Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.6(2023). p.472-82; DOI: https://doi.org/10.14238/pi63.6.2023.472-82

Original Article

Cortisol levels associated with mortality in children with critical illness: a systematic review

Restu Triwulandani Tolibin, Septin Widiretnani, Annang Giri Moelyo

Abstract

Background Critically ill patients, including those with sepsis, have increased cortisol levels due to activation of the hypothalamic-pituitary-adrenal (HPA) axis or critical illness-related corticosteroid insufficiency (CIRCI).

Objective To evaluate for a possible association between cortisol levels and mortality from sepsis in pediatric patients by systematic review of the literature.

Methods A systematic review was conducted on studies involving critically ill children, including those with sepsis. We included studies published between 2011-2020 analyzing data on cortisol levels [total serum cortisol, serum-free cortisol, salivary cortisol, real-time free cortisol, basal serum cortisol and post-adrenocorticotropin hormone (ACTH) stimulation test, or basal salivary cortisol and post-ACTH stimulation test], the predictive score for mortality (*Pediatric Logistic Organ Dysfunction*/PELOD), *Pediatric Risk of Mortality* (PRISM), *Pediatric Index of Mortality* (PIM), *Vasotropic Inotropic Score* (VIS), or *Pediatric Critical Illness Score* (PCIS)], mortality (non-survivor percentage), and CIRCI percentage as an outcomes in patients with critical illness, sepsis, and septic shock.

Results Twenty-one observational studies were included in our systematic review, with a total of 2,212 subjects, 916 of whom had sepsis. Nineteen studies indicated a positive association between elevated cortisol levels and mortality in critically ill children, but 2 studies stated that there was no association with the CIRCI percentage of 32.3 and 84.3% respectively. The median mortality percentage of critically ill patients with elevated cortisol levels and sepsis were 25.81 (range 2.7-60)% and 35.31 (range 6-60)%, respectively. The median percentages of CIRCI in critically ill and sepsis patients were 21.91 (range 0-84.3)% and 21.35 (range 0-84.3)%, respectively.

Conclusion Cortisol levels may increase or decrease in critically ill children. Elevated cortisol levels are associated with mortality in septic children. The effect of CIRCI on mortality in critically ill children cannot be concluded. **[Paediatr Indones. 2023;63:472-82; DOI: https://doi.org/10.14238/pi63.6.2023.472-82**].

Keywords: *cortisol; mortality; sepsis*

The regulation of cortisol production becomes more complex during critical illness due to stress. Critical illness, such as sepsis, causes such severe physical stress that the body must respond to restore homeostasis. The hypothalamus, pituitary, and adrenal glands, which make up the HPA axis, have a central role in regulating the stress response. In critically ill patients, stress mobilizes a variety of neuronal and inflammatory signals that directly or indirectly cause the paraventricular nucleus to stimulate the synthesis andecretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), leading to disruption of the circadian rhythm of cortisol secretion. Furthermore, the hypophyseal portal circulation transports CRH and AVP from the hypothalamus to the anterior pituitary gland. The CRH and AVP hormones trigger corticotropic cells to release ACTH into the systemic circulation.[1-3] The HPA axis activation accompanied by increased cortisol concentration is the best-documented endocrine response to severe systemic stress. In

From the Department of Child Health, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Central Java, Indonesia.

Corresponding author: Restu Triwulandani Tolibin. Pediatric Divison, Faculty of Medicine, Sebelas Maret University/ Dr. Moewardi Hospital, Surakarta, Central Java, Indonesia. Jalan Kolonel Sutarto No. 132, Surakarta, Indonesia. Email: betul2betu@gmail.com.

Submitted October 25, 2022. Accepted December 6, 2023.

critically ill patients, elevated cortisol levels result from activation of the HPA axis, leading to a 6-10 times increase in adrenocortical cortisol synthesis and secretion compared to normal, in response to increased ACTH release from the anterior pituitary gland.[1,2]

Total serum cortisol was found to be higher in patients with severe sepsis (with a well-functioning HPA axis) than in healthy subjects. Mortality was associated with high cortisol levels.[3] High cortisol was associated with a higher risk of mortality as well as higher total basal serum cortisol and PRISM-III scores. High blood pressure is a significant predictor of mortality.[4] Prognostic indicators of children with sepsis could include serum cortisol levels.[5] There was a positive correlation between serum cortisol levels and the PRISM-III score.[6] Serum total cortisol and free cortisol were associated with disease severity as measured by the PRISM-III score.[7]

On the other hand, CIRCI is defined as insufficient cellular corticosteroid activity based on the severity of the patient's disease.[2,8-11] The CIRCI can manifest as glucocorticoid insufficiency, decreased expression, and dysfunction of glucocorticoid receptors that regulate proinflammatory transcription factors, leading to a progressive increase of proinflammatory mediators over time, including decreased production of CRH, ACTH, and cortisol, and decreased cortisol metabolism.[1,2,8] We aimed to evaluate the association between cortisol levels and mortality from sepsis in pediatric patients in a systematic review.

Methods

We performed a systematic review by PRISMA guidelines. We used *PubMed, Directory of Open Access Journal* (DOAJ), *Google Scholar, Scopus*, and *ProQuest* to search for relevant articles published from 2011 to 2020, with the keywords 'cortisol,' 'sepsis,' 'prognosis,' 'mortalit*,' and 'children.' We searched for potential studies and other publications from the bibliography on cohort reports, meta-analyses, and guidelines. We also carried out a hand search of conference/seminar abstracts from the *European Society for Pediatric Endocrinology* and the *Pediatric Endocrine Society*.

Our review was restricted to studies that met the following inclusion criteria: (1) pediatric patients with critical illness, such as sepsis and septic shock; (2) observational studies (cohort, case-control, and cross-sectional) containing at least one pediatric patient with sepsis; (3) available in full-text; and (4) involved analyses of cortisol levels (total serum cortisol, serum-free cortisol, salivary cortisol, real-time free cortisol, basal serum cortisol, and post-ACTH stimulation test, or basal salivary cortisol and post-ACTH stimulation test), with predictive score for mortality (PELOD, PRISM, PIM, VIS or PCIS), mortality (non-survivor percentage), and CIRCI percentage reported as outcomes. Studies were excluded if they (1) did not provide the data required; (2) used languages other than English or Indonesian; or (3) focused on CIRCI. The primary outcome was the percentage of mortality in pediatric patients with sepsis with elevated cortisol levels.

Studies were assessed for quality and risk of bias by two independent reviewers using standardized critical appraisal by the *Newcastle-Ottawa Quality Assessment Form* for cohort, case-control, and cross-sectional studies.[12] Any disagreements that arose between the reviewers were resolved through discussion or with the help of a third reviewer.

Results

We identified 1,903 studies from our initial database literature searches and 3 studies from hand searches. After removing duplicates, we evaluated the articles individually for eligibility at the level of title, abstract, full text, and study design, and excluded studies that did not meet our criteria. Twenty-one studies were included, consisting of 3 cross-sectional studies and 18 cohort studies. The flowchart of study selection is shown in **Figure 1**. Articles included originated from the USA (4), Egypt (3), Turkey (3), Indonesia (3), Canada (2), and India (2) as well as one study each from China, Brazil, Israel, and Vietnam. All included studies were assessed for quality (risk of bias) and were each found to have a low risk of bias.

A total of 21 observational studies published before 2022 were analyzed, with a total of 2,212 enrolled subjects, of whom 57.97% were male and 42.03% were female.[5,6,13-30] The sample consisted of 1,810 subjects with critical illness, including 916 subjects with sepsis and septic shock, and 402 control

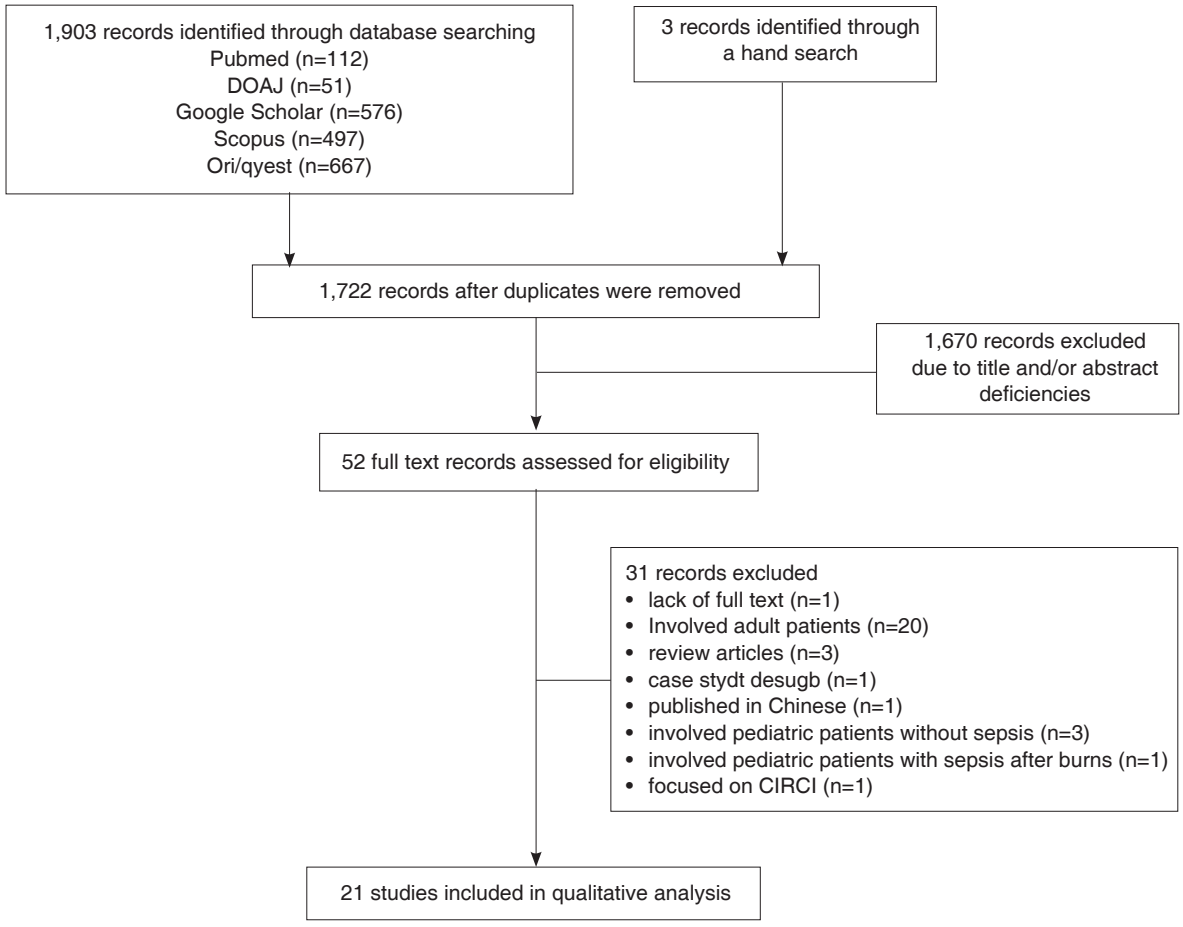

Figure 1. Systematic review flowchart of the study selection process

subjects. The characteristics and outcomes of included studies are shown in **Tables 1** and **2**, respectively. The 21 studies were heterogeneous in terms of study design, population, and outcomes in the form of cortisol levels, mortality, and CIRCI. Nineteen of 21 studies stated that there was a relationship between elevated cortisol levels and mortality in critical illness patients, including those with sepsis, as shown in **Table 3**.[5,6,13-17,19-22,24-30] One study agreed with the statement, but found no relationship between post-serum ACTH stimulation test and mortality in critical illness patients.[17]

Fourteen studies had mortality percentage data critical illness patients with elevated cortisol levels.[5,6,13-20,25-27] Descriptive analysis on these 14 studies revealed a median mortality of 25.81 (range 2.7-60)% in critical illness patients. Only 7 studies had mortality rates of sepsis and septic shock patients with elevated cortisol levels.[6,13,17,25-29] The median mortality was 35.31 (range 6-60)% in sepsis/septic shock patients.

Sixteen studies reported percentages of CIRCI in critical illness patients,[5,13-19,21-26,29,30] comprising a median of 21.91 (range 0-84.3) % of these patients. Only 8 studies had CIRCI percentage in sepsis and septic shock patients,[13,15,21,23-26,29] comprising a median of 21.35 (range 0-84.3) % of such patients.

Discussion

In critical illnesses such as sepsis, cortisol functions directly to reduce norepinephrine reuptake and increase the availability of calcium in the myocardium and blood vessels, causing increased myocardial contractility and vasoconstriction. Cortisol also inhibits prostacyclin and endogenous nitric oxide production, resulting in increased vascular tone,

Table 1. Study design and baseline characteristics of included studies

Author	Year	Study design	Country	Population	Measured in study
Rady, *et al.*[13]	2014	Prospective cohort	Egypt	60 subjects, 30 in the sepsis group and 30 in the control group	Basal serum cortisol and post-ACTH stimulation test, % non-survivor, % CIRCI
Iyer, *et al.*[14]	2017	Retrospective cohort	USA	76 subjects with critical illness using ACTH stimulation test, 12 with sepsis	Basal serum cortisol and post-ACTH stimulation test, PRISM-III score, % non-survivor, % CIRCI
Lin *et al.*[15]	2020	Retrospective cohort	China	74 subjects, 24 in early stage septic shock, 25 in advanced stage septic shock, 25 in the control group	Total serum cortisol, PCIS, % CIRCI
Jacobs *et al.*[16]	2019	Prospective cohort	Canada	506 subjects, 442 in the critical illness group (93 with sepsis) and 64 in the control group	Serum free cortisol, PELOD score, PIM2 score, % non-survivor, % CIRCI
Levy-Shraga *et al.*[17]	2016	Retrospective cohort	Israel	99 subjects with critical illness using ACTH stimulation test, 48 with sepsis and 47 with septic shock	Basal serum cortisol and post-ACTH stimulation test, PCIS, % non-survivor, % CIRCI
Balbao *et al.*[18]	2014	Prospective cohort	Brazil	51 subjects, 36 in the critical illness group (19 with sepsis and septic shock) and 15 in the control group	Basal serum cortisol and post-ACTH stimulation test, basal salivary cortisol and post-ACTH stimulation test, % non-survivor, PRISM-III score, PELOD score, % CIRCI
Aydin *et al.*[19]	2013	Prospective cohort	Turkey	40 subjects with critical illness (10 with sepsis)	Total serum cortisol, PRISM score, PELOD score, % non-survivor, % CIRCI
Demiral *et al.*[20]	2019	Prospective cohort	Turkey	116 subjects, 81 in the critical illness group (11 with sepsis) and 35 in the control group	Total serum cortisol, basal serum cortisol and post-ACTH stimulation test, PRISM-III score, % non-survivor
Zabidi *et al.*[6]	2015	Retrospective cohort	Indonesia	30 subjects with sepsis	Total serum cortisol, % non-survivor
Menon *et al.*[21]	2018	Prospective cohort	Canada	30 subjects with septic shock	Total serum cortisol, serum free cortisol, PRISM score, PELOD score, VIS, % CIRCI
Zimmerman *et al.*[22]	2011	Prospective cohort	USA	186 subjects, 165 in the critical illness group (26 with sepsis) and 21 in the control group	Total serum cortisol, serum free cortisol, real-time free cortisol, PRISM-III score, % CIRCI
Bekhit *et al.*[5]	2019	Prospective cohort	Egypt	81 subjects with critical illness (11 with sepsis)	Total serum cortisol, PRISM-III score, % non-survivor, % CIRCI
Singh *et al.*[23]	2012	Prospective cohort	India	130 subjects, 51 in the septic shock group and 79 in the control group	Basal salivary cortisol and post-ACTH stimulation test, % non-survivor, % CIRCI
Karaguzel *et al.*[24]	2012	Prospective cohort	Turkey	64 subjects, 23 in the septic shock and sepsis group and 23 in the control group	Basal serum cortisol and post-ACTH stimulation test, PRISM-III score, % CIRCI
Alder *et al.*[25]	2018	Prospective cohort	USA	129 subjects with sepsis and septic shock and 35 in the control group	Total serum cortisol, PRISM-III score, % non-survivor, % CIRCI
Nguyen *et al.*[26]	2019	Prospective cohort	Vietnam	74 subjects with septic shock	Total serum cortisol, PRISM-II score, % non-survivor, % CIRCI
Yehya *et al.*[27]	2016	Prospective cohort	USA	155 subjects with critical illness (44 with sepsis)	Total serum cortisol, PRISM-III score, % non-survivor

Table 1. Study design and baseline characteristics of included studies (continued)

Author	Year	Study design	Country	Population	Measured in study
El-Kelany *et al.*[28]	2017	Cross sectional	Egypt	45 subjects with sepsis and 45 in the control group	Total serum cortisol, salivary cortisol, % non-survivor
Pertiwi *et al.*[7]	2017	Cross sectional	Indonesia	42 subjects with critical illness (14 with sepsis)	Total serum cortisol, PELOD score
Rachmawati *et al.*[29]	2011	Cross sectional	Indonesia	30 subjects with sepsis	Basal serum cortisol and post-ACTH stimulation test, PELOD score, % non-survivor, % CIRCI
Wani *et al.*[30]	2019	Prospective cohort	India	114 subjects with critical illness (90 with sepsis)	Total serum cortisol, PRISM-III score, PELOD score, VIS, % non-survivor, % CIRCI

modulating capillary leakage, and augmenting adrenergic receptors in the heart.[15] However, potential adverse side effects of elevated cortisol include hyperglycemia, diffuse neuromuscular weakness (including diaphragmatic muscle weakness) associated with catabolism, and an increased risk of hospital-acquired infection. Elevated cortisol may contribute to poorer outcomes in critically ill patients.[2] This finding seems to be suggested in 19 studies included in this systematic review.[5,6,13-17,19-22,24-30]

One study noted an association between increased basal serum cortisol levels and mortality in critically ill children, but no relationship between post-ACTH stimulation serum cortisol levels and mortality in critically ill children. Levy-Shraga *et al.*[17] stated that the non-survival group had higher basal serum cortisol levels than the survivor group (mean 22.58 and 12.79 g/dL, respectively; P=0.05), but no significant difference in post-test serum cortisol levels ACTH stimulation in both groups. Two studies found no relationship between elevated cortisol levels and mortality in critically ill patients, including those with sepsis. Balbao *et al.*[18] stated that basal serum cortisol levels, basal salivary cortisol levels, salivary cortisol levels post-ACTH stimulation test, and serum cortisol levels post-ACTH stimulation test in the case group were higher than in the control group (P=0.0001). However, the difference in the increase in serum and saliva cortisol after the ACTH stimulation test was not significantly different in the case and control groups. There was a positive relationship between basal serum cortisol levels and basal salivary cortisol (r=0.67; P<0.0001) with serum and salivary cortisol levels post-ACTH stimulation test (r=0.41; P=0.02) in patients with critical illness. A negative relationship was found between post-ACTH stimulation salivary cortisol levels and VIS in the first 48 hours of patient admission to the PICU (r=-0.56; P<0.0008). Furthermore, there was no significant relationship between basal serum cortisol and basal salivary cortisol levels with PRISM-III (P=0.04) and PELOD (P=0.1) scores in the first 24 hours of patient admission to the PICU.

Singh *et al.*[23] also found that basal salivary cortisol levels and salivary cortisol levels after ACTH stimulation test were not associated with mortality. Basal salivary cortisol levels were 19.8 (7.2-42.44) g/dL in the case group with septic shock and 2.6 (1.3-7.6) g/dL (P<0.001) in the control group. However, the salivary cortisol delta or the mean difference between post-ACTH stimulation basal salivary cortisol in the survivor group was higher was 1.45 (SD 2.56) g/dL compared to the non-survivor group of 1.05 (SD 3.27) g/dL (P=0.657).

There was no significant relationship between cortisol levels and mortality in three of the studies, due to the high percentages of CIRCI, which were 37.3% for the Levy-Shraga et al. study,[17] 32.3% for the Balbao *et al.* study,[18] and 84.3% for the Singh *et al.* study.[23] So further study is needed to determine the effect of CIRCI on mortality in children with sepsis.

The cortisol data obtained from 21 studies included total serum cortisol, serum-free cortisol, salivary cortisol, real-time free cortisol, basal serum cortisol and post-ACTH stimulation test, as well as basal salivary cortisol and post-ACTH stimulation test. As such, cortisol output analysis can only be descriptive due to the heterogeneity of the data. We suggest that serum total cortisol levels be preferred over other types of cortisol for use as a predictor

Table 2. Cortisol level, predictive score for mortality, and mortality of patients with critical illness

Study or subgroup	Cortisol		Mortality (without control)	
Rady, *et al.*[13]	Mean basal serum (SD), μg/dL		Non-survivor	50%
	Sepsis	51.39 (30.01)		
	Control	12.83 (1.86)		
	Mean post-serum ACTH 250 μg stimulation test (SD), μg/dL			
	Sepsis	73.38 (29.75)		
	Control	32.80 (6.43)		
Iyer, *et al.*[14]	Median basal serum (IQR), μg/dL	14.9 (0.6-190)	Median PRISM-III score	17 (0-34)
	Median post serum ACTH 250 μg stimulation test (IQR), μg/dL	36.1 (7.3-464)	Non-survivor	29%
Lin *et al.*[15]	Mean total serum (SD), μg/dL		Median PCIS (IQR)	
	Early stage septic shock	32.6 (5.2)	Early stage septic shock	74 (73-76)
	Advanced stage septic shock	50.7 (6.5)	Advanced stage septic shock	71 (67-72)
	Control	NR		
Jacobs *et al.*[16]	Median serum free (IQR), μg/dL		Median PELOD score (IQR)	23 (21-32)
	Critical illness	1.19 (0.775-1.827)	Median PIM2 score (IQR)	5.2 (2.3-14.5)
	Control	NR	Non-survivor	27%
Levy-Shraga *et al.*[17]	Median basal serum (IQR), μg/dL	17.69 (6.05-33.06)	Median PCIS (IQR)	23.5 (0-50)
	Median post serum ACTH 250 μg stimulation test (IQR), μg/dL	42.52 (29.5-74.34)	Non-survivor	24%
Balbao *et al.*[18]	Median basal serum (IQR), μg/dL		Median PRISM-III score (IQR)	9 (1-34)
	Critical illness	25.1 (2.2-62.8)		
	Control	9.2 (3.7-18.7)		
	Median post-serum ACTH 250 μg stimulation test (IQR), μg/dL		Median PELOD score (IQR)	13 (0-30.5)
	Critical illness	39.2 (16.2-120)		
	Control	24.3 (15.3-31.6)		
	Median basal salivary (IQR), μg/dL		Non-survivor	2.9%
	Critical illness	3.41 (0.28-16.25)		
	Control	0.68 (I0.29-1.94)		
	Median post salivary ACTH 250 μg stimulation test (IQR), μg/dL			
	Critical illness	8.71 (1.2-41.8)		
	Control	4.08 (2.35-6.25)		
Aydin *et al.*[19]	Mean total serum (SD), μg/dL	42.1 (21.1)	Mean PRISM score (SD)	16.5 (11.5)
			Mean PELOD score (SD)	15.1 (13.3)
			Non-survivor	27.5%

Table 2. Cortisol level, predictive score for mortality, and mortality of patients with critical illness (continued)

Study or subgroup	Cortisol		Mortality (without control)	
Demiral *et al.*[20]	Mean total serum (SD), µg/dL		Mean PRISM-III score (SD)	7.07 (7.31)
	Critical illness	28.06 (19.23)		
	Control	15.05 (4.09)		
	Mean basal serum (SD), µg/dL		Non-survivor	6%
	Critical illness	10.3 (3.5)		
	Control	NR		
	Mean post serum ACTH 1 µg stimulation test (SD), µg/dL			
	Critical illness	39.9 (12.5)		
	Control	NR		
Zabidi *et al.*[6]	Median total serum (IQR), µg/dL	22.54 (6.46-83.61)	Non-survivor	30%
Menon *et al.*[21]	Median total serum (IQR), µg/dL	22.07 (11.63-41.97)	Median PRISM score (IQR)	6 (5-16)
	Median serum free (IQR), µg/dL	2.21 (0.98-5.18)	Median PELOD score (IQR)	7 (3-11)
			Median VIS (IQR)	16 (10-48)
Zimmerman *et al.*[22]	Mean total serum (SD), µg/dL		Mean PRISM-III score (SD)	8 (6.9)
	Critical illness	20.1 (18.3)		
	Control	10.5 (5.1)		
	Mean serum free (SD), µg/dL			
	Critical illness	3.8 (5.7)		
	Control	1 (0.4)		
	Mean real-time free (SD), µg/dL			
	Critical illness	4.1 (6.7)		
	Control	NR		
Bekhit *et al.*5	Median total serum (IQR). µg/dL	29.03 (15.2-42)	Median PRISM-III score(IQR)	5 (3-8)
			Non-survivor	19%
Singh *et al.*[23]	Median basal salivary (IQR), µg/dL		Non-survivor	62.7%
	Septic shock	0.72 (0.26-1.54)		
	Control	NR		
	Median post salivary ACTH 1 µg stimulation test (IQR), µg/dL			
	Septic shock	0.88 (0.28-2.47)		
	Control	NR		
Karaguzel *et al.*[24]	Mean basal serum (SD), µg/dL		Mean PRISM-III score (SD)	11.6 (4.4)
	Septic shock and sepsis	34.8 (39.7)		
	Control	14.8 (6.6)		
	Mean post serum ACTH 1 µg stimulation test (SD), µg/dL			
	Septic shock and sepsis	52.2 (45.6)		
	Control	NR		

Table 2. Cortisol level, predictive score for mortality, and mortality of patients with critical illness (continued)

Study or subgroup	Cortisol		Mortality (without control)	
Alder *et al.*[25]	Median total serum (IQR), μg/dL		Median PRISM-III score (IQR)	6.6 (3-15)
	Sepsis and septic shock	23.6 (10-49)		
	Control	15 (9-21)		
			Non-survivor	6%
Nguyen *et al.*[26]	Median total serum (IQR), μg/dL	29.03 (15.2-42)	Mean PRISM-II score (SD)	26.6 (10)
			Non-survivor	40.5%
Yehya *et al.*[27]	Median total serum (IQR), μg/dL	19 (2-24)	Median PRISM-III score (IQR)	11 (6-19)
			Non-survivor	10%
El-Kelany *et al.*[28]	Mean total serum (SD), μg/dL		Non-survivor	60%
	Sepsis	49.61 (13.58)		
	Control	13.28 (2.12)		
	Mean salivary (SD), μg/dL			
	Sepsis	2.57 (8.2)		
	Control	0.64 (13)		
Pertiwi *et al.*[7]	Mean total serum (SD)	4.6 (1.06)	Median PELOD score (IQR)	10 (1-20)
Rachmawati *et al.*[29]	Median basal serum (IQR)	32.75 (4.23-378)	Median PELOD score (IQR)	12.5 (0-33)
	Median post serum ACTH 250 μg stimulation test (IQR)	48.20 (16.7-387)	Non-survivor	36.7
Wani *et al.*[30]	Median total serum (IQR)	26.49 (6.6-55.76)	Median PRISM-III score (IQR)	12 (8-18)
			Median PELOD score (IQR)	14 (8.2-18)
			Median VIS (IQR)	60 (20-100)
			Non-survivor	27%

NR=not reported.

Table 3. Analysis of cortisol levels and mortality as well as CIRCI percentage in critical illness patients

Study or subgroup	Association between increased cortisol levels and mortality	CIRCI, %
Rady, *et al.*[13]	+	33.3
Iyer, *et al.*[14]	+	11
Lin *et al.*[15]	+	0
Jacobs *et al.*[16]	+	0
Levy-Shraga *et al.*[17]	+ but no relationship between post-ACTH stimulation serum cortisol levels and mortality	37.3
Balbao *et al.*[18]	-	32.3
Aydin *et al.*[19]	+	27.8
Demiral *et al.*[20]	+	NR
Zabidi *et al.*[6]	+	NR
Menon *et al.*[21]	+	0
Zimmerman *et al.*[22]	+	33
Bekhit *et al.*[5]	+	18.5
Singh *et al.*[23]	-	84.3
Karaguzel *et al.*[24]	+	17
Alder *et al.*[25]	+	0
Nguyen *et al.*[26]	+	9.5
Yehya *et al.*[27]	+	NR
El-Kelany *et al.*[28]	+	NR
Pertiwi *et al.*[7]	+	NR
Rachmawati *et al.*[29]	+	26.7
Wani *et al.*[30]	+	20

NR=not reported

of mortality in septic patients because it is cheaper and more readily available in hospital laboratories, especially in Indonesia.

Mortality and CIRCI analyses had a similar non-uniformity issue. A wide range of mortality rates were obtained because of various diagnoses, not only sepsis or septic shock. Heterogeneous data were also obtained in mortality prediction scores in critically ill patients with elevated cortisol levels. Children with sepsis had increased PRISM, PELOD, PIM, and VIS scores, and decreased PCIS score. The score used to predict mortality varied, but we suggest that the mortality prediction score be preferred because it can distinguish the risk of death in children with sepsis during the first 24 hours of patient hospital admission. A wide range of CIRCI percentages were reported because the diagnoses varied, and were not just sepsis or septic shock.

In conclusion, in critically ill children, cortisol levels may increase or decrease. The effect of CIRCI on mortality in critically ill children cannot be concluded. Elevated cortisol levels are associated with mortality in septic children.

Conflict of interest

None declared.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Marik PE. Endocrinology of the stress response during critical illness. The stress response of critical illness: metabolic and hormonal aspects. Switzerland: Springer International Publishing; 2016. p. 446-54. PMID: 24970271.
2. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, *et al.* Guidelines for the diagnosis and management

of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Critical Care Medicine. 2017;45:2078-88. DOI: https://doi.org/10.1097/CCM.0000000000002737.

3. Téblick A, Peeters B, Langouche L, Van den Berghe G. Adrenal function and dysfunction in critically ill patients. Nature Rev Endocrinol. 2019; 15:417-27. DOI: https://doi.org/10.1038/s41574-019-0185-7.
4. Elbuken G, Karaca Z, Tanriverdi F, Unluhizarci K, Sungur M, Doganay M, *et al.* Comparison of total, salivary, and calculated free cortisol levels in patients with severe sepsis. J Intensive Care. 2016;4:3. DOI: https://doi.org/10.1186/s40560-015-0125-0.
5. Bekhit OE, Mohamed SA, Yousef RM, AbdelRasol HA, Khalaf NA, Salah F. Relation between baseline total serum cortisol level and outcome in pediatric intensive care unit. Sci Rep. 2019;9:6008. DOI: https://doi.org/10.1038/s41598-019-42443-z.
6. Zabidi L, Supriatna M, Mexitalia M. Kadar kortisol serum sebagai indikator prognosis sepsis pada anak. Sari Pediatri. 2015;17:101-6.
7. Pertiwi N, Suryawan W, Arimbawa I, Suparyatha I. Association between serum cortisol levels and Pediatric Logistic Organ Dysfunction score in critically ill patients. Medicina. 2017;48:128-32. DOI: https://doi.org/10.15562/medi.v48i2.41.
8. Patki V, Khilnani P, Zimmerman J. Adrenal dysfunction in critical care settings. Journal of Pediatric Critical Care. 2017;4:52-63. DOI: https://doi.org/10.21304/2017.0403.00214.
9. Uçar A, Baş F, Saka N. Diagnosis and management of pediatric adrenal insufficiency. World J Pediatr. 2016;12:261-74. DOI: https://doi.org/10.1007/s12519-016-0018-x.
10. Soto-Rivera CL, Schwartz SM, Sawyer JE, Macrae DJ, Agus M. Endocrinologic diseases in pediatric cardiac intensive care. Pediatr Crit Care Med. 2016;17:S296-S301. DOI: https://doi.org/10.1097/PCC.0000000000000827.
11. Huang X, Hu W, He X, Zhang G. A potential diagnostic protocol for critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients. J Emerg Crit Care Med. 2018;2:86. DOI: https://doi.org/10.21037/jeccm.2018.10.11.
12. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital. 2020.E17-18. Corpus ID: 79550924.
13. Rady H, Aly Y, Hafez M, Bazaraa H. Adrenocortical status in infants and children with sepsis and septic shock. 2014;62:18-23. DOI: https://doi.org/10.1016/j.epag.2014.02.001.
14. Iyer P, Harrington B, Fadrowski J, Sibinga E, Amankwah E. Correlation between cosyntropin stimulation study and disease severity in children with fluid and catecholamine-refractory shock in the pediatric and cardiovascular intensive care unit. Horm Res Paediatr. 2018;89:31-7. DOI: https://doi.org/10.1159/000484561.
15. Lin M, Zhang B, Lin H, Sun P, Wang S, Guo R, et al. Dynamic changes in serum cortisol and ACTH levels and lymphocyte subset counts in children with septic shock. Preprint (version 1) Research Square. 2020:1-21. DOI: https://doi.org/10.21203/rs.3.rs-39009/v1.
16. Jacobs A, Derese I, Vander Perre S, Wouters P, Verbruggen S, Billen J, *et al*. Dynamics and prognostic value of the hypothalamus-pituitary-adrenal axis responses to pediatric critical illness and association with corticosteroid treatment: a prospective observational study. Intensive Care Med. 2020;46:70-81. DOI: https://doi.org/10.1007/s00134-019-05854-0.
17. Levy-Shraga Y, Pinhas-Hamiel O, Molina-Hazan V, Tamir-Hostovsky L, Eini ZM, Lerner-Geva L, *et al.* Elevated baseline cortisol levels are predictive of bad outcomes in critically ill children. Pediatr Emer Care. 2018;34:613-7. DOI: https://doi.org/10.1097/PEC.0000000000000784.
18. Balbao V, Costa M, Castro M, Carlotti A. Evaluation of adrenal function in critically ill children. Clin Endocrinol. 2014;81:559-65. DOI: 10.1111/cen.12444.
19. Aydin B, Demirkol D, Bas F, Turkoglu U, Kumral A, Karabocuoglu M, *et al.* Evaluation of endocrine function in children admitted to pediatric intensive care unit. Pediatrics International. 2014;56:349-53. DOI: https://doi.org/10.1111/ped.12269.
20. Demiral M, Kiral E, Dinleyici EC, Simsek E. Evaluation of the hypothalamic-pituitary-adrenal axis in a paediatric intensive care unit. Acta Endo (Buc) 2019;15:466-71. DOI: https://doi.org/10.4183/aeb.2019.466.
21. Menon K, McNally D, Acharya A, O'Hearn K, Choong K, Wong HR, *et al.* Random serum free cortisol and total cortisol measurements in pediatric septic shock. J Pediatr Endocrinol Metab. 2018;31:757-62. DOI: https://doi.org/10.1515/jpem-2018-0027.
22. Zimmerman J, Donaldson A, Barker R, Meert K, Harrison R, Carcillo J, *et al*. Real-time free cortisol quantification among critically ill children. Pediatr Crit Care Med. 2011;12:525-31. DOI: https://doi.org/10.1097/PCC.0b013e3181fe4474.
23. Singh S, Rathia S, Awasthi S, Singh, A, Bhatia V. Salivary

cortisol estimation to assess adrenal status in children with fluid unresponsive septic shock. Indian Pediatr. 2013;15:681-4. DOI: https://doi.org/10.1007/s13312-013-0190-1.

24. Karaguzel G, Atay S, Deger O, Imamoglu M, Okten A, Karaguzel G. The effects of three specific conditions related to critical care on adrenal function in children. Intensive Care Med. 2012;38:1689-96. DOI: https://doi.org/10.1007/s00134-012-2662-5.
25. Alder M, Opoka A, Wong H. The glucocorticoid receptor and cortisol levels in pediatric septic shock. Crit Care. 2018;22:244. DOI: https://doi.org/10.1186/s13054-018-2177-8.
26. Nguyen T, Doan T, Tran D. The role of blood cortisol levels in the prognosis for pediatrics septic shock. Arch Pharma Pract. 2019;10:10-14.
27. Yehya N, Vogiatzi M, Thomas N, Srinivasan V. Cortisol correlates with severity of illness and poorly reflects adrenal function in pediatric acute respiratory distress syndrome. J Pediatr. 2016; 177: 212-8.DOI: https://doi.org/10.1016/j.jpeds.2016.05.020.
28. Elbaih A, Elkilany A, Enany M. Salivary cortisol level as a marker of adrenal function in children with systemic inflammatory response syndrome in Egypt. Ann Paediatr Rheum. 2017;6:28-33. DOI: https://doi.org/10.5455/apr.022720171311.
29. Rachmawati R, Widodo D, Tridjaja B, Pudjiaji A. Fungsi adrenal pada sepsis di unit perawatan intensif pediatrik. Sari Pediatri. 2011;12:426-32.
30. Wani WA, Dar SA, Mir MN, Ahmad QI, Ali SW, Charoo BA. Prognostic significance of serum cortisol in catecholamine-resistant pediatric shock. Int J Applied Res. 2019;5:142-8. DOI:10.22271/allresearch.2019.v5.i3c.01.
31. Weiss S, Peters M, Alhazzani W, Agus M, Flori H, Inwald D, *et al*. Surviving Sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children part II. Intensive Care Med. 2020;46:s10-s57. DOI: https://doi.org/10.1007/s00134-019-05878-6.