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OLD COMPLICATION, NEW MARKER: RELATIONSHIP BETWEEN SYSTEMIC IMMUNE INFLAMMATORY INDEX AND POST-PERICARDIOTOMY SYNDROME.

Sercan ÇAYIRLI[a], Berk MUTLU[b], Ömer Faruk RAHMAN[c], Sevil GÜLAŞTI[d], Selim DURMAZ[e], Hasan GÜNGÖR[f]

[a]Sirnak Silopi State Hospital, Clinic of Cardiology, Sirnak, Türkiye.

[b,d,f]Aydın Adnan Menderes University, Faculty of Medicine, Department of Cardiology, Aydın, Türkiye.

[c]Burdur State Hospital, Cardiovasculer Surgery Clinic, Burdur, Türkiye.

[e]Aydın Adnan Menderes University, Faculty of Medicine Department of Cardiovasculer Surgery, Aydın, Türkiye.

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[a]https://orcid.org/0000-0001-9660-9993
[b]https://orcid.org/0000-0002-4285-1722
[c]https://orcid.org/0000-0002-4248-2867
[d]https://orcid.org/0000-0002-7640-1295
[e]https://orcid.org/0000-0001-5618-3270
[f]https://orcid.org/0000-0002-4462-3029

*Correspondence: Sercan ÇAYIRLI

Sirnak Silopi State Hospital, Clinic of Cardiology, Sirnak, Türkiye.

e-mail: sercan_cayirli@hotmail.com

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ABSTRACT

Background: Post-pericardiotomy syndrome (PPS) is a common complication after cardiovascular surgery. Post-operative hospitalizations are prolonged due to PPS and mortality is increased due to pericardial effusion leading to cardiac tamponade. Studies have shown that inflammation plays a role in etiology.

Objectives: The systemic immune-inflammation index (SII) is a new non-invasive marker that has been shown to be effective in predicting inflammatory diseases. In our study, we aimed to investigate the association between the development of PPS and SII in patients undergoing open-heart surgery

Methods: Patients who underwent elective open-heart surgery at our institution between 2017 and 2022 were retrospectively studied. Patients who developed PPS and patients who did not develop PPS were included as two different groups in the study. We investigated whether there was a significant difference between the two groups in terms of SII.

Results: A total of 228 patients were enrolled in the study, 132 in the patient group and 96 in the control group. The mean age was 63.48 years in the patient group and 65.09 years in the control group and no statistically significant difference was found (p 0.34). There were also no significant differences between the two groups in terms of gender (p 0.47), hypertension (p 0.22), hyperlipidemia (p 0.66), coronary artery disease (p 0.76), diabetes (p 0.023), smoking (p 0.35), and chronic obstructive pulmonary disease (p 0.49). The median value for SII was 568.91 (530.17) in the patient group and 634.79 (613.23) in the control group, and no significant difference was found between the groups (p 0.208). Statistically significant differences were found in hemoglobin (p 0.03), hematocrit (p 0.02), and glucose (p 0.018) values between both groups.

Conclusion: The SII is not a useful parameter for predicting post-pericardiotomy syndrome. Comprehensive studies with larger patient populations including subgroup analyzes are needed in this regard.

Key Words: Post-pericardiotomy syndrome, inflammation, bypass

1. INTRODUCTION

Post-pericardiotomy syndrome (PPS), first described in 1950, is now a common complication in patients undergoing open-heart surgery. It has been reported to occur at a rate of 21% to 29% in several case series (1). Although the prognosis is generally considered clinically favorable, pleural and pericardial effusion caused by the syndrome may result in prolonged hospitalization and thus increase the cost burden. Although the etiology of the syndrome has remained a mystery since its inception, recent studies have led to the hypothesis that the disease develops as a result of immune-mediated inflammation. This hypothesis is supported by the finding of elevated levels of neutrophils, leukocytes, erythrocyte sedimentation rate, and C-reactive protein (CRP), which are commonly used as inflammatory markers, in the peripheral blood of patients with the syndrome in several retrospectively studied case series (2).

In recent years, the systemic immune-inflammation index (SII) has been a step ahead of markers commonly used in the diagnosis and follow-up of inflammatory diseases. This marker, first used by Hu et al. in 2014, is calculated by multiplying the number of platelets from peripheral blood by the number of neutrophils and dividing by the number of lymphocytes [SII: (platelets x neutrophils) /

lymphocytes] (3,4). SII, which has been found to be associated with prognosis in many cancer and vasculitis types, is promising in this regard (8,9). Recently, its effects on predicting mortality in patients with chronic coronary syndrome and infective endocarditis have been studied, and it has been used in cardiology (5,6).

We did not find any study in the literature that investigated the association between PPS and SII. In this study, we aimed to investigate the association between SII, a promising marker of inflammation, and PPS in which inflammation is thought to play a role in the etiology.

2. MATERIALS and METHODS

Patients who underwent elective open-heart surgery at our institution between 2017 and 2022 were retrospectively reviewed. Patients who developed PPS and patients who did not develop PPS were included as two different groups in the study. All patients who were followed up after discharge and developed early and late PPS were included in the study. Patients who received a preoperative blood transfusion, patients with active infection, patients who underwent emergency open heart surgery, patients with a history of inflammatory disease, patients with a history of malignant disease, and patients who were already receiving anti-inflammatory therapy were excluded from the study. Our study was approved by the Ethics Committee for Noninterventional Scientific Studies at our institution on 10.06.22 with the decision numbered E-53043469-050.04.04-181181.

Basic demographic characteristics and preoperative medical treatments were recorded. Patients with a systolic blood pressure of >140/90 measured more than twice in the office or who were on antihypertensive treatment were classified as having a history of hypertension. Diabetic patients were defined as patients with a blood glucose >126 mg/dl or on antidiabetic treatment. A history of hyperlipidemia was defined as low-density lipoprotein cholesterol (LDL) >160 mg/dl or total cholesterol >240 mg/dl or triglyceride levels >200 mg/dl or high-density lipoprotein cholesterol (HDL) < 40 or on lipid-lowering medication.

2.1. Diagnosis of the post-pericardiotomy syndrome

Patients were screened and evaluated for eligibility by two different investigators, a cardiologist and a cardiovascular specialist. According to the 2015 European Society of Cardiology Diagnosis and Treatment Algorithm, patients with at least two of the following criteria were classified as PPS: 1) patients with fever without an alternative diagnosis, 2) patients with pericardial or pleural chest pain, 3) patients with pericardial friction rub, 4) patients with pericardial effusion, 5) patients with pleural effusion with elevated inflammatory markers. In addition, patients who were treated with non-steroidal anti-inflammatory drugs and colchicine according to current treatment algorithms after diagnosis and showed clinical improvement and regression of symptoms were also considered as PPS and included in the study.

2.2. Calculation of the systemic immune-inflammation index

The preoperative routine complete blood count values of the patients included in the study were recorded. Using the platelet, neutrophil, and lymphocyte values, the platelet and neutrophil values were multiplied and divided by the lymphocyte values to calculate the SII value.

2.3. Statistical analysis

Statistical analysis was performed with the SPSS 26.0 program (SPSS Inc. Chicago, IL). Parametric tests were used to analyze the data that conformed to the normal distribution, and nonparametric tests were used to analyze the data that did not conform to the normal distribution. Descriptive statistics (number, percentage, mean, standard deviation, median, and IQR [interquartile range]), T-test, Man-Whitney U, and chi-square tests were used to analyze the data. A p-value of < 0.05 was considered statistically significant.

Table 1. Table including demographic and background data of the patients. COPD (chronic obstructive pulmonary disease). PPS (post-pericardiotomy syndrome)

		PPS (n=132)		Control (n=96)		p-value
Age (mean±ss)		63.48 ± 13		65.09 ± 12.07		0.34
Sex (n. %)						0.47
	Male	86	65.2	67	69.8	
	Female	46	34.8	29	30.2	
Hypertension (n. %)		55	41.7	48	50	0.22
Coronary artery disease (n. %)		34	25.8	27	28.1	0.76
Hyperlipidemia (n. %)		43	32.6	28	29.2	0.66
Diabetes mellitus (n. %)		32	24.1	31	32.3	0.23
COPD (n. %)		4	3	5	5.2	0.49
Smoking (n. %)		47	35.6	41	42.7	0.35

3. RESULTS

A total of 228 patients, 132 in the PPS group and 96 in the control group, were enrolled in the study. The mean age was 63.48 ± 13 years in the PPS group and 65.09 ± 12.07 years in the control group and no statistically significant difference was found (p 0.34). There were also no significant differences in gender (p 0.47), hypertension (p 0.22), hyperlipidemia (p 0.66), coronary artery disease (p 0.76), diabetes (p 0.23), smoking (p 0.35), and chronic obstructive pulmonary disease (p 0.49) between the two groups. Patient demographics and background data are summarized in Table I.

All patients who participated in the study were also evaluated for preoperative medication use. When both groups were analyzed, it was found that the use of clopidogrel was higher in the patients who developed PPS than in the control group (p 0.01). Data on this comparison are summarized in Table II.

The groups were compared in terms of complete blood count and biochemical parameters routinely checked preoperatively. Statistically significant differences were observed in hemoglobin (gm/dl) (p 0.03), hematocrit (%) (p 0.02), and glucose (mg/dl) (p

Table 2. Table of preoperative medication use of the patients who participated in the study. PPS (post-pericardiotomy syndrome). ARB (Angiotensin Receptor Blocker). ACE (Angiotensin Converting enzyme). Ca (calcium)

	PPS (n=132)		Control (n=96)		p-value
Acetylsalicylic acid (n. %)	68	%51.5	48	%50	0.89
Clopidogrel (n. %)	28	%21.2	8	%8.3	**0.01**
Warfarin (n. %)	8	%6.1	5	%5.2	0.51
NOAK (n. %)	2	%1.5	1	%1	1
Beta-Blocker (n. %)	77	%58.3	63	%65.6	0.27
ACE inhibitors (n. %)	28	%21.2	16	%16.7	0.49
ARB (n. %)	17	%12.9	12	%12.5	0.54
Ca channel blocker (n. %)	28	%21.2	12	%12.5	0.11
Statin (n. %)	38	%28.8	23	%24	0.45
Furosemide (n. %)	21	%15.9	19	%19.8	0.48
Spironolactone (n. %)	15	%11.4	8	%8.3	0.51

Table 3. Data regarding the comparison of the groups in terms of complete blood count and biochemical parameters routinely checked preoperatively. *(IQR+median.) ** (mean±ss).

	PPS(n=132)	Control (n=96)	p-value
Glucose (mg/dl)	112 (33.3) *	125 (50) *	**0.018**
Hemoglobin (gm/dL)	12.95 ± 1.93 **	12.18 ± 1.96 **	**0.03**
Hematocrit (%)	39.18 ± 5.21 **	36.91 ± 5.54 **	**0.02**
Na (mmol/L)	138 (4) *	138 (4) *	0.443
K (mmol/L)	4.2 (0.6) *	4.3 (0.5) *	0.539
Ca (mg/dl)	9 (0.5) *	8.94 (0.7) *	0.642
Mg (mg/dl)	1.95 (0.28) *	1.9 (0.29) *	0.546
Urea (mg/l)	32 (13.5) *	32 (15.75) *	0.911
Creatinine (mg/dl)	0.8 (0.2) *	0.8 (0.26) *	0.073
Neutrophil (10^3/mkrL)	4985 (2430) *	5180 (2307.5) *	0.61
Thrombocyte (10^3/mkrL)	248621.21±72332.41**	243477.93±72957.31**	0.598
Leucocyte (10^3/mkrL)	8175 (2910) *	7910 (2765) *	0.991
Basophil (10^3/mkrL)	40 (20) *	40 (27.8) *	0.074
Eosinophile (10^3/mkrL)	175 (197.5) *	150 (185) *	0.407
Lymphocyte (10^3/mkrL)	2065 (1032.5) *	1960 (1010) *	0.073
Monocyte (10^3/mkrL)	605 (257.5) *	555 (305) *	0.19

0.018) values between both groups.

The data relating to this comparison are summarized in Table III. The PPS group and control group were compared with each other in terms of SII (p 0.208), platelet/lymphocyte ratio (PLR) (p 0.33), and neutrophil/lymphocyte ratio (NLR) (p 0.06). No statistically significant difference was found between the two groups in terms of these parameters. The data of this comparison are shown in Table IV and Figure 1.

Table 4. SII (Systemic immune inflammatory index). PLR (Platelet lymphocyte ratio). NLR (Neutrophil Lymphocyte ratio). Analysis was performed with the Mann-Whitney U test.

	PPS (n=132)	Control (n=96)	p-value
SII	568.91 (530.17)	634.79 (613.23)	0.208
PLR	116.86 (68.35)	120 (74.78)	0.33
NLR	2.46 (1.7)	2.74 (2.43)	0.06

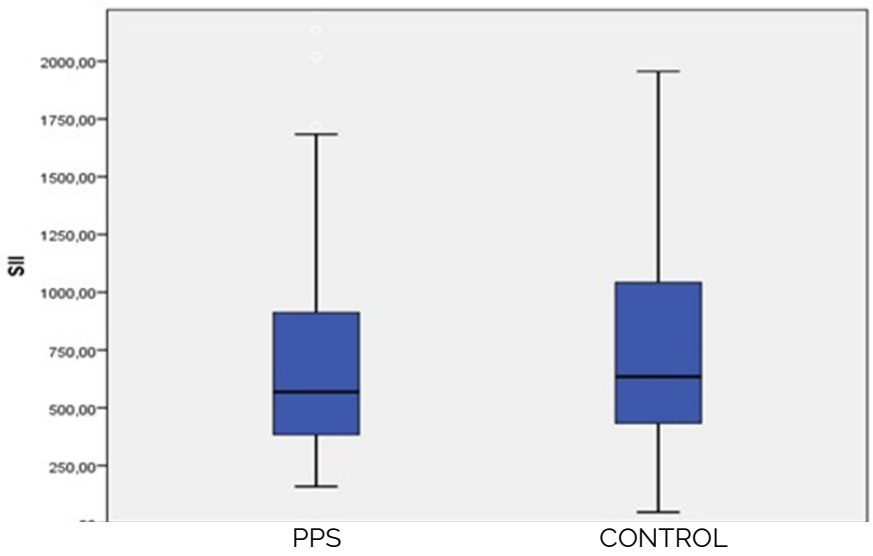

Figure 1. The figure for the comparison of the groups in terms of SII.

4. DISCUSSION

In our study, statistically significant differences were found between groups in clopidogrel use (p 0.01), hemoglobin level (gm/dl) (p 0.03), hematocrit level (%) (p 0.02), and glucose level (mg/dl) (p 0.018). However, when we compared the PPS group with the control group in terms of SII (p 0.208), platelet/ lymphocyte ratio (PLR) (p 0.33), and neutrophil/ lymphocyte ratio (NLR) (p 0.06), no significant difference was found

PPS is one of the most common surgical complications. It has been reported that this syndrome, which is observed in around 10% on average, can be observed in up to 30% in different case series (2). Although it is a complication that has a good prognosis if diagnosed early, delay in diagnosis leads to serious complications that may result in reoperation and death (7). Since it is a common syndrome, many studies have been conducted to investigate under which conditions there is a predisposition to PPS. Among the risk factors, the female gender was found to be the most common factor. The fact that it is generally believed that the pathophysiology of the disease is inflammation mediated by the immune system and the high prevalence of autoimmune diseases in the female sex has led to focus on this topic. Many studies have found an association between the female sex and PPS syndrome (8,9). Another factor is age. Although it is rare in children under 2 years of age, some studies indicate that it peaks in the thirties and decreases with advancing age. There are studies suggesting that an autoimmune response that develops as a result of exposure to immune system stimuli that increase with age may be the responsible pathophysiology (8,10). However, in our study, no significant difference was found between the groups in terms of age and sex.

SII is a popular marker whose association with various diseases has been frequently investigated in recent studies. This marker, first used by Hu et al. in 2014, is calculated by multiplying the number of platelets from peripheral blood by the number of neutrophils and dividing by the number of lymphocytes. After proving useful in predicting mortality in various cancers, its effect has been studied in cardiovascular disease. In a study by Agus et al. that examined its effect in predicting in-hospital mortality in patients with infective endocarditis, the SII was found to be associated with in-hospital mortality (5). In a study by Selçuk et al, 391 patients who underwent isolated coronary artery bypass grafting (CABG) were retrospectively evaluated for the incidence of developing postoperative atrial fibrillation (AF); 97 patients developed postoperative AF and they reported that it was associated with SII. They also found that this marker was superior to the commonly used NLO and PLO (11). There is one study with a large patient population that investigated the association between SII and short- and long-term mortality in patients with the acute coronary syndrome. In this study, Su et al retrospectively studied 4699 patients. As a result of this study, they reported that high SII was associated with 30-day, 90-day, and 1-year mortality rates (12). Our review did not find any study in the literature that examined the association between PPS and SII. We believe our study is important because it is the first study to examine this association and takes the first step in this direction. In our study, no statistically significant association was found between SII and PPS in patients who underwent open heart surgery (p 0.208).

NLO is an older marker and has been frequently investigated in studies. There are studies indicating that it is associated with disease activation in autoimmune diseases such as Sjögren's syndrome, Behçet's disease, and rheumatoid arthritis (13,14,15). An association with cardiovascular disease has also been noted. Ertürk et al. found in a study that NLO was associated with coronary artery disease (16). There are studies suggesting that it is useful for predicting mortality in patients undergoing percutaneous coronary intervention or CABG. Sevuk et al. published a study investigating the association between NLO and PPS. In this study, 72 patients with

PPS and 100 patients without PPS were retrospectively compared. The preoperative and postoperative data of the first complete blood count of the patients were recorded. They found no significant association between NLO and PPS in preoperative values. However, when the postoperative complete blood count data were analyzed, a significant association between NLO and PPS (p 0.01) was found (17). In our study, we also analyzed the relationship between NLO and PPS in preoperative blood counts and found no significant difference (p 0.06), similar to this study.

PLO is another widely used marker associated with SII. There are many studies suggesting that it is associated with inflammation (18). There are studies suggesting that it is also closely associated with cardiovascular diseases. In a previous study from our center, the association between PLO and postoperative AF development was examined. A total of 125 patients who had undergone CABG were retrospectively studied. A statistically significant difference was found between PLO and postoperative AF development (p 0.005) (19). Our review did not find any study in the literature that examined the relationship between PPS and PLO. In our study, the groups were compared in terms of PLO rate, and no significant association was found between PPS and PLO (p 0.33). However, we believe that our study will shed light on further studies on this topic with a larger patient population

Diabetes is one of the biggest problems of our time, affecting the whole world. Studies have reported that serum inflammatory indices are increased in patients with type 2 diabetes and these indices are related to glycosylated hemoglobin (HgbA1c) levels. In a study by Atak et al. that examined 93 patients, PLO was found to be associated with type 2 diabetes and HgbA1c levels (20). In the study FIN-PPS, conducted in Finland, 688 patients who underwent isolated CABG were analyzed. In this study, diabetes was reported to be an independent protective factor against PPS. The authors also stated that this effect might be related to metformin used in diabetes treatment and its anti-inflammatory effect (21). In another study claiming the opposite, Imazio et al. found no significant association between PPS and diabetes (p 0.39) (22). In our analysis, no significant difference was found between groups concerning diabetes history (p 0.23). However, the median value for blood glucose level was 112 (33.3) in the PPS group and 125 (50) in the control group, and this difference was statistically significant (p 0.018).

5. CONCLUSION

Based on the data we obtained, we can say that there is no association between SII and PPS. Given the existing pathophysiological similarities, we believe that multicenter retrospective studies and meta-analyzes with larger patient populations, including subgroup analyzes, are needed.

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Conflicts of Interest: The authors declared that there is no conflict of interest.

Ethical Statement: This study was approved by the Ethics Committee for Noninterventional Scientific Studies at our institution on 10.06.22 with the decision numbered E-53043469-050.04.04-181181.

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