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Original article

Association between severity of sepsis and thyroid function profile

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Abstract. *Background and aim:* Critical illness conditions such as sepsis are often accompanied by altered hormone levels, which may result in decreased thyroid axis activity. This condition aims to provide metabolic substrates for vital organs such as the brain and immune system. Significant alteration of the thyroid axis in critical illnesses such as sepsis known as Low-T3 Syndrome which is associated with increased mortality. This study aims to determine the association between severity of sepsis and thyroid function profile as a predictor of mortality in sepsis patients. *Methods:* An observational study involving 62 subjects with sepsis and septic shock. Serum was measured using Enzyme-linked Immunosorbent Assay (ELISA) method. Statistical analysis used Mann-Whitney, Kruskal-Wallis, and Spearman's correlation tests. Statistical test results are significant if the p-value <0.05. *Results:* The median fT3 level was lower in the septic shock group 13.94 pg/ml (7.71-19.93) compared to the sepsis group 20.15 pg/ml (11.08-37.15) where there was a significant difference (p<0.001). There was a significant correlation between The Sequential Organ Failure Assessment (SOFA) score and fT3 levels (R: -0.270, p=0.032). The non-survivor group had a lower median fT3 level 16.56 pg/ml (7.71-30.03) compared to the survivor group 17.50 pg/ml (10.32-37.15) where there was a significant difference (p<0.036). *Conclusion:* Based on the severity of sepsis, the more severe the sepsis condition, the lower thyroid function levels are obtained where decreased thyroid function levels can be a prognosis indicator to predict mortality in sepsis patients. (www.actabiomedica.it)

Key words: low-T3 syndrome, thyroid, septic shock, sepsis

Introduction

Sepsis is a life-threatening condition of multiorgan dysfunction caused by systemic inflammation (1). This condition is a serious public health problem and one of the most common reasons for treatment in the intensive care unit with the main cause of death and high costs. Sepsis is reported in approximately 1.7 million adult patients in the United States each year with a mortality rate of 30-50%. Another study conducted by Tambajong et al reported a high mortality rate for sepsis patients, around 65.7%, with a national economic burden in Indonesia for 100,000 patients estimated at USD 130 million (2-4).

Critical illness conditions such as sepsis are often accompanied by changes in function or hormone levels where there is the activation of the anterior pituitary function and inactivation of peripheral anabolic pathways of neuroendocrine responses. This reaction aims to support the host defense mechanisms. There are natural defense mechanisms against disease, most of which are accompanied by temporary starvation without having to rely on external support. The initial response to these conditions causes an increase in

metabolic substrates that are directed to the needs of vital organs such as the brain and the immune system. The metabolic response is partly elicited by endocrine changes such as increased activation of the hypothalamic-pituitary-adrenocortical axis and growth hormone, and decreased activity of the thyroid axis (5,6).

In patients with critical illness, there is a significant disturbance of the Hypothalamic–Pituitary–Thyroid axis. This condition is manifested by a decrease in serum hormones total T3 (TT3), free T3 (FT3), total T4 (TT4), and free T4 (FT4) and thyroid stimulating hormone (TSH). This change is known as Low-T3 Syndrome. This condition is an adaptive mechanism to stressful states that is helpful to the patient's clinical course because it can reduce energy use, delay anabolic processes, and activate the immune response. However, these mechanisms can be detrimental especially if the changes are more severe and persist for a long time. Several studies have reported that thyroid hormone changes in critical conditions such as sepsis are associated with increased mortality (6-9).

This study aims to determine the association between the severity of sepsis and the thyroid function profile as a predictor of mortality in sepsis patients. Therefore, this study is necessary to describe the thyroid function profile in sepsis patients without a previous history of thyroid disease and to analyze the association between changes in thyroid function levels and the severity of sepsis. In addition, studies that evaluate thyroid function profiles in sepsis patients, especially for the Indonesian population, are still relatively rare.

Materials and methods

Patient population

This study used a cross-sectional method which was carried out from January to June 2023 at the Dr Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi which is a tertiary referral hospital. The study population was patients diagnosed with sepsis who were hospitalized in internal medicine care. Samples were taken from populations that met the research criteria. The number of samples in this study was 62 subjects who met the inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria of this study were patients diagnosed with sepsis with SOFA score ≥2 who were ≥18 years old at diagnosis. Exclusion criteria were patients with a previous history of thyroid disease, thyroid nodules found on physical examination, pregnancy, receiving hormonal therapy in the last 6 months, receiving massive blood transfusions, and taking drugs that interfere with thyroid hormone metabolism. Septic shock is defined as a sepsis condition that results in persistent hypotension despite adequate fluid resuscitation requiring a vasopressor. The non-survivor group was defined as subjects who died during hospitalization.

Clinical data and sample collection

Demographic and clinical data were taken from patient medical records. Sampling for the study of thyroid hormone examination was performed when the patient was diagnosed with sepsis met the study criteria and was willing to become a research sample by signing an informed consent form. Sample testing was performed at the Hasanuddin University Hospital Research Laboratory Unit. This study used fT3, fT4, and TSH ELISA kits from Elabscience. Serum was measured using the ELISA method with a Thermo Scientific Multiskan FC microplate spectrophotometer with units of measurement fT3 (pg/ml), fT4 (pg/ml), and TSH (mIU/ml).

Statistic analysis

Data analysis was performed using SPSS version 26. The method of analysis consisted of a descriptive method that aimed to describe the characteristics of the research sample by calculating the mean, standard deviation, median, minimum, and maximum values. Kolmogorov-Smirnov test to assess data normality, and Mann-Whitney, Kruskal-Wallis, and Spearman's correlation test is a statistical analysis for data that is not normally distributed. Statistical test results are significant if the p-value <0.05.

Result

Study population

There were 62 subjects studied with 30 men (48.4%) and 32 women (51.6%) distributed in the age group of 18-60 years, 44 subjects (71%), and in the age group >60 years, 18 subjects (29%). There were 46 subjects (74.2%) who had comorbidities (Table 1). In the group of septic shock, there were 24 subjects (38.7%) and 38 subjects (61.3%) with sepsis. There were 32 non-survivors (51.6%) and 30 survivors (48.4%). Based on the focus of infection, the most common infections were from genitourinary infections in 16 subjects (25.8%) and the lowest was from bloodstream infections in 2 subjects (3.2%) (Table 2). The median value of thyroid function levels in the subjects studied where the median value of fT3 levels was 16.81 pg/ml (7.71-37.15), the median value of fT4 was 11.36 pg/ml (1.08- 53.25), and the median TSH level was 0.58 mIU/ml (0.07 - 5.83) (Table 3) where in the analysis of the thyroid function profile based on the focus of infection of the studied subjects found no significant difference in fT3 levels (p=0.974), fT4 (p=0.455) and TSH (p=0.468) (Table 4).

Association between severity of sepsis and thyroid function levels

In this study, the median fT3 level was lower in the septic shock group 13.94 pg/ml (7.71-19.93) compared to the sepsis group 20.15 pg/ml (11.08-37.15) with a significant difference (p<0.001). The same was also shown for fT4 levels where the median was lower in the septic shock group 10.39 pg/ml (1.08-18.47) compared to the sepsis group 15.03 pg/ml

Table 1. Characteristics of research subjects.

Variable	n	%	mean±SD
Age – Year	-	-	52,13±14,42
18-60	44	71,0	45,50±11,37
>60	18	29,0	68,33±5,20
Gender			
Male	30	48,4	-
Female	32	51,6	-
Comorbid			
Yes	46	74,2	-
No	16	25,8	-
Total	62	100	-

Table 2. Frequency distribution of research variables.

Variable	n	%	median (min-max)
Sepsis Degree			
Septic Shock	24	38,7	-
Sepsis	38	61,3	-
Outcome			
Survivor	32	51,6	-
Non-survivor	30	48,4	-
Focus of Infection			
Respiration	15	24,2	-
Abdominal	14	22,6	-
Genitourinary	16	25,8	-
Skin and soft tissue	15	24,2	-
Blood stream infection	2	3,2	-

Table 3. Median value of thyroid function profile of study subjects.

Thyroid Hormone	Median	Minimum	Maximum
fT3 - pg/ml	16,81	7,71	37,15
fT4 - pg/ml	11,36	1,08	53,25
TSH - mIU/ml	0,58	0,07	5,83

Table 4. Thyroid function profile based on focus of infection in sepsis.

Focus of Infection	fT3 (pg/ml)	fT4 (pg/ml)	TSH (mIU/ml)
Respiration	16,39 (7,71-26,89)	14,21 (1,12-48,78)	0,68 (0,31-1,55)
Abdominal	15,26 (11,43-35,69)	12,48 (1,24-53,25)	0,55 (0,11-1,16)
Genitourinary	17,38 (11,08-30,03)	12,80 (4,10-32,97)	0,54 (0,14-5,58)
Skin and soft tissue	16,34 (10,32-37,15)	8,65 (1,08-30,07)	0,57 (0,07-4,55)
Blood stream infection	17,08 (13,77-20,39)	15,77 (14,67-16,87)	0,77 (0,42-1,13)
***p*-value**	0,974	0,455	0,468

*Kruskal-Wallis Test

(1.24-53.25) (p=0.032). In TSH levels, although the median levels were lower in the septic shock group compared to the sepsis group, there was no significant difference (p=0.186) (Table 5).

Table 5. Association between severity of sepsis and level of thyroid function.

Variable	Sepsis	Septic shock	*p*-value
fT3 – pg/ml	20,15 (11,08-37,15)	13,94 (7,71-19,93)	<**0,001**
fT4 – pg/ml	15,03 (1,24-53,25)	10,39 (1,08-18,47)	**0,032**
TSH – mIU/ml	0,60 (0,10-5,83)	0,57 (0,07-3,24)	0,186

*Mann-Whitney Test

Correlation between SOFA scores and thyroid function levels

Correlation analysis between SOFA scores and thyroid function levels found a significant negative correlation between SOFA scores and fT3 levels, where the higher the SOFA score, the lower fT3 levels (R: -0.270, p=0.032) but there was no significant correlation on level of fT4 (R: -0,143, p=0,269) and TSH (R: -0,121, p=0,348) (Figure 1).

Association between thyroid function levels and mortality in sepsis patients

The median fT3 level was lower in the non-survivor group 16.56 pg/ml (7.71-30.03) compared

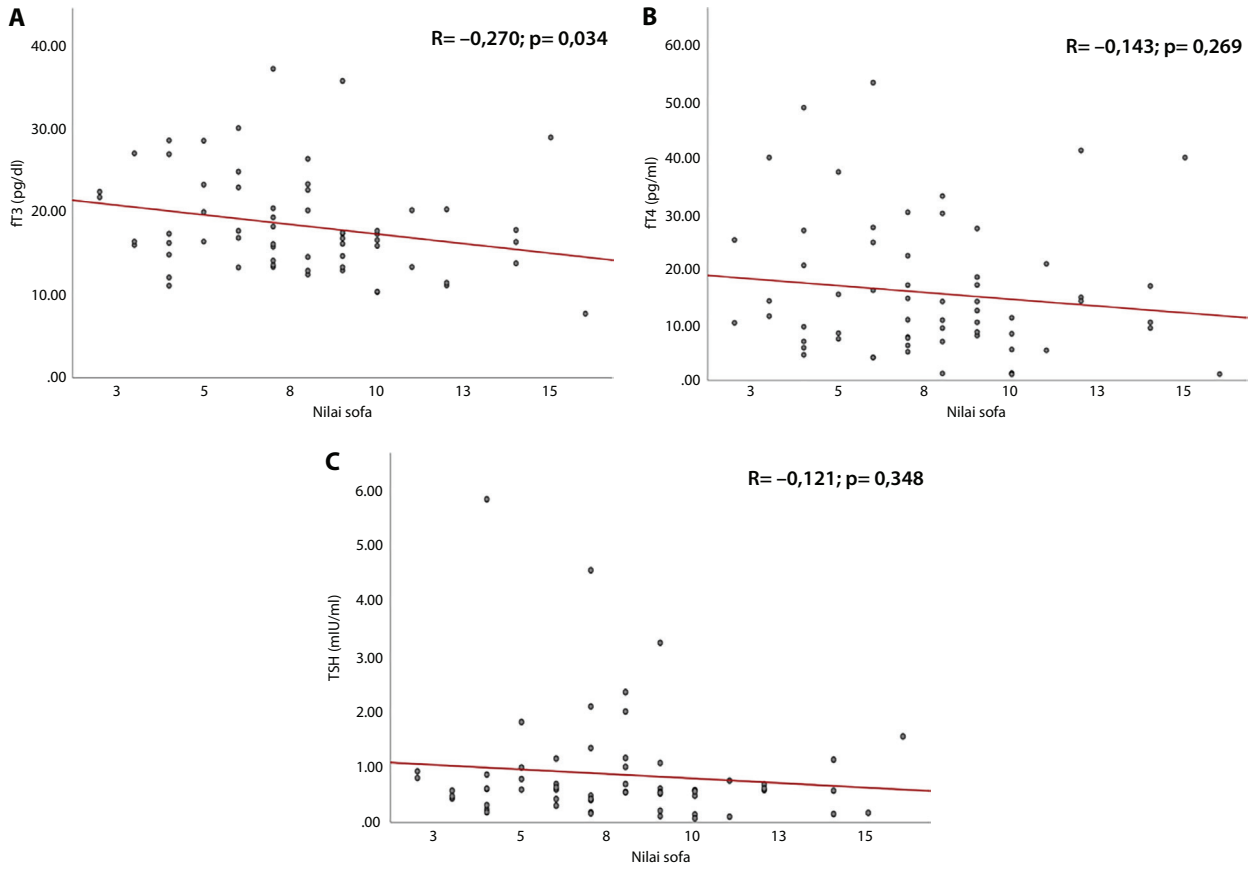

Figure 1. Correlation between the SOFA score and thyroid function levels (a. fT3 levels, b. fT4 levels, c. TSH levels). *Spearman's Correlation test.

Table 6. Association between mortality and thyroid function levels in sepsis patients.

Variable	Non-survivor	Survivor	*p*-value
fT3 – pg/ml	16,56 (7,71-30,03)	17,50 (10,32-37,15)	**0,036**
fT4 – pg/ml	10,81 (1,08-53,25)	12,85 (1,30-39,86)	0,317
TSH – mIU/ml	0,57 (0,07-2,35)	0,65 (0,14-5,83)	0,130

*Mann-Whitney Test

to the survivor group 17.50 pg/ml (10.32-37.15) with a significant difference (p<0.036). The median fT4 and TSH levels were lower in the non-survivor group compared to the survivor group but there were no significant differences (Table 6).

Discussion

Analysis of the association between severity of sepsis and levels of thyroid function

In this study, we observed differences in thyroid function levels were found between the sepsis and septic shock groups where the median value was lower in the septic shock group compared to the sepsis group. Analysis of the association between the severity of sepsis and thyroid function levels showed that there was an association between fT3 (p<0.001) and fT4 (p= 0.032) levels with the severity of sepsis but there was no association with TSH levels.

A study conducted by Hosny M et al (10), who compared fT3, fT4, and TSH levels in patients with sepsis, severe sepsis, and septic shock, found that the mean fT3 level was lower in patients with septic shock and severe sepsis compared to sepsis (p <0.001) but there was no significant difference in fT4 and TSH levels. The pathomechanisms of sepsis involving the effects of systemic inflammation, immune system dysfunction, coagulation and anticoagulation dysfunction, and tissue injury lead to multiorgan disorders (11). It has been proven that critical illness including sepsis is often accompanied by changes in thyroid hormones. This condition is caused by severe acute inflammation, which can disrupt the function of the Hypothalamic–Pituitary–Thyroid axis resulting in a significant decrease in thyroid hormone in multiorgan dysfunction (12).

At the onset of sepsis, there is a decrease in the conversion of T4 to T3 in the tissues, resulting in a decrease in serum T3 levels. This condition is an adaptive response to overcome the changes that occur within a few hours after the onset of acute stress to prevent further catabolism proses thereby reducing unnecessary energy expenditure. However, in conditions of prolonged sepsis, further reductions in T3 levels can be found, T4 levels which also begin to decrease, and TSH levels that are normal or low. These conditions are associated with specific changes in the deiodinase enzyme induced by critical illness (13-15).

Correlation between SOFA Scores and thyroid function levels

In this study, a significant negative correlation was found between the SOFA score and the fT3 level, where the higher the SOFA score, the lower the fT3 level (R: -0.270, p=0.032). A study conducted by Zhang et al (16), who analyzed the correlation between the SOFA score and fT3 hormone levels in sepsis patients involving 138 subjects, reported that there was a significant negative correlation between T3 hormone levels and the SOFA score (R: -0.152, p=0.049). In line with a study conducted by Hosny M et al (10), it was found that fT3 levels decreased along with an increase in the SOFA score in sepsis patients (R: -0.427, p=0.007). The state of multiorgan dysfunction in sepsis can be evaluated using the SOFA score where an increase in the SOFA score is associated with the worsening of multiorgan including changes in the Hypothalamic–Pituitary–Thyroid axis (6,14,17).

Analysis of association between thyroid function levels and mortality in sepsis patients

In this study, the median fT3, fT4, and TSH levels were lower in the non-survivor group compared to the survivor group where there was a significant difference in fT3 levels (p<0.036). A study conducted by Hosny

M et al (10) which analyzed the correlation between fT3, fT4, and TSH levels and mortality in sepsis patients found that the mean fT3 level was lower in the non-survivor group compared to the survivor group ($p < 0.001$), while other thyroid function indicators did not show significant differences. A meta-analysis by Kim JG et al (12) of 8 relevant studies with a total of 1,578 subjects, reported significant differences in serum fT3 and fT4 levels in the non-survivor and survivor groups where the non-survivor group was lower compared to the survivor group (4 studies for fT4; $p = 0.004$ and 3 studies for fT3; $p = 0.0002$) but there was no significant difference in TSH levels. In line with a study conducted by Foks M et al. (18), the levels of fT3 ($p = 0.021$) and fT4 ($p = 0.019$) were lower in the non-survivor group compared to the survivor group, while there was no significant difference in TSH levels. Several literatures have explained that decreased thyroid hormone levels in conditions of severe sepsis are associated with high mortality rates. This condition is caused by a further decline in multiorgan functions such as; cardiovascular and respiratory system dysfunction, immune system dysfunction and coagulation disorders (6). There is a direct correlation between the number of organ failures and mortality in sepsis patients. This condition can be associated with a further decrease in thyroid hormone levels, especially in T3 levels as the active form of thyroid hormone which occurs due to impaired conversion from T4 to T3 in peripheral tissues due to ongoing systemic inflammation (13,19).

Changes in thyroid function levels in critical illnesses such as sepsis without the clinical features typical of thyroid disease do not need to be treated and thyroid function tests can be repeated after the acute condition has improved. A number of studies regarding the benefits of giving thyroid hormone to morbidity and mortality in sepsis patients with decreased thyroid hormone levels have not shown insignificant results. Currently, there is no consensus recommending giving thyroid hormone in this condition considering the low benefits proven by existing research so that treatment focuses more on the underlying disease (5,20,21).

This research still has some limitations. First, the sample size is relatively small. Second, the presence of confounding factors for sources of infection and comorbidities was not analyzed optimally so that they could affect thyroid hormone levels, the degree of sepsis, and mortality in the subjects studied. Third, patients who were treated receive many medications that are difficult to evaluate which may affect the examination of thyroid hormone levels.

Conclusions

Based on the severity of sepsis, the more severe the sepsis condition, the lower thyroid function levels are obtained where the decreased thyroid function levels can be one of the prognostic indicators to predict mortality in sepsis patients. In future studies, it is necessary to carry out further analysis to see the efficacy of thyroid hormone therapy in sepsis patients with Low-T3 Syndrome. Therefore, in critical illness conditions such as sepsis, the level of thyroid function can be used as a factor to assess the severity of sepsis as an early warning for clinicians to provide more comprehensive management to prevent worsening and increase mortality.

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AMA (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). SB (Concept, Design, Critical Review). RH (Concept, Design, Critical Review). AAZ (Concept, Design, Analysis and Interpretation, Critical Review).

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