RISK FOR POST-THROMBOTIC SYNDROME AFTER LOWER-LIMB DEEP VEIN THROMBOSIS: LOCATION OF THE THROMBUS OR RESIDUAL THROMBI?

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Background. Many works aimed to determine factors that influence the onset of postthrombotic syndrome after an acute episode of deep venous thrombosis. We aimed to compare the prognostic value of the most proximal extent of thrombus (proximal and distal DVT) versus the residual thrombosis as identified by venous ultrasonography performed during follow-up.

Method. We conducted a retrospective study of prospectively collected 1183 consecutive cohort patients in the RIETE registry after a first episode of deep venous thrombosis and assessed for postthrombotic syndrome after 12 months.

Results. Multivariate analysis revealed that: residual thrombosis (OR 1.40; 95% CI 0,88–2,21), the presence of cancer (OR 1.38; 95% CI: 0,64–2,97), immobility (OR 1.31; 95% CI 0,70–2,43) and estrogen-containing drugs use (OR 2.08, 95% CI 0,63–6,83), all had a predictive value for the occurrence of PTS.

Conclusion. Our study results revealed that ultrasound finding of residual thrombosis is more predictive than proximal location of thrombus for postthrombotic syndrome after episode of deep venous thrombosis. Real life data from a large group of patients from the RIETE registry substantiates that.

Key words: *post-thrombotic syndrome, deep vein thrombosis, risk factors*

INTRODUCTION

Post-thrombotic syndrome (PTS) is a chronic manifestation of venous insufficiency following a deep vein thrombosis (DVT), usually in the lower limbs [1]. The most serious complication of PTS is the occurrence of a venous ulcer, that is associated with a poor prognosis and has an important socio-economic impact [2]. The reported incidence of PTS varies widely according to patient and DVT characteristics, including the location of the DVT, time lag between DVT and PTS assessment and the use of treatment for DVT [3–10]. A challenging issue in routine clinical practice for clinicians is to try to predict what patients with acute DVT are at an increased risk to develop signs and/or symptoms of PTS several months or years later. As there is no successful curative therapy for PTS, the best treatment lies in its prevention [11–13].

The RIETE (Registro Informatizado Enfermedad Trombo Embólica) registry is an ongoing, multicenter, observational registry of consecutive patients with objectively confirmed acute venous thromboembolism (VTE). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, major bleeding or mortality, and risk factors for these outcomes [14–16]. The rationale and methodology of RIETE have been published elsewhere [17]. In the current study, we aimed to compare the prognostic value of the most proximal extent of thrombus (proximal and distal DVT) versus

* A full list of the RIETE investigators is given in the appendix.

Table 1

Clinical characteristics at baseline, according to the presence or absence of residual thrombosis or PTS during follow-up

Characteristic	Residual thrombus only	PTS signs or symptoms only	Both Conditions	Neither
Patients, N	545	103	64	471
Clinical characteristics,				
Male	327	54	38	234
Age (mean years±SD)	57,4+17,4	58,9±17,9	61,3±15,8	58,6±17,9
Risk factors for VTE,				
Immobility ≥4 days	97	16	12	110
Surgery	41	15	10	74
Active cancer	60	10	4	66
Estrogen use	39	4	2	50
Pregnancy/postpartum	8	1	0	8
None of the above				
Leg varicosities	126	41	24	99
Prior VTE	73	20	56	60
DVT characteristics,				
Proximal	485	91	56	401

the residual thrombosis as identified by venous ultrasonography performed during follow-up.

PATIENTS AND METHODS

Consecutive patients with acute symptomatic DVT or pulmonary embolism (PE) confirmed by objective tests (venous ultrasonography or contrast venography for DVT; helical CT-scan of the chest, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE (ClinicalTrials.gov identifier: NCT02832245). Patients were excluded if they were currently participating in a blind therapeutic clinical trial. All patients (or their relatives) provided written or oral informed consent for participation in the registry, in accordance with local ethics committee requirements.

STUDY DESIGN

For this study, only patients with acute symptomatic and objectively confirmed DVT in the lower-extremities who had been assessed for either residual thrombosis between 3 and 6 months after presentation or for PTS signs and symptoms after 12 months, were considered. PTS was defined with at least 5 points in the Villalta score. We excluded patients with: upper limb DVT and those who developed DVT recurrences during the study period. The major outcome was the occurrence of PTS signs or symptoms in the ipsilateral leg during the first year of follow-up, as assessed by a physician trained in the management of vascular diseases. Signs and symptoms of venous insufficiency collected at the study centres were the same than those required for the Villalta score and instrumental examinations recommended by the International Society on thrombosis and Haemostasis to assess PTS.1 Signs are physician-rated, whereas symptoms are patient self-rated; each item is noted as present or absent. We considered patients to have PTS when having at least 5 symptoms or signs of the Villalta score [1]. Residual thrombosis was defined as a loss of compressibility and presence of organized thrombus on same location at ultrasound examination at 12 months after the DVT episode [2].

STUDY VARIABLES AND DEFINITIONS

The following parameters are recorded in RIETE: patient's baseline characteristics; clinical status including risk factors for VTE. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with or without bathroom privileges) for ⩾4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE. Active cancer was defined as newly diagnosed cancer (<3 months before) or when receiving anti-neoplastic treatment of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support therapy or combined therapies). Recent bleeding was considered in those patients suffering major bleeding <30 days prior to VTE.

FOLLOW-UP

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). After DVT diagnosis, patients were followed-up in the outpatient clinic for at least 12 months. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat venous ultrasonography, lung scanning, helical-CT scan or pulmonary angiography as appropriate.

STATISTICAL ANALYSIS

Qualitative data were reported as numbers (1 or 0). Quantitative data were reported as mean with standard deviation or median with interquartile ranges. We estimated the cumulative rate of PTS at one year using the Kaplan-Meier method. We examined the relationship between each potential risk factor/confounder of PTS and the relative risk of PTS at one year using random-effects Cox model. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were

calculated. P values were considered statistically significant at a level of 0.05 or less. Data were processed and analysed using SPSS software (version 20).

Table 2

Multivariate analysis on risk factors on PTS

Risk factors	B	S.E.	Exp (B)	95% C.I. for EXP (B)	
				Lower	Upper
Proximal thrombosis	-,510	,446	,601	,250	1,440
Cancer	,322	,391	1,380	,641	2,972
Previous surgery	-,545	,321	,580	,309	1,087
Immobility	,269	,316	1,309	,704	2,432
Use of estrogens-containing drugs	,731	,607	2,076	,631	6,826
Varices	-1,044	,229	,352	,225	,551
Travel longer than 8 hours	-,659	,469	,517	,206	1,297
Residual thrombosis	,334	,234	1,397	,883	2,209
Constant	2,695	,585	14,807		

RESULTS

From January 2013 to January 2018, 1183 patients presenting with acute symptomatic DVT in the lower limbs were evaluated for residual thrombosis 3–6 months after DVT diagnosis and for PTS signs and/or symptoms 12 months after DVT diagnosis. Of these, 623 (53%) were men, mean age was 45.3±14.7 years, and 983 (83%) had proximal DVT. Their clinical characteristics are shown in Table 1. During follow-up, 545 patients had signs of residual thrombosis on compression ultrasonography. Twelve months after DVT diagnosis, 167 patients (14%) had developed signs and/or symptoms of post-thrombotic syndrome. Residual thrombosis was found in 545 patients (50.3%).

On multivariable analysis, patients with proximal DVT at baseline did not have a significantly higher risk to develop signs and/or symptoms of PTS one year later (Table 2). Notable results were that the presence of cancer had prognostic value (OR 1.38; 95% CI: 0,64–2,97). Furthermore, immobility and the use of estrogens-containing drugs proved their prognostic values (OR 1.31; 95% CI 0,70–2,43 and OR 2.08; 95% CI 0,631–6,826, respectively). Lastly, residual thrombosis also held a prognostic value (OR 1.40; 95% CI 0,88–2,21), while proximal thrombosis did not show prognostic value (Table 2).

DISCUSSION

Our findings, obtained from a large cohort of consecutive patients with a first episode of lower-limb DVT, reveal that 14% of them had developed PTS signs and/or symptoms one year later. Of these, 2,5% had developed a venous ulcer, the most feared complication after DVT.

The risk of developing PTS after an initial DVT episode is a field that does leave some room for further research. Studies by Tick, et al. and by Yamaki, et al. found proximal thrombosis at entry and residual thrombosis, as independent predictors for PTS [14–15]. Other studies also have reiterated multiple DVT and ipsilateral thrombosis recurrence as positive prognostic factors for PTS, as well as the ilio-femoral localization as more likely to develop PTS [16–18]. Surgery previous to the DVT episode also holds predictive value [19]. The role of compressive stockings in PTS prevention post-DVT has been reaffirmed, and accentuated when used in concordance with the Villalta score assessment. Also, more extensive DVT was associated with PTS [20]. Furthermore, preexisting leg varicosities independently increase the risk of PTS venous ulcers [21]. Poor INR control is also cemented as a risk factor for PTS [22–23]. Galanaud, et al., in 2013, had a great study that affirmed residual venous thrombosis as a positive prognostic factor for PTS [11]. Siragusa, et al., looked at residual thrombosis and the role of discontinuing anticoagulant therapy, and identified that patients without residual thrombosis at one year were relatively safe to discontinue anticoagulant therapy [5]. A review by Kahn in 2014 accentuated the critical role of the clinical scales that were specifically designed for diagnosing PTS after DVT, specifically the Villalta, Ginsberg and Brandjes clinical scales [1]. A study by Michiels, et al., in 2015, affirmed the role of the Villalta score in concordance with compression ultrasonography of the leg veins, as part of regular follow-up evaluation for PTS [24]. A study by Rabinovic, et al., in 2017, affirms that residual thrombosis, together with venous reflux, is a cornerstone of PTS occurrence [25]. This review article, more specifically confirms that residual venous obstruction, together with valvular reflux, cause chronic venous hypertension, itself believed to play a major role in the pathophysiology of PTS [25]. The authors also note the important role of proximal DVT, as well as recurrent ipsilateral DVT, as two principal established risk factors for PTS [25]. Symposium summary, by Henke, et al., in 2010, accentuated the importance of the use of the Villalta scale primarily, with a secondary use of the CEAP classification. The authors also affirm recurrent ipsilateral DVT as a primary risk factor for developing PTS [26]. A study by Tick, et al., in 2010, establishes the male sex, age of ⩾50 years, proximal localization of the thrombus at entry, residual proximal thrombosis and superficial valvular reflux at 6 weeks, as the most important predictors for PTS [27]. More specifically,

residual thrombosis and valvular reflux were established as a predictive factors based on duplex measurements of 17 vein segments, an elaborate examination by any standards [27]. Le Gal, et al. studied the role of residual vein thrombosis as a predictor for thromboembolic events after the initial DVT episode [28]. The study found that patient with minimal vein wall changes at baseline had no significantly increased risk in comparison to patients with no wall changes. They concluded that residual vein obstruction at the time of oral anticoagulation therapy withdrawal was not associated with a higher risk of recurrent DVT [28]. A study by Galanaud, et al. showed that residual thrombosis evidenced by venous ultrasound is associated with PTS [11]. Concordantly, a study by Labropoulos, et al., established recurrent thrombosis as a risk factor for PTS [16]. An excellent research article by Janakiram, et al, in 2013, explored the role of residual venous obstruction as a risk for recurrent DVT. The authors showed that residual venous obstruction is a risk factor, with a significant level of confidence (OR 1.93, 95% CI: 1.29–2.89, I2=64%) [29]. The most notable limitation of our study is the fact that the study is not randomized. A large non-homogenous population of patients formed the study population, with patients selected from international centres. Another limitation of our study is the fact that the absence of data on the type of medicamentous treatment implemented, as well as the absence of data regarding the use of compressive stockings for all patients included. One strength of the study is that the large population of patients with PTS analyzed is certainly one of the largest to date from real life. Although the diagnosis PTS was made in many different centres, the imaging specialists included in the RIETE registry are at a high level, giving weight and certainty to the formed diagnosis with continued low inter-observer variability.

We found that DVT patients with residual thrombosis were at an increased risk to develop PTS, as were patients with cancer. Early identification of at-risk patients would likely help to provide these patients with accurate information on what measures should they reinforce, and which measures should be avoided. In near future we need a more relevant new study trying to identify predictors of PTS.

CONCLUSION

Our study results reveal that ultrasound finding of residual thrombosis is more predictive than proximal location of thrombus for postthrombotic syndrome after episode of deep venous thrombosis. We can still use classical risk factors added to ultrasound findings of residual thrombosis in prediction of postthrombotic syndrome after an episode of deep venous thrombosis. Real life data from a large group of patients from the RIETE registry substantiates that.

Conflict of interest: none declared.

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APPENDIX

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