(9):2956.
37. Grubb A, Björk J, Nyman U, et al. Cystatin C, a marker for successful aging and glomerular filtration rate, is not influenced by inflammation. *Scand J Clin Lab Invest.* 2011;71(2):145-149.
38. Urbonaviciene G, Shi GP, Urbonavicius S, Henneberg EW, Lindholt JS. Higher cystatin C level predicts long-term mortality in patients with peripheral arterial disease. *Atheroscler.* 2011;216(2):440-445.
39. Lassus J, Harjola VP. Cystatin C: a step forward in assessing kidney function and cardiovascular risk. *Heart Fail Rev.* 2012;17(2):251-261.
40. Niccoli G, Conte M, Della Bona R, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate. *Atheroscler.* 2008;198(2):373-380.