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Systemic immune inflammation index: is it a new marker for contrast-induced nephropathy?

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ABSTRACT

Introduction: Worldwide, >200 million patients are affected by peripheral arterial disease (PAD) and endovascular interventional treatments are increasingly being applied. Contrast-induced nephropathy (CIN) is the third most common cause of renal failure in hospitals. However, factors such as renal vasoconstriction, decrease in renal blood flow, endothelial dysfunction, and oxidative stress have been suggested in the etiology of CIN. Studies are showing that inflammatory markers increase in CIN. Systemic immune inflammation index (SII), a newly defined parameter, is calculated by multiplying the platelet and lymphocyte counts and dividing by the neutrophil count. Studies are showing that this parameter influences prognosis in various cancer types. Considering that inflammation may play a role in CIN, we planned this study to investigate the role of SII in patients undergoing percutaneous peripheral vascular interventions.

Material and Method: 300 patients who underwent percutaneous peripheral vascular interventions between August 2018-December 2021 due to peripheral arterial disease were included in the study. The data of the patients were scanned retrospectively from the patient files. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. SII was found by multiplying NLR with platelet count

Results: Contrast-induced nephropathy developed in 41 (12.3%) patients. CIN(+) patients also, had higher CRP levels (5.1±0.7vs 2.4±0.4,P<0.05), NLR (4.07±1.07vs 2.65±0.84, P<.005), SII score (1778±627.57vs 867.14±491.88, P<.005.) the contrast media used was also higher in CIN(+) patients (176.19±48.44 vs 128.72±48.44;P<0.05) Multivariate logistic regression analysis demonstrated that a high SII score was an independent predictor of development of CIN (odds ratio [OR]: 1.002, 95% confidence interval [CI]: 1.001-1.002, P<.0005) together with high NLR (OR: 3.56, 95% CI: 1.905-6.675, P<.005) and CRP (OR: 1.002, 95% CI: 1.001-1.002, P<.005 Receiver operating characteristic curve analysis demonstrated that the best cutoff value of 1224 for SII to predict the development of CIN with 85% sensitivity and 72% specificity (area under ROC curve 0.904 [95% CI: 0.866-0.942], P<.005).

Conclusion: Imbalance in inflammatory cells, the increase in neutrophils, and the decrease in lymphocytes play a role in developing kidney damage. Impaired immune functions due to lymphocytopenia contribute to the development of acute kidney injury. Oxidative stress exacerbates the inflammatory state by increasing inflammatory cell infiltration. AS a result, SII may be a powerful predictor of inflammation and can be used to determine the risk before interventional procedures.

Keywords: contrast-induced nephropathy, inflammation, peripheral vascular interventions, systemic immune inflammation index

INTRODUCTION

Worldwide, >200 million patients are affected by the peripheral arterial disease (PAD and endovascular interventional treatments are increasingly being applied (1). Contrast-induced nephropathy (CIN) is hospitals' third most common cause of renal failure (2). It is usually reversible but related to increased morbidity and mortality (3).

Although factors such as renal vasoconstriction, decrease in renal blood flow, endothelial dysfunction, and oxidative stress have been suggested in the etiology of CIN, it is not known why some patients with the same risk factors develop nephropathy while others do not (4,5). Studies show that inflammatory markers increase in CIN (6-10).

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Systemic immune inflammation index (SII), a newly defined parameter, is calculated by multiplying the platelet and lymphocyte counts and dividing by the neutrophil count. Studies show that this parameter influences prognosis in various cancer types (11-14).

Considering that inflammation may play a role in CIN, we planned this study to investigate the role of SII in patients undergoing percutaneous peripheral vascular interventions.

MATERIAL AND METHOD

The study was initiated with the approval of the Prof. Dr. Cemil Taşçıoğlu City Hospital Institutional Ethical Committee (Date: 2022, Decision No: E-48670771-59.99). All procedures were carried out under the ethical rules and the principles of the Declaration of Helsinki.

Patients who underwent percutaneous peripheral vascular interventions between August 2018-December 2021 due to peripheral arterial disease were included in the study. The data of the patients were scanned retrospectively from the patient files. Risk factors such as age, gender, diabetes mellitus (DM), hypertension (HT), dyslipidemia, smoking, and drugs were scanned from patient files. Exclusion criteria were the presence of active infection, presence of chronic inflammatory or autoimmune disease, known cancer history, presence of chronic liver disease, end-stage renal failure (GFR<10 ml/min), and heart failure (EF<40).

All laboratory parameters before the procedure and three days after the procedure were recorded from the files. CIN was defined as a 25% or >0.5 mg/dl increase in creatinine value on the third day (15).

The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. SII was found by multiplying NLR with platelet count.

SPSS (Statistical Package for Social Sciences, Chicago, IL) for Windows 20.0 was used for statistical analysis. Data about continuous variables were expressed in mean±standard deviation if otherwise is not indicated. Intergroup comparisons were made with Student's t-test (in data with a normal distribution) or with Mann–Whitney U test (in data without a normal distribution). Categorical variables were compared with the Chi-square test. Pearson's correlation coefficient was used for continuous variables with normal distribution, and Spearman's correlation coefficient was used for continuous variables that are not normally distributed p<0.05 was considered significant. The effects of different variables on the development of CIN were calculated with univariate analysis. The model included parameters with a P<.10 in univariate analysis for multivariate regression analysis. The cutoff level of SII and NLR in predicting CIN formation was determined by performing a receiver operating characteristic curve (ROC) analysis. The value corresponding to the highest sensitivity and specificity value in the ROC analysis was accepted as the optimal cutoff value. A 2-sided P<.05 was considered significant.

RESULTS

Of the 300 patients included in the study, 228 (76.3%) were male. The mean age was 62±12.3 years. One hundred sixty patients had diabetes (53.3%), 105 had hypertension (35%), and 202 were smokers (67.3%). The mean creatinine level was 1.06±0.75mg/dl, and CRP was 5.25±1.92. Laboratory findings of the patients can be seen in **Table 1**.

Table 1. Demographic properties of study population

Age (years)	62±12.18
Male (n,%)	228 (76.3%)
Diabetes mellitus (n,%)	160 (53.3%)
Hypertension (n,%)	105 (35%)
Smoking (n,%)	202 (67.3%)
Glucose (mg/dL)	154.3±79.61
Creatinine (mg/dL)	1.06±0.75
AST (U/L)	24.52±12.18
ALT (U/L)	20.24±10.75
T. Cholesterol (mg/dL)	196.29±52.79
HDL (mg/dL)	43.05±10.52
LDL (mg/dL)	136.42±64.37
Triglyceride (mg/dL)	165.99±121.61
Hgb (g/L)	13.65±2.22
Albumin (g/dL)	3.87±0.5
Contrast volume	135.0±40.6
CRP (mg/L)	5.25±1.92
NLR	2.84±1.01
SII	994.76±40.65

Contrast-induced nephropathy developed in 41 (12.3%) patients. the patients with and without CIN are summarized in Table 1. The age of the patients was similar between the two groups. (62.04±11.5 in CIN (-) vs 61.7±15.73 years in CIN (+); P>0.05). The rate of patients with HT and DM was also similar between CIN (-) and CIN (+) (36.8% vs 23.8%, P>0.05; 51.6% vs 64.3%, P>.005, respectively). Other demographic characteristics and the previous medications were similar between both groups. There was no significant difference between the two groups regarding sex and smoking (**Table 2**).

When the hematological parameters were analyzed between the two groups, there was no significant difference in hemoglobin (P>.05).

There was no statistically significant difference between groups in terms of glucose, AST, ALT, total cholesterol, HDL, LDL and triglyceride levels (p>0.05, **Table 1**).

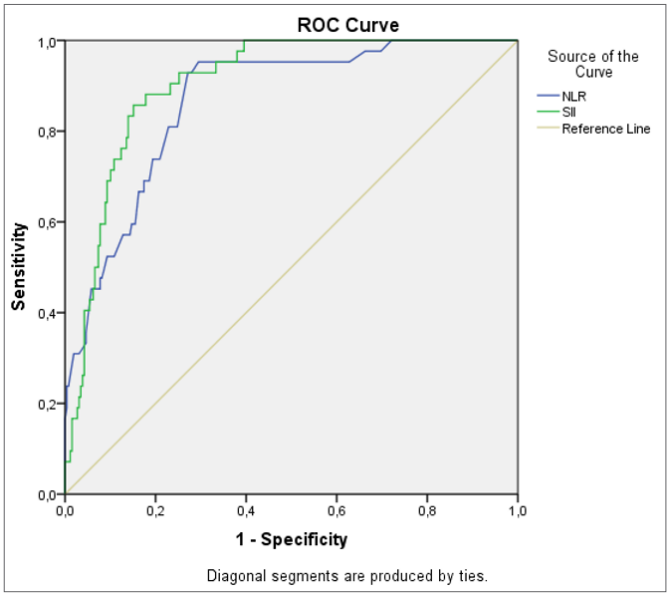
The patients who had CIN had statistically significantly higher creatinine levels (1.89±1.54 vs 0.92±0.17; p<0.05). CIN (+) patients also, had higher CRP levels (5.1±0.7vs 2.4±0.4, P<0.05), NLR (4.07±1.07vs 2.65±0.84, P<.005), SII score (1778±627.57vs 867.14±491.88, P<.005.) the contrast media used was also higher in CIN (+) patients (176.19±48.44 vs 128.72±48.44; P<0.05). CIN (+) patients had significantly higher T.Chol and LDL levels (214.54±57.75vs 193.6±51.65; p=0.043 and 150.19±60.3 vs 134.17±64.83; p_0.021).

Table 2. Comparision of the groups

	CIN(-)	CIN(+)	P
Age (years)	56.81±13.74	62.84±11.72	0.013
Male(n,%)	196 (76.3%)	32 (76.2%)	0.992
Diabetes Mellitus (n,%)	139 (53.9%)	21 (50%)	0.641
Hypertension(n,%)	88 (34%)	17 (40.5%)	0.422
Smoking (n,%)	170 (65.9%)	32 (76.2%)	0.187
Glucose (mg/dl)	154.43±78.38	153.48±87.77	0.493
Creatinine (mg/dl)	0.92±0.17	1.89±1.54	0.023
AST(U/L)	24.92±14.29	22.1±13.1	0.930
ALT(U/L)	20.14±14.72	20.83±10.84	0.357
T.Cholesterol(mg/dl)	193.6±51.65	214.54±57.75	0.043
HDL(mg/dl)	43.12±10.75	42.62±9.03	0.713
LDL(mg/dl)	134.17±64.83	150.19±60.39	0.021
Triglyceride (mg/dl)	164.91±122.42	171.9±117.77	0.954
Hgb (g/L)	13. ±1.02	13.14±2	0.590
Albumin(gr/dl)	3.85±0.55	3.96±0.5	0.810
CRP (mg/L)	2.4±0.4	5.1±0.	0.01
Contrast volume	128.72±48	176.19±48.4	0.001
NLR	2.65±0.84	4.07±1.07	0.00
SII	867.14±491.88	1778±627.57	0.00

The patients who had CIN were grouped in two according to gender. Thirty-two of the patients were male. DM, hypertension, and smoking incidence were similar (**Table 3**). There was no difference in terms of contrast volume, NLR, and SII (152±32 VS 117±55; P=0.125, 2.64±0.4 vs±2.62±0.89; P=0.257, 853.14±468.88 vs. 915.3±526; P=0.467)

The role of several CIN risk factors was also evaluated by multivariate analysis. This included age, gender, DM, HT, contrast volume, serum creatinine, glucose, NLR, CRP, and SII. Multivariate logistic regression analysis demonstrated that a high SII score was an independent predictor of development of CIN (odds ratio [OR]: 1.002, 95% confidence interval [CI]: 1.001-1.002, P<.0005) together with high NLR (OR: 3.56, 95% CI: 1.905-6.675, P<.005) and CRP (OR: 1.002, 95% CI: 1.001-1.002, P<.005. Age was not a significant indicator (OR: 1.000%95 CI: 0.928-1.001,P>0.05). Receiver operating characteristic curve analysis demonstrated that the best cutoff value of 1224 for SII to predict the development of CIN with 85% sensitivity and 72% specificity (area under ROC curve 0.904 [95% CI: 0.866-0.942], P<.005). For NLR, the best cutoff value of 3.17 predicted the development of CIN with a sensitivity of 92% and specificity of 72%, and the area under the curve was 0.867 (95% CI: 0.814-0.919; P<.005; **Figure 1**).



DISCUSSION

The most important finding of this study is that the increase in SII score, a new inflammation parameter, is a robust independent predictor of CIN.

According to previous studies, while the incidence of CIN is below 2% in patients without risk factors, the incidence rises to 90% in patients with risk factors (6). The incidence of CIN was 12.3% in our study. This rate corresponded with the incidence of CIN in patients who underwent angiography for the acute coronary syndrome (16).

In our study, basal creatinine of the CIN (+) group was statistically significantly higher. Preexisting chronic kidney disease is a known risk factor for contrast-induced nephropathy. In a series of 1144 patients, Davidson et al. l. investigated patients undergoing cardiac catheterization and documented a low risk of CIN (increment of creatinine levels of at least 0.5 mg/dL) in patients with normal renal function compared to those with preexisting CKD (creatinine levels exceeding 1.2 mg/dL). These investigators found that the risk for CIN increased significantly (20%) when serum creatinine exceeded 2.0 mg/dL (17).

The age of the CIN (+) group was statistically significantly higher in our study. This is concordant with other studies (18, 19). This is possibly caused by the decline in renal function with increasing age. Vascular stiffens are increased, and vasodilator response is decreased by aging. Also, pluripotent stem cells decreased in advanced age, causing a decrease in vascular repair (20).

Contrast volume is increased in CIN (+) group. High doses and repeated use of contrast material administered within 72 hours increase CIN (+). This is more common in the first-generation contrast agents (21, 22)

In the CIN (+) group, T.Chol. and LDL levels were increased compared with the CIN (-) group. This is consistent with the literature. According to statin use, in a study by Hoshi et al. (23), 2198 patients were analyzed. In the statin pretreatment group, CIN was observed less. Statin may reduce contrast-induced inflammation and may have beneficial effects against CIN. Hyperlipidemia may increase systemic inflammation and disturb tubular function (24).

A high SII score indicates decreased immune system with an increased inflammatory state. To understand the relationship between the SII index and CIN, the roles of neutrophils, platelets, and lymphocytes should be evaluated separately.

Inflammation is a pre-thrombotic condition (25). Endothelial damage caused by inflammation leads to a pre-thrombotic state. In addition, inflammatory cells reduce the amount of critical anticoagulant substances (26)

In this inflammatory process, platelets are activated by chemokines, secreted proteins, and microRNAs (27). Activation of the coagulation system and downregulation of the anticoagulant system causes an increase in platelet levels and an increased risk of CIN (27). Experimental studies have shown that the imbalance in inflammatory cells, the increase in neutrophils, and the decrease in lymphocytes play a role in developing kidney damage (28), stimulation of neutrophils increases vascular permeability, and endothelial damage occurs (29, 30).

Impaired immune functions due to lymphocytopenia contribute to the development of acute kidney injury (30). Oxidative stress exacerbates the inflammatory state by increasing inflammatory cell infiltration (31). Detection of the inflammatory process can be used to determine the risk before interventional procedures.

SII is thought to show inflammatory processes better than NLR and platelet-lymphocyte ratio. This is based on the findings in recent studies showing the relationship of SII with poor outcomes in various diseases (11-13, 32-35).

Xu et al. (36) showed that SII is associated with acute kidney injury in patients with hepatocellular carcinoma who underwent hepatectomy. Bağcı et al. (37) showed that it is an independent marker of CIN in patients with myocardial infarction. Yang et al. (32) claimed that the increase in SII scores was superior to traditional risk factors in predicting mortality and morbidity in coronary arterial disease. Gok et al. (38). Reported a relationship between high SII scores and the severity of pulmonary embolism. Our study found that among the inflammatory markers we examined in peripheral angiography patients, the SII was the most decisive and independent marker associated with CIN development. Moreover, we identified that the optimum cutoff point for the SII was 1224, which predicted the risk of developing CIN with 85% sensitivity and 72% specificity.

This study has some limitations. Few patients were included in the study, and the data were reviewed retrospectively. The study was a single-center study. SII levels were calculated at admission. Control creatinine level was measured three days after contrast use; therefore, it could not be detected if there was an increase after 72 hours.

Table 3. Comparision of the CIN(+) group in terms of gender

	Male (n=32)	Female (n=10)	P
Age (years)	63.35±9.54	61.18±11.72	0.4
Diabetes Mellitus (n,%)	17 (53.1%)	4 (40.3%)	0.641
Hypertension(n,%)	11 (34.4%)	4 (40%)	0.422
Smoking (n,%)	28 (87.5%)	32 (76.2%)	0.182
Glucose (mg/dl)	157.24±81.88	145.57±66.55	0.5
Creatinine (mg/dl)	1.1±0.72	0.93±1.5	0.12
AST(U/L)	24.92±4.29	32.97±6.46	0.881
ALT(U/L)	18.52±12.61	25.64±4.3	0.343
T.Cholesterol (mg/dl)	193.6±51.65	214.54±57.75	0.521
HDL (mg/dl)	43.12±10.75	42.62±9.03	0.513
LDL (mg/dl)	135.3±68.25	130.54±53.2	0.413
Triglyceride (mg/dl)	172.94±133.1	139.08±73.22	0.954
Hgb (g/L)	13.82. ±1.02	13.55±2	0.51
Albumin (g/dl)	3.85±0.55	3.78±0.5	0.243
CRP (mg/L)	2.76±0.4	3.48±0.	0.112
Contrast volume	152±32	117±55	0.125
NLR	2.64±0.83	2.62±0.89	0.257
SII	853.14±468.88	915.3±526	0467

Table 4. Binary logistic regression analysis

	Odds ratio	Cl95%	P
Age	1.000	0.928-1.001	0.057
CRP	1.002	1.001-1.002	0.003
NLR	3.566	1.905-6.675	0.000
SII	1.002	1.001-1.002	0.000

CONCLUSION

This study determined that high SII was an independent indicator of the development of CIN in patients who underwent percutaneous peripheral vascular interventions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Prof. Dr. Cemil Taşçıoğlu City Hospital Institutional Ethical Committee (Date: 2022, Decision No: E-48670771-59.99).

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 declare no conflicts of interest.

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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.

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