Cortisol Levels During First Admission Day Are Associated With Clinical Outcomes in Surgical Critically Ill Patients

Noam Goder, MD[1,2,3]

Fabian Gerstenhaber, MD[2,3]

Amir Gal Oz, MD, MBA[1,3]

Dekel Stavi, MD[1,3]

Yoel Angel, MD, MBA[1,3]

Asaph Nini, MD, MSc[1,3]

Yael Lichter, MD[1,3]

Oded Sold, MD[2,3]

IMPORTANCE: To explore the correlation between cortisol levels during first admission day and clinical outcomes.

OBJECTIVES: Although most patients exhibit a surge in cortisol levels in response to stress, some suffer from critical illness-related corticosteroid insufficiency (CIRCI). Literature remains inconclusive as to which of these patients are at greater risk of poor outcomes.

DESIGN: A retrospective study.

SETTING: A surgical ICU (SICU) in a tertiary medical center.

PARTICIPANTS: Critically ill patients admitted to the SICU who were not treated with steroids.

MAIN OUTCOMES AND MEASURES: Levels of cortisol taken within 24 hours of admission (day 1 [D1] cortisol) in 1412 eligible patients were collected and analyzed. Results were categorized into four groups: low (0–10 µg/dL), normal (10–25 µg/dL), high (25–50 µg/dL), and very high (above 50 µg/dL) cortisol levels. Primary endpoint was 90-day mortality. Secondary endpoints were the need for organ support (use of vasopressors and mechanical ventilation [MV]), ICU length of stay (LOS), and duration of MV.

RESULTS: The majority of patients (63%) had high or very high D1 cortisol levels, whereas 7.6% had low levels and thus could be diagnosed with CIRCI. There were statistically significant differences in 90-day mortality between the four groups and very high levels were found to be an independent risk factor for mortality, primarily in patients with Sequential Organ Failure Assessment (SOFA) less than or equal to 3 or SOFA greater than or equal to 7. Higher cortisol levels were associated with all secondary endpoints. CIRCI was associated with favorable outcomes.

CONCLUSIONS AND RELEVANCE: In critically ill surgical patients D1 cortisol levels above 50 mcg/dL were associated with mortality, need for organ support, longer ICU LOS, and duration of MV, whereas low levels correlated with good clinical outcomes even though untreated. D1 cortisol level greater than 50 mcg/dL can help discriminate nonsurvivors from survivors when SOFA less than or equal to 3 or SOFA greater than or equal to 7.

KEYWORDS: cortisol; critical illness; critical illness-related corticosteroid insufficiency; stress response

INTRODUCTION

Severe illnesses, trauma, anesthesia, and surgery are accompanied by activation of the hypothalamic-pituitary-adrenal axis (HPAA) and increased serum corticotropin and cortisol concentrations (1). This activation is an essential response to stress and contributes to the maintenance of homeostasis (2, 3). In

KEY POINTS

Question: Can day 1 (D1) cortisol levels predict outcome in critically ill surgical patients?

Findings: In this retrospective study, we analyzed the results of cortisol levels, taken within 24 hours from admission, in 1412 patients who were not treated with steroids and compared with 90-day mortality. Very high levels (above 50 mcg/dL) were associated with, and predictive of, 90-day mortality, whereas low levels correlated with good clinical outcomes even though untreated.

Meaning: D1 cortisol levels are informative, associated with clinical outcomes, and can predict mortality.

2008, an international multidisciplinary task force of the Society of Critical Care Medicine (SCCM) coined the term "critical illness-related corticosteroid insufficiency" (CIRCI) to describe impairment of the HPAA during critical illness and recommended using either a delta total serum cortisol of less than 9 µg/dL after IV cosyntropin (250 µg) administration or a random total cortisol level of less than 10 µg/dL as confirmatory diagnostic tests (4). The SCCM and the European Society of Intensive Care Medicine revisited this recommendation and published guidelines for treatment in 2017, suggesting supplemental corticosteroids in treatment of patients with septic shock and ongoing need for vasopressor therapy, as well as in other forms of critical illness (5). This was further reiterated in the Surviving Sepsis Campaign guidelines, last updated in 2021 (6). Trauma and a surgical insult without sepsis also trigger cortisol hypersecretion in response to stress, executed by the afferent nerve signals derived from the surgical site (7). This response mainly occurs in patients undergoing highly invasive procedures (grade III according to the modified Johns Hopkins surgical criteria [8]), in which cortisol levels peak in the first 24 hours postoperatively and can stay high up to 1 week after surgery (9–11). To this end, it is common practice to administer perioperative stress-dose steroids to patients with suspected or confirmed HPAA suppression (12). Furthermore, the administration of the sedative drug Etomidate, a known inhibitor of cortisol synthesis, was found to be associated with increased morbidity and mortality in critically ill patients, including trauma and surgical patients (13–18). Of note, the clinical impact of CIRCI and the recommendation to supplement steroids in cases of inadequate cortisol levels have been repeatedly challenged in the literature and inconsistency in practice remains among intensivists (19–22).

In this retrospective study, we analyzed results of cortisol levels in the first morning following admission of critically ill patients to the surgical ICU (SICU) in a tertiary medical center and compared it with 90-day mortality and with ICU length of stay (LOS).

MATERIALS AND METHODS

This was a retrospective observational study conducted using routinely collected clinical data from patients admitted to the adult SICU at the Tel Aviv Sourasky Medical Center in Israel. The study focused on individuals undergoing general surgery operations, experiencing surgery-related complications, trauma, and gastrointestinal bleeding.

The inclusion criteria encompassed all adult SICU patients who had undergone a cortisol blood test within 24 hours of admission, following the unit's protocol of collecting blood samples between 5:00 and 6:00 AM. Patients who received steroids during admission, at any time before measurement of cortisol, were excluded from the study. Additionally, individuals on chronic steroid therapy were also excluded. A comparative analysis was conducted to assess for potential selection bias that could have originated from exclusion criteria.

Admission day 1 (D1) total cortisol levels were determined by immunoassay and results were grouped as follows: low (0–10 µg/dL), normal (10–25 µg/dL), high (25–50 µg/dL), and very high (above 50 µg/dL). Thresholds for low, normal, and high levels were chosen according to literature for the critically ill population (5, 23, 24). In addition, a Chi-Square Automatic Interaction Detection (CHAID) tree model was employed to detect the best-fitting values that optimize the chi-square value and found that these suggested cut points could be aligned with those reported above and allowed for the addition of a fourth "very high" group (cortisol above 50 µg/dL). Analysis of endpoints was subsequently conducted according to these stratified groups. Primary endpoint was 90-day mortality; secondary endpoints were the need for organ
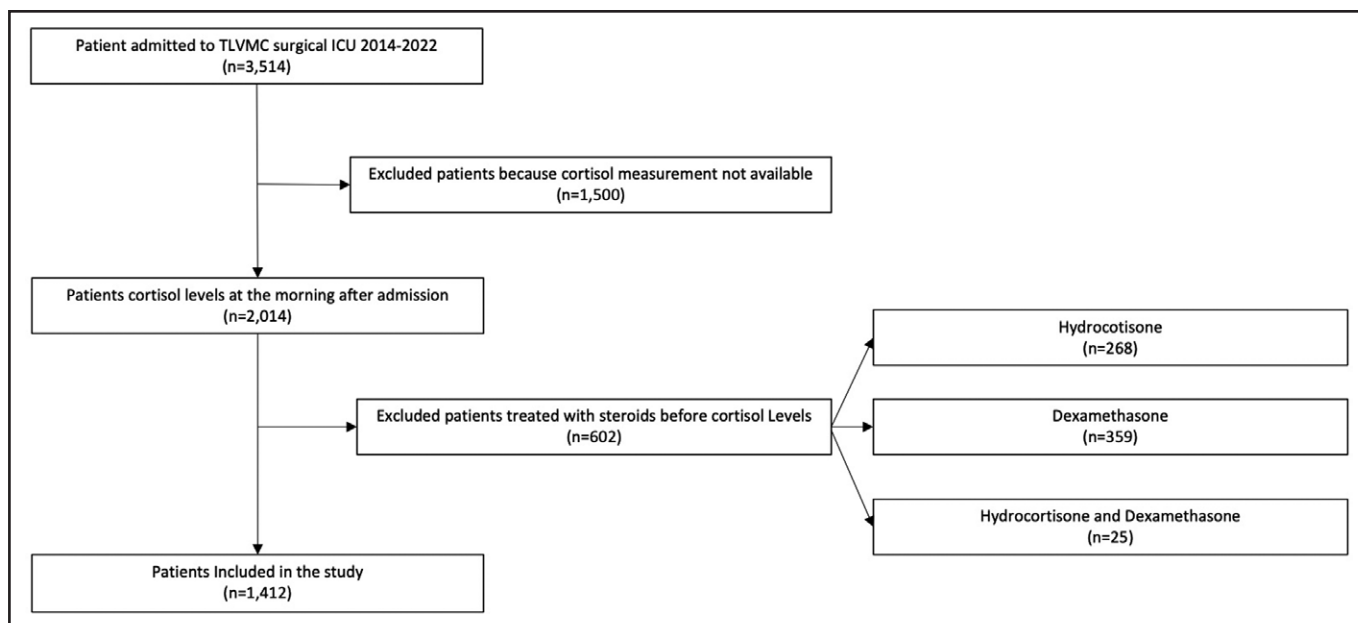
Figure 1. Flowchart of patient inclusion. TLVMC = Tel-Aviv Sourasky Medical Center.

support (use of vasopressors and mechanical ventilation [MV]), ICU LOS, and duration of MV.

The data, collected as part of routine clinical practice, was recorded in the SICU database (MetaVision; IMDsoft, Tel-Aviv, Israel). Retrospective collection and analysis of all data in this study were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975 and received approval from the ethics committee of the Tel Aviv Medical Center (Institutional Review Board No. 0408-23-TLV, August 1, 2023).

Continuous variables are presented as means and sDs for normally distributed data. Categorical variables are reported as counts and percentages of participants within each group.

Difference between cortisol groups was employed using one-way analysis of variance (ANOVA) for continuous variables and with chi-square test for categorical variables. The Kruskal-Wallis test (nonparametric) was used to determine if there are statistically significant differences between two or more groups when the assumptions of the ANOVA were not met. The independent samples Kruskal-Wallis test, a nonparametric statistical test, was employed to evaluate differences in medians across independent groups with ordinal data or non-normally distributed interval data. To assess the impact of cortisol levels on mortality among diverse subpopulations of ICU patients, we employed a CHAID tree analysis, stratifying patients according to low and high Sequential Organ Failure Assessment (SOFA) scores. A logistic regression analysis targeting 90-day mortality included clinically relevant variables: categorized cortisol levels, SOFA score, age, and gender, chosen for their importance in critical care outcomes. Minimal missing data were addressed by reviewing patient records. The model provided odds ratios (ORs) for mortality risk, with statistical significance and 95% CIs. We performed all statistical analyses using IBM SPSS Statistics for Windows, Version 29 (IBM Corp., Armonk, NY).

RESULTS

During the years 2014–2022, a total of 3514 patients were admitted to the Tel-Aviv Medical Center SICU, of which 2014 patients had cortisol level measurement obtained in the morning following admission (**Fig. 1**). Comparative analysis between patients with and without cortisol measurements was conducted to investigate potential differences that could indicate selection bias. Our analysis revealed no significant differences in key parameters, including age (cortisol positive: 63.7 ± 19.8 yr vs. cortisol negative: 64.7 ± 17.5 yr; $p = 0.142$), gender distribution (cortisol positive: 59% males vs. cortisol negative: 58.2% males; $p = 0.653$), and mortality rate (cortisol positive: 10.4% vs. cortisol negative: 10.2%; $p = 0.638$). Additionally, the admission SOFA scores showed no

significant difference between the groups (cortisol positive: median 3 [interquartile range (IQR)] 1–5 vs. cortisol negative: median 2 [IQR 1–6]; $p = 0.456$), indicating a similar severity of illness at admission. We observed a statistically significant difference in the LOS, with patients without cortisol measurements having a median LOS of 2 days (IQR 1–4) compared with 3 days (IQR 2–6) for patients who had cortisol measurements ($p < 0.001$). Six hundred two patients (29.9%) received steroids before blood sampling and were thus excluded from the analysis. Among these, 268 were treated with hydrocortisone; within this subgroup, 167 (62.3%) had very high cortisol levels, 69 (25.7%) had high levels, 23 (8.6%) had normal levels, and 9 (3.4%) had low levels. Dexamethasone was administered to 359 patients in the operating room, with cortisol levels subsequently observed as very high in 4 (1.1%), high in 87 (24.2%), normal in 108 (30.1%), and low in 160 (34.3%). Notably, 25 patients received both hydrocortisone and dexamethasone. Comparatively, these 602 patients showed similar age (64.2 ± 16.9 vs. 64.7 ± 17.5; $p = 0.519$), ICU LOS (median, 2 d [IQR, 1–5 d] vs. 3 d [IQR, 2–6 d]; $p = 0.145$), and mortality rate (8.0% vs. 10.4%; $p = 0.09$), to those not treated with steroids before cortisol measurement. However, these patients were more likely to be male (53.2% vs. 61.5%; $p < 0.001$) and had a slightly higher SOFA score range (median 3 [IQR, 1–7] vs. 3 [IQR, 1–5]; $p = 0.007$).

After exclusion, a total of 1412 patients (70.1%) who were included in the final analysis mean age was 64.7 ± 17.5 years and 61.5% were male. Patients' basic characteristics and primary diagnoses at admission are detailed in **Table 1**.

D1 Cortisol Levels

Cortisol measurements ranged from 0 to 63.4 µg/dL, distributed as very high in 287 patients (20.3%), high in 603 (42.7%), normal in 415 (29.4%), and low in 107 (7.6%). The chi-square value from the CHAID model was 81.8, compared with 77.0 achieved with our selected cut points, confirming that our choice of four groups of cortisol levels were statistically sound and maintained the model's validity (**Fig. S1**, http://links.lww.com/CCX/B338).

Age was found to significantly correlate with D1 cortisol levels, with the Kruskal-Wallis test demonstrating a variation across different age categories ($p < 0.001$). D1 cortisol levels were not associated with gender (Pearson χ^2 test = 6.152; $p = 0.104$) or with body mass index ($p = 0.064$).

D1 Cortisol Levels and Mortality

Death occurred in a total of 147 cases (10.4%), with statistically significant differences in 90-day mortality between the four cortisol level groups. For the group with low cortisol (0–10 µg/dL), death occurred only once (0.9%). For the normal (10–25 µg/dL), high (25–50 µg/dL), and very high (above 50 µg/dL) groups, death occurred in 22 (5.3%), 56 (9.3%), and 68 (23.7%) patients, respectively (Pearson χ^2 test = 77.024; $p < 0.001$). Post hoc analysis indicated that each cortisol level group was significantly different from the others at a p value of less than 0.05.

In a logistic regression analysis of 90-day mortality considering factors such as cortisol levels, SOFA score, age, and gender, a significant difference was found in mortality. Patients with very high cortisol values had an OR for mortality of 2.185 with a 95% CI ranging from 1.242 to 3.845 compared with those with normal cortisol. No statistical difference was found between normal cortisol group and the group of low cortisol with OR 0.244 (0.032–1.878) or high cortisol with OR 1.096 (0.635–1.892). Results are detailed in **Table 2**.

When considering the potential additive effect of cortisol on SOFA scores in predicting survival, we observed cortisol's contribution in two scenarios. First, among the 837 patients with a SOFA score less than or equal to 3, those with cortisol levels greater than 50 µg/dL (726 patients) exhibited a mortality rate of 8.1%, contrasting with a 2.3% mortality rate for those with cortisol levels less than or equal to 50 µg/dL ($p = 0.008$). Additionally, in the group of 250 patients with a SOFA score of 7 and above, there was a 45.4% mortality rate among the 97 patients with cortisol levels above 50 µg/dL, compared with a 24.2% mortality rate among the 153 patients with cortisol levels less than or equal to 50 µg/dL ($p = 0.003$; **Fig. 2**).

Cortisol Levels and Mortality in Different Clinical Groups

In a study of 531 patients who underwent urgent surgery, a significant correlation was observed between D1 cortisol levels and mortality ($p < 0.001$), with 84 deaths reported. Of these, 45.2% had very high cortisol levels, 38.1% were within the high range, and 16.7% were in the normal range, whereas no deaths were noted in the low cortisol group. Among the 525 patients who underwent elective surgeries seven deaths were reported with no significant difference

TABLE 1.
Baseline Patient Characteristics

Demographics	All patients
Number of patients	1412
Age, yr, mean ± SD	64.7±17.5
Weight, kg, mean ± SD	74.8±16.6
Height, cm, mean ± SD	169.1±10.3
Body mass index, median (IQR)	25.5 (22.8–28.7)
Male gender, n (%)	869 (61.5)
Clinical parameters	
ICU length of stay, d, median (IQR)	3 (2–6)
Sequential Organ Failure Assessment score at admission, median (IQR)	3 (1–5)
Deceased, n (%)	147 (10.4)
Diagnosis at admission	
No operation performed, total (%)	356 (25.2)
Out of which, total (%)	
Trauma	121 (34.0)
Upper gastrointestinal bleeding	95 (26.7)
Pancreatitis	26 (7.3)
Lower gastrointestinal bleeding	22 (6.2)
Others	92 (25.8)
Elective operation, total (%)	525 (37.2)
Out of which, total (%)	
Pancreatectomy	136 (25.9)
Hepatectomy	111 (21.1)
Esophagectomy	45 (8.6)
Sarcoma resection	43 (8.2)
Hyperthermic intraperitoneal chemotherapy	33 (6.3)
Gastrectomy	18 (3.4)
Others	139 (26.5)
Urgent operation, total (%)	531 (37.6)
Out of which, total (%)	
Gastrointestinal perforation	75 (14.2)
Trauma	59 (11.2)
Postoperative abdominal sepsis	53 (10.0)
Small bowel obstruction	51 (9.6)
Cholecystitis	33 (6.2)
Upper gastrointestinal bleeding	25 (4.7)
Large bowel obstruction	21 (4.0)
Acute mesenteric ischemia	21 (4.0)
Postoperative bleeding	21 (4.0)
Others	197 (32.4)

IQR = interquartile range.

TABLE 2.
Odds Ratios and 95% CIs for Mortality From Logistic Regression Analysis

| Parameter	OR	Significance	Wald	(95% CI Lower–Upper)
Gender (male)	0.825	0.344	0.894	(0.554–1.229)
Age	1.048	< 0.001	36.76	(1.032–1.064)
Cortisol < 10 µg/dL (low)	0.244	0.176	1.835	(0.032–1.878)
Cortisol 10–25 µg/dL (normal)	1.0 (reference)	0.002	14.674	
Cortisol 25–50 µg/dL (high)	1.096	0.741	0.109	(0.635–1.892)
Cortisol > 50 µg/dL (very high)	2.185	0.007	7.355	(1.242–3.845)
Sequential Organ Failure Assessment	1.323	< 0.001	95.1	(1.251–1.399)

OR = odds ratio.
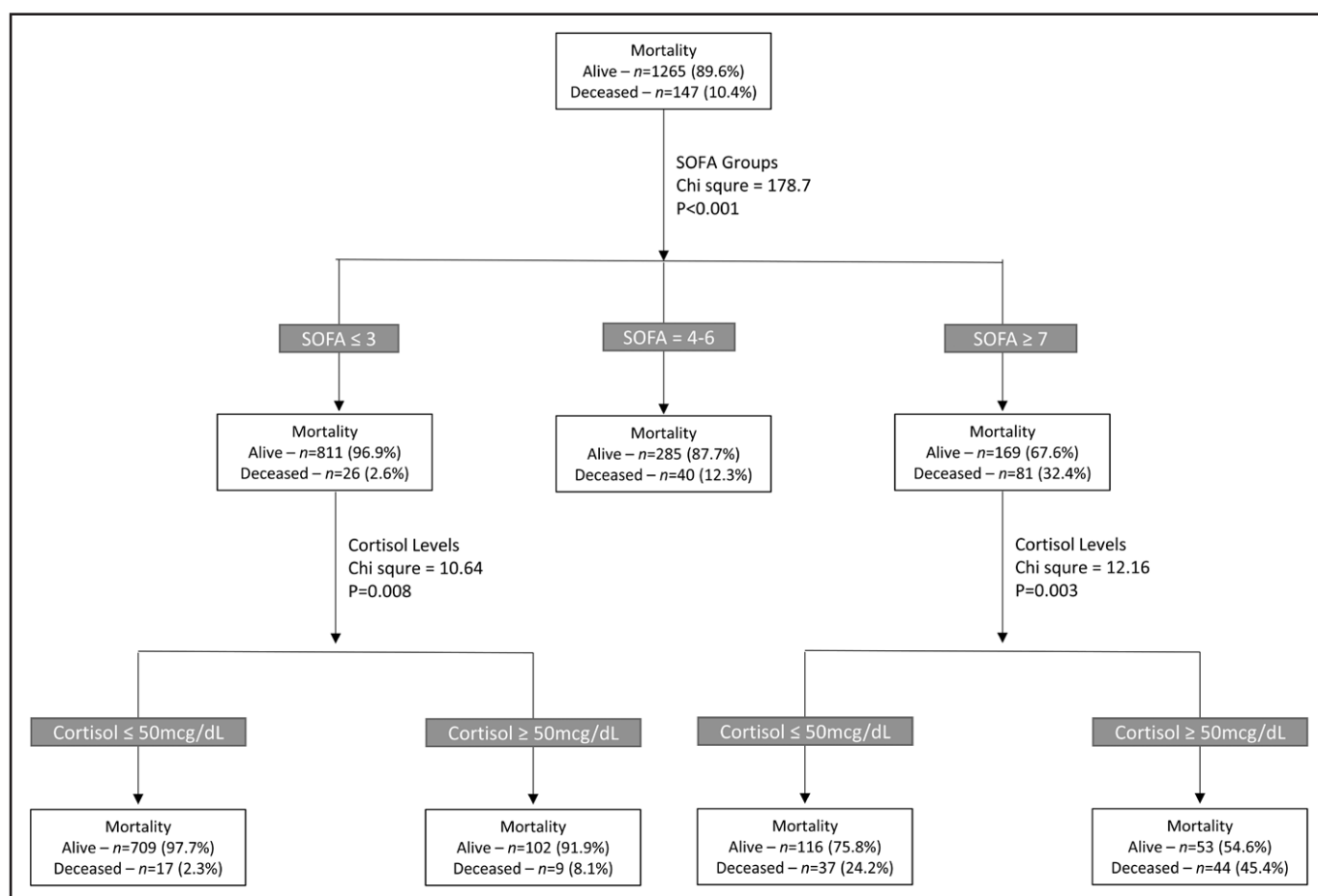
Figure 2. Mortality rate by Sequential Organ Failure Assessment (SOFA) score and by day 1 cortisol levels.

in mortality across cortisol levels ($p = 0.109$). Finally, among the 356 patients who were admitted directly to the SICU without undergoing surgery, there were 56 deaths: 48.2% in the very high group, 37.5% in the high group, 14.3% in the normal group, and no deaths in the low group ($p < 0.001$). Mortality rates by clinical group are shown in **Figure 3**.

D1 Cortisol Levels in Patients Receiving Organ Support

The statistical analysis establishes significant associations between cortisol levels and two critical clinical interventions: vasopressor support (280 patients) and MV (678 patients; both with $p < 0.001$). In the
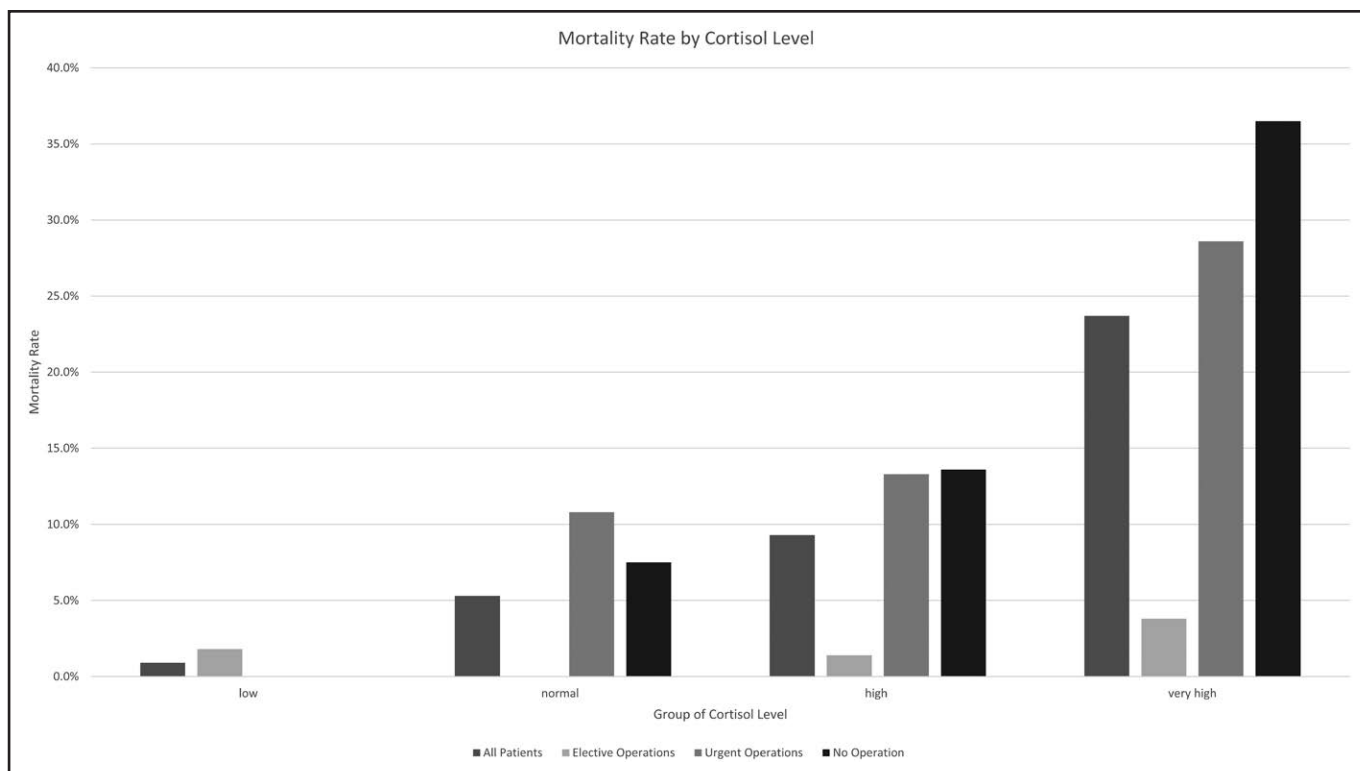
Figure 3. Mortality rate by cortisol level, for all patients and per diagnosis at admission: elective operations, urgent operations, and no operation.

context of vasopressor support, 35.0% of the patients had very high D1 cortisol levels in comparison to 16.7% of those not on vasopressor support who were in this highest cortisol category. In contrast, 94.4% of the patients with low D1 cortisol did not require vasopressor support. A similar trend was observed with MV; 25.8% of ventilated patients had very high cortisol levels compared with 15.3% of nonventilated patients.

D1 Cortisol Levels and Secondary Endpoints

Statistical analysis revealed differences in ICU LOS and duration of MV across low, normal, high, and very high cortisol level groups ($p < 0.001$ for both). Mean ICU LOS was 3.77 days in the low group, 4.45 days in the normal, 6.68 days in the high, and 8.78 days in the very high group, with statistically significant differences ($p < 0.025$) observed between all groups except for the low and normal groups. Mean duration of MV was 5.6 days in the low cortisol group, 5.11 days in the normal, 8.06 in the high, and 8.79 days in the very high group. Patients with very high cortisol levels had significantly longer duration of MV compared with those with low (adjusted $p = 0.026$) and

normal (adjusted $p = 0.001$) levels, with no significant differences between low and normal levels (adjusted $p = 1.000$), or high and very high levels (adjusted $p = 0.670$).

DISCUSSION

In this retrospective observational study, we investigated the relation between postadmission day total cortisol levels and clinical outcomes in a large cohort of critically ill surgical patients. The main results of our study indicate that: 1) majority of patients (63%) have D1 cortisol levels above the upper normal limit of 25 mcg/dL, while CIRCI was uncommon (7.6%); 2) age correlates with D1 cortisol levels; 3) there are statistically significant differences in 90-day mortality between the four cortisol level groups; 4) very high D1 cortisol level (above 50 mcg/dL) is an independent risk factor for mortality, primarily in patients with SOFA less than or equal to 3 or SOFA greater than or equal to 7; 5) higher cortisol levels are associated with ICU morbidity (need for vasopressor support and MV, longer ICU stay and longer duration of MV); and 6) vast majority of patients with low D1 cortisol levels did not require vasopressor support.

Our SICU admits patients who are critically ill due to a variety of conditions that are surgical in essence, or who underwent a major surgical procedure or suffered severe complications during a surgical intervention. To this end, our results that show a majority of patients with high and very high D1 cortisol values, are in keeping with previous literature, including the observed age-related response, with older patients demonstrating a higher surge in D1 cortisol levels (9). We did not find gender or weight related differences. Some patients experience a disruption to the normal HPAA function during critical illness from a variety of etiologies (including surgical) termed CIRCI, with prevalence ranging from 11.8% to as high as 54.3% in a cohort of patients with multitrauma, and experience worse clinical outcomes if untreated (25–31). In our cohort, a lower proportion of patients, only 7.6%, had D1 cortisol levels below 10 mcg/dL, which complies with the diagnosis of CIRCI (4, 5). Despite this, none of these patients suffered refractory shock or exhibited clinical signs of corticosteroid deficiency, and the vast majority (94.4%) did not require any vasopressor support. Of note, the finding of low cortisol level, as a sole indication, did not lead to any clinical intervention or initiation of steroid supplemental therapy. Despite left untreated, only one death (0.9%) occurred in this group of patients with presumed CIRCI, which is significantly lower than any of the other groups of patients with normal, high, or very high D1 cortisol levels. Furthermore, patients in this group suffered less morbidities, needing shorter ICU admission and having shorter duration of MV than patients with high and very high D1 cortisol levels. The latter finding is also contradictory to previous studies that described longer duration of MV in patients with confirmed CIRCI; however, these trials were conducted on small, very specific, patient populations with possible confounders to their results. In a prospective trial by Bagate et al (27), only patients who initially failed to meet criteria for extubation were enrolled, and among them, CIRCI occurred in 33% and was associated with a higher likelihood of subsequent extubation failure. In a retrospective study by Arcellana et al (32), COVID-19 diagnosed with probable or definite CIRCI had longer median days on a ventilator; however, they were all treated with corticosteroids, primarily dexamethasone.

Other studies also showed lack of correlation between CIRCI and worse outcomes. In a systematic review by Salluh et al (39), CIRCI was identified in 10.3% of patients with community-acquired pneumonia (CAP; using a similar cortisol cutoff of < 10 mcg/dL) with no difference in mortality compared with higher values. In a cohort of patients with severe traumatic brain injury, CIRCI was common with 54% of patients having D1 cortisol levels below 10 mcg/dL, with no increase in mortality and even improved survival and favorable functional outcome in 3 months (33). In septic shock patients, 11.8% were diagnosed with CIRCI, but it was the non-CIRCI patients who had higher SOFA scores and 28-day mortality (26). In a prospective cohort of PICU patients, although CIRCI was prevalent it was not associated with an increased mortality rate (34). Furthermore, in a systematic review by Rezai et al (35) in children and adolescents, circulating cortisol levels during acute illness were higher than in controls, indicating an association with disease severity.

Finally, even when circulatory shock is present and CIRCI is confirmed, studies looking at benefits of steroid treatment for patients outcome revealed conflicting results (36–38).

We observed a correlation between higher cortisol levels and 90-day mortality. When analyzing subgroups according to clinical scenario, the correlation was kept in patients with urgent admissions regardless of undergoing a surgical procedure and lost in elective surgery patients. This finding can be attributed to the extremely low mortality rate of 0.01% (7/525 patients) in this group.

We also identified very high D1 cortisol levels as an independent risk factor for mortality that can be specifically used to identify patients at risk of dying when SOFA score is low (3 or less) or 7 or higher. Very high levels were also associated with need for organ support, duration of MV, and longer ICU stay. Numerous other studies identified the relation between high cortisol levels and poor outcomes in both medical and surgical patients. In severe CAP, Salluh et al (39) found that baseline cortisol levels were better predictors of severity and outcome than other routinely measured laboratory parameters or scores as Acute Physiology and Chronic Health Evaluation II, SOFA, and CURB-65 score; Kolditz et al (40) found that serum cortisol was superior to other serum parameters in predicting CAP outcomes, including mortality and a combination of ICU admission and mortality. In trauma

patients, higher cortisol levels were predictive of mortality and cortisol levels were found to have a 77% accuracy in differentiating survivors from nonsurvivors (41). In coronary artery bypass graft surgery, patients with high cortisol levels suffered more postoperative delirium and other complications and had a longer duration of postoperative ICU and hospital stay (42).

To the best of our knowledge, this is the largest cohort of surgical critically ill patients in which cortisol levels were investigated and compared with clinical outcomes. We believe our findings shed new light on the systemic response to stress and surgery. Our study has several limitations. First, as a retrospective observational study, as a retrospective observational study, it cannot establish a causal relationship between cortisol levels and clinical outcomes. Second, we used morning serum cortisol levels, rather than Adrenocorticotropic hormone test, as a marker of CIRCI, which in some studies was found inferior in the ability predict outcome or response to corticosteroids treatment in septic shock (39, 43). However, other studies did not reproduce these results and latest guideline recommendation remains that both tests are of equal value (5). Third, total cortisol level is routinely measured in our center by immunoassay, while mass spectrometry is considered to be "gold standard" and disconcordance between assays can exist, potentially resulting in over and underestimations of true cortisol levels (44); however, guidelines do not question validity of immunoassay results. Furthermore, as all measurements in our cohort were produced by the same assay, so it is unlikely to have altered the observed significant differences between the groups. Fourth, potential bias could arise from the large proportion of excluded patients. The absence of cortisol data in 1500 patients was primarily due to nonadherence to the established protocol, correlating with a shorter LOS. Importantly, differences in other significant variables such as age, gender, and mortality were not found between patients with and without cortisol measurements. Analysis of cortisol levels in patients who received steroids before sampling revealed minor differences with similar mortality rates.

CONCLUSIONS

In critically ill surgical patients D1 cortisol levels above 50 mcg/dL are associated with mortality, need for organ support, longer ICU LOS, and longer duration of MV, whereas low levels correlate with good clinical outcomes even when untreated. D1 cortisol level greater than 50 mcg/dL can help discriminate nonsurvivors from survivors when SOFA is 3 or lower and when SOFA is 7 or higher. Whether serum cortisol level is a marker that can be modified remains an area of interest for future research.

1   Division of Anesthesia, Pain Management and Intensive Care, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

2   Division of Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

3   Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

REFERENCES

1. Lamberts SWJ, Bruining HA, de Jong FH: Corticosteroid therapy in severe illness. *N Engl J Med* 1997; 337:1285−1292

2. Nicolaides NC, Kyratzi E, Lamprokostopoulou A, et al: Stress, the stress system and the role of glucocorticoids. *Neuroimmunomodulation* 2015; 22:6−19

3. Munck A, Guyre PM, Holbrook NJ: Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 1984; 5:25−44

4. Marik PE, Pastores SM, Annane D, et al; American College of Critical Care Medicine: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an International

Task Force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36:1937–1949

5. Annane D, Pastores SM, Rochwerg B, et al: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017; 43:1751–1763

6. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143

7. Desborough JP: The stress response to trauma and surgery. *Br J Anaesth* 2000; 85:109–117

8. Donati A, Ruzzi M, Adrario E, et al: A new and feasible model for predicting operative risk. *Br J Anaesth* 2004; 93:393–399

9. Prete A, Yan Q, Al-Tarrah K, et al: The cortisol stress response induced by surgery: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2018; 89:554–567

10. Raju V, Gibbison B, Klerman EB, et al: Characterizing alterations in cortisol secretion during cardiac surgery. *Annu Int Conf IEEE Eng Med Biol Soc* 2023; 2023:1–6

11. Khanna R, Slovacek H, Liles J, et al: Regulation of cortisol in patients undergoing total joint arthoplasty. *Clin Appl Thromb Hemost* 2021; 27:1076029621987614

12. Liu MM, Reidy AB, Saatee S, et al: Perioperative steroid management: Approaches based on current evidence. *Anesthesiology* 2017; 127:166–172

13. Wagner RL, White PF: Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology* 1984; 61:647–651

14. Ledingham I: Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; 321:1270

15. Jackson WL: Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock?: A critical appraisal. *Chest* 2005; 127:1031–1038

16. Annane D: ICU physicians should abandon the use of etomidate! *Intensive Care Med* 2005; 31:325–326

17. Hildreth AN, Mejia VA, Maxwell RA, et al: Adrenal suppression following a single dose of etomidate for rapid sequence induction: A prospective randomized study. *J Trauma* 2008; 65:573–579

18. Albert SG, Ariyan S, Rather A: The effect of etomidate on adrenal function in critical illness: A systematic review. *Intensive Care Med* 2011; 37:901–910

19. Téblick A, Gunst J, Van den Berghe G: Critical illness-induced corticosteroid insufficiency: What it is not and what it could be. *J Clin Endocrinol Metab* 2022; 107:2057–2064

20. Téblick A, Peeters B, Langouche L, et al: Adrenal function and dysfunction in critically ill patients. *Nat Rev Endocrinol* 2019; 15:417–427

21. Huang C-S, Miles T, Thomas B, et al: A call for standardization: Practice patterns and management of critical illness-related corticosteroid insufficiency in surgical intensive care units. *Injury* 2021; 52:2522–2525

22. Boonen E, Vervenne H, Meersseman P, et al: Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013; 368:1477–1488

23. Marik PE: The diagnosis of adrenal insufficiency in the critically ill patient: Does it really matter? *Crit Care* 2006; 10:176

24. Salgado DR, Verdeal JCR, Rocco JR: Adrenal function testing in patients with septic shock. *Crit Care* 2006; 10:R149

25. Rothwell PM, Udwadia ZF, Lawler PG: Cortisol response to corticotropin and survival in septic shock. *Lancet* 1991; 337:582–583

26. Sanpawithayakul K, Meepornbucha K, Pirompanich P, et al: Prevalence and treatment outcomes of critical illness-related corticosteroid insufficiency (CIRCI) in septic shock patients in medical wards and emergency room in Thammasat University Hospital. *J Endocr Soc* 2023; 7(Suppl 1):bvad114.293

27. Bagate F, Bedet A, Tomberli F, et al: Critical illness-related corticosteroid insufficiency during difficult weaning from mechanical ventilation. *Ann Intensive Care* 2021; 11:65

28. Yang Y, Liu L, Jiang D, et al: Critical illness-related corticosteroid insufficiency after multiple traumas: A multicenter, prospective cohort study. *J Trauma Acute Care Surg* 2014; 76:1390–1396

29. Walker ML, Owen PS, Sampson C, et al: Incidence and outcomes of critical illness-related corticosteroid insufficiency in trauma patients. *Am Surg* 2011; 77:579–585

30. de Jong MFC, Beishuizen A, van Schijndel RJMS, et al: Risk factors and outcome of changes in adrenal response to ACTH in the course of critical illness. *J Intensive Care Med* 2012; 27:37–44

31. Kwok AM, Davis JW, Dirks RC, et al: Prospective evaluation of admission cortisol in trauma. *Trauma Surg Acute Care Open* 2020; 5:e000386

32. Arcellana AE, Arcegono M, Jimeno C: Critical illness-related corticosteroid insufficiency (CIRCI) among patients with COVID-19 at a tertiary hospital: Clinical characteristics and outcomes. *J ASEAN Fed Endocr Soc* 2023; 38:90–99

33. Olivecrona Z, Dahlqvist P, Koskinen L-OD: Acute neuroendocrine profile and prediction of outcome after severe brain injury. *Scand J Trauma Resusc Emerg Med* 2013; 21:33

34. Bekhit OE, Mohamed SA, Yousef RM, et al: Relation between baseline total serum cortisol level and outcome in pediatric intensive care unit. *Sci Rep* 2019; 9:6008

35. Rezai M, Fullwood C, Hird B, et al: Cortisol levels during acute illnesses in children and adolescents: A systematic review. *JAMA Netw Open* 2022; 5:e2217812

36. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124

37. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871

38. Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378:809–818

39. Salluh JIF, Bozza FA, Soares M, et al: Adrenal response in severe community-acquired pneumonia: Impact on outcomes and disease severity. *Chest* 2008; 134:947–954

40. Kolditz M, Halank M, Schulte-Hubbert B, et al: Adrenal function is related to prognosis in moderate community-acquired pneumonia. *Eur Respir J* 2010; 36:615–621

41. Pandya U, Polite N, Wood T, et al: Increased total serum random cortisol levels predict mortality in critically ill trauma patients. *Am Surg* 2014; 80: 1112–1118

42. Mu D-L, Wang D-X, Li L-H, et al: High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: A prospective cohort study. *Crit Care* 2010; 14:R238

43. Bornstein SR, Allolio B, Arlt W, et al: Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101:364–389

44. Briegel J, Sprung CL, Annane D, et al; CORTICUS Study Group: Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. *Intensive Care Med* 2009; 35:2151–2156