Evaluation of various blood biomarkers associated with the outcomes of patients with COVID-19 treated in intensive care units

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Abstract. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) represented a global public health crisis and the most significant pandemic in modern times. Transmission characteristics, and the lack of effective antiviral treatment protocol and protective vaccines, pushed healthcare systems, particularly intensive care units (ICUs), to their limits and led to extreme quarantine measures to control the pandemic. It was evident from an early stage that patient stratification approaches needed to be developed to better predict disease progression. In the present study, the predictive value of clinical and blood biomarkers for the outcomes of patients with COVID-19 hospitalized in the ICU were investigated, taking age and sex into consideration. The present study analyzed blood samples from 3,050 patients with COVID-19 hospitalized in the ICU. The analysis revealed that the levels of procalcitonin, N-terminal pro-B-type natriuretic peptide, D-dimer, ferritin, liver enzymes, C-reactive protein and lactate dehydrogenase were increased and were associated with disease progression, resulting in a prolonged hospitalization period and severe COVID-19 related complications. Additionally, significant age and sex disparities among these biomarkers were documented and discussed in specific cases. On the whole, the results of the present study suggest a potential association of the demographic characteristics and blood biomarkers with prolonged hospitalization in the ICU and the mortality of patients with COVID-19.

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Introduction

Since the initial reports in December, 2019 for a novel type of viral pneumonia in the city of Wuhan, Hubei, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread at an unprecedented rate (1). Current epidemiological data report ~660 million infections and ~6.7 million related deaths worldwide, with a 7-day average of 500-600.000 new cases and an estimated mortality rate of ~10%. Since its outbreak in 2019, the need to develop strategies with which to attenuate the transmission dynamics of SARS-CoV-2 (flattening the curve) has been recognized (2,3). Moreover, it was evident from an early stage that there was a need to stratify patients into risk groups based on disease severity, which would assist clinicians to identify patients at a risk of developing disease-related complications, such as acute respiratory distress syndrome (ARDS) (4-6). For example, even during the first wave of the pandemic, it was evident that older individuals (>65 years of age) were at a higher risk of developing complications of the

disease, with higher mortality rates among infected older individuals than among younger adults and children (7).

To date, several blood biomarkers associated with the cascade of the inflammation processes have emerged as potential contenders for determining the progression of coronavirus disease 2019 (COVID-19). Among these, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) stands out as a crucial biomarker in ventricular heart disorders, and its elevated levels have been identified in the advanced stages of cardiovascular disease, as well as in patients with COVID-19 (7). Similarly, fibrinogen, a renowned acute phase protein, is synthesized abundantly by the liver. It plays a role in the formation of fibrin, constituting the final step in the process of coagulation. Previous research has indicated that changes in fibrinogen levels necessitate attention in patients with COVID-19 (8). Moreover, in addition to fibrinogen, D-dimer, a product of fibrin degradation, has also been assessed. Elevated D-dimer levels have been shown to be associated with pulmonary complications in patients with COVID-19 (9,10). Additionally, in relation to pneumonia or pulmonary embolism in COVID-19, there has been an observed elevation in troponin (Trop max) and ferritin levels (11). In terms of other organ systems, it is noteworthy that patients with COVID-19 display significant alterations in liver functions, as evidenced by increased levels of alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP), as well as elevated creatine kinase (CK) and lactate dehydrogenase (LDH) levels (11). These changes are indicative of cellular inflammation and oxidative stress.

As regards biomarkers related to infections and inflammation, procalcitonin (PCT) the 116 amino acid precursor of the hormone calcitonin, has been considered a biomarker for the early diagnosis of bacterial infections, including COVID-19 (12-14). Moreover, C-reactive protein (CRP), an acute-phase protein that serves as an early marker of inflammation or infection is routinely measured in the early diagnosis of COVID-19, with its levels being associated with disease severity (15). CRP has been found to have a positive association with lung lesions in tomographic scans (16,17). Previous studies have indicated an association between increased CRP values upon admission and disease severity in patients with COVID-19 (18,19). In addition to the inflammation cascade, endothelial function or dysfunction has emerged as a pathological characteristic regarding COVID-19 progression and disease severity. Endothelial cells play a crucial role in maintaining vascular integrity and participate in inflammation processes. Endotheliopathy is observed in cardiovascular diseases, diabetes, obesity and aging in patients with predisposition characteristics for severe disease and is a contributing factor to thrombo-inflammation (20). Although it remains unclear whether endotheliopathy occurs due to the viral infection of endothelial cells or is a consequence of induced inflammation, it significantly contributes to thrombo-inflammation (21,22). Thus, several interventions have been implemented to assess endothelial markers in patients with COVID-19 (23,24). Low levels of magnesium (Mg^{2+}) induce a pro-inflammatory, prothrombotic phenotype in endothelial cells (25). In COVID-19, while serum Mg^{2+} concentrations are lower in mild disease, there are indications of hypomagnesemia in critically ill patients, particularly those in intensive care units (ICUs) (26). Considering other factors, phosphate levels, which contribute to the maintenance of body homeostasis (bone, metabolism, intracellular signaling) have been previously analyzed in relation to COVID-19 (27,28). Finally, the association between the immune response and trace elements has been previously suggested, highlighting the importance of investigating any potential association between certain trace elements and disease outcomes of patients in the ICU (29).

Overall, to date, studies have examined how all this clinical information can be harnessed and organized to provide essential information for optimum healthcare provision in COVID-19 (30,31). Nevertheless, it remains important to comprehend whether there exist additional associations between demographic factors, such as age and sex, and specific clinical attributes, notably blood biomarkers, or any other factors that could provide predictive information as to the outcome of COVID-19 disease severity (32-35). Hence, the present study aimed to evaluate the predictive value of clinical blood biomarkers with regard to the outcomes of hospitalized patients with COVID-19, taking into account age and sex. Moreover, in order to expand upon prior approaches, the present study encompasses an assessment of biomarkers, including PCT, troponin max, vitamin D (Vit-D), CRP, LDH, high-density lipoprotein (HDL), NT-pro-BNP, ALT, AST, ALP and trace minerals (i.e., Mg^{2+}, phosphate, Ca^{2+}, Na^{+}, K^{+}), in order to determine potential associations, together with the influence of sex and age during the course of the hospitalization of patients with COVID-19 in the ICU.

Materials and methods

Study design and ethics approval. The present observational, single-center descriptive study was conducted over a period of 2 years (April, 2020 to April, 2022) in the ICU ward of the Erzurum Regional Training and Research Hospital in Erzurum, Turkey. The study complied with the rules of the 1975 Declaration of Helsinki, as revised in 2013, and it was approved by the Ethics Committee of Erzurum City Hospital and the Turkish Ministry of Health, General Directorate of Health Services (no. 2020-12-22T15_29_35). Written informed consent was obtained from all patients prior to data collection. All data were collected anonymously and contained non-identifiable information.

Data collection and analysis. All data are derived from patients admitted to the ICU ward of the hospital and diagnosed with COVID-19 according to the WHO COVID-19 interim guidelines (7th edition) with laboratory confirmation of SARS-CoV-2 infection through nasopharyngeal/throat swab test by reverse transcription-polymerase chain reaction (RT-PCR) (36). Epidemiological, clinical and laboratory data were extracted from the electronic medical records of the hospital. These data included demographic characteristics (age, sex), blood biomarker parameters, duration of hospitalization (time from admission till the day of discharge) and disease outcomes (survival or mortality). A total of three age groups were considered: Young adults (aged 17-40 years), middle-aged adults (aged 40-70 years) and elderly (aged >70 years). All the data were obtained from the registry system of the hospital.

Table I. Demographic characteristics of the patients with COVID-19 admitted to the ICU over the study period.

A, Age and sex of the patients as regards sex

Characteristic	Sex	
Age cohorts, years	Male (no. of patients)	Female (no. of patients)
17-40	895	905
41-70	467	556
>70	138	89
Length of stay in ICU, days		
0	240	229
1-10	453	505
11-20	363	358
21-30	255	266
>30	189	192

B, Length of stay in the ICU as per age group

Length of stay in ICU, days	Patients aged 17-40 years (no. of patients)	Patients aged 41-70 years (no. of patients)	Patients aged >70 years (no. of patients)
0	323	144	2
1-10	576	342	40
11-20	432	251	38
21-30	265	202	54
>30	204	84	93

Efforts were made to maintain consistent time intervals for data sampling to ensure the comparability of the data. However, any effects on these parameters that occurred prior to admission could not be controlled. Therefore, to certain extent, the data were collected at the same time intervals as the ICU admission and on the first day of hospitalization. Blood data biomarkers referred to PCT, Trop max, pro-BNP (max), fibrinogen, D-dimer Tmax, ferritin, total plasma protein content, albumin, Vit-D, LDH, transaminases (AST, ALT), ALP, low-density lipoprotein (LDL), HDL, CRP and trace minerals (Ca^{2+}, phosphate, Mg^{2+}, K^{+}, Na^{+}). All data were grouped as to age, sex and length of stay in the ICU and compared considering disease outcomes (survival or mortality).

Statistical analysis. Statistical analysis was conducted using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 26.0; IBM Corp). Data were analyzed using the Kruskal-Wallis test with post hoc pairwise comparisons performed using Dunn's test, and are presented as the mean ± standard deviation (SD). Comparisons were made between surviving and deceased patients. Values of $P<0.05$ or $P<0.01$ were considered to indicate statistically significant or highly statistically significant differences with 95% or 99% confidence intervals (CIs), respectively.

Results

Patient demographic characteristics. Over the period of 2 years (April, 2020 to April, 2022), 3,050 data from patients who tested positive for SARS-CoV-2 and were admitted to the Erzurum Regional Training and Research Hospital were recorded and analyzed. There were 1,550 females and 1,500 males. Of these patients, 1,450 recovered and 1,600 patients succumbed due to COVID-19 related complications. The patient demographic characteristics are presented in Table I.

The levels of blood biomarkers and disease outcomes of the patients in the present cohort were then analyzed considering age and sex.

PCT, Trop max, Pro-BNP max, fibrinogen, D-dimer and ferritin. PCT blood levels range between 0 and 0.05 μg/l under normal conditions, and exhibit a tendency to increase in cases of infection (37,38). In the present study, in patients with COVID-19, the PCT levels were 9-fold higher ($P<0.001$, 95% CI) in the deceased compared to the surviving patients (Fig. 1A). The average upper limit of Pro-BNP max was determined at 300 pg/ml in patients <70 years of age and 600 pg/ml in patients >70 years of age. The normal Trop max level is <0.06 ng/ml; however, patients with COVID-19 and deceased patients have been found to have higher values (mean Trop max, 2.5 ng/ml). Herein, the Trop max values exhibited an 11-fold increase ($P<0.001$, 95% CI) and Pro-BNP levels exhibited a 10-fold increase ($P<0.001$, 95% CI) in the deceased patients vs. the surviving patients (Fig. 1A and B). The D-dimer level, which normally ranges between 200-500 ng/ml, increased up to 12,000 ng/ml in the deceased patients, and exhibited a 4-fold increase overall ($P<0.001$, 95% CI) (Fig. 1B). As regards the

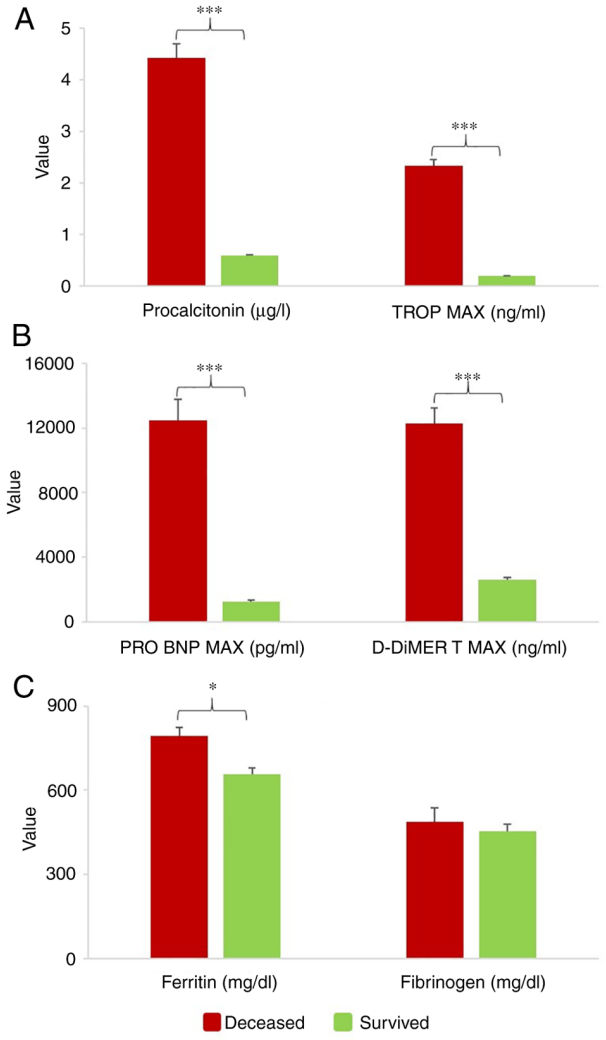

Figure 1. Blood biomarkers associated with inflammation, coagulation, heart failure and differences were recorded among deceased and surviving patients with COVID-19. (A) Procalcitonin and Trop max, (B) Pro-BNP max and D-dimer, (C) ferritin and fibrinogen values. pro-BNP, pro-B-type natriuretic peptide. *P<0.05 and ***P<0.001.

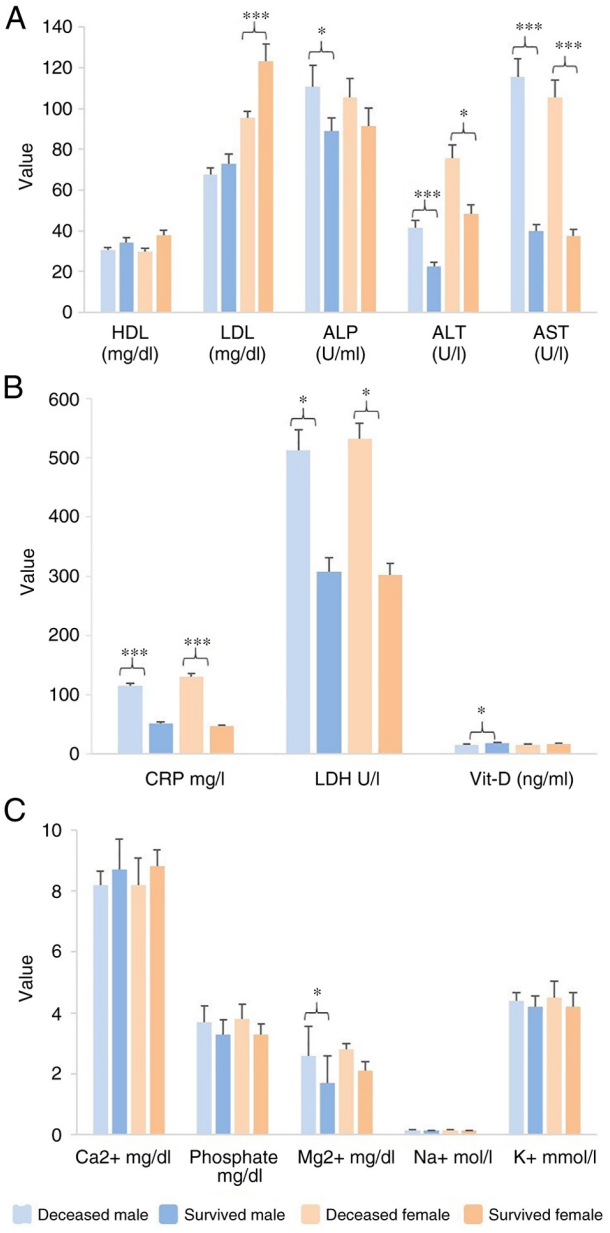

Figure 2. Sex differences as to blood biomarker levels in the deceased and surviving patients in the present study. (A) Lipoprotein and liver enzymes. (B) CRP, LDH and Vit-D. (C) Ca^{2+}, Mg^{2+}, Na^{+} and K^{+} trace elements as to sex. *P<0.05 and ***P<0.001 (95% CI). HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; Vit-D, vitamin D.

ferritin levels, the reference value is 4.63-204 mg/dl in healthy individuals, and herein, it was found to be doubled (P<0.05, 95% CI), being higher in the deceased vs. the surviving patients. Finally, the fibrinogen data were above the reference value range (200-400 mg/dl), and were higher in the deceased patients vs. the surviving patients, although with no statistically significant difference (Fig. 1C).

HDL and LDL. Both the HDL (reference value, 40-60 mg/dl) and LDL (reference value, 60-130 mg/dl) levels were estimated to be ~1.5 lower in the deceased patients compared to the surviving ones (Figs. 2A, 3A and 4A). However, no statistically significant association was found between the HDL levels and age or sex (Figs. 2A and 3A). The decline in HDL levels was inversely linked with the length of stay in the ICU for the deceased patients, and differences were observed for patients with a prolonged (>30 days) ICU stay (Fig. 4A). As regards the LDL levels, a statistically significant difference between the deceased and surviving group (P<0.05, 95% CI) was observed in female patients (Fig. 2A) of all age groups (Fig. 3A).

Liver enzymes. Data analysis revealed sex and age differences in liver enzymes for the deceased and surviving patients in the ICU. Male patients had higher values of AST (reference value, 0-41 U/l), while female patients had elevated ALT values (reference value, 0-35 U/l). Higher levels of ALP, ALT and AST in male patients were associated with a poor prognosis, and similar trends were observed in female patients, particularly for the ALT and AST values in the deceased patients (Fig. 2A). In terms of age, higher levels of ALP, ALT and AST were associated with disease severity and a poor prognosis in young adults (17-40 years of age) and middle-aged adults (40-70 years of age) (Fig. 3A). The highest ALP values were found in cases where patients succumbed due to acute disease complications

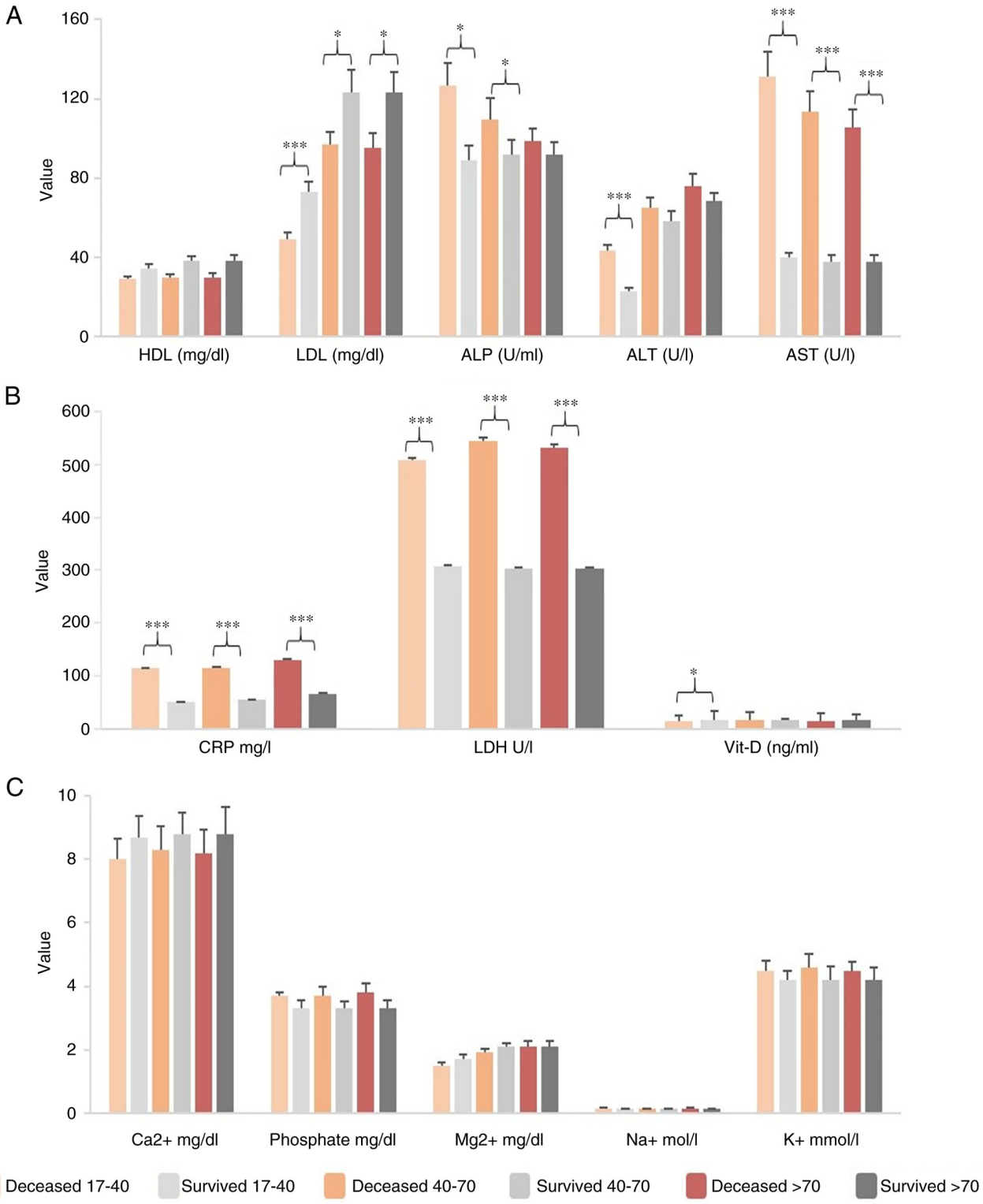

Figure 3. Age differences as regards blood biomarkers in the deceased and surviving patients in the present study. (A) Lipoprotein and liver enzymes. (B) CRP, LDH and Vit-Din. (C) Ca^{2+}, Mg^{2+}, Na^{+} and K^{+} trace elements in the different age groups. *P<0.05 and ***P<0.001 (95% CI). HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; Vit-D, vitamin D.

without ICU hospitalization (Fig. 4A, ALP 0 days). For these cases, the deceased patients regardless of age and se exhibited also a statistically significant increase in AST values (5-fold difference, P<0.001, 95% CI) compared to the surviving ones (Figs. 2A and 3A). Regardless of ICU stay, the deceased patients had significantly higher AST values (~5-fold) and there was a trend for increased ALT levels in patients with extended ICU stays and disease complications (Fig. 4A).

CRP. Statistically significant differences for CRP (reference value, <0.5 mg/l) were observed regardless of sex, age and ICU stay, with increased levels related to disease severity and a

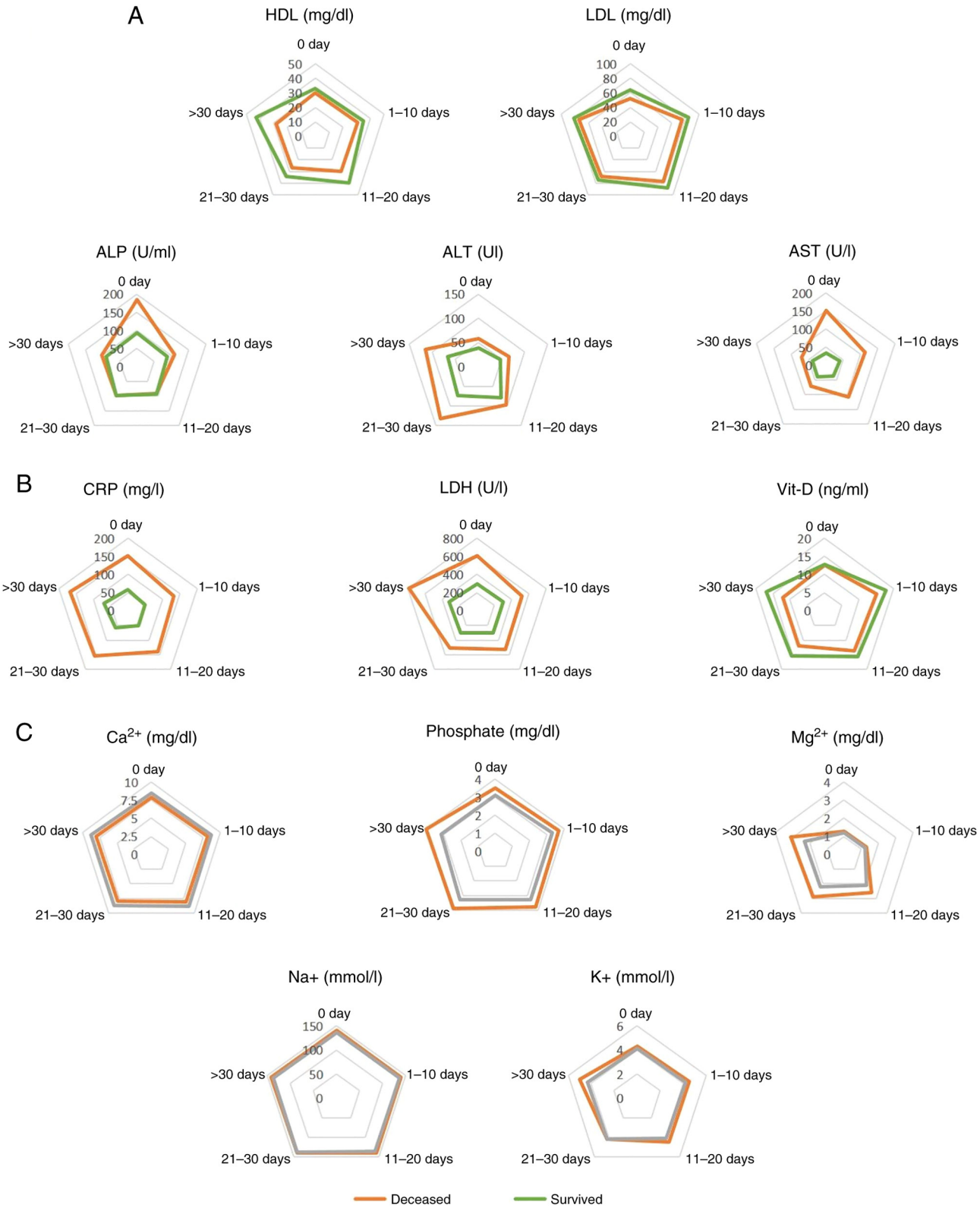

Figure 4. Blood biomarkers in association with the length of stay in the ICU in the deceased and surviving patients. (A) Lipoprotein and liver enzymes. (B) CRP, LDH and Vit-D, and (C) Ca^{2+}, Mg^{2+}, Na^{+} and K^{+} trace elements as to different hospitalization times in the ICU ward. ICU, intensive care unit.

poor prognosis. The CRP values were higher in deceased males compared to surviving males, and were found to be doubled in elderly patients (>70 years of age). They were also found to be associated with a prolonged ICU stay and a poor prognosis, since the values were almost 2-fold higher (P<0.001, 95% CI) between the deceased and surviving patients (Figs. 2B, 3B and 4B).

LDH. There was a statistically significant difference (P<0.05, 95% CI) with a 300% increase in LDH levels between the

deceased and surviving patients (Fig. 2B). There was a significant increase in LDH levels (reference value, 90-240 U/l), particularly in patients >70 years of age and with prolonged hospitalization (>30 days) (Figs. 3B and 4B).

Vit-D. All groups, regardless of sex, age, or ICU stay, had Vit-D levels below the normal reference value (20-50 ng/ml). Younger adults with a Vit-D deficiency had worse outcomes than those without one (Fig. 3B). It was observed that the COVID-19 mortality rate of individuals hospitalized in ICU, especially at a younger age (17-40 years), was inversely proportional to the decrease in Vit-D levels. Additionally, it was found that the Vit-D levels did not differ in males compared to females. In addition, Vit-D levels in patients who completed ICU treatment and were discharged (16.9±0.12 ng/ml in females and 17.5±0.43 ng/ml in males) did not exhibit a significant difference (P>0.05) (Fig. 2B).

Trace elements. The calcium (Ca^{2+}) levels (reference value, 8.8-10.6 mg/dl) were similar in all patients, regardless of the disease outcome, sex, age and ICU stay (Figs. 2C, 3C and 4C). However, the phosphate levels were increased in patients with a prolonged hospitalization in the ICU. In addition, the deceased patients had higher levels of phosphate compared to the survivors (~0.71-fold increase, P<0.05, 95% CI). Hypermagnesemia was frequently observed and could be associated with disease severity and mortality. Hypermagnesemia was more pronounced in males than females, with Mg^{2+} levels being ~2-fold higher in the deceased compared with the surviving male patients (P<0.05, 95% CI). By contrast, the increase in Mg^{2+} levels in females was not statistically significant. Moreover, increased Mg^{2+} levels were observed in cases with a prolonged hospitalization (Figs. 2C, 3C and 4C). As regards potassium (K^+; reference value, 3.5-5.2 mmol/l) and sodium (Na^+) levels (reference value, 135-146 mmol/l), a prolonged hospitalization resulted in increased levels of K^+, although they were within the normal expected values. Similarly, no significant differences were observed in Na^+ levels.

Discussion

Severe COVID-19 can cause various respiratory manifestations ranging from a persistent dry cough and dyspnea to more severe complications, such as pneumonia with a high fever, dyspnea, ARDS and pulmonary infiltrates (4,39). In addition, depending on the comorbidities, it may be associated with organ failure and hemodynamic distress. Therefore, patient stratification is required to analyze potential confounding factors that play a role in inflammation, hemodynamic stress, coagulopathy, pulmonary embolism, kidney or liver dysfunction and heart failure. This will assist clinicians to identify patients who are at risk of being admitted to the ICU and those who may develop severe disease. Previous studies have reported organ dysfunction (11.0%) (40) and coagulopathy (14.6%) (24), which have resulted in high mortality rates (4.3%). Although these studies cover different number of patients and consider factors such as region, age and length of hospital stay, the essential findings are consistent (12,13,17,41). The present study compared the blood parameters of deceased patients with COVID-19 (n=1,600) with those (n=1.450) who were discharged from the ICU. The aim of the present study was to identify statistically significant differences in biomarkers that are commonly used to assess organ dysfunction, coagulation disorders, pulmonary embolism risk, inflammation and general blood biomarkers, and trace elements. Additionally, the present study investigated whether age and sex differences should be considered with certain biomarkers.

The role of PCT in COVID-19 pathogenesis has been proposed, and previous studies have reported that high PCT levels are associated with the severity of COVID-19 (12-14). A recent meta-analysis reported a 5-fold increase in PCT values (42). In the present study, a 9-fold increase was estimated in deceased individuals compared to the survivors, suggesting that elevated PCT levels may be associated with severe disease progression. Pro-BNP levels, which help to assess the risk for heart failure risk and pulmonary embolism, are often elevated in COVID-19 and have been strongly and independently associated with mortality (41). Comparable results were observed in the present study, with a 10-fold increase observed in deceased patients with COVID-19. This increase was consistent regardless of age and sex differences. Fibrinogen, an acute phase protein synthesized in excessive amounts by the liver is involved in fibrin formation, the final step of coagulation process. Previous research has suggested that changes in fibrinogen levels need to be addressed in COVID-19 patients (8). Although changes in fibrinogen levels are considered clinically relevant to disease severity, herein, no statistically significant differences were observed regarding disease outcomes in ICU patients and fibrinogen levels, even when age and sex differences were taken into account. This suggests that fibrinogen may potentially serve as a biomarker for COVID-19 at an early stage prior to ICU admission. Another coagulation factor, D-dimer, which is formed due to fibrin degradation, is known to increase thrombotic events and indicates fibrinolysis. Elevated D-dimer values have previously been associated with a poor prognosis and high mortality rates in COVID-19 (43). These increased values may be attributed to the activation of the coagulation cascade secondary to the systemic inflammatory response syndrome in patients with COVID-19 (44). In the present study, D-dimer levels were found to be ~4-fold higher in deceased patients compared to those who recovered. Another inflammatory biomarker associated with COVID-19 is ferritin (45). Changes in ferritin levels were examined, and an increase was observed, suggesting a potential association between elevated ferritin levels with disease progression and overall survival. Similarly, statistically significant differences in Trop max values were found between the deceased and surviving cohorts. Trop max has been proposed as a potential biomarker for disease progression and worse prognosis in patients with COVID-19 (46).

In addition to specific biomarkers related to infection, inflammation, embolism and coagulopathy, the present study also examined whether differences could be observed in general blood biomarkers when accounting for age and sex differences. For example, previous reports suggest a possible link between Vit-D levels and the prognosis of patients with COVID-19. Vit-D levels tend to be decreased in patients admitted to the ICU, particularly in those who do not survive. The mechanism behind the association between Vit-D and viral infection is not yet fully understood; thus, the role of

Vit-D deficiency in disease prognosis warrants further investigation and monitoring. This effect is considered to be due to the immunomodulatory effect of Vit-D. However, the results obtained thus far have been inconclusive, with other studies not showing any positive impact on death rate, intubation or length of stay with high Vit-D supplementation in the ICU (47). In the present study, Vit-D deficiency was also related to a poor outcomes of patients with COVID-19, although the results varied considering age and sex (48).

In contrast to Vit-D, the LDH and CRP levels exhibited a clear association. LDH levels are elevated in acute hypoxia thus, these levels are expected to be elevated in patients with COVID-19 (49,50). LDH levels also increase with advancing age and the length of stay in the ICU due to the body's tolerance to oxidative stress. This is further exacerbated by multiple organ damage, particularly to the liver and lungs (51). In the present study, the LDH levels were found to be related to disease progression, with a 300% higher value recorded in the deceased compared to the surviving patients, particularly in elderly patients with a prolonged hospitalization period. The rise in LDH levels is also associated an increase in liver enzyme levels and is associated with an increase in CRP levels (51). CRP levels have been reported to be higher in patients with COVID-19 with a poor prognosis (52). Previous research has demonstrated that CRP levels in patients who have succumbed due toCOVID-19 are 10-fold higher than in those who survived (53). The present study observed that the serum CRP levels increased from 60 mg/l in surviving patients to 120 mg/l in the deceased patients, particularly in those >70 years of age. In addition to its association with LDH levels, CRP has also been reported to function in conjunction with increased cytokine levels (IL-1 and IL-6) (51).

In addition to the inflammatory biomarkers, the present study also analyzed enzyme activities in patients with COVID-19. The liver is a potential target for SARS-CoV-2, given the higher expression of ACE2 receptors which the virus exploits. Previous research has indicated that increased ALT and/or AST levels and the AST/ALT ratio >1 are associated with disease progression and an increased mortality rate in hospitalized patients with COVID-19 (54). Similar findings were observed in the present study, with increased AST values associated with male patients and increased ALT values with female patients, while no differences based on age were not recorded.

Furthermore, the analysis of trace elements was conducted to identify potential relevance for patients with COVID-19. Ca^{2+} is responsible for a number of physiological functions, such as blood coagulation, the regulation of muscle contractions, the secretion of hormones and enzymes, and the regulation of the immune system (54,55). Previous studies have reported a significant prevalence of hypocalcemia in patients with COVID-19, with lower levels being associated with Vit-D deficiency (55-57). The results of the present study also demonstrated an association, particularly in cases of disease progression resulting in mortality and extended hospital stays, which may be attributed to the role of the liver in Vit-D metabolism. Phosphate is essential for energy metabolism and abnormal serum phosphate levels have been previously reported in patients hospitalized in ICUs due to COVID-19 (27,28). Although the increase in phosphate levels has not yet been fully explained, the Ca/P ratio holds physiological significance. However, phosphate metabolism is impaired in COVID-19, along with the rise in Ca^{2+}.

This increase in association with the mortality rate may be due to multiple organ damage caused by factors such as hypoxia, viral infection energy need and blood rate (58). Abnormal electrolyte levels, particularly hypermagnesemia, are often associated with decreased renal function, since the kidneys maintain calcium-magnesium-phosphate homeostasis (59,60). Mg^{2+} has been shown to exert anti-inflammatory effects independently and by activating Vit-D (61). Given that the level of Mg^{2+} was higher in the present study in deceased patients with COVID-19, a poor prognosis associated with hypermagnesemia may be considered (62). Although there was a slight increase in Na^{+} and K^{+} levels, the results were not statistically significant.

No significant differences were found between the cohorts regarding the total protein content and serum albumin. A low albumin level usually reflects liver and kidney dysfunction (63). In patients with COVID-19, albumin is an independent risk factor associated with no improvement during follow-up. Furthermore, the activity of the virus is higher in elderly individuals and those with immune system disorders, which supports the theory of low albumin.

The present study has certain limitations which should be mentioned. The findings are specific to a single peripheral hospital in Turkey and may not be extrapolated to other regions or populations due to possible deviations in patient characteristics, healthcare practices, environmental characteristics and other local features (64). Moreover, it is necessary to consider other factors, such as exposure to environmental pollutants and other xenobiotics, which could affect immune response or contribute to the pathogenesis of SARS-CoV-2 and its immunopathology (65-68). Therefore, these factors need to be considered when interpreting the study findings and conducting further research in different settings. As an observational study, there is also a possibility of unmeasured confounders that could affect the outcomes and limit the comprehensive understanding of patient outcomes in critical care settings. Chronic conditions such as diabetes, heart failure, chronic obstructive pulmonary disease (COPD), etc., may influence some of the estimated values in this study prior to the onset of any COVID-19-related conditions. Additionally, COVID-19 may further affect values related to these diseases. Addressing this properly would necessitate creating an extensive dataset and conducting analyses for each of these diseases and multimorbidity conditions (e.g., heart disease, heart disease and diabetes, heart disease and COPD, diabetes and COPD, etc.) and comparing them with COVID-19 cases to extract the specific impact of COVID-19. Furthermore, for thorough evaluation and to further mitigate the impact of underlying diseases, several other indicators such as IL-6, renal function, and white blood cell counts could be employed. However, this would require a different study design that falls outside the scope of the present study. Initially, the present study obtained data on 5,500 patients; however, after excluding chronic and serious diseases (e.g., bacterial infections), the study cohort was narrowed down to 3,050 patients. Future research should take into consideration the aforementioned confounders and indicators, as well as differences in treatment protocols during

various pandemic waves, variations among SARS-CoV-2 variants, disparities in the quality of care across different healthcare systems worldwide, and outcomes in ICU patients both with and without COVID-19.

In conclusion, although pandemic waves appear to be receding and the post-pandemic era, it is essential to gain a comprehensive understanding of the clinical outcomes that have transpired. COVID-19 has undeniably demonstrated the urgent necessity to formulate effective strategies that can promptly stratify patients into risk groups, thereby equipping clinicians in ICU wards with important predictive information regarding the potential progression of COVID-19. The analysis of clinical data from the current observational study revealed that PCT, Trop max, ferritin, D-dimer, CRP and LDH levels are often increased in patients with disease progression, resulting in prolonged hospitalization and fatal COVID-19 related complications. In addition, certain discrepancies related to age and sex have also been documented in specific cases. These parameters could be further monitored in the context of patient monitoring and prediction of disease progression in ICUs toward risk analysis. Future studies may uncover whether interventions aimed at regulating the levels of these markers can significantly affect treatment outcomes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ATa, DAS and ATs conceptualized and designed the study. SG, MEN, OG, CC and AA engaged in the acquisition, analysis and interpretation of the data. MS, TKN, AOD, AID, RM and EH contributed to the interpretation of the data, along with manuscript drafting and finalization. EH and DAS were involved in the interpretation of the data and on critical revisions on the intellectual content. ATa and ATs confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study complied with the guidelines of the 1975 Declaration of Helsinki, as revised in 2013, and was approved by the Erzurum City hospital's Ethics Committee (Erzurum Regional Training and Research Hospital) and the Turkish Ministry of Health, General Directorate of Health Services (approval no. 2020-12-22T15_29_35). Written informed consent was obtained for data analysis and publication. All data were collected anonymously, contained non-identifiable information, and analyzed accordingly. No individual data is presented.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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