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# Markers predicting critical illness and mortality in COVID-19 patients: A multi-centre retrospective study

Risk factors of critical illness and mortality

Tahsin Karaaslan[1], Cumali Karatoprak[2], Esra Karaaslan[3], Gulsah Sasak Kuzgun[1], Mehmet Gunduz[4], Abdusselam Sekerci[5], Banu Buyukaydin[5], Sabahat Alisir Ecder[1]
[1]Department of Nephrology, Medeniyet University, Goztepe Training and Research Hospital
[2]Department of Internal Medicine, Bezmialem Vakif University, Medical Faculty
[3] Department of Chest Diseases, Medipol University Sefakoy Hospital,
[4]Department of Pediatrics, Medipol University Sefakoy Hospital
[5]Department of Internal Medicine, Bezmialem Vakif University, Medical Faculty, İstanbul, Turkey

**Abstract**
Aim: In this study, we aimed to investigate early predictors of critical illness and mortality in patients with coronavirus disease 2019 (COVID-19) based on clinical, biochemical, radiological, and epidemiological findings.
Materials and Methods: This multi-center, retrospective study was conducted in three centers and included a total of 206 confirmed COVID-19 cases using reverse transcription-polymerase chain reaction (RT-PCR). Data of survivors and non-survivors were compared, and predictors of mortality were examined.
Results: Among the patients, 103 (50%) were males with a mean age of 52.8±16.7 years; 88.3% of the patients were discharged in a healthy condition, while 11.7% died. The mean age was significantly higher in non-survivors. Dyspnea occurred in 32.5% of patients, and a significant correlation was found between dyspnea and mortality ($p<0.001$). Thoracic computed tomography (CT) findings were positive in 88.8% of patients. The most frequent imaging findings were ground-glass opacities in 86.4% and consolidation in 33% of patients. The mortality rate was significantly higher in patients with comorbidities ($p<0.001$). There was also a significant correlation between lymphocytopenia and mortality ($p<0.001$). A positive correlation was found between mortality risk and platelet-to-lymphocyte, neutrophil-to-lymphocyte, and red cell distribution width indices. The mortality risk was significantly higher in patients with acute kidney injury (10.7%) ($p<0.001$).
Discussion: These results suggest that advanced age, coexisting diabetes, hypertension, heart failure, chronic kidney disease, or acute kidney injury are associated with an increased mortality risk. The presence of dyspnoea or consolidation on thoracic CT can predict an increased mortality risk in COVID-19 patients.

**Keywords**
COVID-19; Kidney injury; Mortality; Lymphocytopenia; Predictor

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Corresponding Author: Tahsin Karaaslan, Medeniyet University, Goztepe Training and Research Hospital, Department of Nephrology, 34722, Kadikoy, Istanbul, Turkey.
E-mail: drtkaraaslan@hotmail.com P: +90 (505) 935 11 22
Corresponding Author ORCID ID: https://orcid.org/0000-0002-1529-1790

## Introduction

In late December, the first case of novel coronavirus-2019 based on pneumonia of unknown etiology was identified in Wuhan, Hubei Province of China [1]. In February 2020, the World Health Organization (WHO) named the disease as novel coronavirus-2019 (COVID-19). Meanwhile, the International Committee on Taxonomy of Viruses (ICTV) has named the novel virus as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). In March 2020, the WHO announced the COVID-19 pandemic with the concern of alarming levels of spread and severity of the virus. Currently, COVID-19 has become a global health threat due to its rapid spread around the world and the lack of an effective treatment or vaccine. Since December 2019, more than 3 million cases of coronavirus disease 2019 (COVID-19) and about 200,000 deaths have been reported worldwide [2]. Although transmission may occur from asymptomatic patients or during the incubation period, current evidence suggests that severe symptomatic patients mostly transmit the disease. The diagnosis can be made based on clinical signs and symptoms, and laboratory and imaging findings; however, the non-specific nature of the disease may hamper making a definitive diagnosis. The reverse transcription-polymerase chain reaction (RT-PCR) positivity in respiratory samples is the gold standard for the detection of SARS-CoV-2 ribonucleic acid (RNA) [2].

Rapid and accurate diagnosis of COVID-19 enables prioritization of effective treatment modalities, early transfer to intensive care units (ICUs), and early isolation of diseased patients from healthy individuals. In the present study, we aimed to investigate the predictors of critical illness and early mortality in confirmed cases of COVID-19 based on clinical, biochemical, radiological, and epidemiological findings and to identify possible biomarkers of early screening and diagnosis, as well as in identifying patients progressing to critical illness.

## Material and Methods

### *Description*

The fever of each patient was measured with a tympanic thermometer and values above

37.8 $^{0}$C were considered a high fever. Watery defecation, increased stool volume, or increased stool frequency were considered as diarrhea. The diarrhea was bloodless and mucus free. There was no tenesmus. Patients with respiratory failure requiring mechanical ventilation, shock, or other organ failure requiring intensive care follow-up and treatment were defined as critically ill patients.

### *Study design and study population*

This multi-center retrospective study was conducted in three centers located in Istanbul, Turkey from March 1, 2020 to July 30, 2020. The study included patients aged ≥18 years who were under follow-up with a confirmed diagnosis of COVID-19. The cases were confirmed by RT-PCR nucleic acid test (NAT) positivity using nasopharyngeal swabs. Patients with any hematological or solid organ malignancy, RT-PCR-NAT negativity, and missing data including clinical, biochemical, and imaging test results were excluded from the study. All CT images were acquired at the end of inhalation using a 16-slice CT scanner (Somatom scope power, Siemens Healthineers, Forchheim, Germany). Written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Istanbul Medeniyet University, Goztepe Training and Research Hospital (Date: 24/06/2020-No: 2020/0407). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### *Data collection*

Data including demographic and clinical characteristics of the patients were recorded. At the time of hospital admission, the complete blood count analysis results including hemoglobin (Hb), white blood cells (WBC), platelets, absolute neutrophil and eosinophil counts, mean corpuscular volume (MCV), mean platelet volume (MPV), and red cell distribution width (RDW) were noted. C-reactive protein and troponin levels were measured. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and MPV/PC ratio were calculated. The patients were divided into groups according to the WBC (<4.5 x$10^9$/L, 4.5 to 10.5 x$10^9$/L, and >10.5 x$10^9$/L), lymphocyte (<1.0 x$10^9$/L and >1.0 x$10^9$/L), and platelet count (<100 x$10^9$/L, 100 to 400 x$10^9$/L, and >400 x$10^9$/L). They were further divided into subgroups according to creatinine clearance (estimated glomerular filtration rate [eGFR]) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

All patients were classified into two groups as survivors (n=182) and non-survivors (n=24). They were further divided into five subgroups according to age as follows: 18 to 29 years, 30 to 49 years, 50 to 64 years, 65 to 74 years, and >75 years. Thoracic computed tomography (CT) findings including the presence of ground-glass opacities, consolidation, pleural effusion, and lymphadenopathy were evaluated. Intra- and inter-group analyses were performed, and all test results were compared between the survivors and non-survivors.

### *Statistical analysis*

Statistical analysis was performed using the SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation (SD), median (min-max), or number and percentage, where applicable. The Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used to compare abnormally distributed continuous variables. The Chi-square test was performed to examine categorical variables. The Pearson correlation analysis was carried out to analyze possible correlations between variables. A p-value of <0.05 was considered statistically significant.

## Results

A total of 938 confirmed SARS-CoV-2-positive cases were screened. Among these patients, 420 were recruited from Centre 1, 350 from Centre 2, and 168 from Centre 3. According to the inclusion and exclusion criteria, 206 cases were included in the study. Baseline demographic and clinical characteristics of the patients are shown in Table 1. Among the patients, 88.3% (n=182) were discharged in a healthy condition, while 11.7% (n=24) died. The mortality rate was identical in both sexes (11.7%). There was no statistically significant correlation between mortality and gender (p=0.59), while there was a significant correlation between advanced age and mortality (r=+0.369; p<0.001) (Table 1).

**Table 1.** Demographic and clinical characteristics of the patients

| | Age range | Mean±SD | Survivors | Non-survivors | P-value |
|---|---|---|---|---|---|
| Total | 20-93 | 52,8±16,7 | 50,6±15,4 | 69,7±16,0 | <0,001 |
| Female | 20-88 | 54.1± 17.6 | | | |
| Male | 21-93 | 51.6 ± 15.6 | | | |

| | | Survivors | Non-survivors | | Total | |
|---|---|---|---|---|---|---|
| | | | N | % | N | % |
| Distribution by age, years | 18-29 | 22 | 1 | 4,3 | 23 | 11,2 |
| | 30-49 | 64 | 1 | 1,5 | 65 | 31,6 |
| | 50-64 | 56 | 4 | 6,7 | 60 | 29,1 |
| | 65-74 | 28 | 7 | 20 | 35 | 17,0 |
| | >75 | 12 | 11 | 47,8 | 23 | 11,2 |
| | Total | 182 | 24 | | 206 | 100,0 |

| | | Survivors | | Non-survivors | | Total | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Distribution by sex | Female | 91 | 44,2 | 12 | 5,8 | 103 | 50 |
| | Male | 91 | 44,2 | 12 | 5,8 | 103 | 50 |
| | Total | 182 | 88,4 | 24 | 11,6 | 206 | 100,0 |

| | | Survivors | Non-survivors | | Total | |
|---|---|---|---|---|---|---|
| | | | N | % | N | % |
| Distribution by centre | Centre 1 | 86 | 21 | 19,6 | 107 | 51,9 |
| | Centre 2 | 34 | 2 | 5,6 | 36 | 17,5 |
| | Centre 3 | 62 | 1 | 1,6 | 63 | 30,6 |

| | | Survivors | Non-survivors | | Total | |
|---|---|---|---|---|---|---|
| | | | N | % | N | % |
| Distribution according to eGFR | >90 mL/ min/1.73 $m^2$ | 105 | 1 | 0,9 | 106 | 51,5 |
| | 60-89 mL/ min/1.73 $m^2$ | 56 | 4 | 6,7 | 60 | 29,1 |
| | 30-59 mL/ min/1.73 $m^2$ | 13 | 7 | 35 | 20 | 9,7 |
| | 15-29 mL/ min/1.73 $m^2$ | 5 | 5 | 50 | 10 | 4,9 |
| | <15 mL/ min/1.73 $m^2$ | 3 | 7 | 70 | 10 | 4,9 |
| | Total | 182 | 24 | | 206 | 100,0 |

| | | Survivors | Non-survivors | | Total | |
|---|---|---|---|---|---|---|
| | | | N | % | N | % |
| Comorbidity | Hypertension | 46 | 21 | 31,3 | 67 | 32,5 |
| | Diabetes | 33 | 13 | 28,3 | 46 | 22,3 |
| | Heart failure | 9 | 6 | 40 | 15 | 7,3 |
| | CKD | 9 | 11 | 55 | 20 | 9,7 |
| | RTx | 3 | 1 | 25 | 4 | 1,9 |
| | Total | 182 | 24 | | | |

Data are given as mean±SD or number and percentage, unless otherwise stated. SD: standard deviation; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; RTx: renal transplantation.

A total of eight (3.9%) patients were asymptomatic, while 198 (96.1%) had a variety of symptoms. The most common symptoms included fever (n=148, 71.8%), dry cough (n=131, 63.6%), fatigue (n=110, 53.4%), dyspnoea (n=67, 32.5%), myalgia (n=59, 28.6%), diarrhea (n=30, 14.6%), and anosmia/dysgeusia (n=18, 8.7%). No mortality was seen in asymptomatic patients, and an inverse relationship was observed between asymptomatic status and mortality (p=0.004). In this study, we found no significant correlation between fever, dry cough, fatigue, myalgia, diarrhoea, and anosmia/dysgeusia and mortality (p>0.05), while we observed a significant correlation between dyspnoea and mortality (r=+0.320; p<0.001).

**Table 2.** Patient distribution according to symptoms

| | Survivors | | Non-survivors | | Total | | Correlation Mortality P-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Asymptomatic | 8 | 3.9 | 0 | 0 | 8 | 3.9 | 0,297 |
| Symptomatic | 174 | 87.9 | 24 | 12.1 | 198 | 96.1 | |
| Fever | 131 | 72.0 | 17 | 70.8 | 148 | 71.8 | 0,907 |
| Cough | 116 | 63.7 | 15 | 62.5 | 131 | 63.6 | 0,906 |
| Fatigue | 95 | 52.2 | 15 | 62.5 | 110 | 53.4 | 0,344 |
| Dyspnea | 49 | 26.9 | 18 | 75.0 | 67 | 32.5 | <0,001 r=+0,329 |
| Myalgia | 58 | 31.9 | 1 | 4.2 | 59 | 28.6 | 0,005 r= - 0,197 |
| Diarrhea | 26 | 14.3 | 4 | 16.7 | 30 | 14.6 | 0,757 |
| Anosmia/dysgeusia | 17 | 9.3 | 1 | 4.2 | 18 | 8.7 | 0,401 |

Data are given in number and percentage, unless otherwise stated.

Thoracic CT findings were positive in 183 (88.8%) patients and were normal in 23 (11.2%) patients. No mortality was observed in patients with normal CT findings, whereas 24 (13.1%) of 183 patients with positive CT findings died, indicating a statistically significant difference (p<0.001). The most frequent imaging findings were ground-glass opacities in 178 (86.4%) patients and consolidation in 68 (33%) patients. None of the patients developed pneumothorax, while 14 (6.8%) had pleural effusion and 12 (5.8%) had mediastinal lymphadenopathy. There was no statistically significant correlation between ground-glass opacities, pleural effusion, or mediastinal lymphadenopathy and mortality (p>0.05), while we found a statistically significant correlation between consolidation and mortality (p<0.001).

Twenty-two (10.7%) patients developed acute kidney injury (AKI) and one of them (0.5%) required hemodialysis. Among all patients, 20 (9.7%) had chronic kidney disease (CKD). Four (1.9%) patients were renal transplant recipients. The most common comorbidities were hypertension (n= 67, 32.5%), diabetes (n=46, 22.3%), CKD (n=20, 9.7%), and heart failure (n=15, 7.3%). The mortality rate was significantly higher in patients with AKI than those without (p<0.001). Additionally, the mortality rate was significantly higher in patients with CKD than non-CKD patients, in hypertensive patients than non-hypertensive patients, in patients with diabetes than those without diabetes, and in patients with heart failure than those without heart failure (p<0.001 for all).

According to the correlation analysis, there was a strong, negative, and linear correlation between creatinine and eGFR (r=-0.71; p<0.001). Also, there was a positive and significant correlation between the troponin I elevation and an increased mortality risk (r=+0.334; p<0.001) and D-dimer and an increased mortality risk (r=+0.382; p<0.001) (Table 2). On the other hand, there was no significant difference in the MCV, MPV, MPV/PC ratio, WBC, platelet, and eosinophil count between survivors and non-survivors (p>0.05). However, there was a positive and significant correlation between neutrophil count and mortality (r=+0.140; p=0.045), RDW and mortality (r=+0.332; p<0.001), and PLR and mortality (r=+0,320 p<0.001). When we used a median cut-off value of 148.5 for PLR, the significance of the correlation became more prominent (p<0.001). However, we found a negative and significant correlation between lymphocyte count and mortality (r=-0.308; p<0.001) and between Hb and mortality (r=-0.410; p<0.001) (Table 3).

**Table 3.** Complete blood count and biochemical analysis results

| | Mean±SD | Mortality | N | Mean±SD | P-value |
|---|---|---|---|---|---|
| Creatinine (mg/dL) | 1,28±1,5 | Survivor | 182 | 1,0±0,7 | <0,001 |
| | | Non-survivor | 24 | 3,4±3,2 | |
| eGFR (mL/min//1.73 m²) | 82,7±31,4 | Survivor | 182 | 88,79±25,9 | <0,001 |
| | | Non-survivor | 24 | 36,58±32,1 | |
| WBC (x10⁹/L) | 6.329±2.594 | Survivor | 182 | 6.294±2.422 | 0,70 |
| | | Non-survivor | 24 | 6.595±3.714 | |
| Neutrophil (x10⁹/L) | 4.394±2.465 | Survivor | 182 | 4.269±2.310 | 0,045 |
| | | Non-survivor | 24 | 5.339±3.336 | |
| Lymphocyte (x10⁹/L) | 1.358±0.645 | Survivor | 182 | 1.430±0.632 | <0,001 |
| | | Non-survivor | 24 | 0.812±0.455 | |
| Eosinophil (x10⁹/L) | 0.038±0.074 | Survivor | 182 | 0.040±0.076 | 0,23 |
| | | Non-survivor | 24 | 0.021±0.051 | |
| Hb (g/dL) | 13,2±2,1 | Survivor | 182 | 13,5±1,9 | <0,001 |
| | | Non-survivor | 24 | 10,9±2,2 | |
| MCV (fL) | 85,7±5,8 | Survivor | 182 | 84,6±5,3 | 0,95 |
| | | Non-survivor | 24 | 84,7±9,3 | |
| RDW (%) | 13,4±1,7 | Survivor | 182 | 13,15±1,5 | <0,001 |
| | | Non-survivor | 24 | 14,87±2,0 | |
| PLT (x109/L) | 199.9±85.7 | Survivor | 182 | 199.93±79.6 | 0,97 |
| | | Non-survivor | 24 | 199.42±124.9 | |
| MPV (fL) | 9,6±1,4 | Survivor | 182 | 9,60±1,4 | 0,57 |
| | | Non-survivor | 24 | 9,72±1,0 | |
| NLR | 4,4±4,4 | Survivor | 182 | 3,88±3,9 | <0,001 |
| | | Non-survivor | 24 | 8,37±5,9 | |
| MPV/PC | 0,06±0,06 | Survivor | 182 | 0,06±0,06 | 0,28 |
| | | Non-survivor | 24 | 0,07±0,06 | |
| PLR | 179,9±136,7 | Survivor | 182 | 164,01±100,2 | <0,001 |
| | | Non-survivor | 24 | 300,23±265,3 | |
| CRP (mg/dL) | 6,11±6,2 | Survivor | 182 | 5,23±5,7 | <0,001 |
| | | Non-survivor | 24 | 12,76±5,9 | |
| Ferritin (ng/mL) | 1268,6±4328,6 | Survivor | 89 | 523,45±795,9 | <0,001 |
| | | Non-survivor | 21 | 4426,5±9293,4 | |
| Procalcitonin (ng/mL) | 0,7±2,8 | Survivor | 107 | 0,35±1,3 | <0,001 |
| | | Non-survivor | 22 | 2,6±5,9 | |
| D-dimer (ng/mL) | 963,7±1236,9 | Survivor | 112 | 764,8±1099,3 | <0,001 |
| | | Non-survivor | 20 | 1396,7±312,3 | |
| Troponin I (ng/L) | 35,5±96,7 | Survivor | 92 | 20,53±38,6 | |
| | | Non-survivor | 20 | 104,49±203,6 | |
| Leukopenia WBC <4.5 (x10⁹/L) | N=40 %19.4 | Survivor | N=33 (%18.1) | | 0,058 |
| | | Non-survivor | N=7 (%29.2) | | |
| Lymphocyte <0,750 (x10⁹/L) | <0,750...%16 | Survivor | N=21 (%11.5) | | <0,001 |
| | | Non-survivor | N=12 (%50.0) | | |
| | <1.000...%37.9 | Survivor | N=59 (%32.4) | | <0,001 |
| | | Non-Survivor | N=19 (%79.2) | | |
| NLR | <3,19 %51.5 | Survivor | N=104 (%57.1) | | <0,001 |
| | | Non-survivor | N=2 (%8.3) | | |
| | >3,2 %48.5 | Survivor | N=78 (%42.9) | | <0,001 |
| | | Non-Survivor | N=22 (%91,7) | | |

Data are given as mean±SD or number, unless otherwise stated. SD: standard deviation; eGFR: estimated glomerular filtration rate; WBC: white blood cell; Hb: Haemoglobin; MCV: mean corpuscular volume; RDW: red cell distribution width; PLT: platelets; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; MPV/PC: mean platelet volume/platelet count; PLR: platelet-to-lymphocyte ratio; CRP: C-reactive protein.

## Discussion

SARS-CoV-2 is a single-stranded, non-segmented, enveloped RNA, which belongs to the Beta-Coronaviridae family. A definitive diagnosis of SARS-CoV-2 infection is made using RT-PCR-NAT. The PCR positivity rate has been estimated as 63% for nasopharyngeal swabs [3]. In case of repetitive negative RT-PCR testing, immunoglobulin (Ig) M and IgG antibody titers must be checked to confirm the diagnosis [3].

In a retrospective study including 113 deceased patients, Chen et al. [4] reported that advanced age (>65 years) and male gender (73%) were the main risk factors for mortality. In a meta-analysis including 3,027 patients, Zheng et al. [5] showed that advanced age (>60 years) and male gender were the main risk factors for mortality. In our study, the gender distribution was comparable among the participating centers. Unlike previous studies showing male predominance in mortality, in our study, death events were seen equally in both genders (p>0.05). Although 71.9% of our patients were below 65 years of age, 75% of death events occurred in patients over 65 years of age. This finding indicates that advanced age (>65 years) is the main risk factor for mortality, which is consistent with the literature (p<0.001).

There is growing evidence suggesting that clinical presentation may widely vary from asymptomatic infection to severe pneumonia, acute respiratory failure, and even death. In a study including 72,314 patients conducted by the Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention, the rate of asymptomatic patients was 1.2% [1]. In our study, this rate was 3.9%. Thoracic CT revealed ground-glass opacities in half of the asymptomatic cases. The mean NLR was 1.38 in asymptomatic patients and 4.52 in symptomatic patients, indicating a statistically significant difference (p<0.001). Similarly, the mean lymphocyte count was 1.337x10⁹/L in symptomatic patients and 1.865x10⁹/L in asymptomatic patients, indicating a statistically significant difference (p<0.05). In a study including 1,099 confirmed COVID-19 cases, Guan et al. [6] found fever in 87.9%, dry cough in 67.7%, and diarrhea in 3.7% of patients. In our study, the most frequent symptoms included fever (71.8%), dry cough (63.6%), fatigue (53.4%), dyspnoea (32.5%), myalgia (28.6%), diarrhea (14.6%), and anosmia/dysgeusia (8.7%). Correlation analysis revealed no significant correlation between fever, dry cough, fatigue, diarrhea, and anosmia/dysgeusia and mortality (p>0.05). The mortality rate was significantly lower in patients with myalgia (p=0.005). However, an increased severity of dyspnoea was found to be a significant predictor of mortality, consistent with previous studies (p<0.001) [4, 5]. In addition, no mortality was observed in the asymptomatic patient group. Previous studies have also shown that mortality rates ranged from 2.3% to 19.2% [7, 8].

Although thoracic CT mostly reveals non-specific lesions in COVID-19 patients, the most common imaging findings are pure ground-glass opacities, ground-glass opacities, consolidation, interlobular septal thickening, and air bronchograms. In a study examining the diagnostic value and consistency of thoracic CT versus RT-PCR assay in 1,014 COVID-19 patients, Ai et al. [9] reported a positivity rate of 59% for RT-PCR and 88% for thoracic CT. The sensitivity of thoracic CT for COVID-19 was

found to be 97% based on positive RT-PCR results. The authors concluded that thoracic CT could be used as the main tool for the COVID-19 detection in epidemic areas. In our study, 183 (88.8%) of 206 patients had positive thoracic CT scans, while 23 (11.2%) patients had normal CT scans. No mortality was observed in patients with normal CT findings, whereas 24 (13.1%) patients with positive CT findings died, indicating a statistically significantly higher mortality rate in patients with positive CT findings ($p<0.001$). Although we found no significant correlation between the presence of ground-glass opacities, pleural effusion, mediastinal lymphadenopathy and mortality ($p>0.05$), the presence of consolidation was significantly associated with an increased mortality rate ($p<0.001$).

Several studies have demonstrated that chronic comorbidities in COVID-19 patients such as hypertension, diabetes, heart failure, coronary artery disease, asthma, and chronic obstructive pulmonary disease may worsen the prognosis and increase the mortality rate [8]. The SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors and enters into the cells. ACE2 is abundantly present in humans in the epithelia of the lung, heart, kidney, and testicles and, less frequently, in the brain, liver, and small intestines. The relatively high amount of type 2 alveolar epithelial cell line, a major source of ACE2, in males than females has been blamed for the increased mortality rate in males with COVID-19. ACE2 plays a key role in the renin-angiotensin-aldosterone system (RAAS). It functions as the main modulator of RAAS by converting Ang I and II into Ang (1-9) and Ang (1-7), respectively. Previous studies have shown that ACE2 plays a protective role in acute lung injury [10]. Experimental studies have demonstrated that intravenous infusion of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increases the number of ACE2 receptors in the cardiopulmonary circulation [11]. In addition, ACE2 exerts a protective effect on atherosclerosis, hypertension, myocardial hypertrophy, and vasoconstriction. It has been well documented that ACE2 levels decrease with advanced age and in patients with diabetes or hypertension. SARS-CoV-2 infection has been shown to decrease ACE activity. The relatively high mortality rates among the elderly and patients with comorbidities can be attributed to the decreased ACE2 activity in these patients. In a study by Liu et al. [12], they showed that angiotensin II levels increased in COVID-19 patients, which was significantly associated with lung injury. In our study, consistent with previous findings, the most common comorbidities were hypertension (32.5%) and diabetes (22.3%). The rate of AKI at the time of hospital admission was ranged from 1% to 29% in previous studies [13]. Similarly, in our study, the rate of AKI was 10.7%. In another study, Zhang et al. [14] reported that mortality was 3.2-fold higher in COVID-19 patients with AKI. Likewise, the mortality rate was significantly higher among COVID-19 patients with AKI in our study ($p<0.001$). In a meta-analysis including 1,389 COVID-19 patients, Henry et al. [15] observed that the presence of CKD increased infection severity and mortality. In our study, 9.7% of the patients had CKD with a significantly higher mortality rate (55%) ($r=+0.443$; $p<0.001$). The downregulation of ACE2 related to SARS-CoV-2 infection adversely affects the cardiovascular system, as the cardioprotective effects of ACE2 are inhibited. Many studies have also shown that the incidence of myocardial injury varies from 10% to 35%, as evidenced by troponin elevation [16]. In addition, existing heart failure and cardiac events are associated with worse COVID-19 progression and increased mortality [16]. Consistent with these data, we found a positive and significant correlation between the troponin I levels and heart failure ($r=+0.27$; $p<0.001$). In our study, the rate of heart failure was 7.3% and the mortality rate was significantly higher in the patients with heart failure ($p<0.001$).

The underlying mechanisms of leukopenia, thrombocytopenia, and lymphocytopenia in viral infections include the bone marrow and stem cells being directly infected with the virus, increased cell destruction through the immune-mediated mechanisms, increased consumption of platelets, particularly in the lung tissue, and increased apoptosis in T lymphocytes [17]. WBC count is usually normal in SARS-CoV-2 infection, while lymphocytopenia can be seen in 50% to 89.2% of patients. In particular, more prominent lymphocytopenia with an increased WBC and neutrophil counts has been associated with an increased mortality rate [18]. Lymphocytopenia is more severe in ICU patients [7, 8]. The incidence of thrombocytopenia has been reported to range from 5% to 41.7%, and a low platelet count has been associated with more critical illness and an increased mortality rate in COVID-19 patients [19]. Several studies have demonstrated that low absolute eosinophil count is correlated with an increased risk of mortality and, when combined with CRP, it can be used as a valuable biomarker in predicting SARS-CoV-2 infection, as well as for the disease progression follow-up [20]. In general, lymphocytopenia is defined as an absolute lymphocyte count of $<1.0x10^9$/L. In our study, the rate of lymphocytopenia was 37.9%. The mortality rate was 24.4% in patients with a lymphocyte count of $<1.0x10^9$/L, while this rate increased up to 36.4% in patients with a lymphocyte count of $<0.750x10^9$/L. According to the correlation analysis, we found a negative and significant correlation between lymphocyte count and mortality ($r=-0.31$; $p<0.001$). In the present study, 95.1% of the patients had normal or low WBC count. Also, we could not find a significant relationship between the survivors and non-survivors patient group in terms of MCV, MPV, MPV / PC ratio, WBC, thrombocyte and eosinophil counts ($p>0.05$). However, we found a significant association between the neutrophil count and mortality ($r=+0.14$; $p=0.045$). We found a moderate, negative and significant correlation between Hb levels and mortality ($r=-0.41$; $p<0.001$). Consistent with previous studies [21], in our study, RDW increased in deceased patients than survivors. There was also a moderate, positive and significant correlation between RDW and mortality ($r=+0.338$; $p<0.001$). In a study by Qu et al. [22], they showed that PLR was associated with the degree of cytokine storm and might be used as a useful inflammatory indicator when monitoring critically ill patients with COVID-19. Similarly, in the present study, we found a moderate, positive and significant correlation between PLR and mortality ($r=+0.320$; $p<0.001$), indicating a statistically significantly higher mortality rate among the non-survivors ($p<0.001$).

The NLR, which is calculated as the absolute neutrophil count divided by the absolute lymphocyte count, is a potential indicator of systemic inflammatory response [23]. Many studies

have demonstrated that NLR can be utilized as the most useful marker for predicting mortality [21, 19]. In a study, a cut-off NLR value of >3.13 has been shown to be useful in identifying and classifying COVID-19 critical who are likely to develop critical illness [24]. In our study, there was a moderate, positive and significant correlation between NLR and mortality (r=+0.329; p<0.001), and the use of a cut-off value of NLR as >3.13 significantly increased the mortality rate (22%) (r=+0.313; p<0.001). Furthermore, the increase in the CRP, an acute phase reactant used to detect inflammation, procalcitonin, ferritin, RDW, and neutrophil, platelet, and WBC counts is associated with the increased risk for critical illness and mortality. Similarly, we found a significant correlation between CRP and mortality, between ferritin and mortality, and between procalcitonin and mortality in our study (p<0.001 for all).

Although the underlying mechanisms of thrombotic complications have not been fully elucidated yet, a direct viral cytopathic effect, increased Ang II, which has a higher vasoconstrictor effect, decreased Ang (1-7) and Ang (1-9), which have vasodilator effects, and endothelial dysfunction may lead to microvascular thrombosis due to the increased proinflammatory cytokines [25]. All these mechanisms and the existing ACE2 in endothelial and myocardial cells may induce pulmonary and cardiac injuries. Previous studies have shown a significant association between troponins, markers of myocardial injury, and an increased risk for mortality. Similarly, in the current study, we found a significant correlation between the troponin I and D-dimer and an increased mortality risk (p<0.001).

Nonetheless, this study has some limitations. First, the relatively small number of patients in the non-survivor group may have led to bias in the interpretation of the results. Second, this study included only hospitalized patients, which precludes the generalization of the results to all COVID-19-positive patients. In addition, all patient data were recorded at the time of hospital admission and we were unable to perform the measurements later. Therefore, further large-scale, prospective studies using repetitive measurements are warranted to confirm these results.

## *Conclusion*

Our study results suggest that coexisting diabetes, hypertension, heart failure, or CKD are associated with an increased risk for critical illness and mortality. The development of AKI also increases the mortality risk. The disease presenting with symptoms or positive findings on thoracic CT is of clinical relevance alone for the development of critical illness. Patients with dyspnea should be closely followed to prevent mortality or critical illness. The presence of dyspnea or consolidation on thoracic CT can predict the increased mortality risk in COVID-19 patients. In particular, patients with lymphocytopenia (lymphocyte count <0.750x$10^9$/L), an NLR of >5, and a PLR of >149 can be considered for early admission to the ICU.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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