

# Clinical characteristics and outcomes of patients with multiple simultaneous superficial vein thrombi

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## ABSTRACT

**Background:** Although unprovoked superficial venous thrombosis (SVT) has traditionally been considered a local, benign disorder, recent studies demonstrate that patients with SVT are at significant risk for deep venous thrombosis, pulmonary embolism, and other venous thromboembolism (VTE) events. Nevertheless, clinical management remains widely inconsistent. Moreover, patients with multiple, unprovoked SVTs of noncommunicating anatomic sites have not been previously described, and they may be at even increased risk for adverse outcomes. The objective of this study was to describe the clinical characteristics and outcomes of patients with multiple, unprovoked SVTs to elucidate whether this subset of patients possesses a higher risk of thrombophilia, cancer, recurrent VTE, or death compared with patients with unprovoked SVT at a single location.

**Methods:** Twenty-four patients with multiple, unprovoked SVTs were enrolled. Blood tests and computed tomography scans were performed to detect thrombophilia and malignant disease. Patients were followed up with duplex ultrasound and clinical examination for at least 3 months. The prevalence of recurrent VTE and clinical outcomes were compared with a control group of 39 patients with unprovoked SVT in a single vein.

**Results:** Cancer was detected in five patients (20.8%) and thrombophilia in 10 patients (41.7%). During the follow-up period, nine patients (37.5%) exhibited recurrent VTEs, and five patients (16.2%) died. The VTE recurrence rate was significantly greater than in controls ( $P = .03$ ). Patients with a coexisting thrombophilia or cancer had elevated thrombotic load (4.08 vs 2.27 separate vein segments;  $P = .0096$ ) and an increase in VTE recurrence ( $P = .038$ ) compared with patients without any such findings.

**Conclusions:** The results of this study warrant further investigation into this subset of patients through a larger multicenter design, as patients with multiple SVTs are at greater risk for thrombophilia, cancer, recurrent VTE events, and death compared with patients with isolated SVT. (*J Vasc Surg: Venous and Lym Dis* 2018;■:1-7.)

**Keywords:** Superficial vein thrombosis; Multiple location of thrombosis; Risk factors; Clinical outcomes

Superficial venous thrombosis (SVT) has traditionally been considered a predominantly benign disorder with relatively minor complications and a <1% 3-month overall mortality rate.<sup>1</sup> However, a large, prospective epidemiologic study demonstrated that 24.9% of patients who present with SVT also have an associated deep venous thrombosis (DVT) or pulmonary embolism (PE). Furthermore, at 3-month follow-up, 18.2% of patients with SVT and without concurrent DVT or PE developed PE, DVT, extension of SVT, or recurrence of SVT despite that 90.5% received anticoagulation therapy.<sup>2</sup>

SVT may arise as a consequence of a variety of predisposing conditions, such as prolonged immobilization, trauma, obesity, thrombophilia, use of oral

contraceptives or hormonal therapy, prior history of SVT or DVT, intravenous catheter use, malignant neoplasms, and autoimmune disorders—each associated with a unique natural history. Although SVTs are commonly found in patients with varicose veins and may have a benign outcome, the involvement of the proximal great saphenous vein (GSV) is associated with a greater incidence of venous thromboembolism (VTE) events.<sup>3,4</sup> Thus, there exists substantial variability in a patient's prognosis according to the predisposing condition. Consequently, decades of conflicting data concerning the severity of SVT have resulted in inconsistent clinical management in which anticoagulation and compression are rarely prescribed and follow-up and treatment duration are widely incongruent.<sup>5</sup>

Given the broad spectrum of outcomes associated with SVT that range from spontaneous resolution to death, it is imperative to stratify a patient's risk for future adverse events. This approach has been applied to DVT, which is accordingly classified as provoked or unprovoked on the basis of the inciting clinical event to help stratify a patient's risk for complications such as recurrence, thrombophilia, and cancer.<sup>6-8</sup> This distinction is essential because there is a dramatic disparity in the prognoses of patients with provoked and unprovoked DVT associated with a recurrence rate of 22.5% and 52.6% at 10 years, respectively.<sup>9</sup> However, this delineation does not exist

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for SVT. Furthermore, SVTs coexisting at multiple sites may help to further stratify the risk of future complications by indicating a pervasive systemic condition.

Thus, clinical findings such as the absence of provoking risk factors and the detection of multiple, simultaneous thrombi may help to identify those patients who are at greatest risk for development of complications and may benefit most from anticoagulation therapies. To our knowledge, cases in which simultaneous, unprovoked SVTs developing in two or more anatomically distinct locations have never been described. The objective of this study was to examine the demographic and clinical characteristics of this subset of patients and to determine the clinical outcome.

## METHODS

**Study design.** This study was motivated by previous experience with two patients (not included) who presented with SVT at two different sites, one of whom had pancreatic cancer and the other thrombophilia. Because of this observation, we prospectively collected clinical information and blood samples on this subset of patients before initiation of treatment and documented all clinical findings in a database.

This study was approved by the Institutional Review Board, and patients were asked to sign informed consent. Patients who presented with signs and symptoms of SVT were included in the study. Those with recent injury, trauma, or surgery and those taking oral contraceptive pills, with autoimmune disease, or with line placement at the site of thrombosis were excluded. All patients had a duplex ultrasound (DUS) examination to identify the location and extent of the thrombus. Patients who were found to have a thrombus in the deep venous system at baseline were excluded. The examination was performed as described by our group previously.<sup>10</sup> In the lower extremities, the deep veins were examined from the external iliac vein to the medial malleolus. When thrombus was detected in the external iliac vein, the common iliac and inferior vena cava were imaged to identify the proximal length of thrombus. The superficial veins assessed in the lower extremity included the GSV, small saphenous veins (SSVs), lower extremity accessory veins, nonsaphenous lower extremity veins, and other accessory veins. In the upper extremity, the cephalic, basilic, and all other superficial veins from the brachiocephalic to the wrist were imaged in detail. Furthermore, in addition, the inferior epigastric vein and superficial chest vein were also evaluated. In patients in whom there was thrombus of both the upper extremity and lower extremity, all extremities were examined. If the lower extremity was involved, only the lower extremity was examined and the same for upper extremity. When the patient developed a recurrent event in an uninvolved extremity, that extremity was included in the subsequent follow-up. The location

## ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective cohort study
- **Take Home Message:** In 24 patients with multiple, unprovoked superficial venous thromboses (SVTs), those with multiple, simultaneous SVTs had increased risk for thrombophilia, cancer, recurrent venous thromboembolism, and death.
- **Recommendation:** A large multicenter study is needed to confirm that patients with multiple, simultaneous SVTs are at greater risk for thrombophilia, cancer, recurrent venous thromboembolism events, and death compared with those with isolated SVT.

and extent of the thrombus of named veins or their tributary's corresponding anatomic location were marked on a special diagram. The proximal and distal extent of the thrombus was noted in detail using clear fixed anatomic landmarks. This was performed to accurately document thrombus propagation and new VTE events. The images of thrombosed veins and their maximum diameter were recorded. The Fig demonstrates an example of imaging with DUS. Only patients with multiple unprovoked thrombi in separate superficial veins were included. Patients with varicose veins were included but were excluded if thrombus was found within a varicose segment. Before initiation of treatment, blood was drawn from patients to determine the state of thrombophilia. Patients were tested for factor V Leiden, antiphospholipid syndrome, prothrombin gene mutation, protein C and S deficiency, antithrombin deficiency, hyperhomocysteinemia, and factor VIII deficiency (if all other gene mutations were excluded). Blood cultures for infection were not done because these thrombi were not associated with trauma or line placement. Blood tests were repeated only if both the treating physician and the patient agreed on a second testing. If a patient was known to have cancer, the type and stage were recorded. In patients without cancer, blood tests and computed tomography (CT) for chest, abdomen, and pelvis were performed to screen for cancer. Other segments of the body were included if there was a pertinent clinical finding or other imaging indicated a possible mass. Patients identified with thrombophilia or cancer were designated group A, and patients without any such findings were designated group B. The prevalence of recurrent VTE and clinical outcomes were compared with a control group with SVT in a single vein. Only patients who had follow-up were included.

After a treatment plan was instituted, patients were followed up with DUS and clinical examination at 1 month, 3 months, and 12 months and annually thereafter. However, patients were seen immediately if they developed new VTE signs and symptoms. Recurrent VTE

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