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Research Article

Relationship between C-reactive protein, systemic immune-inflammation index, and routine hemogram-related inflammatory markers in low-grade inflammation

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Abstract

Objectives: The term low-grade inflammation is usually used to indicate chronic conditions in which the findings of classic, clinical inflammation are lacking, but there is an elevated C-reactive protein (CRP) level of 3 to 10 mg/L. Recently, the systemic immune-inflammation index (SII) was developed based on lymphocyte, neutrophil, and platelet counts, which can project the inflammatory and immune imbalances. The aim of this study was to examine the SII and new parameters derived from hemograms to determine if they have the potential to detect patients with subclinical low-grade inflammation in an unselected, elderly, outpatient population.

Methods: The CRP level was analyzed with a BN II System nepholometer (Siemens Healthineers, Erlangen, Germany). Participants were stratified according to CRP level: Group 1 had a serum CRP result <3.0 mg/L and Group 2 had a serum CRP result 3.0-9.0 mg/L. Blood samples that had been analyzed with an automated hematology analyzer (Mindray BC-5800; Mindray Biomedical Electronics Co., Ltd., Shenzhen, China) were selected for evaluation of the results. The SII (neutrophil x platelet / lymphocyte), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) were calculated.

Results: The cumulative results of 179 unselected outpatients aged 45 years or older were evaluated. The SII (431 [interquartile range {IQR}: 326] vs 535 [IQR: 291]; p=0.049) and PLR (117 [IQR: 38] vs 126 [IQR: 58]; p=0.031) values were significantly high in Group 2 compared with Group 1. A statistically significant correlation between the SII and the NLR (r=0.807; p<0.001), PLR (r=0.773; p<0.001), and the platelet count (r=0.653; p<0.001) was found. However, there was no correlation between the CRP, SII (r=-0.312; p=0.210), and PLR (r=-0.165; p=0.117).

Conclusion: A high PLR and SII appears to be associated with subclinical low-grade inflammation. These data do not support hematological screening parameters as a substitute for CRP. These findings are limited to the cohort studied here, and may not be entirely applicable to other ethnic origins.

Keywords: C-reactive protein, lymphocyte, neutrophil, platelet

Recent advances in technology led to the quantitation of new parameters with automated hematology analyzers. Some of these parameters have been accepted as additional markers in diagnosing various clinical conditions [1-5]. They are cost effective and easier to perform in a routine setting than tests for some other markers.

C-reactive protein (CRP) is a commonly used inflammation marker in both acute and chronic inflammation. Most healthy individuals have a CRP concentration of 3 mg/L or less; a CRP level higher than 10 mg/L indicates a clinically significant inflammatory disease [6].

Low-grade inflammation typically refers to conditions in which

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Table 1. Characteristics of the entire population by C-reactive protein quartile (n=179)

	Group 1 CRP (<3.0 mg/L)	Group 2 CRP (3.0-9.0 mg/L)	*P* value
Number	88	91	
Gender (male/female)	44/44	45/46	
CRP	<3.0	6.1±1.1	
Age (years)	62.6±9.2	62.5±10.4	0.947+
WBC (10^9/L)	6.8±1.7	6.8±1.5	0.904+
Neutrophil (10^9/L)	3.5(1.4)	3.6(1.1)	0.337++
Lymphocyte (10^9/L)	2.3(0.9)	2.0(1.0)	0.491++
Neutrophil (%)	55.0±10.8	56.2±8.2	0.379+
Lymphocyte (%)	33.3(15.2)	32.2(9.4)	0.262++
RDW (%)	13.4(1.0)	13.3(1.3)	0.173++
PLT (10^9/L)+	267±63	290±76	0.035+*
MPV, fL	9.6(1.4)	9.1(1.2)	0.344++
PCT (%)+	0.25±0.05	0.27±0.06	0.038+*
PDW, fL	16.1(0.4)	16.0(0.5)	0.069++
P-LCR (%)	23.4(9.6)	22.7(8.7)	0.280++
PLR	117(38)	126(58)	0.031++*
NLR	1.7(1.1)	1.7(0.8)	0.301++
SII	431(326)	535(291)	0.049++*

CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocte ratio; PLT: Platelet; P-LCR: Platelet-large cell ratio; PLR: Platelet-to-lymphocte ratio; RDW: Red blood cell distribution width; SII: Systemic immune inflammatory index; WBC: White blood cell.
An independent samples test+ and the Mann-Whitney U test++ were used to compare groups.
Results are expressed as mean±SD or median (interquartile range).

the findings of classical clinical inflammation are absent, but there are chronic conditions in which there is an elevated CRP of 3 to 10 mg/L. Low-grade inflammation differs from acute inflammation in several important ways, such as underlying conditions and molecular triggering mechanisms [7]. The purpose of low-grade inflammation appears to be restoring tissue homeostasis in times of metabolic stress; it does not fight infection or clear necrotic cells, as seen in acute inflammation [8, 9]. Low-grade inflammation, with a general activation of the innate immune system, can silently persist for a long time. It is thought to play a role in the pathogenesis of most age-related diseases, such as Alzheimer's disease, atherosclerosis, cardiovascular disease, and diabetes [9-12].

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) parameters have been reported to be cost-effective measures of many systemic inflammatory processes [3, 4, 13, 14]. Moreover, Lappé et al. [15] demonstrated that the red cell distribution width (RDW), which measures the variation in red blood cell size, is associated with chronic inflammation.

Recently, the systemic immune-inflammation index (SII) was developed. The SII is based on lymphocyte, neutrophil, and platelet counts, which can project the balance of inflammatory and immune status [16].

The objective of this study was to analyze the SII and new parameters derived from hemograms to determine if they have the potential to detect patients with subclinical low-grade inflammation in an unselected, elderly, outpatient population.

Materials and Methods

Ethics approval for this retrospective study was granted by the ethics committee of Uludağ University (no: 2017-17/46).

A search of the database of the hospital laboratory information system, which integrates the information of several databases, including patient demographics, clinical diagnosis, order entry data, and laboratory results, was performed. The laboratory results included the time between specimen collection and test result. We retrieved hematological data, as well as CRP test results for a whole cohort of unselected outpatients aged 45 to 85 years. The exclusion criteria were a history of coagulopathy, recorded hemolysis in patient sample data, turnaround time of test results of more than 1 hour, hemoglobin concentration of less than 90 g/L, white blood cell (WBC) count of less than $3.5x10^9$/L or more than $10.0x10^9$/L, CRP value of more than 9 mg/L, pregnancy, positive culture result, and presence of acute infection.

The CRP level (normal value <3 mg/L) was studied with a BN II nepholometer (Siemens Healthineers, Erlangen, Germany). Participants were stratified according to CRP level. Group 1 had a serum CRP result <3.0 mg/L and Group 2 had a serum CRP result between 3.0 and 9.0 mg/L.

Ethylenediaminetetraacetic acid anticoagulated blood sam-

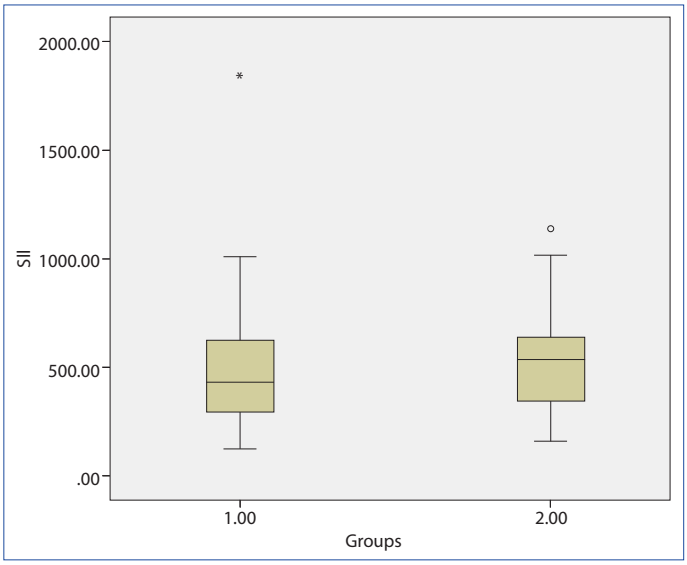

Figure 1. The systemic immune inflammatory level by group. Group 1: serum C-reactive protein (CRP) results <3.0 mg/L, Group 2: serum CRP results between 3.0-9.0 mg/L. SII: System immune-inflammatory index; SII = neutrophil×platelet / lymphocyte.

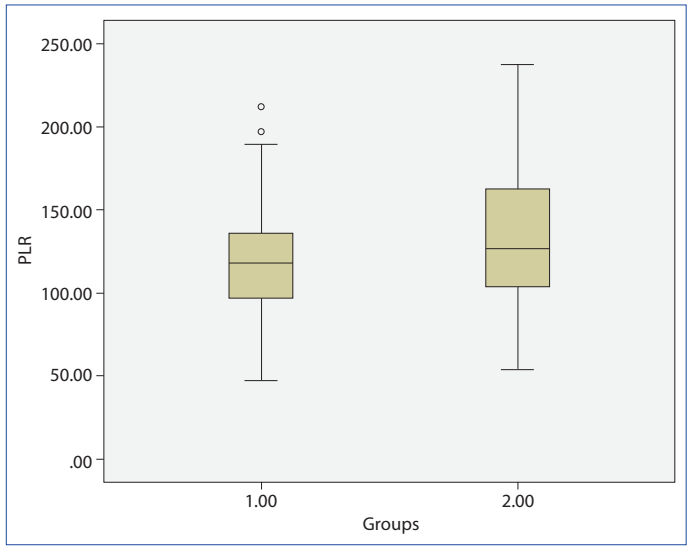

Figure 2. The platelet-to-lymphocyte ratio (PLR) by group. Group 1: serum C-reactive protein (CRP) results <3.0 mg/L, Group 2: serum CRP results 3.0-9.0 mg/L.

ples that were analyzed within 1 hour of venipuncture by an automatic blood counter (Mindray BC-5800; Mindray Biomedical Electronics Co., Ltd., Shenzhen, China) were selected for the evaluation of the results. The SII was calculated using the formula neutrophil x platelet / lymphocyte count. The PLR, NLR, RDW, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), were evaluated.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 21.0 program (IBM Corp., Armonk, NY, USA). The normality of continuous variables was analyzed with the Kolmogorov Smirnov test and the Shapiro-Wilk test. The results were expressed as mean±SD or median (interquartile range [IQR]). An independent samples t-test and the Mann-Whitney U test were used to compare the differences between the 2 groups. The area under curve calculated with receiver operating characteristic curve (ROC) analysis was used to predict low-grade chronic inflammation. In the assessment of correlations, Spearman tests were used. A level of 0.05 was considered to be statistically significant.

Results

Cumulative results for complete hematological testing and CRP level were retrieved for 179 unselected outpatients aged 45 years or older. Age, gender, WBC, neutrophile and lymphocyte concentrations were similar in both groups (Table 1). The median MPV (9.6 fL [IQR: 1.4 fL] vs 9.1 fL [IQR: 1.2 fL]; p=0.344) was non-significantly lower in Group 2 patients when compared with Group 1. The RDW (13.4% [IQR: 1.0%] vs 13.3% [IQR: 1.3%];

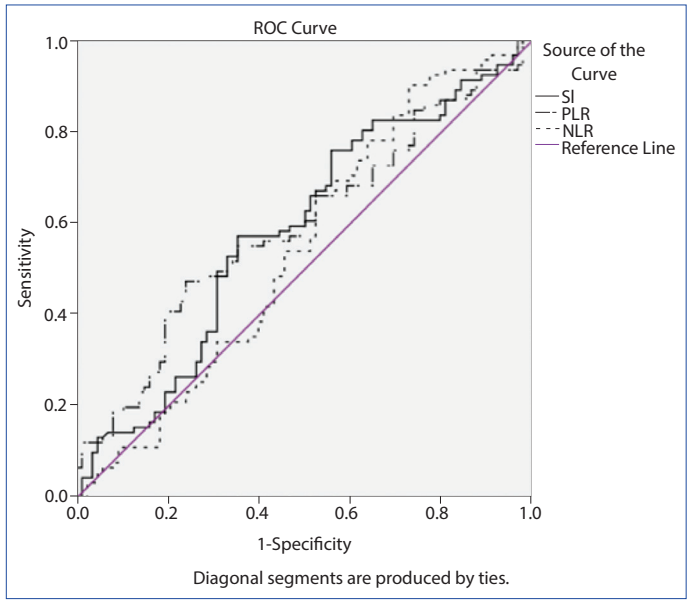

Figure 3. Predictive ability of the systemic immune inflammatory index (SII) compared with the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) according to receiver operating characteristic (ROC) curve analysis. (SII = neutrophil × platelet / lymphocyte). The area under ROC curve was 0.593 for PLR according to CRP (95% confidence interval [CI]: 0.510-0.677), 0.585 (95%CI: 0.501-0.669) for SII, and 0.545 (95% CI: 0.459-630) for NLR.

p=0.173) and the NLR (1.7 [IQR: 1.1] vs 1.7 [IQR: 0.8]; p=0.301) levels were similar between groups (Table 1).

On the other hand, the SII (431 [IQR: 326] vs 535 [IQR: 291]; p=0.049) (Fig. 1), PLR value (117 [IQR: 38] vs 126 [IQR: 58]; p=0.031) (Fig. 2), and PLT (267±63 10^9/L vs 290±76 10^9/L; p=0.035) were significantly higher in Group 2 compared with Group 1 (Table 1).

A statistically significant correlation between the SII and the NLR (r=0.807; p<0.001), the PLR (r=0.773; p<0.001), and the PLT (r=0.653; p<0.001) was found. However, there was no correlation between the CRP value and the SII (r=-0.118; p=0.283).

The area under the ROC curve for the PLR according to CRP was 0.593 (95% confidence interval [CI]: 0.510-0.677), 0.585 (95% CI: 0.501-0.669) for the SII, and 0.545 (95% CI: 0.459-630) for the NLR (Fig. 3).

Discussion

In this study, the SII and the PLR values were higher in low-grade inflammation patients, characterized by a mildly elevated CRP. Similar to increased serum levels of CRP, the evidence indicates that platelet parameters are markers that reflect a systemic inflammatory response [17,18]. Chronic inflammation is typically associated with reactive thrombocytosis, induced by the overproduction of pro-inflammatory cytokines, leading to megakaryocytic proliferation [19]. Platelets play an important role in various inflammatory diseases by interacting with almost all known immune cells. Lymphocytes are involved in the regulatory pathway of the immune system, and inflammation increases lymphocyte apoptosis [20]. Several studies have reported that a high PLR is a parameter that reflects systemic inflammatory response in numerous diseases [21,22]. A PLR increase has also been reported to be associated with cardiovascular complications and poor prognosis in malignancies [23, 24].

The SII assesses 3 of the hemostatic system markers that participate in the inflammatory process at the same time: platelets, lymphocytes, and neutrophils [13,16]. Higher counts of platelets and neutrophils may define underlying inflammation; lower lymphocyte counts may express an uncontrolled inflammatory pathway. Therefore, a combined marker of chronic inflammation, such as the SII, reflecting high neutrophils and platelets, and low lymphocytes, may contribute additional information regarding the inflammatory and immunological balance of the body.

Interest in the SII has grown recently because it has been found to be predictive of the prognoses of patients with diverse oncological conditions [16, 23-25]. There is a strong linkage between obesity, cancer, inflammation, and clinical outcomes [26]. Evidence shows that obesity is related to low-grade chronic inflammation, and the circulating level of CRP rises with body mass index (BMI) [27]. In a recent study, a moderately elevated SII concentration within the normal range was demonstrated to be independently affected by BMI status [13].

Therefore, the SII and PLR do not require additional tests and may be easily calculated from the hemogram, making it easy to be applied to virtually all patients.

This research found a weak negative correlation between the MPV and the SII. A high MPV level indicates the presence of many large platelets, which are more active and related to active inflammatory diseases; a low MPV is associated with a range of chronic diseases, including cancer, systemic lupus erythematosus, and osteoporosis [3, 28-30]. Similarly, Çetin et al. [31] found a negative correlation between the MPV and CRP in an attack-free period in patients with familial Mediterranean fever with low-grade inflammation.

However, this research did not find a correlation between the CRP level and the parameters calculated. In a recent study, Ahbap et al. [32] found that hemodialysis had a significant relationship to the NLR, PLR, and CRP in end-stage renal disease (ESRD) patients on maintenance hemodialysis. Similarly, they reported that the relationship was too small to draw a conclusion that the NLR and PLR were good substitutes for CRP in ESRD patients on maintenance hemodialysis. CRP increases during a chronic low-grade inflammatory response may be due to multiple processes. Inflammation may primarily be caused by the polarization of resistant macrophages that secrete cytokines, rather than by new immune cells.

Conclusion

A high PLR and SII appears to be associated with subclinical low-grade inflammation. Our data do not support the notion that hematological screening parameters can serve as a substitute for CRP. These findings are limited to the cohort studied here, and may not be entirely applicable to other ethnic origins. Well-designed prospective studies are needed.

Limitations

This study has several limitations due to its design as a cross-sectional, retrospective, single-center study. In addition, no information was available on the medication use or coexisting medical conditions of our participants; the subject selection bias cannot be neglected.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Y.Ü.; Design – Y.Ü., K.H.; Supervision – Y.Ü., K.H.; Fundings - Y.Ü., K.H., S.K.G., D.Ü.; Materials – Y.Ü., K.H., S.K.G., D.Ü.; Data collection &/or processing – Y.Ü., S.K.G., D.Ü.; Analysis and/or interpretation – Y.Ü., K.H., S.K.G., D.Ü.; Literature search – Y.Ü., K.H., S.K.G., D.Ü.; Writing – Y.Ü.; Critical review – K.H., S.K.G., D.Ü.

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