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Research Article

A Study On Association of Thyroid Hormone and Intensive Care Unit Mortality in Central India.

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Abstract: Thyroid dysfunction has been linked to mortality in patients hospitalized in the intensive care unit (ICU). We aim to study the thyroid hormone level changes in critically ill ICU patients and predict mortality based on thyroid hormone levels. This prospective observational study was conducted on 80 consecutive patients aged over 18yrs, from November 2021 to May 2022, in patients admitted to ICU at Chirayu medical college and Hospital, Bhopal, and followed up during their ICU stay. Samples were tested for T3, T4, and TSH on day 1 and day 7. In our study of 80 participants, 46(57.5%) were male, and 34(42.5%) were female. About 32 (40%) were non-survivors. The significance value (P value) of T3 levels on day 1 was 0.083, and on day 7 was 0.001; T4 levels on day 1 were 0.85, and on day 7 was 0.001. Similarly, the significance of TSH levels on day 1 was 0.085, and on day 7 was 0.001. Day 1 levels of T3 are significantly correlated with APACHE II Score, and Day 7 levels of T3, T4, and TSH significantly correlated with APACHE II scores in predicting the outcome of the patients with the higher significance of T3 compared to T4 and TSH. Our study showed that low T3 level during critical illness increases mortality risk. Thyroid profiles can be used in predicting mortality and as an independent factor in predicting the outcome of ICU patients.

Keywords: Thyroid function test, ICU care, Mortality prediction, TSH, Low T3, APACHE II.

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1.　INTRODUCTION

Mortality prediction in the Intensive unit care (ICU) is critical for patient care. The accurate prediction of mortality in the ICU not only improves the performance of the ICU but also helps in risk adjustment by identifying the confounding factors which may affect the interventions[1]. Several scoring systems are currently available to evaluate the severity of illness and predict the outcomes[2,3,] especially the mortality[4,5] of critically ill patients. The acute Physiology Chronic Health Evaluation (APACHE) scoring system was initially developed to assess the severity in ICU patients. The advantage of APACHE II is that it can predict mortality in ICU patients. It is still the most commonly used scoring system to predict the outcome[6], but the APACHE II scoring system does not consider hormonal responses to illness. Changes in circulating hormone levels are a common occurrence during critical illness. These changes are linked to the intensity of morbidity and the outcomes of ICU patients[7-9]. Thyroid hormones control and regulate metabolism, growth, and many other bodily functions. There are increasing evidence of thyroid dysfunction and link to the death of patients hospitalized in the intensive care unit (ICU)[10-12]. Euthyroid sick syndrome, or nonthyroidal illness syndrome, can be described as abnormal findings on thyroid function tests that occur in the setting of a nonthyroidal illness (NTI) without preexisting hypothalamic-pituitary and thyroid gland dysfunction. After recovery from an NTI, these thyroid function test result abnormalities should be completely reversible[13]. The 'euthyroid sick syndrome' or 'nonthyroidal sickness syndrome' (NTIS) is characterized by low serum levels of free and total triiodothyronine (T3) and high levels of reverse T3 (rT3), as well as normal or low levels of thyroxine (T4) and thyroid stimulating hormone (TSH)[13-16]. Earlier studies suggest that changes in thyroid tests consistent with nonthyroidal illness in patients with ischemic heart disease are associated with an increase in overall mortality.[14] Low serum T3 is correlated with increased hospital stay, intensive care unit (ICU) admission, and need for mechanical ventilation in patients with acute heart failure[15]. And predicts 30-day mortality in patients with community-acquired pneumonia.[16] The serum T4 value also correlates with outcomes in critically ill patients; values under 3 mcg/dL have been associated with mortality rates over 85 percent[16]. On the contrary, some studies suggested low serum T3 levels may benefit critically ill patients[17]. Few other researchers studied elsewhere showed no association between serum T3 levels and ICU patient mortality[18]. A prospective observational study in China showed T3 levels as an independent and powerful predictor of mortality[19]. Few studies in India have also demonstrated the association of low T3 levels with poor clinical outcomes in critically ill patients[20-22]. Very minimal data is available from India on thyroid hormone levels and ICU mortality. Hence we aimed to study the relationship between thyroid hormone level changes and critical illness in ICU patients, predict mortality based on thyroid hormone levels, and correlate and find the significance of thyroid levels with APACHE II Scores.

2.　MATERIAL AND METHODS

2.1.　Participants

This prospective observational study was conducted on patients admitted to ICU at Chirayu medical college and Hospital, Bhopal, India, from November 2021 to May 2022. A total of 80 patients admitted to the ICU who would stay >7 days were randomly selected and enrolled in the study. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. The research proposal was approved by the institutional ethics committee of Chirayu medical college and Hospital with an Ethical approval number (CMCH/112-09-22). In addition, written informed consent was obtained from all the participants.

2.2.　Inclusion Criteria

Patients admitted to the ICU and who would stay >7 days.

2.3.　Exclusion Criteria

Patients with previous intrinsic thyroid, hypothalamic-pituitary axis disease, usage of iodine contrast agents in the past 8 weeks, patients taking drugs altering thyroid functions, pregnant patients or those who were pregnant in the past 6 months, or patients taking any hormonal therapy except insulin.

2.4.　Measurements

Patients admitted to the ICU, irrespective of their primary diagnosis, were selected for this clinical study as per inclusion/exclusion criteria and were subjected to history taking and clinical examination after obtaining informed consent. Thyroid function test (T3, T4, and TSH) was done on day 1 of their ICU stay. All the patients in the study were followed up in ICU as they were getting treated, and their status was monitored for over a week. After 1 week, patients were again subjected to thyroid function tests (T3, T4, and TSH) on day 7 of their ICU stay. Clinical progression over days was observed in terms of recovery from the illness or death of the patient. Finally, thyroid function tests were analyzed.

2.5.　Hormone Assay

The samples were collected and sent to the central laboratory of Chirayu medical college and Hospital, Bhopal. Trained laboratory technicians measured hormone levels. Samples from all study subjects were assessed simultaneously during the same assay run. Thyroid-stimulating hormone (TSH) was measured by radioimmunoassay and the other hormones (T3, T4) by immunoradiometric assays in the solid phase. [Table.1]

Table 1: Hormone Assay	
Hormone	**Normal Range**
T3	80-180 ng/dL
T4	4.6-12 µg/dL
TSH	0.5 to 4.7 mU/L

T3- triiodothyronine; T4- thyroxin; TSH - thyroid stimulating hormone

2.6. Study outcome

Baseline demographic and clinical characteristics, including the APACHE II score, were collected; the patients were followed up during their hospitalization over a week. The primary outcome of this analysis was death in the ICU due to any cause.

2.7. Statistical Analysis

Analysis was done using SPSS data sheet version 22. Frequency tables, measures of central tendency (mean), and measures of dispersion (Standard Deviation) were calculated. The student's t-test was applied to compare the mean values of quantitative variables when the distribution was normal; $P \leq 0.05$ was considered statistically significant.

3. RESULTS

A total of 80 consecutive patients admitted to the medical ICU were enrolled in our study. The baseline characteristics of survivors and nonsurvivors have been listed in Table 2.

Table 2. Characteristics of ICU Survivors and Non-Survivors				
Characteristics	All participants	Survivors	Non-Survivors	P Value
Number of participants	80	48	32	
Age (years)	39.55 ±20.88	35.61±22.11	46.32±11.30	0.181
Males (%)	46	64.5	46.87	0.001
SBP	109.15±22.50	115.88±15.51	85.91±20.88	0.001
DBP	64.50±28.15	72.14±21.62	55.15±13.12	0.001
APACHE Score	15.20±11.12	13.38±5.25	21.00±8.55	0.001

Table 2. Out of 80 participants, 48 (60%) were survivors, and 32 (40%) were non-survivors. The mean age of the participants was 39.55 ± 20.88 years. The mean APACHE-II score was 15.20±11.12. It was significantly lower among nonsurvivors than survivors (21.00 ± 5.55 vs. 13.83 ± 5.25, P < 0.001). Forty-six patients (57.5%) were male, and 34 (42.5%) were female. Twenty-eight participants (35%) were in the age group of 41-50 years, and 20 patients (25%) were in the age group of 31 to 40 years.

Table 3. Thyroid Levels and Their Significance in mortality prediction				
Test Day	Outcome	Participants (%)	Mean	P Value
Below 30 yearsT3 Day 1	Survivors	48 (60)	46.22	0.083
	Non-Survivors	32 (40)	40.42	
T3 Day 7	Survivors	48 (60)	68.44	0.001
41-50 years	Non-Survivors	32 (40)	32.28	
Above 50 yearsT4 Day 1	14 (17.5)Survivors	48 (60)	4.48	0.851
Sex	Non-Survivors	32 (40)	4.05	
Male T4 Day 7	46 (57.5)Survivors	48 (60)	4.88	0.001
Female	Non-Survivors	32 (40)	3.76	
TSH Day 1	Survivors	48 (60)	0.68	0.085
	Non-Survivors	32 (40)	0.39	
TSH Day 7	Survivors	48 (60)	1.36	0.001
	Non-Survivors	32 (40)	0.43	

Table 3. Thyroid function tests (T3, T4, and TSH) were done on day 1 and day 7. The p-value for T3 levels on day 1 is 0.083, and for day 7 is <0.001*. The p-value for T4 levels on day 1 is 0.851, and for day 7 is <0.001*. Similarly, the p-value for TSH levels on day 1 is 0.083, and for day 7 was 0.001*.

Table 4: Correlation between APACHE II and Thyroid function tests		
Thyroid function test	Days of test	APACHE II (P-Value)
T3		0.003
T4	Day 1	0.432
TSH		0.215
T3		0.001
T4	Day 7	0.012
TSH		0.015

Table 4. APACHE II score, calculated within 24 hours of ICU admission, was compared with a score taken on day 1 and day 7. The results obtained with this comparison are that on day 1, levels of T3 significantly correlated with APACHE II scores, whereas T4 and TSH levels were not statistically significant.

On day 7, T3, T4, and TSH levels were significantly correlated with APACHE II scores in predicting the outcome of the patients. The significance of T3 was higher when compared to T4 and TSH.

Table 5. Univariate odds ratios of variables for predicting ICU mortality				
Predictor	**β Value.**	**OR**	**CI**	
			Lower	**Upper**
T3	-0.928	0.35	0.292	0.528
T4	-0.721	0.51	0.417	0.692
TSH	-0.590	0.45	0.323	0.583
APACHE II	0.892	2.852	1.823	4.325

APACHE II score, Acute Physiology, and Chronic Health Evaluation II score; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating-hormone; CI, Confidence interval; OR, Odds ratio;

Table 5. We also performed a univariate logistic regression analysis to realize the association between ICU mortality and each predictor by calculating each variable's standard coefficient (β) and OR [Table 3]. Among the thyroid hormone indicators, T3 was seen to have the greatest absolute value of standardized β (0.928). The absolute value of T3 was greater than T4 (0.721). It was also greater than the APACHE score, indicating that T3 has a greater power for predicting mortality in ICU patients than the T4 or APACHE score. [Table 6]

Table 6: Correlation between APACHE II and Thyroid function tests		
Thyroid function test	**Days of test**	**APACHE II (P-Value)**
T3		0.003
T4	Day 1	0.432
TSH		0.215
T3		0.001
T4	Day 7	0.012
TSH		0.015

4.   DISCUSSION

The care for critically ill patients in ICU has advanced over the past decades. With the clinical knowledge of the care provider, along with illness scoring systems, the outcome of patients can be predicted. Scoring systems for ICU patients can be classified into scoring systems specific for organ systems/ specific diseases and nonspecific scoring systems that can be used for all patients, irrespective of the diagnosis. APACHE scoring system was a nonspecific scoring system initially developed to assess the severity in ICU patients in 1981. The advantage of APACHE II was that it could predict mortality in ICU patients[6]. The scores range from 0 to 71 points. Physiological variables contribute around 60 points. Around 6 points for age and 5 points for previous health status. The APACHE II score comes with 77% accuracy and is the most common method used to predict the outcomes of patients in ICUs[23]. However, APACHE II scores do not consider hormonal responses, especially the levels of thyroid and cortisol hormones, which show an association with outcomes in critically ill patients[24]. In our study, Thyroid function tests (T3, T4, and TSH) were taken from all subjects on day 1 and day 7. T3, T4, and TSH values were analyzed separately and compared with the APACHE II score in predicting the outcome. On day 1, the observed p values for T3 in predicting the outcome was 0.083, for T4 was 0.851, and for TSH was 0.085. These values are not statistically significant. The p values, seen on day 7 for T3 in predicting the outcome, were 0.001, T4 was 0.001, and TSH was 0.001. All these values are statistically significant in predicting the outcome of the patient. The ability of thyroid function tests to predict hospital survival in 116 critically ill patients was studied, which stated that low T3 and high TSH showed a significant independent predictor of nonsurvival[25]. These findings were similar to our study findings concerning T3 and TSH parameters at the end of 7 days. A study with 163 patients admitted to the intensive care unit over 4 months stated that T3 and T4 concentrations were significantly less in non-survivors on admission and on day 1 but not on day 2 and do not allow accurate prediction of

outcome from critical illness[18]. This study's results contradict our results; in our study on day 7 in ICU, T3, and T4 values are statistically significant in predicting the patient's outcome. Another Study done in the medical/surgical ICU in the United Kingdom over 2 years showed that T4 levels as a superior discriminator of patient outcome than the APACHE II score[10]. This result coincides with our study results at day 7 T4 levels. Further, the thyroid profile was compared with APACHE II scores in predicting the outcome. On day 1, the observed p values for the correlation for T3 were 0.003, T4 was 0.432, and TSH was 0.215. T3 values on day 1 correlated with APACHE II scores in predicting the outcome based on statistical analysis. Thyroid function tests obtained on day 7 were again compared with APACHE II scores in predicting the outcome. The observed p values were 0.001 for T3, 0.012 for T4, and 0.015 for TSH. All these values are statistically significant. Thyroid profiles measured serially in ICU patients can independently predict the outcome of the patients. A study by Chinga-Alayo E and colleagues in three hospitals in the USA with 113 patients admitted to ICU stated that adding thyroid hormones to the APACHE score improves the mortality prediction for ICU patients[23]. This finding correlates with our study findings. Wang et al. did a study on the relationship between thyroid function and ICU mortality and showed that low T3 could predict the mortality of the patients. Adding the T3 level to the APACHE II score could significantly improve the ability to predict ICU mortality[19]. In the Indian scenario, to our knowledge, only a few studies are available to determine the relationship between thyroid hormone levels and the mortality of ICU patients. A study of 100 ICU-admitted patients showed that low T3 was an important marker of prognosis in critically ill patients compared to T4 and TSH levels[20]. Suresh M and colleagues studied 100 ICU-admitted patients and showed a strong relationship between low T3 levels and the severity of critically ill patients[21]. Another study by Gutch M and colleagues concluded that T3 was the strongest predictor of ICU mortality. The combination of fT3 levels and APACHE-II scores provided a higher probability for predicting mortality in ICU patients[22]. A

recent study done by Giri R et al. found that for patients admitted to ICU, fT3 was the strongest predictor of ICU mortality in comparison to all other important parameters included in our study[26]. Our study results are consistent with studies done in India, where low T3 levels strongly predict mortality in ICU patients. The actual mechanisms of association of low T3 levels with poor prognosis of ICU patients are not well defined. The low levels of thyroid hormone in ICU patients who are critically ill could be either an adaptive response or a maladaptive response[27]. Inhibition of the 5'-deiodinase enzyme is a possible mechanism underlying euthyroid sick syndrome resulting in decreased peripheral conversion of T4 to T3. Low T3 levels might reflect a collective measure of pathological processes occurring during critical illness, such as cardiovascular dysfunction and inflammatory status[22]. Further studies are required to establish the role of T3 as a prognostic marker in critically ill patients.

5. LIMITATIONS

Our study has a few limitations. Firstly, the presence of undiagnosed thyroid disorder before ICU admission cannot be ruled out; we could only clinically examine the presence of thyroid nodules during admission. Secondly, though we excluded patients on hormone replacement therapy (except those taking insulin), the interference of other drugs with thyroid function (e.g., furosemide, benzodiazepines, barbiturates, and dopamine) could not be eliminated because most of these drugs play a critical role in ICU patient.

6. CONCLUSION

Thyroid profile can be used in predicting the morality in ICU patients; serial monitoring of thyroid profile will increase the sensitivity in predicting the outcome; outcomes assessed by thyroid profile are comparable with that of APACHE II scores, and thyroid profile can be used as an independent factor in predicting the outcome of the patients. Our study showed that a low thyroid profile, especially T3 levels during critical illness, increases mortality risk. Low T3 is the strongest predictor among the thyroid hormones. Therefore, thyroid profiles can be used in predicting mortality and as an independent factor in predicting the outcome of ICU patients.

7. ETHICAL APPROVAL STATEMENT

The research proposal was approved by the institutional ethics committee of Chirayu medical college and Hospital with an Ethical approval number (CMCH/112-09-22).

8. AUTHORS CONTRIBUTION STATEMENT

All authors contributed to the research and preparation of the manuscript. Pravin Gulab Dandekar and Pranay Anil Jain participated in the study design and wrote the first draft of the manuscript. Pravin Gulab Dandekar and Shefali Jain collected and processed the samples. Pravin Gulab Dandekar, Pranay Anil Jain, and Shefali Jain participated in the study design and performed the statistical analyses. All the authors read and approved the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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