Coronavirus Pandemic

Diagnostic and early prognostic value of serum CRP and LDH levels in patients with possible COVID-19 at the first admission

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Abstract

Introduction: COVID-19 is the infection caused by the new coronavirus. Specific treatment for COVID-19 has not been established, yet. It is important to determine the disease severity of the patients at the first admission. Therefore, the exploration of biomarkers is deemed necessary. We aimed to assess the diagnostic and early prognostic value of CRP and LDH levels in possible COVID-19 patients presenting with a severe clinical picture.

Methodology: We evaluated the correlations of relevant routine laboratory test results with disease severity in COVID-19 patients admitted to our infectious diseases clinic. Patients were divided into severe and non-severe disease groups based on clinical findings, oxygen saturation levels in the arterial blood, biochemical test results, and radiological findings. Differences in the findings between the two disease severity groups were examined to determine potential biomarkers.

Results: Median age and the CRP and LDH levels in the severe disease group were statistically significantly higher compared to the nonsevere group ($p < 0.0001$). No other parameters statistically significant differences have been observed between the two groups ($P > 0.05$).

Conclusions: CRP and LDH levels were positively correlated with lung lesions in early-stage COVID-19, potentially reflecting disease severity. Because LDH and CRP levels can potentially reflect the pulmonary function, they can be potential predictors of COVID-19- related respiratory failure. For avoiding poor prognosis; LDH and CRP should be considered as potential predictors for identifying the need for thoracic CT scans, close monitoring of pulmonary function, and aggressive supportive therapy early in the course of COVID-19.

Key words: COVID-19; SARS-CoV-2; C-reactive protein; lactate dehydrogenase; laboratory findings.

Introduction

Coronaviruses comprise a large virus family causing infections of varying severity ranging from the simple common cold to more severe infectious diseases. Various subtypes of coronaviruses that can be easily transmitted from person to person have been identified in humans. Such subspecies mostly cause common colds in humans. Furthermore, many coronavirus subtypes are detected in animals, causing severe diseases in humans via animal to human transmission [1,2]. Identified in 2003 for the first time and known as the first international health emergency in the 21st century, SARS-CoV caused the deaths of hundreds of people. About ten years later, MERS-CoV from the coronavirus family emerged as another new virus, which has not been identified in humans or animals previously. The most recently identified coronavirus causing severe infections in humans and becoming a

global health issue has been announced by the World Health Organization (WHO) on December 31, 2019, as a new coronavirus (2019-nCoV) that occurred for the first time in China. Later, the 2019-nCoV infection was named as COVID-19. On January 30, 2020; WHO classified the COVID-19 outbreak as an "international public health emergency". Due to the unpreventable spread of 2019-nCoV and the severity of COVID-19 globally; WHO defined the COVID-19 outbreak as a pandemic on March 11, 2020 [3,4]. Assessment of COVID-19 status in our country started on January 10, 2020, and the necessary measures have started to be implemented. The first meeting of the Scientific Advisory Board of the Ministry of Health was held on January 22, 2020. The first COVID-19 case in Turkey was seen on March 11, 2020, after Iran and neighboring countries in Europe. Starting from the detection of the first case, the approach of our country's administrative

and health authorities has been to reduce the damages of the epidemic, contain and suppress the epidemic, and thus prevent the intense demand for health services [1]. According to WHO; 33,502,430 confirmed cases of COVID-19 had been reported worldwide, including approximately 1,004,421 deaths as of 30 September 2020. In our country; 317,272 confirmed cases and approximately 8,130 deaths have been reported [5]. Patients infected with COVID-19 show a variety of manifestations ranging from the asymptomatic presence of the virus in the body to a clinical picture of severe acute respiratory failure and death [2]. Classification of cases as mild, moderate, severe, and critical is useful for effective case management and treatment. COVID-19 patients can be classified as mild, moderate, severe, and critical based on clinical findings, oxygen saturation levels in the arterial blood (SpO2), biochemical test results, and radiological findings [6]. This study aimed to investigate the role of different parameters used in the clinic to determine whether the levels of such parameters would change by disease severity and be potentially used as biomarkers to predict the prognosis of COVID-19. In this study, we evaluated leukocyte and lymphocyte counts and the levels of blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer as potential biomarkers.

Methodology

Ethics Committee Approval

This retrospective observational study was carried out in a single-center after it was approved by the Ankara Health Sciences University clinical research ethics committee. (10.08.2020-93/14).

Study Design and Data Collection

This observational study was conducted at a single-center retrospectively. The study included 220 adults (≥ 18 years old) with confirmed COVID-19; who made their first medical visit to Ankara Pursaklar State Hospital in the period between 2 April 2020 and 20 June 2020, before receiving any antiviral or antibacterial therapy. Medical records of the patients in the electronic archive of the hospital were scanned retrospectively. Nursing records were also reviewed when necessary. Demographic data, comorbidities, clinical symptoms, laboratory findings, computed tomography (CT) scans of the chest, and clinical outcomes of patients were carefully reviewed and analyzed separately. The diagnosis of COVID-19 was confirmed via RT-PCR tests in the oropharyngeal swab

or sputum samples of the patients. Patients with missing laboratory data were excluded from the study. The individuals included in the study were grouped as nonsevere and severe based on clinical features, PO2 values measured by a pulse oximeter, and CT findings. Biochemical and hematological parameters of the study patients were compared between severe and nonsevere disease groups. The serum leukocyte and lymphocyte counts and the levels of LDH, ALT, AST, BUN, CRP, and D-dimer at admission were evaluated for their potential for use as biomarkers.
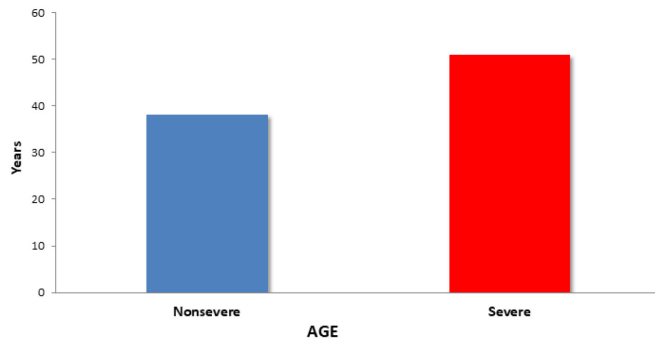
Patients

The patients were assigned to four categories as mild, moderate, severe, and critical groups based on clinical and radiological findings. There were no signs of viral pneumonia and hypoxia in the mild patient group. Patients with minimal pulmonary involvement (< 25%), with SpO2 levels of ≥ 94% on room air, and no signs of severe pneumonia were categorized as the moderate group. Patients with clinical signs of pneumonia (pulmonary involvement of 51-75%) and with one of the following criteria including a respiratory rate of > 30/minute and severe respiratory distress or SpO2 levels of < 93% on room air were assigned to the severe group. The critical group consisted of patients with severe pulmonary involvement (> 75%) in each lung, respiratory failure, need for mechanical ventilation, multiorgan failure, and patients admitted to the intensive care unit [6]. The patients were further categorized into two groups by grouping the patients with critical and severe diseases in the severe group and the patients with mild and moderate diseases in the nonsevere group.

Laboratory tests

The COVID-19 diagnosis was confirmed by RT-PCR (Bio-Rad CFX96, USA) device and Biospedy COVID-19 qPCR Detection Kit (Bioeks, Turkey) in oropharyngeal swab or sputum samples. Blood samples were collected from each participant for routine blood count tests and laboratory analyses; including the white blood cell count (WBC), lymphocyte count, neutrophil count, and the levels of BUN, AST, ALT, LDH, and CRP. Blood counts were performed by using an automated hematology analyzer (Horıba ABX Pentra DF 120, France) in compliance with the manufacturer's instructions. A fully automated clinical chemistry instrument (Beckman Coulter AU 680, USA) was used for analyzing the serum samples. D-dimer was determined on CS2500 automatic coagulation analyzer (Siemens, Germany).
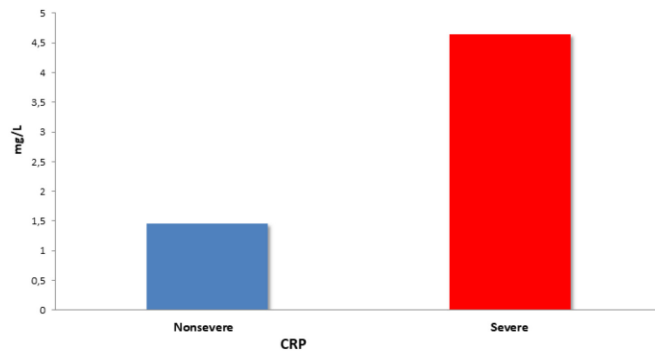
Figure 1. The mean age of the patients in the severe and nonsevere COVID-2019 groups.
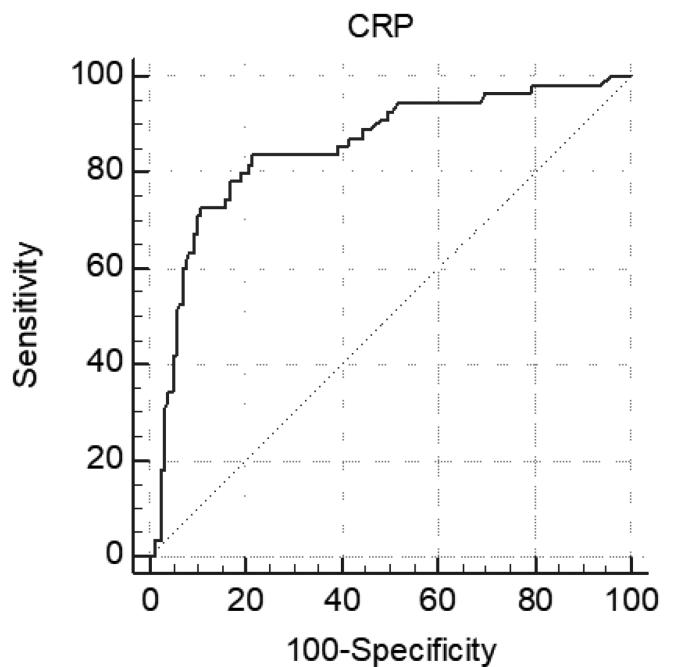

Figure 2. The ROC curve for age for determining disease severity on admission.
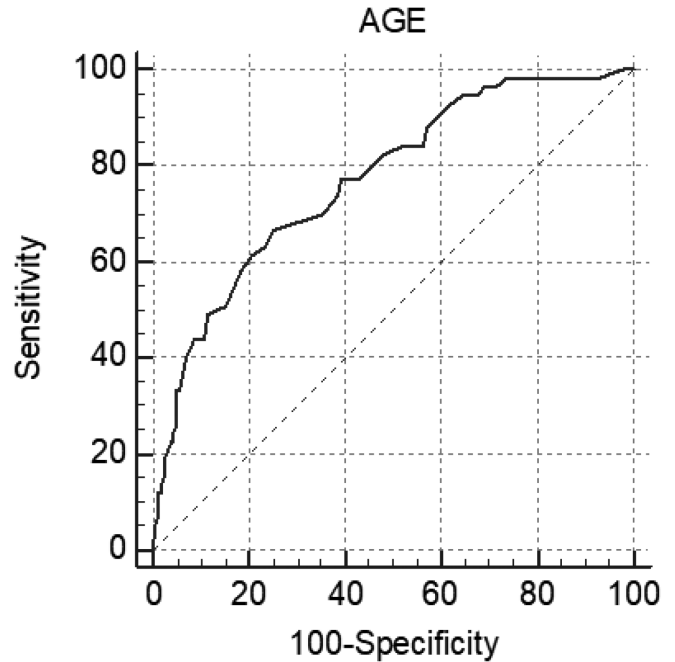
Figure 3. The mean serum C-reactive protein levels of patients with severe and nonsevere COVID-2019.

Figure 4. The ROC curve for C-reactive protein levels for determining disease severity on admission.

Table 2. The area under the curve (AUC) values for age and the serum levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH).

Variables	Cut-off value	AUC(95% CI)	Sensitivity	Specificity	Youden index	p value
AGE	> 46	0.77 (0.70-0.82)	67%	75%	0.42	< 0.0001
CRP	> 1,15	0.84 (0.79-0.89)	84%	78%	0.62	< 0.0001
LDH	> 197	0.72 (0.65-0.78)	73%	65%	0.38	< 0.0001

Table 1. Demographics and clinical characteristics of COVID-19 patients. The mean values of the laboratory test results and corresponding standard deviation values are shown by the severe and nonsevere patient groups.

Parameter	All patients (N = 215)	Nonsevere group (N = 118)	Severe group (N = 57)	P value	(p) OR (95% CI)
Age (Years)	42.07 ±13.423	38.64 ± 11.88	51.57±12.92	**< 0.001**	0.060 (0.002) 1.061 (1.027-1.096)
WBC×10^9/L	5.66 ± 5.44	4.85 ± 1.79	4.8 ± 1.674	0.152	
Lymphocyte×10^9/L	1.62 ± 1.29	1.57 ± 0.65	1.47 ± 0.62	0.180	
LDH (U/L)	205.46 ± 58.31	191.36 ± 37.48	241.53 ± 82.38	**< 0.001**	0.012 (0.003) 1.012 (1.004-1.020)
AST (U/L)	27.91 ± 17.31	27.16 ± 18.06	30.01 ± 14.94	0.518	
ALT (U/L)	27.41 ± 24.84	27.79 ± 27.00	26.32 ± 17.55	0.925	
BUN (mg/dL)	28.35 ±8.69	27.77 ± 8.46	30.00 ± 9.20	0.236	
CRP (mg/dL)	2.29 ± 4.68	1.46 ± 4.64	4.64 ± 3.93	**< 0.001**	0.087 (0.001) 1.211 (1.099-1.334)
D-Dimer (mg/L)	1.55 ± 13.64	1.78 ± 15.78	0.86 ± 1.02	0.493	

Statistical analysis

Continuous variables were presented as mean ± standard deviation, median, or interquartile ranges based on the distribution of the data. Student's t-test or the Mann-Whitney U test was used for testing differences between the two study groups when relevant. The one-way analysis of variance (ANOVA) was used for study group comparisons. Correlation between variables was evaluated using Spearman correlation analysis. The multivariate logistic regression analysis model was established. The dependent variable was considered as severity, and the independent variables that were statistically significant at the group comparison. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated by determining the cut-off values. Receiver operating characteristic (ROC) curves were created and the areas under the curve (AUC) were assessed to determine the accuracy of each independent potential predictor. The sensitivity and specificity of potential predictors of the COVID- 19 severity were determined by using the ROC curves. AUC values of 0.9-1 were accepted to indicate excellent accuracy, 0.8-0.9 very good accuracy, 0.7-0.8 good accuracy, 0.6-0.7 sufficient accuracy, 0.5-0.6 bad accuracy, and AUC values of < 0.5 were accepted to indicate poor accuracy. The SPSS 18.0 software was used for performing the statistical analyses. P-values of lower than 0.05 were accepted to indicate statistical significance.

Results

The study included 215 patients with COVID-19. Of the patients included; 85 had a mild infection, 73 were moderately ill, and 57 had severe disease. No patients met the critical disease criteria. A total of 158 patients from mild and moderate disease severity groups were categorized as the nonsevere group. The remaining 57 patients with severe disease were allocated to the severe group. Of the study patients; 118 (54.9%) were men and 97(45.1%) were women. No significant differences were observed in the male to female ratio between the study groups. The median age of the patients was 42.07 years (range, 21-78 years). The mean age of the patients in the severe group was significantly higher compared to the patients in the non-severe group ($p < 0.0001$) (Table 1 and Figure 1). The mean age and the levels of CRP and LDH measured at the time of admission were statistically significantly different between the two study groups ($p < 0.0001$). The values of the other parameters including the WBC and LYM counts and the serum levels of BUN, AST, ALT, and, D-Dimer were not statistically significantly different between the groups ($p > 0.05$) (Table 1). ROC curves were generated and analyzed and the differences in AUCs between the two study groups were tested to evaluate the sensitivity and specificity of the variables in the prediction of the COVID-19 severity and to determine and compare the accuracy of the study variables in the prediction of adverse clinical outcomes. Table 2 shows the AUC values of age and the CRP and LDH levels. In identifying patients with severe disease; the ROC curves showed that age had 72% sensitivity and 71% specificity (AUC: 0.78, $p < 0.0001$) (Figure 1 and 2), CRP levels had 72% sensitivity and 71% specificity (AUC: 0.78, $p < 0.0001$) (Figures 3 and 4), and LDH levels had 75% sensitivity and 70% specificity (AUC: 0.76, $p < 0.0001$) (Figures 5 and 6). The goodness-of-fit results of the logistic regression model were acceptable (-2LL=166.52; R^2 (Nagelkerke) = 0.371 and Chi-square = 55.76 ($p < 0.001$)). The predictive factors affecting the severity were all significant, they have positive Beta coefficients (OR$_{CRP}$ = 1.211; OR$_{Age}$ = 1.061; OR$_{LDH}$ = 1.012) (Table 1).
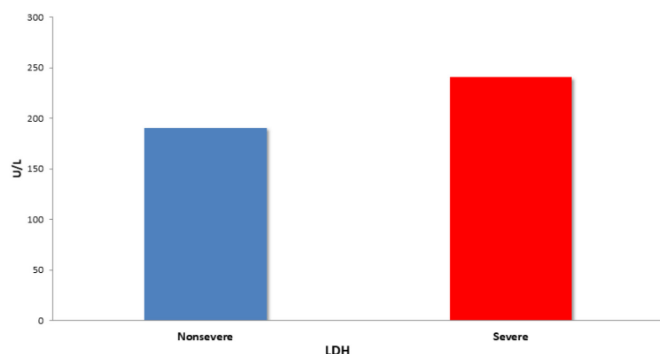
Discussion

The number of patients with COVID-19 and mortality rates due to COVID-19 is rapidly growing around the globe. The rapid spread of the pandemic increases the burden on hospitals. The symptoms of COVID-19 ranges from mild to critical severity levels. Early monitoring of key indicators is crucial to develop treatment strategies. Furthermore, the early assessment of the disease severity is invaluable [7]. Making an accurate diagnosis of COVID-19 is essential for implementing adequate isolation, treatment, and other measures. Although the RT-PCR test is the gold standard in confirming the diagnosis of COVID-19, not every healthcare center may have access to RT-PCR testing opportunities. Therefore, it is essential to determine the condition of patients on time by using hematological and biochemical biomarkers. Biomarkers are the biological parameters measured quantitatively in biological samples collected from patients. Biomarkers are used in the management of many diseases as indicators that reflect the pathological course of the clinical conditions of patients [4,8]. This study has aimed to discuss whether levels of different parameters tested in COVID-19 patients would vary depending on the disease severity and whether they could be used as biomarkers. In this study, the differences between the WBC and lymphocyte counts and the levels of BUN, AST, ALT, and D-Dimer were not found out to be statistically significantly different between the study groups. The importance of the WBC count in determining the severity of COVID-19 has not been proven. Studies show a decrease in the lymphocyte count, especially in severe cases in need of intensive care [9]. D-Dimer; which is the product of the degradation of fibrin, increases as a result of coagulation and the activation of fibrinolysis. D-dimer levels are found to be higher in the blood samples of critical patients and significantly associated with higher

Figure 5. The mean levels of LDH in patients with severe and nonsevere COVID-2019.

rates of mortality [10]. In critical cases, renal function deteriorates and serum levels of renal parameters increase resulting from respiratory failure and coagulation disorders [11]. ALT and AST levels also increase in critical cases due to respiratory failure, coagulation disorders, and organ damage. Studies showed that the prevalence of elevations in the values of liver function tests in critical patients was at least doubled compared to noncritical patients [12,13]. The differences between our study results and the results reported in the literature might have occurred because we refer critically ill patients to external centers. As critical patients were transferred to external centers and were not admitted to our hospital during the study period, we could not access the clinical and laboratory data of such patients. Therefore, our study results have shown differences from the results reported by other studies.

Our study found out that the median age and the levels of LDH and CRP were significantly higher in severe patients compared to nonsevere patients. Age was reported as an independent predictor of adverse outcomes and a predictor of developing a severe or critical disease, suggesting a higher risk of vulnerability to COVID-19 and a higher likelihood of following a severe or critical disease course for older people [14-16].

CRP, which is a non-specific acute phase protein, is produced by the liver. The production of CRP is

Figure 6. The ROC curve for serum LDH levels for determining disease severity on admission.
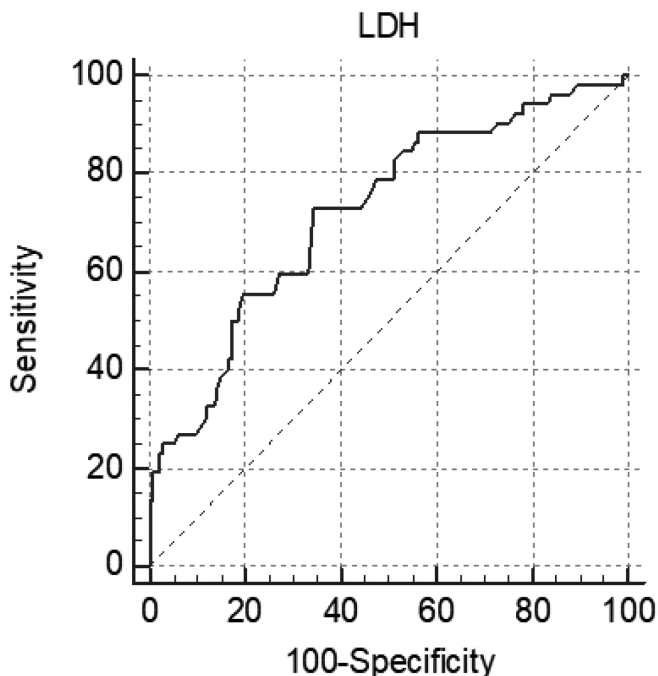
induced by a variety of inflammatory mediators. CRP levels are still utilized in clinical practice as a sensitive biomarker in inflammatory conditions, infections, and tissue damage despite the nonspecificity of the results. Also, increases in CRP levels reflect increasing disease severity [8]. Our study demonstrated that CRP levels were significantly higher in the severe group compared to the levels measured in the non-severe group, pointing out that the CRP level was an independent risk factor for the occurrence of severe COVID-19. In the literature, CRP levels were positively correlated with acute lung injury in COVID-19 patients [17]. A retrospective study conducted at a single-center reported that CRP levels were significantly high in most of the severe patients compared to nonsevere patients [18]. Another study found that COVID-19 patients with high CRP levels were more likely to develop a severe disease [19]. Weiping et al. suggested CRP levels as one of the first biomarkers to reflect physiological complications and as the most significant biomarker for predicting whether COVID-19 would progress [20]. Compatible with our study findings, studies in the literature also have demonstrated that the level of CRP is a robust predictor to diagnose COVID-19 and estimate the disease severity.

LDH is an enzyme involved in glucose metabolism for the conversion of lactate to pyruvate for energy production in living organisms. LDH can be found in almost all types of human cells. LDH is found in high concentrations in the lung, muscle, kidney, and blood cells and the cells of the heart and the liver. LDH is accepted as an inflammatory marker generally indicating acute or chronic tissue damage. The increase in LDH levels has been reported during acute and severe lung injury and interstitial lung infections [21]. Our study demonstrated that the levels of LDH were significantly higher in the severe group compared to the nonsevere group. Compatible with our study results, other studies in the literature reported that increased serum LDH levels were associated with COVID-19 disease. The production of LDH is induced in viral infections or lung damage, including COVID-19-associated pneumonia [22]. LDH levels are reported to be significantly high in cases with tissue damage and higher levels of LDH are reported to depend on the degree of inflammation [23]. Also, studies report significantly higher levels of LDH in critically ill ICU patients compared to non-critical non-ICU patients [24]. A study investigating the association of LDH levels with thoracic CT scan findings found that high LDH levels reflected pneumonia severity [25]. There is growing evidence for the use of LDH as a biomarker to estimate the severity of COVID-19. Another study in the literature reported a significant increase in LDH levels in patients with refractory COVID-19 [26]. A meta-analysis study by Zhang et al. has demonstrated that increased CRP and LDH levels are significantly associated with severity in severe patients and severe patients have significantly higher CRP and LDH levels compared to nonsevere patients [8].

There were some limitations in this study. First, selection bias might occur for this retrospective study, and further prospective studies were needed. Second, this study was based on a single center, and the number of patients participating in the study is not large enough, it should be supported by nationwide studies with a larger patient. Besides, we only included hospitalized patients with follow up CT examinations to ensure more information on clinical and CT characteristics.

Conclusions

Early identification and provision of adequate treatment are crucial factors in the management of COVID-19 patients with a higher likelihood of developing acute respiratory failure so that the development of ARDS and end-organ damage can be avoided. Our study results show that increased CRP and LDH levels are significantly associated with disease severity. Based on our study results; we think that LDH and CRP levels can help identify COVID-19 patients with a high likelihood of developing acute respiratory failure even in patients, who do not complain of dyspnea or who show signs of only slight respiratory failure. Our study results highlight the importance of vigilance in the interpretation of laboratory test results in COVID-19 patients. A high CRP level can be a useful marker to estimate the likelihood of progression to a severe clinical condition in nonsevere COVID-19 patients. To start adequate treatment at early stages in the course of the disease, CRP levels can be used for identifying early-stage COVID-19 patients at risk for developing severe disease. High CRP and LDH levels in COVID-19 patients should indicate the need for close follow-up and ICU admission when necessary. Biomarkers can be beneficial tools for clinicians in the management of COVID-19 patients because biomarkers may reflect the need to start treatment and close follow-up. We believe that serum levels of CRP and LDH on admission are essential parameters in deciding whether thorax CT, home isolation, or hospitalization will be required in the management of COVID-19 patients.

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