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ORIGINAL ARTICLE

Evaluation of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Covid-19 Patients Treated for Cytokine Storm

Sitokin Fırtınası Nedeniyle Tosilizumab ile Tedavi Edilen Covid-19 Hastalarında Nötrofil/Lenfosit Oranı ve Trombosit/Lenfosit Oranının Değerlendirilmesi

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ABSTRACT

Background/Aims: There is a significant increase in proinflammatory cytokine levels in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients entering cytokine storm. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), also increase in inflammatory diseases. The aim was to evaluate the NLR and PLR of coronavirus disease 2019 (COVID-19) patients receiving tocilizumab (TCZ) due to cytokine storm.
Materials and Methods: In this retrospective, cross-sectional study conducted between March and December 2020, adult patients with laboratory-confirmed COVID-19 were analyzed
Results; The mean age of 519 patients included in the study was 61.6 ± 17.0 years, with male predominance (64.7%). 70.7% of patients had at least one type of comorbidity and the most common comorbid conditions were chronic obstructive pulmonary disease (45.9%) and asthma (28.7%). 399 patients who were given TCZ (group 1) and 120 patients who were not given TCZ (group 2) were evaluated. Compared with group 2, group 1 had more male predominance and they were older (p<0.001). The mortality rate, which was found as 48.6% in group 1, was approximately twice as high in the intensive care unit (ICU). NLR and PLR were significantly higher and lymphopenia was more prominent in group 1, especially in ICU patients than group 2 (p<0.001).
Conclusion: High NLR, PLR and lymphopenia was more common in critically ill Covid-19 patients. Therefore, they may be used as a marker to predict poor prognosis. It can be suggested to treat these patients more aggressively in the initial period.

Keywords: Covid-19; inflammation; lymphopenia; NLR; PLR

ÖZ

Giriş/Amaç: Sitokin fırtınasına giren şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) hastalarında proinflamatuar sitokin seviyelerinde önemli bir artış vardır. Nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranı (PLO), inflamatuar hastalıklarda da artar. Amaç, sitokin fırtınası nedeniyle tosilizumab (TCZ) alan koronavirüs hastalığı 2019 (COVID-19) hastalarının NLR ve PLR'sini değerlendirmektir.
Gereç ve Yöntem: Mart ve Aralık 2020 tarihleri arasında yürütülen bu geriye dönük, kesitsel çalışmada, laboratuvar tarafından doğrulanmış COVID-19'lu yetişkin hastalar analiz edildi.
Bulgular: Çalışmaya alınan 519 hastanın yaş ortalaması 61,6 ± 17,0 yıldı ve erkek ağırlıklıydı (%64,7). Hastaların %70,7'sinde en az bir tip komorbidite vardı ve en sık görülen komorbid durumlar kronik obstrüktif akciğer hastalığı (%45,9) ve astımdı (%28,7). TCZ verilen 399 hasta (grup 1) ve verilmeyen 120 hasta (grup 2) değerlendirildi. Grup 2'ye göre grup 1'de erkek ağırlığı daha fazlaydı ve daha yaşlıydılar (p<0.001). Grup 1'de %48,6 olarak saptanan ölüm oranı yoğun bakımda (YBÜ) yaklaşık iki kat daha yüksekti. Grup 1'de özellikle YBÜ hastalarında NLO ve PLO anlamlı olarak yüksekti ve lenfopeni grup 2'ye göre daha belirgindi (p<0.001).
Sonuç: Yüksek NLO, PLO ve lenfopeni, kritik derecede hasta olan Covid-19 hastalarında daha yaygındı. Bu nedenle, kötü prognozu tahmin etmek için bir belirteç olarak kullanılabilirler. Bu hastaların başlangıç döneminde daha agresif tedavi edilmesi önerilebilir.

Anahtar Kelimeler: Covid-19, inflamasyon, lenfopeni, NLO, PLO

Introduction

Severe acute respiratory syndrome (SARS-CoV-2), has become a major public health problem for the whole world. Old age and comorbid diseases, emerged as the most prominent predisposing factors for the development of severe Coronavirus disease 2019 (COVID-19) and related death (1-3). It has been shown that, there is a significant increase in proinflammatory cytokine levels in severe SARS-CoV-2 patients entering cytokine storm (4,5). Interleukin-6 (IL-6) has been known as one of the most important proinflammatory cytokines in patients who died due to SARS-CoV-2 (5). Tocilizumab (TCZ), an agent that inhibits the function of the IL-6 receptor (IL-6R), is recommended to the most ill people with elevated IL-6 (4). However, IL-6 is not a parameter that can be studied in every health institution. As it is known, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), also increase in inflammatory diseases (6,7). It can be preferred because, it is a basic and cheaper method and a test performed in every hospital. Additionally, the NLR and PLR result are obtained by evaluating the complete blood count (CBC) analysis and can enlighten us in terms of different situations. By looking at these parameters, they can be predicted whether

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patients will enter the cytokine storm. Thus, it can be suggested that, these patients will be recognized earlier so, closer follow-up of these patients and by initiation of aggressive treatment earlier may predict better prognosis. In this study, it was aimed to evaluate the prognosis and NLR-PLR of Covid-19 patients with cytokine storm who received TCZ.

Materials and Methods

Design of the study

Medical files of Covid-19 patients between March and December 2020 were evaluated retrospectively.

This research was performed under the guidance of the Declaration of Helsinki and the Good Clinical Practice Guidelines and after obtaining the written consent form from the participants. Ethical Consent: The study was approved by the local ethics committee (2021/008- E-41901325-050.99-2300).

Participants of the study

The medical files of patients with a positive Covid-19 Polymerase Chain Reaction (PCR) were reviewed throughout the study. Age, gender and comorbid diseases of the participants were recorded. The comorbid diseases of the patients such as asthma, chronic obstructive pulmonary disease(COPD), congestive heart failure(CHF), pulmonary thromboembolism(PTE), hypertension(HT), Coronary artery disease, diabetes mellitus and cancer have been questioned. There were no patients with immunodeficiency, rheumatoid arthritis and chronic renal failure, Group 1: Patients with a cytokine storm and who received TCZ included in the study. Group 1 was divided into 2 subgroups; those treated in the ward and intensive care unit (ICU). Group 2: Hospitalized patients without cytokine storm who did not receive TCZ. The admission time of the patients was determined as day 0 and they were followed up until discharge or death (early mortality during hospitalization).

Laboratory studies

The results of laboratory studies CBC, including white blood cell (WBC), NLR and PLR were evaluated based on medical history. Detection of NLR and PLR was found by dividing neutrophil to lymphocyte count and platelet to lymphocyte count respectively.

Groups were compared for these laboratory parameters. In addition, patients treated in the service and intensive care unit as subgroups of group 1 were also compared in this respect.

Statistical Analysis

Percentages and numbers were used to define categorical variables. Anderson-Darling tests, Kolmogorov-Smirnov test and Shapiro-Wilk were used in the normal distribution of numerical variables. When the numerical variables of two independent groups showed normal distribution, independent samples t-test was used for comparison. Mann-Whitney U test was used in the analysis of non-normally distributed variables. Pearson Chi-square and Fisher's Exact tests were used to analyze categorical variables. Mean ± standard deviation and median minimum-maximum values were used for continuous variables. To analyze categorical variables Fisher Freeman Halton test was used. Jamovi-version 1.8.4.0, JASP-version 0.14.1.0 and Jamovi project-2020 (Sydney, Australia) were used for statistical analysis. The level of statistical significance was set as p-value below 0.05.

Results

There were 519 participants with Covid-19 infection in this research. The mean age of the participants was 61.6 ± 17.0 years, and male gender was dominant (64.7%). There was at least one comorbid condition in 367 patients (70.7%).

Respiratory chronic illnesses, including COPD in 238 (45.9%) and asthma in 149 (28.7%) patients were the most common comorbidities (table 1). There were 399 and 120 patients in group 1 and group 2, respectively. When compared in terms of age, patients in group 1 were older than those in group 2 ($p<0.001$) and male predominance was meaningful in group 1 ($p<0.001$) (Table 1). The presence of high comorbidity in group 1 was striking compared to group 2 (77.7% vs 47.5%, $p<0.001$). Although HT was seen more frequently in group 2 ($p<0.001$), when group 1 was examined, the presence of COPD and asthma was significantly higher. ($p<0.001$). Laboratory results of the groups are given in table 2. WBC count, NLR, PLR ($p<0.001$) and platelet count ($p=0.003$) were higher and lymphopenia was more prominent ($p<0.001$) in group 1 than group 2.

When the length of hospital stay was evaluated, the median duration in group 1 (12 days) was significantly higher than in group 2 (7 days) ($p<0.001$). In 57.4% of the patients in the group 1, treatment in ICU was required. The mortality rate among the patients in group 1 was 48.6%. None of the patients in group 2 developed mortality and did not need intensive unit care.

The patients in group 1 were divided into those treated in the wards and intensive care unit, and their outcomes were compared. There were 170 patients (42.6%) who were treated in the wards only. The need for ICU was necessitated in 229 patients (57.4%). Although the median length of hospital stay was longer in ward patients (13 vs. 11 days, $p<0.001$), the mortality rate in ICU patients (83.4%) was significantly higher than in the ward (1.8%) ($p<0.001$).

The hematological results of patients in group 1 are reported in table 3. A significant difference was found between the subgroups of group 1 in terms of WBC count, NLR and PLR values of the patients ($p<0.05$). In addition, when the deceased (n=194, 48.6%) and living patients (patients discharged with recovery; n=205, 51.4%) in group 1 were compared, it was seen that WBC, NLR and PLR values were higher in the deceased patients ($p<0.001$). Since there were no patients in Group 2 who died, such a comparison was not made.

Table 1. Demographic and clinical characteristics of the patients.

	Overall (n=519)	Group 1 (n=399)	Group 2 (n=120)	p
Age (year) Mean ± SD	61.6 ± 17.0	65.0 ± 13.2	50.1 ± 22.5	<0.001
Sex				
Male n (%)	336 (64.7)	283 (70.9)	53 (44.2)	<0.001
Female n (%)	183 (35.3)	116 (29.1)	67 (55.8)	
Comorbidity n (%)	367 (70.7)	310 (77.7)	57 (47.5)	<0.001
Asthma n (%)	149 (28.7)	137 (34.3)	12 (10.0)	<0.001
COPD n (%)	238 (45.9)	232 (58.1)	6 (5.0)	<0.001
Hypertension n (%)	90 (17.3)	53 (13.3)	37 (30.8)	<0.001
Congestive heart failure n (%)	22 (4.2)	19 (4.8)	3 (2.5)	0.412
Coronary artery disease n (%)	51 (9.8)	43 (10.8)	8 (6.7)	0.250
Diabetes mellitus n (%)	100 (19.3)	82 (20.6)	18 (15.0)	0.222
Cancer n (%)	16 (3.1)	14 (3.5)	2 (1.7)	0.384
PTE n (%)	6 (1.2)	4 (1.0)	2 (1.7)	0.626
Others n (%)	42 (8.1)	34 (8.5)	8 (6.7)	0.644

SD: standard deviation; COPD: chronic obstructive pulmonary disease; PTE: pulmonary thromboembolism; group 1: Covid 19 patients with cytokine storm who received tocilizumab; group 2: Covid 19 patients without cytokine storm who didn't receive tocilizumab; p<0.05: significant

Table 2. Comparison of the laboratory values between groups.

Laboratory values	Group 1 (n=399) Median (Range)	Group 2 (n=120) Median (Range)	p
White blood cell count (× 109/L)	9.1 (1.4 – 32.0)	6.9 (2.0 – 23.0)	<0.001
Platelet count (× 109/L)	249.0 (8.0 – 654.0)	204.0 (22.0 – 506.0)	0.003
Lymphocyte count (× 109/L)	0.6 (0.1 – 11.4)	1.4 (0.0 – 4.9)	<0.001
Lymphocyte (%)	6.8 (0.7 – 54.0)	22.1 (0.0 – 64.2)	<0.001
Neutrophil count (× 109/L)	7.9 (1.0 – 30.2)	3.9 (1.0 – 20.6)	<0.001
Neutrophil (%)	88.9 (39.7 – 98.3)	67.9 (25.0 – 95.2)	<0.001
NLR	13.2 (0.8 – 139.2)	3.0 (0.4 – 31.7)	<0.001
PLR	384.7 (22.3 – 2885.7)	154.1 (7.9 – 670.7)	<0.001

NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; p<0.05: Significant

Table 3. Comparison of the laboratory values of the patients in the group 1 treated in the wards and ICU

Laboratory values	Wards (n=170) Median (Range)	ICU (n=229) Median (Range)	p
White blood cell count (× 109/L)	8.0 (1.4–25.5)	10.2 (2.4–32.0)	<0.001
Platelet count (× 109/L)	261.0 (37.0 – 654.0)	244.0 (8.0 – 635.0)	0.533
Lymphocyte count (× 109/L)	0.6 (0.1 – 9.8)	0.6 (0.1 – 11.4)	0.009
Lymphocyte (%)	8.4 (1.9 – 52.8)	5.5 (0.7 – 54.0)	<0.001
Neutrophil count (× 109/L)	6.8 (1.0 – 23.4)	8.9 (1.4 – 30.2)	<0.001
Neutrophil (%)	86.5 (39.7 – 96.6)	90.5 (43.0 – 98.3)	<0.001
NLR	10.5 (0.8 – 48.9)	16.4 (0.8 – 139.2)	<0.001
PLR	355.5 (22.3 – 2885.7)	400.0 (26.5 – 2088.9)	0.033

ICU: Intensive care unit; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; p<0.05: significant

Discussion

Due to the complexity of Covid-19 disease, serious and fatal complications can occur rapidly in its clinical course. Changes in some hematological parameters in the early period may predict these severe conditions (8,9).

The reaction of the immune system against viral infections occurs especially through lymphocytes, and cellular immunity is weakened during systemic infection (10). Recent studies suggest that WBC, NLR and PLR are important parameters in predicting inflammation (11,12,13). Although no significant association between disease severity and PLR has been reported, a significant association between high NLR and age has been reported (12). The cytokine storm can affect many organs and can lead to lung damage and acute respiratory distress syndrome (12-14). It was reported that an increase in NLR was an independent risk factor for severe Covid-19 infection (15,16). In addition, a direct correlation was found between NLR and IL-6 level. Furthermore, NLR can be used as a marker to follow up the outcome of IL-6 blockade (16). In current study, WBC, the neutrophil and platelet count, NLR and PLR were higher in the group 1 than group 2. Consistent with the recent reports (12,17), in the current study, lymphopenia was significantly prominent in the group 1 and severe, especially in patients treated in ICU.

It has been reported that the disease has a more severe course especially in patients with comorbid diseases such as diabetes, hypertension, cardiac and chronic pulmonary diseases and in the elderly (2,3,12,18,19). In the current study also, the patients were older; and more frequently were male in the group 1. In addition, the incidence of COPD and asthma, but not HT, was significantly higher in group 1.

In the current study, no patient in group 2 required an ICU and no death occurred. However, the need for ICU and invasive mechanical ventilation (IMV) was necessitated in 57.4% of the patients, who initially hospitalized in the ward and received TCZ. In fact, all of the patients in the group 1 were the patients receiving TCZ. Initiating this treatment in the early phase of the cytokine storm may be considered to improve the prognosis. Furthermore, while approximately half of these patients in group 1 died, this rate increased to more than 80% in the ICU. The reasons for the high mortality rate can be attributed to the fact that our hospital was a large pandemic hospital, so there were many intensive care units. In addition, because the percentage of the disease was high during the time of the study, especially patients with severe disease were hospitalized. The conditions of the patients followed in the ward were also severe.

Since the rate of patients receiving IMV during the intensive care unit was very high, especially critical patients were followed up in the intensive care unit. In addition, comorbid diseases in most of the patients might have affected the severity of the disease and mortality rates. Studies have reported that mortality

and morbidity are particularly high in males, the elderly and those with comorbidities (1,20). Similarly, most of the patients were men and elderly in current study. In the current study, the rate of comorbidity was significantly higher in the group 1. Especially, COPD and asthma were more common in group 1. On the other hand, HT was more common in group 2. In the previous study, ICU and hospital mortality rates were reported as 48.8% and 53.4%, respectively (20). In other studies, mortality of critically ill patients in ICU, due to COVID-19 ranges from 13.5% to 78% (21-29). In a study conducted in China on ICU patients, ICU mortality rate was 39% for the whole ICU patients (23). However, in the current study, the mortality rate in the patients requiring IMV was high (83.4%).

When the subgroups of group 1 were compared in terms of hematological parameters, WBC, NLR, PLR were found higher in patients treated in the ICU than in the ward. In addition, consistent with the recent reports (12,17-20) in the current study, lymphopenia was common and severe, especially in patients treated in ICU. So, according to these results, patients with higher NLR, PLR, WBC counts and lymphopenia, at baseline required more ICU treatment.

And these parameters can be considered as independent biomarkers for indicating poor clinical outcomes. For this reason, by giving aggressive life support management in the in the early phase of the cytokine storm, the prognosis of the patients can be improved.

Limitations of the Study

This study has several limitations. Due to the very rapid and sudden development of the pandemic and many concerns, in addition to unknowns about the disease, this research was conducted retrospectively. Although history of respiratory diseases of the patients was known, we could not get an idea about other variables that may affect the prognosis, such as body mass index and smoking.

In addition, another limitation is that, although the initial values of the patients were taken in the study, no comparison was made with the parameters on the last day of follow-up. Making this comparison with a larger study will show us the effectiveness of the treatment.

Conclusion

In the current study, respiratory chronic diseases were the most common comorbidities and the patients were significantly older and more frequently were male especially in group 1. WBC, NLR and PLR were higher and lymphopenia was more common in the group 1. More importantly, these parameters were quite evident in critical Covid-19 patients. Therefore, they may be used as a marker to predict poor prognosis in the patients. So, by treating these patients more aggressively in the initial period, their prognosis can be improved.

In fact, by looking at these markers, other inflammatory diseases can be treated more effectively and aggressively in the early period before the disease progresses. As a result, the development of complications in such diseases can be prevented. Further and large-scale studies are needed as uncertainties remain about the disease.

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