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A clinical score to rule out the concomitant presence of deep vein thrombosis in patients presenting with superficial vein thrombosis: The ICARO study

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ABSTRACT

Background: Superficial vein thrombosis (SVT) is commonly encountered in clinical practice. Recent studies have suggested that the concomitant presence of deep vein thrombosis (DVT) or pulmonary embolism (PE) at the time of SVT diagnosis is not uncommon, thus increasing the interest on this disease. Whether this coexistence is predicted by specific risk factors remains unknown.
Aim of the study: To evaluate potential risk factors for DVT coexistence in patients presenting with acute objectively diagnosed SVT of the lower limbs and to develop a simple score entirely based on clinical variables to define the pre-test probability of DVT in these patients.
Methods: A multicenter, retrospective cohort study on SVT patients was conducted. Information was collected on clinical signs and on risk factors for venous thrombosis.
Results: 494 patients (mean age 56.3 ± 17.9 years, 64.2% women) were included. Concomitant DVT was found in 16.0% of patients. After multivariate analysis, we identified 5 independent variables that were used to develop the ICARO score: active malignancy (1.5 points), limb edema (1.5 points), rope-like sign (−1 point), age ≥ 50 years (1 point), unprovoked SVT (−1 point). The prevalence of concomitant DVT was 1.1% in the low-probability category (<0 points), 12.0% in the intermediate-probability category (0 to 1 points), and 32.3% in the high probability category (≥1.5 points).
Conclusions: The concomitant presence of major DVT is not negligible in patients with SVT. Our prediction score entirely based on simple clinical variables may be useful in assessing the risk of concomitant DVT in these patients.

1. Introduction

Superficial vein thrombosis (SVT) is a common disease that most often affects the veins of the lower limbs, but that can also be found in other locations. The great saphenous vein is involved in 60% to 80% of cases, and the small saphenous vein in 10% to 20% [1]. SVT is mainly characterized by the presence of a warm, red, tender, swollen area along the course of a superficial vein, often palpable as a cord usually affecting the lower part of the legs.

Little information is available on the epidemiology of SVT of the lower limbs. It has been estimated to have a prevalence of 3–11% in the general population [2], and in a recent community-based study the annual incidence of symptomatic SVT appeared of 0.64‰ inhabitants/year [3]. Furthermore, its prevalence appears to be approximately two-fold higher than that of deep-vein thrombosis (DVT) and pulmonary embolism (PE) combined in a study conducted among patients attending general practitioners [4].

Predisposing risk factors for SVT are similar to those for DVT or PE and include personal or family history of venous thromboembolism, active malignancy, recent surgery or trauma, immobilization, inherited thrombophilia, use of oral contraceptives, infectious diseases, obesity and cardiac or respiratory failure [5–6].

SVT has long been considered a benign entity with more local than systemic implications. It has become recently more clear, however, that SVT may be a manifestation of a systemic tendency to thrombosis, with a non-negligible risk of recurrence or concomitant DVT or PE at the

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time of SVT diagnosis [7]. Unfortunately, available data on this association are not conclusive, ranging between 6% and 36% for concomitant DVT and up to 33% for PE [1,8]. Furthermore, factors associated with the concomitant presence of major thromboembolic events have not been explored.

To better assess this issue, we conducted a large, multicenter, retrospective cohort study with the aim of identifying clinical variables potentially associated with an increased risk of concomitant DVT in a population of patients with SVT of the lower limbs.

2. Materials and methods

The study was carried on in five Italian centers: Cuneo, Napoli, Palermo, Udine and Varese.

All centers were hospital-based Thrombosis Units or Anticoagulation Clinics that are routinely involved in the management of SVT patients, including diagnosis, evaluation of specific risk factors, management of anticoagulant treatment, and long-term follow-up.

2.1. Inclusion and exclusion criteria

All patients with objectively diagnosed SVT were potentially eligible for the study. Objective diagnosis required compressive B-mode ultrasound or echo-color Doppler, and all the patients were also studied for the concomitant presence of lower limb DVT. All patients with concomitant signs or symptoms of PE and/or with an established diagnosis of PE were excluded from the study. Only ambulatory outpatients were included. Patients were referred to the study-centers by General Practitioner or by the local Emergency Department.

2.2. Data collection

Case report forms for the purpose of this study were prepared by the coordinating center in Varese, Italy and were sent to all participating centers. Local investigators were asked to fill out the form and to send it back to the coordinating center.

For each patient the following data were regularly registered in a computerized database: demographic characteristics (age, gender, body mass index [BMI]), personal or family history of DVT/PE, previous episodes of SVT, presence of solid or hematologic malignancy, recent surgery or trauma (≤3 months), severe varicose veins, local or systemic infections, immobilization (acute), use of hormonal therapies (hormonal therapy for cancer, hormonal replacement therapy or contraceptives), cardiac or chronic respiratory failure. Obesity was defined by a BMI > 30 kg/m^2.

The following information was collected on the thrombotic event: time elapsed between the onset of symptoms and diagnosis; site of SVT, involvement of the sapheno-femoral junction; symptoms and signs at presentation (edema, pain, rope like sign, erythema, paresthesia) and concomitant DVT.

Due to the high risk of extending into deep veins, the sapheno-femoral junction was considered involved when the distance between thrombus and sapheno-femoral junction was <3 cm.

In patients with a previous history of DVT, a DVT recurrence was diagnosed in case of the presence of a newly non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression on ultrasonography [9].

Superficial vein thrombosis was defined as secondary in the presence of one of the following risk factors: malignancy, recent surgery or trauma, local or systemic infections, immobilization, hormonal therapy, obesity, cardiac or respiratory failure and varicose veins. In the absence of the aforementioned predisposing factors, SVT was defined idiopathic.

The study was approved by the local Institutional Review Boards that, due to the retrospective nature of the study, waived the need for informed consent, and patient information was codified to ensure anonymity.

2.3. Statistical analysis

Continuous variables were expressed as mean plus or minus the standard deviation (SD) or as median with minimum and maximum values when data did not have a normal distribution; categorical data are given as counts and percentages.

Prevalence of concomitant DVT and the corresponding 95% confidence interval (CI) were calculated.

We evaluated all of the clinical variables in our database that are potentially associated with the concomitant presence of DVT. To obtain a rule entirely based on clinical variables, we did not use the results of radiological examination and we did not consider the location of SVT since this parameter could be precisely defined only with ultrasonography. We performed univariate analyses to select predictor variables for the multivariate model and to determine the significance and strength of the association between each candidate predictor and presence of major thromboembolic events. We assessed significance by using the chi-square test or fisher exact test for nominal categorical variables and the Mann–Whitney U test for continuous variables. A 2-tailed p value less than 0.05 indicated statistical significance. We then categorized the continuous variables that were statistically significantly associated with concomitant DVT, choosing the most discriminative cut off point or points. We included variables that were statistically significantly associated with concomitant DVT in univariate analysis in a multivariate logistic regression model. Presence of thrombophilic abnormalities was not included in the multivariate model to avoid selection bias since they were searched in only about sixty percent of the whole cohort.

We then removed non-statistically significant variables and calculated a regression coefficient for each statistically significant variable in the final model. We assigned points for the score according to the regression coefficients, with 1 point corresponding to a value close to the smallest regression coefficient and serving as the least common denominator for assigning point values for the score items. At variables with a negative regression coefficient negative points were assigned. We then computed the score for each patient, performing a receiver operating characteristic (ROC) curve analysis [10], and computing the area under the ROC curve and its corresponding 95% CI. Finally, we chose the cut off value that discriminated among the low-, intermediate and high probability groups to identify a concomitant DVT 1) a low-probability group with a prevalence of concomitant DVT of less than 3%; 2) an intermediate probability group with a prevalence of concomitant DVT of more than 10%; 3) a high probability group with a prevalence of concomitant DVT of more than 20%. We assessed the predictive accuracy of the final score categories by the proportion of patients with of concomitant DVT in each group.

3. Results

Four hundred and ninety-four patients with SVT were included in the study. Baseline demographic characteristics and potential risk factors for SVT are summarized in Table 1.

The mean patient age was 56.3 ± 17.9 years, 314 patients (63.7%) were female and 91 patients (19.0%) were obese; 85 patients (17.2%) had a personal history of DVT or PE and 175 patients (36.0%) had a previous episode of SVT. A family history of DVT or PE was recorded in almost one third of patients (31.0%); 216 patients (43.7%) were considered idiopathic.

The mean time between symptoms onset and diagnosis was 7.59 ± 8.80 days and the median time was 5 days (range 1–90 days). The great saphenous vein was involved in 358 patients (72.5%) and involvement of sapheno-femoral junction was observed in 9.3% of patients. The most common symptoms at presentation were pain in 62.3% and warmth in 15.1% of cases. The most common signs included edema (37.6%), erythema (32.7%) and rope like sign (26.3%).

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