Laboratory markers used to predict mortality in severe COVID-19

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Abstract

Purpose: In this study, we aimed to evaluate the laboratory markers used in the diagnosis of COVID-19 and to present the parameters that can be used to predict mortality. Material and method: The cases followed in the intensive care unit due to COVID-19 in our clinic between March 2020 and December 2020 were evaluated retrospectively. A total of 374 patients who met the study criteria were included in the study. The patients were divided into two groups as the patients who were discharged from the intensive care unit with no mortality and patients with a mortal course. Patients with no mortality constituted Group-1, and patients with a mortal course constituted Group-2. Demographic, clinical, and laboratory characteristics of the patients were compared. Results: The number of patients in group-1 consisting of patients with no mortality was 148 (39.5%), and the number of patients in group-2 consisting of patients with mortality was 226 (60.4%). In the group of patients without mortality, 84 (56.8%) of the patients were male, while in the mortality group, 127 (56.2%) were male. In the mortality group, procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate, and INR values were higher, albumin value was lower, and this difference was statistically significant ($p<0.001$). In the logistic regression analysis, PLT and D-dimer were found as the independent variables of mortality. Conclusion: We think that the high procalcitonin and D-dimer values obtained with routinely examined rapid and easily accessible blood tests of Covid-19 patients may contribute to mortality prediction.

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Keywords ; Covid 19, bilirubin, C-reactive protein, white blood cell, neutrophil-lymphocyte ratio, predictive factors

The ongoing covid-19 pandemic causes many deaths regardless of age. This study was conducted with the aim of developing laboratory parameters that can be used to predict mortality. We aimed to guide our valuable colleagues with simple blood tests taken during the first application of the patients. We believe that it is not a subject that has been studied much before.

Introduction

The coronavirus disease caused by the Coronavirus-2 virus (SARS-CoV-2), which is especially destructive in the respiratory tract, still impacts worldwide, although more than one year has passed since the first appearance of the virus and vaccination studies have been carried out. Patients show a broad spectrum of clinical manifestations, ranging from asymptomatic infection to severe respiratory failure resulting in death. In symptomatic patients, clinical manifestations of the disease begin less than a week later, consisting of fever (body temperature 37-38-C), cough, nasal congestion, and fatigue (1). Pneumonia mainly occurs in the second or third week of symptomatic infection (2,3). Common laboratory findings include lymphopenia, the elevation of liver enzymes and lactate dehydrogenase, and inflammation markers such as ferritin, C-reactive protein, and erythrocyte sedimentation rate. Although white blood cells, neutrophils, eosinophils, platelets, and other blood cells, including CD8 cell counts, are partial predictors in distinguishing between mild and severe COVID-19, their significance is still unclear. Parameters and rates obtained from tests such as hemogram and biochemistry, which are fast, easy, and accessible, and routinely studied in the clinic, have been the subject of many studies to detect biomarkers aimed at evaluating the course of the disease.

Although the disease course cannot be predicted precisely, biomarkers that can predict the severity of this disease will make an important contribution to personalized treatment. Early awareness of the clinical course will also help reduce mortality. Our aim in this study is to evaluate the laboratory markers used in patients diagnosed or suspected of COVID-19 and to develop parameters that can be used to predict mortality.

Material and methods

Study design and patients

The cases hospitalized with the diagnosis of COVID-19 in the adult intensive care unit of Şanlıurfa Training and Research Hospital between March 2020 and December 2020 were evaluated retrospectively. Approval for the study was obtained from the Ethics Committee of Harran University with the decision no HRU/XXX decree. The study was conducted per the Declaration of Helsinki. Three hundred seventy-four patients whose data were fully accessed via the hospital information system were included in the study. The patients were divided into two groups: those who were transferred to the pandemic service and those who died. Group-1 consisted of patients without mortality (n=148), and group-2 consisted of patients who died (n=226).

Data

Patients' age, gender, COVID-19 PCR test result, comorbid diseases, intubation status, the day of the intensive care hospitalization, laboratory values during hospitalization in the intensive care unit, white blood cell (WBC), hematocrit (Hct), thrombocyte (Plt), neutrophil, lymphocyte, monocytes, red cell distribution of width (RDW), Mean platelet volume (MPV), c-reactive protein (CRP), total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) values, lactate dehydrogenase (LDH), blood groups, procalcitonin, ferritin, fibrinogen, calcium (Ca), albumin, INR, blood gas parameters (Ph, PO2, PCO2, lactate) duration of stay in the intensive care unit were recorded. In addition, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) values were calculated according to laboratory values.

Statistical analysis: Statistical Package for the Social Sciences (SPSS 25 Inc., Chicago, IL, USA) computer software was used for the biostatistical analyses. The data obtained from the participating patients were expressed as mean, standard deviation values, and as a percentage where necessary. The Kolmogorov Smirnov test was used to examine the normal distribution of the data. Data with normal distribution were analyzed

by student t-test. Group analysis of non-parametric data was performed with the Mann-Whitney U test. Logistic regression test was used for univariate analysis and to calculate odds ratios (OR) with 95% confidence interval (CI). Categorical groups were compared with the chi-square test. Cut-off values were obtained by receiver operating curve (ROC) analysis.

Results

A total of 374 patients who met the study criteria were included in the study. The number of patients in group-1 consisting of patients with no mortality was 148 (39.5%), and the number of patients in group-2 consisting of patients with mortality was 226 (60.4%). The mean age of patients without mortality was 70 (min: 20-max: 93) years, and the mean age of patients who died was 70 (min: 20-max: 92) years, and this difference was not statistically significant (p=0.001). When we took the 65-age value as the cut-off value and grouped it according to the cut-off value, it was seen that 82 (55.4%) of the patients without mortality and 152 (67.3%) of the patients who died were over 65 years old. In the group of patients without mortality, 84 (56.8%) of the patients were male, 64 (43.2%) were female, and in the mortality group, 127 (56.2%) were male, and 99 (43.8%) were female. No significant difference was found between the groups in terms of gender. When we grouped the patients according to their ethnic origins, in the group without mortality, 136 (91.9%) were Turkish, 12 (8.1%) were Syrian, and in the mortality group, 199 (88.1%) were Turkish, and 27 (11.9%) were Syrian. Computed tomography (CT) revealed typical involvement in all patients. When we grouped the patients according to PCR results, there were 75 PCR Negative patients (50.7%), PCR Positive 73 patients (49.3%) in the group without mortality, 98 PCR Negative patients (43.4%), and 128 PCR Positive patients (56.6%) in the mortality group. When the patients were evaluated according to their intubation status, it was seen that 138 patients (93.2%) in the group without mortality did not need intubation, and 10 (6.8%) patients were intubated. In the mortality group, 18 (8%) patients did not need intubation, while 208 (92%) patients were intubated, and the difference was statistically significant (p<0.001). In the mortality group, the mean intubation day was the 2nd day (min:0-max:48), the mean intubation time was 7 (min:0-max:65) days, the difference was statistically significant (p<0.001). When the patients were examined according to their comorbidities, in Group-1, 61 patients (41.2%) had hypertension (HT), 30 patients (20.3%) diabetes mellitus (DM), 50 patients (33.8%) cardiac disease, 44 patients (29.7%) pulmonary disease. Twenty-nine patients (19.6%) had a neurological disease, and seven patients (4.7%) had chronic renal failure (CKD). In Group-2, HT was present in 116 patients (51.3%), DM in 60 patients (26.5%), cardiac disease in 80 patients (35.4%), pulmonary disease in 62 patients (27.4%), neurological disease in 43 patients (19%), and CRF in 16 patients (7.1%), and the difference was not statistically significant.

When the laboratory values of both groups were examined during the intensive care unit admission, in Group-1, WBC was 11.7 (3.26-34.4), Rbc4.8 (2.6-5.9), Hb 12.87±2.06, Htc (%) 38.82±5.85, Neutrophil 9.9 (2-27.1), Lymphocyte 1.1 (0.1-12.5), Monocyte 0.5 (0-2.1), Platelet 290 (59-703), RDW 13.8 (11.7-22), MPV 10.6 (8.6-13.7), Procalcitonin 0.2 (0.02- 23), Ferritin 588 (17-16946), NLR 7.42 (0.76-100), PLR 240 (26.82-2500), CRP 94 (2-338), Total Bilirubin 0.5 (0.1-20), Direct bilirubin 0.1 (0- 19), AST 34 (11-2213), ALT 24 (7-1697), Albumin 3.33±0.44, BUN 47 (18-193), Creatinine 0.95 (0.3-9.4), D-dimer 0.8 (0.15-9.6), Troponin 14 (3-3355), LDH 367 (130-4431), Fibrinogen 491.24±177.15, Na 137 (127-176), K 4.4±0.75, Ca 8.5 (7.3-9.5), Ph 7.43 (6.9-7.51), PO2 was 47 (17-171), PCO2 35 (14-92), Lactate 1.7 (0.83-20), INR 1.1 (0.8-2.7). In Group-2, WBC was 11.6 (0.02-34.64), Rbc4.4 (2.3-6.5), Hb 12.52±2.12, Htc (%) 37.97±6.7, Neutrophil 9.6 (0.4-32.2), Lymphocyte 0.8 (0.2-9.7) , Monocyte 0.45 (0-11), Platelet 219 (20-552), RDW 14.1 (11.8-20.2), MPV 10.9 (8.4-14.3), Procalcitonin 0.24 (0.04-29), Ferritin 743 (21-38486), NLR 5 (0.76-18.4), PLR 125.2 (43.8-545), CRP 120 (0.92-435), Total Bilirubin 0.4 (0.1-7.9), Direct bilirubin 0.2 (0-7.4), AST 43 (10-1243), ALT 26 (5-717), Albumin 3.18±0.53, BUN 54 (12-311), Creatinine 1.1 (0.17-6.4), D-dimer 1.8 (0.2-11.1), Troponin 28 (3-1421), LDH 497 (172) -1918), Fibrinogen 487.68±191.27, Na 138 (125-171), K 4.32±0.91, Ca 8.4 (4.5-10.1), Ph 7.38 (6.9-7.56), PO2 39 (11-181), PCO2 36 (20 -95), Lactate 2.3 (0.7-21), INR 1.1 (0.93-9.9). In the mortality group, procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate and INR values were higher, albumin value was lower, and this difference was found to be statistically significant (p<0.001). When the hospitalization day was evaluated, it was 7 (2-30) days in group-1 and 12 (1-68) days in group-2, the difference was not statistically significant. The demographic, clinical and laboratory characteristics of the patients

are summarized in Table 1. Demographic characteristics and laboratory parameters that were statistically significant between the two groups in the univariant analysis were included in the multivariate logistic regression analysis. In the logistic regression analysis, PLT (OR= 0.992, 95% CI= 0.987-0.996, p=0.000) and D-dimer (OR= 1.230, 95% CI= 1.015-1.491, p=0.035) were found to be independent variables for mortality. (Table 2). D-dimer cut-off value in predicting mortality in the ROC curve analysis of these independent variables: 1.05 (AUC: 0.670, %95Cl: 0.612-0.728, p: <0.001), sensitivity was 68.8%, specificity was 56.7%. AUC for platelets: 0.594, %95Cl: 0.536-0.652, p:0.002 (Figure 1).

Discussion

The COVID-19 disease caused by SARS-CoV-2 continues to show its effects despite the increased use of antiviral treatments and vaccination. In this study, we aimed to develop markers that can be used to predict mortality through laboratory parameters. Studies have reported close to 100% mortality among patients requiring mechanical ventilation (4). Our study is even more important since we observed that our mortality rate was 60.4% in our 1-year intensive care follow-up. In our study, the mortality rate was found to be high in intubated patients; the difference was statistically significant.

If we look at the gender-mortality relationship, the M/F ratio was 1.28 in our study. An in-depth study examining Covid19 effect on Italy, on 123.3 thousand coronavirus deaths, revealed that the fatality rate was much higher for the male gender. If the mortality rate for female patients was 2.5 percent, the corresponding figure for male patients was 3.4 percent. However, the COVID-19 case fatality rate is higher in women than men in a few countries, such as India, one of the worst-affected countries. As of Sept 30, 2020, India had more than 6·4 million recorded COVID-19 cases (5). In India, the COVID-19 case fatality rate among men is 2·9% and 3·3% among women (6*)*. Both group 1 and group 2 patients had comorbid diseases, but the presence of comorbid disease was not significant between the two groups.

When laboratory parameters were examined, procalcitonin, CRP, BUN, D-dimer, troponin, LDH, lactate, high INR, and low albumin were statistically significant in terms of mortality. As a result of logistic regression analysis, low PLT and high D-dimer were determined as independent variables for mortality. In the study conducted by Fan et al. (7), lymphopenia and increased lactate dehydrogenase (LDH) values were associated with higher ICU admission rates. Patients transferred to the ICU had lower lymphocyte counts, lowest monocyte counts, and lowest hemoglobin and higher peak Neutrophil (NEU) counts, and highest LDH levels compared to patients who did not require an ICU stay. Similarly, in SARS disease, high CRP levels, lymphopenia, leukopenia, and elevated aminotransferase, LDH, and creatine kinase levels have been shown in most patients (8). Liver dysfunction is observed more frequently in severe cases of COVID-19 than in those with milder severity, and an increase in Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels have been observed in many ICU patients (9). Infection of liver cells with SARS-CoV-2 cannot be excluded as 2-10% of patients with COVID-19 have diarrhea, and viral RNA is detected in both stool and blood samples, suggesting the possibility of hepatic virus presence (10). High C-reactive protein (CRP), ferritin and lactate dehydrogenase (LDH) levels were found to be correlated with the severity of the disease and prognosis (11,12).

In the study of Wang D et al. (13), the ability of procalcitonin elevation to predict 28-day intensive care mortality was found to be statistically significant.

In the study of Mardani et al. (14), in which they examined 200 patients in a single-center, they reported that ALT, CRP, NEU, LDH, and BUN values had extreme accuracy in predicting PCR positive patients. In the same study, low WBC and lymphocyte counts were evident in PCR-positive patients, but we could not find a significant difference between the patients with a mortal course and the living group in our study.

In the study of Zhao et al. (15), the most common laboratory findings in COVID-19 patients were decreased lymphocyte count, prolonged APTT, elevated LDH, CRP, and erythrocyte sedimentation rate (ESR). Erol et al. (16) examined 101 patients and showed that CRP, LDH, D-Dimer values were significantly higher, and WBC values were significantly lower in the patient group who died. In our study, similar to these results, we found high CRP, D-Dimer LDH values in the patient group who died. Although low platelet levels did not

make a significant difference between the groups in the study of Erol et al., platelet levels were significantly lower in the deceased group in our study. In the study of Deng et al. (17), increased leukocyte count and decreased lymphocyte count in the survival group were associated with mortality. Our study did not observe significant differences in leukocyte counts and lymphocyte counts in both groups.

The predictive value of LDH as an indicator of altered glucose metabolism in patients with sepsis is known (18). In the study conducted by Gao et al. (19), laboratory parameters such as ALT, CRP, AST, and LDH can be used to predict the presence of disease. Tsui et al. (20) examined 323 cases with severe acute respiratory failure and stated that high LDH level was an important prognostic factor. Similarly, we found that LDH levels were significantly higher in the mortality group in our study.

In our study, we concluded that D-dimer elevation is an independent variable for mortality. Similarly, according to a report published in Wuhan, patients with D-dimer levels of 2.0 ng/mL had a higher mortality rate than patients below 2.0 ng/mL (21).

In a meta-analysis including 25 studies published by Huang et al. and 5350 patients in total, high levels of CRP, procalcitonin, D-dimer, and ferritin were associated with poor outcomes (22). COVID-19 infection manifests with a coagulopathy problem characterized by procoagulant factors such as fibrinogen and predominantly high D-dimer levels, increasing mortality. In our study, fibrinogen levels were high in both groups, and the difference was not statistically significant. Likewise, although ferritin values were higher in the mortality group in our study, we could not find a significant difference between the two groups. However, we believe that high ferritin levels are associated with the hyperinflammatory state.

In a meta-analysis of 11 studies and 910 patients reviewed by Aziz et al., a correlation was shown between hypoalbuminemia and severe COVID-19, and it was reported that it would facilitate the early diagnosis of severe disease and help clinicians (23). In our study, we found that hypoalbuminemia was statistically significant in the mortality group.

Similarly, in the study of Erol et al. (16), AST values were higher in non-survivors compared to survivors, and there was no difference in more specific ALT values in the liver. In our study, the AST value was higher in the mortality group, and the difference was not statistically significant (p=0.001). Zhang et al. (9) showed that 2-11% of COVID-19 patients have liver comorbidity and 14-53% of cases have abnormal ALT and AST levels during COVID-19 disease progression. Thus, liver damage appears to be more common in severe cases compared to mild cases of COVID-19. Yang et al. (24) found no difference in the incidence of abnormal liver function between survivors (30%) and non-survivors (28%).

The limitation of our study is that it is retrospective, the number of patients is small, and it is single-centered. In conclusion, full treatment has not been provided yet in the Covid-19 pandemic, which has left its mark on the last century and has caused many deaths. Vaccination and vaccine development studies continue. Nevertheless, we think that the high procalcitonin and D-dimer values obtained with this study, which was carried out with the markers in the rapid and easily accessible blood tests routinely examined in Covid-19 patients, may contribute to the prediction of mortality.

Ethics Committee Approval:

The study was approved by the Harran University Medical Faculty Hospital Local Ethics Committee (approval no: HRU**).**

Conflict of Interest

The authors declared no conflict of interest.

Financial Disclosure

The authors declared that this study had received no financial support.

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