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Base excess, bicarbonate, and lactate levels predict 28-day mortality in patients with COVID-19: a retrospective study

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ABSTRACT

Aim: It is critical to categorize the risk factors that could disclose the severity of COVID-19. This study aimed to determine the effects of arterial blood gases on hospital mortality by examining the results retrospectively measured at the first admission to the emergency department of cases diagnosed with COVID-19.

Material and Method: In this retrospective study, arterial blood gases of patients with COVID-19 were analyzed using univariate analysis to identify factors linked to 28-day all-cause in-hospital mortality. The patients were divided into two groups survivors and nonsurvivors.

Results: The study included 159 survivors and 33 nonsurvivors with COVID-19. Serum levels of lactate, D-dimer, troponin, and CRP were higher and serum levels of base excess, bicarbonate, and albumin to creatinine ratio were lower in nonsurvivor patients than in survivors. The highest AUC was found for lactate and base excess.

Conclusion: The arterial blood gases performed during the first admission to the emergency department are linked with disease severity and can be used to predict disease progression and mortality. Furthermore, patients with higher levels of lactate and lower levels of base excess and bicarbonate should be monitored closely and treated early.

Keywords: COVID-19, base excess, bicarbonate, lactate, mortality

INTRODUCTION

Coronavirus disease (COVID-19) is a viral infection that presents with severe pneumonia and spreads rapidly to many countries as a pandemic (1). The viral agent of the disease was identified as a new coronavirus (2019-nCoV, SARS-CoV-2) (2). COVID-19 has infected over 250 million individuals and killed over 5 million of them (3). The symptoms of COVID-19 are fever, cough, dyspnea, myalgia, sore throat, and dyspnea (4). The clinical course of COVID-19 may differ between individuals. Especially in patients with comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, deaths due to acute respiratory distress syndrome, septic shock, metabolic acidosis, disseminated intravascular coagulopathy and multiple organ failure may occur (5). One of the most delicate challenges in hospitals with a large number of patient admissions is evaluating critical patients. It is crucial to determine which people are at high risk of dying. It is critical to categorize the risk factors that could disclose the severity of COVID-19.

Although the gold-standard test in the diagnosis of the disease is polymerase chain reaction tests (PCR) performed with real-time reverse transcriptases, changes occur in biochemical tests such as urea, creatinine, CRP, ferritin, D-dimer, troponin, lymphocyte and neutrophil levels due to the inflammatory process caused by the virus (6,7). The biochemical tests used routinely provide clinicians with important data about COVID-19. Many studies have been conducted to date on the effect of biochemical parameters on mortality in COVID-19 patients, and some risk factors have been found, such as comorbid diseases, D-dimer, and troponin (8-12). However, the number of publications evaluating the effect of arterial blood gases such as lactate, base excess, and bicarbonate on mortality is very few and the clinical consequences of these results during the first admission remain unclear. We aimed to determine the effects of arterial blood gases and biochemical tests on hospital mortality by examining the results retrospectively measured at the first admission to the emergency department (ED) of cases diagnosed with COVID-19.

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MATERIAL AND METHOD

This study was reviewed and approved by the Human Research Ethical Board of Muğla Sıtkı Koçman University (Date: 24/03/2021, Decision No: 44). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Design

This retrospective, observational study was designed to investigate the relationship between biochemical parameters and 28-day all-cause in-hospital mortality in adult patients with COVID-19 who were referred to the ED of Muğla Training and Research Hospital and hospitalized between March 2020 and February 2021. Diagnoses of COVID-19 were made in accordance with WHO guidelines (13) and confirmed by real-time reverse transcriptase-PCR (RT-PCR) assay. Patients were excluded from the study if they had a diagnosis of pregnancy, anemia, cancer, hematologic or rheumatologic diseases, readmissions, or were aged <18 years. Demographic information, radiological reports, comorbidities, and laboratory results were obtained from the hospital information system and then correlated with clinical outcomes.

Patient Evaluation

After being admitted to the ED, these patients were assessed by an emergency medicine physician as a standard procedure in our hospital. Routine biochemical tests, RT-PCR test, arterial blood gases, and chest computed tomography (CT) of the patients were requested. Patients who underwent a consultant's evaluation were admitted based on the results of laboratory tests and CT scans. Patients were admitted to clinics or the intensive care unit (ICU) depending on the severity of COVID-19.

The radiological diagnosis of COVID-19 was recorded using the "CO-RADS classification," a reporting system for COVID-19, which ranged from 1 (very unlikely) to 5 (very likely) (14). CO-RADS scores of 1–2 were defined as incompatible with COVID-19, a score of 3 was suspicious for COVID-19, and scores of 4–5 were compatible with COVID-19.

Statistical analysis

The Statistical Package for Social Sciences was used to analyze the data (Version 22.0, SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to determine the normality of the quantitative data distribution. Nonparametric tests (such as the Mann–Whitney U–test and the Kruskal–Wallis test) were used on nonnormally distributed data, whereas parametric tests (such as the independent samples t-test and Tukey's post hoc test) were used on normally distributed data. Summary statistics were expressed as the mean, standard deviation, or median (minimum-maximum). Statistical significance was determined for those differences with a p-value of 0.05 or below. Receiver operating characteristic (ROC) curve analysis was used to assess diagnostic accuracy. The area under the ROC curve (AUC) was used to determine the accuracy of these tests. Higher AUC values indicate better test performance. A parameter with an AUC value equal to 1 discriminates individuals perfectly as survivors or nonsurvivors. The Kaplan–Meier test was used to compute the cumulative survival rate, and the log-rank test was used to examine differences in survival across the groups. The data were first analyzed using univariate analysis to identify factors linked to in-hospital mortality. Next, significant factors were employed in a stepwise forward logistic regression analysis. Additionally, sensitivity and specificity analyses for mortality were carried out.

RESULTS

After collecting the medical data, 192 consecutive patients presenting to the ED were selected for further study from a total of 291 records. The exclusions of patients were shown in the flowchart (**Figure 1**). The patients with COVID-19 were divided into two groups who were discharged from the hospital (survivors, n=159) and died in the hospital in 28-day (nonsurvivors, n=33). Nonsurvivors had a median survival time of 8 days (range, 1-28 days). Post hoc power calculations were applied, and the sample size was seen to provide 0.999 power and 1.007 effect size for lactate levels at an α error probability level of 0.05. The mean age of survivors was 55.4±17.5 (range 19-92 years), while the mean age of nonsurvivors was 70.2±13.9 (range 34-99 years). There were age and gender differences between the groups. Nonsurvivors were predominantly male (64%; p <0.001) and older than the survivors (70.2 vs 55.4 years, p <0.001). The baseline characteristics of the patients are shown in **Table 1**.

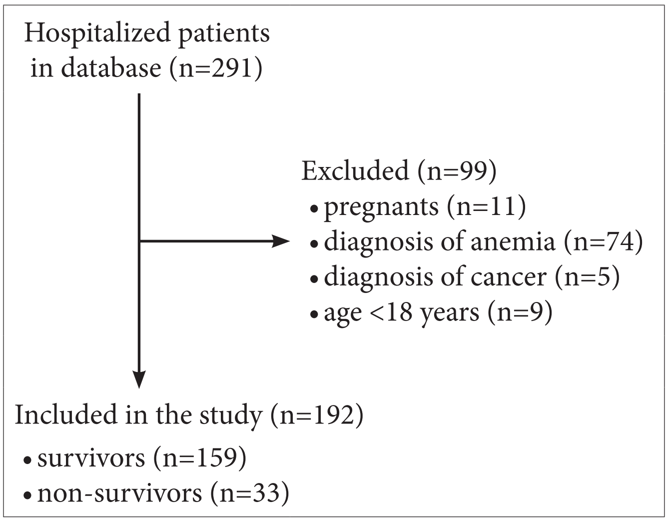

Figure 1. Flowchart of the study

Table 1. Baseline characteristics of the groups according to in-hospital mortality

Variables	Survivors (n=159)	Non-survivors (n=33)	p value
Age (years)	55.4±17.5	70.3±13.9	<0.001
Gender (Women/Men)	78/81	12/21	<0.001
Comorbid disease	52 (32.7%)	30 (90.9%)	<0.001
Hypertension	26 (16.3%)	20 (60.6%)	<0.001
Diabetes mellitus	24 (15.9%)	12 (36.3%)	0.007
Coronary artery disease	15 (9.4%)	7 (21.2%)	0.071
Chronic obstructive pulmonary disease	12 (7.5%)	10 (30.3%)	0.001
Chronic renal failure	2 (1.25%)	7 (21.2%)	<0.001
CT findings			
Incompatible with COVID-19	41 (25.7%)	1 (3.0%)	<0.001
Suspicious for COVID-19	9 (6.8%)	0 (0.0%)	<0.001
Compatible with COVID-19	109 (68.5%)	32 (96.9%)	<0.001
Hospitalization			
Ward	134 (84.3%)	1 (3%)	<0.001
Intensive care unit	25 (15.7%)	32 (97%)	<0.001
Biochemical parameters			
White blood cell (×103/μL)	5.82 (2.36, 25.27)	10.15 (2.44, 23.36)	<0.001
Lymphocyte (×103/μL)	1.34 (0.22, 3.53)	0.61 (0.12, 2.80)	<0.001
Neutrophil (×103/μL)	3.59 (1.00, 21.95)	8.37 (1.91, 20.15)	<0.001
CRP (mg/L)	50.43 (0.60, 361.47)	108.27 (1.57, 364.61)	<0.001
D-Dimer (ng/mL)	880.77 (42, 8651)	2643.54 (142, 8405)	<0.001
Troponin (pg/mL)	9.67 (3, 120)	52.82 (3, 401)	<0.001
Albumin (g/L)	40.74±5.05	31.83±7.58	<0.001
Creatinine (mg/dL)	0.96 (0.48, 5.91)	1.92 (0.36, 7.65)	<0.001
Alb/Cr	43.80±13.93	29.76±16.84	<0.001
Blood gas parameters (arterial)			
pH	7.41±0.07	7.39±0.11	0.616
Base excess (mmol/L)	1.74 (-24.9, 10.6)	-4.32 (-17.3, 4.7)	0.007
Bicarbonate (mmol/L)	27.3±3.8	24.1±6.7	0.003
Lactate (mmol/L)	1.2 (0.4, 15.0)	1.6 (0.5, 12.3)	0.012

Summary statistics are given as the mean ± standart deviation, median (interquartile ranges), and count (percentages). CRP: C reactive protein, Alb/Cr: albumin to creatinine ratio.

A total of 82 (42.7%) patients had comorbidities. The most prevalent comorbidities were hypertension (24.0%) and diabetes mellitus (18.8%). In addition, a history of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure was associated with high mortality (p<0.001, p=0.007, p=0.001, and p<0.001, respectively). However, there was no statistically significant difference in the history of coronary artery disease. CT findings that were compatible with COVID-19 were observed in 141 (73.4%) patients. Fifty-seven patients (29.7%) were hospitalized in the ICU and 135 (70.3%) patients were followed in clinics. Thirty-three patients (17.2%) died in the hospital during 28 days.

The levels of base excess and bicarbonate during the first admission to ED were significantly lower and lactate levels were higher in nonsurvivors compared with survivors (p=0.007, p=0.003, p=0.012, respectively). In terms of the laboratory results, there were statistically significant differences in CRP, D-dimer, troponin, and albumin to creatinine ratio between the groups (**Table 1**, all p-values <0.001).

The areas under the ROC curves (AUCs) were 0.892, 0.842, 0.793, 0.749, 0.741, 0.725, and 0.723 for lactate, base excess, bicarbonate, troponin, D-dimer, albumin to creatinine ratio, and CRP, respectively, for in-hospital mortality (**Figure 2**). The sensitivity, specificity, and accuracy rates for in-hospital mortality based on lactate of 2.0 mmol/L were 84.8%, 81.1%, and 81.7%, respectively (95% CI, AUC: 0.892, p <0.001). The sensitivity, specificity, and accuracy rates for in-hospital mortality based on a base excess of 0.1 mmol/L were 78.7%, 84.2%, and 83.3%, respectively (95% CI, AUC: 0.842, p <0.001). The sensitivity, specificity, and accuracy rates for in-hospital mortality based on bicarbonate of 20.0 mmol/L were 75.7%, 94.9%, and 91.6%, respectively (95% CI, AUC: 0.793, p <0.001).

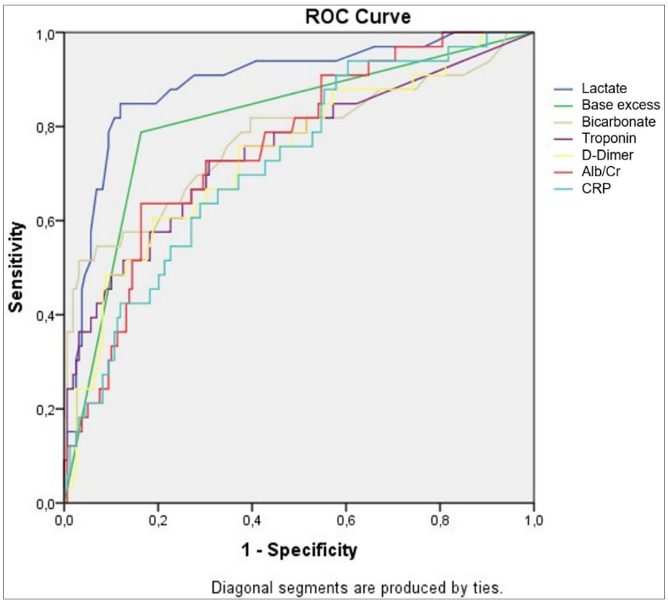

Figure 2. ROC curve for lactate (0.892), base excess (0.842), bicarbonate (0.793), troponin (0.749), D-dimer (0.741), albumin to creatinine ratio (0.725), and CRP (0.723)

A total of 33 patients died in hospital. Twenty-eight of these patients had a lactate level ≥ 2.0 mmol/L, 26 patients had a base excess ≤ 0.1 mmol/L and 25 patients had a bicarbonate ≤ 20.0 mmol/L (Fisher's exact test, all p values <0.001). **Figure 3a**, **Figure 3b**, and **Figure 3c** show the Kaplan–Meier survival curves for lactate, base excess, and bicarbonate according to these cutoff values. Patients with lactate levels above the cutoff value had significantly higher in-hospital mortality rates than those with levels below the cutoff value according to Kaplan–Meier curves (log-rank test=2.663; p <0.001).

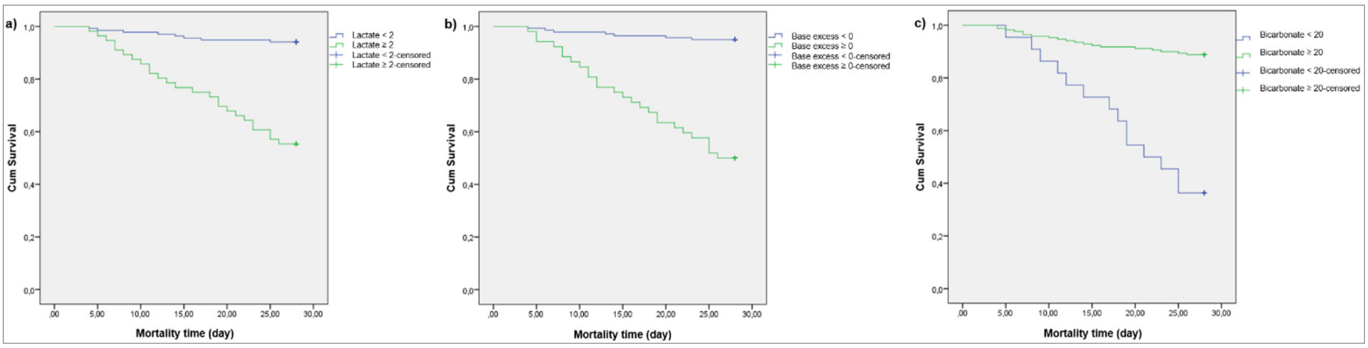

Figure 3. Kaplan–Meier survival curve with (a) lactate ≥ 2 mmol/L, (b) base excess ≤ 0.1 mmol/L, and (c) bicarbonate ≤ 20 mmol/L

Base excess, comorbid disease, lactate, bicarbonate, hypertension, D-dimer, troponin, CRP, Alb/Cr, and age were independent predictors of in-hospital mortality with odds ratios of 12.894, 11.705, 9.368, 7.394, 6.218, 5.213, 4.234, 3.283, 1.149, and 1.048, respectively (Cox regression test, all p values <0.001; **Table 2**).

Table 2. Cox regression analysis for the prediction of in-hospital mortality

Variables	Odds ratio	95% CI	p value
Base excess	12.894	5.584-29.773	<0.001
Comorbid disease	11.705	4.112-33.322	<0.001
Lactate	9.368	4.219-20.802	<0.001
Bicarbonate	7.394	3.917-18.741	<0.001
Hypertension	6.218	3.087-12.524	<0.001
D-Dimer	5.213	2.590-10.493	<0.001
Troponin	4.234	2.105-8.516	<0.001
CRP	3.283	1.562-6.901	0.002
Alb/Cr	1.149	1.083-1.219	<0.001
Age	1.048	1.025-1.071	<0.001

CRP: C reactive protein, Alb/Cr: albumin to creatinine ratio

DISCUSSION

In this study, arterial blood gases and biochemical tests were evaluated as mortality risk factors in patients with COVID-19 during the first admission to the ED. The most significant finding of the study was that base excess, lactate, bicarbonate, hypertension, D-dimer, troponin, CRP, Alb/Cr, and age were independent mortality predictors in patients.

With respect to demographic factors such as age and sex, Dong et al. (15) divided patients with COVID-19 into two groups, severe and mild, and found that severe cases were significantly older with a greater proportion of males. In our study, nonsurvivor patients were prevalently male and older than survivor patients which were consistent with findings in the literature that older men are more susceptible.

Comorbidities in patients with COVID-19 are another significant mortality predictor as described in previous meta-analysis studies (16,17). In a study by Guan et al. (18), the presence of any coexisting illness was more common among patients with severe disease than among those with the nonsevere disease. In our study, 82 (42.7%) of the patients had comorbidities, with hypertension (24.0%) being the most common. We observed that comorbidities were independent predictors of mortality similar to previous studies (OR: 11.705, p<0.001).

Arterial blood gases are reliable tests to evaluate mortality in COVID-19, as described in previous studies (19-22). In a study by Bruno et al. (19), a decreasing lactate concentration over time was inversely associated with ICU mortality. Another study by Dheir et al. (20) showed higher levels of pH and lactate in patients who died. Kieninger et al. (21) identified blood pH value, mean arterial pressure, base excess, troponin, and procalcitonin as highly significant prognostic factors of in-hospital mortality. However, no significant difference was found for other parameters expected to be relevant prognostic factors, such as high lactate levels. This conflicting result of lactate may be attributed to the low sample size of the study. Kunt et al. (22) studied a very large range of parameters in nonsurvivor patients. They found higher levels of lactate, D-dimer, fibrinogen, CRP, and troponin and lower levels of partial pressure of carbon dioxide, base excess, and bicarbonate in patients who died in the hospital. In our study, higher serum levels of lactate, D-dimer, troponin, and CRP and lower levels of base excess, bicarbonate, and albumin to creatinine ratio were associated with in-hospital mortality in accordance with the literature. Cox-regression analysis represented higher odds ratios for base excess and lactate levels than those studies (odds ratios for BE: 12.894 and lactate: 9.368, respectively, p<0.001).

Previous studies have demonstrated biochemical parameters as relevant prognostic factors in COVID-19 (11,23,24). Bonetti et al. (24) found higher levels of CRP, D-dimer, and troponin in patients who died in the hospital and concluded that these parameters are highly predictive of in-hospital death and may be useful for guiding risk assessment and clinical decision-making. Pan et al. (11) also found that sex, SpO2, breath rate, diastolic pressure, neutrophils, lymphocytes, CRP, procalcitonin, lactate dehydrogenase, and D-dimer were significantly correlated with death events. In the current study, CRP, D-dimer, and troponin levels were found to be significantly higher in the nonsurvivor group than in the survivor group, in line with these findings. To the best of our knowledge, this is the first study to have evaluated the albumin to creatinine ratio in predicting COVID-19 mortality, and the results showed that lower levels of Alb/Cr were found in nonsurvivor patients. Renal and liver pathologies should have driven this decrease.

The main strength of this study was the well-designed comparison of biochemical parameters in patients with COVID-19 during the first admissions to the ED. However, there were some limitations to the study. Primarily, our study design was retrospective, single-center, and had limited data. Second, this was a cross-sectional study, which cannot describe the cause and effect relationship between laboratory parameters and clinical outcomes. Nevertheless, despite these limitations, this study can be considered valuable with respect to mortality predictors and the determination of cutoff values and odds ratios between arterial blood gases in a comparison of survivors and nonsurvivors.

CONCLUSION

Arterial blood gases performed during the first admission to the ED are linked with disease severity. Blood levels of base excess, lactate, and bicarbonate can be used to predict disease progression and mortality. Furthermore, patients with older age, male sex, hypertension, higher levels of lactate, D-dimer, troponin, CRP, and lower levels of base excess, bicarbonate, and albumin to creatinine ratio should be monitored closely and treated early. These parameters have the potential to give frontline clinicians better triage of COVID-19 patients in the ED. Overall, our findings can be useful in clinical practice and should be confirmed by large-scale studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Muğla Sıtkı Koçman University, Human Research Ethics Committee (Date: 24/03/2021, Decision No: 44).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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