ORIGINAL ARTICLE

Association between Cortisol Level at the Time of Shock and Hypoadrenalism after Hospital Discharge among Septic Shock Survivors: A Pilot Study

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Background: Septic shock survivors are susceptible to adrenocortical dysfunction due to multiple physiological alterations during sepsis. However, no clinical studies have focused on hypoadrenalism.

Objective: To evaluate the prevalence of hypoadrenalism among septic shock survivors 28 days after hospital discharge and to identify clinical factors associated with subsequent adrenal function.

Materials and Methods: This prospective cohort pilot study included adult septic shock patients between June 2019 and December 2021. The patients with previously known hypoadrenalism, corticosteroids used within three months, or other types of shock were excluded. Clinical characteristics and severity of illness, including SOFA, APACHE III score, and shock parameters, were assessed during the shock resuscitation. Cosyntropin stimulation was performed after 28 days of hospital discharge in septic shock survivors to evaluate adrenal function. Hypoadrenalism was defined as having a peak cortisol level of less than 14.5 μg/dL or serum morning cortisol at baseline <3 μg/dL.

Results: Of the 81 septic shock patients, 36 survivors were enrolled, with a mean age of 64±17.6 years. The mean SOFA and APACHE III score was 7.44±2.76 and 67.1±25.5, respectively. Twelve patients (33.3%, 95% confidence interval [CI] 19.1 to 51.0) had hypoadrenalism after 28 days of hospital discharge. Cortisol level at the time of shock was not associated with the prevalent hypoadrenalism (adjusted odds ratio 0.99, 95% CI 0.98 to 1.01). However, log cortisol level positively correlated with a peak incremental response of log serum cortisol after cosyntropin stimulation (β=0.45, 95% CI 0.02 to 0.89, p=0.04) after adjusting with serum lactate, SOFA score, serum albumin, and hydrocortisone use.

Conclusion: The prevalence of hypoadrenalism among septic shock survivors is notably high, which raises concern over the need for adrenocortical evaluation during follow-up. Cortisol level at the time of shock may serve as a surrogate marker in predicting adrenal reserve in these patients.

Keywords: Hypoadrenalism; Cortisol; Septic shock; ACTH stimulation

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Septic shock is a potentially fatal medical condition characterized by a life-threatening organ dysfunction and circulatory failure due to dysregulated host response to infection. Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg or higher and a serum lactate level greater than 18 mg/dL despite adequate volume resuscitation[1]. Overall mortality in patients with septic shock was around 30% to 60%, depending on the severity[2-5].

One of the most crucial factors in modulating the inflammatory response and immunological function in septic shock is cortisol, the end product of the hypothalamic-pituitary-adrenal (HPA) axis activation[6]. It was well-documented that higher plasma cortisol level during sepsis or septic shock was associated with mortality[7-9]. However, the underlying pathophysiological explanation of this association is extremely complex and poorly understood[10,11]. Cortisol elevation during critical illness is thought to be from multiple central and peripheral regulators, including increased cortisol production from the pituitary-independent process[12], decreased peripherally enzymatic cortisol clearance[13], and impaired cellular and tissue responsiveness to cortisol in sepsis and septic

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shock[14-17]. Interestingly, a study conducted in prolonged critically ill patients revealed that the persistently high cortisol in such patients could lead to sustained suppression of adrenocorticotropic hormone (ACTH), which can ultimately cause central hypoadrenalism[18]. After intensive care discharge, plasma ACTH may rise to above-normal levels that frequently exceed those presented during critical illness to ensure adrenocortical recovery[19]. However, whether and when the HPA axis will revert to normal function in these patients remains unclear. Moreover, persistent hypoadrenalism caused by direct damage to the HPA axis from the critical illness itself has also been reported[10,14]. Some patients experienced structural harm to their adrenal cortex, pituitary, or hypothalamus because of the primary disease for which they were admitted to intensive care. Hypoadrenalism in such patients has been linked to infectious, hemorrhagic, infiltrative, surgical, and drug-induced adrenalitis or hypophysitis[20]. However, no clinical studies have focused on hypoadrenalism in patients with septic shock after hospital discharge. The objectives of the present study were to evaluate the prevalence of hypoadrenalism after 28-days of hospital discharge among septic shock survivors. We also aimed to identify the clinical factors associated with hypoadrenalism and cortisol response to cosyntropin, which could represent the integrity of the HPA axis after discharge from septic shock.

Materials and Methods

Study setting and population

We conducted a prospective cohort pilot study from June 2019 to December 2021 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, a tertiary academic hospital in Northeastern Thailand. We included all adult septic shock patients (≥18 years old) who came to the emergency room and were admitted to the medical intensive care unit (ICU). Patients with known adrenal insufficiency and corticosteroids used within three months of admission (except for hydrocortisone use during the current episode of septic shock) were excluded from the present study. The patients diagnosed with other types of shock or referred from other hospitals were also excluded. Written informed consent was given by all participants or legally authorized representatives after enrollment. Septic shocks were treated as per standard of care according to clinical guidelines. We then prospectively followed the patients who survived the septic shock event for at least 28 days after hospital discharge. The patients who were at risk of developing new hypoadrenalism during the follow-up period, e.g., hospitalized for any acute illness or received any forms of glucocorticoids, were withdrawn from the final analysis. The present study was approved by the Human Research Ethics Committee of Khon Kaen University per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE631354).

Data collection and definition

According to the Sepsis-3 consensus definition, septic shock was defined as a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) of 65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation[1]. Shock control rate by 6 hours was defined as maintaining MAP ≥65 mmHg, urine output ≥0.5 mL/kg/hour consecutively for 2 hours, and lactate clearance ≥10% from the initial lactate level[21]. Shock reversal was defined as maintaining MAP ≥65 mmHg without vasopressor long-lasting than 24 hours (from the start time of vasopressor until the time vasopressor had been stopped)[22].

The patient characteristics were extracted from the detailed medical record. Data collection included: age, sex, body mass index (BMI), comorbidities, Charlson comorbidity index, Sequential Organ Failure Assessment (SOFA) score, the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score, site of infection, pathologic organism, appropriation of antibiotic treatment, serum lactate level, serum cortisol level, blood chemistry, amount of fluid received in 1 and 3 hours after triage time at the emergency room, urine output, duration of norepinephrine, and the use of hydrocortisone during shock. We collected all the clinical and laboratory results at the time of septic shock diagnosis and for 72 hours after admission. All the septic shock survivors who were eligible for the final analysis underwent a short low-dose ACTH stimulation test (cosyntropin stimulation test) after 28 days of hospital discharge. Cortisol levels were sampled before, 30, and 60 minutes after intravenous injection of 1 µg cosyntropin (Synacthen®). Serum cortisol was evaluated using the Electrochemiluminescence II immunoassay technique (Elecsys II) with Cobas e602 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Hypoadrenalism was diagnosed if serum total cortisol level failed to reach 14.5 µg/dL at any time either before or after cosyntropin injection, or serum morning cortisol at baseline <3 µg/dL[20]. The cortisol cutoff of 14.5 µg/dL was based on the recommendation by Javorsky et al. for the Elecsys II cortisol assay, which has been validated against LC-MS/MS[23]. Study data were collected and managed using REDCap (Research Electronic Data Capture) hosted at Khon Kaen University[24]. REDCap is a secure, web-based software platform that supports data capture for research studies.

Statistical analysis

The continuous variables were present as mean ± standard deviation (SD) or median and interquartile range

(IQR) depending on the data's normality. The categorical variables were described as counts and percentages (%). Two-sample t-test or Wilcoxon rank-sum test was used to compare continuous variables. The Chi-square test or Fisher's exact test was used for categorical variables. Multivariable logistic regression was performed to estimate the effect of clinical factors on the occurrence of hypoadrenalism. Multicollinearity was examined using variance inflation factors. In addition, we evaluated the correlation between peak incremental cortisol response following cosyntropin injection and various clinically significant variables. Multivariable linear regression analysis estimated the relationship between two or more explanatory variables and a peak incremental cortisol response. Due to the skewed distribution of total cortisol levels, logarithmic transformation was applied to approximate a normal distribution, stabilize variance, and reduce the influence of outliers, thereby ensuring the validity of parametric statistical tests[25]. All the statistical analyses were performed by using R software version 4.2.2. The level of statistical significance was set at a p-value less than 0.05 (two-tailed).

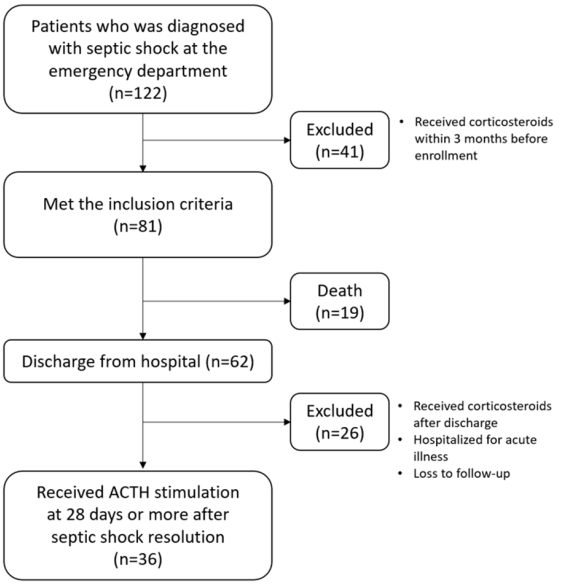

Figure 1. Study design and flow.

Results

Of the 122 patients diagnosed with septic shock, 81 met the inclusion criteria, and 62 (76.5%) survived the septic shock events and were discharged from the hospital. However, 26 patients were withdrawn from the final analysis (loss to follow-up, at risk of developing new hypoadrenalism during the follow-up), resulting in 36 patients who underwent ACTH stimulation test after 28 days of hospital discharge (Figure 1). The mean age of participants was 64±17.6 years, and 21 (58.3%) were male. The median BMI was 21.9 (IQR 19.6 to 22.9) kg/m^2. The mean SOFA scores, APACHE III, and Charlson comorbidity index at admission were 7.44±2.76, 67.1±25.5, and 4.28±2.69, respectively. The most common site of infection was urinary tract infection (33.3%), followed by intraabdominal infection (22.2%) and respiratory tract infection (19.4%). The causative organisms were identified as 41.7% of Gram-negative bacteria, 11.1% of Gram-positive bacteria, and 50% of culture-negative pathogens. The median hospital and ICU length of stay were 8 (IQR 6 to 13) and 5 (IQR 3 to 7) days, respectively. There were 12 patients (33.3%) who received hydrocortisone while being shocked (Table 1). The median hydrocortisone duration was 2.77 (IQR 1.54 to 3) days among patients receiving hydrocortisone.

Hypoadrenalism after 28 days of hospital discharge

The median interval between the ACTH stimulation test date and hospital discharge date was 35 (IQR 29 to 49.5) days. The median albumin level at the ACTH stimulation date was 4.0 (IQR 3.5 to 4.4) g/dL. There were 12 patients (33.3%, 95% confidence interval [CI] 19.1 to 51.0) who failed ACTH stimulation and were defined as having hypoadrenalism after 28 days of hospital discharge. Neither severity of illness nor parameters during shock resuscitation was associated with hypoadrenalism (Table 1). The authors performed an explanatory multivariable logistic regression. Pre-defined clinically significant covariates, including serum cortisol, serum lactate, SOFA score, serum albumin, and hydrocortisone use, were added to the model. None of these variables showed an association with the presence of hypoadrenalism (Table 2).

Peak incremental cortisol response after ACTH stimulation test

The peak incremental of total cortisol following cosyntropin injection in patients with hypoadrenalism was significantly lower than those without (Table 1). Log cortisol level at the time of shock was correlated with peak incremental response of log cortisol after ACTH stimulation, r=0.37, p=0.03 (Figure 2). Multivariable linear regression analysis revealed that log cortisol at the time of shock was associated with peak incremental response of log cortisol following ACTH stimulation (β=0.45, 95% CI 0.02 to 0.89, p=0.04) after adjusting with covariates, including serum lactate, SOFA score, serum albumin, and hydrocortisone use (Table 3).

Discussion

In the current study, we found that one-third (33.3%) of septic shock survivors had a prevalent hypoadrenalism after 28 days of hospital discharge, which was extremely

Table 1. Patient characteristics by adrenocortical status after 28 days of hospital discharge

Characteristics	All patients (n=36)	No hypoadrenalism (n=24)	Hypoadrenalism (n=12)	p-value
Baseline				
Age, mean (SD), years	64 (17.6)	67.5 (14.2)	57 (22)	0.09
Male, No. (%)	21 (58.3)	12 (50)	9 (75)	0.28
BMI, median (IQR), kg/m^2	21.9 (19.6 to 22.9)	21.9 (19.6 to 23.1)	21.6 (20.3 to 22.7)	0.91
SOFA, mean (SD), points	7.44 (2.76)	7.33 (2.51)	7.67 (3.31)	0.74
SOFA score at 72 hours, mean (SD), points	4.03 (2.67)	3.92 (2.59)	4.25 (2.93)	0.73
APACHE III, mean (SD), points	67.1 (25.5)	69.5 (28.5)	62.2 (18.2)	0.43
Charlson comorbidities index, mean (SD), points	4.28 (2.69)	4.83 (2.78)	3.17 (2.21)	0.08
Comorbidities, No. (%)				
Diabetes	13 (36.1)	10 (41.7)	3 (25)	0.47
Cardiovascular diseases	8 (22.2)	7 (29.2)	1 (8.3)	0.22
Neurologic diseases	7 (19.4)	6 (25)	1 (8.3)	0.38
CKD stage 3 to 5	5 (13.9)	3 (12.5)	2 (16.7)	0.99
Cirrhosis	3 (8.3)	2 (8.3)	1 (8.3)	0.99
Site of infection, No. (%)				
Urinary tract infection	12 (33.3)	8 (33.3)	4 (33.3)	0.99
Intra-abdominal infection	8 (22.2)	6 (25)	2 (16.7)	0.69
Respiratory tract infection	7 (19.4)	5 (20.8)	2 (16.7)	0.99
Unknown sites	5 (13.9)	5 (20.8)	0 (0)	0.15
Other sites	5 (13.9)	1 (4.2)	4 (33.3)	0.03
Causative pathogen, No. (%)				
Gram-negative	15 (41.7)	11 (45.8)	4 (33.3)	0.72
Gram-positive	4 (11.1)	2 (8.3)	2 (16.7)	0.58
Culture negative	18 (50)	12 (50)	6 (50)	0.99
Appropriate antibiotic, No. (%)	33 (91.7)	22 (91.7)	11 (91.7)	0.99
Serum lactate at the time of shock, median (IQR), mg/dL	27.6 (23.6 to 40.5)	29.2 (23.6 to 44.4)	26 (23.5 to 32.3)	0.42
Serum cortisol at the time of shock, median (IQR), µg/dL	24.8 (12.6)	26.3 (13.1)	21.9 (11.4)	0.33
Serum albumin, mean (SD), g/dL	3.2 (0.7)	3.3 (0.6)	3.1 (0.9)	0.54
Hypoalbuminemia <2.5 g/dL, No. (%)	2 (5.6)	1 (4.2)	1 (8.3)	1.00
Fluid received, median (IQR), mL				
At 1 hour	1,000 (590 to 1,000)	1,000 (590 to 1,000)	1,000 (575 to 1,000)	0.90
At 3 hours	1,550 (1,500 to 2,000)	1,500 (1,450 to 2,000)	1,750 (1,500 to 2,000)	0.50
Norepinephrine duration, median (IQR), hours	34 (22.2 to 61.8)	34 (23.6 to 58.8)	37 (21.9 to 64.4)	0.65
Hydrocortisone use, No. (%)	12 (33.3)	9 (37.5)	3 (25)	0.70
Shock control rate at 6 hours, No. (%)	16 (44.4)	12 (50)	4 (33.3)	0.55
Shock reversal rate at 72 hours, No. (%)	30 (83.3)	21 (87.5)	9 (75.0)	0.38
Hospital length of stay, median (IQR), days	8 (6 to 13)	9.5 (6.5 to 13.2)	7.5 (6.0 to 11.2)	0.66
Intensive care unit length of stay, median (IQR), days	5 (3 to 7)	5 (3.75 to 7.25)	4.5 (3 to 7)	0.51
After 28 days of hospital discharge				
Peak incremental cortisol after ACTH stimulation test, mean (SD), µg/dL	5.49 (2.75)	6.62 (2.21)	3.24 (2.34)	<0.01

SD=standard deviation; IQR=interquartile range; BMI=body mass index, SOFA=sequential organ failure assessment; APACHE=acute physiology, age, chronic health evaluation; CKD=chronic kidney disease

high relative to less than 1% reported from the general population[26]. Moreover, we found that the peak incremental of log-transformed total cortisol following ACTH stimulation test after 28 days of hospital discharge, which represented the capability of adrenal glands to respond to stimulus and produce cortisol, was associated with the log cortisol level at the time of shock. These findings suggested that cortisol level at the time of shock may be a predictor in identifying patients at risk of hypoadrenalism after discharge from septic shock, who are prone to readmission or are more

Table 2. Multivariable logistic regression analysis of predicting hypoadrenalism after 28 days of hospital discharge

Variables	Prevalence of hypoadrenalism		
	Adjusted odds ratio (OR)	95% confidence interval (CI)	p-value
Serum cortisol	0.99	0.98 to 1.01	0.37
Serum lactate	1.00	0.99 to 1.00	0.25
SOFA score	1.02	0.95 to 1.10	0.58
Serum albumin	0.97	0.74 to 1.26	0.82
Hydrocortisone use	0.85	0.59 to 1.23	0.40

SOFA=sequential organ failure assessment; ICU=intensive care unit

Table 3. Multivariable linear regression analysis of predictors of peak incremental response of log serum cortisol following cosyntropin stimulation test after 28 days of hospital discharge

Variables	Peak incremental response of log cortisol		
	Coefficient (β)	95% confidence interval (CI)	p-value
Log serum cortisol	0.45	0.02 to 0.89	0.04*
Serum lactate	0.004	-0.01 to 0.02	0.47
SOFA score	0.01	-0.10 to 0.12	0.80
Serum albumin	0.27	-0.12 to 0.66	0.17
Hydrocortisone use	0.32	-0.23 to 0.87	0.24

SOFA=sequential organ failure assessment; ICU=intensive care unit

Adjusted r^2=0.13

* Statistically significant

likely to experience another shock episode.

Evaluating adrenocortical dysfunction in patients during sepsis or post-sepsis is extremely challenging. Most authors recommended against the use of ACTH stimulation test in assessing HPA axis integrity during critical illness, as it is confounded by the pronounced decline in plasma cortisol binding proteins, particularly albumin and plasma cortisol binding globulin (CBG)[10,11,27]. To date, It is yet unknown how long this abnormal protein binding behavior persists after the critical event. However, we believed that serum albumin might be used as a surrogate marker, which led us to assume that our patients have reversed these pathophysiological alterations, as shown by the recovery of serum albumin from 3.2 g/dL during the shock phase to 4.0 g/dL at the time of ACTH stimulation. Therefore, the biochemical diagnosis of hypoadrenalism using the same ACTH-stimulated cortisol threshold used in the general population should be reliable in our patients. The high prevalence of hypoadrenalism after septic shock demonstrated in the current study highlights the underappreciated significance of this condition. There is evidence showing that almost one-third of all sepsis survivors are readmitted to the hospital within 90 days, while nearly half of the patients over 50 years of age are readmitted within 90 days[28,29]. Moreover, the mortality rate during one year of hospital discharge after sepsis ranges between 28 to 44%[30-32]. These negative consequences in post-sepsis were thought to be attributed to persistent changes in inflammatory mediators and prolonged immunosuppression[33,34]. Our findings suggested that adrenocortical dysfunction might also be involved as the cause of these poor outcomes.

There are numerous potential factors related to hypoadrenalism post-septic shock. A prior study has been conducted in long-stay critically ill patients requiring intensive care for at least one week. The authors found that the prolonged elevation in systemic cortisol availability in such patients, either from centrally activated pro-opiomelanocortin (POMC) mediated cortisol production[12], or reduced cortisol clearance[13] could result in sustained suppression of ACTH response to corticotropin-releasing hormone (CRH) and central hypoadrenalism[18]. A study on adrenal tissues obtained post-mortem from patients who died after being critically ill for several weeks demonstrated structural abnormalities, including lipid droplet depletion, loss of adrenocortical zonation, and decreased ACTH-regulated gene expression[35]. If these patients survive, adrenal abnormalities may begin to recover as early as one week after ICU discharge, as evidenced by a consistent rise in both ACTH and cortisol levels to supra-normal levels[19]. Conversely, some patients may develop persistent hypoadrenalism after septic shock. There has been a report of severe hypotension-related necrosis to the brain or pituitary that results in irreversible adrenal insufficiency[36]. The primary insult related to septic shock, such as sepsis associated with widespread infection involving the hypothalamus, pituitary, or adrenal cortex, could also lead to permanent adrenocortical dysfunction[10]. These injuries could result from direct organ involvement of the organisms, or bilateral adrenal gland hemorrhages secondary to fatal bacterial infections[37]. Hypoadrenalism may also follow particular drug therapy in the ICU, including antibiotics, anti-fungal, inotropes, opioids, and glucocorticoids[10]. Previous treatments with glucocorticoids could induce prolonged suppression of CRH and ACTH synthesis and result in late-onset secondary adrenal insufficiency that may outlast exposure to such treatment[38]. Unfortunately, the current study was unable to identify an association between any potential contributing factors and the prevalent hypoadrenalism. Future research with a larger sample size and a different time frame of adrenocortical assessment after hospital discharge should add more perspectives to this issue.

In our study, we used the 1 µg ACTH (low-dose) stimulation test rather than the standard 250 µg dose. This decision was based on evidence suggesting that the low-dose test has greater sensitivity for detecting subtle

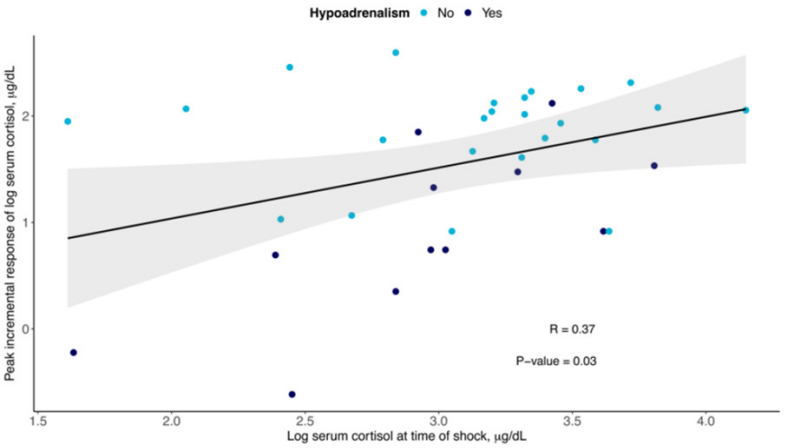

Figure 2. Scatter plot of Pearson's correlation between log serum cortisol at the time of shock and peak incremental response of log serum cortisol following cosyntropin stimulation after 28 days of hospital discharge.

or central adrenal insufficiency, which we hypothesized to be more relevant in our cohort of septic shock survivors. Given that post-sepsis hypoadrenalism may result from central suppression of the hypothalamic-pituitary-adrenal axis rather than primary adrenal failure, the 1 µg test was considered more appropriate for assessing residual adrenal reserve. However, it is important to acknowledge that this approach might influence the comparability of our findings with studies using the standard-dose test and should be interpreted within this context.

It was established that higher plasma cortisol level at the time of sepsis or septic shock was associated with poor outcomes. Annane et al. reported that cortisol levels greater than 34 µg/dL were independent predictors of 28-day mortality in patients with septic shock[7]. Sam et al. also reported that serum cortisol levels of more than 45 µg/dL (1,242 nmol/L) were associated with both in-hospital mortality and 90-day mortality in patients with severe sepsis[8]. Recently, De Castro et al. found that basal cortisol measured within the first 24 hours of sepsis was the best prognostic factor for in-hospital and 28-day mortality, even superior to the SOFA or APACHE II scores[9]. However, our study showed that if the patients had survived the septic shock, serum cortisol might have instead served as a favorable indicator of HPA axis integrity. We demonstrated that log cortisol level at the time of shock was significantly correlated with peak incremental of log cortisol response following ACTH stimulation. This relationship remained significant after adjustment with potential confounders, including serum lactate, SOFA score, serum albumin, and hydrocortisone use. Of clinical relevance, these findings suggested that higher cortisol levels at the time of shock could indicate greater adrenal gland reserve during critical illness. Despite the paradoxically low ACTH, Boonen et al. showed that cortisol production from the adrenal glands was still increased by 83% in the first 180 minutes of critical illness[13]. Coinciding with this ACTH-cortisol dissociation, POMC was believed to be an alternative activator of cortisol production, as a several-fold elevation of POMC was found from the acute to the prolonged phase of sepsis and upon recovery.12 Another study revealed a normal ACTH response to CRH in the first few days of critical illness, followed by substantially suppressed ACTH responses in the latter phase[18]. These findings collectively showed that the HPA axis was unquestionably active at the start of a severe illness, and that cortisol level measured at that time should still partially reflect the functional reserve of the adrenal glands.

Although our findings demonstrate a statistically significant correlation between log-transformed cortisol levels at the time of shock and the peak incremental cortisol response following ACTH stimulation, a closer examination of the scatter plot (Figure 2) reveals that this association appears to be primarily driven by patients without hypoadrenalism. In contrast, the correlation in patients who were later diagnosed with hypoadrenalism was less evident. This observation suggests heterogeneity in the adrenal responsiveness across subgroups and highlights a potential limitation in generalizing the predictive value of cortisol during shock for all patients. The differential pattern also underscores the need for further investigation using larger cohorts to validate whether early cortisol levels can reliably stratify risk for persistent hypoadrenalism and to explore subgroup-specific predictive thresholds.

The current study is the first prospective study demonstrating the high prevalence of hypoadrenalism in septic shock survivors, which could raise more awareness among physicians in the attempt to identify adrenal status

when monitoring these patients after being discharged. However, there are some limitations worth mentioning. The major limitation was the sample size. This pilot study included only a small population, which might have resulted in low power of analysis. In addition, since we cannot perform an HPA axis assessment prior to the patient enrollment, some patients may already have unrecognized pre-existing adrenocortical dysfunction before the onset of the septic shock event. Additionally, free cortisol and ACTH testing, which would have provided more insightful data regarding the pathophysiology and clinical implications of post-sepsis hypoadrenalism, were not carried out in our investigation. Further prospective studies on novel strategies to identify, prevent, and treat post-sepsis hypoadrenalism are needed, and should not only focus on short-term outcomes but should also include long-term follow-up that continues much beyond the hospital stay.

Conclusion

The prevalence of hypoadrenalism among septic shock survivors is notably high. The significance of adrenocortical evaluation during follow-up after septic shock should be emphasized, and cortisol level at the time of shock may serve as a surrogate marker in predicting HPA axis integrity in these patients.

What is already known on this topic?

Septic shock is a potentially fatal medical condition.

One-third of all sepsis survivors are readmitted to the hospital within 90 days.

What this study adds?

One-third of septic shock survivors had a prevalent hypoadrenalism after 28 days of hospital discharge.

Adrenocortical dysfunction might also be involved as the cause of mortality rate during one year of hospital discharge after sepsis.

Higher cortisol levels at the time of shock might indicate greater adrenal gland reserve during critical illness.

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Conflicts of interest

The authors declare no conflict of interest.

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