

Discrepancy between biomarkers of lung injury and 1-year mortality in COVID-19

Basak Atalay¹  | Abdurrahman Cesur²  | Mehmet Agirbasli³ 

¹Department of Radiology, School of Medicine, Istanbul Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey

²School of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

³Department of Cardiology, School of Medicine, Istanbul Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey

Correspondence

Mehmet Agirbasli, Department of Cardiology, School of Medicine, Istanbul Medeniyet University, Medeniyet University Hospital, Goztepe 34726, Istanbul, Turkey.
Email: agirbasli@gmail.com

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Abstract

Background: COVID-19 global pandemic started in late 2019 with the first wave. In this cross-sectional and observational study, we evaluated the associations between the biomarkers, COVID-19 pneumonia severity and 1-year mortality.

Methods: A sample of 276 polymerase chain reaction (PCR)-positive patients for SARS-CoV-2 was included. Computerized tomography severity score (CT-SS) was used to assess the severity of COVID-19 pneumonia in 222 cases. Multivariate analyses were performed to find the predictors of CT-SS, severe CT-SS (≥ 20) and 1-year mortality. Biomarkers of ferritin, high-sensitive C-reactive protein (CRP), lactate dehydrogenase (LDH), cardiac troponin (cTn), neutrophil-to-lymphocyte ratio (NLR), uric acid (UA) and D-dimer were routinely measured.

Results: Severe CT-SS (>20) was observed in 86 (31.2%) cases. Mortality was observed in 75 (27.2%) patients at 1 year. LDH displayed the highest predictive accuracy for severe CT-SS (AUC 0.741, sensitivity = 81% and specificity = 68%, cut-off value: 360 mg/dl). Linear regression analysis displayed that LDH predicted CT-SS [$B = 11$ (95% CI for $B = 5-17$, $p < .001$)]. Age was the most significant parameter that was associated with severe CT-SS (OR 0.96, 95% CI 0.92–0.99, $p = .015$). D-dimer was the only biomarker that predicted with 1-year mortality (OR 1.62, 95% CI 1.08–2.42, $p = .020$).

Conclusion: LDH is a sensitive and specific biomarker to determine patients with severe lung injury in COVID-19. D-dimer is the only biomarker that predicts 1-year mortality. Neither LDH nor CT-SS is associated with 1-year mortality.

KEYWORDS

biomarkers, COVID-19, CT severity score, first wave, mortality

1 | INTRODUCTION

SARS-CoV-2 caused coronavirus disease 2019 (COVID-19). COVID-19 global pandemic started in late 2019 with the first wave.¹ Lung damage is common in COVID-19 such as histologically-proven pneumonitis or interstitial damage and fibrosis. Pneumonia is the

leading cause of morbidity and mortality in COVID-19. Lung involvement in patients with COVID-19 could range from asymptomatic to overt adult respiratory distress syndrome requiring intubation. Determining the severity of lung involvement is important for the effective utilization of health care resources. Lung damage in COVID-19 can be assessed with several noninvasive

imaging methods such as chest radiography, computed tomography (CT) and lung ultrasonography. Radiological findings are largely based on CT of the chest. A suspected diagnosis of SARS-CoV-2 pneumonia is radiologically based upon the findings of ground-glass opacities (GGO), crazy-paving and consolidation in Chest CT images.² Several scoring systems check and score the typical findings in accordance with the standards published by the Fleischner Society.³ The lung involvement and the radiological findings vary in relation to the phase and severity of COVID-19. In the early phases, the GGO is frequently observed whereas in later phases as in severe and critical patients, consolidation is the predominant finding.² The CT findings represent the damage in the epithelium and the alveoli, which are infiltrated by inflammatory exudate.⁴ Chest CT has a higher sensitivity and greater proficiency in determining the characteristic findings, particularly during the early stages of the disease.⁵ Yet, CT scan cannot be used as a routine screening tool in the emergency room (ER) due to the cost and the radiation exposure. In addition to the clinical assessment in the ER, pulse oximeter (<94%) and respiratory rate (>22/min) set the decision points for admission in COVID-19.⁶ However, the assessment of pulse oximeter and respiratory rate can be difficult and subjective in the ER. Both variables can change with the position of the patient and environmental factors. Confirmatory biomarkers are needed to screen, diagnose and manage patients with severe lung damage in the ER. Similarly, the predictors of poor COVID-19 outcomes during the first wave of the pandemic remain to be elucidated. The pathophysiology of severe and rapid lung damage, in most cases, remains uncertain. Histological and autopsy studies report that SARS-CoV-2 induces endotheliitis in the heart, lung, kidney, liver and other tissues.⁷ Inflammation, microvascular dysfunction and thrombosis co-exist in the pulmonary vascular system in COVID-19. Several biomarkers are used to risk stratify the hospitalized patients with COVID-19.⁸ These biomarkers represent different biological systems such as inflammation (ferritin, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR) and high-sensitive C-reactive protein (CRP), tissue injury (lactate dehydrogenase (LDH) and cardiac troponins), oxidative stress (uric acid) and thrombosis (D-dimer).

Over the last 2 years, the COVID-19 phenotype has changed significantly. The availability of effective vaccines and resources, effective treatment algorithms and identification of novel variants with different clinical features have all added to the complexity of COVID-19. The predictors of severe outcomes in the first wave of COVID-19 remain to be of interest.

There is a need for easily available and cheap biomarkers for severe lung involvement COVID-19. In the present

study, we report the predictors of severe CT-SS and 1-year mortality in COVID-19.

2 | MATERIALS AND METHODS

The study was performed in Istanbul, Turkey. The first case of COVID-19 in Turkey was reported on 11 March 2020 in Istanbul. Shortly after the start of the pandemic, the hospital became a designated COVID-19 center. We reviewed the charts of patients who had been diagnosed with COVID-19 and admitted to the hospital during the first wave of the pandemic. A cross-sectional observational study was performed in a large tertiary care university hospital. Patients aged between 18 and 80 years were included. Patients were polymerase chain reaction (PCR) positive for SARS-CoV-2. Demographic, clinical and laboratory parameters were recorded with direct interviews and with using the institutional electronic medical database. All patients included in the present study had: (i) a positive nasopharyngeal swab PCR test for SARS-CoV-2, (ii) chest X-ray or thoracic CT findings that were compatible with COVID-19 pneumonia and (iii) requirement for hospital admission due to COVID-19 according to the Ministry of Health criteria.

The study was approved by the Ethics Committee and the Ministry of Health (protocol number 2022-04-09T11_42_37). The committee waived the requirement of informed consent due to the study design and anonymity of the database. The study conforms to the STROBE Statement for the reports of observational studies. Reporting of the study conforms to broad EQUATOR guidelines.⁹

2.1 | Imaging parameters

All patients were scanned in the supine position with a 16-detector CT scanner (GE Optima CT660 GE Healthcare). CT scan parameters were as follows: X-ray tube parameters 120 kVp, 300 mAs; rotation time 0.6 s; pitch 1.0; section thickness 5 mm; intersection space 5 mm; additional reconstruction with a slice thickness of 1.5 mm.

2.2 | Grading of computerized tomography evidence of disease

Chest computed tomography severity score (CT-SS) was used for grading CT findings. CT-SS was developed by Yang et al¹⁰ to assess the severity of COVID-19 pneumonia. The lung segments were assessed for the presence and

dissemination of GGO, crazy-paving pattern and consolidation. Totally 20 lung segments and percent (%) involvement were scored on chest CT images as follows: 0%–score 0, <50%–score 1, or equal to or more than 50%–score 2, respectively. Finally, the sum of all 20 segment scores was added to a maximum score of 40 range. Univariate and multivariate logistic regression analysis was performed to predict CT-SS. Severe COVID-19 pneumonia is defined as a CT score ≥ 20 (Figure 1).

2.3 | Laboratory investigations

The nasopharyngeal swab was obtained on admission. Real-time reverse-transcription PCR using Coronex COVID-19 rt-qPCR detection kit (Gensutek) was used. The diagnosis of COVID-19 was ascertained with a positive PCR test and thorax imaging findings that were compatible with COVID-19 pneumonia. Biomarker concentrations of ferritin, CRP, LDH, cardiac troponin, uric acid and D-dimer were routinely determined with electrochemiluminescence immunoassay methods, using biochemical analysis kits and Roche Cobas 6000 analysis device (Roche Diagnostics). Other laboratory analyses were done with conventional biochemical methods.

2.4 | Statistical analyses

Data for continuous parameters were given as mean $\pm$ SD or median and interquartile range, depending on the distribution of the data. Categorical variables were presented as percentages. For continuous variables, patterns of distribution were analysed with a visual inspection of histograms and with the Shapiro–Wilk test. Comparisons between groups were done with the Student's *t* test or Mann–Whitney *U* test were used to compare independent samples with parametric or nonparametric distribution, respectively. For categorical variables, the χ^2 test or Fisher's exact test were used to compare the groups. Correlation analyses were performed with the Pearson or Spearman test for parametric and nonparametric variables, respectively. A receiver-operator curve was drawn to analyse the accuracy of various biomarkers to predict severe CT-SS (≥ 20). Linear regression analysis was performed to find the predictors of CT-SS. Covariates were selected from basic parameters that are assessed in the emergency room such as age, LDH, D-dimer, haemoglobin WBC and NLR. Variables with nonparametric distribution were log-transformed before analysis (LDH, D-dimer, WBC). $p < .05$ were accepted as statistically significant. All statistical analyses were done with SPSS 25.0 (IBM Inc).



FIGURE 1 The axial (A,B) and coronal (C–E) reformatted computerized tomography (CT) images demonstrate an example of severe CT-SS. Patchy areas of ground-glass opacities were noted in several segments in both lungs. All 20 segments were scored from 0 to 2 based on the percent involvement. All scores were added to a total CT severity score of 31

3 | RESULTS

A sample of 276 PCR-positive patients with COVID-19 who were admitted to the hospital from April 1 to 30, 2020 to March 1 to 30, 2021 were identified. The study was performed through a detailed retrospective chart review. CT-SS was used to assess the severity of COVID-19 pneumonia in 222 cases, and 86 cases (39%) displayed severe CT-SS.

Figure 1 demonstrates an example of severe CT-SS. Patchy areas of ground-glass opacities were noted in several segments in both lungs. All 20 segments were scored from 0 to 2 based on the percent involvement. The higher percentage of involvement ($\geq 50\%$) scored 2 points for each segment. All scores were added to a total CT severity score of 31.

Demographic, clinical and laboratory results of the study groups were summarized in Table 1. Patients with severe CT-SS displayed higher fibrinogen, troponin and hs-CRP concentrations as compared to patients with CT-SS < 20 (Table 2).

3.1 | CT-SS and biomarkers

We tested all 6 biomarkers by ROC analysis for severe CT-SS. The sensitivities and specificities of all 6 biomarkers to detect severe CT-SS by ROC analysis were determined (Table 3). Of all biomarkers tested, LDH [AUC 0.741 (0.672–0.809) $p < .001$, sensitivity = 81% and specificity = 68% for a cut-off value 360 mg/dl] displayed the highest predictive accuracy for severe CT-SS. AUC for other biomarkers of inflammation and organ injury remained < 0.7 (Table 3). Gender differences were noted in the specificity and sensitivity of LDH in predicting severe lung damage. In both female and male patients, LDH displayed higher AUC than other biomarkers (Figure 2). Linear regression analysis was performed to find the predictors of CT-SS. Covariates were age, LDH, D-dimer, haemoglobin and WBC. Variables with non-parametric distribution were log-transformed (LDH, D-dimer and WBC). LDH was the only predictor of CT-SS (Figure 3).

Severe CT-SS (> 20) was observed in 86 (31.2%) cases. Logistic regression analysis was performed to find the predictors of severe CT-SS. Covariates were 7 biomarkers (Hs-CRP, D-dimer, LDH, troponin, ferritin, uric acid and NLR), gender and age. Age was the most significant parameter that was associated with severe CT-SS. Age displayed negative association with CT-SS (OR 0.96, 95% CI 0.92–0.99, $p = .015$, Nagelkarke $R^2 .36$) (Table 4).

3.2 | One-year mortality

Mortality was observed in 75 (27.2%) patients at 1 year. Multivariate binary logistic regression analysis has performed the predictors of 1-year mortality. Covariates were age, CT-SS, biomarker concentrations of ferritin, hs-CRP, LDH, cardiac troponin, NLR, UA and D-dimer. Among covariates of 7 biomarkers, CT-SS, gender and age, D-dimer was the only biomarker that was associated with mortality (OR 1.62 95% CI 1.08–2.42, $p = .20$, Nagelkarke $R^2 .73$) (Table 5).

4 | DISCUSSION

Severe lung damage and 1-year mortality are indicators of poor outcomes after COVID-19. The study indicates that there is a discrepancy between the biomarkers of lung damage and 1-year mortality in COVID-19. LDH is a sensitive and specific biomarker to determine patients with severe lung damage in COVID-19. Yet, neither LDH nor CT-SS is associated with 1-year mortality. D-dimer is the only biomarker that was associated with mortality in the first wave of COVID-19.

D-dimer is a fibrin degradation product and a small protein fragment. D-dimer is present in the circulation after a blood clot is degraded by fibrinolysis.⁸ COVID-19 patients display an interesting paradox. Clinical phenotype in COVID-19 is characterized by a hypercoagulable state with decreased fibrinolytic capacity and a paradoxical increase in D-dimer.¹¹

Several retrospective studies report that D-dimer levels are associated with the disease severity and mortality in COVID-19.¹²

The hallmark of the lung damage in COVID19 is intra-alveolar fibrin deposition. D-dimer is a protein degradation product of fibrin that is formed by plasmin during fibrinolysis.¹² D-dimer serves as an indirect biomarker of thrombosis. Fibrinolysis and proteolytic breakdown of the fibrin in the capillary beds of the lung segments increase the D-dimer levels in the circulation. Observational studies report that the lungs are the potential sources of D-dimer in COVID-19.^{11–13}

A retrospective study from Wuhan, China reports the COVID-19 outcome from 676 laboratory-confirmed cases. The study comes from the first wave of the pandemic.¹⁴ Patients are divided into 3 groups according to the extent of lung lesions: mild (0%–30%), moderate (30%–60%) and severe ($> 60\%$). Severe lung damage is more common in the mortality group compared with the survivors (65.9% vs. 16.0%). D-dimer is the biomarker that predicts the mortality in the study.¹⁴

TABLE 1 Demographic and laboratory characteristics of patients

	Median	IQR	Mean	SD
Age (years)	65.0	25.0	63.4	17.9
Uric acid (mg/dl)	5.7	3.3	6.3	2.8
Lactate dehydrogenase (units/L)	364.0	261.0	572.5	1097.2
Urea (mmol/L)	39.0	39.5	59.4	39.5
Creatinine (mg/dl)	0.9	0.5	1.2	1.1
Hs-troponin (ng/L)	18	90	879	5647
C-reactive protein	11.8	12.4	16.5	31.1
D-dimer	1.5	2.1	2.8	4.4
White blood cell	7.5	5.1	8.8	5.5
Haemoglobin	12.2	3.2	11.9	2.3
Haematocrit	37.0	9.0	36.8	8.1
Platelet	209	129	218	99
Mean platelet volume	10.1	1.7	10.1	1.4
Platelet distribution width	16.3	0.7	16.7	5.1
Neutrophil-to-lymphocyte ratio	4.3	5.7	9.5	17.9
Computerized tomography of chest score	16.0	17.3	16.1	10.3

Abbreviations: SD, standard deviation; IQR, interquartile range.

TABLE 2 Comparison of laboratory characteristics between low and high CT score groups

	Low CT score	High CT score	<i>p</i>
Hs-troponin (ng/L)	50.3 (313.8)	38.0 (526.1)	.048 ^m
C-reactive protein	14.6 (16.2)	16.4 (17.3)	.007 ^m
D-dimer	2.1 (2.4)	2.5 (5.5)	<.001 ^m
LDH (units/L)	358.0 (298.5)	516.0 (387.0)	<.001 ^m
Ferritin	340.8 (1827.0)	1367.5 (1497.6)	<.001 ^m
Uric acid (mg/dl)	6.9 (3.2)	7.0 (4.3)	.512 ^m
White blood cell	6.8 (5.2)	8.4 (4.5)	.043 ^m
Haemoglobin	12.4 (3.2)	12.1 (3.1)	.302 ^m
Platelet	201 (123)	220 (156)	.288 ^m

Abbreviations: L: liter, dl: deciliter, m: Mann-Whitney U Test.

A multicenter cohort study of 3418 critically ill COVID-19 patients from the US confirms the results of the Wuhan study. D-dimer levels are independently associated with mortality, even after adjustments for disease characteristics and severity.¹⁵ Early autopsy and pathological studies help the clinicians to understand the pathophysiology of D-dimer elevation in COVID-19. The lung specimens demonstrate widespread capillary fibrinous microthrombi and fibrin at the microvascular level.¹⁶

Global data indicate that there are differences in the risk factors, phenotype and outcome of COVID-19 among countries.¹⁷ The vaccination for COVID-19 in Turkey initially started early in 2021 with the CoronaVac vaccine. Healthcare workers and old people

with chronic diseases were prioritized in the order of vaccination. Pfizer-BioNTech vaccine doses were widely available later in 2021. After the vaccination COVID-19 disease course and phenotype changed significantly. Similarly, novel variants, effective therapies and global responses evolved in the course of pandemics. The phenotype of COVID-19 changed significantly since the first wave of COVID-19. The delta and omicron variants have reached global circulation after 2021. The first variants were dominant throughout the world at the time of our study. The diagnostic and prognostic effects of biomarkers differ according to the globally dominant variants.

LDH is a widely available biochemical parameter that is part of the routine laboratory panel. Estimating

TABLE 3 ROC statistics of biomarkers to predict high CT score

Biomarker	AUC in men	AUC in women	AUC	% 95 CI for AUC		p	Sensitivity (%)	Specificity (%)	Cut-off value
				Lower	Upper				
LDH	0.702	0.788	0.741	0.672	0.809	<.001	81	68	360 mg/dl
Hs-CRP	0.584	0.717	0.645	0.550	0.739	.007	67	54	12 mg/dl
D-dimer	0.521	0.625	0.565	0.484	0.645	.121	68	42	1.0 mg/dl
HsCTn	0.574	0.541	0.561	0.476	0.646	.166	52	48	10.0 ng/L
Ferritin	0.679	0.709	0.696	0.616	0.775	<.001	77	63	405 mg/dl
Uric acid	0.522	0.531	0.528	0.441	0.614	.512	53	57	6 mg/dl

the extent of lung damage is challenging in the absence of imaging findings. CT cannot be offered to every patient visiting ER with a clinical suspicion of COVID-19. The cost and radiation exposure are common concerns. The study indicates that LDH is a sensitive and specific biomarker to predict a severe CT-SS. LDH displays better performance than hs-CRP, D-dimer, cTn, uric acid and ferritin in predicting severe CT-SS. In the first wave of pandemics, respiratory rate or room air oxygen saturation are used as initial screening parameters. LDH is a routinely and easily available biomarker universally. Adding LDH level to the initial evaluation algorithms can be useful. LDH can be utilized in screening patients for severe CT-SS.

Various scoring methods (including artificial intelligence) have been proposed to grade the CT findings in COVID-19^{10,18–21} CT-SS is developed for assessing the severity of COVID-19 pneumonia.¹⁰ Chest CT findings of COVID-19 partially overlap with other viral infections. COVID-19 reporting and data system (CO-RADS) is a scheme that evaluates the extent of the lung involvement. The reporting system ranges from very low to very high levels of suspicion (CO-RADS 1–5),²⁰ Francone et al⁴ and Pan et al¹⁸ use semiquantitative CT severity scoring systems. Five lobes of each lung are evaluated for the extent of the involvement and all 5 lobes are scored from 0 to 5. The global CT-SS is the sum of each lobar score, which varies from 0 to 25⁴ GGOs are the main findings in the early phase of COVID-19. Crazy-paving and consolidation patterns are the characteristics of the late phase of the disease.

In a recent observational study, CT-SS and age of the patients from the first and the second waves of the pandemic are compared. CT-SS and age of the patients are higher in the second wave compared with the first wave of the pandemic.²² In the current study, we observe a negative correlation between age and CT-SS. The differences in the observations can be attributed to the alterations of COVID-19 phenotype between the waveforms of the disease.

LDH is a valuable biomarker in a wide range of pathological conditions in the respiratory system. Bronchial asthma, chronic obstructive pulmonary disease, pulmonary tuberculosis, bronchopneumonia, pneumocystis jirovecii pneumonia, avian influenza and acute respiratory distress syndrome are all associated with elevated LDH levels.^{23–30} The current study findings suggest that LDH can be useful in the clinical assessment of COVID-19 patient in the ER. Yet LDH or CT-SS are not associated with short-term mortality after COVID-19. D-dimer predicts 1-year mortality. These observations contribute to a nascent body of literature suggesting that COVID-19 is multisystem disease.

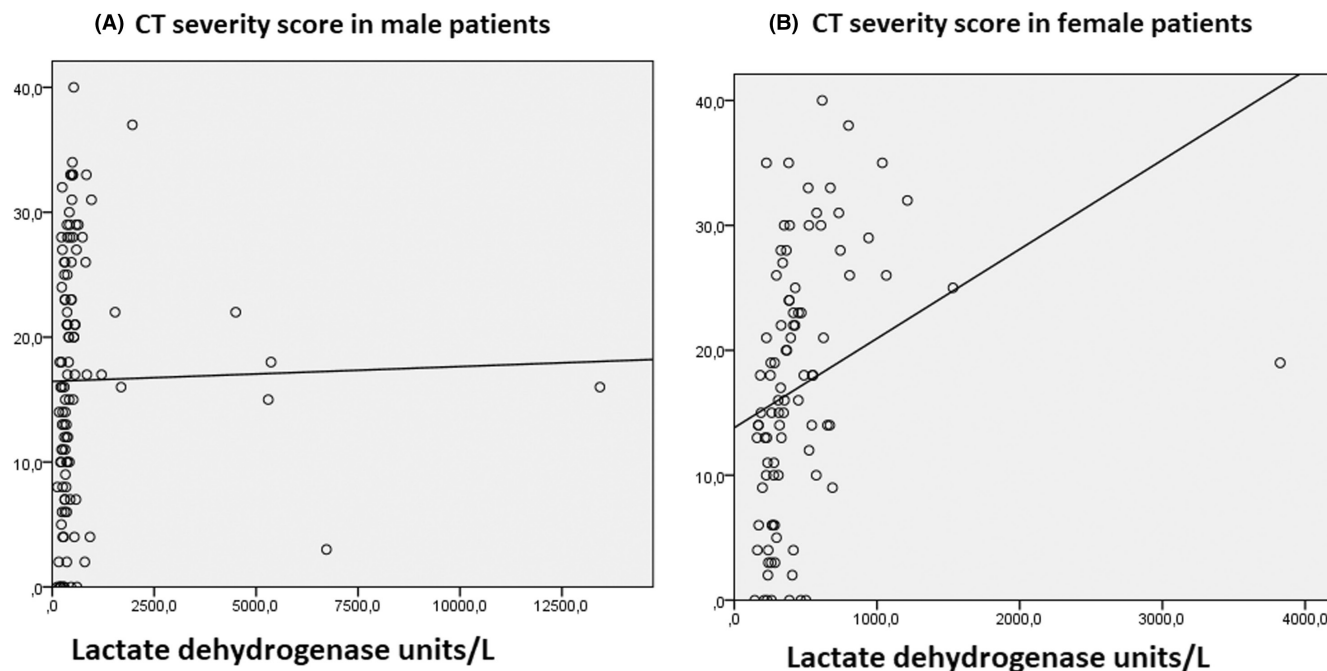


FIGURE 2 A linear regression curve estimation analysis was drawn to analyse the lactate dehydrogenase (LDH) level to predict severe COVID-19 pneumonia CT score in males (A) and females (B)

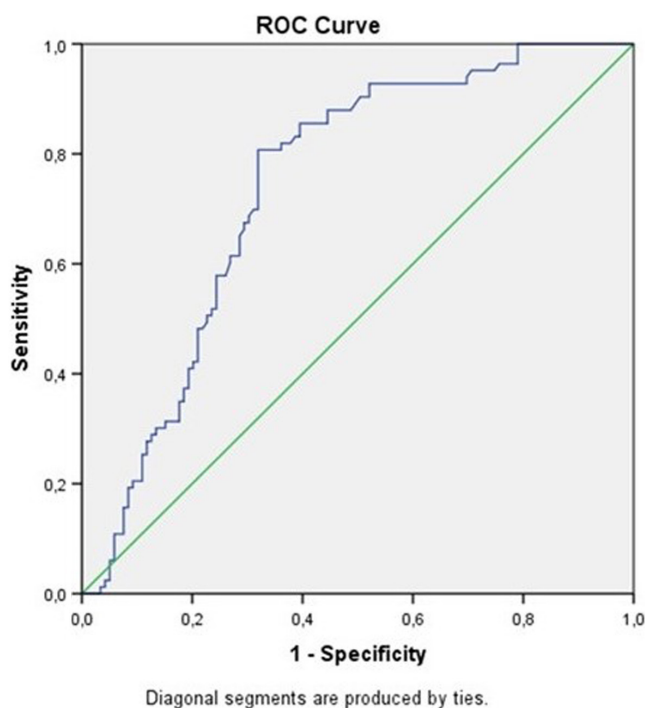


FIGURE 3 A receiver-operator curve (ROC) was drawn to analyse the accuracy of lactate dehydrogenase (LDH) to predict severe COVID-19 pneumonia (score ≥ 20)

5 | LIMITATIONS

We examine a representative sample of COVID-19 patients from Istanbul, Turkey. One of the study's limitations is that the sample size is small and cross-sectional.

TABLE 4 Logistic regression analysis was performed to find the predictors of severe CT-SS (>20)

	Sig.	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Age (years)	0.015	0.956	0.922	0.991
Gender	0.403	1.669	0.503	5.540
Hs-CRP (mg/dl)	0.956	0.999	0.968	1.031
D-dimer (mg/dl)	0.028	1.398	1.037	1.884
LDH (units/L)	0.049	0.999	0.998	1.000
Troponin	0.087	1.000	1.000	1.000
Ferritin	0.401	1.000	1.000	1.000
Uric acid (mg/dl)	0.135	1.184	0.949	1.476
NLR	0.284	1.022	0.982	1.064
Constant	0.471	2.451		

Note: Severe CT-SS was observed in 86 (31.2%) cases. Among covariates of 7 biomarkers, gender and age, age was the most significant parameter that was associated with CT-SS. Age displayed negative association with CT-SS. Nagelkarke R^2 .36.

Abbreviations: CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

Each country has differences in treatment algorithms during the COVID-19 pandemic. Therapies can affect biomarker levels. Further disparities exist among different regions and socioeconomic statuses within the countries. Another limitation is that the confounding effects of genetic and environmental risk factors cannot be excluded. Pertaining to the laboratory studies, preanalytical

TABLE 5 The predictors of 1-year mortality

	Sig.	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Age (years)	0.530	1.017	0.966	1.070
hs-CRP (mg/dl)	0.805	1.006	0.957	1.058
D-dimer (mg/dl)	0.020	1.618	1.080	2.424
LDH (units/L)	0.264	1.003	0.998	1.007
Troponin	0.165	1.000	1.000	1.001
Ferritin	0.141	1.000	1.000	1.001
Uric acid (mg/dl)	0.141	1.261	0.926	1.719
NLR	0.147	1.053	0.982	1.130
CT-SS	0.383	0.955	0.862	1.059
Gender	0.985	0.981	0.137	7.028
Constant	0.025	0.001		

Note: Logistic regression analysis was performed to find the predictors of 1-year mortality. Mortality was observed in 75 (27.2%) patients at 1 year. Multivariate binary logistic regression analysis was performed the predictors of 1-year mortality. Covariates were age, CT-SS, biomarker concentrations of ferritin, hs-CRP, LDH, cardiac troponin, NLR, UA and D-dimer. D-dimer was the only biomarker that was associated with mortality (Nagelkarke R^2 .73).

Abbreviations: Hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; CT-SS, computed tomography severity score.

and analytical factors can affect biomarker levels. The biomarker levels were obtained on the same admission with COVID-19. Since the study period, the COVID-19 phenotype has changed significantly. Vaccination, novel variants, effective therapies and global response to pandemics have all modulated the phenotype of COVID-19. Naturally, biomarkers' diagnostic and prognostic forecast values will also change according to the globally dominant variants.

6 | CONCLUSIONS

COVID-19 is a proinflammatory condition that can result in the elevation of biomarkers in several critical pathways. In this study, we investigated the biomarkers in relation to the severity of pneumonia and 1-year mortality in hospitalized COVID-19 patients. One-year mortality was high in the first wave of COVID-19. D-dimer was the only parameter that predicted the 1-year mortality. LDH was a sensitive and specific biomarker of severe CT-SS. Yet, neither LDH nor CT-SS was associated with 1-year mortality. We need larger studies to test the efficacy of novel criteria and algorithms that can improve the outcome of COVID-19.

CONFLICT OF INTEREST

Authors have no conflicts to disclose.

ORCID

Basak Atalay  <https://orcid.org/0000-0003-3318-3555>

Abdurrahman Cesur  <https://orcid.org/0000-0001-5212-410X>

Mehmet Agirbasli  <https://orcid.org/0000-0002-4873-4391>

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