

The importance of biomarkers in determining the prognosis of patients requiring intensive care hospitalization due to COVID-19 infection

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ABSTRACT

Objective: This study aims to investigate the effect of biomarkers such as CRP, ferritin, troponin, lymphopenia, and D-dimer in predicting disease severity and clinical outcome. Identifying an effective and predictive biomarker will help to evaluate patients' risk and improve overall clinical management of patients with COVID-19

Material and Methods: In this retrospective cohort study, 1458 patients who were taken to intensive care follow-up due to COVID-19 across the province of Bursa were evaluated. Age, gender, and laboratory data such as ferritin, D-dimer, White Blood Cell (WBC), C-reactive protein, troponin values, chronic diseases, length of stay in the intensive care unit, and mortality were recorded. The relation of these variables with mortality was analyzed.

Results: There was no significant difference between the groups regarding age and length of stay in the intensive care unit ($p=379$, $p=0.094$). There was a statistically significant difference between the groups for ferritin, CRP, D-dimer, troponin, and WBC variables ($p<0.001$). In the ROC analysis, it was seen that the sensitivity value for ferritin was 86.08%, the specificity value was 85.23%, and the AUC: 0.902 had a high level of diagnostic value.

Conclusion: An increase in acute phase reactants was associated with mortality in patients followed up for COVID-19. This may be related to the increased cytokine response triggered by the disease.

Keywords: COVID-19, mortality, acute phase reactants, disease severity

INTRODUCTION

Coronavirus spreading from China to the world, rapidly gained a global magnitude (1). Around the world, approximately 582,928,015 cases and 6,415,652 deaths were reported (2). Since the first COVID-19 case in Turkey was seen on 10th March 2020, the cumulative number of cases was 16,295,817, and the number of deaths was 99,678 (3).

Although COVID-19 infection progresses with a good prognosis in many patients, also, it can progress to acute respiratory distress syndrome (ARDS), and end-stage organ failure in individuals with advanced age and comorbidities. For this reason, the need for intensive care and mechanical ventilator follow-up may arise in individuals with severe infection (4, 5). This requirement has forced to test researchers in many health services such as intensive care and ventilators in many countries during the pandemic. As COVID-19 cases increased, the number of patients followed in intensive care compelled many countries, especially China, Italy, France and Spain (6, 7). In 2020, while Spain, France and especially Italy were affected by the pandemic, southern Mediterranean countries experienced a relatively more comfortable pandemic process with a limited number of patients admitted to intensive care units compared to these European countries (8,9). The necessity of developing strategies and making choices for the effective use of the capacity of increasing intensive care needs has emerged. Accurate identification of critically ill COVID-19 patients has gained importance for the need for intensive care. Studies have reflected different findings and experiences on the follow-up and treatment processes of COVID-19 patients in intensive care, mechanical ventilator management, and intensive care indications (5).

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In the light of studies investigating that COVID-19 disease is associated with mortality, cardiovascular disease, diabetes mellitus, chronic lung diseases, hypertension, chronic renal failure, and diseases that require immunosuppressive therapy were considered as important comorbidities (10-13). In a meta-analysis of 1558 patients and six studies conducted in China, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, and hypertension were found to be the most important independent risk factors for mortality, respectively (14). In a retrospective study of COVID-19-related mortality in Italy, the mean number of pre-existing comorbidities was 2.7, and no comorbid disease was found in only three (0.3%) patients. Older age and male gender were considered independent risk factors in studies conducted in China, Italy, and USA, due to a disproportionately high number of deaths (13, 15-16). The increased mortality prevalence, especially in males, may be due to males' predisposition to cardiovascular disease. In a comment by the Center for Disease Control and Prevention, it was emphasized that men and women interpret COVID-19 differently, increased incidence of smoking in men with other comorbidities seen in men are independent risk factors for COVID-19, and treatment initiation and adherence to treatment are more unsuccessful for men than women (16-18).

In the literature, factors associated with estimating the severity of COVID-19 infection are age, comorbidities, and high inflammatory markers (19,20). Literature research indicates that one of the predictive acute phase reactants associated with predicting the severity of coronavirus disease is ferritin (21). In cases with a high pathogenic load, the increase in ferritin will reduce the iron supply to the microorganism, thus playing a protective role in the body's defense. Ferritin not only reduces the iron supply for the pathogen, but also regulates the release of cytokines and prevents them from entering the cytokine storm. Ferritin is a component of iron metabolism that protects the host in pathogen infections (22-24). Iron is an essential micronutrient for both energy production at the mitochondrial level and nucleic acid replication at the nuclear level (25). For these processes to take place, microorganisms compete with the body's cells for iron binding (26). When the innate immunity is activated, and cytokine cascades begin, interleukines stimulate hepcidin expression in the liver and reduce intestinal absorption, thus storing ferritin accumulated in macrophages and limiting iron bioavailability (27, 28).

C-reactive protein (CRP) is an acute phase reactant synthesized in the liver secondary to inflammation or an infectious process. Unlike profound changes in plasma levels during the catabolism of most acute phase proteins, CRP remains almost constant in plasma. During acute infection, serum concentrations increase, making CRP a striking marker for inflammatory processes such as sepsis. CRP contributes to the pro-inflammatory process by activating inflammatory cytokines in the body (29,30). CRP levels increase in patients with COVID-19, and the median CRP value of survivors is 40mg/dL, and the median CRP value of those who died due to COVID-19 is 125mg/dL, demonstrating that CRP has a strong relationship with disease severity and prognosis (31).

CRP and serum ferritin play an important role in the initiation of inflammatory processes. The main finding of immune pathology in COVID-19 is cytokine storm. The virus

multiplies rapidly in the endothelial and epithelial cells of the body, which causes the synthesis of cytokines and chemokines. Studies have shown that high levels of cytokines and chemokines released during infections are associated with poor outcomes of respiratory viral infections (32,33). Overproduction of inflammatory cytokines increases the severity of COVID-19 infection by contributing to the picture leading to ARDS and multi-organ failure (34,35).

Among the hematological markers, lymphopenia was clearly associated with disease severity (36). The lymphocyte counts of patients who died from COVID-19 were found to be significantly lower than those who survived. Lymphopenia and involvement of specific T-cells have been associated with both its characteristic and poor prognosis for COVID-19 (37-40). In the previous pandemic of SARS, the peak of viral load occurred 7 days later, followed by elevation in IL-6 and IL-8, regression to the lowest lymphocyte count, and subsequent pulmonary leakage, suggesting that lymphopenia may mediate the immune system dysregulation rather than direct damage to clinical symptoms (41).

During sepsis, a decrease in antithrombin is observed followed by upregulation of the tissue factor resulting in an increase in plasma thrombin, while at the same time, decreased production of Prothrombin-C and upregulation of type 1 plasminogen activator inhibitor further inhibit fibrinolysis. All these changes lead to a high level of coagulation tendency. With the addition of increased coagulation and hypotension with sepsis, it brings with it life-threatening multi-organ failure. The D-dimer is a measure of the coagulation process and assesses the severity of the host response, making it an important role in the classification of patients with sepsis. One study showed that the higher the D-dimer levels, the higher the risk for the patient for septic shock and the greater the likelihood of sepsis (42-44). Studies are showing that D-dimer elevation > 1 ug/L among coagulation parameters is the strongest independent predictor of mortality (13,45).

Although the clinical manifestations of COVID-19 are mainly related to the respiratory tract, with the increase in the number of infected patients, major cardiac complications have been reported in a significant number of COVID-19 patients (14, 46, 47). Acute cardiac injury, defined as the marked elevation of cardiac troponins, is a frequent complication reported in 8-12% of COVID-19 patients (48). In the explanations made so far regarding the cardiovascular impact of COVID-19, it has been suggested that chronic cardiovascular diseases may occur as a result of the imbalance between the increased metabolic demand caused by the infection and the decreased cardiac reserve in the case of a viral infection (49). Studies evaluating COVID-19 patients with signs of cardiac injury show that it is associated with poor prognosis and that arrhythmic events are not uncommon (50, 51). High cardiac troponin levels in COVID-19 patients indicating cardiac injury, were associated with mortality in critically ill patients (52, 53).

This study aims to investigate the effect of biomarkers such as CRP, ferritin, troponin, lymphopenia, and D-dimer in predicting disease severity and clinical outcome. Identifying an effective and predictive biomarker will help to evaluate patients' risk and improve overall clinical management of patients with COVID-19, particularly in the local region.

MATERIAL AND METHODS

The study was assessed retrospectively in PCR-positive patients who were evaluated in the emergency services of public hospitals and COVID-19 outpatient clinics and admitted to the intensive care unit due to COVID-19 in Bursa between January 1 and June 1, 2021. During the study planning process, approval was obtained from the Bursa City Hospital ethics committee, and the principles of Research and Publication Ethics were followed. Age, gender, and laboratory data of the patients included in the study such as ferritin, D-dimer, White Blood Cell (WBC), C-reactive protein, troponin values, chronic diseases, length of stay in the intensive care unit, and mortality were recorded. Patients under the age of 18, patients with positive thorax imaging for COVID-19 but negative PCR test results and treated as possible COVID-19 cases, and patients whose file data could not be accessed were excluded from the study.

Statistical analysis: The data of the study were analyzed using the 'The jamovi project (2021). jamovi (Version 2.0.0) (Computer Software). Descriptive statistics were expressed as mean \pm standard deviation or median values and an interquartile range (IQR) of 25–75 %, while categorical variables were expressed as numbers and percentages (%). Kolmogorov–Smirnov test and Shapiro–Wilk test were used for the normality distribution of the data. While the significance of the difference between the groups in terms of continuous numerical variables in which parametric test statistics assumptions were provided was examined with Student's t test, the significance of the difference in terms of continuous numerical variables where parametric test statistics assumptions were not met was evaluated with the Mann-Whitney U and Kruskal-Wallis tests. Chi-square and Fisher's exact test were used to analyze whether there was a relationship between categorical variables. The variables that may be effective for mortality were evaluated using the "enter" method in logistic regression analysis. The ROC curve was drawn to investigate the diagnostic value of the ferritin, lymphocyte, CRP, D-dimer, and troponin. $p < 0.05$ was considered statistically significant. Results were given at 95 % confidence interval.

RESULTS

In our study, the data of a total of 1576 patients were analyzed retrospectively. 9 patients were excluded from the study because they were under the age of 18, and the data of 109 patients could not be accessed.

Table 1: Descriptive statistics of the study population

	Mortality	N	Median	Minimum	Maximum	Percentiles	
						25th	75th
Ferritin	Yes	625	999.00	23.000	2000.0	719.450	1560.00
	No	833	232.80	21.000	2000.0	116.890	437.60
CRP	Yes	625	100.30	1.300	439.0	51.000	161.40
	No	833	52.90	0.700	339.9	13.900	114.70
D-Dimer	Yes	625	3.29	0.100	89.0	1.180	8.60
	No	833	1.42	0.190	45.0	0.760	3.54
Troponin	Yes	625	56.00	0.100	9893.9	16.270	152.80
	No	833	24.00	0.200	6092.0	9.550	55.72
WBC	Yes	625	4.90	0.190	70.6	3.150	9.62
	No	833	6.90	0.260	87.6	3.730	12.12
SEX		N	Median	Minimum	Maximum	25th	75th
Age	Male	844	70.00	20.0	97.0	61.00	78.0
	Female	614	74.00	22.0	100.0	64.00	81.0
ICU Time	Male	844	6.00	0.0	88.0	3.00	12.0
	Female	614	6.00	0.0	126.0	3.00	13.0

CRP: C-reactive protein, WBC: White blood cell, ICU: Intensive care unit

A total of 1458 patients were included in the study. 57.9% (n:844) of the 1458 patients included in the study were male, with a median age of 71(IQR:25-75)(62-79), median ferritin value 493.5 (IQR:25-75)(187.15-987), CRP median value 74 (IQR:25-75)(24.625-132), D-dimer median value 1.97 (IQR:25-75)(0.87-5.48), troponin median value 31.44 (IQR:25-75)(12-83.95), WBC median value was 5.92 (IQR:25-75)(3.4-11.39), median length of stay in the intensive care unit was 6 (IQR:25-75) (3-12) days (**Table-1**).

When we look at the comorbidity distribution of the patients, it was seen that 35.4% (n:516) did not have any additional disease, 21.2% (n:309) of the patients with comorbidities had HT, 10% (n:146) DM, 7.2% (n:105) COPD (**Figure-1**). Mortality developed in 42.9% (n:625) of the patients during their follow-up, and we found that 64.3% (n:402) of the patients were male (**Figure-2**). Mortality was grouped into developing and non-developing patients, and statistical analyses were performed. Continuous variables did not fit the normal distribution with the Kolmogorov-Smirnov test, and statistically significant differences between the groups were calculated with the Mann-Whitney U test (**Table-2**). There was no significant difference between the groups in terms of age and length of stay in the intensive care unit ($p=379$, $p=0.094$). There was a statistically significant difference between the groups for ferritin, CRP, D-dimer, troponin and WBC variables ($p<0.001$).

In the Chi-Square test performed for gender and comorbidity variables, a statistically significant difference was observed in both variables ($p<0.001$, $p<0.001$). The distribution of gender and comorbidity variables by binomial logistic regression analysis is given in **Table-3**. Male gender, malignancy, HT and DM were found to have significant effects on mortality ($p<0.001$, OR:1.598, $p=0.01$, OR:5.819, $p<0.001$, OR:3.708, $p<0.001$, OR:2.657).

Regarding the diagnostic values for mortality in patients admitted to the intensive care unit due to COVID-19 in the ROC analysis, it was seen that the sensitivity value for ferritin was 86.08%, the specificity value was 85.23%, and the AUC: 0.902 had a high level of diagnostic value. ROC curve is given in **Figure-3** and ROC analysis results are shown in **Table-4**. In addition, graphical distributions of ferritin, CRP, D-dimer, troponin and WBC variables according to mortality are demonstrated in **Figure-4**.

Table 2: Association of variables with mortality

Independent Samples T-Test			
		Statistic	p
Age	Mann-Whitney U	253320	0.379
ICU Time	Mann-Whitney U	247010	0.094
Ferritin	Mann-Whitney U	51173	<.001
CRP	Mann-Whitney U	175977	<.001
D-Dimer	Mann-Whitney U	178795	<.001
Troponin	Mann-Whitney U	180814	<.001
WBC	Mann-Whitney U	226065	<.001

Table 3: Results of Binomial Logistic Regression Analysis

Model Coefficients - Mortality						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.024	0.116	-8.816	<.001	0.359	0.286	0.451
Comorbidities:							
KOAH – No Comorbidities	0.146	0.225	0.646	0.518	1.157	0.744	1.799
HT – No Comorbidities	0.977	0.149	6.541	<.001	2.657	1.983	3.561
Renal Failure – No Comorbidities	-0.371	0.306	-1.213	0.225	0.690	0.379	1.257
SVO – No Comorbidities	0.593	0.268	2.214	0.027	1.810	1.071	3.059
DM – No Comorbidities	1.310	0.198	6.634	<.001	3.708	2.517	5.460
Asthma – No Comorbidities	0.457	0.333	1.372	0.170	1.579	0.822	3.035
Neurological – No Comorbidities	0.180	0.456	0.394	0.694	1.197	0.490	2.924
Malignancy – No Comorbidities	1.761	0.687	2.562	0.010	5.819	1.513	22.385
Cardiac Failure – No Comorbidities	0.481	0.179	2.689	0.007	1.618	1.139	2.298
SEX:							
Male – Female	0.469	0.112	4.172	<.001	1.598	1.282	1.991

Model Fit Measures			
Model	Deviance	AIC	R ² _{Mcf}
1	1886	1908	0.0529

Table 4: ROC analysis results

Cutpoint	Sensitivity (%)	Specificity (%)	Youden's index	AUC
Scale: Ferritin				
445	92.48%	75.87%	0.684	0.902
503	89.76%	80.91%	0.707	0.902
576	86.08%	85.23%	0.713	0.902
616.7	84%	86.79%	0.708	0.902
Scale: CRP				
18.27	90.4%	30.49%	0.209	0.662
31.13	85.12%	38.66%	0.238	0.662
62.2	68.16%	54.14%	0.223	0.662
72.2	63.84%	58.7%	0.225	0.662
Scale: D-Dimer				
1.44	71.36%	50.06%	0.214	0.657
1.9	63.84%	58.34%	0.222	0.657
2.12	60.32%	64.23%	0.245	0.657
2.74	55.2%	69.99%	0.252	0.657
Scale: Troponin				
28.52	64.96%	55.94%	0.209	0.653
36.2	59.52%	64.23%	0.237	0.653
36.32	59.52%	64.35%	0.239	0.653
47.69	52.96%	71.67%	0.246	0.653
Scale: WBC				
0.5	99.04%	1.2%	0.00240	0.434
2	89.76%	12.61%	0.02365	0.434
16.83	10.24%	87.76%	-0.02005	0.434
19.15	8.32%	91.12%	-0.00564	0.434

CRP: C-reaktif protein, WBC: White blood cell, AUC: Area under curve,

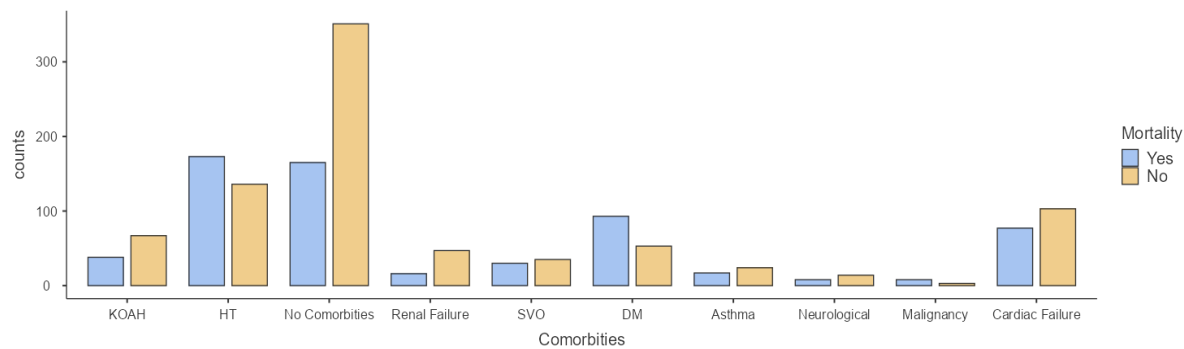


Figure 1: Distribution of comorbidities in patients with mortality

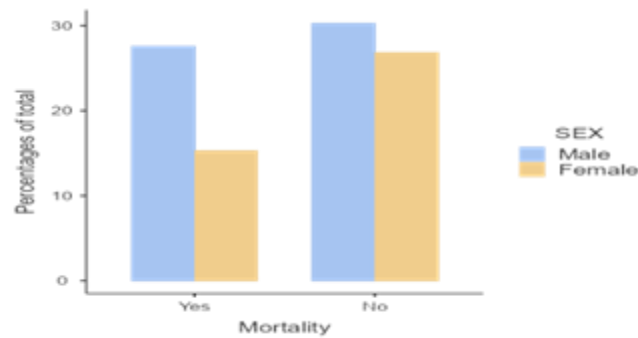


Figure 2: Mortality and sex distribution

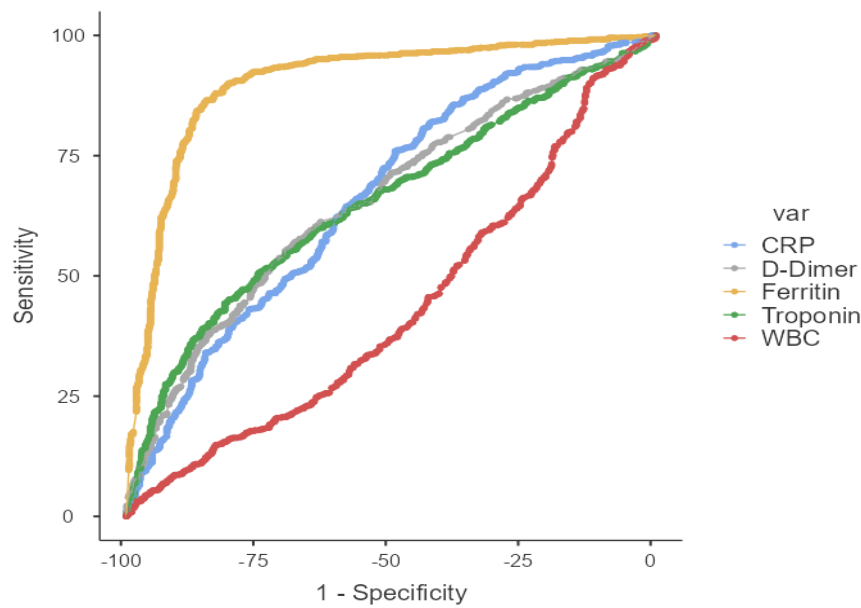


Figure 3: ROC Curve: Combined

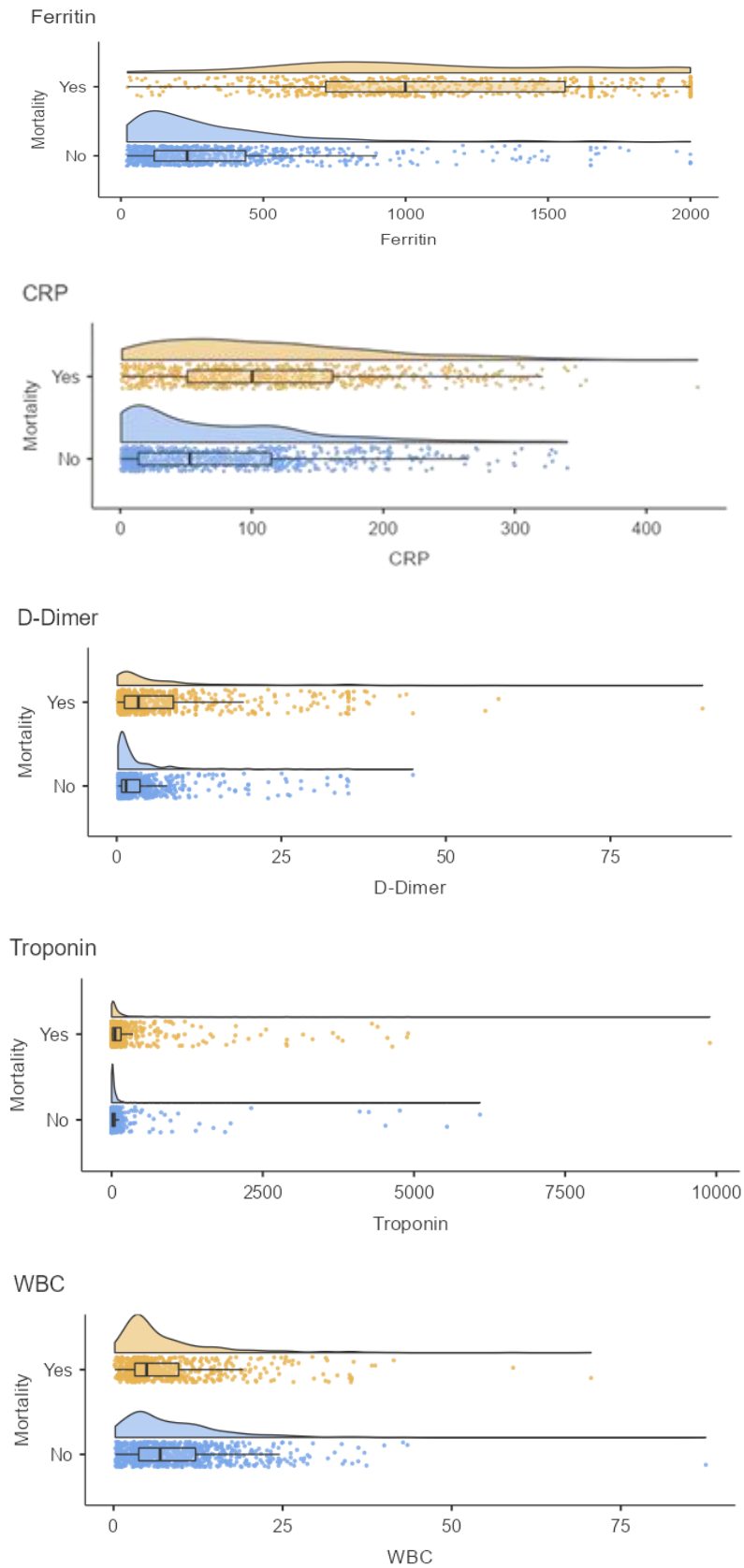


Figure 4: Mortality Distributions of Laboratory Variables

DISCUSSION

In our study, we defined the sociodemographic characteristics, laboratory findings, length of hospital stay, and mortality in critically ill patients with COVID-19. In our study, risk factors associated with death in patients with COVID-19 in intensive care were also identified.

It was previously reported that advanced age is an important determinant of mortality. Overall, the data analyzed also suggest that serious illness can be expected in the elderly (54-57). The age range in severe patients is 52 to 66 years in most of the Chinese studies (53, 58). Similarly, in the study conducted in Italy, the mortality rate increases with age; 12% in patients older than 70 years and 20% in patients older than 80 years (8). In addition, in our study the increasing age of the patients was an independent predictor of COVID-19 mortality, and a significant correlation was found with the severity of the disease. The relationship between advanced age and the mortality of COVID-19 has been found in many studies in the literature (34,59,60). This may be because older people are more vulnerable to Coronavirus and are more likely to have chronic illnesses (34, 58, 61).

Our study was comparable to the previous ones and revealed the male predominance of 69% in the previous study on 336 COVID-19 patients in Pakistan, 71% in the retrospective study on 239 cases in Italy and Lombardy, and 75% in the study conducted in Wuhan, China with 28 cases (62-64). In our study, as stated previously by Zheng et al, we found that the group with the most severe course of COVID-19 was higher in men, in terms of gender distribution (65)

Most of the patients in our study had one or more comorbidities. Hypertension, diabetes mellitus, and coronary artery disease were the most common chronic diseases in the patients. In a multicenter study conducted in China, it was observed that approximately half of the patients had comorbid diseases, the most common comorbidity was hypertension, followed by diabetes mellitus and coronary artery disease, respectively (66).

In our study, the ferritin elevation was seen in mortal COVID 19 patients; Previously, ferritin's predictive power of death was similar in Algeria with a series of 157 patients, in New York in a cohort of 330 cases, and in a retrospective review of 942 patients (62,67,68). In a study on ferritin by Pastora et al. in 2020, it has been shown that the ferritin level of COVID 19 patients is below 400 in those who do not have severe involvement, and that it can increase 1.5-5.3 times the normal limit of 400 in severe involvement (69).

Although our data on C-reactive protein is significantly higher in the mortality threshold group, it is compatible with the literature that high CRP indicates a longer hospitalization period, poor prognosis in terms of the course of the disease, the need for intensive care follow-up, and predicts mortality (70, 71). The increase in CRP reflects the magnitude of the systemic inflammatory syndrome present in severe forms of the disease. The increase in CRP reflects the severity of the systemic inflammatory syndrome present in severe forms of the disease. It is believed that, in addition to multi-organ failure, the onset of ARDS results in the release of inflammatory cytokines that create a "cytokine storm" responsible for acute tissue damage, and in the research

conducted in 2020, the high CRP was proved to be a predictor of both the need for invasive mechanical ventilators and to detect the patients who would need intensive care unit follow-up in the ward (72,73).

Although the cut-off value of the normal level differed in relation to the significantly low lymphocyte count in the COVID-19 patient group who died in our analysis, it showed similar results with studies using a cut-off point of $<1100 \mu\text{L}$ (12, 66, 74-76). Interestingly, it was seen that the relationship between lymphopenia and COVID 19 was stronger in young patients than in elderly patients. The possible hypothesis to explain the low lymphocyte count in the young was that the immune system is affected by a wider range of active lymphocyte kinetics at the young than in the elderly (20, 32).

These results are also consistent with data reported by Rodriguez et al., which revealed the presence of common biological abnormalities such as elevated inflammatory marker levels (elevated CRP and lymphopenia) in a meta-analysis (77). The frequency of lymphopenia observed by us suggests that COVID-19 may act on lymphocytes, particularly T lymphocytes, perhaps leading to the depletion of CD4 and CD8 cells. This idea has been demonstrated in severe acute respiratory syndrome (SARS) (78). Given its cost-effectiveness and easy-to-perform, such as complete blood count, lymphopenia can serve as a prognostic tool to predict the severity and poor prognosis of COVID-19 in a primary clinic. Therefore, it may be a useful biomarker to consider for risk-adjusted medical resource allocation during this pandemic period.

In retrospective cohorts, baseline d-dimer levels were increased in 33% of COVID 19 patients admitted to the hospital earlier (11, 12, 34, 53). In a pooled analysis of these 4 studies involving 553 patients, baseline D-Dimer levels were associated with COVID-19 severity. Another analysis showed that D-dimer levels could be a useful marker for predicting mortality in hospitalized COVID-19 cases (79,80). Tang et al. reported that D-dimer level was associated with 28-day mortality in a series of 449 patients with COVID-19 (81). In an analysis of 343 patients, one study reported that D-dimer level was associated with death above a D-dimer cut-off value of $>2 \mu\text{g/mL}$ (82). The mechanisms underlying the D-dimer increase in COVID-19 patients are not fully understood. In retrospective cohorts, Tang et al. found that 71.6% of non-survivors met the criteria for coagulopathies from sepsis, compared to 0.6% of survivors (45). Accordingly, there are some evidence that COVID-19 is associated with a prothrombotic condition leading to an increased risk of venous thromboembolism (83, 84). The increase in D-dimer levels can simply explain this prothrombotic state. Several case reports have shown an association between COVID-19 and thrombosis formation at the microvascular level (85, 86). In a study of 81 severe COVID-19 patients admitted to the intensive care unit in China, 25% of the 81 people who were not under prophylaxis had venous thromboembolism (87). In a more recent prospective study, the incidence of venous thromboembolism was reported as 27% in 184 patients admitted to the intensive care unit (88). Therefore, thromboprophylaxis is required in all hospitalized COVID-19 patients. An awareness call on the need for adapted thromboprophylaxis in COVID-19 patients was recently published (89). In our study, the troponin level

was found to be significantly higher in the group, that resulted in mortality in the population with COVID-19 compared to the other group. In a study similar to our result, with 55% sensitivity and 80% specificity, troponin elevation was associated with an almost five-fold increase in mortality (90). A meta-regression showed that the relationship between high troponin level and mortality rate did not change according to age, male gender, hypertension, diabetes or coronary artery disease, which showed that some of the factors we mentioned were associated with mortality rate and myocardial damage (91-95). In addition to heart damage, COVID-19 can lead to arrhythmia, myocardial ischemia and thromboembolism (96,97). Natriuretic cardiac biomarkers are elevated in COVID 19 patients, indicating a poor prognosis (98).

Limitations

Various limitations should be considered when interpreting the results of our study. A causal relationship could not be established due to the retrospective and non-randomized nature of the study. This study included patients from 14 different public hospitals in Bursa, and there were unmeasurable differences in approach to patient care between the hospitals. The effect of changes in ICU admission criteria, differences in ICU staff specialties, the threshold for initiating invasive mechanical ventilation, and initiating several additional treatments at the discretion of the treating physician could not be determined. Since the mean duration of any treatment for COVID-19 is less than 10 days, we chose the laboratory values at day-1 of admission to the ICU, day-10 of ICU stay, and the highest values during ICU stay. Given the variable frequency of laboratory sample collection, we are unable to determine whether these values accurately represent pre- and post-treatment values in all study groups. We believe that our population represents a real-world cohort and what we have found regarding current COVID-19 is generalizable.

CONCLUSION

To our knowledge, this is the largest cohort study of critically ill patients with COVID-19 admitted to the intensive care unit in Turkey. COVID-19 has high mortality rates, and patients with advanced age and comorbidities may require care in the intensive care unit. We found that ferritin, hs-troponin, d-dimer and C-reactive protein levels were significantly higher in patients who died at the time of admission. In addition, hospitalization lymphocyte was significantly lower in patients who died compared to patients who were discharged.

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Author Contributions: SM, SE, HA, CD: Study design, Literature review, Patient therapies, SE: Data collection, Analysis, Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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