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Letter to the Editors-in-Chief

Clinically relevant bleeding and thrombotic events in non-cirrhotic splanchnic vein thrombosis. Long-term follow up

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1. Introduction

Splanchnic vein thrombosis (SVT) involves thrombosis that occurs in the trunk of the portal vein, including the left and right branches as well as possible extension to the splanchnic vein, the upper mesenteric artery or the intra-hepatic branches of the portal vein [1]. SVT is considered a type of deep vein thrombosis of atypical localization since it shares the same physiopathological mechanism as the classical venous thromboembolism (VTE) known as the Virchow triad [2]. Anticoagulant treatment is important for the management of this disease, although its use is sometimes limited by the presence of haemorrhagic factors [3].

A recent prospective 2-year follow up study in a large sample of patients evaluated the risk of bleeding, thrombotic events and the causes of mortality of patients with SVT [4] providing further knowledge of this disease. The aims of the present study were to evaluate the long-term complications and identify the risk factors related to complications in patients with non-cirrhotic SVT.

2. Material and methods

2.1. Study design

Retrospective study from 2008 to 2015 of patients diagnosed with non-cirrhotic SVT in Hospital Virgen del Rocio, Seville, Spain. The search was carried out according to the International Disease Classification (IDC) 10 using code I81 for portal thrombosis, D73.5 for splenic thrombosis, K55.0 for mesenteric thrombosis and I12.0 for hepatic thrombosis. We grouped all registries, verified the absence of duplication, and two investigators individually reviewed them excluding cirrhotic patients.

The inclusion criteria of the study were: 1) age > 18 years, 2) non-cirrhotic SVT by imaging techniques (abdominal Doppler ultrasound, abdominal computerized tomography (CT) or magnetic resonance (MR)). Patients with hepatic cirrhosis were excluded from the study due to differential physio-pathological characteristics. The Ethical Committee of the hospital approved this retrospective study.

2.2. Study variables

We collected demographic data, associated comorbidities, risk factors for VTE (active cancer, immobilization, hormone treatment, pregnancy-puerperium, recent surgery) and biomarkers (creatinine, albumin, platelets, bilirubin and haemoglobin). All non-cirrhotic SVT were included in the study regardless of whether they had or not received anticoagulant treatment. Patients were managed according to guidelines, which recommend anticoagulation for at least 3 months [5]. In each patient, the clinician balanced the risk of bleeding versus recurrence while honouring patient preferences when deciding starting, continuing or withdrawing treatment. Two investigators reviewed all the complications, and these were classified as: bleeding, death and thrombotic events. Bleeding events were classified as: mild or clinically relevant bleeding (CRB) (including major and non major CRB) [6]. Thrombotic events were divided into venous thrombotic events (SVT recurrence at a canalized location or not previously affected, deep vein thrombosis and pulmonary embolism) or arterial events (acute coronary syndrome, stroke or transient ischaemic attack). Response to treatment was evaluated in patients undergoing control-imaging studies, with complete resolution being considered as the absence of residual thrombus, partial resolution was the presence of residual thrombus and stabilization was deemed as the absence of changes and evolution to portal cavernoma (chronic SVT). We registered all-cause mortality, death related to thrombosis and/or anticoagulant treatment.

2.3. Statistical analysis

Quantitative variables are expressed as mean (standard deviation) or median (range or interquartile range [IQR]) if necessary. Complications were expressed as accumulated incidence and rate of incidence, calculated as the number of events per 100 patients-year of observation with a confidence interval (CI) of 95% using the Clopper-Pearson exact method. The rate of events was defined as the number of patients with events divided by the total number of 100 patients-year at risk.

The Students' *t*-test (or the Mann-Whitney *U* test when necessary) and the χ^2 test (or the Fisher exact test when appropriate) were used to compare continuous or categorical variables. We analysed the time to complications with the Kaplan-Meier (Mantel-Cox Log rank) method. Proportional hazards regression analysis was performed using the Cox model to evaluate the crude and adjusted hazard ratios (HR). A p value < 0.05 was considered statistically significant. The statistical analyses were carried out using IBM SPSS Statistics v19.

3. Results

3.1. Demographic data

Seventy patients were included (all Caucasian) with a mean age of 52.6 years, and 64% were men (Fig. 1). The median follow up was 11.9 months (IQR: 3.5–37.1) that implies 140.6 patients-year. SVT was localized in the portal, splenic, mesenteric or multiple veins in 47.2%, 10%, 7.1% and 35.7%, respectively (Baseline characteristics in Table 1).

All the solid tumours (n = 28, 40%) were localized in the abdomen: pancreas (n = 10), colon (n = 7), rectum (n = 4), biliary tract (n = 2),

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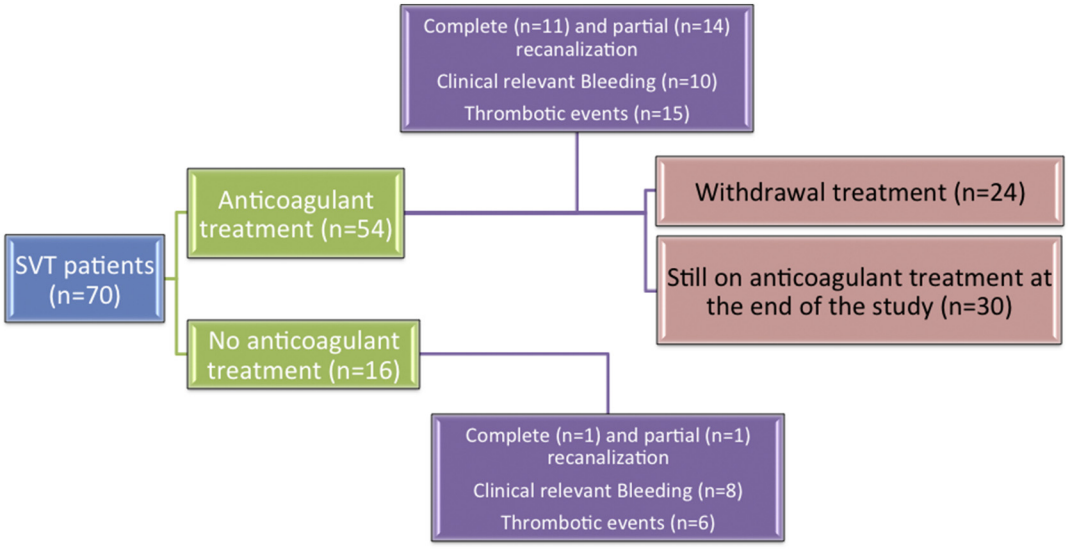

Fig. 1. Flowchart patients.

ovary (n = 1), sarcoma (n = 1), bladder (n = 1), prostate (n = 1) and stomach (n = 1). Four patients had haematological disease: 3 essential JAK2 positive thrombocytosis and 1 diffuse large cell lymphoma.

Fifty-four patients (77.2%) received anticoagulant treatment. The median length of anticoagulant treatment was 6.7 months (IQR: 1.4–13.5). Of these, 8 patients (14.8%) initiated treatment with VKA and the 46 remaining patients (85.2%) initiated treatment with LMWH. In 16 cases (22.8%), the clinician decided to not start anticoagulant treatment mainly due to a history of bleeding, small sized SVT or evidence of chronic portal cavernomatosis. Most of patients (86%) had follow-up imaging, and resolution of the thrombus was partial or total in 39.7%, being higher in patients receiving anticoagulant treatment (47.8%) compared to those not receiving this treatment (8.3%) (p = 0.013; relative risk [RR]: 10; 95%CI: 1.2–84.62).

A total of 25 bleeding events were found (35.7%): 7 mild bleeding (10%) and 18 CRB (25.7%) (13 major bleeding and 5 NMCRB). The rate of CRB was 16.03 per 100 patients-year (95%CI: 9.5–25.34), being greater in patients with a transitory risk factor (19.32 per 100 patients-year;

Table 1
Baseline characteristics of the study cohort and rates of complications.

Characteristic	Total non-cirrhotic SVT cohort (n = 70)
Age, mean (SD)	52.6 (16)
Gender (male), n (%)	45 (64.3%)
Family history of VTE, n (%)	1 (1.4%)
Previous history of VTE, n (%)	8 (11.4%)
Current smoker, n (%)	25 (35.7%)
Incidental, n (%)	33 (47.1%)
Alcohol, n (%)	16 (22.9%)
Previous bleeding, n (%)	17 (24.3%)

Rates of bleeding, thrombotic events and mortality in patients with splanchnic vein thrombosis (SVT), and attending risk factors. Rate: n/subject per 100 patients-year at risk[a] (95%CI[b])

Outcome	Transient risk factor[c] (n = 30)	Cancer (n = 32)	Unprovoked (n = 8)	Total (n = 70)	Transient risk factor[c] (n = 30)
Clinically relevant bleedings events	10 events; 19.32 per 100 patients-year (9.26–35.52)	6 events 16.66 per 100 patients-year (6.09–36.14)	2 events 8.21 per 100 patients-year (0.99–29.66)	18 events 16.03 per 100 patients-year (9.5–25.34)	10 events; 19.32 per 100 patients-year (9.26–35.52)
Major bleeding events	7 events; 11.39 per 100 patients-year (4.58–23.47)	4 events 11.03 per 100 patients-year (3–28.25)	2 events 8.21 per 100 patients-year (0.99–29.66)	13 events 10.65 per 100 patients-year (5.67–18.2)	7 events; 11.39 per 100 patients-year (4.58–23.47)
Thrombotic events	11 events 16.66 per 100 patients-year (8.32–29.8)	8 events 23.12 per 100 patients-year (9.98–45.56)	2 events 7.05 per 100 patients-year (0.85–25.48)	21 events 16.28 per 100 patients-year (10.1–24.89)	11 events 16.66 per 100 patients-year (8.32–29.8)
Mortality	5 events 6.25 per 100 patients-year (2.29–13.84)	13 events 46.81 per 100 patients-year (26.04–78.04)	0	18 events 12.85 per 100 patients-year (7.86–19.92)	5 events 6.25 per 100 patients-year (2.29–13.84)

SVT: splanchnic vein thrombosis; DVT: deep vein thrombosis, PE: pulmonary embolism; BMI: body mass index; n: number. Adjudicated events were events that had been reviewed and confirmed by the Central Adjudication Committee.
Clinically relevant bleeding: Major bleeding or clinically relevant non-major bleeding.
[a] Denominator was the total subjects per 100 patients-year at risk during the time period.
[b] 95%CI = 95% confidence interval, two-tailed Clopper-Pearson exact method.
[c] Transient risk factors included recent surgery, intra-abdominal infection, use of hormone therapy.