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Systemic inflammatory indexes (NLR, DNLR, PLR and SII) role in predicting COVID-19 progression

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has caused a worldwide emergency. The disease is characterized primarily by symptoms of the respiratory system, but also by systemic inflammation. Since the onset of the disease, there has been a need for biomarkers to predict the severity of the clinical picture and the outcome of the disease. The aim of this study is to evaluate systemic inflammatory markers for predicting severity of COVID-19.

Methods: The study was conducted at the Sarajevo Canton Health Center on a total of 170 adults suffering from COVID-19. 70 subjects had mild clinical picture, while the control group consisted of 100 subjects with moderate clinical picture. The results of complete and differential blood counts, C-reactive protein (CRP), and systemic inflammatory indexes (SII) (neutrophil/lymphocyte ratio [NLR], derived NLR [dNLR], platelet/lymphocyte ratio [PLR], and SII) were used to compare the groups. IBM SPSS Ver. 23 was used for statistical analysis and data processing.

Results: The proportion of male patients in the group with a milder clinical picture was higher than the proportion of male patients with a moderate clinical picture, $p = 0.016$. The values of leukocytes and neutrophils were higher in patients with a moderate clinical picture ($p = 0.006$ and $p < 0.001$, respectively). The values of all inflammatory indexes (NLR, dNLR, PLR and SII) were higher in patients with a moderate clinical picture of COVID-19 than in patients with a mild clinical picture ($p < 0.001$ for NLR, dNLR, and SII; $p = 0.023$ for PLR). In the research, patient age showed no correlation and CRP showed no correlation with SII.

Conclusion: SII show higher values in patients with a moderate compared with a mild clinical picture of COVID-19. These parameters can be cost-effective and useful indicators in patient classification, diagnosis, and probably in monitoring patients with COVID-19.

Keywords: Systemic inflammatory indexes; coronavirus disease 2019; clinical picture

INTRODUCTION

The 2019 coronavirus pandemic (COVID-19) has caused a global health economic emergency. The disease is characterized by severe acute respiratory syndrome and systemic inflammation and often requires intensive patient care due to multiorgan failure (1).

The clinical presentation of COVID-19 varies widely, ranging from asymptomatic patients to patients with mild upper respiratory tract inflammation to severe pneumonia, leading to respiratory failure and, in the worst cases, death (2,3).

Although primarily a respiratory infection, COVID-19 is considered a systemic disease and has significant effects on the hematopoietic system and hemostasis. Lymphopenia, neutrophilia, thrombocytopenia, and impaired erythropoiesis are hallmarks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Thrombocytopenia and hypercoagulability of the blood are common features in patients with a severe form of the disease (4).

There is a need to identify biomarkers that reliably predict the severity of disease caused by SARS-CoV-19 virus infection. Ideally, the biomarkers should be able to be used as a point of care or in routine diagnostics. Previous studies have shown that the relationship between leukocyte formula (leukogram) and COVID-19 plays an important role in the pathogenesis of the disease (5-8). Indexes of systemic inflammation, including neutrophil/lymphocyte ratio (NLR) and derived NLR (dNLR), platelet/lymphocyte ratio (PLR), and systemic inflammatory index (SII) are

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well-established inflammatory indexes used to predict the severity and mortality of various inflammatory diseases (9).

The aim of this study was to analyze the characteristics and role of basic systemic inflammatory markers in COVID-19 primary care patients, their behavior at certain stages of the disease, but also their prognostic significance in determining the severity and outcome of the disease itself.

METHODS

The study was conducted at the Sarajevo Canton Health Center on a total of 170 adults who had COVID-19 from July 07, 2020, to November 30, 2021. 70 patients had a mild clinical picture, whereas the control group consisted of 100 patients with an intermediate clinical picture. The basis for dividing patients into two groups was their clinical presentation. Mild COVID-19 patients required treatment at home with possible visits to the primary care physician, whereas moderate COVID-19 patients were hospitalized (oxygen saturation below 95%). The presence of SARS-CoV-2 virus in patients was confirmed by real-time polymerase chain reaction (PCR) method. Inclusion criteria were positive epidemiologic history, the presence of general symptoms such as fever, malaise, and dry cough, characteristic changes on chest radiographs, and a positive reverse transcription -PCR for the presence of SARS-CoV-2 nucleic acid. Exclusion criteria were patients younger than 18 years, pregnant women, and patients with concomitant diseases that may alter the inflammatory response of COVID-19 patients (e.g., obesity, diabetes mellitus, autoimmune diseases, and malignancies). Demographic data, epidemiological history, data on applied therapy during treatment, and data on radiological diagnosis were obtained from the Health Information System.

The results of complete and differential blood counts, C-reactive protein (CRP), and SII were used for comparison between groups. Systemic inflammation indexes analyzed included: (NLR; neutrophils/lymphocytes), (dNLR; neutrophils/[leukocytes-neutrophils]), (PLR; platelets/lymphocytes), and systemic inflammation index (SII; [neutrophils × platelets]/lymphocytes). Blood samples from patients participating in the study were collected in tubes containing the appropriate anticoagulant and treated according to standard laboratory procedures. Analyses were performed using a Siemens Advia 2120 hematological analyzer and a Siemens Dimension EXL 200 biochemical analyzer.

The study was approved by the Ethics Committee of the Sarajevo Canton Health Center (number: 01-06-5847-3/20). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

IBM SPSS v. 23 was used for statistical analysis and data processing. We used descriptive statistics and nonparametric significance tests. Data did not follow a normal distribution and were presented as median and interquartile range, whereas categorical variables were presented as percentages (%). Differences between groups were examined with the Mann–Whitney U test and the Kruskal–Wallis H test. Correlations between parameters were examined using the Spearman correlation test. $p < 0.05$ was considered statistically significant for all tests.

RESULTS

170 patients were enrolled in the study, 100 with moderate and 70 with mild clinical picture of COVID-19. The average age in the group of subjects with mild clinical picture was 56.4 ± 21.6 and 57.9 ± 22.1 in the subjects with moderate clinical picture. The proportion of male patients in the group with mild clinical picture (63%) is higher than the proportion of male patients with moderate clinical picture (44.3%), $p = 0.016$. The demographic characteristics and the values of the determined parameters of all patients are shown in Table 1.

The values of leukocytes and neutrophils were higher in patients with a moderate clinical picture ($p = 0.006$ and $p < 0.001$, respectively). The values of lymphocytes, platelets, and CRP showed no significant difference between patients with moderate and patients with mild clinical picture.

The values of all inflammatory indexes (NLR, dNLR, PLR, and SII) were higher in patients with a moderate clinical picture of COVID-19 than in patients with a mild clinical picture ($p < 0.001$ for NLR, dNLR, and SII; $p = 0.023$ for PLR).

The study also analyzed the mutual correlations between the studied parameters (Table 2). In addition to the expected correlations due to the direct dependence of inflammatory indexes on the hematological parameters from which they are calculated, correlations of inflammatory indexes with CRP, age of patients, and with each other were shown.

According to the Spearman correlation test, the age of the patients showed no significant correlation with the SII. In contrast to age, CRP showed a significant positive correlation with NLR, dNLR, and SII ($p < 0.001$ for all three) and with PLR ($p = 0.018$). Each of the SII studied showed a significant positive correlation with each of the remaining three, $p < 0.001$ for all correlations.

DISCUSSION

The main finding from the results of our study is that patients with COVID-19 with a moderate clinical picture had higher values of SII (NLR, dNLR, PLR, and SII) compared with patients with a mild clinical picture, whereas other laboratory parameters used in daily practice, such as lymphocytes, platelets, and CRP, showed no significant difference between these two groups of patients. The reason why these parameters did not show significance can be explained on the basis of the clinical picture - mild and moderate. The study did not include patients with a severe clinical picture, certainly characterized by very severe inflammation, whether primary, viral, or secondary bacterial infection.

COVID-19 is a highly contagious disease that has killed millions of people in a relatively short period of time (10) and has severely impacted health systems around the world, particularly the health systems of developing countries such as Bosnia and Herzegovina.

Identification of risk factors, concomitant diseases, and classification of patients according to the severity of the disease using the index of systemic inflammation at diagnosis and progression of the disease from COVID-19 can effectively

TABLE 1. Demographic parameters, CRP, hematological and systemic inflammatory indexes values in patients with mild and moderate clinical picture of COVID-19

Parameters	COVID-19		Mann Whitney
	Mild clinical picture	Moderate clinical picture	*p*-value
Age	56.4±21.6	57.9±22.1	0.554
Gender			
Male, *n* (%)	63 (63)	31 (44.3)	
Female, *n* (%)	37 (37)	39 (55.7)	
Leukocytes (×10^9/L)	6.93 (4.98–9.72)	8.91 (5.87–11.58)	0.006
Lymphocytes (×10^9/L)	1.37 (1.00–1.90)	1.20 (0.80–1.72)	0.117
Neutrophils (×10^9/L)	4.35 (3.06–6.67)	6.34 (4.13–9.98)	<0.001
Platelets (×10^9/L)	192.5 (122.3–265.8)	217.7 (150.5–277.0)	0.168
CRP (mg/L)	44.0 (22.20–86.77)	46.9 (11.13–100.1)	0.889
NLR	3.35 (2.32–4.15)	4.05 (2.79–11.06)	<0.001
dNLR	1.93 (1.51–2.41)	2.78 (2.11–6.67)	<0.001
PLR	128.3 (94.8–194.2)	152.3 (109.5–280.4)	0.023
SII	527.6 (355.9–962.4)	982.5 (503.5–2347.5)	<0.001

CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, dNLR: Derived NLR, PLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory indexes

TABLE 2. Correlations between age, CRP and inflammatory indexes in patients with mild and moderate clinical picture of COVID-19 (n=170)

Index	Age	CRP (mg/L)	NLR	dNLR	PLR
CRP (mg/L)					
Rho	0.035	/	/	/	/
p-value	0.655				
NLR					
Rho	0.047	0.393**	/	/	/
p-value	0.541	<0.001			
dNLR					
Rho	0.123	0.356**	0.905**	/	/
p-value	0.110	<0.001	<0.001		
PLR					
Rho	0.001	0.183*	0.571**	0.514**	/
p-value	0.992	0.018	<0.001	<0.001	
SII					
Rho	−0.003	0.277**	0.788**	0.717**	0.755**
p-value	0.971	<0.001	<0.001	<0.001	<0.001

CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, dNLR: Derived NLR, PLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory indexes

contribute to appropriate management and reduction of mortality (11). It should be emphasized here the economic factor of these indexes, which are obtained by calculation from other standard and cheap laboratory analyses, while providing more meaningful diagnostic information (12).

Preliminary laboratory results in our study showed that the values of SII were higher in patients with a moderate clinical picture than in patients with a mild clinical picture. According to the results, leukocytosis and neutrophilia were prominent in patients with a moderate clinical picture, whereas lymphopenia was less prominent.

Various age-related physiological and immunological changes associated with comorbidities are influential factors in the elderly population that may lead to disease exacerbation COVID-19 (9). In our study, groups were matched by age. The association between age, systemic inflammatory markers, and CRP was not found in our study. We suspect that the reason for this is that our study included patients without concomitant diseases. It should also be noted that the mean age of the patients was 56.4 ± 21.6 years for mild disease and 57.9 ± 22.1 years for moderate disease. Thus, this is the reason why we obtained these results for these two groups in comparison with the results of previous studies with a larger number of COVID-19 patients, in which it was demonstrated that elderly patients with existing concomitant diseases have a higher risk of developing a severe clinical picture and a fatal outcome (13-15).

In addition to age, there are significant gender differences in the moderate form of COVID-19, with more men dying than women. The incidence and severity of disease of COVID-19 is also higher in men than in women. This trend may be attributed to a better response and stronger immune system in women (16). In our study, more males were in the mild disease group than in the moderate disease group (63% vs. 44.3%), but we did not perform a detailed sex analysis. Our data showed more pathologic levels of inflammatory parameters in the moderate disease group, although there were fewer male participants in this group than in the mild disease group.

Neutrophils play a key role in the body's defense against bacterial and fungal infections. However, their role in defense against viruses is not yet fully understood. Unusually for viral infection, the immunophenotype of severe COVID-19 is characterized by lower lymphocyte counts and increased neutrophil counts, with the ratio of neutrophils to lymphocytes correlating with disease severity (17). These data are consistent with the results of our study.

Lymphopenia was equally pronounced in patients with moderate disease and in patients with milder disease. Lymphopenia is thought to be a consequence of the effect of the virus on the infection of T-cells with ACE2 receptors (9,18). T-cell imbalance is key to diagnosing the severity of COVID-19. Decreased levels of CD4 + and CD8 + T cells may increase some metrics, such as NLR (19).

CRP has been shown to be a good marker of COVID-19 disease severity (20,21). CRP had significantly higher levels in patients with severe COVID-19 compared with mildly infected patients. In our study, there was no significant difference in CRP levels between patients with moderate and mild disease. One possible reason for this difference is the

difficulty in determining the stage of disease at which CRP levels were measured in our and other studies, as well as unreliable data on the treatment given to patients before admission to the Health Center.

The diagnostic significance of SII (NLR, dNLR, PLR, and SII) has been demonstrated in other studies. The results of the study by Karimi et al. suggest that most of the systemic inflammatory markers studied can predict the prognosis of COVID-19, with NLR appearing to be the most robust of them (22). The findings of Xia et al. (23) suggest that both NLR and SII are potential new diagnostic biomarkers in severe patients with COVID-19. How useful SII can actually be for monitoring the clinical course of COVID-19 is also demonstrated by the study of Hosseninia et al. who showed that WBC count, MLR, SIRI, and AISI were associated with mortality in COPD patients with COVID-19 (24).

It is unnecessary to list all the studies that demonstrated the usefulness and practicality of SII (25-27). We have mentioned only a few that we came across while writing this article. A consensus and definitive conclusion on the use of these indexes in daily practice regarding COVID-19 is needed. According to our results, the SII used showed no correlation in these two groups of patients of the indicated age, although their higher values are observed in moderate-severe disease, suggesting that their value increases with the progression of COVID-19. Therefore, the recommendations for clinical practice are that systemic inflammatory indices should be used in the elderly patients with a more severe and severe clinical picture, which is in accordance with the results of previously performed studies.

The limitations of our study are that it was performed on patients from one center, included only patients from the Sarajevo Canton area and did not perform a sex-specific analysis. For the analysis in this study, the laboratory results of the patients at the time of admission were used, but it is unclear at what stage of the disease each of the patients was, regardless of the severity of the clinical picture. Furthermore, considering the level of health care at which the study was conducted, patients with a severe clinical picture of COVID-19 were not included in the study. The limitation of the study conducted is reflected in the fact that a relatively small number of COVID-19 patients from one institution were included compared with other studies conducted. The reason for the small number of COVID-19 patients in our study is that patients with comorbidities were excluded. Our aim was to provide the most credible results possible and to show SII values only in patients with COVID-19.

CONCLUSION

SII show higher values in patients with a moderate compared with a mild clinical picture of COVID-19. These parameters can be cost-effective and useful indicators in patient classification, diagnosis, and probably in monitoring patients with COVID-19.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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