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Original Article

Platelet-to-lymphocyte ratio predicts contrast-induced nephropathy in acute myocardial infarction

Akut miyokard infarktüsünde trombosit/lenfosit oranı kontrast nefropatisini öngörür

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ABSTRACT

Aim: Contrast-induced nephropathy (CIN) is responsible for an increased mortality rate and correlates with increases in hospital stays and the risk of cardiovascular complications. The platelet to lymphocyte ratio (PLR) was introduced as a potential marker to determine the balance between thrombosis and inflammation and was associated with increased cardiovascular morbidity and mortality. We investigated whether PLR on admission is an independent risk factor that predicts the development of CIN in patients with ST-segment elevation myocardial infarction (STEMI) underwent primary percutaneous coronary intervention (pPCI).

Material and Methods: 1348 consecutive patients with acute STMI who were admitted to our institution and underwent pPCI were retrospectively evaluated. Data obtained from hospital files and computer records. CIN development was accepted as the endpoint.

Results: A total of 127 (9.4%) patients experienced CIN. 16 patients underwent renal replacement theraphy. In-hospital mortality rate was found 2.7% (n = 37). Patients were divided into two groups based on development of CIN. Age (P = 0.001), baseline GFR (P < 0.001), grade 3 and more chronic kidney disease (P < 0.001), baseline creatinin (P < 0.001), EF (P < 0.001), presence of DM (P < 0.001) were different between groups. In multivariate analyses, PLR (odds ratio [OR] 1.012, 95% confidence interval [CI] 1.006-1.017, P < 0.001) was independently predicted CIN development.

Conclusion: PLR is easily available, widely used, and relatively cheap biomarker, and is an independent predictor of CIN development in patients with STEMI undergoing pPCI.

Keywords: platelet/lymphocyte ratio, ST-segment elevation acute myocardial infarction, contrast-induced nephropathy

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ÖZ

Amaç: Kontrast madde nefropatisi (CIN) uzamış hastanede yatış süresi, artmıs kardiyovasküler komplikasyonlar ve mortalite ile ilişkilidir. Trombosit/lenfosit oranı (PLR) tromboz ve inflamasyon arasındaki dengeyi gösteren potansiyel bir belirteç olarak tanımlanmış ve artan kardiyovasküler morbidite ve mortalite ile ilişkili bulunmuştur. Biz bu çalışmada PLR'nin primer perkütan koroner girişim (pPCI) yapılan ST yükselmeli miyokard infarktüsü (STEMI) hastalarda CIN gelişimini tahmin etmede bağımsız bir risk faktörü olup olmadığı araştırdık.

Gereç ve Yöntemler: Kurumumuza akut STEMI ile başvuran ve pPCI yapılan 1348 hasta geriye dönük olarak değerlendirildi. Hastane dosya ve bilgisayar kayıtlarından veriler elde edildi. CIN gelişimi sonlanım noktası olarak kabul edildi.

Bulgular: 127 (%9.4) hastada CIN gelişmişti. 16 hastaya renal replasman tedavisi uygulandı. Hastane içi mortalite oranı %2,7(n = 37) bulunmuştur. Hastalar CIN gelişimine göre iki gruba ayrıldı. Yaş (P = 0,001), bazal GFR (P < 0,001), grade 3 ve üzeri kronik böbrek hastalığı (P < 0,001), bazal kreatinin (P < 0,001), EF (P < 0,001), DM varlığı (P < 0,001) gruplar arasında farklı idi. Çok değişkenli analizlerde, PLR (odds ratio [OR] 1.012, %95 güven aralığı [CI] 1,006-1,017, P < 0,001) CIN gelişimini bağımsız olarak öngördü.

Sonuçlar: PLR, kolay ulaşılabilir yaygın olarak kullanılan ve nispeten ucuz biyomarkerdir ve STEMI nedeniyle pPCI uygulanan hastalarda CIN gelişiminin bağımsız bir belirleyicisidir.

Anahtar Kelimeler: trombosit/lenfosit oranı, ST yükselmeli miyokard infarktüsü, kontrast madde nefropatisi

Introduction

Contrast-induced nephropathy (CIN) is the third most common cause of renal insufficiency in hospitalized patients. CIN is responsible for an increased mortality rate of 14% and, for most patients, correlates with increases in hospital stays and the risk of cardiovascular complications [1]. The risk of CIN is even higher in patients referred for primary coronary angioplasty in the context of acute coronary syndromes. While it seems that intraarterial administration of contrast medium is associated with a higher risk of CIN than intravenous infusion primary coronary angioplasty appears to be a particularly high-risk procedure, as it affects a population at greater risk of CIN (i.e. older patients with co-morbidities, such as diabetes, heart failure and chronic renal failure). The main pit- fall is that renal function is often unknown at the time of contrast exposure because primary coronary angioplasty has to be performed without delay, leaving no time for renal function assessment. Moreover, the short delay between patient admission and primary coronary angioplasty significantly limits the use of pedigree renal protection measures, such as intravenous hydration (at least prior to the procedure) [2]. Identifying patients at high risk of CIN before PCI is of utmost clinical importance to make timely pre-procedural decisions regarding the therapeutic intervention to minimizing the risk.

The platelet to lymphocyte ratio (PLR) was introduced as a potential marker to determine the balance between thrombosis and inflammation, oncologic and cardiac disorders. Increased platelet and decreased lymphocyte counts in the circulation have been associated with increased cardiovascular morbidity and mortality [3]. Because of the potential role of inflammation in the development of CIN.

In the present study, we investigated whether PLR on admission is an independent risk factor that predicts the development of CIN in patients with ST-segment elevation myocardial infarction (STEMI) underwent primary percutaneous coronary intervention (pPCI).

Material and methods

The study population consisted of 1348 consecutive patients with acute STEMI who were admitted to our institution and underwent p-PCI within 12 h of the onset of symptoms between January 2013 and March 2015. This retrospective study was conducted in accordance with the principles of The Declaration of Helsinki. Inclusion criteria were presence of typical ongoing chest pain lasting for >30 minutes and ST elevation of at least ≥2 mm in at least 2 contiguous leads or new-onset complete left bundle-branch block. The baseline demographic, clinical and angiographic features, in-hospital

outcomes, admission laboratory test results were obtained from hospital files and computer records. Exclusion criteria were acute renal failure or end-stage renal failure requiring dialysis, known malignant or chronic inflammatory disease, recipient of transplanted organs, contrast dye exposure within the last 10 days, and chronic treatment with steroid or nonsteroidal anti-inflammatory drugs.

All of pPCI procedures were performed either femoral or radial approach with a 6F guiding catheter. 300 mg chewable aspirin and 600 mg loading dose of clopidogrel on admission, and 70 U/kg intravenous standard heparin were administered to all patients. Non-ionic, iso-osmolar or non-ionic, low-osmolar contrast media (CM) were used. The use of glycoprotein IIb/IIIa receptor blocker (tirofiban) was left to the primary operator's discretion. Occlusion of the infarct related artery was crossed by using a guidewire, direct stenting was implanted whenever possible; in the remaining cases, manual thrombus aspiration and/or balloon predilatation were carried out. The type of stent used was left to the operator's judgment. If the lesion anatomy was not suitable for stenting, only balloon dilatation was performed. After the procedure all patients were transferred to coronary intensive care unit and guideline-based cardiac medications were administered at the maximum tolerated doses. A successful intervention was described as a reduction in the stenosis or obstruction to less than 50% with Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow after p-PCI. If could not achieved, it was deemed unsuccessful.

Hypertension was defined as use of blood pressure lowering drugs at admission, systolic pressure >140 mm Hg, or diastolic pressure >90 mm Hg in measurements. Anemia was defined as baseline hemoglobin levels <13 g/dL in males and <12 g/dL in females. Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease Formula [4]. Patients were considered to have hyperlipidemia if they were being treated with lipid-lowering drugs at the time of admission or had abnormal fasting lipid test results according to guidelines [5]. Patients being treated with glucose-lowering drugs or had a fasting plasma glucose concentration >7 mmol/L or a nonfasting plasma glucose concentration >11.1 mmol/L were considered to have diabetes. CIN was defined as either an increase in serum creatinine greater than 25% or an absolute raise in serum creatinine of 0.5 mg/dL within 72 hours of administration of radiocontrast [6].

Multivessel disease was described as the presence of >50% stenosis in at least two or more major epicardial arteries. Cardiogenic shock was defined as marked and persistent (>30 minutes) hypotension with systolic arterial pressure being < 90 mmHg nonresponsive to fluid replacement, or the need of inotropes or intra-aortic balloon pumping to maintain blood pressure >90 mmHg due to left ventricular dysfunction, right ventricular infarction, and mechanical complications.

Echocardiography was performed in all patients and the left ventricular ejection fraction was calculated by using the modified biplane Simpson's method. In-hospital heart failure was recognised in the presence of Framingham criteria for the diagnosis of heart failure and left ventricular systolic and/or diastolic dysfunction on echocardiography. In-hospital cardiovascular mortality defined as unexplained sudden death, death from acute MI, heart failure, and arrhythmia. CIN development was accepted as the endpoint.

Statistical analysis

All analyses were performed using SPSS for Windows version 20.0 (IBM Corporation). Continuous variables are presented as mean+standard deviation and categorical variables are presented as percentages. Group means for continuous variables were compared using either the unpaired Student's t test or the Mann-Whitney U test according to normality. Categorical variables were compared by the Chi-square test. Pearson test was used for correlation analysis. Receiver-operating characteristic (ROC) analyses were used to detect the cut-off value of PLR in the prediction of CIN. To determine the independent predictors of CIN, parameters that were found to be significant in the univariate analysis were evaluated by stepwise forward logistic regression analysis. Two-sided P values <0.5 were considered significant.

Results

The mean age of the patients studied was 57.3±11years and 32.3% of the patients were women. A total of 127 (9.4%) patients experienced CIN. 16 patients underwent renal replacement therapy. In-hospital mortality rate was found 2.7% (n = 37). Patients were divided into two groups based on development of CIN. The baseline demographic, angiographic and clinic characteristics of the patient groups are shown in Table 1.

Table 1. Baseline demographic, angiographic, and clinical characteristics of patient groups based on development of CIN.

	CIN (+) group n=127	CIN (-) group n=1221	P value
Age (years)	64±12	56±11	<0.001
Sex (male), n (%)	93 (73.2)	820 (67.2)	0.97
GFR ≤ 60, n (%)	58 (45.7)	147 (7.9)	<0.001
Anterior infarction, n (%)	60 (47.6)	485 (39.7)	0.05
Suspected vessel,n (%)			
LAD	65 (51.2)	528 (43.2)	
CX	13 (10.2)	187 (15.3)	0.26
RCA	45 (35.4)	478 (39.1)	
Others	4 (3.2)	28 (2.4)	
DM,n (%)	76(59.8)	227(19.4)	<0.001
HT,n (%)	51 (32.3)	402(32.9)	0.48
HL,n (%)	24(18.9)	251 (20.6)	0.37
Smoking,n (%)	23 (18.1)	261 (21.4)	0.23
PCI history,n (%)	21(16.5)	150(12.3)	0.11
By-pass history,n (%)	6(4.7)	25(2.0)	0.64
Anemia, n (%)	50(39.4)	353(28.9)	0.11
Unsuccesful intervention, n (%)	22(17.3)	84(6.9)	<0.001
Multivessel disease, n (%)	19(15)	256 (21)	0.66
Shock on admission, n (%)	8(6.3)	24(2.0)	0.07
Predilatation, n (%)	107 (84.3)	873(71.5)	0.02
Stent lenght ,mm	23.1±6.8	21.5±6.4	0.04
Trofiban usage,n(%)	63 (49.6)	594(48.6)	0.83
In-hospital mortality, n(%)	19(15)	18(1.5)	<0.001
GFR (mL/min/1,73m2)	67.6±45.6	99±30.6	<0.001
EF (%)	40.4±8.7	50.2±1.3	<0.001
WBC (103/µL)	14±7	12±4.6	0.004
Hemoglobin (g/dl)	12.9±2.1	13.6±1.7	0.001
Neutrophil (103/ µL)	11.5±6.5	9.1±3.8	<0.001
Lymphocyte (103/ µL)	1.711±0.94	2.057±0.48	0.004
Platelet (103/ µL)	241.2±42.3	179.5±51.8	<0.001
Total cholesterol (mg/dl)	178.5±32.4	178.9±43.4	0.74
LDL (mg/dl)	105±35.1	108.9±37.2	0.51
HDL (mg/dl)	37.4±10.2	38.2±9.8	0.44
TG (mg/dl)	153±76.1	158.9±96.7	0.94
Contrast volume (ml)	172.5±95.3	144.7±85.1	0.001
Basal creatinin (mg/dl)	1.18±0.43	0.87±0.26	<0.001
Peak troponin (ng/mL)	37.8±16.8	32.4±18.4	<0.001
CRP (mg/L)	11.6±4.1	3.5±0.4	<0.001
Platelet to lymphocyte ratio	187.1±141.6	114.1±67.4	<0.001

CIN, contrast-induced nephropathy; CRP; C reactive protein; CX, circumflex artery ;DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; HT, hypertension; HL, hyperlipidemia;; HDL, high-density lipoprotein; LAD, left anterior descending artery; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; RCA, right coronary artery ;TG, triglyceride;WBC, white blood cell.

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Age (P = 0.001), baseline GFR (P < 0.001), grade 3 and more chronic kidney disease (P < 0.001), baseline creatinine (P < 0.001), EF (P < 0.001), presence of DM (P < 0.001) were different between groups. Patients who developed CIN (group 1) had more unsuccessful intervention (P < 0.001) than group 2.

Predilatation was done more often in group 1 (P = 0.02). Longer stents were implanted in group1 (23.1 ± 6.8 cm, P = 0.04). The PLR was significantly higher in the CIN group than in the non-CIN group (187.1 ± 141.6 vs 114.1 ± 67.4, P < 0.001). Amount of contrast media (172.5 ± 95.3 vs 144.7 ± 85.1 mL, P < 0.001) was higher in the CIN than non-CIN group. Patients in group 1 had higher CRP values (P < 0.001) In-hospital mortality was higher in group 1 (P < 0.001). PLR was significantly correlated with CRP in our study (r = 0.224, P < 0.001) Independent predictors of CIN development are presented in Table 2.

Table 2. The predictors of the development of CIN in the multivariable logistic regression analyses.

Parameters	OR (%95 CI)	P value
Age	1.081(1.031-1.134)	0.011
GFR <60	0.057(0.009-0.367)	0.003
DM	0.350 (0.129-0.950)	0.039
Multivessel disease	0.228 (0.076-0.690)	0.009
EF	1.061 (1.010-1.114)	0.018
CRP	1.403 (1.286-1.531)	<0.01

CIN, contrast-induced nephropathy; CRP; C reactive protein; DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate.

In multivariate analyses, PLR (odds ratio [OR] 1.012, 95% confidence interval [CI] 1.006-1.017, P < 0.001) was independently predicted CIN development.

The area under the ROC curve for PLR was 0.74, and a PLR of >119.2 predicted CIN with sensitivity of 72% and specificity of 63% (0.735, 95% CI 0.691-0.779, P < 0.001; Figure 1).

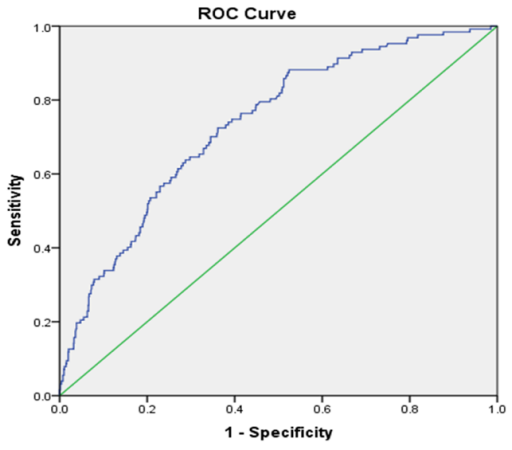

Figure 1. Receiver operating characteristic curve of PLR for predicting CIN development

Discussion

Our study findings showed that PLR, a readily accessible parameter, is an independent risk factor for CIN in patients with STEMI. The incidence of CIN in this study (9.4%) was in agreement with previous reports [7]. Previous studies indicated that a higher PLR value emerged as a significant independent predictor of long-term survival in patients who presented with STEMI. Among the factors we identified for the prediction of CIN development, impaired renal function (GFR <60mL/min/1.73m2), EF, CRP and DM were in line with the literature [8]. Moreover, patients having greater extent of atherosclerosis revealed by multivessel affection and increased size of tents used were also significant predictors of CIN in our study population. It may be related to decreased ventricular function, remote ischemia and intraprocedural hemodynamic impairments that result in renal hypoperfusion. We also identified shock on admission as a predictor of CIN but its role should be discussed since shock implies potential kidney failure. It is more a predictor of multifactorial acute renal failure rather than CIN. But, decreased renal perfusion pressure whatever the cause aggravates CIN development. PLR was found to be a predictor of CIN development after angiography in patients without ST elevation myocardial infarction [9]. However, different from our population there was enough time to evaluate renal function and to take adequate renal protective measures since interventions were planned but not urgently done. Additionally, in STEMI patients the renal function could not be accurately evaluated because acute hemodynamic changes and the contrast medium dose have to be governed primarily by the complexity of lesions that need to be opened, not by renal function. Also, we did not exclude patients with impaired renal function or patients in shock or patients with depressed left ventricular function and analysed blood test results droven at emergency department on admission. Our study population is a homogeneous group of unselected patients with STEMI undergoing pPCI which is directly relevant to most patients undergoing pPCI in the general population.

CIN is considered an intrinsic acute kidney injury, usually with conserved diuresis, but in severe cases acute tubular necrosis and even end-stage renal disease may develop. However, irreversible renal function losses occur in rare cases. The physiopathology of CIN is multifactorial and is still incompletely understood. Direct toxicity of contrast media, contrast induced modification in renal microvascular haemodynamics (increase vasoconstriction and decrease vasodilatation in the renal medulla), oxidative stress reperfusion injury, tubular obstruction and inflammation are suggested mechanisms contribute to its pathogenesis [10,11].

Infarcted heart activates damage-associated signaling pathways and triggers an intense sterile inflammatory response. Remote organ inflammation is evidenced by upregulation of VCAM-1 in renal glomeruli and by the recruitment and infiltration

of inflammatory cells throughout the kidney 24 h following myocardial infarction [12]. Unlike neutrophils, a lower lymphocyte count has been observed in acute myocardial infarction and lower lymphocyte count were found to be related to more cardiovascular events during the follow up [13]. Moreover, activated platelets recognised as inflammatory cells release inflammatory and mitogenic substances and promote the recruitment of more platelets and leukocytes. Formation of neutrophil-platelet aggregates plugs the microcirculation and cause reperfusion-related injury. Platelet activation in STMI is associated with increased generation of circulating microparticles acknowledged as intercellular communicators and links between inflammation and thrombosis [14]. PLR reflects both hyperactive coagulation and inflammatory pathways, and both of them are the suspected underlying mechanisms of CIN.

We found that the volume of contrast medium was significantly higher in patients experienced CIN but was not an independent predictor of CIN development. However, Nymann et al. proved that an adjustment of contrast amount to the GFR allows a reduction of the incidence of CIN in STMI [15]. Evolution of clinical practice and progress in contrast agent development, more usage of low or iso-osmolar agents may be explanations. Pre-exisiting renal dysfunction is another independent predictor of CIN development in our cohort. A greater incidence of baseline chronic kidney disease was observed in those patients who eventually developed postprocedural CIN. PLR has role in the evaluation of inflammation in end stage renal disease and it can predict inflammation and albuminuria in patients with diabetic nephropathy [16].

The present study has some limitations. It is cross-sectional retrospective and reflects single center experience. Complete follow-up data is not adequate. We measured PLR only once at admission and without correction for potential variability in PLR levels. To reflect the inflammatory status of patients we assessed CRP values but more sensitive markers could be evaluated.

As a conclusion the present study results demonstrated that PLR is easily available, widely used, and relatively cheap biomarker, and is an independent predictor of CIN development in patients with STEMI undergoing pPCI. It may also allow risk stratification and selection of a treatment strategy in patients with STEMI prior to or during coronary interventional procedures.

Declaration of conflicting interests

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