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Serum cortisol as a predictor of major adverse outcomes in patients with COVID-19

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RESEARCH

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ABSTRACT

Background
Several biomarkers were found to predict the severity and outcome of COVID-19 infection.

Aims
To determine the serum cortisol response in patients with Coronavirus Disease 2019 (COVID-19) and its correlation with disease outcomes.

Methods
A prospective study among confirmed COVID-19 patients aged 18 years old and above. Morning cortisol levels were measured within 24 hours of admission. Relationship between cortisol levels and outcomes (intensive care unit (ICU) admission, intubation, and death) were analysed.

Results
A total of 206 patients positive for COVID-19 (mean age of 53.6±15.2 years) were included in the study. Mortality was recorded in 21 (30.4 per cent) patients with cortisol levels of ≥570nmol/L, 6 (8.8 per cent) among patients with 181–569nmol/L cortisol level, and 8 (11.6 per cent) among patients with ≤180nmol/L cortisol. Patients with cortisol levels of ≥570nmol/L were more likely to be admitted to the ICU, be intubated and longer hospital stay. Serum cortisol and ferritin levels were the most significant predictors of mortality.

Conclusion
On admission, the morning cortisol level was predictive of mortality, ICU admission, intubation, and length of hospital stay in patients with COVID-19 and may be listed as an independent predictor for worse outcomes of COVID-19 infection.

Key Words
Cortisol, COVID-19, outcomes, severity, mortality

What this study adds:

1. What is known about this subject?
Several biomarkers were suggested to predict the severity and outcome among patients with COVID-19 infection.

2. What new information is offered in this study?
Serum cortisol is predictive of mortality, ICU admission, intubation and length of hospital stay in patients with COVID-19 and can be used as an independent predictor for the disease.

3. What are the implications for research, policy, or practice?

The findings of this research will facilitate a more focused and aggressive intervention and early ICU admission.

Background

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) harshly affected the world in the early 2020.[1] Although majority of patients develop a self-limited course of infection, few develop severe complications that lead to death secondary to acute respiratory distress syndrome and multi-organ failure. Provocation of inflammatory reactions, thrombogenicity, and dysregulated renin angiotensin aldosterone system are proposed mechanisms of the pathogenesis of severe COVID-19.[2]

Systemic infection activates the immune system, which leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of adrenal glucocorticoids, which play an important role in protecting the body against an overactivation of inflammatory cytokines that is thought to be the main cause of adverse outcomes associated with COVID-19 (cytokine storm syndrome).[3] Initially, HPA axis activation is triggered by the release of corticotropin-releasing hormone (CRH) under the influence of proinflammatory cytokines; tumour necrotic factor (TNFα), interleukin 1 (IL-1), and interleukin 6 (IL-6) and interferons and T cell cytokines (IL-2 and INF-γ); then, the CRH stimulates the adrenal glands to release corticosteroids.[4] Ultimately, corticosteroids act by suppressing the immune response to minimize the detrimental effects of inflammatory cytokines.[5]

Viral infections, such as influenza, can trigger the inflammatory response early in the course of the disease, which is accompanied by HPA axis activation. The induced inflammatory response is dominated by macrophage activation and monocyte and T cell infiltration that can be damaging to the host.[6,7]

In subjects with infection of Middle East respiratory syndrome coronavirus (MERS-CoV), another beta coronavirus that genomically has 50 per cent resemblance to SARS-CoV-2, the causative agent of COVID-19, it has been shown that it can trigger an immunogenic response to adrenocorticotropic hormone, a similar mechanism that might apply to SARS-CoV-2.[8,9]

Recently, dexamethasone was found to decrease mortality in subjects with moderate or severe COVID-19, indicating the crucial value of steroids in regulating and protecting the body against undesirable immune system activation.[10] Tan et al. reported that higher cortisol levels in subjects with COVID-19 in the first 48h of admission was associated with higher mortality rates. Furthermore, they found that elevated cortisol levels were better predictors of severity than other laboratory markers associated with COVID-19, such as C-reactive protein (CRP) level, D-dimer level, and neutrophil-to-leukocyte ratio.[11] However, this study was conducted in a relatively older age group (mean: 66.3 years; SD: 15.7) and different populations and divided the patients in a relatively higher cortisol level (744nmol/L) cut-off, remaining as a solo study.

Therefore, the present study aimed to prospectively determine the response of the HPA axis after infection with SARS-CoV-2 and correlate it with mortality, ICU admission, need of intubation, and length of hospital stay.

Method

We conducted a prospective cohort observational study in patients who were diagnosed with COVID-19 and admitted to our institution through the Emergency Department (ED). All patients with confirmed COVID-19 who met the ED criteria of admission (fever, cough, shortness of breath, and malaise) were included in the study. All COVID-19 swab test was done on admission. Patients who did not need admission, patients who were known to have adrenal insufficiency, patients with Cushing syndrome, patients who were on steroids for >2 weeks in the last two years, patients with previous pituitary or adrenal disease or surgery, patients who received steroids during admission before cortisol and adrenocorticotropic hormone (ACTH) sampling, patients without confirmatory COVID-19 test, and patients with cortisol and ACTH sample withdrawn >24h from admission were excluded from the study.

Demographic data (age and gender, clinical presentation, and vital signs were recorded, including maximum recorded temperature (Tmax), heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure. Previous chronic disease; comorbidities, including endocrine diseases, diabetes, and hypertension; pulmonary diseases, including bronchial asthma; chronic obstructive lung disease; and interstitial lung disease or cardiac diseases, including heart failure, ischemic heart disease, and valvular heart diseases, were also recorded. Medications used before and during admission were verified.

COVID-19 was confirmed by nasopharyngeal swab by reverse transcription polymerase chain reaction, which is a

test used with Roche MagNA Pure 96 (MP96) using MagNA Pure 96 DNA and Viral NA Small Volume Kit and Applied Biosystems QuantStudio7 Flex, the instrument with software version 1.3 in a singleplex format.

Cortisol, ACTH, or corticotropin level was measured within the 24 h of hospitalization and between 7:00 and 9:00 in the next morning of admission. For the cortisol level, we used "ADVIA Centaur," which is a solid-phase, competitive chemiluminescent enzyme immunoassay from Siemens. The reference range for morning sample was 118–618nmol/L (4.3–22.4µg/dL). We used ACTH immunoassay for quantitative determination in human ethylenediaminetetraacetic acid (EDTA) plasma. Electrochemiluminescence immunoassay was performed using Elecsys and Cobase immunoassay analysers from Roche. The reference of plasma samples that were drawn between 7 and 10 AM was 1.6–13.9pmol/L (7.2–63.3pg/mL). Laboratory tests, including complete blood count, electrolytes, renal and liver function, D-dimer and CRP levels, and IL-6 level, were performed in all patients.

We measured the outcomes to the date of completion of data collection on June 30, 2020. The outcome categories were as follows: ICU admission, intubation, and death. Moreover, we calculated the length of hospital stay of each patient.

Statistical analysis was conducted using the Statistical Package for Social Sciences version 23.0 (SPSS Inc., IBM, Armonk, New York, USA). Data were reported as numbers and percentages for categorical variables and mean, standard deviation (SD), and median for continuous variables. The chi-square test was used to determine the significant difference in proportions. Test of significance between means (SD) for normally distributed variables was performed using the independent t-test. Test of significance between median for skewed variables was performed using the nonparametric Mann–Whitney U test. Pearson correlation test was used to determine the relationship between linearly related variables, and nonparametric Spearman test was used for nonlinear variables. Kaplan–Meir survival analysis was conducted to determine the survival rate, and a curve was plotted. A logistic regression analysis was conducted to determine the most significant factors associated with mortality among patients positive for COVID-19. A p value <0.05 was considered statistically significant. Prior to recruitment, all procedures and protocols were reviewed and approved by the Institutional Review Board of the institution.

Results

Baseline characteristics

A total of 206 patients positive for COVID-19 were included in the study, with a mean age of 53.6 ± 15.2 years (median, 54.0 years). There were 152 men (73.8 per cent) and 54 (26.2 per cent) women, and 112 (54.4 per cent) were non-Saudi nationals. Moreover, 79 (38.3 per cent) patients had hypertension, 79 (38.3 per cent) had diabetes mellitus, 31 (15.0 per cent) had dyslipidaemia, 18 (8.7 per cent) had chronic kidney disease, and 17 (8.3 per cent) had heart disease.

Subjects were divided into tertiles based on 9AM cortisol levels: lower cortisol level tertile (≤180nmol/L), mean of 68.1 and standard error of mean (SEM) of 5.21); middle tertile (181–569nmol/L), mean of 387.2 (SEM, 12.77); and upper tertile (≥570nmol/L), mean of 936.6 (SEM, 48.07). The 69 patients who had serum cortisol levels (≤180nmol/L were tested for adrenal insufficiency and those with a negative synacthen test were excluded. The sensitivity and specificity of cortisol were 80 per cent and 64.3 per cent, respectively (AUC=0.703, 95 per cent CI 0.603–0.804).

Laboratory results for all 206 patients positive for COVID-19 according to tertiles were shown in Table 1. Analysis of variance showed patients who were in the upper cortisol tertile had significantly higher mean Tmax (p=0.013), higher mean serum creatinine level (p=0.004), higher serum ferritin level (p=0.002), higher CRP level (p=0.010), and higher ACTH level (p<0.001) compared to patients who were in the middle and lower cortisol tertiles. There were no significant differences across sex and nationality (p=0.781 and p=0.759, respectively) and in the proportion of patients with comorbid conditions according to cortisol tertiles (Table 2).

Cortisol level and adverse outcomes (mortality, ICU admission, intubation, and length of hospital stay)

Death occurred in 21 (30.4 per cent) patients who were in the upper cortisol tertile compared to 6 (8.8 per cent) patients in the middle cortisol tertile and 8 (11.6 per cent) in the lower cortisol tertile (p=0.001). Of 35 patients who died, all patients in the low and middle cortisol tertiles died within 28 days, and 18 of 21 (86 per cent) patients in the upper tertile.

More patients who belonged to the upper cortisol tertile (n=40, 58.0 per cent) were admitted to the ICU compared to patients in the middle (n=17, 25.0 per cent) and lower cortisol tertile (n=35, 50.7 per cent) (p<0.001). Furthermore, there were also a significantly larger number of patients who were in the upper cortisol tertile who were intubated

(n=28, 40.6 per cent) compared to patients who were in the middle (n=8, 11.8 per cent) and lower cortisol tertiles (n=13, 18.8 per cent) (p<0.001). The length of hospital stay was significantly longer among patients in the upper cortisol tertile (mean, 12.76 days) compared to patients in the middle (8.41 days) and lower (9.89 days) cortisol tertiles (p=0.011) (Table 3). Kaplan–Meir survival analysis showed that patients who were in the upper cortisol tertile had a 71 per cent survival at five weeks after hospital admission compared to 88 per cent with the middle cortisol tertile group and 94 per cent with the lower cortisol tertile group (Figure 1).

Bivariate Pearson correlation analysis showed that death was significantly associated with an elevated cortisol level (r=0.340, p<0.001), increased ferritin level (r=0.266, p<0.001), increased CRP level (r=0.171, p=0.019), and longer hospital stay (r=0.280, p=0.001). Using death as the dependent factor and cortisol, ferritin, and CRP levels and length of hospital stay as independent factors, stepwise logistic regression analysis showed that cortisol (beta=0.324, p<0.001, 95 per cent CI 0–0) and ferritin (beta=0.270, p=0.002, 95 per cent CI 0–0) levels were the most significant factors for mortality.

Discussion

Cortisol is an adrenal hormone that is activated after acute infections and plays a crucial role in the inflammatory response of the body.[12,13] In this prospective study on patients with COVID-19, we found that higher morning cortisol levels were associated with higher mortality rate. The risk of death was almost three times higher in those with cortisol level >570nmol/L compared with those with lower readings. In parallel, the rates of ICU admission, intubation and length of hospital stay were also higher in subjects with elevated cortisol levels, indicating that cortisol can be used as a predictor of adverse outcomes in patients with COVID-19.

In addition to cortisol level, we found that the admission levels of WBC, haemoglobin, erythrocyte sedimentation rate, CRP, lymphocyte, D-dimer, AST, urea, creatinine, potassium, ferritin, procalcitonin, and IL-6 were found to be associated with worse outcome in terms of ICU admission, mechanical ventilation, or mortality. After applying a stepwise regression analysis, only cortisol and ferritin levels were found to be predictors of mortality.

Based on the study conducted by Tan et al.,[11] in which the cortisol level was set to ≥744nmol/L, we also found significantly higher mortality rate (40.5 per cent versus 11.0 per cent, p<0.001), intubation rate (45.2 per cent versus 18.3 per cent), and ICU admission rate (64.3 per cent versus 39.6 per cent) among patients with high cortisol level (≥744nmol/L) compared to patients with low cortisol levels (<744nmol/L). No significant difference in the length of hospital stay was noted when the cortisol cut-off level was set to 744nmol/L. Tan et al. have examined the relationship between cortisol level and risk of mortalities in three United Kingdom centers and found that risk of death for patients with a mean age of 66 years with cortisol >570µg/dL was higher than those with lower values. Our data showed a similar finding in relatively younger age group (mean, 55 years).[11] We reached a similar conclusion in different populations, which further enhances the predictive value of cortisol level in subjects with COVID-19. In our cohort, we have further shown a positive correlation with other prespecified adverse outcomes, e.g., risk of intubation and length of hospital stay. Using tertiles to represent the data might be more clinically relevant rather than a higher cut-off level of cortisol. Furthermore, our data showed no differences in preadmission comorbidities of patients positive for COVID-19 in all three cortisol tertiles.

Chen et al. reported that CRP, ferritin, lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) levels were significantly higher in severe cases compared to mild cases.[14] Other significant findings, including increased serum amyloid A level, neutrophil-to-lymphocyte ratio, prothrombin time, D-dimer level, fibrin degradation product, and inflammatory cytokine interleukin 2R (IL-2R), TNF-α, and interleukin 10 (IL-10) levels have been reported in other studies.[15]

High cortisol level was observed to be significantly elevated in critically ill patients and shown in several trials to be predictive of severity of illness, including the need of ICU admission and mortality in patients without COVID-19.[16-18] In patients with septic shock, the mortality was significantly higher in those with cortisol level >1242nmol/L.[19] Annane's study suggests that basal plasma cortisol levels are higher in patients who have the highest risk of mortality.[20] Furthermore, cortisol was found to be superior to Acute Physiology and Chronic Health Evaluation (APACHE II) score in predicting worse outcome in patients admitted in the ICU.[21]

The study was conducted under strict methodology by obtaining morning cortisol level on the first day of admission and excluding patients with adrenal or pituitary diseases or who were on steroid before admission. Furthermore, patients with adrenal insufficiency were

excluded by performing the short Synacthen test whenever the 9AM cortisol level was <138nmol/L.

This trial has a relatively small number of patients and conducted in one center; however, the predictive value was obvious after conducting the analysis. Moreover, depending on only one cortisol reading, which might reduce the reliability of the test, the widespread use of steroids in treating patients with COVID-19 after the RECOVERY report makes it difficult from an ethical point of view to withhold steroid therapy to obtain another cortisol level measurement.[22] Furthermore, we were not able to assess the duration of symptoms of patients before hospitalization, and we were not able to document the exact point or time when the patient sought medical attention. However, from our experience of caring patients with COVID-19, patients who were admitted are those who presented to our emergency room with severe symptoms (including shortness of breath, fever not responding to treatment, cough and other symptoms) which usually started three to five days after a diagnosis was made for COVID-19, or those with no previous diagnosis who were first diagnosed in the emergency room. Therefore, the cortisol measurement we reported is a real-world data that provides a practical guide for practicing physicians dealing with COVID-19 patients presenting to acute care hospitals.

Conclusion

We believe that serum cortisol may be listed as a marker to predict worse outcomes in subjects with COVID-19 disease. Mortality increased by threefold with cortisol levels of >570nmol/L, providing a level that can be used in clinical settings as it is a single measurement, cheap, and an affordable test that can be easily performed in most hospitals. However, additional studies are needed to evaluate the effect of steroid use on patient's outcome depending on the initial cortisol level, which might be of clinical relevance.

References

1. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: Challenges for global health governance. JAMA. 2020;323:709-710.
2. Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting disease severity and outcome in COVID-19 patients: A review of multiple biomarkers. Arch Pathol Lab Med. 2020;144(12):1465-1474.
3. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846-848.
4. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335(1):2-13.
5. Ronchetti S, Migliorati G, Bruscoli S, et al. Defining the role of glucocorticoids in inflammation. Clin Sci (Lond). 2018;132(14):1529-1543.
6. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20(6):355-362.
7. Song JW, Zhang C, Fan X, et al. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat Comm. 2020;11(1):3410.
8. Teblick A, Peeters B, Langouche L, et al. Adrenal function and dysfunction in critically ill patients. Nat Rev Endocrinol. 2019;15:417-427.
9. Pal R. COVID-19, hypothalamo–pituitary–adrenal axis and clinical implications. Endocrine. 2020;68:251-252.
10. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. 2020. doi: 10.1056/NEJMoa2021436
11. 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.
12. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351-1362.
13. Besedovsky H, Sorkin E, Keller M, et al. Changes in blood hormone levels during the immune response. Proc Soc Exp Biol Med. 1975;150:466-470.
14. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-2629.
15. Ji M, Yuan L, Shen W, et al. Characteristics of disease progress in patients with coronavirus disease 2019 in Wuhan, China. Epidemiol Infect. 2020;148:e94.
16. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med. 2004;350(16):1629-1638.
17. Wade CE, Lindberg JS, Cockrell JL, et al. Upon-admission adrenal steroidogenesis is adapted to the degree of illness in intensive care unit patients. J Clin Endocrinol Metab. 1988;67(2):223-227.
18. Christ-Crain M, Stolz D, Jutla S, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med. 2007;176:913-920.

19. Sam S, Corbridge TC, Mokhlesi B, et al. Cortisol levels and mortality in severe sepsis. Clin Endocrinol (Oxf). 2004;60(1):29-35.
20. Annane D, Sébille V, Troché G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283(8):1038-1045.
21. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med. 1995;23(1):78-83.
22. Wilkinson E. RECOVERY trial: the UK covid-19 study resetting expectations for clinical trials. BMJ. 2020;369.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

Approval for the conduct of the study was issued by the Institutional Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Table 1: Analysis of variance (ANOVA) of anthropometric and laboratory parameters according to cortisol tertiles in 206 patients with COVID-19

	Lower cortisol tertile (<180nmol/L) N=69 Mean±SD (median)	Middle cortisol tertile (level from 180 to 569nmol/L) N=68 Mean±SD (median)	Upper cortisol tertile (level >570nmol/L) N=69 Mean±SD (median)	p values
Age	52.9±14.8 (51.0)	52.69±16.19 (54.00)	55.26±14.69 (58.00)	0.547
BMI	28.5±5.3 (27.6)	30.25±7.61 (29.59)	29.64±6.38 (28.35)	0.293
Maximum recorded temperature	37.5±0.9 (37.4)	37.73±0.86 (37.70)	37.98±0.89 (38.00)	0.013*
Heart rate	99.8±20.7 (100.0)	98.81±17.42 (99.50)	99.64±18.47 (100.00)	0.948
Respiratory rate	28.8±6.9 (30.0)	24.93±6.37 (22.00)	26.25±6.71 (24.00)	0.003*
Systolic blood pressure	118.9±22.4 (117.00)	119.77±19.28 (121.00)	119.49±24.77 (117.00)	0.971
Diastolic blood pressure	69.2±17.2 (68.00)	69.82±13.27 (70.00)	69.74±19.88 (68.00)	0.977
White cell count	8.85±6.42 (7.50)	7.66±4.28 (6.85)	7.80±3.98 (7.00)	0.312
Hemoglobin	13.30±2.01 (13.70)	13.31±2.19 (13.60)	12.87±2.49 (13.00)	0.421
Lymphocytes	1.43±1.40 (1.00)	1.25±0.62 (1.10)	1.23±1.55 (0.80)	0.572
Platelets	276.55±130.95 (241.0)	259.89±102.60 (243.50)	247.24±105.43 (234.00)	0.318
Neutrophils	6.73±5.33 (5.90)	5.24±2.85 (4.90)	6.51±5.41 (5.60)	0.145
Ferritin	1112.80±1326.8 (764.0)	814.50±752.50 (593.00)	1554.11±1456.98 (1283.95)	0.002*
C-reactive protein	123.31±78.95 (113.0)	87.61±69.16 (82.90)	125.79±83.26 (107.00)	0.010*
Erythrocyte sedimentation rate	71.35±32.34 (70.0)	71.15±33.78 (71.50)	75.25±39.33 (74.00)	0.855
D-dimer	2.04±5.33 (1.03)	1.78±3.02 (0.84)	1.90±2.86 (1.05)	0.875
Adrenocorticotropic hormone	1.63±2.56 (0.30)	2.91±2.44 (2.20)	3.91±3.15 (3.15)	<0.001*
Creatinine	86.03±33.58 (78.00)	116.99±103.85 (84.00)	221.51±415.96 (87.00)	0.004*
Sodium	137.57±4.68 (138.00)	137.27±4.36 (138.00)	136.19±6.49 (136.00)	0.274
Potassium	4.25±0.56 (4.30)	4.28±0.75 (4.30)	4.31±0.71 (4.30)	0.901
Fasting blood glucose	9.14±4.51 (7.68)	8.61±4.52 (7.10)	8.89±3.98 (7.60)	0.782
Corrected calcium	2.36±0.20 (2.33)	2.32±0.15 (2.33)	2.30±0.17 (2.29)	0.184
Vitamin D	45.10±32.25 (35.9)	43.18±30.89 (36.90)	43.45±23.00 (39.40)	0.951
Procalcitonin	0.84±2.21 (0.14)	1.28±3.46 (0.18)	3.38±12.71 (0.33)	0.21
Interleukin-6	434.54±1020.73 (105.40)	194.30±760.45 (48.73)	182.65±301.92 (100.20)	0.254

Note: *Significant p values – significant differences in the means in the samples done by Analysis of variance (ANOVA)

Table 2: Correlation between comorbidities in 206 patients with COVID-19 and cortisol tertiles

Comorbidities	Low tertile (<180nmol/L) N=69	Middle tertile (180–569 nmol/L) N=68	High tertile (≥570nmol/L) N=69	Correlation coefficients	p values*
Hypertension	24 (34.8%)	30 (44.1%)	25 (36.2%)	1.459	0.482
Diabetes	23 (33.3%)	30 (44.1%)	26 (37.7%)	1.704	0.426
Dyslipidemia	9 (13.2%)	9 (13.2%)	13 (18.8%)	1.121	0.571
Heart disease	4 (5.8%)	6 (8.8%)	7 (10.1%)	0.905	0.636
Respiratory diseases	5 (7.2%)	5 (7.4%)	8 (11.6%)	1.062	0.588
Chronic kidney disease	1 (1.4%)	5 (7.4%)	6 (8.7%)	3.734	0.155

Note: * p values done by chi-square test

Table 3: Outcomes of patients with COVID-19 according to cortisol tertiles. Intensive care unit, ICU

Outcome	Low tertile (<180 nmol/L) N=69	Middle tertile (180–569 nmol/L) N=68	High tertile (≥570 nmol/L) N=69	p values*
Total death, %	8 (11.6%)	6 (8.8%)	21 (30.4%)	0.001
Ventilated, %	13 (18.8%)	8 (11.8%)	28 (40.6%)	<0.001
ICU, %	35 (50.7%)	17 (25.0%)	40 (58.0%)	<0.001
Length of hospital stay (mean±SD)	9.89±6.26	8.41±5.24	12.76±9.22	0.011

Figure 1: Kaplan–Meir survival analysis showed that patients who were in the upper cortisol tertile had a 71% survival at 5 weeks after hospital admission compared to 88% with the middle cortisol tertile group and 94% with the lower cortisol tertile group (Figure 1)