Correlation of SOFA Score and Hormone Value for Predicting 28-days Mortality for Septic Patients

Zulkifli[1], Agustina Br Haloho[1], Ziske Maritska[2], Dipta Anggara[3*]

[1] Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2] Department of Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[3] Specialized Residency Training, Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

*Corresponding author:

Dipta Anggara

Specialized Residency Training, Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

Email:

anggara_dimension@yahoo.com

ABSTRACT

Introduction. Sepsis is a group of symptoms of organ dysfunction that can be life-threatening because of dysregulation of body response toward ongoing infection. Organ dysfunction in sepsis can be measured by Sequential Organ Failure Assessment (SOFA) and T3 hormone. The study was aimed to identify the correlation of T3 in predicting mortality of 28 days patients in Intensive Care Unit RSMH Palembang.

Method. This study design is cohort prospective. The inclusion criteria consist of a patient diagnosed with sepsis and septic shock in the Intensive Care Unit, 18-64 years old. Patients with a history of thyroid disease, pregnant or post-pregnancy, the patient admitted in referral from other hospitals, and patients with a history of psychiatry medication and thyroid medication were excluded. Data collected is the patient whose stay in Intensive Care Unit RSMH followed in 28 days from January 2021 until the sample was fulfilled (39 samples). Analyzing data was SPSS version 23 with chi-square analysis and Fisher's Exact to identify the relationship. Pearson correlation to identify correlation coefficient, and Medical application to measure AUC, cutoff value, sensitivity, and specificity.

Result. The result showed that age (p=0,445). gender (p=1,00), need of ICU (p=0,228), isolation-nonisolation ward (p=0,437) didn't have any significant relationship toward mortality. SOFA score correlate statistically with positive correlation and medium strength (0,633) toward mortality of sepsis patient (p=0,000). T3 hormon correlate positively with medium strength (0,514) toward mortality of sepsis patient (p=0,001). T3 hormone toward SOFA correlate negatively (-0,365) with significant correlation (p=0,22). T3 hormone has AUC 0,291 with sensitivity 3,3% and specificity 67,7%.

Conclusion. T3 hormone has a significant negative correlation to mortality in sepsis patients but cannot be used to predict mortality with a low AUC value (0,291).

Keywords. sepsis, sequential organ failure assessment (SOFA), intensive care unit, triiodotironin (T3).

Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1-3] Sepsis is one of the leading causes of morbidity and mortality in the Intensive Care Unit (ICU).[4] The mortality rate can reach 30 % in sepsis and 80% in septic shock. Every year, at least 1.7 million adults in America experience sepsis, and nearly 270,000 Americans die of sepsis each year.[5] An observational study conducted in Indonesia from 2013 to 2016 found that the patient died from 14,076 patients, 8,200 (58.3%)) the patient died. The cost burden of sepsis patients per 100,000 patients is estimated to be as high as $130 million USD[6]. Based on patient data at Dr. Mohammad Hoesin General Hospital (RSMH) Palembang, in 2017, found that the incidence of sepsis was 30.1%, and 28-day mortality was 46.8%.[7]

Organ dysfunction in sepsis can be assessed using sequential organ failure assessment (SOFA), which can be assessed from the time the diagnosis of sepsis is established.[1-3] The SOFA score measures the amount and severity of dysfunction in six organ systems. The six organ systems include respiration, coagulation, hepatobiliary, cardiovascular, central nervous system, and kidneys. An increase in SOFA score of 2 points or more is associated with in-hospital mortality of more than 10%.[8] The higher the SOFA score in septic patients, the higher the risk of possible death. The SOFA score requires several clinical examination variables and laboratory data such as PaO_2, platelet count, creatinine level, and bilirubin level.[9]

The level of stress in the body due to sepsis will change every endocrine system, including the thyroid hormone, namely the T3 hormone. The thyroid hormone itself is very influential in metabolism and the immune system.10 Starting from a decrease in T3 hormone levels, which immediately change in the first few hours, the body enters a septic state, then a decrease in thyroxine hormone (T4) level if the sepsis persists more extended finally thyroid hormone stimulating hormone (TSH).[11] This condition in the literature is known as a euthyroid sick syndrome or nonthyroidal illness syndrome.[12] Several studies have shown that septic patients who have no previous history of thyroid disease have deficient levels of the hormone T3. Kumar et al. and Padhi et al. showed that in the acute phase of sepsis, blood levels of T3 hormone were deficient even though there was no history of thyroid disease in the previous patient. In addition, the T3 hormone value showed more changes than the T4 and TSH hormone values in the acute phase, where the T4 and TSH hormone values still tended to be expected when the patient entered the intensive care room. There are few studies on T3 hormone levels in Indonesia; there is a study conducted in Denpasar by Djoko et al. regarding T3 hormone levels as a predictor of death in Pediatric Intensive Care Unit (PICU) patients.[15] T3 hormone examination is widely available in every hospital in Indonesia,

including in Palembang. Therefore, this study aimed to assess the correlation between SOFA scores and T3 hormone levels to predict 28-day mortality of sepsis patients in the intensive ward of RSMH Palembang.

Methods

This study is a prospective cohort study. The data taken is the data of patients who were treated in the RSMH intensive care room and then followed for 28 days. The study starts from January 2021 until the number of samples is met. The study sample was taken by consecutive sampling on patients who met the inclusion and exclusion criteria. After calculating the minimum sample is 39 samples. All adult patients (18-64 years) diagnosed with sepsis and septic shock who were admitted to the RSMH intensive care unit were included in the study sample. Patients with a history of thyroid disease on anamnesis or physical examination found thyroid abnormalities, pregnant, recently gave birth <6 months. Other hospital ICU referrals, history of use of psychiatric drugs, currently on therapy or history of thyroid hormone therapy, consumption of amiodarone and phenytoin drugs will be excluded from the study sample.

This study will measure T3 hormone levels and SOFA scores on the mortality of septic patients in 28 days in the intensive ward of RSMH Palembang. The sampling method uses a sample of venous blood in the cubital fossa as 3 mL into the EDTA tube. The EDTA tube was brought to the RSMH laboratory, where the T3 hormone was checked using Abbott's reagent. Longitudinal patient observations were made, whether death occurred or not within 28 days. The data will be analyzed using SPSS version 22 software. Chi-Square test with 95% confidence level to assess the relationship between categorical variables (age, mean age, gender, length of stay, patient origin, and intensive care unit) and 28-day mortality of sepsis patients. To assess the mortality of sepsis patients using the Chi-Square statistical test, it was stated to be significant if $p < 0.05$. Descriptive statistical tests were used to assess the mean SOFA score and T3 hormone levels in sepsis patients, and the mean and ranges of SOFA scores and T3 hormone levels were obtained. To assess the correlation between SOFA scores and T3 hormone levels with 28-day mortality in sepsis patients, the Pearson correlation test was used.

Results

In this study, 39 subjects met the inclusion criteria. A total of 30 subjects did not survive, and nine subjects survived within 28 days of treatment (Figure 1) In this study, 30 (76.9%) subjects died, while 9 (23.1%) subjects survived. In the sex distribution of research subjects on mortality, there were 15 (50%) male subjects and 15 (50%) female subjects in the group who died, while there were 4 (44.4%) subjects

with male gender and 5 (55.6%) subjects with female sex in the surviving group. In the Chi-Square analysis, it was found that gender did not have a significant relationship with mortality with a p-value = 1.00. In the sex distribution of research subjects on mortality, there were 15 (50%) male subjects and 15 (50%) female subjects in the group who died, while there were 4 (44.4%) subjects with male gender and 5 (55.6%) subjects with female sex in the surviving group. In the Chi-Square analysis, it was found that gender did not have a significant relationship with mortality with a p-value = 1.00. In the distribution of the COVID-19 status of research subjects on mortality, there were 13 (43.3%) subjects with COVID-19 and 17 (56.7%) subjects with non-COVID-19 in the group who died, while there were as many as 2 (22.2) %) subjects with the type of care for covid and 7 (77.8%) subjects with the type of care for non-covid in the group that survived. In the results of Chi-Square analysis, it was found that the COVID-19 status of the research subjects did not have a significant relationship with mortality with a p-value = 0.437 (Table 1).
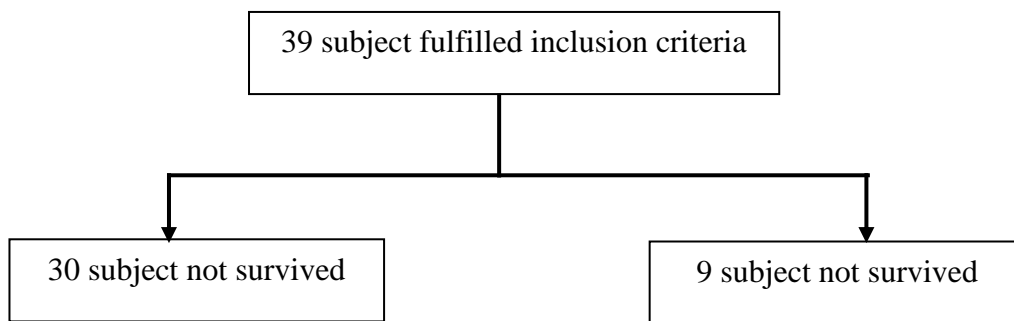
```
          ┌─────────────────────────────────────┐
          │ 39 subject fulfilled inclusion       │
          │            criteria                  │
          └─────────────────────────────────────┘
              │                           │
              ▼                           ▼
   ┌──────────────────────┐   ┌──────────────────────┐
   │ 30 subject not        │   │ 9 subject not        │
   │    survived           │   │    survived          │
   └──────────────────────┘   └──────────────────────┘
```

Figure 1. Patients flow diagram

Table 1. Sample characteristics

Variable	Mortality		P
	Not-Survived	Survived	
Gender			
Male	15 (50%)	4 (44,4%)	1.00
Female	15 (50%)	5 (55,6%)	
Admission			
Emergency	11 (36,7%)	1 (11,1%)	0.228
ICU	19 (63,3%)	8 (88,9%)	
COVID-19 Status			
Covid	13 (43,3%)	2 (22,2%)	0.437
Non Covid	17 (56,7%)	7 (77,8%)	

In the SOFA score of the sepsis research subjects, the mean SOFA score was 8.26 with a standard deviation of 3.370. According to a study conducted by Lestari et al, in 2019 about the correlation between PCO and sepsis patients based on SOFA scores involving 59 sepsis patients who were studied prospectively and obtained a mean SOFA score of 10.00 with a standard deviation of 3.5.7 The results of this study are in line with research It has been mentioned that a high mean SOFA score affects patient mortality and the SOFA score profile in this study is close to that of this study. From the results of the correlation analysis of SOFA scores on mortality, it was found that SOFA scores were statistically correlated with a positive correlation direction with moderate strength (0.633) on mortality in sepsis patients. Based on a study made by Gaini in 2019, stated that SOFA and qSOFA scores both increased significantly in the group who died. SOFA demonstrated good accuracy (AUROC = 0.83 95% CI, 0.76 - 0.90) for 28-day mortality compared to qSOFA (AUROC = 0.67, 95% CI, 0.54 - 0.80) and SIRS (AUROC = 0.62, 95% Cl 0.49 - 0.74). Gaini's research results found that a SOFA score 2 could predict 28-day mortality in sepsis patients better than qSOFA and SIRS[16], while another study conducted by Raith in 2017 also found that SOFA had a better AUROC value than qSOFA and SIRS in predicting mortality with the following ratio SOFA (AUROC = 0.753 99% CI 0.750 – 0.757), qSOFA: 0.607 (99% CI 0.603 – 0.611) and SIRS: 0.589 (99% CI 0.585 – 0.593).[17] The results of this study are in line with Ghaini's study who found that SOFA was a strong predictor of mortality in septic patients.

Table 2. SOFA Score and T3 Hormone correlation with mortality

	Mean $\pm$ SD	Corellation coefficient	p
SOFA Score	8,26 $\pm$ 3.370	0.633	0.000
T3 Hormone	0,426 $\pm$ 0.0794	0.514	0.001

Table 3. Area Under ROC Curves (AUC) to predict mortality

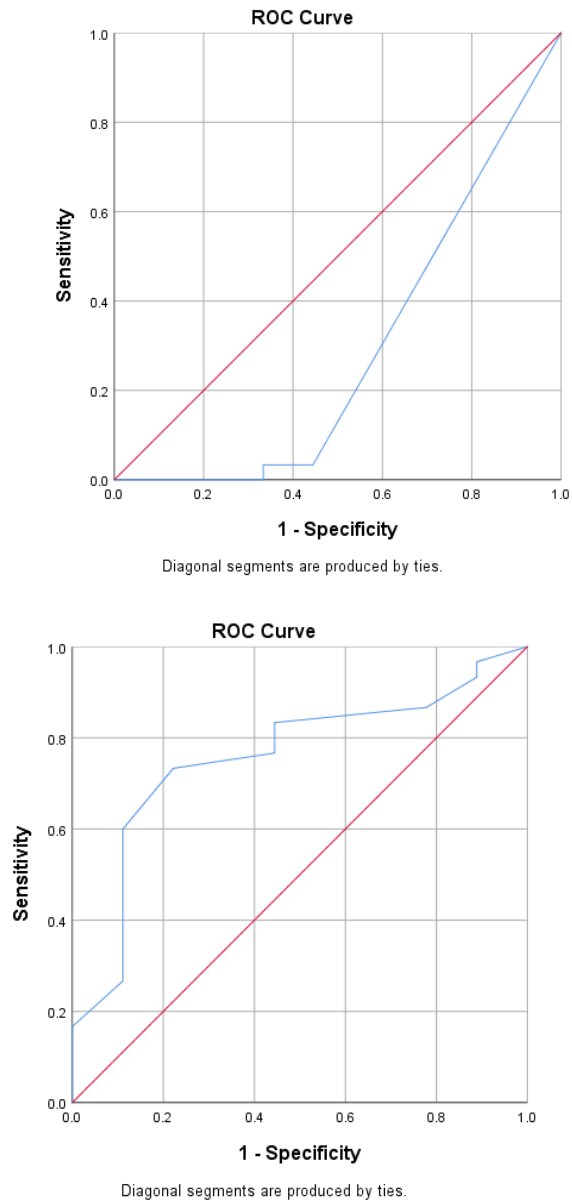| Variable	AUC	Cutoff Value	Sensitivity	Specificity	Confidence Interval 95%	
					Lower	Upper
T3	0,291	0,515	3,3	66,7	0,066	0,516
SOFA	0,757	7,5	73,3	78,8	0,583	0,931

Figure 2. SOFA score and T3 hormone ROC curve as mortality predictor

Discussion

This study found the mean T3 hormone level was 0.426 with a standard deviation of 0.0794. According to a study conducted by Feilong et al, in 2012 on the relationship between thyroid hormone and mortality in the ICU with a sample of 480 sepsis patients admitted to the Xinhua ICU which was studied prospectively and the results obtained were 1.11 mean T3 hormone levels with a standard deviation of 0.33.[18] The results of this study are also reinforced by research by Hosny, in 2015, regarding the predictive

value of thyroid hormone levels in sepsis patients, the results obtained were 0.855 mean T3.[19] hormone levels. From research conducted by Mayer et al, in 2011, stated the median value of decreased T3 hormone levels in septic patients ranged from 0.7 to 1.2. The results of this study are in line with the research that has been mentioned that the average T3 hormone level in sepsis patients shows a decrease in T3 hormone levels from the normal value. moderate power (0.514) on mortality in sepsis patients. This explains that the higher the T3 level, the mortality rate of sepsis patients will increase.

According to a study conducted by Feilong et al, in 2012 on the relationship between thyroid hormone and the ICU with a sample of 480 sepsis patients treated at the Xinhua ICU which was studied prospectively and stated the correlation of T3 hormone levels to mortality, it was found that T3 hormone levels were statistically correlated with the direction of T3 hormone levels. positive correlation with strong strength (AUC = 0.722 (95% CI, 0.28 - 0.51). The results of this study are in line with Feilong's study which stated that there was a relationship between T3 hormone levels and mortality in sepsis patients.[20]

In this study, the cut off point for the T3 hormone obtained from the ROC analysis was > 0.515 with a sensitivity of 3.3% and a specificity of 67.7%. This means that the T3 hormone does not have the ability as a marker to predict the mortality of septic patients within 28 days, will die by 3.3% and is correct in predicting the mortality of sepsis patients who will not die in 28 days by 67.7%. The AUC value of 0.291 indicates that the T3 hormone cannot be used as a mortality marker. In contrast to the SOFA score variable, the cut-off point value obtained from the ROC analysis was > 7.5 with a sensitivity of 73.3% and a specificity of 78.8%. This means that the SOFA score has the ability as a marker that can predict sepsis patients will die within 28 days, 73.3% of patients will die correctly and 78.8% of them are correct in predicting sepsis patients will not die. The AUC value of 0.757 indicates that the SOFA score as a marker is included in the category with sufficient accuracy (Table 3 and Figure 2). According to a study conducted by Yang et al in 2012, low levels of T3 hormone can increase the mortality rate (p = 0.001) with a sensitivity of 61.7% and a specificity of 63%.[21] Based on a study conducted by Feilong et al in 2012, among the levels of other thyroid hormones, fT3 was the strongest predictor (AUC=0.762) with a sensitivity of 62.14% and a specificity of 78.02% (p<0.001) compared to T3 hormone levels (AUC=0.617 with a sensitivity of 72.53% and a specificity of 45, 79% (p=0.001).[20] The SOFA score has an AUC value of 0.757 with a sensitivity of 73.3% and a specificity of 78.8%.[14] This is in line with the research conducted by Liu et al in 2020 which stated that SOFA scores can be a predictor of mortality with strong power (AUC=0.890) with a threshold value of 3 on the SOFA score (Youden's index=0.73) had a sensitivity of 90% and a specificity of 83.18%.[22] It can be concluded that patients with SOFA score 3 can be predictors of strong

for patient inhospital mortality rate.

Conclusion

The conclusion of this study is that there is a correlation between SOFA scores on mortality, it was found that SOFA scores were statistically significant in the direction of positive correlation with moderate strength (0.633) on mortality in sepsis patients. The results of the correlation analysis of T3 hormone levels on mortality, it was found that T3 hormone levels were also statistically significantly correlated with a positive correlation direction with moderate strength (0.514) on mortality in sepsis patients.

References

1. Simpson SQ. SIRS in the time of sepsis-3. American College of CHEST Physicians. Chest journal. 2018; 153: 34-8.
2. Singer M, Deutschman C, Warren SC, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). Jama. 2016; 315(8): 801–810.
3. PERDICI. Penatalaksanaan sepsis dan syok septik optimalisasi FASTHUGBID. 1st ed. Pangalila FJV, Manshoer A, editors. Jakarta; 2017; 1-3.
4. Sakr Y, Jaschinki U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, et al. Sepsis in intensive care unit patients: worldwide data from the intensive care over nations audit. Open Forum Infect Dis. 2018; 5(12): 313.
5. Data reports | Sepsis | CDC [Internet]. [cited 2020 Jul 30]. Available from: https://www.cdc.gov/sepsis/datareports/index.html
6. Purba AKR, Mariana N, Aliska G, Wijaya SH, Wulandari RR, Hadi U, et al. The burden and costs of sepsis and reimbursement of its treatment in a developing country: An observational study on focal infections in Indonesia. IJID. 2020; 96: 211-218.
7. Lestari MI, Sedono R, Zulkifli dan Maritska Z. How closely is protein carbonyl (PCO) level correlated with sepsis-related organ function assessment (SOFA) score?. Int J App Pharm. 2020; 12(3): 79-82.
8. Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE, et al. Prognostic accuracy of the sequential organ failure assessment for mortality in patients with suspected infection. Annals of Internal Med. 2018; 168 (4): 266–75.

9. Kumar KV, Kapoor U, Kalia R, Chandra NS, Singh P, Nangia R. Low triiodothyronine predicts mortality in critically ill patients. J Clin Endocrinol Metab. 2013; 17(2): 285.

10. Economidou F, Douke E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. Hormones.2011; 10(2): 117-24.

11. Hosny M, Rashad R, Atef D, Abed N. Predictive value of thyroid hormone assessment in septic patients in comparison with C-reactive protein. The egyptian journal of critical care medicine.2015; 3: 55-61.

12. Sinha, Ray. Sepsis-3: How usefu'l is the new definition?. J anesthesiol clin pharmacol.2018; 34(4); 542-543.

13. Hunter J. Inflammatory shock syndromes. In: L Marino P. The ICU Book. 4th ed. New York: Lippincot Williams & Wilkins; 2014; 264.

14. Kharbanda M, Ramasubban. Septic shock. In: Chawla R. Todi S, editors. ICU protocols a stepwise approach. New York: Springer; 2012; 396.

15. Dellinger R, Levy M, Rhodes A, Annane D, Gerlach H, Opal S, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Critical Care Med. 2013; 41(2): 580-637.

16. Gaini S, Relster MM, Pedersen C, Johansen IS. Prediction of 28-days mortality with sequential organ failure assessment (SOFA), quick SOFA (qSOFA) and systemic inflammatory response syndrome (SIRS) – A retrospective study of medical patients with acute infectious disease. Denmark: Int J Infect Dis. 2019; 1–7

17. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. Adelaide: JAMA. 2017; 290-300.

18. Wang F, Pan W, Wang H, Wang S, Pan S, Ge J. Relationship between thyroid function and ICU mortality: a prospective observation study. Shanghai: Crit. Care. 2012; 16: R11.

19. Yang JW, Han ST, Song SH, Kim MK, Kim JS, Choi SO, et al. Serum T3 level can predict cardiovascular events and all-cause mortality rates in CKD patients with proteinuria. Gangwon-do: Ren Fail. 2012; 364-72.

20. Wang F, Pan W, Wang H, Wang S, Pan S, Ge J. Relationship between thyroid function and ICU mortality: a prospective observation study. Shanghai: Crit. Care. 2012; 16: R11.

21. Yang JW, Han ST, Song SH, Kim MK, Kim JS, Choi SO, et al. Serum T3 level can predict cardiovascular events and all-cause mortality rates in CKD patients with proteinuria. Gangwon-do: Ren Fail. 2012; 364-72.

22. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Sichuan: Am J Emerg Med. 2020; 2074–80.