The Predictive Role of Corticosteroid-Binding Globulin and Thyroid Hormone in Pediatric Septic Shock

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ABSTRACT

Background: Septic shock, a condition caused by a dysregulated host response to systemic infection, may cause life-threatening organ dysfunction. During sepsis, concentrations of corticosteroid-binding globulin (CBG) in the serum progressively decrease. Therefore, the CBG nadir could play a role in septic shock-related organ failure and mortality. Non-thyroidal illness is a non-thyroidal illness syndrome that refers to changes in thyroid function tests in the inpatients of intensive care units having critical illnesses because of transient changes in the hypothalamic-pituitary-thyroid axis that can be explained as a homeostatic mechanism to conserve energy.

Aim of the Work: to evaluate the relation of serum CBG and thyroid hormone levels to organ dysfunction and mortality rates in pediatric patients with septic shock.

Patients and Methods: We conducted a prospective observational study on 91 pediatric patients with proved sepsis during the period from May 2023 to November 2023 at pediatric intensive care unit (PICU) of Ain shams university hospitals, serum CBG level was measured after at least 6 hours of initiation of inotropes. Thyroid hormones were measured for all patients. The primary outcome was overall ICU mortality and morbidity. Secondary outcomes were 28 and 90-day- mortality, need for mechanical ventilation, renal replacement therapy, need for cardiac inotropic support including the dose and duration of cardiac support infusion, and the need for shock dose steroids.

Results: Ninety-one patients were included and subdivided into two groups: survivors (42.9%) and non-survivors (57.1%). A cutoff value of 222.3 mg/dl was calculated for serum CBG levels using the Receiver Operating Characteristic curve (ROC) and Interactive Dot Diagram to differentiate between survivors and non-survivors creating a sensitivity and specificity of 98.08 and 3 1.58 % respectively. Primary outcome: The overall ICU mortality rate due to septic shock was significantly higher in patients with serum CBG levels less than 222.3 mg/dl, p-value=0.000. Secondary outcomes: 28-day mortality rates were higher in patients with CBG levels < 222.3 mg/dl, p-value = 0.00. Also, the need for mechanical ventilation was higher in patients with serum CBG levels < 222.3 mg/dl. There was no significant difference between patients with serum CBG levels <222.3 mg/dl and patients with serum CBG levels > 222.3 mg/dl regarding the need for noradrenaline and dopamine use However, patients with serum CBG <222.3 mg/dl needed higher noradrenaline and dopamine doses when used and a higher need for adrenaline and milrinone use, with longer infusion duration. The prevalence of non-thyroidal illness was 46.1%. Patients with non-thyroidal illness (changes in thyroid hormones levels during critical illness without clinical manifestations) had higher SOFA scores. There was no significant difference between the patients with normal thyroid profiles and non-thyroidal illness patients regarding mortality, dose of cardiac inotropic support, or organ dysfunction.

Conclusion:

Septic shock patients with CBG < 222.3 mg/dl had a higher need for ventilatory support, vasopressors, and 8.4-fold higher ICU mortality. Non-thyroidal illness is common in septic shock patients with higher SOFA scores but is not associated with a higher mortality rate.

Keywords: Corticosteroid-Binding Globulin, Thyroid Hormones, pediatric Septic Shock.

INTRODUCTION

Septic shock is a condition where the body's response to a systemic infection becomes dysregulated, leading to life-threatening organ dysfunction. This condition is typically identified empirically by persistent hypotension, which requires vasopressors to maintain a mean arterial pressure of over 65 mmHg, even after fluid resuscitation ***(Meyer et al., 2022).***

Disruption of the hypothalamic-pituitary-adrenal axis may result in cardiovascular and other organ dysfunction in patients with sepsis, eventually increasing the risk of death ***(Annane, 2016).***

The vasoconstrictive effect that is associated with catecholamines is potentiated by corticosteroids, which has a positive effect on vascular tone. This happens due to an increase in the number of adrenergic receptors and by preventing receptor desensitization. During septic shock, if there is adrenal insufficiency, it can lead to adrenergic receptor downregulation, a decrease in the number of both α- and β-adrenergic receptors, or their desensitization ***(Burry et al., 2004).***

Cortisol is a hydrophobic molecule largely bound to corticosteroid-binding globulin (CBG) in the circulation ***(Verbeeten et al., 2018)***. When human CBG molecules were incubated with leucocytes from patients in septic shock, cleavage of the CBG molecules was noticed, suggesting that CBG is targeted by elastases secreted by activated neutrophils in the physiologic settings of inflammation ***(Nenke et al., 2015).***

Acidosis and hyperthermia reduce CBG: cortisol binding, which is common in systemic inflammatory states such as sepsis and septic shock, this may enhance the delivery of cortisol to the interstitial space ***(Meyer et al., 2020).***

Serum CBG levels fall proportional to sepsis severity ***(Nenke et al., 2015).*** Deficiency in serum CBG levels can hinder cortisol transportation to inflamed areas, resulting in organ failure, and raised mortality rates observed in septic shock

Thyroid hormones affect the innate and adaptive immune response during infection. Clinical studies have revealed that thyroid hormones have a regulatory effect on the activity of neutrophils, macrophages, natural killer cells, dendritic cells (innate immune system), and B- and T-lymphocytes (adaptive immune system) ***(Lasa et al., 2022).***

Non-thyroidal illness (NTI) is characterized by lower levels of triiodothyronine (fT3) without any compensatory increase in thyroid stimulating hormone (TSH). It is unclear whether the association between the severity of NTI and poor outcomes in pediatric critical illness is due to an adaptive protective response or contributes to poor outcomes. The peripheral component of NTI, which involves the inactivation of thyroid hormone, may be a beneficial adaptation. At present, there is insufficient evidence to support the treatment of NTI in children. However, recent findings suggest that reactivation of the central component of NTI could provide benefits, and this hypothesis should be tested in randomized trials ***(Jacobs et al., 2019).***

AIM OF THE WORK

To observe the role of corticosteroid-binding globulin and thyroid hormones in sepsis and to evaluate the effect of serum CBG levels and serum thyroid hormone levels on organ dysfunction and mortality rate in pediatric patients with septic shock.

- **Ethical considerations**:
  -Approval of Ain Shams University Research Ethics Committee was obtained **(FMASU MS 301 /2023)**.
  -Guardians of all participants were instructed about the aim of the study and informed written consent was obtained before enrollment.
  -Patient data confidentiality was preserved during all study procedures.
  -The patient and parents have the right to withdraw at any time.
  -There was no conflict of interest regarding the study or publication.
  -There is no financial support or sponsorship.
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- **Sample size**: The sample size is calculated according to ***(Meyer et al., 2022)*** with 16% SD , alpha error 0.1 and prediction of 90%. 91patients were enough as a sample size.

$$\boldsymbol{Necessary\ sample\ size} = \frac{(\boldsymbol{z-score})\mathbf{2}\ \boldsymbol{x\ StdDev\ x}(\mathbf{1}-\boldsymbol{StdDev})}{(\boldsymbol{margin\ of\ error})\mathbf{2}}$$

- **Inclusion criteria**:

  -Eligible patients were 1month -18years of both sex and were receiving intravenous (IV) vasopressors for septic shock in the ICU.
  -Receiving vasopressor for at least 6 hours to maintain a mean arterial pressure > 65 mmHg.
- **Exclusion criteria:**
  -Known conditions that alter cortisol secretion e.g (burn, stress…), including the use of systemic glucocorticoids for ≥3 months.
  -Disorders of the Hypothalamic Pituitary Aaxis.
  -The use of systemic glucocorticoids in the PICU for indications other than septic shock.
  -Hypo or hyperthyroidism.

  Study procedure:
  This is an observational prospective study in pediatric patients with septic shock. Patients were followed up till death (up to 90 days) to evaluate morbidities and survival.

- All the studied cases were subjected to the following:
  i. Detailed history including: source of sepsis; history of GI infection (fever, vomiting, diarrhea) or chest infection (cough, dyspnea, chest pain), history of other systemic disorders and symptoms of adrenal insufficiency before this admission (fatigue, muscle weakness, loss of appetite, weight loss, and abdominal pain).
  ii. Physical examination including : weight, height, and body mass index, signs of septic shock (high-grade fever or hypothermia, confusion, pallor, cold clammy skin delayed capillary refilling time, weak peripheral pulsation, tachycardia, hypotension, and oliguria), signs of adrenal insufficiency (hypotension, hypoglycemia, and sweating), and for signs of hypothyroidism (bradycardia, cold intolerance).
- Diagnosis of sepsis was based on the following criteria:

-the presence of a clinically or microbiologically documented infection; ≥2 points on the pediatric Sequential [sepsis-related] Organ Failure Assessment (SOFA) score which was calculated within 24h of admission. This score assesses 6 organ systems:

respiratory, hematological, hepatic, cardiovascular, neurological, and renal. Each system took a score from 0 to 4.

- **Laboratory Evaluation:**
  i. Plasma CBG concentrations were measured by enzyme-linked immunosorbent assay (ELISA) kit with a standard curve range of 2.5-320 mg/dl and sensitivity of 1.34 mg/dl, with intra-assay CV <8% and inter-assay CV <10%, from BT LAB Bio-Technology Laboratory company, Shanghai, China.
  ii. Complete Blood Count (CBC) parameters were assayed on the Alinity HQ analyzer.
  iii. CRP was measured using cobas ® 6000 analyzer, Roche company.
  iv. Liver profile (ALT, AST, direct and total bilirubin) were measured using cobas ® 6000 analyzer, Roche company
  v. Kidney functions (BUN and serum. creatinine) were measured using cobas ® 6000 analyzer, Roche company
  vi. Total CK, and CK-MP were measured using cobas ® 6000 analyzer, Roche company.
  vii. Thyroid hormones (FT3, FT4, and TSH) were assayed using an enzyme-linked immunosorbent assay (ELISA) kit, from Thermo Fisher Scientific Company.

- **Outcomes:** The primary outcome was overall ICU mortality & morbidity. Secondary outcomes were 28 and 90-day- mortality, need for mechanical ventilation, renal replacement therapy, need for cardiac inotropic supports including the dose and duration of cardiac support infusion, and the need for shock dose steroids. All were correlated with serum CBG levels.

- **Statistical Analysis:** The Statistical Package for Social Science (IBM SPSS) version 27 was used to analyze data. Mean, standard deviation and range were used to represent quantitative data with parametric distribution, while the median and interquartile range (IQR) were used for non-parametric data. Qualitative variables were expressed as numbers and percentages. For comparisons between groups of qualitative data, the Chi-square test and/or Fisher exact test were used when the expected count in any cell was less than 5. An independent t-test was used for comparison between two independent groups with quantitative data and parametric distribution. The Mann-Whitney test was used for non-parametric distribution. The Kruskall-Wallis test followed by a post hoc analysis using the Mann-Whitney test was used to compare more than two groups regarding quantitative data and non-parametric distribution. The best cut-off point was evaluated using the receiver operating characteristic curve (ROC), along with its sensitivity, specificity, positive predictive value, negative predictive value, and area under curve (AUC) of the studied marker. The confidence interval was set at 95%, and the accepted margin of error was 5%. Therefore, a p-value of less than 0.05 was considered significant.
- The studied cases were subclassified into two subgroups; survivors group and non survivors group.

RESULTS:

our will be demonstrated in the following tables and figures.

Table (1): Demographic data and anthropometrics of the studied patients

		Total no.=91
Age (months)	Median (IQR)	24 (5 - 84)
	Range	1 – 180
Sex	Female	47 (51.6%)
	Male	44 (48.4%)
Weight (kg)	Median (IQR)	10 (6 - 21)
	Range	2.5 - 62.5
Weight-SDS	Median (IQR)	- 0.95 (- 2.24 - 0.08)
	Range	- 2.26 – 4.05
Height (cm)	Mean ± SD	88.32 ± 33.62
	Range	12.7 – 162
Height-SDS	Median (IQR)	- 1.26 (- 2.26 - - 0.12)
	Range	- 2.94 – 4.77
Body Mass Index	Mean ± SD	16.50 ± 4.27
	Range	6.4 – 26
BMI SDS	Mean ± SD	0.34 (-4.99 - 3.52)
	Range	-3.14 – 4.28

This table shows91 patients with a median age of 24 months ranging from 1 to 180 months, 51.61% were females and 48.4% were males. Their median weight standard deviation score (Wt SDS) was -0.95 ranging from -2.26 to 4.05 SDS, median height SDS (Ht SDS) was -1.26 ranging from - 2.94 to 4.77 SDS, and median body mass index SDS (BMI SDS) was 0.34 ranging from -3.14 to 4.28.

Table (2): Initial diagnosis of the studied patients

Initial diagnosis (source of sepsis)	Total no.=91
Pneumonia	35 (38.5%)
Gastroenteritis	18 (19.8%)
Encephalitis	8 (8.8%)
Enterocolitis	4 (4.4%)
Intestinal perforation	3 (3.3%)
Pyelonephritis	3 (3.3%)
Pancreatitis	2 (2.2%)
Central line infection	2 (2.2%)
Peritonitis	2 (2.2%)
Disseminated fungal infection	2 (2.2%)
Fulminant hepatitis	1 (1.1%)
Necrotizing Pneumonia	1 (1.1%)
Perforated appendix	1 (1.1%)
Liver abscess	1 (1.1%)
Neck abscess	1 (1.1%)
Intestinal obstruction	1 (1.1%)
Surgical site infection	1 (1.1%)
Multiple abscesses	1 (1.1%)
Cholangitis	1 (1.1%)
Perforated sigmoid	1 (1.1%)
Viral septicemia	1 (1.1%)
Typhlitis	1 (1.1%)

This table shows the main source of sepsis of studied patients was pneumonia (38.5%) followed by Gastroenteritis (19.8%).

Table (3): Outcome distribution in studied patients

		Total no.=91	p value
Mortality	Survivors	39 (42.9%)	<0.01
	Non-survivors	52 (57.1%)	
28 days mortality	No	46 (50.5%)	
	Yes	45 (49.5%)	
90 days mortality	No	84 (92.3%)	
	Yes	7 (7.7%)	
Organ dysfunction	No	14 (15.6%)	
	Yes	76 (84.4%)	

This table shows 39 cases were survivors and 52 cases were non survivors with statistically significant p value <0.01.

Table (4): Comparison between survivors and non-survivors regarding different laboratory parameters and SOFA score.

		Mortality		P-value
		Survivors No.=39	Non-Survivors No.=52	
CBG (mg/dl)	Median (IQR)	69.45 (35.7-250)	40 (20.87-88.21)	0.010
	Range	7.35 – 378	6.55 – 333	
T3 (pg/ml)	Mean ± SD	2.22 ± 1.04	2.03 ± 0.91	0.333
	Range	0.39 - 4.1	0.56 - 5.61	
T4 (ng/dl)	Mean ± SD	1.27 ± 0.38	1.26 ± 0.52	0.922
	Range	0.49 - 2.14	0.25 - 2.9	
TSH (ulU/ml)	Median (IQR)	1.79 (0.89-2.74)	2 (0.55-2.99)	0.866
	Range	0.01 - 5.32	0.05 - 9.29	
Interpretation	Normal	23 (59%)	18 (34.6%)	0.080
	Non-thyroidal illness	14 (35.9%)	28 (53.8%)	
	Subclinical hypothyroidism	2 (5.1%)	3 (5.8%)	
	Subclinical hyperthyroidism	0 (0%)	3 (5.8%)	
SOFA score	Median (IQR)	5 (4-6)	8.5 (7-10.5)	0.000
	Range	2 – 10	5 – 13	

This table shows there was no statistically significance between survivors and non survivors regarding laboratory parameters except a significant decrease of CBG among non survivors with p value =0.010.

Table (5): Comparison between survivors and non-survivors regarding different treatment modalities

Treatment		Mortality		P-value
		Survivors No.=39	Non-Survivors No.=52	
Noradrenaline	Yes	29 (74.4%)	43 (82.7%)	0.333
Milrinone	Yes	6 (15.4%)	11 (21.2%)	0.485
Dopamine	Yes	5(12.8%)	5 (9.6%)	0.629
Adrenaline	Yes	12 (30.8%)	20 (38.5%)	0.447
Shock dose steroids	Yes	8 (20.5%)	29 (55.8%)	0.001
Ventilated	Yes	7 (17.9%)	51 (98.1%)	0.000

Hemodialysis	Yes	5 (12.8%)	8 (15.4%)	0.729

This table shows there was no statistically significance between survivors and non survivors regarding different treatment modalities except a significant increase of shock dose steroids and ventilation among non survivors with p value =0.010.

Table (6): Sensitivity, specificity positive predictive value and negative predictive value for serum CBG assay:

Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
≤ 222.3	0.659	98.08	31.58	66.2	92.3

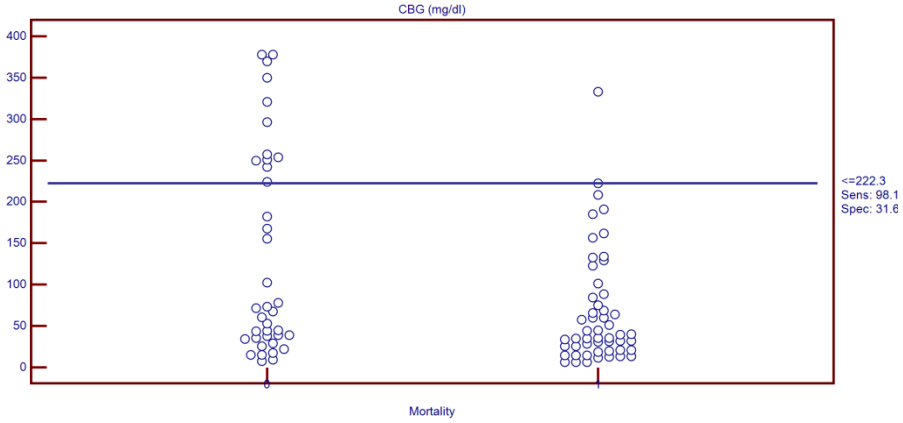

Figure (1): Cutoff point of CBG level among studied patients

AUC: Area under curve, Receiver Operating Characteristic curve (ROC), and Interactive Dot Diagram for CBG level to differentiate between survivors and non-survivor cases.

DISCUSSION

This prospective observational study on 91 children diagnosed with septic shock discovered that a deficiency of CBG, defined as a plasma CBG concentration lower than 222.3 mg/dL, predicted ICU mortality independently and increased the risk by 8.4 times. Additionally, CBG deficiency was linked to the need for ventilator and vasopressor support, both of which are indicators of the severity of the illness. The overall mortality rate was 57.1%, the 28-day mortality rate was 49.5%, and the 90-day mortality was 7.7%. The mortality rate of sepsis in the PICU of developing countries is higher than 50% ***(Sarthi et al., 2007)***. The high SOFA score of our patients at admission reflected the severity of sepsis which resulted in an increased mortality rate (***Kaur et al., 2007)***. Also, the type of our patients (septic patients on cardiac support) is associated with a high mortality rate ***(Markovitz et al., 2005)***.

Regarding our primary outcomes: the ICU mortality rate was higher in patients with serum CBG levels < 222.3 mg/dl, lower serum CBG levels were observed among pediatric patients with septic shock compared to controls in one study ***(Ho et al., 2006)***. IL-6 is one of the cytokines involved in septic shock, IL-6 injection inhibited CBG secretion and CBG mRNAs in mice hepatocytes ***(Emptoz et al., 1997)***. Low plasma CBG level was associated with poor outcomes in patients with sepsis in other studies ***(Jiang et al., 2022)***, ***(Meyer et al 2019), (Nenke et al***

2015). Cortisol is essential to survive stressors such as systemic inflammation including sepsis ***(Annane et al., 2016).*** CBG is a glycoprotein with a high affinity for cortisol binding; it binds 80% of circulating cortisol. Pyrexia and acidic media reversibly reduce CBG cortisol binding, while neutrophil elastase (NE) cleavage irreversibly reduces it. This may enhance the delivery of cortisol to inflammatory sites during sepsis. In addition, inflammatory cytokines in sepsis suppress CBG hepatic synthesis ***(Lee et al., 2023)***. So, serum CBG levels fall in proportion to sepsis severity ***(Nenke et al 2015).*** Deficiency of serum CBG level may impair cortisol transport to inflammatory sites, leading to organ failure and increased mortality seen in septic shock ***(Meyer et al 2019).***

Serum CBG levels were lower in patients with impaired renal functions. Kidneys are one of the major sites of CBG synthesis so impaired renal function may affect CBG synthesis ***(Scorcchi et al., 1993).***

Twenty-eight and 90-day mortality rates, the need for mechanical ventilation and vasopressors were higher in patients with serum CBG levels < 222.3 mg/dl, These results can be explained by the presence of CBG in most of the endothelial cells of blood vessels within the myocardium, endocardial cells, and smooth muscle cells of arterial walls ***(Schäfer et al., 2015).*** So CBG deficiency seen in sepsis impairs the delivery and effect of cortisol on the cardiovascular system resulting in higher doses and duration needed for cardiac support. However, studies on adult septic patients failed to find a correlation between serum CBG levels and inotropic support use during septic shock ***(Beishuizen et al., 2001).***

Hydrocortisone administration in septic shock is still controversial. The administration of shock dose steroids to our patients was associated with a higher overall mortality rate. Studies conducted on pediatric patients with septic shock described a positive correlation between the use of shock dose hydrocortisone and septic shock mortality ***(Nichols et al., 2017), (Casartelli et al., 2016) (Yehya et al., 2016), (Atkinson et al., 2014), (Klowak et al., 2023).*** Corticosteroid administration could increase the incidence of secondary bacterial infection, diminish wound healing, and increase the risk of gastrointestinal bleeding, hyperglycemia, and immune suppression resulting in higher mortality ***(Atkinson et al., 2014), (Patel et al., 2012), (Hanna et all., 2013).*** Shock dose hydrocortisone was associated with faster resolution from shock, shorter duration of ventilation, and earlier discharge from PICU without affecting the mortality rate in some studies ***(Vankatesh et al., 2018), (Briegel et al., 1999).*** Contrarily, lower mortality rates were observed with shock-dose steroid therapy in adult sepsis, which could be attributed to corticosteroids' action in decreasing inflammation and improving tissue perfusion to restore organ function and reverse shock ***(Baur et al., 2008), (Boyer et al., 2006), (Pourmand et al., 2019).*** We did not measure serum cortisol levels in our study as it was not intended to address the value of cortisol concentrations in septic shock; particularly as shock dose hydrocortisone was delivered on intensivist judgment to approximately 40% of the patients, and the cortisol concentrations in that setting would be highly variable and subject to pharmacokinetic considerations. Cortisol concentrations are associated with illness severity and vasopressor sensitivity but are not recommended for use in determining the need for hydrocortisone therapy ***(Nenke et al., 2015), (Rotman et al., 2006), (Annane et al., 1998), (Christ et al., 2007)), (Annane et al., 2000), (Lipener et al., 2007).***

Non-thyroidal illness (NTI) is a condition of decreased thyroid hormone levels without disruption of thyroid hormone function that occurs in severe systemic illness ***(Yanni et al., 2019).*** It is an adaptive mechanism of the body responding to stress to reduce metabolic demands and inhibit anabolism (38). Non-thyroidal illness was observed in 46.1% of the recruited subjects which was lower than the rates observed in other studies 70%, 62.9%, 65%, and 96% ***(El-Nawawy et al., 2024), (El-Ella et al., 2019), (Abdelgawad et al., 2022), (Cornu et al., 2021).***

NTI was associated with a higher sofa score compared with patients who had a normal thyroid profile in agreement with other studies ***(Abdelgawad et al., 2022), (Sun et al., 2023), (Hosny et al., 2015).***

Alterations in thyroid hormones lead to disruption of oxygen consumption in different systems including cardiovascular, sympathetic nerves, respiratory, and digestive systems, which in turn will result in more organ failure ***(Angelousi et al., 2011).*** In our study, NTI did not correlate with mortality, dose of cardiac supports, or organ dysfunction which raises the question of whether the peripheral non-thyroidal illness component, with inactivation of thyroid hormone, may represent a beneficial adaptation ***(Jacobs et al., 2019).*** Other studies on pediatric sepsis observed higher mortality rates in patients with NTI ***(Abdelgawad et al., 2022),*** We only measured thyroid hormones once in this study at the time of patient recruitment without further follow-up of thyroid hormone levels especially around the time of mortality in non-survivors or time of discharge in survivors. In a study on adult septic patients, no difference in T3 and free thyroxin (fT4) levels on admission in non-survivors compared with survivors was observed. However, during follow-up, fT4 levels decreased significantly in non-survivors, while they increased in survivors, in addition, on the day of death, non-survivors had lower T3 and fT4 levels as compared with survivors elucidating that decrease in fT4 levels in the course of the disease may point to an adverse outcome, unlike single fT4 readings which failed to predict mortality ***(Meyer et al., 2011).*** So serial measurements of thyroid hormones in larger cohorts of pediatric septic shock patients may be needed to prove or deny the current belief in prognostic importance of NTI in pediatric septic shock after excluding the effects of other confounders affecting thyroid functions including drugs that might affect thyroid hormone levels ***(Abdelgawad et al., 2022), (Sun et al., 2023)***.

CONCLUSION

Serum CBG level is associated with a higher mortality rate in pediatric septic shock and may be used as a future marker to predict poor outcomes. Non-thyroidal illness is common among septic shock patients with higher SOFA scores but is not associated with a higher mortality rate in our study. Further studies on NTI in pediatric sepsis are required including serial measurements of thyroid hormones to understand the impact of NTI on septic shock mortality.

RECOMMENDATIONS:

- **i.** Further studies on large numbers of patients with sepsis to confirm the role of CBG as a predictor of severity of illness and mortality rate in septic pediatrics.
- **ii.** Further studies septic patients to assess the role of steroid therapy in pediatric sepsis.
- **iii.** Further follow up of CBG and thyroid hormones levels changes during the admission in PICU**.**

LIMITATIONS:

- **i.** The small sample size.
- **ii.** Drugs that patients had in PICU might have an affect on thyroid hormone levels.
- **iii.** Some cases could have sub clinical abnormalities in thyroid functions before the onset of critical illness, and this could affect the results.

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References:

1. **ANNANE, D., ABDELGAWAD, T. A., MAGDY, S. M., MAHMOUD, R. A. A., TAHA, S. I. A. & ALI, S. Y. A. E. 2022**. Frequency of non-thyroidal illness syndrome in pediatric patients with sepsis and septic shock. *Egyptian Pediatric Association Gazette,* 70**,** 32.
2. **ANGELOUSI, A. G., KARAGEORGOPOULOS, D. E., KAPASKELIS, A. M. & FALAGAS, M. E. 2011**. Association between thyroid function tests at baseline and the outcome of patients with sepsis or septic shock: a systematic review. *Eur J Endocrinol,* 164**,** 147-55.
3. **ANNANE, D. 2016.** The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update. *Front Endocrinol (Lausanne),* 7**,** 70.
4. **ANNANE, D., BELLISSANT, E., SEBILLE, V., LESIEUR, O., MATHIEU, B., RAPHAEL, J. C. & GAJDOS, P. 1998**. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. *Br J Clin Pharmacol,* 46**,** 589-97.
5. **SÉBILLE, V., TROCHÉ, G., RAPHAËL, J. C., GAJDOS, P. & BELLISSANT, E. 2000.** A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *Jama,* 283**,** 1038-45.
6. **ATKINSON, S. J., CVIJANOVICH, N. Z., THOMAS, N. J., ALLEN, G. L., ANAS, N., BIGHAM, M. T., HALL, M., FREISHTAT, R. J., SEN, A., MEYER, K., CHECCHIA, P. A., SHANLEY, T. P., NOWAK, J., QUASNEY, M., WEISS, S. L., BANSCHBACH, S., BECKMAN, E., HOWARD, K., FRANK, E., HARMON, K., LAHNI, P., LINDSELL, C. J. & WONG, H. R. 2014.** Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. *PLoS One,* 9**,** e112702.
7. **BAUER, S. R., LAM, S. W., CHA, S. S. & OYEN, L. J. 2008**. Effect of corticosteroids on arginine vasopressin-containing vasopressor therapy for septic shock: a case control study. *J Crit Care,* 23**,** 500-6.
8. **BEISHUIZEN, A., THIJS, L. G. & VERMES, I. 2001.** Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Medicine,* 27**,** 1584-1591.
9. **BOYER, A., CHADDA, K., SALAH, A. & ANNANE, D. 2006.** Glucocorticoid treatment in patients with septic shock: effects on vasopressor use and mortality. *Int J Clin Pharmacol Ther,* 44**,** 309-18.
10. **BRIEGEL, J., FORST, H., HALLER, M., SCHELLING, G., KILGER, E., KUPRAT, G., HEMMER, B., HUMMEL, T., LENHART, A., HEYDUCK, M., STOLL, C. & PETER, K. 1999.** Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med,* 27**,** 723-32.
11. **BURRY, L. D. & WAX, R. S. 2004**. Role of corticosteroids in septic shock. *Ann Pharmacother,* 38**,** 464-72.
12. **CASARTELLI, C. H., GARCIA, P. C., BRANCO, R. G., PIVA, J. P., EINLOFT, P. R. & TASKER, R. C. 2007**. Adrenal response in children with septic shock. *Intensive Care Med,* 33**,** 1609-13.
13. **CHRIST-CRAIN, M., STOLZ, D., JUTLA, S., COUPPIS, O., MÜLLER, C., BINGISSER, R., SCHUETZ, P., TAMM, M., EDWARDS, R., MÜLLER, B. & GROSSMAN, A. B. 2007.** Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med,* 176**,** 913-20.
14. **CORNU, M. G., MARTINUZZI, A. L. N., ROEL, P., SANHUEZA, L., SEPÚLVEDA, M. E., OROZCO, M. S., SÁNCHEZ, C. A. & GULINO, M. 2021**. Incidence of low-triiodothyronine syndrome in patients with septic shock. *Revista Brasileira de Terapia Intensiva,* 32**,** 514-520.
15. **EL-ELLA, S. S. A., EL-MEKKAWY, M. S. & EL-DIHEMEY, M. A. 2019**. Prevalence and prognostic value of non-thyroidal illness syndrome among critically ill children. *Anales de Pediatría (English Edition),* 90**,** 237-243.
16. **EL-NAWAWY, A., ELWAFA, R., KHALIL ABOUAHMED, A., RASHEED, R. A. & OMAR, O. M. 2024.** Evaluation of non-

thyroidal illness syndrome in shock patients admitted to pediatric intensive care unit in a developing country. *Eur J Pediatr,* 183**,** 769-778.

17. **EMPTOZ-BONNETON, A., CRAVE, J. C., LEJEUNE, H., BRÉBANT, C. & PUGEAT, M. 1997.** Corticosteroid-binding globulin synthesis regulation by cytokines and glucocorticoids in human hepatoblastoma-derived (HepG2) cells. *J Clin Endocrinol Metab,* 82**,** 3758-62.
18. **HANNA, W. & WONG, H. R. 2013.** Pediatric sepsis: challenges and adjunctive therapies. *Crit Care Clin,* 29**,** 203-22.
19. **HO, J. T., AL-MUSALHI, H., CHAPMAN, M. J., QUACH, T., THOMAS, P. D., BAGLEY, C. J., LEWIS, J. G. & TORPY, D. J. 2006**. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab,* 91**,** 105-14.
20. **HOSNY, M., RASHAD, R., ATEF, D. & ABED, N. 2015**. Predictive value of thyroid hormone assessment in septic patients in comparison with C-reactive protein. *The egyptian journal of critical care medicine,* 3**,** 55-61.
21. **JACOBS, A., VANHOREBEEK, I. & VAN DEN BERGHE, G. 2019**. Nonthyroidal illness in critically ill children. *Current Opinion in Endocrinology, Diabetes and Obesity,* 26**,** 241-249.
22. **JIANG, Z., ELSARRAG, S. Z., DUAN, Q., LAGORY, E. L., WANG, Z., ALEXANIAN, M., MCMAHON, S., RULIFSON, I. C., WINCHESTER, S., WANG, Y., VAISSE, C., BROWN, J. D., QUATTROCELLI, M., LIN, C. Y. & HALDAR, S. M. 2022.** KLF15 cistromes reveal a hepatocyte pathway governing plasma corticosteroid transport and systemic inflammation. *Sci Adv,* 8**,** eabj2917.
23. **KAUR, G., VINAYAK, N., MITTAL, K., KAUSHIK, J. S. & AAMIR, M. 2014.** Clinical outcome and predictors of mortality in children with sepsis, severe sepsis, and septic shock from Rohtak, Haryana: A prospective observational study. *Indian J Crit Care Med,* 18**,** 437-41.
24. **KLOWAK, J. A., BIJELIĆ, V., BARROWMAN, N. & MENON, K. 2023.** The Association of Corticosteroids and Pediatric Sepsis Biomarker Risk Model (PERSEVERE)-II Biomarker Risk Stratification With Mortality in Pediatric Septic Shock. *Pediatr Crit Care Med,* 24**,** 186-193.
25. **LASA, M. & CONTRERAS-JURADO, C. 2022**. Thyroid hormones act as modulators of inflammation through their nuclear receptors. *Front Endocrinol (Lausanne),* 13**,** 937099.
26. **LEE, J. H., MEYER, E. J., NENKE, M. A., FALHAMMAR, H. & TORPY, D. J. 2023.** Corticosteroid-binding globulin (CBG): spatiotemporal distribution of cortisol in sepsis. *Trends Endocrinol Metab,* 34**,** 181-190.
27. **LIPINER-FRIEDMAN, D., SPRUNG, C. L., LATERRE, P. F., WEISS, Y., GOODMAN, S. V., VOGESER, M., BRIEGEL, J., KEH, D., SINGER, M., MORENO, R., BELLISSANT, E. & ANNANE, D. 2007**. Adrenal function in sepsis: the retrospective Corticus cohort study. *Crit Care Med,* 35**,** 1012-8.
28. **MARKOVITZ, B. P., GOODMAN, D. M., WATSON, R. S., BERTOCH, D. & ZIMMERMAN, J. 2005.** A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med,* 6**,** 270-4.
29. **MEYER, E. J., NENKE, M. A., DAVIES, M. L., CHAPMAN, M., RANKIN, W., RUSHWORTH, R. L. & TORPY, D. J. 2022.** Corticosteroid-Binding Globulin Deficiency Independently Predicts Mortality in Septic Shock. *J Clin Endocrinol Metab,* 107**,** 1636-1646.
30. **MEYER, E. J., NENKE, M. A., RANKIN, W., LEWIS, J. G., KONINGS, E., SLAGER, M., JANSEN, T. C., BAKKER, J., HOFLAND, J., FEELDERS, R. A. & TORPY, D. J. 2019**. Total and high-affinity corticosteroid-binding globulin depletion in septic shock is associated with mortality. *Clin Endocrinol (Oxf),* 90**,** 232-240.
31. **MEYER, E. J., TORPY, D. J., CHERNYKH, A., THAYSEN-ANDERSEN, M., NENKE, M. A., LEWIS, J. G., RAJAPAKSHA, H., RANKIN, W. & POLYAK, S. W. 2020.** Pyrexia and acidosis act independently of neutrophil elastase reactive center loop cleavage to effect cortisol release from corticosteroid-binding globulin. *Protein Sci,* 29**,** 2495-2509.

32. **MEYER, S., SCHUETZ, P., WIELAND, M., NUSBAUMER, C., MUELLER, B. & CHRIST-CRAIN, M. 2011.** Low triiodothyronine syndrome: a prognostic marker for outcome in sepsis? *Endocrine,* 39**,** 167-74.
33. **NENKE, M. A., RANKIN, W., CHAPMAN, M. J., STEVENS, N. E., DIENER, K. R., HAYBALL, J. D., LEWIS, J. G. & TORPY, D. J. 2015**. Depletion of high-affinity corticosteroid-binding globulin corresponds to illness severity in sepsis and septic shock; clinical implications. *Clin Endocrinol (Oxf),* 82**,** 801-7.
34. **NICHOLS, B., KUBIS, S., HEWLETT, J., YEHYA, N. & SRINIVASAN, V. 2017**. Hydrocortisone Therapy in Catecholamine-Resistant Pediatric Septic Shock: A Pragmatic Analysis of Clinician Practice and Association With Outcomes. *Pediatr Crit Care Med,* 18**,** e406-e414.
35. **PATEL, G. P. & BALK, R. A. 2012.** Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med,* 185**,** 133-9.
36. **POURMAND, A., WHITESIDE, T., YAMANE, D., RASHED, A. & MAZER-AMIRSHAHI, M. 2019**. The controversial role of corticosteroids in septic shock. *Am J Emerg Med,* 37**,** 1353-1361.
37. **RADMAN, M. & PORTMAN, M. A. 2016.** Thyroid Hormone in the Pediatric Intensive Care Unit. *J Pediatr Intensive Care,* 5**,** 154-161.
38. **ROTMAN-PIKIELNY, P., ROUACH, V., CHEN, O., GUR, H. G., LIMOR, R. & STERN, N. 2006**. Serum cortisol levels in patients admitted to the department of medicine: Prognostic correlations and effects of age, infection, and comorbidity. *Am J Med Sci,* 332**,** 61-67.
39. **SARTHI, M., LODHA, R., VIVEKANANDHAN, S. & ARORA, N. K. 2007.** Adrenal status in children with septic shock using low-dose stimulation test. *Pediatr Crit Care Med,* 8**,** 23-8.
40. **SCHÄFER, H. H., GEBHART, V. M., HERTEL, K. & JIRIKOWSKI, G. F. 2015**. Expression of corticosteroid-binding globulin CBG in the human heart. *Horm Metab Res,* 47**,** 596-9.
41. **SCROCCHI, L. A., HEARN, S. A., HAN, V. K. & HAMMOND, G. L. 1993**. Corticosteroid-binding globulin biosynthesis in the mouse liver and kidney during postnatal development. *Endocrinology,* 132**,** 910-6.
42. **SUN, C., BAO, L., GUO, L., WEI, J., SONG, Y., SHEN, H. & QIN, H. 2023.** Prognostic significance of thyroid hormone T3 in patients with septic shock: a retrospective cohort study. *PeerJ,* 11**,** e15335.
43. **VENKATESH, B., FINFER, S., COHEN, J., RAJBHANDARI, D., ARABI, Y., BELLOMO, R., BILLOT, L., CORREA, M., GLASS, P., HARWARD, M., JOYCE, C., LI, Q., MCARTHUR, C., PERNER, A., RHODES, A., THOMPSON, K., WEBB, S. & MYBURGH, J. 2018**. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *New England Journal of Medicine,* 378**,** 797-808.
44. **VERBEETEN, K. C. & AHMET, A. H. 2018**. The role of corticosteroid-binding globulin in the evaluation of adrenal insufficiency. *J Pediatr Endocrinol Metab,* 31**,** 107-115.
45. **YANNI, G. N., DESTARIANI, C. P., LUBIS, A. N. & DELIANA, M. 2019.** Thyroid Hormone Profile in Children with Sepsis: Does Euthyroid Sick Syndrome Exist? *Open Access Maced J Med Sci,* 7**,** 1110-1113.
46. **YEHYA, N. & THOMAS, N. J. 2016**. Relevant Outcomes in Pediatric Acute Respiratory Distress Syndrome Studies. *Front Pediatr,* 4**,** 51.