ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

ORIGINAL ARTICLE
Endocrinol Res Pract. 2024;28(2):94-99

Assessment of Serum Cortisol Levels in Coronavirus Disease 2019 Inpatients and Investigation of the Potential Impact of Alterations in Serum Cortisol Levels on Prognosis

ABSTRACT

Objective: The novel coronavirus caused a disease that mainly affected the respiratory system. The effect of severe acute respiratory syndrome coronavirus 2 on the hypothalamic–pituitary–adrenal axis is unknown. This study assesses the prognostic accuracy of serum cortisol levels and prediction tools in predicting mortality rates in patients with coronavirus disease 2019 (COVID-19).

Methods: We prospectively analyzed 106 inpatients (53 COVID-19 positive, 53 non-COVID-19; mean 59.9 ± 17.3 years; 38 males and 68 females) with serum cortisol and adrenocorticotropic hormone levels compared with prognostic scores. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores determined the disease's severity. The predictive value of serum cortisol, APACHE, and SOFA on mortality was assessed using receiver operating characteristic curve analysis and the area under the curve (AUC).

Results: No significant age or sex differences were found between groups. Serum cortisol levels were similar. The APACHE-II scores in the COVID-19 group were higher than in the other group, while SOFA scores showed no significant difference. The AUC for the APACHE-II score in predicting mortality was 0.765 (95% CI 0.672-0.842), with an optimal cutoff (>9) demonstrating 62.5% sensitivity and 86.7% specificity for overall participants. No correlation was found between serum cortisol levels and prediction tools such as APACHE-II and SOFA.

Conclusion: The measurement of serum cortisol did not provide additional prognostic information beyond that established by the APACH-II score. This study highlights the significance of assessing novel prognostic tools for predicting outcomes in hospitalized patients with COVID-19.

Keywords: Coronavirus, SARS-CoV-2, APACHE-II, Cortisol

Ensar Aydemir[1]
Yasemin Ünsal[2]
Coşkun Ateş[3]
Mehmet Refik Göktuğ[4]
Özen Öz Gül[3]
Soner Cander[3]

[1]*Division of Endocrinology and Metabolism, Edirne Sultan Murat I State Hospital, Edirne, Turkey*
[2]*Division of Endocrinology and Metabolism, Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Ankara, Turkey*
[3]*Division of Endocrinology and Metabolism, Bursa Uludağ University Faculty of Medicine, Bursa, Turkey*
[4]*Department of Internal Medicine, Muş State Hospital, Muş, Turkey*

Corresponding author:
Ensar Aydemir
✉ ensaraydemir@gmail.com

Received: July 18, 2023
Revision Requested: August 10, 2023
Last Revision Received: November 18, 2023
Accepted: November 27, 2023
Publication Date: January 29, 2024

Cite this article as: Aydemir E, Ünsal Y, Ateş C, Refik Göktuğ M, Öz Gül Ö, Cander S. Assessment of serum cortisol levels in coronavirus disease 2019 inpatients and investigation of the potential impact of alterations in serum cortisol levels on prognosis. *Endocrinol Res Pract.* 2024;28(2):94-99.

DOI: 10.5152/erp.2024.23312

Introduction

As a novel coronavirus reported in Wuhan, China, in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for worldwide mortality owing in particular to respiratory failures such as pneumonia, acute respiratory distress syndrome (ARDS), and sepsis.[1] On March 11, 2020, the World Health Organization (WHO) declared that the SARS-CoV-2 was a pandemic. The Ministry of Health of the Republic of Turkey announced that the first COVID-19 case was detected in Turkey on the same day. As of this writing, coronavirus is responsible for 399 600 607 confirmed cases and 5 757 562 deaths globally since 2019.[2] Turkey has recorded more than 11 million cases - seventh country in the world. Most patients with coronavirus disease 2019 (COVID-19) in Turkey recovered or were discharged, accounting for 99.2%. The official death toll in Turkey is more than 80 000.[3]

The SARS-CoV-2 virus enters host cells by attachment to the metallocarboxyl peptidase angiotensin receptor 2.[4] Angiotensin receptor 2 is expressed particularly in the vascular endothelial cells of many organ systems such as the kidney, lung, and heart.[5] Virus can induce hyperactivation of proinflammatory cytokines and chemokines, causing life-threatening complications such as cytokine storm and ARDS.[5]

Symptoms of COVID-19 range from mild symptoms like cough, fever, myalgia, and headache to severe symptoms such as life-threatening pneumonia, respiratory failure, and multiorgan dysfunction.[6-8] The COVID-19 hospitalization rate was reported to be higher in patients with comorbid diseases such as diabetes mellitus (DM), hypertension (HT), cardiovascular disease

Copyright @ Author(s) – Available online at http://endocrinolrespract.org
This journal is licensed under a Creative Commons (CC BY-NC-SA) 4.0 International License.

(CVD), and chronic lung diseases (CLD).[9-11] The mortality rates vary internationally up to 18%. Mortality rates in our country have been reported as 0.7%.[12]

National COVID-19 guidelines recommended avoiding the choice of glucocorticoids in the early stages of the pandemic, except in cases such as severe COVID-19, resistant shock, and ARDS. The novel guideline recommends glucocorticoid therapy in COVID-19 patients who need oxygen administration due to respiratory distress.[13]

The genetic sequence of SARS-CoV-2 is 80% similar to SARS-CoV-1. Severe acute respiratory syndrome coronavirus 1 causes transient central hypocortisolism by affecting the hypothalamus-pituitary-adrenal axis due to reversible hypophysitis or direct hypothalamic damage.[5] Tan et al[9] showed a relationship between high total cortisol levels and COVID-19 mortality rate. In the RECOVERY study, it was reported that glucocorticoid therapy decreased mortality rates of COVID-19 patients receiving oxygen support.[14]

This study aimed to investigate the correlation between plasma cortisol levels and the severity of COVID-19 using prognostic markers.

Material and Methods

Study Design

This study was conducted at Bursa Uludağ University Faculty of Medicine Hospital from December 2020 to May 2021. The current study was a methodologic study and assessed the relationship between plasma cortisol levels and prognosis by using prognostic scores such as "Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system" and "Sequential Organ Failure Assessment (SOFA) Score" in COVID-19 and non-COVID-19 patients. This study was approved by the ethics committee of the Bursa Uludağ University Ethics Board (Approval number: THIZ-2021-458).

Participants

All adult inpatients (≥18 years old) who tested for COVID-19 were included. Participants were informed about the research and obtained consent before participating. Patients were divided into 2 groups with and without COVID-19 (non-COVID-19 group). They were matched in terms of sex.

Eligibility Criteria

This study included individuals who exhibited symptoms such as fever, cough, and shortness of breath. These patients exhibited pulmonary infiltrates on chest imaging and tested positive for COVID-19 through polymerase chain reaction testing. They were subsequently admitted to the hospital for further management. Morning fasting plasma cortisol levels were measured within 24 hours of admission in patients admitted to the clinic without any prior steroid treatment. The non-COVID-19 cohort consisted of patients presenting to the endocrinology clinic for ongoing medical care. The main reasons for their admission were inadequate glycemic control of diabetes and investigation of undiagnosed conditions of uncertain underlying causes. Among these cases, none of the patients presented with a diagnosis of pneumonia.

Exclusion criteria included the age of less than 18 years; underlying Cushing's syndrome or disease; primary or secondary adrenal insufficiency, adrenocortical carcinoma, end-stage renal disease, chronic liver disease (hypoalbuminemia or international normalized ratio prolongation), active malignancies and metastases; use of drugs affecting the serum cortisol levels such as glucocorticoids; and alcohol abuse.

Serum Cortisol Analysis

Serum cortisol levels were evaluated by acquiring a venous blood sample after at least 8 hours of overnight fasting, during a state of rest, within the time frame of 8:00 AM and 9:00 AM. Samples were stored at −80°C until analysis. Serum cortisol levels were measured using the chemiluminescent microparticle immunoassay method on an Architect system (Abbott, Ill, USA).

Data Collection

Blood electrolytes, kidney and liver function, plasma cortisol, ACTH, and blood gas analysis were collected from all inpatients at admission. In addition, d-dimer, ferritin, and troponin I were collected from all COVID-19 inpatients. All the tests were done in the hospital's central laboratory. Online calculators were used to calculate the SOFA and APACHE-II scores.[15] Patient baseline characteristics were extracted from medical records, including comorbid diseases and demographic information such as vaccination status at initial diagnosis.

Measurement Criteria and Tools

The APACHE-II and SOFA scores are widely used in intensive care to predict the prognosis of critically ill patients. The APACHE II score, ranging from 0 to 71 points, is derived by analyzing 12 physiological characteristics, age, and the presence of chronic diseases. The tool is used to determine the likelihood of mortality.[16,17] Conversely, the SOFA score is a prognostic scoring system that ranges from 0 to 24. It is used to assess the presence of organ dysfunction. The SOFA score assesses many physiological systems, including respiratory, coagulation, liver, cardiovascular, central nervous system, and renal function.[17]

Statistical Analysis

The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Descriptive analyses were performed using means ± standard deviations for the normality of the continuous data, the medians and the interquartile ranges (IQRs) for analyzing quantitative variables, and frequencies for categorical data. Group comparisons were analyzed using the chi-square test and Fisher's exact test. The Mann–Whitney *U*-test compared independent groups with non-normally distributed data. Comparison of cortisol levels in the 2 groups of participants in the study (COVID-19 positive and negative) was analyzed using the Mann–Whitney *U*-test. Statistical analysis was conducted using the IBM Statistical Package

MAIN POINTS

- There was no statistically significant association observed between serum cortisol levels and mortality caused by coronavirus disease 2019 (COVID-19) among adult inpatients.
- There was no statistically significant correlation found between blood cortisol levels and prediction measures such as Acute Physiology And Chronic Health Evaluation II (APACHE-II) and Sequential Organ Failure Assessment (SOFA).
- The APACHE-II score shown effectiveness as a predictive tool among diverse hospitalized patients.
- The use of predictive tools such as APACHE-II and SOFA in the context of patients admitted to hospital with COVID-19 needs to demonstrate a consistent and reliable ability to serve as prognostic indicators.

for the Social Sciences Statistics software (version 29.0, IBM corp., Armonk, NY, USA). The area under the curve (AUC) in receiver operating characteristic (ROC) analysis was estimated to evaluate the efficacy of prognostic scores, particularly APACHE-II and SOFA, to predict overall mortality.

P-values of less than .05 were considered statistically significant.

Results

Population Characteristics

A hundred six patients met study eligibility; 53 were selected for the non-COVID-19 group and 53 for the COVID-19 group. The baseline clinical and demography characteristics of all participants are shown in Table 1. Among the 106 participants, the mean (SD) age was 59.9 (17.3) years, and 68 (64.1%) were female. All patients had at least 1 comorbid condition, with DM (n = 58/106, 54.7%), HT (n = 49/106, 46.2%), CVD (n = 24/106, 22.6%), and CLD (n = 15/106, 14.2%) most frequently documented. Prevalences of DM and CLD varied between patients with and without COVID-19.

Seventy-seven (72.6%) participants had received at least 1 dose of vaccine with the inactivated SARS-CoV-2 vaccine (CoronaVac) and/or Pfizer-BioNTech messenger RNA (mRNA) vaccine. There were 17 (16%) patients who had never been vaccinated and 12 (11.3%) whose vaccination status was unknown. Of the 37 vaccinated patients in the COVID-19 group, 24 (64.8%) received only the CoronaVac vaccine, 5 (13.5%) received CoronaVac, and then Pfizer-BioNTech mRNA vaccines, and 8 (21.6%) received only Pfizer-BioNTech mRNA vaccine. A similar rate of vaccination status was observed in the patients who received at least 1 dose of the CoronaVac vaccine between both groups ($P = .083$). We found a significant difference in vaccination rates with the Pfizer–BioNTech vaccine between the participants with and without COVID-19 (13 vs. 33, $P < .001$).

Laboratory Findings

The COVID-19 group had significantly lower serum lymphocyte and platelet count, total protein, albumin, potassium, and ACTH levels but higher C-reactive protein (CRP), aspartate aminotransferase, and total bilirubin levels compared to the non-COVID-19 group ($P < .05$). In addition, serum cortisol levels of patients with COVID-19 were similar to that of the non-COVID-19 group (12.56 ± 6.64 µg/dL vs. 10.93 ± 4.20 µg/dL. $P = .134$). No statistical difference was observed either in serum cortisol between the vaccinated and unvaccinated patients with COVID-19 (12.5 ± 6.5 µg/dL vs. 12.9 ± 6.9. $P = .851$). There was no significant difference in lymphocyte, CRP, d-dimer, ferritin, and ACTH between the 2 subgroups of COVID-19 patients.

Prognostic Scores, Hospital Stay, Mortality, and Risk Factors

The median APACHE-II and SOFA scores were 5 (IQR 3-9) and 1 (IQR 0-2), respectively. Eight patients died (7.5%). The median APACHE-II and SOFA in the survivors and nonsurvivors were 5 (IQR 3-8) and, 10 (IQR 6-11) ($P = .013$), and 1 (IQR 0-2) and 2 (IQR 0.25-3.75) ($P = .063$), respectively. The APACHE-II and SOFA in the COVID-19 and non-COVID-19 groups were 6 (IQR 4-10) and 5 (IQR 3-7) ($P = .03$), and 1 (IQR 0-2.5) and 0 (IQR 0-1) ($P = .09$), respectively. In the subgroup analysis, no significant differences were observed in the APACHE-II and SOFA scores between the vaccinated and unvaccinated inpatients with COVID-19.

The study found that the median cortisol levels in all patients were 11.1 (IQR 7.1-15.2) mg/dL. In the COVID-19 group, the median cortisol levels were 13 (IQR 6.9-17.2) mg/dL, whereas in the non-COVID-19 group, the median cortisol levels were 11 (IQR 7.4-13.4) mg/dL. However, the difference in cortisol levels between the 2 groups was not statistically significant ($P = .210$).

In the AUC analysis, we found that the APACHE-II scoring system showed the highest AUC value of 0.765 (95% CI 0.608-0.921) in predicting overall population mortality. However, the value of the Youden index was for APACHE-II ($J = .258$) with a sensitivity of 62.5% and specificity of 63.3%, the optimal cutoff value of 6.5 µg/dL ($P = .001$) (Figure 1). When comparing the AUCs using the De Long test, no differences were found between SOFA, APACHE-II, and cortisol levels at admission in the COVID-19 group (Table 2).

The in-hospital mortality rate in our study was 7.5%, with a mean time to discharge or admission to another clinic as intensive care unit, non-pandemic clinic, of 11.38 ± 7.24 days, whereas survivors had a median length of 7.5 days. Among 5 patients (4.7%) admitted to the ICU, 100% died.

On the univariate analysis, we found no significant results associated with outcomes.

Discussion

In this study, we investigated clinical, biochemical, and prognostic scores in the COVID-19 and non-COVID-19 groups, evaluated the prognostic effect of serum cortisol concentration for the clinical progression of the inpatients with COVID-19, and analyzed the correlations between serum total cortisol level and other parameters in 53 inpatients with COVID-19. We found that participants with COVID-19 exhibited a higher level of APACHE-II score than the participants without COVID-19. However, there were similar APACHE-II and SOFA scores levels between vaccinated and unvaccinated patients with COVID-19. Serum cortisol levels were not correlated with prognostic scores.

During the early stages of the United Kingdom pandemic, Tan et al[9] incorporated 3 prominent medical centers. The study included a cohort of approximately 400 patients who were either confirmed positive for COVID-19 through nasopharyngeal sampling or showed a notable clinical and radiological suspicion of COVID-19. As a crucial aspect of the study, basal cortisol samples were systematically collected within 48 hours of the patient's hospital admission. Tan et al[9] reported that high serum total cortisol concentrations were associated with mortality from COVID-19. In contrast to these findings, this study demonstrates no significant relationship between serum cortisol levels and mortality. The effects of increased vaccination rates may explain this result, decreased COVID-19-associated mortality rates, and the emergence of new coronavirus variants.

A recent study reported no difference in the morning salivary cortisol levels between COVID-19 and non-COVID-19 patients. Nevertheless, cortisol levels measured at other times of the day were higher in COVID-19 patients. The disruption of diurnal rhythm is associated with increased interleukin 6 concentration.[10] In this study, morning cortisol concentrations have been shown insufficient to predict the severity of mild-to-moderate COVID-19, similar to those observed among non-COVID patients. Interestingly, Amiri-Dashatan et al[18] reported that increased serum cortisol levels are positively correlated with the severity of COVID-19. However,

Table 1. Demographic, Clinical, and Biochemical Characteristics of the Patients at Baseline

Characteristic	Overall (n = 106)	COVID-19 Group (n = 53)	Non-COVID-19 Group (n = 53)	*P*
Age ± SD, years	59.9 ± 17.3	62.8 ± 18.1	57.1 ± 16	.093
Female sex, n (%)	68 (64.1)	34	34	
Comorbidities, n (%)				
Hypertension	49 (46.2)	22 (41.5)	27 (50.9)	.330
Diabetes mellitus	58 (54.7)	15 (28.3)	43 (81.1)	<.001*
Cardiovascular disease	24 (22.6)	10 (18.9)	14 (26.4)	.353
Chronic lung disease	15 (14.2)	7 (13.2)	8 (15.1)	.012*
Vaccination, n (%)				
None	17 (16)			
SinoVac				.083
None	40 (37.7)	20 (37.7)	20 (37.7)	
1 dose	1 (0.9)	1 (1.8)	0	
2 doses	34 (32.1)	14 (26.4)	20 (37.7)	
3 doses	19 (17.9)	14 (26.4)	5 (9.4)	
BioNTech				<.001*
None	48 (45.2)	36 (67.9)	12 (22.6)	
1 dose	23 (21.7)	8 (15)	15 (28.3)	
2 doses	13 (11.3)	5 (9.4)	18 (33.9)	
Treatment, n (%)				
Anticoagulants	45 (42.5)	42 (79.2)	3 (5.7)	<.001*
Antibiotics	49 (46.2)	33 (62.3)	16 (30.2)	<.001*
Favipravir	36 (34)	36 (67.9)	-	
Steroids	23 (21.7)	22 (41.5)	1 (1.9)	<.001*
Plasmapheresis	2 (1.9)	2 (3.8)	-	
Respiratory support, n (%)	18 (17)	16 (30.2)	2 (3.8)	<.001*
Nasal cannula	10 (55.6)	9 (17)	1 (1.9)	
Face mask	4 (22.2)	4 (7.5)	-	
HFOT	3 (16.7)	3 (5.7)	-	
IMV	1 (5.6)	-	1 (1.9)	
Laboratory values, mean ± SD or median (IQR)				
WBC, $\times 10^3/\mu L$	7.98 (5.55-10.17)	6.96 (4.91-11.23)	8.16 (6.52-10.04)	.730
Lymphocytes, $\times 10^3/\mu L$	1.69 (1.04-2.43)	1.23 (0.76-1.75)	2.12 (1.6-2.94)	<.001*
Platelets, $\times 10^3/\mu L$	222 (176-270)	201 (166-255)	232 (201-271)	.028*
CRP, mg/dL	17.6 (2-59.9)	51.6 (17.6-86.2)	2.5 (2-18)	<.001*
Creatinine, mg/dL	0.84 (0.7-1.25)	0.86 (0.68-1.26)	0.83 (0.73-1.21)	.840
Bilirubin, mg/dL	0.5 (0.3-0.7)	0.6 (0.4-0.8)	0.4 (0.3-0.6)	.024*
Troponin I, ng/L	9.2 (2.5-29.4)	10.2 (2.4-37)	6.2 (3.6-9.8)	.446
Ferritin, µg/L	225 (87-613)	242 (96-571)	162 (79-728)	.611
ACTH, ng/L	13 (9-22)	11.5 (7-21.5)	14 (10.5-26)	.037
Cortisol, µg/dL	11.7 ± 5.6 11.1 (7.1-15.2)	12.5 ± 6.6 13 (6.9-17.2)	10.9 ±4.2 11 (7.4-13.4)	.134 .210
Prognostic scores				
APACHE-II	5 (3-9)	6 (4-10)	5 (3-7)	.030*
SOFA	1 (0-2)	1 (0-2.5)	0 (0-1)	.090
In-hospital stay, days	7 (3-10)	7 (3-10)	9 (6-11)	.032*

ACTH, adrenocorticotropic hormone; APACHE-II, Acute Physiology And Chronic Health Evaluation; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HFOT, high flow oxygen therapy; IMV, invasive mechanical ventilation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; WBC, white blood cells.
*$P < .05$.

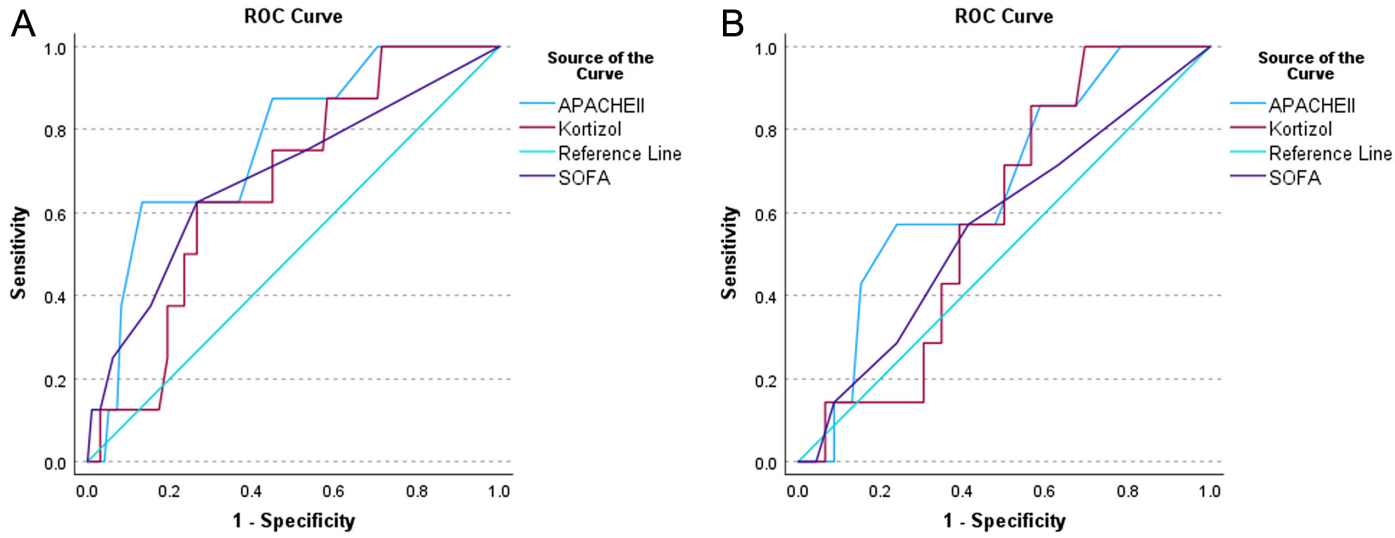

Figure 1. Comparison of ROC curves for serum cortisol levels, APACHE-II, and SOFA scores predicting in-hospital mortality among overall patient (A) and the COVID-19 subgroup (B). APACHE-II, Acute Physiology and Chronic Health Evaluation; COVID-19, coronavirus disease 2019; SOFA, Sequential Organ Failure Assessment.

there is no comparison with non-COVID-19 patients in this analysis. In a recent study from Iran, low serum cortisol levels at the admission of intensive care unit increased mortality rates in COVID-19 patients.[19]

The majority of patients had at least 1 comorbid disease, most commonly HT and diabetes. The prevalence of DM in COVID-19 patients also varies across geographical regions. According to the International Diabetes Federation diabetes atlas tenth edition, the prevalence of DM in Turkey is 14.5%.[20] However, the rate of diabetic patients was higher in our cohort. In accordance with the present results, previous studies have demonstrated that patients suffering from COVID-19 with diabetes had higher rates of hospitalization and mortality than patients without diabetes. Hyperglycemia increases the risk of mortality by decreasing the immune response.[21]

Despite the higher prevalence of HT in the participants with COVID-19, no correlation was found with mortality. These results are in line with those of previous studies.[22-24] However, different results have also been reported in early studies.[25]

This study has been unable to demonstrate that the SOFA score predicted mortality.[26,27] Zou et al[28] found that the APACHE-II score demonstrated better in predicting in-hospital mortality due to COVID-19 than the SOFA score. Our study also found that the APACHE-II score was higher in the deaths group than in the survivors group. Considering the APACHE-II score (range 3-10) has a greater range of values than the SOFA score (range 0-2.5) may be advantageous. The discrepancy in the range of the 2 scores could contribute to why the APACHE-II and SOFA scores were statistically different.

This study demonstrated that serum cortisol levels of participants with COVID-19 are not associated with in-hospital mortality. Nonetheless, an attempt to perform an accurate clinical assessment solely based on cortisol level measurements remains a compelling proposition. The study showed that only the APACHE-II score is a sensitive prognostic score of in-hospital deaths of all inpatients. However, the SOFA and APACHE-II scores are not good predictors of prognosis in COVID-19 patients. In this context, we showed no association between in-hospital mortality and cortisol levels, APACHE-II, and SOFA scores in hospitalized patients with COVID-19. The prognostic value of the

Table 2. The Area Under Curve of Serum Cortisol Levels, Acute Physiology and Chronic Health Evaluation II, and Sequential Organ Failure Assessment Models in Predicting In-Hospital Mortality

Models	AUC of ROC	95% CI of AUC	Youden Index J	Sensitivity, %	Specificity, %	Cutoff value	*Z* statistic	*P*
Overall								
Cortisol, µg/dL	0.642	0.542-0.733	0.367	62.5	74.2	>21	1.154	.249
APACHE-II	0.765	0.672-0.842	0.492	62.5	86.7	>9	0.698	.001*
SOFA	0.687	0.590 - 0.773		62.5	73.5	>1	1.701	.089
COVID-19 group								
Cortisol	0.592	0.448-0.725	0.304	100	30.4	>7.1	0.975	.329
APACHE-II	0.663	0.520-0.787	0.332	57.1	76.1	>9	1.532	.125
SOFA	0.567	0.424-0.702	0.158	57.1	58.7	>1	0.556	.578

APACHE-II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the curve; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment.
*$P < .05$.

prognostic scores employed in our study, when applied to patients diagnosed with COVID-19, remains to be determined.

The present study has several limitations. First, this study did not include severe COVID-19 patients who received steroids at first admission. Second, the vaccination information of patients not allowed access to the national database could not be obtained. Third, most patients in the non-COVID-19 group consisted of diabetic patients hospitalized in the endocrine clinic. Fourth, sex matching of the patients was performed, but age matching could not be achieved exactly between the groups. Despite the strict isolation protocols implemented in hospitals during the COVID-19 pandemic, executing certain medical procedures, including collecting multiple cortisol samples from patients or administering dynamic tests, has become unfeasible.

This study demonstrated that serum cortisol levels of participants with COVID-19 are not associated with in-hospital mortality. Nonetheless, an attempt to perform an accurate clinical assessment solely based on cortisol level measurements remains a compelling proposition. The study showed that only the APACHE-II score is a sensitive prognostic score of in-hospital deaths of all inpatients. However, the SOFA and APACHE-II scores are not good predictors of prognosis in COVID-19 patients. In this context, we showed no association between in-hospital mortality and cortisol levels, APACHE-II, and SOFA scores in hospitalized patients with COVID-19. The prognostic value of the prognostic scores employed in our study, when applied to patients diagnosed with COVID, remains to be determined.

Ethics Committee Approval: This study was approved by the ethics committee of the Bursa Uludağ University Ethics Board (Approval number: THIZ-2021-458).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A., Y.Ü., C.A., M.R.G., Ö.Ö.G, S.C.; Design – E.A., Y.Ü., C.A., M.R.G., Ö.Ö.G., S.C.; Literature Search – E.A., Y.Ü., C.A., M.R.G., Ö.Ö.G., S.C.; Writing Manuscript – E.A., Y.Ü., C.A., M.R.G., Ö.Ö.G., S.C.; Critical Review – E.A., Y.Ü., C.A., M.R.G., Ö.Ö.G., S.C.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

References

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579(7798):265-269. [CrossRef]
2. Worldometer COVID-19 coronavirus pandemic, countries. Accessed December 3, 2021. https://www.worldometers.info/coronavirus/
3. Republic of Turkiye Ministry of Health COVID. *19 Information Platform*. Accessed December 13, 2021. https://covid19.saglik.gov.tr/
4. Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. *Endocrine*. 2020;68(2):251-252. [CrossRef]
5. Somasundaram NP, Ranathunga I, Ratnasamy V, et al. The impact of SARS-Cov-2 virus infection on the endocrine system. *J Endocr Soc*. 2020;4(8):bvaa082. [CrossRef]
6. Pullen MF, Skipper CP, Hullsiek KH, et al. Symptoms of COVID-19 outpatients in the United States. *Open Forum Infect Dis*. 2020;7(7):ofaa271. [CrossRef]
7. Çalıca Utku A, Budak G, Karabay O, Güçlü E, Okan HD, Vatan A. Main symptoms in patients presenting in the COVID-19 period. *Scott Med J*. 2020;65(4):127-132. [CrossRef]
8. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. [CrossRef]
9. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(8):659-660. [CrossRef]
10. Yavropoulou MP, Filippa MG, Mantzou A, et al. Alterations in cortisol and interleukin-6 secretion in patients with COVID-19 suggestive of neuroendocrine-immune adaptations. *Endocrine*. 2022;75(2):317-327. [CrossRef]
11. Troxel AB, Petkova E, Goldfeld K, et al. Association of convalescent plasma treatment with clinical status in patients hospitalized with COVID-19: A meta-analysis. *JAMA Netw Open*. 2022;5(1):e2147331. [CrossRef]
12. World Health Organization. *COVID-19 Dashboard*. Geneva: World Health Organization; 2020. Accessed December 20, 2021. https://covid19.who.int/
13. Türkiye cumhuriyeti sağlık bakanlığı halk sağlığı genel müdürlüğü. *Eriskin Rehberi*. Accessed April 14, 2020. https://hsgm.saglik.gov.tr/tr/covid19
14. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. [CrossRef]
15. *MDCalc*. Accessed December 20, 2021. https://www.mdcalc.com/
16. Vandenbrande J, Verbrugge L, Bruckers L, et al. Validation of the Acute Physiology and Chronic Health Evaluation (APACHE) II and IV Score in COVID-19 Patients. *Crit Care Res Pract*. 2021;2021:5443083. [CrossRef]
17. Beigmohammadi MT, Amoozadeh L, Rezaei Motlagh F, et al. Mortality predictive value of Apache II and SOFA scores in COVID-19 patients in the Intensive Care Unit. *Can Respir J*. 2022;2022:5129314. [CrossRef]
18. Amiri-Dashatan N, Koushki M, Parsamanesh N, Chiti H. Serum cortisol concentration and COVID-19 severity: a systematic review and meta-analysis. *J Investig Med*. 2022;70(3):766-772. [CrossRef]
19. Ahmadi I, Estabraghnia Babaki H, Maleki M, et al. Changes in physiological levels of cortisol and adrenocorticotropic hormone upon hospitalization can predict SARS-CoV-2 mortality: a cohort study. *Int J Endocrinol*. 2022;2022:4280691. [CrossRef]
20. International Diabetes Federation. *IDF Diabetes Atlas*. 10th ed; vol 2021; 2021.
21. Wang J, Meng W. COVID-19 and diabetes: the contributions of hyperglycemia. *J Mol Cell Biol*. 2020;12(12):958-962. [CrossRef]
22. Killerby ME, Link-Gelles R, Haight SC, et al. Characteristics associated with hospitalization among patients with COVID-19 – Metropolitan Atlanta, Georgia, March-April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(25):790-794. [CrossRef]
23. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. [CrossRef]
24. Kim L, Garg S, O'Halloran A, et al. Risk factors for Intensive Care Unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis*. 2021;72(9):e206-e214. [CrossRef]
25. Lippi G, Wong J, Henry BM. Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis. *Pol Arch Intern Med*. 2020;130(4):304-309. [CrossRef]
26. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. *Am J Emerg Med*. 2020;38(10):2074-2080. [CrossRef]
27. Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. *Med (Baltim)*. 2021;100(32):e26900. [CrossRef]
28. Zou X, Li S, Fang M, et al. Acute physiology and chronic health evaluation II score as a predictor of hospital mortality in patients of coronavirus disease 2019. *Crit Care Med*. 2020;48(8):e657-e665. [CrossRef]