REVIEW ARTICLE

How to predict and diagnose postthrombotic syndrome

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KEY WORDS

deep vein thrombosis, diagnosis, postthrombotic syndrome, risk factors

ABSTRACT

Postthrombotic syndrome (PTS) is the most frequent complication of deep vein thrombosis (DVT). From 20% to 50% of the patients will develop PTS after DVT, and from 5% to 10%, severe PTS. PTS is diagnosed on clinical grounds, based on the presence of signs and symptoms of venous insufficiency in the leg ipsilateral to DVT. The Villalta scale, a clinical scale that incorporates venous symptoms and signs, is a recommended standard for the diagnosis of PTS. Identifying which patients are at high risk of developing PTS would help improve the management of patients with DVT and allow physicians to provide patients with individualized information on their expected prognosis. Clinical predictors of PTS have been progressively characterized, but the ability to predict which patient with DVT is likely to develop PTS remains limited. A number of risk factors for PTS have been identified; of these, proximal location of DVT and a previous ipsilateral DVT are the most important. This review discusses the knowledge gained over the last decade on the diagnosis and predictors of PTS.

Introduction Postthrombotic syndrome (PTS) is the most common chronic complication of deep vein thrombosis (DVT). PTS develops in 20% to 50% of the patients within the first 2 years after the diagnosis of DVT,[1,2] even when patients are adequately treated with anticoagulants. The severity varies from minimal discomfort to severe clinical manifestations such as chronic pain and intractable edema. Severe PTS, which includes leg ulceration, develops in 5% to 10% of the patients.[2-4]

The estimated incidence of venous thromboembolism (VTE) is from 0.7 to 2 per 1000 person-years.[5,6] More than one-third of the cases occur in persons older than 60 years of age.[7] VTE is a growing public health problem largely due to the aging population. Hence, it is expected that the prevalence of PTS in the population will increase.

The pathophysiology of PTS is not fully understood, but likely involves the interplay of damage to delicate venous valves in the days to weeks following acute DVT, residual venous thrombosis or obstruction due to incomplete fibrinolysis, and impaired microcirculation due to persistent venous hypertension.[8-10]

This review focuses on the diagnosis and risk determinants of PTS after DVT in adult patients.

How to diagnose postthrombotic syndrome? **Clinical presentation** PTS is termed a "syndrome" because it is associated with a cluster of symptoms and signs that vary from patient to patient. Symptoms include aching pain, heaviness, swelling, cramps, itching, or tingling along the affected limb and, infrequently, the so called venous claudication, consisting of a bursting pain in the leg when walking.[11] These may be present in varying combinations and can be persistent or intermittent. Typically, symptoms are made worse by standing or walking and improve with rest and recumbency. Signs include edema, usually an early clinical sign, followed at different times by lipodermatosclerosis (a brawny, tender induration of the subcutaneous tissue of the medial lower limb) and eczematous skin changes. Some patients develop secondary superficial varicose veins as the syndrome evolves. Venous ulcers may develop, often precipitated by a minor trauma. Further typical features of ulceration are a chronic and indolent course, and its main location in the medial ankle region. Stasis ulcers are rich in fibrin, superficial, show inflamed edges, and often tend to recur once fully healed.[4,11,12] The clinical presentation of PTS is nonspecific, and conditions other

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Received: May 16, 2014.
Revision accepted: May 20, 2014.
Published online: May 23, 2014.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2014; 124 (7-8): 410-416

TABLE 1 Main scoring systems for postthrombotic syndrome (PTS)

Villalta scale					CEAP classification	
symptoms	none	mild	moderate	severe	clinical	
pain	0 point	1 point	2 points	3 points	C0	no signs of venous disease
cramps	0 point	1 point	2 points	3 points	C1	telangiectasias or reticular veins
heaviness	0 point	1 point	2 points	3 points	C2	varicose veins
paresthesiae	0 point	1 point	2 points	3 points	C3	edema without skin changes
pruritis	0 point	1 point	2 points	3 points	C4a	pigmentation or eczema
					C4b	lipodermatosclerosis/atrophie blanche
					C5	healed venous ulcer
					C6	active venous ulcer
					S	superscript "s" added to any of the above for symptomatic PTS, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
					A	superscript "a" added to any of the above for asymptomatic PTS
signs	none	mild	moderate	severe	etiologic	
pretibial edema	0 point	1 point	2 points	3 points	Ec	congenital
skin induration	0 point	1 point	2 points	3 points	Ep	primary
hyperpigmentation	0 point	1 point	2 points	3 points	Es	secondary (postthrombotic)
redness	0 point	1 point	2 points	3 points	En	no venous cause identified
venous ectasia	0 point	1 point	2 points	3 points		
pain on calf compression	0 point	1 point	2 points	3 points		
	present				anatomic	
venous ulcer	yes/no				As	superficial veins
					Ap	perforator veins
					Ad	deep veins
					An	no venous location identified
					pathophysiologic	
					Pr	reflux
					Po	obstruction
					Pr,o	reflux and obstruction
					Pn	no venous pathophysiology identifiable

In the Villalta scale, each symptom is self-rated by the patient and each clinical sign is rated by the clinician as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe), except an ulcer, which is marked as present or absent. All numeric points are summed to yield a total score: a score of 0–4 indicates the absence of PTS and a score of ≥5 indicates PTS (5–9, mild PTS; 10–14, moderate PTS; and >14 or the presence of an ulcer, severe PTS). CEAP encompasses clinical presentation, etiology of the venous disease, the type of veins involved, and the presence or absence of venous reflux and obstruction.

than DVT, such as primary venous insufficiency, chronic congestive heart failure, or trauma may produce similar symptoms or signs in the lower extremities.[10]

Timing of diagnosis Most cases of PTS develop within 2 years of acute DVT.[1,2,13] However, 2 studies demonstrated a gradual increase in the incidence of PTS during the first 4 to 5 years after DVT,[3,14] whereas another found no further increase in the overall incidence of PTS after 1 year, but a gradual increase in PTS severity over time.[15] Venous ulcer incidence ranges from 1% to 2% after 2 to 5 years[2,3,13,16] and from 2% to 10% up to 10 years after DVT, with a gradual increase in incidence over time.[17,18]

As the initial pain, leg heaviness, and swelling associated with acute DVT may take 3 to 6 months to resolve, the optimal timing of diagnosis of PTS is under debate. Over half of the patients meeting the criteria for moderate or severe PTS at 1 month are later reclassified as having milder or no disease.[2] Therefore, current recommendations advise that a diagnosis of PTS be deferred at least until 3 months after acute DVT.[19]

Scoring systems for postthrombotic syndrome There is no gold-standard objective test to diagnose PTS. The condition is primarily diagnosed on clinical grounds in a patient with characteristic manifestations of PTS and a previous episode of DVT. Six different scales have been used to define PTS in clinical studies: CEAP (clinical, etiologic, anatomic, pathophysiologic) classification; Widmer classification; venous clinical severity score; Villalta scale; Ginsberg definition; and Brandjes scoring

TABLE 2 Risk factors for postthrombotic syndrome

established risk factors
recurrent ipsilateral DVT
proximal DVT (particularly involving iliac or femoral veins)
obesity (BMI >30 kg/m^2)
presence of varicose veins prior to DVT
possible risk factors (more studies needed to confirm)
older age
female sex
residual DVT symptoms 1 month post-DVT diagnosis
residual thrombosis
valvular reflux or incompetence
asymptomatic DVT
≥20% of time spent below therapeutic INR range during first few months of anticoagulation
type of anticoagulant used
elevated inflammatory markers (CRP, IL-6, ICAM-1)
elevated D-dimer
certain SNPs
not risk factors
type of DVT event (provoked vs. unprovoked)
thrombophilia (including factor V Leiden, lupus anticoagulant, protein C or protein S deficiency, prothrombin 20210A mutation, and elevated factor VIII)
duration of anticoagulation

Abbreviations: BMI – body mass index, CRP – C-reactive protein, DVT – deep vein thrombosis, ICAM-1 – intracellular adhesion molecule-1, IL-6 – interleukin 6, INR – international normalized ratio, SNP – single nucleotide polymorphism

system.[19,20] The scales that are most commonly used in clinical practice are the CEAP and Villalta scales.[21,22] The CEAP classification was developed for chronic venous disease (CVD) in general, and combines findings into 7 classes of CVD with subcategories to denote etiologic, anatomic, and pathophysiologic attributes (TABLE 1). In order to improve standardization of the diagnosis of PTS and allow greater ability to perform cross-study comparisons, international guidelines now recommend using the Villalta scale to diagnose PTS and grade its severity[19] (TABLE 1). The Villalta scale shows several advantages over other PTS classifications: specific design for PTS,[1,20,22] high interobserver accordance,[15,20] and accuracy in reflecting patient-perceived quality of life and the clinical course of PTS.[12,13,15,20,23,24] However, the Villalta scale is a clinical measure, and hence does not provide information about the anatomic distribution of the original DVT, whether there is residual thrombosis with obstruction or reflux on ultrasonography, and the presence of healed ulcer is not considered. These important ancillary features are reported in the CEAP classification that can be used for research purposes jointly with the Villalta scale for PTS evaluation.[19,25] A recent systematic review that aimed to assess each of the scoring systems used to diagnose and classify PTS concluded that the Villalta score, combined with a venous disease-specific quality-of-life questionnaire, should be considered the gold standard for the diagnosis and classification of PTS.[26]

Imaging studies In the absence of clinical features of PTS in a patient with previous DVT, demonstrating the presence of venous abnormalities such as valvular reflux, persistent venous obstruction, or venous hypertension on invasive or noninvasive imaging does not indicate a diagnosis of PTS.[27] This is because, while many patients with symptomatic PTS have detectable venous abnormalities, many DVT patients who do not have symptoms of PTS can also be shown to have such abnormalities.[13,28] Therefore, there is no indication to routinely perform invasive or noninvasive venous testing in patients with a clear clinical diagnosis of PTS. Objective confirmation may be necessary to confirm the diagnosis of PTS in patients without a history of DVT, or if invasive intervention is contemplated.

Duplex sonography of the affected limb has become the initial investigation of choice. It can qualitatively identify the sites of reflux and stenosis. The presence of an echoic lumen, reduced compressibility, impaired augmentation of flow on distal compression, and reduced or absent phasity are qualitative parameters that can help identify previous DVT.[29] Quantitative assessment of the overall severity of reflux when multiple segments are involved can be performed. One of the most important drawbacks of duplex sonography is its inability to properly assess iliac vein thrombus.

Other modalities are used less often owing to limited availability, cost, or invasiveness. Intravascular ultrasound can provide better images of iliac vein and inferior vena cava thrombi.[30] Ascending venography is an invasive method of obtaining a panoramic view of lower limb venous outflow in the infrainguinal area. Ambulatory venous pressure (AVP) provides an overall assessment of venous dysfunction.[29] AVP is maximal in limbs having venous obstruction with reflux. Investigations such as magnetic resonance imaging and computed tomography provide 3-dimensional view of the venous tree.

Risk factors for postthrombotic syndrome

Because risk factors for PTS are incompletely understood, it is difficult to predict which patients with DVT will develop PTS. Improving our understanding of risk factors is an important initial step toward the development of effective management strategies for PTS.

Defining risk factors for PTS is an area of ongoing research: some have been well established, some have been found not to increase the risk for PTS, while others warrant a more rigorous study (TABLE 2).

Established risk factors for postthrombotic syndrome

Ipsilateral DVT recurrence was found to be the strongest risk factor for the development of PTS (5- to 10-fold increased risk).[1,3,31] This finding underlines the importance of preventing the recurrence of DVT by providing adequate intensity and duration of anticoagulation following the initial event, as well as of evidence-based

thrombophylaxis to prevent DVT in high-risk situations.

With regard to the relationship between the location of the initial DVT and the subsequent development of PTS, in most studies, the risk of PTS was higher in patients with proximal rather than distal DVT,[2,16,32,33] whereas in others, the site or extent of thrombosis did not predict the development of PTS.[1,31,34] Proximal DVTs are a heterogeneous group, comprising both iliofemoral and femoropopliteal DVT. This distinction is important because, in iliofemoral DVT, the obstruction is often above the entry of the profunda femoral vein, thereby impairing collateral flow and conferring a greater risk of PTS than popliteal DVTs.[35]

A higher body mass index (BMI) is not only a risk factor for VTE, but also increases the risk of PTS by 2-fold and is associated with more severe PTS.[2,3,13,16,35-37] This is an interesting finding because obesity is a modifiable risk factor, and thus, weight reduction might potentially reduce the occurrence or severity of PTS.

The presence of varicose veins prior to the development of DVT is associated with an increased risk of PTS.[13,35] Therefore, the assessment of preexisting symptoms and signs of CVD at the time of DVT diagnosis might be of interest to identify patients at a higher risk of PTS.

Possible risk factors for postthrombotic syndrome

The risk of VTE is known to increase with age, but there does not appear to be a definite association with PTS. Reports in the literature are conflicting: although some studies have observed an association,[2,17,31,34-36] others have not.[10,16] Similarly, some studies have shown men to be at a higher risk for PTS, while others have shown an increased risk in women.[2,16,34,35]

The presence of residual DVT symptoms may also predict an increased risk for PTS. Kahn et al.[2] found that patients with residual DVT symptoms 1 month after the diagnosis of DVT were 4 times more likely to develop PTS than those without residual symptoms at 1 month.[2]

It is plausible that residual thrombosis as well as physiological changes, including reflux in the affected vein, promote the development of PTS. Johnson et al.[38] showed residual occlusion to be present in 80% of postthrombotic limbs and reflux in 83% (in 65% of the limbs, both occlusion and reflux were present). Prandoni et al.[9] reported a relative risk (RR) of 1.6 for the development of PTS with the presence of residual vein thrombosis, and 1.7 if both residual vein thrombosis and popliteal vein reflux were present.[9] In a recent study, the RR for PTS was 1.9 (95% confidence interval [CI], 1.4–2.6) in patients with residual vein thrombosis alone; 1.1 (95% CI, 0.7–1.9) in patients with popliteal vein reflux alone; and 1.8 (95% CI, 1.3–2.7) in those with both residual vein thrombosis and popliteal vein reflux.[34] However, other studies found conflicting results. Yamaki et al.[39] studied venous obstruction and measured reflux by duplex scanning in a population of patients who completed 6 years of follow-up after DVT. They reported that the presence of reflux, as reflected by elevated peak reflux velocity in the proximal veins, mainly the popliteal (>25.4 cm/s) and femoral veins (>24.5 cm/s), seems to constitute an independent predictor of advanced signs of PTS. However, the proportion of patients with persistent venous occlusion was reported to be the same in patients with CEAP scores of C0–3 and C4–6. Haenen et al.[8] showed reflux in the proximal deep veins to be associated with worse CEAP scores, but no such relation was shown for reflux in the superficial veins and distal deep veins and no relation was observed between vein noncompressibility or the combination of reflux and noncompressibility and PTS. In a second study, the same group showed superficial venous reflux to be the most important risk factor for the onset of PTS symptoms, and 64% of patients with severe PTS were shown to have a combination of superficial and deep reflux.[40] In a recently published study of 114 patients followed with ultrasound and air plethysmography,[41] 4 risk factors for PTS were identified as best predictors: extensive clot load on presentation; clot regression at 6 months not exceeding 50%; venous filling index exceeding 2.5 ml/s; and abnormal outflow rate measured by a 2-second maximum outflow volume (<60% of the volume depleted after 2 s). Patients with 3 or more of these risk factors had a significant risk of developing PTS with a sensitivity of 100%, specificity of 83%, and positive predictive value of 67%. Patients scoring 2 or less risk factors did not have PTS at 5 years, with a negative predictive value of 100%.

DVT is sometimes diagnosed in asymptomatic patients by performing screening tests in high-risk settings, for example, postoperatively. A meta-analysis pooled 7 studies of patients with asymptomatic postoperative DVT and reported that the overall RR of developing PTS was 1.6 (95% CI, 1.24–2.02) as compared with patients without DVT.[42] These findings indicate that asymptomatic DVT can lead to PTS, which could help explain the lack of a clinical history of DVT in some patients who have evident postthrombotic limbs. It remains to be determined whether the treatment of asymptomatic thrombi impacts on either the incidence or severity of PTS.

Some data suggests that PTS may be promoted by inadequate initial anticoagulation. Van Dongen et al.[3] showed that patients who spent more than 50% of their time beneath the therapeutic range during the first 3 months after DVT diagnosis were at an increased risk for developing PTS (odds ratio [OR], 2.71; 95% CI, 1.44–5.10).[3] These results have recently been confirmed in a cohort study of patients with unprovoked DVT, which showed the overall frequency of PTS in patients with subtherapeutic anticoagulation to be 33.5%, compared with 21.6% in those with an international normalized ratio (INR) below 2 for 20% or less of the time ($P = 0.01$).[43] During the first 3 months of therapy, the adjusted OR

for developing PTS if a patient had subtherapeutic anticoagulation was 1.84 (95% CI, 1.13–3.01); the corresponding OR for the full period of anticoagulation was 1.88 (95% CI, 1.15–3.07). Therefore, improving the quality of anticoagulant treatment during the first 3 to 6 months after DVT diagnosis might be of importance to prevent PTS occurrence.

The role of the type of anticoagulant used for the treatment of DVT in relation to PTS is a matter of ongoing study. A meta-analysis of 9 studies that compared prolonged treatment with LMWH versus oral anticoagulation reported a lower incidence of venous ulceration in LMWH-treated patients.[44] The underlying mechanism could be an anti-inflammatory effect of LMWH or the prevention of the recurrence of subclinical DVT. Along the same lines, the use of new oral anticoagulants (NOACs; direct thrombin or factor Xa inhibitors), by delivering a more predictable quality of therapeutic anticoagulation than that of vitamin K antagonists, could plausibly reduce the occurrence of PTS after DVT,[18,45] but this has not been studied. Clinical and pharmacoeconomic studies are needed to assess the effect of NOACs on the risk of PTS.

Recent research efforts have focused on certain biomarkers as predictors of PTS. Elevated interleukin 6 and C-reactive protein (CRP) are linked to higher venous outflow resistance and incomplete thrombus resolution,[46] and the levels of intercellular adhesion molecule-1 are higher in patients with PTS compared with those without PTS.[47] Median CRP levels, measured 12 months after acute DVT, were increased in patients with PTS compared with those without PTS, and CRP levels exceeding 5 mg/l at 12 months were associated with an OR of 8.0 (95% CI, 2.4–26.4) for PTS development in a prospective cohort study that included 228 patients.[48] Further study is needed to assess the incremental benefit of inflammatory biomarkers as part of a clinical prediction rule for PTS.

D-dimer is a fibrin degradation product that, when elevated, indicates active clot breakdown and can be an indirect marker of coagulation activation.[49] A recent systematic review included 11 studies that investigated the association between D-dimer levels and PTS.[50] The majority of studies suggested an increased risk of PTS (statistically significant in 4 of them) with higher D-dimer levels; however, no firm conclusion could be reached owing to heterogeneity between studies regarding the method and timing of D-dimer measurement and the definition of PTS. To further evaluate D-dimer as a predictor of PTS, clinical studies need to standardize the use of either qualitative or quantitative D-dimer, as well as the timing and circumstances (e.g., on vs. off anticoagulants) of D-dimer testing.

In recent years, advances have been made in the field of the genetics of VTE by identifying associations between genes or variants (single nucleotide polymorphysms [SNPs]) and the occurrence of VTE. A recent study investigated the role of the SNP 4G/5G of the gene coding for plasminogen activator inhibitor 1 (PAI-1) in the persistence of thrombotic lesion and the occurrence of PTS.[51] Patients with the 4G/5G polymorphism had increased PAI-1 activity and increased incidence of persistent thrombosis or the development of PTS or both. A large prospective cohort study by our group, examining the association between various SNPs and PTS is ongoing.

Factors not associated with increased risk of post-thrombotic syndrome Reports in the literature have not demonstrated an association between PTS and the type of DVT (unprovoked vs. reversible risk factors vs. cancer-related).[3,15,31]

This association between inherited and acquired thrombophilic disorders and PTS has not been substantiated. A recent systematic review and meta-analysis of 16 studies did not demonstrate a significant association between any of the known thrombophilias and the risk of PTS in patients with DVT.[52]

Duration and intensity of long-term anticoagulation does not appear to modulate the risk of developing PTS. While secondary prophylaxis with oral anticoagulants for 6 months compared with 6 weeks offered an advantage regarding the rate of VTE recurrence in the DURAC I trial, it did not appear to influence the rate of PTS after a 10-year follow-up.[17] These findings were confirmed in a recent study.[34] In a study involving patients with unprovoked DVT who were treated with oral anticoagulants for an average of 2 years, there was no difference in PTS occurrence among patients randomized to a lower target INR (1.5–1.9) compared with conventional-intensity INR (2.0–3.0).[13]

Conclusion After acute DVT, up to half of the patients will develop PTS, in most cases, within 1 to 2 years of the acute event. Recurrent ipsilateral DVT and proximal DVT increase the risk of developing PTS, as does increased BMI. Preliminary studies suggest that poor quality of initial oral anticoagulation could be associated with the development of PTS as well as finding residual obstruction and valvular reflux on duplex ultrasonography.

Despite the progress made in recent years, it is still not possible to reliably predict, on an individual basis, who will develop PTS after acute DVT. Further studies of clinical determinants and biological markers of an increased risk of PTS are needed to ultimately achieve improvements in long-term prognosis after DVT.

Acknowledgments Anat Rabinovich, MD, is supported by the Richard and Edith Strauss Clinical Fellowship in Medicine award from the Faculty of Medicine, McGill University. Susan Kahn, MD, was a recipient of a National Research Scientist Award from the Fonds de la Recherche en Santé du Québec.

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ARTYKUŁ POGLĄDOWY

Zespół pozakrzepowy – czynniki ryzyka i rozpoznawanie

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STRESZCZENIE

Zespół pozakrzepowy (ZPZ) jest najczęstszym powikłaniem zakrzepicy żył głębokich (ZŻG). ZPZ rozwija się u 20–50% pacjentów po przebytej ZŻG, a u 5–10% ma ciężki przebieg. ZPZ rozpoznaje się na podstawie podmiotowych i przedmiotowych objawów niewydolności żylnej w kończynie, w której wcześniej stwierdzono zakrzepicę. Standardem w rozpoznawaniu ZPZ jest skala Villlalty, integrująca kliniczne objawy niewydolności żylnej. Wyselekcjonowanie pacjentów obciążonych wysokim ryzykiem rozwoju ZPZ może potencjalnie poprawić efekty leczenia ZŻG i określić indywidualne rokowanie u pacjenta. Pomimo coraz większej wiedzy dotyczącej klinicznych czynników prognostycznych ZPZ, nadal brakuje narzędzi pozwalających przewidzieć, u którego pacjenta z rozpoznaną ZŻG wystąpi ZPZ. Spośród wielu poznanych czynników ryzyka ZPZ najważniejsze są proksymalna lokalizacja ZŻG i przebyta ZŻG w tej samej kończynie. Niniejszy artykuł poglądowy podsumowuje wiedzę z ostatniej dekady na temat diagnostyki i czynników prognostycznych ZPZ.

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Praca wpłynęła: 16.05.2014.
Przyjęta do druku: 20.05.2014.
Publikacja *online*: 23.05.2014.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2014; 124 (7-8): 410-416