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Prognostic significance of Non - Thyroidal illness syndrome in Sepsis

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ABSTRACT

Background and Objectives. Sepsis is a common diagnosis among ICU patients. Therefore, the present study aimed at assessing the prognostic significance of non-thyroidal illness syndrome (NTIS) in sepsis.

Materials and Methods. The study was done as a retrospective analysis on adult patients of age greater than 18 years who were admitted with sepsis to an urban tertiary care ICU at Saveetha Medical College and Hospital.

Results. In our study, we found that NITS can cause either alone T3 fall or alone T4 fall or both T3 and T4 falls together among sepsis patients; however, only the latter strongly correlates with poor primary outcome (28-day mortality) than former (either). We also found that advancing age among septic cases leads to greater combined fall in T3 and T4 values along with increased mortality rate especially among females where the death rate rises statistically significantly if any one of them is less than certain level even though such increase may not be significant enough when only either t3 or t4 falls below specific value among women folk too. Overall mortality rate observed in my series was 55% because majority had severe infection causing much sickness so they were very sick indeed already being complicated by severe sepsis plus having APACHE II score indicating more severity which associated itself again highly significant lower levels these hormones compared against low levels single hormone like what happens usually during such conditions.

Conclusion. In conclusion from this research work it can be suggested that NTIS should be taken

into consideration as an indicator for poor prognosis in patients suffering from septicemia since they require aggressive management unlike those without NTIS while still underlining importance of doing tsh alongside t3t4 among case of critical illness but treating ntis is not within scope our project.

Keywords: Non-thyroidal illness syndrome, Sepsis, Septic shock, Thyroid hormones, Prognosis, Intensive care unit.

Abbreviations: systemic inflammatory response syndrome - SIRS; Intensive Care Units - ICU; thyroid-stimulating hormone - TSH; total triiodothyronine -T3; thyroxine -T4.

INTRODUCTION

Sepsis, a syndrome characterized by a dysregulated host response to infection, remains a formidable challenge within intensive care units (ICUs) worldwide [1]. Despite advancements in medical care, the mortality rate for severe sepsis remains distressingly high, particularly in developed countries where it hovers around 50%. However, the situation is even graver in India, where the mortality rate for severe sepsis spikes to an alarming 65.2%. This disparity underscores the urgent need for improved prognostic tools and therapeutic strategies to combat this life-threatening condition [2].

Predicting outcomes in sepsis is paramount for clinicians, as it facilitates the timely implementation of appropriate interventions and resource allocation in ICU settings. Numerous prognostic factors have been identified, encompassing a wide array of demographic, clinical, and biochemical parameters. Among these factors, the non-thyroidal illness syndrome (NTIS) has garnered increasing attention in recent years due to its complex interplay with the pathophysiology of critical illness [3].

NTIS, also known as euthyroid sick syndrome, reflects the body's adaptive response to severe illness, characterized by alterations in thyroid hormone metabolism and function. In critically ill patients, the intricate balance of thyroid hormone production, transport, and utilization becomes disrupted, leading to characteristic changes in serum thyroid hormone levels [4]. Key among these changes is the reduction in serum concentrations of total triiodothyronine (T3) and free triiodothyronine (fT3), accompanied by elevated levels of reverse triiodothyronine (rT3). This dysregulation is further exacerbated as the severity of illness escalates, with serum T3 levels declining progressively while fT3 levels exhibit a less pronounced reduction [5].

Despite these well-documented alterations in thyroid hormone profiles during critical illness, the clinical significance of NTIS in the context of sepsis remains a subject of ongoing debate. While

some studies have suggested a potential association between low thyroid hormone levels and adverse outcomes in septic patients, conflicting findings have been reported in the literature [6]. Moreover, the specific prognostic relevance of NTIS in adult sepsis patients, particularly within the unique demographic and clinical landscape of Eastern India, remains largely unexplored [7]. Thus, the primary objective of the proposed study is to elucidate the prognostic significance of NTIS in adult sepsis patients in Eastern India. By meticulously examining the association between thyroid hormone levels—including T3, fT3, thyroxine (T4), and thyroid-stimulating hormone (TSH)—and clinical outcomes in this population, the study aims to fill critical gaps in our understanding of the pathophysiology and prognostication of sepsis. Ultimately, the insights gleaned from this research endeavor hold the potential to inform more targeted and effective therapeutic interventions, thereby improving the management and outcomes of sepsis patients in this region and beyond.

MATERIALS AND METHODS

Study Design and Setting. A retrospective analysis was conducted on adult patients (18+) admitted with sepsis to an urban tertiary care institution. Patients were divided into two categories: systemic inflammatory response syndrome (SIRS) and APACHE II computed in the absence of an underlying infection. Furthermore, individuals were classified as having sepsis, which includes severe sepsis and septic shock, according to international consensus guidelines. The patients were treated in accordance with international guidelines for severe sepsis and septic shock. Crystalloids were used for fluid resuscitation, resulting in a central venous pressure of 8-12 mm Hg. Vasoactive medications were used to keep the mean arterial pressure between 65 and 90 mm Hg, with norepinephrine being the first choice.

Patients with diagnosed thyroid disorders and palpable abnormalities in the thyroid gland (such as enlarged thyroid and thyroid nodules), psychiatric conditions, pregnancy, individuals receiving hormonal therapy other than insulin, those taking amiodarone, corticosteroids, or dopamine, or those who had given birth within the previous 6 months were all excluded.

Thyroid hormone analysis was utilized to diagnose non-thyroidal sickness syndrome (NTIS) in the study participants. Patients with low levels of T3 alone or low levels of T3 plus T4, as evaluated by blood T3 and T4 levels, were assigned to the NTIS group. Measurements taken in the laboratory: Blood samples were taken within 24 hours after admission to the medical ICU to assess thyroid hormone levels, including total triiodothyronine (T3), total thyroxine (TT4), and thyroid-stimulating hormone (TSH). The electrochemiluminescence method was used to perform the third-generation TSH assay. The institution's thyroid hormone reference ranges were as follows: T4 (5.13-14.06 micrograms per deciliter), T3 (84.63-201.08 nanograms per deciliter), and TSH (0.46-4.68 microinternational units per milliliter). Additional blood tests, such as arterial blood gas analysis, serum chemistry, complete blood count, C-reactive protein,

and procalcitonin, were performed simultaneously. Prior to antibiotic administration, blood samples were obtained for culture, with a positive result indicating the presence of aerobic, anaerobic, or fungal microorganisms.

Data Collection and Processing. The data was obtained from standardized collection forms, which included information on demographics, co-morbidities (such as diabetes, hypertension, liver disease, and chronic obstructive pulmonary disease), initial hemodynamics, primary site of infection, laboratory results, microbiological reports, Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and outcome variables. Patients who were released within 28 days underwent follow-up. **Statistical analysis.** Quantitative data were represented using the median and interquartile range, whereas categorical variables were represented using frequency percentages. The Mann-Whitney U test was used to assess quantitative data with a non-normal distribution, and the Chi-square test was used for categorical variables. A p-value < 0.05 was considered statistically significant. The analysis was carried out using SPSS version 25.0.

RESULTS

With the analysis of 200 patients in a tertiary care center, 102 persons are males and 98 are females. Of this 52 (51.08%) males and 58 (59.2%) female patients had mortality and p value was 0.02 (Table 1).

With normal values of T3 (84.63-201.08 ng/dl) the mortality rate was less compared to survival rate, but with moderate values of T3 (25-84.62 ng/dl) the survival rate was low (44.1%) compared to the death (55.9%). But in very low values of T3 (<24.99) the mortality was very high compared to the survival rate. So, we conclude that, as the levels of T3 decreases the mortality rate increases exponentially (Table 2).

The value of T4 also decreases in sepsis but to the lesser extent. As the T4 decreases in the sepsis, the very low values of T4 <1microgram/dl the mortality rate was very high. The p value was 0.029. The low value of both T3 and T 4 in patient has very high mortality when compared to decreased values of T3 and T4 alone (Table 3).

As the APACHE II score increasing the T3 and T4 values decreases which indicate the patient has the increase in severity of sepsis, so there is an increase in mortality.

Discussion

Sepsis is a complex illness that is characterized by the body's organized inflammatory reaction to infections. Hypoxia, tissue hypoperfusion, systemic symptoms, and finally death follow (10). Severe sepsis alters thyroid gland function, which impacts the endocrine system. A thyroid hormone metabolism imbalance known as euthyroid sick syndrome (ESS) or non-thyroidal sickness syndrome (NTIS) is frequently seen in critically ill individuals who do not have intrinsic

thyroid disease. While FT4 may be low or normal in these patients, serum free T3, TSH, and other TSH values are low (11). Furthermore, non-thyroidal disease raises reverse T3 (rT3) levels because it converts less readily to diiodothyronine (T2), which is linked to a decrease in 5'monodeiodinase activity [12]. Thyroid dysfunction is present in critically ill sepsis patients admitted to the intensive care unit (ICU) and is linked to morbidity and mortality [13]. Because thyroid hormones control immunity and body metabolism, the severity and acuteness of the disease process will determine how much of a hormonal disturbance occurs [14]. Studies conducted in the past have demonstrated that fT3 levels are considerably lower in non-survivors than in survivors. Likewise, data from past publications did not link fT3 to patient outcome in the intensive care unit. As a result, there are multiple conflicting findings about the relationship between thyroid hormone and ICU sepsis patients' morbidity and mortality [15]. The purpose of this study was to ascertain whether NTIS was linked to higher 28-day death rates in sepsis-affected patients.

Within 28 days, 55% of the trial participants passed away. An examination of survivors and non-survivors revealed that the former were younger than the latter. In line with this, Padhi et al. [17] discovered that age is a significant predictor of death. Bello et al. found that age had a significant correlation with sepsis-related death in a different research [7]. Sex did not predict death from sepsis in our study. Padhi et al.'s [16] finding that male gender was a major predictor of death supports this conclusion. However, Guo et al. [18] state that there is no correlation between sex and an ICU patient's outcome. T3 and T4 levels were shown to differ between survivors and non-survivors, suggesting a potential function for NTIS in this illness. A systematic review that examined the relationship between baseline thyroid function tests and the prognosis of patients suffering from sepsis or septic shock included nine investigations, of which two were adult and seven were prospective cohort studies. Our findings are in line with six of the nine studies that found that admission FT3 and FT4 tended to be lower in individuals who experienced unfavorable outcomes than in those who did not [19].

NTIS is strongly associated with sepsis. 60% to 70% of individuals who are really sick may be affected. According to our research, 65% of septic patients experienced NTIS [21]. In a similar vein, El-Ella et al. prospectively monitored 65 children who developed sepsis and found that 63% of those patients exhibited "low T3-T4" syndrome [20]. In a similar line, 67% of Padhi et al.'s septic patients had NTIS (16). Numerous confounding factors, such as known thyroid disorders, mental health conditions, hormone therapy, and amiodarone use, have been ruled out of this study in order to analyze thyroid function.

When compared to all other full indicators of thyroid functions, such as FT3, TT3, FT4, TT4, TSH, rT3, and T3/rT3, Wang et al.'s study on the association between ICU mortality and thyroid function revealed that FT3 was the most effective predictor of ICU mortality. According to Ray et al., there is no association between FT3 levels and unfavorable outcomes in ICU patients; yet,

data indicates that TSH, TT3, TT4, FT4, and other markers predict ICU mortality in the adult general population [21]. Thyroid function test abnormalities are seen in patients with acute or chronic systemic diseases, and this disorder is known as non-thyroxine syndrome (NTIS). Early in the critical illness period, there are alterations such as lowered T3, increased T4-rT3 ratio, and normal TSH levels; later in the illness phase, central hypothyroidism with reduced blood concentrations of T4 and T3 occurs [22]. Thyrotropic hormone serum levels rise throughout the first part of the recovery phase, which eventually results in a return to normal thyroxine concentration.

El-Ella et al. looked at the occurrence and diagnostic utility of NTIS in critically unwell children. According to their findings, FT4 was substantially more prevalent in non-survivors than in survivors (50% versus 19.2%, P =.028). NTIS was able to predict mortality independently (OR = 3.91; 95% CI = 1.006--15.19; P =.0491). The combination of FT3, FT4, and TSH reductions is the greatest independent predictor of death (OR = 16.9; P =.026). T3 was lower in non-survivors than in survivors in our study. Thyroid hormone (T3 and T4) suppression was higher in non-survivors. This has significant ramifications because it indicates that a decreased T3 in sepsis is an indicator of a poor prognosis.

The thyroid hormone levels and APACHE II score in this study showed a clear difference between the survivors and non-survivors. The APACHE II score increased significantly ($p<0.001$) in non-survivors compared to survivors. Our results are in line with those of Kothiwale et al., who discovered that deceased patients had higher average APACHE II scores [23]. Likewise, we observed a negative correlation between the APACHE II score and T3 levels. According to Chinga-Alayo et al., there is a significant negative correlation ($p < 0.0005$) between FT3 and the ICU death rate, as evidenced by SOFA scores and APACHE II scores [24]. Due to 5'monodeiodinase suppression, which reduces the amount of T4 that can be converted into T3, the majority of critically sick patients with NTIS have decreased fT3 concentrations. 5'-monodeiodinase is inhibited by a number of substances, such as glucocorticoid treatment, circulating deiodenase inhibitors (free fatty acids), and cytokines. Long-term sickness causes hypothalamic pituitary suppression, which lowers TSH release and thyroid gland T4 production, ultimately resulting in low fT4 levels. Consequently, lower TSH and fT4 levels are indicative of a serious chronic illness or a dismal prognosis.

In conclusion: When NTIS is absent in septic cases that need more intensive care, it is a sign of a poor prognosis in sepsis cases. This study further emphasizes the importance of measuring T3, T4, and the TSH ranges in these instances. For TSH, a sole measurement is insufficient. The NTIS therapy portion has been removed from the study's purview; please rewrite

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AUTHOR'S CONTRIBUTIONS

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All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1: Demographic Characteristics and Mortality Outcomes in Sepsis Patients

	Survivor (n%)	Non-survivor (n%)	p-value
Age	53 [43-62]	56 [47-66]	0.020
Male	50 (49.0%)	52 (51.0%)	0.258
Female	40(40.8%)	58 (59.2%)	

Table 2: Association of Triiodothyronine (T3) Levels with Mortality in Sepsis Patients

		Survivor (n%)	**Non-survivor (n%)**	**p-value**
T3	84.6 - 201.8 ng/dl	40 (57.1%)	30 (42.9%)	
	83 - 25 ng/dl	41(44.1%)	52 (55.9%)	0.005
	< 24.99 ng/dl	9 (24.3%)	28 (75.7%)	

Table 3: Impact of Thyroxine (T4) Levels on Mortality Outcomes in Sepsis Patients

		Survivor (n%)	**Non-survivor (n%)**	**p-value**
T4	5.13 - 14.0 microgram/dl	67 (51.9%)	62 (48.1%)	
	4.99 - 1.0 microgram/dl	22 (32.4%)	46 (67.6%)	0.029
	< 1 microgram/dl	1 (33.3%)	2 (66.7%)	

Table 4: APACHE II Score (changes)

APACHE II Score (changes)								
	5-9	**10-14**	**15-19**	**20-24**	**25-29**	**30-34**	**>35**	**p- value**
84.6 - 201.8 ng/dl	5 (7.1%)	30 (42.9%)	16 (22.9%)	5 (7.1%)	6 (8.6%)	6 (8.6%)	2 (2.9%)	
83 - 25 ng/dl	6 (6.5%)	17 (18.3%)	23 (24.7%)	11 (11.8%)	13 (14.0%)	12 (12.9%)	11 (11.8%)	0.001
< 24.99 ng/dl	2 (5.4%)	2 (5.4%)	5 (13.5%)	6 (16.2%)	9 (24.3%)	10 (27.0%)	3 (8.1%)	
5.13 - 14.0 microgram/dl	11 (8.5%)	38 (29.5%)	28 (21.7%)	11 (8.5%)	14 (10.9%)	16 (12.4%)	11 (8.5%)	
4.99 - 1.0 microgram/dl	2 (2.9%)	11 (16.2%)	16 (23.5%)	11 (16.2%)	12 (17.6%)	12 (17.6%)	4 (5.9%)	0.045
<1 microgram/dl	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	1 (33.3%)	