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The Prognostic Role of Non-Thyroidal Illness Syndrome in Critically Ill Patients: A Retrospective Cohort Study

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Abstract

Aim: Non-thyroidal illness syndrome (NTIS), characterized by reduced triiodothyronine (T3) levels in the absence of intrinsic thyroid disease, is common among critically ill patients. However, its independent association with intensive care unit (ICU) mortality remains uncertain. This study investigated the association between NTIS and ICU outcomes in adult patients admitted to a tertiary-level medical ICU.

Study Design: We retrospectively analyzed adult patients (≥18 years) admitted to a tertiary-level medical ICU between May 2021 and May 2023. NTIS was defined as reduced serum T3 with normal or low thyroid-stimulating hormone (TSH) and thyroxine (T4) levels. Patients with known thyroid disease, corticosteroid therapy within the preceding seven days, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) positivity, prior ICU admission, ICU stay <24 hours, or recent radiocontrast exposure were excluded. Demographic, clinical, and laboratory characteristics were compared between patients with and without NTIS.

Results: Of 109 patients, 85 (78%) had NTIS. ICU mortality was numerically higher among NTIS patients (30.5%) compared with those without NTIS (16.6%), although the difference was not statistically significant. The NTIS group had higher Sequential Organ Failure Assessment (SOFA) scores (median 8.5 vs. 6; p=0.054) and more frequent need for mechanical ventilation (55.2% vs. 41.6%; p=0.124). No significant differences were observed in ICU length of stay (p=0.17) or hospital mortality (p=0.178).

Conclusions: Non-thyroidal illness syndrome was not independently associated with ICU mortality but showed a strong correlation with markers of illness severity. These findings suggest that NTIS may serve as a biomarker of critical illness severity rather than an independent predictor of mortality.

Keywords: Euthyroid sick syndrome; Intensive care unit (ICU); Thyroid hormones; Outcome.

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Introduction

Non-thyroidal illness syndrome (NTIS), also known as euthyroid sick syndrome (ESS), is a dysregulation of thyroid hormone metabolism commonly observed in critically ill patients without intrinsic thyroid disorders.[1] It is primarily characterized by decreased serum triiodothyronine (T3) levels, with thyroid-stimulating hormone (TSH) and thyroxine (T4) levels remaining normal or low.[2] NTIS may rep-

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resent either an adaptive or maladaptive endocrine response to systemic illness, with potential implications for prognosis and therapeutic decision-making.[3] The prevalence of NTIS ranges from 70% to 80% across all forms of critical illness, indicating that the vast majority of critically ill patients experience some degree of thyroid dysfunction. This highlights the importance of understanding and managing NTIS in critical care settings.[4] The central debate revolves around a key question: *Is NTIS a protective, energy-conserving adaptation, or a maladaptive process that actively contributes to adverse outcomes?*

In critical illness, the hypothalamic-pituitary-thyroid (HPT) axis undergoes adaptive suppression, influenced by cytokine activity, altered deiodinase expression, impaired hormone transport, and reduced peripheral conversion of T4 to T3. These alterations are especially pronounced in conditions such as sepsis, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and acute kidney or liver failure—clinical states frequently encountered in intensive care units (ICUs).[3-6] To date, the literature remains strikingly divided. While previous studies have highlighted the prognostic relevance of NTIS, particularly in non-ICU populations, it remains unclear whether NTIS functions as an independent predictor of ICU mortality, keeping the question at the forefront of critical care research.[7,8] Some researchers propose that NTIS is an epiphenomenon secondary to illness severity, whereas others argue it may be a modifiable marker of adverse outcomes.[9-11]

This persistent uncertainty highlights a critical gap in our understanding: the need to clarify the relationship between NTIS and illness severity in a general, heterogeneous ICU population, a setting less frequently studied compared to specific disease cohorts. Therefore, this study aimed to elucidate the prognostic significance of NTIS in a tertiary-level medical ICU. The primary objective was to determine whether NTIS is independently associated with ICU mortality. The secondary objective was to characterize the relationship between NTIS and validated markers of organ dysfunction and clinical severity, with the hypothesis that NTIS primarily serves as a robust biomarker of systemic stress rather than an independent driver of mortality in this vulnerable patient group.

Materials and Methods

Study Design and Population

This retrospective cohort study was approved by the Ankara University Human Research Ethics Committee Ethics Committee (Approval No: I01-73-24, Date: February 6, 2024) and conducted in the tertiary-level medical intensive care unit of a university hospital between May 2021 and May 2023.

Adult patients (≥18 years) without SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection who were admitted to the ICU during the study period were screened for eligibility. Patients with available thyroid function tests (TFTs) measured within the first 48 hours of ICU admission were included in the evaluation. Patients were excluded if they had any of the following criteria: known hypothyroidism or hyperthyroidism; use of systemic corticosteroids within seven days before or during the ICU stay; a positive SARS-CoV-2 Reverse Transcription Polymerase Chain Reaction (RT-PCR) test; readmission during the study period; ICU stay shorter than 24 hours; or recent exposure to radiocontrast agents. Eligible patients were included in the final analysis and stratified into two groups based on the presence or absence of NTIS. NTIS was defined as reduced free triiodothyronine (fT3) levels in combination with normal or low free thyroxine (fT4) and thyroid-stimulating hormone levels, measured within 48 hours of ICU admission.

Serum concentrations of TSH, fT3, and fT4 were determined using a direct chemiluminescence immunoassay (ADVIA Centaur XP, Siemens Healthineers, Tarrytown, NY, USA). The reference ranges used in our laboratory were: TSH, 0.38-5.33 mIU/mL; fT3, 3.99-6.71 pmol/L; and fT4, 7-22 pmol/L.

Data Collection

Demographic and clinical data were extracted from electronic medical records. Recorded variables included age, sex, comorbidities, admission diagnoses, need for invasive mechanical ventilation, and lengths of ICU and hospital stay. The Sequential Organ Failure Assessment (SOFA) score was calculated at ICU admission, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated using data from the first 24 hours of ICU stay. For the secondary analysis, patients were categorized as survivors or non-survivors and compared according to their thyroid hormone profiles and clinical variables.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

A total of 413 adult patients (≥18 years) without SARS-CoV-2 infection were evaluated between May 2021 and May 2023 (Fig. 1). Of these, 214 patients had thyroid function tests available within the first 48 hours of ICU admission. One hundred and five patients were excluded from the evaluation for the following reasons: known hypothyroidism (n=38), hyperthyroidism (n=13), use of systemic corticosteroids within seven days before or during ICU stay (n=54), or other exclusion criteria.

After applying the exclusion criteria, 109 patients were included in the final analysis. Of these, 85 (78.0%) were classified as having NTIS and 24 (22.0%) as not having NTIS. The median age of the entire cohort was 72 years (IQR: 57-83 years), with no significant difference between groups (72 years [IQR: 57-82.7] in the NTIS group vs. 74 years [IQR: 64-83] in the non-NTIS group; p=0.70). Gender distribution was balanced across both groups, with 55 patients (50.4%) being male overall, and similar proportions in the NTIS (50.5%) and non-NTIS (50.0%) groups (p=0.95).

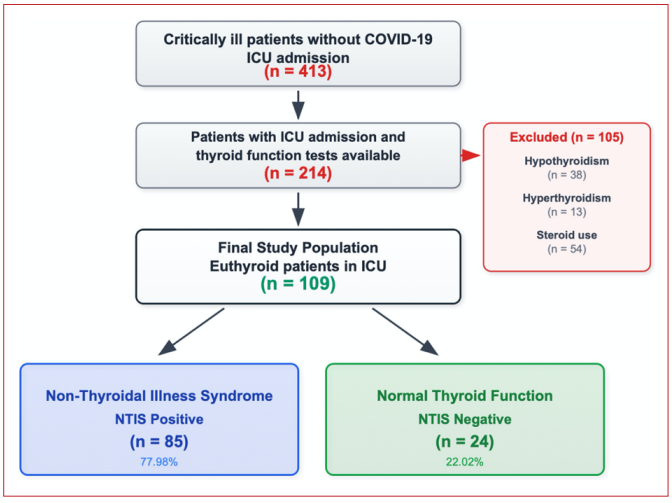

Figure 1. Bilateral pulmonary opacities demonstrating acute respiratory distress syndrome in the patient.

The distribution of comorbidities was also similar between groups. Hypertension was the most prevalent comorbidity, affecting 59.6% of all patients, with comparable rates in the NTIS (60.0%) and non-NTIS (58.3%) groups (p=0.88). Diabetes mellitus was present in 44.0% of patients overall, with a numerically higher prevalence in the non-NTIS group (37.5%) compared with the NTIS group (23.5%), although this difference was not statistically significant (p=0.46). Chronic obstructive pulmonary disease affected 26.6% of patients, with a notably higher prevalence in the non-NTIS group (41.6% vs. 22.3%; p=0.17). Other comorbidities, including chronic heart failure (26.6%), malignancy (21.1%), coronary artery disease (9.1%), and hepatic failure, showed similar distributions between groups (all p>0.05).

Primary admission diagnoses were similarly distributed. Pneumonia was the most common diagnosis, accounting for 55.9% of cases overall, with similar rates in the NTIS (54.1%) and non-NTIS (62.0%) groups (p=0.50). Sepsis was diagnosed in 47.7% of patients at admission, with comparable proportions between groups (48.2% NTIS vs. 45.8% non-NTIS; p=0.83). Acute kidney injury (AKI) was present in 20.1% of patients, with a higher prevalence in the NTIS group (23.5%) compared to the non-NTIS group (8.3%; p=0.10). Acute respiratory distress syndrome affected 16.5% of patients, with a similar distribution between groups (11.7% in the NTIS group vs. 33.3% in the non-NTIS group; p=0.12).

Assessment of disease severity revealed similar APACHE II scores between groups, with a median score of 24 (IQR: 17-31.7) in NTIS patients and 21 (IQR: 13-27) in non-NTIS patients (p=0.42). However, SOFA scores showed a clinically relevant trend toward greater severity in the NTIS group, with median scores of 8.5 (IQR: 5-10.7) compared with 6.0 (IQR: 4-8) in the non-NTIS group (p=0.054), approaching statistical significance.

Invasive mechanical ventilation was required in 56 patients (51.3%) overall. Although not statistically significant, ventilation requirements differed numerically between groups, with 47 patients (55.2%) in the NTIS group and 19 patients (79.1%) in the non-NTIS group requiring mechanical ventilation (p=0.124). This apparent paradox may reflect the complex interplay between illness severity, admission diagnoses, and the development of NTIS during critical illness. ICU length of stay was comparable between groups, with a median of 9 days (IQR: 4.25-15) in NTIS patients and 7 days (IQR: 4-12) in non-NTIS patients

Table 1. Characteristics, management, thyroid hormone levels, and outcomes of patients with and without non-thyroidal illness syndrome (NTIS)

	Total (n=109)	With NTIS (n=85)	Without NTIS (n=24)	p
Age*	72 [57-83]	72 [57-82.7]	74 [64-83]	0.70
Male gender**	55 (50.4)	43 (50.5)	12 (50)	0.95
APACHE II*	24 [17-31]	24 [17-31.7]	21 [13-27]	0.42
SOFA*	7 [5-10]	8.5 [5-10.7]	6 [4-8]	0.054
Comorbidities**				
Hypertension	65 (59.6)	51 (60)	14 (58.3)	0.88
Diabetes mellitus	48 (44)	39 (45.8)	9 (37.5)	0.46
COPD	29 (26.6)	20 (23.5)	9 (37.5)	0.17
Chronic heart failure	29 (26.6)	19 (22.3)	10 (41.6)	0.063
Malignancy	29 (26.6)	21 (24.7)	8 (33.3)	0.39
Coronary artery disease	23 (21.1)	19 (22.3)	4 (16.6)	0.392
Hepatic failure	10 (9.1)	8 (9.4)	2 (8.3)	0.87
Admission diagnosis**				
Pneumonia	61 (55.9)	46 (54.1)	15 (62)	0.50
Sepsis	52 (47.7)	41 (48.2)	11 (45.8)	0.83
AKI	22 (20.1)	20 (23.5)	2 (8.3)	0.10
ARDS	10 (9.1)	9 (10.5)	1 (4.2)	0.32
fT3	2.43 [1.91-2.86]	2.34 [1.87-2.58]	3.48 [3.25-3.82]	<0.001
fT4	14.60 [10.8-16.8]	13.05 [9.91-16.35]	16.20 [15-18.7]	0.002
Thyroid stimulating hormone	1.12 [0.59-2.06]	1.13 [0.59-2.12]	1.09 [0.56-1.98]	0.96
Invasive mechanical ventilation**	56 (51.3)	47 (55.2)	19 (79.1)	0.124
ICU length of stay*	9 [4-14]	9 [4.25-15]	7 [4-12]	0.24
Hospital length of stay*	15 [10-25]	17.5 [10-28]	13 [10-20]	0.17
ICU mortality**	30 (27.5)	26 (30.5)	4 (16.6)	0.178

APACHE II: Acute Physiology and Chronic Health Evaluation II; NTIS: Non-thyroidal illness syndrome; COPD: Chronic obstructive pulmonary disease; fT3: Free triiodothyronine; fT4: Free thyroxine; ICU: Intensive care unit; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment Score; TSH: Thyroid-stimulating hormone. *Median [interquartile range]; **n (%).

p-values <0.05 were considered statistically significant.

(p=0.24). Similarly, total hospital length of stay showed no significant difference between groups, with median durations of 17.5 days (IQR: 10-28) in the NTIS group and 13 days (IQR: 10-20) in the non-NTIS group (p=0.17).

ICU mortality was observed in 30 patients (27.5%) overall. Although mortality was numerically higher in the NTIS group, the difference did not reach statistical significance. Specifically, 26 patients (30.5%) in the NTIS group died during their ICU stay compared with four patients (16.6%) in the non-NTIS group (p=0.178). These findings suggest that while NTIS may be associated with markers of disease severity, it does not independently predict mortality in this critically ill population. A detailed summary of clinical and laboratory characteristics is provided in Table 1 and Figure 2.

Kaplan-Meier survival curves demonstrated no statistically significant difference in cumulative survival between groups (log-rank p=0.22), as shown in Figure 3.

Discussion

In this retrospective cohort study conducted in a tertiary-level medical ICU, we evaluated the relationship between non-thyroidal illness syndrome and ICU outcomes in critically ill adult patients. A key methodological strength of this study is the systematic exclusion of patients with recent corticosteroid exposure, addressing an important confounding factor that has been inadequately controlled in many previous investigations. Exogenous corticosteroids exert direct suppressive effects on hypothalamic thyrotropin-releasing hormone secre-

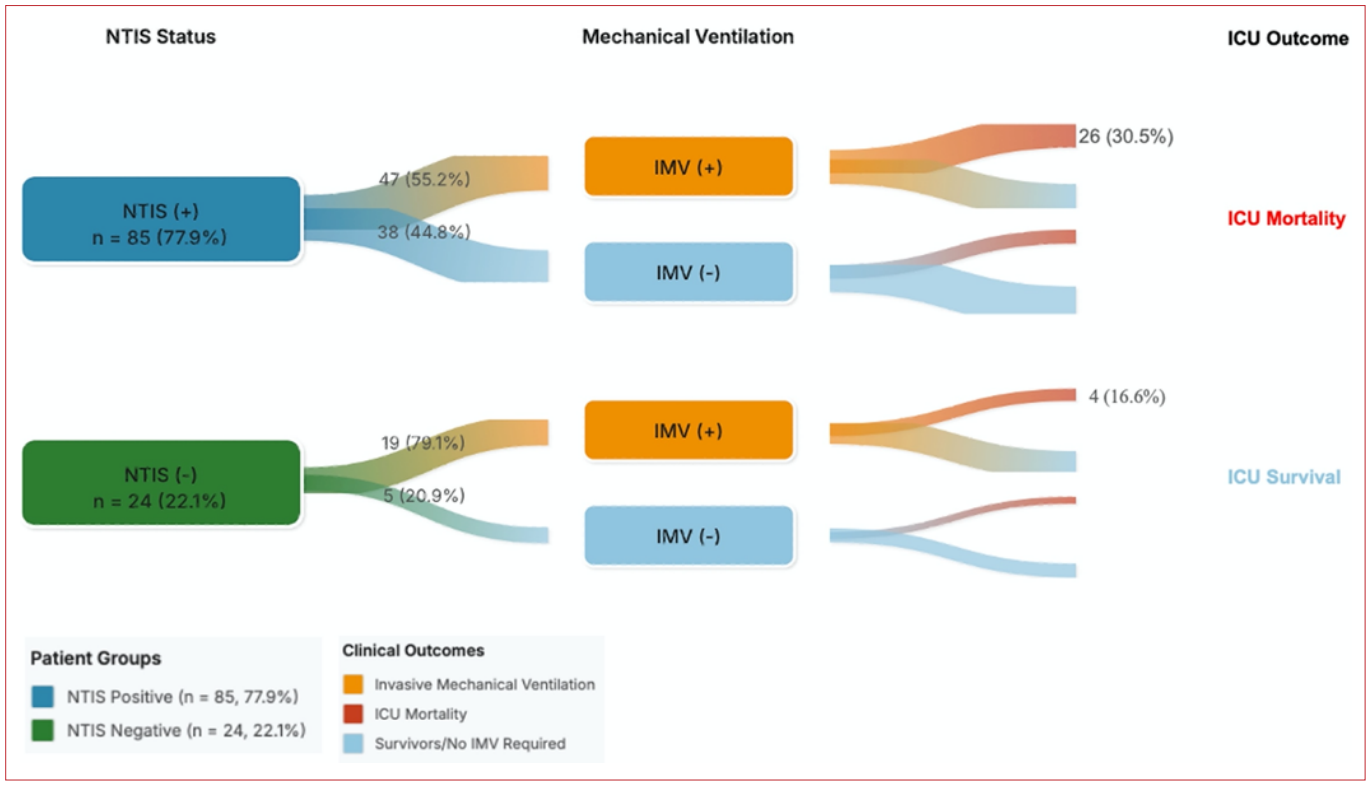

Figure 2. Sankey diagram illustrating the flow of critically ill patients from NTIS status to IMV and ICU mortality. Among the 85 patients with NTIS, 47 (55.2%) required invasive mechanical ventilation and 26 (30.5%) died in the ICU. Among the 24 patients without NTIS, 19 (79.1%) received mechanical ventilation and four (16.6%) died. Arrow widths are proportional to the number of patients in each transition, with all numeric values explicitly annotated. NTIS was not significantly associated with ICU mortality or mechanical ventilation in univariate analysis, although a numerical trend was observed. NTIS: Non-thyroidal illness syndrome; IMV: Invasive mechanical ventilation; ICU: Intensive care unit.

tion and pituitary thyroid-stimulating hormone release, thereby inducing iatrogenic thyroid dysfunction that mimics NTIS. Although ICU mortality rates were numerically higher among patients with NTIS, this difference did not reach statistical significance. Nonetheless, NTIS was significantly associated with higher SOFA scores and showed a trend toward increased need for invasive mechanical ventilation. These findings support the notion that NTIS may reflect illness severity rather than serving as an independent predictor of ICU mortality.

The prevalence of NTIS in our cohort (78%) is consistent with previous reports indicating that NTIS is highly prevalent in critical care settings, particularly among patients with sepsis, organ failure, and respiratory compromise.[4,7,9] For example, Zargar et al.[4] reported a prevalence of NTIS as high as 80% in patients with severe non-thyroidal illness, emphasizing its frequent occurrence in acutely ill populations. Similarly, Iglesias et al.[12] found altered thyroid function tests in 74% of hospitalized elderly patients, many of whom had systemic illnesses requiring ICU-level care.

Regarding ICU mortality, our findings align with those of Krug et al.,[10] who demonstrated that NTIS was not an independent predictor of mortality in ICU patients when adjusted for illness severity. Likewise, Praveen et al.[13] reported that although NTIS was more common among non-survivors, its significance disappeared in multivariate analysis, suggesting that it may be a bystander phenomenon reflecting systemic stress.

Conversely, other studies have suggested a prognostic role for NTIS in critical illness. Guo et al.[14] showed that low fT3 levels were independently associated with increased 28-day mortality in ICU patients, particularly when combined with elevated inflammatory markers and organ dysfunction scores. Similarly, Bello et al.[7] found that NTIS was associated with prolonged mechanical ventilation in ICU patients, a finding that parallels the increased ventilation requirements observed in our NTIS group. A recently published single-center study also demonstrated a high prevalence of NTIS (62.6%) among critically ill patients with Coronavirus Disease 2019 (COVID-19) but did not find a statistically signifi-

cant association with mortality, reinforcing the hypothesis that NTIS may mirror the severity of systemic illness rather than directly contribute to adverse outcomes.[15]

The discrepancy between studies may stem from differences in study populations, timing of hormone measurements, exclusion criteria (e.g., corticosteroid use), and whether adjustments were made for confounders such as disease severity scores. In our study, despite the absence of multivariate adjustment, the elevated SOFA scores and greater use of mechanical ventilation among NTIS patients suggest that NTIS closely parallels clinical deterioration.

In addition to its prognostic associations, NTIS has been shown to correlate with objective measures of disease severity. For example, Wang et al.[16] demonstrated a significant association between lower fT3 levels and higher severity scores, including SOFA and APACHE II, in ICU patients with NTIS. Similarly, Tognini et al.[17] reported that NTIS was linked to short-term survival in a hospitalized elderly population, underscoring the clinical relevance of thyroid hormone alterations beyond critical illness alone.

From a pathophysiological perspective, the changes observed in NTIS—namely, reduced peripheral conversion of T4 to T3 and central suppression of the hypothalamic-pituitary-thyroid axis—are believed to represent an adaptive response to acute systemic illness.[3,5,6] This hormonal adaptation may serve to reduce metabolic demands during critical illness, but whether it is ultimately protective or maladaptive remains uncertain. Although not statistically significant, visual trends illustrated in Figure 2 suggest a directional relationship between NTIS and markers of clinical severity, such as mechanical ventilation and elevated SOFA scores.

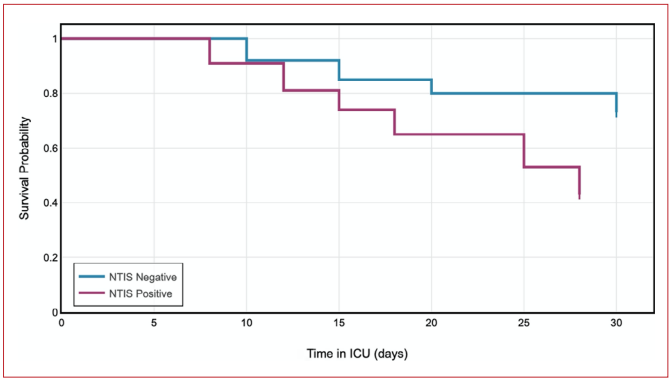

Figure 3. Kaplan-Meier survival curves for patients with or without NTIS, showing the probability of ICU survival over time stratified by NTIS status. The blue line represents NTIS-negative patients (n=24), the purple line represents NTIS-positive patients (n=85). Censored observations are indicated by tick marks. The p-value was determined using the log-rank test. NTIS: Non-thyroidal illness syndrome; ICU: Intensive care unit.

Therapeutic implications of NTIS remain controversial. While some authors have explored thyroid hormone replacement in selected populations, such as patients undergoing cardiac surgery or those with trauma, the routine use of levothyroxine or liothyronine in NTIS is not currently supported by major guidelines due to inconsistent evidence and potential risks.[6] Our findings reinforce this conservative approach, as the absence of an independent association with mortality suggests that correcting NTIS may not improve outcomes and could potentially disrupt beneficial adaptive responses. Nevertheless, the potential utility of NTIS as an early biomarker for ICU triage and disease progression remains an area of growing interest. The potential development of NTIS-based risk prediction models, integrating hormonal parameters with traditional severity scores, represents an intriguing avenue for future research. Such models could enhance early warning systems and guide resource allocation in critical care settings.

Limitations

Several limitations warrant acknowledgment. The relatively small sample size, particularly in the non-NTIS group (n=24), may have limited the statistical power to detect clinically meaningful differences. The single-center, retrospective design restricts generalizability and introduces potential selection bias. Additionally, the absence of long-term follow-up prevents assessment of the effects of NTIS on hospital mortality and functional outcomes.

Furthermore, unmeasured confounders, including nutritional status, medication effects, and genetic polymorphisms affecting thyroid hormone metabolism, may have influenced our results. The absence of reverse T3 measurements represents a missed opportunity to more comprehensively characterize the thyroid hormone profile in critical illness.

Conclusion

In this cohort of critically ill patients, NTIS was highly prevalent but did not independently predict ICU mortality. Instead, NTIS appeared to function as a biomarker of illness severity, correlating strongly with established severity measures while showing similar mortality rates across groups. These findings support the hypothesis that NTIS represents an adaptive response to critical illness rather than a pathological process requiring intervention.

Our results suggest that routine thyroid function testing solely for mortality prediction may not be necessary in critically ill patients. However, NTIS assessment could complement existing severity scores in clinical risk stratification, particularly when resources for comprehensive monitoring are limited. The development of integrated assessment tools incorporating thyroid function alongside traditional severity scores could enhance prognostic accuracy and guide clinical decision-making in critical care settings.

Future research should focus on prospective multicenter studies with sufficient power to detect clinically meaningful differences, serial hormone measurements to clarify temporal relationships, and mechanistic investigations to advance our understanding of NTIS pathophysiology. Only through such comprehensive approaches can the role of thyroid dysfunction in critical illness be fully elucidated, thereby optimizing patient care.

Ethics Committee Approval: Ethics committee approval was obtained from the Ankara University Human Research Ethics Committee Ethics Committee (Approval No: I01-73-24, Date: 06.02.2024).

Informed Consent: Informed consent was obtained from all study participants.

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