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Thyroid hormone as a clinical predictor in acute exacerbation of COPD: Relationship with %FEV1, exacerbation severity, and hospital stay duration

Yanuar,[1]* Hendrastutik Apriningsih,[1] Ana Rima Setijadi,[2] Reviono,[1] Artrien Adhiputri[2]

[1]Pulmonology and Respiration Medicine Department, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia
[2]Pulmonology Department, Dr. Moewardi Hospital, Surakarta, Indonesia

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***Corresponding author:**
yanuarabdulhay@gmail.com

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Original Article

ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of mortality worldwide. Acute Exacerbations of COPD (AECOPD) significantly impact patient outcomes and healthcare costs. Thyroid hormone dysregulation has been proposed as a potential systemic effect of AECOPD. However, the relationship between thyroid hormones and AECOPD clinical predictors, such as %FEV1, exacerbation severity, and hospitalization duration, remains unclear.
Objective: This study aimed to investigate the relationship between thyroid hormones and key clinical predictors in patients with Acute Exacerbation of COPD (AECOPD), including %FEV1, exacerbation severity, and Length of Stay (LOS).
Method: This is a cross-sectional study which included 32 patients admitted for AECOPD from November 2023 to January 2024 at Sebelas Maret University Hospital. Thyroid function was assessed by measuring serum levels of Thyroid-Stimulating Hormone (TSH), Free Triiodothyronine (FT3), and Free Thyroxine (FT4). We evaluated the association between thyroid hormone levels and Forced Expiratory Volume in 1 second (FEV1), severity of exacerbation, and Length of Stay (LOS).
Results: The study found a significant positive correlation between FT3 and %FEV1 (r=0.414, p=0.019), indicating a relationship between higher FT3 and better lung function. A significant negative correlation was observed between FT3 and exacerbation severity (r=-0.506, p=0.003), then FT3 and LOS (r=-0.350, p=0.050). FT4 also negatively correlated with exacerbation severity (r=-0.367, p=0.039). The optimal cut-off for FT3 to predict severe exacerbation was <2.65 pmol/L, with a sensitivity of 80.8% and specificity of 100%.
Conclusion: The study indicates a significant relationship between thyroid hormones, particularly FT3, and clinical outcomes in AECOPD patients. These findings suggest that thyroid hormone assessment could be useful in predicting the severity of acute COPD exacerbations, contributing to more targeted management strategies.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide, with Acute Exacerbations (AECOPD) significantly contributing to the healthcare burden.[1–3] Acute exacerbations are characterised by a sudden worsening of respiratory symptoms that often necessitate hospitalisation.[1] These episodes lead to increased healthcare costs and reduced quality of life for patients.[4,5]

Thyroid hormones are crucial in regulating metabolism, muscle function, and cellular growth.[6,7] Thyroid dysfunction may lead to systemic effects, impacting various physiological processes and it might influence COPD due to its role in regulating energy metabolism and muscle

strength.[8–10] Additionally, COPD patients often experience systemic inflammation, which might impact thyroid hormone levels.[5,10,11] Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-1 (IL-1) are known to be elevated in COPD, and these pro-inflammatory cytokines can disrupt thyroid function by inhibiting the synthesis and secretion of TSH and altering the conversion of Thyroxine (T4) to Triiodothyronine (T3).[8,11]

Recent studies have indicated a possible relationship between thyroid dysfunction and COPD.[9] Other studies found that non-thyroidal illness syndrome (NTIS) is common amongst patients with AECOPD, suggesting a potential link between systemic inflammation in COPD and thyroid function.[10,12] Previous research showed a correlation between thyroid hormone levels and COPD outcomes, such as increase in exacerbation frequency and prolonged intubation.[7,8] Given these findings, knowledge about prognosis of disease and factors that predict poor outcome is important to help physicians to advise patients regarding the expected natural course of an illness.[13]

This study aims to investigate the correlation between thyroid hormone levels and key clinical outcomes in patients with acute exacerbation of COPD, focusing on the association with lung function (FEV1), exacerbation severity, and duration of hospital stay. This research is essential to be conducted as current COPD management strategies do not routinely consider thyroid function as a contributing factor to exacerbations. Evaluating thyroid hormone levels in COPD patients may help identify individuals at higher risk of severe exacerbations. Additionally, this study could pave the way for future research into targeted therapeutic interventions, potentially improving clinical outcomes for patients with both COPD and thyroid dysfunction. This study contributes to improving early detection and personalised management strategies, which align with Indonesia's public health goals and the Sustainable Development Goals (SDGs), particularly SDG 3 (Good Health and Well-Being). A better understanding of the interplay between thyroid function and COPD may support the development of more effective healthcare policies and interventions, ultimately reducing the burden of chronic respiratory diseases in Indonesia.

METHODS

Research Methods

This study was an observational analytic study with a cross-sectional approach. It examined the relationship between TSH, FT3, FT4 levels, and the degree of exacerbation, length of stay, mortality rate, and %FEV1 in patients with acute exacerbation of COPD.

Study location and period

The research was conducted in the pulmonary inpatient ward at UNS Hospital from November 2023 to January 2024.

Study subjects

The population targeted in this study were those diagnosed with acute exacerbation of COPD at UNS Hospital between November 2023 and January 2024. The subjects, specifically patients admitted to UNS Hospital with acute exacerbation of COPD, were determined using Lameshow's formula for observational studies. The formula $n= Z\alpha 2pq/d2$ where n represented the sample size, $Z\alpha$ was the confidence level of 10% (1.64), p was the proportion in the known group (14.2% from Garcia-Olmost's 2013 cohort study in Spain), q was 1 minus p, and d was the margin of error (10%). Based on this formula, the minimum required sample size for the study was 32 patients.

The sampling method employed was consecutive sampling, whereby samples meeting the inclusion and exclusion criteria were taken sequentially until the minimum sample size was reached. No randomization was applied in this study.

Patients aged 40 years and older were included in the study, as the pathogenesis of COPD required chronic exposure, and epidemiologically, COPD incidence occurred in individuals over this age. Further, only inpatients diagnosed with acute exacerbation of COPD clinically and

confirmed by spirometry results showing FEV1/FVC < 0.7, measured on day 7 post-hospitalization and treated in the Pulmonary Ward at UNS Hospital were included. Patients with incomplete medical records, those who did not consent to participate, patients with stable COPD, and those with other significant respiratory or cardiac conditions such as asthma, pulmonary tuberculosis, pulmonary fibrosis, lung cancer, acute myocardial infarction, congestive heart failure, or those requiring surgery were excluded from the study.

The independent variables examined in this study included components of the thyroid function panel, specifically TSH, FT4, and FT3 levels. The dependent variables included the degree of clinical exacerbation of COPD, the length of stay, and %FEV1 values.

Acute exacerbation of COPD was defined as the presence of chronic and progressive shortness of breath, cough, and sputum production, which worsened with activity and were associated with recurrent lower respiratory tract infections and exposure to risk factors. This condition was confirmed by spirometry showing FEV1/FVC<0.7 post-bronchodilator. Exacerbation was characterized as an acute worsening of symptoms requiring a change in therapy, marked by increased breathlessness and/or worsening of cough and sputum within 14 days.

Thyroid dysfunction was assessed by measuring TSH, which is produced by the pituitary gland to stimulate the thyroid to produce T4 and T3. The normal TSH range is 0.25-5 μIU/mL. Free T4, the inactive form of thyroxine, has a normal range of 10.6–19.4 pmol/L, while FT3, the active form of thyroid hormone, has normal values of 4–8.3 pmol/L.

The degree of exacerbation was classified according to the Anthonisen criteria into mild, moderate, and severe categories based on symptoms.[1,14] Mild exacerbation was characterized by the presence of one cardinal symptom plus additional features such as increased wheezing, cough, fever without an identifiable cause, recent upper respiratory tract infection, or an increase in respiratory rate of more than 20% from baseline. The cardinal symptoms of COPD exacerbation include increased dyspnea (shortness of breath), increased sputum production, and sputum purulence (thicker or more discolored sputum). Moderate exacerbation included two cardinal symptoms, whereas severe exacerbation involved all three cardinal symptoms and may be accompanied by respiratory failure, hypoxemia, or hypercapnia.[1,14]

Length of stay (LOS) was defined as the total number of days from admission to discharge. Criteria for discharge readiness included clinical stability, discontinuation of parenteral therapy for 24 hours, reduced need for inhaled bronchodilators to fewer than four times per day, discontinuation of oxygen therapy for 24 hours unless home oxygen was indicated, the ability to walk safely and perform daily activities, and a clear understanding of medications by the patient or caregiver.[15] A prolonged LOS was defined as more than 7 days, while an extended LOS was defined as more than 4 days.[16] Based on the length of hospitalization, subjects were divided into two groups.[16,17]

The %FEV1 value, which indicates the percentage of forced expiratory volume in the first second of a forced breath compared to predicted values, was measured using spirometry and based on data from the Pneumobile Project Indonesia. The %FEV1 variable was categorized into two groups based on its mean value (48.62 ± 17.45); a group with %FEV1 < 50 and a group with %FEV1 > 50. This classification aligns with statistical norms to facilitate data analysis and has also been used in previous study.[7,18]

Data collection and analysis

Demographic data, smoking history, comorbidities, and spirometry results were recorded. Serum TSH, FT3, and FT4 were measured using standard laboratory methods. The severity of exacerbation was assessed based on clinical presentation, and the length of hospital stay was recorded in days. Statistical analyses included Pearson correlation to assess relationships between thyroid hormone levels and FEV1, exacerbation severity, and length of hospital stay. A receiver operating characteristic (ROC) curve was used to determine the cut-off value of FT3 for predicting severe exacerbations. Statistical analyses were performed using SPSS version 26 for Windows, with statistical significance set at $p < 0.05$.

Ethical

Ethical approval was obtained from the Research Ethics Committee from Faculty of Medicine Universitas Sebelas Maret, with approval number 02/UN27.06.11/KEP/EC/2024. Informed consent was acquired from each participant after providing a detailed explanation of the study procedures.

RESULTS

Subject characteristics

The study included 32 subjects with an average age of 67.34 ± 12.97 years, ranging from 44 to 93 years. Males comprised 68.8% of the sample, while females accounted for 31.3%. The majority of the participants had a normal body weight, with a smaller proportion classified as obese. Pneumonia was identified as the primary precipitating factor for exacerbations, observed in 81.3% of cases. Reported comorbidities included hypertension (28.1%), diabetes mellitus (12.5%), and cardiovascular diseases (43.8%). The detailed characteristics of the study participants are presented in Table 1.

Table 1. Characteristics of participants

Characteristics	n(%)/mean ± SD	Minimum	Maximum
Age	67.34 ± 12.97	44.00	93.00
Gender			
Female	10 (31.3%)		
Male	22 (68.8%)		
Body mass index (kg/m^2)	22.31 ± 5.25	14.6	38.00
Underweight	2 (6.3%)		
Normoweight	9 (28.1%)		
Overweight	16 (50.0%)		
Obese	5 (15.6%)		
Pneumonia	26 (81.3%)		
Comorbidity			
Hypertension	9 (28.1%)		
Diabetes mellitus	4 (12.5%)		
Non-specific cardiovascular disease	14 (43.8%)		
Smoking habit (pack/year)			
>40	3 (9.4%)		
20-40	13 (40.6%)		
1-20	5 (15.6%)		
0	11 (34.4%)		
Thyroid hormone			
Thyroid stimulating hormone (uUl/ml)	0.61 ± 0.54	0.09	2.12
Free triiodothyronine (pmol/l)	3.05 ± 1.10	1.25	7.33
Free tetraiodothyronine (pmol/l)	18.38 ± 4.83	7.73	28.97
FEV1/Forced expiratory volume in 1 second (%)	48.62 ± 17.45	20.00	82.00
FEV1<50%	19 (59.4%)		
FEV1>50%	13 (40.6%)		
Degree of exacerbation severity			
Severe	6 (18.8%)		
Mild-moderate	26 (81.3%)		
Length of stay	4.09 ± 1.00	3.00	6.00
≥4 days	22 (68.8%)		

Table 1. Characteristics of participants (continued)

Characteristics	n(%)/mean ± SD	Minimum	Maximum
<4 days	10 (31.3%)		

SD: standard of deviation; kg/m²: kilograms per meter square

Correlation between thyroid hormone levels and %FEV1, clinical exacerbation severity, and length of hospital stay amongst study subjects

The study found no significant correlation between TSH or FT4 levels and %FEV1 (Table 2). However, FT3 demonstrated a moderate positive correlation with %FEV1 (r=0.414; p=0.019), indicating that higher FT3 levels were associated with better lung function. No significant correlation was observed between TSH levels and the severity of clinical exacerbations. In contrast, FT3 (r=-0.506; p=0.003) and FT4 (r=-0.367; p=0.039) showed significant negative correlations with clinical exacerbation severity, suggesting that lower FT3 and FT4 levels were associated with more severe exacerbations (Table 2). In addition, free triiodothyronine exhibited a weak negative correlation with length of stay (r=-0.350; p=0.050), indicating that lower FT3 levels were associated with longer hospitalization periods.

Table 2. Analysis of the relationship between thyroid hormone levels and %FEV1, clinical grade and length of stay in subjects with acute exacerbation of COPD

	FEV 1 %		Exacerbation severity level		Length of stay	
Variable	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
TSH (uUl/ml)	0.024[b]	0.898	0.115[b]	0.547	0.260[b]	0.165
FT3 (pmol/l)	0.414[a]	0.019*	-0.506[b]	0.003*	-0.350[b]	0.050*
FT4 (pmol/l)	-0.161[a]	0.379	-0.367[b]	0.039*	-0.101[b]	0.582

a: Pearson Product Moment correlation test; b: Spearman rank correlation; *: significant at p<0.05; TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free tetraiodothyronine; FEV1: forced expiratory volume in 1 second

Comparison of thyroid hormone levels based on %FEV1, clinical severity, and length of hospitalization in patients with acute COPD exacerbation

Patients with acute COPD exacerbation were categorized into two groups according to the observed dependent variables. Specifically, for the clinical severity variable, subjects were divided into severe and non-severe (mild-moderate) groups. The FT3 variable (p=0.019) showed a statistically significant difference between patients with severe clinical severity and those with mild-moderate severity (p <0.05). This finding indicates that FT3 thyroid hormone levels may serve as a potential predictor of clinical severity in patients experiencing an acute COPD exacerbation (Table 3).

Table 3: Comparison of thyroid hormone levels based on clinical severity in acute COPD exacerbation

Variable	Severe (mean±SD)	Mild/Moderate (mean±SD)	p-value
TSH (uUl/ml)	0.86 ± 0.76	0.55 ± 0.48	0.337[a]
FT3 (pmol/l)	2.13 ± 0.43	3.26 ± 1.10	0.019*[b]
FT4 (pmol/l)	16.39 ± 5.54	18.84 ± 4.65	0.268[b]

Note: a = Mann-Whitney test, b = independent t-test; * indicates significance at p<0.01.

Determination of FT3 cut-off value for severe clinical severity

Receiver Operating Characteristic (ROC) curve analysis was used to evaluate whether FT3 could serve as a predictor of severe clinical severity in patients with AECOPD (Figure 1). The analysis showed that FT3 had an area under the curve (AUC) of 0.897 (p=0.003), suggesting a strong

predictive value for severe clinical severity (Table 4). The optimal cut-off value of FT3 to predict severe clinical severity was determined to be <2.65.

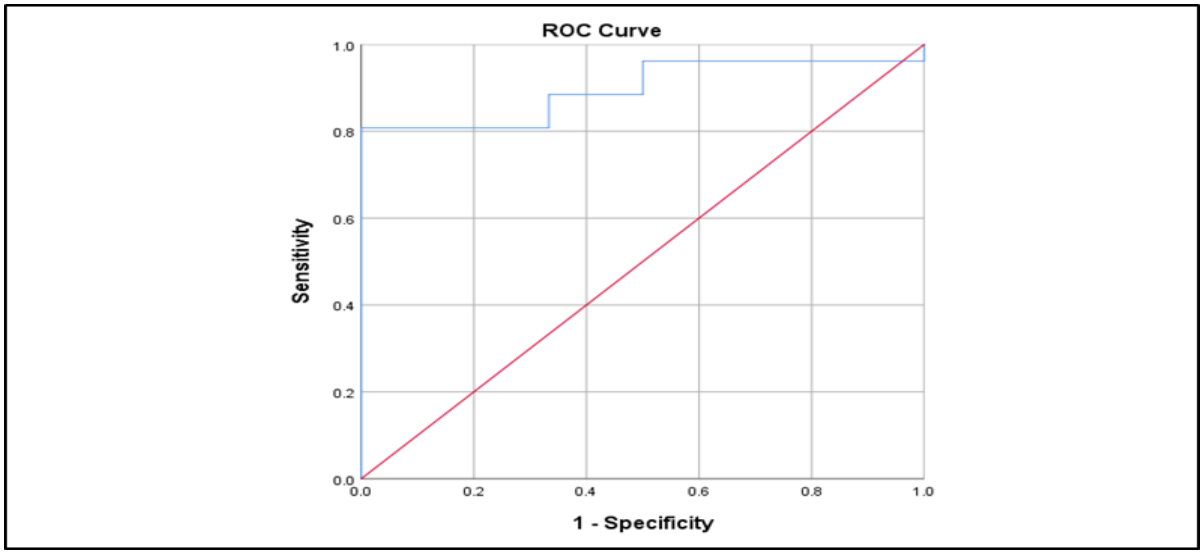

Figure 1. Receiving operating characteristic (ROC) curve for FT3 levels based on the clinical grade of patients with acute exacerbation of chronic obstructive pulmonary disease.

Table 4: Description of the results of determining the FT3 cut-off based on the clinical grade of patients with acute exacerbation of COPD.

Variable	AUC	95% CI		*Cut-off*	Sensitivity	Specificity
		Minimum	Maximum			
FT3	0.897	0.788	1.000	<2.65	80.8%	100% p=0.003

AUC: Area under the curve; CI: Confidence interval; *significant at p<0.05; FT3: free triiodothyronine

DISCUSSION

Our study investigated the correlation between thyroid hormone levels and clinical outcomes in patients with AECOPD and found that FT3 levels were significantly associated with several key clinical parameters in AECOPD patients. Higher FT3 levels were positively correlated with FEV1, indicating better lung function. Conversely, FT3 levels showed a significant negative correlation with exacerbation severity and length of hospital stay, suggesting that lower FT3 levels may be indicative of more severe exacerbations and prolonged hospitalization. These findings highlight the potential role of FT3 as a clinical marker for disease severity and prognosis in AECOPD.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are episodes of acute syptom worsening that lead to significant morbidity and mortality.[1,4,12] The triggers for these exacerbations are multifactorial, including infections, environmental factors, and systemic inflammation.[1,3] Systemic inflammation is often implicated in the pathogenesis of AECOPD, and is associated with elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, which have been shown to affect thyroid function by inhibiting thyroid-stimulating hormone (TSH) and altering the conversion of T4 to T3.[5,8,19] Previous studies have concluded that thyroid function is significantly associated with the severity of acute exacerbations in COPD patients. Higher TSH levels were positively correlated with better lung function (FEV_1%pred) and negatively correlated with the length of hospitalization, suggesting that thyroid dysfunction may contribute to poorer clinical outcomes. Additionally, forced vital capacity (FVC) has been identified as a protective factor against thyroid dysfunction in AECOPD patients. These findings highlight the importance of monitoring thyroid function in COPD management, as it may influence both disease progression and recovery.[7] A study by Chaudhary et al. reported a 25% prevalence of thyroid dysfunction among COPD patients, with the highest rates found in those with frequent

exacerbations and in those at more advanced stages of the disease. The study emphasized that thyroid dysfunction in COPD is linked with increased exacerbation frequency and a reduced quality of life.[20]

We found that the relationship between thyroid hormones and COPD outcomes was complex, with some significant correlations and others that were not statistically significant. The most notable finding from our study was the correlation between FT3 and several key outcomes in AECOPD. Higher level of FT3 was associated with improved lung function, as indicated by a positive correlation with FEV1. This finding is consistentwith previous studies, which have also reported a positive correlation between thyroid hormone levels and lung function in COPD.[7] These results suggest that thyroid hormones, particularly FT3, may play a role in modulating respiratory function in patients with COPD, potentially through their effects on muscle strength and energy metabolism.[7,8,12]

Free triiodothyronine also demonstrated a significant negative correlation with the clinical severity of AECOPD, indicating that higher FT3 levels were associated with less severe exacerbations. This finding is consistent with previous studies which reported that Non-Thyroidal Illness Syndrome (NTIS) was common amongst patients with severe AECOPD, suggesting that thyroid dysfunction might be linked to exacerbation severity.[10,12] Additionally, we found a negative correlation between FT3 levels and the duration of hospital stay, implying that higher FT3 levels were associated with shorter hospitalization periods. These result suggest that FT3 levels could be a predictive marker for the length of hospitalization in patients experiencing AECOPD.

While FT3 showed significant correlations with several clinical outcomes, TSH and FT4 did not show significant correlations with FEV1, clinical severity, or length of hospital stay. The absence of a significant relationship between TSH and FT4 and these outcomes may be attributed to several factors.[18] One possible explanation is the influence of medications, such as dexamethasone, which is commonly used in the management of AECOPD.[7,8] Dexamethasone and other corticosteroids can alter thyroid hormone levels, potentially affecting TSH and FT4 concentrations.[8,10,21] This effect may introduce bias into the analysis and complicate the interpretation of results. In addition, the timing of sample collection might have contributed to the non-significant findings, as thyroid hormone levels can vary throughout the day and may be influenced by the patient's clinical condition and treatment status. Another possible explanation is the complexity of systemic inflammation in COPD. While FT3 displayed a consistent pattern, the relationship between TSH, FT4, and AECOPD outcomes may be more variable, reflecting the multifactorial nature of the disease and its exacerbations.[9,18,21]

In addition to examining the relationship between thyroid hormone levels and clinical outcomes in AECOPD, we analyzed whether specific thyroid hormone levels could serve as predictors for key clinical parameters, including lung function, severity of exacerbations, and length of hospital stay. Thyroid function may influence exacerbation severity through multiple mechanisms. First, thyroid hormones regulate the metabolic rate and energy production in cells, including in respiratory muscles. A deficiency in these hormones can lead to respiratory muscle weakness, impairing secretion clearance and increasing susceptibility to respiratory infections. Second, thyroid dysfunction contributes to systemic inflammation by altering cytokine levels and modulating the immune response, thereby exacerbating airway inflammation in COPD. Finally, thyroid hormone imbalances may affect cardiovascular function, further increasing the risk of complications during exacerbations.[8,10,12]

The analysis revealed that FT3 levels may serve as a predictive marker for clinical outcomes in AECOPD. Higher levels of FT3 were positively associated with FEV1 values, suggesting that FT3 may reflect better pulmonary function and a potentially less severe disease state. This aligns with previous studies reporting a positive correlation between thyroid hormone levels and respiratory muscle function.[5,7,8]

FT3 demonstrated a significant negative correlation with clinical severity, indicating that lower FT3 levels may be associated with more severe AECOPD.[11,12] Previous study have further highlighted that NTIS occurs due to impaired hypothalamic-pituitary-thyroid axis regulation,

leading to decreased peripheral conversion of T4 to T3, which exacerbates muscle dysfunction and respiratory failure in COPD patients.[8,10,12] These findings reinforce the hypothesis that thyroid dysfunction, particularly low FT3 levels, may serve as a predictor of exacerbation severity and poorer clinical outcomes in COPD patients. Monitoring thyroid function during exacerbations may provide additional insights into disease progression and guide therapeutic interventions. Furthermore, previous study found that reduced FT3 levels were associated with systemic inflammation and metabolic dysregulation, contributing to a higher likelihood of severe exacerbations in COPD patients. This suggests that monitoring FT3 may be a useful tool in assessing the severity of exacerbations and guiding clinical decision-making. Similarly, FT3 levels showed a significant negative correlation with the length of hospital stay. This implies that patients with higher FT3 levels tended to have shorter hospital stays as well as faster recovery process. These results suggest that FT3 may serve as a prognostic marker and could be useful in clinical practice for risk stratification and resource allocation during AECOPD.[7]

An additional analysis was conducted to identify a potential cut-off point for FT3 levels that may help in predicting severe clinical outcomes in AECOPD. Using receiver operating characteristic (ROC) analysis, we determined that an FT3 level below 2.65 pmol/L was associated with a higher risk of severe clinical outcomes. This cut-off had a sensitivity of 80.8% and a specificity of 100%, indicating a high degree of accuracy in predicting severe exacerbations. Low serum concentrations of FT3 and FT4 increased the incidence and mortality of invasive mechanical ventilation in patients with respiratory failure.[5,7,8] Previous study demonstrated that NTIS has a predictive role for prolonged weaning in COPD patients undergoing invasive mechanical ventilation.[8] These findings suggest that thyroid hormone levels may influence prognosis during acute exacerbations of COPD.

Our findings support the hypothesis that thyroid hormones, particularly FT3, may serve not only as biomarkers but also play a pathophysiological role in the clinical course of AECOPD. Free triiodothyronine is the biologically active form of thyroid hormone, essential for mitochondrial activity and energy metabolism. In the context of COPD, systemic inflammation and hypoxia are known to impair peripheral conversion of T4 to T3, resulting in low FT3 levels, a phenomenon consistent with non-thyroidal illness syndrome (NTIS) or "low T3 syndrome".[7,12] Furthermore, reduced FT3 levels have been shown to impair skeletal muscle function, including respiratory muscles, leading to worsened ventilation and prolonged recovery.[6] This is especially relevant in AECOPD, where respiratory muscle fatigue contributes to dyspnea and increased hospitalization. The observed correlation between low FT3 and longer hospital stay in our study reinforces this physiological mechanism.

Additionally, the interplay between thyroid hormones and systemic inflammation may create a self-reinforcing cycle. Elevated cytokines such as IL-6 and TNF-α not only contribute to COPD exacerbations but also suppress deiodinase activity, thereby reducing T3 production.[8,10] This may explain why patients with severe exacerbations, marked by intense inflammation, often exhibit suppressed FT3 levels. From a clinical perspective, our study suggests that FT3 may serve as a practical and accessible biomarker to stratify AECOPD severity, especially in settings where other prognostic tools, such as blood gas analysis (BGA) or procalcitonin, are unavailable. The high specificity (100%) and good sensitivity (80.8%) of FT3 at the <2.65 pmol/L threshold for predicting severe exacerbation further support its potential utility.

A recent prospective study also found that FT3 levels were independently associated with the need for invasive ventilation and ICU admission in AECOPD patients.[13] Such evidence strengthens the argument for incorporating thyroid function testing—particularly FT3—into the routine assessment of hospitalized COPD patients. Future studies should explore whether early identification and management of low FT3 can improve clinical outcomes. Interventional trials examining thyroid hormone supplementation in selected COPD patients with NTIS may offer new avenues for treatment, as suggested by prior endocrine research.[5] Longitudinal research tracking thyroid status throughout both stable and exacerbation phases would also help clarify the direction of causality. In summary, our study contributes to the growing body of literature suggesting that thyroid function, especially FT3, not only reflects but may also influence the

clinical trajectory of AECOPD. Given its prognostic value and mechanistic links to inflammation and muscle function, FT3 deserves attention as a possible clinical predictor and therapeutic target in this vulnerable population.

One limitation of this study is the inability to use the GOLD criteria for assessing exacerbation severity, due to the limited availability of arterial blood gas analysis at the research hospital. Additionally, %FEV1 was measured on day 7 post-hospitalization. This approach was intended to obtain a more reliable baseline measurement of lung function; however, it may not fully reflect the extent of impairment during the acute phase of exacerbations. Future research should consider assessing %FEV1 both during and after exacerbation episodes to provide a more comprehensive understanding of disease progression and recovery. A key consideration in this study is the comparison between our study population and those in previous studies, which primarily investigated stable COPD patients. We recognize that acute exacerbations introduce a distinct inflammatory profile compared to the stable phase of COPD. Although some prior studies have focused on stable patients, we have carefully selected references that include discussions on acute exacerbations or systemic effects that may persist across different disease phases. Our findings highlight the unique role of thyroid hormones during acute exacerbations, particularly their potential utility as a clinical predictor of disease severity. Future studies should elucidate these differences by incorporating longitudinal assessments comparing the stable and exacerbation phases within the same patient cohort. The use of corticosteroids, such as dexamethasone, during AECOPD treatment may have influenced thyroid hormone levels, leading to potential bias. The timing of sample collection and variability in patient conditions at the time of sampling could have contributed to the observed results. Lastly, the relatively small sample size and observational study design may limit the generalizability of our findings.

CONCLUSION

Thyroid function, particularly FT3 levels, is associated with lung function, exacerbation severity, and hospital stay duration in patients with AECOPD. These associations highlight the importance of considering thyroid function assessment into the clinical management of COPD and suggest a potential role for FT3 as a predictive marker of severe exacerbations. Further research with larger sample sizes and prospective study designs is suggested to confirm these findings and explore underlying mechanisms.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVALABILITY

All relevant data supporting the findings of this study are available in the supplementary materials provided with this article.

SUPPLEMENTAL DATA

The supplementary material includes additional tables (Table S1 and Table S2) presenting extended statistical analysis, as well as raw dataset files containing patient demographics and laboratory results. These files are provided as supplementary documents accompanying this article.

AUTHOR CONTRIBUTIONS

Y led the research project, designed the study, and was responsible for the data collection and analysis. He also carried out the manuscript preparation. HA, provided guidance throughout the study, contributed to the research design, reviewed the data analysis, and edited the manuscript. ARS, supported the development of the study design and provided analysis and took part in the manuscript preparation. R reviewed the manuscript and contributed to the study's methodology. AA, assisted in the data collection and contributed to the manuscript preparation. All authors reviewed and approved the final manuscript. Each author brought their expertise to different aspects of the research, from conception to final publication.

DECLARATION OF USING AI IN THE WRITING PROCESS

Artificial intelligence (AI) was utilized in the editing process, specifically for translation from the original language to English. The final version of the manuscript was reviewed and revised by the authors to ensure accuracy and clarity.

LIST OF ABBREVIATIONS

COPD: Chronic Obstructive Pulmonary Disease; %FEV1: Percent Forced Expiratory Volume in one second; FVC : Force Vital Capacity; AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease; LOS : Length of Stay; AUC: Area Under the Curve; ROC: Receiver Operating Characteristic; NTIS: Non-Thyroidal Illness Syndrome; TSH: Thyroid Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Thyroxine; TNF-α : Tumor necrosis factor-alpha**;** IL-6: interleukin-6; IL-1: interleukin-1; T4: thyroxine; T T3 : triiodothyronine; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

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