Risk Factors for Superficial Thrombophlebitis: A Retrospective Case Control Study

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We dedicate this article to the memory of our dear colleague and friend, Dr. Eilon Krashin, a man of knowledge and endless curiosity.

ABSTRACT **Background:** Data regarding risk factors for superficial thrombophlebitis (STP) cases presenting to a hospital is limited.

Objectives: To investigate and stratify clinical and laboratory risk factors for STP.

Methods: We conducted a retrospective case control study comparing patients presenting to the emergency department with STP and age- and gender-matched controls. We collected data on multiple risk factors and five blood indices.

Results: The study comprised 151 patients and matched controls. Patients with STP were more likely to have varicose veins (43.7% vs. 5.3%, $P < 0.001$), recent immobilization (14.6% vs. 1.3%, $P < 0.001$), obesity (36.4% vs. 18.5%, $P = 0.001$), a history of venous thromboembolism (VTE) or STP (27.2% vs. 0.7%, $P < 0.001$), and inherited thrombophilia (9.3% vs. 1.3%, $P = 0.002$). Following multivariate analysis, all five risk factors remained significant, with a history of VTE or STP associated with the largest risk (odds ratio [OR] 35.7), followed by immobilization (OR 22.3), varicose veins (OR 12.1), inherited thrombophilia (OR 6.1), and obesity (OR 2.7). Mean platelet volume was higher (8.5 vs 7.9 fl, $P = 0.003$) in STP cases

Conclusions: A history of VTE or STP, immobilization, varicose veins, inherited thrombophilia, and obesity serve as independent clinical risk factors for STP presenting to hospital.

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KEY WORDS: risk factors, superficial thrombophlebitis (STP), superficial vein thrombosis, thrombophilia, thrombophlebitis

Superficial thrombophlebitis (STP) is a common disorder characterized by inflammation of a superficial vein associated with thrombosis. STP is diagnosed clinically as tender, rigid, and discolored superficial vein [1]. Previously considered a benign condition, STP is now known to coexist with venous thromboembolism (VTE) in up to 36% of cases [2].

STP shares many risk and etiologic factors with VTE, including immobility secondary to prolonged travel or surgery, a hypercoagulable stage, vessel wall trauma, pregnancy, and estrogen-based hormonal treatment. Previous episodes of STP increase the risk for recurrent events [3]. Inherited thrombophilia may predispose to STP, with factor V leiden mutation, prothrombin 20210 mutation, and deficiencies in antithrombin III, protein C, and protein S being the most common [4]. However, varicose veins remain the most prevalent predisposing factor, associated with up to 88% of affected patients [5].

While one large study assessed known risk factors for STP in a healthy population cohort [6], to the best of our knowledge, no prior study was designed to assess risk and contributing factors to STP cases presenting to a hospital setting. Moreover, no prior study assessed the association of routine blood indices with STP. We conducted a retrospective case control study based on an emergency department setting to assess for risk and contributing factors to STP.

PATIENTS AND METHODS

PATIENT POPULATION

The study cohort included adult patients presenting to the emergency department at Meir Medical Center between May 2010 and May 2018. All cases discharged with a diagnosis of STP were evaluated for inclusion. Diagnosis was based on clinical evaluation, namely a tender and erythematous superficial vein. Cases were excluded if STP was secondary to active malignancy, included obvious trauma such as intravenous cannulation, or occurred during pregnancy or the puerperium. In addition, where duplex ultrasound was performed, cases of STP involving the saphenofemoral junction were excluded. STP patients were then age- and sex-matched to patients presenting on the same day to the internal emergency department due to a non-thrombotic diagnosis, based on the earliest available admission.

DATA COLLECTION

Data for both cases and controls was collected on the date of presentation and included smoking history, varicose veins, recent (within 30 days of admission) immobilization of at least 4 days due to disease or major surgery, obesity (body mass index > 30 kg/m^2), history of VTE or STP, history of antiaggregant use, history of anticoagulant use, history of oral contraceptives (OCT) or estrogen hormone replacement therapy (HRT) use, known inherited thrombophilia (factor V Leiden mutation, prothrombin 20210 mutation, hyperhomocysteinemia, protein S deficiency, protein C deficiency, or antithrombin deficiency), cardiovascular disease, and autoimmune or rheumatic disorders. In addition, for patients with blood tests collected on admission, data on the following blood indices was included white blood cell count, hemoglobin levels, platelet count, mean corpuscular volume (MCV), and mean platelet volume (MPV).

STATISTICAL ANALYSIS

Chi-square test was used to assess differences between categorical variables. Variables significant in the univariate analysis were included in a multinomial logistic regression model to determine the adjusted odds ratio (OR) for each risk factor in patients with STP compared with controls, as well as the significance of each adjusted association. Nagelkerke R2 was used to determine variance based on the risk factors in the model. Risk factors were added serially by prevalence to the model to determine their relative contribution to variance between cases and controls. Paired *t*-test was conducted to compare blood indices. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 27 (SPSS, IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered statistically significant. Baseline characteristics of the patients and blood indices are presented as mean and standard deviation (SD) for continuous variables and count (%) for categorical variables.

RESULTS

The first cohort included 151 patients with superficial thrombophlebitis and their age- and sex-matched controls. Characteristics of participants are presented in Table 1. For both groups, 60.9% of patients were female and mean age at admission was 56 years. Following statistical analysis, no significant difference was observed between the two groups for smoking rate, use of OCT or HRT, antiaggregant therapy, anticoagulant therapy, and history of autoimmune or rheumatic disease ($P > 0.05$). Controls were more likely to have cardiovascular disease (19.9% vs. 9.9%, $P = 0.01$). Patients with STP were more likely to have varicose veins (43.7% vs. 5.3%, $P < 0.001$), recent immobilization (14.6% vs. 1.3%, $P < 0.001$), obesity (36.4% vs. 18.5%, $P = 0.001$), history of VTE or STP (27.2% vs. 0.7%, $P < 0.001$), and inherited thrombophilia (9.3% vs. 1.3%, $P = 0.002$). Significant variables were included in a logistic regression model [Table 2]. Following regression, the association to cardiovascular disease was no longer significant. All five risk factors for STP remained significant, with a history of VTE or STP associated with the largest risk (adjusted OR 35.7, 95% confidence interval [95%CI] 4.6–278.0), followed by immobilization (adjusted OR 22.3, 95%CI 4.8–103.9), varicose veins (adjusted OR 12.1, 95%CI 5.2–28.2), inherited thrombophilia (adjusted OR 6.1, 95%CI 1.1–33.1), and obesity (adjusted OR 2.7, 95%CI 1.4–5.1). Roughly half the variance between cases and controls was attributed to these risk factors (Naglkerke R2 =4 9.8%), with varices contributing to 26.5% of the variance, followed by history of VTE or STP (11.5%), immobilization (7.4%), obesity (3%), and inherited thrombophilia (1.4%).

Table 1. Characteristics of study participants

Variable	Thrombophlebitis	Controls
Female	92 (60.9%)	92 (60.9%)
Age (years)	56 ± 16	56 ± 16
Smoking history (current or past)	56 (37.1%)	51 (33.8%)
Varicose veins	66 (43.7%)	8 (5.3%)
Recent immobilization	22 (14.6%)	2 (1.3%)
Obesity	55 (36.4%)	28 (18.5%)
Previous STP / VTE	41 (27.2%)	1 (0.7%)
Antiaggregant therapy	37 (24.5%)	37 (24.5%)
Anticoagulant therapy	13 (8.6%)	6 (4.0%)
OCT / HRT therapy	4 (2.6%)	2 (1.3%)
Inherited thrombophilia	14 (9.3%)	2 (1.3%)
Cardiovascular disease	15 (9.9%)	30 (19.9%)
Autoimmune / rheumatic disease	18 (11.9%)	18 (11.9%)

Data is presented as mean and standard deviation (SD) for continuous variables and count (%) for categorical variables

HRT = hormone replacement therapy, OCT = oral contraceptive therapy, STP = superficial thrombophlebitis, VTE = venous thromboembolism

A nested analysis was then performed for patients with available blood counts, comparing five blood indices between STP cases and their matched controls [Table 3]. No significant difference was found for hemoglobin levels, platelet count, and MCV. Mean white blood cell count was slightly higher for controls (8.8 vs. 7.8 cells × 109/L, $P = 0.03$), while MPV was larger for STP cases (8.5 vs. 7.9 fl, $P = 0.003$).

DISCUSSION

Superficial thrombophlebitis is a relatively common condition, which is estimated to occur in more than one per 1000 cases [7], with many patients presenting to the emergency department. A large body of evidence has demonstrated an associa-

Table 2. Adjusted odds ratios for thrombophlebitis following multinomial logistic regression

Variable	Adjusted OR (95% CI)	*P*-value
Varicose veins	12.1 (5.2–28.2)	< 0.001
Recent immobilization	22.3 (4.8–103.9)	< 0.001
Obesity	2.7 (1.4–5.1)	0.003
Previous STP / VTE	35.7 (4.6–278.0)	0.001
Inherited thrombophilia	6.1 (1.1–33.1)	0.04
Cardiovascular disease	0.5 (0.2–1.2)	0.13

STP = superficial thrombophlebitis, VTE = venous thromboembolism

Table 3. Blood indices at admission

Variable	Thrombophlebitis	Controls
WBC count (cells x 109/L)	7.8 ± 2.8	8.8 ± 3.6
Hemoglobin (g/dl)	13.0 ± 1.8	12.8 ± 2.2
Platelet count (cells x 109/L)	240.4 ± 72.9	262 ± 90.6
MCV (fl)	87.2 (± 6.1)	85.2 ± 8.2
MPV (fl)	8.5 ± 1.5	7.9 ± 0.8

STP = superficial thrombophlebitis, VTE = venous thromboembolism

tion between STP and venous thromboembolic complications [2, 8-11]. Therefore, defining contributing factors for STP and their attributable risk is mandated, especially as some of these conditions may be preventable.

One previous study [6] assessed risk factors for superficial vein thrombosis among Italian blood donors, demonstrating a significant association for age, varicose veins, plaster cast/bed rest, and transfusion. However, this study was population based, and the role of several important potential predisposing conditions, including inherited thrombophilia and autoimmune conditions, were not assessed. Our study therefore explored risk factors for STP within a hospital setting.

Our retrospective case control study demonstrated that five risk factors are independently associated with STP presenting to the emergency department: varicose veins, recent immobilization, obesity, previous STP or VTE, and inherited thrombophilia. Varices were the most common risk factor, affecting 43.7% of patients, with an adjusted OR of 12.1. In addition, although other risk factors had higher OR, varices were associated with the greatest attributable risk (26.5%). This suggests treatment of varices may potentially affect STP disease burden. A history of VTE or STP was associated with the largest risk (adjusted OR 35.7), suggesting a potential role for extended anticoagulant treatment to mitigate risk of future STP. The value of these approaches remains to be determined in future interventional studies.

Inherited thrombophilia was associated with the smallest effect on attributed risk (1.4%). However, as these and other genetic factors are not routinely assessed, they may contribute to the large share of the risk (50.2%) unaccounted for by well-defined risk factors. Last, while obesity was relatively common in the STP cohort (36.4%), it was associated with the lowest risk (adjusted OR 2.7%) among the five risk factors and accounted for only 3% of the variance between cases and controls.

A nested analysis demonstrated higher MPV among STP cases (8.5 vs. 7.9 fl). MPV serves as a potential marker for thrombotic events, as larger platelets have a higher tendency for aggregation [12,13]. Prior studies have demonstrated a link between higher MPV and arterial thrombotic events [14-17] as well as VTE [18]. However, to the best of our knowledge, this is the first study to suggest such an association for STP. In addition, WBC count was lower for STP cases, although this association may be biased by leukocytosis in infectious presentations in the control group.

CONCLUSIONS

A history of VTE or STP, immobilization, varicose veins, inherited thrombophilia, and obesity serve as independent and significant risk factors for STP presenting to the emergency department. In addition, STP may be associated with an increase in MPV. Further investigation into the effect of risk mitigation on thrombophlebitis is warranted.

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Capsule

Determining behavior by following tau

Although some of the symptoms of Alzheimer's disease are conserved among patients, multiple phenotypes exist, including amnestic, visuospatial, language, and behavioral/dysexecutive symptoms. Understanding the mechanisms mediating the different behavioral phenotypes of Alzheimer's disease will help in the development of specific treatments. **Therriault** and colleagues studied the pattern of tau pathology spreading in multiple cohorts of patients with different phenotypes and showed that each phenotype was associated with a specific connectivity-based pattern of tau aggregation. The results suggest that intrinsic brain connectivity drives tau aggregation patterns, thus determining the behavioral phenotype of the disease.

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Eitan Israeli

Capsule

Making ethanol in the gut

Nonalcoholic fatty liver disease (NAFLD) affects about one-fourth of the global population, and it has been proposed that microbially derived ethanol may be involved. **Meijnikman** and colleagues measured the amount of gut microbiota-derived ethanol in the portal vein and found that it was significantly higher in individuals with NAFLD who had undergone fasting. After eating, blood ethanol concentrations increased further, and the liver appeared to metabolize much of it. Next, 20 individuals with NAFLD were given an alcohol dehydrogenase inhibitor, which resulted in even higher levels of ethanol in the peripheral blood. However, this response was ablated in individuals who were first treated with antibiotics, confirming a role for the gut microbiota.

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Eitan Israeli

Capsule

A bacterial driver of arthritis

Autoantibodies can be detected in individuals at risk for developing rheumatoid arthritis (RA) before the development of clinical disease. The source of these autoantibodies, however, remains unclear. **Chriswell** and colleagues found that immunoglobulin G and A autoantibodies from individuals who are at risk for RA cross-react against gut bacteria in the Lachnospiraceae and Ruminococcaceae families. Further analysis identified a bacterial strain from the *Subdoligranulum* genus that was associated with autoantibody development. Mice colonized with this *Subdoligranulum* isolate developed arthritis with a pathology similar to human RA. These findings suggest that this *Subdoligranulum* strain may be a major contributor to RA autoantibody development.

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Eitan Israeli