ORIGINAL ARTICLE

# RELATIONSHIP BETWEEN MODIFIED SYSTEMIC IMMUNE-INFLAMMATION INDEX AND CONTRAST-INDUCED NEPHROPATHY IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

## ST Segment Yükselmeli Miyokard İnfarktüsü Olan Hastalarda Modifiye Sistemik İmmün İnflamasyon İndeksi ile Kontrastın Neden Olduğu Nefropati Arasındaki İlişki

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## ABSTRACT

**Objective:** Developing contrast induced nephropathy after primary PCI in patients with ST segment elevation myocardial infarction is a risky condition in terms of mortality and morbidity. Various studies have shown that the systemic inflammatory index predicts (SII) the development of CIN. Mean platelet volume (MPV) is an important indicator known to be associated with the platelet function and activation. Therefore, we revised SII and named it modified SII (mSII) by using NLR multiply MPV.

**Material and Methods:** This study includes patients who underwent pPCI due to STEMI in our cardiology department between February 2015 and February 2021. Modified SII was obtained by using MPV instead of platelet in the formula (mSII= NLR x MPV). Patients who underwent pPCI with STEMI were divided into two groups, those with CIN and those without CIN, and compared. Informed consent was obtained from all patients.

**Results:** In the logistic regression analysis, it was observed that the mSII, NLR, GFR and contrast medium amount was independent predictor of CIN. The optimal threshold mSII for predicting CIN was >42.5, with a 78.1% sensitivity and 52.3% specificity ([AUC]: 0.639, 95%CI: 0.602- 0.674, p< 0.001). Pairwise comparison of ROC curves, it was observed that the predictive value of mSII for the development of CIN was better than NLR. (z-test = 3.144, P = 0.001)

**Conclusion:** We think that mSII, which we have shown to be superior to SII in predicting the development of CIN and is very easy to calculate, is a parameter that can be considered in predicting the development of CIN after pPCI in STEMI patients.

**Keywords:** *Systemic Inflammatory Index; Nephropathy; Contrast Agent*

## ÖZET

**Amaç:** ST yükselmeli miyokard infarktüsü hastalarında primer PKG sonrası kontrast maddeye bağlı nefropati gelişmesi mortalite ve morbidite açısından riskli bir durumdur. Çeşitli çalışmalar sistemik inflamatuar indeksin (Sİİ) kontrast maddenin indüklediği nefropati (KİN) gelişimini öngördüğünü göstermiştir. Ortalama trombosit hacmi (MPV), trombosit fonksiyonu ve aktivasyonu ile ilişkili olduğu bilinen önemli bir göstergedir. Bu nedenle Sİİ'yi revize ettik ve NLR çarpımlı MPV'yi kullanarak değiştirilmiş Sİİ (mSİİ) olarak adlandırdık.

**Gereç ve Yöntemler:** Bu çalışmaya Şubat 2015 ile Şubat 2021 tarihleri arasında kardiyoloji bölümümüzde ST elevasyonlu miyokard infarktüsü (STEMI) nedeniyle primer perkütanöz girişim (pPKG) uygulanan hastalar dahil edilmiştir. Modifiye Sİİ, formülde trombosit yerine MPV kullanılarak elde edildi (mSİİ= NLR x MPV). STEMI ile pPKG uygulanan hastalar KİN'li ve KİN'siz olmak üzere iki gruba ayrılarak karşılaştırıldı.

**Bulgular:** Lojistik regresyon analizinde mSİİ, NLR, GFR ve kontrast madde miktarının KİN'in bağımsız belirleyicisi olduğu görüldü. KİN'i öngörmek için optimal eşik mSİİ, %78,1 duyarlılık ve %52,3 özgüllük ile >42,5 idi ([AUC]: 0,639, %95CI: 0,602-0,674, p<0,001). ROC eğrileri ikili olarak karşılaştırıldığında mSİİ'nin KİN gelişimini öngörme değerinin NLR'den daha iyi olduğu görüldü. (z testi = 3,144, P = 0,001)

**Sonuç:** KİN gelişimini öngörmede Sİİ'ye üstün olduğunu gösterdiğimiz ve hesaplanması oldukça kolay olan mSİİ'nin, STEMI hastalarında pPKG sonrası KİN gelişimini öngörmede dikkate alınabilecek bir parametre olduğunu düşünüyoruz.

**Anahtar Kelimeler:** *Sistemik İnflamatuar İndeks; Nefropati; Kontrast Madde*

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## INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) remains one of the leading causes of death over the worldwide (1). Primary percutaneous coronary intervention (pPCI) is the primary treatment modality for patients presenting with STEMI (2). Contrast-induced nephropathy (CIN) is defined as acute deterioration of renal function after exposure to contrast agents (3). Although the incidence is variable in studies, CIN has been reported to be 5% to 25% after pPCI (3,4). The incidence of CIN due to pPCI in STEMI patients is higher due to possible hemodynamic instability, the complexity of the procedure, and the lack of precautionary measures (5,6). CIN after pPCI prolongs hospital stay and is associated with increased mortality and morbidity (7).

Various inflammatory markers such as white blood cell count, neutrophil count, procalcitonin, C-reactive protein (CRP) have been shown to be potentially effective in predicting the development of CIN (8,9). In a recent study, systemic inflammatory index (SII) has also been reported as an important marker in predicting the development of CIN (9). SII is obtained by the formula, which is, neutrophil lymphocyte ratio (NLR), multiplied by platelet count (NLR x platelet count). It is known that the platelet function and activation are more important than the platelet count especially those in the normal reference values (10). Mean platelet volume (MPV) is an important indicator known to be associated with the platelet function and activation (11). Therefore, we revised SII and named it modified SII (mSII) by using NLR multiply MPV.

In this study, we aimed to evaluate the association between mSII and CIN, in patients with STEMI undergoing pPCI.

## MATERIAL AND METHODS

This study includes 698 patients who underwent pPCI due to STEMI in our cardiology department between February 2015 and February 2021. Study protocol was approved by the hospital's local ethics committee in accordance with the Helsinki Declaration and Good Clinical Practice Guidelines (Yozgat Bozok University ethical committee, 2024-GOKAEK-245_2024.06.05_17). All patients were followed with daily creatinine test in the hospital for at least 72 hours. Patients with a glomerular filtration rate less than 30 mL/min/1.73 at presentation, active infection, systemic inflammatory disease, history of autoimmune or chronic inflammatory disease, cardiogenic shock or pulmonary edema were excluded from the study.

Demographic and health data of the patients such as age, gender, body mass index (BMI), hypertension (HT), diabetes mellitus (DM), hyperlipidemia, smoking, previous coronary artery disease, heart failure, peripheral artery disease was obtained. A 12-lead electrocardiogram was performed at admission. STEMI was defined as a ST-segment elevation of 1 mm (2 mm for V1-V3) in two or more contiguous leads followed by an increase in cardiac troponins (12). Blood samples were taken at the time of admission, after 24 and 72 hours. Heart rate, systolic blood pressure, diastolic blood pressure, routinely measured glucose, blood urine nitrogen, creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL-C), triglycerides, high-sensitivity C- reactive protein (hsCRP), hemoglobin, neutrophil count, lymphocyte count and platelet count values were recorded. The use of antihypertensive drug or a systolic blood pressure of 140 mm Hg or a diastolic blood pressure of 90 mmHg were accepted as criteria for the diagnosis of hypertension (13). Antidiabetic drug use or fasting plasma glucose higher than 126 mg/dl were accepted as criteria for the diagnosis of Diabetes Mellitus (14). Transthoracic echocardiography was performed for all patients. Left ventricular ejection fraction was calculated by Simpson's method. Any major coronary vessel narrowed by 50% or more in diameter was defined as significant stenosis. Patients were labeled as having multivessel disease if they had more than 50% stenosis in two or more than two pericardial coronary arteries. Complete revascularization was defined as TIMI III flow with less than 20% residual stenosis in the major epicardial coronary arteries. Syntax score was calculated using an online calculator (http: //www. syntaxscore.com). The systemic immune-inflammation index was calculated using the formula, neutrophil count / lymphocyte x platelet count (9). The SII value was calculated using the hemogram parameters obtained at admission. NLR was calculated by dividing the neutrophil count by the

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lymphocyte count. Modified SII was obtained by using mean platelet volume (MPV) instead of platelet in the formula (mSII= NLR x MPV). CIN was defined as according to baseline creatinine level a 25% or 0.5 mg/dl increase in creatinine levels after 72 hours admission, without any other etiology. Patients who underwent pPCI with STEMI were divided into two groups, those with CIN and those without CIN, and compared.

### Statistics

Data analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, IL) and MedCalc statistical software (trial version 12.7.8, Mariakerke, Belgium). Continuous variable data were expressed as mean ± standard deviation. Chi-square test was used for categorical variables and Student's t test was used for continuous variables when evaluating the differences between groups. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. To estimate the risk of CIN and to compare the optimal cut-off point of SII and mSII, a receiver operating characteristic (ROC) curve was constructed, with point sensitivity and specificity determined according to the Youden J index. A multivariate logistic regression model was used to identify independent predictors of CIN. The significant variables that were found to be in the univariate analysis (P < 0.05) were included in a multiple logistic regression analysis. A 2-tailed P <0 .05 was considered as significant.

## RESULTS

A total of 698 patients were included in the analysis between May 2017 through April 2021. A total of 87 patients developed CIN. Clinical, angiographic and demographic characteristics are shown in Table 1. Such as age, gender (female), DM, pain balloon time, ejection fraction, TIMI flow grade, contrast amount, stent length was observed different between the groups, while hyperlipidemia, smoking, obesity, heart rate, systolic and diastolic blood pressure, MI type, infarct related artery was not different between the two groups Laboratory findings are given in Table 2. Baseline creatinine, BUN, glucose, uric acid, neutrophil, MPV, peak troponin, peak CKMB, NLR, SII, mSII were higher while lymphocyte, and GFR was lower in the group developing CIN.

Univariate and multivariate logistic regression analysis results are given in Table 3. In the logistic regression analysis, it was observed that the mSII, NLR, GFR, was independent predictor of CIN. The optimal threshold mSII for predicting CIN was >42.5, with a 78.1% sensitivity and 52.3% specificity (area under the curve [AUC]: 0.639, 95%CI: 0.602- 0.674, p< 0.001). The optimal threshold mSII for predicting CIN was >4.49, with a 73.6% sensitivity and 46.8% specificity (area under the curve [AUC]: 0.589, 95%CI: 0.551-0.625, p=0.003). Pairwise comparison of ROC curves, it was observed that the predictive value of mSII for the development of CIN was better than NLR (z-test= 3.144, p= 0.001) (Figure 1).

## DISCUSSION

In this study, we showed that mSII is a suitable parameter for predicting the development of CIN after pPCI. Accordingly, modified SII emerged as the hematological parameter that independently predicted the development of CIN after pPCI. In the ROC analysis, we observed that mSII had better predictive power than NLR.

In addition to the natural risk factors of the patient, the amount of contrast material used and other physical and chemical markers play a role in the development of CIN (3,6). Acute renal failure is defined as CIN, manifested by a 25% or 0.5 mg/dL (44.2 mmol/L) increase in serum creatinine within 3 days after administration of contrast medium (15). The frequency of CIN in STEMI patients varies between studies (16). Two main mechanisms have been reported for the pathogenesis of CIN: renal vasoconstriction causing medullary hypoxia and direct cytotoxic effects of contrast agents (16,17). Following exposure to contrast media, the effects of various mediators such as angiotensin, vasopressin, and endothelin and the reduction in nitric oxide production (15). Those changes could cause renal vasoconstriction, impaired vasodilation, and decreased medullary blood flow that contributes to the development and progression of CIN (3,6). In studies, STEMI patients who underwent pPCI, a significant relationship was found between parameters indicating inflammatory status such as NLR, SII and the development of CIN (9). In our study, we observed a significant relationship between these parameters and CIN.

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**Table 1.** Clinical and Demographic characteristics of groups

| Variables | | Group 1 (n=611) | Group 2 (n=87) | p value |
|---|---|---|---|---|
| Age, years, (mean) | | 57.4±11.8 | 63.7±12.2 | **<0.001** |
| Female sex, n (%) | | 104(17.0) | 23(26.4) | 0.033 |
| Hypertension, n (%) | | 277(45.3) | 47(54.0) | 0.128 |
| Dyslipidemia (%) | | 273(44.3) | 35(35.6) | 0.079 |
| Diabetes mellitus, n (%) | | 118 (19.3) | 31(35.6) | **0.001** |
| Family History (%) | | 141(23.1) | 21(24.1) | 0.826 |
| Body mass index | | 28±3.1 | 27.1±4.1 | 0.143 |
| Heart rate (bpm) | | 75±14 | 73± 19 | 0.156 |
| History of CAD (%) | | 68(11.1) | 11(12.1) | 0.677 |
| History of PCI (%) | | 65(10.6) | 12(13.6) | 0.380 |
| History of CABG (%) | | 19(3.1) | 4(4.6) | 0.467 |
| History of PAD (%) | | 57(9.3) | 6(6.9) | 0.080 |
| Smoking, n (%) | | 342(56.0) | 40(46.0) | 0.080 |
| Systolic blood pressure (mmHg) | | 78±17 | 75±24 | 0.357 |
| Diastolic blood pressure (mmHg) | | 132±27 | 129±39 | 0.372 |
| Ejection fraction (%) | | 48.5±7.4 | 44.5±9.0 | **<0.001** |
| MI pattern | anterior | 272(44.5) | 38(43.7) | 0.564 |
| inferior | 320(52.4) | 48(55.2) | | |
| Non anterior | 19(3.1) | 1(1.1) | | |
| IRA | LMCA | 1(0.2) | - | 0.680 |
| | LAD | 281(46) | 37(42.5) | |
| | CX | 95(15.5) | 14(16.1) | |
| | RCA | 219(35.8) | 36(41.4) | |
| | Other | 11(1.8) | - | |
| Paint to PCI time (minute) | | 170±113 | 177±101 | 0.591 |
| Contrast medium amount (ml) | | 179±48 | 205±68 | <0.001 |
| Stent size (mm) | | 3.0±0.3 | 3.0±0.4 | 0.967 |
| Stent length (mm) | | 20.7±7.9 | 17.6±7.8 | 0.001 |
| Syntax score | | 15.5±6.6 | 17.6±7.8 | <0.001 |
| TIMI flow <3 (%) | | 45(7.4) | 14(16.1) | 0.006 |
| Asa n (%) | | 73(11.9) | 9(10.3) | 0.664 |
| Beta blocker n (%) | | 83(13.6) | 19(21.8) | 0.060 |
| Statin n (%) | | 132(21.6) | 12(13.8) | 0.118 |
| RAS blocker n (%) | | 139(22.7) | 22(25.3) | 0.599 |
| Calcium channel blocker (%) | | 39(6.4) | 7(8.0) | 0.559 |

CX: circumflex artery, IRA: infarct related artery, LM: left main, LAD: left ascending artery, MI: myocardial infarction, PAD: peripheral artery disease, PCI: percutaneous coronary intervention, RCA: right coronary artery, RAS: renin-angiotensin system, CAD: coronary artery disease, bpm: beats per minute, mm: milimeter, ml: milileter, TIMI: Thrombolysis in Myocardial Infarction.

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**Table 2.** Findings during the admission and process characteristics

| Variables | Group 1 (n=611) | Group 2 (n=87) | p value |
|---|---|---|---|
| BUN (mg/dL) | 32.4±11.1 | 44.3±23.1 | <0.001 |
| Initial creatinine | 0.9±0.2 | 1.1±1.1 | **<0.001** |
| 72thhour creatinine (mg/dL) | 0.95±0.2 | 1.7±0.8 | **<0.001** |
| Glomerular filtration rate mL/min/1.73m$^2$ | 90.0±22.3 | 69±33.9 | **<0.001** |
| Glucose(mg/dL) | 142±67 | 169±83 | 0.001 |
| Uric acid | 4.9±1.1 | 6.1±1.7 | **<0.001** |
| Hemoglobin(g/dL) | 13.7±1.6 | 13.2±2.1 | **0.112** |
| White cell count ($10^3$/mL) | 11.7±3.3 | 12.6±4.2 | **0.018** |
| Neutrophil count ($10^3$/mL) | 9.0±2.7 | 9.7±2.6 | 0.035 |
| Lymphocyte count ($10^3$/mL) | 1.9±0.7 | 1.8±0.7 | 0.041 |
| NLR | 5.1±2.2 | 5.6±2.0 | **0.029** |
| Platelet count ($10^3$/mL) | 254±60 | 259±57 | 0.469 |
| hs-CRP | 11±9 | 16±12 | **<0.001** |
| Mean platelet volume | 8.9±1.0 | 9.2±1.2 | **0.011** |
| Total cholesterol (mg/dL) | 178±41 | 169±47 | 0.099 |
| HDL-C (mg/dL) | 36±10 | 34±11 | 0.244 |
| LDL-C (mg/dL) | 117±37 | 109±42 | **0.109** |
| Triglycerides (mg/dL) | 133±83 | 115±77 | **0.089** |
| CKMB peak | 195±145 | 265±245 | **<0.001** |
| Troponin at peak | 93±87 | 132±116 | **<0.001** |
| SII | 1197±436 | 1327±393 | **0.009** |
| Modified SII | 45.9±21.6 | 54.8±21.4 | **<0.001** |

BUN, blood urea nitrogen; HDL, high-density lipoprotein; hs-CRP, high- sensitivity C-reactive protein; LDL, low-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; RAS, renin–angiotensin system; SII, systemic immune-inflammation index; mg/dL, miligram/deciliter; mL/min, mililiter/minute;

**Table 3.** Univariate and multivariate analysis for prediction of contrast induced Nephropathy

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | B | 95%CI | p value | OR | 95%CI | p value |
| Diabetes mellitus | 0.432 | 0.267-0.701 | 0.001 | | | |
| Sex | 0.571 | 0.339-0.961 | 0.035 | | | |
| Age | 1.043 | 1.024-1.062 | 0.001 | | | |
| GFR | 0.966 | 0.957-0.976 | <0.001 | 0.969 | 0.957-0.982 | **0.001** |
| Glucose | 1.004 | 1.002-1.007 | 0.001 | | | |
| Ejection fraction | 0.937 | 0.911-0.964 | 0.001 | | | |
| Syntax score | 1.043 | 1.011-1.076 | 0.009 | | | |
| NLR | 1.113 | 1.010-1.226 | 0.030 | 0.467 | 0.304-0.717 | **0.001** |
| Modified SII | 1.017 | 1.008-1.027 | <0.001 | 1.074 | 1.036-1.114 | **<0.001** |
| SII | 1.001 | 1.000-1.076 | 0.009 | | | |
| hs-CRP | 1.038 | 1.019-1.057 | <0.001 | | | |
| Troponin at peak | 1.004 | 0.998-1.045 | 0.004 | | | |
| Contrast medium amount | 1.013 | 1.010-1.117 | <0.001 | 1.014 | 1.010-1.018 | **0.001** |

GFR, Glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; hsCRP, high- sensitivity C-reactive protein

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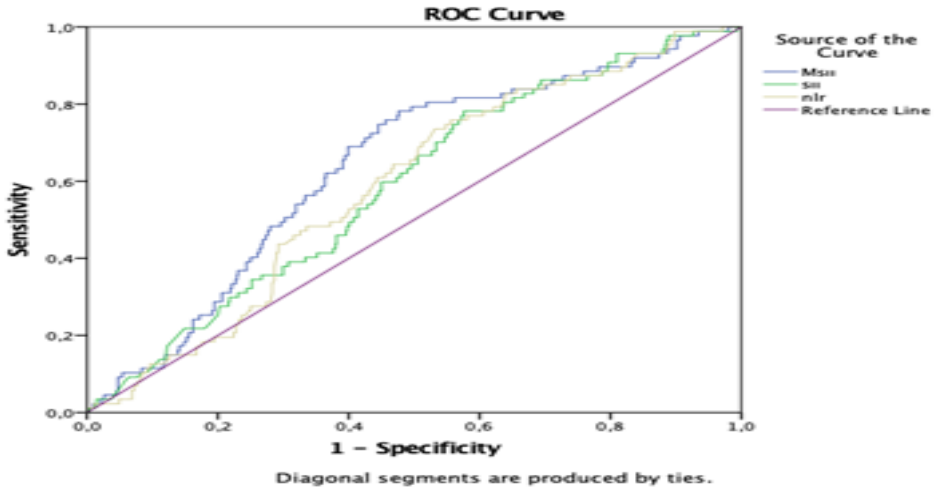


**Figure 1.** The comparison of the area under the curves (AUC) of ROC curve analyses for modified SII and NLR

Neutrophil, lymphocyte, and platelet counts are biomarkers that inexpensive and easy-to-measure. SII is derived using the formula neutrophil count / lymphocyte count x platelet count; is a recently derived biomarker that had shown to reflect inflammatory and immune balance in cardiovascular diseases (7,8,18,19). It is a known situation that there is no significant relationship between platelet count and activation if platelet count is in normal range (19). Once more, in various studies, there was no significant relationship between platelet count and cardiovascular events, but it was observed that this relationship was evident with MPV (18,19). Mean platelet volume (MPV) is an easy to measure marker reflecting platelet activation or reactivity. Larger platelets are enzymatically and metabolically more active and have a higher potential thrombotic ability as compared with smaller platelets (20,21). MPV is an important predictive and prognostic indicator in cardiovascular disease (22). Large platelets have a higher thrombosis potential (6). Increasing MPV values have been accepted as an independent risk factor for myocardial Infarction (MI) and stroke (22,23). In addition, it has been seen that increased MPV is associated with recurrent ischemia and mortality (24). For this reason, we obtained the modified mSII by using MPV instead of the platelet count used in obtaining SII in our study and evaluated its relationship with CIN. In our analysis, we observed that the newly obtained mSII is a superior parameter to NLR and SII in showing CIN.

Diabetes mellitus has been reported to be an independent risk factor for CIN in many studies, this increased risk is most likely due to microvascular damage caused by DM (18,19,25,26). In our study, we determined that DM independently predicted CIN, supporting previous literature findings. Various studies have also shown a relationship between lower ejection fraction and GFR and the development of CIN (27-28). Our findings also support these results.

An important limitation of our study is that it has a single-center and retrospective design. The limited number of patients and the lack of long-term follow-up of the patients are another limitation. Prospective and long-term follow-up studies are needed in a larger population.

## CONCLUSION

In this study, a significant correlation was found between the mSII calculated at admission and the development of CIN after pPCI in STEMI patients. This relationship was shown to be better than NLR, SII, which was previously known to have a significant relationship with CIN. This finding suggests that pre-procedural mSII may help predict the risk of developing CIN in patients with STEMI. Accordingly, we suggest that mSII, which we have shown to be superior to SII in predicting the development of CIN and is very easy to calculate, to take precautions for the development of CIN before and after pPCI in STEMI patients.

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