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Original Article

Triiodothyronin (T3) as a parameter of mortality in sepsis patients in the PICU

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Abstract

Background Thyroid hormone stimulates the regulation of β-adrenergic receptors in order to increase the inotropic effect of the heart myocardium. Euthyroid sick syndrome is a disorder of non-metabolic thyroid function, which is characterized by a decrease in triiodothyronine (T3) levels in patients with non-thyroid systemic disease, such as sepsis. Low serum T3 hormone level is a potentially high-risk factor for mortality from sepsis.

Objective To assess for a relationship between decreased serum T3 levels and mortality in pediatric sepsis patients admitted in the PICU.

Methods This study used a nested case-control design. The subjects were children aged 1 month-18 years who were diagnosed with sepsis in the pediatric intensive care unit at Sanglah Hospital, Denpasar, Bali, from September 2017 to January 2019.

Results A total of 90 children were included, of whom 44 died and 46 survived. Median age was 10.5 (IQR 44) months in subjects who died and 9 (IQR 50) months in those who survived. The majority of subjects in both groups had well-nourished nutritional status. Bivariate analysis revealed that significantly more subjects who died had low serum T3 (≤1 ng/dL), PELOD-2 score ≥5, than subjects who survived. Multivariate analysis revealed that serum T3 ≤ 1 ng/dL (OR 55.1; 95%CI 9 to 334.8; P<0.001) and PELOD-2 score ≥ 5 (OR 6.5; 95%CI 1.6 to 26.7; P=0.01) were significant risk factors for sepsis mortality.

Conclusion Low serum T3 level and high PELOD-2 score are risk factors for death in sepsis. **[Paediatr Indones. 2019;59:298-302; doi: http://dx.doi.org/10.14238/pi59.6.2019.298-302]**.

Keywords: *sepsis; euthyroid sick syndrome; outcome; T3 serum*

Sepsis is a major cause of infant and child mortality. It is a systemic disease caused by the spread of microbes or toxins into the bloodstream leading to a systemic response. The cause of death in septic patients depends on various factors, such as the type of bacteria, duration from the occurrence of illness until treatment onset, primary illness before the sepsis occurred, and the current immunization status of the patient.[1] Leon-Sanz *et al*.[2] performed a cross-sectional study about the relationships between thyroid status and prevalence, therapy, outcome, risk of failed therapy, and length of stay in septic patients. They showed a difference in septic characteristics between pediatric and adult patients. Malnutrition was also one of the factors that can affect the risk of death in sepsis. Other factors that can affect the outcome of sepsis were age, poor nutritional status, prematurity, invasive treatment, chronic diseases, and immunodeficiency.[2]

Serum T3 level influences the compensating body response to chronic disease and sepsis. Serum

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T3 activates stress hormones as well as increases the effectiveness of β-adrenergic receptors, as an inotropic activator of cardiac smooth muscle.[3] In recent years, more study has been done on the relationship between non-metabolic thyroid dysfunction (euthyroid sick syndrome) and mortality in septic patients. Decreased T3 levels in blood were found to increase the risk of death three times higher in septic patients.[3]

A previous study reported that T3 had an important role in determining mortality rate in European geriatric patients with euthyroid sick syndrome who had sepsis and other chronic diseases.[4] Angeloussi *et al*.[5] in Europe conducted a systematic review of nine prospective cohort studies, comprised of studies on adults (2), neonates (3), and children (4). They found a significant correlation between septic patient outcome and reduced T3 levels in blood.[6] However, a prospective cohort study in India found no significant relationship between hormone levels and survival rate in children with sepsis.[5]

Demographic and climate differences between Indonesia and Europe can affect T3 levels. In Indonesia, efforts to meet iodine intake requirements have not been uniform throughout the country, and may be a cause of T3 deficiency in blood. A study in Semarang, Indonesia reported no significant difference between thyroid hormone levels and outcome in septic patients. But they used a cross-sectional method with a small sample size, so the results cannot be generalized to the entire population.[7]

Since Indonesia has different demographicss, climates, and populations compared to Europe, European study results may not be applicable to Indonesia. In addition, considering the dearth of research conducted specifically in children, and the relatively small sample size in Indonesian studies, we aimed to further assess if T3 levels in blood are a risk factor of mortality in children with sepsis.

Methods

This study used a nested case-control study design. We calculated the sample size using unpaired, categorical, comparative analytic sample, taking into account a possible 10% drop out rate. Subjects were included by consecutive sampling. Ninety subjects' blood specimens were taken by laboratory personnel trained at the Sanglah Laboratory Denpasar, Bali, at first day of sepsis diagnosis, and stored at -200C in the laboratory. Age was divided into 3 groups based on epidemiology : <12 month, 12-144 month, >144 months. Nutritional status was the ratio between current body weight in kg divided by ideal weight plotted in the CDC and WHO curve, and classified into obesitiy, well-nourished, moderate malnutrition, severe malnutrition, and failure to thrive.

Procalcitonin was analysed using the ELISA method (ng/mL) and categorized as > 36 ng/mL and ≤ 36 ng/mL. Procalcitonin data was taken from medical record. The PELOD-2 was a scoring system used to determine the risk of mortality patients based on the laboratory data on medical record, classified as score ≥5 or <5. All data was taken at the time of initial diagnosis and subjects' conditions were followed until the end of treatment, then they were divided into the died (case) and survived (control) groups. Serum T3 levels in both groups were measured by electrochemiluminescent immunoassay (ECLIA) method (ng/dL), and categorized as low (≤ 1 ng/dL) or normal (> 1 ng/dL).

All data were analyzed with *SPSS v.21*. We conducted bivariate analysis using the Chi square test. If P value was <0.002 we continued to multivariate analysis using logistic regression. This study was approved by the Ethics Committee of Universitas Udayana Medical School/Sanglah Hospital, Denpasar.

Results

This was a nested case-control study of 90 children aged 1 months-18 years who were treated in the PICU Sanglah Hospital Denpasar, Bali, from September 2017 until the samples was fulfilled in January 2019. The flow of study results can be seen from **Figure 1**.

The charateristics of the subjects based on the group of not survive and survive showed procalcitonin level in not survive (died) at median of 63 (IQR 88.9) and 22 (IQR 35.8) in survive. The T3 serum in died was 0.7 (IQR 0.38) and 1.4 (IQR 0.83) in survived groups. The PELOD-2 score was 4 (IQR 4) in died groups, and 2 (IQR 2) in survived. The characteristics of full subjects are shown in **Table 1**.

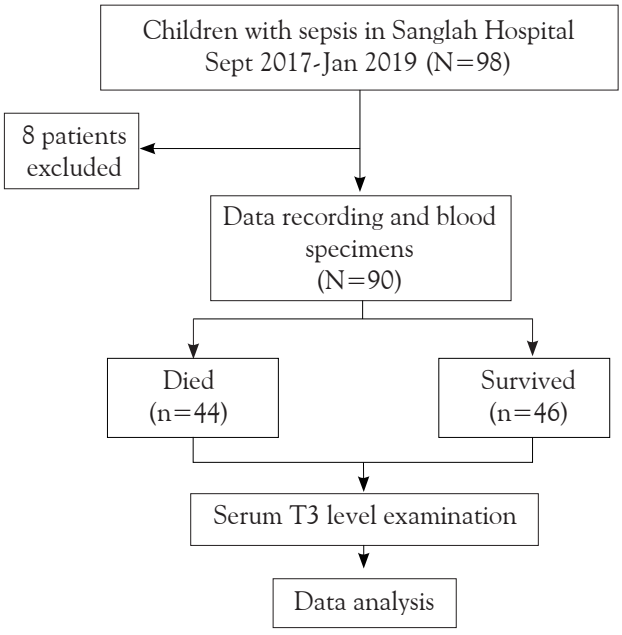

Figure 1. Flow chart of the study scheme

Table 1. Characteristics of subjects by outcomes

Characteristics	Died (n=44)	Survived (n=46)
Median age (IQR), months	10.5 (44)	9 (50)
Age, n (%)		
<12 mo	23 (52.3)	27 (58.7)
12-144 mo	20 (45.5)	16 (34.8)
>144 mo	1 (2.3)	3 (6.5)
Sex, n (%)		
Male	22 (50)	22 (50)
Female	25 (54.3)	21 (45.7)
Nutritional status, n (%)Obese		
Well-nourished	2 (4.5)	2 (4.3)
Moderate malnutrition	20 (45.5)	23 (50)
Severe malnutritioN	13 (29.5)	17 (37)
Failure to thrive	5 (11.4)	1 (2.2)
	4 (9.1)	3 (6.5)
Median procalcitonin (IQR), ng/mL	63 (88.9)	22 (35.9)
Median T3 serum (IQR), ng/dL	0.7 (0.38)	1.4 (0.83)
Median PELOD-2 score (IQR)	5 (4)	2 (2)

Bivariate analysis were analysed using Chi-square test, with normality test using Kolmogorov Smirnov and Shapiro-Wilk tes for data distribution. From bivariate analysis there was two component which had P value < 0,002 which were serum T3 and PELOD-2. The all results of bivariate analysis are shown in **Table 2**.

Table 2. Bivariate analysis of sepsis outcomes and variables

Variables	Groups		OR	95%CI	P value
	Died (n=44)	Survived (n=46)			
Serum T3, n (%)					
Low	42 (95.5)	13 (28.3)	53.3	11.236 to 252.910	<0.001
Normal	2 (4.5)	33 (71.7)			
PELOD-2 score, n (%)					
≥5	26 (59.1)	5 (10.9)	11.8	5.9 to 35.8	<0.001
< 5	18 (40.9)	41 (89.1)			
Procalcitonin, n (%)					
>36 ng/mL	28 (63.6)	14 (30.4)	4	1.66 to 9.63	0.002
≤36 ng/mL	16 (36.4)	32 (69.6)			
Sex, n (%)					
Male	22 (50)	25 (54.3)	0.8	0.3 to 1.9	0.8
Female	22 (50)	21 (45.7)			
Age, n (%)					
<12 months	23 (52.3)	27 (58.7)	1	0.4 to 2.4	0.9
12-144 months	20 (45.4)	16 (34.8)	0.9	0.6 to 1.5	0.5
> 144 months	1 (2.3)	3 (6.5)	Ref	-	-
Nutritional status, n (%)					
Obese	2 (4.5)	2 (4.3)	0.8	0.5 to 1.3	0.6
Well-nourished	20 (45.5)	23 (50.0)	Ref	-	-
Moderate malnutrition	13.(29.5)	17 (37.0)	0.7	0.2 to 1.7	0.4
Severe malnutrition	5 (11.4)	1 (2.2)	0.7	0.7 to 1.7	0.8
Failure to thrive	4 (9.1)	7 (7.8)	0.8	0.8 to 1.4	0.6

From multivariate analysis we found low T3 serum level and high of PELOD-2 score were high predictors to dead in sepsis patient (P<0.001) (**Table 3**).

Table 3. Multivariate analysis

Variables	Step I			Step IV		
	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Low serum T3 (≤1 ng/dL)	56.4	8.7 to 364.4	<0.001	55.1	9 to 334.8	<0.001
PELOD-2 score (≥5)	5.5	1.3 to 23.5	0.02	6.5	1.6 to 26.7	0.01

Discussion

Median serum T3 level in septic patients who died was 0.7 (IQR 0.38)ng/dL. Bivariate analysis revealed that 95.5% of these subjects had serum T3 ≤ 1 ng/dL, while only 28.3% did in the survived group. Further multivariate analysis revealed that serum T3 ≤ 1 ng/dL had a significant association with mortality (OR 55.1; 95% CI 9-334.8; P <0.001). Our results were in agreement with a systematic review performed in Europe who analyzed 7 pediatric studies and 2 adult studies. They showed that decreased total T3 level below 1 ng/dL increased the risk of death in 8 studies with OR 38-42, while 1 study did not have a significant correlation.[5] Previous studies also noted no significant relationship between thyroid hormone levels in septic patients and outcomes. This result could have been affected by their smaller sample sizes of 30 and 49 subjects, respectively.[6,7]

The Pediatric Logistic Organ Dysfunction (PELOD)-2 is an updated scoring system for assessing organ dysfunction in critically ill patients in order to predict mortality in septic patients. We found that sepsis patients who died had the median PELOD-2 score of 5 (IQR 4). Bivariate analysis revealed that significantly more sepsis patients with PELOD-2 score >5 died than survived (59.1% *vs.* 10.9%, respectively; (P<0.001). Multivariate analysis revealed that septic patients with PELOD-2 score ≥ 5 had a significantly higher risk of mortality than those with score of <5 (OR 6.5; 95%CI 1.6 to 26.7; P=0.01). In contrast, a previous study found that the PELOD-2 score had to be more than 20 to indicate higher risk of mortality in sepsis patients. This difference may have been due to their larger sample size of 209 subjects.[8]

The PELOD-2 score analysis was also in line with a study conducted at Sanglah Hospital, Denpasar. Daily PELOD scores were used as predictors of mortality. They found that higher PELOD score was associated with the faster mortality. They also noted that low PELOD score occured on day 23, moderate score on day 12, and high score on day 7.[9] The difference in our study was that we only evaluated PELOD-2 score on the first day of the treatment, not daily, and .the previous study used PELOD as predictors, but from our study we used PELOD-2 score which modified from PELOD score.

A limitation of our study was that serum T3 level was measured only at the beginning of treatment, not when the patient experienced the outcome. Also, the primary diseases in this study were not considered as one of the factors to cause death in sepsis.

Our results provide evidence that septic patients with decreased serum T3 levels and high PELOD-2 score are at greater risk of mortality. As such, low T3 level can be used as a risk factor of mortality in septic patients, but must be supported by the evidence of organ failure.

In conclusion, low serum T3 (< 1 ng/dL) and high PELOD-2 score (>5) were significant risk factors for mortality in pediatric sepsis patients. Procalcitonin is not a significant risk factor for mortality.

Conflict of interest

None declared.

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