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RESEARCH

# NONTHYROIDAL ILLNESS SYNDROME IN SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS IN THE ELDERLY

## ABSTRACT

***Introduction:*** Aging is often associated with decreased serum triiodothyronine levels. There is growing evidence that critical illness can cause thyroid dysfunction and nonthyroidal illness syndrome. Elderly patients with severe chronic obstructive pulmonary disease exacerbations may be more prone to thyroid function impairment. We evaluated nonthyroidal illness syndrome incidence in elderly patients with chronic obstructive pulmonary disease during severe exacerbations and the possible impact on short-term prognosis.

***Materials and Method:*** Elderly patients (≥65 years) admitted with a diagnosis of acute respiratory failure due to an acute exacerbation were included in the study. All patients were evaluated for thyroid function and its relationship with clinical outcomes.

***Results:*** Forty-four patients with a median age of 71.5 years were included. Nonthyroidal illness syndrome incidence was 65.9% (n = 29) and it was related with increased noninvasive ventilation failure rate (p=0.04). Compared with survivors, nonsurvivors had lower triiodothyronine levels (p=0.02). Only the Glasgow coma score and noninvasive ventilation failure were found to be independent predictors of hospital mortality in logistic regression analysis.

***Conclusion:*** In this study, nonthyroidal illness syndrome was found to be relatively common in elderly patients with chronic obstructive pulmonary disease having severe exacerbations. The presence of nonthyroidal illness syndrome in these high-risk patients may affect response to treatment, and eventually, outcomes.

***Key Words:*** Pulmonary Disease, Chronic Obstructive; Disease Progression, Aged; Euthyroid Sick Syndromes; Triiodothyronine; Mortality.

ARAŞTIRMA

# İLERİ YAŞ KOAH HASTALARINDA AĞIR ALEVLENMEDE NONTİROİDAL HASTALIK SENDROMU

## ÖZ

***Giriş:*** Yaşlanma genellikle serum triiodotironin seviyesinde azalma ile ilişkilidir. Ayrıca kritik hastalık varlığında tiroid disfonksiyonu ve nontiroidal hastalık sendromu geliştiğine dair kanıtlar gün geçtikçe artmaktadır. Özellikle kronik obstrüktif akciğer hastalığı olan ileri yaştaki hastalar bu durumun gelişmesi için yatkın olabilir. Bu çalışmada ileri yaştaki kronik obstrüktif akciğer hastalığı olan olgularda ağır alevlenme esnasında nontiroidal hastalık sendromu gelişim sıklığını ve kısa dönem prognoza etkilerini değerlendirmeyi amaçladık.

***Gereç ve Yöntem:*** Kronik obstrüktif akciğer hastalığı akut alevlenmesi ile akut solunum yetmezliği gelişen yaşlı hastalar (≥65yaş) çalışmaya dahil edilmiştir. Hastaların demografik ve klinik özellikleri ile hastane başvurusundaki tiroid fonksiyonları kaydedilmiş ve klinik sonuçlara etkisi değerlendirilmiştir.

***Bulgular:*** Kırk dört hasta (ortanca yaş 71,5) çalışmaya dahil edilmiştir. Nontiroidal hastalık sendromu görülme sıklığı %65,9 (n=29) olarak bulunmuştur ve nontiroidal hastalık sendromu olan hastalarda noninvaziv ventilasyon başarısızlığı daha sık saptanmıştır (p=0,04). Sağkalan hastalar ile karşılaştırıldığında ölen hastaların ortanca triiodotironin seviyelerinin daha düşük olduğu görülmüştür (p=0,02). Hastane mortalitesi için yapılan lojistik regresyon analizinde sadece Glasgow koma skoru ve noninvaziv ventilasyon başarısızlığı bağımsız faktörler olarak bulunmuştur.

***Sonuç:*** Bu çalışmada ileri yaştaki kronik obstrüktif akciğer hastalığı ağır alevlenmesinde nontiroidal hastalık sendromu varlığı sık saptanmıştır. Yüksek riskli gruplarda nontiroidal hastalık sendromu tedaviye yanıtı ve dolayısı ile klinik sonuçları etkileyebilir.

***Anahtar Sözcükler:*** Kronik Obstrüktif Akciğer Hastalığı; Alevleme; Yaşlı; Nontiroidal Hastalık Sendromu; Triiodotironin; Mortalite.

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## Introduction

Aging is an important factor associated with impaired thyroid function, and several changes in thyroid hormone secretion, metabolism, and action occur with increasing age (1). Impaired thyroid function can present as subclinical hypothyroidism, overt hypothyroidism, and nonthyroidal illness syndrome (NTIS). Nonthyroidal illness syndrome is characterized by low serum triiodothyronine (T3) levels with normal or low thyroid stimulating hormone (TSH) levels. It is relatively common in elderly patients, with an incidence of approximately 32%–62% in the hospitalized geriatric population (2-4). The serum T3 level is accepted as a prognostic biomarker for acutely ill elderly patients and is reported to be the most sensitive independent predictor for short-term mortality (2). Alterations in thyroid function during hospitalization have been associated with long-term mortality in elderly patients (3). Therefore, clinical consequences of thyroid dysfunction should be well defined in elderly patients at a higher risk of death.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, resulting in premature death because of its complications (5). It's expected to be the third cause of death in 2020. Chronic obstructive pulmonary disease is now considered to be a systemic disease because of ongoing systemic chronic inflammation. Several effects occurring outside the lungs are often associated with extrapulmonary abnormalities and have been described as systemic effects of COPD. Cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, diabetes, osteoporosis, depression, and lung cancer are the most commonly described comorbid conditions. Among endocrinological disorders, thyroid abnormalities are often observed in patients with COPD (6,7). Impaired thyroid function can present as subclinical hypothyroidism, overt hypothyroidism, and NTIS. Of these, NTIS is the most common issue observed in COPD, reported in 20% of stable patients and 70% of patients experiencing an exacerbation (8). However, there are limited data regarding the impact of NTIS in patients with COPD having severe exacerbations.

Low T3 levels are now accepted as a predictor for poor outcomes during critical illness (9). Here we evaluated NTIS incidence in elderly patients with COPD during critical illness and its correlation with short-term prognosis.

## Methods

### Patients

The study was approved by local ethics committee. Elderly patients (≥65years) admitted to the intensive care unit (ICU) with a diagnosis of acute respiratory failure due to COPD exacerbation were included into the study between May 2011 and January 2013. Patients with a known history of thyroid disease, patients previously administered drugs that may affect thyroid function (oral corticosteroids, amiodarone, and lithium), and patients who stayed in ICU for <24 h were excluded. The study flowchart is presented in Figure 1. Patients' demographic characteristics and clinical characteristics including pulmonary function tests from within the previous year (if available), Glasgow coma score (GCS), acute physiology and chronic health evaluation (APACHE) II score, blood gas values, mechanical ventilatory support, length of stay in the ICU and hospital, and hospital mortality were recorded.

### Mechanical Ventilation Support

After ICU admission all patients required mechanical ventilatory support due to hypercapnic respiratory failure. Mechanical ventilation support was initiated either invasively or noninvasively according to the degree of respiratory failure and the patient's clinical condition. Invasive mechanical ventilation was initiated if intubation was necessary. Noninvasive ventilation (NIV) was performed by experienced ICU staff using pressure support with an oronasal mask. NIV failure was defined as requiring endotracheal intubation at any time.

### Thyroid Function Assessment

Thyroid function assessment was performed within the first 24 h of admission to ICU. Venous blood serum was separated, serum levels of free T3, free thyroxine (T4), and TSH were determined using an immunoassay (Advia Centaur, Siemens). The normal ranges were considered to be 2.30–4.20 pg/mL for T3, 0.74–1.52 pg/mL for T4 and 0.55–4.48 μIU/mL for TSH. NTIS was diagnosed according to the *Turkish Society of Endocrinology and Metabolism* guideline (10) and defined as decreased serum T3 levels with normal or decreased TSH levels.

### Statistical Analysis

The primary study outcome was the frequency of NTIS in severe exacerbations in elderly patients with COPD. Secondary outcomes were NIV failure, length of ICU and hospital stay,

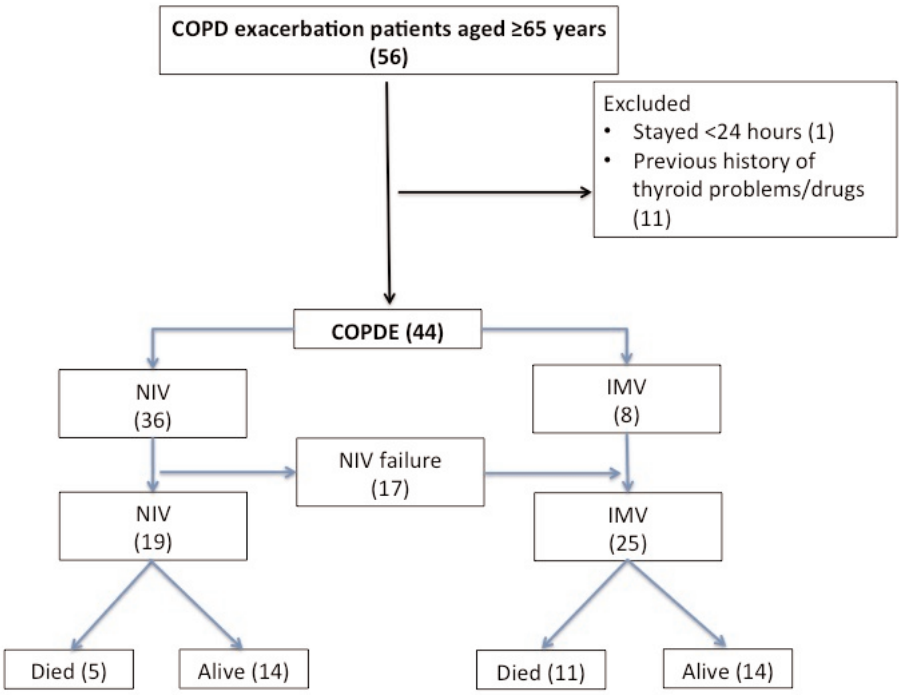


**Figure 1—** Study flowchart.

and hospital mortality. All continuous variables were expressed as medians with interquartile range (IQR). For bivariate analysis, categorical variables were compared using the chi-square test and continuous variables were compared using the Mann–Whitney U test. Logistic regression analysis with backward elimination was used to obtain independent predictors for hospital mortality. A two-sided p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows program, version 17 (SPSS Inc., Chicago, IL, USA).

## Results

Forty-four patients >65 years were included in the study; their general characteristics are presented in Table 1. The median age was 71.5 (63.5–77.8) years. Spirometric measurement was available in the medical records of 23 patients, and all patients had airflow obstruction with a median forced expiratory volume in 1 sec (FEV1) of 0.83 L. The most common comorbidities were hypertension (61.4%) and congestive heart failure (50%). All patients had severe hypercapnic respiratory failure during admission with a median partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 73.8 (62.0–84.0) mmHg and a pH of 7.26 (7.19–7.33). In 36 patients, initial ventilatory support was with NIV; among them, 17 required intubation during follow-up. The median T3 level of the study population was 1.93 (1.60–2.38) pg/ml, and T3 levels were below normal in 29 patients. There was a negative correlation between T3 levels and APACHE II score (r=-0.491, p=0.008; Figure 2). However there was no association between T3 levels and the partial pressure of oxygen in arterial blood ($PaO_2$; data not shown). Intubated patients (n=25) had lower T3 levels than patients with NIV (1.8 vs 2.31).

Nonthyroidal illness syndrome incidence in the study population was 65.9% (n=29). Six patients had low serum T4 levels and these patients had significantly higher APACHE II scores (41 vs 23; p=0.014). Bivariate analysis between NTIS positive and negative groups is shown Table 2. Median (IQR) T3 levels were 1.8 (1.3–1.9) pg/mL in the NTIS positive group, whereas they were 2.6 (2.3–2.8) pg/mL in the NTIS negative group. On admission, NTIS positive patients had a lower pH than NTIS negative patients [7.22 (7.15–7.30) and

**Table 1—** General Characteristics of The Study Population (n = 44)

| | |
|---|---|
| Male gender | 32 (72.7) |
| Age (years) | 71.5 (65.5–77.8) |
| Smoking history | |
| Smokers | 9 (20.5) |
| Ex-smokers | 23 (52.3) |
| Never smokers | 12 (27.3) |
| FEV1* | |
| Liters | 0.85 (0.58–1.26) |
| % of predicted | 31.7 (19.6–42.6) |
| GCS | 15 (8–15) |
| APACHE II score | 24 (18–34) |
| Admission arterial blood gases | |
| pH | 7.26 (7.19–7.33) |
| $PaCO_2$ (mmHg) | 73.8 (62.0–84.0) |
| $PaO_2$ (mmHg) | 52.5 (39.4–64.6) |
| Thyroid function | |
| T3 (pg/mL) | 1.93 (1.60–2.38) |
| T4 (pg/mL) | 1.04 (0.90–1.22) |
| TSH (μIU/mL) | 0.68 (0.18–1.25) |
| Presence of NTIS | 29 (65.9) |
| Initial ventilatory support | |
| Noninvasive | 36 (81.8) |
| Invasive | 8 (18.2) |
| NIV failure | 17 (38.6) |
| Length of ICU stay (days) | 15.0 (9.5–22.5) |
| Length of hospital stay (days) | 16.0 (11.5–24.0) |
| Hospital mortality | 16 (36.4) |

*Available in 23 patients.

7.31 (7.28–7.36) respectively, p=0.01]. Patients with NTIS had a higher NIV failure than patients without NTIS (60.9% and 23.1% respectively; p = 0.04). There were no statistically significant differences between the two groups for the length of ICU and hospital stay or hospital mortality.

Sixteen patients (36.4%) died during their hospital stay. Table 3 shows the characteristics of survivors and nonsurvivors. Compared with survivors, nonsurvivors had lower GCS scores [15 (14.5–15.0) vs 8 (4.5–12.5); p<0.01], higher APACHE II scores [20 (16–27) vs 27 (23–41); p=0.02], a higher NIV failure rate (21.4% vs 68.8%; p < 0.01) and lower T3 levels [2.0 (1.73–2.55) vs 1.8 (1.13–2.0) pg/mL; p=0.02]. Only GCS score and NIV failure were found to be independent predictors of hospital mortality in logistic regression analysis (Table 4).

## Discussion

There is growing evidence that critical illness causes thyroid dysfunction. We hypothesized that elderly patients

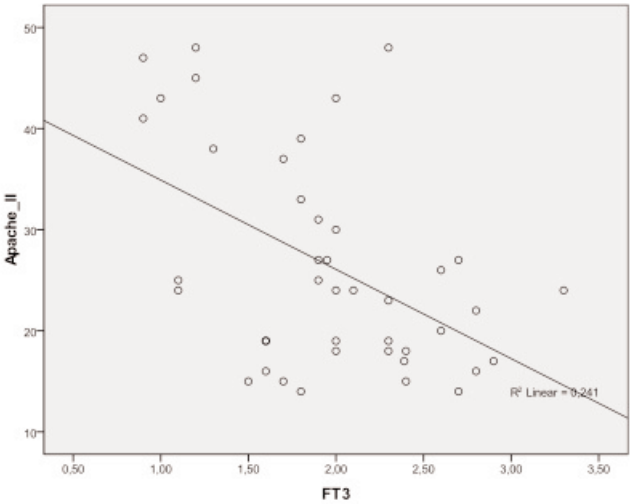


**Figure 2—** Negative correlation between T3 levels and APACHE II (r = -0.491; p < 0.01)

with COPD who are critically ill due to a severe exacerbation may be more prone to thyroid function impairment. In this study, we found that NTIS was relatively common (65.9%) in this patient population. Nonthyroidal illness syndrome incidence has been reported to be as high as 60%–70% in critically ill patients (11). Plikat et al reported NTIS incidence to be 44.1% in medical ICUs, and in another study by Wang et al low levels of thyroid hormones were found in nearly half of the patients (9,12).

Thyroid dysfunction in pulmonary diseases has been studied less. NTIS incidence was approximately 50% in patients with respiratory failure in one study (13). With regard to patients with COPD, there are different incidence rates for stable periods and exacerbations; however, most studies show that exacerbations result in decreased T3 levels (8,14). A study performed by Karadag et al reported that NTIS incidence was 20% in patients with stable phase COPD; however, it was 70 % in patients with exacerbations (8). Reportedly, average T3 levels were lower in patients with COPD exacerbations than in both stable COPD cases and controls (14). Another study demonstrated that thyroid function was restored after the exacerbation resolved (15). These data show that COPD exacerbations are disease periods characterized by prominent thyroid dysfunction. Significant inflammatory responses may be responsible for changes in the neuroendocrine axis and hormonal profile, which could cause a decrease in T3 levels during exacerbations.

**Table 2—** Bivariate Analysis of Patients According to Presence of NTIS

| | NTIS (-) n=15 | NTIS (+) n=29 | p |
|---|---|---|---|
| GCS | 15 (15–15) | 11 (6–15) | 0.01 |
| APACHE II score | 19 (17–24) | 27 (19–39) | 0.02 |
| Admission arterial blood gases | | | |
| pH | 7.31 (7.28–7.36) | 7.22 (7.15–7.30) | 0.01 |
| $PaCO_2$ (mmHg) | 77.0 (62.0–86.1) | 71.8 (61.3–83.9) | 0.68 |
| $PaO_2$ (mmHg) | 49.4 (43.2–67.3) | 53.0 (38.5–64.1) | 0.76 |
| Initial ventilatory support | | | |
| Noninvasive | 13 (86.7) | 23 (79.3) | 0.70 |
| Invasive | 2 (13.3) | 6 (20.7) | |
| NIV failure | 3 (23.1) | 14 (60.9) | 0.04 |
| T3 (pg/mL) | 2.60 (2.30–2.80) | 1.80 (1.25–1.93) | <0.01 |
| T4 (pg/mL) | 1.23 (1.16–1.34) | 0.98 (0.82–1.10) | <0.01 |
| TSH (μIU/mL) | 0.52 (0.14–1.36) | 0.73 (0.19–1.04) | 0.85 |
| Hospital mortality | 3 (20.0) | 13 (44.8) | 0.19 |

**Table 3—** Bivariate Analysis According to Hospital Mortality

| | Survivors n = 16 | Nonsurvivors n = 28 | p |
|---|---|---|---|
| Male gender | 11 (68.8) | 19 (65.5) | 0.73 |
| Age (years) | 74.0 (66.5–79.5) | 71.0 (62.0–74.0) | 0.09 |
| GCS | 8 (4.5–12.5) | 15 (14.5–15) | <0.01 |
| APACHE II score | 20 (16–27) | 27 (23–41) | 0.02 |
| Admission arterial blood gases | | | |
| pH | 7.23 (7.20–7.35) | 7.28 (7.19–7.33) | 0.62 |
| $PaCO_2$ (mmHg) | 76.6 (63.4–86.6) | 73.4 (60.9–81.2) | 0.40 |
| $PaO_2$ (mmHg) | 51.7 (39.0–61.3) | 54.2 (40.2–66.5) | 0.57 |
| Initial ventilatory support | | | |
| Noninvasive | 11 (68.8) | 25 (89.3) | 0.12 |
| Invasive | 5 (31.3) | 3 (10.7) | |
| NIV failure | 11 (68.8) | 6 (21.4) | <0.01 |
| Length of ICU stay (days) | 17.5 (12.3–35.0) | 13.0 (9.0–20.5) | 0.25 |
| Length of hospital stay (days) | 17.5 (12.3–35.0) | 15.0 (11.0–22.0) | 0.24 |
| NTIS | 13 (81.3) | 16 (57.1) | 0.19 |
| T3 (pg/mL) | 1.80 (1.12–2.00) | 2.0 (1.73–2.55) | 0.02 |
| T4 (pg/mL) | 0.98 (0.73–1.17) | 1.12 (0.92–1.28) | 0.12 |
| TSH (μIU/mL) | 0.53 (0.22–1.80) | 0.72 (0.16–1.03) | 0.59 |

**Table 4—** Independent Factors for Hospital Mortality

| | Odds ratio | 95% Confidence Interval | p |
|---|---|---|---|
| APACHE II score | 0.92 | 0.81–1.05 | 0.26 |
| GCS | 0.72 | 0.53–0.98 | 0.04 |
| NIV failure | 36.3 | 3.23–408.10 | <0.01 |
| T3 | 0.19 | 1.02–2.32 | 0.19 |

Our study indicates that there was a negative correlation between T3 and APACHE II score. These results are similar to previously reported data in the literature; the study performed by Plikat et al showed that patients with reduced serum T3 had the highest APACHE II scores (12). Furthermore, examining thyroid hormone levels in addition to calculating the APACHE score may improve the prediction of mortality for patients in ICU (16). In the present study NTIS was associated with lower GCS and higher APACHE II scores. These scores are considered to be important measures of disease severity and predictors of outcomes in critical illness. Similar to other critical states, clinicians should consider that patients with COPD with high APACHE II scores and low GCS have a higher risk of NTIS during exacerbations.

Previous data have shown that the degree of hypoxemia is correlated with the T3/T4 ratio in patients with COPD (17). In our study, all patients were hypoxemic and either noninvasively or invasively required mechanical ventilatory support; however, we could not identify a correlation between the degree of hypoxemia and T3 levels. This may be because most of our patients had severe COPD with a predicted FEV1 <30% and were probably chronically hypoxemic.

Low T3 levels and the presence of NTIS have been reported as predictors of outcomes in respiratory failure (13,18). We found that NTIS was associated with lower pH and an increased NIV failure rate. The correlation between thyroid impairment and respiratory failure was evaluated in different patient populations. Plikat et al evaluated 247 (33.2%) of 743 patients in ICU whose thyroid hormone test results were available and found that impaired thyroid function was more common in mechanically ventilated patients than in those without mechanical ventilation (12). For respiratory failure cases, presence of NTIS increased invasive mechanical ventilation requirement (13). Other studies showed that NTIS was correlated with prolonged ventilation (19,20). All these studies evaluated invasive mechanical ventilation. However, in our study most patients were under NIV, and this is the first study evaluating the correlation between NTIS and NIV failure. Thyroid hormones are critical determinants of metabolic activity in adults, and they can regulate metabolic rate and, particularly, respiratory drive. The impaired respiratory drive in patients with a low T3 status may result in NIV failure.

Hospital mortality in COPD exacerbation was found to be 36.4% in this study. Hospital mortality in patients with COPD exacerbations is approximately 11%–24%; however, it is increased seven-fold in severe exacerbations (21). Reportedly, age is an additional risk factor for mortality; in one study, patients with COPD>75 years had increased mortality (22). Another factor associated with increased hospital mortality is the requirement for mechanical ventilation support: mortality is increased to 25% in patients who need NIV support. High mortality rate in our study may be associated with the coexistence of additional risk factors such as severe exacerbation, increased age, and mechanical ventilation requirement.

Nonsurvivors had lower GCS and higher APACHE II scores, a higher NIV failure rate, and lower T3 levels. In the logistic regression model for hospital mortality, only GCS score and NIV failure were independent predictors for mortality. NIV failure is accepted as a major risk factor for increased mortality in COPD exacerbations (23). In the European COPD audit study, the risk factors for hospital mortality were older age, presence of acidotic respiratory failure, subsequent ventilatory support requirement, and presence of comorbidity (24). Our study population had most of those factors associated with mortality. Low GCS is considered to be a risk factor for NIV failure. For elderly hypercapnic respiratory failure cases with NIV, a GCS of >9 points is associated with a better survival (25).

Our study has several limitations. First, the study was performed with a limited number of patients in one center. Second, we only included elderly patients; therefore, there was no comparison with younger patients with COPD. However, comparison with younger patients is not easy because COPD is a progressive disease and most patients with severe COPD are >65 years. Third, we did not evaluate survivors after exacerbation for reversal of thyroid dysfunction.

However, we believe that our study has important strengths. This is the first study evaluating the effect of NTIS on NIV therapy in a geriatric population. In addition, all patients had a severe COPD exacerbation with acute respiratory failure; therefore, we are confident that our sample represents critically ill elderly patients. Last, COPD will be one of the major cause of death worldwide in future years and we think that our results have great value for the management of elderly COPD patients.

In conclusion, we suggest that the presence of NTIS may have an adverse effect on outcomes in elderly patients with severe COPD exacerbations. Whether the low T3 level in these conditions is an adaptive physiologic response or a result of a maladaptive state is yet unclear. Because there is no evidence for tissue hypothyroidism to date, thyroid replacement therapy is not advised. However, it should be considered that the magnitude of these changes is associated with the underlying disease severity, and further studies are required to evaluate the significance of NTIS in the critically ill elderly population.

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