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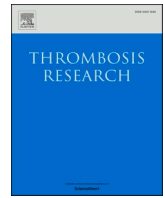
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Review Article

Acute phase determinant of post-thrombotic syndrome: A review of the literature

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ABSTRACT

Background: Post-thrombotic syndrome (PTS) is the main long-term complication of deep vein thrombosis (DVT). Several therapies are being evaluated to prevent or to treat PTS. Identifying the patients most likely to benefit from these therapies presents a significant challenge.

Objectives: The objective of this review was to identify risk factors for PTS during the acute phase of DVT.

Eligibility criteria: We searched the PubMed and Cochrane databases for studies published between January 2000 and January 2021, including randomized clinical trials, meta-analyses, systematic reviews and observational studies.

Results: Risk factors for PTS such as proximal location of DVT, obesity, chronic venous disease, history of DVT are associated with higher risk of PTS. On the initial ultrasound-Doppler, a high thrombotic burden appears to be a predictor of PTS. Among the evaluated biomarkers, some inflammatory markers such as ICAM-1, MMP-1 and MMP-8 appear to be associated with a higher risk of developing PTS. Coagulation disorders are not associated with risk of developing PTS. Role of endothelial biomarkers in predicting PTS has been poorly explored. Lastly, vitamin K antagonist was associated with a higher risk of developing PTS when compared to direct oral anti-coagulants and low molecular weight heparin.

Conclusions: Several risk factors during the acute phase of VTE are associated with an increased risk of developing PTS. There is a high-unmet medical need to identify potential biomarkers for early detection of patients at risk of developing PTS after VTE. Inflammatory and endothelial biomarkers should be explored in larger prospective studies to identify populations that could benefit from new therapies.

1. Introduction

Deep vein thrombosis (DVT) of the lower limbs is a prevalent and serious condition, with an estimated annual incidence of 9.3 cases per 10,000 individuals [1]. Post-thrombotic syndrome (PTS), usually resulting in severe chronic venous disease, is the most feared local complication, substantially impacting patients' quality of life. The incidence of PTS, which typically appear within 2 years following DVT, varies widely, ranging from 20 % to 80 % [2–4]. The pathophysiology of PTS is associated with venous reflux and venous hypertension, which

results from both valve insufficiency and thrombotic obstruction [5,6]. From medico-economic perspective, PTS represents a significant health care burden [7,8] as evidenced by a study that revealed an average incremental adjusted healthcare cost of \$7000 per patient per year for those developing PTS [9]. In routine clinical practice, the identification of patients with DVT at risk of developing PTS, particularly post-thrombotic ulcers, remains challenging. Several clinical scales and definitions have been developed and used in various studies to diagnose PTS following proximal DVT. Some scales, such as Villalta score [10], Brandjes scale [11] and Ginsberg score [12] were specifically created for

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assessing PTS. Notably, the Villalta score incorporates a composite criterion that takes into account clinical signs, early symptoms, and skin complications (lipodermatosclerosis and active ulcers), that may develop later. To facilitate comparability across published clinical studies, various expert committees recommend the use of the Villalta score for PTS diagnosis [2,13]. This score offers both quantitative and qualitative assessments of PTS, sensitivity to changes in symptomatology over time, correlation with quality of life alterations [14] and exhibits good interobserver agreement [13]. However, it is important to note that the Villalta score has not been validated for use during the acute phase of DVT.

Currently there is no effective treatment to cure PTS, with venous compression providing only marginal symptom relief [15]. Several endovascular techniques aimed at preventing PTS occurrence by restoring thrombosed vein patency during the acute phase are under development. The challenge in validating the efficacy of these emerging procedures is identifying the population that should be treated, thereby targeting patients with DVT at risk of developing PTS. The aim of this review is to identify the risk factors for PTS during the acute phase of DVT, and shed light on unexplored areas of investigation.

2. Methods

To compile this review, we conducted a thorough search of the PubMed and Cochrane databases for English-language studies published from January 2000 through December 2022. We focused on randomized clinical trials, meta-analyses, systematic reviews, and observational studies. The MeSH terms used in our search were ‘predictor’, ‘determination’, ‘determinant’, ‘syndrome’, ‘post-thrombotic syndrome’, ‘venous stasis syndrome’, ‘varicose ulcer’, ‘postphlebotic syndrome’, ‘venous ulcers’ and ‘predictive factor’. Additionally, we manually examined references from selected articles, reviews and meta-analyses. Three investigators assessed the articles for eligibility and data extraction (LK, TM and NG). First, we excluded articles based on titles and abstract in order to select eligible articles for full text review. Only studies in which PTS was diagnosed by Villalta scale [10], Ginsberg measure [12], Brandjes scale [11], CEAP (clinical, etiological, anatomic, pathophysiological) classification [16] a French classification for the evaluation of chronic venous disease not specific to PTS, Venous Clinical Severity Score (VCSS) [17] or Widmer Scale [18] were included in our analysis.

2.1. Predictive markers at diagnosis

2.1.1. Clinic

2.1.1.1. Proximal location of deep vein thrombosis. In multiple series, a consensus emerges that iliofemoral involvement in case of DVT is associated with an increased risk of developing PTS [14,19–24]. Kahn et al. [14] found a significant association between common femoral or iliac DVT and a higher Villalta score with a 2.23 point increase compared to distal DVT (95 % confidence interval, CI 1.29–3.16; $p < 0.001$) within 2 years of diagnosis. Tick et al. [19] showed a significantly higher incidence of PTS in patients with iliofemoral DVT compared to popliteal DVT (risk ratio, RR, 1.3, 95 % CI 1.1–1.6). Two studies provided evidences that iliofemoral DVT is the most reliable predictor of PTS development with an odds ratio (OR) of 2.97 using the Villalta score [24] and 3.4 (95 % CI 1.4–8.6) using the CEAP classification [23]. A long-term study spanning two decades on over 1500 patients revealed that patients aged 40 or younger with proximal DVT were nearly three times more likely to develop PTS than patients with distal DVT [20]. In that study, PTS was assessed on clinical and ultrasonographic arguments for venous insufficiency. However, in patients over 40 years, this discrepancy was not observed though this hypothesis remains controversial. It’s important to note that some studies do not identify the proximal nature of DVT as a risk factor for PTS [25–28]. Ende-Verhaar

et al. [28] did not find a difference between proximal and popliteal DVT as a risk factor for developing PTS, but this result might differ if popliteal DVT were grouped with proximal DVT for comparison to distal DVT. In other studies [25–27], the proximal location of the DVT and the incidence of PTS may rely on two explanations. First, patients who had recurrence during follow-up were not excluded from the analysis, despite ipsilateral recurrence is a strong risk factor for developing PTS [14]. Second, patients were older [25–27] when compared to the Siddiqui et al. population [24] (56.9 versus 41.3 years).

2.1.1.2. Obesity. The role of obesity as predictive marker for PTS is supported by several studies. Patients with PTS tend to have a higher body mass index (BMI) compared to those without PTS. [24,29,30] Rattazzi et al. [30] reported a higher BMI ($p = 0.005$) in patients with PTS, but there was no difference in the prevalence of metabolic syndrome between patients with and without PTS (20 % vs. 26 % respectively, $p = 0.64$). Kahn et al. [14] found a clear correlation between BMI and the development of PTS with an increase on Villalta score (0.14 point per 1 kg/m², $p < 0.001$). Obesity, defined by a BMI ≥ 30 kg/m² has been identified as a major risk factor for developing PTS [28,31,32]. In the REVERSE study, obesity remains the only independent predictor of PTS (OR 2.6, 95 % CI 1.3–5.0) among other variables [33]. One study also identified overweight defined by a BMI ≥ 25 kg/m² as a risk factor for PTS [34]. Specific BMI thresholds associated with significantly increased risk of PTS have been established, such as ≥ 35 kg/m² (OR 2.1, 95 % CI 0.9–4.9) [24] and > 28 kg/m² (OR 3.5, 95 % CI 1.0–12.1) [29]. Furthermore, obesity significantly increases by twofold the risk of venous ulcers associated with PTS, as shown by Galanaud et al. [35]. The role of obesity in PTS development can be explained by its impact on chronic venous disease, as excess weight increases venous hypertension and promote reflux in veins where valves are already damaged by thrombosis [36–38].

2.1.1.3. Chronic venous disease. Pre-existing chronic venous disease is a recognized confounding factor due to the symptom overlap with PTS. Hence, it is often excluded in studies assessing PTS predictors [25]. Multiple studies have concurred that pre-existing chronic venous disease is a risk for developing PTS [19,33,39,40], including the subsequent development of ulcers (OR 3.2, 95 % CI 1.7–6.1) [35]. Notably, even mild pre-existing chronic venous disease increases the risk of PTS development (OR 1.9, 95 % CI 1.1–3.4) [33].

2.1.1.4. Sex. The literature presents some ambiguity regarding the association between sex and the risk of developing PTS. For some studies, sex does not emerge as a significant risk factor [8,29,34]. Other studies report that women have 1.5 to 1.7-fold greater risk of PTS, even after adjusting on other risk factors [19,28]. Female sex is independently associated with higher Villalta scores, with a 0.79 point (95 % CI 0.13–1.46) increase compared to men [14]. On the other hand, male sex is also identified as a risk factor (OR 1.6, 95 % CI 1.0–2.8), but this study primarily focused on clinical rather than functional signs of PTS, using the CEAP classification [22]. Galanaud et al. [35] found that men also had a higher prevalence of PTS associated ulcers (OR 2.5, 95 % CI 1.3–5.1).

2.1.1.5. History of DVT. While most studies on predictive criteria for PTS focus on patients with a first episode of DVT, a study included patients regardless of their DVT history and revealed that recurrent DVT was a significant risk factor for PTS (OR 3.25, 95 % CI 2.03–5.21) [41]. Ipsilateral DVT history was also associated with higher Villalta scores with a 1.78 point (95 % CI 0.69–2.87, $p < 0.001$) increase compared to patients without previous ipsilateral DVT [14]. Several other studies have reported DVT recurrences as a significant risk factor of developing PTS [26,27,34], irrespective of whether the DVT was provoked or unprovoked [28]. Finally, history of DVT or pulmonary embolism was

associated with PTS associated ulcers [35].

2.1.1.6. Severe symptoms at diagnosis. The initial symptoms of DVT vary among individuals and often influence treatment choices, particularly with regard to endovascular techniques. Although not validated for use at the acute phase of DVT, the Villalta score can also serve as a tool to assess symptom severity as in this study involving 122 consecutive patients diagnosed with a first DVT episode [35]. The mean Villalta score at diagnosis was higher in the PTS group (8.1 ± 3.7) compared to those without PTS (2.6 ± 2.7 , $p < 0.001$) [42].

2.1.1.7. Cancer-associated venous thrombosis. Nishimoto et al. [43] observed in 148 patients with cancer that acute DVT in context of cancer is at increased risk of developing PTS (OR 3.66, 95 % CI 2.30–5.84). Moreover, another study including 15 patients with cancer with acute DVT did not find that malignant disease was a risk factor for PTS (OR 1.48, 95 % CI 0.39–5.65) [41].

2.1.2. Biological

2.1.2.1. Platelets. Gabriel et al. included 135 patients with a history of unprovoked DVT and found similar baseline platelet counts (206.0 G/L vs. 214.5 G/L respectively, $p = 0.594$) in both patients developing PTS or not after a 12-month follow-up [44]. Galanaud et al. did not find that platelet count was associated with a risk of PTS-related ulcer (OR 2.5, 95 % CI 0.7–8.2) [35].

2.1.2.2. Coagulation. Inherited and acquired thrombophilia play a significant role in venous thromboembolism (VTE) but data regarding their involvement in PTS are inconsistent [45]. In a Canadian study, presence of factor V Leiden mutation (FVL) or prothrombin gene mutation G20210A (FII G20210A) was an independent predictor of both a lower risk (OR 0.33, 95 % CI 0.15–0.73) of developing PTS and a lower Villalta score (linear correlation coefficient -1.6 , 95 % CI -3.20 , -0.06) [46]. Nishimoto et al. found also that protein C (PC), protein S (PS) and antithrombin deficiencies and antiphospholipid syndrome were independent risk factors for developing PTS (OR 2.07, 95 % CI 1.06–4.04, $p = 0.03$) [43]. However a meta-analysis in 2014 [47] did not find any link between thrombophilia and PTS, including FVL (13 studies), FII G20210A (10 studies), activated protein C (PC) resistance (1 study), PS deficiency (5 studies), PC deficiency (5 studies), antithrombin deficiency (3 studies), high factor VIII levels (4 studies) and antiphospholipid syndrome (6 studies). Similarly, in study published in 2019, including 1657 patients diagnosed with DVT in the MEGA study [28], the presence of FVL, FII G20210A, factor XIII variants or high factor VIII levels did not affect the risk of PTS after 1 year. One study investigated whether biomarkers and unfavorable properties of fibrin clot could predict PTS development. In a cohort study of 182 consecutive patients with DVT, they determined 3 months after the index event the fibrin clot permeability and lysis and measured inflammatory markers, thrombin generation, fibrinolysis proteins and the histidine-rich glycoprotein (HRG), a plasma protein with anti-inflammatory, anticoagulant and anti-fibrinolytic effects [48]. Forty-eight patients (26.4 %) developed PTS after 12 to 14 months of follow-up. A more prothrombotic feature and an impaired fibrinolysis at baseline, evidenced by shorter lag phase and higher maximum absorbance during plasma clot formation, lower plasma clot permeability and prolonged clot lysis time were linked to the development of PTS [48]. HRG levels at baseline were also higher in patients who developed PTS and correlated with the Villalta score [48]. This study suggests that in patients with DVT some biomarkers such as high HRG levels and fibrin clot characteristics may predict the development of PTS.

2.1.2.3. D-dimer. D-dimer, fibrin degradation products, are commonly measured for DVT diagnosis [49] but their role as a predictor of PTS

remains inconclusive. Roberts et al. [42] included 122 consecutive patients with a first episode of DVT and assessed PTS 6 months after withdrawn anticoagulation. In this cohort, baseline median D-dimer level was significantly higher in those who developed PTS (3260 ng/mL, interquartile range 820–8000 ng/mL) compared to those who did not (1540 ng/mL, IQR 810–2520 ng/mL $p < 0.001$). D-dimer levels were measured with STA®-Liatest® D-Di (Diagnostica Stago, Asnières, France), excluding results with any other technique and those obtained after anticoagulation had been started. On the other hand, Gabriel et al. [44] included 135 patients with a history of DVT with a 12-month follow-up. Positivity of baseline D-dimers level (DG-Ddimer kit®, Diagnostic Grifols, S.A., Barcelona, Spain; positivity if D-dimer levels >260 ng/mL) did not differ between PTS and non-PTS groups (84.3 % vs. 76.1 %, $p = 0.061$). Further research is necessary to determine the prognostic value of D-dimers measured at DVT diagnosis or during follow-up on the PTS occurrence. However, it's worth noting that D-dimer is not a specific biomarker, as it can also increase in pregnancy, inflammatory diseases, and sepsis [49]. Additionally, varying reagents used in healthcare laboratories can affect D-dimers results as highlighted by the International Society on Thrombosis and Haemostasis during the COVID-19 outbreak [50,51]. D-dimer assays can yield different results indeed, due to varying affinity for high or low molecular weight fibrin degradation products and cross-linked and non-cross-linked fibrin derivatives.

2.1.2.4. Inflammatory markers. Inflammation is implicated in the pathogenesis of PTS leading to remodeling and fibrotic responses in the veins. Nevertheless, the C-reactive protein (CRP) showed no correlation with the risk of developing PTS in the REVERSE study and SOX trial populations [52,53]. In the SOX trial, aimed to assess the efficacy of elastic compression stockings (ECS) for PTS prevention, baseline ICAM-1 levels, a transmembrane protein facilitating attachment of leukocytes to the endothelial cells and their migration into the affected tissue, were higher in patients who developed PTS [53]. In contrast, no link was noted between PTS and other inflammatory biomarkers baseline levels like interleukin-6 or interleukin-10. Some acute phase reactants at the early stage of DVT such as metalloproteinases (MMP) 1 and MMP-8 showed higher baseline levels in patients who developed PTS suggesting their involvement in venous valve alteration and the predisposition to secondary varicose veins and non-healing venous ulcers [54].

2.1.2.5. Endothelial markers. A few studies have evaluated endothelial markers in the acute phase of VTE and their association with PTS. Two studies evaluated soluble E-selectin (sE-selectin) levels during the acute phase of DVT and found no association with DVT [55,56]. However, their role in predicting PTS remains unexplored. Bittar et al. reported elevated levels of sE-selectin in patients with severe PTS at the PTS assessment [57].

2.1.2.6. ABO group. A study found that among the 192 patients who developed PTS after a first episode of proximal DVT, 142 (75 %) were non-O blood group, conferring a significantly higher risk of developing PTS (HR 1.53, 95 % CI 1.05–2.24, $p = 0.028$) compared to O blood group patients [58].

2.1.3. Imaging

2.1.3.1. Ultrasound. While there has been limited research on ultrasound parameters as a predictor of PTS, one noteworthy study demonstrated that a higher proportion of patients who developed PTS exhibited complete vein obstruction compared to those who did not develop PTS (53 % vs. 29 %, $p = 0.016$) [24]. Additionally, a higher initial clot load assessed using Haenan's clot score [59] was identified as a risk factor for PTS [60].

2.1.4. Anticoagulant therapy

Currently all DVT are managed with anticoagulant therapy to prevent extension and recurrence. Various anticoagulant treatments are available, both oral (direct oral anticoagulants, DOAC, and vitamin K antagonists, VKA), and parenteral (low molecular weight heparin (LMWH), unfractionated heparin, fondaparinux, danaparoid and argatroban).

2.1.4.1. VKA vs. DOAC. In a meta-analysis published in 2020, which incorporated seven comparative studies, encompassing 2364 participants, the use of rivaroxaban (an oral factor Xa inhibitor) for treating DVT was associated with a lower risk of PTS compared to conventional VKA (pooled unadjusted OR 0.53, 95 % CI, 0.43–0.65, $p < 0.00001$) [61]. Furthermore, Coleman et al. [62] investigated adults treated after a primary diagnosis of VTE and compared the outcomes between rivaroxaban ($n = 10,463$) and warfarin ($n = 26,494$) during a 16 ± 9 months of follow-up. Rivaroxaban was associated with a lower risk of PTS in comparison to warfarin (HR 0.77, 95 % CI 0.70–0.84, $p < 0.00001$). Søgaard et al. [63] involved 19,957 oral anticoagulation-naïve patients with incident VTE treated with either warfarin or rivaroxaban. Although non-statistically significant, the propensity-weighted rate of PTS after 3-year follow-up was 0.53 per 100 person-years with rivaroxaban versus 0.55 per 100 person-years with warfarin (HR 0.88, 95 % CI 0.66–1.17). This association remained consistent across different VTE types: DVT vs. PE, provoked vs. unprovoked VTE or when censoring patients with recurrent VTE. One explanation may be given by this retrospective study conducted in Brazil on DVT treated with either warfarin ($n = 26$) or rivaroxaban ($n = 51$) [64]. Venous recanalization rates at 30, 90, and 180 days were lower with warfarin compared to rivaroxaban, respectively 10 %, 52.5 %, and 78.9 %, vs. 55.3 %, 83.5 %, and 92.4 % ($p = 0.041$). In conclusion, consistent results support the reduction of PTS incidence with rivaroxaban compared to warfarin. It is important to note that, no study has evaluated the impact of apixaban vs. other anticoagulants on PTS.

2.1.4.2. LMWH versus VKA. A pooled analysis of randomized controlled trials [65] reported less PTS occurrence (OR 0.8, 95 % CI 0.7–0.9) and a lower incidence of venous ulcers (relative risk (RR) 0.1, 95 % CI 0.02–0.7) with an extended LMWH therapy compared to a VKA therapy.

2.1.4.3. Time in therapeutic range (TTR). One potential explanation for the observed differences between VKAs and DOACs or LMWHs may be related to the challenge in maintaining an international normalized ratio within the therapeutic range. A low TTR was found to be significantly associated with PTS [24] and two studies emphasized on the impact of a low TTR during the initial 3 months of VKA therapy. The first study reported that patients with a TTR < 50 % had a twofold increase of PTS [34], confirmed by the second study for patients with a TTR < 80 % (OR 1.83, 95 % CI 1.13–3.01) [66].

2.1.5. Elastic compression stockings

A recent meta-analysis [72] analyzing seven randomized controlled trials comparing the use of ECS to placebo to reduce PTS occurrence [11,12,32,73–76] showed that the use of ECS was associated with a statistically significant reduction in PTS (RR 0.73, 95 % CI 0.53–1.00, $p = 0.05$). Among these studies, four assessed the risk of severe PTS, and no difference was found (RR 0.61, 95 % CI 0.29–1.31, $p = 0.21$) [11,26,75,76].

2.1.6. Other treatments

2.1.6.1. Venoactive drugs. Concerning rutosides, the current body of evidence is limited and of low quality in terms of reducing PTS symptoms [67]. About another venoactive drug, in a clinical trial by

Schastlivtsev et al. [68], referred to as the RIDILOTT study, patients with their first femoro-popliteal DVT were randomly assigned to either diosmin 600 mg once daily for 12 months on top of standard regimen (including rivaroxaban for 6 months and ECS for 12 months) or standard regimen alone. Diosmin exhibited a significantly lower PTS occurrence at 12 months (8.9 % vs. 48.9 %, RR 0.14, 95 % CI 0.04–0.43, $p < 0.001$). Lobastov et al. [69] enrolled patients with their first episode of femoro-popliteal DVT confirmed by duplex ultrasound scanning in an open-label study with blinded outcome assessment. Sixty participants were randomly assigned to micronized purified flavonoid fraction (MPFF) 1000 mg per day on top of standard regimen (including rivaroxaban) or standard regimen alone. MPFF exhibited a significantly lower PTS occurrence at 6 months (20 % vs. 57 %, $p = 0.007$) and a lower Villalta score (2.9 ± 2.7 vs. 5.8 ± 3.0 , $p < 0.0001$). Notably, a more rapid rate of recanalization of the femoral vein ($p < 0.0001$), while non-significant trends for the common femoral vein ($p = 0.130$) and popliteal vein ($p = 0.204$) were observed in the MPFF group compared to the control group.

2.1.6.2. Statins. Statins are effective lipid-lowering therapies with pleiotropic effects and are evaluated in VTE prevention [70]. In a study conducted by María San Norberto et al. [71] 234 patients with DVT were included in an open label study. They were randomly assigned either rosuvastatin plus LMWH or LMWH alone. All patients underwent lower limb duplex ultrasound scanning and biomarkers at diagnosis and after a 3-month follow-up. The final analysis included 230 patients. Rosuvastatin exhibited a significantly lower PTS occurrence at 6 months (38.3 % vs. 48.5 %, $p = 0.019$) and a lower Villalta score (3.45 ± 6.03 vs. 7.79 ± 5.58 , $p = 0.035$). Additionally, a study by Cucuruz et al. [41] following 579 patients after DVT found those taking statin for another reason presented less risk of developing PTS (OR 0.27 95 % CI 0.15–0.50, $p = 0.001$).

2.2. Prediction model for risk stratification of PTS

Several predictive models for assessing the risk of PTS have been proposed in the literature. Mean M et al. [77] developed a PTS prediction rule based on five predictors, including age ≥ 75 years, prior varicose vein surgery, multilevel thrombosis, concomitant antiplatelet or non-steroidal anti-inflammatory drug therapy and the number of leg symptoms and signs. Based on computations 16.3 % of the patients with acute DVT were classified as low-risk of PTS (score 0–3), 31.2 % as moderate-risk (score 4–5) and 52.5 % as high-risk (score ≥ 6). The prediction model showed a good predictive accuracy (area under the curve, 0.77; 95 % CI 0.71–0.82), since 24.4 % of the patients in the low-risk category developed a PTS within 24 months after their index DVT, 38.4 % in the moderate and 80.7 % in the high-risk categories. In the Netherlands a two-step risk assessment model was developed [40], which included at baseline the presence of: age > 56 years, BMI > 30 kg/m², varicose veins, smoking, female sex, provoked DVT, ilio-femoral DVT, history of DVT and at a sub-acute phase the presence of age > 56 years, BMI > 30 kg/m², varicose veins, smoking and residual vein obstruction. Each variable was weighted to reflect their level of involvement in the risk of PTS, varicose veins counting for 4 at baseline and 3 at the sub-acute phase, whereas all the other variables counting for 1. External validation of this score showed a good predictive accuracy (area under the curve, 0.64; 95 % CI 0.60–0.69). In the SOX-PTS cohort, patients with a SOX-PTS score ≥ 4 had a significantly higher risk of developing PTS (OR 5.9, 95 % CI 2.1–16.6) compared to those with a score of 0 [78]. The SOX-PTS score has been validated by Rabinovich A et al. in the ATTRACT trial [79] in patients with acute DVT by computing 1 point for iliac vein involvement; 2 points for BMI ≥ 35 kg/m² and 1 or 2 point for baseline Villalta score ≥ 10 points or ≥ 14 respectively. The prediction model showed a good predictive accuracy (area under the curve, 0.63; 95 % CI 0.59–0.67). Lastly, a study

conducted in New Zealand [60] identified four key risk factors for PTS prediction including: initial clot load, clot regression at 6 months, venous filling index, and outflow rate. Patients scoring 2 or less did not have PTS after 5-year follow-up with a negative predictive value of 100 %, compared to those scoring 3 or more, who had a significant risk of developing PTS with a 100 % sensitivity, 83 % specificity, and 67 % positive predictive value [53].

3. Discussion

3.1. Summary of evidence

This review presents an extensive examination of clinical (Table 1), biological (Table 2) and radiological factors during the acute phase of VTE that may serve as predictive indicators for the development of PTS in patients with DVT. Notably, the proximal nature of DVT, particularly the ilio-femoral localization in young patients, obesity, history of DVT and chronic venous disease carry a substantial risk of developing PTS. Sex, while not definitively established as a risk factor presents inconclusive results, with some studies suggesting that men may be more susceptible to severe PTS. Contradictory results were observed in the association between active cancer and acute thrombosis with the risk of PTS [41,43]. Further, larger studies dedicated to assessing the risk of PTS in patients with active cancer are needed. Finally, some studies linked the initial severity of the symptoms related to the acute DVT to the PTS occurrence.

Biological factors such as D-dimer and inflammatory markers have been insufficiently explored, yielding inconsistent results. However, ICAM-1 or MMP-1 and MMP-8, have shown potential in predicting PTS when elevated during the acute phase. Additionally, research indicates that vascular endothelium plays a crucial role in regulating thrombotic and fibrinolytic processes. Studies in animal models reveal that genetic deletion of MMP-9 may reduce vascular inflammation and fibrosis in the vein wall potentially preventing PTS [80]. The accelerated thrombus resolution observed in MMP-9 knockout mice may also be related to a

Table 1

Clinical risk factors of post-thrombotic syndrome at the acute phase of thrombosis.

| | |
|------------------------------|--|
| Proximal location of DVT | Femoral or iliac DVT is associated with a 2.23 points increase of Villalta score compared to distal DVT [14]. Iliofemoral DVT is a predictor of PTS development with OR of 2.97 vs distal DVT [24]. Iliofemoral DVT is associated with a 1.3-fold higher risk of PTS than popliteal DVT [19]. Patients below 40 years with iliofemoral DVT appear to be at increased risk of developing PTS [20]. |
| Obesity | Villalta score increases of 0.14 point per 1 kg/m ² [14]. Obesity is a predictor of developing PTS with OR of 2.6 [33]. Risk of PTS increased with BMI \geq 35 kg/m ² [24] (OR 2.13, 95 % CI 0.92–4.92); $>$ 28 kg/m ² (OR 3.54, 95 % CI 1.07–12.08) [29]. Obesity increases the risk of PTS associated ulcer by at least twofold [35]. |
| Chronic venous disease | Pre-existing chronic venous disease increases the risk by two-fold of severe PTS and therefore ulcers [19,33,39,40]. Pre-existing chronic venous disease is a risk factor for developing PTS (OR 1.917, 95 % CI 1.075–3.419) [33]. |
| History of DVT | Previous ipsilateral DVT is associated with an increase in Villalta score of 1.78 point (95 % CI 0.69–2.87) [14]. History of DVT is associated with an increased risk of developing PTS associated ulcer [35]. |
| Severe Symptoms at Diagnosis | Villalta score is higher during acute phase of DVT. [42]. Initial leg swelling (OR 4.15, 95 % CI 2.25–7.66) is an independent risk factors for developing PTS [42]. |

DVT: deep venous thrombosis, OR: odds ratio, BMI: body mass index; CI: confidence interval; PTS: post-thrombotic syndrome.

Table 2

Biological risk factors of post-thrombotic syndrome at the acute phase of thrombosis.

| | |
|----------------------|---|
| Coagulation | Initial fibrin clot characteristics are associated with an increased risk of ulcers (HR 5.37, 95 % CI 1.3–21.5) [48]. HRG levels are higher in patients who develop PTS, and correlate with PTS severity [48]. |
| Fibrinolysis | Initial D-dimer levels show inconsistent results to predict PTS [42,44]. |
| Inflammatory markers | Initial ICAM-1 levels are associated with the risk of developing PTS [53]. Initial MMP-1 and MMP-8 levels are associated with the risk of developing PTS [54]. |
| ABO group | Individuals with non-O blood group are at increased risk of developing PTS (HR 1.53, 95 % CI 1.05–2.24) [58]. |

HR: hazard ratio; HRG: histidine-rich glycoprotein, PTS: post-thrombotic syndrome.

compensatory MMP-2 increased activity [81]. Thus, therapies targeting MMPs during the acute phase of VTE may be valuable in reducing the thrombus–vein wall interaction. Thrombus resolution facilitated by angiogenesis and MMP-9 is critical for neovascularization within the thrombus [82]. This contributes to restoring a patent vein lumen, [83] with increased local expression of vascular endothelial growth factor and basic fibroblast growth factor [84]. Role of endothelial biomarkers in predicting PTS has been poorly explored. Further exploration of endothelial markers, such as sE-selectin, holds promise [55–57]. Preliminary findings suggest decreased flow-mediated dilation values in patients with unprovoked DVT [85,86], indicating impaired vasodilatory response and endothelial function alterations in both arteries and veins. Direct access to endothelial cells, particularly endothelial progenitor cells (EPCs), could provide valuable insights, as bone marrow-derived EPCs have been found in thrombi during resolution [83]. Endothelial colony-forming cells (ECFCs) seem a good candidate as an endothelium liquid biopsy [87]. They play an important role in adult neovascularization and have been proposed to be EPCs derived from the vessel wall [88]. Previous studies have demonstrated that thrombin adsorbed to fibrin clots may contribute to recruit ECFC [89] and that ECFCs isolated from patients after unprovoked VTE exhibited elevated oxidative stress, cellular senescence, and reduced proliferative potential [90]. Thus, ECFCs alterations or defective recruitment could allow thrombus extension and contribute to PTS occurrence. Few studies have focused on ultrasound parameters, making the initial thrombotic load a potential field of investigations. Regarding available treatments, the literature suggests that patients treated with VKAs face a higher risk of developing PTS compared to those treated with DOACs (mainly rivaroxaban) or LMWH. The mechanisms of action of these drugs differ, suggesting potential for further exploration into the anti-factor Xa activity of heparins and DOACs in reducing vascular sequelae. Finally, VKAs are associated with non-negligible inefficacy risk due to INR balance challenges. Venoactiv drugs do not appear to reduce PTS occurrence and should not be used for this purpose. Some studies evaluated statins in combination with anticoagulants, indicating a potential reduction in PTS that warrants further exploration. Several teams have developed prediction models that include various parameters during the acute phase of DVT, which should be evaluated prospectively. Recently, Iding et al. [91], using an unsupervised hierarchical clustering approach with 23 commonly available clinical characteristics in 825 patients after VTE, and identified among 4 phenotypes, one distinct phenotype of patients with a higher risk of PTS, recurrent VTE, and cancer. This phenotype ($n = 128$) included patients with previous VTE (65.6 %), known thrombophilia (18.8 %) and the highest prevalence of chronic venous disease (21.1 %) and hematologic disease (7 %) compared to other phenotypes. Moreover, in this phenotype, the prevalence of transient provoking risk factors was the lowest (16.4 %). There is an urgent need for observational cohort studies with comprehensive bio-banking and precise collection of clinical and radiological parameters

to determine predisposing factors for PTS. Studies on venous recanalization techniques are ongoing [92–94], but their effectiveness may be challenging to demonstrate, potentially due to the need to select high risk patients initially. Results from such studies could also shed light on new therapeutic approaches for PTS prevention, including antiplatelet therapy or statins.

3.2. Limitations

A significant limitation of this review lies in the evaluation of the PTS score. While, learned societies recommend using the Villalta score for greater consistency, many of the cited studies have not utilized it. Future research on this subject should adhere to this standard and employ the recommended Villalta [13] score to enable comparisons between studies.

4. Conclusion

PTS remains challenging to predict, yet it significantly impacts patients' quality of life and causes considerable morbidity. This study has revealed several key factors associated with PTS including proximal DVT location, varicose veins, obesity and treatment with VKA. There is a high-unmet medical need to identify potential biomarkers for early detection of patients at risk of developing PTS early after VTE, and to develop effective therapies to prevent PTS. Inflammatory and endothelial biomarkers should be explored in larger prospective studies to identify populations that could benefit from new therapies.

CRediT authorship contribution statement

Lina Khider: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Benjamin Planquette:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **David D. Smadja:** Writing – review & editing. **Olivier Sanchez:** Writing – review & editing, Supervision, Methodology. **Carla Rial:** Writing – review & editing. **Guillaume Goudot:** Writing – review & editing. **Emmanuel Messas:** Writing – review & editing. **Tristan Mirault:** Writing – original draft, Validation, Supervision, Methodology, Investigation. **Nicolas Gendron:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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