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Correlation Between Free Triiodothyronine (FT3) with PELOD-2 Score and PICU Length of Stay in Critically Ill Pediatric

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ABSTRACT

Background: Thyroid function disorders, particularly reduced FT3 levels, are frequently observed in critically ill patients. FT3 plays a crucial role in metabolic regulation during critical illness. The extent of the decrease in FT3 levels directly corresponds to the severity of the disease, as indicated by the PELOD-2 score, and indirectly influences the length of stay in the Pediatric Intensive Care Unit (PICU). This study aims to examine the relationship between free triiodothyronine (FT3) levels and both the PELOD-2 score and the length of stay in critically ill pediatric patients.
Methods: Cross-sectional study was conducted at Dr. M Djamil Hospital's Pediatric Intensive Care Unit (PICU) from June to September 2022. The study included critically ill pediatric patients who accept the informed consent and were well-nourished, while individuals with a history of thyroid disease, those using exogenous/thyroid hormone/antithyroid drugs, individuals with chronic diseases, and those with Down's syndrome were excluded. The levels of FT3 and PELOD-2 scores were measured within 48 hours of admission, while the length of stay was obtained from medical records. Data analysis was performed using the SPSS program, utilizing the Spearman correlation test.
Result: Thirty subjects were included in the study. The mortality rate was 30%. The median FT3 level was 1.5 pg/mL. FT3 levels were low in 26 of 30 samples. There was a significant negative correlation (p = 0,001) between FT3 levels and PELOD-2 scores with moderate value (r = -0.567) and no significant correlation between FT3 levels and PICU length of stay.
Conclusion: The lower FT3 level measured, the higher PELOD-2 score found in critically ill children.

Keywords: FT3, PELOD-2 score, length of stay, critically ill pediatric

INTRODUCTION

Critical illness refers to a state wherein a patient's reliance on intensive medical assistance becomes imperative to sustain the functionality of essential organs and ensure survival. Without timely medical intervention, this condition can lead to a heightened mortality risk due to one or multiple processes resulting in organ damage.[1] Numerous physiological responses occur within the body during critical illness, including the endocrine system. Specifically, the hypothalamus-pituitary-adrenocortical (HHA) axis becomes activated, resulting in increased secretion of prolactin (PRL) and growth hormone (GH). Additionally, there is a decrease in the activity of the hypothalamic-pituitary-thyroid (HPT) axis. This alteration is believed to be an adaptive or advantageous reaction, as it conserves energy, slows down anabolism, and enhances the immune

response, safeguarding the host from further biological consequences.[2] Thyroid dysfunction that occurs while critically ill in patients without previous thyroid disorders is called Non Thyroidal Illness (NTI). Abnormalities often found are decreased levels of FT3 with normal or decreased TSH.[3] This condition is caused by increased TNF-alpha, interleukin-6, reactive oxygen species, and decreased leptin, selenium, and thyroid-binding globulin affinity.[4]

The FT3 can penetrate cells and execute its biological functions, making it a superior indicator of the overall thyroid function compared to T3. Evaluating free hormone levels provides a more accurate picture of thyroid status than assessing bound hormones (T3). This is attributed to the occurrence of reduced levels of thyroid hormone-binding protein, which can influence the outcomes of bound hormone level analyses.[5] Decrease of FT3 in critically ill can cause a decrease in tissue oxygen consumption, metabolic rate, pulse rate, cardiac output, response to catecholamines, lipolysis, gluconeogenesis, glycogenolysis, intestinal motility and impaired response to hypoxia and hypercapnia in the brain.[6]

A study by El Ella *et al.* (2018) in Spain reported that NTI occurred in 62.9% of subjects and can predict mortality. The most common patterns were low levels of free triiodothyronine (FT3), normal thyroxine (T4), and thyroid stimulating hormone (TSH).[7] Destariani et al. (2018) reported in pediatric patients with sepsis or septic shock, a decrease in FT3 levels was found in 48.75% of the sample and a mortality rate of 92.3%. Subjects with low FT3 levels have a mortality risk of 6.31 times compared to normal FT3 levels.[8] In numerous prior investigations, researchers have examined the link between FT3 levels and the extent of illness severity in critically ill children, aiming to ascertain the nature and intensity of the relationship between these two variables. Among these studies, one noteworthy measure used is the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score. The findings from examining FT3 levels and PELOD-2 scores on critically ill children's initial and third days indicated a negative correlation. It was observed that as the PELOD-2 score increased, signifying greater illness severity, FT3 levels decreased. Importantly, a higher PELOD-2 score has been associated with increased mortality rates.[9] The presence of thyroid dysfunction also is commonly observed in individuals who have undergone cardiopulmonary bypass surgery due to congenital heart disease. A vast majority of the cases exhibit reduced levels of T3, T4, and TSH. This NTI state is also linked to increased mortality rates, prolonged hospital stays, and extended periods of ventilator usage.[10]

Previous studies in Indonesia have yet to explore the relationship between FT3 levels and the PELOD-2 score as well as the duration of hospitalization in children. Given the evidence of reduced thyroid function in critically ill children from prior studies and the high mortality rate observed in the PICU, researchers aim to explore the potential impact of critical illness on thyroid hormone imbalances, specifically focusing on FT3 levels, and examine their correlation with disease severity as measured by PELOD-2 scores and the length of treatment.

MATERIALS & METHODS

This cross-sectional study took place at Dr. M Djamil Hospital Padang from June to September 2022. The study focused on pediatric patients, aged 1 month to 18 years, who were admitted to the Pediatric Intensive Care Unit (PICU) due to severe medical conditions and received treatment. The inclusion criteria for this study were individuals who voluntarily agreed to participate and had a good nutritional status based on the WHO Z-Score 2007 curve (-2 SD to +2 SD) and CDC 2000 (90% to 110%). Exclusion criteria included individuals with a history of hypothyroidism or hyperthyroidism, those taking thyroid hormones or antithyroid drugs within the

past 3 weeks, individuals with Down's syndrome, patients with known HIV infection, congestive heart failure, chronic kidney disease, diabetes mellitus (excluding ketoacidosis diabetikum), thalassemia, and liver cirrhosis. Blood samples were collected from eligible patients who met the predetermined inclusion criteria and did not have any of the exclusion criteria. The samples were obtained within 48 hours of the patient's initial admission, and at the same time, the PELOD-2 score was assessed. The FT3 examination used the VIDAS® Enzyme Linked Fluorescent Assay (ELFA) method. Relevant information and the duration of hospitalization were extracted from the patient's medical records. Descriptive statistics were used to present the data, and the Shapiro-Wilk test was applied to assess normality. Correlation analysis was performed using the Spearman correlation test. All analysis was performed on Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS Inc. Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULT

This research was conducted from June 2022 to September 2022 with 30 subjects. 4 subjects were excluded due to incomplete data for assessing the PELOD-2 score. The study found that the age of most subjects was 1-5 years old, 11 out of 30 subjects. The distribution of male and female subjects was equal. The most reported diagnoses were pneumonia (15 subjects), followed by sepsis/septic shock (9 subjects), meningitis and acute kidney injury (4 subjects) and others. The mortality rate was 9 out of 30 subjects (Table 1).

Table 1. Characteristics of Subjects

Characteristics	(n= 30)
Age group (year)	
< 1	11
1-5	8
5-15	9
> 15	2
Gender	
Male	15
Female	15
Diagnosis	
Pneumonia	15
Sepsis/septic shock	9
Meningitis	4
Acute kidney injury	4
Hypertensive crisis	3
Dengue hemorraghic fever (DHF)	2
Multisystem Inflammatory Syndrome in Children (MISC)	2
Intracranial bleeding	2
Ecephalitis, cardiogenic shock, epidural abscess, diaphragmatic hernia, diabetic ketoacidosis and pericardial efussion	1
Survivor	21
Non-survivor	9

The median FT3 concentration among the participants in this research was recorded as 1.5 pg/mL (Table 2). Notably, the age group of individuals above 15 years exhibited the highest median FT3 level at 2.25 pg/mL. Notably, 26 out of 30 subjects demonstrated low FT3 levels, while the remaining 4 exhibited normal FT3 levels.

Table 2. FT3 Levels Based on Age Group in Critically Ill Children

Age group (year)	Normal range, (pg/mL)	FT3				Total, n
		Median (pg/mL)	Low, n	Normal, n	High, n	
< 1	2,92 - 5,14	1,5	10	1	-	11
1-5	2,73 – 4,94	1,5	8	-	-	8
5-15	2,73 – 4,62	1,9	7	2	-	9
> 15	2,67 – 4,5	2,25	1	1	-	2
Total		-	26	4	-	30

In this study, a significant relationship was observed between FT3 levels and the PELOD-2 score, indicating that as FT3 levels decreased, the PELOD-2 score increased. The correlation between these variables was found to be moderate ($r = -0.567$) and statistically significant ($p < 0.05$). Furthermore, a weak correlation ($r = -0.395$) was identified between lower FT3 levels and longer length of stay; however, this correlation was not statistically significant ($p > 0.05$) (Table 3) (Figure 1).

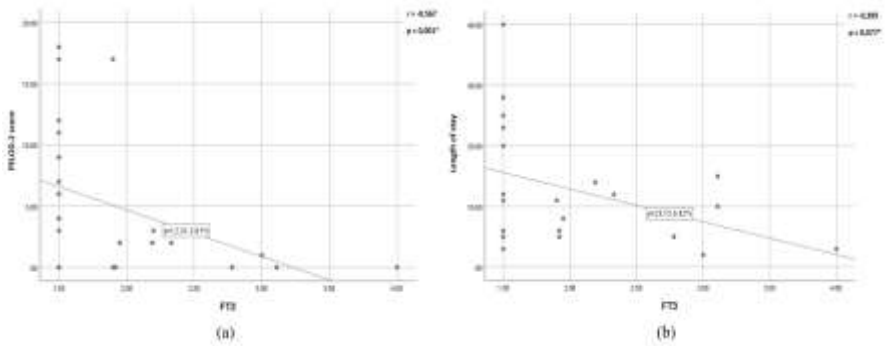
Table 3. Correlation Between FT3 with PELOD-2 Score and PICU Length of Stay

Variable		FT3
PELOD-2 score	r	-0,567
	p-value	0,001
Length of stay	r	-0,395
	p-value	0,077

DISCUSSION

This study's findings highlight that most participants belong to the age group below 5 years (19 out of 30). This aligns with a previous study conducted by Tanurahardja et al. in Jakarta in 2014, where they reported that the age group below 5 years constituted 56.6% of their study population.[11] A larger study in India by Maheswari et al. in 2020 also reported that the prevalence of their highest age group was under 5 years (69.5%).[12] This study revealed a balanced distribution between males and females, which differs from previous studies conducted in Indonesia by Tanurahardja et al. and Rismala et al. These earlier studies reported a higher prevalence of males, specifically 53.3% and 56.4%, respectively.[11,13]

This study's most commonly observed diagnoses were pneumonia, sepsis/septic shock, meningitis, AKI, hypertensive crisis, DHF, and MISC. These findings are consistent with a previous study conducted at PICU Dr M Djamil Hospital by Rachmawati et al. in 2017, which reported similar prevalent diagnoses, including septic shock (11 subjects), pneumonia (8 subjects), meningitis (7 subjects), encephalitis (6 subjects), diabetic ketoacidosis (3 subjects), and heart failure (2 subjects), among others.[14] Contrary to our findings, Rismala et al. study in Jakarta in 2019 reveal a distinct pattern. Surgical abnormalities were more prevalent (65%) than non-surgical ones (35%). Among the various organ dysfunctions observed, hematology accounted for the highest percentage (41.72%), followed by neurology and cardiovascular (20.75%), respiration (15.51%), and renal (12.99%).[13] The findings of this study revealed a mortality rate of 30% (9 out of 30 samples). The current mortality rate is quite similar to the rate recorded in 2016, which was 33.9%.[14] When comparing the mortality rates of critically ill children across different countries, the rates varied as follows: 2.89% in America, 2.8% in Sweden, 4% in South Africa, and 7.14% in Iran.[15–17] The mortality rates in the PICUs of three hospitals in Indonesia were as follows: 10.7% in Cipto Mangunkusumo General Hospital, 52.3% in Dr. Sardjito General Hospital, and 67% in Abdul Wahab District Hospital.[13,18]



***Spearman's correlation test**

Figure 1. Scatter plots showing (a) relationships between FT3 levels and the PELOD-2 score and (b) relationships between FT3 levels and length of stay.

This study revealed a median FT3 level of 1.5 pg/mL, notably lower than the FT3 level reported by El Ella et al., which was 2,619 ± 0.9 pg/mL.[7] Age group of participants over 15 years had the highest median FT3 level, measuring 2.25 pg/mL. Interestingly, a substantial majority of the research subjects, approximately 86.6%, exhibited low FT3 levels. This percentage is notably higher compared to previous studies conducted by Muruli et al. in 2018 in India (75%) and El Ella et al. in 2019 in Egypt (57.1%).[7,19]

This study provides evidence for the impact of critical illness on reducing FT3 hormone levels. The researcher took measures to ensure the generalizability of the findings by excluding potential factors that could affect FT3 levels while assuming normal FT3 levels in the subjects. It is worth noting that the daily intake of iodine can also influence FT3 hormone levels. In this study, it was observed that 90% of the subjects (n=27/30) were from West Sumatra, while the remaining 10% (n=3) came from outside the region. Notably, the household iodine adequacy rate in West Sumatra was found to be 90.3%, which exceeds the national adequacy rate of 70.4% and the WHO standard rate of 90%.[20] This indicates that the iodine intake among the participants in the sample is generally adequate.

This study identified four samples with normal FT3 levels based on age. Interestingly, these four samples displayed a PELOD-2 score of zero. The PELOD score is a scoring system designed to evaluate multiple organ dysfunction syndrome (MODS) in critically ill patients and predict outcomes in PICU patients. A low PELOD score indicates minimal organ involvement. It is hypothesized that the normal FT3 levels observed in these four samples could be attributed to the absence of significant organ dysfunction.

This study discovered a negative correlation between FT3 levels and PELOD-2 scores in critically ill children (r = -0.567). This implies that as FT3 levels decrease, the PELOD-2 scores tend to increase, and vice versa. We observed reduced activity of the hypothalamus-pituitary-thyroid axis and deiodinase function in critically ill patients, which can be seen as adaptive or beneficial responses. These changes help conserve energy, delay anabolism, and activate immune responses, protecting the patients from additional biological effects.[2]

No prior research has specifically examined the correlation between FT3 levels and PELOD-2 scores in critically ill children receiving care in the PICU. In contrast, some studies have explored thyroid hormone function in critically ill children with specific conditions. The study conducted by Marks et al. focused on assessing thyroid hormone function in patients following cardiac surgery. A significant association was observed between FT3I (free T3 index) levels during nighttime and the PELOD-2 score ($p = 0.047$).[21] In another study conducted by Calcaterra et al., they reported a negative association between FT3 levels and various biomarkers, such as urea, creatinine, NTproBNP, d-dimer, ferritin, procalcitonin, and the Overall Severity Score (OSS) in children diagnosed with Multisystem Inflammatory Syndrome in Children (MISC). The strength of this relationship varied from weak to moderate, as indicated by the correlogram analysis. The OSS utilized in this study encompasses organ involvement, including the kidneys, heart, digestive system, central nervous system, lungs, immune system, and skin, which aligns closely with the components of the PELOD-2 score.[22]

In a study conducted by Shao et al. on pediatric patients with diabetic ketoacidosis, an investigation revealed a negative correlation between FT3 levels and beta-hydroxybutyric acid (β-HB) levels, anion gap (AG) values, and HbA1c levels ($r = -0.642$, $r = -0.377$, and $r = -0.309$, respectively; $p < 0.01$). A positive correlation was also observed between FT3 levels and HCO3- and prealbumin levels ($r = 0.681$ and $r = 0.309$, respectively; $p < 0.01$). The study findings suggested that low

FT3 levels were linked to a more severe acidosis in DKA cases.[23]

In the study by Muruli et al. they assessed the severity of the disease using the PRISM III score. Their findings revealed a negative correlation between FT3 levels and the PRISM III score at both initial admission and discharge. The correlation coefficients were reported as -0.33 ($p = 0.009$) and -0.28 ($p = 0.045$) for initial admission and discharge, respectively.[19] The PRISM III score demonstrates comparable calibration to the PELOD-2 score in effectively distinguishing between survivor and non-survivor groups and predicting mortality. This was confirmed through the Hosmer-Lemeshow goodness-of-fit test (PRISM III: $\chi2 = 5.667$, $p = 0.368$; PELOD-2: $\chi2 = 9.582$, $p = 0.276$).[24]

In this study, the free hormone variable (FT3) investigation was deemed more effective in assessing thyroid hormone function. This is because free hormones can penetrate cells and carry out their biological functions. Moreover, free-hormone analysis is considered superior in describing thyroid function as it is unaffected by proteins. In contrast, levels of thyroid hormone-binding proteins can often decrease, potentially impacting the accuracy of measurements involving bound hormone levels.[5] Previous studies have consistently documented decreased levels of albumin and transthyretin, both of which are thyroid hormone-binding proteins, in critically ill children.[25,26]

This study observed a weak negative correlation ($r = -0.395$, $p = 0.077$) between FT3 levels and the length of stay in the PICU. However, this correlation was not statistically significant, possibly due to the limitations of the lowest FT3 level that could be measured in this study, which was 1.5 pg/mL. Consequently, further analysis could not evaluate the direction of the correlation in subjects with FT3 values below 1.5 pg/mL. It is worth noting that this cutoff value is higher than a previous study by Calcaterra et al., where the lowest measurement limit was 1.25 pg/mL.[22]

Limited research exists on the direct association between FT3 levels and length of stay in pediatric studies. Yanni et al. conducted a study with the variable of T3 on children with sepsis in PICU and found no significant difference in the length of stay between individuals with low or normal T3 levels ($p = 0.5$).[27] In another study conducted by Marks et al. involving patients in the pediatric intensive care unit (PICU) after cardiac surgery, a noteworthy finding was the presence of a significant negative correlation between FT3I levels from days 3 to 7 post-surgery and the duration of PICU stay ($r = -0.871$ to -0.517, $p < 0.05$).[21] There were no deaths reported in their study. However, in contrast, our study observed 2 subjects who passed away within less than 7 days and 9 subjects who died during the observation period. This disparity may introduce bias in our study's length of stay analysis.

The lack of a significant correlation between FT3 levels and length of stay suggests that some patients with low FT3 levels may have had a relatively short stay. Further investigation revealed that this particular patient had been referred from a previous hospital, indicating a potential bias in the length of stay in the PICU, which may have led to shorter stays in certain cases.

CONCLUSION

Decreased FT3 levels were found in most subjects (26 out of 30). The lower FT3 level measured, the higher PELOD-2 score was found in critically ill children.

Declaration by Authors

Ethical Approval: Approved by Health Research Ethics Committee Dr. M Djamil Hospital (LB.02.02/5.7/381/2022)

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