SCIE DOI: 10.14744/scie.2022.93446
South. Clin. Ist. Euras. 2022;33(3):316-319

Original Article

Serum Cortisol May Serve as a Novel Predictor of Hospital Length of Stay for COVID-19 Patients

Fatih Türker,[1] Süleyman Ahbab,[1] Betül Çavuşoğlu,[2] Atay Can Kula,[1] Raife Dilhan Alçelik,[1] Hayriye Esra Ataoglu[1]

[1]Department of Internal Diseases, Haseki Training and Research Hospital, İstanbul, Türkiye
[2]Department of Internal Diseases, Taksim Training and Research Hospital, İstanbul, Türkiye

Submitted: 18.10.2021
Accepted: 07.02.2022

Correspondence: Fatih Türker, Haseki Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği İstanbul, Türkiye
E-mail: fatihturker1985@hotmail.com

Keywords: Cortisol; COVID-19; length of stay.

ABSTRACT

Objective: There are several clinical outcomes associated with coronavirus disease 2019 (COVID-19) infection, including pneumonia, acute respiratory distress syndrome, and death. The aim of this study is to evaluate whether serum cortisol levels affect COVID-19 prognosis.

Methods: A retrospective study was conducted with COVID-19 pneumonia patients hospitalized in an internal medicine clinic at the Haseki Training and Research Hospital in Istanbul from March 13 to May 31, 2020. Demographics, laboratory test results, and clinical outcomes of the patients were recorded. The patients were divided into two groups based on whether they were hospitalized for 1–9 days or ≥10 days. Both groups were classified according to their average age and duration of hospitalization/discharge, and laboratory parameters were analyzed.

Results: This study was conducted on 129 COVID-19 pneumonia patients, 13 of whom died during the study period. The mean age was 68.7±10.9 years for nonsurvivors and 55.7±15.9 years for survivors (p=0.001). Serum cortisol levels were significantly elevated in patients with a long hospital stay. While there was no significant difference in the hemogram or biochemical parameters of the two groups, correlation analysis showed a close relationship between serum cortisol levels and length of hospitalization.

Conclusion: Cortisol is a reliable predictor of the length of hospital stay and prognosis of COVID-19 patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in late 2019 and declared a global pandemic by the World Health Organization (WHO) in March 2020.[1] Novel coronavirus disease 2019 (COVID-19) continues to have a significant impact on the world, resulting in various clinical outcomes, from pneumonia to acute respiratory distress syndrome and mortality. The value of acute phase reactants to COVID-19 prognosis is well known.[2] Cortisol is the primary glucocorticoid in the adrenal cortex and is synthesized from cholesterol and secreted in response to biochemical stress.[3] Most (95%) of cortisol in the blood is bound to cortisol-binding globulin and albumin, while the remaining 5% is in free form. Serum cortisol levels can be a marker of disease progression and prognosis.[4] Critically ill patients often have high plasma cortisol concentrations proportional to disease severity. Serum cortisol levels increase during disease along with activation of the hypothalamic–pituitary–adrenal axis and reduced production of cortisol binding protein.[5,6] The role of serum cortisol in community-acquired pneumonia has been extensively studied, and the results indicate that it is an independent biomarker of adverse patient outcomes and mortality.[7–10] Thus, analysis of serum cortisol levels may aid the prognosis of COVID-19 pneumonia in clinical settings. The potential association between serum cortisol levels and prolonged hospitalization during SARS-CoV-2 infection remains unclear. The aim of this study is to evaluate whether serum cortisol impacts the duration of hospitalization for COVID-19 patients with pneumonia.

MATERIALS AND METHODS

Study participants and laboratory analyses

This study was approved by the Local Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. This retrospective cohort study was conducted according to the principles of good clinical practice and the declaration of Helsinki. The study included 129 COVID-19 pneumonia patients (58 males and 71 fe-

males) who were hospitalized in the pandemic unit of the internal medicine clinic of Haseki Training and Research Hospital from March 18 to May 31, 2020. Patients with repeated hospital admissions, pregnancy, age <18 years, steroid treatment, adrenal insufficiency, or Cushing's syndrome were excluded from the study. According to the hospital laboratory, the normal range of serum cortisol levels was 7–29 pg/dL. The patients were divided into two groups based on whether they were hospitalized for 1–9 days or ≥10 days. Both groups were classified by average age and duration of hospitalization/discharge. Patients' data were obtained from the electronic hospital management system. Standardized data collection included patients' demographics, medical history, laboratory examination, and mortality information. Blood samples were taken on the first day of hospitalization after a 12-h fasting period. Laboratory parameters, including serum glucose, creatinine, uric acid, alanine aminotransferase, lactate dehydrogenase (LDH), albumin, C-reactive protein (CRP), procalcitonin, d-dimer, ferritin, fibrinogen, cortisol, and complete blood count parameters, were analyzed.

Statistical analysis

Data are expressed as the mean±standard deviation. Statistical analysis was performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA). Basic descriptive statistics were measured, including the means, standard deviations, ranges, and percentages. The normality of the distribution was examined by the Kolmogorov–Smirnov test. Mean values between two independent groups were compared using the Mann–Whitney U test for continuous variables and by the Chi-squared test for categorical parameters. Comparisons between more than two subgroups were performed by ANOVA and the Kruskal–Wallis tests. Bivariate correlations were explored by Pearson's (continuous variables) test. Differences were considered statistically significant if the two-tailed p-value was less than 0.05.

RESULTS

This study was conducted using 129 patients (58 males and 71 females) who were hospitalized in the Haseki Training and Research Hospital's internal medicine pandemic unit, 13 of whom died during the study period. Basic biochemical parameters were compared between the nonsurvival and survival groups. Nonsurvivors and survivors had a mean age of 68.7±10.9 years and 55.7±15.9 years, respectively (p=0.001). While 10 patients died in the group that was hospitalized for 1–10 days, 3 patients died in the group that was hospitalized for >10 days (Table 1). Creatinine and uric acid levels were statistically higher in the nonsurvival group. While not statistically significant, cortisol levels were high in the survival group (Table 2). In total, 75 patients were hospitalized for <10 days, and 54 patients were hospitalized for ≥10 days. Basic biochemical parameters were compared between the two groups, and serum cortisol and creatinine levels were significantly higher in patients with ≥10-day hospital stay. No significant differences were found in

Table 1. Relationship between hospitalization day as survival and nonsurvival

Hospitalization day	Nonsurvival	Survival	Total
1–10 day, n (%)	10 (13.3)	65 (86.7)	75
10 days and over, n (%)	3 (5.6)	51 (94.4)	54
Total	13	116	129

Table 2. Basic biochemical parameters between nonsurvival and survival groups

Hospitalization day	Nonsurvival	Survival	Total
Age	68.7±10.9	55.7±15.9	0.001
Creatinine (mg/dL)	2.49±2.7	1.18±1.5	0.003
Uric acid (mg/dL)	6.4±2.4	4.8±2.1	0.1
Glucose (mg/dL)	209.5±110.1	137.7±66.1	0.01
ALT (U/L)	22.2±22	29.5±35.5	0.28
LDH (U/L)	325.7±55.7	287.8±147.3	0.1
Albumin (g/L)	3.4±0.3	3.8±0.9	0.1
CRP (mg/L)	53.2±51	94.1±100.9	0.5
Procalcitonin (ng/mL)	0.1±0.4	1±5.3	0.3
Hemoglobin (g/dL)	11.5±2.3	12±1.9	0.49
White blood cell (10^3 UL)	7.6±4.8	7±4.2	0.86
D-dimer (mg/L)	2.3±2.2	1.6±3.1	0.5
Ferritin (ng/mL)	332.6±339.6	279.9±291.5	0.69
Fibrinogen (mg/dL)	448.8±150.2	464±117.5	0.49
Cortisol (pg/dL)	12.2±0.8	16±5.5	0.28

P<0.05. ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

Table 3. Basic biochemical parameters between hospitalization period below and above 10 days

	Hospitalization below 10 days	Hospitalization above 10 days	p
Age	55.5±16.4	59.1±15	0.2
Creatinine (mg/dL)	1.04±1.2	1.7±2.2	0.05
Uric acid (mg/dL)	4.9±2.1	4.9±2	0.8
Glucose (mg/dL)	137.6±73.8	144.5±66.7	0.5
ALT (U/L)	30.7±42.6	26.6±19.9	0.4
LDH (U/L)	292.1±146	290.5±128.4	0.9
Albumin (g/L)	3.6±0.5	3.5±0.4	0.1
CRP (mg/L)	58.9±70	72.5±79.3	0.3
Procalcitonin (ng/mL)	0.1±0.6	1±6.3	0.3
Hemoglobin (g/dL)	12±1.9	12.2±2	0.6
White blood cell (10^3 UL)	7.1±3.5	6.9±5	0.8
D-dimer (mg/L)	2±3.9	1.2±1.8	0.1
Ferritin (ng/mL)	245.1±278.6	304.6±307.1	0.3
Fibrinogen (mg/dL)	440.5±110.4	480.3±124.4	0.07
Cortisol (pg/dL)	14.3±4.5	17.3±5.3	0.02

P<0.05. ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

Table 4. Correlation analysis between cortisol and biochemical parameters

	LDH	CRP	Procalcitonin	D-dimer	Ferritin	Fibrinogen
Cortisol (p-value)	0.005	0.001	0.2	0.2	0.02	0.004
Cortisol (r-value)	0.364	0.415	0.164	0.287	0.297	0.378

P<0.05. LDH: Lactate dehydrogenase; CRP: C-reactive protein.

Table 5. Multivariate regression analysis between cortisol and biochemical parameters

	Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7	
	p	OR	p	OR	p	OR	p	OR	p	OR	p	OR	p	OR
Serum corti-sol	0.07	1.1	0.07	1	0.04	1.1	0.04	1.1	0.05	1.1	0.02	1.2	0.03	1.1
Fibrinogen	0.212	1	0.191	1	0.08	1	0.08	1	0.09	1	0.06	1	0.09	1
D-dimer	0.209	0.6	0.208	0.6	0.225	0.6	0.226	0.6	0.277	0.6	0.202	0.6		
LDH	0.340	1	0.287	1	0.331	1	0.338	1	0.325	1				
Creatinine	0.552	1.1	0.530	1.1	0.496	1.2	0.517	1.1						
Age	0.539	1	0.538	1	0.573	1								
CRP	0.689	1	0.595	1										
Ferritin	0.945	1												

P<0.05. LDH: Lactate dehydrogenase; CRP: C-reactive protein.

the other biochemical parameters (Table 3). There was a positive correlation between LDH, CRP, ferritin, fibrinogen, and high cortisol levels (Table 4). Multivariate regression analysis was performed to assess the relationship between serum cortisol and fibrinogen, D-dimer, LDH, creatinine, age, CRP, and ferritin levels. Based on the regression analysis, elevated serum cortisol levels were significantly higher than other biochemical parameters in patients with ≥10-day hospitalization (p=0.03, OR=1.1) (Table 5).

DISCUSSION

This retrospective study showed a relationship between prolonged hospitalization and increased serum cortisol levels. Cortisol correlated with LDH, CRP, ferritin, and fibrinogen levels in patients with prolonged hospital stay. Regression analysis showed that serum cortisol was significantly higher in patients who stayed in the hospital for ≥10 days. Cortisol was also higher in the survival group than in the nonsurvival group. Prior studies have associated elevated LDH, CRP ferritin, and fibrinogen levels with poor prognosis and prolonged hospital stay in COVID-19 clinics.[2] This study found a correlation between high LDH, CRP ferritin, fibrinogen, cortisol, and long-term hospitalization.

Serum cortisol levels and bioavailability increase through activation of the hypothalamic–pituitary–adrenal axis, and cortisol metabolism decreases as a result of stressful physiologic conditions such as burns, surgery, sepsis, and critical illnesses.[5] The increase in cortisol causes adaptive changes in stress responses, metabolism, and immune regulation.[9–11] Elevated serum cortisol concentrations play an important role in the clinical disease course.[12–14] The prognostic role of serum cortisol in community-acquired pneumonia is known, with increased cortisol levels correlating with the severity of the disease.[15] Elevated cortisol is an independent biomarker that can predict adverse outcomes and mortality in this group of patients.[7,10,15] The effect of COVID-19 on cortisol is currently unknown, and studies on the role of cortisol in predicting COVID-19 patient hospital length of stay are insufficient. The correlation between acute phase reactants and increased cortisol may allow cortisol to serve as a marker of prolonged hospitalization. Elevated LDH, CRP, ferritin, and fibrinogen levels are associated with severe COVID-19.[16] This study did not show a relationship between acute phase reactants and the mortality of survival and nonsurvival groups. Probably, this was because there were a lower number of cases in the nonsurvival group. However, serum cortisol levels and inflammatory parameters may be useful for predicting prolonged hospital stays and disease severity in COVID-19 patients. In this study, serum cortisol was a better independent predictor of prolonged hospital stays than other biochemical markers, likely because it is a marker of illness severity. This study has some limitations. Cortisol levels can vary between individuals due to differences in stress response. Pulsatile cortisol release may not be the same in COVID-19-infected as healthy patients. This study should be supported by prospective studies. Overall, it was observed that elevated cortisol levels could predict disease severity and long-term hospitalization of COVID-19 patients.

CONCLUSION

Serum cortisol levels should be evaluated together with inflammatory markers to predict the severity of COVID-19 pneumonia and length of hospital stay.

Ethics Committee Approval

This study approved by the Haseki Training and Research Hospital Clinical Research Ethics Committee (Date: 17.04.2020, Decision No: 2020-44).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: H.E.A.; Design: S.A.; Supervision: A.C.K.; Fundings: R.D.A.; Data: A.C.K., B.Ç.; Analysis: H.E.A.; Literature search: F.T.; Writing: F.T., B.Ç.; Critical revision: F.T., S.A., B.Ç.

Conflict of Interest

None declared.

REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470–3. [CrossRef]
2. Yormaz B, Ergun D, Tulek B, Ergun R, Korez KM, Suerdem M, et al. The evaluation of prognostic value of acute phase reactants in the COVID-19. Bratisl Lek Listy 2020;121:628–33. [CrossRef]
3. Oswald LM, Zandi P, Nestadt G, Potash JB, Kalaydjian AE, Wand GS. Relationship be-tween cortisol responses to stress and personality. Neuropsychopharmacology 2006;31:1583–91. [CrossRef]
4. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 2020;8:659–60.
5. Teblick A, Peeters B, Langouche L, Van den Berghe G. Adrenal function and dysfunction in critically ill patients. Nat Rev Endocrinol 2019;15:417–27. [CrossRef]
6. Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, et al. Redefining the stress cortisol response to surgery. Clin Endocrinol (Oxf) 2017;87:451–8.
7. Salluh JI, Shinotsuka CR, Soares M, Bozza FA, Lapa e Silva JR, Tura BR, et al. Cortisol levels and adrenal response in severe community-acquired pneumonia: a systematic review of the literature. J Crit Care 2010;25:541.e1–8. [CrossRef]
8. Lagadinou M, Salomou EE, Zareifopoulos N, Marangos M, Gogos C, Velissaris D. Prog-nosis of COVID-19: Changes in laboratory parameters. Infez Med 2020;28:89–95.
9. Widmer IE, Puder JJ, König C, Pargger H, Zerkowski HR, Girard J, et al. Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab 2005;90:4579–86. [CrossRef]
10. Kolditz M, Höffken G, Martus P, Rohde G, Schütte H, Bals R, et al; CAPNETZ study group. Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study. BMC Infect Dis 2012;12:90. [CrossRef]
11. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol 2013;132:1033–44. [CrossRef]
12. Ehrhart-Bornstein M, Hinson JP, Bornstein SR, Scherbaum WA, Vinson GP. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. Endocr Rev 1998;19:101–43. [CrossRef]
13. Kanczkowski W, Chatzigeorgiou A, Grossklaus S, Sprott D, Bornstein SR, Chavakis T. Role of the endothelial-derived endogenous anti-inflammatory factor Del-1 in inflammation-mediated adrenal gland dysfunction. Endocrinology 2013;154:1181–9. [CrossRef]
14. Kanczkowski W, Alexaki VI, Tran N, Großklaus S, Zacharowski K, Martinez A, et al. Hypothalamo-pituitary and immune-dependent adrenal regulation during systemic inflammation. Proc Natl Acad Sci U S A 2013;110:14801–6. [CrossRef]
15. Christ-Crain M, Stolz D, Jutla S, Couppis O, Müller C, Bingisser R, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 2007;176:913–20. [CrossRef]
16. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF, et al. Hyperferritinemia in critically ill COVID-19 patients - Is ferritin the product of inflammation or a pathogenic mediator? Clin Chim Acta 2020;509:249–51.

Serum Kortizol, COVID-19 Hastaları İçin Hastanede Yatış Süresini Tahmin Etmek İçin Yeni Bir Belirteç Olabilir

Amaç: COVID-19 enfeksiyonu pnömoniden akut respiratuar distres sendromuna ve mortaliteye kadar çeşitli klinik durumlara yol açabilir. Bu çalışmanın amacı, serum kortizol düzeylerinin COVID-19 hastalığının prognozuna etkisinin olup olmadığını değerlendirmektir.

Gereç ve Yöntem: 18.03.2020-31.05.2020 tarihleri arasında İstanbul Haseki Eğitim ve Araştırma Hastanesi dahiliye kliniklerinde yatan COVID-19 pnömoni hastalarını içeren geriye dönük bir çalışma yürütüldü. Hastaların demografik verileri, laboratuvar testleri ve klinik sonuçları kaydedildi. Hastalar yatışlarına göre 1–10 gün ve ≥10 gün olmak üzere iki gruba ayrıldı. Her iki grup da yaş ortalamalarına ve hastanede kalış/taburcu olma sürelerine göre sınıflandırıldı. Laboratuvar parametreleri analiz edildi.

Bulgular: Bu çalışma 129 hasta üzerinde yapıldı. Exitus olan hasta sayısı 13, hayatta kalanların sayısı 116 idi. Exitus olanların yaş ortalaması 68.7±10.9, taburcu olanların yaş ortalaması 55.7±15.9 idi (p=0.001). Hastanede uzun süreli yatanhastalarda serum kortizol düzeyleri daha yüksek saptandı. Hemogram ve biyokimyasal parametrelerde gruplar arasında anlamlı fark yoktu. Yapılan korelasyon analizinde serum kortizol düzeyleri ile yatış süresi arasında yakın bir ilişki saptandı. Korelasyon ve regresyon analizine göre yüksek serum kortizol düzeyleri anlamlı bulundu.

Sonuç: Serum kortizol seviyeleri COVID-19 hastalarında hastanede kalış süresini ve prognozu tahmin edebilir.

Anahtar Sözcükler: COVID-19; kortizol; yatış süresi.