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Thyroid-stimulating hormone concentration as an independent risk factor of venous thromboembolism regardless of thyroid function

Koncentracja hormonu tyreotropowego jako niezależny czynnik ryzyka żylnych powikłań zakrzepowo-zatorowych bez względu na czynność tarczycy

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Abstract

Introduction: Thyroid dysfunction has been recognised as playing a role in the coagulation cascade, but the clinical implications of this phenomenon are unclear. The aim of our study was to assess the predictive power of TSH measurement on the presence or absence of venous thromboembolism (VTE).

Material and methods: From January 2009 to August 2012, all consecutive patients hospitalised for suspected VTE were included in the study. VTE was confirmed either by pulmonary angiography or compressive ultrasound. We investigated the predictive power of TSH concentration on the risk of VTE in univariate and multivariate analysis including the existing risk factors (age, D-dimer).

Results: A total of 232 patients were eligible for final analysis, with a median age of 70 years (IQR 58–80) and male-to-female ratio of 124:108. VTE was confirmed in 124 patients (53.4%). TSH concentration was significantly higher in cases with VTE (median 2.17 *vs.* 1.76 mIU/L, p = 0.0104), but free T4 concentrations were not found to be significantly different. Receiver operating curve analysis identified the cut-off of TSH > 2.686 mIU/L as a predictor of VTE with the prevalence of VTE 47.1 *vs.* 66.7% below and above this cut-off, p = 0.011. Multivariate logistic regression identified five independent predictors of VTE: male gender (odds ratio, OR = 2.22), D-dimer > 0.5 mg/L OR = 16.42), CRP > 5 g/L (OR = 9.178), TSH > 2.686 mIU/L (OR = 2.269), and age (OR = 0.9767/year).

Conclusions: Among patients with suspected venous thromboembolism TSH concentration was found to be an independent predictor of VTE in addition to gender, D-dimer, C-reactive protein (CRP), and age. **(Endokrynol Pol 2015; 66 (6): 474–479)**

Key words: *venous thromboembolism; thyrotropin; free thyroxine*

Streszczenie

Wstęp: Stwierdzono, że dysfunkcja tarczycy odgrywa pewną rolę w kaskadzie krzepnięcia, lecz kliniczne następstwa tego zjawiska nie są do końca znane. Celem niniejszego badania była ocena na ile pomiar stężenia TSH pomoże przewidzieć obecność lub brak żylnych powikłań zatorowo-zakrzepowych.

Materiał i metody: Badaniem objęto wszystkich pacjentów hospitalizowanych z powodu podejrzenia żylnych powikłań zatorowo-zakrzepowych w okresie od stycznia 2009 do sierpnia 2012 roku Powikłania te potwierdzono za pomocą angiografii płuc lub USG kompresyjnego. Autorzy przebadali w analizie jednoczynnikowej oraz wieloczynnikowej, z uwzględnieniem istniejących czynników ryzyka (wiek, D-dimery), na ile pomiar stężenia TSH pomoże przewidzieć ryzyko wystąpienia powikłań zatorowo-zakrzepowych.

Wyniki: Dwustu trzydziestu dwóch pacjentów spełniało kryteria do analizy ostatecznej; średnia wieku wynosiła 70 lat (IQR 58–80), stosunek mężczyzn do kobiet 124/108. Powikłania zatorowo-zakrzepowe potwierdzono u 124 pacjentów (53, 4%). Stężenie TSH było znacznie wyższe u pacjentów, u których wykryto żylne powikłania zatorowo-zakrzepowe (średnia 2,17 *vs.* 1,76 mIU/l; p = 0,0104), stężenie wolnej T4 nie wykazało znaczących różnic. Analiza krzywej ROC wykazała wartość graniczną TSH na poziomie > 2,686 mIU/l jako czynnik prognostyczny żylnych powikłań zatorowo-zakrzepowych z przewagą ich występowania u 47,1 *vs.* 66,7% pacjentów ze stężeniem TSH poniżej i powyżej wartości granicznej, p = 0,011. Wieloczynnikowa regresja logistyczna określiła pięć niezależnych czynników prognozujących obecność żylnych powikłań zatorowo-zakrzepowych: płeć męska (iloraz szans (OR), OR = 2,22); D-dimery > 0,5 mg/l (OR = 16,42); CRP > 5 g/l (OR = 9,178); TSH > 2,686 mIU/l (OR = 2,269) oraz wiek (OR = 0,9767/rok).

Wnioski: Wśród pacjentów z podejrzeniem żylnych powikłań zatorowo-zakrzepowych, stężenie TSH okazało się niezależnych czynnikiem prognostycznym obecności tych powikłań, oprócz płci, D-dimerów, białka C-reaktywnego (CRP) oraz wieku.
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Słowa kluczowe: *żylne powikłania zatorowo-zakrzepowe; tyreotropina; wolna tyroksyna*

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Introduction

Venous thromboembolism (VTE) represents an important cause of morbidity and mortality in developed countries. In recent decades several risk factors for VTE, both genetic and acquired, have been described [1, 2]. The relationship between thyroid hormones and the coagulation–fibrinolytic system was reported for the first time a century ago. In 1913, Kaliebe reported an episode of cerebral vein thrombosis in a patient with thyrotoxicosis [3].

The pathogenesis of coagulopathies associated with thyroid diseases may include direct and indirect effects of excess or deficiency of thyroid hormones on platelet maturation and function, as well as on the synthesis and action of coagulation factors and on altered blood viscosity [4]. Thyroid autoimmunity may also modify the processes of primary and secondary haemostasis [3]. Overall, the interference of thyroid hormones with the homeostasis of the coagulation-fibrinolytic system seems to be complex and its pathogenetic mechanism might be individually determined in a particular patient depending on the aetiology of thyroid dysfunction as well as on other factors influencing the final risk of VTE.

It is generally assumed that serum free thyroxine (fT4) levels are related to altered coagulation parameters, especially FVIII, fibrinogen, FIX, and von Willebrand factor (VWF). It remains unknown whether this effect on coagulation is partially mediated by TSH. Recently, more evidence has been provided showing that TSH itself can have a direct effect in peripheral tissues such as bone, adipose tissue, and muscle, mediated via the TSH receptor [5, 6]. Therefore, the question of whether TSH also affects the coagulation system remains to be answered [7].

Changes in coagulation–fibrinolytic disorders occur in patients with thyroid diseases and may range from subclinical laboratory abnormalities to clinically significant disturbances of coagulation and, more rarely, life-threatening haemorrhages or thrombotic events [4] According to recent literature, patients with hypothyroidism seem to have an increased risk of bleeding [8], and patients with hyperthyroidism might be at risk of thrombotic events. However, this finding has not been replicated across different patient populations [9].

Thus, there are data supportive of the hypothesis that thyroid function-induced disturbances have an impact on the coagulation-fibrinolytic system, but it is unclear whether the assessment of TSH or thyroid function in clinical practice might represent a useful tool to estimate the risk of VTE in a particular patient. In the present study, we prospectively assessed TSH and free T4 concentration in patients with clinical suspicion of VTE.

Material and methods

All consecutive patients hospitalised with clinical suspicion of VTE in a single centre between January 2009 and August 2012 were prospectively considered for the study. The inclusion criteria were as follows: hospitalisation for suspected VTE in cases with symptoms and signs of deep venous thrombosis (calf pain or tenderness, swelling, warmth, redness or discoloration, dilatation of superficial veins) and/or pulmonary embolism (dyspnoea, tachypnoea, chest pain, cough, haemoptysis, cyanosis, collapse, or circulatory instability). The decision regarding suspicion of VTE was made by the admitting physician. Additionally, each patient had at least one confirmatory test. VTE was confirmed or excluded by a test selected by the clinical context. Pulmonary CT angiography was carried out in all cases with suspected pulmonary embolism. In positive cases, a lower extremity venous ultrasound (LEVU) was performed. Patients with suspected deep venous thrombosis had a LEVU and were not routinely screened for concomitant pulmonary embolism. LEVU was performed in a supine position for the femoral and popliteal veins and in the sitting position for the deep calf veins. Deep venous thrombosis (DVT) is defined as a failure to fully collapse the lumen of a deep vein with compression. In all cases the following deep veins were examined: iliac vein, superficial femoral veins, popliteal veins, and the upper third of the deep calf veins.

Patients with no confirmatory VTE test or cases hospitalised for diagnoses other than VTE and eventually developing VTE during hospitalisation were not included. We also excluded patients with a history of known thyroid disease and cases without available complete laboratory results.

All laboratory parameters were tested on admission or during the first 24 hours of hospitalisation. D-dimer, CRP, full blood count, serum thyrotropin (TSH), and free thyroxine (fT4) were assessed by standard automated laboratory analysers using commercially available kits, with normal TSH defined between 0.5 and 5.0 mIU/L and free thyroxine (fT4) between 11.5 and 22.7 pmol/L. Since the aim of our study was focused only on the screening of TSH and fT4, in these cases thyroid antibodies could not be evaluated because such examinations are not reimbursed by the public healthcare companies.

Statistical analysis

Results of parameters with normal (Gaussian) distribution confirmed by d´Agostino-Pearson test are given as a mean and standard deviation but most commonly the median and interquartile range are provided. All nonparametric parameters were compared by Mann-Whitney rank

Table I. *Summary statistics of the study group*
Tabela I. *Miara rozkładu cech badanej grup*

Summary statistics table of the study qroup (n = 232)	Non VTE group (n = 108)		VTE group (n = 124)		p
	Median	IQR	Median	IQR	
Age	74 5	60.500 to 83.000	68	53.000 to 78.000	0.0051
Male gender	33%	0.000 to 1.000	50.40%	0.000 to 1.000	0.0146
Body mass index [kg/m^2]	26.67	27.18 to 32.03	28.68	25.41 to 32.81	0.1369
D dimer [mg/L FEU]	1.5	0.740 to 4.405	6.57	2.545 to 12.590	<0.0001
CRP [g/L]	21.35	5.30 to 78.59	31	16.2 to 84.53	0.0072
fT4 [pomo/L]	15.03	12.940 to 17.230	14 84	13.745 to 16.855	0.0725
TSH [mlU/L]	1.763	0.769 to 2.686	2.17	1.293 to 3.620	0.0104
Neutrophil count	6 61	4.74 to 9.07	6.82	5.08 to 9.180	0.777
Lymphocyte count	1.375	1.00 to 1.80	1.53	1.058 to 2.030	0.2621
Neutrophil lymphocyte ratio	4.715	3.171 to 7.156	4.133	3.031 to 7.383	0.5171
Platelet count x 10(9)/L	246	194 to 293.5	220	177 to 280	0 154 1
Mean platelet volume	10.6	10.1o to 11.40	10.5	9.90 to 1.125	0.298
International normalized ratio (INR)	1.07	1.008 to 1.162	1.09	1.01 to 1.19	0.4873
	%		%		
TSH above normal range [> 4.87 mlU/L]	11.2		13.2		0.8275
TSH below normal range [< 0.5 mlU/L]	14 3		6.14		0 0803
TSH >2.686 [mlU/L]	24.5		42.1		0.0106
D dimer above normal range	87		99.2		< 0.0001
CRP >5 q/L	76.4		95.9		< 0.0001

sum test. The risk of VTE in various categorical groups was compared using the chi square test. Subsequently, the receiver operating curve analysis was carried out to identify the TSH cut-off point with the best predictive power for VTE. Multivariate logistic regression analysis was performed with VTE as a dependent variable. For independent variables we selected parameters with significant differences between the VTE and non-VTE groups (gender, D-dimer, C reactive protein, TSH levels above the identified cut-off). Odds ratios with 95% confidence intervals were calculated for each parameter. Finally, we calculated the Spearman correlation coefficient between TSH and INR and the mean platelet volume. We used the statistical software package MedCalc v. 14, by MedCalc Software, Ostend, Belgium.

Results

A total of 232 patients met the inclusion criteria and were available for the final analysis. VTE was confirmed in 124 patients (53.4%) and excluded in 108 (46.6%). A summary of statistics comparing both groups is displayed in Table I.

Univariate analysis showed that cases with VTE were more often male and had significantly lower age, higher D-dimer and C reactive protein, and higher TSH concentration (Fig. 1, Table I) However, free T4 concentration was not different (fT4 14.84 *vs.* 15.03 pmol/L, p = 0.0725), and the prevalence of VTE did not differ between the first and the fourth free T4 quartiles (44.4 *vs.* 51.16%, p = 0.1276).

The ROC curve analysis of TSH as a predictor of VTE found that TSH > 2.686 mIU/L had a sensitivity of 42.1% and specificity of 75.5%, AUROC = 0.602 (0.525–0.679). TSH concentration below and above this cut-off was significantly associated with the risk of VTE 47.1 *vs.* 66.7%, p = 0.011 (Fig. 2).

Multivariate logistic regression using parameters significantly different between the VTE and non-VTE group included age, gender, CRP, D-dimer, and TSH. All five parameters were confirmed as independent predictors of VTE: age (odds ratio, OR = 0.9767/year, 95% confidence interval (CI) 0.9576–0.9961), D-dimer > 0.5 mg/L FEU (OR = 16.64, 95% CI 2.04–135.46), CRP > 5 g/L (OR = 9.29, 95% CI 2.5–34.4), TSH > 2.686 mIU/L (OR = 2.307, 95% CI 1.17–4.54), and male gender (OR 2.01, 95% CI 1.06–3.81), with 70.05% of cases correctly classified (Table II).

Considering the underlying mechanism of VTE in cases with increased TSH, we confirmed that cases with TSH above the normal range had significantly

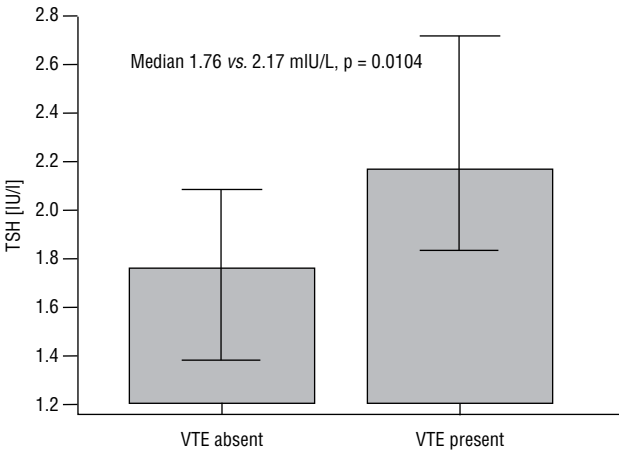

Figure 1. *TSH concentration in nonVTE and VTE groups in 232 consecutive patients*

Rycina 1. *Stężenie TSH w grupie 232 pacjentów nonVTE i z VTE*

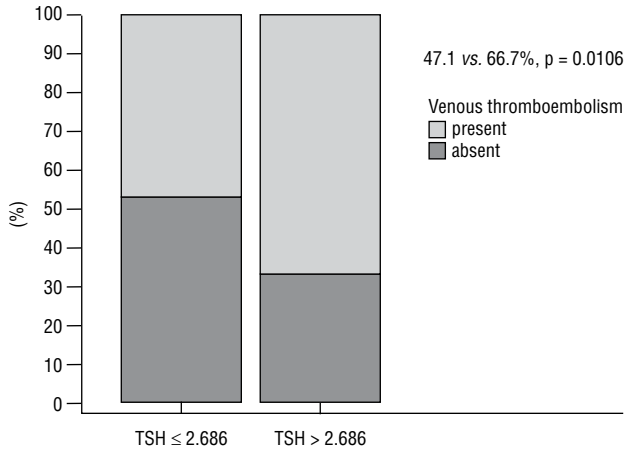

Figure 2. *Prevalence of VTE in cases below or above the identified TSH cutoff 2.686 mIU/L*

Rycina 2. *Przewaga VTE w przypadkach niższej lub wyższej stwierdzonej wartości granicznej TSH 2,686 mIU/l*

Table II. ***Multivariate logistic regression of predictive factors of venous thromboembolism in 232 consecutive cases***

Tabela II. ***Wieloczynnikowa regresja logistyczna czynników predykcyjnych dla żylnej choroby zakrzepowo-zatorowej w grupie 232 pacjentów***

	Oddsratio	95% confidence interval	p
D dimer above normal	16.6463	2.0456 to 135.4606	0.0086
CRP above normal	9.2909	2.5048 to 34.4626	0.0009
TSH > 2.686 mIU/L	2.3079	1.1722 to 4.5438	0.0155
Male	2.0108	1.0620 to 3.8073	0.032
	0.9767	0.9576 to 0.9961	0.0189

P < 0.0001, 70.05% of cases correctly classified,
AUROC = 0.773 (0.709–0.828)

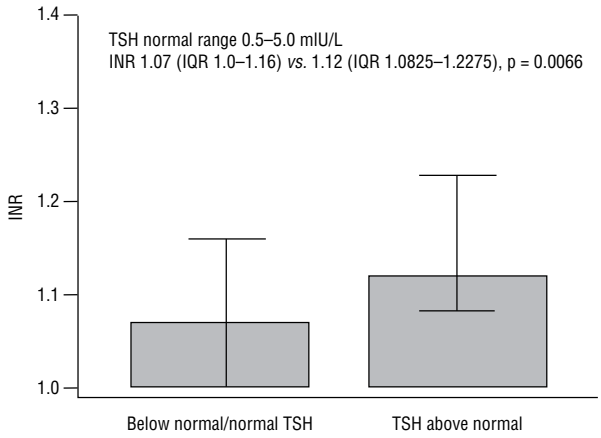

Figure 3. *INR values in cases with low and normal TSH vs. high TSH*

Rycina 3. *Wartości INR dla pacjentów z niskim lub prawidłowym stężeniem TSH vs. wysokim stężeniem TSH*

higher INR compared to cases with normal or low TSH, median 1.12 *vs.* 1.07, p = 0.0066 (Fig. 3). There was also a significant positive correlation between INR and mean platelet volume (rho = 0.185, p = 0.0070). However, we found no significant correlation between TSH and INR or TSH and mean platelet volume, rho = 0.113, p = 0.11 and rho = 0.008, p = 0.90.

Discussion

In the present study, we prospectively evaluated the clinical value of TSH measurement in determining the risk of VTE in patients hospitalised with clinical suspicion of VTE. We found that patients with TSH > 2.69 mIU/L regardless of the thyroid dysfunction had an elevated risk of VTE compared with patients with TSH below this cut-off. In addition, TSH above this cut-off was an independent predictor of VTE as well as age, D-dimer, CRP, and male gender. Cases with TSH above the normal range had slightly higher INR, but we found no correlation between TSH and INR or mean platelet volume.

Clinically overt hypothyroidism and hyperthyroidism can modify the haemostatic system in opposite directions [10]. Disorders of the coagulation-fibrinolytic system usually range from mild to moderate and rarely cause severe laboratory abnormalities. Some reports showed that patients with overt hyperthyroidism

had shortened activated partial thromboplastin time, higher fibrinogen levels, and significant increases in the turnover of factor FII, FVII, and FX [11]. Similarly, patients with hyperthyroidism were found to have decreased levels of FIX, von Willebrand factor (VWF), antithrombin, and PAI-1, as well as decreased levels of t-PA, suggesting reduced plasma fibrinolytic capacity and predisposing them to a hypercoagulable state [12, 13]. Furthermore, studies have demonstrated that in hyperthyroid patients the balance between t-PA and PAI-1 appears to favour PAI-1, resulting in impaired endothelial function. Therefore, patients with hyperthyroidism may often have accompanying endothelial dysfunction and hypercoagulable states that contribute to the development of venous thrombosis and increased risk of PE [14].

Coagulation abnormalities in patients with thyroid deficiency consist of a defect of primary haemostasis, which results in a bleeding tendency that is usually mild (e.g. nose or gingival bleeding, menorrhagia, easy bruising), but which can, rarely, be severe (e.g. haemorrhages following trauma or surgery) [15]. Coagulation tests in patients with hypothyroidism usually show prolongation of the APTT and a normal or slightly shortened PT, reflecting the abnormalities of the related coagulation factors [16, 17] Hypothyroidism, which is usually associated with depression of a variety of coagulation factors, was first observed by Egeberg and Simone, who found a significant decrease of factor VIII, IX, and XI levels in hypothyroid patients [18]. Other studies described low levels of plasma coagulation factors VII, X, and XII [16].

Conversely, one recent retrospective study based on National Hospital Discharge Survey data showed contradictory results. Danescu et al. reported that among 633,000 US patients discharged from non-Federal hospitals with hyperthyroidism during the years 1979–2005, the risk of PE and DVT was not significantly higher than in all other patients with no thyroid dysfunction (relative risk 0.98, 95% CI 0.96–1.01). A high risk of VTE was shown in patients with hypothyroidism but not in those with hyperthyroidism.

In a large population-based case-control study (MEGA-study) into the aetiology of VTE levels of fT4, TSH, and antiTPO and coagulation factors FII, FVII, FVIII, FIX, FX, and VWF, antithrombin, protein C and S, and fibrinogen were determined. High levels of fT4 were associated with increased concentrations of procoagulant factors, and not with levels of the anticoagulant factors. High levels of fT4 were also associated with the risk of VTE, up to an OR of 2.2 (95% CI 1.0–4.6) for levels above 24.4 pmol/L relative to fT4 levels between 15.5 and 18.9 pmol/L. Low TSH levels were also, but less evidently, associated with thrombosis, while there was no association with antiTPO and VTE risk [19].

Thus, arguments from observations published thus far are rather conflicting and the underlying mechanism is therefore speculative. More specifically, it is not clear whether it is related to the effect of thyroid hormones or this effect is a direct effect of TSH, or if TSH itself is only a biomarker reflecting the overall increased risk of VTE from other causes. The results of our study suggest that this effect is independent of the thyroid function since free T4 levels were not significantly associated with the risk of VTE. From our data and from the available evidence we might speculate that increased TSH could influence both the coagulation cascade and the platelet volume and function. Slightly elevated INR in cases with high TSH could be one part of the mechanism, but alone it does not seem to shift the coagulation balance. The other part of the mechanism could be the platelet function. Recent reports showed that in subjects with subclinical hypothyroidism defined by elevated TSH levels above the normal rage, there was an increase in the mean platelet volume (MPV). Thus, in cases with TSH above the normal range, and even among subjects with upper TSH tertiles, the increased risk of VTE could be explained by larger and more activated platelets [20, 21]. However, in our study we measured the platelet count and the mean platelet volume and we did not observe any significant differences. We found a positive correlation between INR and the mean platelet volume but no correlation between TSH and INR or MPV. This finding might be due to the methodology of MPV measurement, which in our case was done only on automated analysers. The same was true for the differential while blood cell count, which had no predictive value for VTE in our study (Table I).

When comparing our results with the above-mentioned studies one must keep in mind that our study was carried out on a different study population, namely hospitalised cases with high risk of VTE and with no clinical indices of thyroid dysfunction. It was specifically designed to assess the clinical benefit of determining TSH and fT4 as a putative predictive factor of VTE risk in this clinical context. We found that TSH, but not free T4, above a defined cut-off is associated with higher risk of VTE. However, TSH values are in the normal range in the vast majority of cases and our cut-off was in the mid-range of normal values. Thus, TSH appears to be a biomarker of VTE independently of the thyroid function and other well-known VTE predictors (D-dimer, age, gender, CRP). However, the question remains whether TSH values are influenced by the thyroid function or by other factors in the context of an acute illness and comorbidities, or both. This finding must therefore be confirmed by a prospective study designed specifically to assess the complementary role of TSH to the currently used risk assessment indexes

(Wells score, etc.), which is not provided by our study and is currently underway.

A similar concept of TSH as a biomarker was already described in another non-thyroid pathology: metabolic bone disease [22]. The level of TSH concentration within the normal range was found to be a marker of bone health and a predictor of hip fractures in women [23].

The surprising finding of age as a protective factor of VTE can be explained by our particular study population. Older patients had a higher probability of alternative causes of this clinical condition, namely lung infection and/or cardiac failure, cellulitis, or anaemia, and therefore their relative prevalence of VTE was lower compared to younger patients. The same was true about the elevated C reactive protein as a risk factor of VTE. Some studies previously reported that normal CRP could have a role in excluding pulmonary embolism [24, 25]. Elevated CRP was probably caused by multiple factors such as infection, which is itself a risk factor for VTE, but also by the deep venous thrombosis. Moreover, cases with normal CRP were more likely to have an alternative diagnosis, such as anaemia or congestive heart failure, which could have a similar clinical picture to VTE.

Our study has several limitations. The study group included patients with several comorbidities, which could influence the clinical and the laboratory picture. The exact impact and quantification of present comorbidities on the risk of VTE itself could not be assessed. Furthermore, TSH values could also be influenced by the comorbidities and the context of an acute illness. It was therefore impossible to evaluate the effect of acute illness and comorbidities on the concentration of TSH. Nevertheless, TSH in our study was associated with VTE independently of age, the strongest predictor of concomitant diseases and TSH values.

In conclusion, TSH seems to be related to an increased risk of VTE independently of age, gender, CRP, and D-dimer and independently of thyroid function. Further studies are needed to provide definite answers on the usefulness of TSH measurement in the prediction of VTE and on the mechanism underlying this association.

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