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Analyzing The Relationship Between Systemic Inflammatory Index, Neutrophil Lymphocyte Ratios and Covid-19 Infection

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Research Article

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ABSTRACT

Background: There are important parameters in understanding the severity of COVID-19 infection. We aimed to observe the role of systemic inflammatory index and neutrophil lymphocyte ratios in Covid-19 infections and the changes seen during the infection process.

Methods: This retrospective single-center study was conducted between April 2020 and May 2020. Clinical, demographic and laboratory data of patients with COVID-19 were analyzed. All COVID-19 case confirmation made with reverse transcription polymerase chain reaction. Neutrophil/lymphocyte ratio and SII change and relationship were examined.

Results: 140 patients were included in our study and 50 of them were female. There was no statistically significant difference in SII according to gender (p>0.05) but there was a difference in SII between age categories (p=0.009). A statistically significant difference was found (p=0.003) regardless of the presence of comorbidities. Tobacco users had a significantly lower SII (p=0.028). A statistically significant difference was found between SII and Covid Severity Index (p=0.020). A statistically significant difference was found in the SII values of those receiving favipiravir treatment and those receiving hydroxychloroquine treatment (p<0.001). A statistically significant difference was found between those who received treatment in the outpatient clinic and those who received treatment in the intensive care unit (p=0.043). A statistically significant difference in the SII values was found between the patients who died and those who survived (p= 0.009)

Conclusion: The Systemic Inflammatory Index is a parameter that can be used for the Covid-19 patient follow-up and estimating mortality..

Keywords: Covid-19, Emergency Medicine, Systemic Inflammatory Index, Neutrophil Lymphocyte Ratio

Sistemik İnflamatuar İndeks, Nötrofil Lenfosit Oranları ve Covid-19 Enfeksiyonu Arasındaki İlişkinin Analizi

Süreç

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ÖZ

Amaç: COVID-19 enfeksiyonunun ciddiyetini anlamada önemli parametreler bulunmaktadır. Çalışmamızda amacımız Sistemik inflamatuar index (SII) ve nötrofil lenfosit oranlarının Covid-19 Enfeksiyonu ve bu enfeksiyon sürecindeki değişim ile ilişkilerini ortaya koymaktır.

Yöntemler: Nisan 2020-Mayıs 2020 tarihleri arasında yapılan retrospektif tek merkezli bir çalışmadır. COVID-19 hastalığı tüm vakalarda ters transkripsiyon polimeraz zincir reaksiyonu ile doğrulanan hastaların demografik, klinik ve laboratuvar verileri incelendi. Nötrofil/lenfosit oranı ve SII değişimi ve ilişkisi incelendi.

Bulgular: Çalışmamızda 50'si kadın toplam 140 hasta bulunmaktadır. İstatistiksel olarak Cinsiyetlere göre SII 'de farklılık bulunmaz iken (p>0.05), yaş katagorileri arasında SII 'de anlamlı farklılık saptanmıştır (p=0,009). Komorbidite olup olmaması durumunda, SII 'de istatistiksel anlamlı farklılıklar saptandı (p=0,003). Tütün kullananların SII nin daha az olduğu ve bunun anlamlı olduğu bulundu (p=0.028). SII ile Covid Severity İndexin, karşılaştırılmasında; gruplar arası istatistiksel anlamlı farklılık bulundu (p=0.020). Favipravir tedavisi alanlar ile hidroksiklorokin tedavisi alanların SII değerlerinde istatistiksel anlamlı farklılık bulundu (p<0.001). Klinikte tedavi alanlar ile yoğun bakımda tedavi alanlar arasında istatistiksel olarak anlamlı farklılık bulundu (p=0,043) Hastalardan ölenlerin ve yaşayanların SII'lerinin gruplar arasında istatistiksel olarak anlamlı farklılık bulundu (p= 0.009).

Sonuç: Sistemik İnflamatuar İndeks, Covid-19 hastalarının takibinde ve mortalite tahminlerinde kullanılabilir bir parametredir.

Anahtar sözcükler: Acil Servis, Sistemik İnflamatuvar İndeks, Covid-19, Covid-19, Nötrofil Lenfosit Oranı

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Introduction

Coronavirus disease affected a lot of people wordwide [1]. Updated technical guidelines on critical preparedness, preparedness and response; advice on mask use; infection prevention and control; and laboratory tests have been updated by WHO [2]. The main route of transmission is via respiratory droplets. Patients often present with atypical presentations of respiratory symptoms such as dry cough, fever, fatigue, and sometimes loss of taste and smell. The disease severity classified as mild-moderate-severe-critical by assessing laboratory tests and symptoms [1,3-6]. Most people (approximately 81%), patients experience cough and low-grade fever as mild or moderate symptoms. Patients with critical cases or severe symptoms account for 5% and 14% of all infected subjects, respectively. However, multiple organ failure, acute respiratory distress syndrome (ARDS) or severe pneumonia may develop requiring hospitalization, that might cause death [7]. Approximately 1 out of 5 hospitalized patients, in which the mortality rate is 61.5%, need to be applied to an intensive care unit (ICU) [8, 9]. Therefore, identifying any early biomarkers of severity may enable early aggressive treatment and reduce death rate.

Although Covid-19 is a systemic disease, lung involvement has major clinical consequences. Thorax Computed Tomography (CT) has played a major role in both the diagnosis and management of patients. Inflammatory markers are other parameters that provide information about the course of the disease. CRP, Ferritin and Procalcitonin are the most common and easily accessible parameters. Previous studies have shown that inflammatory markers and thorax tomography findings provide useful information about the course of the disease.

In this study, other than the aforementioned parameters, we focused on routine blood tests and parameters in complete blood count. Common blood tests to evaluate inflammatory processes often used in early diagnosis of various diseases. [1,3,4]. An easy and inexpensive test is complete blood count which provides information about different cell types and their morphological features; such as platelets (PLT), mean platelet volume and white blood cells (monocytes, neutrophils, lymphocytes). Furthermore, combination of those parameters' ratios can be used as indicators of inflammation, thus proposed as biomarkers to aid in diagnosis, progression and stratifying the risk in inflammatory diseases [4,5]. Latterly, platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) have been shown to be helpful in diagnosis. Also systemic inflammation response index (SII) and monocyte lymphocyte ratio (MLR) can be used. However, there are only few studies evaluating the prognostic capacity of these indicators to assess severity in COVID-19 patients [2,6,7]. In our study, we analyzed of the role of systemic inflammatory index and neutrophil lymphocyte ratios in COVID-19 patients to predict the mortality of COVID-19 disease.

Material methods

This is a retrospective single-center study conducted in State Hospital between April 2020 and May 2020. 140 patients taken in our study. The study was approved by the Ministry of Health COVID-19 Scientific Committee and the local ethics committee. Data were collected from the hospital's electronic information system. All the COVID-19 cases were confirmed with reverse transcription polymerase chain reaction (RT-PCR). The demographic-clinical-laboratory data were recorded. Peripheral venous blood samples were evaluated in the biochemical laboratory of State Hospital after standard operative procedures. Biochemical parameters were measured with an ARCHITCT 16200 automated biochemistry analyzer (Abbott Laboratories, Illinois, United States). Hemogram and inflammation parameters were evaluated. Afterwards, the change and relationship of the whole blood cell indicators of systemic inflammation, calculated as NLR and SII ((neutrophils × platelets)/lymphocytes), were examined.

Statistical Analysis

Distribution of parameters was assessed using Kolmogorov-Smirnov test. Non-parametric assumptions were met. Therefore, comparisons between two groups were conducted using Mann-Whitney U test. Moreover, Post hoc comparisons were carried out using Dunn-Bonferonni test after Kruskal Wallis test was implemented for comparison of more than two groups.

Results

140 patients were included, 50 of them were female. Demographic information of these patients is shown in Table 1 and laboratory values in Table 2. There was no difference in SII amongst male and females ($p>0.05$). However, a difference in SII was found amongst the age categories in the Kruskal-Wallis test result ($p=0.009$) (Figure 1). There was a difference in CLASS levels amongst the 18-35 and >65 age groups ($p=0.017$).

There was no relationship between comorbidities and SII (p>0.05) (Figure 2). However, higher SII levels were found in those with a comorbidity than in those without a comorbidity (mean: 1,395 vs. 556, p=0.003).

In terms of tobacco use, it was found that tobacco users had a significantly lower SII (mean: 1,059 vs. 1,444) (p=0.028).
Using the Kruskal-Wallis test, the Covid Severity Index and SII was found to be different amongst the groups (p=0.020) (Figure 3). Subgroups were examined by post hoc pairwise comparison using the Dunn-Bonferonni test; a difference found between the moderate and severe subgroups (p=0.017).

Regarding the treatments received by the patients, a difference found between favipravir (mean (sd) 1781 (2024)) and hydroxychloroquine (mean (sd): 727 (750)) using the Mann-Whitney U test (p<0.001).

In our study, patients were grouped as outpatient follow-up, treatment in the clinic/ward, treatment in the intensive care unit, and treatment with ECMO and mechanical ventilation. The SII values are shown in Table 3, and the differences amongst the groups were measured with Kruskal-Wallis test, and it was statistically significant (p=0.006).

In the post hoc pairwise comparison (Dunn-Bonferonni test), a difference found amongst inpatients and intensive care unit patients (p=0.043), as well as, between inpatients and mechanical ventilation patients (p=0.032).

When the difference of the SIIs of those who died and those who survived were examined with the Mann-Whitney U test, a statistically significant difference was found (mean dead vs. alive: 1917 vs. 1121, p= 0.009).

Table 1: Demographic Information

		Count
Gender	Female	50
	Male	90
Age	18-35	25
	36-50	33
	51-65	36
	65	46
Group-tobacco	No tobacco use	45
	Tobacco use	95
Comorbid disease	Comorbidities absent	35
	Comorbidities present	105
Comorbid disease	Comorbidities absent	35
	Respiratory disease	19
	Cardiovascular disease	37
	Hypertension	16
	Chroic renal Failure	5
	Chronic hepatic failure	2
	Diabetes	20
	Rheumathologic disease	1
	Solid tumor	4
	Hematologic disease	1
COVID SEVERITY INDEX	mild	14
	moderate	52
	severe	68
	critical	6
Thorax CT involvement	No CT findings	7
	Less than 25% involvement	34
	25-50% involvement	47
	Less than 75% involvement	40
	More than 75% involvement	12
Treatment	No treatment	1
	Favipiravir	61
	Oseltamivir	0
	Hydroxychloroquıne	78
	Azithromycin	0
Form of treatment (outpaitent, inpatient, intensive care unit, ventilator)	Outpaitent	5
	Inpatient	70
	Intensive care unite	51
	Mechanic ventilation	12
	ECMO	2
Treatment	No treatment	0
	Favipiravir	61
	Oseltamivir	0
	Hydroxychloroquıne	78
	Azithromycin	0
Outcome	Deceased	11
	Survived	129

COVID-19: Coronavirus disease, CT: Computerized Tomography, ECMO: Extracorporeal Membrane Oxygenation.

Table 2: Laboratory Findings

	Mean	Standard Deviation	Median	Percentile 25	Percentile 75
White blood cell	8,53	4,50	7,26	5,55	10,40
Neutrophil	5,93	4,05	4,70	3,17	7,80
Monocyte count	,82	,63	,67	,49	,98
Lymphocyte	1,82	1,04	1,61	1,10	2,16
Neutrophil lymphocyte count	4,18	4,05	2,80	1,71	5,15
hemoglobin	12,58	2,39	12,95	11,05	14,45
Mean corpuscular volume	82,85	6,53	82,20	78,90	86,20
platelet	254,20	100,65	232,50	181,50	316,00
Red cell Distribution Width	14,50	2,10	13,95	13,10	15,15
Mean Platelet Volume	12,23	21,18	10,30	9,70	11,20
Plateled Distribution Width	12,57	2,06	12,20	11,30	13,90
Procalsitonin	,26	,09	,24	,19	,31
URIC ACID	5,71	2,20	5,60	4,30	6,90
CREATININ	1,14	1,02	,85	,72	1,05
UREA	21,63	21,73	14,00	11,00	21,50
Alanine Aminotransferase	32,90	93,28	19,50	12,50	33,00
PROCALCITONIN	,70	5,28	,05	,02	,10
SEDIMENTATION	20,60	11,83	17,00	12,00	24,00
FERRITIN	244,74	409,15	89,50	40,85	208,20
INR	1,30	,88	1,11	1,01	1,25
APTT	30,43	7,13	29,35	26,00	32,40
FIBRINOGEN	420,86	116,59	439,00	332,00	511,50
D-DİMER	1,27	2,35	,67	,31	1,50
C Reactive Protein	17	11	15	8	25
SII	1184,10	1529,97	667,33	358,45	1175,87

APTT: Activated Partial Thromboplastine time, INR: International normalized ratio, SII: Sistemic İnflamatory index.

Table 3: SII values of outpatient follow- up, treated in clinic/ward, treated in intensive care unit, treated with mechanical ventilation and ECMO.

		Mean	Standard Deviation	Median	Percentile 25	Percentile 75
Form of treatment (outpaitent, inpatient, intensive care unit, ventilator)	Outpatient	712,53	332,82	766,11	452,92	915,45
	Inpatient	749,44	740,16	508,33	334,04	770,91
	Intensive Care Unit	1679,61	2142,14	796,86	399,60	1711,19
	Mechanic Ventilation	1860,96	1513,19	1332,93	591,34	3357,42
	ECMO	1217,36	743,62	1217,36	691,55	1743,18

ECMO: Extracorporeal Membrane Oxygenation.

Discussion

The COVID-19 pandemic has been the biggest problem in our world for the last two years. Although the developments in the treatment strategy still continue, there is still no definitive treatment. For this reason, the evaluation of treatment and the prediction of prognosis are very important. In this study, we focused on routine blood tests and parameters in complete blood count. In our study, we analyzed the relationship between systemic inflammatory index, neutrophil lymphocyte ratios and COVID-19 to predict the mortality in COVID-19.

The relationship between SII and COVID-19 was evaluated for the first time by Alessandro et al. [1]. In this study, it was concluded that the increase in proinflammatory cytokines, especially in the presence of T cell lymphopenia make severe COVID-19 cases prone to cytokine storm which results multiple organ failure and death [1]. It was found that NLR and dNLR values were increased in patients with severe COVID-19 disease. It was describe for the first time that SII, like other blood cell count originated indices of inflammation, was significantly associated with disease severity [1]. Similar to this study, we found significant differences in SII between age categories in our study. In addition, similar to the results of the study by Alessandro et al., we found that SII levels in patients without comorbid disease were statistically significantly different from those with comorbidity [1].

In a study by Huang et al., inflammatory parameters between SARS-CoV, MERS-CoV and COVID-19 were compared [4]. Similar to the previous findings, we observed that the SII values of the patients who received inpatient treatment in the clinic were higher. Due to these similar results, SII was thought to have a diagnostic role in patients infected with SARS-CoV2 [1,4].

In a study by Kong et al., higher neutrophil levels and lower lymphocyte counts were observed in severe cases [5]. The severe group had elevated biomarkers for infection as well [5]. NLR was also used as a common factor for systemic infection and inflammation for evaluating bacterial infection's severity and the pneumonia's clinical prognosis. Highest NLR group's patients showed a 5.9-fold increased risk of severe COVID-19 incidence [5]. Similarly, in our study, we found statistically significant differences when we compared the severity assessment of the disease on thorax CT with the SII values.

In a study by Wu Z. et al., the characteristic findings of COVID-19 were examined [6]. This study presented the largest case series of COVID-19 (72,314 cases) ever published [6]. In this study, the findings of the disease, clinical course, mild to severe critical classification, and mortality rates were reported [6]. These classifications and groupings were used in the same way in our study as in subsequent studies [6].
The study by Wang D. et al. was a pioneering study in examining the relationship between inflammatory markers and clinical findings [7]. This study showed that the presence of comorbidity may be a risk factor for poor outcome [7]. Similarly, in our study, the SII values of those with comorbidities were high.

Zhou V et al. described the discharge criteria for the first time: no fever 3 days, significant improvement of both lungs in thorax CT, clinical improvement in respiratory symptoms, and negative 2 throat swab samples for SARS-CoV-2 RNA taken 24 hours apart [8]. Significant changes were observed during the inflammatory processes, and the relationship of these changes with mortality was also evaluated [8]. Similar to the results of our study, it was found that there was a significant relationship between the mortality rate and SII.

In a study by Usul E. et al., the role of biomarkers obtained from peripheral blood samples in those diagnosed patients with COVID-19 admitted to the emergency department was evaluated. Platelet lymphocyte ratio, SII, peripheral blood parameters, NLR were compared in patients with and without COVID-19 infection. in this study age was not considered as a risk factor. On the contrary, in our study, a statistically significant difference was found in the relationship between age groups and SII values using the Kruskal-Wallis test [9]. In addition, unlike the results of our study, in the study by Usul E. et al, it was determined that platelet, leukocyte, neutrophil, NLR and SII values were higher in patients with negative test results, and hemoglobin was higher in patients with positive test results. In the study by Usul E. et al., and in our study, SII values were found to be higher in patients with comorbidity, and a statistically significant difference was observed in the relationship between SII values and presence of comorbidity [9].

The systematic review and meta-analysis by Paliogiannis B. et al. aimed to compare the PLR and NLR with the NLR values of patients with frequent acute COPD exacerbations and stable COPD patients [10]. All studies evaluated PLR and NLR was

evaluated in four studies [10]. Combined results indicated that both PLR and NLR values were significantly higher in patients with unstable COPD [10].

In a study by Walsh et al., the survival rate of patients with colorectal cancer was examined with NLR [11]. It was found that survival and NLR are directly related in malignancies [11]. Therefore, SII predicts the severity of the disease and the treatment algorithm not only for COVID-19, but also for common respiratory diseases such as malignancy and COPD.

Limitation

The present study is limited by lack of control groups. Thus, further studies should be conducted to evaluate the difference between case and control groups. Furthermore, some novel inflammation biomarkers such as presepsin were not assessed in this study.

Conclusion

The Systemic Inflammatory Index is a parameter that can be used in the follow-up of patients with COVID-19 and in estimating its mortality.

While explaining the test results to the patients, NLR is calculated and reported as an appendix. A similarly, calculating the SII would be useful for both the physicians and patients.

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