Evaluation of Clinical Laboratory Findings with Computed Tomography Segmentation-Volume Analysis Results in COVID-19 Patients

COVID-19 Hastalarında Klinik Laboratuvar Bulgularının, Bilgisayarlı Tomografi Segmentasyon-Hacim Analizi Sonuçları ile Birlikte Değerlendirilmesi

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ABSTRACT

Objective: COVID-19 is a disease caused by SARS-COV-2 and early diagnosis and classification of the COVID-19 are critical for the better prognosis. This study aimed to combine laboratory data of COVID-19 patients with Computed Tomography Segmentation-Volume Analysis (CT-SVA). Thus, we hope to contribute to the early diagnosis and classification of the disease.
Methods: Patients were divided into two groups according to disease severity as mild/moderate (n=41) and severe/critical (n=42). Some laboratory parameters were recorded and evaluated together with CT-SVA.
Results: The results of the study have shown that sodium, C-reactive protein, D-dimer, ferritin, fibrinogen, interleukin 6, procalcitonin, white blood cells, neutrophil, neutrophil-lymphocyte ratio values were significantly higher at first admission in the severe/critical diseased group ($p<0.05$), while albumin, lymphocyte, and venous blood pH values were significantly lower ($p<0.05$). CT-SVA results have shown negative correlation with albumin, while having a positive correlation with C-reactive protein, D-dimer, ferritin, fibrinogen, interleukin 6 and procalcitonin. The results of the performed Receiver Operating Characteristics analysis revealed that CT-SVA has a cut-off value of 15.92 with a sensitivity of 87.1% and a specificity of 80.0% in predicting disease severity. Binary logistic regression model has included CT-SVA, D-dimer, ferritin, interleukin 6, and neutrophil-lymphocyte ratio. The model correctly classified 88.1% of cases. CT-SVA, D-dimer, ferritin, interleukin 6, and neutrophil-lymphocyte ratio were detected to be the independent predictors of disease severity.
Conclusion: Evaluation of laboratory parameters together with CT-SVA results will help identification of cases with a poor prognosis and accelerate intervention.

Keywords: COVID-19, computed tomography, laboratory parameters, inflammation, biomarker, risk factor

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ÖZET

Amaç: COVİD-19, SARS-COV-2'nin neden olduğu bir hastalıktır ve COVİD-19'un erken teşhisi ve sınıflandırılması daha iyi prognoz için kritik öneme sahiptir. Bu çalışma, COVİD-19 hastalarında laboratuvar verilerinin Bilgisayarlı Tomografi Segmentasyon-Hacim Analizi (CT-SVA) ile birleştirilmesini amaçlamıştır. Böylece hastalığın erken teşhisine ve sınıflandırılmasına katkı sağlamayı umuyoruz.
Yöntem: Hastalar, hastalık şiddetine göre hafif/orta (n=41) ve şiddetli/kritik (n=42) olarak iki gruba ayrıldı. Bazı laboratuvar parametreleri kaydedildi ve CT-SVA ile birlikte değerlendirildi.
Bulgular: Çalışmanın sonuçları, şiddetli/kiritik vakaların yer aldığı grup için ilk başvuruda sodyum, C-reaktif protein, D-dimer, ferritin, fibrinojen, interlökin 6, prokalsitonin, beyaz kan hücreleri, nötrofil, nötrofil-lenfosit oranı değerlerinin anlamlı olarak yüksek olduğunu ($p<0.05$) ve albümin, lenfosit ve venöz kan pH değerlerinin ise anlamlı olarak düştüğünü gösterdi ($p<0.05$). CT-SVA sonuçları albümin ile negatif korelasyon gösterirken, C-reaktif protein, D-dimer, ferritin, fibrinojen, interlökin 6 ve prokalsitonin ile pozitif korelasyon göstermiştir. Gerçekleştirilen ROC analizinin sonuçları, 15,92 cut-off değeri ile CT-SVA'nın hastalık şiddetini öngörmede % 87,1 duyarlılık ve % 80,0 özgüllüğe sahip olduğunu ortaya koydu. İkili lojistik regresyon modeli CT-SVA, D-dimer, ferritin, interlökin 6 ve nötrofil-lenfosit oranını içermekteydi. Model, vakaların % 88,1'ini doğru bir şekilde sınıflandırdı. CT-SVA, D-dimer, ferritin, interlökin 6 ve nötrofil-lenfosit oranı, hastalık şiddetinin bağımsız belirleyicileri olarak saptandı.
Sonuç: Laboratuvar parametrelerinin CT-SVA sonuçları ile birlikte değerlendirilmesi, kötü prognozlu olguların belirlenmesine ve müdahalenin hızlandırılmasına yardımcı olacaktır.

Anahtar Sözcükler: COVİD-19, bilgisayarlı tomografi, laboratuvar parametreleri, inflamasyon, biyobelirteç, risk faktörü

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INTRODUCTION

COVID-19 is a disease caused by SARS-COV-2 and the virus causes besides mucous membrane inflammation and endothelial cell damage the activation of the clotting cascade and further regulatory pathways (1). The complications of the disease are thought to be caused by viral toxin production, cytokine storm and hyperinflammation (2).

Laboratory parameters are essential for COVID-19 diagnosis and treatment worldwide discovery. Early diagnosis and classification of the COVID-19 are critical for the better prognosis and as well the therapeutic interference, as cortisol, as heparin and i.e. monoclonal antibodies. The present study is focused on early, correct and personalized evaluation and identification of the most useful prognostic factors in COVID-19 patients treated in our hospital by classifying them according to disease severity and evaluating multiple factors like sodium, albumin, C-reactive protein (CRP), D-dimer, ferritin, fibrinogen, interleukin 6 (IL-6), procalcitonin, white blood cell (WBC), lymphocyte, neutrophil, neutrophil lymphocyte ratio (NLR) and venous blood gas values. Initial measurements on admission and final measurements at discharge were compared. The thorax computed tomography (CT) results and laboratory findings of the patients were highly correlated with disease severity and simultaneous usage of these findings in symptomatic cases were thought to be useful in accelerating patients' management.

METHODS

Study Population

The study was approved by the Health Sciences University Gulhane Scientific Research Ethics Committee with a 05.11.2020/406 date and number. Written informed consent was obtained from all participants. The requests of the 2018 version of the Declaration of Helsinki were complied with while conducting this study. Study data was stored in an encrypted computer folder accessible to researchers. Blood results used drawn from patients who were positive for Polymerase Chain Reaction (PCR) at the time of admission to the hospital and before discharge (500 copies/mL considered positive for SARS-CoV-2.).

Sodium, albumin, CRP, D-dimer, ferritin, fibrinogen, IL-6, procalcitonin, WBC, lymphocyte, neutrophil, NLR and venous blood gas values were analyzed from these blood and the results were recorded. The demographic features, hospital stay duration, presence of any chronic diseases, intubation status, intensive care unit stay information was also recorded. Classification of the patients was made according to the criteria defined in guidelines published by the ministry of health (5). The patients were divided into two as mild/moderate ill group and severe/critical diseased group according to disease severity. Accordingly; patients with a) Fever, myalgia, cough, and sore throat; with respiration rate <30/min, SpO_2 levels >90% and, b) Mild-moderate pneumonia symptoms in lung CT were classified in the mild/moderate ill group. On the other hand, patients with a) Fever, myalgia, cough, and sore throat, having tachypnea (≥30/min), SpO_2 levels ≤ 90% and, b) Having bilateral diffuse pneumonia in lung CT and, c) Patients with intensive care unit needs were classified in the severe/critical diseased group. The study started with 300 patients and was completed with 83 patients. No uptake was observed in the CT images of 87 patients, laboratory parameters of 67 patients were not available, image of 63 patients was too bad to be segmented. As a result 41 in the mild/moderate ill group and 42 in the severe/critical diseased group were included in the study.

Radiological examination

The impaired lung volumes caused by COVID-19 in the lungs was evaluated by the radiology department of our hospital by following a semi-automated segmentation approach. As the number of CT scans is high, and COVID-19 infected regions with the surrounding tissues have a complex structure; an open-source ITK-Snap tool, a semi-automated segmentation method, was used for the assessment of the lungs injury in COVID-19 diagnosed patients; the ratio between the volume of the non-COVID-19 infected volume and the overall lung volume was calculated (3). Calculation of the affected lung volume due to the disease was carried out in 2 steps. First; the interested volume (Region of Interest) was determined, and the best threshold value of grey level was selected to discriminate the target volume from the surrounding tissues. There is not an optimum thresholding value valid for all CT scans. Therefore, a thresholding value was adjusted according to the characteristics of each CT scan. Thus, binary imaging in 3D was obtained per CT scan. Second; an active contour algorithm that minimizes energy function iteratively was used to calculate its volume (Figure I) (4).

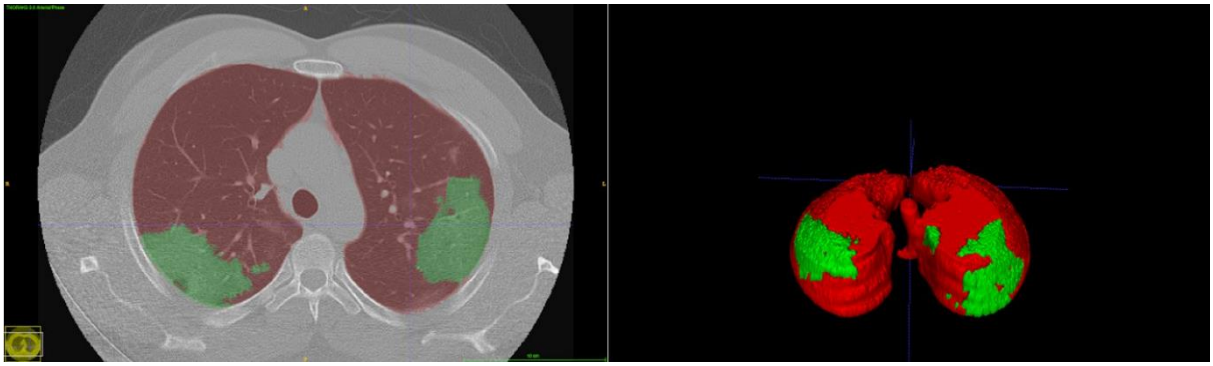

Figure I: 2D lung and ve affected area segmentation (left) and construciton of 3D lung volumes (right). Example of lung volumes calculated by semi-automatic segmentation tool, ITK-Snap, on computed tomography images by pre-setting a threshold value and a color in order to obtain quantative evaluation of segmented volumes, the non-COVID-19 infected (green) and the overall lung (red).

The located balloon inside the binary image is grown at each iteration until the physician decides that the interested volume is sufficiently covered. In the end, target volume was calculated using the built-in functionalities of the tool. To quantify the prognosis of the patients and compare it with other patients, the ratio rather than actual value was calculated for each patient by considering the lung capacity and the amount of volume affected by COVID-19. All CT examinations were obtained in the 64-row CT scanner (Aquillon 64, Toshiba, Japan) with the specified parameters without using contrast agents. CT scans were obtained with the following parameters; 100-120 kv, 50-150 mAs, 2-3 mm slice thickness, 1-2 mm slice interval, 500 ms rotation time, holding breath, arms up, 300-400 mm FOV, covering the whole lung from apex to basal. The images obtained were sent to hospital picture archiving and communication system (PACS).

Statistical analysis

All statistical analyses were carried out with SPSS 22.0 program. Shapiro-Wilk tests were used to determine if the laboratory parameters were distributed normally. Parametric data were given as mean+SD.Values were compared with the Independent-Samples T-test. Values belonging to the same patient group were compared with Paired-Samples T-test. CT-SVA results were evaluated in terms of correlation with laboratory parameters by applying the Pearson Test. A binary regression analysis was done for the detection of independent predictors of disease severity. For detecting the laboratory parameters suitable for the logistic regression model; first, the binary relationships between all laboratory parameters were evaluated, and then the most clinically relevant laboratory parameters were included in the model.

Laboratory parameters found to be highly related with disease prognosis were analyzed with Receiver Operating Characteristics (ROC) analysis for prediction of disease severity together with CT-SVA results. The sensitivity and specificity cut-offs were calculated for limit values. p<0.05 was accepted as the statistical significance level.

RESULTS

About 30/ 42 of severe/critically diseased group were transferred to the intensive care unit (ICU) from the inpatient clinics and 16 of them died. The remaining 12 severe/critically diseased group were directly followed up in the ICU from the time of admission and where 10 of them dies. The levels of D-dimer, fibrinogen, ferritin, IL-6 ve procalcitonin were significantly higher in the patients who died when compared to patients who were treated and discharged (p values were; <0.001, <0.001, =0.005, <0.001, <0.001 respectively). The demographic features of the study group are summarized in Table I.

Table I: Demographic characteristics of the patients with COVID-19

Parameters	Mild/Moderate Group	Severe/Critical Group	Total	*p* values
Patients (n)	41	42	83	
Male/Female (n)	26/15	26/16	52/31	0.447
Age (years) (mean±SD)	67.23±8.89	65.40±10.29	66.36±9.50	0.474
Hospital Stay (day) (mean±SD)	11.11±5.33	13.87±8.99	12.11±7.45	0.051
Intensive Care Stay (n) (%)	0	42 (100%)	42 (50.60%)	<0.001*
Intubation (n) (%)	0	25 (59.52%)	25 (30.12%)	<0.001*
Treated (n) (%)	41 (100%)	16 (38.09%)	57 (68.67%)	<0.001*
Ex (n) (%)	0	26 (61.90%)	26 (31.33%)	<0.001*

SD: Standart Deviation. *p* <0.05 was considered statistically significant. **p* values indicate differences between the parameters.

The levels of albumin, venous blood gas pH, and lymphocyte were significantly lower in the severe/critically diseased group while sodium, CRP, D-dimer, ferritin, fibrinogen, IL-6, procalcitonin, neutrophil, WBC, and NLR values were significantly higher in this group (p<0.05 for all laboratory parameters) (Table II).

Table II: Computed Tomography Segmentation-Volume Analysis and Laboratory Parameters of the patients with COVID-19

Parameters	Mild/Moderate Group (n:41) (mean±SD)	Severe/Critical Group (n:42) (mean±SD)	*p* values
CT-SVA (%)	13.61±12.20	31.80±12.52	<0.001*
Sodium (mEq/L)	135.34±4.25	137.17±6.55	0.025
Albumin (g/L)	3.36±0.44	3.06±0.49	<0.001*
CRP (mg/L)	110.87±86.11	152.84±101.77	0.004*
D-dimer (mg/L)	0.74±0.42	2.81±3.33	<0.001*
Ferritin (ng/mL)	300.25±211.32	652.51±424.86	<0.001*
Fibrinogen (mg/dL)	492.85±126.83	620.06±172.78	<0.001*
IL-6 (pg/mL)	60.26±54.62	206.49±276.32	<0.001*
Procalcitonin (ng/mL)	0.59±1.28	3.37±9.16	<0.001*
HCO3 (mEq/L)	22.54±3.91	22.16±5.76	0.702
Lactate (mmol/L)	2.16±1.51	2.31±1.54	0.425
pCO2 (mmHg)	36.31±6.71	38.41±11.23	0.221
pH	7.41±0.07	7.35±0.26	0.041*
pO2 (mmHg)	48,83±26.52	46.81±18,46	0.775
Lymphocyte (x10^3/µL)	1.08±0.59	0.84±0.48	0.001*
Neutrophil (x10^3/µL)	6.69±8.94	7.83±5.42	0.008*
WBC (x10^3/µL)	8.50±10.07	9.31±5.77	0.039*
NLR	7.47±7.33	12.43±10.53	<0.001*

SD: Standart Deviation. CRP: C Reactive Protein, CT-SVA: Computed Tomography Segmentation-Volume Analysis, WBC: White Blood Cell, NLR: Neutrophil-Lymphocyte Ratio, IL-6: Interleukin 6, *p* <0.05 was considered statistically significant. **p* values indicate differences between the parameters.

The laboratory results of all patients on admission and their latest results before discharge were also compared. The laboratory parameters with significant differences between the initial and final values are shown in Figure II.

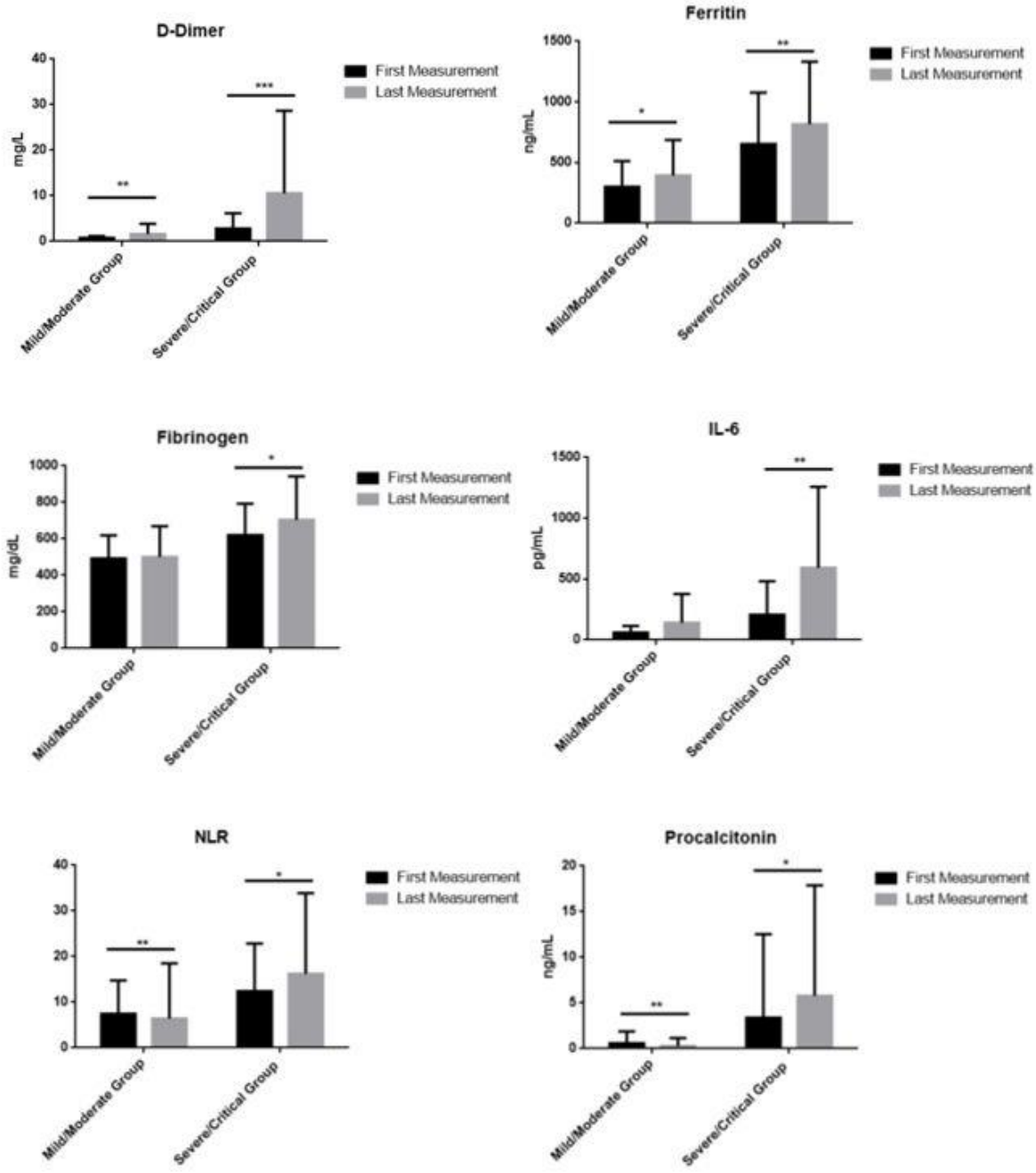

Figure II: Comparison of first and last test results of COVID-19 patients, **p*<0.05, ***p*<0.01, ****p*<0.001. CRP: C-reactive protein, NLR: Neutrophil Lymphocyte Ratio, IL-6: Interleukin 6

CT-SVA results have shown negative correlation with, albumin (p=0.007), while they had positive correlations with levels of CRP (p=0.036), D-dimer (p<0.001), ferritin (p<0.001), fibrinogen (p=0.031), IL-6 (p=0.001) and procalcitonin (p=0.009).

The results of the performed ROC analysis were summarized in table III and revealed that CT-SVA has a cut-off value of 15.92 with a sensitivity of 87.1% and a specificity of 80.0% in predicting disease severity.

Table III: The value of parameters and Computed Tomography Segmentation-Volume Analysis predicting SARS-CoV-2 infection severity

Parameters	AUC (95%)	Cut off	*p* values	Sensitivity (%)	Specificity (%)
CT-SVA	0.837 (0.776-0.899)	15.92	<0.001	87.1	80.0
Sodium	0.603 (0.523-0.683)	136	0.01	54.5	61.1
Albumin	0.225 (0.142-0.308)	3.32	<0.001	31.3	34.6
CRP	0.770 (0.684-0.856)	109	<0.001	71.6	73.1
D-dimer	0.777 (0.696-0.858)	0.895	<0.001	70.1	69.2
Ferritin	0.810 (0.733-0.886)	351	<0.001	73.1	71.2
Fibrinogen	0.740 (0.652-0.827)	525	<0.001	62.7	67.3
IL-6	0.788 (0.707-0.870)	65	<0.001	73.1	75
Procalcitonin	0.774 (0.687-0.860)	0.211	<0.001	74.6	73.1
HCO_3	0.472 (0.368-0.577)	22.9	0.6	46.3	46.2
Lactate	0.545 (0.441-0.649)	2.05	0.4	50.7	57.7
pCO_2	0.508 (0.404-0.612)	37.5	0.88	50.7	53.8
pH	0.450 (0.347-0.554)	7.41	0.35	40.3	57.7
pO_2	0.498 (0.391-0.606)	39.8	0.98	56.7	53.8
Lymphocyte	0.353 (0.254-0.452)	0.85	0.01	38.9	44.2
Neutrophil	0.642 (0.544-0.741)	4.85	0.01	59.7	59.6
WBC	0.619 (0.519-0.719)	6.5	0.03	58.2	57.7
NLR	0.704 (0.612-0.796)	6.775	<0.001	64.2	63.5

CRP: C Reactive Protein, CT-SVA: Computed Tomography Segmentation-Volume Analysis, WBC: White Blood Cell, NLR: Neutrophil-Lymphocyte Ratio, IL-6: Interleukin 6, AUC: Area Under The Curve. *p* <0.05 was considered statistically significant.

Binary logistic regression models have included CT-SVA, D-dimer, ferritin, IL-6, and NLR. The model correctly classified 88.1% of cases. CT-SVA, D-dimer, ferritin, IL-6, and NLR were detected to be the independent predictors of disease severity.

DISCUSSION

COVID-19 has a wide clinical spectrum from asymptomatic infection to severe pneumonia. Lung CT evaluation and laboratory parameters provide great contributions to the quick diagnosis of disease. In our study group; mild/moderate ill group had mild-moderate pneumonia in their lung CTs while severe/critical diseased group had diffuse bilateral pneumonia.

Severe/critical COVID-19 includes cytokine storm and some mechanisms that cause hypoalbuminemia (6). IL-6 level which is accepted as the most important predictor of the severe COVID-19 infection has been shown to cause increases in acute phase reactants like CRP and fibrinogen, and inhibits the synthesis of albümin (7). In previous studies; lower serum albumin in COVID-19 patients was related to poor prognosis and the impaired function of liver cells, which is followed by reduced albumin synthesis (8, 9). The results of the present study are in concordance with previous results as albumin levels of severe/critical diseased group were significantly lower than mild/moderate ill group (p<0.001). When final measurements were compared to the values at admission; albumin levels of severe/critical diseased group decreased more than the albumin levels of mild/moderate ill group (p<0.001). At the same time; as the lung damage level detected by CT-SVA worsened, albumin levels decreased.

Previous studies have shown that IL-6, CRP ve procalcitonin levels were significantly higher in the severe/critically diseased group, peripheral blood IL-6 levels were suggested as an independent predictor for progression of COVID-19, and CRP shows a positive correlation with disease severity. Further, the relationship between elevated levels of procalcitonin and ferritin and severity of SARS-CoV-2 infection was stated (10, 11). Our results have shown that IL-6, CRP, ferritin, and procalcitonin levels are elevated as the disease becomes more severe (p <0.001, =0.004, <0.001, <0.001 respectively). Also, the initial and final measurements of these laboratory parameters have shown that they support a bad prognosis in severe/critical diseased group.

In addition IL-6 and ferritin were detected as independent predictors of disease severity (p <0.001, and p= 0.002 respectively). Ferritin levels also showed a positive correlation with lung damage (p<0.001). Similar to a previous study on COVID-19, high procalcitonin levels in severe patients in our study support the possibility of bacterial coinfection in this group (11).

D-dimer and fibrinogen levels in COVID-19 patients have brought attention. Previous studies have stated higher levels of D-dimer and fibrinogen in severe patients when compared to mildly symptomatic patients (12, 13). Our results were also similar to the previous studies, in addition we also found that the levels of these two markers were increased in correlation with bad prognosis in time (p<0.001 for both) (Figure II). We also found that the level of D-dimers shows a positive correlation with lung damage (p<0.001).

In a previous study, peripheral blood lymphocytes of the severe/critical diseased group were detected to be extremely low at admission to the hospital while their WBC and neutrophil counts were significantly higher when compared to mild/moderate ill group. NLR was also defined as a powerful prognostic factor for predicting COVID-19 severity (14). Other studies also supported these findings as they stated that WBC and NLR values were higher in the critical patients while lymphocyte numbers were significantly low (15,16,17). Our results are also similar to the previous ones as lymphocyte numbers were significantly lower in the severe/critical diseased group while WBC and NLR values were significantly higher when compared to mild/moderate ill group (p values; 0.001, 0.039, <0.001 respectively). We also determined that NLR is one of the independent predictors of disease severity. These findings show that NLR increase is closely related to a bad prognosis. We also detected significantly lower pH values in blood gas analysis results of critical patients when compared to mild/moderate ill group (p=0.041). No significant differences were detected in other blood gas parameters. Previous studies with COVID-19 patients have also reported low pH levels in arterial blood gas analyses and related this situation to respiratory acidosis caused by lung damage (18,19,20). Another study in COVID-19 patients in the ICU has shown that relatively higher arterial blood pH is strongly correlated with survival (21).

Several authors have reported in recent literature the role of chest X-ray and CT in patients affected by COVID-19 disease, the evolution of these features over time, and the radiologist's performance in distinguishing COVID-19 from other viral infections (22,23).

Various methods have been proposed to quantify disease extent on chest CT, including the extent of emphysema, pulmonary fibrosis, and acute respiratory distress syndrome (ARDS). The CT score of lung disease burden has been previously reported as a risk factor for mortality in ARDS (24). However, there is little data on the prognostic value of CT in COVID-19. Visual semi-quantitative quantification of disease extent on CT correlated with clinical severity (25). Colombia et al. reported that in patients with confirmed COVID-19 pneumonia, extent of CT lung abnormality by visual or software digitization were predictors of ICU admission or death. They reported that the proportion of well-ventilated lungs as assessed by chest CT obtained in the emergency department is associated with a better prognosis in patients with COVID-19 pneumonia, independent of other clinical parameters (26). The size of the lung lesions is directly related to clinical symptoms. That's why a thorax CT in screening of COVID-19 is indispensable. COVID-19 has different imaging findings in different levels of pathogenesis (27). The most common CT finding in COVID-19 affected patients is ground-glass opacity and it is related to disease severity (28). The correlation of laboratory parameters which can be analyzed in a fast, practical, and cost-effective way with lung CT findings which is accepted as a cardinal sign of COVID-19 infection severity has been a subject of interest.

This study is a report in which segmentation-volume analysis is performed according to thorax CT results in COVID-19 patients and the damaged lung volume is calculated as a "%" ratio to correlate with laboratory parameters. The results of this original research revealed that segmentation-volume analysis gives the ratio of damaged lung tissue to total tissue volume and it has an important role in detecting the degree of clinical prognosis. Over 15.92% damage detected in the lungs by this method had an 87.1% predictive value for worsening of the clinical presentation. Also, lung damage detected under 15.92% is a predictive value of over 80% in patients who will be cured and discharged. On the other hand, when combined with laboratory parameters, CT-SVA is capable to provide a great contribution to the estimation of clinical prognosis. When CT-SVA results were combined with D-dimer, ferritin, IL-6, and NLR results, it had a predictive value of 88.1% for serious prognosis.

As a result, our data have shown that CT-SVA will be valuable in predicting the outcome of severe cases of COVID-19. Also, evaluation of laboratory parameters together with CT-SVA will provide an important contribution to the prediction of clinical outcomes. Follow-up of severity predictors will help clinicians to recognize patients at high risk for bad prognosis and accelerate early interventions. The limitations of the present study is being a single center cohort and inclusion of a limited number of parameters. Besides this, our study is based on lung involvement according to thorax CT results, so it will not proveide a major contribution to prediction of prognosis or mortality in COVID-19 patients without lung involvement. However, this study will be a valuable pioneer study for future multi-centered cohort studies including more hematological and inflammatory parameters.

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Conflict of interest

No conflict of interest was declared by the authors.

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