Predictive Value of Monocyte to High-Density Lipoprotein Cholesterol Ratio for Contrast-Induced Nephropathy in Patients with ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention

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ABSTRACT

Introduction: Contrast-induced nephropathy (CIN) is a serious complication in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (p-PCI). The monocyte to high-density lipoprotein (HDL) cholesterol ratio (MHR) has recently been defined as an inflammation and oxidative stress marker. The aim of this study was to evaluate the predictive value of MHR for risk of CIN in patients with ST who underwent p-PCI.

Patients and Methods: Data of a 2120 patients who were hospitalised with the diagnosis of STEMI and underwent p-PCI were retrospectively evaluated. A relative increase in serum creatinine levels of ≥ 25% or an absolute increase of ≥ 0.5 mg/dL from the baseline within 72 h of contrast exposure was defined as CIN. MHR was calculated on emergency admission. The risk of CIN was evaluated across MHR values.

Results: The incidence of CIN was 6.6% (n= 139). Age (p= 0.001), baseline creatinine levels (p< 0.001), DM (p< 0.001), HT (p< 0.001) and anaemia (p= 0.001) were higher in patients with CIN. The patients were divided into 2 groups based on the development of CIN. Peripheral monocyte count, HDL levels and MHR did not differ between the groups. After correction for all baseline confounders, neither peripheral monocyte count nor MHR were found to be independent predictors of CIN development in our multivariate logistic regression analyses.

Conclusion: Because MHR does not differ much from that in stable patients at the early phase of infarction, it cannot be a potential predictor of CIN development in patients with STEMI who underwent p-PCI.

Key Words: Contrast-induced nephropathy; primary percutaneous coronary intervention; ST segment elevation myocardial infarction; monocyte to high-density lipoprotein cholesterol ratio

Primer Perkütan Koroner Girişim Uygulanan St-segment Yükselmesi Miyokart İnfarktüsü Hastalarında Kontrast Nefropatisi Gelişimi İçin Monosit/Yüksek Yoğunluklu Lipoprotein Oranının Öngörülü Değeri

ÖZET

Giriş: Kontrast madde nefropatisi (KMN) primer perkütan koroner girişim (p-PKG) uygulanan ST yükselmeli miyokart infarktüsü (STEMİ) hastalarda ciddi bir komplikasyondur. Monosit/yüksek dansiteli lipoprotein (HDL) oranı (MHR) son zamanlarda inflamasyon ve oksidatif stres işaretleyici tanımlamıştır. Bu çalışmanın amacı, p-PKG uygulanan hastalarda KMN riski için MHR öngörü değerini araştırmaktır.

Hastalar ve Yöntem: STEMİ tanısı ile hastaneye yatırılan ve p-PKG uygulanan 2120 hasta retrospektif olarak değerlendirildi. Kontrast maruziyeti sonrası 72 saat içinde başlangıç serum kreatininde ≥ %25 göreceli artış veya ≥ 0.5 mg/dL mutlak artış olması KMN olarak tanımlandı. MHR acil servis başvurusunda hesaplandı. KMN riski ile MHR arasındaki ilişki değerlendirildi.

Bulgular: KMN insidansı (n= 139) %6.6 idi. Yaş (p= 0.001), bazal kreatinin (p< 0.001), DM (p< 0.001), HT (p< 0.001), anemi (p= 0.001) KMN olan hastalarda daha yüksekti. Hastalar CIN gelişimine göre iki gruba ayrıldı. Periferik monosit sayısı, HDL ve MHR gruplar arasında farklılık yoktu. Tüm temel karıştırıcı faktörler için düzeltme yapıldıktan sonra, periferik monosit sayısı ve MHR bizim çok değişkenli lojistik regresyon analizi sonrasında KMN gelişmesinin bağımsız belirleyicileri olarak saptanmadı.

Sonuç: MHR infarktüsün erken safhasında stabil hastalardan çok farklı olmadığından, p-PKG uygulanan STEMİ hastalarında KMN gelişimi için potansiyel belirleyicisi olarak değerlendirilemez.

Anahtar Kelimeler: Kontrast nefropatisi; primer perkütan koroner girişim; ST-segment yükselmeli miyokart infarktüsü; monosit/yüksek dansiteli lipoprotein oranı

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INTRODUCTION

Acute myocardial infarction (AMI) activates adrenergic signalling and triggers an inflammatory response, which aids in clearing necrosis and facilitates healing. Monocytes, the major immune cell type in atherosclerotic plaques, are recruited to the infarcted myocardium, transform into macrophages and regulate these vital cascades. However, exaggerated monocytosis, acting as a mediator of injury, impedes recovery, accelerates non-culprit atherosclerotic plaque progression and provokes unfavourable cardiovascular events, mainly re-infarct and ventricular dysfunction[1].

Contrast-induced nephropathy (CIN) is an important complication of unplanned coronary interventions due to the renal toxicity of iodinated contrast media (CM). Urgent coronary revascularisation increases its occurrence. Although most patients developing CIN after percutaneous coronary intervention are asymptomatic with conserved diuresis, it is strongly associated with short-term and long-term adverse clinical outcomes after myocardial infarction[2]. Hence, the identification of patients at a high risk for CIN development is of utmost clinical relevance.

Lately, the circulating monocyte to HDL cholesterol ratio (MHR) has been defined as an indicator of enhanced inflammation and oxidative stress[3]. Moreover, MHR is associated with a worse cardiovascular profile and has emerged as an independent predictor of cardiovascular outcomes in patients with chronic kidney disease[4]. However, its role in patients who have developed CIN has not been evaluated yet.

The purpose of this study was to investigate whether MHR on admission is associated with an increased risk of CIN after primary percutaneous coronary intervention (p-PCI) in patients with acute ST segment elevation myocardial infarction (STEMI).

PATIENTS and METHODS

The study population consisted of 2.120 consecutive patients with acute STEMI who were admitted to Siyami Ersek Thoracic and Cardiovascular Surgery Center and underwent p-PCI within 12 h of the onset of symptoms between January 2011 and March 2015. Inclusion criteria were THE presence of typical ongoing chest pain lasting for > 30 min 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 and admission laboratory test results were obtained from hospital files and computer records. Lipid parameters were measured on emergency admission. The monocyte count was obtained using the data elicited from complete blood count differential analysis. The reference value for monocytes in our laboratory is 2%-10%.

All p-PCI procedures were performed using a femoral or radial approach with a 6F guiding catheter. In total, 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 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 using a guidewire, and direct stenting was performed whenever possible; in the remaining cases, manual thrombus aspiration and/or balloon predilatation were performed. 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 the 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 stenosis or obstruction to less than 50% with thrombolysis in myocardial infarction (TIMI) grade 2 or 3 flow after p-PCI. If this could not be achieved, it was deemed unsuccessful.

Hypertension was defined as the use of blood pressure-lowering drugs on admission, systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg. Anaemia was defined as baseline haemoglobin levels < 13 g/dL in males and < 12 g/dL in females. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Formula[5].

Patients were considered to have hyperlipidaemia if they were being treated with lipid-lowering drugs at the time of admission or had abnormal fasting lipid test results according to guidelines[6]. Patients who were being treated with glucose-lowering drugs or had a fasting plasma glucose level of > 7 mmol/L or a non-fasting plasma glucose level of > 11.1 mmol/L were considered to have diabetes. CIN was defined as an increase in serum creatinine levels of > 25% or an absolute increase in serum creatinine levels of 0.5 mg/dL within 72 h of administration of radiocontrast[7].

Multivessel disease was described as the presence of 50% stenosis in at least 2 or more major epicardial arteries. Cardiogenic shock was defined as marked and persistent (> 30 min) hypotension with systolic arterial pressure < 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 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. The study protocol was approved by the local ethical committee and was consistent with the Declaration of Helsinki. Because all data were retrospectively collected from hospital records, we did not take informed consent from patients.

In-hospital cardiovascular mortality defined as unexplained sudden death or death from acute MI, heart failure and arrhythmia. CIN development was accepted as the endpoint.

The Number Cruncher Statistical System (NCSS) 2007 (NCSS, LLC, Kaysville, Utah, USA) program was used for statistical analysis. Continuous variables are presented as mean values ± SDs, whereas categorical ones are presented as percentages. Student's t-test was used for comparing parameters that show normal distribution, and Mann-Whitney U test was used for comparing variables that do not show normal distribution. Pearson's chi-square test and Fisher's exact test were used for comparing categorical variables. Pearson's test was performed to identify the correlation between MHR and CRP. Multivariate logistic regression analysis was performed to identify independent predictors of CIN. Variables with unadjusted $p< 0.1$ by univariate analysis were identified and included in the full model. Significance was determined at $p< 0.05$.

RESULTS

In total, 2.120 patients were evaluated in the study. The mean age of the patients was 56.9 ± 11 years, and 17.4 % of the patients were women. In total, 139 (6.6%) patients experienced CIN. Seventeen patients underwent renal replacement therapy. The in-hospital mortality rate was 2.2% (n= 47). Patients were divided into 2 groups based on CIN development. The baseline demographic, angiographic and clinical characteristics of the patient groups are shown in Table 1. Age ($p= 0.001$), baseline GFR ($p< 0.001$), baseline creatinine level ($p< 0.001$), EF ($p< 0.001$), DM ($p< 0.001$), HT ($p< 0.001$) and anaemia ($p= 0.001$) were different between the groups. Patients who developed CIN (group 1) experienced more shock on admission ($p< 0.001$) and had more unsuccessful intervention ($p< 0.001$) than group 2 (who did not develop CIN). Patients in group 1 had higher CRP levels ($p < 0.001$) In-hospital mortality was higher in group 1 ($p< 0.001$). The peripheral monocyte count and MHR were not different between the groups ($p= 0.22$ and 0.77, respectively). CRP levels and MHR did not correlate ($r= 0.072$, $p= 0.50$). Peripheral monocyte count ($p= 0.22$), HDL level ($p= 0.30$) and MHR ($p= 0.77$) did not differ between the groups. Independent predictors of CIN development are presented in Table 2. Neither peripheral monocyte count nor MHR was found to be an independent predictor of CIN development in patients with STEMI who underwent p-PCI according to our multivariate logistic regression analyses.

DISCUSSION

The present study demonstrates that MHR, an easily available test, is not an independent predictor of CIN development in patients with STEMI treated with p-PCI. There is no correlation between MHR and well-known risk factors for CIN. In addition, MHR on admission does not correlate with markers of inflammation in an acute setting.

The physiopathology of CIN is multifactorial and not fully understood. Many patient- and procedure-related risk factors have been proposed to explain the development of nephropathy after exposure to iodinated contrast, such as baseline renal insufficiency, heart failure, periprocedural haemodynamic instability and myocardial infarction. Direct toxicity of CM, contrast-induced modification in renal microvascular haemodynamics (increased vasoconstriction and decreased vasodilatation in the renal medulla), oxidative stress reperfusion injury, tubular obstruction and inflammation are suggested to be mechanisms that contribute to its pathogenesis.

The incidence of CIN in our STEMI population was 6.6%. Depending on the definition criteria, the incidence of CIN has been found to vary from 6.4% to 27.7% in the literature[8]. Among the factors we identified for the prediction of CIN development, impaired renal function (GFR< 60 mL/min/1.73 m^2), EF, CRP levels, DM and age were in line with those reported in the literature. Although the volume of CM was significantly higher in the CIN group, it did not predict CIN development. In our cohort, this could be explained by the usage of low-osmolarity agents that are deemed to be less nephrotoxic. In addition, there was a trend toward an increased risk of CIN in patients with multivessel disease. This may be related to more extensive vessel involvement in diabetic patients ($p< 0.001$) and a significant negative correlation of EF and multivessel disease in our population ($r= -0.85$, $p< 0.001$).

It is known that renal injury and repair comprise a delicate balance between cell loss and proliferation and inflammatory response determines tissue destruction or recovery. The infarcted heart activates damage-associated signalling pathways and triggers an intense sterile inflammatory response in order to initiate repair. Early mechanical reperfusion by p-PCI preserves myocardial salvage, primarily through a reduction in infarct size and transmurality. Systemic inflammatory response following acute myocardial infarction consists of circulating mediators and activation of inflammatory cells and platelets. Monocytes are the key players in this inflammatory damage and mediate a negative effect on myocardial remodelling. Furthermore, remote organ inflammation is evidenced by the upregulation of VCAM-1 in renal glomeruli and by the recruitment and infiltration of leukocytes throughout the kidney 24 h following myocardial infarction[9]. Karasawa et al. showed that the inflammatory subset of peripheral monocytes accumulates in injured renal tissue and contributes to renal damage. Moreover, these monocytes undergo differentiation into macrophages that produce pro-inflammatory cytokines[10]. On the other hand, the non-inflammatory subset of monocytes transforms into vascular elements, including endothelial cells, and plays an important role in the maintenance of renal vascular homeostasis[11]. Moreover, LDL exacerbates vascular inflammation and causes endothelial dysfunction by stimulating the production of oxygen radicals. Increased oxygen radicals impair perfusion and oxygen supply in the renal medulla[12]. LDL also upregulates endothelin receptor expression by inducing vasoconstriction results in renal medullary hypoxia, and this plays a major role in CIN development[13]. Chen et al. showed that LDL levels are higher in patients with CIN than those without CIN[14]. Moreover,

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

	CIN (+) group n= 139	CIN (–) group n= 1981	p value
Age (years)	65 ± 12	56 ± 11	0.001
Sex (male), n (%)	101 (71.9)	1650 (83.2)	0.001
GFR ≤ 60, n (%)	53 (38.1)	151 (7.6)	< 0.001
Anterior infarction, n (%)	65 (46.8)	776 (39.2)	0.29
Suspected vessel, n (%)			
LAD	72 (51.8)	848 (42.8)	
CX	15 (10.8)	304 (15.3)	0.16
RCA	47 (33.8)	778 (39.3)	
Others	5 (3.5)	51 (2.5)	
DM, n (%)	63 (45.3)	513 (25.9)	< 0.001
HT, n (%)	56 (40.3)	483 (24.4)	< 0.001
HL, n (%)	26 (18.7)	545 (27.5)	0.24
Smoking, n (%)	26 (18.7)	653 (33)	0.001
PCI history, n (%)	25 (18)	262 (13.2)	0.13
Bypass history, n (%)	3 (4.3)	45 (2.3)	0.12
Anaemia, n (%)	57 (41)	550 (27.8)	0.001
Unsuccessful intervention, n (%)	24 (17.3)	124 (6.3)	< 0.001
Multivessel disease, n (%)	34 (24.5)	372 (18.8)	0.10
Shock on admission, n (%)	10 (7.2)	41 (2.1)	< 0.001
Predilatation, n (%)	115 (82.7)	1470 (74.2)	0.25
Trofiban usage, n (%)	68 (48.9)	982 (49.6)	0.93
In-hospital mortality, n (%)	21 (15.1)	26 (1.3)	< 0.001
GFR (mL/min/1.73 m^2)	70.6 ± 44.2	99.9 ± 32.4	< 0.001
EF (%)	41.5 ± 10	46.6 ± 10	< 0.001
WBC (10^3/μL)	13.8 ± 6.9	12 ± 4.3	0.20
Haemoglobin (g/dL)	12.9 ± 2.1	13.6 ± 1.6	< 0.001
Neutrophil (10^3/μL)	11.3 ± 6.4	9.3 ± 4.7	0.02
Monocyte (10^3/μL)	0.67 ± 0.47	0.65 ± 0.39	0.22
Total cholesterol (mg/dL)	166.4 ± 43.7	179.4 ± 43.8	0.03
LDL (mg/dL)	99 ± 36.5	110 ± 38	0.01
HDL (mg/dL)	36.9 ± 10.2	37.8 ± 10.1	0.30
TG (mg/dL)	141.3 ± 71.3	158.8 ± 97.7	0.09
Contrast volume (mL)	163.3 ± 96	144.5 ± 83.9	0.03
Basal creatinine (mg/dL)	1.2 ± 0.45	0.87 ± 0.26	< 0.001
Peak creatinine (mg/dL)	2.0 ± 1.7	1.0 ± 0.23	< 0.001
Peak troponin (ng/mL)	38.3 ± 16.3	32.4 ± 18.3	< 0.001
CRP (mg/L)	11.2 ± 4.7	3.4 ± 2.3	< 0.001
MHR	18.9 ± 12.2	18.1 ± 9.1	0.77

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: Hyperlipidaemia, 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.

Table 2. Predictors of CIN development in 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.

Liu et al. concluded that LDL is an independent risk factor of CIN in patients undergoing p-PCI[15]. In contrast, HDL exerts antioxidant, anti-inflammatory and antithrombotic effects in the endothelium and increases nitric oxide bioavailability. It prevents inflammation on the vasculature, and more importantly, it inhibits signalling pathways associated with monocyte adhesion and transmigration[16]. Prestimulated monocytes through the cardiosplenic axis or programmed monocytes in the blood can be rescued from activation by HDL[17]. Besides steady states, on acute infarction, MHR becomes more valuable because one acts as a mediator of injury and the other tries to revert it. Finding a valuable peripheral marker to identify patients at risk is the purpose. However, no study in the literature has demonstrated a renoprotective role of HDL in patients at risk of CIN. Moreover, extended-release niacin treatment reduces triglyceride levels and increases high-density lipoprotein cholesterol levels but does not show any protective effect on kidney function[18].

Notably, after infarction, there is preponderance of the proinflammatory and proatherosclerotic monocyte subset ($CD14^{++}CD16^{+}$). In experimental models, the attenuation of this monocyte response significantly has been found to significantly cell survival[19]. Exaggerated monocytosis during AMI impairs recovery, and curbing monocye transmigration may improve cardiac and renal functions. However, recently, Ruparella et al. have demonstrated that after acute myocardial infarction, total peripheral circulating monocyte levels at presentation did not differ from those in control patients with stable atherosclerosis but increased thereafter. Moreover, there was no preponderance of the inflammatory subset of monocytes on admission; however, this was observed at 48 h[20]. Further, the magnitude of monocyte reaction at 48 h when compared with that on admission correlates with the extent of irreversible myocardial injury. Monocytes contribute to every stage of atherosclerosis and even play a role in final plaque rupture. However no study has demonstrated an association between circulating monocyte counts and cardiovascular disease[21]. Increased MHR is inversely related to renal functions and is associated with a worse cardiovascular profile in patients with renal chronic kidney disease. Dysregulated monocyte function and functional alterations in HDL particles due to inflammatory uremic milieu are the casual explanations of this association[4]. After monocyte subset analysis, Rogacev et al. concluded that only the $CD14^{++}CD16^{+}$ monocyte count but not the total monocyte count predicted cardiovascular events in stable subjects referred for elective coronary angiography[22]. Likewise, we found that the peripheral total MHR on admission did not predict CIN occurrence. The diverse and temporal nature of monocyte response during myocardial infarction diminish the predictive power of admission and total values.

Independent of the lipid-lowering effect, pleiotropic effects of statins reduce the risk of CIN by ameliorating ischaemia-reperfusion injury and suppressing the apoptosis of renal tubular cells. Recently, Abaci et al. concluded that statins have no effect on the incidence of CIN in stable cases without evident inflammation. However, they reduce the incidence of CIN by an anti-inflammatory, antioxidant effect in patients with acute coronary syndromes[23].

The present study has some limitations. It is cross-sectional and retrospective and reflects a single-centre experience. Complete follow-up data are not adequate. More importantly, the monocyte count was taken on admission within 12 h of the start of chest pain and MHR was calculated. A single value was used rather than a temporal trend. However, in order to evaluate the predictive power of MHR, we evaluated admission values. To reflect the inflammatory status of patients, we assessed CRP levels, but more sensitive markers could be evaluated.

In conclusion, our results showed that MHR does not differ much from that in stable patients at the early phase of AMI (≤ 12 h). Therefore, it cannot be a potential predictor of CIN development in patients with STEMI who underwent p-PCI.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: RZ, AT

Analysis/Interpretation: AG

Data Acquisition: YV, RZ

Writting: RZ

Critical Revision: RZ, EB, NH

Final Approval: All of authors

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