

Prognostic Implication of Adrenocortical Response during the Course of Critical Illness

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Background: Critical illness-related corticosteroid insufficiency (CIRCI) and adrenocorticotrophic hormone (ACTH)-cortisol dissociation are hormonal conditions frequently observed in patients in the intensive care unit (ICU). The aim of this study was to evaluate the association between ACTH-cortisol dissociation and clinical outcomes of critically ill patients.

Methods: We retrospectively reviewed the medical records of 94 ICU patients who underwent two rapid cosyntropin tests during hospital admission and compared the clinical aspects of patients with and without ACTH-cortisol dissociation. ACTH-cortisol dissociation was defined as plasma ACTH and serum cortisol concentrations of <22 pmol/L and >600 nmol/L, respectively.

Results: Dissociation was present in 30 of the 94 patients (31.9%). Patients with ACTH-cortisol dissociation in the initial test had significantly higher hospital mortality rate than those in the control group (55% vs. 25.7%, $P=0.013$). There was no difference in hospital mortality between patients classified as having CIRCI and those who were not. In multivariate adjusted Cox regression analysis, the mortality risk was higher in the group with ACTH-cortisol dissociation (hazard ratio, 2.98; 95% confidence interval, 1.34 to 6.63; $P=0.007$). Patients with dissociation in two consecutive stimulation tests showed the highest hospital mortality rate among groups classified according to stimulation test results (100% vs. 31.3%).

Conclusions: The hospital mortality was higher in ICU patients diagnosed with ACTH-cortisol dissociation. It is clinically feasible to evaluate the presence of ACTH-cortisol dissociation by analyzing rapid ACTH stimulation test results in critically ill patients.

Key Words: adrenocorticotrophic hormone; critical illness; mortality; steroids

INTRODUCTION

In 2017, a multispecialty task force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) defined the term “critical illness-related corticosteroid insufficiency (CIRCI).” CIRCI refers to the dysregulation of the hypothalamic-pituitary-adrenal axis, altered cortisol metabolism, and peripheral tissue resistance to glucocorticoids. Although the cortisol level is elevated due to decreased cortisol clearance, the target tissue resistance to cortisol is caused by inadequate glucocorticoid receptor alpha activity [1]. The SCCM and ESICM task force in 2017 also proposed that the following conditions may be used as the diagnostic criteria for CIRCI [2]: a delta cortisol (change in baseline

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cortisol at 60 minutes) of $<9 \mu\text{g/dl}$ after cosyntropin (250 μg) stimulation and a random plasma cortisol of $<10 \mu\text{g/dl}$.

Previous studies have reported a CIRCI prevalence of 30%–70% in critically ill patients [3–5]. CIRCI in these patients is accompanied by elevated levels of inflammatory markers and coagulopathy and is associated with prolonged intensive care unit (ICU) stay and higher ICU mortality [2]. Although the patients in previous studies were heterogeneous and the CIRCI diagnostic criteria were not unified, the clinical outcomes of critically ill patients with inadequate cortisol response were worse than those in patients with an adequate response [3,5–7]. A low random plasma cortisol level could be considered indicative of CIRCI, but the association between cortisol level and clinical outcome was not consistent in previous studies [8–10].

Adrenocorticotropic hormone (ACTH)-cortisol dissociation refers to elevated cortisol levels and low ACTH levels. A decrease in cortisol clearance leads to a decrease in ACTH due to negative inhibitory feedback, which may occur in the chronic phase among critically ill patients. ACTH-cortisol dissociation has been reported in ICU patients [11]; however, to our knowledge, no study has assessed whether it predicts the clinical outcome of critically ill patients as an indicator of abnormal adrenocortical response, such as CIRCI. We attempted to identify changes in the appearance of adrenocortical dissociation and CIRCI in patients who underwent more than one ACTH stimulation test. Therefore, we investigated whether ACTH-cortisol dissociation can predict clinical outcomes in critically ill patients and evaluated the dynamic correlation between two consecutive rapid ACTH stimulation tests.

MATERIALS AND METHODS

Study Population and Cosyntropin Stimulation Test

We retrospectively analyzed the medical information of patients admitted to the ICUs of a tertiary university hospital between 2006 and 2018. These ICUs included surgical, medical, and emergency ICUs. The study included 104 critically ill patients who underwent two rapid cosyntropin stimulation tests during hospitalization, all of whom underwent the first test during ICU admission. Cosyntropin stimulation test was performed in patients with suspected relative adrenal insufficiency (RAI). Since there are no definite diagnostic criteria for RAI, stimulation test was performed when the clinician suspected the disease. Usually the affected patients had clinical signs such as hyponatremia or refractory shock, fever or general weakness. The test was conducted in the following method. Basal ACTH and cortisol levels were measured by collect-

KEY MESSAGES

- Adrenocortical dissociation in critically ill patients was related to the worse clinical outcome.

ing the blood sample of the patient before the injection of cosyntropin. The blood used for ACTH measurement was collected in a pre-chilled lithium-heparin tube and carried in an ice box for minimizing degradation of ACTH. The patient was injected intravenously with 250 μg of tetracosactrin (Synacthen). After 30 and 60 minutes after the injection of the drug, the patient's blood sample was collected separately and the cortisol level was measured.

Data Collection and Processing

Demographic data including age, sex, and body mass index were collected. The clinical variables included comorbidities, vital signs at the time of admission to the ICU, and blood test results. The severity of patient illness was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score on the first day of ICU admission based on vital signs and laboratory results. The management in the ICU included invasive mechanical ventilation (MV), continuous renal replacement therapy (CRRT), and use of vasoactive agents. We also investigated the presence of septic shock and bacteremia at the time of the cosyntropin stimulation test and whether the patient had acquired a nosocomial infection during their ICU stay. Information was collected to determine if there was a history of steroid use and whether the patient received etomidate before ICU admission. The clinical outcomes of the patients included 30-day ICU mortality, ICU mortality, in-hospital mortality, ICU length of stay (LOS), and hospital LOS. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1802-006-918) and patient consent was waived with retrospective design of the study.

Adrenocortical dissociation refers to a condition in which the ACTH concentration is decreased while the cortisol concentration is increased. There remains no consensus regarding the cutoff value to define this condition; therefore, the definition of adrenocortical dissociation used in the present study was an ACTH concentration of $<22 \text{ pmol/L}$ (100 pg/ml), 25th percentile and cortisol concentration $>600 \text{ nmol/L}$ (21.75 $\mu\text{g/dl}$), 75th percentile of total population. We compared the clinical outcomes of patients who were evaluated as having adrenocortical dissociation and patients without dissociation in the first cosyntropin stimulation test.

Statistical Analysis

Statistical analyses were performed using STATA ver. 13.0 (StataCorp., College Station, TX, USA). Categorical variables were described as number (percent) and continuous variables as mean and standard deviation. For univariate analysis, continuous variables were assessed by Student t-tests, while categorical variables were assessed by Pearson chi-square or Fisher exact tests. Patient survival in the hospital was compared using Kaplan-Meier analysis and log-rank tests. Cox regression analysis was performed for the multivariate analysis of factors affecting hospital mortality. The P-values <0.05 were considered statistically significant.

RESULTS

Among patients admitted to the medical, surgical, emergency, or cardiopulmonary ICUs of a tertiary hospital between 2006 and 2018, a total of 104 patients underwent two cosyntropin stimulation tests during their hospital stays. Among these pa-

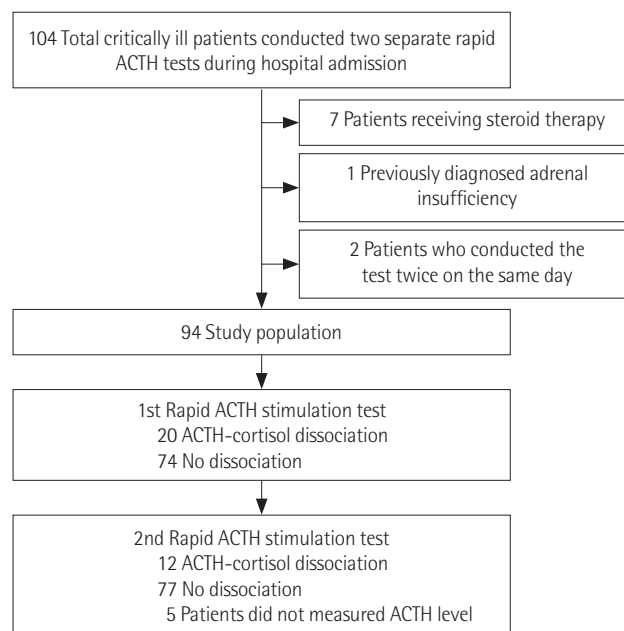


Figure 1. Study population selection flow. ACTH: adrenocorticotrophic hormone.

Table 1. Clinical characteristics of the study population

Variable	Total patients (n=94)	Hospital survivor (n=64)	Hospital non-survivor (n=30)	P-value
Female sex	31 (33.0)	24 (37.5)	7 (23.3)	0.173
Age (yr)	64.6±16.1	65.4±16.4	64.2±16.0	0.745
BMI (kg/m ²) ^a	19.6±8.0	18.9±8.1	21.3±7.7	0.194
Comorbidity				
Malignancy	36 (38.3)	22/64 (34.5)	14 (46.7)	0.253
Chronic liver disease	8 (8.5)	4 (6.3)	4 (13.3)	0.251
Diabetes	19 (20.2)	12 (18.8)	7 (23.3)	0.606
Hypertension	27 (28.7)	11 (17.2)	16 (53.3)	<0.001
Serum albumin (g/dl)	2.6±0.6	2.6±0.5	2.6±0.7	0.931
Serum creatinine (mg/dl)	1.7±1.5	1.5±1.5	2.0±1.6	0.142
Admission APACHE II score	24.8±8.3	24.4±8.4	25.8±8.1	0.446
Septic shock	50 (53.2)	32 (50.0)	18 (60.0)	0.365
Bacteremia	18 (19.2)	12 (18.8)	6 (20.0)	0.886
ICU-acquired infection ^b	19 (20.2)	4/28 (14.3)	15/66 (22.7)	0.351
Previous steroid use	30 (31.9)	20 (31.3)	10 (33.3)	0.840
Previous etomidate use	24 (25.5)	16 (25.0)	8 (26.7)	0.863
MV	87 (92.6)	58 (90.6)	29 (96.7)	0.298
CRRT	29 (30.9)	15 (23.4)	14 (46.7)	0.023
Type of ICU				0.741
MICU	41 (43.6)	28 (68.3)	13 (31.7)	
SICU	11 (11.7)	8 (72.7)	3 (27.2)	
CPICU	1 (1.1)	0	1 (100)	
EICU	41 (43.6)	28 (68.3)	13 (31.7)	

Values are presented as number (%) or mean±standard deviation.

BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; MV: mechanical ventilation; CRRT: continuous renal replacement therapy; MICU: medical ICU; SICU: surgical ICU; CPICU: cardiopulmonary ICU; EICU: emergency ICU.

^aTotal patients: n=85; Hospital survivor: n=58; Hospital non-survivor: n=27; ^bHospital survivor: n=28; Hospital non-survivor: n=66.

tients, seven with current steroid replacement therapy, one with a previous diagnosis of adrenal insufficiency, and two patients who underwent the test on the same day were excluded. Finally, 94 critically-ill patients were included in the analysis (Figure 1).

Patient Baseline and Clinical Characteristics

Table 1 shows the baseline and clinical characteristics of these 94 patients. Their mean age was 64.6 ± 16.1 years and 33% were female. The mean APACHE II score was 25.0 ± 8.3 and

53.2% of the patients had septic shock. Among 87 total patients requiring MV, 19.5% of patients ($n = 17$) were administered etomidate during rapid sequence intubation, and 80.5% ($n = 70$) cases used midazolam during the intubation procedure. During ICU admission, 92.6% of the patients required invasive MV and 30.9% received CRRT. Patients with hypertension showed higher hospital mortality (17.2% vs. 53.3%, $P < 0.001$) and patients who received CRRT also showed higher mortality (23.4% vs. 46.7%, $P = 0.023$).

Table 2. Adrenocortical responses of the study population in cosyntropin stimulation tests

Variable	Total patients (n=94)	Hospital survivor (n=64)	Hospital non-survivor (n = 30)	P-value
Day from admission to the 1st test	18.0±24.9	16.1±21.8	21.9±30.6	0.296
ACTH baseline (pmol/L)	27.2±94.6	19.5±44.9	43.4±154.6	0.256
Cortisol baseline (nmol/dl)	565.8±561.2	530.9±580.0	640.3±520.3	0.381
Cortisol after 30 minutes (nmol/dl)	802.6±617.5	794.5±649.3	820.0±553.5	0.853
Cortisol after 60 minutes (nmol/dl)	841.5±561.0	822.2±568.8	882.7±551.0	0.629
ΔMax (cortisol) (nmol/dl)	309.9±422.6	336.8±482.7	252.7±248.0	0.371
Cortisol baseline/serum albumin (nmol/mg)	2.2±2.3	2.1±2.6	2.6±2.5	0.269
Cortisol after 30 minutes/serum albumin (nmol/mg)	3.1±2.5	3.1±2.5	3.3±2.6	0.619
Cortisol after 60 minutes/serum albumin (nmol/mg)	3.3±2.4	3.2±2.2	3.6±2.6	0.438
ΔMax (cortisol)/serum albumin (nmol/mg)	1.2±1.6	1.3±1.8	1.0±1.1	0.414
Day from admission to the 2nd test	49.3±62.7	47.3±58.1	53.7±72.6	0.645
ACTH baseline (pmol/L) ^a	11.3±12.2	12.1±12.5	44.8±53.0	0.419
Cortisol baseline (nmol/dl)	399.6±205.1	344.6±184.1	517.0±200.9	<0.001
Cortisol after 30 minutes (nmol/dl)	603.5±245.5	567.6±231.6	680.0±260.4	0.038
Cortisol after 60 minutes (nmol/dl)	694.4±421.7	679.3±474.9	726.5±280.8	0.616
ΔMax (cortisol) (nmol/dl)	300.6±417.6	338.2±474.0	220.3±247.7	0.204
Cortisol baseline/serum albumin (nmol/mg)	1.5±0.9	1.2±0.7	2.0±1.1	<0.001
Cortisol after 30 minutes/serum albumin (nmol/mg)	2.2±1.0	2.0±0.9	2.6±1.3	0.013
Cortisol after 60 minutes/serum albumin (nmol/mg)	2.6±2.1	2.5±2.3	2.8±1.4	0.527
ΔMax (cortisol)/serum albumin (nmol/mg)	1.1±2.0	1.3±2.3	0.8±1.0	0.279

Values are presented as mean ± standard deviation.

ACTH: adrenocorticotrophic hormone.

^aTotal patients: n=89; Hospital survivor: n=59.

Table 3. Clinical outcomes in groups with ACTH–cortisol dissociation in the first cosyntropin stimulation test

Variable	Total patients (n=94)	ACTH–cortisol dissociation (n=20)	No dissociation (n=74)	P-value
Hospital mortality	30/94 (31.9)	11/20 (55.0)	19/74 (25.7)	0.013
28-Day mortality	6/58 (10.3)	3/10 (30.0)	3/48 (8.3)	0.025
90-Day mortality	14/90 (15.6)	7/19 (36.8)	9/71 (12.7)	0.014
ICU mortality	13/37 (35.1)	7/10 (70.0)	6/27 (22.2)	0.017
Hospital LOS	113.9±138.6	90.9±106.4	120.2±146.1	0.406
ICU LOS	31.0±55.3	34.1±47.8	30.2±57.4	0.780

Values are presented as number/total number (%) or mean ± standard deviation.

ACTH: adrenocorticotrophic hormone; ICU: intensive care unit; LOS: length of stay.

Adrenocortical Responses of Study Population in Cosyntropin Stimulation Tests

We also compared the rapid ACTH stimulation test results of survivors and non-survivors. There was no significant difference in ACTH and cortisol basal levels between the two groups when comparing the first test. However, in the second test, the baseline cortisol level and the cortisol level after 30 minutes for the non-survivor group were statistically significantly higher. Similar results were obtained when comparing cortisol levels after correcting for serum albumin levels (Table 2).

Effect of ACTH-Cortisol Dissociation on Clinical Outcomes

We compared the clinical outcome between patients with and without ACTH cortisol dissociation in first stimulation test, as shown in Table 3. The dissociation and no-dissociation groups had similar demographic and clinical characteristics (Supplementary Table 1), the overall hospital mortality was 31.9% and

the ICU mortality rate was 14.9% (14/94, data not shown). The hospital mortality rates were 55% and 25.7% in the dissociation and control groups, respectively. The mortality rate was higher in the dissociation group compared to the 28-day mortality rate only in patients who underwent two tests within 28 days. There was no difference in hospital LOS between the two groups although the mean value of the dissociation group was lower. The 90-day mortality rate in patients who underwent two cosyntropin tests within 90 days was also higher in the dissociation group and consistent with the analysis of patients who underwent two cosyntropin tests during the ICU period (Table 3). These results were consistent in patients without etomidate (Supplementary Table 2).

We also compared the clinical outcomes of the CIRCI group defined by the 2017 SCCM/ESICM criteria but found no statistically significant difference. The outcomes were similar between patients with decreased and increased cortical response in the second test (Supplementary Table 3). Kaplan-Meier time series analysis showed a higher mortality rate in the dissociation group than that in the control group ($P=0.009$, log-rank test) (Figure 2). A Cox regression univariate analysis of factors determining hospital mortality revealed that ACTH-cortisol dissociation was associated with higher hospital mortality. Furthermore, ACTH-cortisol dissociation was significantly associated with higher hospital mortality in multivariate analysis adjusted for age, sex, presence of cancer, APACHE II score, hypertension and medical history of malignancy (Table 4).

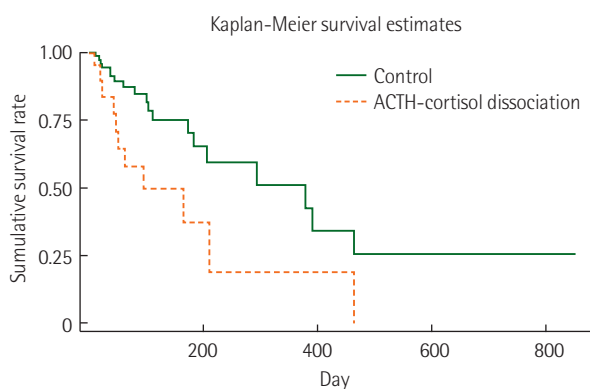


Figure 2. Kaplan-Meier survival analysis of patients. Adrenocorticotrophic hormone (ACTH)-cortisol dissociation group refers to critically-ill patients with ACTH less than 22 pmol/L and cortisol greater than 600 nmol/L in the first rapid Cosyntropin stimulation test and control denotes that groups of critically ill patients without ACTH-cortisol dissociation in the first test.

Differences in Clinical Outcomes According to Changes in ACTH-Cortisol Dissociation in Cosyntropin Stimulation Tests

To analyze the effect of ACTH-cortisol dissociation on clinical prognosis, we divided the patients into four groups. The first

Table 4. Cox regression analysis of hospital mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Female sex	0.53 (0.23–1.24)	0.144	1.05 (0.38–2.89)	0.930
Age	1.00 (0.99–1.03)	0.566	0.98 (0.96–1.01)	0.202
ACTH-cortisol dissociation	2.55 (1.21–5.38)	0.014	3.18 (1.54–6.96)	0.004
Septic shock	1.66 (0.80–3.47)	0.174	1.99 (0.88–4.54)	0.099
APACHE II score	1.02 (0.98–1.06)	0.374	1.04 (0.98–1.10)	0.184
Malignancy	1.63 (0.79–3.35)	0.188	3.20 (1.30–7.82)	0.011
Hypertension	2.24 (1.08–4.66)	0.031	3.74 (1.43–9.73)	0.007

HR: hazard ratio; CI: confidence interval; ACTH: adrenocorticotrophic hormone; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 5. Differences in clinical outcomes among groups classified according to changes in ACTH-cortisol dissociation status

Variable	Analyzed patients (n=89)				P-value
	Group 1 (n=62)	Group 2 (n=3)	Group 3 (n=15)	Group 4 (n=9)	
Test interval (day)	34.5±59.0	5.3±3.2	30.5±23.6	28.9±16.1	0.120
Hospital mortality	15/62 (24.2)	3/3 (100.0)	8/15 (53.3)	4/9 (44.4)	0.009
28-Day mortality (n=54)	3/42 (7.2)	1/3 (33.3)	2/6 (33.3)	0/3	0.136
90-Day mortality (n=88)	6/61 (10.3)	3/3 (100.0)	4/15 (26.7)	1/9 (11.1)	<0.001
ICU mortality (n=34)	4/20 (20.0)	3/3 (100.0)	4/7 (57.1)	2/4 (50.0)	0.030
Hospital LOS	114.8±142.4	37.3±14.6	106.9±118.2	171.0±184.0	0.579
ICU LOS	21.8±22.6	26.3±8.1	38.5±54.6	83.7±147.7	0.607

Values are presented as mean ± standard deviation or number/total number (%).

ACTH: adrenocorticotrophic hormone; Group 1: no dissociations in both tests; Group 2: ACTH-cortisol dissociation in both tests; Group 3: ACTH-cortisol dissociation in the first test; Group 4: ACTH-cortisol dissociation in the second test; ICU: intensive care unit; LOS: length of stay.

group consisted of patients without ACTH-cortisol dissociation in both tests, the second group showed dissociations in both tests, the third group showed dissociation in the first test only, and the fourth group showed dissociation in only the second test. Three patients had ACTH-cortisol dissociation in both cosyntropin stimulation tests (group 2); they comprised 3.2% of the total patient population and had 100% hospital mortality. Fifteen patients showed dissociation in the only first test (group 3) and had a hospital mortality rate of 53.3%. The patients with dissociation in the second test (group 4), had a 44.4% in-hospital mortality. Groups 1, 3, and 4 had an overall hospital mortality rate of 31.3%. The hospital mortality rate of patients without dissociation in two tests was the lowest, at 24.2%. These differences between groups were similar for 90-day and ICU mortality (Table 5).

DISCUSSION

The present study investigated the relationship between adrenocortical dissociation and hospital mortality in critically ill patients. Adrenocortical dissociation, defined as the combined condition of increased cortisol and suppressed ACTH levels, was associated with increased in-hospital mortality. Every participant in this study underwent two separate cosyntropin stimulation tests during hospitalization and patients with adrenocortical dissociation at least one of the two tests showed worse clinical outcome than those in patients without dissociation in both tests. The association between dissociation and hospital mortality was consistent across time-series and multivariate analyses. In addition, the non-survivor group had an increased basal cortisol level in the second stimulation test. This dissociation occurred during critical illness and was sustained for more than 1 week [12]. We demonstrated that

dissociation, reflecting a prolonged stress response, associated with the prognosis of critically ill patients.

Previous reports on Korean ICUs have reported a RAI rate of 70.6% among septic shock patients [9] and 43.9% among critically ill patients [5]. These earlier studies defined RAI as an increase in serum cortisol level of less than 9 µg/dl from the baseline after the injection of 250 µg cosyntropin [5,9]. The frequency of adrenocortical dissociation in the present study was 21.3%. In addition, the proportions of patients diagnosed with CIRCI according to the SCCM/ESICM criteria were as follows: cortisol increase less than 9 µg/dl after stimulation was 53.2% with and 16.0% with less than 10 µg/dl random serum cortisol level. The frequencies of adrenal dysfunction such as RAI, CIRCI, and dissociation vary according to the diagnostic criteria. These findings suggest the usefulness of the assessment of adrenal dysfunction in critically ill patients.

Some limitations should be considered in interpreting the results of this study. The first is the inherent nature of its retrospective design. Second, there was heterogeneity in the patient population. This study included patients without septic shock. We also analyzed patients who entered the medical, surgical, and emergency ICUs. Third, compared to previous studies on the effect of RAI or CIRCI on the prognosis of critically ill patients [5,9,13,14], the patients included in this study stayed in the ICU for an average of 30 days or longer. Fourth, because of the nature of the retrospective study, the detailed use of various medications including steroids were not assessed. Finally, we defined adrenocortical dissociation as the 25th percentile of ACTH and 75th percentile of cortisol in this study population, but these cutoff values require validation in a prospective large-scale study.

The strength of this study was its analysis of the dynamic correlations in patients who underwent two stimulation tests.

We assessed changes in two tests and, unlike previous studies, did not find any difference in ICU survival or LOS [13]. To our knowledge, this is the first study to compare the clinical outcome of patients diagnosed with CIRCI using the suggested cutoff value of SCCM/ESICM 2017 guideline. There was no significant difference in the clinical prognosis of patients with CIRCI. Adrenocortical dissociation showed a worse outcome; therefore, the ACTH level should also be considered in the clinical interpretation of cosyntropin stimulation test results. In addition, these results can be universally applied to critically ill patients and compared to previous studies in homogeneous patient groups such as those with septic shock, cardiogenic shock, and trauma.

It is unclear whether steroid replacement is effective in patients with adrenocortical dissociation. Steroid resistance in the peripheral tissue may contribute to the increased cortisol level in patients with dissociation, and supplementation of additional systemic steroids in these cases may have consequences. Only 40% of patients with adrenocortical dissociation underwent steroid replacement and there was no significant difference in in-hospital mortality between dissociation patients who did and did not receive systemic steroids (62.5% vs. 50.0%, $P = 0.670$). Although there was no significant difference in mortality, it is possible that steroid replacement may have affected the prognosis of these patients.

In conclusion, the results of our retrospective cohort study showed an increased hospital mortality among patients with adrenocortical dissociation defined as an elevated basal cortisol level and suppressed ACTH level. Although the patients with ACTH-cortisol dissociation in rapid ACTH stimulation tests is associated with poor outcome in our study, validation in a multicenter prospective study is required to confirm these findings of ACTH-cortisol dissociation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: JL, SML. Data curation: JHS. Formal analysis: JHS. Methodology: JL, JHS, JHK, SML. Project administration: JL. Visualization: JHS. Writing - original draft: JHS. Writing - review & editing: JHS, JL, JHK, SML.

SUPPLEMENTARY MATERIALS

The online-only supplement data are available with this article online: <https://doi.org/10.4266/acc.2018.00339>.

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Supplementary Table 1. Comparison of groups with and without adrenocorticotrophic hormone–cortisol dissociation

Variable	Total patients (n=94)	Dissociation (n=20)	No dissociation (n=74)	P-value
Sex (female)	31/94 (33.0)	6/20 (30.0)	25/74 (33.8)	0.749
Age (yr)	64.6±16.1	63.4±19.3	64.9±15.2	0.712
BMI (kg/m ²) ^a	19.6±8.0	19.1±9.3	19.8±7.7	0.744
Comorbidity				
Malignancy	36/94 (38.3)	6/20 (30.0)	30/74 (40.5)	0.390
Chronic liver disease	8/94 (8.5)	1/20 (5.0)	7/74 (9.5)	0.526
Serum albumin (g/dl)	2.6±0.6	2.6±0.8	2.6±0.5	0.981
Serum creatinine (mg/dl)	1.7±1.5	1.8±1.6	1.6±1.5	0.603
APACHE II score	24.8±8.3	27.7±8.1	24.0±8.2	0.079
Septic shock	50/94 (53.2)	11/20 (55.0)	39/74 (52.7)	0.855
Bacteremia	18/94 (19.2)	5/20 (25.0)	13/74 (17.6)	0.454
ICU-acquired infection	19/94 (20.2)	3/20 (15.0)	16/74 (21.6)	0.513
Previous steroid use	30/94 (31.9)	8/20 (40.0)	22/74 (29.7)	0.382
Previous etomidate use	24/94 (25.5)	6/20 (30.0)	18/74 (24.3)	0.606
MV	87/94 (92.6)	18/20 (90.0)	69/74 (93.2)	0.624
CRRT	29/94 (30.9)	6/20 (30.0)	23/74 (31.1)	0.926

Values are presented as number/total number (%) or mean ± standard deviation.

BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; MV: mechanical ventilation; CRRT: continuous renal replacement therapy.

^aTotal patients: n=85; Dissociation: n=19; No dissociation: n=66.

Supplementary Table 2. Clinical outcomes of ACTH–cortisol dissociation in etomidate-free population

Patient not treated with etomidate	ACTH–cortisol dissociation (n=14)	No dissociation (n=56)	P-value
Hospital mortality	8/14 (57.1)	14/56 (25.0)	0.020
28-Day mortality (n=44)	3/8 (37.5)	2/36 (5.6)	0.035
90-Day mortality (n=66)	6/14 (42.9)	5/52 (9.6)	0.003
ICU mortality (n=28)	6/8 (75.0)	4/20 (20.0)	0.006
Hospital LOS	69.1±65.3	124.1±153.3	0.196
ICU LOS	37.5±56.2	27.9±46.0	0.506

Values are presented as number/total number (%) or mean ± standard deviation.

ACTH: adrenocorticotrophic hormone; ICU: intensive care unit; LOS: length of stay.

Supplementary Table 3. Differences in clinical outcome according to CIRCI defined by various criteria

Variable	CIRCI (increase in cortisol level <248.3 nmol/L from baseline) (n = 50)	No CIRCI (n = 44)	P-value
Hospital mortality	16/50 (32.0)	14/44 (31.8)	0.985
28-Day mortality	6/36 (16.7)	1/22 (4.6)	0.235
90-Day mortality	8/43 (18.6)	8/47 (17.0)	0.844
ICU mortality	5/19 (26.4)	8/18 (44.4)	0.248
Hospital LOS	116.7 ± 153.4	110.7 ± 121.4	0.836
ICU LOS	48.1 ± 82.3	64.4 ± 77.6	0.538
	CIRCI (increase in cortisol level <275.9 nmol/L from baseline) (n = 15)	No CIRCI (n = 79)	
Hospital mortality	2/15 (13.3)	28/79 (35.4)	0.132
28-Day mortality	0/9	7/49 (14.3)	0.581
90-Day mortality	1/15 (6.7)	15/75 (20.0)	0.291
ICU mortality	1/5 (20)	12/32 (37.5)	0.638
Hospital LOS	144.5 ± 218.4	144.5 ± 218.4	0.354
ICU LOS	47.5 ± 94.3	27.9 ± 44.5	0.209
	Decrease in Δcortisol in the 2nd test (n = 51)	Increase in Δcortisol in the 2nd test (n = 43)	
Hospital mortality	15/51 (29.4)	15/43 (34.9)	0.571
28-Day mortality	3/51 (5.9)	4/43 (9.3)	0.529
90-Day mortality	8/51 (15.7)	8/43 (18.6)	0.708
ICU mortality (n = 37)	9/19 (47.3)	4/18 (22.2)	0.109
Hospital LOS	108.3 ± 113.8	120.5 ± 164.6	0.672
ICU LOS	32.4 ± 53.9	29.3 ± 57.5	0.788

Values are presented as number/total number (%) or mean ± standard deviation.

CIRCI: critical illness-related corticosteroid insufficiency; ICU: intensive care unit; LOS: length of stay.