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ORIGINAL RESEARCH INTENSIVE CARE

The impact of thyroid hormone levels and APACHE II scores on the clinical outcome in critically ill patients

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ABSTRACT

Background & objective: Thyroid hormone levels are often raised during stress and acute illness. APACHE II score has been linked to adverse outcome after severe disease. We analyzed the impact of the level of free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormones (TSH), and APACHE II scores on the outcome of critically ill patients admitted to Intensive Care Unit (ICU).

Methodology: A cohort prospective study was conducted on critically ill patients in the ICU. Patients' baseline data, thyroid hormone levels, including fT3, fT4, TSH, and APACHE II score within 24 h of admission were compared between 30-day survivors and non-survivors. Multivariate Cox proportional hazards regression analysis was conducted to assess the risk factors for mortality.

fT3Non-survivors were significantly older than survivors (55.81 ± 12.61 vs 41.40 ± 11.40, P = 0.003). The APACHE II score was higher in non-survivors (25.88 ± 9.28 vs 22.13 ± 10.42, P = 0.299). Thyroid hormone levels showed no significant difference between the two groups. The area under the receiver-operating curve for APACHE II was 0.610 (0.403-0.818), and for fT3 was 0.523 (0.311-0.735).

Conclusion: Although there was no significant difference in thyroid hormone levels between the survivors and non-survivors, the results of this study show that low fT3 levels and high APACHE II scores had a more significant association with adverse clinical outcomes in critically ill patients.

Abbreviations: APACHE - Acute Physiology and Chronic Health Evaluation; ESS - Euthyroid Sick Syndrome; ft3 - Free Triiodothyronine; ft4 - Free Triiodothyronine; NTIS - Non-Thyroidal Illness Syndrome; TSH - Thyroid Stimulating Hormone

Keywords: Critically ill; Mortality; fT3 level; fT4 level; APACHE II score

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1. INTRODUCTION

The number of critically ill patients needing hospitalizations is expected to rise with increased life expectancy, improved health technology, and more resources.[1] In a study conducted by Garland et al. (2013), it was found that in 2007, about 0.72% of men and 0.47% of women underwent treatment in intensive care units (ICU) each year. In addition, the increase in the number of ICU patients is also expected to increase along with economic growth.[1]

Changes in various organ systems and functions are closely related to the severity of the disease and the clinical outcomes that will occur, especially in patients in the ICU.[1] One of them is a disorder related to thyroid function, which plays an important role in the continuity of body growth by modulating metabolism and the body's immune system. It is known that in critical conditions, there are changes in hormone levels circulating in the body.[2] Abnormalities of thyroid function are found in patients without abnormalities of the thyroid gland or pituitary gland. They are often found in patients with trauma, severe infections, after major surgery, malignancy, and inflammatory conditions known as 'Euthyroid Sick Syndrome' (ESS). ESS is also known by another term, 'Non-Thyroidal Illness Syndrome' (NTIS).[3] NTIS was first reported around 1970 as a change in serum thyroid hormone levels that occurs in critical illnesses. A relationship between different thyroid hormone parameters with critical illness and clinical outcomes, including thyroxine (T4), thyrotropin-releasing hormone (TRH), cortisol,[4] Thyroid-Stimulating Hormone (TSH).[6] Until now, NTIS is still an incompletely understood phenomenon, but a decrease in triiodothyronine (T3) is the dominant marker obtained in the acute phase of NTIS, as well as its relationship with morbidity and mortality.[3]

Some studies prove that thyroid hormone disorders are closely related to the death of ICU patients, especially the free hormone triiodothyronine (fT3) and fT3 levels correspond to disease severity assessed using APACHE II scores.[4]

APACHE is the most common and widely used critical severity scoring system. It was first compiled and used in 1981 with 34 individual variables. This score was further developed and became the APACHE II score in 1985, with 12 variables assessed in the first 24 h after critical patient admission to the ICU. Scores ranged from 0 to 71, where the higher the score indicated, the higher the severity of the subject's illness.[5]

Because of the two factors mentioned above, abnormalities in thyroid function in critical patients, especially T3 disruption, the relationship of thyroid hormone with clinical output or death in critical patients needs to be known with certainty. We examined the relationship between T3 thyroid hormone and APACHE II score and its relationship with clinical output in critical patients. This is consistent with the concept of ESS, which states that thyroid dysfunction is related to the severity of the disease. The study conducted is expected to provide additional knowledge and can contribute to clinical practice in Indonesia.

2. METHODOLOGY

2.1. Study design

A cohort prospective study was conducted in July 2020. Subjects were adult patients older than 18 y of age, admitted to the ICU during the study period. Subjects with abnormal thyroid glands upon palpation, those on hormonal therapy except insulin, pregnant cases, or those having a history of childbirth in the past six months were excluded. Written consent was obtained from the patients or their relatives prior to their inclusion.

The sample size calculation showed that the minimum requirement was 31 subjects. Consecutive sampling was carried out until the minimum number was met. The study was approved by the Research Ethics Committee of Soetomo General Hospital.

2.2. Laboratory measurements

Blood samples for fT3, fT4, and TSH levels were taken within 24 h of admission to the ICU. Assays were done using the electro-chemiluminescence immunoassay (ECLIA) method using Cobas E601 (Roche Diagnostics, Swiss). Normal reference ranges used were; fT3 = 2.0-4.4 pg/mL; fT4 = 0.93-1.71 ng/dL; TSH = 0.27-4.20 uIU/mL.

Other blood tests such as complete blood count, C-reactive protein, procalcitonin, arterial blood gas analysis, and serum chemistry were performed simultaneously.

Standardized data collection forms that included demographical information and diagnosis groups were used for data collection in this study.

2.3. Data analysis

Acquired data were analyzed using IBM SPSS Statistics for Windows version 25 (IBM Corp, Armonk, USA). Patients were divided into 30-day survivors and non-survivors. Continuous variables were analyzed for normality distribution using the Kolmogorov-Smirnov test, and data were expressed as mean ± standard deviation.

Depending on the normality of data, bivariate analysis

of baseline data, thyroid hormone levels, and APACHE II score between the two groups were conducted using an independent t-test or Mann-Whitney U-test. The strength of the correlation between thyroid hormone levels and APACHE II score with clinical outcomes was measured using Pearson or Spearman's rank order, as appropriate.

Cumulative survival rates were analyzed using Kaplan-Meier curves and log-rank tests. Multivariate Cox proportional hazards regression methods were performed to determine independent factors of mortality during a 30-day follow-up period. The area under the Receiver Operating Characteristic (ROC) curve was used to determine the discrimination cutoff points for the 30-day mortality rate. P < 0.05 was considered statistically significant.

3. RESULTS

A total of 31 patients were included in this study. The mean age of patients was 48.84 ± 13.99 y. Regarding gender, 15 (48.39%) of the patients were male, and 16 (51.6%) patients died during the 30-day follow-up period and were categorized under the 'non-survivors' group. The baseline characteristics of survivors and non-survivors are shown in Table 1. Non-survivors were comparatively older and predominantly females. The most common diagnosis in survivors was lung disease, while in non-survivors it was cardiovascular disease. The mean APACHE II score among non-survivors was higher than in the survivors. Using statistical analysis, we found that the difference in age between survivors and non-survivors was statistically significant (P = 0.003). No

Table 1: Baseline characteristics of patients

Parameters	Survivors (n = 15)	Non-survivors (n = 16)	P value
Age (y) (range)	41.40 ± 11.58 (19-62)	55.81 ± 12.61 (37-81)	.003*
Male	8 (53.33)	7 (43.75)	.724
GCS	9.80 ± 5.09	8.44 ± 4.69	.364
Mean arterial pressure (mmHg)	83.42 ± 25.02	84.33 ± 33.78	.933
Pulse rate (ppm)	113.20 ± 14.36	118.13 ± 26.54	.530
Respiratory rate (bpm)	28.93 ± 7.63	29.44 ± 6.65	.846
Diagnosis group			
Cardiovascular	2 (13.33)	5 (31.25)	.394
Pulmonology	4 (26.67)	3 (18.75)	.685
Neurology	3 (20.00)	2 (12.50)	.653
Metabolic	3 (20.00)	2 (12.50)	.653
Digestive	2 (13.33)	2 (12.50)	1.000
Others	1 (6.67)	2 (12.50)	1.000
APACHE II score (mean ± SD)	22.13 ± 10.42	25.88 ± 9.28	.299
APACHE II score (range)	(10-48)	(10-43)	

**GCS: Glasgow Coma Scale, ppm: pulse per minute, bpm: breath per minute, APACHE II: Acute Physiologic and Chronic Health Evaluation; **P < 0.05 considered as significant.*

Table 2: Laboratory parameters of patients

Laboratory Parameters	Survivors (n = 15)	Non-survivors (n = 16)	*P* value
Routine laboratory findings			
White Blood Count (x10^9)	18.15 ± 11.75	18.12 ± 10.43	.906
Hemoglobin (g/dL)	11.94 ± 3.33	10.73 ± 2.93	.291
Platelet (x10^3/µL)	297.73 ± 154.77	332.00 ± 183.00	.611
Hematocrit (%)	35.53 ± 9.79	32.25 ± 7.94	.313
Random Blood Glucose (mg/dL)	206.60 ± 196.36	259.75 ± 187.55	.260
BUN (mg/dL)	53.29 ± 44.43	46.88 ± 36.99	.771
Creatinine (mg/dL)	5.42 ± 10.11	3.55 ± 2.93	.206
Albumin (g/dL)	3.51 ± 1.04	3.44 ± 1.02	.858
C-reactive protein (mg/L)	124.98 ± 152.41	70.05 ± 81.34	.449
ALT (U/L)	142.85 ± 298.68	349.44 ± 924.90	.614
AST (U/L)	162.38 ± 287.45	411.94 ± 1065.50	.726
Thyroid function tests			
fT3 (pg/mL)	1.78 ± 0.75	1.92 ± 0.94	.643
fT4 (ng/dL)	1.17 ± 0.35	1.17 ± 0.46	.979
TSHs (uIU/mL)	1.43 ± 2.11	1.07 ± 1.08	.843

*ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; fT3: Free triiodothyronine; fT4: Free thyroxine; TSHs: Thyroid Stimulating Hormone; **P < 0.05 considered as significant; Data presented as mean ± SD*

Table 3: Correlation between APHACHE II score with fT3, fT4 and TSHs

Variable	Independent	r	P value
APACHE II score	fT3	-0,162	.383
	fT4	-0,301	.100
	TSHs	-0,199	.282

P < 0.05 considered as significant.

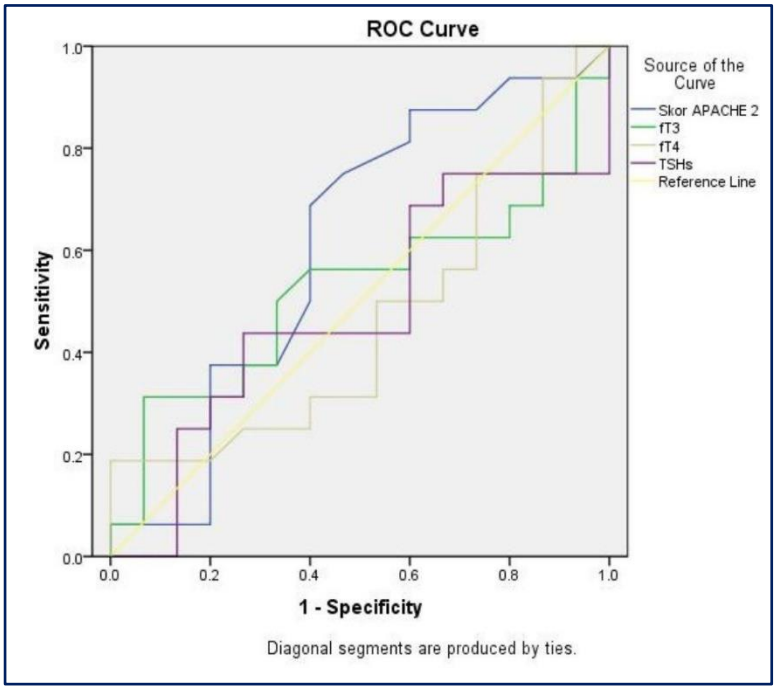

Figure1: ROC curve of APACHE II, fT3, fT4, and TSHs in relation with mortality rate.

statistical significance was observed between survivors and non-survivors concerning gender, common clinical parameters, diagnosis group, and APACHE II score (Table 1).

The laboratory parameters between survivors and non-survivors are shown in Table 2. We found no significant differences in the complete blood count values, random blood glucose, albumin, renal function tests, liver function tests, and CRP among both groups. Regarding thyroid function test results, there was no significant difference among survivors and non-survivors.

3.1. Correlation between APACHE II score and thyroid hormone levels for clinical outcome

Further analyses were conducted to determine the correlation between the APACHE II score and the thyroid function test parameters. We found a negative correlation between APACHE II score with fT3, fT4, and TSHs. However, these findings were not statistically significant (fT3: Pearson's r = -0.162, P = 0.383; fT4: Pearson'sr = -0.301, P = 0.100; TSH: Spearman's rho = -0.199, P = 0.282) (Table 3).

The Kaplan-Meier test was conducted to measure the survivability of patients in correlation with APACHE II score, fT3, fT4, and TSHs. Receiver operating characteristics (ROC) curve analysis (Figure 1) was made, and we found that only APACHE II score and fT3 levels had Area Under the Curve (AUC) values above 0.500, respectively 0.610 (0.403-0.818) for APACHE II and 0.523 (0.311-0.735) for fT3. A cutoff value of 18 and 1.69 for APACHE II and fT3 was chosen to provide the best outcome in critically ill patients.

Based on the APACHE II score, thirteen non-survivors were categorized on a high APACHE II score (above 18 points), and three non-survivors were categorized on a low APACHE II score (18 points and below). The Kaplan-Meier survival curve showed that the low APACHE II group had a high survival rate, while the high APACHE II group had a low survival rate (Figure 2). The decrease in the survival value of APACHE II was quite drastic on day 11 and thereafter was constant (Figure 2). We observed a higher Hazard

Table 4: Correlation between APACHE II score, fT3 and fT4 levels to analyze mortality of critically ill patients

Model	Variable	Coefficient	P-value	RR	Lower	Upper
Model 1	fT3	0.320	0.497	1.376	0.548	3.458
	APACHE II	0.047	0.251	1.048	0.967	1.136
Model 2	fT4	0.363	0.715	1.437	0.206	10.031
	APACHE II	0.045	0.265	1.047	0.966	1.134

**Significant for P < 0.05.*

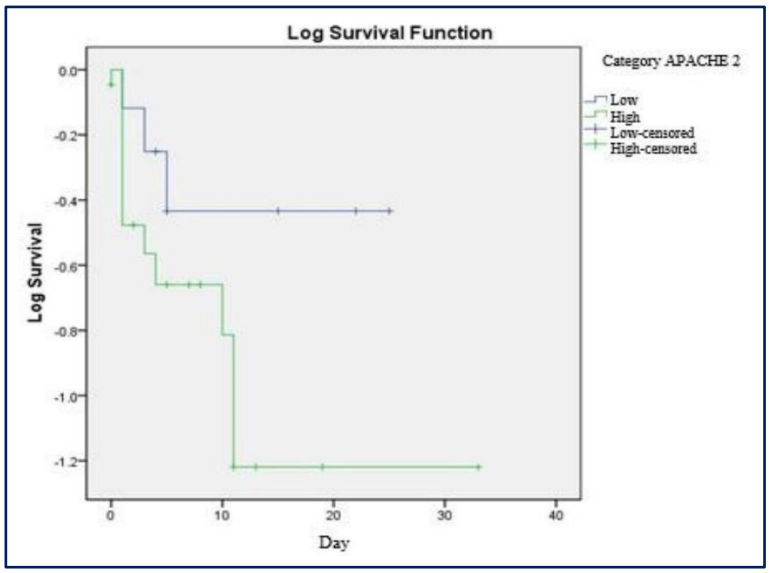

Figure 2: Kaplan-Meier's curve is high (green) and low (blue) APACHE II score.

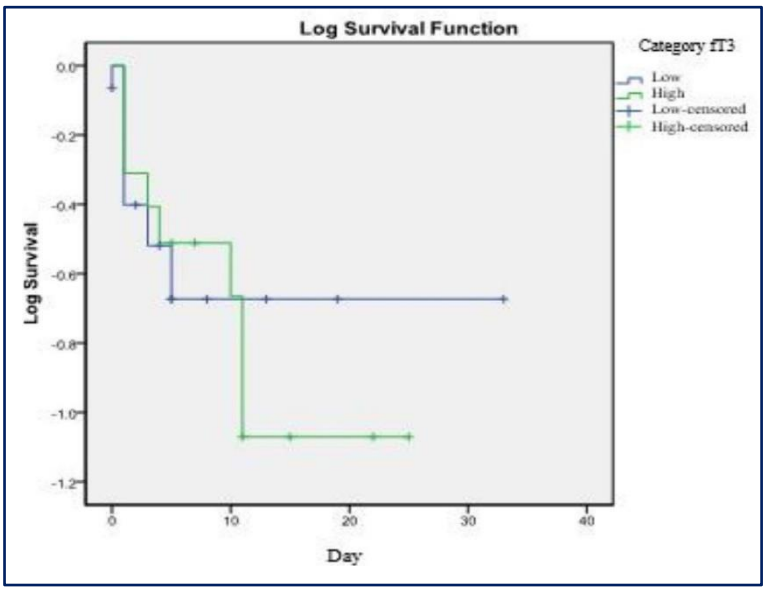

Figure 3: Kaplan-Meier's curve of high (green) and low (blue) fT3 level. (Low category: fT3 level < 1.69 pmol/L; High category: fT3 level > 1.69 pmol/L).

Ratio in groups with high APACHE II scores compared to those with low APACHE II scores (0.60 ± 0.32 vs 0.27 ± 0.16).

Based on the fT3 cutoff value of 1.69, seven non-survivors were categorized as low fT3 group, and nine non-survivors were categorized as high fT3 group. Regarding the fT3 survival curve (Figure 3), we observed that during the first ten days, the group with high fT3 hormone had a higher survival rate than the group with low fT3 (HR 0.40 ± 0.14 vs 0.41 ± 0.18, respectively). However, after ten days, the hazard ratio values for both groups were the same.

3.2. Correlation between APACHE II score, fT3 and fT4 levels to analyze mortality of critically ill patients

Using logistic regression, we formulate two models to analyze the mortality in patients using APACHE II paired with fT3 (Model 1) and with fT4 (Model 2). We found that APACHE II played a more significant role in the outcome when co-administered with fT3 compared to fT4. However, this finding was not statistically significant (Table 4).

4. DISCUSSION

Previous studies have conflicting evidence regarding the correlation of thyroid hormones with clinical outcomes and which hormone is the best predictor of mortality among critically ill patients.[2,5–7]

In our study, we observed NTIS among critically ill patients characterized by low fT3 levels and low or normal fT4 and TSHs level within 24 h of admission. These findings are consistent with the description of acute phase NTIS from previous studies where the fT3 level is low, the reverse T3 (rT3) level is elevated, and fT4 and TSH levels vary.[8,9]

Our study shows a significant difference in age among survivors and non-survivors. This finding is in line with previous studies where age could be a risk factor for mortality among critically ill patients.[10,11] Regarding the APACHE II score, the mean score among non-survivors is higher than in survivors. This finding is similar to previous studies where a higher APACHE II score correlates with increased mortality among critically ill patients.[12–14]

The difference in laboratory parameters between survivors and non-survivors in this study is not statistically significant. These findings are different from those of a study by Padhi et al., where blood urea nitrogen (BUN) and creatinine values were higher, and albumin levels were lower among non-survivors of

critically ill NTIS patients.[15] One might argue that laboratory parameters alone may not be a significant predictor of a patient's clinical outcomes.

This study found no significant difference in thyroid hormone levels among survivors and non-survivors. We argued that changes in thyroid hormone levels in critically ill patients are complex and dynamic. One study by Jarek et al. stated that total T3 concentration measured on the first day of treatment was unable to predict clinical outcome, while on day two, it was a good predictor of clinical outcome.[16] Another study conducted in trauma patients showed that changes in thyroid hormone levels begin 6-12 h after injury and reach a maximum of about 1-4 days afterward.[17] This may explain the dynamic changes in thyroid hormones with respect to time.

There is no standardized cutoff value used for APACHE II. In this study, we used the cutoff of 18 points to provide the best outcome. Bouch and Thompson reported that a score of 25 predicted a mortality of 50%, while a score over 35 predicted a mortality of 80%.[12] In this study, we observed higher mortality rates among groups with high APACHE II scores than those with low APACHE II scores.

Our study also found that changes in thyroid hormone levels in the first 10-day period are in line with the worsening of the patient's disease as indicated by the APACHE II score. This finding is in line with previous studies where low fT3 and fT4 values were correlated with an increased mortality rate among patients.[15,18] Another study also suggests that improvement of thyroid hormone levels during the course of the disease may improve the survivability of the patients.[19]

5. LIMITATIONS

This study has several limitations. First, we did not conduct any diagnostic examination related to autoimmune hypothyroidism upon admission. Secondly, we did not analyze possible comorbidities of subclinical hypothyroidism due to degenerative factors. Thirdly, we did not analyze the relationship between systemic diseases that may be a confounding factor in the patient's thyroid function test and APACHE II score.

6. CONCLUSION

In conclusion, although there was no significant difference in thyroid hormone levels to the patient's outcome, we found that low fT3 level and high APACHE II score had a more significant effect on clinical outcomes in critically ill patients, especially during the first ten days of admission. Further research with a larger sample size and periodic hormonal assessment is needed to determine the role of 'non-thyroidal illness syndrome' in outcome prediction among critically ill patients.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Ethics considerations

This study received approval from the Research Ethics Committee of Soetomo general hospital before it began (Date: June 2020; Approval No: 0053/LOE/301.4.2/VII/2020).

Written informed consent was obtained from the patients who participated in this study.

11. Authors' contribution

All authors took part in concept; acquisition, analysis, and interpretation of data; drafting the manuscript; final approval

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