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# COVID-19 Pneumonia-Related ARDS – Can We Predict Mortality with Laboratory Parameters?

## COVID 19 Pnömonisi Sonrası Gelişen ARDS'de Laboratuvar Parametreleri Mortaliteyi Öngörmede Kullanılabilir Mi?

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**Abstract**

**Objective:** To examine the laboratory characteristics of COVID-19 pneumonia-related ARDS patients who lived or died.

**Materials and Methods:** Retrospectively, two-center of patients who were hospitalized in the intensive care unit were researched in Abant Izzet Baysal University Education and Research Hospital in Bolu, Turkey. Between March 31 and December 31, 2020, data on the demographic characteristics, routine laboratory results, including arterial blood gas tests, and clinical outcomes were collected for both the survivor and non-survivor groups.

**Results**: The median age of the 509 patients was 70 years (interquartile range, 59-79 years); 326 patients (64%) were men, and 161 patients (31.6%) tested positive for RT-PCR. While 232 (45.6%) patients in the non-survivor group died, 277 patients were discharged (54.4%) as survivors. The mortality markers of WBC, RBC, HGB, Ph, $pO_2$, $pCO_2$, $HCO_3$, PLT, PCT, NEU, ALT, and D-dimer did not differ significantly ($p>0.05$). CRP, RDW, LDH, ferritin, urea, and creatinine levels were substantially higher and associated with death in the non-survivor group (p 0.05).

**Conclusion**: A greater risk of death was linked to older age and the number of days spent in the hospital, most likely as a result of persistent underlying issues and weakened immune responses. Risk variables for the progression were CRP, LDH, RDW, ferritin, urea, and creatinine. With the help of laboratory parameters to predict mortality, we can define earlier the changes in immune insufficiency, coagulation problems, hepatic injury, and kidney injury.

**Keywords**: ARDS, COVID 19, Laboratory Parameters, Mortality.

**&**

**Öz**

**Amaç**: Yaşayan veya ölen COVİD-19 pnömonisine bağlı ARDS hastalarının laboratuvar özelliklerini incelemek.

**Gereç ve Yöntemler:** Bolu Abant İzzet Baysal Üniversitesi Eğitim ve Araştırma Hastanesi'nde yoğun bakım ünitesinde yatan hastaların iki merkezi retrospektif olarak araştırıldı. 31 Mart ile 31 Aralık 2020 tarihleri arasında hem hayatta kalan hem de hayatta kalmayan gruplar için demografik özellikler, arteriyel kan gazı testleri dahil rutin laboratuvar sonuçları ve klinik sonuçlara ilişkin veriler toplandı.

**Bulgular**: 509 hastanın ortanca yaşı 70 (çeyrekler arası aralık, 59-79 yıl) idi; 326 hasta (%64) erkekti ve 161 hastanın (%31,6) RT-PCR testi pozitif çıktı. Hayatta kalan grupta 232 (%45,6) hasta hayatını kaybederken, 277 hasta (%54,4) sağ olarak taburcu edildi. WBC, RBC, HGB, Ph, pO2, pCO2, HCO3, PLT, PCT, NEU, ALT ve D-dimer mortalite belirteçleri anlamlı farklılık göstermedi ($p>0,05$). Hayatta kalmayan grupta CRP, RDW, LDH, ferritin, üre ve kreatinin düzeyleri önemli ölçüde daha yüksekti ve ölümle ilişkiliydi ($p < 0,05$).

**Sonuç**: Daha büyük ölüm riski, ileri yaş ve hastanede geçirilen gün sayısıyla bağlantılıydı; büyük ihtimalle kalıcı altta yatan sorunlar ve zayıflamış bağışıklık tepkilerinin bir sonucuydu. İlerlemeye ilişkin risk değişkenleri CRP, LDH, RDW, ferritin, üre ve kreatinindi. Mortaliteyi tahmin etmeye yönelik laboratuvar parametrelerinin yardımıyla bağışıklık yetersizliği, pıhtılaşma sorunları, karaciğer hasarı ve böbrek hasarındaki değişiklikleri daha erken tanımlayabiliriz.

**Anahtar Kelimeler:** ARDS, COVID 19, Laboratuvar Parametreleri, Mortalite.

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## Introduction

Since the outbreak of Coronavirus disease 2019 (COVID- 19), the approach of severe and critical patients has remained a clinical challenge. Despite of the respiratory support, antiviral drugs and immunmodulators, it's still likely to develop acute respiratory distress syndrome (ARDS) for the patients and eventually invasive ventilation. The mortality rates of cases range from 1.7 to 2.23 percent belong to the geographic location, the virus's rate of transmission, and the proportion of the population at risks (1-3). In addition, some factors that affected these criteria were the health system's readiness, the availability of hospitals, and the number of beds in intensive care units (ICUs) (4). These results might also be due to variances in the categorization and reporting of COVID-19 cases and related fatalities. The WHO dashboard presently only includes real-time polymerase chain reaction (RT-PCR)-positive cases, which might cause the actual situation to be underestimated (1). A high proportion of PCR-negative people with clinical and radiographic traits consistent with COVID-19 are identified and handled as such in clinical practice (5). Furthermore, rates of false negative PCR tests are anticipated to vary between 2 and 29 percent (6).

Numerous investigations have demonstrated that COVID-19 pneumonia has had certain specific epidemiological and clinical features in the past (7,8). However, the risk factors for poor clinical outcomes have not yet been found, particularly in COVID-19 pneumonia-related ARDS. Even though several researchs have shown death rates and risk factors globally, we still don't have much information on the characteristics of proven or strongly suspected cases in Turkey, specifically forecasting fatality. In this research, the laboratory features of pneumonia-related ARDS in COVID-19 to death from two tertiary ICU units in Bolu, Turkey, are presented. We sought to explain the demographic and laboratory factors that distinguished critically sick patients who would survive from those who wouldn't, as these factors were crucial in predicting death.

## Materials and Methods

### Study Design

This multicenter registry study was approved by the Clinical Researches Ethics Committee of Bolu Abant Izzet Baysal University (2020/327). The clinical outcomes of patients were evaluated retrospectively from data hospitalized in tertiary ICU at Abant Izzet Baysal University Hospital and Izzet Baysal State Hospital in Bolu, Turkey. No informed consent was required, because of the retrospective design of the study. All patients were managed according to the guidelines of the Ministry of Health of Turkey (2). The demographic features, routine laboratory findings including arterial blood gas analyses, and clinical outcomes were recorded between March 31 and December 31, 2020.

### Case Definition

The WHO COVID-19 case definition sheet was used to include the patients in the study. As a result, a confirmed case was defined as the presence of a positive nucleic acid amplification test or a positive fast antigen detection test, as well as clinical and radiographic features strongly suggesting COVID-19 (9). Despite matching clinical and radiographic signs in very likely occurrences, an RT-PCR assay was unable to confirm (9). The final diagnosis was made using the following criteria (9–11).

### Procedures

Numerous procedures were administered to the patients, such as coagulation, hemograms, ferritin, C-reactive protein (CRP), D-dimer tests, and biochemical testing. The patients' vital status, length of hospital stay, and demographic data were also compared between the two of groups. Children, pregnant women, and patients who were in hospitals for other ARDS-related conditions were not included. 65 years of age or older were considered to be older. All patients had throat swabs obtained at the time of admission, and they were all tested using RT-PCR assays by a method that has previously been used to identify SARS-CoV-2 infection.

### Data Management

The majority of the clinical data for this research was obtained on the discharge day of hospitalization in the survivor group and on the death day in the non-survivor group. WHO interim guidance was used to define COVID-19 pneumonia-related ARDS (9).

### Statistical Analysis

The analysis of the data obtained as a result of the research was made in the SPSS 20 statistical package program. In addition to the Kolmogorov-Smirnov test, conformity to the normal distribution was evaluated based on the skewness and kurtosis coefficients and the range of ±2. Parametric data were compared with the Independent Sample t-test and expressed as standard deviation. The homogeneity of the variances was examined by Levene's test. Nonparametric data were compared with the Mann-Whitney U test and expressed as median (Q1-Q3). The relationship between categorical variables was examined with Chi-Square. Receiver Operative Characteristics (ROC) analysis was used to determine the cut-off values in estimating mortality. $p < 0.05$ was considered statistically significant.

## Results

In this study, from March 31 to December 31, 2020, a total of 509 patients (mean age 67.25±16.00; 326 men [64%]; 161 RT-PCR positives [31.6%]) were hospitalized as ARDS in tertiary ICU and were retrospectively enrolled. They completed both thorax CT and laboratory viral nucleic acid testing (RT-PCR assay with throat swab samples). The patient's electronic medical records in our hospital information system were used to obtain the RT-PCR data. Despite having negative RT-PCR findings, radiologists discovered that 348 (68.4%) of the patients had traits that suggested they were highly susceptible to COVID-19. While 232 (45.6%) patients died in the non-survivor group, 277 patients were released (54.4%) as survivors.

There was no significant difference in mortality for white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), potential of hydrogene (pH), partial oxygen pressure ($pO_2$), partial carbon dioxide pressure ($pCO_2$), bicarbonate ($HCO_3$), platelet (PLT), plateaucrit (PCT), neutrophil (NEU), alanine transferase (ALT), and D-dimer indicators. ($p>0.05$) (Table 1).

Their mean ages, days spent in hospitals, C reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), glucose, ferritin, urea, and creatinine levels were significantly higher ($p<0.05$) in the non-survivor group, despite their lower results for albumin, oxygen saturation ($SO_2$), lymphocyte (LYM), and monocyte (MONO).

The ROC analysis revealed that the albumin, $SO_2$, LYM, and MONO values were significant; however, the chi-square assumptions did not support the establishment of a relationship between these parameters and mortality. Table 2 presents the predictive value of many factors in relation to AUC, sensitivity, specificity, and 95% confidence intervals.

In patients with the non-survivor group of ARDS, CRP, RDW, ferritin, urea, LDH, and creatinine values were significantly higher and those on cut-off were related to mortality ($p<0.05$). The ROC curves of the parameters are shown in Figure 1.

**Table 1.**

Comparison Of Hemogram, Biochemical and Blood Gas Parameters

| | **Survivor (n=277, %54.4)** | **Non-Survivor (n=232, %45.6)** | **All patients (n=509)** | **p-value** |
|---|---|---|---|---|
| Gender | | | | |
| Female | 74 (%40.4) | 109 (%59.6) | 183 (%36.0) | **<0.001[a,*]** |
| Male | 203 (%62.3) | 123 (%37.7) | 326 (% 64.0) | |
| | | $\bar{X}\pm ss$ | | |
| WBC, $10^9$/L | 13.79±6.88 | 13.54±9.25 | 13.68±8.04 | 0.717 |
| RBC, $10^{12}$/L | 4.08±0.74 | 4.02±0.81 | 4.06±0.77 | 0.390 |
| HGB, g/dL | 11.53±2.28 | 11.44±2.27 | 11.49±2.27 | 0.648 |
| Albumin, g/L | 32.91±6.33 | 29.62±6.22 | 31.39±6.48 | **<0.001[b]** |
| CRP, mg/L | 53.58±72.62 | 105.82±85.59 | 78.22±83.13 | **<0.001[b]** |

| | | Median (Q1-Q3) | | |
|---|---|---|---|---|
| Age, years | 62.97±16.59<br>66 (54-74) | 72.36±13.64<br>75 (66-82) | 70 (59-79)<br>67.25±16.00 | **<0.001**[b,*] |
| Days of hospitalized | 6.46±10.28<br>2 (1-7) | 12.45±18.06<br>6 (2-15) | 4 (1-10)<br>9.19±14.65 | **<0.001**[b,*] |
| pH | 7.42 (7.39-7.47) | 7.42 (7.37-7.48) | 7.42 (7.37-7.47) | 0.508 |
| $pO_2$, mmHg | 81.4 (49.5-106.4) | 70.8 (43.7-96.95) | 75.2 (45.25-101.5) | 0.079 |
| $pCO_2$, mmHg | 39 (34.8-44.3) | 40.35 (33.15-48.2) | 39.60 (33.9-45.55) | 0.342 |
| $SO_2$, % | 97.7 (92.8-99.2) | 93.8 (83.9-98.75) | 97.0 (88.65-99.0) | **<0.001**[b] |
| $HCO_3$, mEq/L | 24.02 (21.9-27) | 24.02 (21-26.45) | 24.02 (21.6-26.9) | 0.426 |
| LYM, $10^9$/L | 1.19 (0.79-1.76) | 0.84 (0.53-1.25) | 1.03 (0.5-1.6) | **<0.001**[b] |
| PLT, $10^9$/L | 223 (177-276.5) | 222 (147-299) | 223 (167-288) | 0.502 |
| PCT, % | 0.22 (0.18-0.28) | 0.23 (0.16-0.31) | 0.23 (0.17-0.29) | 0.953 |
| NEU, $10^9$/L | 9.63 (7.15-14.87) | 9.9 (6.4-14.7) | 9.75 (6.95-14.8) | 0.362 |
| MONO, $10^9$/L | 0.73 (0.48-1.06) | 0.597 (0.3-0.91) | 0.66 (0.37-1.04) | **<0.001**[b] |
| RDW, % | 13.9 (13-15.8) | 15.2 (13.8-17.5) | 14.45 (13.2-16.7) | **<0.001**[b] |
| ALT, U/L | 22 (14-39) | 21 (14-45) | 22 (14-41) | 0.707 |
| AST, U/L | 29 (19-48) | 34 (20-64) | 30 (20-54) | **0.029**[b] |
| Glucose, mg/dL | 143 (114-176) | 152 (112-230) | 146 (113-197) | **0.045**[b] |
| Ferritin, µg/L | 172.5 (63.6-511.3) | 556.3 (284.0-899.4) | 369.2 (117.3-779.4) | **<0.001**[b] |
| Urea, mg/dL | 39 (28-58) | 66 (41-107) | 47 (32-82.5) | **<0.001**[b] |
| D-dimer, | 3.18 (1.32-8.19) | 2.865 (1.49-5.29) | 2.92 (1.4-6.54) | |
| LDH, U/L | 309.5 (240-447) | 432.5 (311-616) | 365 (263.75-525.75) | **<0.001**[b] |
| Creatinine, mg/dL | 0.87 (0.73-1.17) | 1.15 (0.78-2.04) | 0.97 (0.74-1.47) | **<0.001**[b] |

White blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), potential of hydrogene (pH), partial oxygen pressure (pO2), partial carbon dioxide pressure ($pCO_2$), bicarbonate ($HCO_3$), platelet (PLT), plateaucrit (PCT), neutrophil (NEU), alanine transferase (ALT), C-reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), oxygen saturation ($SO_2$), lymphocyte (LYM), and monocyte (MONO). [a]Chi-Square test, [b]Independent Sample t test/Mann-Whitney U test.

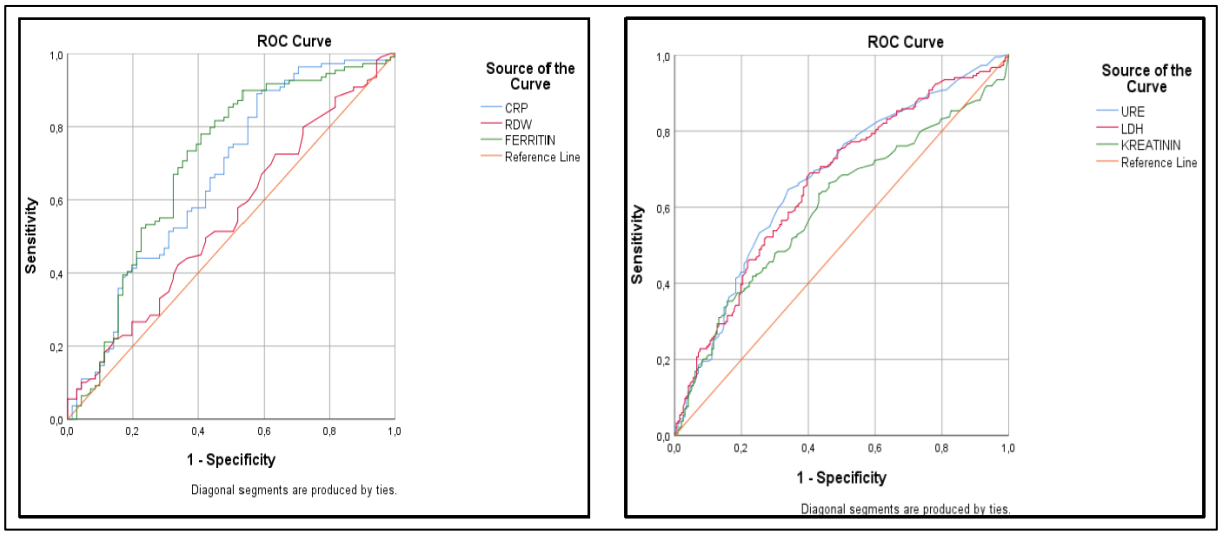
**Table 2.**

Cut-Off Values of Parameters and Their Relation to The Mortality

| **Parameters** | **AUC (%95 CI)** | **Cut-Off** | **P value** | **Sensitivity (%)** | **Specificity (%)** |
|---|---|---|---|---|---|
| CRP, mg/L | 0.708 (0.661-0.755) | 34.65 | <0.001 | 74.2 | 62.3 |
| RDW, % | 0.653 (0.606-0.700) | 14.35 | <0.001 | 65.4 | 59.6 |
| AST, U/L | 0.557 (0.506-0.607) | 30.50 | 0.029 | 53.3 | 53.7 |
| Glucose, mg/dL | 0.552 (0.500-0.604) | 145.50 | 0.045 | 52.8 | 52.0 |
| Ferritin,µg/L | 0.698 (0.619-0.778) | 343.37 | <0.001 | 67.3 | 67.1 |
| Urea, mg/dL | 0.711 (0.665-0.756) | 50.00 | <0.001 | 65.7 | 69.3 |
| LDH, U/L | 0.663 (0.609-0.718) | 349.50 | <0.001 | 68.5 | 60.1 |
| Creatinine, mg/dL | 0.632 (0.582-0.682) | 0.985 | <0.001 | 62.9 | 62.5 |
| Albumin, g/L | 0.350 (0.301-0.399) | 31.55 | <0.001 | 40.4 | 40.3 |
| SO2, % | 0.404 (0.353-0.455) | 96.85 | <0.001 | 40.1 | 39.7 |
| LYM, $10^9$/L | 0.357 (0.309-0.406) | 1.01 | <0.001 | 39.0 | 38.8 |
| MONO, $10^9$/L | 0.395 (0.345-0.445) | 0.655 | <0.001 | 42.9 | 42.8 |
| | **Sub-Groups Based on Defined Cut-Off** | **Survivor, n (%)** | **Non-survivor, n (%)** | **$X^2$ value** | **P value*** |
| CRP | 0-34.640<br>≥34.641 | 157 (%73.0)<br>95 (%36.3) | 58 (%27.0)<br>167 (%63.7) | 64.049 | **<0.001** |

| | | | | | |
|---|---|---|---|---|---|
| RDW | 0-14.340 | 164 (%67.2) | 80 (%32.8) | 31.437 | **<0.001** |
| | ≥14.341 | 111 (%42.4) | 151 (%57.6) | | |
| AST | 0-30.490 | 146 (%57.7) | 107 (%42.3) | 2.403 | 0.128 |
| | ≥30.491 | 126 (%50.8) | 122 (%49.2) | | |
| Glucose | 0-145.490 | 141 (%56.6) | 108 (%43.4) | 1.177 | 0.283 |
| | ≥145.491 | 130 (%51.8) | 121 (%48.2) | | |
| Ferritin | 0-343.360 | 53 (%59.6) | 36 (%40.4) | 21.789 | **<0.001** |
| | ≥343.361 | 26 (%26.0) | 74 (%74.0) | | |
| Urea | 0-49.00 | 190 (%70.6) | 79 (%29.4) | 61.533 | **<0.001** |
| | ≥49.01 | 84 (%35.7) | 151 (%64.3) | | |
| LDH | 0-349.490 | 119 (%67.2) | 58 (%32.8) | 31.327 | <0.001 |
| | ≥349.491 | 79 (%38.5) | 126 (%61.5) | | |
| Creatinine | 0-0.984 | 173 (%66.8) | 86 (%33.2) | 32.556 | <0.001 |
| | ≥0.985 | 104 (%41.6) | 146 (%58.4) | | |

C reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), oxygen saturation (SO2), lymphocyte (LYM), and monocyte (MONO). *Chi-Square analysis, AUC: Area under the curve. CI: Confidence interval,




C reactive protein (CRP), red blood cells distribution width (RDW), lactate dehydrogenase (LDH)

**Figure 1.** Receiver operating characteristic (ROC) curve for mortality

## Discussion

In this retrospective study, the laboratory characteristics associated with clinical outcomes in patients with COVID-19 pneumonia-related ARDS and those who progressed from ARDS to death between two groups as a survivor and non-survivor group were evaluated. We aimed to predict the laboratory parameters that are linked to the onset of ARDS and the progression of ARDS to mortality in COVID-19 pneumonia. The older age and days of hospitalized stay were even associated with a higher risk of developing ARDS and mortality; this was not statistically significant. In patients with the non-survivor group of ARDS; CRP, RDW, LDH, ferritin, urea, and creatinine values were significantly higher and related to mortality ($p<0.05$).

The illness caused by COVID-19 spread rapidly, and significant studies have been done to determine which patients will be affected and what their clinical outcomes would be. We know that this virus mostly impacted the respiratory system, with some patients quickly developing ARDS which was mostly related to mortality; other organ functions were less affected (11). Thus, it is necessary for early detection and accurate therapy of COVID-19 pneumonia-related ARDS.

Patients with ARDS have been seen in ICUs across the world. Around 5% of patients infected with the new 2019 coronavirus disease necessitate hospitalization owing to ARDS, with a case-fatality rate ranging from

30% to 60% (11-13). Previous observational studies in Turkey found death rates ranging from 8.5 percent to 50%, depending on the healthcare environment, the age of the study group, and the severity of the condition (14-16). These studies were generally done in a single-center setting with a small number of patients. One big research, which used Ministry of Health records and included 16,942 hospitalized old people, found death rates ranging from 17.9% to 32.2% depending on when public limitations were in place (15). The research, however, did not give any clinical data about the patients. Our study evaluated a fatality rate of 45.5%. The groups in our research were not limited to mild to moderate cases but included a wide spectrum of severe patients with ARDS. This might explain why the death rate is so high when compared to prior findings from Turkey and other countries (17-19).

Several studies have evaluated the risk factors for mortality (20-23). The most well-known predictor of death in older age and countries with significant old populations have been proven to have higher case-fatality rates. The in-hospital mortality rate for patients aged 80 and over was estimated to be 32.8 percent in Turkey (15,16). Similarly, the non-survivors and survivors in our research had mean ages of 72.3 and 62.9 years, demonstrating that age was an independent variable associated with death. The median hospital stay was 6.4 days in the survivor group and 12.4 in the non-survivor group, as expected. Older age and days of hospital stay were significantly higher in the non-survivor group than in the survivor group but these were not predictable for mortality. Low immune response and comorbidities are all age-related disorders that may play a role infor the increased risk.

Some hematological and biochemical parameters about the prognosis of COVID-19, multiple recent studies have researched laboratory features of hospitalized patients. (17-19,23) Chidambaram et al. (22) looked at clinical and laboratory indicators related to mortality in a meta-analysis utilizing 109 published publications, 42 of which looked at mortality. Increased levels of CRP, LDH, and D-dimer were associated with a higher risk of severe disease and death. Huang et al. (23) found that increased serum CRP, PCT, D-dimer, and ferritin were linked with a poor outcome in a meta-analysis involving a total of 5350 patients. Another meta-analysis found that procalcitonin had the best predictor of mortality and disease severity (24). This may be caused by bacterial coinfection and cytokine storm according to the authors. In that study, parameters related to mortality were respiratory failure, high WBC-CRP-creatinine-LDH-D dimer-lactate, and low albumin, thrombocytopenia, and lymphopenia. In a recent study in Turkey, BUN and albumin levels at admission, as well as D-dimer and procalcitonin levels during follow-up, were shown to be linked with mortality (25). We found that CRP, LDH, RDW, ferritin, urea, and creatinine values were significantly higher and related to mortality like these studies. These parameters may be linked to the cytokine storm triggered by a viral infection, whereas coagulation activation is related to the long-term inflammatory response. Acute renal impairment caused by the infection, hypoxia, and shock might have resulted in elevated urea and creatinine levels.

Furthermore, because our study was single-center and had a limited sample size, our findings may not apply to all COVID-19 pneumonia-related ARDS patients. Secondly, we did not evaluate the comorbidities that can affect mortality. Also, the findings relied on data that were recorded at the time of hospitalization in the ICU, so there were no follow-up parameters. Finally, patients' ventilator parameters were not noted for both two groups even if that setting is being recommended to personalize at the bedside. To investigate the phenotypic, larger cohort studies are needed for ARDS caused by COVID-19.

## Conclusion

In this study, we found that various laboratory indicators were linked to death in COVID-19 pneumonia-related ARDS and that clinicians should consider these factors while managing these patients. After these findings have been validated in prospective research, it may be advantageous to develop algorithms based on them.

**Ethics Committee Approval**: This study was approved by the Clinical Researches Ethics Committee of Bolu Abant Izzet Baysal Unıversity, (Approval No: 2020/327).

**Informed Consent**: Consent was not obtained as it was a retrospective study.

**Conflict of Interest**: Authors declared no conflict of interest.

**Financial Disclosure**: Authors declared no financial support.

**Author Contributions**: Idea/Concept: E.O., M.E.D.; Design: E.O., M.E.D., S.O., Supervision: E.O, S.O.; Funding: E.O, S.O.; Materials: M.E.D., S.O.; Data Collection/Processing: E.O., S.O, M.E.D; Analysis/Interpretation: D.K, M.K., Z.B.; Literature Review: M.K, D.D.K, Z.B.; Drafting/Writing: E.O.; Critical Review: E.O., M.E.D., S.O., M.K., D.K., Z.B. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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