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ORIGINAL RESEARCH

Thyroid Status and Pulmonary Thromboembolic Extent: Is There an Association in Patients with Pulmonary Embolism?

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Background: Thyroid dysfunction has been associated with thrombotic diseases. However, the association between thyroid status and pulmonary thromboembolic extent remains unclear in patients with pulmonary embolism (PE). Thus, this study investigated the association between thyroid status and pulmonary thromboembolic extent and elucidated the clinical significance of thyroid status assessment in patients with PE.

Methods: We retrospectively analyzed data from 118 patients with PE. Pulmonary thromboembolic extent was assessed with computerized tomography obstruction index.

Results: Serum free triiodothyronine (FT3) levels were significantly higher in PE patients with greater pulmonary thromboembolic extent than in those with lesser pulmonary thromboembolic extent (4.33[4.04–4.98] vs 4.17[3.33–4.66] pmol/L, p=0.017), but not for serum free thyroxine (FT4) levels (15.33[13.43-16.94] vs 15.36[13.75-17.82] pmol/L, p=0.908) and serum thyroid stimulating hormone (TSH) levels (1.84[1.01-3.00] vs 1.49[0.74-2.58] uIU/mL, p=0.273). Multivariable linear regression analysis revealed that higher serum FT3 levels were independently associated with greater pulmonary thromboembolic extent in patients with PE (β=0.235, p=0.013).

Conclusion: Higher serum FT3 levels were associated with greater pulmonary thromboembolic extent in patients with PE. This finding suggests that the possibility of extensive pulmonary thromboembolic extent should be noticed for PE patients with higher serum FT3 levels.

Keywords: pulmonary embolism, pulmonary thromboembolic extent, thyroid status

Introduction

Thyroid hormones, essential hormones secreted by the thyroid gland, play a crucial role in maintaining metabolic homeostasis.[1] Clinical evaluations of thyroid hormone levels directly reflect thyroid functional status.[2] Thyroid hormones have an important influence on coagulation system,[3] with hyperthyroidism demonstrating causal relationships with reduced anticoagulant factor levels.[4] Coagulation and fibrinolytic system alterations occur in hyperthyroid and hypothyroid states, and high thyroid hormone levels promote procoagulant activity and suppress fibrinolysis.[5] In recent years, accumulating evidence has established notable associations between thyroid dysfunction and thrombotic diseases.[6–8] Interestingly, thyroid dysfunction has been linked to clinical outcomes in patients with pulmonary embolism (PE).[9] However, to our knowledge, limited study has examined the association between thyroid status and pulmonary thromboembolic extent in patients with PE. Therefore, this study examined this association to elucidate the clinical significance of thyroid status assessment in patients with PE.

Methods

The study retrospective included 118 patients diagnosed with PE at the Affiliated Hospital of Youjiang Medical University for Nationalities between January 2020 to October 2024. All patients with PE were identified based on

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clinical diagnostic information through electronic medical records. The diagnosis of PE was confirmed by computerized tomography pulmonary angiography (CTPA).[10] Patients with PE receiving thrombolytic therapy prior to admission were excluded from this study. The study was approved by the Ethical Committee at the Affiliated Hospital of Youjiang Medical University for Nationalities and followed the principles of Declaration of Helsinki. Given the retrospective nature of the study, a waiver of informed consent was granted by the Ethical Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities. The data of patients were maintained with confidentiality.

The study data, which included demographic and clinical characteristics, laboratory investigation results, and imaging examination results, were collected from electronic medical records. The demographic and clinical characteristics included sex, age, height, weight, smoking history, medication history, and comorbidity.The laboratory investigation results included prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), D-dimer, free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH), and the imaging examination results included color Doppler ultrasonography for lower-extremity deep venous thrombosis (LEDVT) assessment and CTPA. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Pulmonary thromboembolic extent was assessed by computerized tomography obstruction index, and the computerized tomography obstruction index was calculated according to CTPA findings using the formula: $\Sigma(n \cdot d) / 40 \times 100\%$, where n represents the value of the proximal thrombus in the pulmonary arterial tree, corresponding to the number of affected distal segmental branches (minimum, 1; maximum, 20), and d represents the degree of obstruction (minimum, 0; maximum, 2).[11]

Categorical variables are reported as frequency (percentage), and continuous variables are reported as median (interquartile range) given their nonnormal distribution. Differences in continuous variables were analyzed by Mann-Whitney *U*-test, and differences in categorical variables were analyzed by chi-square test. Univariable linear regression analysis was initially used to analyze potential factors associated with pulmonary thromboembolic extent in patients with PE. Subsequently, multivariable linear regression analysis was applied to identify independent factors, following verification of key regression assumptions including linearity, independence, residual normality, homoscedasticity, and multicollinearity. All statistical analyses adopted two-tailed test with statistical significance defined at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA).

Results

The results of comparison in characteristics of patients with PE stratified by the median of pulmonary thromboembolic extent are presented in Table 1. Significantly higher serum FT3 levels were observed in PE patients with greater pulmonary thromboembolic extent than in those with lesser pulmonary thromboembolic extent (4.33[4.04–4.98] vs 4.17[3.33–4.66] pmol/L, p=0.017); however, serum FT4 levels (15.33[13.43-16.94] vs 15.36[13.75-17.82] pmol/L, p=0.908) and serum TSH levels (1.84[1.01-3.00] vs 1.49[0.74-2.58] uIU/mL, p=0.273) showed no significant differences. In addition, PE patients with greater pulmonary thromboembolic extent exhibited significantly higher frequency of LEDVT history (p=0.006), higher plasma D-dimer levels (p=0.002), and lower plasma PT levels (p=0.045) than in those with lesser pulmonary thromboembolic extent. Sex (p=0.379), age (p=0.998), BMI (p=0.587), smoking history (p=0.923), chronic obstructive pulmonary disease (COPD) history (p=0.182), APTT (p=0.072), and TT (p=0.258) showed no significant differences between the groups.

The results of univariable and multivariable linear regression analyses between thyroid status and pulmonary thromboembolic extent in patients with PE are detailed in Table 2. Univariable linear regression analysis revealed that LEDVT history (β=0.264, p=0.004), higher plasma D-dimer levels (β=0.355, p<0.001), and higher serum FT3 levels (β=0.204, p=0.027) were significantly associated with greater pulmonary thromboembolic extent in patients with PE; however, no significant associations were found between serum FT4 levels (β=-0.057, p=0.541) or serum TSH levels (β=-0.070, p=0.454) and pulmonary thromboembolic extent in patients with PE. In subsequent multivariable linear regression analysis adjusted for sex, age, BMI, smoking history, LEDVT history, COPD history, PT, APTT, TT, and D-dimer, higher serum FT3 levels maintained an independent association with greater pulmonary thromboembolic extent in patients with PE (β=0.235, p=0.013), and higher plasma D-dimer levels were independently associated with greater pulmonary thromboembolic extent in patients with PE (β=0.332, p<0.001).

Table 1 The Characteristics of Patients with PE Stratified by the Median of Pulmonary Thromboembolic Extent

Variables	Pulmonary Thromboembolic Extent (%)		p value
	≤17.5	>17.5	
n	61	57	
Males, n (%)	37(60.7)	39(68.4)	0.379
Age (year)	66(52–76)	66(55–75)	0.998
Body mass index (kg/m²)	22.3(20.6–24.1)	22.1(20.4–23.6)	0.587
Smoking history, n (%)	23(37.7)	21(36.8)	0.923
Lower-extremity deep venous thrombosis history, n (%)	17(27.9)	30(52.6)	0.006
Chronic obstructive pulmonary disease history, n (%)	17(27.9)	10(17.5)	0.182
Prothrombin time (s)	12.5(11.6–13.9)	11.8(11.0–13.2)	0.045
Activated partial thromboplastin time (s)	31.9(28.1–35.5)	29.1(25.1–34.2)	0.072
Thrombin time (s)	17.4(16.2–19.1)	16.9(16.0–18.6)	0.258
D-dimer (ug/mL)	2.02(0.87–3.87)	3.87(1.83–5.60)	0.002
Free triiodothyronine (pmol/L)	4.17(3.33–4.66)	4.33(4.04–4.98)	0.017
Free thyroxine (pmol/L)	15.36(13.75–17.82)	15.33(13.43–16.94)	0.908
Thyroid stimulating hormone (ulU/mL)	1.49(0.74–2.58)	1.84(1.01–3.00)	0.273

Table 2 Univariable and Multivariable Linear Regression Analyses Between Serum FT3 Levels and Pulmonary Thromboembolic Extent in Patients with PE

Variables	Univariable Analysis		Multivariable Analysis	
	Standardized Coefficient β	p value	Standardized Coefficient β	p value
Sex	0.003	0.976	−0.016	0.876
Age	0.019	0.842	0.101	0.314
Body mass index	0.033	0.720	−0.006	0.951
Smoking history	−0.001	0.990	0.006	0.956
Lower-extremity deep venous thrombosis history	0.264	0.004	0.112	0.239
Chronic obstructive pulmonary disease history	−0.129	0.164	−0.083	0.418
Prothrombin time	−0.059	0.525	0.043	0.761
Activated partial thromboplastin time	−0.070	0.449	−0.016	0.910
Thrombin time	−0.121	0.191	−0.105	0.248
D-dimer	0.355	<0.001	0.332	<0.001
Free triiodothyronine	0.204	0.027	0.235	0.013
Free thyroxine	−0.057	0.541	–	–
Thyroid stimulating hormone	−0.070	0.454	–	–

Discussion

Thyroid hormones are involved in the regulation of coagulation disorders, and hyperthyroidism enhances coagulation activity and increases thrombotic risk,[12] whereas overt hypothyroidism may predispose patients to an increased risk of bleeding.[13] Hyperthyroidism has been reported to be associated with cardiovascular diseases such as myocardial infarction, atrial fibrillation, and myocarditis.[14–16] It has been shown that increased thyroid hormones may result in coronary vascular degeneration and plaque instability, manifesting as more high-grade coronary stenoses, plaque burden, and high-risk plaque features.[17] Clinical observation in euthyroid patients with acute myocardial infarction has revealed an inverse correlation between serum FT3 levels and international normalized ratio,[18] suggesting that higher serum FT3 levels may be associated with thrombosis risk. A positive correlation between serum FT3 levels and factor IX activity has been demonstrated in patients with hypothyroidism,[19] implying FT3 may mediate the enhancement of coagulation through factor IX activation.

Experimental evidence by Shih et al indicated that triiodothyronine (T3) treatment increased the production of fibrinogen and multiple coagulation factors, suggesting T3 promotes blood clotting dependent the transcriptional regulation of fibrinogen and coagulation proteins.[20] In hypothyroid animal models, T3 administration modulates the transcription of coagulation factors in hepatic and vascular tissues, resulting in longer PT and shorter APTT.[21] Notably, T3 has been also shown to increase the amounts of coagulant proteins including factor II, factor X, and fibrinogen.[22] Thus, the effects of FT3 on coagulation pathways may provide mechanistic insights into the observed association between higher serum FT3 levels and greater pulmonary thromboembolic extent in patients with PE.

D-dimer, a biomarker of intravascular thrombosis, has been regarded as a predictor of disease severity in patients with acute PE.[23,24] Türedi S et al demonstrated a positive association between D-dimer levels and pulmonary embolism severity in acute PE.[25] Our study identified an independent association between with higher plasma D-dimer levels and greater pulmonary thromboembolic extent in patients with PE, suggesting the clinical utility of D-dimer for evaluating pulmonary thromboembolic extent in patients with PE.

This investigation has several limitations. First, the relatively small sample size may weaken the statistical power and the generalizability of findings. Second, the cross-sectional design cannot provide causal inference regarding the association between serum FT3 levels and pulmonary thromboembolic extent in patients with PE. Third, echocardiographic measurements have been associated with clinical outcomes in patients with PE;[26] however, our study did not evaluate the role of echocardiographic measurements in patients with PE.

In summary, this study revealed a positive association between serum FT3 levels and pulmonary thromboembolic extent in patients with PE. This finding indicates that PE patients exhibiting higher serum FT3 levels may require additional notice for possible extensive pulmonary thromboembolic extent. However, the prognostic value of serum FT3 levels needs be further confirmed by prospective studies in patients with PE.

Data Sharing Statement

Data are available upon reasonable request from the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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