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ORIGINAL RESEARCH

Non-thyroid disease syndrome: a strong prognostic predictor of death in patients with pneumonia

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Abstract

Introduction: Non-thyroid disease syndrome (NTDS) is a common syndrome in critical diseases and is characterized by below-normal levels of free T3 (fT3) and free T4 (fT4) in the absence of primary thyroid gland pathology. Pneumonias are a group of respiratory system infections that are associated with a high incidence of mortality. Rapid biomarkers are needed to determine the diagnosis and prognosis in patients with pneumonia to optimize treatment potential. This study investigated the effect of changes in thyroid hormone and procalcitonin (PCT) levels on prognosis and mortality in patients with pneumonia.

Method: This study was conducted as a retrospective observational study in a tertiary hospital. Between 2019 and 2020, 1118 patients with pneumonia were included in the study. For all participants, PSI scores were calculated and disease severity was determined according to these scores. Patient demographic and disease data were recorded.

Discussion and Conclusion: Low fT3 hormone levels in patients diagnosed with pneumonia upon arrival at the emergency department had an important effect on prognosis. Our results indicated that fT3 levels had a reliable predictive effect on prognosis, disease severity, and mortality. In addition, we found that fT3 was superior to PCT in predicting mortality.

Keywords

Emergency Service; Pneumonia; Euthyroid Sick Syndromes; Diagnosis

1. Introduction

Non-thyroid disease syndrome (NTDS) is defined as the detection of free T3 (fT3) or free T4 (fT4) levels below normal in patients with conditions not characterized by primary pathology in the thyroid gland. Thyroid-stimulating hormone (TSH) levels may be normal, high, or low in this condition [1]. NTDS can occur frequently in chronic diseases such as chronic heart failure, chronic kidney failure, and malignancies. In critical diseases, it is established that changes occur on the hypothalamo-hypophyseal axis due to the body's pro-inflammatory response to the disease [2, 3]. During a critical disease process, the body decreases thyroid hormone levels by both central and peripheral mechanisms, causing changes in the metabolism and transfer of thyroid hormones and leading to the low fT3 and fT4 levels that characterize NTDS. This is the most-seen endocrine pathology in critical patients [5]. Research has shown that as the critical disease increases its severity, fT3 and fT4 levels continue to decrease gradually [6] due to an adaptive reaction that arises to prevent the usage of excessive energy, even in mild-severity illnesses [2].

With its high mortality rate, pneumonia is considered the most serious of all respiratory tract infections. It is the sixth leading cause of death worldwide and is the leading cause of infectious disease-related death. The mortality rate is between 1% and 5% in the outpatient setting, 12% in patients admitted to the hospital, and 40% in patients in the Intensive Care Unit (ICU) [3].

As preventive medicine measures have developed, survival rates in patients with pneumonia have increased. With new advances in medicine have come the development of new parameters that quantify the pneumonia disease process. CURB-65 and the Pneumonia Severity Index (PSI) are commonly used to assess the clinical process of pneumonia, though the accuracy of these scoring parameters is debated.

In healthy individuals, a normal serum procalcitonin (PCT) concentration is below 0.1 ng/mL; any infectious or inflammatory damage can increase this value [3, 4]. In patients with community-acquired pneumonia and lower respiratory tract infections, PCT is a useful and trustworthy method of both predicting prognosis and following the disease process [1, 3, 7].

The changes that occur to thyroid hormone levels as a result of NTDS can potentially play a role in clinical decision-making

in patients with critical illness. As the first contact of a critically-ill patient with medical care usually occurs in the emergency department (ED), strong measures for aiding in the decision-making process regarding outcomes, illness severity, and risk of mortality are necessary [8]. Thus, a strong argument is made for assessing if thyroid hormone levels can be used in the ED as prognostic indicators in patients with critical illness.

The purpose of this study was to investigate the effectiveness of using measures of thyroid hormone levels in the diagnostic process for patients with pneumonia. We aimed to contribute to the literature on NTDS, which thus far has not been widely reported on, and to accelerate the diagnosis and treatment process of critical patients. Toward this goal, a retrospective study of thyroid function tests and PCT levels of patients diagnosed with pneumonia and admitted to the ICU or non-critical care was performed.

2. Material and method

2.1 Study design

This was a descriptive study performed retrospectively in a single center that accepts 300,000 patients annually. The setting was a university-affiliated tertiary care center located in a city of 5.5 million people.

2.2 Study setting

Medical records of patients diagnosed with pneumonia between January 1, 2019, and January 1, 2020, were analyzed.

2.3 Inclusion criteria

Patients aged 65 years and older diagnosed with pneumonia in the ED were included in the study.

2.4 Exclusion criteria

Patients younger than 65 years of age, with a history of thyroid disease (including biopsy and surgery), and patients on medications that affect serum thyroid hormone levels were excluded from the study. Patients with missing data were excluded as well.

Of 1,761 patients, 571 were excluded due to inadequate data or unknown outcome. Seventy-two patients who received dopamine therapy in their previous care were excluded due to the effect of dopamine on fT3 levels. A final sample population of 1,118 patients was included in the study.

2.5 Data collection

The hospital's database was scanned for cases that included a pneumonia diagnosis and the electronic medical record was used to gather information on antecedent illnesses, laboratory results, and prognosis. The results of PCT and thyroid examinations performed on the patients in the ED were evaluated. The amount of time that elapsed between the patients' arrival at the ED and the time of the laboratory tests was not measured.

Patient outcome was recorded for all patients, described as the destination of the patient from the ED, either to inpatient, intensive, or outpatient care. Admission to the ICU was determined by the intensive care specialist, and admission to non-critical inpatient care and discharge were determined by the pulmonologist.

2.6 Limitations

Patients aged 65 or over were included in the study. Patients without a previous thyroid disorder diagnosis, patients without a history of thyroid operation including biopsy, and patients with missing data were excluded. Information regarding patient vaccination status could not be obtained. In addition, some medical records were unclear regarding the initial onset of symptoms and the duration of disease onset before arrival at the ED, which limited certain calculations. Since our retrospective study was outside the COVID-19 pandemic period, there were no COVID-19 pneumonia patients in our study.

2.7 Biochemical parameters

All patients underwent laboratory testing. For the purposes of our study, the results of leukocyte, thrombocyte, PCT, and thyroid function tests were evaluated and their relationship with patient prognosis was investigated.

2.8 Statistical analysis

The data obtained were analyzed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, USA) software. Frequency distributions for categorical variables and descriptive measures for numeric variables including average and standard deviation were given. As the data did not conform to a normal distribution, the Mann-Whitney U test was used to determine a difference between two independent groups, and the Kruskal-Wallis test was used to determine a difference between more than two independent groups. Bonferroni correction was used to determine the groups that made the difference. A P value below 0.05 was considered statistically significant. Roc analysis was performed to determine the most suitable threshold values for PCT and fT3. A threshold value for PCT above 0.3 ng/mL for both mortality and ICU admission and a threshold value for fT3 below 2.3 ng/dL for mortality and 1.8 ng/dL for ICU admission were determined. The threshold value for thrombocytes of 150,000 was determined based on laboratory reference. We categorized these continuous variables based on the determined threshold values. Binary logistic regression analysis was then performed to investigate fT3, PCT, and thrombocyte levels as predictors for ICU admission and mortality. A multivariate regression model was established using PCT, fT3, and thrombocyte levels for predicting mortality and PCT and fT3 levels for predicting ICU admission.

3. Results

This study included 1118 patients above the age of 65. Of these, 190 (17.0%) were discharged and referred to an outpatient setting, 878 (78.6%) were admitted to non-critical inpatient care, and 50 (4.4%) were admitted to the ICU. Eighty-two (7.3%) of the 1118 patients died as a result of their illness.

When the relationship between laboratory values and mortality was examined, it was found that fT3, PCT, and thrombocyte levels were associated with mortality. Levels of fT4 and

leukocytes were not associated with mortality (Table 1).

TABLE 1. Evaluation of Thyroid hormones, Procalcitionin, Platelet and WBC according to survival status.

Test Name	Mortality	Mean (SD)	*P*
T3	No	2.209 (1.035)	**< 0.01**
	Yes	1.342 (0.642)	
T4	No	1.202 (0.260)	0.636
	Yes	1.145 (0.377)	
Procalsitonin	No	2.185 (6.958)	**< 0.01**
	Yes	20.352 (27.020)	
Platelet	No	260.302 (122.826)	**< 0.01**
	Yes	187.242 (114.499)	
WBC	No	13.185 (8.024)	0.733
	Yes	12.832 (8.146)	

Binary logistic regression analysis indicated that a PCT level above 0.3 ng/mL, fT3 level below 2.3 ng/dL, and thrombocyte level below 150000 were statistically significant predictors of mortality (Table 2). The success of PCT, fT3, and thrombocyte levels in predicting mortality was calculated as 92.9% using the multivariate logistic regression model.

TABLE 2. Multivariete regression model as a predictor of mortality.

Variable	*P*	Odds ratio	95% CI
Trombosit < 150000	0.027	2.371	1.102–5.103
T3 < 2.3	0.003	5.095	1.754–14.799
Prokalsitonin > 0.3	0.001	3.883	1.714–8.797

When the relationship of the laboratory parameters with patient hospitalization status was examined, fT3, PCT, and thrombocyte levels were associated with admission to both non-critical care and the ICU (Table 3).

In the paired comparison, fT3, PCT, and thrombocyte levels were found to be significant predictors of ICU admission (Table 4). Binary logistic regression analysis indicated that a PCT above 0.3 ng/mL and fT3 below 1.85 ng/dL were significant in predicting ICU admission. Thrombocyte level, on the other hand, was excluded from the model as a confounding factor because it was insignificant in the multivariate regression model, although it was significant on its own. PCT above 0.3 ng/mL and fT3 below 1.8 ng/dL were found significant in predicting admission to the ICU. The success of PCT and fT3 in predicting intubation was found to be 96.1% using the multivariate logistic regression model (Table 5).

4. Discussion

Community-acquired pneumonia is one of the most frequent diseases requiring hospitalization as well as a significant cause of mortality worldwide. Rapid diagnosis and determination of the prognosis in these patients are vitally important [8].

It has been well-documented that in critical diseases there are certain changes on the hypothalamo-hypophyseal axis related to the body's pro-inflammatory response [2, 3]. NTDS is the most frequent endocrinologic pathology seen in critical diseases [5].

The theory that the hormonal changes that occur as a result of NTSD can predict the prognosis in critical diseases is still controversial [9, 10]. Some studies have shown a correlation between low T3 and T4 levels in critical pediatric and geriatric patients [9, 11]. On the other hand, other studies have not found fT3 and fT4 levels as predictive of patient prognosis before hospitalization [12].

In this study, pneumonia severity was evaluated by PSI score and the decision to admit (non-critical or ICU) or discharge was made based on the determination of severity. The results indicated that fT3 levels were significantly lower in patients admitted to the ICU than in patients admitted to non-critical care or discharged. Based on this result, we can infer that as the severity of the disease process increases, fT3 levels continue to decrease. Similar results were not found for fT4 levels. In a study conducted by Liu *et al.* [13], serum fT3 levels were found to be a prognostic factor for predicting ICU admission. Based on the results of our study, fT3 levels measured in the ED may provide some guidance in the decision to admit or discharge patients with pneumonia.

In the literature, multiple studies have investigated the relationship between thyroid testing and critical diseases, though our study was the first to detect a relationship between thyroid hormone levels and disease severity in patients diagnosed with pneumonia.

In the prospective study by Neamtu *et al.* [14] on 65 children with sepsis, T3 and T4 levels were found to be low in 63% of the patients. In a study conducted by Lodha *et al.* [12] that evaluated 24 children either with sepsis or in septic shock, lower fT3, fT4, and TSH levels were found in patients in septic shock compared to patients in a less severe septic state. A systematic review by Angelousi *et al.* [15] found that reduced thyroid hormone levels were caused by critical diseases and could be used as a prognostic indicator of disease severity. The results of our study are in agreement with previous research.

Thyroid hormones have also been found to play a significant role in predicting mortality. Levels of T3 in particular provide important prognostic information. In our study, when comparing fT3 levels in patients who died and patients who survived, a statistically significant decrease in fT3 level was found in patients who died of their illness. No statistically significant difference was present in fT4 values. In a study by Liu *et al.* [13] on patients with community-acquired pneumonia, low T3 levels were found to be an independent prognostic indicator of mortality within 30 days. Peeters *et al.* [16] detected low T3, T4, and TSH levels and high fT3 levels in cases of mortality. Meyer *et al.* found lower T3 and T4 levels only in cases of mortality and in follow-up measurements [1]. Slag *et al.* [17], in their study on critical patients, identified low T3 and T4 values as important prognostic indicators. In our study, contrary to the literature, thyroid test values obtained at first contact in the ED were predictive of mortality; thus, low fT3 levels could be used as a prognostic tool for mortality risk and guide follow-up care in critical patients.

A myriad of criteria is used to predict the prognosis of

TABLE 3. Evaluation of Parameters according to the hospitalization status of the patients.

Test name	Comparison of patient outcomes	Mean (SD)	*P*
T3	Outpatient	2.294 (0.757)	**0.002**
	Inpatient	2.149 (1.085)	
	ICU	1.478 (0.874)	
T4	Outpatient	1.178 (0.284)	0.676
	Inpatient	1.204 (0.262)	
	ICU	1.150 (0.340)	
Prokalsitonin	Outpatient	1.205 (3.532)	**< 0.01**
	Inpatient	2.107 (6.252)	
	ICU	41.920 (26.318)	
Trombosit	Outpatient	280.388 (121.013)	**0.006**
	Inpatient	252.429 (124.874)	
	ICU	195.921 (75.969)	
WBC	Outpatient	14.403 (9.858)	0.106
	Inpatient	12.737 (7.549)	
	ICU	16.193 (7.199)	

TABLE 4. Paired comparison of tests related to patient outcomes.

Test name	Comparison of patient outcomes	P1	P2
T3	ICU vs Inpatient	0.013	**0.040**
	ICU vs Outpatient	0.001	**0.002**
	Inpatient vs Outpatient	0.021	0.062
Procalcitonin	ICU vs Inpatient	0.434	1.000
	ICU vs Outpatient	< 0.01	**< 0.01**
	Inpatient vs Outpatient	< 0.01	**< 0.01**
Platelet	ICU vs Inpatient	0.028	0.084
	ICU vs Outpatient	0.003	**0.008**
	Inpatient vs Outpatient	0.035	0.104

P1: comparison between outcomes.
P2: significant values have been adjusted by the Benferroni correction for multiple tests.
ICU, Intensive Care Unit.

TABLE 5. Multivariete Regression Model as a Predictor of ICU admission.

Variable	*P*	Odds ratio	95% CI
Prokalsitonin > 0.3	0.005	17.816	2.347–135.246
T3 < 1.8	< 0.001	5.757	2.254–14.709

patients with pneumonia in the ED. One of the most well-known criteria is PCT level [18]. It is not only used frequently in patients with pneumonia to determine culprit pathology but has also been used in multiple studies to ascertain the mortality risk for patients admitted to the ICU. In addition to this, it is well-established that PCT levels rise meaningfully in patients with sepsis or septic shock [19]. PCT is one of the most frequently used infectious parameters in patient follow-ups. In a wide-range multicentric cohort study, PCT levels were found to correspond with PSI and CURB-65 scores, and low levels of PCT (0.1 ng/dL) were associated with low mortality risk for patients admitted to the ICU. In our study, the relationship between increased PCT levels and mortality in patients with pneumonia appeared to correlate with other studies conducted on inpatient and ICU admission and mortality rate [7, 18, 19].

When the threshold values for PCT (>0.1 ng/dL) and fT3 were compared, fT3 was found to be significantly superior to PCT ($P < 0.01$). Our study is the first to compare these two parameters in their role of providing prognostic information in critical patients.

5. Conclusions

We detected that in patients who were diagnosed with pneumonia upon arrival at the ED, low fT3 hormone levels had an important predictive effect on prognosis, illness severity, and mortality. In addition, we found that fT3 was superior to PCT in predicting mortality. Understanding the underlying mechanism by which fT3 levels plummet in patients with pneumonia should be a goal of future research. After further studies, we think that ft3 may be a parameter indicating patient severity for patients with pneumonia presenting to the emergency department.

AUTHOR CONTRIBUTIONS

ESB and AÇ designed the study. CA, HA and SH collected the data. ESB and GY analyzed the data. ESB analyzed the results and prepared the drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee on May 12, 2020 (Number: 663).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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