



The Relationship of Hemogram and Inflammatory Biomarkers to Length of Stay in Hospital and Clinical Course in Patients with COVID-19

COVID-19 Olgularında Hemogram ve Enflamasyon Biyobelirteçlerinin Hastane Yatış Süresi ve Klinik Seyirle İlişkisi

Banu BÜYÜKAYDIN

Bezmiâlem Vakıf University, Department of Internal Medicine, İstanbul, Turkey

ABSTRACT

Objective: It was aimed to research the relationship between neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), inflammatory markers and length of stay in hospital (LOS) with clinical results in hospitalized patients with Coronavirus disease-2019 (COVID-19).

Methods: Total leukocyte, neutrophil, lymphocyte and platelet counts (/mm³), hemoglobin (g/dL), mean platelet volume, C-reactive protein (CRP) (mg/L), ferritin (ng/mL), lactate dehydrogenase (LDH) (U/L) creatine kinase (U/L), D-dimer (ng/mL), troponin-I (pg/mL), alanine aminotransferase (U/L), aspartate aminotransferase (U/L) and serum creatinine (mg/dL) measurements were recorded. NLR and PLR were calculated. Applied treatments, intensive care unit requirement, and mortality rates were determined. For LOS and mortality, the sensitivity of biochemical parameters was evaluated.

Results: One hundred seventy-one patients (87 females, 84 males) were evaluated. The mean age was 57.9±14.6 years, and the mean LOS was 8.83±6.4 days. There was a positive correlation between NLR and PLR (p<0.05). NLR was correlated with CRP, LDH, ferritin, D-dimer, and troponin-I (p<0.05). LOS was longer in patients with high serum creatinine, CRP, LDH, ferritin, and troponin-I (p<0.05). The need of intensive care unit was observed in 14.6% of the patients and mortality rate was 9.9%. The most used medications were Azithromycin and Hydroxychloroquine.

ÖZ

Amaç: Hospitalize Coronavirüs hastalığı-2019 (COVID-19) olgularında nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR) ve enflamatuvar göstergelerin hastane yatış süresi (HYS) ve klinik seyirle olan ilişkisini araştırmaktır.

Yöntemler: Çalışmaya dahil edilen olguların total lökosit, nötrofil, lenfosit ve trombosit sayıları (/mm³), hemoglobün düzeyi (g/dL), ortalama trombosit hacmi, C-reaktif protein (CRP) (mg/L), ferritin (ng/mL), laktat dehidrogenaz (LDH) (U/L), kreatin kinaz (U/L), D-dimer (ng/mL), troponin-I (pg/mL), alanin aminotransferaz (U/L), aspartat aminotransferaz (U/L) ve serum kreatinin (mg/dL) sonuçları kaydedildi. NLR ve PLR hesaplandı. Uygulanmış olan antiviral tedaviler kaydedildi. Yoğun bakım ünitesi takibi ve mortalite oranları belirlendi. Biyokimyasal parametrelerin kendi aralarındaki korelasyon analizleri yapıldı ve parametrelerin HYS ve mortalite öngörüsü için duyarlılıkları analiz edildi.

Bulgular: Toplam 171 hastanın (87 kadın, 84 erkek) verileri değerlendirildi. Ortalama yaş 57,9±14,6 yıl, ortalama HYS 8,83±6,4 gündü. NLR ile PLR pozitif yönde koreleydi (p<0,05). NLR ile CRP, LDH, ferritin, D-dimer ve troponin-I arasında pozitif yönde korelasyon vardı (p<0,05). HYS, artmış serum kreatinin, CRP, LDH, ferritin ve troponin-I olan olgularda daha uzundu (p<0,05). Yirmi beş olgu (%14,6) yoğun bakım ünitesinde takip edilmiş, 17 olgunun takibi (%9,9) mortalite ile sonuçlanmıştı. Tedavide Azitromisin ve Hidroksiklorokin kullanımı yüksek orandaydı.

Address for Correspondence: Banu BÜYÜKAYDIN, Bezmiâlem Vakıf University, Department of Internal Medicine, İstanbul, Turkey

E-mail: bbuyukaydin@hotmail.com **ORCID ID:** orcid.org/0000-0003-2843-4209

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In patients with advanced age, prolonged LOS, and increased inflammation, the frequency of using Favipravir and Tocilizumab was higher.

Conclusion: In patients with COVID-19, inflammatory parameters are useful to predict LOS. Increased NLR and PLR seem to be related with poor prognosis.

Keywords: COVID-19, length of stay in hospital, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, intensive care unit follow up, mortality

Favipravir ve Tocilizumab tedavileri uygulanan olgularda ileri yaş, uzamış yatış süresi ve artmış enflamatuvar göstergeler mevcuttu.

Sonuç: COVID-19 olgularında HYS'yi öngörmek için enflamatuvar parametreler kullanılabilir. Artmış NLR ve PLR kötü klinik seyirle ilişkili gözükmemektedir.

Anahtar Sözcükler: COVID-19, hastane yatış süresi, nötrofil-lenfosit oranı, platelet-lenfosit oranı, yoğun bakım takibi, mortalite

Introduction

At the end of 2019, a new Coronavirus was determined as a result of virus sequence analyses performed in cases of pneumonia of unknown cause in Wuhan, China. This infection, defined as Coronavirus disease-2019 (COVID-19), has become a serious threat to human health due to the rapid increase in its incidence, high contagiousness and high mortality. Although 81% of the cases have a mild course, a severe course is observed in 14% of cases and a critically severe course is observed in 5% (1). Prognosis is poor and mortality is high in critically severe cases (2). Fever, cough, dyspnea, fatigue, and myalgia are among the clinical symptoms, and the ground-glass appearance on computed tomography is accepted as the typical finding (3,4). Its pathogenesis includes the inflammatory process associated with vasculitis, the complement cascade and pro-inflammatory cytokines, and the process results in serious organ damage, particularly lung and cardiovascular damage (5,6).

Due to the high rates of infection-related mortality, early recognition of cases that will progress is very important, and biomarkers to be used for this purpose are among the research topics. Normal or decreased neutrophil and lymphocyte count, thrombocytopenia, increased transaminase, lactate dehydrogenase (LDH), creatine kinase (CK) and troponin levels, and changes in D-dimer and albumin have been shown as risk factors for referral to intensive care unit (ICU) in COVID-19 cases (3,7). Increased neutrophil-lymphocyte ratio (NLR) has been associated with poor prognosis, and platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio have been evaluated among inflammatory response indicators (8). The change in mean platelet volume (MPV) associated with this infection is among the research topics, although its prediction is low (9).

Clinical course and response rates to the treatment show unpredictable differences among cases. Length of stay (LOS) in hospital has been associated with patient age, current comorbidities, severity of symptoms and lymphopenia level (10-12). The prolongation of the hospitalization period increases the risk of complications, especially hospital infection. Clinical and laboratory tools to be used to predict this period are among the research topics.

There is not yet an approved treatment method and a vaccine with proven safety against COVID-19. The use of protective equipment, symptomatic supportive treatment, and advanced

life support in serious disease and treatment of complications are the accepted approach models (13). It is recommended that uncomplicated mild cases are treated outside the hospital, whereas complicated cases with additional risk factors and severe respiratory failure are hospitalized (14).

In our study, we aimed to investigate the relationship between NLR, PLR, inflammatory indicators, medical treatments and LOS with clinical course in hospitalized patients with COVID-19.

Method

In our study, the files of the patients, who were clinically and radiologically diagnosed with COVID-19 between March 20 and May 20, 2020 hospitalized, were retrospectively evaluated with the permission of the institutional ethics committee, number with 54022451-050-05-04- 02/09/2020. The patients were included in the study according to the protocol number order. No additional intervention was made in patient selection. Patient age, gender and LOS period were recorded.

Cases with malignancy recorded were not included in the study. Related was the thought that the current diagnosis and the treatments might affect the parameters evaluated. Total leukocyte, neutrophil, lymphocyte and thrombocyte counts (/mm³), hemoglobin level (g/dL) and MPV were recorded among the hemogram parameters measured on the day of hospitalization. NLR and PLR were calculated and included in the study. C-reactive protein (CRP) (mg/L) and ferritin (ng/mL) levels as acute phase indicators, together with LDH (U/L), CK (U/L), D-dimer (ng/mL), troponin-I (pg/mL), alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L) and serum creatinine, (mg/dL) were recorded.

Among the treatments applied, the presence of Azithromycin, Oseltamivir, Hydroxychloroquine, Favipravir and Tocilizumab was investigated. Anti-coagulant treatments, especially low molecular weight heparin, were determined. The numbers of patients followed up in the ICU and developing mortality were recorded. The possible relationships of the evaluated biochemical parameters with each other and their sensitivity in predicting the length of hospital stay and mortality were analyzed. In addition, the effects of the treatments used on the parameters evaluated were investigated.

Statistical Analysis

IBM 22.0 version was used for statistical analysis. The Mann-Whitney U test was used for non-parametric analysis. Descriptive analyses were presented as mean and standard deviation. The chi-square and Fisher’s exact test were employed for categorical analyses. Non-parametric Spearman’s test was used for the correlation between LOS and biochemical parameters, and Pearson correlation test was used for the correlation of biochemical parameters among themselves. P<0.05 was considered statistically significant for all data.

Results

Data of 171 patients (87 female, 84 male) were evaluated. The mean age was 57.9±14.6 years. The mean LOS was found to be 8.83±6.4 days. A very low statistically significant relationship was found between the age of the patient and LOS in the same direction (rs: 0.18, p=0.018). The mean values and statistical differences of biochemical parameters according to gender are presented in Table 1. When all cases were evaluated together, the NLR correlated negatively with the hemoglobin level and positively with the platelet count (r=-0.176, p=0.021, r=0.163, p=0.033). A statistically significant positive correlation was found between NLR and PLR (r=0.645, p<0.05). NLR was also significantly correlated in the same direction with CRP, LDH, ferritin, D-dimer, and troponin-I (r=0.341, r=0.216, r=0.226, r=0.4, r=0.264, p<0.05). PLR was positively correlated with neutrophil absolute count and d-dimer and negatively correlated

with MPV (r=0.199, r=0.168, r=-0.305, p<0.05). There was a negative correlation between MPV and the absolute number of platelets (r=-0.425, p<0.05). Total leukocyte and neutrophil absolute counts were positively correlated with D-dimer, LDH, ferritin, and troponin-I (r=0.274, 0.329, r=0.213, 0.275, r=0.213, 0.271, r=0.274, 0.308, p<0.05).

LOS was longer for patients with higher serum creatinine, CRP, LDH, ferritin and troponin-I levels (p<0.05). Twenty-five cases (14.6%) (13 women, 12 men) were followed up in the ICU. Table 2 shows the changes of the parameters between cases with and without ICU follow-up. Azithromycin usage rate was 91.8% (157 cases), Hydroxychloroquine usage rate was 97.1% (166 cases). For oseltamivir, this rate was 30.4% (52 cases). 63.7% of the cases had received anticoagulant treatment, mostly (60.2%) low molecular weight heparin. Favipravir treatment for 60 cases (35.1%) and Tocilizumab treatment for 12 cases (7%) were added to the existing treatment. Favipravir rate was 84% and Tocilizumab usage rate was 32% in patients with ICU. While there was a positive correlation between the number of ICU admissions and Favipravir use, this number was negatively correlated with Tocilizumab (p<0.05). In 60 cases given Favipravir, age, LOS, CRP, ALT, AST, LDH, ferritin and troponin-I levels were statistically significantly higher, and the absolute number of lymphocytes was lower (p<0.05), compared to the patients who did not use it. In these cases, NLR was statistically significantly higher, while PLR was similar between the two groups (p<0.05, p=0.451). LOS, CRP, ALT, AST, LDH and ferritin levels were found to be statistically significantly

Table 1. The averages of evaluated biochemical parameters

| | Female | Male | p |
|---------------------------------|---------------|---------------|-------|
| Age | 59.7±14.1 | 56.01±17.98 | 0.1 |
| LOS-day | 8.34±5.82 | 9.33±6.36 | 0.265 |
| Total leukocyte-mm ³ | 7.88±4.18 | 7.34±3.2 | 0.721 |
| Neut-mm ³ | 5.44±3.74 | 5.27±2.98 | 0.506 |
| Lymph-mm ³ | 1.59±0.79 | 1.27±0.57 | <0.05 |
| Hb-g/dL | 12.68±1.64 | 13.94±2.09 | <0.05 |
| PLT-mm ³ | 244±86.4 | 201.9±69.2 | <0.05 |
| MPV | 7.71±1.35 | 7.93±1.36 | 0.135 |
| NLR | 4.34±3.93 | 5.21±4.31 | 0.058 |
| PLR | 198.26±137.5 | 193.5±117 | 0.607 |
| CRP-mg/L | 57.42±56.01 | 64.04±55.5 | 0.349 |
| D-dimer-ng/mL | 498.83±574.42 | 416.42±798.04 | 0.03 |
| ALT-U/L | 28.38±25.16 | 35.68±36.91 | 0.057 |
| AST-U/L | 32.57±29.47 | 37.44±33.64 | 0.365 |
| Creatinin-mg/dL | 1.03±0.78 | 1.11±0.73 | <0.05 |
| LDH-U/L | 287.48±124.43 | 294.18±133.4 | 0.888 |
| CK-U/L | 84.93±67.71 | 171.95±272 | <0.05 |
| Ferritin-ng/mL | 371.04±830.03 | 418.45±520.26 | <0.05 |
| Troponin-I-pg/mL | 34.10±170.27 | 15.51±34.09 | 0.257 |

LOS: Length of stay in hospital, Neut: Neutrophil count, Lymph: Lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase

Table 2. The changes of parameters between the patients in clinical service and intensive care unit

| | Clinical service (n=146) | ICU (n=25) | p |
|---------------------------------|--------------------------|-----------------|---------|
| Age | 56.77±14.09 | 64.6±16.17 | p<0.05 |
| LOS-day | 7.76±4.12 | 15.08±11.85 | p<0.05 |
| Total leukocyte-mm ³ | 7.11±3.41 | 10.59±3.93 | p<0.05 |
| Neut-mm ³ | 4.78±2.97 | 8.68±3.78 | p<0.05 |
| Lymph-mm ³ | 1.47±0.7 | 1.22±0.7 | p=0.057 |
| Hb-g/dL | 13.37±1.97 | 12.89±1.96 | p=0.208 |
| PLT-mm ³ | 219.12±79.25 | 249.56±88.26 | p=0.087 |
| MPV | 7.82±1.39 | 7.77±1.12 | p=0.946 |
| NLR | 3.97±3.15 | 9.43±5.87 | p<0.05 |
| PLR | 182.59±111.89 | 273.79±179.52 | p<0.05 |
| CRP-mg/L | 53.07±52.79 | 104.47±52.87 | p<0.05 |
| D-dimer-ng/mL | 346.11±285.17 | 1102.08±1530.38 | p<0.05 |
| ALT-U/L | 29.9±29.11 | 44.08±42.23 | p=0.068 |
| AST-U/L | 31.78±26.42 | 53.33±49.15 | p<0.05 |
| Creatinin-mg/dL | 1.04±0.72 | 1.23±0.95 | p=0.317 |
| LDH-U/L | 265.7±96.74 | 437.2±185.58 | p<0.05 |
| CK-U/L | 106.58±130.94 | 258.92±412.49 | p<0.05 |
| Ferritin-ng/mL | 290.6±396.36 | 985.35±1400.31 | p<0.05 |
| Troponin-I-pg/mL | 10.52±18.09 | 108.38±310.1 | p<0.05 |

ICU: Intensive care unit, LOS: Length of stay in hospital, Neut: Neutrophil count, Lymph: Lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase

higher, and the absolute count of lymphocytes was found to be lower in 12 patients who were given tocilizumab ($p<0.05$). In these cases, NLR and PLR were not different from those who did not use tocilizumab ($p=0.063$, $p=0.127$).

Mortality rate for our patient group was 17 cases (7 women, 10 men) (9.9%). The results of these cases with the remaining patient group are presented in Table 3. All cases with mortality were followed up in the ICU. In these cases, Favipravir usage rate was 82.4% and Tocilizumab usage rate was 29.4%.

Discussion

In our study, 171 hospitalized COVID-19 cases were evaluated and the mean LOS was found to be 8.83 ± 6.4 days. LOS varies among countries. While an average of 19 and 21 days of LOS was reported in studies originating from China and Vietnam, this time is 7-8 days in those originating from Europe and the United States (15,16). This difference is thought to be due to differences in disease prevention and control approaches among countries. In our study, LOS was similar between male and female patient groups. Although a statistically very low relationship was found, it was observed that LOS increased as the age of the patients increased. This period is thought to be prolonged due to the higher rate of comorbid diseases and the risk of developing a more severe clinical picture in older patients.

In many studies, it has been observed that advanced age is the main factor in hospitalization risk (17,18). In our study, it was

remarkable that the average age of the patients who were taken to the ICU and developed mortality was significantly higher. CRP, LDH, ferritin and troponin-I values at the time of hospitalization were among the other factors affecting LOS in our case group. High CRP and LDH levels have been previously associated with a severe clinical course and prolonged hospitalization (19). There are studies in which high ferritin level is associated with severe clinical course and high troponin-I level with mortality (20,21).

In our study, a positive correlation was found between NLR and PLR, which are among the parameters investigated in the prediction of clinical progression in the literature. NLR was also significantly positively correlated with platelet count, CRP, LDH, ferritin, D-dimer, and troponin-I. PLR was positively correlated with the absolute number of neutrophils and D-dimer. The absolute number of lymphocytes was lower in male patients but there was no significant difference between the two genders in terms of NLR and PLR. NLR and PLR are among for the prognostic indicators, especially cardiovascular diseases and malignancies (22). In studies and meta-analyses on NLR - related COVID-19, it has been reported that high neutrophil count and decreased lymphocyte count and NLR are useful in predicting disease severity (23). In a study in which 548 COVID-19 cases were analyzed, it was reported that increased neutrophil count and NLR were found in critically ill patients and cases with mortality, and low eosinophil, lymphocyte and platelet counts were observed during hospitalization of these cases (24). As a new systemic inflammation indicator, PLR is one of the factors

Table 3. The changes of parameters in cases with or without of mortality

| | Non exitus (n=154) | Exitus (n=17) | p |
|---------------------------------|--------------------|-----------------|---------|
| Age | 56.84±14.21 | 67.71±15.11 | p<0.05 |
| LOS-day | 8.07±4.48 | 15.71±13.71 | p<0.05 |
| Total leukocyte-mm ³ | 7.25±3.50 | 10.92±3.9 | p<0.05 |
| Neut-mm ³ | 4.95±3.11 | 8.97±3.63 | p<0.05 |
| Lymph-mm ³ | 1.45±0.71 | 1.25±0.64 | p=0.257 |
| Hb-g/dL | 13.36±1.94 | 12.79±2.24 | p=0.319 |
| PLT-mm ³ | 222.74±83.16 | 231±60.3 | p=0.394 |
| MPV | 7.8±1.37 | 7.93±1.2 | p=0.501 |
| NLR | 4.3±5.67 | 8.97±5.66 | p<0.05 |
| PLR | 191.8±124.44 | 233.24±152.2 | p=0.136 |
| CRP-mg/L | 55.9±54.17 | 103.89±51.88 | p<0.05 |
| D-dimer-ng/mL | 376.14±395 | 1191.12±1702.3 | p<0.05 |
| ALT-U/L | 29.99±28.53 | 50±49.54 | p=0.146 |
| AST-U/L | 31.99±25.81 | 62.19±58.31 | p=0.069 |
| Creatinin-mg/dL | 1.03±0.7 | 1.4±1.11 | p=0.083 |
| LDH-U/L | 273.89±106.08 | 443.71±201.29 | p<0.05 |
| CK-U/L | 106.53±128.9 | 335.5±488.18 | p<0.05 |
| Ferritin-ng/mL | 299.79±401.28 | 1231.22±1624.65 | p<0.05 |
| Troponin I-pg/mL | 11.33±20 | 147.15±372.17 | p<0.05 |

LOS: Length of stay in hospital, Neut: Neutrophil count, Lymph: Lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase

that increase thrombosis development and responsible for the cytokine and chemokine cascade (25). In COVID-19 cases, high PLR has been reported to be associated with severe clinical course and prolonged LOS (26). In our case group, the total leukocyte and neutrophil absolute counts, as well as NLR and PLR levels were statistically significantly higher in the patients who were followed up in the ICU. It was also remarkable that NLR was higher in cases developing mortality, in line with the literature. The fact that PLR was not observed to be significant in mortality prediction. It can be explained by the relatively low number of patients.

In our study, it was striking that CK and ferritin levels were higher in male patients and acute phase-related CRP, LDH, D-dimer, ferritin, CK, troponin-I levels in case groups with ICU and mortality were apparently high. It was observed that acute phase response increased in patients developing renal dysfunction. However, the predictive effect of transaminase levels and renal functions on ICU admission and mortality was not observed. Our results related to acute phase parameters were consistent with the literature. In these cases, CRP, LDH, CK and troponin levels were associated with disease severity (27). In a cohort analysis performed with 799 patients, the presence of significantly high concentrations of ALT, AST, creatinine, CK, LDH, troponin-I, N-terminal pro-brain natriuretic peptide, and D-dimer was reported in patients with mortality (28). In clinical practice, evaluating D-dimer, LDH, transaminases together with interleukin-6 (IL-6) levels among routine tests is among

the cases recommendations to predict high-risk patients and to identify cases that may benefit from anti-IL-6 and Tocilizumab treatment (29). Cytokine storm is thought to be responsible for acute lung injury and multiorgan failure in these cases. Other inflammatory markers that are being investigated in this process include IL-2, IL-7, tumor necrosis factor-alpha (α), interferon-c inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α , granulocyte-colony stimulating factor, procalcitonin and ferritin (30-32).

For our cases, the rate of follow-up in the ICU was 14.6%, and the mortality rate was 9.9%. ICU rates for our cases were consistent with the literature. We think that all hospitalized patients should be included in the analysis and re-evaluated in order to determine our hospital mortality rate. So far, it has not been determined what percent of infected people are hospitalized. ICU rate has been reported as 10-20% in hospitalized patients, with intubation 3-10%. Also the reported mortality risk was 5,5% for China and 6,5% for worldwide, this rate increases up to 49% in critical cases (33,34). However, the actual mortality rate of COVID-19 has not been determined yet. Risk factors for poor prognosis appear to be patient age and the presence of comorbidities (30). Therefore, the use of scoring systems and patient management according to the results is the recommended to predict disease severity (35). Apparatus and biomarkers that will rapidly and early identify the disease course are among the research topics (36).

Today, an effective treatment method against COVID-19 has not yet been defined. However, due to the similarity of this virus, which is a single-stranded RNA virus, to the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) and Middle East Respiratory Syndrome, the current treatment is based on the experience gained from these two diseases (37). Chloroquine and Hydroxychloroquine have an important place among the treatments. Although the antiviral activity of these drugs is not known exactly, there is information in *in vitro* studies that they prevent the virus to bind and enter the cell (38). Favorable results have been reported in a study in which Azithromycin, a macrolide antibiotic, was used together with Hydroxychloroquine, and it was presented among the recommendations (39,40). The combination of Azithromycin and Hydroxychloroquine is also included in the first stage in the current treatment protocol of our country's Ministry of Health along with relevant literature. Therefore, the rate of using this combination quite high in our case group.

Favipravir treatment is among the recommendations for patients with tachypnea and SpO₂ level below 90% in room air, with bilateral diffuse involvement in imaging, and patients whose clinical condition and pneumonia symptoms progressed while receiving Hydroxychloroquine treatment. In our study, the patients who received Favipravir treatment were older, and the LOS duration was longer and the acute phase response was significantly higher in these cases. Favipravir acts by inhibiting viral RNA-dependent RNA polymerase and has been shown to have good clinical efficacy against COVID-19 (41). Favipravir appears to be a promising agent for treatment. Along with its clinical research, the studies continue in comparative and combination models with placebo and other antiviral agents (42).

Tocilizumab is a recombinant IL-6 receptor monoclonal antibody. In the development of severe alveolar damage and dysfunction in these cases, high IL-6 level among inflammatory mediators was observed as predictive of mortality (31). Clinical studies investigating its effectiveness are promising (43). Because it was a case-based medication, Tocilizumab was used at a rate of 7% for the entire patient group and 32% for the patients who were hospitalized in the ICU. Due to the low rate of use for this patient group, it was not possible to indicate a result on its clinical efficacy, but promising studies related to this treatment continues (44).

Treatment modalities with favorable results reported in the literature. Among these Oseltamivir, Baricitinib, Remdesivir, Ritonavir and Lopinavir, Ivermectin, Darunavir, Camostat Mesylate, Cepharanthin, Selamectin, Mefloquine Hydrochloride, Losartan and Telmisartan, SARS-CoV - specific human monoclonal antibody, protease inhibitors, convalescent plasma and passive immunization. In these cases, supportive and symptomatic treatments, including anticoagulation, are applied on the basis case (45,46).

Study Limitations

Because of the retrospective nature of the study, analyses could only be made over the parameters registered in the system. There is no sufficient and reliable information about possible comorbidities of cases that are among the factors that may affect LOS duration. The fact that the relationship between LOS and inflammation and NLR and PLR was not investigated with multivariate analysis. The absence of objective data on the status of COVID-19-associated disease severity, respiratory support need, existing lung damage and the absence of risk scoring associated with inflammation and thrombosis are other limitations of the study.

Conclusion

The COVID-19 pandemic continues to affect the world with increasing case and mortality rates. In this study, the correlation of leukocyte count, neutrophil absolute count, NLR, and PLR with inflammatory markers was determined. NLR and PLR were observed to be predictive in cases with ICU hospitalization, and NLR in cases developing mortality. Future studies are needed regarding the role of these biomarkers in the pathogenesis of the disease.

Ethics

Ethics Committee Approval: Bezmialem Vakif University Clinical Research Ethics Committee Approval Number: 54022451-050-05-04- 02/09/2020.

Informed Consent: There is no informed consent because of retrospective manner.

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References

1. Weifeng Shang, Junwu Dong, Yali Ren, Ming Tian, Wei Li, Jianwu Hu, Yuanyuan Li The Value of Clinical Parameters in Predicting the Severity of COVID-19 J Med Virol 2020; 21;10.1002/jmv.26031 Online ahead of print.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323:1239.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497-506.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 82:1708-20.
5. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18:844-47.

6. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect.* 2020; 9:1–1.
7. Zhang G, Zhang J, Wang B, et al. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res.* 2020; 21:74.
8. Ai-Ping Yang, Jian-Ping Liu, Wen-Qiang Tao, Hui-Ming Li. The Diagnostic and Predictive Role of NLR, d-NLR and PLR in COVID-19 Patients *Int Immunopharmacol* 2020; 84:106504.
9. Yunbao Pan, Guangming Ye, Xiantao Zeng, et al. Can Routine Laboratory Tests Discriminate SARS-CoV-2-infected Pneumonia From Other Causes of Community-Acquired Pneumonia? *Clin Transl Med* 2020; 10:161-8.
10. Dawei Wang, Bo Hu, Chang Hu et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China *JAMA* 2020; 323:1061-69.
11. Vinayak Mishra, Ajit Deo Burma, Sumit Kumar Das, Mohana Balan Parivallal, Senthil Amudhan, Girish N Rao. COVID-19-Hospitalized Patients in Karnataka: Survival and Stay Characteristics *Indian J Public Health* 2020; 64: 221-24.
12. Xiaofan Liu, Hong Zhou Yilu Zhou et al. Risk Factors Associated With Disease Severity and Length of Hospital Stay in COVID-19 Patients *J Infect* 2020; 81:95-97.
13. Center for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease COVID-19 2020.
14. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected 2020.
15. Pham Quang Thai, Do Thi Thanh Toa, Dinh Thai Son, et al. Factors Associated With the Duration of Hospitalisation Among COVID-19 Patients in Vietnam: A Survival Analysis *Epidemiol Infect* 2020; 10:e114.
16. Wise J. A third of COVID-19 patients admitted to UK hospitals die. *British Medical Journal* 2020; 30: m1794.
17. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention *JAMA* 2020; 323: 1239–42.
18. CDC (Centers for Disease Control and Prevention) Severe outcomes among patients with coronavirus disease 2019 (COVID-19) – United States, February 12–March 16, 2020. *MMWR. Morbidity and Mortality Weekly Report* 69, 343–346.
19. Xiaofan Liu, Hong Zhou, Yilu Zhou et al. Risk Factors Associated With Disease Severity and Length of Hospital Stay in COVID-19 Patients *Comment J Infect* 2020; ;81:95-97.
20. Ian Huang Raymond Pranata, Michael Anthonius Lim, Amaylia Oehadian, Bacht Alisjahbana C-reactive Protein, Procalcitonin, D-dimer, and Ferritin in Severe Coronavirus disease-2019: A Meta-Analysis *Ther Adv Respir Dis* 2020; 14:1753466620937175.
21. Alvaro Lorente-Ros, Juan Manuel Monteagudo Ruiz, Luis M Rincón, et al. Myocardial Injury Determination Improves Risk Stratification and Predicts Mortality in COVID-19 Patients *Cardiol J* 2020 Jun 26, Online ahead of print.
22. M.E. Afari, T. Bhat, Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update, *Expert Rev. Cardiovasc. Ther* 2016;14: 573–77.
23. Furong Zeng, Linfeng Li, Jiling Zeng, Yuhao Deng, Huining Huang, Bin Chen, Guangtong Deng Can We Predict the Severity of Coronavirus Disease 2019 With a Routine Blood Test? *Pol Arch Intern Med* 2020;130:400-6.
24. Ruchong Chen, Ling Sang, Mei Jiang, J et al Longitudinal Hematologic and Immunologic Variations Associated With the Progression of COVID-19 Patients in China Medical Treatment Expert Group for COVID-19 *Allergy Clin Immunol.* 2020; 146:89-100.
25. Rayes J, Bourne JH, Brill A, Watson SP. The dual role of platelet innate immune cell interactions in thrombo-inflammation. *Res Pract Thromb Haemost.* 2019;4:23-35.
26. Rong Qu, Yun Ling, Yi-Hui-Zhi Zhang J et al. Platelet-to-lymphocyte Ratio Is Associated With Prognosis in Patients With Coronavirus disease-19 *Med Virol.* 2020;17:10.
27. Du R-H, Liang L-R, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J.* 2020; 55:2000524.
28. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020; 368:m1091.
29. Zhang C, Wu Z, Li J-W, et al. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents.* 2020. 55:105954.
30. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
31. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395:1033–34.
32. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus- infected pneumonia in Wuhan, China. *JAMA.* 2020;323:1061–69.
33. Guan W-j, Ni Z-y, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–20.
34. World Health Organization. Coronavirus disease (COVID-19): situation report—125. <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200524-covid-19-sitrep-125.pdf?sfvrsn=80e7d7f0-2>.
35. Centers for Disease Control and Prevention, Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>.

36. Michael P McRae, Glennon W Simmons et al. Clinical Decision Support Tool and Rapid Point-of-Care Platform for Determining Disease Severity in Patients With COVID-19 medRxiv. 2020 22;04.16.20068411.
37. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem*2020;21:730-8.
38. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. 2003. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 3:722–7.
39. Gautret P, Lagier JP, Parola P, Hoang VT et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 20:105949.
40. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med.* 2020;2600: 30127-2.
41. Bryner J. 2020. Flu drug used in Japan shows promise in treating COVID-19. Live Science, New York, NY. <https://www.livescience.com/flu-drug-could-treat-coronavirus.html>.
42. Clinicaltrials.Gov. Clinical trials on Favipiravir role in SARS-COV-2 infection. 2020 <https://clinicaltrials.gov/ct2/results?cond=covid+19&term=Favipiravir+&cntry=&state=&city=&dist>
43. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl Acad. Sci. U S A* 2020;117:10970-10975.
44. Chctr.Org. Favipiravir Combined With Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial 2020 www.chictr.org.cn/showprojen.aspx?proj=51126
45. Chris R Triggler, Devendra Bansal, Elmoubasher Abu Baker Abd Farag, Hong Ding , Ali A Sultan COVID-19: Learning From Lessons To Guide Treatment and Prevention Interventions- Review *mSphere*2020;5:e00317-20.
46. Lo'ai Alanagreh, Foad Alzoughool, Manar Atoum. Review Pathogens The Human Coronavirus Disease COVID-19: Its Origin, Characteristics, and Insights Into Potential Drugs and Its Mechanisms *Pathogens* 2020; 29:331.