Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Splanchnic Vein Thrombosis on Survival: 15-Year Institutional Experience With 1561 Cases

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BACKGROUND: Previous studies regarding survival in patients with splanchnic vein thrombosis (SVT) are limited. This study measured overall survival in a large cohort of SVTs through linkage to population-based data.

METHODS AND RESULTS: Using a previously derived text-search algorithm, we screened the reports of all abdominal ultrasound and contrast-enhanced computed tomography studies at The Ottawa Hospital over 14 years. Screen-positive reports were manually reviewed by at least 2 authors to identify definite SVT cases by consensus. Images of uncertain studies were independently reviewed by 2 radiologists. One thousand five hundred sixty-one adults with SVT (annual incidence ranging from 2.8 to 5.9 cases/10 000 patients) were linked with population-based data sets to measure the presence of concomitant cancer and survival status. Thrombosis involved multiple veins in 314 patients (20.1%), most commonly the portal vein (n=1410, 90.3%). Compared with an age-sex-year matched population, patients with SVT had significantly reduced survival in particular with local cancer (adjusted relative excess risk for recent cases 12.0 [95% CI, 9.8–14.6] and for remote cases 9.7 [7.7–12.2]), distant cancer (relative excess risk for recent cases 5.7 [4.5–7.3] and for remote cases 5.4 [4.4–6.6]), cirrhosis (relative excess risk 8.2 [5.3–12.7]), and previous venous thromboembolism (relative excess risk 3.8 [2.4–6.0]). One hundred fifty (23.9%) of patients >65 years of age were anticoagulated within 1 month of diagnosis.

CONCLUSIONS: SVT is more common than expected. Most patients have cancer and the portal vein is by far the most common vein involved. Compared with the general population, patients with SVT had significantly reduced survival, particularly in patients with concomitant cancer, cirrhosis, and previous venous thromboembolic disease. Most elderly patients did not receive anticoagulant therapy.

Key Words: cancer ■ cirrhosis ■ computerized tomography ■ relative survival ■ splanchnic vein thrombosis

Splanchnic vein thrombosis (SVT) is a potentially life-threatening thrombotic condition that includes thromboses in any of the portal, splenic, hepatic, or mesenteric veins. SVT has an estimated annual incidence of 0.5 to 1 cases per million people per year.[1] SVT presents a clinical challenge for physicians because of a paucity of studies evaluating treatment of SVT and because acute symptoms may go unrecognized with patients not getting diagnosed during the acute phase of the disease.[2,3]

The influence of SVT on survival is uncertain. Deaths associated with SVT could be because of direct causes (such as ascites, liver failure, and infarcted bowel) or indirect causes (such as induction of a thrombogenic state increasing risk of venous thrombosis at other sites, or increased risk of cardiovascular events), but studies are limited. Three studies have used primary data collection to examine survival of patients with SVT but included few participants (ranging from 28 to 97).[2,4,5] The largest primary data-collection study

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016600

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The incidence of splanchnic vein thrombosis, in particular portal vein thrombosis, is more common than expected.
- Our study indicates the incidence is on the rise.
- Splanchnic vein thrombosis is associated with reduced survival, most notably when associated with local cancers; often no anticoagulation is given.

What Are the Clinical Implications?

- Patients with cancer will represent a significant proportion of patients with splanchnic vein thrombosis.
- Treatment decisions are complicated by end-of-life presentations and comorbidities.
- Our retrospective data suggest better outcomes when oral anticoagulation is provided, but randomized trials are needed, with detailed documentation of exclusions because currently most patients do not get offered or cannot receive anticoagulation.

Nonstandard Abbreviations and Acronyms

LMWH	low molecular weight heparins
RER	relative excess risk
SVT	splanchnic vein thrombosis

regarding SVT survival involved 604 cases, followed for a median of 2 years, and recorded 106 deaths.[6] These primary data-collection studies were susceptible to missing deaths from loss to follow-up. Three SVT studies have used population-based death registries to completely measure patient survival, but identified cases using diagnostic codes having uncertain accuracy.[7–9]

To our knowledge, no study has examined the influence of patient and thrombus characteristics on death risk in SVT. In addition, the influence of treatment on survival in patients with SVT is also unknown. This study attempted to understand more about the survival of patients with SVT and its influencing factors by creating a complete cohort of patients at an academic hospital. We linked these data with population-based data sets to examine the incidence, treatment, and complete survival of patients with SVT. The resultant collection of patients represents the largest primary-data cohort of patients with SVT described in the literature to date and provides insights into current trends in management of SVT.

METHODS

Study Setting

The study took place at The Ottawa Hospital (TOH). The study was approved by the TOH Research Ethics Board. Patients were not required to provide consent. TOH is the quaternary–tertiary care/academic hospital for the Champlain region of Ontario, Canada with 1.3 million people. All patients with cancer in the region are managed at TOH. We have 8% of our 1200 inpatient beds dedicated to cancer care and we treat >4000 new patients with cancer per year. Despite our tertiary mandate, we care for 75% of all patients in our region and 70% of our care is considered nontertiary. The data from this study cannot be made available for other researchers because the ownership is not with the authors, but rather with the province of Ontario and TOH.

Identifying Patients with SVT

We screened the reports of all abdominal ultrasounds and contrast-enhanced computed tomography scans conducted between July 1, 2001 and December 31, 2015 for SVT. This used a text search algorithm that we had derived in a simple random sample of 4999 abdominal ultrasound reports in which 16 (0.3%) cited an SVT. This analysis found that the reports of these cases each contained the text "PORTAL" with "THROMB" elsewhere in the same sentence (100% sensitivity). The specificity and positive predictive value of this text algorithm was 99.4% and 28.1%, respectively. Cases involving patients <18 years of age were excluded.

All reports between 2001 and 2015 identified by our text-search were reviewed independently by 2 reviewers (IT, JB) to determine whether a definite diagnosis of SVT was made. Reports using any of the following descriptors were considered diagnostic of SVT: "acute thrombus"; "acute thrombosis"; "acute intraluminal filling defect"; "fresh thrombus"; "definite thrombus"; "evidence of thrombosis"; "in keeping with thrombosis"; and "consistent with thrombosis." Reports were classified as "equivocal" if they used any of the following terms in association with a thrombus of any splanchnic vein: "suggestive," "probably," "compatible with," "suspicious," "appears to be," "suspected," "likely," "possibly," "implied by," "indicative of," "could be," "believe to be," "might be," "presumably," "may be," "worrisome for," "question of," "favor thrombosis," "thrombus considered," "seems to be," "questionable for," "concerning for," "may represent," and "features of." The original computed tomography or ultrasound images of these equivocal cases were independently reviewed by 2 radiologists (AK, SJ) to make a final determination regarding SVT diagnosis. These reviews

were conducted without knowledge of clinical treatments and outcomes. If there were divergent opinions regarding clot status following radiological review, images were reviewed simultaneously by both radiologists to determine the final diagnosis by consensus. Only cases of definite SVTs were included in this study. If patients had multiple diagnoses of SVT, only the first case was retained for the study.

Data Collection

For each SVT case, clot characteristics were abstracted from the radiology report including location (portal vein [including its branches], splenic vein, mesenteric veins [superior or inferior], or hepatic veins); whether it was occlusive; presence of tumor thrombus (rather than simply bland thrombus); presence of characteristics suggesting chronicity; and whether previous imaging studies demonstrated nondiagnostic findings suggestive of SVT.

From our hospital's data warehouse, we extracted basic information including time and location of the SVT diagnosis (with the latter classified as outpatient, emergency department, or inpatient). For patients who were diagnosed while in the emergency department or as an inpatient, we determined whether full anticoagulation was provided after the diagnosis of SVT.

All cases were then anonymously linked to population-based data sets using encrypted patient healthcare numbers. We linked to the Registered Patients Database (which captures the date of all Ontarian deaths, including those outside of the province) to determine if and when patients died. We linked to the National Ambulatory Care Reporting System (which captures all emergency department visits) and the Discharge Abstract Database (which captures all hospitalizations and same-day surgeries) to determine whether, before the diagnosis of SVT, patients had ever been diagnosed with cirrhosis; had undergone epigastric surgery in the previous 6 months; or had been diagnosed with acute or chronic pancreatitis in the previous 6 months. We linked to the Ontario Cancer Registry (which captures all incident diagnoses of cancer—except for nonmelanomatous skin cancer—in Ontarians) to determine if and when patients had been diagnosed with a myeloproliferative disorder (including chronic myelogenous leukemia, polycythemia vera, essential thrombocytosis, primary myelofibrosis, and chronic neutrophilic leukemia) or cancer before their SVT. Cancer diagnoses made up to 1 month following SVT diagnosis were classified as having been present when the latter was identified. Cancers were classified as "local" if they involved the stomach, liver, gallbladder, biliary tract, pancreas, small intestine, kidney, or adrenals; all others were classified as "distant." Cancers were classified as "recent" if they had been diagnosed in the 6 months before SVT; all others were classified as "remote." Finally, for patients over the age of 65, we linked to the Ontario Drug Benefit Database (which captures all pharmacy dispensations for seniors) to determine whether patients had been dispensed anticoagulant treatment 6 months before or within 1 month after their SVT diagnosis. Details regarding the coding algorithms used to identify these covariates is provided in Table S1

Statistical Analysis

We limited our analysis to patients >18 years of age. SVTs were categorized as chronic if the radiologist noted that an abnormality was, or *may* have been, present on previous imaging or if previous imaging from an external institution had reported SVT. The annual incidence of SVT at our hospital was measured using the annual number of unique patients seen at our hospital as the denominator. Two reviewers examined the reports of all patients to determine SVT status; we did double abstraction of the initial 223 randomly selected cases to measure interrater reliability regarding SVT details. A priori, we decided to have only 1 reviewer abstract details from each report if high interrater reliability was present.

The primary treatment outcome of the study was relative survival, or the risk of all-cause death in our cohort compared with an age-sex-time matched population (measured with life tables from Statistics Canada) using methods from Dickman et al.[10] This unadjusted "relative survival" was calculated as the ratio of the observed survival (calculated as the base of the natural logarithm [*e*] raised to the observed number of deaths divided by the total observation time) to the expected survival (from the provincial life tables). Multivariable relative survival models were used to measure the association of prespecified characteristics (including patient characteristics [age, sex, and previous conditions including cancer, cirrhosis, venous thromboembolic disease, epigastric surgery, pancreatitis] and SVT characteristics [diagnosis year and location, evidence of occlusive, chronic, or tumorous changes, number of veins involved]) with relative survival. Relative survival models are additive hazards models in which the total hazard of death is the sum of the known hazard in the general population and the excess hazard in patients with SVT.[10] Parameter estimates for the full relative survival model were estimated with a Poisson error structure using PROC GENMOD in SAS 9.3 and were exponentiated to calculate the relative excess risk.[11]

In patients >65 years of age, we added parameters for anticoagulation in the prior 6 months and within the first 30 days following diagnosis to the model.

Anticoagulation was classified as any exposure to oral anticoagulants (including warfarin and direct oral anticoagulants) or low molecular weight heparins (LMWH). To explore possible reasons for nontreatment, we randomly audited the hospital record of 60 patients with SVT who had been diagnosed in the hospital and received no acute treatment. Patients diagnosed with SVT in the hospital who were fully anticoagulated were classified as having received postdiagnosis LMWH regardless of whether oral anticoagulants were started later. The treatment analysis excluded 4 patients who died within the first month of their SVT diagnosis before being exposed to anticoagulants (either in the hospital when diagnosed or as an outpatient) to avoid time-dependent bias.[12]

RESULTS

During the study period, 567 031 reports were screened for splanchnic vein thrombosis (Figure 1). Seven thousand two hundred forty-two reports were screen-positive, within which there were 195 duplicate reports, 2249 duplicate patients, and 54 patients who were <18 years of age. In the remaining 4744 adult patients, 3093 (65.2%) definitively had no SVT, 90 (1.9%) had a possible SVT (even after manual review of the imaging studies), and 1561 (32.9%) had a definite SVT. Manual review was performed in 423 cases because of equivocal reports. Agreement between the 2 reviewers regarding SVT detail was excellent; in a random sample of 223 reports, there

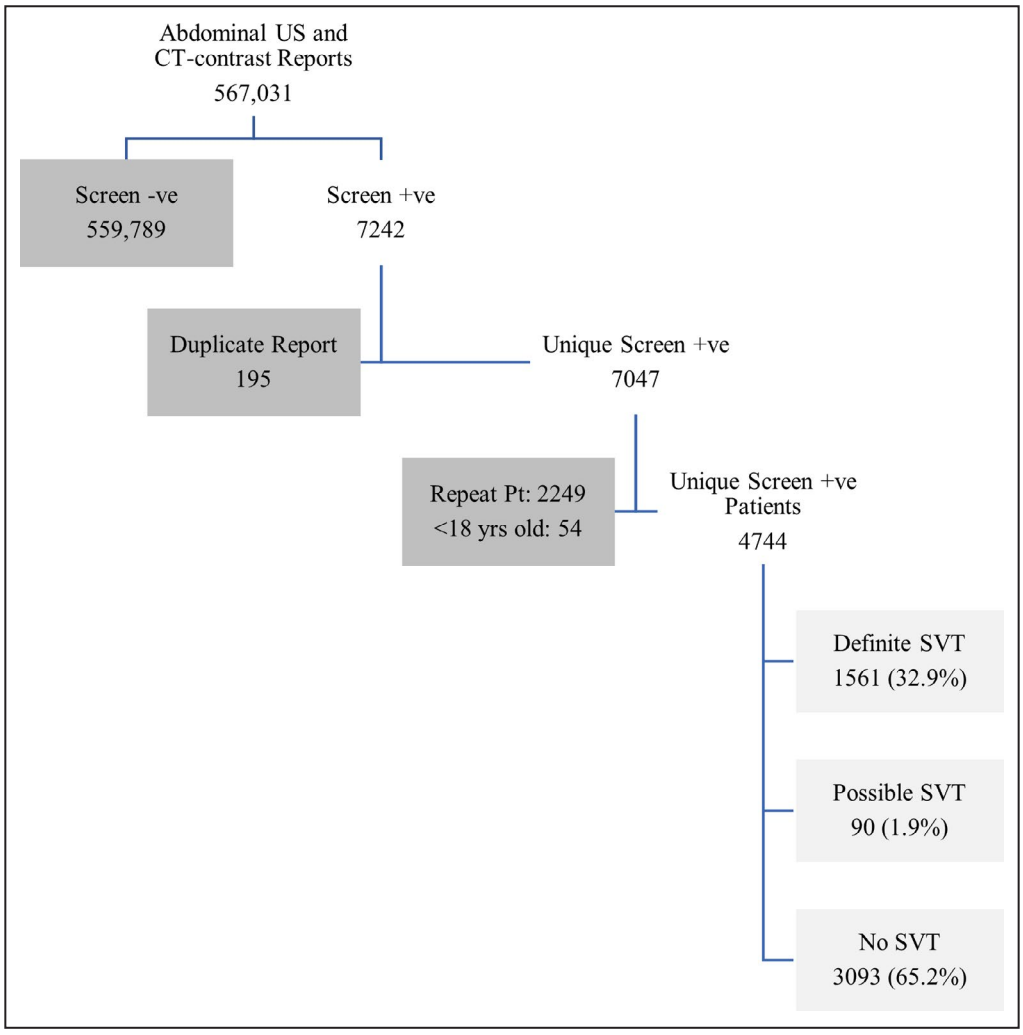

Figure 1. Creation of the TOH-SVT cohort.
This figure illustrates the creation of the study cohort. We identified 567 031 reports of abdominal ultrasound or contrast-enhanced computed tomography between July 1, 2001 and December 31, 2015. A text-search algorithm derived to identify SVT (Table S1) was used to screen all reports, of which 7242 were positive. One hundred ninety-five of these were duplicate reports and 2249 included duplicate patients. This left 4744 patients with at least 1 screen positive radiology report of which 1561 definitively had an SVT after manual review of the report and/or the imaging study. CT indicates computed tomography; Pt, patient; SVT, splanchnic vein thromboses; TOH, The Ottawa Hospital; US, ultrasound; +ve, positive; and –ve=negative.

Table 1. Description of 1561 Patients With Definite Splanchnic Vein Thrombosis

Variable	Level	Group			All
			Linked (N=1488)		
		Unlinked	Age <65	Age 65+	
		N=73 (4.7%)	N=861 (55.2%)	N=627 (40.2%)	N=1561 (100%)
Mean age (SD)	…	56.7±14.3	51.5±10.1	74.3±6.6	60.9±14.3
Women	…	35 (47.9%)	354 (41.1%)	274 (43.7%)	663 (42.5%)
Location	Inpatient	28 (38.4%)	319 (37.0%)	226 (36.0%)	573 (36.7%)
	Emergency	16 (21.9%)	202 (23.5%)	141 (22.5%)	359 (23.0%)
	Outpatient	29 (39.7%)	340 (39.5%)	260 (41.5%)	629 (40.3%)
Imaging modality	CT	48 (65.8%)	623 (72.4%)	453 (72.2%)	1124 (72.0%)
	US	25 (34.2%)	238 (27.6%)	174 (27.8%)	437 (28.0%)
SVT location*	Portal	67 (91.8%)	772 (89.7%)	571 (91.1%)	1410 (90.3%)
	Mesenteric	16 (21.9%)	137 (15.9%)	106 (16.9%)	259 (16.6%)
	Splenic	7 (9.6%)	138 (16.0%)	99 (15.8%)	244 (15.6%)
	Hepatic	≤5 (0–6.8%)	23 (2.7%)	19 (3.0%)	42–47 (2.7–3.0%)
Total locations	1	59 (80.8%)	690 (80.1%)	498 (79.4%)	1247 (79.9%)
	>1	14 (19.2%)	171 (19.8%)	129 (20.6%)	314 (20.1%)
Thrombus traits	Occluded	14 (19.2%)	123 (14.3%)	88 (14.0%)	225 (14.4%)
	With tumor	6 (8.2%)	82 (9.5%)	85 (13.6%)	173 (11.1%)
	Chronic	19 (26.0%)	254 (29.5%)	153 (24.4%)	426 (27.3%)
Prior cancer†	None	…	414 (48.1%)	178 (28.4%)	…
	Distant, remote	…	153 (17.8%)	152 (24.2%)	…
	Distant, recent	…	64 (7.4%)	72 (11.5%)	…
	Local, remote	…	92 (10.7%)	82 (13.1%)	…
	Local, recent	…	138 (16.0%)	143 (22.8%)	…
Conditions	Cirrhosis	…	30 (3.5%)	13 (2.1%)	…
	VTE disease‡	…	24 (2.8%)	19 (3.0%)	…
	Epigastric surgery‡	…	18 (2.1%)	10 (1.6%)	…
	Pancreatitis‡	…	10 (1.2%)	≤5 (0–0.8%)	…
	Myeloproliferative disease§	…	≤5 (0–0.6%)	≤5 (0–0.8%)	…
Rx – prior 6 mo	Oral‖	…	…	32 (5.1%)	…
	LMWH	…	…	8 (1.3%)	…
- Within 1 mo, acute*¶	Oral‖	…	…	43 (6.9%)	…
	LMWH	…	…	86 (13.7%)	…
- Within 1 mo, Chronic*	Oral‖			15 (2.4%)	
	LMWH			26 (4.2%)	

A total of 1556 individual patients were diagnosed with SVT between July 1, 1991 and December 31, 2015. Patients are clustered based on whether they could be linked to population-based data sets and by age relative to 65 years. All medications for patients above this age threshold are recorded in the population-based data sets. CT indicates computed tomography; SVT, splanchnic vein thrombosis; US, ultrasound; VTE, venous thromboembolic; and LMWH, low molecular weight heparin.

*Note that these groups are not mutually exclusive.

†"Local" = cancers of the stomach, liver, gallbladder, biliary tract, pancreas, small intestine, kidney, and adrenals; "Distal" = all other cancers; "Recent" = diagnosed no more than 6 months before SVT; "Remote" = diagnosed more than 6 months before SVT.

‡In 6 months before SVT diagnosis based on administrative data set diagnostic and procedural codes.

§Based on Ontario Cancer Registry data.

‖Includes both warfarin and direct oral anticoagulants.

¶Four patients died within 1 month of diagnosis without treatment.

were only 18 disagreements regarding SVT status in each of the 7 venous locations (Table S2). Given that this involved 1561 comparisons (ie, 223×7) and the very high kappa measures for these comparisons, we had only 1 reviewer record the patient details on all subsequent reports.

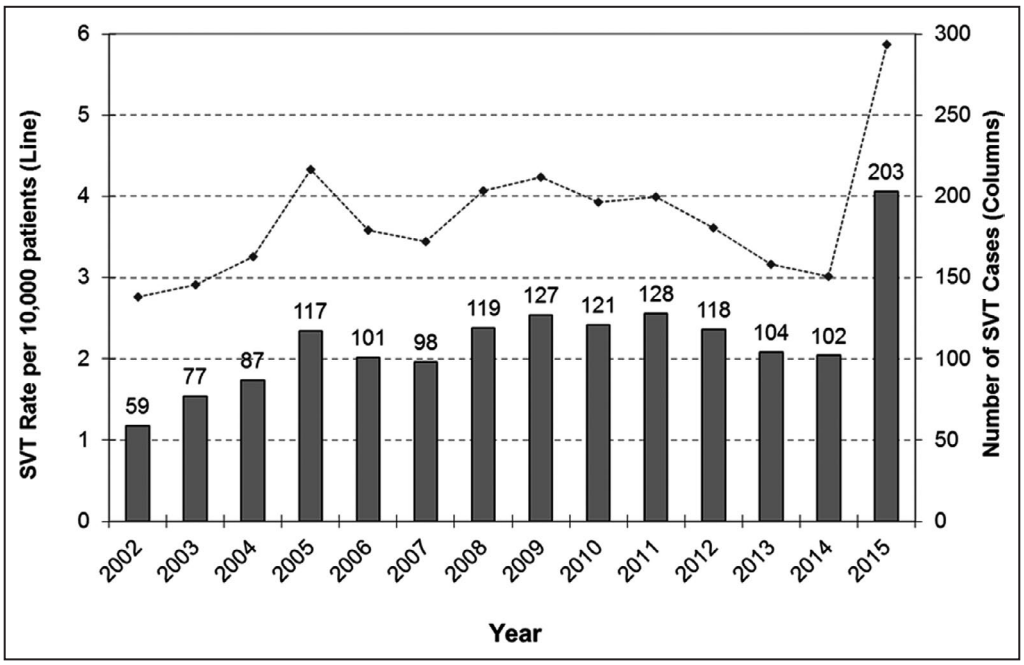

Figure 2. Annual number and incidence of SVT at the study hospital.
This plot presents by year (horizontal axis) the number of SVT identified at the study hospital (right vertical axis) along with SVT rate (left vertical axis), calculated as the number of cases per 10 000 unique patients seen at the hospital that year (for example, for year 2002, 59 cases were divided by number of unique patients for that year times 10 000 to give the SVT rate of 2.8 per 10 000 patients in that year). SVT indicates splanchnic vein thromboses.

The 1561 patients with a definite SVT are described in Table 1. Mean age was 61 years, with less than half being women. Approximately 78% of patients were inpatients or outpatients when they were diagnosed, with the remainder from the emergency department. In more than a quarter of cases, thrombi appeared chronic or were likely present on previous imaging. SVTs were occlusive almost 15% of the time. One thousand four hundred eighty-eight patients (95.4%) could be linked to population-based data sets; patients who could not be linked did not vary notably in their characteristics (Table 1). In the linked patients, cancer was present before SVT diagnosis in 1056 patients (71.0%); cancer was equally distributed between local and distant tumors and was more prevalent in older patients.

In patients >65 years of age (in whom treatment status could be determined), anticoagulation with either oral agents or with heparins was uncommon before SVT diagnosis. Initiation of any treatment within 1 month of diagnosis occurred in 150 patients (23.9%). Treatment using oral agents or heparins was less likely if the SVT had chronic characteristics. The chart audit (n=60) revealed that treatment was withheld because of active bleeding in 35%, palliative status in 35%, chronic SVT in 15%, and for undocumented reasons in 15%.

SVT incidence fluctuated during the study period but ended with a notable spike at the end of the study period (Figure 2). Before 2015, the annual number of people newly diagnosed with SVT varied between a low of 59 (in 2002) and a high of 128 (in 2011). This translated to hospital-based SVT rates varying between 2.8 and 4.3 SVT per 10 000 patients. In 2015, however, the number of thrombi and the associated rate increased notably to 203 and 5.9 per 10 000 patients, respectively.

Thrombosis location varied between patients, with portal vein thromboses being most common (n=1410, 90.3%) and hepatic vein thromboses being rare (n=43, 2.8%) (Figure 3). Patients most commonly had thromboses isolated to a single vein location (n=1247, 79.9%). The most frequent combined location was portal vein and mesenteric vein (n=112, 7.2%). Eighty patients (5.1%) had thrombus in the portal, mesenteric, and splenic veins.

Influence of SVT on Patient Survival

Survival in patients with SVT was significantly lower than that in the age-sex-time matched population (Figure 4). This relative survival varied significantly over time and by age, cancer status, and patient location. In almost all subgroups, relative survival decreased as time from SVT diagnosis increased. In patients without a previous diagnosis of cancer, relative survival was lower in older patients but was relatively invariant to patient location at diagnosis. In

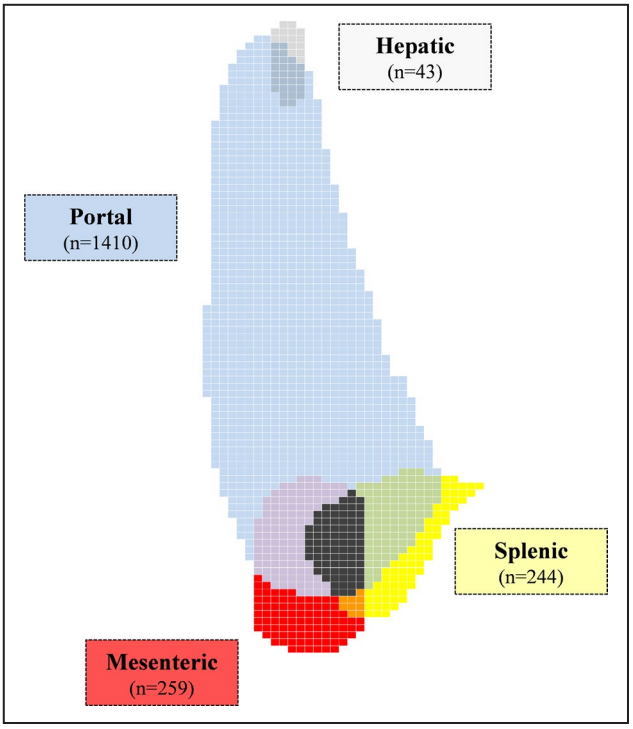

Figure 3. SVT locations in 1561 patients.
This Venn diagram presents the location of all 1561 patients diagnosed with a SVT between July 1, 2001 and December 31, 2015. Each patient is represented as a square with thrombus location indicated by colors (blue=portal; yellow=splenic; red=mesenteric; speckled=hepatic). Patients with thrombus in multiple locations are represented by colors that are combinations of the constituent locations; for example, a patient simultaneously having a thrombus in the portal vein (blue) and mesenteric vein (red) is indicated by a purple square. Porto–mesenteric–splenic vein thrombi are indicated in black. Not indicated on the diagram is: (1) 1 patient with a simultaneous hepatic vein and mesenteric vein thrombus (represented in the diagram as a hepatic vein thrombus) and (2) another patient with a simultaneous hepatic vein, portal vein, and splenic vein thrombus (represented in the diagram as a portal–hepatic vein thrombus). The shape of subgroups was done to reflect the anatomy of the splanchnic veins. One simply needs to count the squares to know the overlapping cases because each square represents 1 patient. SVT indicates splanchnic vein thrombosis.

patients with a previous cancer diagnosis, relative survival was less influenced by patient age (especially with inpatients) and relative survival was better among outpatients. Distinction in relative survival between remote and recent cancer diagnosis was most apparent among local cancers.

Patient and SVT characteristics were significantly associated with relative survival (Table 2). Relative excess risk (RER) increased progressively as patients aged. A diagnosis of cancer before SVT greatly increased RER, most prominently in patients diagnosed with cancers local to the splanchnic region. Cirrhosis was associated with an RER of 8.2 (95% CI, 5.2–12.7). Recent venous thromboembolic disease was associated with an increased RER almost 4 times unity. Relative survival was not influenced by recent epigastric surgery, pancreatitis, or myeloproliferative disease. RER increased very slightly over time and was greatest for inpatients. SVT that was occlusive or appeared tumorous was significantly associated with increased RERs (1.41 [1.16–1.64] and 1.36 [1.13–1.64], respectively). Chronic-appearing SVT had better survival than those whose SVT was acute (RER, 0.67; 95% CI, 0.58-0.79).

When the relative survival analysis was limited to patients age >65 years of age, qualitatively similar results were found but some important changes were seen (Table 2) including: age effect decreased (likely because of the much smaller age range); epigastric surgery and myeloproliferative disease negatively influenced relative survival; and time, as well as thrombus location/characteristics, had a smaller effect on relative survival. Factors that persisted included the negative influence of cirrhosis, previous venous thromboembolic disease, and a prior diagnosis of cancer, most notably when local.

In patients >65 years of age, treatment with LMWH in the 6 months before SVT diagnosis was associated with more than a 6-fold increase of the RER, but this observation is based on only 8 patients. After diagnosis, the association of treatment for acute SVT differed by agent; warfarin or direct oral anticoagulants were associated with an almost three-quarters reduction in the RER (RER, 0.26; 95% CI, 0.14–0.50) while LMWH was associated with an increased RER risk of death (RER, 1.42; 95% CI, 0.98–2.10). Treatment of chronic SVT had no association with relative survival.

DISCUSSION

Our study had several notable findings. First, we found that, relative to an age-sex-year matched population, SVT was associated with a significantly reduced survival that worsened over time and was most evident in those with cancer, cirrhosis, and previous venous thromboembolic disease. We are the first to report that survival in patients with cancer and SVT varies by cancer location and timing, with recently diagnosed and local cancers conferring the worst prognosis. We noted a very high prevalence of cancer before the diagnosis of SVT with a prevalence exceeding 50% in those <65 years of age and almost 75% in the elderly. Second, although we confirmed that SVT frequently involves multiple sites, we determined 80% were isolated to a single vein. This is slightly higher than 60% estimated in smaller studies.[13] The portal vein was involved in 90% of cases. Third, we confirmed that SVT is an uncommon diagnosis, occurring in <0.06% of the 338 000 patients seen annually at our institution. However, our data also

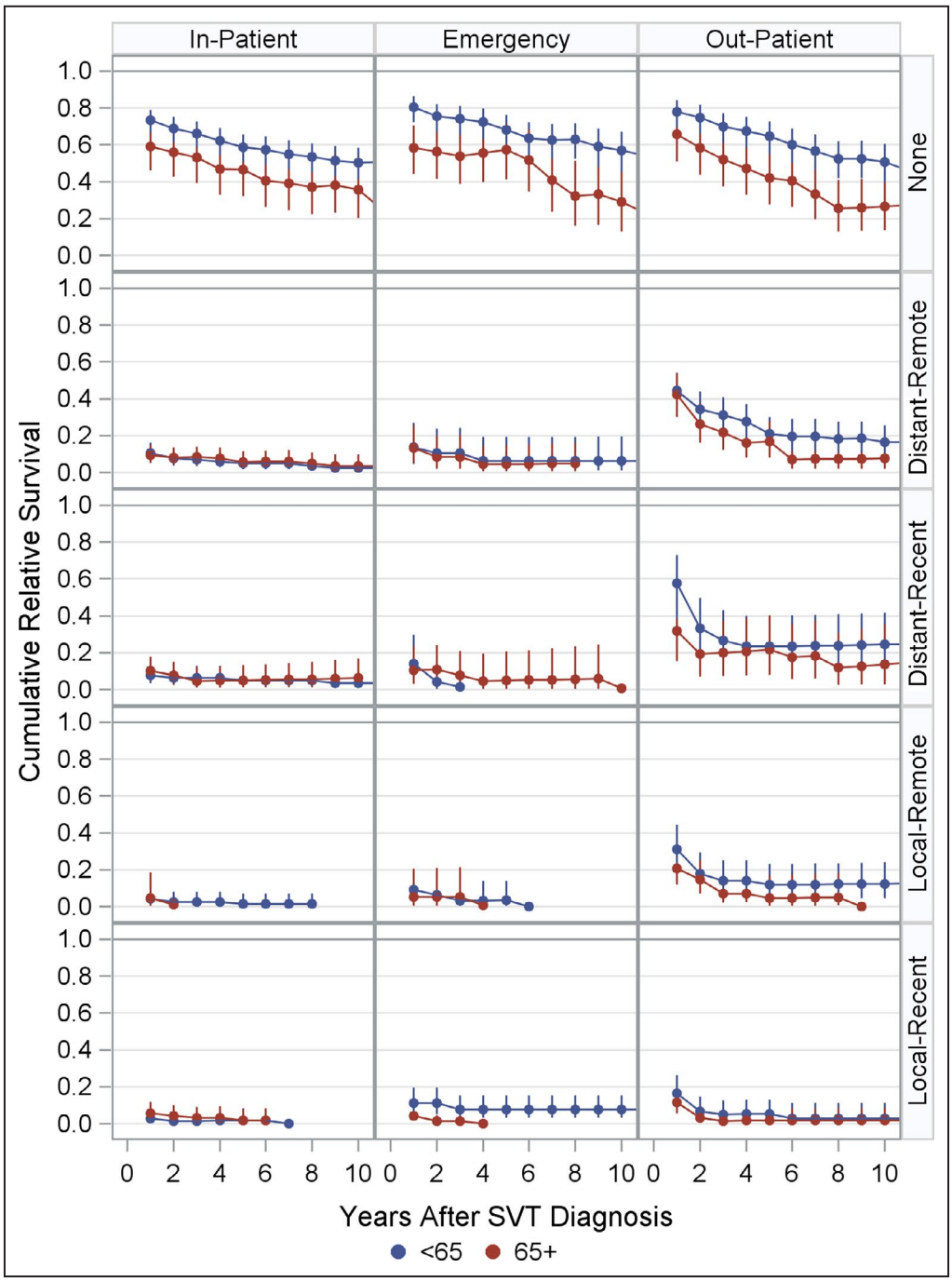

Figure 4. Association of SVT with relative survival by patient location at diagnosis, cancer status at time of diagnosis, and age.
Relative survival plots for patients above and below 65 years of age are stratified by patient location at time of diagnosis (top) and cancer status (side). "Local" cancers involve stomach, liver, gallbladder, biliary tract, pancreas, small intestine, kidney, and adrenals (with all others classified as "Distant"). "Recent" cancers are diagnosed <6 months before SVT (with all others classified as "Remote"). Each graph plots the cumulative relative survival (vertical axis) against years after SVT diagnosis (horizontal axis) with 95% CIs. Cumulative relative survival indicates patient survival relative to an age-sex-year matched population (with values <1 indicating survival less than that expected based on the patient age and sex as well as diagnosis year). SVT indicates splanchnic vein thrombosis.

suggest that SVT could be much more common than has been previously suggested. A Swedish study based on diagnostic codes reported a population-based portal vein thrombosis incidence of 0.7 per 100 000 population.[8] With a service population for our institution of 1.3 million people, the 1561 cases we identified

Table 2. Adjusted Association of Patient and Thrombosis Characteristics with Relative Survival

Variable	Level	All Patients			Patients >65 years		
		Parameter Estimate (SE)	Relative Excess Risk (95% CI)	*P* value	Parameter Estimate (SE)	Relative Excess Risk (95% CI)	*P* value
Intercept		−2.86 (0.12)	…	0.0000	−2.17 (0.2)	…	0.0000
Patient characteristics							
Age (y)	<55	…	…	0.0000	…	…	0.6817
	55≤65	0.43 (0.09)	1.54 (1.28, 1.84)	…	…	…	…
	65≤75	0.52 (0.09)	1.68 (1.40, 2.01)	…	…	…	…
	75+	0.60 (0.10)	1.81 (1.48, 2.23)	…	−0.05 (0.12)	0.95 (0.75, 1.21)	…
Women	…	0.06 (0.07)	1.06 (0.93, 1.21)	0.3725	0.10 (0.12)	1.11 (0.88, 1.4)	0.3888
Cancer Dx‡	None	…	…	0.0000	…	…	0.0000
	Distant–remote	1.68 (0.10)	5.37 (4.40, 6.55)	…	1.33 (0.19)	3.8 (2.61, 5.52)	…
	Distant–recent	1.74 (0.12)	5.69 (4.46, 7.25)	…	1.49 (0.22)	4.44 (2.9, 6.78)	…
	Local–remote	2.27 (0.12)	9.66 (7.68, 12.2)	…	2.01 (0.22)	7.49 (4.91, 11.4)	…
	Local–recent	2.48 (0.1)	12.0 (9.80, 14.6)	…	2.15 (0.19)	8.54 (5.92, 12.3)	…
Cirrhosis	…	2.10 (0.22)	8.17 (5.26, 12.7)	0.0000	2.04 (0.43)	7.67 (3.3, 17.8)	0.0000
VTE disease*	…	1.34 (0.23)	3.82 (2.42, 6.05)	0.0000	1.94 (0.38)	6.96 (3.32, 14.6)	0.0000
Epigastric surgery*	…	0.41 (0.29)	1.51 (0.86, 2.66)	0.1538	0.95 (0.53)	2.58 (0.92, 7.22)	0.0714
Pancreatitis*	…	0.55 (0.35)	1.74 (0.88, 3.45)	0.1136	0.43 (1.07)	1.54 (0.19, 12.6)	0.6865
MPD	…	0.38 (0.61)	1.47 (0.44, 4.87)	0.5291	2.93 (1.04)	18.7 (2.46, 143)	0.0047
Thrombosis characteristics							
Year	<2008	…	…	0.0751	…	…	0.9178
	2008–2011	0.11 (0.08)	1.12 (0.96, 1.31)	…	−0.06 (0.14)	0.95 (0.72, 1.24)	…
	2012+	0.19 (0.08)	1.21 (1.02, 1.43)	…	−0.04 (0.15)	0.96 (0.72, 1.28)	…
Dx location	Outpatient			0.0000			0.1142
	Emergency	0.25 (0.09)	1.29 (1.08, 1.54)	…	0.29 (0.15)	1.34 (1.00, 1.81)	…
	Inpatient	0.38 (0.08)	1.46 (1.26, 1.70)	…	0.24 (0.17)	1.27 (0.91, 1.77)	…
Occluded	…	0.34 (0.1)	1.41 (1.16, 1.70)	0.0004	0.29 (0.17)	1.34 (0.97, 1.86)	0.0753
Tumor	…	0.31 (0.1)	1.36 (1.13, 1.64)	0.0013	−0.31 (0.16)	0.73 (0.54, 0.99)	0.0463
Chronic	…	−0.39 (0.08)	0.67 (0.58, 0.79)	0.0000	0.22 (0.16)	1.25 (0.91, 1.72)	0.1746
>1 SVT	…	−0.14 (0.09)	0.87 (0.73, 1.03)	0.1046	0.22 (0.15)	1.24 (0.93, 1.67)	0.1488
Rx–prior 6 mo	Oral†	…	…	…	0.32 (0.26)	1.37 (0.82, 2.3)	0.2289
	LMWH	…	…	…	1.88 (0.42)	6.58 (2.89, 15)	0.0000
–within 1 mo, acute	Oral†				−1.36 (0.31)	0.26 (0.14, 0.50)	0.0000
	LMWH				0.35 (0.19)	1.42 (0.98, 2.10)	0.0623
–within 1 mo, chronic	Oral†	…	…	…	−0.04 (0.45)	0.96 (0.40, 2.35)	0.9369
	LMWH	…	…	…	−0.30 (0.32)	0.74 (0.39, 1.40)	0.3557

All parameter estimates and risks are adjusted, thus are independent of all the other covariates presented. Dx indicates diagnosis; LMWH, low molecular weight heparin; MPD, myeloproliferative disease; Rx, drug; SVT, splanchnic vein thrombosis; and VTE, venous thromboembolic disease.

*In 6 months before SVT diagnosis based on administrative data set diagnostic and procedural codes.

†Includes both warfarin and direct oral anticoagulants.

‡"Local"=cancers of the stomach, liver, gallbladder, biliary tract, pancreas, small intestine, kidney, and adrenals; "Distal"=all other cancers; "Recent"=diagnosed no more than 6 months before SVT; "Remote"=diagnosed more than 6 months before SVT.

returns an incidence of 120 per 100 000 population. Several biases exist in this statistic that would bias this estimate both down (not all people in our area undergo abdominal imaging, thereby missing asymptomatic SVT; our study did not capture all abdominal imaging of patients in our area; we did not include cases in patients <18 years of age) and up (some cases identified in our cohort may have come from outside our service population). However, SVT incidence from our radiographically based data is much higher than previously reported. Fourth, we found a large increase in the incidence of SVT at our institution at the end of our study period. Further study will be required to determine whether this increase is a temporary spike or part of an ongoing trend of either increased detection or higher incidence of SVT. Finally, the proportion of patients who

received anticoagulant therapy in this study was much lower than reported by others. Treatment of acute SVT with warfarin or direct oral anticoagulants was positively associated with survival, but treatment with LMWH or of chronic SVT had no association with relative survival. Similar to our results, other studies have found decreased survival associated with SVT, which varied by patient characteristics, being highest in those with cancer and cirrhosis.[8,9] Reduced survival associated with SVT was also identified in a systematic review of liver transplantation studies.[14] Our findings in patients with cancer contrasts with the findings of Sutkowaska et al,[15] whose cancer prevalence in 341 SVTs was only 11%. This could be because of selection bias since their cohort was created from patients who underwent thrombophilia testing and clinicians are unlikely to pursue thrombophilia testing in patients with SVT with a known malignancy. Other studies identified cancer rates of 35% to 41%; these data came from a multicenter population-based study of only 174 portal vein thromboses identified by *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, and from a 31-center study that over 4 years only identified 177 SVT cases.[8,16] Further research is required to determine whether the SVT was an active contributor to mortality or whether other characteristics are confounders in the association of SVT with death.

A multicenter, prospective, registry study suggests that 77% of patients will receive treatment, but <30% were treated in our population.[6] Our random chart audit of hospital-based SVT suggested good reasons for this; many had concomitant active bleeding or were considered palliative at the time of diagnosis. The higher proportion of treated patients with SVT in Ageno's registry may be because of their recruitment methods. Although elderly patients were anticoagulated uncommonly in our unselected cohort, treatment of acute SVT with oral anticoagulants was associated with a significant improvement in relative survival. We are unable with our study design to determine whether this is because of a "healthy-patient effect," in which treatment is indicative of those with less serious comorbidities and a better prognosis. Certainly, our chart audit suggested that patients who were not treated frequently had grave prognoses. Cohort studies that have reported on treatment likely also had selection bias in which treatment was provided to patients with a better prognosis than those who were left untreated. Therefore, although our study does not provide evidence that refutes guidelines recommending anticoagulation in SVT, it does emphasize the importance of performing a large randomized controlled trial in this population. A recent small randomized trial suggests that rivaroxaban or other direct oral anticoagulants would be justified in such a study.[17]

Our study has several strengths. First, we actively searched for SVT by applying a very sensitive text-search algorithm to the reports of all abdominal ultrasound and computed tomography studies at our center. We believe that this method more completely identifies SVT than that based on diagnostic codes. We also made greater efforts to accurately apply reasonable diagnostic criteria. Extra review was performed on imaging studies in which there was an element of doubt, and we were careful to categorize the SVT as acute or chronic based on imaging appearances. Although it is possible that the sensitivity of the algorithm we used was overestimated and that we missed some cases, it is very unlikely that cases were overcalled because of the detailed review of all potential cases found by the search algorithm. Furthermore, our results suggest that registry studies published to date may be limited by diagnostic inaccuracy, because relying on reports alone, without review of equivocal cases, could result in misclassification in up to 10% of cases. Second, we consider our survival data to be very important since this is, to our knowledge, the largest unselected cohort of SVT published. Large cohorts are required for precise outcome estimates in the entire population and subgroups. Primary data collection ensured that each patient in the cohort definitively had SVT, which is not true of the studies that rely upon diagnostic codes in administrative data sets or patient registries, which are not capable of enrolling consecutive patients. We also linked to population-based data sets for what is considered the criterion standard determinations of both survival and cancer status for database research. However, we were unable to precisely determine details regarding each SVT (including symptom status and baseline comorbidities) because 40% of the cohort were outpatients at the time of their diagnosis (and were without complete medical record documentation). We dealt with this issue by using administrative database codes to identify noncancer comorbidities. Future studies are required to determine whether the symptomatic status of the SVT, and other comorbidities, influence survival or response to therapy.

Our study has limitations. First, although our case identification process was strong, it could be criticized that we did not have 2 independent radiologists interpret all imaging studies for SVT status. We instead relied upon the interpreting radiologist's opinion. If they indicated definitively in their report that an SVT was present, that patient was identified as an SVT case. However, as stated above, we did review the primary imaging study if the radiologist indicated uncertainty regarding SVT status. This could introduce some misclassification bias to our study. Second, we cannot accurately determine the cause of the SVT in the patients without cancer. Third, with respect to the treatment data, we could only link treatment data to those >65 years of age and did not perform detailed, individual chart reviews on all patients. Although most patients did not receive treatment, oral

anticoagulants were associated with survival, which we could not demonstrate for LMWH. This is likely because very few patients received LMWH (therefore wide confidence intervals on the survival outcome), and patients taking LMWH may have had advanced oncological disease negating the need for biopsy confirmation; such cases would not make it into the population-based cancer registry and would be missed by our study. Finally, we chose not to provide information on cancer treatment or cancer types. We chose to provide information on whether the cancer was local (ie, in the region of the splanchnic bed) or distant because we thought that these factors could influence both the incidence and outcomes of SVT. The same reasoning applies to our cancer classification of recent versus remote. If we analyzed treatment, we would subdivide the cohort further and have very small numbers, which does not provide for an informative analysis.

In summary, our large, unselected, and completely followed cohort found that patients with SVT have significantly reduced survival compared with an age-sex-time matched population. This was most apparent in patients with cancer (especially if it is local and recently diagnosed), cirrhosis, or recent venous thromboembolic disease. Treatment was less frequent than expected, but oral anticoagulants were positively associated with survival. We have more precisely defined the distribution and frequency of SVT than prior studies. Further study is required to determine whether SVT contributes to death, and the role of anticoagulation in its management.

ARTICLE INFORMATION

Received August 10, 2020; accepted November 6, 2020.

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Sources of Funding

This study was supported by Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information (CIHI); however, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily of CIHI.

Disclosures

Dr Wells has received honoraria for speaking engagements, as well as grant support for investigator-initiated and run clinical studies, from Bayer Healthcare and BMS/Pfizer. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Summary of codes used in study.

Diagnostic codes in Discharge Abstract Database (DAD) for **cirrhosis** (any position):

ICD9 - '4561','5712','5715'

ICD10 - 'I859','I981','K703','K717','K746'

Diagnostic codes in Discharge Abstract Database (DAD) for **pancreatitis** in 6 months prior to case identification (any position):

ICD9 - '5770','5771'

ICD10 - 'K85','K86'

Diagnostic codes in Discharge Abstract Database (DAD) and NACRS for **venous thromboembolic disease** in 6 months prior to case identification (any position)*:

ICD9 - '415','451','453'

ICD10 - 'I802','I803','I801','I828','I809','I829','I808','O223',
'O229','O871','I269','I260'

Diagnostic codes in Ontario Health Insurance Plan (OHIP) for **venous thromboembolic disease** in 6 months prior to case identification (any position)*:

'415','451','453'

Drug identification numbers for **anticoagulants**:

00001550,00009296,00009318,00009326,00009342,00010308,00026166,00026174,00031348,00476870,00585629,
00585637,00585645,00585653,00861634,00918338,00918354,01918311,01918338,01918346,01918354,01918362,02007959,
02152460,02152479,02152487,02152495,02152509,02152517,02229741,02240205,02240206,02242680,02242681,02242682,
02242683,02242684, 02242889, 02245618, 02287498, 02335646, 02344114, 81918338,81918346,82240205, 09857463,
02242685,02242686,02242687,02242697,02242881,02242882,02242883,02242884,02242885,02242886,02242887,02242888,
02242924,02242925,02242926,02242927,02242928,02242929,02244462,02244463,02244464,02244465,02244466,02244467,
02245817,02245818,02265273,02265281,02265303,02265311,02265338,02265345,02265346,02265354,02265362,02265370,
02287501,02287528,02311070,02311089,02311097,02311100,02311119,02311127,02311135,02316986,02335611,02335638,
02335654,02335662,02335670,02335689,02344025,02344033,02344041,02344068,02344076,02344084,02344092,02344106,
02377233,02378604,02378612,02397714,02441535,02480808,

Procedural codes in DAD for **epigastric surgery**:

CCP - '506','5076','5016','5126','5159','5133','5219','5783','562','5742','6294',
'6212','5334','6385','6388','6399','6387','6333','1155','6390','6326','6490',
'6401','645'

CCI – '1IS51GRKA','1KE51GQGE','1KE51LA','1KE57LAGX','1KE76MUXX','1KQ50GRBD',
'1KQ80LA','1MG87LA','1NK76RE','1KN76RJ','1NK87RE','1OA13GQW0','1OA27JA','1OA59HAA'
'1OA9HAX7','1OA87LA','1OB13GQW0','1OB89LA','1OD89DA','1OE50BABD',
'1OE50BANR','1OE50HABD','1OE50HANR','1OE52BATS','1OE52LATS','1OE55BANR',
'1OE55HATS','1OE57BAAM','1OE57BABD','1OE57BAGX','1OE76SR','1OJ27JA','1J52BATS',
'1OJ52HATS','1OJ87LA'

Cancer location codes:

C48-RETROPERITONEUM+PERITONEUM C64-KIDNEY C74-ADRENAL C16-STOMACH C17-SMALL INTESTINE C22-LIVER C23-GALLBLADDER C24-BILIARY TRACT C25-PANCREAS

*** Based on** Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. Vasc Med 2015; 20: 364-368.

Table S2. **Summary of intra-rater reliability of radiological report review for splanchnic vein thrombosis.**

Splanchnic Vein	Kappa (95%CI)	Reviews That Disagreed, n (%)
Main portal	0.945 (0.883, 1)	3 (1.6%)
Right hepatic portal	0.877 (0.771, 0.983)	5 (2.6%)
Left hepatic portal	0.88 (0.763, 0.996)	4 (2.1%)
Portal vein confluence	0.853 (0.652, 1)	2 (1.1%)
Inferior mesenteric	0.853 (0.652, 1)	0 (0%)
Superior mesenteric	0.921 (0.767, 1)	1 (0.5%)
Splenic	0.853 (0.652, 1)	2 (1.1%)
Hepatic	0.665 (0.047, 1)	1 (0.5%)

This analysis included 223 reports that were double abstracted.