Covid-19 Hastalığında Laboratuvar Parametrelerinin Tanısal Değerinin ROC Eğrisi ile İncelenmesi

Analyzing the Diagnostic Value of Laboratory Parameters with ROV Curve in Covid-19

Mehmet Gürbilek[*]   **Çiğdem Damla Deniz**[**]   **Mehmet Sinan İyisoy**[***]

Gamze Demirel[****]   **Nahide Baran**[*****]   **Mehmet Özcan**[******]

[*]   Necmettin Erbakan Üniversitesi Üniversitesi, Tıbbi Biyokimya, Konya, Türkiye

[**]   Şehir Hastanesi, Tıbbi Biyokimya, Konya, Türkiye

[***]   Necmettin Erbakan Üniversitesi Üniversitesi, Tıp Eğitimi ve Bilişimi Anabilim Dalı, Konya, Türkiye

[****]   Selçuk Üniversitesi Kadir Yallagöz Sağlık Yüksekokulu, Beslenme ve Diyetetik, Konya, Türkiye

[*****]   Cihanbeyli Devlet Hastanesi, Radyoloji, Konya, Türkiye

[******]   Konya Meram Devlet Hastanesi, Enfeksiyon Hastalıkları, Konya, Türkiye

ÖZET

Amaç: Koronavirüs Hastalığı (Covid-19) Aralık 2019'da ortaya çıktığından beri pandemiye dönüşmüştür. Covid-19 enfeksiyonu; pulmoner inflamasyonu tetikleyebilir ve aynı zamanda akut akciğer hasarına neden olabilir. Şiddetli pnömoni görülen vakalarda uzun hastanede kalış süresi ve yüksek ölüm oranı tespit edilmiştir. Bu nedenle, vakaları hızlı ve erken tanı koyacak şekilde biyobelirteç varlığına ihtiyaç vardır. Çalışmamızda Covid-19 hastalarında kullanılan laboratuvar parametreleri ve radyolojik bulguları ROC eğrisi analizi ile değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamız Mayıs 2020-Temmuz 2020 tarihleri arasında hastanemizde Covid-19 tanısı alan erişkin hastalarda geriye dönük olarak planlandı. Hastaların rutin biyokimyasal ve hematolojik laboratuvar testlerinin sonuçları taranarak veriler elde edildi. Laboratuvar verileri ve radyolojik bulgular, alıcı çalışma karakteristiği ROC eğrisi ve Cox regresyon analizi kullanılarak karşılaştırıldı.

Mehmet Gürbilek	: https://orcid.org/0000-0002-6281-8807
Çiğdem Damla Deniz	: https://orcid.org/0000-0002-6052-4645
Mehmet Sinan İyisoy	: https://orcid.org/0000-0001-5895-9984
Gamze Demirel	: https://orcid.org/0000-0001-6037-378X
Nahide Baran	: https://orcid.org/0000-0001-6387-423X
Mehmet Özcan	: https://orcid.org/0000-0002-4553-5565
Etik Kurul İzni	: 2022/3633 (8239)

Yazışma adresi: Gamze Demirel
Necmettin Erbakan Üniversitesi
Üniversitesi Tıbbi Biyokimya,
Konya, Türkiye
E-mail: gamzedemirel@selcuk.edu.tr

Bulgular: Yaş ortalaması 47,3 ± 17,65 (aralık: 19-78) yıl olan bin olgu (%54 erkek) incelendi. Covid-19 için RT-PCR sonucu tüm vakalarda pozitifti. İlerlemiş pulmoner tutulumu olan hastalarda üre ($p <$ 0.0001), glomerüler filtrasyon hızı ($p <$ 0.0001), laktat dehidrogenaz (LDH) ($p <$ 0.0001), aspartat aminotransferaz (AST) ($p <$ 0.0001), Nötrofil-Lenfosit Oranı ($p <$ 0.0001), Trombosit-Lenfosit Oranı ve C-reaktif protein (CRP) ($p <$ 0.0001) anlamlı olarak saptandı. Ayrıca ileri akciğer tutulumu olan hastalarda hemoglobin (Hb) ($p <$ 0,0001), beyaz küre sayısı (WBC) ($p <$ 0,0001), serum albümin (Alb) düzeyi ($p <$ 0,0001) ve lenfosit sayısı ($p <$ 0,0001) diğerlerine kıyasla daha düşüktü. WBC ve CRP çok değişkenli modelde anlamlı bulundu, sırasıyla $p = 0,002$ ve $p <$ 0,0001. Alb (AUC = 0.77), D-dimer (AUC = 0.68), LDH (AUC = 0.69) ve CRP (AUC = 0.77) Covid-19 için ileri akciğer tutulumu olan vakaları tahmin etmede çok iyi bir doğruluğa sahipti.

Sonuç: Covid hastalarında tanıyı koyabilmek için; hastaları sınıflandırmak ve hastalığın ilerlemesini tespit edebilmek adına göstergelere ihtiyaç vardır. Bulgularımız, Covid-19 hastalarında akciğer tutulumunun şiddetini tahmin etmek için spesifik olarak Alb, D-dimer, LDH ve CRP düzeylerinin kullanılabileceğini göstermektedir.

Anahtar Sözcükler: ROC eğrisi; Covid-19; Biyobelirteçler; Biyokimya; Teşhis

ABSTRACT

Objective: Since the emergence of Coronavirus Disease 2019 (Covid-19) in December 2019, it has turned into a pandemic. Covid-19 infection; can trigger pulmonary inflammation and also cause acute lung injury. In cases with severe pneumonia, long hospital stays and high mortality rates were detected. Therefore, there is a need for biomarkers to diagnose cases quickly and early. In our study, we aimed to evaluate the laboratory parameters and radiological findings used in Covid-19 patients with ROC curve analysis.

Material and Method: Our study was planned retrospectively in adult patients diagnosed with Covid-19 in our hospital between May 2020 and July 2020. Data were obtained by scanning the results of routine biochemical and hematological laboratory tests of the patients. Laboratory data and radiological findings were compared using receiver operating characteristic ROC curve and Cox regression analysis.

Results: One thousand cases (54% males) with a mean age of 47.3 ± 17.65 (range: 19-78) years were analyzed. RT-PCR result for Covid-19 was positive in all cases. Significantly, in patients with advanced pulmonary involvement urea ($p <$ 0.0001), glomerular filtration rate ($p <$ 0.0001), lactate dehydrogenase (LDH) ($p <$ 0.0001), aspartate aminotransferase (AST) ($p <$ 0.0001), Neutrophil-Lymphocyte Ratio ($p <$ 0.0001), Platelet-Lymphocyte Ratio and C-reactive protein (CRP) ($p <$ 0.0001) were significantly different. In addition, in patients with advanced lung involvement, hemoglobin (Hb) ($p <$ 0.0001), white blood cell count (WBC) ($p <$ 0.0001), serum albumin (Alb) level ($p <$ 0.0001) and lymphocyte count (p) $<$ 0.0001) was lower, compared to others. WBC and CRP were significant in the multivariate model, $p = 0.002$ and $p <$ 0.0001, respectively. Alb (AUC = 0.77), D-dimer (AUC = 0.68), LDH (AUC = 0.69) and CRP (AUC = 0.77) had very good accuracy in predicting cases with advanced lung involvement for Covid-19.

Conclusions: In order to make the diagnosis in Covid patients; indicators are needed to classify patients and detect disease progression. Our findings show that specifically Alb, D-dimer, LDH and CRP levels can be used to predict the severity of lung involvement in Covid-19 patients.

Keywords: ROC curve; Covid-19; Biomarkers, Biochemistry; Diagnosis

INTRODUCTION

Coronaviruses are enveloped RNA viruses belonging to the Coronaviridae family and commonly found in living groups (1). Coronavirus disease 2019 (Covid-19); it is a disease that was first reported from the city of Wuhan, Hubei Province of China, with compelling consequences for health systems worldwide, causing serious respiratory diseases such as pneumonia and lung failure (2). It is important to predict the prognosis of patients in order to prevent difficult conditions that may help the treatment. There is a need for a parameter that can provide fast, simple and easy results in order to follow the treatment response and prevent mortality. To analyze the disease, samples were taken from the lower respiratory tract and the results were identified as a new

strain of Covid-19. Disease; with all data received in February 2020, it was named Covid-19 by WHO (3). Respiratory droplets and human-to-human contact were identified as the main mode of transmission of the virus. (4).

When the symptoms of Covid-19 disease are examined, it has been observed that severe acute respiratory tract infection may occur in the early stages of the disease. In addition, acute respiratory distress syndrome (ARDS) and different complications may develop rapidly in some patients, all of which may result in multiple organ failure (5). Defining the pathophysiology of the disease is very important because it will continue to guide in many stages, such as the prevention of possible infections (6). To recognize the factor; characterization specific to the host, etiology and determination of the resulting host responses are the points that need to be defined. In Covid-19, there are studies being conducted to identify individuals with complications such as ARDS, who may even be at greater risk for death (7).

Previous disease-based studies have confirmed that ground-glass appearance and consolidation in the lung, with data from radiological findings, is the hallmark of people with Covid-19 infection. In addition, in CT and radiographic examinations; bilateral ground glass and consolidation are included among the most common findings in the disease (8).

After the identification of the factor causing the epidemic, various laboratory parameters were analyzed and some of them became important (2). For example, in infection; when blood parameters were examined, it was observed that the synthesis of many plasma proteins increased (9).

When diagnosing Covid-19, biomarkers identified with PCR results should be used together with computerized tomography (CT) images of individuals (8). In our study, we aimed to highlight the diagnostic value of some laboratory parameters in their follow-up due to their easy measurement and clinical value in Covid-19 patients. We aimed to evaluate the laboratory parameters and radiological findings used in Covid-19 patients with ROC curve analysis. Modeling or estimating coronavirus test results based on routine laboratory tests can shorten the time and also be promising in the treatment applied.

MATERIALS and METHODS

Study Design and Population

This study was conducted with the approval of the ethics committee numbered 2022/ 3633 (8239) on Covid-19 patients who applied to our hospital between May 2020 and July 2020. The inclusion criteria were: 1) being diagnosed of Covid-19, 2) age of > 18 years. The exclusion criteria were: 1) reverse transcription polymerase chain reaction was not studied, 2) the patient's prediagnosis was changed and Covid-19 was excluded, 3) laboratory data could not be accessed, 4) the absence of radiological image results of the patient. Patients who met the definitive case definition of Covid-19 and agreed to participate in the study were included in the study. Routine laboratory test results, radiological findings and demographic data such as age and sex were extracted from the medical records of the patients.

Serum Biomarkers

Blood samples were drawn immediately after the patients' admission to the emergency department. The serum biomarkers evaluated upon admission included white blood cell WBC count in $10^3/mm^3$, hemoglobin (HB) value in g/dL, hematocrit (HCT) value in %, platelet (PLT) in $10^3/mm^3$, lymphocyte (LYM) in $10^3/mm^3$, neutrophil (NEU) in fL, mean platelet volume (MPV) in fL, platelet distribution width (PDW) in fL were measured in SYSMEX XT2000 Hematology Analyzer (Sysmex, Germany), D-dimer mg/L were measured in Siemens BCS XP (Siemens, Marburg, Germany); C-reactive protein (CRP) in mg/L were measured were

measured in Siemens BN2 nephelometer using nephelometric method via Siemens kits; serum albumin (Alb) level in g/L, uric acid level in mg/L, urea level in mg/dL, Creatinin level in mg/dL, serum laktat dehidrogenaz (LDH) level in U/L, Aspartat aminotransferaz (AST) level in U/L and Alanin aminotransferaz (ALT) level in U/L were measured in Beckman Coulter AU480 (Chemistry analyzer, USA). Moreover, the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) which are the markers of systemic inflammation were calculated.

Statistical analysis

Analyzes were done with SAS University Edition 9.4. *P* < 0.05 was considered significant. In the analysis of numerical variables logistic regression and the ROC curve were used.

RESULTS

One thousand cases with the mean age of 47.3 ± 17,65 years were studied (54% male). 51.7 percent of the total 29 patients who died were male and 48.3 percent were female.

Table 1 shows the ROC analysis results. The cut-off point of Alb was 38.94 and the sensitivity and specificity were 70.6% and 70.7%. Positive predictive value of Alb was 32.3% and negative predictive value was 92.4%.

The cut-off point of CRP which is widely used in infections was 4.68 and the sensitivity and specificity were 75.4% and 69.3%. Positive predictive value of Alb was 46.2% and negative predictive value was 88.9% (Table 1).

Table 1. ROC analysis results of laboratory parameters of COVID-19 patients.

Variable	Cut-off point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC
Albumin	38.94	70.6	70.7	32.3	92.4	0.77
HB	14.4	52.8	74.3	41	82.3	0.66
WBC	5.48	60.8	49.5	29	78.9	0.55
PLT	167	79.6	33.6	28.8	82.9	0.53
LYM	1.74	63.1	62.9	36.4	83.5	0.66
NEU	3.4	59.4	45.7	27	76.9	0.51
MPV	10.4	56.3	50.1	27.5	77.3	0.52
PDW	11.7	45.3	60.2	27.7	76.6	0.52
D-dimer	0.4	65.9	65.4	41.4	83.7	0.68
Urea	27.3	66.2	50.3	30	82.2	0.6
Creatinin	0.97	78.2	29.1	27.2	79.8	0.53
GFR	103	58.1	76	43.9	84.9	0.73
LDH	220	70.7	61.3	40.1	85.1	0.69
AST	24	59.2	65.2	36.7	82.4	0.65
ALT	17	49	66.6	33.3	79.3	0.59
Uric Acid	4.7	65	58.9	28	87.3	0.61
NLR	1.8	63.9	58.1	34	82.6	0.62
PLR	131.7	71.5	48.7	32	83.5	0.63
CRP	4.68	75.4	69.3	46.2	88.9	0.77

AUC, Area Under the Curve; HB, Hemoglobin; WBC, White blood cells; PLT, Platelet; LYM, Lymphocyte; NEU, Neutrophil; MPV, Mean Platelet Volüme; PDW, Platelet Distribution Width; GFR, Glomerular Filtration Rate; LDH; Lactate Dehydrogenase; AST; Aspartat Amino transferaz; ALT, Alanine Aminotransferase; NLR; Neutrophil-Lymphocyte Ratio; PLR; Platelet-to-Lymphocyte Ratio; CRP, C-Reactive Protein.

According to the results of the multivariate model, FER hazard ratio (HR)= 1.001, 95% confidence interval (CI) = 1.000–1.001, P < 0.004), CRP (HR = 1.005, 95% CI = 1.001–1.009, P < 0.02) and, Lactate (HR = 1.153, CI = 0.988-1.288, P <0.02) were found significant. In addition, a univariable survival analysis was performed for each variable. The univariate logistic regression showed the following results: FER (HR = 1.001, 95% CI = 1.000–1.001, P = 0.0004), CRP (HR = 1.005, 95% CI = 1.001–1.008, P < 0.005), Lactate (HR = 1.141, CI = 1.016-1.243, P = 0.009), Alb (HR = 1.016, CI = 0.74-1.399, P =0.922),

Cer (HR = 1.056, CI = 1.017-1.100, P = 0.006, Prealb (HR = 0.978, CI = 0.917-1.035, P =0.469), Trf (HR = 1, CI = 0.995-1.006, P = 0.897), Age (HR = 1.032, CI = 1.004-1.064, P =0.033), SOFA (HR = 1.104, CI = 0.971-1.247, P = 0.123), APACHE (HR = 1.012, CI = 0.974-1.051, P = 0.5267). Table 2 presents the results of the multivariate and univariate Logistic regression analysis.

ROC curves for all laboratory parameters are presented in Figure 1. Area Under the Curve value (AUC) of the ALB, HB, LYM, D-dimer, GFR, LDH and CRP were 0.77, 0.66, 0.66, 0.68, 0.73, 0.69 and 0.77, respectively.

Table 2. Univariable and Multivariable Analysis Results.

Faktors	Univariable Analysis			Multivariable Analysis		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Albumin	1.27	1.19–1.36	< 0.0001			
HB	1.043	1.3–1.57	< 0.0001			
WBC	1.023	0.97–1.07	0.360	0.868	0.79-0.95	0.002
PLT	1.001	0.99–1.002	0.566			
LYM	2.015	1.668–2.434	< 0.0001			
NEU	0.93	0.87–1.001	0.0538			
MPV	0.92	0.79-1.073	0.29			
PDW	0.95	0.89-1.02	0.17			
D-dimer	0.94	0.89-1	0.06			
Urea	0.95	0.94-0.97	<0.0001			
Creatinin	0.329	0.15-0.69	0.003			
GFR	1.052	1.04-1.06	< 0.0001			
LDH	0.99	0.98-0.99	< 0.0001			
AST	0.97	0.96-0.98	< 0.0001			
ALT	0.99	0.98-1.001	0.08			
Uric Acid	1.15	1-1.33	0.04			
NLR	0.77	0.69-0.86	< 0.0001			
PLR	0.99	0.99-0.99	< 0.0001			
CRP	0.93	0.91-0.95	< 0.0001	1.041	1.025-1.057	< 0.0001
Age	0.92	0.91-0.93	< 0.0001	1.06	1.05-1.08	< 0.0001
Cinsiyet	1.63	1.24-2.16	0.0005	0.54	0.37-0.79	0.001

95 % Confidence Interval (CI); Odds Ratio (OR); HB, Hemoglobin; WBC, White blood cells; PLT, Platelet; LYM, Lymphocyte; NEU, Neutrophil; MPV, Mean Platelet Volüme; Platelet Distribution Width; GFR, Glomerular Filtration Rate; LDH; Lactate Dehydrogenase; AST; Aspartat Aminotransferaz; ALT, Alanine Aminotransferase; NLR; Neutrophil-Lymphocyte Ratio; PLR; Platelet-to-Lymphocyte Ratio; CRP, C-Reactive Protein
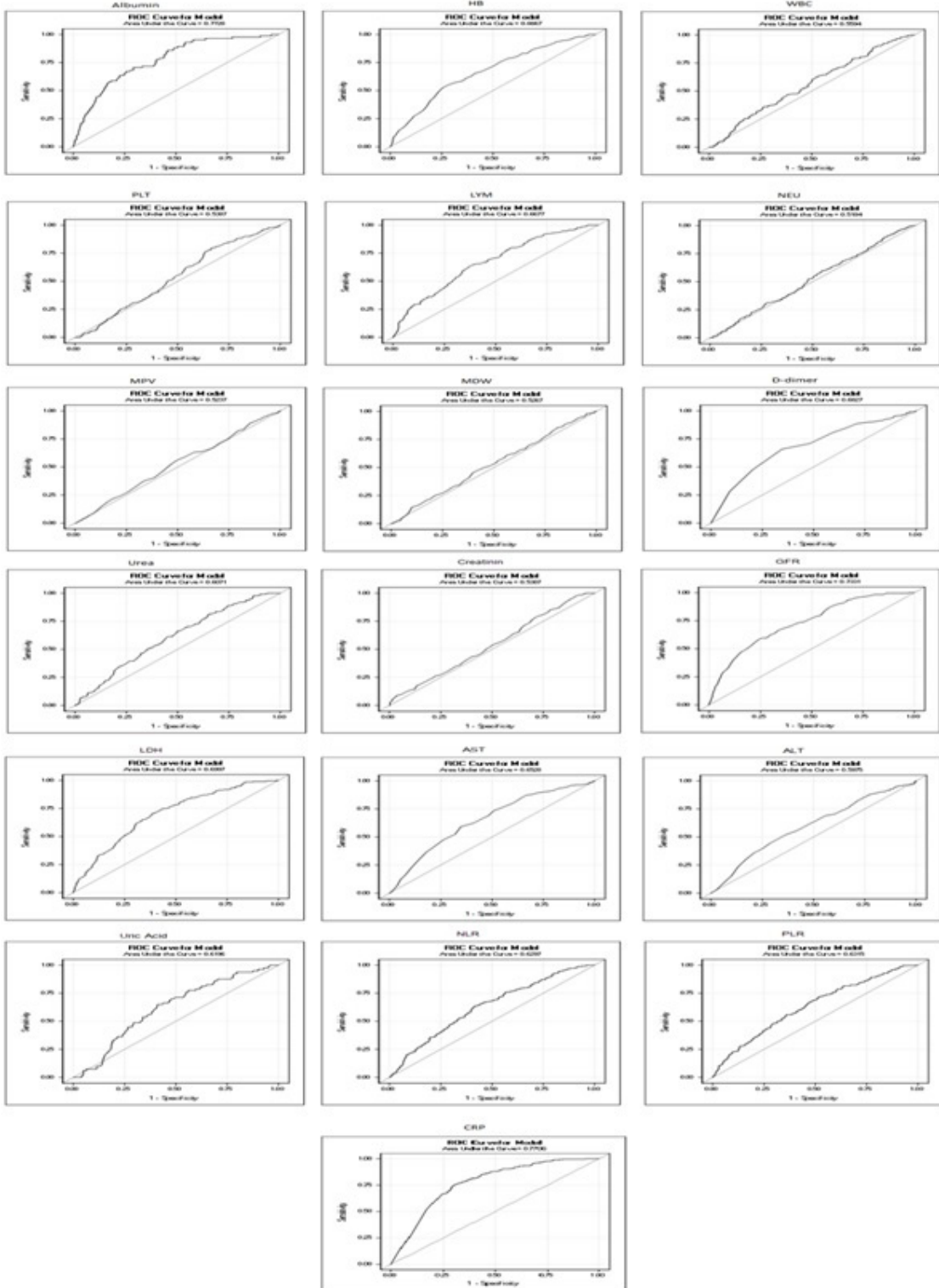
Fig 1: ROC curves of all parameters

HB, Hemoglobin; WBC, White blood cells; PLT, Platelet; LYM, Lymphocyte; NEU, Neutrophil; MPV, Mean Platelet Volüme; Platelet Distribution Width; GFR, Glomerular Filtration Rate; LDH; Lactate Dehydrogenase; AST; Aspartat Aminotransferaz; ALT, Alanine Aminotransferase; NLR; Neutrophil-Lymphocyte Ratio; PLR; Platelet-to-Lymphocyte Ratio; CRP, C-Reactive Protein

DISCUSSION

Early detection of risk factors that cause Covid-19 disease can help people working in the clinical field to make appropriate treatments (10, 11). Looking at the existing literature based on coronavirus cases; reported differences in many biochemical parameters of patients (including, for example, lymphocyte count, neutrophil count, and D-dimer status) (12). In our study; we compared laboratory data and radiological findings, ROC curve, and Cox regression analysis. In addition, we aimed to evaluate the laboratory parameters and radiological findings used in Covıd-19 patients with ROC curve analysis.

In a study conducted; coronavirus disease has been associated with many factors. Age, lymphopenia, leukocytosis, LDH, creatine kinase, D-dimer, serum ferritin are some of them. D-dimer, high-sensitivity cardiac troponin I, serum ferritin, LDH and IL-6 levels, which are defined as the factors that change the course of the disease, were shown to be higher in non-survivors. It has been shown that D-dimer levels higher than 1 μg/mL are associated with the fatal outcome of the disease (13). Similarly; it has been stated that the risk factors for ARDS are age, fever, increased inflammation index and coagulopathy disorders (14).

In a meta-analysis; it has been shown that increased PCT values are associated with the severity of the Covid-19 disease (15). When the parameters of the Covid-19 disease are compared; changes in IL-6, D-Dimer, GLU, thrombin time (TT), fibrinogen (FIB) and CRP were observed differently in people with mild and severe disease. (16). In another study, an increase in LDH levels was associated with the rate of hospitalization in intensive care units (17). When considered on the basis of SARS disease, the relevant laboratory data; CRP, lymphopenia, LDH and creatine kinase levels were increased (18). In another similar study; in cases with positive RT-PCR for Covid-19, ALT, AST, CRP, NEU, LDH and Urea were determined respectively; it has been shown to be quite reliable in testing the disease (19).

In another study; CT findings in Covid-19 patients have been shown to be overwhelming at the important initial stage. In the same study; CRP has been associated with the course of the disease. According to the data of the research; high sensitivity CRP was detected in 166 (85.6%) of 194 patients. It has also been shown that risk factors for the course of the disease are advanced age, neutrophilia, and high LDH and D-dimer (20). In the other study; high creatine kinase level and muscle pain have been reported as symptoms of Covid-19 infection (21).

In addition; Covid-19 disease is associated with being prothrombotic and elevated D-dimer levels, and it has been shown that coagulation parameters being different from normal are associated with the course of the disease (22). It has been stated that Neu is another change that occurs in Covid-19 patients (23). Differently; PCT levels in patients with Covid-19 have generally been found to be within the normal range. However, the increase in the level of PCT was found to be associated with the course of the disease (15). According to the data of another study; showed that changes in markers such as AST, ALT, bilirubin and Alb can be used as laboratory findings in Covid-19 patients (24).

In our retrospective study, which we conducted in adult patients diagnosed with Covid-19 in our hospital between May 2020 and July 2020, the results of routine biochemical and hematological laboratory tests of the patients were scanned. In our study, based on all these data, CRP, Alb, HGB, WBC, PLT, LYM, NEU, MPV, PDW (Hemogram); D-Dimer, Urea, Creatinine, GFR, LDH, AST, ALT, Uric acid results were scanned and radiological findings were compared with the ROC curve. Our findings show that specifically Alb, D-dimer, LDH, and CRP levels can be used to predict the severity of lung involvement in Covid-19 patients. We believe that these data we have obtained for the determination of laboratory parameters related to radiological findings will contribute to the clinical recovery of Covid-19 patients. The recovery time of the patients will be

accelerated and it will be contributed to the disappearance of contagion in the early period. In addition, it will contribute to the

literature by revealing the diagnostic value of laboratory parameters in Covid-19 patients.

REFERENCES

1. Liu, J., Dai, S., Wang, M., et al. Virus like particle-based vaccines against emerging infectious disease viruses. Virologica Sinica, 2016; 31(4), 279-287.

2. Wu, Z., and McGoogan, J. M. 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(13), 1239-1242.

3. Nishiura, H., Jung, S. M., Linton, N. M., et al. The extent of transmission of novel coronavirus in Wuhan, China, 2020.

4. Wan, S., Yi, Q., Fan, S., et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). 2020: MedRxiv.

5. Chen, N., Zhou, M., Dong, X., et al.. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet, 395(10223), 507-513.Chung, M., et al. (2020). "CT imaging features of 2019 novel coronavirus (2019-nCoV)." Radiology 2020: 295(1): 202-207.

6. Weissleder, R., Lee, H., Ko, J. et al. COVID-19 diagnostics in context. Science translational medicine, 2020: 12(546).

7. Zhu, N., Zhang, D., Wang, W., et al. A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine. 2020.

8. Ng, M. Y., Lee, E. Y., Yang, J., et al. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiology: Cardiothoracic Imaging, 2020: 2(1), e200034.

9. Steven Black, I. K., David Samols "C-reactive Protein." J Biol Chem. 2019: 279(47):48487-90.

10. Zumla, A., and Niederman, M. S. The explosive epidemic outbreak of novel coronavirus disease 2019 (COVID-19) and the persistent threat of respiratory tract infectious diseases to global health security. Current opinion in pulmonary medicine. 2020.

11. Liu, J., Liu, Y., Xiang, P., et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine, 2020: 18, 1-12.

12. Wang, D., Li, R., Wang, J., et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. BMC infectious diseases, 2020: 20(1), 1-9.

13. 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. The lancet, 2020: 395(10229), 1054-1062.

14. Wu, C., Chen, X., Cai, Y., et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine, 2020: 180(7), 934-943.

15. Lippi, G. and M. Plebani. "PROCalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis." Clinica chimica acta; international journal of clinical chemistry. 2020: 505: 190.

16. Gao, Y., Li, T., Han, M., et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID‐19. Journal of medical virology, 2020: 92(7), 791-796.

17. Fan, B. E. "Hematologic parameters in patients with COVID‐19 infection: a reply." American journal of hematology. 2020.

18. Wang, J. T., Sheng, W. H., Fang, C. T.et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerging infectious diseases, 2004: 10(5), 818.

19. Branson, B., Tavakoli, R., Khaledi, M., et al. The Correlations Between Epidemiological and Clinical Characteristics, laboratory tests and CT Scan reports in the diagnosis of cases 2019 novel coronavirus pneumonia. A Diagnostic Accuracy Study. Authorea Preprints. 2021.

20. Tan, C., Huang, Y., Shi, F., et al. C‐reactive protein correlates with computed tomographic findings and predicts severe COVID‐19 early. Journal of medical virology, 2020: 92(7), 856-862.

21. Chan, K. H., Farouji, I., Hanoud, A. A., et al. Weakness and elevated creatinine kinase as the initial presentation of coronavirus disease 2019 (COVID-19). The American journal of emergency medicine, 2020; 38(7), 1548-e1.

22. Tang, N., Li, D., Wang, X., et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis, 2020: 18(4), 844-847.

23. Lai, C. C., Liu, Y. H., Wang, C. Y., et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. Journal of Microbiology, Immunology and Infection, 2020: 53(3), 404-412.

24. Chai, X., Hu, L., Zhang, Y., et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. biorxiv.Chan, K. H., et al. (2020). "Weakness and elevated creatinine kinase as the initial presentation of coronavirus disease 2019 (COVID-19)." The American journal of emergency medicine. 2020: 38(7): 1548. e1541-1548. e1543.