ORIGINAL ARTICLE

Serum Cortisol Level and Clinical Outcomes in Critically Ill Neonates

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Objective: To determine serum cortisol levels and their association with clinical outcomes in critically ill neonates admitted to the neonatal intensive care unit (NICU) at Hatyai Hospital. Clinical outcomes included neonatal mortality, length of hospital stay, and duration of ventilator use.

Materials and Methods: A retrospective cohort study was conducted between January 2022 and December 2024, involving 120 critically ill term neonates with conditions like neonatal sepsis with septic shock or respiratory failure. Patients were categorized by serum cortisol levels: Group 1 (cortisol of less than 18 µg/dL, 80 patients) and Group 2 (cortisol of 18 µg/dL or more, 40 patients). Baseline characteristics and clinical outcome data were collected. Statistical analysis compared the two groups and identified factors associated with mortality.

Results: Baseline characteristics were similar, except that Group 1 had a higher proportion of older neonates (age 2 to 20 days) (p=0.002). Mortality was higher in Group 2 (20.0%) compared to Group 1 (7.5%). Univariate analysis showed that age of 1 day or less, birth asphyxia, modified sick neonatal (MSN) score of 10 or less, use of more than two vasoactive inotropic drugs, and renal, electrolyte, and calcium abnormalities were significantly associated with death. Multivariate analysis revealed that age 2 to 20 days (adjusted OR 0.14, 95% CI 0.03 to 0.54, p=0.005) and MSN score of 10 or less (adjusted OR 10.31, 95% CI 1.87 to 56.87, p=0.007) were independently associated with mortality. Serum cortisol level was not a significant independent predictor of mortality (adjusted OR 2.19, 95% CI 0.57 to 8.33, p=0.251). There were no significant differences in ventilator duration, hospital length of stay, or NICU length of stay between the two groups. Time to NICU discharge did not differ significantly between infants with cortisol levels of less than 18 µg/dL and those with levels of 18 µg/dL or more (log-rank test, p=0.059).

Conclusion: Serum cortisol level was not an independent predictor of mortality or other clinical outcomes. MSN scores and young age may predict mortality outcome for critically ill neonate.

Keywords: Serum cortisol; Clinical outcome; Critically sick neonate

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Cortisol is a vital glucocorticoid involved in regulating metabolism, inflammation, blood pressure, and stress response. During critical illness, cortisol production typically rises to meet the heightened physiological demand. The body's cortisol production increases to cope with physiological stress. However, in critically ill neonates, especially those with conditions like sepsis with persistent hypotension or respiratory failure, cortisol levels can be abnormally high or low, reflecting a dysregulated stress response. The term "Critical Illness-Related Corticosteroid Insufficiency" (CIRCI) describes this condition, which can be caused by impairment of the hypothalamic-pituitary-adrenal (HPA) axis or peripheral cellular unresponsiveness to cortisol[1-4].

The diagnostic criteria for CIRCI in the pediatric population remain poorly defined. Current classifications utilize the concepts of 'Relative' and 'Absolute' Adrenal Insufficiency (RAI and AAI) to describe the failure of the adrenal glands to produce adequate cortisol levels[1,5,6]. AAI is typically defined by a random baseline cortisol level of less than 18 µg/dL during acute stress, such as sepsis or respiratory failure. While several conditions are associated with neonatal adrenal insufficiency, a definitive consensus on the definition of CIRCI in neonates has not yet been established. Although some neonatal studies utilize lower thresholds (e.g., 15 µg/dL)[7], the author adopted the 18 µg/dL criterion to align with established pediatric CIRCI guidelines[1,3,8], ensuring higher sensitivity in identifying neonates who may benefit from exogenous hydrocortisone to reverse catecholamine-resistant shock.

CIRCI has been identified as a risk factor for

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poor outcomes in critically ill neonates, including increased mortality, prolonged hospitalization, and extended ventilator use[9-11]. Studies in pediatric and adult populations have shown an association between adrenal insufficiency and adverse outcomes, such as longer ICU and hospital stays and higher readmission rates[12-16].

The present study aimed to investigate the association between serum cortisol levels and clinical outcomes in a cohort of critically ill neonates. Specifically, the author sought to describe the cortisol levels in neonates with severe illness (as sepsis with shock and respiratory failure) and to evaluate if these levels correlate with clinical outcomes, including neonatal mortality, length of stay, and ventilator duration.

Materials and Methods

Study design and setting

The present was a retrospective cohort study conducted at the neonatal intensive care unit (NICU) of Hatyai Hospital between January 2022 and December 2024. The study included term neonates, with gestational age of 37 or more weeks and age of less than 28 days, diagnosed with neonatal sepsis, septic shock, and respiratory failure requiring mechanical ventilation. In cases of persistent hypotension refractory to fluid resuscitation and inotropic support, serum cortisol levels were measured before the initiation of corticosteroid therapy. Hydrocortisone was administered as the first-line treatment in all such cases.

Serum total cortisol levels were measured using a chemiluminescent immunoassay (CLIA) (Abbott Alinity). The assay has a reported dynamic range of 0.8 to 60 µg/dL. The intra-assay and inter-assay coefficients of variation (CV) were 10%. All samples were processed at the central laboratory of Hatyai Hospital immediately after collection.

Sample size

The sample size was calculated using the formula for comparing two proportions in a cohort study. To detect a difference in the proportion of mortality between the two cortisol groups, assuming an expected mortality proportion of 0.39 in the higher cortisol group of 18 µg/dL or more, and 0.063 in the lower cortisol group of less than 18 µg/dL[17], with an alpha (α) of 0.05 and a beta (β) of 0.05 or power of 95%, and a group ratio of 2:1, a minimum total sample size of 120 subjects was determined, consisting of 80 subjects in the cortisol of less than 18 µg/dL group and 40 subjects in the cortisol of 18 µg/dL or more group.

Inclusion and exclusion criteria

Inclusion:

(a) Term neonates aged less than 28 days at the time of onset.

(b) Confirmed neonatal sepsis, based on clinical signs or positive blood culture, with associated septic shock*.

* Septic shock was defined as sepsis with cardiovascular dysfunction requiring fluid resuscitation of 20 mL/kg or more, and the initiation of inotropic support (e.g., dopamine, epinephrine, or norepinephrine) to maintain blood pressure within the normal range for gestational age, associated with signs of poor tissue perfusion such as prolonged capillary refill time of more than three seconds, oliguria, or metabolic acidosis.

(c) Presence of respiratory failure requiring mechanical ventilation.

(d) Availability of serum cortisol levels measured prior to the administration of systemic corticosteroids.

Exclusion: Neonates with a diagnosis of primary adrenal insufficiency, congenital heart disease, chromosomal abnormalities, or a history of previous steroid use.

Data collection

The author collected data on age, gender, maternal gestation age, Apgar score, diagnosis, modified sick neonatal (MSN) score[18] (included respiratory effort, heart rate, temperature, capillary refilling time, random blood sugar, SpO_2 at room air, gestational age, and birth weight), number of vasoactive inotropic drugs (VID), blood culture, sputum culture, liver and renal function, metabolic profiles, and serum cortisol. Clinical outcomes included death, ventilator duration, length of stay in the NICU, and total length of hospital stay.

Birth asphyxia was clinically defined in the present study as an Apgar score of less than 7 at the first minute of life, indicating the need for immediate neonatal resuscitation at birth.

Statistical analysis

Data were analyzed to compare baseline characteristics and clinical outcomes between the two cortisol groups. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as

Table 1. Baseline characteristics of the critically ill neonates by cortisol level

Characteristics	Total (n=120)	Cortisol level (µg/dL)		p-value
		<18 (n=80)	≥18 (n=40)	
Age (days); median [IQR] (min-max)	2 [1, 2] (1 to 20)			
Age group; n (%)				0.002*
≤1 day	35 (29.17)	16 (20.00)	19 (47.50)	
2 to 20 days	85 (70.83)	64 (80.00)	21 (52.50)	
Male sex; n (%)	74 (61.67)	47 (58.75)	27 (67.50)	0.353
Body weight (g); median [IQR] (min-max)	3,058 [2,838, 3,300] (2,000 to 4,595)			
Gestational age (weeks); median [IQR] (min-max)	39 [38, 40] (37 to 42)			
Birth asphyxia[a]; n (%)	24 (20.00)	16 (20.00)	8 (20.00)	1.000
Diagnosis; n (%)				0.573
Sepsis with septic shock	62 (51.67)	40 (50.00)	22 (55.00)	
Sepsis with septic shock and others condition (PPHN, MAS)	58 (48.33)	40 (50.00)	18 (45.00)	
MSN score; n (%)				0.794
≤10	52 (43.33)	34 (42.50)	18 (45.00)	
>10	68 (56.67)	46 (57.50)	22 (55.00)	
Vasoactive inotropic drug(s); n (%)				0.184
1	46 (38.33)	34 (42.50)	12 (30.00)	
≥2	74 (61.67)	46 (57.50)	28 (70.00)	
Positive blood culture; n (%)	9 (7.50)	3 (3.75)	6 (15.00)	0.059
Positive sputum culture; n (%)	15 (12.50)	8 (10.00)	7 (17.50)	0.242
Liver abnormality[b]; n (%)	15 (12.50)	8 (10.00)	7 (17.50)	0.242
Renal abnormality[c]; n (%)	45 (37.50)	27 (33.75)	18 (45.00)	0.230
Electrolyte abnormality[d]; n (%)	56 (46.67)	34 (42.50)	22 (55.00)	0.196
Calcium abnormality[e]; n (%)	47 (39.17)	32 (40.00)	15 (37.50)	0.791
Glucose abnormality[f]; n (%)	66 (55.83)	43 (53.75)	24 (60.00)	0.585

IQR=interquartile range; PPHN=persistent pulmonary hypertension of the newborn; MAS=meconium aspiration syndrome; MSN=modified sick neonatal

(a) Birth asphyxia: a 1-minute Apgar score <7; (b) Liver abnormality: abnormal AST >150 U/L, ALT >50 U/L (<7 days) or AST >80 U/L, ALT >45 U/L (8 to 28 days); (c) Renal abnormality: oliguria definition by urine output <0.5 mL/kg/hour for 6 to 12 hours with increase serum creatinine 0.3 mg/dL within 48 hours; (d) Electrolyte abnormality: abnormal of sodium (less than 135 or more than 145 mEq/L) or abnormal of potassium (less than 3.5 or more than 6.5 mEq/L); (e) Calcium abnormality: serum calcium less than 8 mg/dL after corrected with serum albumin; (f) Glucose abnormality: Hypoglycemia (plasma glucose <40 mg/dL) or hyperglycemia (plasma glucose >150 mg/dL)

* p<0.05 is considered statistically significant

medians and interquartile ranges (IQR) due to their non-normal distribution, and comparisons between groups were performed using the Mann-Whitney U test.

Univariate analysis was conducted to identify factors associated with neonatal mortality. Variables with a p-value less than 0.10 in the univariate analysis or those clinically relevant were subsequently entered into a multivariate logistic regression model using the enter method to determine independent predictors of mortality, with results reported as adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Time-to-event data, specifically the time from NICU admission to discharge, was evaluated using Kaplan-Meier survival analysis, and differences between groups were compared using the log-rank test. All statistical analyses were performed using Stata Statistical Software, version 15 (StataCorp LLC, College Station, TX, USA), and a p-value of less than 0.05 was considered statistically significant.

Results

One hundred and twenty critically ill neonates were included in the present study. Eighty neonates had a cortisol level of less than 18 µg/dL and were in Group 1, while 40 neonates had a cortisol level of 18 µg/dL or more and were in Group 2.

Baseline characteristics

Table 1 summarizes the baseline characteristics of the study population. The two groups were comparable across most demographic and clinical variables, including gender, body weight, gestational age, birth asphyxia, diagnosis, MSN score, and use of VID, including laboratory results such as blood culture, sputum culture, liver function test, renal

Table 2. Characteristics of critically ill neonates with death outcome

Characteristics	Total (n=120)	Alive (n=106); n (%)	Dead (n=14); n (%)	p-value
Age group				0.001*
≤1 day	35	25 (71.43)	10 (28.57)	
2 to 20 days	85	81 (95.29)	4 (4.71)	
Sex				0.149
Male	74	68 (91.89)	6 (8.11)	
Female	46	38 (82.61)	8 (11.67)	
Body weight (g)				0.189
<2,500	7	5 (71.43)	2 (28.57)	
≥2,500	113	101 (89.38)	12 (10.62)	
Birth asphyxia	24	18 (75.00)	6 (25.00)	0.034*
Diagnosis				0.648
Sepsis with septic shock	62	56 (90.33)	6 (9.67)	
Sepsis with septic shock and others condition (PPHN, MAS)	58	50 (86.21)	8 (13.79)	
MSN score				0.001*
≤10	52	40 (76.92)	12 (23.08)	
>10	68	66 (97.06)	2 (2.94)	
Vasoactive inotropic drug(s)				0.011*
1	46	45 (97.83)	1 (2.17)	
≥2	74	61 (82.43)	13 (17.57)	
Positive blood culture	9	7 (77.78)	2 (22.22)	0.282
Positive sputum culture	15	15 (100)	0 (0.00)	NA
Liver abnormality	15	11 (73.33)	4 (26.67)	0.075
Renal abnormality	45	36 (80.00)	9 (20.00)	0.028*
Electrolyte abnormality	56	43 (76.79)	13 (23.21)	<0.001*
Calcium abnormality	47	37 (78.72)	10 (21.28)	0.009*
Glucose abnormality	66	53 (86.89)	9 (13.63)	0.632

PPHN=persistent pulmonary hypertension of the newborn; MAS=meconium aspiration syndrome; MSN= modified sick neonatal
* p<0.05 is considered statistically significant

function test, electrolyte, calcium, and glucose. The only statistically significant difference was in age at diagnosis, with neonates in Group 1, which were 1 day or younger, thus, significantly younger than Group 2, which were 2 to 20 days (p=0.002).

Clinical outcomes

The overall mortality rate was 11.67% (14 deaths out of 120 neonates). Mortality was higher in Group 2 at 20.00%, compared to Group 1 at 7.50%.

Factors associated with death

Univariate analysis (Table 2) showed that several factors were significantly associated with death. Those were age of less than 1 day (p=0.001), birth asphyxia (p=0.034), MSN score of more than 10 (p=0.001), use of more than 2 VID (p=0.011), and renal (p=0.028), electrolyte (p<0.001), and calcium abnormalities (p=0.009).

Multivariate analysis was performed to adjust for these factors. In this model, age 2 to 20 days (adjusted OR 0.14, 95% CI 0.03 to 0.54, p=0.005) and MSN score of 10 or less (adjusted OR 10.31, 95% CI 1.87 to 56.87, p=0.007) remained statistically significant predictors of mortality. Serum cortisol level of 18 µg/dL or more was not a significant independent predictor of mortality in the multivariate model (adjusted OR 2.19, 95% CI 0.57 to 8.33, p=0.251) (Table 3).

Other clinical outcomes, including ventilator duration, hospital length of stay, and NICU length of stay, showed no significant difference between the two cortisol groups (Table 4). Critically ill neonate with cortisol of less than 18 µg/dL (Group 1) exhibited a wider range of hospital stay, with extreme outliers exceeding 100 days, compared to those with cortisol of more than 18 µg/dL (Group 2). Ventilator or NICU stay remained low, with fewer extreme outliers than Group 1 (Figure 1).

Kaplan-Meier survival analysis was performed

Table 3. Association between cortisol level and factors associated with death in critically ill neonates (adjust)

Characteristic	Total (n=120)	Dead (n=14); n (%)	Crude OR			Adjusted OR		
			OR	95% CI	p-value	AOR	95% CI	p-value
Cortisol								
<18 µg/dL	80	6 (7.50)	1			1		
≥18 µg/dL	40	8 (20.00)	3.08	0.99 to 9.61	0.052	2.19	0.57 to 8.33	0.251
Age								
≤1 day	35	10 (28.57)	1			1		
2 to 20 days	85	4 (4.71)	0.12	0.04 to 0.43	0.001	0.14	0.03 to 0.54	0.005
Birth asphyxia	24	6 (25.00)	3.67	1.13 to 11.86	0.030	1.43	0.35 to 5.82	0.622
MSN score ≤10	52	12 (23.08)	9.90	2.11 to 46.53	0.004	10.31	1.87 to 56.87	0.007

OR=odds ratio; AOR=adjusted odds ratio; CI=confidence interval; MSN= modified sick neonatal

Table 4. Clinical outcomes in critically ill neonates

Clinical outcomes (days)	Total (n=120); median (IQR)	Cortisol; median (IQR)		p-value*
		<18 (n=80)	18 or more (n=40)	
Ventilator duration	3 (2, 5)	3 (2, 5)	3 (1, 5)	0.465
LOS in hospital	10 (7, 17.5)	9.5 (7, 17)	11.5 (5.25, 19.75)	0.778
LOS in NICU	4 (2, 6)	4 (2.25, 6)	4 (1, 6.75)	0.524

IQR=interquartile range; LOS=length of stay; NICU=neonatal intensive care unit
* Wilcoxon rank-sum test

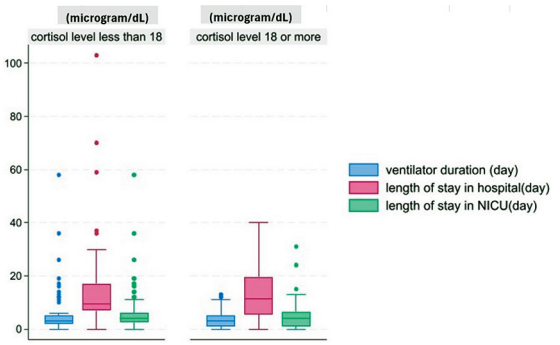

Figure 1. Association between the level of cortisol and clinical outcomes in critically ill neonates.

The side-by-side box-and-whisker plots illustrate three clinical outcomes: ventilator duration, hospital length of stay, and NICU length of stay. The horizontal line within each box represents the median value, while the boundaries of the box indicate the interquartile range (IQR). The whiskers extend to 1.5 times the IQR. Circles beyond the whiskers represent extreme outliers. Notably, neonates in the cortisol <18 µg/dL group exhibited several extreme outliers in hospital length of stay, exceeding 100 days. No statistically significant differences in median values were observed between the two groups for any outcome (p>0.05).

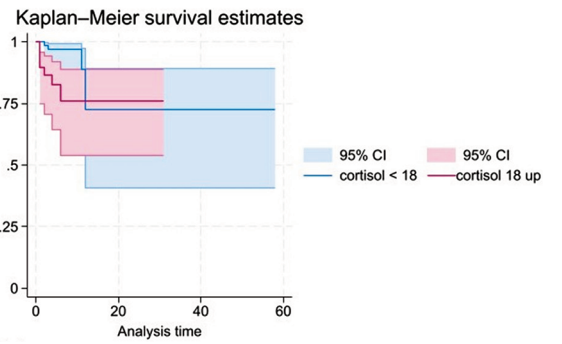

Figure 2. Kaplan-Meier survival estimates of time from NICU admission to discharge.

Kaplan-Meier estimates of time from NICU admission to discharge stratified by cortisol level (<18 vs. ≥18 µg/dL). Shaded areas indicate 95% confidence intervals. No statistically significant difference was observed between groups (log-rank test, p=0.059).

to evaluate the time from NICU admission to discharge according to cortisol level (less than 18 versus 18 µg/dL or more). Infants with cortisol levels of 18 or more showed a shorter time to discharge compared with those with cortisol levels of less than 18. However, the difference between groups did not reach statistical significance (log-rank test, p=0.059) (Figure 2).

Discussion

The present study investigated the relationship between serum cortisol levels and clinical outcomes in a cohort of critically ill neonates. The present study findings demonstrate that while a higher cortisol level (18 µg/dL or more) was associated with a higher mortality rate in the initial univariate analysis, this association did not remain an independent predictor when adjusted for other clinical factors in the multivariate model. This suggests that the initial observed association was confounded by the clinical

severity of the illness. The observed trend of higher mortality in the high-cortisol group (18 µg/dL or more) presents a clinical paradox. Traditionally, adrenal insufficiency (cortisol less than 18 µg/dL) is viewed as a risk factor for poor outcomes. However, the present study data suggest that in critically ill neonates, an elevated cortisol level may not be a protective mechanism but rather a biological marker of maximal physiological stress. In life-threatening states, the HPA axis is stimulated to its limit, resulting in high circulating cortisol that reflects the severity of the fatal disease rather than a failing adrenal response[19].

The finding that mortality was higher in the group with a cortisol level of 18 µg/dL or more is notable. This contrasts with the definition of adrenal insufficiency (cortisol of less than 18 µg/dL) being a risk factor for poor outcomes[20,21]. This suggests that a single cortisol measurement in a critically ill neonate may not accurately reflect the complex interplay of the HPA axis and the severity of illness. A high cortisol level may not represent an appropriate or protective stress response, but rather be a marker of a maximally stressed, highly fatal disease state. Studies showed a poor correlation between baseline cortisol and the cortisol response in pediatric septic shock, arguing for the ACTH Stimulation test[15,22]. An elevated cortisol level may simply be a marker of a more severe, life-threatening stress response, rather than a protective mechanism. It is plausible that in these critically ill patients, the clinical manifestations of the disease, such as a low MSN score and the number of vasoactive drugs required, are better indicators of disease severity and are more directly correlated with mortality than the cortisol level itself.

The present study results highlight that clinical parameters, particularly the MSN score, which quantifies the severity of sepsis, and age at presentation, were the most significant independent predictors of mortality. A total MSN score of 10 or less has a good sensitivity and specificity in predicting mortality of admitted neonates when used early during the course of hospitalization[18]. The strong association between a low MSN score and death (adjusted OR 10.31) underscores the importance of the clinical severity of the underlying illness. Furthermore, the significant association between younger age (less than 1 day) and a higher risk of death may be related to the unique physiological characteristics of the immediate postnatal period, where neonates are more vulnerable to severe illness and have a less mature stress response system[21]. Studies have shown that elevated basal cortisol levels positively correlate with the "Pediatric Risk of Mortality III" (PRISM III) score[23-25]. Clinical severity scores are superior predictors of mortality than a single cortisol level.

Studies in adults have found an association between adrenal insufficiency, prolonged length of hospital stay, and prolonged use of a ventilator[14,26]. In the present study, the lack of a significant association between cortisol levels and other outcomes like ventilator duration and length of stay is consistent with the finding that clinical severity, as measured by MSN score, is the primary driver of these outcomes. The clinical evaluation and management of critically ill neonates should therefore prioritize addressing the underlying clinical condition and its severity rather than focusing solely on a single cortisol value. This is consistent with existing literature suggesting that even with normal cortisol levels, clinical findings of unresponsiveness to vasopressors can be a warning sign of relative adrenal insufficiency, and that clinical response should be considered paramount in diagnosis and management.

Limitation

The retrospective nature of the present study limits the ability to establish causality. The cortisol measurements were single, baseline values and do not capture the dynamic nature of the HPA axis response to illness. Future prospective studies with serial cortisol measurements and ACTH stimulation tests could provide a more comprehensive understanding of the role of cortisol in this population.

Conclusion

The present study of critically ill neonates demonstrates that a single high serum cortisol level of 18 µg/dL or more is associated with a higher mortality in univariate analysis but is not an independent predictor of death in the multivariate model. Instead, clinical severity, as indicated by a low MSN score and younger age at diagnosis, was the most significant independent predictor of mortality. These findings suggest that comprehensive clinical assessment using validated scoring systems is more reliable than a standalone cortisol measurement for prognosticating outcomes and guiding management in the NICU setting. The present study findings suggest that clinical manifestations are more important than a single serum cortisol measurement in predicting outcomes for critically ill neonates.

What is already known about this topic?

Critical illness (like sepsis and septic shock) is known to activate the HPA axis, which typically leads to elevated cortisol secretion as a normal stress response. Diagnosing AI in neonates is particularly difficult because their normal cortisol reference ranges are lower than in adults, and the clinical signs (like hypotension/shock) are non-specific and overlap with sepsis or other conditions. Cortisol and clinical outcomes show conflicting results, such as very high baseline cortisol levels may correlate with increased mortality and specific poor short-term outcomes, low basal cortisol or poor response to ACTH stimulation test is often associated with higher mortality.

What does this study add?

Low cortisol (CIRCI) is a direct, independent cause or predictor of death in all critically ill neonates. It suggested that the initial association observed in studies is a confounding effect of the underlying disease severity. A comprehensive clinical assessment of multi-organ dysfunction (as captured by MSN score) is more reliable than a single hormone level for predicting outcome. This supports prioritization clinical evaluation and management, over solely relying on a laboratory test that is known to be dynamically complex. The cortisol status itself does not appear to drive key morbidity outcomes, which are instead likely dictated by the primary illness and its severity (MSN score).

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Author contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Data availability statement

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethic Committee for Research in Human Subject Hatyai Hospital (HYH EC 020-68-01, approval No. 42/2025).

Clinical trial registration

Not applicable. This study was a retrospective study and was not registered as a clinical trial.

Use of artificial intelligence

Artificial intelligence (ChatGPT and OpenAI) was used to assist in language editing of the manuscript. No AI tools were used for data analysis or interpretation. All content was critically reviewed by the author, who takes full responsibility for its accuracy and integrity.

Conflicts of interest

The authors declare no conflict of interest.

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