DOI: 10.4274/mjima.galenos.2021.2021.62
Mediterr J Infect Microb Antimicrob 2021;10:62
Erişim: <http://dx.doi.org/10.4274/mjima.galenos.2021.2021.62>

Evaluation of the Relationship Between Lactate Dehydrogenase/Lymphocyte Ratio with Interleukin-6 Levels in Hospitalized Patients with COVID-19

Hastanede Yatan COVID-19 Tanılı Hastalarda Laktat Dehidrogenaz/Lenfosit Oranı ile İnterlökin-6 Düzeyi İlişkisinin Değerlendirilmesi

Umay BALCI, Kübra DEMİR ÖNDER, Ayşegül SEREMET KESKİN

University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Antalya, Turkey

Abstract

Introduction: Clinical picture of Coronavirus disease-2019 (COVID-19) ranges from mild respiratory symptoms to severe respiratory failure and death. To determine the severity of the disease; lymphocyte count, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer and interleukin-6 (IL-6) levels are the parameters that are used. In this study, it was aimed to evaluate effect of LDH/lymphocyte ratio on prognosis and whether there was a correlation between LDH/lymphocyte ratio and IL-6 in hospitalized patients with COVID-19.

Materials and Methods: Patients who were aged 18 years and older, were positive for Severe acute respiratory syndrome-Coronavirus-2 polymerase chain reaction test, had COVID-19 pneumonia findings on tomography, and hospitalized for at least three days were included in the study.

Results: The mean age of the patients was 59.35±15.23 year and 56 (59.6%) of patients were male. Fifty seven (60.6%) of the patients had comorbid diseases. The 14- and 28-day mortality rates were 14.9% and 27.7%, respectively. There was a statistically significant correlation between hospitalization in intensive care unit and LDH, lymphocyte count, LDH/lymphocyte ratio, CRP, highest D-dimer, initial IL-6, neutrophil/lymphocyte ratio, and highest IL-6 values ($p<0.05$). The IL-6 level, highest D-dimer level, LDH/lymphocyte ratio and CRP level of the patients who died were significantly higher than those who were survivors ($p<0.05$). A positive and significant correlation was found between the LDH/lymphocyte ratio and both the first admission and the highest IL-6 levels. In ROC analysis, LDH/lymphocyte ratio values of 0.53 and above [AUC: 0.758 (95% CI: 0.660-0.855)] were found to have a specificity of 61% and sensitivity of 70.7% in showing the IL-6 level of 80 pg/ml and above at first admission.

Conclusion: In this study, a significant correlation was found between the LDH/lymphocyte ratio and the IL-6 values. As a result of this study, even if IL-6 cannot be measured, the ratio of LDH/lymphocyte that can be measured in most centers, is thought to be an important marker in predicting poor clinical course.

Keywords: COVID-19, interleukin-6, lactate dehydrogenase/lymphocyte

Öz

Giriş: Koronavirüs hastalığı-2019'da (COVID-19) klinik; hafif solunum semptomlarından ciddi solunum yetmezliği ve ölüme kadar geniş bir spektrumda seyreder. Lenfosit sayısı, laktat dehidrogenaz (LDH), C-reaktif protein (CRP), D-dimer ve interlökin-6 (IL-6) düzeyleri laboratuvar olarak hastalığın şiddetini öngörmede incelenen parametrelerdir. Bu çalışmada amacımız COVID-19 tanılı hastalarda LDH/lenfosit oranının prognoz üzerine etkisini ve LDH/lenfosit oranı ile IL-6 arasında korelasyonun olup olmadığını araştırmaktır.

Gereç ve Yöntem: Şiddetli akut solunum sendromu-Koronavirüs-2 polimeraz zincir reaksiyonu testi pozitif, 18 yaş ve üstünde, tomografisi COVID-19 pnömonisi ile uyumlu, en az üç gün hastane yatışı yapılan hastalar çalışmaya dahil edildi.

Cite this article as: Balcı U, Demir Önder K, Seremet Keskin A. Evaluation of the Relationship Between Lactate Dehydrogenase/Lymphocyte Ratio with Interleukin-6 Levels in Hospitalized Patients with COVID-19. Mediterr J Infect Microb Antimicrob. 2021;10:62.

Address for Correspondence/Yazışma Adresi: Umay Balcı MD, University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Antalya, Turkey
Phone: +90 506 204 64 15 E-mail: umossdr@hotmail.com ORCID ID: orcid.org/0000-0003-2369-0692
Received/Geliş Tarihi: 14.06.2021 Kabul Accepted/Kabul Tarihi: 26.09.2021
©Copyright 2021 by the Infectious Diseases and Clinical Microbiology Specialty Society of Turkey
Mediterranean Journal of Infection, Microbes and Antimicrobials published by Galenos Yayınevi.

Presented in: It was presented as an oral presentation at the 9th Turkey EKMUD International Scientific Platform 20-23 May 2021 - Online Congress.

Published: 1 October 2021

Bulgular: Çalışmaya alınan 94 hastanın yaş ortalaması $59,35 \pm 15,23$ yıl idi ve 56'sı (%59,6) erkekti. Hastaların 57'sinde (%60,6) komorbid hastalık mevcuttu. On dört ve 28 günlük mortalite sırasıyla %14,9 ve %27,7 idi. Hastaların yoğun bakım yatışı ile LDH, lenfosit, LDH/lenfosit oranı, CRP, en yüksek D-dimer, ilk başvurudaki IL-6, nötrofil/lenfosit oranı, en yüksek IL-6 değerleri arasında istatistiksel olarak anlamlı ilişki saptandı ($p < 0,05$). Mortal seyredenlerin IL-6, en yüksek D-dimer, LDH/lenfosit oranı ve CRP değerleri sağ kalanlardan anlamlı düzeyde yüksek bulundu ($p < 0,05$). Laktat dehidrogenaz/lenfosit oranı ile hem ilk başvuru hem de en yüksek IL-6 düzeyleri arasında pozitif yönde anlamlı korelasyon saptandı. ROC analizinde LDH/lenfosit oranının 0,53 ve üzeri değerlerinin [eğri altında kalan alan 0,758 (%95 güven aralığı: 0,660-0,855)] ilk başvuru IL-6'nın 80 pg/ml ve üzerindeki değerini göstermede %61 spesifik ve %70,7 sensitif olduğu saptandı.

Sonuç: Laktat dehidrogenaz/lenfosit oranı ile IL-6 değerleri arasında aynı yönde anlamlı korelasyon tespit edilmiştir. Bu çalışma sonucunda, IL-6 bakılmasına bile çoğu merkezde bakılabilen LDH/lenfosit oranının kötü klinik gidişi tahmin etmede önemli bir belirteç olduğu düşünüldü.

Anahtar Kelimeler: COVID-19, interlökin-6, laktat dehidrogenaz/lenfosit

Introduction

While clinical findings in Coronavirus disease-2019 (COVID-19) show a wide spectrum from mild respiratory symptoms to severe respiratory failure and death, the rate of severe infection is reported to be 4-5%^[1]. The mortality rate in hospitalized patients is 15-20%, and this rate is 40% in intensive care units (ICUs)^[2]. Advanced age, comorbidities, lymphopenia, increased lactate dehydrogenase (LDH) and D-dimer levels are associated with high ICU admission and high mortality rate^[3,4].

There are many studies in the literature on biomarkers to determine the severity and progression of the disease. Lymphocyte, LDH, C-reactive protein (CRP), D-dimer and interleukin-6 (IL-6) are the parameters examined in this regard^[1,3,5,6]. Lactate dehydrogenase and lymphocyte are easily accessible laboratory parameters in clinical practice. In a study evaluating the relationship between LDH/lymphocyte ratio and progression and mortality, LDH/lymphocyte ratio [>345 (0.345)] was reported as the only independent risk factor^[3].

Interleukin-6 may be an ideal biomarker for monitoring disease severity, but it cannot be used widely because IL-6 levels cannot be studied in every hospital^[7].

In this study, our aim was to investigate the effect of LDH/lymphocyte ratio on prognosis and whether there was a correlation between LDH/lymphocyte ratio and IL-6 in patients with COVID-19.

Methods

In this study, patients over 18 years of age who were hospitalized and followed up with a positive Severe acute respiratory syndrome-Coronavirus-2 polymerase chain reaction test at University of Health Sciences Turkey, Antalya Training and Research Hospital between 15.09.2020 and 28.02.2021 were retrospectively analyzed. Patients who had COVID-19 pneumonia in their first admission thorax tomography, were hospitalized for at least three days, received favipiravir for 10 days, had their IL-6 level checked at least once during their follow-up, and completed the follow-up period were included in the study. Patients with procalcitonin level above 2 ng/ml

during hospitalization were not included in the study because there would be an increase in IL-6 secondary to sepsis. The IL-6 level measured within five days of hospitalization was recorded as the "first admission IL-6 level". Initial reference values of LDH, lymphocyte, CRP, D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ferritin and procalcitonin were included in the study. In addition, the highest IL-6 and D-dimer values during the follow-up, if any, were also recorded. Since lymphocyte and LDH levels might be affected after receiving steroid treatment, the LDH/lymphocyte ratio at the first admission was used as the basis.

Of the patients who met the inclusion criteria; LDH, lymphocyte, CRP, AST, ALT, ferritin, D-dimer, IL-6, procalcitonin, highest D-dimer and IL-6 levels in the follow-up period, LDH/lymphocyte ratio, length of stay of the patients, hospitalization in ICU, need for mechanical ventilator and mortality data were recorded.

The study was approved by the University of Health Sciences Turkey, Antalya Training and Research Hospital Ethics Committee (decision no: 5/11, date: 15/04/21).

Statistical Analysis

The study data were analyzed using the 2010 version of the IBM Statistical Package for the Social Sciences (SPSS) Statistics 18 Copyright SPSS Inc. 1989. The normal distribution of continuous variables was examined with Kolmogorov-Smirnov test. Categorical variables in the study were presented as frequency and percentage, and continuous variables as mean, median, standard deviation, interquartile range, minimum and maximum values. Mann-Whitney U test was used because parametric test assumptions were not provided in the mean comparisons of two independent groups. The relationship between continuous variables was analyzed with the Spearman correlation test. ROC analysis was performed to determine the threshold value for determining the LDH/lymphocyte ratio and IL-6 level, and the area under the curve (AUC), sensitivity and specificity values were calculated. The statistical significance level was accepted as 0.05 in the study.

Results

The mean age of 94 patients included in the study was 59.35 ± 15.23 years and 56 (59.6%) were male. Comorbid disease

was present in 57 (60.6%) of the patients. The most common comorbidities were hypertension (HT) 37.2% (n=35) and diabetes mellitus (DM) 33% (n=31) (Table 1).

The most common symptoms at admission were shortness of breath in 69.1% (n=65) of the patients, dry cough in 64.9% (n=61), and fever in 57.4% (n=54). Smoking was detected at a rate of 20.2% (n=19) (Table 1).

The rate of hospitalization in ICU was 48.9% (n=46) and the rate of patients requiring mechanical ventilation was 31.9% (n=30). The 14- and 28-day mortality rates were 14.9% (n=14) and 27.7% (n=26), respectively. Median (minimum-maximum) LDH level was 341 (90-1641)U/l, lymphocyte count was 800 (100-3900)/mm³, LDH/lymphocyte ratio was 0.65 (0.09-4.18), IL-6 level at admission was 44.51 (2-1252) and the highest IL-6 level was 58.70 (2-1949) pg/ml. Demographic-clinical data and laboratory values of the patients are shown in Table 1.

There were significant relationships between hospitalization in ICU and LDH level (p<0.001), lymphocyte count (p<0.001), LDH/lymphocyte ratio (p<0.001), CRP level (p=0.001), highest D-dimer level (p<0.001), ferritin level (p=0.003), IL-6 level at first admission (p<0.001), neutrophil/lymphocyte (N/L) ratio (p=0.001), and the highest IL-6 level (p<0.001) (Table 2).

There were significant relationships between mechanical ventilation and LDH level (p=0.046), lymphocyte count (p<0.001), LDH/lymphocyte ratio (p<0.001), CRP level (p=0.001), highest D-dimer level (p<0.001), IL-6 level at first admission (p<0.001), N/L ratio (p=0.001), and the highest IL-6 level (p<0.001) (Table 3).

Lymphocyte count (p=0.018), IL-6 level (p<0.001), highest D-dimer level (p<0.001), LDH/lymphocyte ratio (p=0.007) and CRP level (p<0.001) of the patients who died were found to be significantly different than the patients who survived (Table 4).

According to the ROC analysis, in showing the need for hospitalization in ICU in patients with severe COVID-19; LDH/lymphocyte ratio values of 0.44 and above had a sensitivity of 71.7% and a specificity of 77.1% [AUC: 0.770 (95% confidence interval (CI): 0.673-0.867)] (Figure 1).

The LDH/lymphocyte ratio values of 0.58 and above had a sensitivity of 57.7% and a specificity of 75% [AUC: 0.679 (95% CI: 0.551-0.807)] in predicting mortality (Figure 2).

The IL-6 values at first admission of 58.7 pg/ml and above had a sensitivity of 71.7% and a specificity of 81.3% [AUC: 0.835 (95% CI: 0.755-0.915)] in predicting hospitalization in ICU.

When the cut-off value of IL-6 was accepted as 53 pg/ml, its sensitivity was 92.3% and its specificity was 70.6% [AUC: 0.860 (95% CI: 0.781-0.939)] in predicting mortality.

Table 1. Demographic and clinical characteristics

Variables (n=94)	n (%)	Mean±SD/Median (min-max)
Age, year		59.35±15.23/61 (26-91)
Male	56 (59.6)	
Comorbid disease	57 (60.6)	
HT	35 (37.2)	
DM	31 (33.0)	
CAD-HF	16 (17.0)	
Obesity	10 (10.6)	
CKD	6 (6.4)	
Allergic asthma	6 (6.4)	
HPL	3 (3.2)	
Solid organ tm	3 (3.2)	
Hematological malignancy	2 (2.1)	
Other comorbidities	4 (4.4)	
Presence of symptoms		
Shortness of breath	65 (69.1)	
Dry cough	61 (64.9)	
Fever	54 (57.4)	
Weakness	47 (50.0)	
Myalgia	31 (33.0)	
Headache	22 (23.4)	
Throat ache	22 (23.4)	
Diarrhea	12 (12.8)	
Loss of taste	7 (7.4)	
Loss of smell	4 (4.3)	
Smoking	19 (20.2)	
ICU hospitalization	46 (48.9)	
MV need	30 (31.9)	
Length of stay, days		9.15±7.70/8.5 (0-28)
14-day mortality	14 (14.9)	
28-day mortality	26 (27.7)	
28-day survival	68 (72.3)	
LDH (U/l)		383.56±191.12/341 (90-1641)
Lymphocyte (/mm ³)		919.15±587.18/800 (100-3900)
LDH/lymphocyte		0.65±0.74/0.65 (0.09-4.18)
CRP (mg/l)		119.20±98.37/102.5 (5-510)
Initial D-dimer (μl)		720.36±1179.23/331 (33-6153)
Highest D-dimer (μl)		1936.56±3050.30/725 (72-23108)
Ferritin (μl)		544.57±716.14/442.50 (29-6258)
Initial IL-6 (pg/ml)		106.85±202.86/44.51 (2-1252)
Highest IL-6 (pg/ml)		151.33±298.97/58.70 (2-1949)
N/L		11.70±14.17/6.40 (1-76)

COAH: Chronic obstructive pulmonary disease, cerebrovascular disease, rheumatologic disease, advanced liver disease, HT: Hypertension, DM: Diabetes mellitus, CAD-HF: Coronary artery disease-heart failure, CKD: Chronic kidney disease, ICU: Intensive care unit, MV: Mechanical ventilation, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, min-max: Minimum-maximum, N/L: Neutrophil/lymphocyte, SD: Standard deviation

Table 2. The relationship between hospitalization in intensive care unit and other independent variables

Variables (n=94)	No hospitalization in ICU (n=48) Median (IQR)	Hospitalization in ICU (n=46) Median (IQR)	p value
LDH	297 (124)	444,5 (251)	<0.001
Lymphocyte	900 (575)	600 (500)	<0.001
LDH/lymphocyte	0.313 (0.238)	0.711 (0.644)	<0.001
CRP	61.75 (93)	127.00 (119)	0.001
Initial D-dimer	267.00 (256)	461.50 (799)	0.009
Highest D-dimer	419.00 (524)	1606.50 (3454)	<0.001
Ferritin	297.00 (393)	530.00 (444)	0.003
Initial IL-6	25.31 (39)	103.35 (115)	<0.001
Highest IL-6	27.80 (40)	128.50 (152)	<0.001
N/L	5.05 (5)	8.00 (14)	0.001

Mann-Whitney U test.

IQR: Interquartile range, CRP: C-reactive protein, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, N/L: Neutrophil/lymphocyte, ICU: Intensive care unit

Table 3. The relationship between need for mechanical ventilation and other independent variables

Variables (n=94)	No mechanical ventilation (n=64) Median (IQR)	Mechanical ventilaiton (n=30) Median (IQR)	p value
LDH	319.5 (194)	444.5 (256)	0.046
Lymphocyte	900 (600)	600 (525)	<0.001
LDH/lymphocyte	0.355 (0.345)	0.687 (1.032)	0.001
CRP	5.95 (54)	8.80 (19)	<0.001
Initial D-dimer	284.00 (309)	457.00 (808)	0.025
Highest D-dimer	570.00 (826)	2822.00 (4934)	<0.001
Ferritin	368.00 (462)	525.00 (501)	0.307
Initial IL-6	29.05 (66)	129.00 (141)	<0.001
Highest IL-6	33.12 (73)	161.00 (210)	<0.001
N/L	5.95 (6)	8.80 (19)	0.009

Mann-Whitney U test.

IQR: Interquartile range, CRP: C-reactive protein, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, N/L: Neutrophil/lymphocyte, MV: Mechanical ventilation

In correlation analysis; a moderate and positive correlation was found between the LDH/lymphocyte ratio and IL-6 level at first admission ($r=0.384$; $p<0.001$) and the highest IL-6 level ($r=0.385$; $p<0.001$) (Figure 3, 4). There was a low and negative correlation between LDH/lymphocyte ratio and length of hospital stay, but this relationship was not found to be statistically significant ($r=0.151$; $p=0.250$) (Table 5).

The LDH/lymphocyte ratio values of 0.53 and above [AUC: 0.758 (95% CI: 0.660–0.855)] were found to have a specificity of 61% and sensitivity of 70.7% in showing IL-6 level of 80 pg/ml and above (Figure 5).

Figure 1. ROC analysis for lactate dehydrogenase (LDH)/lymphocyte ratio in predicting intensive care unit admission. LDH/lymphocyte ratio cut-off ≥ 0.44 [area under the curve: 0.770 (95% confidence interval: 0.673–0.867)], sensitivity 71.7%, specificity 77.1%

Figure 2. ROC analysis for lactate dehydrogenase (LDH)/lymphocyte ratio in predicting mortality. LDH/lymphocyte ratio cut-off ≥ 0.58 [area under the curve: 0.679 (95% confidence interval: 0.551–0.807)], sensitivity 57.7%, specificity 75%

The LDH/lymphocyte ratio values of 0.58 and above [AUC: 0.686 (95% CI: 0.549–0.824)] were found to have a specificity of 59.1% and sensitivity of 73.6% in showing the highest IL-6 value of 150 pg/ml and above.

Table 4. Relationship between mortality and other independent variables

Variables (n=94)	Exitus (n=26) Median (IQR)	28-day survival (n=68) Median (IQR)	p value
LDH	429.5 (304)	320 (212)	0.059
Lymphocyte	600 (550)	800 (600)	0.018
LDH/lymphocyte	0.685 (0.707)	0.366 (0.352)	0.007
CRP	129.35 (113)	79.00 (100)	0.001
Initial D-dimer	500.50 (580)	284.50 (308)	0.057
Highest D-dimer	2822.00 (5162)	648.00 (864)	<0.001
Ferritin	521.00 (464)	384 (477)	0.397
Initial IL-6	131.40 (132)	29.05 (69)	<0.001
Highest IL-6	161.00 (148)	33.50 (75)	<0.001
N/L	7.01 (13)	6.10 (7)	0.083

Mann-Whitney U test.

IQR: Interquartile range, CRP: C-reactive protein, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, N/L: Neutrophil/lymphocyte

Figure 3. Correlation graph of lactate dehydrogenase/lymphocyte ratio with initial interleukin-6 value

LDH: Lactate dehydrogenase

Discussion

The mortality rate in patients hospitalized due to COVID-19 is between 15-20%. While the mortality is high in patients with advanced age and comorbidities, COVID-19 can sometimes be mortal in patients without comorbidities^[2,8,9]. In our study, the mean age was found to be high as 59.35 ± 15.23 years. Comorbidity was present in 60% of the patients, and the most common comorbidities were HT and DM. The most common symptoms in studies are reported as fever, cough and malaise. Shortness of breath is often related with a poor prognosis^[4,10].

Figure 4. Correlation graph of lactate dehydrogenase/lymphocyte ratio with the highest interleukin-6 value

LDH: Lactate dehydrogenase

Table 5. Correlation of lactate dehydrogenase/lymphocyte ratio with length of hospital stay and interleukin-6

Variables (n=94)	r	p value
Length of hospital stay (days)	0.151	0.250
Initial IL-6	0.384	<0.001
Highest IL-6	0.385	<0.001

Spearman correlation analysis.

IL-6: Interleukin-6

Figure 5. ROC analysis for lactate dehydrogenase (LDH)/lymphocyte ratio in predicting values of interleukin-6 above 80 at first admission. LDH/lymphocyte ratio cut-off ≥ 0.53 [area under the curve: 0.758 (95% confidence interval: 0.660-0.855)], specificity 61% and sensitivity 70.7%

The most common symptoms in our patients were dyspnea, cough and fever, respectively. Consistent with the literature, the mortality rates at 14- and 28 days were found to be 14.9% (14) and 27.7% (26), respectively.

Cytokine storm, which is accepted as the main cause of disease severity and death in patients with COVID-19, is characterized by excessive activation of immune cells, excessive production of inflammatory cytokines and chemical mediators. High levels of circulating cytokines in cytokine storm cause severe lymphopenia, thrombosis in various organs, and mononuclear cell infiltration^[11]. Numerous studies show that decreased lymphocyte count is associated with disease severity^[12,13]. It has been reported that IL-6 levels increase 1-2 days before decline in the number of CD4 and CD8 lymphocytes^[13]. High serum IL-6 levels are associated with lymphopenia, impaired lymphocyte cytotoxicity and endothelial activation^[7]. Some biomarkers associated with pathophysiology help predict prognosis in COVID-19. These parameters are reported as high D-dimer, CRP, LDH and cardiac troponin 1^[10,14]. In our study, low lymphocyte count, LDH/lymphocyte ratio, high CRP, D-dimer and IL-6 were found to be risk factors associated with hospitalization in ICU, mechanical ventilation and mortality.

In studies, abnormalities in markers of cellular damage, especially high LDH level, were associated with disease severity. It is stated that LDH may be associated with respiratory function and may be an important predictor of airways. When LDH values of 450 U/l and above were accepted as cut-off, it was shown to have 75% sensitivity and 70% specificity in predicting moderate and severe Acute respiratory distress syndrome^[15]. In our study, the median LDH value was found to be 341 U/l (90-1641). LDH levels were found to be significantly higher in patients who needed hospitalization in ICU and mechanical ventilation.

There are few studies in the literature on the LDH/lymphocyte ratio in COVID-19 patients. The mean LDH/lymphocyte ratio in patients with COVID-19 was found to be 0.17 ± 0.31 in the study by Serin et al. It was reported that the LDH/lymphocyte ratio was diagnostic for COVID-19 when the cut-off ≥ 0.06 was accepted, with a sensitivity of 76.40% and a specificity of 59.60%. When cut-off ≥ 0.21 was accepted, the sensitivity of the LDH/lymphocyte ratio in predicting mortality was 70.59% and the specificity was 73.88%. In the light of these results, it is stated that the LDH/lymphocyte ratio is an easily accessible marker that can be used to predict mortality and diagnose COVID-19^[1]. In another study evaluating the LDH/lymphocyte ratio and the prognosis and mortality of COVID-19, when the cut-off was accepted as >345 (0.345), LDH/lymphocyte ratio was found to be an independent risk factor for poor prognosis^[3]. In our study, the median LDH/lymphocyte ratio was 0.65 (0.09-4.18). Lactate dehydrogenase/lymphocyte ratio was found to be higher in the patients who were hospitalized in ICU, needed

mechanical ventilation and in the patients with mortality. When the cut-off values of LDH/lymphocyte ratio was accepted as 0.44, it was found to have a sensitivity of 71.7% and specificity of 77.1% in predicting hospitalization in ICU. In demonstrating mortality, the sensitivity was 57.7% and the specificity was 75% when the cut-off was accepted as 0.58.

In studies on IL-6, a cytokine that plays an important role in the pathogenesis of COVID-19, high IL-6 level was found to be associated with poor prognosis and mortality, and it was stated that IL-6 was a good biomarker in the follow-up of patients with COVID-19^[16]. In our study, the median IL-6 value was found to be 44.51 pg/ml (2-1252) at the first admission and it was also found to associated with hospitalization in ICU, mechanical ventilation and mortality. In studies, it was reported that IL-6 was superior to CRP, ferritin, liver enzymes and other laboratory markers in predicting respiratory failure and mortality when the cut-off value of IL-6 was accepted as 80 and 86 pg/ml, and it was reported that the threshold value of 80 pg/ml had a prognostic value for cytokine storm^[7]. In a study conducted in Spain, it was reported that patients with serum IL-6 levels greater than 35 pg/ml had an increased risk of mortality and need for mechanical ventilation^[17]. In a study conducted in our country, a cut-off value of 54 pg/ml of IL-6 was found to predict a poor prognosis, with sensitivity and specificity of 89% and 86%, respectively^[18]. In our study, when the cut-off value of IL-6 at first admission was accepted as 58 pg/ml, IL-6 had a sensitivity of 71.7% and specificity of 81.3% in predicting hospitalization in ICU. When the cut-off value of IL-6 at first admission was accepted as 53 pg/ml, IL-6 had a sensitivity of 92.3% and specificity of 70.6% in predicting mortality.

In the study of Karayel et al.^[19] in which they investigated the correlation between IL-6 and other inflammatory markers and the severity of lung computed tomography findings during admission to ICU; a positive and statistically significant relationship was found between IL-6 level and procalcitonin levels, and this situation was associated with bacterial sepsis in patients. In our study, patients with procalcitonin levels above 2 ng/ml were not included in the study, since IL-6 elevation might be associated with bacterial sepsis. In the study of Karayel et al., there was also a weak negative correlation between IL-6 level and CT score, lymphocyte count and NLR ratio, and a positive and weak correlation was found between IL-6 level, age and CRP^[19]. In our study, positive correlation was found between LDH/lymphocyte ratio and IL-6 level, and the difference was statistically significant.

During the course of COVID-19, some patients develop macrophage activation syndrome (MAS), which is characterized by a cytokine storm due to a hyperinflammatory response, or in other words, acquired (secondary) hemophagocytic lymphohistiocytosis. Rapid and effective treatment approaches

become very important in cytokine storm, which causes a very severe clinical picture that is life-threatening. For this reason, accurate and timely identification of the patient group that can benefit from glucocorticoid and anti-cytokine therapies is important for effective and safe treatment planning. Although there are no standard diagnostic criteria for cytokine storm, helpful findings in demonstrating the development of MAS are defined in the COVID-19 treatment guideline of the Ministry of Health of the Republic of Turkey. These are; persistent fever, persistently elevated or increasing CRP, ferritin values above the upper limits of normal and continuing to increase (>700 $\mu\text{g/l}$), elevated D-dimer, lymphopenia, thrombocytopenia and neutrophilia, and impaired liver function tests (ALT, AST, LDH)^[20]. In a study, it was reported that there was a 14% decrease in mortality when 30 mg dexamethasone or 125 mg methylprednisolone was given for 2-5 days to 64 patients with cytokine storm findings (IL-6 ≥ 40 pg/ml and/or two of the following: CRP ≥ 100 mg/l, D-dimer ≥ 1000 ng/ml, ferritin ≥ 500 ng/ml and LDH ≥ 300 U/l)^[21]. In that study, tocilizumab was also used as an anti-inflammatory drug in 15 patients with IL-6 levels higher than 40 pg/ml, and although the survival rate was 73% in those using tocilizumab, there was no statistically significant difference in terms of overall results^[21].

In our study, it was found that cut-off values of 0.53 and above for LDH/lymphocyte ratio showed 61% specificity and 70.7% sensitivity in predicting the value of IL-6 level of 80 pg/ml and above. When the cut-off value of 0.58 and above for LDH/lymphocyte ratio was accepted, it was determined that it showed 59.1% specificity and 73.6% sensitivity in predicting the highest IL-6 values of 150 pg/ml and above during the follow-up.

The limitation of our study was that only hospitalized patients were evaluated, so a comparison between outpatients and inpatients could not be made.

Conclusion

In our study, it was determined that the increased LDH/lymphocyte ratio and IL-6 levels were related with hospitalization in ICU, mechanical ventilation and mortality, and the difference was statistically significant. A similar and moderate correlation was found between the LDH/lymphocyte ratio and IL-6 level at admission and the highest IL-6 level. In the light of these results in our study, it was thought that the LDH/lymphocyte ratio, which could be measured in most centers and at the first admission, was an important marker in predicting poor clinical course.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Antalya Training and

Research Hospital Ethics Committee (decision no: 5/11, date: 15/04/21).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.B., K.D.Ö., A.S.K., Design: U.B., K.D.Ö., A.S.K., Data Collection or Processing: U.B., K.D.Ö., A.S.K., Analysis or Interpretation: U.B., K.D.Ö., A.S.K., Literature Search: U.B., K.D.Ö., A.S.K., Writing: U.B., K.D.Ö., A.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Serin I, Sari ND, Dogu MH, Acikel SD, Babur G, Ulusoy A, Onar MI, Gokce EC, Altunok O, Yaylaci Mert F, Karakilic A, Baltik M, Gulesir B. A new parameter in COVID-19 pandemic: initial lactate dehydrogenase (LDH)/Lymphocyte ratio for diagnosis and mortality. *J Infect Public Health*. 2020;13:1664-70.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19) a review. *JAMA*. 2020;324:782-93.
3. Li G, Xu F, Yin X, Wu N, Li Y, Zhang T, Chen D, Liu K, Qiu Q. Lactic dehydrogenase-lymphocyte ratio for predicting prognosis of severe COVID-19. *Medicine (Baltimore)*. 2021;100:e24441.
4. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81:e16-25.
5. Li C, Ye J, Chen Q, Hu W, Wang L, Fan Y, Lu Z, Chen J, Chen Z, Chen S, Tong J, Xiao W, Mei J, Lu H. Elevated Lactate Dehydrogenase (LDH) level as an independent risk factor for the severity and mortality of COVID-19. *Aging (Albany NY)*. 2020;12:15670-81.
6. Zhang J, Hao Y, Ou W, Ming F, Liang G, Qian Y, Cai Q, Dong S, Hu S, Wang W, Wei S. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. *J Transl Med*. 2020;18:406.
7. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J*. 2020;56:2003006.
8. Zacharioudakis IM, Zervou FN, Prasad PJ, Shao Y, Basu A, Inglima K, Weisenberg SA, Aguerro-Rosenfeld ME. Association of SARS-CoV-2 genomic load trends with clinical status in COVID-19: A retrospective analysis from an academic hospital center in New York City. *PLoS One*. 2020;15:e0242399.
9. Trunfio M, Venuti F, Alladio F, Longo BM, Burdino E, Cerutti F, Ghisetti V, Bertucci R, Picco C, Bonora S, Di Perri G, Calcagno A. Diagnostic SARS-CoV-2 cycle threshold value predicts disease severity, survival, and six-month sequelae in COVID-19 symptomatic patients. *Viruses*. 2021;13:281.
10. Marin BG, Aghagholi G, Lavine K, Yang L, Siff EJ, Chiang SS, Salazar-Mather TP, Dumenco L, Savari MC, Aung SN, Flanagan T, Michelow IC. Predictors of COVID-19 severity: a literature review. *Rev Med Virol*. 2021;31:1-10.
11. Hu B, Huang S, Yinhe L. The cytokine storm and COVID-19. *Med Virol*. 2021;93:250-6.
12. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939

- COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol.* 2020;108:17-41.
13. Wang W, Liu X, Wu S, Chen S, Li Y, Nong L, Lie P, Huang L, Cheng L, Lin Y, He J. Definition and risks of cytokine release syndrome in 11 critically ill COVID-19 patients with pneumonia: analysis of disease characteristics. *J Infect Dis.* 2020;222:1444-51.
 14. Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, Hussein MH, Killackey MT, Fawzy MS, Kandil E. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: a meta-analysis of 6320 patients. *PLoS One.* 2020;15:e0238160.
 15. Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, Nuccetelli M, Vadacca G, Guidetti D, Vercelli A, Magnacavallo A, Bernardini S, Terracciano C. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in COVID-19 patients. *Clin Chim Acta.* 2020;509:135-8.
 16. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol.* 2020;11:1441.
 17. Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. *Mol Immunol.* 2020;128:64-8.
 18. Satış H, Özger HS, Aysert Yıldız P, Hızal K, Gulbahar Ö, Erbaş G, Aygencel G, Guzel Tunccan O, Öztürk MA, Dizbay M, Tufan A. Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19. *Cytokine.* 2021;137:155302.
 19. Karayel A, Özgültekin A, Yağcı B, Sarı A, Balık Y, Aksaray S, Ekinci O. Do the IL-6 levels and other inflammatory parameters correlate with the lung computed tomography involvement scores in critical Covid-19 patients? *Turk J Intensive Care.* 2020;18:41-7.
 20. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. COVID-19 (Sars-Cov-2 Enfeksiyonu) Antisitokin-Antiinflamatuvar Tedaviler, Koagülopati Yönetimi. Son Erişim Tarihi: 07.11.2020. Erişim Adresi: <https://COVID19.saglik.gov.tr/TR-66341/antisitokin-antiinflamatuvar-tedaviler-koagulopati-yonetimi.html>
 21. López Zúñiga MÁ, Moreno-Moral A, Ocaña-Granados A, Padilla-Moreno FA, Castillo-Fernández AM, Guillamón-Fernández D, Ramírez-Sánchez C, Sanchez-Palop M, Martínez-Colmenero J, Pimentel-Villar MA, Blázquez-Roselló S, Moreno-Sánchez JJ, López-Vilchez M, Prior-Sánchez I, Jódar-Moreno R, López Ruz MÁ. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. *PLoS One.* 2021;16:e0243964.