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A comparison of on-admission blood cell count-derived parameters on the development of contrast-induced nephropathy in acute coronary syndromes

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Abstract

Contrast-induced nephropathy (CIN) is a clinical entity closely associated with cardiac mortality and morbidity. We aimed to investigate the relationship between CIN after acute coronary syndrome and other bio-inflammatory parameters (Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio) as well as biomarkers such as AST/ALT, SIRI (Systemic Immnun Response Index), AISI (Aggregate Index of Systemic Inflammation), APRI (AST to platelet ratio index), SII (Systemic Immun Inflammation Index) NLR (Neutrophil to lymphocyte ratio), N/LPR (Neutrophil/ (lymphocyte x platelet), PLR (Platelet to lymphocyte ratio), MLR (Monocyte to lymphocyte ratio) and MPVLR (Mean platelet volume to lymphocyte ratio). In this retrospective cross-sectional study, we included 228 patients older than 18 years of age and underwent coronary angiography for acute coronary syndrome between January 2021 and May 2022. We applied the logistic regression analyzes to evaluate the relationship between patients' demographic, clinical characteristics, laboratory parameters, and contrast-induced nephropathy, and to evaluate the predictive power of the AST/ALT, AISI, SIRI, SII, NLR, PLR, MLR, N/LP ratio, MPVLR and other inflammatory based parameters on this primary endpoint. In the univariate analyses, prior history of coronary artery bypass, acute coronary syndrome type, prior ACEi/ARB usage, white blood cell count, hospitalization stay length, contrast amount, MLR, PLR, white blood cell to platelet ratio (WBCPR) were significantly associated with CIN. [p:0.039, p:0.017, p:0.025, p:0.044, p<0.001, p:0.003, p: 0.045, p: 0.044, p:0.044, respectively]. However, multivariable logistic regression analysis showed that WBCPR [OR 0.00 (95% CI 0.00- 0.01) p:0.005] and MLR [OR 13.522 (95% CI 2.15-84.72) p:0.005] might be statistically a significant independent predictor of CIN beside contrast amount [OR 1.92 (95% CI 01.23-3.02) p:0.004]. The WBCPR can be a new valuable independent predictor of CIN. Also, MLR and contrast amount may be a good independent predictor of CIN in acute coronary syndrome.

Keywords: Contrast-induced nephroapthy, acute coronary syndrome, monocyte/lymphocyte ratio, white blood cell/platelet ratio

Introduction

Contrast-induced nephropathy (CIN) is a clinical entity closely associated with cardiac mortality and morbidity. Despite advances in percutaneous coronary intervention (PCI) techniques in patients with acute coronary syndromes, complications such as CIN, stroke, emergency coronary artery bypass surgery, and vascular access site bleeding may occur during or after the procedure [1]. The risk of CIN increases in conditions such as chronic kidney disease (CKD), diabetes mellitus (DM), congestive heart failure (CHF), anemia, hemodynamic instability, decreased plasma volume, female gender, advanced age, contrast type, and amount [2,3].

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There are many studies in the literature on laboratory parameters associated with contrast nephropathy, especially in the acute coronary syndrome population. In a meta-analysis study, high CRP, NLR, hs-CRP and RDW levels, and low hematocrit levels, were associated with contrast nephropathy in acute coronary syndrome [4]. In other studies examining patients undergoing intervention for acute coronary syndrome, age, urea, glomerular filtration rate, creatinine, and PLR, were associated with contrast nephropathy [5-7]. Recently, it has been shown that SII was associated with CIN in non-ST elevation myocardial infarction [8]. Aspartate aminotransferase (AST) is a non-specific cardiac biomarker that increases early in acute coronary syndromes. In addition to acute inflammatory diseases, AST levels can be elevated in many chronic diseases such as inflammatory bowel diseases and chronic liver diseases [9]. The AST/ALT ratio, which is also known as the De-Ritis ratio, has been shown to predict the prognosis in cases such as bladder cancer, kidney cancer, pancreatic cancer, acute myocardial infarction, cardiac arrest, and ischemic stroke [10,11]. It has been shown in a recent study that the AST/ALT ratio also a predictor of acute kidney failure after radical retropubic prostatectomy [12]. Systemic immune response index (SIRI), calculated as neutrophil count x monocyte count/lymphocyte count, is an available parameter to predict the prognosis in acute and chronic inflammatory diseases, in endovascular interventions due to ischemic stroke, and to predict mortality in conditions such as breast cancer and lung cancer [13-15]. Moreover, there are new parameters such as AISI (Aggregate Index of Systemic Inflammation) and neutrophil/lymphocyte x platelet ratio (N/LP ratio). AISI, calculated by NLR x platelet count x monocytes, has a prognostic value, especially in respiratory tract inflammatory diseases such as interstitial fibrosis, asthma, lung cancer, or different inflammatory diseases such as COVID-19 disease [16,17]. The N/LP ratio predicts acute renal failure after abdominal surgery and cardiovascular surgery [18,19]. MLR and MPV to lymphocyte ratio (MPVLR) is also found as a good inflammatory marker in acute coronary syndromes and is a predictor of contrast-induced nephropathy [20,21]. Platelet to white blood cell count (P/WBC), is also a new inflammatory prognostic parameter predicting mortality in HBV-associated decompansated cirrhosis [22]. Since CIN is a complex porcess of inflammatory reactions including a ischemia, hypoxia, vasoconstriction, and direct toxic effect on renal tubular cells, we aimed to compare De-Ritis ratio, AISI, SII, APRİ, N/LP ratio, PLR, MLR, P/WBC and other blood derived parameters in predicting CIN in acute coronary syndromes.

Material and Methods

We evaluated acute coronary syndrome patients over 18 years old who underwent coronary angiography between 01/01/2021 and 01/05/2022. Patients who had severe chronic kidney disease (GFR<15 ml/min/1.73m2) or undergoing dialysis, chronic liver disease, died within the first 24 hours of the angiography procedure, came with cardiac arrest and were resuscitated, underwent bypass surgery after coronary angiography, had no creatinine values in the first 72 hours after admission, had acute or chronic inflammatory diseases such as autoimmune disease or cancer diagnosis, or had a history of infection or antibiotic therapy within the last one month were excluded. We recorded the demographic data, essential clinical characteristics of the patient, and serum CRP, creatinine, GFR, AST, ALT, hemoglobin, platelet count, platelet count, and hs-Trop I value before coronary angiography at admission. Contrast-induced nephropathy was defined as an increase in creatinine of >0.5 mg/dL from baseline or more than a 25% increase in creatinine from baseline within 72 hours of the procedure. Iohexol, a non-ionic, water-soluble contrast agent was used for coronary angiography. We calculated GFR with the automatic MDRD formula. We used the latest definition of universal myocardial infarction to diagnose myocardial infarction [23]. The primary endpoint targeted in our study was coronary angiography-induced contrast nephropathy. Coronary angiographic digital images of patients presenting with ACS were examined and classified as left main coronary artery, left anterior descending artery, circumflex artery, and right coronary artery, and other vessels according to the culprit lesions. The culprit lesions were treated percutaneously. The drugs used by the patients were also classified and recorded.

This study was conducted in Baskent University Hospital in accordance with the Declaration of Helsinki. Başkent University Institutional Review Board approved the study with Project no: KA21/519. The data used in the study were anonymous, so informed consent was not required.

Statistical Analysis

We analyzed the data using IBM SPSS Statistics volume 25.0 (SPSS Inc, IBM, USA). Histogram graphs, skewness-kurtosis values, and normality tests were used to check whether the data were normally distributed. In terms of descriptive statistics, it includes the mean for normally distributed parameters, the median for non-parametric quantitative variables, and numbers and percentages for categorical variables. Mann-Whitney U test and Chi-square or Fisher's exact test were used to compare non-normally distributed variables and categorical variables, respectively. Demographic, clinical, and blood count-derived parameters on admission were analyzed with univariate analysis, and the variables with a p-value <0.2 were included in a binary logistic regression analysis to determine their role in independently predicting contrast-induced nephropathy.

Results

Of 228 patients, 182 (79.8%) were male and 46 (20.2%) were female. Among the CIN-negative patients (n=198), 160 (80.8%) were male and 38 (19.2%) were female. The mean age of the CIN-negative patients was 62.39, whereas it was 61.83 in CIN-positive patients.

In the result of univariate analyses, coronary artery bypass surgery history (CABG), acute coronary syndrome type, prior ACEi/ARB usage, hospital stay length, contrast amount, MLR, PLR, and WBCPR were significantly associated with CIN in acute

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coronary syndrome patients treated percutaneously [p:0.039, p: 0.017, p:0.025, p:0.044, p <0.001, p:0.003, p:0.045, p:0.044, p: 0.044] whereas De-Ritis ratio, APRI score, SII, SIRI, AISI, NLR, N to PL ratio and MPVLR were not associated with CIN in acute coronary syndrome patients treated percutaneously [p:0.605, p:0.621, p:0.116, p:0.270, p:0.213, p:0.115, p: 0.270, p:0.213, p:0.115, p: 0.246, p:0.223, respectively][Table 1]. Although there was a significant relationship between prolongation of hospital stay and contrast nephropathy, it was thought to be meaningless in determining the prognostic value because it was a natural result of the cause-effect relationship. Thus, we found inappropriate to include the hospital stay length in the logistic regression analysis. In the binary logistic regression analysis, only MLR and WBCPR were found to be statistically

Table 1. Comparison of the baseline demographics and clinical characteristics between CIN negativeand CIN positive patients

Variables	CIN negative patients (N=198) Mean (±SD)/Median (IQR)/frequency (%)	CIN positive patients (N=30) Mean (±SD)/Median (IQR)/frequency (%)	P value
Baseline characteristics			
Age (year)	62.39 (±11.53)	61.83 (±13.76)	0.679#
Sex category (male/female)	158/40 (79.7%/20.2%)	24/6 (80%/20%)	0.980**
Hypertension	106 (53.5%)	18 (60%)	0.509**
Diabetes mellitus	64 (32.3%)	8 (26.6%)	0.537**
Hyperlipidemia	50 (25.3%)	12 (40%)	0.091**
Coronary artery disease	60 (30.3%)	11 (36.6%)	0.484**
Congestive heart failure	24 (12.1%)	4 (13.3%)	0.850**
Atrial fibrillation	8 (4%)	0 (0%)	0.262**
Prior myocardial infarction	42 (21.2%)	8 (26.6%)	0.501**
Prior CABG surgery	16 (8.1%)	6 (20%)	0,039**
Smoking	120 (60.6%)	16 (53.3%)	0.449**
Chronic pulmonary disease	22 (11.1%)	0 (0%)	0.055**
Peripheral artery disease	4 (2%)	2 (6.6%)	0.138**
Serebrovascular disease	4 (2%)	0 (0 %)	1.000**
Culprit lesion			
-LAD	80 (40.4%)	13 (43.3%)	
-Cx	44 (22.2%)	3 (10%)	
-RCA	62 (31.3%)	12 (40%)	
-LAD+ Cx	2 (1%)	0 (0%)	0.552**
-Cx+ RCA	2 (1%)	0 (0%)	
-LAD+ RCA	2 (1%)	0 (0%)	
-Saphenous	4 (2%)	2 (6.7%)	
- IM	2 (1%)	0 (0%)	
ACS type			
-Unstable angina pectoris	5 (2.5)	0 (0%)	
-Non ST elevation	45 (22.7%)	14 (46.6%)	0.017**
-ST elevation	148 (74.8%)	16 (53.4%)	
Prior BB usage	60 (30.3%)	8 (26.6%)	0.685**
Prior CCB usage	38 (19.2%)	4 (13.3%)	0.440**
Prior ACEi/ARB usage	64 (32.3%)	16 (53.4%)	0.025**
Prior Statin usage	44 (22.2%)	10 (33.3%)	0.182**
Clinical and laboratory characteristics			
Urea (mg/dL)	17 (6-51)/(8)	17 (10-31)/(7)	0.453*
Preoperative creatinine (mg/dL)	1.01 (±0.28)	1.11 (±0.35)	0.080#
GFR (mL/min/1.73m2)	78.15 (±22.19)	73.03 (±25.28)	0.250#
Serum Sodium (Na) (mmol/L)	138.06 (±2.63)	137.83 (±2.36)	0.663#

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AST (U/L)	23 (10-411)/(28)	24.5 (11-174)/(21)	0.482*
ALT (U/L)	23 (8-97)/(21)	19.5 (6-67)/(23)	0.238*
CK-MB (U/L)	23.05 (0.70-558.10)/(40.95)	21,05 (7,79-123,70)/(46.53)	0.929*
Trop I (ng/L)	0.11 (0.00-213.00)/2.88	0.34 (0.01-48.79)	0.096*
Hemoglobin (g/dL)	14.77 (±1.74)	14.83 (±1.80)	0.864#
White blood cell count (103/µL)	11.35 (±3.60)	9.93 (3.42)	0.044#
Platelet (103/µL)	234 (117-673)/(94)	230.05 (139-325)/(61)	0.938*
MPV (fL)	8.05 (±1.47)	7.81 (±1.20)	0.390#
RDW (%)	12.50 (9.80-25.70)/(2,9)	12.00 (10.8-16.6)/(3.5)	0,477*
Neutrophile (103/µL)	6.63 (1.59-21.70)/(4.15)	6.37 (3.34-14.80)/(3.53)	0.280*
Lymphocyte (103/µL)	2.94 (±1.66)	2.43 (±1.59)	0.120#
Monocyte (103/µL)	0.78 (±0.32)	0.82 (±0.37)	0.533#
CRP (mg/L)	3.20 (0.30-176)/(7.05)	3.85 (0.5-120.1)/(9.90)	0.840*
HDL (mg/dL)	38 (13-93)/(11)	37 (25-79)/(13)	0.989*
LDL (mg/dL)	121.40 (±31.89)	112.77 (±31.33)	0.168#
Triglyceride (mg/dL)	129 (21-630)/(87)	156.5 (55-295)/(119)	0.269*
LV ejection fraction on admission			
>50%	84 (42.4%)	12 (40%)	
41-50%	88 (44.4%)	10 (33,.%)	0.136**
<40%	26 (13.1%)	8 (26.7%)	
Hospital stay length (day)	3 (2-9)/(1)	4 (3-8)/(2)	<0.001#
Contrast amount (mL)			
0-100	12 (6.1%)	0 (0%)	
101-200	92 (46.5%)	8 (26.7%)	
201-300	68 (34.3%)	16 (53.3%)	0.003**
301-400	20 (10.1%)	2 (6.7%)	
401-500	6 (3%)	2 (6.7%)	
>500	0 (0%)	2 (6.7%)	
De-Ritis ratio	1.179 (0.418-9.676)/(0.694)	1.000 (0.545-4.625)/(1.470)	0.605*
APRI	0.100 (0.017-1.633)/(0.139)	0.098 (0.043-0.628)/(0.088)	0.621*
SII	529.085 (139.600-4591.814)/(740.326)	645.142 (143.004-1592.752)/(761.513)	0.116*
SIRI	1.541 (0.528-29.583)/(2.129)	1.680 (0.283-10.055)/(3.583)	0.270*
AISI	356.934 (85.993-7484.658)/(496.359)	440.373 (39.685-2785.388)/(742.507)	0.213*
NLR	2.356 (0.576-19.466)/(3.158)	2.773 (0.489-7.382)/(4.373)	0.115*
MLR	0.261 (0.099-1.933)	0.321 (0.084-1.125)/(0.316)	0.045*
PLR	87.733 (32.220-440.131)/(73.261)	117.861 (39.945-282.352)/(86.089)	0.044*
NLPR	0.010 (0.001-0.166)/(0.015)	0.013 (0001-0.044)/(0.021)	0.246*
WBCPR	0.048 (±0.016)	0.041 (±0.011)	0.044#
MPVLR	3.37 (0.995-20)/(2.56)	3.75 (1.07-13.8)/(3.89)	0.223*

Abbreviations: LAD: Left coronary artery, Cx: circumflex artery, RCA: Right coronary artery, IM:Intermediate coronary artery, ACS: acute coronary syndrome, BB: Beta blocker, CCB: Calcium channel blocker, ACEi/ARB: Angiotensin converting enzymes inhibitors/ Anjiotension II receptor blockers, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, AST: aspartate transaminase, ALT: Alanin transaminase, CK-MB: Creatinine kinase –miyocardial band, Trop I: Troponın I, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, De-Ritis ratio: AST/ALT, APRI: AST to platelet ratio index, SII: Systemic Immun Inflammation Index, NLR:Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, NLPR: Neutrophil/ (lymphocyte x platelet), WBCPR: White blood cell count to platelet ratio, MPVLR: Mean platelet volume to lymphocyte ratio, SD: Standard derivation, IQR: Interquartile range (max-min)

#: Student- t test

***: Mann-Whitney U test**

****: Chi-Square test**

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significant predictors of the CIN in acute coronary syndrome patients treated percutaneously [OR 13.522 (95% CI 2.15-84.72) p:0.005; OR 0.00 (95% CI 0.00- 0.01) p:0.005, respectively]. Moreover, contrast amount was also an independent predictor of CIN in this population [OR 1.92 (95% CI 01.23-3.02) p:0.004] [Table 2]. As a result of the logistic regression analysis of the parameters derived from the blood count and other statistically significant parameters predicting CIN at the time of admission to the hospital, the p-value of Hosmer-Lemeshow was found to be 0.940 and the Nagelkerke R2 value was found to be 0.293, which indicate regression model compatibility.

Table 2. Multivariable logistic regression analysis of the baseline characteristics and laboratory parameters

Variables	B	SE	Wald	df	OR	P value	95% CI	
							Lower bound	Upper bound
Baseline characteristics								
ACS type	-7.55	0.429	3.099	1	0.470	0.078	0.203	1.089
Prior CABG surgery	0.527	0.652	0.651	1	1.693	0.559	0.471	6.082
Prior COPD	-18.429	8265.394	0.000	1	1.410	0.998	0.000	.
Peripheral arterial disease	-0.848	1.076	0.621	1	2.335	0.431	0.283	19.239
Prior ACEi/ARB usage	0.715	0.475	2.266	1	2.045	0.132	0.806	5.190
LV ejection fraction on admission	0.416	0.343	1.426	1	1.516	0.225	0.774	2.969
Contrast amount	0.657	0.229	8.220	1	1.929	0.004	1.231	3.022
Laboratory parameters								
Trop I	-0.019	0.015	1.672	1	0.981	0.196	0.953	1.010
MLR	2.604	0.936	7.737	1	13.522	0.005	2.158	84.729
WBC/platelet ratio (WBCPR)	-52.115	18.626	7.829	1	2.330	0.005	0.000	0.000

Abbreviations: ACS: Acute coronary syndrome, CABG: Coronary aryery bypass greft surgery, COPD: Chronic obstructive pulmonary disease, ACEi/ARB: Angiotensin converting enzymes inhibitors/ Anjiotension II receptor blockers, Trop I: Troponın I, MLR: Monocyte to lymphocyte ratio, WBCPR: White blood cell count to platelet ratio, SE: Standard error, OR: Odds ratio, CI: Confidence interval

Discussion

There are different studies investigating many parameters, such as NLR, PLR, RDW, MPVLR, and SII, which may be associated with CIN in acute coronary syndromes. However, a recent study showed a significant association between CIN and NLR, CRP, and lower hematocrit levels, except for PLR [4-6,8]. Herein our study, MLR, PLR, WBC, and WBCPR were associated with CIN. Besides, CABG surgery, acute coronary syndrome type, contrast amount, hospital stay length, and prior ACEi/ARB usage were significantly associated with CIN. Nevertheless, there was no significant association between SII and CIN in our study. According to logistic regression analysis, WBCPR and MLR might be good predictors of CIN, in addition to contrast amount in this population.

Although there were too many studies investigating inflammatory parameters derived from blood count cells about CIN in the literature, our study is maybe the first study ascertaining and comparing other inflammatory parameters such as AISI, SII, SIRI, APRI, NLR, PLR, MLR, MPVLR, and others for CIN in acute coronary syndrome. Although there is a recent study stating that SII has a predictive value in predicting CIN in acute coronary syndrome [9], we did not find a significant association between SII and CIN. Besides, it is stated in the literature that AST/ALT ratio can be used to determine kidney damage in cancer patients or to predict post-operative acute kidney damage [10,12], we found that the AST/ALT ratio was not useful in predicting CIN in the acute coronary syndromes, as in SII.

Recently, MPVLR, a new parameter was associated with CIN and a good predictor of CIN in the acute coronary syndromes [9]. In our study, we could not find a significant association between MPVLR and CIN. Since there was a study about the association between acute kidney injury and neutrophil to platelet x lymphocyte ratio (N/LPR), we also investigated the N/LP ratio [18,19]. However, in our study, there was no significant association between the N/LP ratio and CIN. Recent studies also showed that MLR was an independent predictor of coronary inflammation and could be a good prognostic indicator of CIN in the acute coronary syndromes [20,21]. Complying with the last-cited study results about MLR and CIN, in our study, MLR was an independent predictor of CIN in the acute coronary syndromes.

It has been stated in the literature that the platelet/WBC ratio, which is a new parameter, can be a good prognostic tool in HBV-related chronic cirrhosis. There has been no study of this parameter in the literature on CIN, which is another complex inflammatory process [22]. We calculated a new formula for

white blood cell to platelet ratio (WBCPR) and found that there might be a significant association between CIN and WBCPR. In this study, we enquired the role of WBCPR in predicting CIN after percutaneous treatment in acute coronary syndrome. In this study, we aimed to investigate the role of the WBCPR in predicting CIN after percutaneous treatment in acute coronary syndromes. As a result, MLR and WBCPR were significantly associated with CIN in percutaneously treated coronary syndrome patients and could be good independent predictors of CIN in this group. The on-admission blood count-derived parameters can be calculated easily and quickly from routine blood tests in every patient with acute coronary syndromes. Thus, MLR can be a good prognostic parameter of CIN in acute coronary syndromes. WBCPR, a possibly new and independent indicator of CIN in patients with acute coronary syndromes, can be a useful parameter to predict CIN in these groups. In addition to MLR and WBCPR, contrast amount is surely associated with CIN and is a useful prognostic marker of CIN in this population.

Limitations

There were some limitations in our study. The primary limitation of the study is that it is retrospective and has a relatively small population. Secondly, we collected the on-admission data that could be affected from the timing of the patient admission to hospital. Thirdly, the comparison of patients with NSTEMI and STEMI specifically, rather than acute coronary syndrome, could have been made by including a larger patient population. Therefore, new, prospective, and larger population studies are needed to determine the true effects of blood cell-derived parameters on CIN in acute coronary syndromes.

Conclusion

CIN continues as a serious complication that may develop in acute coronary syndrome. In patients who are planned for percutaneous treatment in acute coronary syndrome, we can conclude that a new parameter, WBCPR, together with MLR, is a more valuable predictor for the development of CIN in these patients. Moreover, this study reiterates that it would be beneficial to keep the amount of contrast low.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was conducted in Başkent University Hospital, and performed in compliance with the Declaration of Helsinki. Başkent University Institutional Review Board approved the study with Project no: KA21/519.

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