

## PAPER DETAILS

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# The role of the systemic inflammatory response index (SIRI) in the prediction of chronic total occlusion: useful or not?

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## ABSTRACT

**Aims:** Inflammation is very important in the pathogenesis of atherosclerosis and coronary artery disease (CAD). Chronic total occlusion (CTO) is a chronic form of CAD and is common in patients with severe CAD. The aim of this study was to determine the association of the systemic inflammatory response index (SIRI), a marker of inflammation, with CTO.

**Methods:** Our study was retrospective and included 100 CAD patients with CTO and 100 CAD patients without CTO. SIRI was compared between the two groups.

**Results:** Among the basic clinical and laboratory characteristics of the patients, age, white blood cell, and neutrophil counts were statistically higher in the CTO group ( $p=0.044$ ,  $p=0.044$ ,  $p=0.036$ , respectively). SIRI parameters were similar between the groups, and no statistical difference was observed ( $p=0.111$ ). According to the ROC analysis, the optimum cut-off value for SIRI was  $>1040$  (sensitivity 70.0% and specificity 44.0%).

**Conclusion:** SIRI is not a useful predictor for the detection of CTO.

**Keywords:** Systemic inflammatory response index, chronic total occlusion, coronary artery disease

## INTRODUCTION

Cardiovascular diseases (CVD) are the major cause of death worldwide in 2020.<sup>1</sup> Therefore, early detection of coronary artery disease (CAD) is important, and coronary angiography is the main diagnostic modality. Chronic total obstruction (CTO) is a common finding on coronary angiography and refers to total occlusion of at least one epicardial artery for more than 3 months and the absence of blood flow in the distal part of the vessel.<sup>2</sup> In one study, approximately 1/3 of patients undergoing coronary angiography (CAG) had CTO.<sup>3</sup> In a study by Christofferson et al.<sup>4</sup> 52% of patients with severe CAD had one CTO, and 12% had more than one CTO. Intervention in vessels with CTO requires an experienced and trained operator, along with the variety and adequacy of the materials used for successful revascularization. Therefore, pre-procedural planning becomes important. The ACC/AHA guideline recommends intervention for CTO in patients with persistent angina despite revascularization of all other non-CTO vessels and optimal medical therapy if the coronary anatomy is suitable for revascularization (class 2b).<sup>5</sup> Therefore, it becomes very important to find predictive markers for CTOs with limited indications for

intervention and difficult revascularization compared to other vessels. One study emphasized the importance of evaluating the inflammatory status in selecting low-risk CTO patients for intervention.<sup>6</sup>

In recent years, many studies have shown the relationship between atherosclerosis and inflammation. For example, neutrophil-to-lymphocyte ratio (NLR), erythrocyte distribution width (RDW), and systemic inflammatory index (SII) parameters, which are indicators of inflammation, have been associated with CAD,<sup>7-10</sup> and a significant association with CTO has also been shown.<sup>11-14</sup> Another inflammatory marker, the systemic inflammatory response index (SIRI), is also associated with CAD, and its elevation has been associated with three-vessel disease.<sup>10</sup>

Considering that CTO is more common in patients with chronic-severe CAD and the association of other inflammatory parameters with CTO, it is not far from the mind that SIRI may be associated with CTO. In addition, we did not find any studies in the literature on the relationship between SIRI and CTO. Therefore, we planned this study with the hypothesis that SIRI may be a good predictor of CTO.

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## METHODS

The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 17.01.23, Decision No: 780). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study was retrospective and included all patients over the age of 18 years who were admitted to the cardiology outpatient clinic between 1/2022 and 12/2022 with stable angina pectoris and who underwent coronary angiography. Patients under 18 years of age, history of acute coronary syndrome, history of previous by-pass operation, history of chronic renal and hepatic failure, history of known inflammatory and rheumatologic diseases, history of known malignancy, history of known anemia (Hb <13 g/dl (male), Hb <12 g/dl (female)), blood transfusion in the last three months, and active infection were excluded.

A total of 200 patients with coronary artery disease who met the inclusion criteria were included in the study. For the CTO group, 100 consecutive patients with 100% stenosis in at least one epicardial artery and for the control group, 100 consecutive patients with coronary artery disease but without 100% occlusion in any epicardial artery were selected.

In all patients, CAG was performed using the Judkins technique with multiple projections using 6 or 7 French (F) catheters through the right or left femoral approach. Iopromide (Ultravist-370®) or Iohexol (Omnipaque® 350 mg/mL) were used as opaque agents. CTO was defined as 100% occlusion of at least one epicardial artery for more than 3 months and the absence of blood flow distal to the vessel.<sup>2</sup> The results of all patients' CAGs were evaluated by two experienced cardiologists.

Blood samples for laboratory examination were collected from the antecubital vein before angiography and after a 12-hour fasting period between 08.00-10.00 hours. A comprehensive metabolic panel and complete blood count (neutrophils, lymphocytes, monocytes, platelets, hemoglobin, RDW, low-density lipoprotein, high-density lipoprotein cholesterol, and triglycerides) were evaluated. With these results, SIRI was calculated by multiplying the number of platelets by the number of neutrophils and dividing by the number of lymphocytes, and SII was calculated by multiplying the number of monocytes by the number of neutrophils and dividing by the number of lymphocytes.

### Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) and MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd., Ostend, Belgium). Descriptive

statistics were given as the number of units (n), percentage (%), mean, and standard error. Pearson chi-square analysis was used to compare categorical variables. Homogeneity of variances, one of the prerequisites of parametric tests, was checked by the "Levene" test. The normality assumption was checked with the "Shapiro-Wilk" test. When the differences between the two groups were to be evaluated, the "Student's t Test" was used when the parametric test preconditions were met, and the "Mann Whitney-U test" was used when they were not met. The performance of RDW, SIRI, and SII parameters in predicting CTO was evaluated by Receiver Operating Characteristic (ROC) curve analysis.  $p < 0.05$  was considered statistically significant.

## RESULTS

In the CTO group, the number of patients with CTO in 1 vessel was 87, while the number of patients with CTO in more than 2 vessels was 13. CTOs were most frequently observed in the right coronary artery, with 52 CTOs. This was followed by the left coronary artery with 32 and the circumflex artery with 31.

Basic clinical and laboratory characteristics of the patients are presented in [Table 1](#). Patients in the CTO group were found to be older ( $p=0.044$ ). White blood cell and neutrophil counts were also statistically higher in the CTO group ( $p=0.044$ ,  $p=0.036$ , respectively).

	Non-CTO group n=100	CTO group n=100	p
Age	60±8.56	62.41±9.19	0.044
Sex (F/M) n (%)	25 (58.1)/75 (47.8)	18 (41.9)/82 (52.2)	0.228
Body mass index	29.64±4.2	29.64±3.68	0.892
Hypertension, n (%)	48 (48.5)	51 (51.5)	0.671
Diabetes mellitus, n (%)	40 (50.0)	40 (50.0)	0.999
Hyperlipidemia, n (%)	41 (50.6)	40 (49.4)	0.885
Coronary artery disease, n (%)	32 (46.4)	37 (53.6)	0.457
Glucose	154.34±74.4	143.43±64.47	0.324
GFR	88.48±13.84	84.64±15.31	0.109
LDL	120.57±34.1	127.28±40.46	0.256
TG	208.74±86.98	216.09±111.84	0.832
HDL	40.76±10.18	39.66±12.1	0.426
WBC	7628.7±1831.26	8157±1859.12	0.044
Hb	14.97±1.37	15.08±1.28	0.568
Platelets	260.97±65.49	255.44±62.9	0.543
Neutrophil	4554.5±1402.21	4991.8±1475.48	0.036
Lymphocyte	2249.3±728.26	2308.4±775.5	0.741
Monocyte	584.7±175.81	625.7±206.63	0.166

GFR: Glomerular filtration rate, Hb: Hemoglobin, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglycerides, WBC: White blood count.

**Table 2** shows the comparison of SIRI, SII, and RDW parameters of these groups, and no statistical difference was observed ( $p=0.111$ ,  $p=0.404$ ,  $p=0.507$  respectively).

	Non-CTO group n=100	CTO group n=100	p
SIRI	1355.7±933.04	1529.57±1024.94	0.111
SII	590.22±343.21	607.83±305.55	0.404
RDW	13.18±1.09	16.74±1.97	0.507

RDW: Red cell distribution width, SII: Systemic Inflammatory Index, SIRI: Systemic Inflammatory Response Index.

**Table 3** shows the performance of these parameters in predicting CTO. The optimum cut-off value for SIRI was >1040 (sensitivity 70.0% and specificity 44.0%), the optimum cut-off value for SII was >483 (sensitivity 65.0% and specificity 47.0%), and the optimum cut-off value for RDW was >13.3, (sensitivity 25.0% and specificity 85.0%).

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)
SIRI	0.565 (0.493-0.635)	0.109	>1040	70.0 (60.0-78.8)	44.0 (34.1-54.3)
SII	0.534 (0.462-0.605)	0.406	>483	65.0 (54.8-74.3)	47.0 (36.9-57.2)
RDW	0.527 (0.455-0.598)	0.508	>13.3	25.0 (16.9-34.7)	85.0 (76.5-91.4)

RDW: Red cell distribution width, SII: Systemic Inflammatory Index, SIRI: Systemic Inflammatory Response Index.

## DISCUSSION

The main conclusion of our study is that SIRI is useless as a predictor of CTO in patients with stable CAD.

The underlying mechanism of CAD is atherosclerosis. Atherosclerosis has a very complex and incompletely elucidated pathophysiology. Clinical and experimental studies have shown that inflammation plays a critical role in atherosclerosis and CAD.<sup>15</sup> The inflammation that causes atherosclerosis involves various mediators, particularly monocytes and cholesterol particles. During the development of atherosclerotic plaque, monocytes expressed in damaged endothelium are activated by binding to adhesion molecules.<sup>16</sup> The activated monocytes then migrate to the arterial intima, where they differentiate into macrophages and form foam cells characteristic of atherosclerosis by phagocytosis of modified lipoproteins and lipid loading.<sup>17</sup>

Neutrophils and lymphocytes, other elements of the immune system, are also active in atherosclerosis. Neutrophils mediate the inflammatory reaction by

releasing numerous bioactive substances, such as arachidonic acid metabolites and platelet-inhibiting factors,<sup>18</sup> leading to the progressive development and fragility of the plaque.<sup>19</sup> On the other hand, lymphocytes have also been shown to be important for the development of atherosclerosis.<sup>20,21</sup> Therefore, the monocytes, neutrophils, and lymphocytes used to calculate the SIRI are important components of the inflammatory and atherosclerotic processes.

SIRI is a relatively new parameter and is considered an indicator of inflammation. This parameter was first used in cancer patients, and it was demonstrated that it could be used to predict the survival of patients with pancreatic adenocarcinoma receiving chemotherapy.<sup>22</sup> In the following years, its relationship with CAD was also investigated. In one study, SIRI was found to be significantly elevated in patients with severe CAD.<sup>10</sup> In another study, SIRI elevation was found to be associated with single-vessel and complex coronary artery disease.<sup>23</sup> Inflammatory markers, such as SII and RDW, have been the subject of interest in CAD-related studies. Different studies have found a significant association between elevated SII and CAD severity.<sup>9,24,25</sup> RDW have also been found to be associated with the presence of CAD and CAD severity in patients with stable angina pectoris.<sup>8</sup>

CTO is a chronic-advanced form of CAD and occurs against a background of atherosclerosis. Since inflammation plays an important role in the pathogenesis of atherosclerosis, the association of inflammatory parameters such as SII and RDW with CTO has also been investigated. SII has been shown to be an easy and practical indicator for identifying high-risk CTO patients.<sup>14</sup> RDW has been shown to be associated with infarct-related artery (IRA)-CTO<sup>12</sup> and non-IRA-CTO<sup>13</sup> in patients with acute coronary syndrome (ACS) and has also been independently correlated with inadequate coronary collateral circulation in patients with stable CAD.<sup>26</sup>

Based on previous studies, it is possible to conclude that SII and RDW have a close relationship between CAD and CTO. In our study, we predicted that SIRI, which has been correlated with the presence and severity of CAD, would also show a positive correlation with CTO. According to the data we obtained, SIRI was higher in the group with CTO compared to the group without CTO. However, this elevation was not statistically different. Moreover, not only SIRI but also SII and RDW did not reach statistical significance in CTO patients compared to non-CTO patients.



In contrast to previous studies, the lack of a significant association between RDW and CTO may be due to the difference in the study population. The patient group selected in our study was stable CAD, while previous studies showing the relationship between RDW and CTO were performed in patients with acute coronary syndromes.<sup>12,13</sup> Therefore, a significant relationship between CTO and RDW may have been found due to the physiopathological process of ACS. Similarly, in the study with SII and CTO, the study group was different from our study.<sup>14</sup> The patient group selected for CTO was highly heterogeneous and included patients with ACS, stable CAD and previous bypass surgery. In addition, this study emphasized the relationship between SII and high-risk CTO rather than the relationship between CTO and SII.

The failure of SIRI and other parameters to detect CTO in our study suggests that the level of inflammation in CTO patients may not be higher than in non-CTO patients. In a previously published study, it was reported that the main pathophysiological basis of CTO is soft plaque rupture, followed by thrombotic coronary occlusion and organization of thrombotic material, and to a lesser extent, progression of partial atheroma plaque.<sup>27</sup> Therefore, although CTO develops in the background of atherosclerosis, the basic physiopathologic process may not be inflammation. We think that this is the reason why SIRI and other parameters were not found to be predictors of CTO in our study.

### Limitations

This study has some limitations that should be considered. First of all, the most important limitation was that it was a retrospective study conducted at a single center. In addition, due to the retrospective design of the study, although broad exclusion criteria were used, all other factors that may affect these parameters may not have been revealed. Finally, high-sensitivity C-reactive protein (hsCRP), an inflammatory marker that provides prognostic information in predicting cardiovascular events, was not included in the study.<sup>28</sup> A clearer result could have been obtained by correlating hsCRP values with other inflammatory parameters, especially SIRI. We think that prospective studies, including hsCRP along with all inflammatory parameters and with a larger number of patients, are needed.

### CONCLUSION

Although SIRI is valuable in predicting the severity of CAD, the same is not true for CTO. The main conclusion from our study is that SIRI is an inflammatory predictor that is not useful in the detection of CTO.

### ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 17.01.23, Decision No: 780).

**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 have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**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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