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Risk and prognosis of venous thromboembolism in patients with liver disease

PhD dissertation

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Kirstine Kobberøe Søgaard, 2015

Dissertation papers

I. Søgaard KK, Horváth-Puhó E, Grønbæk H, Jepsen P, Vilstrup H, Sørensen HT. Risk of Venous Thromboembolism in Patients With Liver Disease: A Nationwide Population-Based Case-Control Study. *Am J Gastroenterol*. 2009;104:96-101.

The study was conducted during a research year in 2006-2007, but according to regulations it may subsequently be included in a PhD dissertation.

II. Søgaard KK, Horvath-Puho E, Montomoli J, Vilstrup H, Sørensen HT. Cirrhosis is associated with increased 30-day mortality after venous thromboembolism. *Clin Transl Gastroenterol*. 2015 Jul 2;6:e97.

III. Montomoli J, Erichsen R, Søgaard KK, Farkas DK, Münster AMB, Sørensen HT. Venous thromboembolism and subsequent risk of cancer in patients with liver disease: a population-based cohort study. *BMJ Open Gastro* 2015:2:e000043

IV. Søgaard KK, Farkas DK, Pedersen L, Sørensen HT. Splanchnic venous thrombosis is a marker of cancer and a prognostic factor for cancer survival. *Blood*. 2015 Aug 20;126(8):957-63 18.

V. Søgaard KK, Darvalics B, Horváth–Puhó E, Sørensen HT. Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study. *Submitted.*

Abbreviations

CI: Confidence interval

CLD: Chronic liver disease

CRS: Civil Registration System

DCR: Danish Cancer Registry

DVT: Deep venous thrombosis

HR: Hazard ratio

ICD: International Classification of Diseases

MPN: Myeloproliferative neoplasm

MRR: Mortality rate ratio

DNPR: Danish National Patient Registry

OR: Odds ratio

PE: Pulmonary embolism

PVT: Portal vein thrombosis

RR: Relative risk

SIR: Standardized incidence ratio

SVT: Splanchnic venous thrombosis

VTE: Venous thromboembolism

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1. INTRODUCTION

Venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular disease in the Western world after acute myocardial infarction and stroke[1]. The annual incidence is approximately 1-2 persons per 1000 persons in the general population, but it may be up to 1 per 100 in certain subgroups, such as the elderly[2] and cancer patients[3,4]. Several risk factors for VTE have been identified, including a number of major diseases[5,6]. Chronic liver disease (CLD) was recently acknowledged to be a potential risk factor for VTE[7], but the impact of liver disease on VTE outcomes is unclear. Though VTE has been identified as a marker of occult cancer in the general population of VTE patients, it remains unclear if VTE is an indicator of cancer in patients with liver disease. Such information is clinically relevant because cirrhosis is associated with both an increased risk of VTE[7] and an increased risk of malignancy[8].

Splanchnic venous thrombosis (SVT) is a subtype of venous thrombosis that occurs in the abdominal veins (i.e., portal, hepatic, splenic, mesenteric veins). SVT is rare, and our understanding of the disease and its clinical course is limited[9-14]. Patients with SVT often have substantial comorbidity, including a high prevalence of liver disease, and they may be at particularly high risk of cancer and death[15]. However, the prognosis after SVT, including the relative impact of SVT on these outcomes, is largely unknown.

In this dissertation, we examined whether liver disease is associated with an increased risk of VTE and whether it has an impact on the prognosis - more specifically on short-term mortality after VTE. We also examined the occurrence of cancer after venous thrombosis in patients with liver disease and among persons with SVT. Finally, we estimated the incidence of SVT and its associated mortality.

2. BACKGROUND

This section provides a brief introduction to the coagulation system and coagulopathy associated with liver disease. It also contains some background information on risk and prognosis related to different types of venous thrombosis, specifically their associations with liver disease, cancer, and death.

2.1 Risk and prognosis

The studies in this dissertation focus on two main epidemiological terms: risk and prognosis. Overall, risk refers to the probability of an event. When studying risk in clinical epidemiological studies, we examine the occurrence of a disease in a group of people without the condition at the start of follow-up. The purpose may be to identify new risk factors for a given disease or to quantify how strong the causal relation is between two diseases[16]. Prognosis focuses on the course of the disease following the clinical diagnosis and may help predict the outcome in patients with a given disease[16]. Prognosis is often measured by time to death and we can evaluate whether specific underlying characteristics (e.g., age, cancer, or other underlying disease) modify the mortality risk. Using historical data from a clinical setting allows us mainly to study the clinical course rather than the natural history of the disease.

2.2 The coagulation system

The coagulation system is a highly complex biological system that exerts its effects through procoagulant and anticoagulant factors[17]. Under normal conditions there is continuous activation of coagulation factors, which is counterbalanced by the concurrent activation of fibrinolytic inhibitors[17]. Sometimes this normal balance cannot be maintained, resulting in abnormal bleeding or the formation of a thrombus[17]. In the case of endothelial injury, the formation of a blood clot prevents bleeding. Initially, vasoconstriction will reduce blood flow. Platelets then aggregate at the site of injury to form a plug (*primary hemostasis*), which is

stabilized by the conversion of fibrinogen to a fibrin clot (*secondary hemostasis*). A simultaneous inhibition of the coagulation ensures that the clotting does not disseminate to veins throughout the body[17].

2.3 Presentations of venous thromboembolism

Deep venous thrombosis and pulmonary embolism and their risk factors

DVT in the lower leg in is the most common type of venous thrombosis. When a thrombus forms in a vein, it will either resolve spontaneously (i.e., through the body's own counteracting fibrinolysis), or remain attached to the vessel wall. If thrombus formation progresses, a piece of the clot may break off and potentially cause a fatal embolism[18].

As defined by Virchow in 1856, the pathogenesis of a venous thrombosis includes hypercoagulability, stasis of venous blood flow, and endothelial injury[19]. Some of the most common risk factors for initiation and progression of a DVT and PE are advanced age, malignancy, and recent surgery[19]. These characteristics are prevalent in up to a third of patients diagnosed with VTE[20]. Other risk factors include immobilization, pregnancy, use of oral contraceptives or hormone replacement therapy, and heredity (e.g., factor V Leiden mutation, prothrombin G20210A gene variant, and deficiencies in protein C, protein S, or antithrombin) or acquired thrombophilia (e.g., antiphospholipid syndrome or myeloproliferative disorders)[1].

Splanchnic venous thrombosis

Splanchnic venous thrombosis (SVT) is a rare presentation of venous thrombosis, comprising portal vein thrombosis (PVT), hepatic vein thrombosis (also called Budd-Chiari syndrome), splenic vein thrombosis, and mesenteric vein thrombosis[21]. Our understanding of SVT is limited and based mainly on case reports, prevalence studies, and cohort studies with small sample sizes and incomplete or short-term follow-up. The reported annual incidence of SVT is 1-10 per million persons[22,23]. Nevertheless, findings from an autopsy study indicated that the condition may be more common, with 1 per 100 deceased having PVT[24].

Similar to other types of venous thrombosis, all three components of Virchow´s triad may be at play. Gastrointestinal cancer (e.g., hepato-biliary cancer), an inflamed or infectious abdominal tissue/organ (e.g., cirrhosis or pancreatitis), and abdominal surgery may all directly cause endothelial injury or indirectly result in a hypercoagulable state[21]. A solid tumor or abscess and hepatomegaly or splenomegaly can compress the vessels, thereby causing venous stasis[21]. In addition, congestive heart failure may result in venous stasis transferring from the inferior vena cava to the portal system[25].

Mortality after venous thromboembolism

The 30-day mortality risk after isolated DVT is low but may be up to 30% when a PE develops[20]. PVT is a serious condition with 30-day mortality varying from approximately 3% to 50%. The poor outcome after PE and PVT is likely determined and explained by several factors[26]. The mortality may be directly caused by the thromboembolic event[20], related to underlying comorbidities associated with increased mortality[20,26], and/or potentially explained by subsequent events, such as other cardiovascular events, cancer, or episodes of major bleeding[26]. We recently examined the impact of several comorbidities on mortality after thrombosis in a nationwide Danish cohort including all patients diagnosed with DVT or PE[20]. Among a wide range of serious chronic conditions, only the presence of cancer, diabetes, and CLD yielded higher mortality rates after VTE compared to the absence of these factors[20].

The prognosis after SVT is poorly understood, but patient characteristics and underlying comorbidity (particularly prevalent cancer or cirrhosis) are thought to impact the prognosis[15,26]. Moreover, the location of the thrombus and degree of extension is important for survival after SVT[15]. Treatment with anticoagulant therapy in patients with venous thrombosis is complicated because of the high prevalence of cancer and cirrhosis, and such fragile patients are more likely to be left untreated[27].

2.4 Liver disease and venous thromboembolism

Definition of liver disease

Liver disease is a broad term covering all diseases of the liver[28]. The severity of disease varies from transient and reversible affection of the liver tissue to chronic impaired liver function eventually causing death[28]. The most frequent liver diseases include fatty liver disease, viral hepatitis, alcoholic hepatitis, and cirrhosis[28]. Cirrhosis is a chronic degenerative liver disease in which normal liver cells are replaced with fibrotic tissue[29]. The main causes of cirrhosis in the Western world are long-term alcohol abuse, chronic liver infections such as viral hepatitis B and C, autoimmune diseases, and non-alcoholic steatohepatitis[30]. The clinical presentation of cirrhosis is multifaceted, varying from non-specific symptoms (e.g., loss of appetite, nausea, fatigue) and clinical stigmata of hepatic decompensation (e.g., jaundice, ascites, esophageal varices, hepatic encephalopathy)[29,31,32]. Patients are at increased risk of both hepatocellular carcinoma and extrahepatic cancers[8]. Overall, cirrhosis has a serious outlook[33]. Patients with cirrhosis have excess mortality from both cirrhosis-related conditions (e.g., variceal bleeding and hepatic coma) and non-cirrhotic causes (e.g., malignancy, ischemic heart disease, infections, respiratory disease, and accidents)[34]. Cirrhosis is among the 15 leading causes of death in the US, contributing to more than 35,000 deaths annually[35].

Cirrhosis and risk of venous thromboembolism

The liver has multiple functions, including the synthesis of both procoagulants and anticoagulants[36]. For many years the clinical paradigm was that patients with cirrhosis were mainly at risk of hemorrhagic crises, including bleeding from esophageal varices and an increased tendency to bleed during invasive procedures[37]. In contrast, cirrhosis patients were generally thought to be protected against venous thrombosis[38]. However, clinicians were challenged by the increasing recognition of thrombotic events in patients with cirrhosis, and the standard laboratory tests measuring coagulopathy seemed to be less useful in these patients[38]. Patients with cirrhosis, or other diseases causing failure of the liver to function normally, have thrombocytopenia and impaired synthesis of coagulation factors (e.g., fibrinogen,

prothrombin, and Factors V, VII, and X). Both primary hemostasis and secondary hemostasis are likely affected in patients with cirrhosis, but thrombocyte deficiency and dysfunction probably plays a less important role because elevated levels of von Willebrand factor and its reduced breakdown may ensure adequate platelet function[39]. In vivo, other factors (e.g., tissue factor, antithrombin, and protein C/S) also affect the hemostatic balance (Table 1) [40].

Coagulation	Promoting bleeding	Promoting thrombosis
Primary hemostasis	↓ platelets platelet dysfunction	↑ von Willebrand factor
Secondary hemostasis	↓ factors II, VII, IX, X, XI, XII dysfibrinogenemia	↑ factor VIII ↓ protein C/S, antithrombin
Fibrinolysis	↑ tissue plasminogen activator ↑ thrombin-activatable fibrinolysis inhibitor ↓ antiplasmin	↑ plasminogen activator inhibitor ↓ plasminogen

Table 1 - Coagulation imbalance in cirrhosis (modified from Yang et al.[40])

Within the last decade or so, the concept of hemostasis in patients with cirrhosis has completely changed[36]. Impaired liver function is now acknowledged to alter hemostasis in several ways. The net result is a complex coagulopathy, including the possibility of both hemorrhagic and thromboembolic events[38,41]. Moreover, the reduced portal flow in patients with cirrhosis[42], together with other local or systemic factors, may favor the development of thrombosis in splanchnic veins[42].

In clinical practice, PVT is the most common type of venous thrombosis in patients with cirrhosis. The prevalence of PVT in patients with cirrhosis may be as high as 25%, with variance depending on inclusion and exclusion criteria and the diagnostic tool used[43]. DVT and PE are less common in patients with cirrhosis; between 0.5% and 0.9% of patients with cirrhosis experience these types of thrombotic events[44,45].

2.5 Venous thrombosis and cancer

The association between cancer and VTE was noted by Bouillard in 1823[46] and later described by Trousseau in 1865[47]. Since that time, there has been considerable evidence for a clinical association between cancer and venous thrombosis[48,49]. The pathomechanism underlying cancer-associated hypercoagulability includes the expression of procoagulant proteins, the synthesis of inflammatory cytokines, and a direct effect through compression of venous blood flow by a malignant tumor[50]. In patients with cancer, clots may form spontaneously in the venous system, and be the first sign of occult cancer in some cases[51,52]. More specifically, persons with lower-limb DVT, PE, or superficial venous thrombosis have a 2- to 4-fold increased risk of being diagnosed with cancer in the first year after the thromboembolic event compared to the general population[51-55]. Some cancers, including ovary, pancreatic, and liver cancer, exhibit a particularly strong association with VTE[51,52]. No previous study has examined whether the association also applies to patients with liver disease (i.e., whether VTE is also a marker of cancer in patients with liver disease). The detection of underlying cancer has important implications for the management of VTE. Patients diagnosed with thrombosis shortly before being diagnosed with cancer are also more likely to have advanced disease and higher mortality than cancer patients without VTE at the time of diagnosis[56].

SVT has been described in case reports as the first presentation of liver and pancreatic cancer[57-59]. These cancers also exhibit a particularly strong association with other types of venous thrombosis, and a direct effect of the tumor (e.g., vessel wall injury or compression of splanchnic veins) could be the leading mechanism underlying cancer-related SVT. Nevertheless, in a cohort of 413 patients diagnosed with thrombosis in the hepatic veins or inferior vena cava in an Indian hospital between 1989 and 2013, there were only eight incident cases of hepatocellular carcinoma over a median follow-up of 5 years[13]. A meta-analysis of studies examining the prevalence of myeloproliferative neoplasm (MPN) among patients with portal or hepatic vein thrombosis reported that the thrombosis often occurred prior to the cancer diagnosis[12]. The association between SVT and subsequent cancer risk has not been studied in a population-based setting or related the risk to that of a comparison cohort.

2.6 Literature review

We reviewed the existing literature concerning the following aspects of the occurrence and outcome of venous thrombosis in patients with liver disease:

1) Liver disease as a risk factor for VTE (study I)
2) Liver disease as a prognostic factor for the outcome of VTE and PVT (study II)
3) Cancer occurrence in patients with VTE and liver disease (study III)
4) Cancer occurrence after a diagnosis of SVT (study IV)
5) Mortality after a first SVT diagnosis (study V)

We searched PubMed using Medical Subject Headings (MeSH) and free-text search (some VTE subtypes are not assigned specific MeSH terms) using “AND/OR” combinations. Titles and abstracts were reviewed and relevant papers including information on the population, intervention (or exposure), comparison, and outcome (PICO criteria) were selected. We also reviewed the reference lists in the selected papers to identified additional relevant articles. An overview of the literature is provided in Table 2.

Study I was published in 2009 and, at that time, knowledge on VTE risk among patients with cirrhosis was sparse, with only a few studies indicating a potential association[44,60,61]. Of these studies, only two used a comparison cohort to estimate the relative risk of VTE, but they came to different conclusions[60,61]. Shortly before our paper was published, a third study reported no association between cirrhosis and VTE[62].
We used the following search string to review potential new references post-publication: "Liver Diseases"[MeSH] AND "Embolism and Thrombosis"[MeSH] AND "Risk Factors"[MeSH]. We identified three additional population-based studies (from the Netherlands[6], Taiwan[63], and Singapore[64]) that confirmed our findings.

In study II, we used the following search string: ("Embolism and Thrombosis"[MeSH] OR "portal vein thrombosis") AND "Liver Cirrhosis"[MeSH] AND "Mortality"[MeSH]. The search was not successful at identifying relevant studies. From our previous work, we were aware of two studies that addressed the impact of several chronic diseases, including liver disease, on mortality after VTE[20,65].

In study III, the search included the MeSH terms "Liver Diseases"[Majr] AND "Embolism and Thrombosis"[Majr] AND "Neoplasms"[Majr] AND “epidemiology”. The search output revealed that no previous study had specifically addressed whether VTE was a marker of occult cancer in patients with liver disease. Accordingly, no studies are included in the literature table below.

In study IV, we searched the literature using the following search string: ("Myelodysplastic Syndromes"[MeSH] OR "Myelodysplastic-Myeloproliferative Diseases"[MeSH] OR" Hematologic Neoplasms"[MeSH] OR "Neoplasms"[MeSH]) AND ("Budd-Chiari Syndrome"[MeSH] OR "Hepatic Veno-Occlusive Disease"[MeSH] OR ”splanchnic vein thrombosis” OR ”splanchnic venous thrombosis” OR "portal vein thrombosis" OR "portal venous thrombosis" OR "mesenteric venous thrombosis" OR "mesenteric vein thrombosis" OR "abdominal venous thrombosis" OR "abdominal vein thrombosis") AND “epidemiology”. Our search revealed that past evidence was based mainly on case reports and cohort studies with small sample sizes. No previous study aimed to clarify whether SVT was a marker of cancer using a comparison cohort.

In study V, we used the same search string for SVT as in study IV, but combined it with "Survival Analysis"[MeSH]. Again, after reviewing titles and abstracts, very few studies were relevant, and only one study used a comparison cohort to examine relative survival measures.

Table 2 - Literature review

Study I - Cirrhosis and risk of VTE			
Author/Journal/Year	Setting/Design	Population/Exposure/Outcome	Statistical Analysis/Results
Heit et al.[60] *Arch Intern Med*, *2000*	Population-based nested case-control study Olmsted inception cohort, USA, 1976-1990	VTE cases n=625 (serious liver disease n=5) Hospital controls without VTE n=625 Matched for age, sex, and calendar year	In a multivariate* logistic regression model, serious liver disease was associated with a reduced VTE risk, OR 0.10 (95% CI: 0.01-0.71). *Including surgery, trauma, malignancy, central venous catheter, prior superficial vein thrombosis, neurological disease, varicose veins, chronic heart failure, and VTE
Huerta et al.[61] *Arch Intern Med*, *2007*	Nested case-control study Clinical Practice Research Database, United Kingdom, 1994-2000	VTE cases n=6,550 (CLD n=39) Controls from General Practice Research Database n=10,000 (CLD n=29) Matched for age, sex, and year	Logistic regression analyses had an overall OR of 1.65 (95% CI: 0.97-2.82); for DVT OR 1.24 (95% CI: 0.65-2.37); for PE OR 1.75 (95% CI: 0.91-3.36). Notably, the authors' conclusion was no association.
Gulley et al.[62] *Dig Dis Sci*, *2008*	Case-control study Regenstrief Medical Record system US, 1995-2005	Cirrhosis n=963 Hospital controls without cirrhosis n=12,405 Matched for age, race, and gender	In a multivariate analysis cirrhosis was not associated with VTE risk, OR 0.86 (95% CI: 0.28-2.63).
Wu and Nguyen[66] *Clin Gastroenterol Hepatol*, *2010*	Cross-sectional study Nationwide Inpatient Sample, US, 1998-2006	Compensated cirrhosis n=408,253 Decompensated cirrhosis n=241,626 Hospital controls without cirrhosis n= 575,057	Using multiple logistic regression analysis (adjusting for age, Charlson comorbidity, gender, calendar year, and race), the study showed no overall risk of VTE among patients with compensated cirrhosis and a 10% increased risk of decompensated cirrhosis. Patients <45 years of age had an elevated risk; OR for VTE among patients with compensated cirrhosis 1.23 (95% CI: 1.04-1.46), for patients with decompensated cirrhosis OR 1.39 (95% CI: 1.15-1.69) compared to absence of liver disease.
Al-Dorzi et al.[67] *Thrombosis*, *2013*	Prospective cohort study Tertiary care center, Saudi Arabia, 2006-2008	ICU patients with cirrhosis n=75 (2 VTE events) ICU patients without cirrhosis n=723 (55 VTE events)	Cox proportional regression analysis showed no association with increased VTE risk. The adjusted HR was 0.40 (95% CI: 0.10–1.67). The adjusted model included age, gender, creatinine, use of LMWH, platelet count, INR, admission diagnosis, trauma, fracture, presence of central line, sepsis, spinal cord injury status, malignancy, surgery, previous VTE, and stroke.
Ocak et al.[6]	Case-control study	VTE cases n=4,311 (liver disease n=27)	The study examined the association between several major illnesses. For

J Thromb Haemost, 2013	MEGA study, the Netherlands, 1999-2004	Controls n=5,768 (liver disease n=22) Self-reported history of liver disease Matched for age and sex	liver disease the OR of VTE was 1.7 (95% CI: 1.0–2.9), for DVT the OR was 1.7 (95% CI: 0.9-3.2), and for PE the OR was 1.6 (95% CI: 0.8-3.3). The study addressed the impact of immobilization; OR 6.2 (95% CI: 5.4-7.0) in absence of major illnesses and OR 8.3 (95% CI: 2.8-24.4) in patients with liver disease.
Ng KJ et al.[63] *J Thromb Haemost, 2015*	Matched cohort study Taiwan National Health Research Institute, Taiwan, 2007-2010	Patients with cirrhosis n= 2,223 (26 VTE events) Comparisons without cirrhosis n=22,230 (1,115 VTE events) Propensity score matching using a standard greedy-matching algorithm	Multivariate Cox regression model (adjusted for age, sex, urbanization level, SES, diabetes, hypertension, coronary artery disease, hyperlipidemia, malignancies, congestive heart failure, atrial fibrillation, smoking, obesity, peripheral artery disease, and CCI score) yielded a HR of 1.71 (95% CI:1.05-2.78). In a subanalysis, the adjusted HR for advanced cirrhosis was 4.36 (95% CI 1.36-14.01).
Yang et al.[64] *Thromb Res, 2015*	Cohort study Singapore General Hospital, Singapore, 2004-2011	Hospitalized patients n=199,904 (n=6,372 with CLD) Diagnosis of CLD, VTE, and other covariates were derived from ICD-9-AM discharge diagnosis codes	VTE prevalence was 1.5% among patients with non-cirrhosis CLD, 2.0% among patients with cirrhosis, and 0.8% among patients without CLD. In a logistic regression model adjusted for age, gender, ethnicity, long stayer, cancer, infectious disease, diabetes, anemia, cardiovascular disease, cerebrovascular disease, renal disease, and pulmonary disease, the OR for VTE was 1.4 (95% CI: 1.2-1.7) among non-cirrhosis CLD and 1.5 (95% CI: 1.2-2.0) for cirrhosis.
Study II - Cirrhosis and 30-day mortality after VTE			
Author/Journal/Year	Setting/Design	Population/Exposure/Outcome	Statistical Analysis/Results
Heit et al.[65] *Arch Intern Med*, *1999*	Population-based cohort study Olmsted inception cohort, US, 1966-1990	Patients with DVT or PE n=2,218 Outcome was risk of death among subgroups of patients (no information on number of CLD) Expected survival was calculated based on age- and sex-specific mortality rates	Predictors of death within 7 days were examined using univariate logistic regression, OR for CLD was 1.72 (95% CI: 0.84-3.51). Predictors of death among patients surviving more than 7 days using univariate Cox proportional hazard regression, HR for CLD was 2.13 (95% CI: 1.34-3.40).
Søgaard et al. [20] *Circulation, 2014*	Population-based cohort study, Denmark, 1980-2011	Patients with VTE n=128,223 (severe liver disease n=415) Comparison group from general population without VTE n=640,760 (severe liver disease n=703)	Adjusted Cox regression analysis was used to estimate MRRs. Stratified analyses showed that severe liver disease modified overall mortality. Patients with DVT and liver disease had a MRR of 1.84 (95% CI: 1.47-2.30) and DVT patients without liver disease had a MRR of 1.55 (95% CI: 1.53-1.57). Patients with PE and liver disease had a MRR of 3.64 (95% CI: 2.59-5.12), PE patients without liver disease had a MRR of 2.77 (95% CI: 2.74-2.81).

Study IV – SVT as a marker of cancer and a prognostic factor for cancer survival			
Author/Journal/Year	Setting/Design	Population/Exposure/Outcome	Statistical Analysis/Results
Smalberg et al.[12] *Blood, 2012*	Meta-analysis of 32 studies, Publications 1980-2011	The studies in the meta-analysis included between 10 and 237 patients In total, 1,062 patients with Budd-Chiari syndrome and 855 patients with PVT Outcome MPN	Budd-Chiari syndrome was the presenting symptom of MPN in 37 of 50 patients. PVT was the presenting symptom of MPN in 47 of 64 patients. Five studies included a comparison group, but after review none performed the relevant analyses estimating if MPNs were more frequently diagnosed among persons with SVT than population controls.
Ren et al.[14] *Eur J Gastroenterol and Hepatol, 2013*	Meta-analysis of 16 studies, Publications before 2012	The studies in the meta-analysis included between 12 and 177 patients In total, 1,159 patients with Budd-Chiari syndrome Outcome was prevalence of hepatocellular carcinoma	The prevalence of hepatocellular carcinoma varied between 2% and 52%. Only two studies were based on European and American populations, in these studies the prevalence was 11%. Pooled estimates for hepatocellular carcinoma were 4% for thrombosis of hepatic veins and 26.5% for obstruction of the inferior vena cava. The study concluded that routine surveillance for hepatocellular carcinoma is warranted, especially for obstruction of the inferior vena cava.
Paul et al.[13] *Aliment Pharmacol Ther, 2015*	Single center cohort study All India Institute of Medical Sciences, New Delhi India, 1989-2013	In total, 413 patients diagnosed with thrombosis in hepatic veins or inferior vena cava	Patients with prevalent cancer were excluded (n=8). During a median follow-up of 5 years, eight cases of hepatocellular carcinoma were diagnosed, corresponding to a 10-year incidence of 3.5%.
Study V - Survival after SVT			
Author/Journal/Year	Setting/Design	Population/Exposure/Outcome	Statistical Analysis/Results
Thatipelli et al.[15] *Clin Gastroenterol Hepatol, 2010*	Cohort study, Mayo Clinic, US, 1980-2000	Patients with SVT (portal, mesenteric, splenic, and hepatic vein thrombosis) n=832 Expected mortality was calculated based on age- and sex-specific mortality rates	The combined 10-year survival after SVT was 60% at end of follow-up, which was lower than that expected in the general population. Patients with hepatic vein thrombosis had the highest survival rate, and portal vein thormbosis had the lowest survival rate. Patients with multi-segmental thrombosis or underlying cancer had a particularly poor prognosis.
Ageno et al.[26] *JAMA Intern Med, 2015*	Mulitnational cohort study, 2008-2014	604 patients with SVT Outcome was incidence of major bleeding, thrombotic events, and all-cause mortality.	Patients were followed for a median of 2 years. Incidence rates per 100 person-years were 3.8, 7.3, and 10.3 for major bleeding, thrombotic events, and all-cause mortality, respectively. Cirrhosis and cancer patients had higher incidence rates for all three outcomes than patients with unprovoked SVT or patients with transient risk factors.

3. AIMS OF THE DISSERTATION

Although an increasing number of studies describe the burden of VTEs in patients with liver disease[6,60-64,66,67], the existing literature has several important limitations, including small study sizes[60,61,67], selection bias[67], problems with follow-up[66], and limited confounder adjustment[61]. Previous studies regarding the outcome of SVT have also been of limited size[9,11], without confounder adjustment [9,11,15], and with a lack of relevant comparison cohorts[26]. Accordingly, several unanswered questions remain: Are patients with liver disease at increased risk of VTE? Does liver disease affect the short-term course after VTE? It is well known that VTE may be a marker of occult cancer[51-53] and that patients with liver cirrhosis are at an increased risk of cancer, but does the association with VTE and occult cancer also apply to patients with liver disease? Is SVT also a marker of occult cancer and does it help predict outcome in cancer patients? What is the incidence of SVT, and is it associated with an increased risk of dying if we adjust for underlying etiology and comorbidity?

Seeking to answer some of the above questions, we examined some of the less common presentations of VTE. We addressed the risk and prognosis of venous thrombosis in patients with cirrhosis (studies I and II) and examined their risk of subsequent cancer (study III). We also examined associations between SVT and the subsequent risk of cancer and death (study IV), and calculated the incidence of SVT and the absolute and relative mortality after SVT (study V).

4. MATERIAL AND METHODS

The material and methods used in the five studies are described in detail below and summarized in Table 3.

4.1 Setting and data sources

Denmark has a national health service that provides tax supported healthcare for all residents, guaranteeing free access to general practitioners and hospitals, and partial reimbursement for prescribed medicine. The studies in this dissertation were based on the nationwide Danish administrative and medical registries and conducted as population-based studies. We used civil personal registration (CPR) numbers to link data between registries described below.

The Danish National Patient Registry [68] (DNPR) contains information on all hospitalizations since 1977 and on outpatient and emergency room visits since 1994 and 1995, respectively. All registrations are uniquely identified by their CPR number, and the capture dates of admission and discharge, imaging examinations, endoscopic or surgical procedures, and discharge diagnoses are entered by the treating physician. Diseases are coded according to the International Classification of Diseases (ICD), 8th revision until the end of 1993 and the 10th revision thereafter. Information on imaging examinations is considered complete from 2002 and onwards. Surgical procedures have been recorded with the Nordic Medico Statistical Committee Classification (NOMESCO) of Surgical Procedures codes since 1996[69]. We used the DNPR to identify our study cohorts and to find information on underlying comorbidities or conditions, as well as imaging examinations and endoscopic or surgical procedures dating back to 1977.

The Danish Civil Registration System[70] (CRS) dates back to 1968 and was established to assign CPR numbers to all Danish residents and keep track of the population. This registry is updated daily and maintains electronic records on the dates of immigrations, emigrations, and deaths of Danish residents. We used the CRS to create comparison cohorts from the general population and to obtain the date of all-cause mortality.

The Danish Cancer Registry[71] (DCR) has recorded incident cancer cases in Denmark since 1943. The cancer diagnoses are classified according to ICD-10, and stage classified as "localized", "advanced" (regional or distant spread), and "unknown" until 2003 but according to the tumor node metastasis (TNM) staging system thereafter.

The Danish National Health Service Prescription Database[72] has provided nationwide coverage of all reimbursed medications since 2004, coded according to the Anatomical Therapeutic Chemical (ATC) classification. We used this database to obtain data on the use of anticoagulant medication: vitamin K antagonist (VKA) and low-molecular-weight heparin (LMWH).

The Danish Register of Causes of Death[73] contains information from all Danish death certificates since 1943, coded according to the Danish version of the ICD-8 (from 1972 through 1993) or ICD-10 (from 1994 through 2011). We obtained information on causes of death for patients with VTE using the specific immediate cause of death as well as the underlying cause of death.

Table 3 - Summary of methods in the five dissertation papers

	Study I	Study II	Study III	Study IV	Study V
Objectives	To examine if liver disease is associated with an increased risk of DVT or PE	To examine 30-day mortality among patients with cirrhosis and DVT, PE, or PVT	To examine cancer risk after VTE in patients with liver disease	To examine cancer risk after SVT and compare mortality among cancer patients with and without SVT	To examine mortality among SVT patients and explore whether specific prevalent diseases modify the mortality
Design and period	Population-based case-control study, 1980-2005	Population-based matched cohort, 1994-2011	Population-based cohort study using national cancer incidence rates, 1980-2010	Population-based cohort study using national cancer incidence rates and a matched cohort study, 1994-2011	Population-based matched cohort, 1994-2013
Data sources	DNPR, CRS	DNPR, CRS, DNDRP, Danish Register of Causes of Death	DNPR, CRS, DCR	DNPR, CRS, DCR	DNPR, CRS, Danish Register of Causes of Death
Study population	99,444 patients with VTE and 496,872 population controls	745 VTE patients with cirrhosis and 3,647 VTE patients without cirrhosis	1,867 patients with non-cirrhotic liver disease and VTE and 888 patients with cirrhosis ad VTE	Risk analysis: 1,191 patients with SVT Prognostic analysis: 259 patients with liver cancer, 116 patients with pancreatic cancer, 107 patients with MPN	1,915 patients with SVT and 18,267 comparisons from the general population
Matching criteria	Gender, age, and county; we matched up to 5 comparisons from the general population per case using risk set sampling	Gender, age, calendar year of diagnosis, and type of VTE; we matched up to 5 comparisons without cirrhosis per patient with VTE using risk set sampling	Standardization by gender, age, and calendar year of diagnosis.	Risk analysis: standardization by gender, age, and calendar year of diagnosis Prognostic analysis: gender, year of birth, year of diagnosis, cancer type, and stage; we matched up to 5 comparisons with cancer but no SVT for each SVT patient	Gender, age, calendar year, cancer, cirrhosis, pancreatitis, atrial fibrillation or flutter, VTE, other alcoholism-related disease, and IBD; we matched up to 10 comparisons from the general population per patient with SVT using risk set sampling
Exposure	Liver disease (cirrhotic and non-cirrhotic)	VTE including DVT, PE and, PVT	Liver disease (cirrhotic and non-cirrhotic) and VTE (including superficial venous thrombosis)	SVT	SVT

	Study I	Study II	Study III	Study IV	Study V
Covariates	Cancer, fracture/trauma, surgery, pregnancy obesity, psychiatric disease, and diagnoses included in Charlson Comorbidity Index	Cancer, fracture/trauma, surgery, heart failure, chronic pulmonary disease, peptic ulcer, diabetes, alcoholism-related disease, psychiatric disorders, obesity, infections gastroesophageal varices, VKA, and LMWH	Fracture/trauma, surgery, childbirth or pregnancy, obesity, inflammatory bowel disease, psychiatric disease, and other alcoholism-related disease	Liver disease, gastroesophageal varices, ascites, pancreatitis, diabetes, COPD, VTE, congestive heart failure and myocardial infarction, surgery, and ultrasound/CT scan	Myocardial infarction, peripheral vascular disease, cerebrovascular disease, stroke, dementia, chronic pulmonary disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate to severe renal disease, AIDS, surgery, and ultrasound/CT/MR scan
Outcome	VTE including DVT and PE	30-day mortality (all-cause and immediate cause)	Cancer	Cancer and mortality (all-cause)	Mortality (all-cause and cause-specific)
Statistical analyses	Conditional logistic regression	Cox proportional hazards regression	Standardized incidence rate ratios	Standardized incidence rate ratios and Cox proportional hazards regression	Stratified Cox proportional hazards regression
Confounder control	Matching, stratification, adjustment	Matching, stratification, adjustment	Standardization, stratification	Standardization, matching, stratification	Matching, adjustment, stratification
Subgroup analyses	Unprovoked VTE, calendar year of VTE	Type of VTE and type of cirrhosis, comorbidity level, and cancer	Type of VTE, gender, age group, period of VTE, presence/absence of alcoholism-related disease, presence/absence of risk factors for VTE Exclusion of patients diagnosed with cancer within 30 days after their VTE diagnosis	Ultrasound and/or CT scan confirmed diagnosis	Ultrasound and/or CT scan confirmed diagnosis

4.2 Definition of study populations, exposures, covariates, and outcomes

The population of interest in all studies was patients with venous thrombosis, but we included different subtypes of VTE in the studies. In study I, we included DVT and PE; in study II, we included DVT, PE, and PVT; in study III, we included DVT, PE, and superficial venous thrombosis; and in studies IV and V, we included all types of SVT (including portal, hepatic, and mesenteric vein thrombosis). Liver disease, cirrhotic and non-cirrhotic, was the exposure in studies I-III.

We included several covariates in our datasets. Some of these variables were used for matching[16], some only had a descriptive purpose[16], some were selected for confounder adjustment, and some were used to examine effect modification. In studies I, II, and V, we used diseases included in the Charlson Comorbidity Index (CCI) diagnosed any time before the thrombotic event to categorize patients' overall burden of disease. In addition to individual diseases, we created three levels of comorbidity: low, CCI score of 0; moderate, CCI score of 1-2; and severe, CCI score ≥ 3.

The outcome of interest was risk of VTE (study I), risk of cancer (studies III and IV), or risk of mortality (studies II, IV, and V).

We used some general features in the selection of our study cohorts, including risk set sampling[16], matching[16], and restriction[16]. The principle behind risk set sampling, which we used to create our matched control group in study I, is that a person is included in the "risk set" (i.e., the population at risk) until he/she experiences the event of interest or is censored for other reasons[16]. Therefore, individuals of the same age and gender with an index date in the same calendar period but without a previous VTE were eligible as comparisons and allowed to contribute person-time until the occurrence of a VTE (thereafter they were designated as VTE cases). A similar method was used to create comparison cohorts for the cohort studies (studies II and IV). In the case-control study the outcome was VTE, and in the cohort studies VTE patients were followed until the occurrence of the event (cancer or death), emigration, or end of follow-up, whichever came first.

We used restriction in all studies by excluding patients who were also diagnosed with VTE before the study period in order to avoid cases of recurrent thrombosis or complications of previous VTEs. In study IV, we excluded patients with cancer diagnoses prior to the admission for SVT in order to capture only incident cancers.

We also reduced the risk of confounding by matching for age, gender, and calendar period (studies I, II, and V) or by indirect standardization (studies III and IV). In study V, we also used the previous medical history of SVT patients and persons in the general population to perform more detailed matching.

Study I

Study I was conducted as a case-control study including all patients with a first-time diagnosis of DVT or PE between 1980 and 2005. The exposure was liver disease and the outcome VTE. For each case, we randomly selected five population controls matched for age, gender, and county. The controls were assigned an index date identical to that of the corresponding case with DVT or PE. The exposure was defined using discharge diagnoses of liver disease registered before the index date for DVT or PE going back to 1977. We grouped liver disease into liver cirrhosis or non-cirrhotic liver disease. We used the following covariates: cancer, fracture/trauma, surgery, pregnancy, psychiatric disease (as a proxy for antipsychotic drug use), obesity, and all diseases included in the CCI (excluding cancer and liver disease). We classified patients as having *provoked VTE* if they had a diagnosis of cancer before or within 90 days after VTE, or a discharge diagnosis of fracture or trauma, surgery, or pregnancy within 90 days prior to the admission leading to the VTE diagnosis. Patients without any of these conditions were designated as having *unprovoked VTE.* However, the term “unprovoked” may be somewhat misleading. In addition to the classical risk factors, other underlying conditions may be involved in the development of thrombosis (e.g., inflammation, infection, cardiovascular risk factors), and these factors may be identified by targeted scrutiny of VTE risk factors[74,75].

Study II

In study II, we defined the study population as patients diagnosed with DVT, PE, or PVT during admission or an outpatient contact between 1994 and 2011. We excluded patients diagnosed only in emergency departments without subsequent admission because VTE diagnosis in emergency departments has an expected low positive predictive value. In this study, the exposure was liver cirrhosis, which we classified as alcoholic, biliary, or other cirrhosis. VTE patients without liver cirrhosis served as the comparison cohort and were matched for age, gender, calendar year of VTE diagnosis, and VTE subtype. We included the following covariates that were either risk factors for VTE or predictors of VTE-related mortality: cancer (diagnosed prior to or on the date of the VTE-related hospital contact), fracture, trauma, or surgical procedures (registered within 90 days prior to the hospital contact for VTE), heart failure, chronic pulmonary disease, ulcer disease, diabetes, alcoholism-related disease, psychiatric disease, obesity, infections (diagnosed during the VTE-related hospital contact), and gastroesophageal varices with and without bleeding (previous or concurrent diagnoses). We also calculated the CCI level, excluding mild and severe liver disease. Finally, we retrieved information on the post-discharge use of VKA and LMWH from the prescription database. The outcome of interest was 30-day mortality, and we examined both all-cause mortality and immediate cause of death.

Study III

In study III, we defined our exposure as non-cirrhotic liver disease and cirrhotic liver disease combined with a first time VTE discharge diagnosis during the 1980-2010 period. Patients were followed for the occurrence of cancer. Instead of sampling a comparison cohort from the general population, we used national cancer incidence rates for the comparison and performed an indirect standardization (standardizing by age, gender, and calendar period). We categorized the patients according to type of VTE (DVT, PE, or superficial venous thrombosis), presence of classical risk factors for VTE (fracture/trauma,

surgery, childbirth or pregnancy, diagnosed within 90 days before admission), obesity, inflammatory bowel disease, psychiatric disease, and other alcoholism-related disease diagnosed any time before or during the hospital contact for VTE.

Study IV

Study IV included two different study populations. In the first part of the study, we defined a cohort of patients with a first-time diagnosis of SVT between 1994 and 2011. Similar to study III, we used indirect standardization to calculate standardized incidence ratios (SIRs). We categorized the patients according to overall comorbidity level using CCI and obtained information on diagnoses of liver disease (including varices and ascites), pancreatitis, diabetes, chronic obstructive pulmonary disease (as a proxy for smoking), DVT and PE, congestive heart failure, or myocardial infarction diagnosed any time before SVT. We also obtained information on surgical procedures performed within 90 days prior to the thrombosis. We retrieved registered abdominal ultrasound and computerized tomography (CT) scans performed within 30 days before or during the hospital contact for SVT. The above information was obtained from patients' medical histories only for the SVT cohort. The outcome of interest was cancer.

In the second part of the study, we defined a subgroup of SVT patients later diagnosed with liver cancer, pancreatic cancer, or MPN. We used the DCR to identify up to five comparisons for each patient, matched for gender, age (5-year intervals), year of diagnosis (5-year intervals), cancer type, and stage (stage was not applicable for MPNs). In this analysis we compared all-cause mortality in the two groups.

Study V

In study V, we defined our study cohort by a discharge diagnosis of SVT and used a matched comparison cohort (matched for gender, age, calendar year, liver cancer, pancreatic cancer, other GI cancer, MPN, non-GI cancer, cirrhosis, pancreatitis, atrial fibrillation or flutter, congestive heart failure, DVT/PE, other

alcoholism-related disease, and inflammatory bowel disease). We matched up to 10 comparisons from the general population per individual with SVT. We also included information on diagnoses (any time before SVT) of myocardial infarction, peripheral vascular disease, cerebrovascular disease, stroke, dementia, chronic pulmonary disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate to severe renal disease, and AIDS. Pregnancy or childbirth within 90 days of admission was also included in the covariate set. We obtained information on surgical procedures and endoscopies performed within 90 days prior to the index date. We also retrieved registered abdominal ultrasound/CT/magnetic resonance (MR) scans performed within 30 days before or during the hospital contact for SVT. The main outcome of interest in study V was all-cause mortality, but we also examined specific causes of death.

4.3 Statistical analysis

In all studies, we constructed frequency tables with demographics and other characteristics. Age and follow-up time were presented as medians with interquartile ranges. Study I was conducted as a case-control study, whereas studies II-V were cohort studies.

Conditional logistic regression analysis (study I)

We used logistic regression to compute odds ratios (ORs) of VTE for patients with liver disease compared to patients without liver disease. Because of the matched design, we used a conditional logistic regression analysis[76]. Because we used risk set sampling, ORs translate into unbiased estimates of corresponding rate ratios in a similar cohort study[16]. We were interested in determining whether the relative risk differed for the subtypes of VTE. In agreement with a dichotomous outcome (e.g., DVT or PE), we used polytomous logistic regression[77]. In the stratified analysis, we disregarded the matching and adjusted for matching factors using unconditional logistic regression.

Cox proportional hazard regression analysis (studies II, IV, and V)

In time-to event analyses, we compared mortality in patients with DVT, PE, or SVT to the mortality among members of the comparison cohort. We used Cox proportional hazards regression to compute mortality rate ratios (MRRs), specifically hazard ratios (HRs), as measures of relative mortality risk. An underlying assumption for Cox regression analysis is proportional hazards over time; therefore, we tested the proportionality of hazards visually using log-log plots. In study II, we confirmed proportional hazards for DVT and PE, but the assumption was not fulfilled for PVT. Accordingly, we split the 30 days of follow-up into 0-7 days and 8-30 days.

In studies II and V, we used matching to sample the comparison cohort. Consequently, we conducted a stratified Cox regression analysis. In study II, we also conducted a conventional regression analysis, dissolving the matching and including the matching factors as covariates in the model. The results were in agreement.

Absolute risks (studies II-V)

Three methods are commonly used to calculate the absolute risk. The first method is a simple computation of the proportion of people having the outcome. This is often not a very realistic measure, as it assumes complete follow-up of all included persons in addition to the assumption that censoring and deaths do not occur. The second method is the Kaplan-Meier method, which we used to calculate absolute mortality risks in studies II and V. The method takes censoring into account but assumes that patients who are censored have the same prognosis as those who continue to be followed. The absolute risk computed by Kaplan-Meier is generally higher than the estimated risk calculated using the first method. We had information on follow-up at the patient level and were able to censor those no longer at risk because they experienced the outcome of interest (i.e., died), or left the cohort. In studies III and IV, we used a third approach because our outcome was cancer and not death. We calculated absolute risk or the cumulative incidence of cancer in patients with SVT, treating death as a competing risk. This method takes into account that only one event can occur, that patients are not at risk of being diagnosed with cancer if they die. The absolute risk computed using this method will likely provide an estimate that falls between that of the first basic method and that of the Kaplan-Meier method.

Standardized incidence ratios (studies III and IV)

SIRs are also measures of relative risk. The method enables a comparison between an observed cancer incidence rate in a defined cohort, with that expected in the general population. The expected number of cancer cases is calculated by applying the national cancer incidence rates (by age, gender, and calendar period) to the study cohort. We used SIRs in study IV to examine whether patients with SVT had a higher relative risk of being diagnosed with cancer shortly after the thrombotic event compared to the expected risk in the general population. We standardized by age, gender, and calendar period, thereby handling the potential confounding by age and gender. However, the method did not allow further adjustment as a regular regression model would have because we did not use a defined comparison cohort.

Stratified analyses (studies I-V)

We used stratified analyses in all studies with the overall purpose of eliminating confounding or analyzing the presence of effect modification. Strata were created according to categories of the variable of interest (dichotomous yes/no, or using multiple levels) and the analyses repeated within these strata. Examples of stratified analyses are an analysis repeated according to gender strata, age category, or calendar period of diagnosis. In study II, we stratified according to type of cirrhosis (alcoholic, biliary, and other or non-specified) to explore if there were differences, as these patients likely have different risk profiles. We also stratified by comorbidity level and cancer, as they were potential effect modifiers. In study IV, we compared the SIRs in a cohort of SVT patients to the national cancer incidence rates. Though we did not have information on the prevalence of the covariates in the general population, stratified analyses based on sparse data were less imprecise than they would have been in a corresponding cohort study with a comparison group. In study V, we estimated the overall prognosis among patients with SVT but also examined the mortality in strata based on the location of thrombosis.

5. RESULTS

Our main findings are summarized in this section.

5.1 Study I

We provided strong evidence of an association between liver disease and an increased risk of VTE. Our findings were based on 99,444 VTE cases and 496,872 population controls. The prevalence of cirrhosis and non-cirrhotic liver disease was 0.6% and 1.1%, respectively, among cases and 0.2% and 0.4% among population controls. The OR of VTE for patients with liver cirrhosis was 1.74 (95% CI: 1.54-1.95) compared to matched controls from the general population (Table 4). In particular, the ORs of DVT and PE were elevated 2- and 1.4-fold, respectively. Notably, patients younger than 55 years of age had an OR of 3.58 (95% CI: 2.62-4.88) for VTE. The risk of unprovoked VTE (i.e., without one of the major classical risk factors) was even higher than the risk of overall VTE (OR 2.06, 95% CI: 1.79-2.38). In addition, patients with non-cirrhotic liver disease were at increased risk of developing VTE (OR 1.87, 95% CI: 1.73-2.03; Table 4).

Table 4 - OR (95% CI) of VTE for patients with liver disease compared to the general population

	All VTE		Unprovoked VTE	
Variable	**Crude RR**	**Adjusted* OR**	**Crude RR**	**Adjusted† OR**
Liver cirrhosis	2.60 (2.34-2.88)	1.74 (1.54-1.95)	2.88 (2.52-3.29)	2.06 (1.79-2.38)
Non-cirrhotic liver disease	2.54 (2.36-2.73)	1.87 (1.73-2.03)	2.84 (2.59-3.11)	2.10 (1.91-2.31)

* Adjusted for cancer, fractures, trauma, surgery, pregnancy, Charlson Index, psychiatric diseases, and obesity.
† Adjusted for Charlson Index, psychiatric diseases, and obesity.

5.2 Study II

The main results in study II are shown in Figure 1, namely that cirrhosis patients had higher 30-day mortality after DVT or PE than the comparison cohort, and that mortality after PVT was high regardless of underlying cirrhosis. In relative measures, the adjusted 30-day MRR was 2.17 (95% CI: 1.24-3.79) for DVT, 1.83 (95% CI: 1.30-2.56) for PE, and 1.30 (95% CI: 0.80-2.13) for PVT (Table 5).

Table 5 - Thirty-day mortality among 4,392 patients with a first-time diagnosis of VTE

	Patients, n	Deaths, n	Mortality risk, % (95% CI)	Unadjusted MRR[a] (95% CI)	Adjusted MRR[b] (95% CI)
Deep venous thrombosis	2,514	83	3 (3-4)		
No cirrhosis	2,095	55	3 (2-3)	1.00	1.00
Cirrhosis (all types)	419	28	7 (5-10)	2.65 (1.68-4.17)	2.17 (1.24-3.79)
Alcoholic	320	18	6 (4-9)	2.41 (1.41-4.12)	1.92 (0.91-4.03)
Biliary[c]	22	2	9 (2-32)	3.24 (0.78-13.41)	2.80 (0.67-11.75)
Other or non-specified[d]	77	8	10 (5-20)	3.22 (1.51-6.86)	2.36 (1.06-5.22)
Pulmonary embolism	1,242	240	19 (17-22)		
No cirrhosis	1,035	167	16 (14-19)	1.00	1.00
Cirrhosis (all types)	207	73	35 (29-42)	2.51 (1.90-3.30)	1.83 (1.30-2.56)
Alcoholic	142	51	36 (29-44)	2.72 (1.98-3.74)	1.76 (1.11-2.77)
Biliary[c]	18	4	22 (9-49)	1.25 (0.46-3.40)	1.00 (0.36-2.75)
Other or non-specified[d]	47	18	38 (26-54)	2.54 (1.55-4.14)	2.30 (1.40-3.78)
Portal vein thrombosis	636	100	16 (13-19)		
No cirrhosis	517	77	15 (12-18)	1.00	1.00
Cirrhosis (all types)	119	23	19 (13-28)	1.34 (0.84-2.13)	1.30 (0.80-2.13)
Alcoholic	75	16	21 (14-33)	1.55 (0.90-2.65)	1.52 (0.84-2.75)
Biliary[c]	8	1	13 (2-61)	0.85 (0.12-6.21)	0.57 (0.08-4.30)
Other or non-specified[d]	36	6	17 (8-33)	1.05 (0.46-2.42)	1.17 (0.50-2.72)

[a] Adjusted for matching factors by study design (gender, age, calendar period).

[b] Adjusted for matching factors by study design (gender, age, calendar period), cancer, fracture/trauma, surgery, congestive heart failure, chronic pulmonary disease, diabetes, ulcer disease, alcoholism-related disease, and infection.

[c] Biliary cirrhosis includes primary, secondary, and other or non-specified biliary cirrhosis.

[d] Includes 13 patients with hepatitis B or C virus.

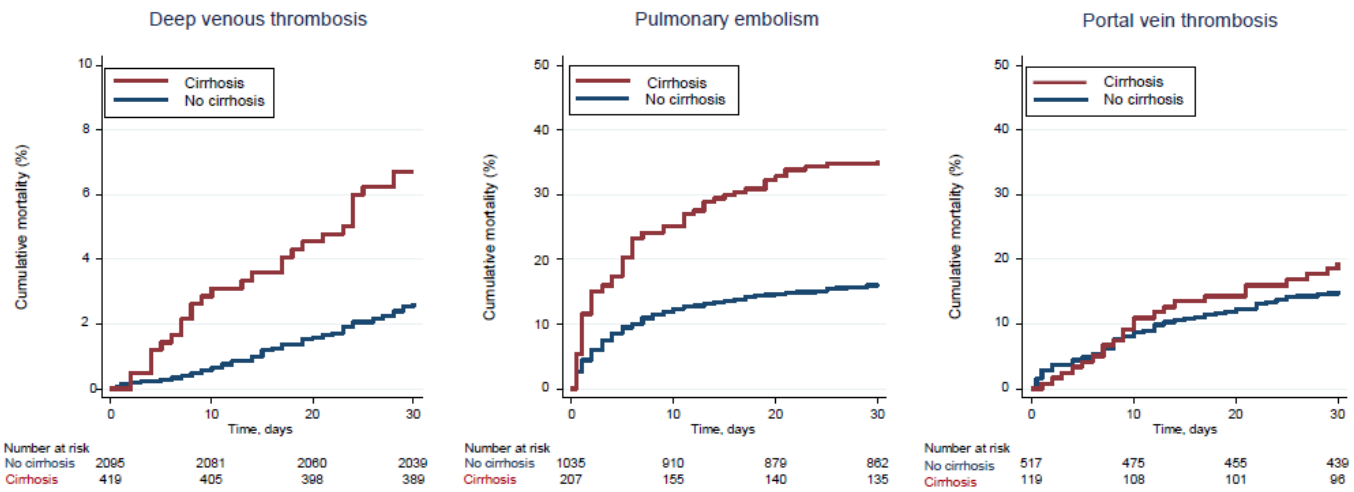


Figure 1 - Thirty-day mortality risk (%) among patients with VTE

Other interesting findings included a clear difference in the prescribing patterns for anti-coagulant medicine within 30 days of discharge for patients with and without cirrhosis. In patients without cirrhosis, the proportion of patients receiving VKA was 53%, 55%, and 33% for DVT, PE, and PVT, respectively. The corresponding frequencies for patients with cirrhosis were 31%, 29%, and 16%. In contrast, patients with cirrhosis and DVT were more likely to redeem a prescription for LMWH than patients without cirrhosis (9% versus 6%).

The main causes of death registered in patients with cirrhosis and PE included PE (most frequent), liver disease (including complications), cardiovascular disease, respiratory failure, and infectious diseases. Notably, the proportions of deaths due to PE were similar among patients with and without cirrhosis (25% and 24%, respectively).

5.3 Study III

We identified 1,867 patients with non-cirrhotic liver disease and 888 with cirrhosis and a first-time VTE diagnosis. The most frequent location of thrombosis was in the deep veins of the lower leg, followed by PE and superficial vein thrombosis (Table 6). Non-cirrhotic liver disease included diagnoses of alcoholic hepatitis (32%), viral hepatitis (17%), fatty liver disease (9%), and other non-cirrhotic liver diseases (42%). The most frequent cause of cirrhosis was alcohol abuse (48%), whereas the remaining patients had other or unspecified cirrhosis.

Table 6 - Characteristics of patients with liver disease and VTE

Variable	Non-cirrhotic liver disease and VTE N = 1,867	Cirrhosis and VTE N = 888
Male, n (%)	1,027 (55%)	519 (58%)
Type of VTE, n (%)		
Deep vein thrombosis	1,183 (63%)	477 (54%)
Pulmonary embolism	535 (29%)	343 (39%)
Superficial venous thrombosis	149 (8%)	68 (8%)
Alcoholism-related disease, n (%)	421 (23%)	388 (44%)

A total of 158 cancers were diagnosed among patients with non-cirrhotic liver disease and 88 among patients with liver cirrhosis, corresponding to an almost 2-fold and 3-fold increased cancer risk, respectively. In absolute numbers, treating death as a competing risk, the 1-year risk of any cancer was 2.7% for patients with non-cirrhotic liver disease and 4.3% for patients with cirrhosis. The cancers diagnosed during the first year of follow-up were detected mainly during the first 3 months after the VTE, with SIRs of 9.96 (95% CI: 6.85-13.99) and 13.11 (95% CI: 8.31-19.67) (Table 7). Thereafter, the SIRs decreased considerably in both patient groups. However, the 3-12 month SIR remained increased almost 2-fold among patients with non-cirrhotic liver disease and 3.5-fold among patients with liver cirrhosis. One or more years after the VTE, an increased risk persisted in both groups of liver disease patients (Table 7).

Table 7 - SIRs of cancer diagnosed among patients with liver disease and VTE

	Observed cancers and standardized incidence ratios (95% CI)							
	0–<3 months		3–<12 months		1+ years		Overall	
Non-cirrhotic liver disease	33	9.96 (6.85-13.99)	17	1.90 (1.11-3.05)	108	1.50 (1.23-1.81)	158	1.88 (1.60-2.19)
Deep vein thrombosis	21	10.36 (6.41-15.84)	11	1.97 (0.98-3.53)	78	1.65 (1.30-2.06)	110	2.00 (1.65-2.42)
Pulmonary embolism	11	10.64 (5.30-19.04)	4	1.52 (0.41-3.89)	21	1.14 (0.70-1.74)	36	1.63 (1.14-2.25)
Superficial venous thrombosis	1	3.95 (0.10-21.98)	2	2.78 (0.34-10.04)	9	1.46 (0.67-2.77)	12	1.68 (0.87-2.93)
Liver cirrhosis	23	13.11 (8.31-19.67)	15	3.52 (1.97-5.81)	50	1.95 (1.45-2.57)	88	2.78 (2.23-3.42)
Deep vein thrombosis	13	11.86 (6.31-20.28)	12	4.30 (2.22-7.52)	31	1.69 (1.15-2.40)	56	2.52 (1.90-3.27)
Pulmonary embolism	10	19.17 (9.18-35.26)	2	1.87 (0.23-6.75)	11	2.35 (1.17-4.21)	23	3.67 (2.33-5.51)
Superficial venous thrombosis	0	-	1	2.51 (0.06-13.99)	8	3.02 (1.30-5.96)	9	2.83 (1.30-5.38)

In a supplemental analysis we provided site-specific cancer SIRs, revealing that several gastrointestinal cancers (including hepatic, biliary, pancreatic, and esophageal) and lung cancer occurred more frequently than expected (see the supplemental table in the full version in the Appendix).

5.4 Study IV

Several results in study IV deserve attention. Importantly, the patients included in the main analysis on the risk of cancer after SVT diagnosis were burdened by comorbidity. More than half of the patients had either moderate or severe comorbidity, and a third had undergone surgery less than 90 days before the VTE. Some diseases were particularly frequent, including liver disease (20%), heart disease (15%), diabetes (15%), and previous pancreatitis (12%).

Both in absolute and relative measures, the 3-month cancer risk was notable in our cohort of SVT patients: 8.0% and 33-fold increased risk, respectively (Table 8). The increased risk was confined to liver cancer, pancreatic cancer, and MPN; however, the risk remained increased 2-fold with 1 or more years of follow-up compared to the risk in the general population.

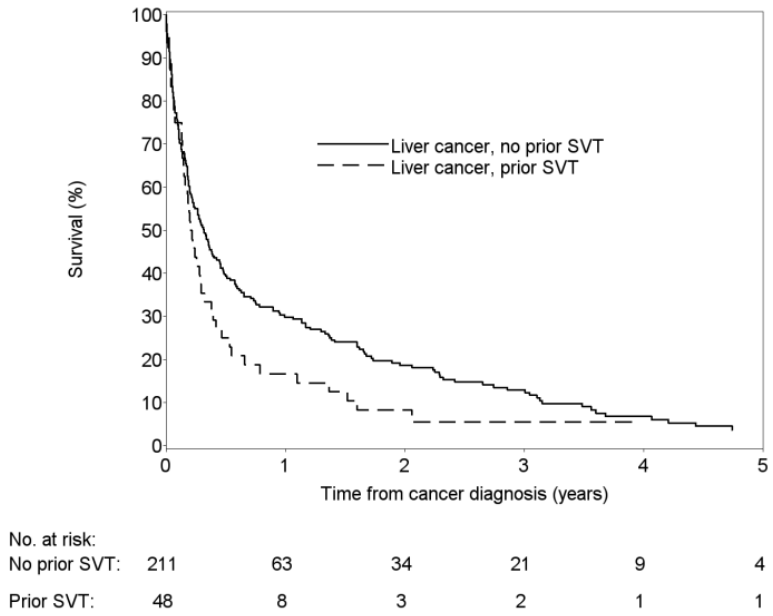
Table 8 - SIRs for cancer in 1,191 patients with SVT

	Observed cancers and standardized incidence ratios (95% CI)							
Cancer site	**0-<3 months**		**3-<12 months**		**1+ year**		**Overall**	
Any	95	33 (27-40)	18	2.7 (1.6-4.3)	70	2.1 (1.6-2.6)	183	4.2 (3.6-4.9)
Liver[a]	41	1805 (1295-2449)	5	92 (30-215)	2	7.4 (0.9-27)	48	138 (101-182)
Pancreas[b]	17	256 (149-409)	0	-	3	4.0 (0.8-12)	20	21 (13-32)
MPN[c]	8	764 (329-1505)	3	119 (25-348)	12	88 (45-153)	23	133 (85-200)

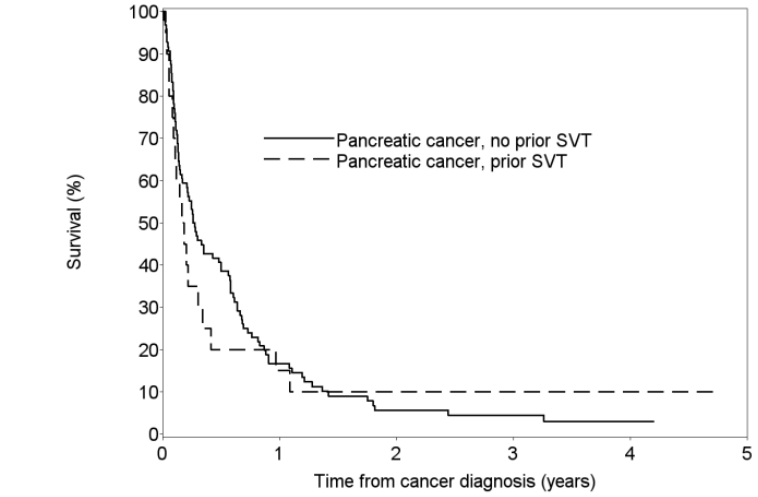
[a] Hepatocellular carcinoma (n=38), intrahepatic bile duct carcinoma (n=2), and unspecified liver cancer excluding metastasis (n=8).
[b] Pancreatic head (n=4), pancreatic body (n=1), more locations (n=2), unspecified (n=13).
[c] Polycythemia (n=15), essential thrombocytemia (n=8), primary myelofibrosis (n=0).

In a subanalysis, we examined cancer risk according to the site of thrombosis. PVT was by far the most frequent SVT (78%), and this group of patients also accounted for most of the subsequently diagnosed cancers (n=161). The overall SIR for patients with PVT was 4.7 (95% CI: 4.0-5.5), which included the diagnosis of all liver cancer cases (n=48), almost all pancreatic cancer cases (n=19), and the majority of MPNs (n=15). Among patients with hepatic vein thrombosis (11%), 21 patients were subsequently diagnosed with cancer, most frequently MPNs (n=8). Only one case of cancer was diagnosed after mesenteric vein thrombosis.

In addition, we showed that SVT was a prognostic factor for survival in patients with liver or pancreatic cancer (Figure 2). At 3 months, 44% of patients with liver cancer and SVT had survived, whereas 55% of matched liver cancer patients without SVT had survived (MRR 1.5, 95% CI: 0.9–2.3). SVT remained a prognostic factor for liver cancer patients at the 1 year follow-up (survival 17% versus 30%; Figure 2). SVT was also a prognostic factor for 3-month survival in patients with pancreatic cancer. Survival was 35% for patients with pancreatic cancer and SVT and 53% for matched pancreatic cancer patients without SVT (MRR 1.5, 95% CI: 0.8–2.9). Survival at 1 year was similar for pancreatic cancer patients with and without SVT (15% versus 17%; Figure 2).



No. at risk:						
No prior SVT:	211	63	34	21	9	4
Prior SVT:	48	8	3	2	1	1



No. at risk:						
No prior SVT:	96	16	5	4	2	1
Prior SVT:	20	3	1	1	1	

Figure 2 - Survival curves for cancer patients with and without SVT

Footnote: Survival curves for patients with a diagnosis of liver cancer or pancreatic cancer *and* splanchnic venous thrombosis (SVT), and for a matched comparison cohort of cancer patients *without* SVT (matched for cancer type and stage, sex, age (5-year intervals), and year of diagnosis (5-year intervals).

5.5 Study V

In our cohort of SVT patients, the proportion having had recent surgery was high (40%), and the patients generally had a high comorbidity burden, including alcoholism-related disease, cardiovascular disease, and cancer. Our descriptive data suggested that each of the SVT subtypes had specific characteristics that were more frequent than among the other SVT subtypes (Figure 3).

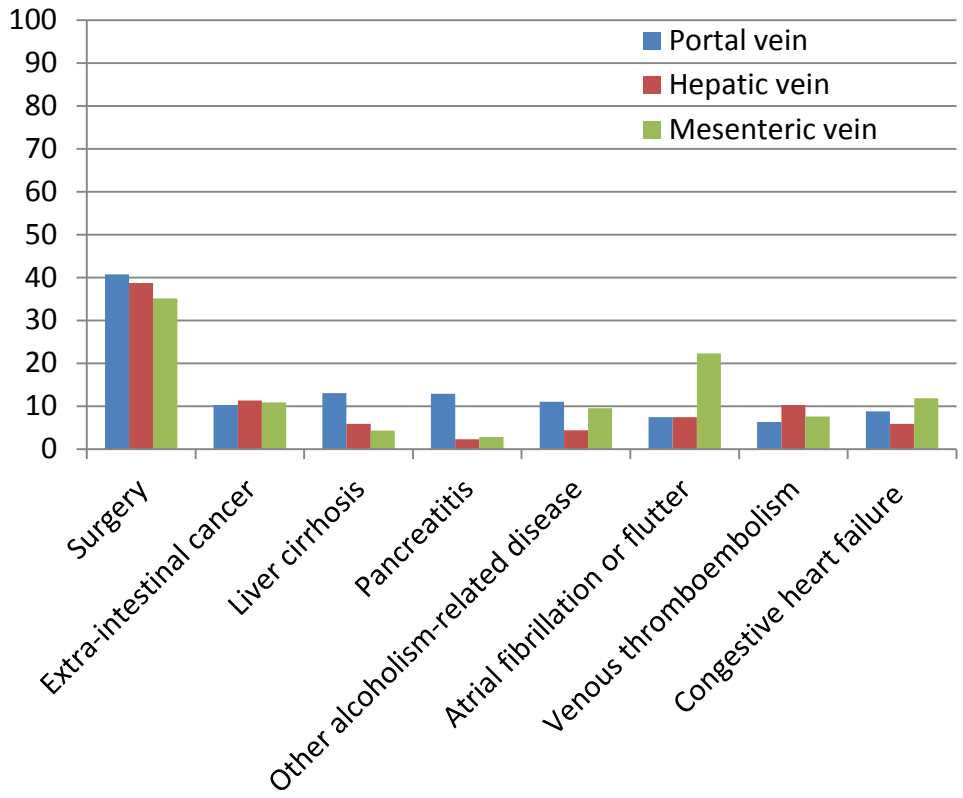


Figure 3 - Frequencies (%) of selected conditions according to location of thrombosis

We calculated mortality risks and MRRs for the overall cohort and for several subgroups according to the site of thrombosis and underlying disease. Overall, SVT patients had markedly higher 5-year mortality than the matched comparison group. The 30-day, 31 to 364-day, and 1 to 5-year risks were 20.6%, 21.7%, and 25.4%, respectively, for SVT patients and 0.7%, 4.7%, and 17.7% for the comparison group. The MRRs for

the three follow-up periods were 40.7 (95% CI: 32.4-51.1), 7.4 (95% CI: 6.4-8.6), and 2.4 (95% CI: 2.1-2.8), respectively (Table 9). However, prognosis differed for the different types of thrombosis. Patients with portal or hepatic vein thrombosis had a higher risk of mortality beyond 5 years of follow-up, but patients with mesenteric vein thrombosis had an excess risk mainly during first 30 days (Table 9).

Table 9 - Mortality after SVT compared to the general population comparison cohort

	Mortality rate ratio (95% CI)		
	30 days	**31-364 days**	**1-5 years**
Comparison cohort	1.00	1.00	1.00
Splanchnic venous thrombosis	40.7 (32.4-51.1)	7.4 (6.4-8.6)	2.4 (2.1-2.8)
Portal vein	26.9 (20.8-34.7)	7.4 (6.3-8.8)	2.6 (2.2-3.1)
Hepatic vein	32.6 (14.8-71.8)	7.6 (4.6-12.6)	2.4 (1.5-3.7)
Mesenteric vein	435.0 (138.8-1369.3)	6.1 (2.4-15.5)	0.6 (0.2-1.9)
Subgroups			
Liver cancer	1.7 (0.2-15.6)	3.3 (1.5-7.0)	0.4 (0.1-3.6)
Pancreatic cancer	3.7 (1.6-8.2)	2.2 (1.1-4.3)	0.9 (0.2-3.1)
Other gastrointestinal cancer	39.0 (17.0-89.4)	3.7 (2.1-6.4)	1.8 (0.9-3.3)
Myeloproliferative neoplasm	20.0 (1.8-220.5)	2.4 (0.5-11.2)	1.8 (0.5-6.5)
Extra-intestinal cancer	37.9 (21.5-66.9)	6.0 (4.1-8.8)	3.1 (2.0-4.8)
Liver cirrhosis	12.4 (7.3-21.0)	7.3 (5.1-10.4)	1.5 (1.0-2.4)
Pancreatitis	25.9 (11.5-58.3)	7.8 (4.8-12.9)	2.5 (1.6-3.8)
Atrial fibrillation or flutter	60.1 (32.7-110.8)	5.8 (3.7-9.2)	2.8 (1.7-4.6)
Congestive heart failure	47.8 (25.7-89.1)	5.8 (3.8-8.8)	2.8 (1.8-4.2)
Venous thromboembolism	40.4 (13.7-119.4)	6.3 (3.6-10.8)	1.4 (0.8-2.7)
Alcoholism-related disease	29.4 (15.4-56.3)	5.0 (3.3-7.7)	2.4 (1.6-3.7)
Inflammatory bowel disease	41.0 (9.0-187.6)	4.4 (1.5-13.3)	2.4 (0.8-7.4)

6. DISCUSSION

6.1 Main conclusions

In study I, we provided firm evidence that patients with liver disease have an increased risk of VTE compared to the general population. We then showed in study II that persons with liver cirrhosis have increased 30-day mortality after a hospital contact for DVT or PE compared to other patients with similar thromboembolic events. In study III, we showed that VTE is also a marker of occult cancer in patients with liver disease.

Importantly, in study IV we found that SVT may be the first manifestation of occult cancer, with an increased occurrence of liver and pancreatic cancer shortly after SVT. Specifically for liver and pancreatic cancer, patients that experienced SVT prior to the diagnosis of cancer had a poorer outcome than corresponding cancer patients without SVT. Moreover, we showed that SVT may precede the diagnosis of MPNs. Notably, some MPNs were diagnosed more than 1 year after SVT, possibly indicating delayed diagnosis. Finally, in study V we found that our cohort of patients with SVT had higher absolute and relative mortality than the comparison cohort, even after extensive matching for underlying chronic diseases that could potentially impact mortality.

6.2 Comparison with existing literature

In the following sections, we relate our findings to the existing literature (Table 2).

Study I

When we conducted study I (published in 2009, included in my research year report), the evidence of a possible association was based primarily on studies presenting the prevalence or incidence of VTE in patients with CLD. Therefore, in a field in which speculations regarding the possible importance of VTE

among liver disease patients dominated, our study provided evidence-based knowledge confirming the association. More recently, our results have been confirmed in three recent population-based studies[6,63,64].

The first study was case-control study conducted in the Netherlands using data from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study[6]. The study included 4,311 patients with a first VTE and 5,768 controls (consisting of partners of patients and persons identified via a random-digit-dialing method). The main exposure was self-reported history of major illness, and the ORs of VTE were calculated for the different diseases. All of the investigated major illnesses were associated with an increased risk of VTE, and the ORs varied from 1.5 (95% CI: 1.2-1.8) to 4.9 (95%CI: 2.4-9.9)[6]. The study included 27 patients with liver disease and 22 controls with liver disease, and the unadjusted OR of VTE for patients with liver disease was 1.7 (95% CI: 1.0-2.9). Our unadjusted results were higher (cirrhosis OR=2.6; non-cirrhotic liver disease OR=2.7), but their unadjusted risks were comparable to our adjusted ORs (cirrhosis OR=1.7; non-cirrhotic liver disease OR=1.9). Though they did not adjust for confounders, the effect of immobilization (i.e., bedridden for minimum 4 days, hospitalization, or surgery within 3 months prior to the index date), BMI, and thrombophilia (factor V Leiden, FVIII, FIX, and von Willebrand factor) was addressed in stratified analyses. When combined with immobilization or von Willebrand factor, the ORs of VTE for liver disease patients were 8.3 (95% CI: 2.8-24.4) and 8.0 (95% CI: 2.6-24.7), but these analyses were based on small numbers. The Dutch study[6] used VTE diagnoses from anticoagulation clinics with higher positive predictive values for DVT than our hospital discharge diagnoses (97% versus 71%), but the values for PE were comparable (78% versus 82%)[48,78]. Furthermore, the Dutch study used only self-reported information on major illnesses, whereas we relied on hospital discharge diagnoses for all covariates, with a generally high validity. Though self-reported information may be reliable for diseases such as myocardial disease and stroke, it is less reliable for liver disease because of the strong relation with alcohol abuse. Moreover, patients with cirrhosis may be more difficult to reach through the random-digit-dial method. Though we could expect less misclassification of liver disease in our

registry compared to self-reported disease, any potential misclassification of covariates should be non-differential and have a minimal impact on the relative risks provided in both studies.

The second study was designed as a cohort study comparing the risk of VTE among patients with liver cirrhosis and a comparison group identified in the National Health Insurance program in Taiwan[63]. A sample population of 1,000,000 was randomly selected between 2005 and 2010. A total of 2,223 patients with liver cirrhosis were identified using ICD-9-CM codes and followed from 2007 onwards alongside a comparison cohort of 22,230 patients without cirrhosis. Patients with cirrhosis were matched to non-cirrhotic patients using propensity scores (standard greedy-matching algorithm). At the end of follow-up in 2010, 26 patients with liver cirrhosis and 1,115 patients without liver cirrhosis had been admitted with VTE[63]. HRs were calculated for VTE using Cox proportional hazard regression analysis adjusting for age, sex, urbanization level, socioeconomic status, diabetes, hypertension, coronary artery disease, hyperlipidemia, malignancies, congestive heart failure, atrial fibrillation, smoking, obesity, peripheral artery disease, and CCI score. The HR of VTE for patients with liver cirrhosis was 1.71 (95% CI: 1.05-2.78) compared to persons without cirrhosis[63]. Interestingly, despite different settings and analyses, this result was in complete agreement with the OR of 1.74 (95% CI 1.54-1.95) in our study. In a second analysis, the association was examined for a subgroup of patients with advanced cirrhosis, revealing that these patients had an even higher HR (4.36, 95% CI: 1.36-14.01) than the main analysis. However, this subanalysis was based on a small number of events (5 VTEs among 293 patients with cirrhosis and 15 among 2,930 without cirrhosis). Similar to our approach, this study used diagnostic codes, and their internal validation of the codes against medical records indicated very high agreement with positive predictive values of 94% (95% CI: 84%-99%) for VTE and 98% (95% CI: 93%-100%) for liver cirrhosis. The authors highlighted overall limitations that included the use of administrative data and the validity of the codes, as well as the chance of unmeasured confounding and overmatching.

We acknowledged that a lack of information on immobility and the severity of cirrhosis was a limitation in our study. After publication, we received a comment questioning our results because we did not address thrombophilia. Therefore, post-publication we conducted a sensitivity analysis to determine if a risk of unmeasured confounding seemed likely. This simulation exercise showed that it was unlikely for unmeasured confounding to explain the associations that we found (described in detail in the section 6.3, confounding).

The third study was conducted using data from Singapore General Hospital, which is a tertiary care hospital serving approximately one-third of the total population of Singapore[64]. The study was based on all hospitalizations during 2004-2011 (n=199,904). The study population included 193,532 patients without CLD and 6,372 patients with CLD (1,296 with cirrhosis and 5,076 with non-cirrhosis CLD). VTE was present in a total of 1,744 patients. CLD and VTE were identified using ICD-9-AM codes, and a subset of 50 diagnoses for each disease entity were validated against information from chart reviews. The positive predictive value was 96% for VTE and 98% for CLD. The study found a higher prevalence of VTE among patients with non-cirrhosis CLD (1.5%) or cirrhosis (2.0%) than among other patients (0.8%), and the corresponding ORs of VTE were 1.4 (95% CI 1.2-1.7) and 1.5 (95% CI: 1.2-2.0)[64]. These ORs were adjusted for age, gender, ethnicity, long stayer (defined by length of admission >21 days), cancer, infectious disease, diabetes, anemia, cardiovascular disease, cerebrovascular disease, renal disease, and pulmonary disease. The authors did not present the unadjusted ORs, so it is unclear how strongly the results were biased by the confounders. Considering the results from the logistic regression in the paper, long-stayer was a strong confounder and may explain why their estimates were somewhat lower than ours. The validity of diagnoses was reported to be almost perfect, regardless of whether the diagnosed had such high predictive values, as a lower specificity would only tend to attenuate the risk estimates. Similar to our study, non-differential misclassification of diagnoses may have had the consequence of balancing any difference in risk between the two liver disease categories.

Study II

No previous study specifically examined 30-day mortality after VTE in patients with cirrhosis compared to a general population comparison cohort. However, we recently examined the effect of several comorbidities on overall mortality after VTE in a Danish nationwide cohort[20]. We found that few diseases yielded higher MRRs compared to the absence of those diseases. Patients with prior diagnosis of severe liver disease had an overall MRR of 1.84 (95% CI: 1.47-2.30), whereas patients without severe liver disease had a MRR of 1.55 (95% CI: 1.53-1.57). Similar for PE, the MRR for patients with severe liver disease was 3.64 (95% CI: 2.59-5.12) and without liver disease 2.77 (95% CI: 2.74-2.81)[20]. However, we only provided these results for the complete follow-up (i.e., not specifically for different follow-up periods). Therefore, our study II expands on the current understanding of liver disease and its effect on short-term VTE mortality. Nearly one-third of patients with PVT have cirrhosis[15,79], which has been identified as a prognostic factor for increased mortality in patients with PVT[15,79]. However, the effect of cirrhosis on mortality is mainly addressed in smaller cohorts without a comparison cohort.

There is no evidence-based knowledge regarding the treatment of thrombosis in patients with cirrhosis, and the clinical benefit or harm of thromboprophylaxis in patients with cirrhosis remains unclear. Thus, clinicians often struggle with making decisions on how to treat the thrombosis while avoiding major bleeding. A few studies estimated the occurrence of hemorrhagic episodes after PVT and anti-coagulant treatment; somewhat surprisingly the risk of bleeding seems to be low. Among 67 patients with PVT, malignancy, liver failure, and cardiopulmonary disorders were the main causes of death, and variceal bleeding was only recorded in four patients and heparin-induced thrombocytopenia in two patients[79].

A few small cohort studies (including between 19 and 235 cirrhosis patients) reported the use of prophylaxis[80] and treatment with anticoagulation after PVT[81-83] as being relatively safe in these patients. However, the results may be limited by confounding by indication, arising when patients with a high a priori bleeding risk are not treated but patients with a low risk of bleeding are more likely to receive treatment. Overall, a few studies, including ours, indicate that cirrhosis patients with thrombosis are less likely to

receive standard treatment, particularly in the case of incidentally diagnosed SVT[27]. However, incidental VTE appears to be just as serious as symptomatic venous thrombosis[84-86], and this probably also applies to SVTs.

Study III

Liver disease is associated with an increased risk of cancer[8]. Compared to the general population, patients with liver disease have an overall 2-fold increased risk of any cancer[8,34,87-89]. Patients with liver cirrhosis who are cancer-free at diagnosis have a 1-year incidence of 1.2% and 2.2% for hepatocellular carcinoma and extra-hepatic cancer, respectively[87]. Moreover, as shown in study I and confirmed by others[6,63,64], liver disease is associated with an increased risk of VTE. In study III, we showed that patients with liver disease have an increased risk of a cancer diagnosis after a venous thromboembolic event. The absolute risk of cancer at 1 year was higher in patients with cirrhosis than in patients with non-cirrhotic liver disease. In agreement, our estimated relative risks (i.e., SIRs) were higher among patients with liver cirrhosis than among patients with non-cirrhotic liver disease compared to the general population. The cancer risk was most pronounced shortly after the VTE, but an excess risk of cancer diagnosis remained during subsequent months. Specifically, among patients with liver disease and VTE, we observed more cases of gastrointestinal cancer (hepatic, biliary, pancreatic, esophageal cancers) and lung cancer than we expected.
Generally, we found a similar association with cancer after VTE in our cohort of patients with liver disease compared to cohorts from the general population hospitalized with VTE. However, if we look more closely at the risk beyond 1 year of follow-up, the patients with liver disease had a higher long-term risk of cancer. This finding may be explained by the fact that liver disease *per se* is associated with an increased risk of cancer or that the associated lifestyle factors, including smoking and drinking, increase the risk of several cancers, thereby acting as effect modifiers. The implications of the findings from study III point towards individualized work-ups for cancer patients presenting with VTE. Though patients with liver disease are known to be at an increased risk of VTE, such an event may actually reflect the presence of underlying

occult cancer. Currently, it is not clear if extensive screening for earlier detection of cancer among patients with liver disease and VTE will improve the outlook for the patients. Regardless of the presence of VTE, these patients have a poor 5-year survival, and VTE (or at least PVT) indicates severe liver disease.

Study IV

No previous study has used a comparison cohort to investigate if patients with SVT have a higher occurrence of subsequent cancer. However, a link had been suggested in case reports and smaller cohort studies[13,57-59]. One of the largest studies included 413 patients with thrombosis in the hepatic veins or inferior vena cava diagnosed in India between 1989 and 2013[13]. A total of eight patients were diagnosed with hepatocellular carcinoma during a median follow-up of 5 years. Two meta-analyses examined the prevalence of MPNs[12] and hepatocellular carcinoma[14] among patients with subtypes of SVT. The first[12] included 32 studies and a total of 1,062 patients with Budd-Chiari syndrome and 855 patients with PVT (the largest study included 237 patients). Budd-Chiari syndrome was found to be the presenting symptom of MPN in 37 of 50 (74%) patients, and PVT was the presenting symptom of MPN in 47 of 64 (73%) patients[12]. The second meta-analysis[14] included 16 studies with a total of 1,159 patients with Budd-Chiari syndrome (maximum of 177 study participants). The majority of included studies reported period prevalence (with undefined periods), i.e., simply proportions of patients subsequently diagnosed with hepatocellular carcinoma. One study reported the incidence of carcinoma among patients with Budd-Chiari syndrome but excluded the first year of follow-up[90]. Regardless, there was substantial heterogeneity among the included studies, and the prevalence of hepatocellular carcinoma varied between 2% and 52% (median number of carcinomas in the included studies = 7). The pooled estimate for hepatocellular carcinoma was 4% for thrombosis in the hepatic veins and 26.5% for obstruction of the inferior vena cava.

The association between cancer and VTE is well-described - we provided evidence of a similar association between SVT and cancer, potentially an even stronger association. We highlighted that SVT may be a marker of occult malignancy, but also showed that the SIRs remained increased more than 1 year after the

thrombosis. Cancers diagnosed 1 year after the diagnosis of SVT could include cancers overlooked at the time of the SVT. We did not have clinical details on the type of work-up the patients received; therefore, we can only speculate whether these cancers could have been identified earlier and, if so, whether an earlier diagnosis would have improved survival among SVT patients. Thus, despite our findings of a strong association between SVT and cancer occurrence, the clinical impact is not clear.

The conclusion of the first meta-analysis was that a specific JAK2 mutation should be included in the diagnostic workup of SVT patients to help identify MPNs[12]. The second meta-analysis advocated for routine surveillance for hepatocellular carcinoma in patients with Budd-Chiari syndrome, especially those with obstruction of the inferior vena cava[14]. A Danish registry-based study found that patients in whom cancer was discovered within 1 year after an episode of DVT or PE were more likely to have advanced cancer disease and higher mortality than patients with cancer who did not have VTE[56]. Proposals for implementing new screening procedures are only rational if they are cost-effective and improve cancer-related survival. After the publication of study IV, a study examining the potential effect of screening for occult cancer in unprovoked VTE was published in The New England Journal of Medicine[91]. The study was a multicenter randomized controlled trial in Canada of 854 patients with VTE, including DVT and/or PE. The analyses were restricted to unprovoked VTE (similar to our definition, but patients with known hereditary or acquired thrombophilia, paralysis, paresis, or recent immobilization were also excluded). The primary outcome was incident cancer diagnosed in patients who initially had a negative screening for occult cancer. Patients were assigned to undergo basic blood testing, chest x-ray, screening for breast, cervical, and prostate cancer, or a CT scan (including virtual colonoscopy and gastroscopy, biphasic enhanced CT of the liver, parenchymal pancreatography, and uniphasic enhanced CT of the bladder). Patients were followed for 1 year. A total of 33 patients received a new cancer diagnosis, but the proportions were similar in the two groups (3.2%, 95% CI: 1.9%-5.4% versus 4.5%, 95% CI: 2.9%-6.9%; p=0.28)[91].The absolute difference in missed occult cancers between the two screening modalities was 0.25% (95% CI: -1.12-1.63). The conclusion of the study was that routine screening with CT of the abdomen and pelvis does not provide a clinically relevant benefit.

However, their interpretation of the results deserves further consideration. First, the precision of the estimates revealed that the study had problems with power. Second, relying solely on significance testing, when interpreting the results, may have led to inaccurate conclusions regarding clinical relevance[92]. A single p-value provides a dichotomous perception of the picture, allowing only a yes/no answer to a question, which is often too simple an answer. In contrast, a risk estimate with 95% CI, absolute risk difference, and the numbers needed to treat (NNT) provides better insight into the magnitude of effect size, the precision of the estimates, and whether a clinically relevant benefit exists for the extended diagnostic work-up. If we look closer at the proportion of missed cancers in the study published in in The New England Journal of Medicine[91] and calculate the absolute risk difference divided by 100 (i.e., [4.5%-2.3%]/100%,) we can estimate the NNT or *numbers needed to screen*. The data suggest that 46 patients would need to undergo the more extended evaluation to detect one additional cancer. A similar randomized controlled trial comparing different screening modalities would be optimal, but will likely be difficult to conduct because of the low incidence of SVT.

The SOMIT trial (screening for occult malignancy in patients with idiopathic VTE) included 201 patients with a first-time VTE and no recognized risk factor for VTE, including cancer identified by routine physical examination at the time of VTE diagnosis. Patients were divided into two groups: 99 were allocated to receive “extensive screening” and 102 served as a comparison group. The result of extensive screening (versus no further testing) in apparently cancer-free patients with VTE confirmed a higher chance of detecting underlying cancer. The absolute difference in cancer-related mortality was based on a few events and, thus, had low precision (1.9%, 95% CI: -5.5%–10.9%)[93]. In a cohort study, 864 patients with acute VTE underwent an initial routine clinical examination for cancer, and if this was negative then cancer markers were measured and an abdominal and pelvic ultrasound performed[94]. Almost half of the malignancies (n=27) were only identified by the extended work-up, and these cancers were diagnosed at an earlier stage than those detected by routine clinical evaluation[94]. Though our setting was different from the cohort studies described above, we found that patients diagnosed with SVT before their liver cancer diagnosis

were more frequently diagnosed at a localized stage than liver cancer patients without preceding SVT. In contrast, among the patients with pancreatic cancer in our data, SVT indicated a more advanced cancer stage. We can only speculate about the reasons for the dissimilarity in stage distribution for liver and pancreatic cancer. Maybe the difference is due to variance in the cancer-related potential to induce thrombosis. Liver cancer may cause thrombosis at an early stage due to external compression of veins, whereas pancreatic cancer causes thrombosis at a later stage only when intrinsic hypercoagulability becomes prominent[95]. Another possibility is that underlying factors among patients (e.g., presence of cirrhosis among patients who develop hepatocellular carcinoma) influence the degree of surveillance they receive (regardless of SVT). More specifically, patients who develop hepatocellular carcinoma probably have more hospital contacts and undergo more ultrasound examinations than the more heterogeneous patient group that develops pancreatic cancer. Finally, ultrasound may have greater sensitivity in detecting malignant tumors in the liver than in the pancreas.

Cancer patients are at higher risk of recurrent thrombosis and hemorrhagic episodes during oral anti-coagulant therapy with VKAs compared to non-cancer patients[96-98]. Thus, regardless of a possible impact on survival, the detection of cancer may impact the choice of anticoagulant treatment[27].

In conclusion, the absolute cancer risk among SVT patients was pronounced, and given that SVT is more strongly related to subsequent cancer diagnoses than DVT and PE, we think an individualized extended work-up may be relevant for subgroups of SVT patients.

Study V

Because SVT is an uncommon condition, survival after SVT has been described primarily in cohorts of limited study size (33-604 patients) including selected patient groups (patients with cirrhosis or hepatocellular carcinoma, non-cirrthotic liver disease, non-malignant SVT, and liver transplantation candidates)[26,79,82,99-102]. An international cohort comprising 604 SVT patients from 32 different centers followed patients for a median of 2 years[26]. The incidence of several outcomes was assessed, including

episodes of major bleeding, reccurrent thrombosis or other thrombotic events, and mortality. The reported incidence rates per 100 person-years for the three outcomes were 3.8, 7.3, and 10.3, respectively[26]. Subgroups of patients with cirrhosis or cancer had higher incidence rates for all three outcomes than patients with unprovoked SVT or patients with transient risk factors. Other studies have shown that PVT is associated with more severe disease in patients with cirrhosis and may be a marker of disease progression[103]. The overall 10-year survival has been reported to be as low as 54%[79]. Though descriptive numbers give us an idea of the severity of diseases, such studies cannot eliminate confounding, i.e., the presence of other factors that may explain the high mortality in patients with SVT. In addition, the natural histories of SVT subtypes may be quite different and probably need to be considered different diseases instead of being grouped together as one disease. Our literature search identified only one cohort study that estimated the relative mortality after SVT compared to mortality in the general popoulation. The study compared mortality among 832 SVT patients diagnosed at the Mayo Clinic between 1980 and 2000 to that of the general population using age- and sex-specific mortality rates in the US white population[15]. The 10-year survival rates varied according to site of thrombosis, from 63% for portal vein thrombosis to 82% for hepatic vein thrombosis. Compared to the expected survival rates calculated from mortality in the general population, SVT patients had lower survival. Patients with multi-segmental thrombosis or active malignancy had higher mortality than patients with one-site thrombosis only or an absence of cancer. In addition, the outcome was worse for patients who did not receive anticoagulation therapy compared to patients who received treatment. In agreement with these findings, we found a higher mortality rate among patients with portal vein thrombosis compared to those with hepatic vein thrombosis. Notably, patients in the Mayo Clinic cohort with PVT had a higher prevalence of cirrhosis and cancer than patients with hepatic or mesenteric vein thrombosis, but patients with hepatic vein thrombosis mainly comprised young women and patients with MPNs[15]. In our cohort, the predominant underlying cause of thrombosis in all patients was recent surgery (portal vein 41%, hepatic vein 39%, mesenteric vein 35%). PVT patients had a higher prevalence of cirrhosis, pancreatitis, and alcoholism-related disease in general, but the prevalence of extra-

GI cancer was similar for all subgroups of SVT. Other notable differences included a higher prevalence of atrial fibrillation or flutter and congestive heart failure among patients with mesenteric vein thrombosis. Thus, our study adds to the existing literature by addressing confounding and by estimating the risk of short- and long-term mortality.

6.3 Methodological considerations

The studies in this dissertation were designed to examine risk and prognosis, more specifically whether there is a causal relation between the exposure (liver disease in studies I-III; SVT in studies IV and V) and outcome (VTE in study I; mortality in studies II and V; cancer in studies III and IV). In any study aiming to examine causal associations, there is a risk that findings are explained or influenced by systematic and random errors. Systematic errors (e.g., selection bias and information bias) cannot be controlled for by statistical analysis; however, sensitivity analyses may be helpful in quantifying systematic errors for effect estimates[104]. The risk of confounding can be reduced in the design phase by randomization, restriction, and matching, as well as in the analytic phase by standardization, stratification, and adjustment (using regression models). The influence of random errors can be reduced by conducting large studies with a high number of events. Together, these considerations will increase the precision of the effect measures and reduce the risk of demonstrating associations due to chance only (described in section 6.2, study IV). Some overall considerations are described below, but the more specific discussions are included in the five dissertation papers.

Selection bias

Selection bias may occur as a consequence of the procedure used to select study participants or from factors affecting study participation[105]**.** In general, the structure of the Danish healthcare system reduces concerns regarding critical selection bias. However, when using data from administrative registries, we

have no influence on the methods used to collect the data[106]. Our study cohorts may include all patients *diagnosed* with a given disease in the population but may not capture all persons *with* the disease in the population. In particular, there may be undercoding of diseases among severely ill patients and of conditions that are asymptomatic and, therefore not diagnosed. We used hospital discharge diagnoses (covering inpatient admissions or outpatient clinic visits) to identify patients with cirrhosis, venous thrombosis, and cancer. These specific diagnoses are not made by the general practitioner without referral to the hospital; therefore, we likely captured all patients *diagnosed* with these conditions during the defined study periods in Denmark. However, the diagnostics for cirrhosis, VTE or SVT, and cancer often involve the use of imaging procedures. Work-up for one condition may lead to diagnosis of the other. For example, symptoms related to cirrhosis may result in imaging examinations that reveal either SVT or cancer. In contrast, standard blood tests in patients worked up for thrombosis may reveal signs of hepatic involvement, initiating further work-up for liver disease or cancer.

The risk of selection bias also differs according to the study design used. For example, substantial misclassification of VTE in study I could have caused selection bias, as we selected our cohort based on the outcome. We had complete follow-up for our patients, meaning that we knew if they left our "nationwide cohort" and for what reasons, e.g., emigration, death, censoring by end of the defined follow-up period, or because the event of interest occurred[70]. Also, a differential loss to follow-up is unlikely among the patients we defined as exposed and unexposed (e.g., as in study II, VTE patients with cirrhosis compared to other VTE patients; or in study V, SVT patients compared to a matched comparison cohort).

Information bias

We derived information on all study variables from our nationwide medical registries; therefore, as in any registry-based study, there is a risk of information bias. Though we are not particularly concerned about measurement bias, observer bias, or reporting bias, some misclassification is likely present. The coding in

our hospital registries is performed by the treating physicians, and some degree of erroneous classification of disease is unavoidable. The importance and effect of such misclassification depends on whether it occurs equally (non-differential) or for a particular subgroup of patients (differential). Severe misclassification of the outcome may cause information bias in a cohort design, but as mentioned above it can lead to selection bias in a case-control study. Though the validity of diagnoses is always crucial for absolute effect measures, the importance varies for relative risk estimates according to type of design.

Overall, the validity of diagnoses of cancer and comorbidities, as well surgical procedures reported in the DNPR, have been shown to be consistently high[106]. Specifically, the validity for cirrhosis was previously shown to be 85% using diagnostic criteria for cirrhosis[107], or after the evaluation of medical charts[108]. Approximately 20-25% of the patients registered with VTE may not fulfill the strict diagnostic criteria (covering typical clinical symptoms in combination with confirmatory test results from ultrasound or CT scans)[78]. The validity of SVT diagnoses has not yet been examined. We aimed to strengthen the validity of SVT diagnoses by restricting the study to patients registered with a specific anatomic location. The majority of SVT patients in our cohort had imaging examinations with ultrasound/CT/MR scans in close relation to the admission for SVT, and we likely included confirmed diagnoses. We argue (e.g., in study I) that the potential misclassification was non-differential, that the risk of being diagnosed with VTE would not have depended on the presence/absence of cirrhosis. Non-differential misclassification most often biases towards the null, but differential misclassification is less predictable. We included information on causes of death in studies II and V, but all-cause mortality is unlikely to be misclassified though the immediate causes are likely prone to some degree of misclassification. Accordingly, we highlighted that these immediate causes of death should be interpreted with caution.

Confounding

Classically, confounding is described as a mixing of effect[16] (i.e., the relation observed between exposure and outcome is not solely due to the effect of the exposure itself). Thus, the effect may be explained, to some extent (partially or completely), by a third factor related to both the exposure and the outcome without being an intermediate step between the two. As mentioned above, confounding can be dealt with at different stages or steps of the study. In the early definition of the study cohort, restriction and matching can be used to reduce incomparability of cases and controls or between two cohorts. During the analysis, standardization, stratification, and adjustment may be useful in minimizing the risk of confounding. In this dissertation, we reduced risk of confounding by restriction (studies I-IV), matching (studies II and V), standardization (studies III and IV), adjustment (studies I, II and V), and stratification (studies I-IV).

The registration of confounding factors is often not complete. The consequence of such underreporting of prevalent disease may be residual confounding. Such misclassification of confounders will cause imperfect adjustment in the regression analysis. Another issue to consider when conducting studies on cancer risk and mortality is the risk of confounding by lifestyle factors, such as alcohol abuse and smoking. Unfortunately, the reporting of these lifestyle factors in our registries was only recently standardized. These factors are likely important, as they are associated with both an increased risk of several cancers (e.g., esophageal, gastric, liver, lung, and urinary tract cancers)[109] and poorer outcomes of several medical conditions and surgery[110-113]. Therefore, although we sought to reduce substantial confounding by matching for characteristics, including diseases from the CCI score system and others considered relevant, unmeasured confounding by known and unknown confounders is likely.

As mentioned previously, we questioned whether our results demonstrating liver disease as a risk factor for VTE could be due to unmeasured confounding, more specifically thrombophilia. Even though we did not agree that thrombophilia was necessarily a confounder, but rather an intermediate step from the pathway between cirrhosis and VTE, we performed a simulation exercise[114] to assess if this seemed likely.

We set the prevalence of cirrhosis to 0.3%[115] and the prevalence of the unmeasured confounder thrombophilia in the general population to 3%[116]. The curves in Figure 4 indicate that, if thrombophilia was 10-times more frequent among patients with cirrhosis, the required strength of the association between thrombophilia and VTE would have to be 5 or more to fully explain our results. If the prevalence of thrombophilia was only 4-times higher among patients with cirrhosis than the general population, then the strength of thrombophilia as a confounder would have to be around 10 to explain our results, if the actual association was a null-result. Both of these settings are probably unrealistic, and we remain confident that our robust association is not due solely to unmeasured confounding.

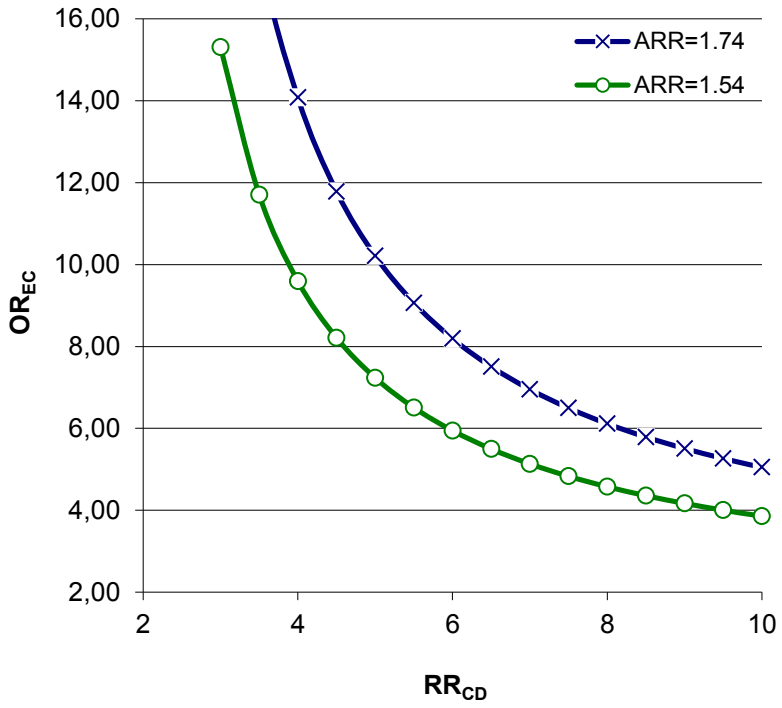


Figure 4 - Simulation of required strength of unmeasured confounding

Sensitivity analyses simulating different situations in the association between an unmeasured confounder, cirrhosis (OR_{EC}), and VTE (RR_{CD}). The graphs depict the adjusted ORs for liver disease and VTE (blue line) and the lower limit of the 95% CI (green line).

Statistical methods and their validity

In this dissertation, we conducted two primary types of observational studies. We conducted a case-control study using logistic regression (study I) and cohort studies using Cox regression (studies II, IV, and V), and indirect standardization (studies III and IV). All statistical methods are widely used and well-acknowledged in the field of epidemiology[16]. Though the designs and methods are conceptually different, they may answer the same question by providing approximations of relative risks.

Logistic regression provides the OR for a disease occurring in one group compared to a reference group, whereas Cox regression provides incidence rate ratios (or MRRs if the outcome is mortality). Notably, the OR will often overstate any effect size compared to incidence rate ratios. In practical terms, this means that the OR is lower than the relative risk when OR < 1, but it will be greater than the relative risk when OR > 1. Nevertheless, substantial divergence occurs between the two effect measures only when the prevalence of the outcome is high. Accordingly, in case the outcome of interest is rare, the OR corresponds to the incidence rate ratio obtained in a cohort study[16].

The third type of analysis we conducted was indirect standardization by computation of SIRs, another estimate of the relative risk (described in detail in section 4.3, standardized incidence ratios). This method was originally developed to calculate standardized mortality ratios (SMRs), comparing mortality in one group of patients to that of the national death statistics[117]. However, this method may also be applied to national statistics, such as cancer statistics. In two studies in this dissertation, we estimated the SIRs of cancer among patients with liver disease and VTE (study III) and in patients with SVT (study IV). Because the rates are based on a high number of events, at least for the most common cancers sites, this method generally provides very robust estimates[117]. Though regression analyses such as Cox may produce estimates of low precision in stratified analyses, SIRs are based on rates from the entire cohort, not only the subgroup defined by the stratifying factor, and may have high precision even in stratified analyses. The events in the exposed cohort will often be of limited size in absolute numbers and not affect the rates in the general

population. However, a few issues may be considered with respect to how well the SIRs approximate a relative risk and how the results may be biased.

First, the criterion and ascertainment of outcome must be similar for the exposed cohort and the general population. In our case, the criteria for cancer diagnoses are comparable for both groups, and the setting of the national healthcare system and complete follow-up ensures that differences in ascertainment do not impact our results. Nevertheless, surveillance bias may impact the short-term cancer risk. Persons admitted to the hospital who undergo clinical examination including imaging procedures may have a greater chance of detecting an underlying cancer. In contrast, the general population will not undergo such screening. Surveillance bias may also have an impact on the apparent long-term risks. Being admitted for a condition that leads to thorough diagnostics may be "protective" for long-term cancer risk, as the cancer cases have been "weeded out" among the exposed during the index hospitalization but not from the general population serving as a comparison[118].

Second, the method allows "adjustments" for age, gender, and calendar time by standardization, but the classical concept of further adjustment is not feasible. However, the importance of bias depends on the prevalence of a confounder among the general population and the size of the true risk estimate. As shown by Jones and Swerdlow[119] in Figure 5, bias can occur if an exposure is highly prevalent in the general population or if the relative risk associated with an exposure is high. If the observed SMR (or in our case SIR) reflecting the relative risk is <1.5, then little relative bias will be present, regardless of how frequent the exposure is in the general population. When the prevalence of the exposure in the general population is < 5%, then bias in observed SIRs will be approximately 10% for a SIR of 3. In contrast, for SIRs > 5, substantial bias may occur, regardless of how low the prevalence of the exposure is.

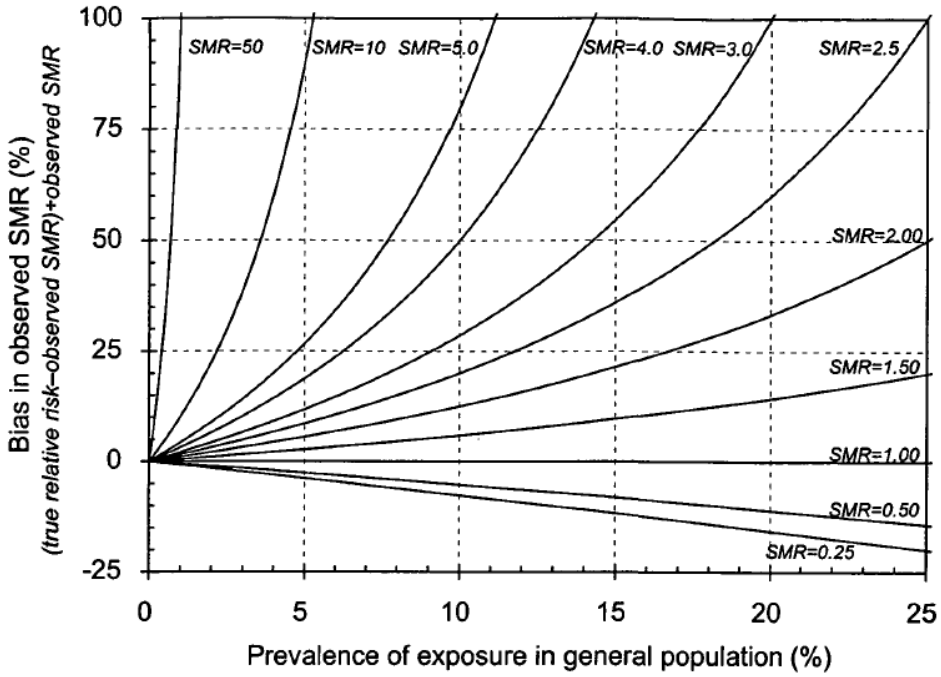


Figure 5 - Bias in observed standardized mortality ratios (SMRs) in relation to population prevalence of exposure[119]

Third, the overall expected number of outcomes is calculated based on the entire exposed cohort and their age and gender distribution and contributing person-time. Subgroup analyses with estimation of SIRs for different strata may lead to biased estimates. We can imagine a situation in which the relative risk of an outcome is equal for different age strata, whereas the prevalence (or probability) of cancer (or death) increases with age for exposed individuals and also for persons in the general population. The variance in prevalence by age may result in an artefactual trend in the SIRs across strata. The net effect is a conservative bias that increases with age[119]. In practice this means that the subgroup with the lowest prevalence will set the upper limit, resulting in increasing age being biased towards the null.

Finally, SIRs derived from different study cohorts should not be compared directly. When two cohorts differ in their age structure, the combined SIRs may reveal conflicting results even though SIRs in subgroups, such as age strata, are similar. This occurs because the calculation of SIRs includes the person-time, which will often be cohort-specific. As shown in the table below, the combined SIRs suggest an overall decreased risk in population 1, but an increased risk in population 2.

Table 10 – Simulation showing how overall SIRs depend on person-time

	Population 1				Population 2			
Age	**Person-years**	**Observed**	**Expected**	**O/E ratio**	**Person-years**	**Observed**	**Expected**	**O/E ratio**
35-39	15855	35	51.47	0.68	3171	7	10.29	0.68
40-44	22810	84	120.00	0.70	4562	17	24.00	0.70
45-49	24424	128	194.87	0.66	6106	32	48.72	0.66
50-54	26460	256	360.98	0.71	6615	64	90.24	0.71
55-59	20496	340	414.12	0.82	5124	85	103.53	0.82
60-64	8342	237	211.63	1.12	6900	196	175.21	1.12
65-69	2869	140	97.96	1.43	7437	363	253.59	1.43
70-74	1137	117	69.90	1.68	7530	775	461.15	1.68
Total	122393	1337	1520.93	0.88	47445	1539	1166.73	1.32

(Table adapted by Tsai et al.[120])

A potential limitation of registry-based studies

The studies in this dissertation were based on data from nationwide registries. As described above, these data are a highly valuable source and may be used to answer almost an unlimited number of research questions. However, we also have to acknowledge that no study or setting is perfect. A shortcoming in our registry-based data is the lack of clinical information, making it difficult to assess disease severity and disease progression. Consequently, our definitions or categories of disease will be relatively broad. This limitation is sometimes stressed by reviewers, particularly clinicians, who in their daily practice base their decisions on a patient's entire clinical presentation, including severity of disease.

We did not have information to classify cirrhosis patients according to Child-Pugh score or Model for End-Stage Liver Disease (MELD). These classification or scoring systems reflect disease severity and are widely used by clinicians in patient evaluation, but they are also used as predictors of mortality in studies of cirrhosis[121]. Instead, we classified patients according to underlying etiology (e.g., alcohol or autoimmune) and adjusted for comorbid conditions known to affect the risk and prognosis of VTE. However, we were not able to determine if the association only concerned patients with a specific disease severity.

We categorized patients with thrombosis into subgroups according to the location of the thrombosis, but we did not have information on the extent of thrombosis. For PE, the location and extent of the embolus is likely crucial, as a large central embolus is highly fatal but a peripheral or sub-segmental embolus may or may not be associated with a better outcome[122,123]. The location and extent of SVT is also likely associated with a higher mortality risk[15]. Clinicians evaluate if the thrombosis is acute or if there are signs of a more chronic condition with cavernous transformation, which relates to the development of esophageal varices[124]. Though we included information on varices, we did not have information on the extent of thrombosis.

Despite our inability to classify patients according to severity and to give clear recommendations regarding treatment or diagnostic work-up, we think our findings are important.

6.4 Clinical implications

This dissertation adds to our current understanding of the complexity of thrombotic events in patients with cirrhosis. We have shown that patients with cirrhosis have an increased risk of VTE, and that 30-day mortality after VTE is higher in patients with cirrhosis than in the general population of VTE patients. We have provided evidence of increased cancer occurrence in patients with liver disease and VTE, pointing towards an individualized diagnostic work-up in patients presenting with VTE. Furthermore, we have shown that SVT is predictor of occult cancer and a prognostic factor for short-term survival in patients with liver and pancreatic cancer. Though our results does not reveal if earlier detection of cancer may improve cancer survival, the discovery of underlying cancer will likely influence the management of thrombosis, as cancer patients have higher recurrence and complication rates.

The incidence of SVT has varied substantially in previous studies, so the national incidences of SVT subtypes that we provided contribute to the perception of disease occurrence in a hospital-based setting. We presented mortality according to site of SVT and the impact of thrombosis on short- and long-term mortality in several patient subcohorts. Such knowledge may help clinicians make decisions regarding how to treat or follow the incident cases of SVT in different patient groups and hopefully facilitate further research on this topic.

7. SUMMARY

The five studies in this dissertation were conducted as nationwide registry-based studies. The aim of the dissertation was to extend our understanding of VTE in liver disease, more specifically to clarify whether liver disease is a risk factor for VTE and has an impact on mortality after VTE. We also aimed to provide insights into the clinical course of SVT, particularly regarding cancer risk and mortality.

Study I was based on 99,444 patients with VTE and 496,872 matched population controls. Among the cases, 544 had liver cirrhosis and 1,109 had non-cirrhotic liver disease (1,058 and 2,211 among controls, respectively). We calculated ORs for VTE and found that liver disease was associated with an approximately 2-fold increased risk, even after adjusting for several confounding factors. The risk of unprovoked VTE (i.e., VTE occurring in patients without cancer, recent surgery, or pregnancy) was approximately 15% higher than the overall risk of VTE. In particular, liver disease increased the odds of having VTE among persons younger than 55 years of age.

In study II, we included 745 patients with cirrhosis and DVT, PE, or PVT and a comparison cohort of 3,647 patients without cirrhosis matched by gender, age, and type of VTE. We estimated the impact of cirrhosis on 30-day mortality after VTE. Cirrhosis was associated with an up to 2-fold increase in mortality after DVT and PE. While absolute mortality risk was high after PVT, there was no difference in mortality for patients with and without cirrhosis. We also noted a difference in prescriptions for post-discharge anti-coagulant medicine, which depended on cirrhosis diagnosis. Fewer patients with cirrhosis received VKA than persons without cirrhosis. Finally, the proportion of deaths due to PE was similar among patients with and without cirrhosis.

In study III, we examined the risk of cancer among 1,867 patients with non-cirrhotic liver disease and 888 patients with liver cirrhosis subsequent to hospitalization with DVT, PE, or superficial venous thrombosis. We showed that the patients had a highly elevated risk of being diagnosed with cancer shortly after VTE, but an increased risk also persisted beyond 1 year of follow-up.

In study IV, we compared the cancer risk in a cohort of 1,191 SVT patients to that expected based on Danish national cancer incidence rates. In a second analysis, we compared prognosis among cancer patients (liver cancer n=259, pancreatic cancer n=116, and MPN n=107) with and without SVT preceding their cancer diagnosis (matched by age, gender, cancer type, and stage). The 3-month risk of cancer was 8.0% in our SVT cohort, corresponding to a more than 30-fold increased risk of cancer compared to the expected risk. The most predominant cancers diagnosed within the first 3 months were liver cancer, pancreatic cancer, and MPNs. In addition to this highly elevated short-term risk, the patients remained at a two-fold higher risk of being diagnosed with cancer one or more years of after the SVT. In the prognostic analysis, the mortality was higher for liver cancer and pancreatic cancer patients with SVT at 3 months, and SVT remained a poor prognostic indicator for liver cancer up to 1 year. However, our results did not reveal whether the increased mortality was a direct cause of SVT or other underlying characteristics.

Study V was based on 1,915 patients with SVT and 18,267 comparison persons from the general population matched for several chronic diseases. We calculated mortality risks and MRR for the overall cohort and several subgroups. Overall, SVT patients had markedly higher 5-year mortality than the comparison group. The absolute risk was substantial for the first 30 days, as well as 31-364 days and 1-5 years. The relative mortality was increased approximately 40-fold for SVT patients, and though the excess mortality decreased, the patients remained at a two-fold increased risk 5 years after the event. We also noted some variations in prognosis for different types of thrombosis.

In conclusion, we showed that liver cirrhosis is a risk factor for VTE and is associated with increased 30-day mortality after DVT and PE. We demonstrated that, similar to the general population, VTE is a marker of occult cancer in patients with liver disease. We found that a diagnosis of SVT is a predictor of occult cancer, particularly liver and pancreatic cancer, as well as MPNs. We also provided evidence of SVT as a prognostic factor for short-term survival in patients with liver and pancreatic cancer. Finally, we showed that patients with SVT have markedly higher short- and long-term mortality than patients with similar underlying disease without SVT.

8. DANSK RESUMÉ

Denne afhandling bygger på resultater fra fem studier, der alle er udført som nationale register-baserede studier. Målet med afhandlingen var at udvide forståelsen af venøse blodpropper hos patienter med leversygdom, herunder belyse om leversygdom er en risiko faktor for venøse blodpropper og om leversygdom påvirker overlevelsen efter venøse blodpropper. Derudover, var målet at opnå viden og indsigt i det kliniske forløb efter venøse blodpropper i maveregionen, herunder særligt risikoen for kræft og død.

Den første undersøgelse byggede på næsten 100.000 patienter med venøse blodpropper i ben eller lunge og 5 gange så mange kontroller fra baggrundsbefolkningen. Selv efter vi tog højde for alvorlige underliggende sygdomme hos personerne i undersøgelsen, fandt vi at patienter med leversygdom havde en næsten dobbelt så stor risiko for venøse blodpropper sammenlignet med baggrundsbefolkningen.

Den anden undersøgelse var baseret på næsten 4.500 patienter venøse blodpropper i ben, lunge, eller maveregion, hvoraf 745 også havde skrumpelever. Vi fulgte personerne fra indlæggelse med blodproppen og 30 dage frem. Vi fandt at personer med skrumpelever havde en ca. dobbelt så stor dødelighed efter blodprop i ben og lunge sammenlignet med patient gruppen uden skrumpelever. Det så ikke ud til at skrumpelever påvirkede 30-dages dødeligheden efter en blodprop i maveregionen, men dødeligheden var betydelig både blandt personer med og uden skrumpelever. Vi fandt også at personer med skrumpelever var mindre tilbøjelige til at få behandling med blodfortyndende medicin.

Det tredje studie var en undersøgelse af 2.755 patienter med lever sygdom, der fik ny diagnosticeret venøs trombose i ben eller lunge. Vi sammenlignede forekomsten af kræft efterfølgende med det vi havde forventet ud fra kræft forekomsten i baggrundsbefolkningen. Det var særligt lever kræft og andre kræftformer i mavetarm regionen der var en overhyppighed af. Dvs. også blandt patienter med leversygdom, kan en venøs blodprop således være tegn på underliggende kræft.

Den fjerde undersøgelse inkluderede ca. 1200 patienter med en venøs blodprop i maveregionen. Vi fulgte patienterne fra diagnose tidspunktet, og især indenfor de første 3 måneder var der en markant større forekomst af kræft end vi forventede, men overhyppigheden af kræft varede ved mere end et år efter diagnosen af blodproppen. Vi viste også, at de blodproppatienter, der efterfølgende fik diagnosticeret kræft havde en dårligere overlevelse end andre patienter med samme kræfttyper uden forudgående blodprop. Det kan dog ikke umiddelbart udledes at den forøgede dødelighed skyldes blodproppen i sig selv, idet underliggende faktorer hos patienterne også kan have medvirkende årsag.

Den femte undersøgelse var baseret på næsten 2.000 patienter med venøs blodprop i maveregionen og næsten 10 gange så mange kontroller fra baggrundsbefolkningen (matched på underliggende kroniske sygdomme). Vi undersøgte om personer med disse særlige blodpropper i maveregionen havde en ringere overlevelse end tilsvarende personer i en sammenligningsgruppe. Vi fandt at patienterne havde en markant højere dødelighed, særligt indenfor de første 30 dage, men den forblev forøget mere en 5 år efter indlæggelsen for blodproppen.

Sammenfattende fandt vi således at leversygdom kan være en risiko factor for at udvikle venøs blodprop i ben og lunge, og også hænge sammen med en forøget 30-dages dødelighed efter disse blodpropper. Hos patienter med leversygdom, kan en venøs blodprop være tegn på underliggende kræft. Derudover kan venøse blodpropper i maveregionen også bruges til at forudsige at patienten har stor risiko for at have en udiagnosticeret kræft eller udvikle kræft på længere sigt, og måske også forudsige en ringere overlevelse efter kræft. Endeligt viste vi i denne afhandling at disse blodpropper i maveregionen er forbundet med en høj dødelighed, selv om der tages højde for at personerne har en høj forekomst af kroniske sygdomme.

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10. APPENDIX

The Appendix includes the full versions of studies I-V.

Study I

Study II

Study III

Study IV

Study V

Study I

Risk of Venous Thromboembolism in Patients With Liver Disease: A Nationwide Population-Based Case–Control Study

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OBJECTIVES: **It is known that liver disease can cause an imbalance in the coagulation system, but available data on liver disease and risk of venous thromboembolism are conflicting. We examined the risk of venous thromboembolism in patients hospitalized with liver diseases.**

METHODS: **We conducted a nationwide Danish case–control study of incident cases of venous thromboembolism from 1980 to 2005 using population-based data from the National Registry of Patients, and from the Civil Registration System. We used conditional logistic regression to compute the relative risk of venous thromboembolism in patients with liver disease compared to population controls. We then excluded patients with known malignancy (diagnosed either before or up to 3 months after the venous thromboembolism) or fractures, trauma, surgery, or pregnancy within 90 days before the venous thromboembolism to estimate the risk associated with unprovoked venous thromboembolism.**

RESULTS: **A total of 99,444 patients with venous thromboembolism and 496,872 population controls were included in the study. Patients with liver disease had a clearly increased relative risk of venous thromboembolism, varying from 1.74 (95% CI, 1.54–1.95) for liver cirrhosis to 1.87 (95% CI, 1.73–2.03) for non-cirrhotic liver disease. The risks were higher for deep venous thrombosis compared with pulmonary embolism. In the analysis, restricted to 67,519 patients with unprovoked venous thromboembolism and 308,614 population controls, we found slightly higher relative risks: 2.06 (95% CI, 1.79–2.38) for liver cirrhosis and 2.10 (95% CI, 1.91–2.31) for non-cirrhotic liver disease.**

CONCLUSIONS: **Patients with liver disease have a substantially increased risk of venous thromboembolism.**

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INTRODUCTION

Venous thrombosis and its complications (pulmonary embolism and post-thrombotic syndrome) are common (incidence = 1 per 1,000 persons per year) and have a high mortality rate (1–5). Among established risk factors are fractures, recent surgery, malignant disease, pregnancy, use of estrogens, and use of antipsychotic drugs (1,2,6–9). Approximately 0.5% of hospital admissions for patients with liver cirrhosis are associated with a venous thromboembolic event (10).

Patients with liver cirrhosis have endogenous coagulopathy and thrombocytopenia (11), and it has been suggested that they have a reduced risk for venous thromboembolism (VTE) (6). However, the evidence is limited to two studies with conflicting results. In a small case–control study from the United States, Heit *et al.* (6) found a substantially reduced relative risk of 0.10 of VTE in patients with serious liver disease. In contrast, a recent case–control study from Britain found a nonsignificantly increased relative risk 1.65 of VTE in patients with chronic liver

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disease (9). The studies were not designed specifically to examine the risk of VTE associated with liver diseases.

Information on the association between VTE and liver disease is needed to better understand the clinical course of liver patients and the role of the liver in maintaining hemostasis. We, therefore, undertook a nationwide population-based case–control study to determine if liver disease is associated with an increased or decreased risk of VTE.

METHODS

We used the Danish National Registry of Patients, which contains records on 99.4% of all hospital discharges since 1 January 1977 (12), and the Danish Civil Registration System. The civil registration number, a personal identifier assigned to all Danes at birth, links records across registries.

Cases of venous thromboembolism

The Danish National Registry of Patients records civil registration numbers, dates of hospital admission and discharge, surgical procedures, and up to 20 discharge diagnoses. The discharge diagnoses are classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter (12). Of the registered discharge diagnoses one is registered as primary and the others as secondary (12). We searched the Registry for all discharge diagnoses of deep venous thrombosis in the lower limb (code 451.00 in ICD-8 and code I80.1–I80.3 in ICD-10), and pulmonary embolism (code 450.99 in ICD-8 and codes I26.0 and I26.9 in ICD-10) between 1 January 1980 and 31 December 2005.

The start date was chosen to avoid considering prevalent VTE cases that had occurred before the Registry's establishment as incident cases. If a patient had had several VTE hospitalizations, the date of the first VTE diagnosis was used. We included 99,444 patients with a first recorded hospitalization for deep venous thrombosis in the lower limb or for a pulmonary embolism (primary as well as secondary discharge diagnoses). The diagnostic approach to VTE has been previously described (13).

We first assessed the association between liver disease and overall risk of VTE and then conducted a separate analysis for unprovoked VTE. We defined unprovoked VTE as occurring in patients without a diagnosis of cancer before or within 90 days after the thromboembolic event, as well as in patients without a discharge diagnosis of fractures, trauma, surgery, or pregnancy within 90 days before the hospitalization for VTE (14).

Population controls

For each case we selected five population controls from the Danish Civil Registration System, matched by age, gender, and county. This Registry is updated daily and maintains electronic records on vital status (dead or alive), date of death, and the residence of all Danish citizens since 1 April 1968. The controls were selected using risk set sampling (15) and assigned an index date identical to the VTE admission date for the matched case. Thus, in addition to fulfilling the matching criteria, the controls had to be alive on the index date and must not have had a VTE before this date. A total of 496,872 population controls were included in the study.

Liver diseases

On the basis of diagnoses in the Danish National Registry of Patients, we defined two groups according to expected severity of liver disease: (i) Liver cirrhosis and (ii) non-cirrhotic liver disease. We included all discharge diagnoses of liver disease from 1 January 1977 until the date of VTE diagnosis among patients or the index date among controls. Patients with a liver transplant were excluded. The diagnosis codes used in the study are provided in the Appendix.

Confounders

To classify patients as having unprovoked VTE, we collected data on cancer, fractures, trauma, surgery, and pregnancy from the Danish National Registry of Patients. We also retrieved data on diagnoses included in the Charlson Index, as a measure of the overall burden of illness among cases and controls. As well, we retrieved data on obesity (1,2,16–19) and psychiatric diseases (as a marker of antipsychotic drug use) (2,20,21), which have been reported as risk factors for VTE. Only diagnoses recorded before the admission date for VTE, or the index date for controls, were included. The relevant diagnosis codes used are provided in the Appendix.

Statistical analyses

We analyzed the data first by constructing contingency tables for the main study variables. We used conditional logistic regression to compute odds ratios, as a measure of relative risks, of VTE for patients with liver disease compared to patients without liver disease. We then stratified by gender, age category (≤54, 55–74, and 75+ years), and 5-year intervals (1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2005) and conducted a separate analysis on unprovoked VTE. We also fitted conditional logistic regression models, and used polytomous logistic regression to determine if relative risks differed for deep venous thrombosis and pulmonary embolism after adjustment for covariates, age, and gender. We used Wald statistics to compute *P* values for the difference in risk between deep venous thrombosis and pulmonary embolism.

In addition, the analysis using all VTE events was adjusted for cancer, recent fractures, trauma, surgery, and pregnancy. Because of our use of risk set sampling, the odds ratios are unbiased estimates of corresponding rate ratios in a similar cohort study (22,23).

RESULTS

Descriptive data

All patients with venous thromboembolism. For the overall case–control analysis, we identified 99,444 individuals

Table 1. Characteristics of all patients with VTE and population controls

Variable	Venous thromboembolism cases (%), *N*=99,444	Population controls (%), *N*=496,872
Female	52,344 (52.6)	261,470 (52.6)
Male	47,100 (47.4)	235,402 (47.4)
≤54	23,217 (23.4)	116,121 (23.4)
55–74	41,064 (41.3)	205,316 (41.3)
≥75	35,163 (35.4)	175,435 (35.3)
Liver cirrhosis	544 (0.6)	1,058 (0.2)
Non-cirrhotic liver disease	1,109 (1.1)	2,211 (0.4)
Cancer	16,758 (16.9)	31,005 (6.2)
Fractures or trauma	8,799 (8.9)	6,443 (1.3)
Surgery	13,577 (13.7)	10,331 (2.1)
Pregnancy	840 (0.8)	727 (0.2)
Psychiatric diseases	4,425 (4.5)	9,731 (2.0)
Obesity	3,452 (3.5)	6,134 (1.2)

Table 2. Charlson Index diseases among all patients with VTE and population controls

Variable	Venous thromboembolism cases (%), *N*=99,444	Population controls (%), *N*=496,872
Myocardial infarction	6,723 (6.8%)	17,817 (3.6%)
Congestive heart failure	7,292 (7.3%)	13,675 (2.8%)
Peripheral vascular disease	5,521 (5.6%)	11,287 (2.3%)
Cerebrovascular disease	8,530 (8.6%)	25,870 (5.2%)
Dementia	1,385 (1.4%)	4,918 (1.0%)
Chronic pulmonary disease	8,500 (8.6%)	19,212 (3.9%)
Connective tissue disease	3,702 (3.7%)	8,677 (1.8%)
Ulcer disease	4,835 (4.9%)	15,014 (3.0%)
Diabetes type 1 and 2	5,304 (5.3%)	14,159 (2.9%)
Diabetes with end-organ damage	1,702 (1.7%)	4,248 (0.9%)
Hemiplegia	473 (0.5%)	981 (0.2%)
Renal disease	1,795 (1.8%)	3,284 (0.7%)
AIDS	104 (0.1%)	57 (0.01%)

with VTE (53,514 with deep venous thrombosis and 45,930 with pulmonary embolism) and 496,872 population controls. Among both cases and controls, there were slightly more women than men and one-third were older than 75 years. VTE patients had a higher prevalence of all risk factors compared to controls (**Tables 1** and **2**).

Patients with unprovoked venous thromboembolism. In the case–control analysis of unprovoked VTE, we identified 67,519 cases with VTE (36,959 with deep VTE and 30,560 with pulmonary embolism) and 308,614 population controls. Slightly more cases were women than men and one-third of both cases and controls were older than 75 years. Similar to all VTE cases, patients with unprovoked VTE had a higher prevalence of all comorbidities (data not presented) and liver diseases (**Table 3**) compared to population controls.

Table 3. Characteristics of patients with unprovoked VTE and population controls

Variable	Venous thromboembolism cases (%), *N*=67,519	Population controls (%), *N*=308,614
Female	34,539 (51.2)	156,240 (50.6)
Male	32,980 (48.9)	152,374 (49.4)
Age ≤54	16,483 (24.4)	79,011 (25.6)
Age 55–74	27,811 (41.2)	128,336 (41.6)
Age ≥75	23,225 (34.4)	101,267 (32.8)
Liver cirrhosis	353 (0.5)	570 (0.2)
Non-cirrhotic liver disease	758 (1.1)	1,232 (0.4)

Risk of venous thromboembolism

All patients with venous thromboembolism. Compared with the general population controls, patients with liver disease had an approximately doubled risk of VTE, varying from 1.74 (95% CI, 1.54–1.95) for patients with liver cirrhosis to 1.87 (95% CI, 1.73–2.03) for patients with non-cirrhotic liver disease, after adjustment (**Table 4**). Among liver cirrhosis cases the adjusted relative risk was 2.02 (95% CI, 1.78–2.31) for deep venous thrombosis and 1.41 (95% CI, 1.20–1.65) for pulmonary embolism ($P<0.0001$). For patients with non-cirrhotic liver disease the adjusted relative risk was 2.15 (95% CI, 1.97–2.36) for deep venous thrombosis and 1.33 (95% CI, 1.18–1.49) for pulmonary embolism ($P<0.0001$).

The relative risk was similar in a sub-analysis of patients with hepatocellular carcinoma within the group of patients with liver cirrhosis (1.75 (95% CI, 1.56–1.97)). To examine whether antithrombotic prophylaxis affected the risk, we conducted a sub-analysis stratifying the data by 5-year intervals. This indicated decreasing risk over time, with the highest risk in the period 1990–1994 (**Table 5**).

Patients with unprovoked venous thromboembolism. The relative risks of unprovoked VTE were approximately 15% higher than the risks of any VTE (**Table 4**): 2.06 (95% CI, 1.79–2. 38) in patients with liver cirrhosis and 2.10 (95% CI,

Table 4. Relative risks[a] (odds ratios) and 95% CIs for VTE

	All venous thromboembolism		Unprovoked venous thromboembolism	
Variable	Crude RR	Adjusted[b] RR	Crude RR	Adjusted[c] RR
Liver cirrhosis	2.60 (2.34–2.88)	1.74 (1.54–1.95)	2.88 (2.52–3.29)	2.06 (1.79–2.38)
Non-cirrhotic liver disease	2.54 (2.36–2.73)	1.87 (1.73–2.03)	2.84 (2.59–3.11)	2.10 (1.91–2.31)
Liver cirrhosis and HCC	2.64 (2.38–2.93)	1.75 (1.56–1.97)	2.90 (2.54–3.32)	2.08 (1.81–2.40)

HCC, hepatocellular carcinoma.
[a]Computed with conditional logistic regression. [b]Adjusted for cancer, fractures, trauma, surgery, pregnancy, Charlson Index, psychiatric diseases, and obesity. [c]Adjusted for Charlson Index, psychiatric diseases, and obesity.

Table 5. Relative risks[a] (odds ratios) and 95% CIs for all VTE cases, stratified by 5-year intervals

	All venous thromboembolism (cirrhosis)		All venous thromboembolism (non-cirrhotic liver disease)	
Variable	Crude RR	Adjusted[b] RR	Crude RR	Adjusted[b] RR
Year 1980–1984	2.93 (2.28–3.77)	1.72 (1.30–2.30)	2.36 (1.84–3.03)	1.54 (1.16–2.05)
Year 1985–1989	2.50 (1.96–3.21)	1.71 (1.30–2.27)	2.49 (2.05–3.04)	1.82 (1.46–2.27)
Year 1990–1994	2.90 (2.28–3.70)	1.99 (1.51–2.61)	3.15 (2.63–3.77)	2.31 (1.89–2.82)
Year 1995–1999	2.27 (1.78–2.89)	1.59 (1.22–2.06)	2.90 (2.48–3.39)	2.17 (1.83–2.58)
Year 2000–2005	2.53 (2.08–3.07)	1.71 (1.38–2.12)	2.23 (1.99–2.50)	1.67 (1.47–1.90)

[a]Computed with conditional logistic regression. [b]Adjusted for cancer, fractures, trauma, surgery, pregnancy, Charlson Index, psychiatric diseases, and obesity.

1.91–2.31) in patients with non-cirrhotic liver disease. The relative risks were slightly higher in men than women and in patients younger than 55 years. The adjusted relative risks varied from 3.32 (95% CI, 2.83–3.89) in patients aged less than 55 years with non-cirrhotic liver disease to 3.58 (95% CI, 2.62–4.88) in patients in this age group with liver cirrhosis (data not presented). Similar risks were found in a sub-analysis stratified on whether the diagnosis of VTE was primary or secondary (data not presented).

DISCUSSION

This large nationwide population-based case–control study provided strong evidence that all categories of liver disease were associated with an increased risk of VTE, regardless of the presence of other risk factors.

Our findings differ from those of a smaller case–control study of 625 VTE cases and 625 population controls. In that study, hepatitis and liver cirrhosis were combined into one category. The study showed a substantially reduced risk of VTE of 0.10 (95% CI, 0.01–0.71) (6), but was based on very few exposed cases and therefore resulted in an imprecise relative risk estimate. In a recent study based on data from general practices in the UK, including 6,550 VTE patients and 10,000 population controls, Huerta *et al.* (9) reported an increased relative risk of 1.65 (95% CI, 0.97–2.82). As in our study, adjustments were made for potential confounding factors in the statistical analyses. However, only one category was used for all chronic liver diseases combined.

Our study's major strengths are its population-based design, large size, complete follow-up, and nationwide coverage. The tax-supported National Health Service eliminates referral bias. There was no information bias as data were collected for purposes independent of our study. Still, the accuracy of our findings depends on the quality of the coding of VTE and liver disease diagnoses and comorbidities. This has been evaluated in previous studies of the Danish National Registry of Patients (24,25). The predictive value of coding diseases compared to diagnoses confirmed by scrutiny of clinical records has been shown to be 90% for pulmonary embolism (26) and slightly lower for venous thrombosis and liver diseases (26,27). However, any deficit in coding specificity would bias our risk estimates toward the null (28), so that the estimates we report are minimum estimates in that respect. This notwithstanding, there may be nondifferential misclassification between the two categories of liver disease, which would have the effect of leveling out the risk estimates for different liver diseases, but could not in itself explain the similarity of the estimates.

Data on confounding variables were collected from the Danish National Registry of Patients, and had a high validity for most of the included covariates (12). In accordance with the procedure used in another epidemiologic study (14), exclusion of diagnoses of cancer, fractures, trauma, and pregnancy, together with surgical procedures, was used to define

unprovoked VTE. Although we did not have data on lifestyle factors such as smoking and alcohol intake, there is no firm evidence that these are risk factors for VTE (6,9).

We cannot specify the mechanism by which liver disease increases the risk of VTE. However, both endogenous changes associated with liver disease and external factors may be involved. Northup *et al.* (10) recently showed that severity of liver disease, as reflected in low serum albumin, was a predictor for developing thromboembolic events. This may indicate that the liver also produces low amounts of anticoagulants. It is well established that exogenous estrogens are a risk factor for venous thrombosis (29–31) and endogenous estrogen levels are elevated in cirrhosis (32,33). Recently, the metabolic syndrome has been implicated as a risk factor for VTE (34), and nonalcoholic fatty liver disease and to some extent cirrhosis of unknown etiology are considered hepatic manifestations of this syndrome (35,36): our patients with non-cirrhotic liver disease indeed had higher frequencies of diabetes and obesity. It is also likely that the immobility associated with liver disease, secondary to or contributing to muscle weakness (37), increases the risk of VTE. Cirrhosis patients have a markedly increased frequency of severe infective and hemorrhagic complications (38), and it is well known that all severely ill patients have a substantially increased risk of deep venous thrombosis (39,40). As information on Child–Pugh scores was not available, it was not possible to subclassify cirrhosis patients, and to examine the impact of the severity of cirrhosis.

We found decreasing risks of VTE over time both for cirrhosis and non-cirrhotic liver disease; this may be because of the now standard use of antithrombotic prophylaxis (41).

In any case, it is remarkable that the risk estimates were nearly identical for the categories of liver disease, although, as expected, patients belonging to each category have very different degrees of metabolic disturbances and frequency of complications. As discussed above, the similarity of risk estimates is probably not entirely an artifact, and makes it difficult to suggest any mechanism common to all liver patients.

VTE is associated with significant short-term mortality (9), and liver disease is a relative contraindication for anticoagulation therapy. In the clinical handling of patients with liver disease, absolute risk estimates of VTE would be useful, but cannot be derived form this case–control study. Furthermore, the lack of clinical detail in our data prevents us from providing guidelines on this important issue.

In conclusion, our study shows that liver diseases are strong risk factors for VTE, and that other unidentified risk factors for venous thrombosis supersede any decrease in coagulation associated with liver disease.

CONFLICTS OF INTEREST

Guarantor of the article: Kirstine K. Søgaard, MD.

Specific author contributions: Kirstine K. Søgaard participated in the design of the study, the analysis, and the interpretation of results, and has drafted the paper. Erzsébet Horváth-Puhó contributed to the design of the study and to the analysis and interpretation of the data. Peter Jepsen participated in the analysis and interpretation of data, and revised the paper. Henning Grønbæk participated in the interpretation of results and revised the paper. Hendrik Vilstrup participated in the interpretation of results, and critically revised the paper. Henrik T. Sørensen participated in the design of the study, organized the statistical analysis, assisted in the interpretation of results, and critically revised the paper. All authors read and approved the final paper.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Liver disease can cause imbalances in the coagulation system.
- ✓ Existing studies of the association between liver disease and venous thromboembolism are few and conflicting.

WHAT IS NEW HERE

- ✓ All sorts of liver diseases are risk factors for VTE.

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APPENDIX

ICD CODES

Outcome:

Deep venous thrombosis in the lower limb (ICD-8: 451.00) (ICD-10: I80.1–I.80.3)

Pulmonary embolism (ICD-8: 450.99) (ICD-10: I26.0, I26.9)

Exposures:

Reference group: no liver disease.

(1) Liver cirrhosis:

Cirrhosis hepatitis, nonalcoholic (ICD-8: 571.09)

Alcoholic liver cirrhosis (ICD-10: K70.3)

Nonalcoholic liver cirrhosis (ICD-8: 571.90–571.92, 571.99; ICD-10: K71.7, K74.3, K74.4, K74.5, K74.6)

(2) Non-cirrhotic liver disease:

Steatosis hepatis alcoholica (ICD-8: 571.10)

Alcoholic liver disease excluding cirrhosis (ICD-10: K70.0- K70.9 excluding K70.3)

Nonalcoholic liver disease excluding cirrhosis (ICD-8: 570.00–573.09 excluding 571.09, 571.10, 571.90–571.92, 571.99; ICD-10: R74.0, K71.0–K77.8 excluding K71.7, K74.3, K74.4, K74.5, K74.6)

Hepatitis viralis (ICD-8: 70.01–70.09; ICD-10: B15–B19)

Confounders:

Cancer (ICD-8: 140–209; ICD-10: C00–C99)

Fractures or trauma (ICD-8: 800–929, 950–959; ICD-10: S00–T14)

Pregnancy or delivery (ICD-8: 630–680; ICD-10: O00–O99)

Disease included in the Charlson Index:

Myocardial infarction (ICD-8: 410; ICD-10: I21–I23)

Heart failure (ICD-8: 42709–42711, 42719, 42899, 78249; ICD-10: I50, I110, I130, I132)

Peripheral vascular disease (ICD-8: 440–445; ICD-10: I70–I74, I77)

Cerebrovascular disease (ICD-8: 430–438; ICD-10: I60–I69, G45, G46)

Dementia (ICD-8: 29009–29019, 29309; ICD-10: F00–F03, F051, G30)

Chronic obstructive pulmonary disease (ICD-8: 490–493, 515–518; ICD-10: J40–J47, J60–67, J684, J701, J703, J841, J920, J961, J982, J983)

Connective tissue disease (ICD-8: 712, 716, 734, 446, 13599; ICD-10: M05, M06, M08, M09, M30–M36, D86)

Ulcer disease (ICD-8: 53091, 53098, 531–34; ICD-10: K221, K25–28)

Diabetes (ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9)

Diabetes with end-organ damage (ICD-8: 249.01–249.05, 249.08, 250.01–250.05, 250.08; ICD-10: E10.2-E10.8, E11.2–E11.8)

Hemiplegia (ICD-8: 344; ICD-10: G81, G82)

Renal disease (ICD-8: 403, 404, 580-584, 59009, 59319, 75310-75319, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-19, Q61)

AIDS (ICD-8: 079.83; ICD-10: B21–24)

Psychiatric diseases (ICD-8: 291–301, 304; ICD-10: F10.4–F10.9, F11-F69)

Obesity (ICD-8: 277.99; ICD-10: E66)

Study II

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Cirrhosis is Associated with an Increased 30-Day Mortality After Venous Thromboembolism

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OBJECTIVES: Patients with cirrhosis are at increased risk of venous thromboembolism (VTE), but the impact of cirrhosis on the clinical course following VTE is unclear. In a nationwide cohort study, we examined 30-day mortality among patients with cirrhosis and VTE.

METHODS: We used Danish population-based health-care databases (1994–2011) to identify patients with incident VTE, i.e., deep venous thrombosis (DVT), pulmonary embolism (PE), and portal vein thrombosis (PVT). Among these, we identified 745 patients with cirrhosis and 3647 patients without cirrhosis (matched on gender, year of birth, calendar year of VTE diagnosis and VTE type). We assessed the 30-day mortality risk among VTE patients with and without cirrhosis, and the mortality rate ratios (MRRs), using an adjusted Cox model with 95% confidence interval. We obtained information on immediate cause of death for patients who died within 30 days after VTE.

RESULTS: The 30-day mortality risk for DVT was 7% for patients with cirrhosis and 3% for patients without cirrhosis. Corresponding PE-related mortality risks were 35% and 16%, and PVT-related mortality risks were 19% and 15%, respectively. The adjusted 30-day MRRs were 2.17 (1.24–3.79) for DVT, 1.83 (1.30–2.56) for PE, and 1.30 (0.80–2.13) for PVT. Though overall mortality was higher in patients with cirrhosis than patients without cirrhosis, the proportions of deaths due to PE were similar among patients (25% and 24%, respectively).

CONCLUSIONS: Cirrhosis is a predictor for increased short-term mortality following VTE, with PE as the most frequent cause of death.

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INTRODUCTION

Deep venous thrombosis (DVT) is a common medical event with 30-day mortality between 3 and 30%, depending on whether pulmonary embolism (PE) develops.[1] By contrast, portal vein thrombosis (PVT) is less common, but a potential serious condition with 30-day mortality varying from ~3 to 50%.[2] Patients with venous thromboembolism (VTE) often have underlying comorbidities that may increase their risk of dying from a thrombotic event. In a large population-based cohort study of patients with DVT or PE, we recently examined the effect of several comorbidities on mortality after thrombosis.[1] In stratified analyses, only presence of cancer, diabetes, and chronic liver disease yielded higher mortality rates after the thrombotic event, compared with absence of these factors.[1] Among patients with PVT, prevalent cancer or cirrhosis are predictors of increased mortality.[2,3]

Patients with cirrhosis are at increased risk of DVT and PE compared with the general population.[2,4–6] This increased risk of thrombosis is likely due to a combination of external factors among cirrhosis patients (immobilization, surgical procedures, severe infections and a high comorbidity burden)[7,8] and intrinsic factors (disturbance of the coagulation system and increased estrogen levels).[7–9] In addition, local factors may result in venous stasis (e.g., compression by a solid tumor, abscess, or by hepato- or splenomegaly) causing PVT. Cirrhosis in itself has a grave prognosis because of cirrhosis-related complications and comorbidities.[10,11] In case of venous thrombosis in patients with cirrhosis, initiation of standard treatment with anticoagulant medications may be impeded considering their increased bleeding tendency. Therefore, it is important to know whether cirrhosis affects mortality after venous thrombosis.

We undertook this nationwide cohort study to examine whether cirrhosis affects 30-day mortality after DVT, PE, or PVT, clarifying the clinical course of venous thrombosis among patients with cirrhosis.

METHODS

Setting and data sources. This nationwide cohort study was conducted in Denmark during 1994–2011, within a total underlying cohort of 7.1 million people. It was based on data from the Danish National Patient Registry (DNPR), which contains information on all hospitalizations since 1977 and on outpatient and emergency room visits since 1995.[12] Recorded information includes civil registration number (unique personal identifier assigned to all Danish citizens),[13] dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses. Discharge diagnoses are coded according to the *International*

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Classification of Diseases, 8th revision, until the end of 1993 and 10th revision thereafter. From the Danish National Health Service Prescription Database,[14] we ascertained data on use of anticoagulant medication (vitamin K antagonist (VKA) and low-molecular-weight heparin (LMWH)) in our cohort since 2004 coded according to the *Anatomical Therapeutic Chemical* classification.

The DNPR can be linked to the Danish Civil Registration System, which, in addition to issuing civil registration numbers, has monitored deaths and emigration from the country since 1968.[15]

We used the Danish Register of Causes of Death[16] to obtain information on causes of death for patients with VTE. The register contains information from all Danish death certificates since 1943, coded according to the Danish version of the *International Classification of Diseases* (ICD-8 from 1972 through 1993, and ICD-10 from 1994 through 2011).

VTE cohorts. We searched the DNPR for all hospital discharge diagnoses of DVT, PE, and PVT. We also included hospital outpatient clinic diagnoses, since an increasing proportion of VTE patients are treated only in the outpatient setting.[17] Patients diagnosed only in emergency departments were excluded ($n=12{,}184$) owing to the expected low positive predictive value of diagnoses in this setting.[18] Patients who were diagnosed with a VTE during 1977–1993 also were excluded, to avoid cases of recurrent thrombosis or complications of previous VTE.

Based on medical history preceding a hospital contact for VTE or on status at the time of this contact, as recorded in the DNPR, we identified patients with cirrhosis and patients without cirrhosis registered (comparison cohort). Cirrhosis was further classified as alcoholic, biliary (primary, secondary, and non-specified biliary cirrhosis), and other or non-specified cirrhosis. Because of substantial differences in baseline characteristics among patients with cirrhosis and patients in the comparison cohort, we matched the VTE patients with and without cirrhosis by age, gender, calendar year of VTE diagnosis, and type of VTE. We were able to match 96% ($n=713$) of patients with cirrhosis with five patients each in the comparison cohort.

Covariates. From the DNPR we obtained information on several covariates that are established risk factors for VTE or predictors of VTE-related mortality. Classical risk factors include cancer (diagnosed prior to the thromboembolic event or on the date of the VTE-related hospital contact), fracture or trauma, and surgical procedures (registered within 90 days before the hospital contact for VTE).[19] As a measure of overall morbidity status, we characterized patients using the diseases included in the Charlson Comorbidity Index (except the categories mild and severe liver disease) diagnosed at any time before the thrombotic event (low comorbidity level = Charlson Comorbidity Index score of 0, moderate comorbidity level = Charlson Comorbidity Index score of 1–2, and severe comorbidity level = Charlson Comorbidity Index score of 3 or higher).[20,21]

We also examined diagnoses or conditions related to VTE and/or cirrhosis that may affect 30-day mortality after VTE. These were heart failure, chronic pulmonary disease, ulcer disease, diabetes, alcoholism-related disease, psychiatric disorders, and obesity.[22–25] Patients with cirrhosis are prone to infections because of their compromised immune system,[26] and prevalent infections have a strong impact on prognosis.[27] We therefore also included infections diagnosed during the VTE-related hospital contact (i.e., pneumonia, urinary tract infections, and skin, soft tissue, and bone infections). To further characterize VTE patients with cirrhosis, we collected information on previous or concurrent diagnoses of gastroesophageal varices with and without bleeding. Finally, we retrieved information on post-discharge use of VKA and LMWH from the prescription database.

Mortality data. We ascertained the vital status of the VTE patients from the Danish Civil Registration System[13] and the specific immediate cause of death from the Danish Register of Causes of Death.[16] Patients who died on the day of their VTE-related hospital contact were included, assuming 0.5 days of follow-up. All codes used in the study are provided in the Supplementary Appendix S1 (published online).

Statistical analysis. We calculated the frequency of demographic variables (gender, age categories (<55 years, 55–75 years, and >75 years), calendar-year periods (1994–1999, 2000–2005, and 2006–2011)) at VTE diagnosis, as well as the frequency of comorbidities diagnosed at any time before the VTE diagnosis.

We followed the patients from the date of their first VTE-related hospital contact until date of death from any cause, 30 days of follow-up, emigration, or censoring on 31 December 2011, whichever came first. The Kaplan–Meier survival method was used to compute 30-day mortality risk after DVT, and/or PE, and PVT among patients with and without cirrhosis. We used Cox proportional hazards regression to compute 30-day mortality rate ratios (MRRs) and 95% confidence intervals (CIs) for VTE patients according to presence of cirrhosis. Using log–log plots, we visually confirmed proportionality of hazards for DVT and PE throughout the 30 days of follow-up, whereas there was non-proportionality of the overall follow-up for PVT. Therefore, we divided follow-up after PVT into 0–7 days and 8–30 days. In accordance with the matched design, we also used a stratified Cox regression model (which revealed similar results). We adjusted for gender, age categories, and calendar-year periods (by study design), in addition to the classical risk factors (as described above) and other comorbidities (heart failure, chronic pulmonary disease, ulcer disease, diabetes, alcoholism-related disease, and concurrent infections).

We also conducted analyses stratified according to type of cirrhosis (alcoholic, biliary, and other or non-specified), comorbidity level, and cancer (potential effect modifiers). To quantify whether patients with cirrhosis were less likely than their comparisons to receive treatment with anticoagulant medication post discharge, we used χ^2-test for homogeneity of proportions.

We calculated the proportions of deaths due to PE among patients with and without cirrhosis. For patients with cirrhosis, we described the prevalence of immediate causes of death within 30 days following VTE diagnosis.

Statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Board (record number 1-16-02-1-08 and 2012-41-0793). Danish registry data generally are available for research purposes, and use of the data does not require informed consent according to Danish law.

RESULTS

General characteristics of the study population. The study population of patients with a first-time hospital contact for VTE included 745 patients with cirrhosis and 3647 patients without cirrhosis. Among all 4392 patients, 2514 had DVT (one with PVT and no with PE), 1242 had PE (91 with DVT and three with PVT), and 636 had PVT (without DVT or PE). Among patients with cirrhosis, types of cirrhosis were alcoholic cirrhosis in 537 (72%) patients, biliary cirrhosis in 48 (6%) patients, and other or non-specified cirrhosis in 160 (22%) patients (among these, 13 patients also had a diagnosis of viral hepatitis B or C). Overall, the median time since first cirrhosis diagnosis and VTE was 3 years (interquartile range 0–8). Owing to matching, the gender and age distribution of the study population reflected the characteristics of patients with liver disease. More than half (56%) of study population were men, and only 15% of patients were older than 75 years. Patients with cirrhosis were more likely to have pre-existing comorbidities, compared with patients without liver disease. In particular, cirrhosis patients had a higher prevalence of alcoholism-related diagnoses, chronic pulmonary disease, ulcer disease, diabetes, and psychiatric disorders than patients without cirrhosis (Table 1). Among cirrhosis patients, 25 patients (3%) had previous liver cancer diagnosis and 166 patients (22%) had previous or concurrent diagnosis of gastroesophageal varices ± bleeding. Of note, the frequency of varices was similar among patients who died within 30 days and patients who survived beyond 30 days.

Deep venous thrombosis. Within 30 days of follow-up, DVT patients with cirrhosis were at higher risk of death than DVT patients without cirrhosis (Figure 1). The 30-day mortality risk following a DVT diagnosis was 7% (95% CI: 5–10%) among patients with cirrhosis and 3% (95% CI: 2–3%) among patients without cirrhosis (Table 2). In a subgroup analysis of patients with cancer, 30-day mortality risks were slightly higher in DVT patients with cirrhosis (absolute risk = 15% (95% CI: 8–26%)) compared with DVT patients without cirrhosis (absolute risk = 9% (95% CI: 6–12%)). Cirrhosis increased the risk of dying after a DVT event (adjusted MRR = 2.17 (95% CI: 1.24–3.79)) (Table 2). All types of cirrhosis seemed to increase mortality rates compared with patients without cirrhosis, although for patients with biliary cirrhosis the estimate was based on a small number of deaths (Table 2). The impact of cirrhosis on the relative mortality after DVT was higher among patients without other pre-existing comorbidities than patients with moderate or severe comorbidity level, compared with patients without cirrhosis but with similar comorbidity level (Table 3). Correspondingly, the MRR was higher for patients without previous cancer than in patients with cancer (Table 3), which likely reflects confounding by baseline risk.

Pulmonary embolism. Throughout the 30 days of follow-up, PE patients with cirrhosis had higher mortality risks than PE patients without cirrhosis (Figure 1). The 30-day mortality risk following PE was 35% (95% CI: 29–42%) among patients with cirrhosis and 16% (95% CI: 14–19%) among patients without cirrhosis (Table 2). Among PE patients with cancer, we still found higher 30-day mortality risks in patients with cirrhosis (absolute risk = 45% (95% CI: 31–62%)) than in patients without cirrhosis (absolute risk = 22% (95% CI: 18–28%)). After adjustment, the 30-day MRR was 1.83 (95% CI: 1.30–2.56) in PE patients with cirrhosis compared with PE patients without cirrhosis (Table 2). Alcoholic cirrhosis and other or non-specified cirrhosis were associated with a higher mortality rate, whereas biliary cirrhosis was not (Table 2). Comorbidity level modified mortality risk among cirrhosis patients with PE; i.e., patients without comorbidities had a higher MRR compared with patients with a more severe comorbidity level (Table 3). Similarly, patients without previous cancer had higher MRR than patients with cancer (Table 3).

Portal vein thrombosis. The 30-day mortality risks were almost similar for PVT patients with or without cirrhosis (Figure 1). The risks were 19% (95% CI: 13–28%) among patients with cirrhosis and 15% (95% CI: 12–18%) among patients without cirrhosis (Table 2). For patients with PVT, cirrhosis was not associated with an elevated mortality, and the estimates did not change much after adjustment for potential confounders. The adjusted 30-day MRR was 1.30 (95% CI: 0.80–2.13) in PVT patients with cirrhosis compared with PVT patients without cirrhosis (Table 2). The 7-day MRR was 1.08 (95% CI: 0.49–2.38) and the 8- to 30-day MRR was 1.51 (95% CI: 0.80–2.86). Results from the sub-analysis according to cirrhosis type showed that alcoholic cirrhosis was mainly responsible for the increased MRR after PVT, but the association was not statistically significant (Table 2).

Use of anticoagulant medicine post discharge. Information on post discharge use of medication was available for patients diagnosed after 2004, totaling 430 (58%) patients with cirrhosis and 2111 (58%) patients without cirrhosis. Overall, 145 (34%) patients with cirrhosis and 1160 (55%) without cirrhosis were treated with either VKA or LMWH within 30 days after discharge. In general, more patients with DVT and PE received treatment with VKA than patients with PVT did (Table 1). However, use of VKA was less frequent among VTE patients with cirrhosis than among their corresponding comparison patients without cirrhosis (DVT: 31% vs. 53%, P value < 0.001; PE: 29% vs. 55%, P value < 0.001; PVT: 16% vs. 33%, P value $= 0.004$). Whereas the proportions among PE and PVT patients with and without cirrhosis treated with LMWH were similar (PE: 6% vs. 8%, P value $= 0.472$; PVT: 5% vs. 9%, P value $= 0.225$), more DVT patients with cirrhosis than without cirrhosis were treated with LMWH (9% vs. 6%, P value $= 0.045$).

Table 1 Characteristics of 4392 patients with a first-time diagnosis of venous thromboembolism

	Deep venous thrombosis, *n* (%)		Pulmonary embolism, *n* (%)		Portal vein thrombosis, *n* (%)	
	Cirrhosis *N* = 419	No cirrhosis *N* = 2095	Cirrhosis *N* = 207	No cirrhosis *N* = 1035	Cirrhosis *N* = 119	No cirrhosis *N* = 517
Men	232 (55)	1160 (55)	112 (54)	560 (54)	71 (60)	311 (60)
Age (years)						
<55	143 (34)	693 (33)	36 (17)	181 (17)	36 (30)	142 (27)
55–75	217 (52)	1101 (53)	136 (66)	669 (65)	70 (59)	309 (60)
>75	59 (14)	301 (14)	35 (17)	185 (18)	13 (11)	66 (13)
Calendar period						
1994–1999	101 (24)	529 (25)	40 (19)	208 (20)	16 (14)	67 (13)
2000–2005	155 (37)	752 (36)	55 (27)	286 (28)	36 (30)	152 (29)
2006–2011	163 (39)	814 (39)	112 (54)	541 (52)	67 (56)	298 (58)
Classical risk factors						
Cancer[a]	68 (16)	355 (17)	38 (18)	253 (24)	26 (22)	149 (29)
Surgery	118 (28)	467 (22)	76 (37)	271 (26)	71 (60)	219 (42)
Fracture/trauma	61 (15)	195 (9)	21 (10)	82 (8)	13 (11)	24 (5)
Comorbidity level						
No comorbidity	133 (32)	1189 (57)	55 (26)	448 (43)	43 (36)	189 (37)
Moderate comorbidity	188 (45)	652 (31)	99 (48)	399 (39)	62 (52)	197 (38)
Severe comorbidity	98 (23)	254 (12)	53 (26)	188 (18)	14 (12)	131 (25)
Selected comorbidities						
Congestive heart failure	39 (9)	76 (4)	24 (12)	70 (7)	5 (4)	43 (8)
Chronic pulmonary disease	61 (15)	187 (9)	51 (25)	165 (16)	9 (8)	51 (10)
Ulcer disease	109 (26)	106 (5)	43 (21)	56 (5)	26 (22)	59 (11)
Diabetes	79 (19)	112 (5)	36 (17)	76 (7)	22 (18)	86 (17)
Obesity	36 (9)	122 (6)	20 (10)	69 (7)	4 (3)	36 (7)
Psychiatric disorder	78 (19)	141 (7)	36 (17)	55 (5)	9 (8)	32 (6)
Alcoholism-related disease	242 (58)	126 (6)	105 (51)	55 (5)	35 (29)	65 (13)
Infections	31 (7)	100 (5)	25 (12)	116 (11)	3 (3)	18 (3)
Post discharge medication[b]						
Vitamin K antagonists	67 (31)	575 (53)	39 (29)	373 (55)	13 (16)	117 (33)
Low-molecular-weight-heparins	20 (9)	61 (6)	8 (6)	52 (8)	4 (5)	33 (9)

Owing to matching, the gender and age distribution of the study population reflected the characteristics of patients with liver disease.
[a]Liver cancer accounted for 11 of the cancer cases among cirrhosis patients.
[b]Medication use only available after 2004, analysis restricted to patients surviving discharge. VTE patients with cirrhosis were less likely to receive vitamin K antagonists than their comparisons without cirrhosis (*P* value < 0.001), whereas DVT patients with cirrhosis were more likely to receive low-molecular-weight heparins than their comparisons (*P* value = 0.045).

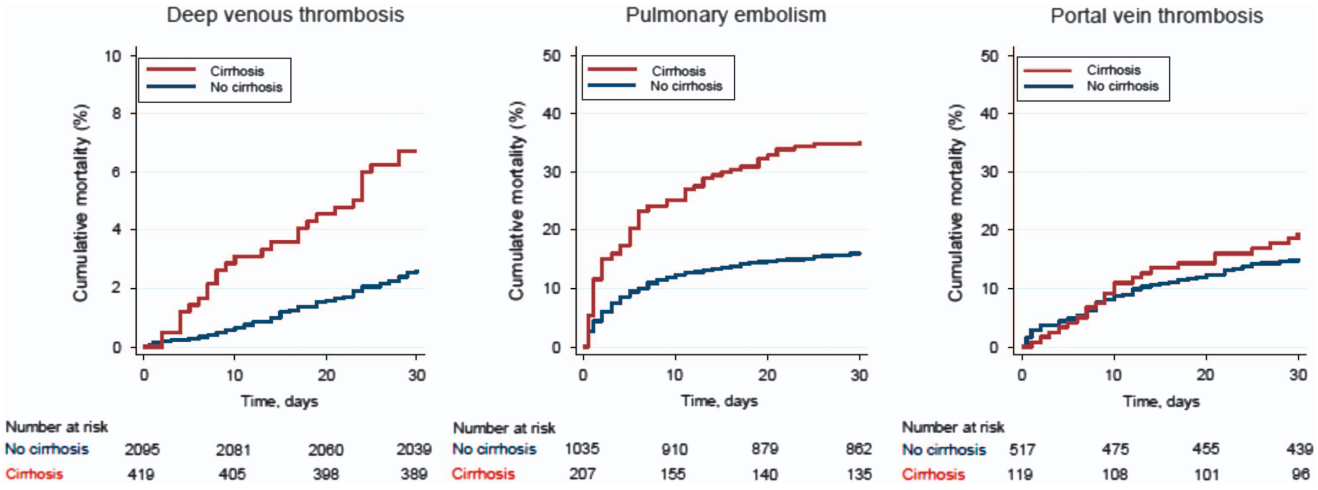

Figure 1 Thirty-day mortality risk (%) among patients with venous thromboembolism. Note that different scales were used for mortality risk (%).

Table 2 Thirty-day mortality among 4392 patients with a first-time diagnosis of venous thromboembolism

	Patients (*n*)	Deaths (*n*)	Mortality risk (%) (95% CI)	Unadjusted MRR[a] (95% CI)	Adjusted MRR[b] (95% CI)
Deep venous thrombosis	*2514*	*83*	*3 (3–4)*	—	—
No cirrhosis	2095	55	3 (2–3)	1.00	1.00
Cirrhosis (all types)	419	28	7 (5–10)	2.65 (1.68–4.17)	2.17 (1.24–3.79)
Alcoholic	320	18	6 (4–9)	2.41 (1.41–4.12)	1.92 (0.91–4.03)
Biliary[c]	22	2	9 (2–32)	3.24 (0.78–13.41)	2.80 (0.67–11.75)
Other or non-specified[d]	77	8	10 (5–20)	3.22 (1.51–6.86)	2.36 (1.06–5.22)
Pulmonary embolism	*1242*	*240*	*19 (17–22)*	—	—
No cirrhosis	1035	167	16 (14–19)	1.00	1.00
Cirrhosis (all types)	207	73	35 (29–42)	2.51 (1.90–3.30)	1.83 (1.30–2.56)
Alcoholic	142	51	36 (29–44)	2.72 (1.98–3.74)	1.76 (1.11–2.77)
Biliary[c]	18	4	22 (9–49)	1.25 (0.46–3.40)	1.00 (0.36–2.75)
Other or non-specified[d]	47	18	38 (26–54)	2.54 (1.55–4.14)	2.30 (1.40–3.78)
Portal vein thrombosis	*636*	*100*	*16 (13–19)*	—	—
No cirrhosis	517	77	15 (12–18)	1.00	1.00
Cirrhosis (all types)	119	23	19 (13–28)	1.34 (0.84–2.13)	1.30 (0.80–2.13)
Alcoholic	75	16	21 (14–33)	1.55 (0.90–2.65)	1.52 (0.84–2.75)
Biliary[c]	8	1	13 (2–61)	0.85 (0.12–6.21)	0.57 (0.08–4.30)
Other or non-specified[d]	36	6	17 (8–33)	1.05 (0.46–2.42)	1.17 (0.50–2.72)

CI, confidence interval; MRR, mortality rate ratio.
[a]Adjusted for matching factors by study design (gender, age, calendar period).
[b]Adjusted for matching factors by study design (gender, age, calendar period), cancer, fracture/trauma, surgery, congestive heart failure, chronic pulmonary disease, diabetes, ulcer disease, alcoholism-related disease, and infection.
[c]Biliary cirrhosis includes primary, secondary, and other or non-specified biliary cirrhosis.
[d]Includes 13 patients with hepatitis B or C virus.

Table 3 Adjusted thirty-day mortality rate ratios among 4392 patients with a first-time diagnosis of venous thromboembolism, stratified analyses

	Adjusted MRR (95% CI)		
	Deep venous thrombosis	Pulmonary embolism	Portal vein thrombosis
No liver disease	1.00	1.00	1.00
Cirrhosis (all types)	2.17 (1.24–3.79)	1.83 (1.30–2.56)	1.30 (0.80–2.13)
Comorbidity[a]			
Low	6.11 (1.34–27.77)	4.13 (1.93–8.87)	3.04 (1.21–7.65)
Moderate	2.21 (0.96–5.09)	1.69 (1.08–2.65)	0.83 (0.39–1.80)
Severe	1.36 (0.60–3.08)	1.05 (0.53–2.09)	1.43 (0.44–4.65)
Cancer[b]			
No	2.94 (1.37–6.31)	2.20 (1.45–3.33)	1.65 (0.91–2.98)
Yes	1.61 (0.72–3.61)	1.69 (0.86–3.32)	0.70 (0.25–1.99)

CI, confidence interval; MRR, mortality rate ratio.
[a]Adjusted for matching factors by study design (gender, age, calendar period), fracture/trauma, surgery, alcoholism-related disease, and infection.
[b]Adjusted for matching factors by study design (gender, age, calendar period), fracture/trauma, surgery, congestive heart failure, chronic pulmonary disease, diabetes, ulcer disease, alcoholism-related disease, and infection.

Cause of death. Among the 745 patients with cirrhosis and venous thrombosis, 124 (17%) patients died within 30 days after their hospital diagnosis of venous thrombosis. Among these patients, an immediate cause of death was registered in 106 (85%). The main causes of death registered among these patients were PE ($n=27$, 25%), liver disease (including complications) ($n=21$, 20%), cardiovascular disease ($n=12$, 11%), respiratory failure ($n=13$, 12%), and infectious disease ($n=10$, 9%) (Table 4). Among the 27 patients with cirrhosis who died of PE, 21 had alcoholic cirrhosis, 2 had biliary cirrhosis, and 4 had other cirrhosis (not presented in a table). Among the 3647 venous thrombosis patients without cirrhosis, 299 (8%) patients died within 30 days after their hospital diagnosis of venous thrombosis, with PE as the cause of death registered for 60 patients (60 of 255 with a registered cause of death, 24%).

DISCUSSION

This is the first nationwide population-based cohort study to report the impact of cirrhosis on 30-day mortality following DVT, PE, or PVT. We found that patients with cirrhosis had higher absolute mortality risks after any thromboembolic event than their matched comparisons, but the risk difference was more pronounced for PE than for DVT and PVT. Patients with cirrhosis also had a higher relative mortality rate after DVT and PE than matched patients without cirrhosis, whereas it was not clear whether cirrhosis patients had higher mortality after PVT than patients in the comparison cohort. PE was the most frequent cause of death within 30 days among patients with cirrhosis and VTE, and most of the deceased had alcoholic cirrhosis.

Clearly, the site and extension of a venous thrombosis impact on mortality risk.[28] Presence of underlying chronic comorbidities among patients with VTE is also a prognostic factor for mortality after a thrombotic event. We recently examined the effect of several comorbidities on mortality among 128,223 patients with DVT or PE and 640,760 persons

Table 4 Immediate cause of death among 106 patients with venous thromboembolism and cirrhosis

Cause of death (*n*)
Pulmonary embolism (27)
Portal vein thrombosis (2)
Acute mesenteric vascular event (2)
Liver disease (including complications) (21)
Cirrhosis (7)
Bleeding esophageal varices (6)
Hepatorenal syndrome (3)
Alcoholic hepatitis (1)
Alcoholic liver disease (1)
Liver failure (2)
Alcoholic cardiomyopathy (1)
Other gastrointestinal disease (9)
Chronic alcoholic pancreatitis (3)
Gastroduodenal ulcer (2)
Peritoneal bleeding (1)
Biliary cancer (1)
Cholecystolithiasis (1)
Anorectal disease unspecified (1)
Cardiovascular disease (12)
Respiratory failure or disease (13)
Infections (10)
Other diseases (6)
Stroke (2)
Renal insufficiency (2)
Fracture (1)
Anemia (1)
Gangrene (1)
Dehydration (1)
Unknown cause of death (2)

from the general population.[1] Extensive stratified analyses revealed that among numerous considered comorbidities, only presence of cancer, diabetes, and chronic liver disease resulted in a higher mortality after VTE, compared with absence of these factors.[1] In general, patients with cirrhosis have a substantial excess short-term mortality.[27,29–31] This increased mortality likely stems from a high comorbidity burden,[11] increased susceptibility to bacterial infections,[32,33] and complications of cirrhosis.[34] In addition, the patients with cirrhosis had a high prevalence of classical risk factors for VTE, but also other comorbidities, particularly alcoholism-related complications. Their risk profile may therefore have impacted on the course of VTE including the choice of treatment. There is still inadequate evidence regarding effectiveness and safety of anticoagulant treatment in patients with cirrhosis and VTE,[35–38] and the establishment of a risk–benefit ratio for pharmacological VTE prophylaxis, and treatment therefore remains a critical problem. Most of the evidence regarding treatment with anticoagulants stems from studies including PVT patients. Treatment patterns with anticoagulants within the first month after splanchnic venous thrombosis were described in a multinational cohort study including 244 patients with isolated PVT.[39] Although 81 (33%) patients did not receive treatment, 143 (59%) were treated with LMWH and 77 (32%) patients with VKA, alone or in combination. A larger proportion of patients with active cancer or cirrhosis received prolonged LMWH, which is in agreement with the guidelines for DVT and PE.[17,39] As the frequencies of patients treated with anticoagulants were not provided separately for patients with and without cirrhosis, our results are not comparable.

The main strengths of our registry-based study were its size and setting within the uniformly organized Danish health-care system, permitting a nationwide population-based design. A number of limitations must also be considered, including the accuracy of VTE and cirrhosis diagnoses in the patient registries and the ability to control for confounders such as underlying comorbid conditions. The VTE diagnosis in the DNPR has been found to have a positive predictive value of 71% for DVT and 82% for PE[18] compared with strict diagnostic criteria (including a combination of typical clinical symptoms in combination with confirmatory diagnostic imaging test results). However, any misclassification of thrombosis diagnoses should not differ between patients with and without cirrhosis (i.e., it is non-differential). The positive predictive value of cirrhosis codes in the DNPR was previously found to be 85%, using either the diagnostic criteria for cirrhosis[40] or through comparison with medical charts.[41] In regard to confounder control, the positive predictive values of other diseases[41] and surgical procedures[42,43] are also high.

Another study limitation is that we could not classify patients according to cirrhosis severity because the data necessary for severity scoring are not available in the patient registries. Instead, we stratified patients broadly by type of cirrhosis. Of note, we had only a few cases of hepatitis C-associated cirrhosis, as hepatitis C virus is rare in Denmark.[44]

Patients with cirrhosis may be frail persons who likely have a high mortality when admitted with any acute illness, and confounding by baseline risk may have impacted our results. We performed comprehensive adjustment for potential confounders, which clearly attenuated the relative VTE mortality risks. Still, we cannot rule out residual confounding that could lead to overestimation of the association between cirrhosis and mortality following VTE. The impact of cirrhosis on relative mortality was more pronounced for DVT than PE, which may reflect a high mortality after PE *per se,* regardless of underlying disease.

In conclusion, during 30 days of follow-up after a diagnosis of DVT, PE or PVT, we found higher mortality risk and rates in DVT and PE patients with cirrhosis than in VTE patients without cirrhosis. PE was the main cause of death among patients with cirrhosis, but the proportion of deaths due to PE was similar to that of other VTE patients.

CONFLICT OF INTEREST

Guarantor of the article: Kirstine Kobberøe Søgaard, MD.
Specific author contributions: Study concept and design, analyses, interpretation of data, manuscript writing, manuscript revision, editing, and decision to publish: Kirstine Kobberøe Søgaard; study concept and design, supervising in analyses, interpretation of data, revision of manuscript, editing, and decision to publish: Jonathan Montomoli, Hendrik Vilstrup, Henrik Toft Sørensen; study concept and design, participated in data analysis, interpretation of data, revision of manuscript, editing, and decision to publish: Erzsébet Horváth-Puhó. All authors had full access to all data.

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Potential competing interest: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Short-term mortality is high after VTE.
- ✓ Patients with cirrhosis are at increased risk of DVT, PE, and PVT compared with the general population.
- ✓ Knowledge about the influence of cirrhosis on VTE mortality is limited.

WHAT IS NEW HERE

- ✓ The 30-day mortality risk among patients with cirrhosis was 7%, 35%, and 19% for DVT, PE, and PVT, respectively.
- ✓ The adjusted 30-day MRRs for cirrhosis were 2.17 (95% CI: 1.24–3.79) for DVT, 1.83 (95% CI: 1.30–2.45) for PE, and 1.30 (0.80–2.13) for PVT.
- ✓ Cirrhosis is a prognostic factor for short-term mortality after DVT and PE, with PE as a frequent cause of death.

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Study III

BMJ Open Gastroenterology

Venous thromboembolism and subsequent risk of cancer in patients with liver disease: a population-based cohort study

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ABSTRACT

Objective: Venous thromboembolism (VTE) may be a marker of occult cancer in the general population. While liver disease is known to increase the risk of VTE and cancer, it is unclear whether VTE in patients with liver disease is also a marker of occult cancer.

Design: A population-based cohort study.

Setting: Denmark.

Participants: We used population-based health registries to identify all patients with liver disease in Denmark with a first-time diagnosis of VTE (including superficial or deep venous thrombosis and pulmonary embolism) during 1980–2010. Patients with non-cirrhotic liver disease and patients with liver cirrhosis were followed as two separate cohorts from the date of their VTE.

Measures: For each cohort, we computed the absolute and relative risk (standardised incidence ratio; SIR) of cancer after VTE.

Results: During the study period, 1867 patients with non-cirrhotic liver disease and 888 with liver cirrhosis were diagnosed with incident VTE. In the first year following VTE, the absolute risk of cancer was 2.7% among patients with non-cirrhotic liver disease and 4.3% among those with liver cirrhosis. The SIR for the first 90 days of follow-up was 9.96 (95% CI 6.85 to 13.99) among patients with non-cirrhotic liver disease and 13.11 (95% CI 8.31 to 19.67) among patients with liver cirrhosis. After 1 year of follow-up, SIRs declined, but remained elevated in patients with non-cirrhotic liver disease (SIR=1.50, 95% CI 1.23 to 1.81) and patients with liver cirrhosis (SIR=1.95, 95% CI 1.45 to 2.57).

Conclusions: VTE may be a marker of occult cancer in patients with liver disease.

Summary box

What is already known about this subject?

- Venous thromboembolism (VTE) may be a marker of cancer.
- Liver disease is a risk factor for VTE and cancer.
- It is not clear if VTE is a marker of cancer among patients with liver disease.

What are the new findings?

- VTE in patients with liver disease may be a marker of cancer.
- Among patients with liver disease with VTE, the observed number of cancers was 10–13 times higher than expected for the first 90 days of follow-up, compared with the general population.
- Our data suggest that 37 patients with non-cirrhotic liver disease and 23 patients with liver cirrhosis diagnosed with VTE would need to be worked up in order to detect one additional cancer within 1 year following VTE.

How might it impact on clinical practice in the foreseeable future?

- The study highlights the importance of a diagnostic workup for cancer in patients with liver disease presenting with VTE.

INTRODUCTION

There is strong evidence that venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), occurs as a complication of cancer,[1 2] and that it may also be a marker of occult cancer.[3–6]

Several studies have reported a twofold to fourfold increased 1-year risk of cancer among patients diagnosed with DVT or PE, compared with the general population.[3–6] In these studies, the relative risk for cancer in the second and subsequent years after the VTE event declined to 1.1–1.4.[3–6] A recent population-based study showed that patients diagnosed with superficial venous thrombosis (SVT) also have a higher than expected occurrence of cancer.[5]

VTE in patients with liver disease is an increasingly recognised clinical challenge.[7]

Previous studies have shown that liver disease increases the risk of VTE,[8–11] and

that patients with liver disease have a twofold increased lifetime risk of all cancers compared to the general population.[12–16] In particular, patients with liver cirrhosis and an initial negative screening exam for liver cancer have an estimated 1-year incidence of hepatocellular carcinoma and extrahepatic cancer of 1.2% and 2.2%, respectively.[14] However, to the best of our knowledge, it remains unknown whether VTE is a marker of occult cancer in patients with liver disease.

We therefore conducted the present study to examine if patients with liver disease diagnosed with VTE have a higher occurrence of cancer than the general population.

METHODS

This cohort study was conducted within the setting of the entire Danish population. During the study period (1 January 1980 to 31 December 2010), the total population count was 7.9 million persons. The National Health Service provides tax-funded medical care for all Danish residents. Since 1968, a unique personal registration number has been assigned to every Danish resident at birth or on immigration, which allows unambiguous linkage between registries.[17]

Study population

The Danish National Patient Register (DNPR), established in 1977, contains discharge diagnoses from Danish hospital departments.[18] Hospital outpatient and emergency room visits have been included since 1995. Information recorded in the DNPR includes patients' personal registration number, dates of hospital admission and discharge, surgical procedures and up to 20 discharge diagnoses, classified according to the International Classification of Diseases, 8th revision (ICD-8) until 31 December 1993, and 10th revision (ICD-10) thereafter.[18] The discharge diagnoses are coded as primary or secondary, according to the reason for admission.[18] We used the DNPR to identify patients with a first-time inpatient or outpatient diagnosis of VTE during the study period, including both primary and secondary diagnoses. VTE events included a lower-limb SVT, a lower-limb DVT and PE. Since improvements in diagnosing VTE and cancer using ultrasound, computed tomographic scans and other technologies occurred during the study period, we categorised patients by diagnosis date, that is, diagnosis before versus after 31 December 1993. This corresponds with the date that the ICD-10 replaced the ICD-8.

We excluded patients who were diagnosed with VTE in the emergency room without a subsequent inpatient diagnosis, since the working diagnoses used in that setting have a positive predictive value of only 31%.[19] We also excluded all patients with a cancer diagnosis other than non-melanoma skin cancer and dysplasia or carcinoma in situ of the uterine cervix before the date of VTE diagnosis.

The study population was then further restricted to patients with VTE with a recorded diagnosis of liver disease before or during the same hospital contact in which VTE was diagnosed. Two patient cohorts were then established based on liver disease severity: patients with non-cirrhotic liver disease and patients with liver cirrhosis.[10] Non-cirrhotic liver disease encompassed all liver diseases except liver cirrhosis, for example, viral hepatitis, alcoholic hepatitis, non-alcoholic fatty liver disease and autoimmune hepatitis. Patients coded with both non-cirrhotic liver disease and liver cirrhosis before their VTE event were included in the liver cirrhosis cohort. The duration of liver disease before the VTE event was calculated as the time between the first diagnosis of non-cirrhotic liver disease or liver cirrhosis and the date of VTE diagnosis.

Covariates

We used the DNPR to ascertain the presence of the following conditions: fracture, trauma, surgery, childbirth, or pregnancy recorded in the 90 days before the VTE event, or a previous hospital diagnosis of obesity, inflammatory bowel disease or psychiatric disorder (as a marker of antipsychotic drug use) at any time before or during the hospital contact for VTE.[20] Patients with at least one of the conditions listed above were classified as having risk factors for VTE.[20] Patients with none of the above diagnoses were considered to be without risk factors for VTE other than liver disease. We also categorised patients according to the presence/absence of alcoholism-related disease codes in the DNPR, that is, alcohol abuse or alcoholism-related diseases other than alcoholic liver disease.

Cancer outcomes

To identify cancer outcomes, all members of the two patient cohorts were linked to the Danish Cancer Registry, which has recorded incident cancers in Denmark since 1943.[21] We searched for all cancers (excluding non-melanoma skin cancer and dysplasia or carcinoma in situ of the uterine cervix) using ICD-10 codes.[13] The ICD codes used in this study are provided in the online supplementary appendix.

Statistical analysis

In the primary analysis, patients were followed from their date of VTE diagnosis until a cancer diagnosis, death or 31 December 2011, whichever came first. The follow-up time was classified into the following periods: 0–1 year, 1+ years and total follow-up. The first year after VTE was further classified into two periods: 0–90 days and 91–365 days.

We calculated absolute risks (or cumulative incidence) for all cancers, treating death as a competing risk.[22] We also calculated the inverse of the absolute risk for the first year of follow-up, in order to quantify the number of patients with VTE with liver disease that would need a diagnostic workup in order to detect one additional

cancer,[23] assuming that this workup would identify all occult cancers detectable within 1 year after VTE diagnosis.

We then used national cancer incidence rates to compute the expected number of cancer cases according to gender, age and year of diagnosis. Multiplying the number of person-years at risk by the incidence rates yielded the number of cancer cases expected, if patients with VTE and liver disease had the same risk of cancer as the general population. Next, we calculated the standardised incidence ratio (SIR)—the ratio of the observed number of cancers to the expected number of cancers—as a measure of relative risk of cancer after VTE diagnosis in patients in the two cohorts. CIs for SIRs were computed assuming that the observed number of cases in a specific category followed a Poisson distribution.[22] When the observed number was less than 10, the exact 95% CIs were used; otherwise Byar's approximation was used.[22] In addition to the risk of any cancer, we also computed SIRs for the selected cancers.

We examined the impact of non-cirrhotic liver disease and liver cirrhosis on cancer risk after VTE among patient subgroups. Our approach was to compute SIRs in different subgroups classified according to the type of VTE event (SVT, DVT, PE), gender, age group (<60 years, 60+ years), period of VTE (1980–1993, 1994–2010), presence/absence of alcoholism-related disease, and presence/absence of risk factors for VTE.

Finally, we performed a secondary analysis in which we excluded patients who were diagnosed with cancer within 30 days after their VTE diagnosis. The purpose of this analysis was to avoid including VTEs that were detected after diagnostic workup in patients suspected to have cancer.

All statistical analyses were conducted using the SAS statistical software package, V.9.2 (SAS Institute, Cary, North Carolina, USA). The study was approved by the Danish Data Protection Agency, record number 2011-41-5809. Data obtained from Danish registries are generally available to researchers, and their use does not require informed consent.

RESULTS

Descriptive data

We identified 2755 patients with liver disease with a first-time VTE diagnosis (table 1).

Among these patients, 1867 (68%) had non-cirrhotic liver disease (median follow-up after VTE diagnosis: 4.2 years), and 888 (32%) had liver cirrhosis (median follow-up after VTE diagnosis: 1.3 years). Median age was 53 years among patients with non-cirrhotic liver disease and 62 years among patients with liver cirrhosis. In both cohorts, the largest group of patients had DVT, followed by PE, and then SVT.

The majority of patients were diagnosed with VTE in the period 1994–2011: 1501 (80%) patients with non-cirrhotic liver disease and 553 (62%) of those with liver cirrhosis.

Table 1 Characteristics of patients with venous thromboembolism and liver disease

Variable	Patients with non-cirrhotic liver disease and VTE N=1867	Patients with liver cirrhosis and VTE N=888
Median age, years	53	62
Superficial venous thrombosis	50	57
Deep vein thrombosis	49	59
Pulmonary embolism	63	67
Median follow-up time (IQR), years	4.20 (1.30–8.40)	1.28 (0.09–4.32)
Person-years at risk, total	10 539	2794
Male, n (%)	1027 (55)	519 (58)
Type of VTE, n (%)		
Superficial venous thrombosis	149 (8)	68 (8)
Deep vein thrombosis	1183 (63)	477 (54)
Pulmonary embolism	535 (29)	343 (39)
Period of VTE diagnosis, n (%)		
1980–1993	366 (20)	335 (38)
1994–2010	1501 (80)	553 (62)
Risk factors for VTE*, n (%)		
Absent	776 (42)	424 (48)
Present	1091 (58)	466 (52)
Alcoholism-related disease, n (%)	421 (23)	388 (44)

*Patients with at least one of the following conditions: fracture, trauma, surgery, childbirth or pregnancy diagnosed in the 90 days before VTE admission or a previous hospital diagnosis of obesity, inflammatory bowel disease or psychiatric disorder (as a marker of antipsychotic drug use) at any time before or during the hospital contact for VTE.
VTE, venous thromboembolism.

More than 50% of patients in both cohorts were male and had at least one risk factor for VTE other than liver disease. Among patients with non-cirrhotic liver disease, 322 (17%) had alcoholic hepatitis, 593 (32%) had viral hepatitis, 163 (9%) had fatty liver disease, and 789 (42%) had other non-cirrhotic liver diseases. Furthermore, 503 (27%) patients had a history of non-cirrhotic liver disease of less than 1 year at the time of VTE diagnosis, 455 (24%) patients had a history from 1 to 5 years, and 909 (49%) had a history longer than 5 years. Among patients in the liver cirrhosis cohort, 422 (48%) were diagnosed with alcoholic liver cirrhosis, 39 (4%) with primary or secondary biliary cirrhosis, and 427 (48%) with other or unspecified cirrhosis. A total of 327 (37%) patients had a history of liver cirrhosis of less than 1 year at the time of VTE diagnosis, 269 (30%) had a history from 1 to 5 years, and 292 (33%) had a history longer than 5 years.

Cancer risk

During follow-up after VTE diagnosis, 158 cancers were diagnosed among patients with non-cirrhotic liver disease and 88 among those with liver cirrhosis.

Corresponding absolute risks were 14.7% (overall follow-up time: 31.7 years) and 13.1% (overall follow-up time: 24.8 years), respectively (figure 1). The SIR was 1.88 (95% CI 1.60 to 2.19) for patients with non-cirrhotic liver disease, and 2.78 (95% CI 2.23 to 3.42) for patients with liver cirrhosis (tables 2 and 3).

In both cohorts, cancer risk was higher in the first year of follow-up than in the second and subsequent years. The 1-year absolute risk of cancer was 2.7% for patients with non-cirrhotic liver disease and 4.3% for patients with liver cirrhosis (figure 1). According to these results, 37 patients with non-cirrhotic liver disease with a VTE event or 23 patients with liver cirrhosis with a VTE event would need to receive diagnostic workup in order to detect one cancer within the first year following their VTE. During the first year of follow-up, cancer SIRs were markedly increased both among patients with non-cirrhotic liver disease (SIR=4.08 (95% CI 3.03 to 5.38)) and among patients with liver cirrhosis (SIR=6.32 (95% CI 4.47 to 8.68)). This increased risk stemmed mainly from cancers detected during the first 90 days after the VTE event; for patients with non-cirrhotic liver disease, the 90-day SIR was 9.96 (95% CI 6.85 to 13.99), and for patients with liver cirrhosis the 90-day SIR was 13.11 (95% CI 8.31 to 19.67) (tables 2 and 3).

After the first 90 days, the SIR decreased considerably in both study cohorts. Still, the 91 to 365 days SIR was 1.90 (95% CI 1.11 to 3.05) among patients with non-cirrhotic liver disease and 3.52 (95% CI 1.97 to 5.81) among patients with liver cirrhosis. Beyond 1 year of follow-up, the risk of cancer remained 1.5 and 2 times increased among patients with non-cirrhotic liver disease and among those with liver cirrhosis, respectively.

Subgroup analysis

All types of VTE were associated with a subsequently increased overall risk of cancer. However, while DVT and PE were associated with a markedly increased cancer risk in the first 90 days of follow-up, risk estimates for SVT were not available or were very imprecise due to the low number of events. Moreover, the risk of cancer after VTE remained increased in different patient subgroups (tables 2 and 3). In both cohorts of patients, the 90-day SIR was higher among men than women, and also among patients without risk factors for VTE, compared with those with risk factors other than liver disease (tables 2 and 3).

The markedly increased risk during the first year was mainly due to the higher than expected occurrence of, in particular, liver and biliary cancers. However, we also found an increased SIR of other GI cancers, lung, brain and nervous system cancers than expected, though based on small numbers with limited precision (see online supplementary table S1).

Secondary analysis

In the secondary analysis excluding patients diagnosed with cancer within 30 days after the date of VTE (n=17

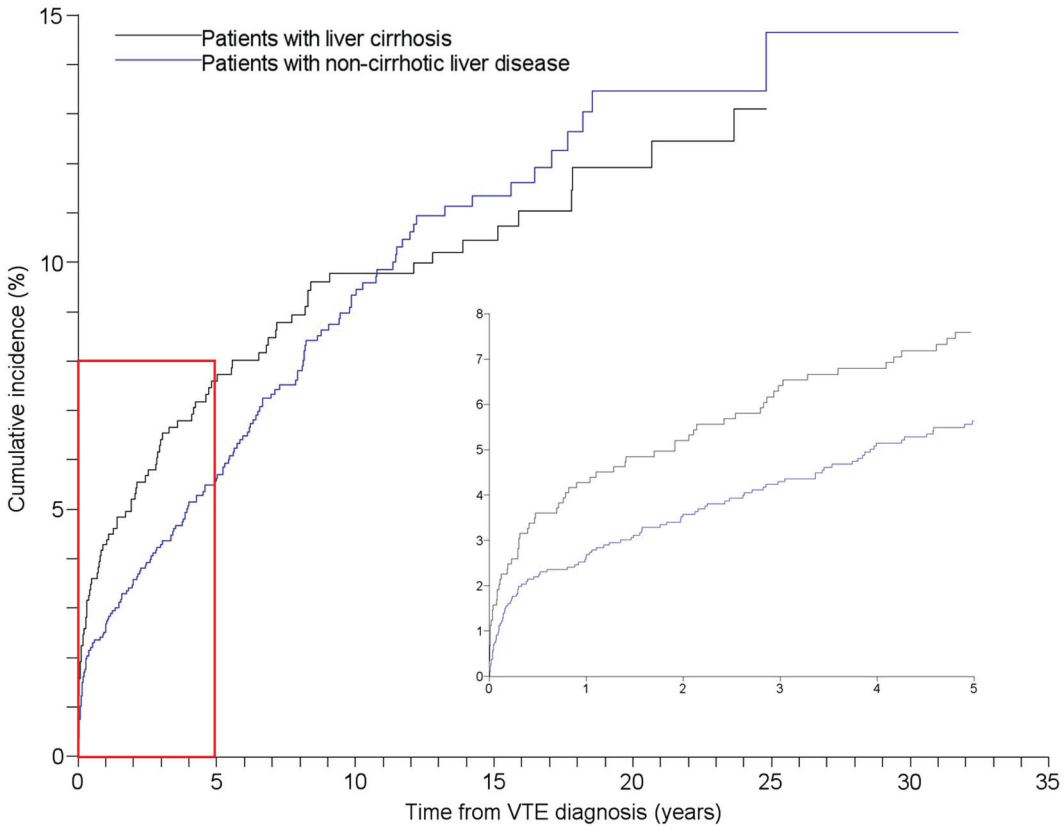

Figure 1 Cumulative incidence for all cancers among patients with liver disease following venous thromboembolism (VTE).

Table 2 Standardised incidence ratios with 95% CIs of cancer diagnosed among 1867 patients with venous thromboembolism and non-cirrhotic liver disease

	0–90 days		91–365 days		1+ years		Overall	
	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)
All patients	33	9.96 (6.85 to 13.99)	17	1.90 (1.11 to 3.05)	108	1.50 (1.23 to 1.81)	158	1.88 (1.60 to 2.19)
Type of VTE								
SVT	1	3.95 (0.10 to 21.98)	2	2.78 (0.34 to 10.04)	9	1.46 (0.67 to 2.77)	12	1.68 (0.87 to 2.93)
DVT	21	10.36 (6.41 to 15.84)	11	1.97 (0.98 to 3.53)	78	1.65 (1.30 to 2.06)	110	2.00 (1.65 to 2.42)
PE	11	10.64 (5.30 to 19.04)	4	11.52 (0.41 to 3.89)	21	1.14 (0.70 to 1.74)	36	1.63 (1.14 to 2.25)
Gender								
Male	19	11.20 (6.74 to 17.49)	9	1.99 (0.91 to 3.78)	60	1.53 (1.17 to 1.97)	88	1.94 (1.56 to 2.39)
Female	14	8.66 (4.73 to 14.53)	8	1.82 (0.78 to 3.58)	48	1.46 (1.08 to 1.94)	70	1.80 (1.40 to 2.28)
Age (years)								
<60	8	9.98 (4.30 to 19.66)	6	2.52 (0.93 to 5.50)	53	1.63 (1.22 to 2.14)	67	1.88 (1.46 to 2.39)
60+	25	9.95 (6.44 to 14.69)	11	1.68 (0.84 to 3.00)	55	1.39 (1.05 to 1.81)	91	1.88 (1.51 to 2.30)
Period of VTE diagnosis								
1980–1993	4	7.41 (2.02 to 18.98)	2	1.45 (0.18 to 5.23)	34	1.74 (1.21 to 2.44)	40	1.87 (1.33 to 2.54)
1994–2010	29	10.45 (7.00 to 15.02)	15	1.99 (1.11 to 3.28)	74	1.41 (1.11 to 1.77)	118	1.88 (1.56 to 2.25)
Alcoholism-related disease								
Yes	5	8.34 (2.70 to 19.44)	0	–	31	2.37 (1.61 to 3.37)	36	2.34 (1.64 to 3.24)
No	28	10.32 (6.85 to 14.91)	17	2.35 (1.37 to 3.77)	77	1.31 (1.03 to 1.63)	122	1.77 (1.47 to 2.12)
Risk factors for VTE*								
Absent	17	10.30 (6.00 to 16.49)	10	2.22 (1.06 to 4.08)	56	1.57 (1.18 to 2.03)	83	1.98 (1.58 to 2.45)
Present	16	9.62 (5.50 to 15.62)	7	1.58 (0.63 to 3.26)	52	1.44 (1.07 to 1.89)	75	1.77 (1.40 to 2.22)

*Patients with at least one of the following conditions: fracture, trauma, surgery, childbirth or pregnancy diagnosed in the 90 days before VTE admission or a previous hospital diagnosis of obesity, inflammatory bowel disease or psychiatric disorder (as a marker of antipsychotic drug use) at any time before or during the hospital contact for VTE.
DVT, deep vein thrombosis; O, observed; PE, pulmonary embolism; SIR, standardised incidence ratio; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

Table 3 Standardised incidence ratios with 95% CIs of cancer diagnosed among 888 patients with venous thromboembolism and liver cirrhosis

	0–90 days		91–365 days		1+ years		Overall	
	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)
All patients	23	13.11 (8.31 to 19.67)	15	3.52 (1.97 to 5.81)	50	1.95 (1.45 to 2.57)	88	2.78 (2.23 to 3.42)
Type of VTE								
SVT	0	–	1	2.51 (0.06 to 13.99)	8	3.02 (1.30 to 5.96)	9	2.83 (1.30 to 5.38)
DVT	13	11.86 (6.31 to 20.28)	12	4.30 (2.22 to 7.52)	31	1.69 (1.15 to 2.40)	56	2.52 (1.90 to 3.27)
PE	10	19.17 (9.18 to 35.26)	2	1.87 (0.23 to 6.75)	11	2.35 (1.17 to 4.21)	23	3.67 (2.33 to 5.51)
Gender								
Male	16	15.78 (9.02 to 25.63)	9	3.73 (1.71 to 7.09)	34	2.22 (1.54 to 3.10)	59	3.15 (2.40 to 4.06)
Female	7	9.44 (3.79 to 19.46)	6	3.25 (1.19 to 7.09)	16	1.55 (0.88 to 2.51)	29	2.24 (1.50 to 3.22)
Age (years)								
<60	6	16.56 (6.08 to 36.11)	2	2.01 (0.24 to 7.25)	26	2.31 (1.51 to 3.39)	34	2.70 (1.87 to 3.77)
60+	17	12.21 (7.11 to 19.55)	13	3.99 (2.12 to 6.82)	24	1.66 (1.07 to 2.48)	54	2.83 (2.13 to 3.69)
Period of VTE diagnosis								
1980–1993	11	21.36 (10.65 to 38.22)	5	4.44 (1.44 to 10.34)	18	1.77 (1.05 to 2.79)	34	2.87 (1.99 to 4.02)
1994–2010	12	9.68 (5.00–16.91)	10	3.19 (1.53 to 5.88)	32	2.07 (1.41 to 2.92)	54	2.72 (2.04 to 3.55)
Alcoholism-related disease								
Yes	9	13.99 (6.41 to 26.58)	2	1.23 (0.15 to 4.43)		2.01 (1.23 to 3.10)	31	2.53 (1.72 to 3.60)
No	14	12.60 (6.88 to 21.14)	13	4.95 (2.63 to 8.46)	30	1.91 (1.29 to 2.73)	57	2.93 (2.22 to 3.80)
Risk factors for VTE*								
Absent	14	16.49 (9.01 to 27.68)	7	3.33 (1.33 to 6.85)	28	2.14 (1.42 to 3.09)	49	3.05 (2.26 to 4.03)
Present	9	9.93 (4.55 to 18.87)	8	3.72 (1.60 to 7.32)	22	1.75 (1.10 to 2.65)	39	2.50 (1.78 to 3.41)

*Patients with at least one of the following conditions: fracture, trauma, surgery, childbirth or pregnancy diagnosed in the 90 days before VTE admission or a previous hospital diagnosis of obesity, inflammatory bowel disease or psychiatric disorder (as a marker of antipsychotic drug use) at any time before or during the hospital contact for VTE.
DVT, deep vein thrombosis; O, observed; PE, pulmonary embolism; SIR, standardised incidence ratio; SVT, superficial venous thrombosis VTE, venous thromboembolism.

for patients with non-cirrhotic liver disease and n=15 for patients with cirrhotic liver disease), the SIRs for cancer during the entire follow-up period were 1.70 (95% CI 1.43 to 2.00) and 2.35 (95% CI 1.84 to 2.96) for the remaining patients with non-cirrhotic and cirrhotic liver disease, respectively. In the first 90 days after VTE, the SIR for cancer was 7.48 (95% CI 4.27 to 12.15) among patients with non-cirrhotic liver disease and 7.28 (95% CI 3.14 to 14.34) among patients with liver cirrhosis.

DISCUSSION

In this population-based cohort study of 2755 patients with liver disease with VTE, we found an increased risk of a cancer diagnosis subsequent to a VTE event. The 1-year absolute cancer risk was higher in patients with liver cirrhosis than in patients with non-cirrhotic liver disease. Similarly, we found higher relative risks among patients with liver cirrhosis than among patients with non-cirrhotic liver disease, compared with the general population. The increased relative risk of cancer was particularly high during the first 90 days of follow-up after VTE, but remained elevated during subsequent months. In particular, the risk for liver and biliary cancers was markedly increased both in patients with non-cirrhotic liver disease and in patients with liver cirrhosis.

To the best of our knowledge, this is the first study to investigate cancer risk in patients with liver disease and VTE. Our finding of an overall increased risk of cancer in patients with liver disease with VTE is similar to the cancer risk reported in previous studies of patients hospitalised with VTE in the general population. However, the SIRs for cancer after the first year of follow-up in our study were higher than previously reported.[3–6] The finding of an elevated cancer risk beyond 1 year may reflect the fact that liver disease and associated lifestyle factors increase cancer risk.[13–16 24] Therefore, the higher SIRs for cancer after the first year of follow-up in our study, compared to previous studies, may be explained partially by other risk factors for cancer more likely to be present among patients with liver disease.[25]

Our study aimed to clarify the role of VTE as a marker of occult cancer among patients with liver disease. The results of this study may increase awareness of the high risk of cancer in patients with liver disease with a first episode of VTE. The results suggest that diagnostic workup for an occult cancer should be individualised according to underlying patient clinical characteristics. Moreover, detection of an underlying cancer may not only have implications for VTE management, including its treatment, but also lead to diagnosis of cancer at an earlier stage.[26] However, it remains controversial whether extensive screening for the early detection of occult cancer after VTE improves prognosis.[27–29] The clinical utility for diagnostic workup for cancer in patients with liver disease diagnosed with VTE is not clear because of the poor 5-year survival among those patients.[30] Patients with liver cirrhosis may therefore not benefit substantially from earlier cancer detection in terms of improved survival, since they are likely to die of other comorbidities or cirrhosis-related complications.

The validity of our findings depends on several factors. The use of population-based registries minimised selection and referral biases and ensured complete follow-up. Registry data on cancer,[21] liver diseases[31] and comorbidity[32] have high positive predictive value when validated against medical charts. Moreover, the VTE diagnoses in the DNPR have positive predictive values of approximately 70–80% when compared with strict clinical criteria.[19] Of note, we included only patients with SVT diagnosed in the inpatient or outpatient hospital setting, who may have a higher baseline risk of cancer than patients diagnosed in general practitioners' offices. Although the data quality in the registry of liver disease and VTE diagnosis have been reported to be high,[19 31] the diagnostic accuracy of these diagnoses may have improved during the study period. However, the cancer risk was similar in the two periods. Both heightened diagnostic effort and the effects of occult cancer may explain the association in the short term. However, the increased risk was remarkably persistent many years after a thromboembolic episode. Therefore, diagnostic bias should not be prominent. Moreover, if detection bias (ie, a greater likelihood of detecting cancers during a hospital contact) had occurred, the period of increased cancer diagnosis would have been followed by a compensatory deficit. We did not see such a pattern. Although liver disease has been reported to be a strong risk factor for cancer, our data did not allow us to separate the effect of liver disease, alcohol consumption, smoking and comorbidity on long-term risk of cancer.[33]

In summary, our findings indicate that VTE may be a marker of occult cancer in patients with liver disease. In particular, patients with liver cirrhosis are at a markedly increased risk of being diagnosed with cancer during the first year following a VTE diagnosis.

Contributors JM was involved in the study idea and design, statistical analysis, data interpretation and manuscript preparation. RE and KKS were involved in the study concept and design, data interpretation and manuscript review. DKF was involved in the statistical analysis and manuscript review. A-MBM was involved in the critical analysis of the data and manuscript review. HTS was involved in the study idea and design, critical analysis of the data, manuscript review and study supervision. All authors approved the final draft submitted for publication.

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Study IV

CLINICAL TRIALS AND OBSERVATIONS

Splanchnic venous thrombosis is a marker of cancer and a prognostic factor for cancer survival

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Key Points

- SVT is a marker of occult cancer, in particular myeloproliferative neoplasms, liver cancer, and pancreatic cancer.
- SVT is a prognostic factor for short-term survival in patients diagnosed with liver or pancreatic cancer.

It is unknown if splanchnic venous thrombosis (SVT) is a marker of occult cancer and a prognostic factor for cancer survival. Using Danish medical registries, we conducted a nationwide cohort study including all patients with first-time SVT (n = 1191) between 1994 and 2011. We followed the patients for subsequent cancer diagnoses and calculated absolute risks and standardized incidence ratios (SIRs). We formed a matched comparison cohort of cancer patients without SVT, and assessed the prognostic impact of SVT on cancer survival by applying the Kaplan–Meier method and Cox regression. We followed the patients for a median of 1.6 years, and found that SVT was a marker of occult cancer. The 3-month cancer risk was 8.0% and the SIR was 33 (95% confidence interval, 27-40), compared with the general population. Increased risk was mainly found for liver cancer (risk = 3.5%; SIR = 1805), pancreatic cancer (risk = 1.5%; SIR = 256), and myeloproliferative neoplasms (risk = 0.7%; SIR = 764). The overall SIR remained increased twofold after 1 or more years of follow-up. SVT was also a prognostic factor for survival in patients with liver and pancreatic cancer. The clinical impact may be a more thorough diagnostic work-up in patients presenting with SVT. (*Blood*. 2015;126(8):957-963)

Introduction

Venous thromboembolism may be a marker of occult cancer. Patients with a lower-limb deep venous thrombosis (DVT) or pulmonary embolism (PE) have a two- to fourfold increased risk of a cancer diagnosis in the first year after the thromboembolic event, compared with the general population.[1-3] Recently, a similar association was demonstrated for superficial venous thrombosis.[4] Patients, in whom thrombosis occurs before cancer diagnosis, are more likely to have advanced disease and higher mortality than cancer patients without venous thromboembolism at time of diagnosis.[5] Splanchnic venous thrombosis (SVT) (ie, thrombosis of portal veins, hepatic veins [Budd-Chiari syndrome], mesenteric veins, and/or splenic veins)[6] also may precede diagnosis of a malignant neoplasm. A few case reports have described SVT as the first sign of liver and pancreatic malignancies.[7-9] A meta-analysis of 32 studies, each including between 10 and 237 patients with portal or hepatic vein thrombosis (HVT), showed that thrombosis often occurred prior to diagnosis of myeloproliferative neoplasms.[10]

The association between SVT and subsequent cancer risk has never been studied in a population-based setting using a comparison cohort. Moreover, the prognostic impact of SVT on cancer survival remains unknown.[11] We therefore examined cancer risk after a first-time SVT diagnosis, compared with cancer risk in the general Danish population. In addition, we compared survival among cancer patients with and without SVT. The present study may extend our understanding of the development of SVT and may have implications for diagnostic work-up for cancer among patients presenting with this indication.

Methods

Data sources and study population

The Danish National Health Service provides tax-funded medical care to all Danish residents and guarantees free access to hospitals and outpatient clinics.[12] We used data from the Danish National Patient Registry,[13] recorded according to International Classification of Diseases (ICD) codes (8th and 10th revision). We identified all hospital inpatients and outpatients with a first-time ICD-10 code of SVT from 1994 through 2011. We retrieved information on comorbidities characterizing the patients from 1977 onwards, using ICD-8 and ICD-10 codes. We categorized the patients according to overall comorbidity level, using diseases included in the Charlson Comorbidity Index.[14,15] We obtained information on diagnoses of liver disease (including varices and ascites), pancreatitis, diabetes, chronic obstructive pulmonary disease (as a proxy for smoking), venous thromboembolism (ie, DVT and PE), congestive heart failure, and myocardial infarction (MI) diagnosed at any time before SVT, and information on surgical procedures performed within 90 days before the thrombosis. We also retrieved registered abdominal ultrasound and computerized tomography (CT) scans performed within 30 days before or during the hospital contact with SVT. Registration of these diagnostic tests is complete since 2002.

Cancer outcomes

To identify patients with cancer, we linked the study cohort (using the patients' unique personal identification number)[16] to the Danish Cancer Registry,[17] which contains data on prospectively recorded incident cancers diagnosed in Denmark since 1943, including month and year of diagnosis, and information on cancer stage at diagnosis. We searched for all cancer diagnoses, myeloproliferative

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neoplasms (including polycythemia vera, primary myelofibrosis, and essential thrombocytemia), and myelodysplastic syndromes (MDS).[18] We excluded patients diagnosed with cancer (except for nonmelanoma skin cancer), myeloproliferative neoplasm, or MDS before the diagnosis date of SVT.

In the prognostic analysis, we examined survival among patients in our cohort who were later diagnosed with liver cancer, pancreatic cancer, or myeloproliferative neoplasm, and compared this with survival among matched cancer patients without SVT. We used the Danish Cancer Registry to identify up to five comparisons for each patient, matched by cancer type and stage (except for myeloproliferative neoplasm as there is no standard staging system), sex, age (5-year intervals), and year of diagnosis (5-year intervals).

All diagnosis codes and variable categorizations used are provided in the supplemental Appendix, available on the *Blood* Web site.

Statistical analysis

Descriptive data are presented as frequencies or as median values with interquartile ranges (IQRs). We followed each patient from date of first diagnosis of SVT until date of cancer diagnosis, emigration, death, or December 31, 2011, whichever came first.

We computed the absolute risk (cumulative incidence) of cancer in patients with a SVT diagnosis, treating death as a competing risk. Standardized incidence ratios (SIRs) (with 95% confidence intervals [CIs]) were used as a measure of relative risk, comparing cancer incidence observed among patients with SVT with that expected based on national cancer incidence rates by age, sex, and calendar year. SIRs were stratified by: patient characteristics, type of thrombosis, primary and secondary diagnoses, covariates, and cancer stage. We repeated the analyses for the subgroup of patients who had an ultrasound or CT scan within 30 days before or during their hospital contact with SVT.

The survival analysis was restricted to the most frequent cancers in the study cohort. We characterized the patients according to diseases occurring before their cancer diagnosis.

We summarized survival of cancer patients, by constructing Kaplan–Meier survival curves. We used Cox proportional hazard regression to compare risk of death among cancer patients with and without SVT, by computing mortality rate ratios and associated 95% CIs (adjusting for cancer type and stage, sex, age, and year of diagnosis).

All statistical analyses were conducted using the SAS statistical software package, version 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency, record #1-16-02-1-08. Danish registry data are generally available to researchers. According to Danish law, the use of registry data for research purposes does not require informed consent.

Results

Risk analysis

Patient characteristics. We identified 1191 patients with SVT; 924 (78%) had portal vein thrombosis (PVT), 141 (12%) had HVT, and 126 (10%) had mesenteric thrombosis. Median age was 61 years (46-74 years) and 52% were men. Nearly all patients, 1026 (86%) received their thrombosis diagnosis during a hospital admission, whereas only 165 (14%) were diagnosed in an outpatient clinic.

The majority of patients in our cohort had a moderate (34%) or severe (23%) level of comorbidity. In particular, we found a high prevalence of liver disease (20%), diabetes (15%), heart disease (15%), and previous pancreatitis (12%). In addition, 33% of the patients had undergone a surgical procedure less than 90 days prior to their thrombotic event (Table 1). Information on cancer stage was available for 111 (74%) of the 150 patients with nonhematologic cancers. Of these, 52 (47%) had localized cancer and 59 (53%) had regional spread or distant metastasis.

Overall cancer risk. During median follow-up of 1.6 years (IQR, 0-5 years), we identified 183 incident cancers, corresponding to an overall SIR of cancer of 4.2 (95% CI, 3.6-4.9). The majority of cancers were diagnosed among patients with PVT (n = 161, 88%), with an overall SIR of 4.7 (95% CI, 4.0-5.5) (Table 2). In total, 21 cancers (11%) were diagnosed among patients with HVT, corresponding to an overall SIR of 2.9 (95% CI, 1.8-4.4) (Table 2). One cancer was diagnosed in a patient with mesenteric vein thrombosis. During the first 3 months of follow-up, 95 cancers were diagnosed and among these, 53 were diagnosed within the first month. Three-month and 5-year absolute risks of cancer among SVT patients were 8.0% and 14.8%, respectively. During the first 3 months of follow-up, the SIR was 33 (95% CI, 27-40); between 3 and 12 months the ratio was 2.7 (95% CI, 1.6–4.3); and beyond 1 year of follow-up it remained increased twofold, compared with the risk in the general population (Table 1; Figure 1).

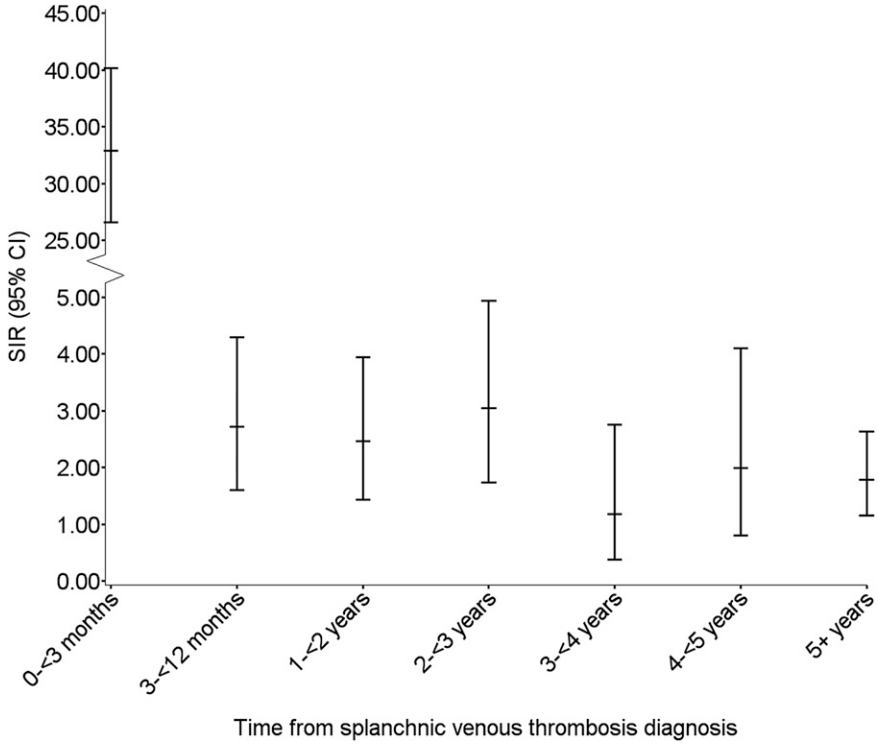
We observed no difference in cancer risk between men and women. Although the majority of cancers were diagnosed in patients older than 40 years, the excess risk was more pronounced in patients younger than

Table 1. Characteristics and SIRs for cancer in 1191 patients diagnosed with SVT from 1994 to 2011 in Denmark

	Patients, N (%)	Observed cancers, N	SIR (95% CI)
i. All patients	1191(100)	183	4.2 (3.6-4.9)
Women	567 (48)	77	4.1 (3.2-5.1)
Men	624 (52)	106	4.3 (3.5-5.2)
Age group (y)			
<40	213 (18)	22	9.5 (5.9-14)
41-64	479 (40)	86	4.5 (3.6-5.6)
65+	499 (42)	75	3.4 (2.7-4.3)
Calendar period			
1994-1999	216 (18)	40	3.0 (2.2-4.1)
2000-2005	364 (31)	62	3.7 (2.8-4.7)
2006-2011	611 (51)	81	6.0 (4.8-7.5)
SVT as primary diagnosis	674 (57)	104	3.8 (3.1-4.6)
SVT as secondary diagnosis	517 (43)	79	4.9 (3.9-6.1)
SVT confirmed by ultrasound and/or CT scan*	624 (71)	107	7.7 (6.3-9.4)
ii. Comorbidity level			
Low	512 (43)	88	4.7 (3.8-5.8)
Moderate	401 (34)	63	3.8 (2.9-4.8)
Severe	278 (23)	32	4.0 (2.7-5.6)
Liver disease			
Yes	234 (20)	37	6.8 (4.8-9.3)
No	957 (80)	146	3.9 (3.3-4.5)
Pancreatitis			
Yes	137 (12)	16	3.2 (1.8-5.2)
No	1054 (88)	167	4.4 (3.7-5.1)
Diabetes			
Yes	178 (15)	36	6.1 (4.3-8.5)
No	1013 (85)	147	3.9 (3.3-4.6)
Chronic obstructive pulmonary disease			
Yes	102 (9)	15	6.0 (3.4-9.9)
No	1089 (91)	168	4.1 (3.5-4.8)
Venous thromboembolism			
Yes	98 (8)	11	3.2 (1.6-5.8)
No	1093 (92)	172	4.3 (3.7-5.0)
Heart failure or previous MI			
Yes	178 (15)	27	4.4 (2.9-6.3)
No	1013 (85)	156	4.2 (3.6-4.9)
Surgical procedure within previous 90 d			
Yes	399 (33)	61	4.9 (3.7-6.3)
No	792 (67)	122	4.0 (3.3-4.7)

*Examination performed 30 days before or during the hospital contact, among a subgroup of 881 patients diagnosed between 2002 and 2011.

Figure 1. SIRs for cancer overall.



age 40. The risk of cancer subsequent to SVT increased during the study period, which likely reflected improved diagnostics with a higher accuracy of diagnoses. Between 1994 and 1999, the SIR was 3.0 (95% CI, 2.2-4.1) and between 2006 and 2011 it was 6.0 (95% CI, 4.8-7.5).

SVT was the primary reason for the hospital contact for 674 patients (57%). Stratification by thrombosis as the primary vs secondary reason for admission yielded SIRs of 3.8 (95% CI, 3.1-4.6) and 4.9 (95% CI, 3.9-6.1), respectively. Patients with liver disease, diabetes, or recent surgery were at higher risk of cancer than patients without these diseases or recent surgery (Table 1). In sub-analyses based on patient characteristics, only chronic obstructive pulmonary disease modified the SIRs after more than 1 year of follow-up (data not presented).

Liver and pancreatic cancer. The increased cancer risk during the first 3 months following an SVT diagnosis stemmed mainly from excess risk of liver cancer (absolute risk = 3.5%; SIR = 1805 [95% CI, 1295-2448]) and pancreatic cancer (absolute risk = 1.5%; SIR = 256 [95% CI, 149-409]), and occurred in patients with PVT. Although the prevalence of liver disease in the overall cohort was 20%, it was present in 50% of the patients diagnosed with liver cancer. Only 4 (20%) of the

Table 2. SIRs for cancer in 1191 patients with SVT, stratified by type of thrombosis

	Overall observed cancers and SIRs (95% CI)							
	Portal vein thrombosis		Hepatic vein thrombosis		Mesenteric vein thrombosis		Overall	
Cancer site								
Any	161	4.7 (4.0-5.5)	21	2.9 (1.8-4.4)	1	0.5 (0.0-2.5)	183	4.2 (3.6-4.9)
Liver	48	175 (129-232)	0	—	0	—	48	138 (101-182)
Myeloproliferative neoplasms	15	111 (62-184)	8	289 (125-570)	0	—	23	133 (85-200)
Pancreas	19	25 (15-40)	1	6.3 (0.2-35)	0	—	20	21 (13-32)
Hodgkin malignant lymphoma	1	13 (0.3-71)	0	—	0	—	1	9.7 (0.3-54)
Gallbladder or biliary tract	3	18 (3.8-53)	0	—	0	—	3	14 (2.9-41)
Metastases and nonspecified cancer in lymph nodes	4	6.5 (1.8-17)	1	7.1 (0.2-40)	0	—	5	6.3 (2.0-15)
MDS	2	14 (1.7-51)	0	—	0	—	2	11 (1.3-38)
Kidney	1	1.9 (0.1-10.5)	1	10 (0.3-55)	0	—	2	3.0 (0.4-11)
Leukemia	3	5.0 (1.0-15)	0	—	0	—	3	3.9 (0.8-11)
Non-Hodgkin malignant lymphoma	3	2.8 (0.6-8.2)	1	4.4 (0.1-25)	0	—	4	3.0 (0.8-7.5)
Lung, bronchi, or trachea	11	3.1 (1.5-5.5)	1	1.5 (0.0-8.3)	0	—	12	2.7 (1.4-4.7)
Colon	5	2.2 (0.7-5.1)	1	2.0 (0.1-11)	0	—	6	2.0 (0.7-4.4)
Breast	4	1.3 (0.4-3.3)	0	—	1	3.8 (0.1-21)	5	1.2 (0.4-2.8)
Bladder	8	4.9 (2.2-9.7)	0	—	0	—	8	3.9 (1.7-7.7)
Stomach	3	6.0 (1.2-17.5)	1	9.2 (0.2-52)	0	—	4	6.3 (1.7-16)
Rectum	0	—	2	7.7 (0.9-28)	0	—	2	1.3 (0.2-4.5)
Uterus	1	2.0 (0.1-11)	0	—	0	—	1	1.5 (0.0-8.4)
Prostate	6	1.6 (0.6-3.5)	0	—	0	—	6	1.3 (0.5-2.9)

Table 3. SIRs for cancer in 1191 patients with SVT

Cancer site	Observed cancers and SIRs (95% CI)							
	0 to <3 months		3 to <12 months		12+ months		Overall	
Any	95	33 (27-40)	18	2.7 (1.6-4.3)	70	2.1 (1.6-2.6)	183	4.2 (3.6-4.9)
Liver	41	1805 (1295-2449)	5	92 (30-215)	2	7.4 (0.9-27)	48	138 (101-182)
Myeloproliferative neoplasms	8	764 (329-1505)	3	119 (25-348)	12	88 (45-153)	23	133 (85-200)
Pancreas	17	256 (149-409)	0	—	3	4.0 (0.8-12)	20	21 (13-32)
Hodgkin malignant lymphoma	1	172 (4.3-956)	0	—	0	—	1	9.7 (0.3-54)
Gallbladder or biliary tract	2	132 (16-476)	1	28 (0.7-155)	0	—	3	14 (2.9-41)
Metastases and nonspecified cancer in lymph nodes	5	86 (28-201)	0	—	0	—	5	6.3 (2.0-15)
MDS	1	75 (1.9-415)	0	—	1	6.8 (0.2-38)	2	11 (1.3-38)
Kidney	2	47 (5.6-168)	0	—	0	—	2	3.0 (0.4-11)
Leukemia	2	38 (4.6-138)	0	—	1	1.7 (0.0-9.3)	3	3.9 (0.8-11)
Non-Hodgkin malignant lymphoma	3	34 (7.0-99)	0	—	1	0.9 (0.0-5.3)	4	3.0 (0.8-7.5)
Lung, bronchi, or trachea	4	13 (3.6-34)	1	1.4 (0.0-8.0)	7	2.0 (0.8-4.2)	12	2.7 (1.4-4.7)
Colon	2	9.5 (1.1-34)	1	2.1 (0.1-12)	3	1.3 (0.3-3.8)	6	2.0 (0.7-4.4)
Breast	1	3.6 (0.1-20)	0	—	4	1.2 (0.3-3.2)	5	1.2 (0.4-2.8)
Bladder	0	—	2	6.1 (0.7-22)	6	3.8 (1.4-8.3)	8	3.9 (1.7-7.7)
Stomach	0	—	1	9.8 (0.3-55)	3	6.1 (1.3-18)	4	6.3 (1.7-16)
Rectum	0	—	0	—	2	1.6 (0.2-5.8)	2	1.3 (0.2-4.5)
Uterus	0	—	1	8.9 (0.2-50)	0	0	1	1.5 (0.0-8.4)
Prostate	0	—	1	1.6 (0.0-8.7)	5	1.4 (0.4-3.2)	6	1.3 (0.5-2.9)

20 patients with pancreatic cancer had previous pancreatitis. Of note, among patients diagnosed with liver cancer with known stage during the first 3 months following the thrombotic event, 16 had localized cancer (SIR = 2451 [95% CI, 1400-3981]) and 9 had advanced cancer (SIR = 1191 [95% CI, 546-2263]). Among patients diagnosed with pancreatic cancer, 2 had localized cancer (SIR = 227 [95% CI, 27-820]) and 11 had advanced cancer (SIR = 263 [95% CI, 131-470]). We found a persistent increased cancer risk beyond 3 months of follow-up, but the estimates were imprecise (Table 3).

Hematologic cancer. The majority of hematologic cancers diagnosed in our cohort was myeloproliferative neoplasms, and were diagnosed among patients with HVT. The absolute risk of a myeloproliferative neoplasm diagnosis during the first 3 months was 0.7% and the SIR was 764 (95% CI, 329-1505) (Table 3). Beyond 1 year of follow-up, the patients still had a pronounced excess risk of myeloproliferative neoplasms (SIR = 88 [95% CI, 45-153]). After 5 years of follow-up, the absolute risk of myeloproliferative neoplasms was 2.2%, and at end of follow-up it was 3.5%. We also observed an excess risk of lymphoma,

Table 4. Characteristics of 91 patients with SVT before cancer diagnosis and 391 cancer patients without a prior SVT

	Cancer type, n (%)					
	Liver cancer		Pancreatic cancer		Myeloproliferative neoplasm	
	Prior SVT (n = 48)	No prior SVT (n = 211)	Prior SVT (n = 20)	No prior SVT (n = 96)	Prior SVT (n = 23)	No prior SVT (n = 84)
Female	11 (23)	36 (17)	9 (45)	45 (47)	17 (74)	54 (64)
Male	37 (77)	175 (83)	11 (55)	51 (53)	6 (26)	30 (36)
Median follow-up (IQR), d	76 (38-182)	115 (35-496)	31 (8-63)	97 (39-259)	2196 (1161-3133)	2499 (1699-3026)
Age at cancer diagnosis, y						
<40	2 (4)	0	0	0	10 (43)	19 (23)
40-64	23 (48)	96 (45)	12 (60)	56 (58)	11 (48)	55 (65)
65+	23 (48)	115 (55)	8 (40)	40 (42)	2 (9)	10 (12)
Median age (IQR), y	65 (58-72)	66 (60-73)	61 (57-70)	63 (57-72)	42 (34-53)	47 (41-55)
Year of cancer diagnosis						
1994-1999	3 (6)	10 (5)	0	0	1 (4)	1 (1)
2000-2005	16 (33)	67 (32)	3 (15)	25 (26)	10 (44)	41 (49)
2006-2011	29 (61)	134 (63)	17 (85)	71 (74)	12 (52)	42 (50)
Comorbidity level						
Low	8 (17)	62 (29)	6 (30)	54 (56)	10 (44)	56 (67)
Moderate	22 (46)	76 (36)	6 (30)	33 (35)	4 (17)	27 (32)
Severe	18 (37)	73 (35)	8 (40)	9 (9)	9 (39)	1 (1)
Liver disease	32 (67)	81 (38)	4 (20)	1 (1)	7 (30)	2 (2)
Pancreatitis	2 (4)	7 (3)	5 (25)	6 (6)	1 (4)	0
Diabetes	18 (38)	56 (27)	8 (40)	20 (21)	2 (9)	2 (2)
Chronic obstructive pulmonary disease	4 (8)	25 (12)	4 (20)	12 (13)	0	4 (5)
Heart failure or previous MI	10 (21)	24 (11)	3 (15)	6 (6)	1 (4)	1 (1)
Ascites	14 (29)	29 (14)	4 (20)	4 (4)	5 (22)	0
Varices	14 (29)	30 (14)	4 (20)	0	7 (30)	0
Surgical procedure within previous 90 d	35 (73)	100 (47)	15 (75)	50 (52)	15 (65)	13 (15)

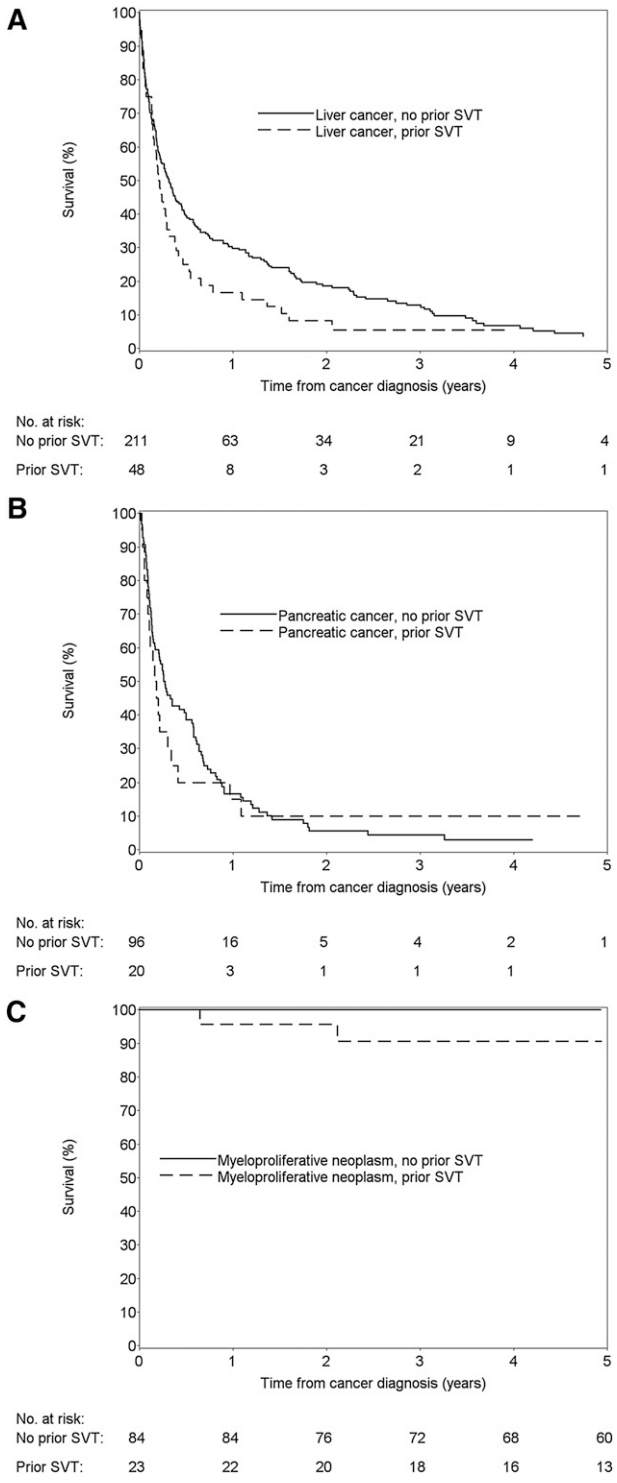


Figure 2. Survival curves for cancer patients with and without SVT. (A-C) Survival curves for patients with a diagnosis of liver cancer (A), pancreatic cancer (B), or myeloproliferative neoplasm (C) and SVT, and for a matched comparison cohort of cancer patients without SVT (matched by cancer type and stage, sex, age [5-year intervals], and year of diagnosis [5-year intervals]).

leukemia, and MDS during the first 3 months of follow-up. Thereafter, the risk did not differ from the expected risk (Table 3).

Other cancers. The number of lung, stomach, gallbladder/biliary tract, and urinary tract cancers observed during follow-up in patients diagnosed with SVT was higher than expected. The overall risk of being diagnosed with these smoking-related cancers was increased threefold to 14-fold compared with the expected (Table 3). Cancers of the colon, rectum, breast, uterus, and prostate were only weakly or not associated with SVT (Table 3).

Patients with ultrasound and/or CT scan-confirmed diagnosis of SVT. Among the 881 patients diagnosed with SVT after 2002, 624 events (71%) were confirmed by abdominal ultrasound and/or CT scan. In this subgroup, the overall cancer risk was even higher (7.7 [95% CI, 6.3-9.4]) than for the entire SVT cohort (Table 1). During the first 3 months of follow-up, the SIR for cancer was 52 (95% CI, 41-66); between 3 and 12 months of follow-up, the ratio was 4.3 (95% CI, 2.2-7.5); and beyond 1 year of follow-up it remained increased twofold. The proportion of SVT confirmed by ultrasound or CT scan increased from 66% in 2002 to 85% in 2011. For patients with a confirmed diagnosis between 2002 and 2006, the overall cancer SIR was 4.7 (95% CI, 3.4-6.5), and between 2007 and 2011 it was 12 (95% CI, 9.4-15).

Survival analysis

Characteristics. The survival analyses included 259 patients with liver cancer, 116 patients with pancreatic cancer, and 107 patients with myeloproliferative neoplasms. Among these patients, SVT preceded the cancer diagnosis in 48 (all with PVT), 20 (19 with PVT and 1 with HVT), and 23 (15 with PVT and 8 with HVT) patients, respectively. Compared with matched cancer patients without SVT, more patients diagnosed with SVT before their cancer diagnosis had a high comorbidity level, including liver disease and associated complications, diabetes, and more had undergone surgical procedures within 90 days (Table 4).

Survival. Patients with liver or pancreatic cancer had a poor outcome, regardless of presence of SVT before cancer diagnosis (Figure 2A-B).

The 3-month survival after liver cancer diagnosis was 44% for patients with and 55% for patients without SVT, corresponding to a mortality rate ratio of 1.5 (95% CI, 0.9-2.3). After 1 year of follow-up, thrombosis was still a prognostic factor for liver cancer patients; survival was 17% among patients with thrombosis and 30% among patients without thrombosis. At the end of follow-up, the mortality rate ratio for liver cancer was 1.6 (95% CI, 1.1-2.3).

SVT was also a prognostic factor for patients with pancreatic cancer. The 3-month survival after pancreatic cancer diagnosis was 35% for patients with and 53% for patients without SVT, yielding a 3-month mortality rate ratio for pancreatic cancer of 1.5 (95% CI, 0.8-2.9). Among patients with pancreatic cancer, SVT was not a prognostic factor for 1-year survival (15% for patients with and 17% for patients without thrombosis). The overall mortality rate ratio for pancreatic cancer was 1.4 (95% CI, 0.8-2.5).

In contrast, patients with myeloproliferative neoplasms had a much better prognosis (Figure 2C), regardless of the presence of an SVT. Due to the few deaths among these patients, we did not analyze the impact of SVT on relative mortality.

Discussion

In this cohort study, we found SVT to be a strong marker of occult cancer. In particular, we observed a higher incidence of liver cancer, pancreatic cancer, and myeloproliferative neoplasms than expected during the first 3 months after a PVT or HVT diagnosis. Although excess cancer occurrence decreased after 3 months, SVT remained a marker of slightly increased cancer risk during subsequent follow-up, especially for myeloproliferative neoplasms. SVT was a prognostic factor for short-term

survival in patients with liver and pancreatic cancer, but did not impact survival in patients with myeloproliferative neoplasms.

The pathogenesis of cancer-related SVT includes cancer-associated hypercoagulability, vessel-wall injury (tumor invasion), and stasis (splanchnic vein compression).[19] Our finding of a greatly increased short-term risk of cancer in patients with SVT may have several explanations. The substantial fall in risk after 3 months of follow-up implies that cancer preceded the thrombosis. An unrecognized malignancy likely triggered thrombus formation, and in some patients it may have been the first sign of cancer. Supporting this assumption, we found that more patients had SVT registered as the primary, rather than secondary, reason for their hospital contact. In other patients, the thrombosis may have been coincidentally detected in the diagnostic work-up for cancer,[11] which could be the case for patients diagnosed with both diseases during the first month of follow-up. The persistent increased risk of liver cancer is likely related to underlying diseases such as liver cirrhosis,[20] whereas the increased risk of myeloproliferative neoplasms beyond 1 year of follow-up may indicate that diagnosis of these neoplasms was delayed.[21] We had no information on test results for the JAK2V617F mutation, but it is possible that the finding of this mutation was related to diagnosis of myeloproliferative neoplasms in some patients.[10] Alcohol abuse is a risk factor for SVT, but is also associated with smoking.[22] Because smoking is a strong risk factor for cancer,[23] a combination of alcohol abuse and smoking may be the link behind the increased risk observed for lung, stomach, and bladder cancers. The increased risk of cancer during the study period likely reflects improved diagnostics, with more frequent use of CT scans.

Our study was conducted in a setting in which a national health service provides unfettered access to health care, allowing us largely to avoid referral and selection biases.[24] Other strengths were our inclusion of the entire Danish population and complete individual-level follow-up through access to patients' full hospital histories, as well as to outpatient clinic histories since 1994. Whereas diagnoses in the Danish Cancer Registry generally have high validity, with up to 95% to 98% completeness and accuracy of recorded diagnoses,[13,17] the registration of SVT in the Danish National Patient Registry has not been validated previously. We sought to strengthen the validity of SVT diagnoses by including only those registered with a specific anatomic location (excluding unspecified abdominal venous thrombosis). Moreover, we found that the majority (71%) of SVT diagnoses in our cohort were based on ultrasound examinations or CT scans, and hence were confirmed diagnoses. Finally, the use of registry data precluded detailed information on clinical care of patients.

Screening with abdomino-pelvic ultrasound, CT, or fluoro-2-deoxy-D-glucose–positron emission tomography combined with CT increases the chance of detecting an occult cancer in patients with venous thromboembolism.[25,26] The most recent guideline by the United Kingdom National Institute for Health and Clinical Excellence (NICE CG144; 2012), recommends considering an abdomino-pelvic CT scan in patients aged over 40 years presenting with venous thromboembolism.[27] We speculate if abdominal CT or PET/CT scans should be mandatory in the diagnostic work-up in patients with SVT. Nevertheless, proposals for implementing new diagnostic work-up procedures for occult cancer are only reasonable if they improve cancer-associated survival and are cost-effective. Based on the existing literature, screening for occult cancers in patients with lower-limb DVT and PE may help identify cancers at an early stage, but does not necessarily improve cancer-related survival.[28] However, the detection of underlying cancer potentially influences the management of venous thromboembolism,[29] as recurrence and complications are more frequent among cancer patients.[30,31]

In conclusion, we found evidence that SVT is a strong marker of occult cancer and a predictor of poor prognosis for patients with liver and pancreatic cancer.

Authorship

Contribution: K.K.S. and H.T.S. conceived the study idea, designed the study, and directed the analyses, which were carried out by D.K.F. and L.P.; K.K.S. reviewed the literature, organized the writing, and wrote the initial drafts; and all authors participated in the interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version.

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Splanchnic venous thrombosis is a marker of cancer and a prognostic factor for cancer survival

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Study V

Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study

Short title: Splanchnic vein thrombosis and survival

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Running head: Survival after splanchnic vein thrombosis

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Summary

Background: Splanchnic vein thrombosis (SVT) is a rare condition with a poorly understood prognosis.

Objectives: We conducted a population-based cohort study (1994-2013), using data from Danish nationwide medical registries, to examine the short- and long-term prognosis of SVT.

Methods: We identified 1,915 incident cases of SVT and a matched comparison cohort of 18,267 persons without SVT. We used the Kaplan-Meier method to calculate absolute risk of death among patients in both cohorts. Using stratified Cox regression, we computed mortality rate ratios (MRRs) with 95% confidence intervals (CIs), comparing SVT patients with the comparison cohort. *Results:* We identified 1,500 (78%) patients with portal vein thrombosis, 204 (11%) with hepatic vein thrombosis, and 211 (11%) with mesenteric vein thrombosis. The mortality risks were markedly higher for SVT patients than for matched members of the comparison cohort during the first 5 years of follow-up (30-day risk: 20.6% vs. 0.7%; 31-364-day risk: 21.7% vs. 4.7%; and 1-5-year risk: 25.4% vs. 17.7%). The corresponding MRRs were 40.7 (95% CI: 32.4-51.1), 7.4 (95% CI: 6.4-8.6), and 2.4 (95% CI: 2.1-2.8), respectively. Notably, the MRR remained twofold increased after more than 5 years of follow-up.

Conclusions: Splanchnic vein thrombosis has a poor short- and long-term prognosis. Despite extensive matching on several diseases, we found an increased mortality for all subtypes of splanchnic vein thrombosis. Reasons for the increased mortality observed in patients with splanchnic vein thrombosis need further clarification.

Keywords: Epidemiology; Portal system; Budd-Chiari syndrome; Prognosis

Introduction

Splanchnic vein thrombosis (SVT) - thrombosis of portal, hepatic, or mesenteric veins is a rare presentation of venous thrombosis [1]. The limited data available on incidence of SVT show a large range, *i.e.*, between 1 per million [2] and 1 per 100.000 [3] persons per year. A Swedish autopsy study found a prevalence of portal vein thrombosis of 1 per 100 persons [4], suggesting that this type of thrombosis is much more common than perceived. The elements of Virchow´s triad, including hypercoagulability, endothelial injury (*e.g.*, tumor invasion, surgical trauma, infection, or inflammation), and venous stasis (*e.g.*, compression caused by a solid tumor, abscess, hepato- or splenomegaly, or depressed cardiac output) are also applicable in the pathogenesis of SVT [1,5].

Cirrhosis, hepato-biliary cancers, and intra-abdominal infection or inflammation are among the most important local precipitating factors for SVT [1]. Congestive heart failure and atrial fibrillation increase the risk of venous thromboembolism [6] and may also increase risk of SVT. The most common systemic risk factors are myeloproliferative neoplasms and prothrombotic genetic conditions (*e.g.,* mutation in Factor V Leiden or prothrombin) [7]. Finally, pregnancy and oral contraceptives also may cause SVT [1], although young women likely represent only a small number of SVT patients. Patients presenting with SVT are mainly diagnosed and treated in hematological and gastroenterological departments, depending on their underlying disease. Some also are diagnosed accidentally when undergoing an abdominal ultrasound or computerized tomography (CT) scan for another indication [8]. In some cases, SVTs are found only at autopsy [4].

The prognosis after SVT is poorly understood. Underlying comorbidities [9] and location of thrombosis likely impact prognosis [10]. The aim of our study was to examine survival in a nationwide population-based cohort of patients with incident SVT and to explore whether specific prevalent diseases modify this outcome.

Patients and Methods

Setting and Data Sources

We conducted a population-based nationwide Danish cohort study of incident cases of SVT diagnosed between 1994 and 2013 (the cumulative Danish population in this period was 7,3 million persons), using data from the Danish National Patient Registry (DNPR) [11], and the Danish Civil Registration System [12]. The Danish National Health Service provides tax-funded medical care to all Danish residents and guarantees free-of-charge access to hospitals and outpatient clinics [13].

Study Population

The DNPR contains data on all hospital inpatient contacts since 1977, registered according to the *International Classification of Diseases* (ICD) 8th and 10th version [11]. The ICD-10 was introduced in Denmark in 1994. The DNPR also covers data from outpatient clinic visits since 1994. We therefore started our study in 1994. For each hospital contact, the treating physician assigns a primary discharge diagnosis and may also assign up to 19 secondary diagnoses. Surgical procedures have been coded in the DNPR using the Nordic Medico Statistical Committee Classification (NOMESCO) system since 1996 [14]. The DNPR also captures imaging examinations (both invasive and non-invasive), and data since 2002 are considered to be complete.

We identified all hospital inpatients and outpatients diagnosed with a first-time SVT during 1994 through 2013, including both primary and secondary diagnoses. Patients with only an emergency room SVT diagnosis were excluded from the analysis. We also did not include patients who were diagnosed with SVT before 1994, to avoid capturing recurrent thrombosis. All diagnosis codes used are provided in the supplemental Appendix, for online only.

Comparison Cohort

We used the DCRS and DNPR to create a population-based comparison cohort. For each patient with SVT we randomly matched 10 persons from the Danish general population on sex, year of birth (5-year intervals), date of SVT diagnosis, and several comorbidities. The underlying comorbidities used for the matching included cirrhosis, pancreatitis, liver cancer, pancreatic cancer, other gastrointestinal cancer, myeloproliferative neoplasms, extra-intestinal cancer, atrial fibrillation or flutter, venous thromboembolism, congestive heart failure, other alcohol-related disease (not cirrhosis and pancreatitis), and inflammatory bowel disease diagnosed any time before the index date. The index date for each member of the comparison cohort corresponded to the hospital admission date or hospital outpatient contact date for the matched incident SVT case.

Patient Characteristics

In addition to the matching factors, we obtained information on diseases (diagnosed prior to SVT/index date) included in the Charlson Comorbidity Index [15, 16]: myocardial infarction, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate to severe renal disease, and AIDS. In addition, we included information on pregnancy or childbirth within 90 days before index date. We also obtained information on surgical procedures performed within 90 days before the index date and on documented abdominal ultrasound, angiography, CT scan or magnetic resonance (MR) scan, performed within 30 days before or after the hospital contact for SVT. Finally, we calculated the frequency of patients that were diagnosed with ischemic colitis or infarction during same admission or subsequently.

Statistical Analysis

We characterized SVT patients and the comparison cohort members by sex, age category, calendar period of diagnosis, and covariates. We calculated median age at the index date and median follow-up period (interquartile range (IQR)) for all patients and for 30-day survivors. We followed both cohorts from SVT/index date until death from any cause, emigration, 30 November 2013, or 20 years of follow-up, whichever came first. Using the Kaplan-Meier method [17], we computed mortality risks for several subcohorts (*e.g.* cancer and cirrhosis patients), and for several follow-up periods (30 days, 31-364 days, 1-5 years, >5-20 years). In addition, we illustrated graphically the mortality (absolute risk) observed in the SVT and comparison cohorts.

In accordance with the matched design, we used a stratified Cox proportional hazard regression model to compute mortality rate ratios (MRRs) with 95% confidence intervals (CIs) (as a measure of relative risk for mortality), comparing SVT patients with members of the matched comparison cohort [18]. We used log-log plots to examine the proportionality of hazards visually, and found that the assumptions were fulfilled for all analyzed follow-up periods. We computed MRRs for the first 30 days of follow-up, 31-364 days, 1-5 years, and >5-20 years. The MRRs were adjusted for all matching factors by study design. In a second analysis, we also adjusted for recent surgery.

We described the immediate causes of death among patients (when available), and compared cause-specific mortality rates among SVT patients and the comparison cohort.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). The Danish Data Protection Agency approved the study (record no. 1-16-02-1-08). Data in Danish registries are available to researchers, and their use does not require ethics approval or informed consent.

Results

We identified 1,915 patients with a first-time SVT, including 1,500 (78.3%) with portal vein thrombosis, 204 (10.7%) with hepatic vein thrombosis (two patients had concurrent portal vein thrombosis), and 211 (11.0%) with mesenteric vein thrombosis (four patients had concurrent portal vein thrombosis). The corresponding incidence rates were 22 per 100,000 persons, 3 per 100,000 persons, and 3 per 100,000 persons, respectively. Among SVT patients, there were slightly more men (53.2%) than women, and the median age was 63 years (IQR: 49–74 years). The matched comparison cohort included 18,267 persons from the general population, with a similar gender and age distribution through matching. The SVT patients were followed for a median of 1.3 years (IQR: 0.1–4.8 years), while the matched comparison cohort was followed for a median of 4.0 years (IQR: 1.7–8.0 years). For 30-day survivors of SVT (n=1,511), the median follow-up time was 2.5 years (IQR: 0.7-6.1). In total, 1,620 patients (84.6%) were diagnosed with SVT during an inpatient admission and the remaining 295 patients (15.4%) during an outpatient clinic visit. Overall, 77.1% of patients had their diagnosis confirmed by imaging.

The matching of medical characteristics was successful, and accordingly the distributions of underlying diseases or conditions such as liver cirrhosis, pancreatitis, other alcohol-related diseases, cancer, atrial fibrillation or flutter, and deep venous thrombosis or pulmonary embolism were nearly equal among SVT patients and members of the comparison cohort.

We also classified patients according to recent surgery and other underlying comorbidities (not used as matching criteria). In particular, the frequency of recent surgery was higher for SVT patients than for the matched comparison cohort. Among patients with SVT, 763 had had recent surgery (39.8%), including 282 (14.7%) with abdominal surgery. Also, 429 (22.4%) had gastrointestinal endoscopy within 90 days before SVT diagnosis. Several of the other comorbidities, including cardiovascular diseases, ulcer disease, mild liver disease, diabetes, and renal disease, were more prevalent also among SVT patients than among members of the comparison cohort (Table 1). Figure 1 depicts frequencies of underlying comorbidities according to

thrombosis location. Frequency of recent surgery was high among patients with all types of thrombosis. However, some characteristics were predominant in specific thrombosis types (e.g. cirrhosis and pancreatitis for portal vein thrombosis, venous thromboembolism for hepatic vein and congestive heart failure for mesenteric vein thrombosis) (Figure 1).

Among SVT patients, a total of 91 patients were diagnosed with ischemic colitis or infarction during or after the admission for SVT. The frequency was particularly high for patients with mesenteric vein thrombosis (n=37, 17.5%), but also notable for patients with portal vein thrombosis (n=51, 3.4%), and hepatic vein thrombosis (n=3, 1.5%).

1-year Mortality

The 30-day and 31-364 day mortality risks were 20.6% and 21.7% for SVT patients, compared with 0.7% and 4.7% for the comparison cohort (Table 2 and Figure 2). The 30-day mortality risk was particularly high for patients with mesenteric vein thrombosis (63.1%), followed by portal vein thrombosis (15.6%), and hepatic vein thrombosis (13.2%) (Figure 3A-3C). The mortality risks during 31-364 days remained markedly elevated for portal vein thrombosis (23.1%), hepatic vein thrombosis (16.5%), and mesenteric vein (10.8%) (Table 2). The overall 30-day MRR was 40.7 (95% CI: 32.4-51.1), comparing SVT patients with the comparison cohort. For portal vein thrombosis, the 30-day MRR was 26.9 (95% CI: 20.8–34.7) and for hepatic vein thrombosis it was 32.6 (95% C: 14.8–71.8). During 31-364 days of follow-up, the overall MRR was 7.4 (95% CI: 6.4-8.6), with similar estimates for subtypes of SVT.

When we examined mortality risks and MRRs according to underlying disease (i.e. the matching factors), we found that 30-day mortality and 31-364-day mortality were markedly higher among SVT patients, compared with members of the comparison cohort with similar comorbidity (Tables 2 and 3).

Because recent surgery was more frequent among SVT patients than in the comparison cohort, we additionally adjusted for surgery in a second analysis (Supplementary Table 1). Even though the additional adjustment attenuated the risk estimates, it did not change the conclusions.

1-5 year Mortality and >5 year Mortality

The absolute mortality risk 1-5 years after the index date was 25.4% for SVT patients and 17.7% for members of the comparison cohort. Thus mortality was high in both cohorts, but the risk difference between the cohorts was smaller than during the first year of follow-up (Table 2). Mortality among patients with portal vein thrombosis (27.2%) and hepatic vein thrombosis (20.9%) had the greatest impact on the combined risk for all SVT patients. The overall 1-5 year MRR was 2.4 (95% CI: 2.1-2.8), varying according to thrombosis site. The MRRs for thrombosis of the portal vein, hepatic vein, and mesenteric vein were 2.6 (95% CI: 2.2-3.1), 2.4 (95% CI: 1.5-3.7), and 0.6 (95% CI: 0.2-1.9), respectively (Table 3).

During the 1-5 year follow-up period, SVT was associated with increased mortality risks and MRRs among patients with cancer (except for liver and pancreatic cancer), cirrhosis, pancreatitis, other alcohol-related diseases, atrial fibrillation or flutter, and congestive heart failure (Table 3). After 5 years of follow-up, 458 (24%) SVT patients [356 (24%) of 1500 with portal vein thrombosis, 88 (43%) of 204 with hepatic vein thrombosis, and 14 (7%) of 211 with mesenteric vein thrombosis)] and 7,640 (42%) members of the comparison cohort were still alive. The >5 year MRR for any SVT was 2.1 (95% CI: 1.6-2.6), based on MRRs of 2.2 (95% CI: 1.7-2.9) for portal vein thrombosis, 1.6 (95% CI: 0.9-2.8) for hepatic vein thrombosis, and 1.9 (95% CI: 0.4-9.3) for mesenteric vein thrombosis.

Cause of Death

An immediate cause of death was registered for 663 SVT patients and 3,074 persons in the comparison cohort. The most frequent cause of death in SVT patients was circulatory system disease (n=161, 24.3%), respiratory system disease (n=97, 14.6%), cancer (n=82, 12.4%), SVT (n=63, 9.5%), liver disease (n=60, 9.0%), and sepsis (n=53, 8.0%). Among the patients with SVT recorded as immediate cause of death, 55 died within the first 30 days after SVT, 5 died between 31 and 364 days, and 3 died one or more years after their SVT diagnosis. Of note, bleeding was registered as the immediate cause of death in only 19 SVT patients; 5 died within the first 30 days, 2 died between 31 and 364 days, 7 died between 1 and 5 years, and 5 persons died more than five years after their SVT diagnosis. Compared with persons in the matched cohort, SVT patients had a markedly elevated MRR for cardiovascular diseases [5.8 (95% CI: 4.7-7.1)], cancer [5.8 (95% CI: 4.4-7.8)], respiratory system diseases [4.7 (95% CI: 3.6-6.1)], liver disease [14.9 (95% CI: 9.6-23.1)], and bleeding [3.8 (95% CI: 2.1-7.0)].

Discussion

This Danish nationwide 20-year follow-up study included 1,915 patients with a first-time SVT and a matched comparison cohort of 18,267 persons from the general population. We found that patients with SVT had markedly higher short- and long-term mortality than members of the comparison cohort, despite extensive matching by underlying diseases associated with mortality.

Knowledge of the impact of SVT on life expectancy is very limited and poorly understood. Existing studies have been restricted to selected cohorts (*e.g*. patients with cirrhosis or myeloproliferative neoplasms), without a general population comparison cohort [9, 19-21]. We are aware of only one large study that compared mortality among SVT patients to expected mortality in the general population, based on age- and sex-specific mortality rates in the US Caucasian population [10]. The study included 832 patients

diagnosed with portal, mesenteric, splenic, and hepatic vein thrombosis at the Mayo Clinic over a 20-year period (1980-2000). Patients with SVT had an overall 10-year survival of 60% by the end of follow-up, lower than that expected in the general population. Patients with multi-segmental thrombosis or underlying cancer had a particularly poor prognosis. Stratification by location of thrombosis showed important differences in mortality. Patients with portal vein thrombosis had the highest mortality, as well as the highest prevalence of cancer and cirrhosis. In contrast, patients with hepatic vein thrombosis had the lowest overall 10-year mortality. However, this group of patients primarily included younger women and patients with myeloproliferative neoplams [10]. In our study, patients with portal vein thrombosis had higher mortality risks than those with hepatic vein thrombosis during all follow-up periods. Compared with the matched comparison cohort, the mortality was especially elevated during first 30 days, but remained increased for patients with both portal and hepatic vein thrombosis. In contrast, we found that patients with mesenteric thrombosis had by far the highest 30-day mortality risk (though based on small numbers), but after one year their relative mortality paralled that of the general population cohort.

Bleeding has been reported as a frequent complication among patients with SVT, particularly variceal bleeding occurring in patients treated with warfarin [10]. While we did not examine bleeding rates in our study, bleeding was registered as the primary cause of death for relatively few patients (although cause-of-death data should be cautiously interpreted).

Reasons for the increased mortality observed in patients with SVT need further clarification. Although we matched our SVT patients to a comparison cohort by diseases associated with both SVT and prognosis, we lacked detailed information on disease severity (*e.g.* cancer stage, severity and type of heart failure, etc.). It is thus likely that thrombosis occurred as a complication of more advanced disease or its treatment. We noted that surgery and several chronic diseases (not included as mathcing factors due to collinearity) were more prevalent among SVT patients than in the comparison cohort. This may have contributed to the higher short- and long-term mortality that we observed. However, additional adjustment for recent surgery

did not change the conclusions for any of subtypes of SVT. It follows that we found cancer, cardiovascular diseases, and respiratory diseases to be frequent causes of death.

Any study relying on medical databases has inherent limitations. The crucial issue in our study was potential misclassification of SVT diagnoses. While validity of the risk estimates depends mainly on adjustment for confounders, absolute mortality risk estimates rely on accuracy of SVT diagnoses. We are not aware of previous specific studies that validated diagnostic coding of SVT diagnoses in medical registries. However, in earlier research we described a cohort of patients diagnosed with portal vein thrombosis during 1992-2005 [22]. While this was not designed as a validation study, diagnoses were confirmed among 67 of 70 (96%) patients registered with portal vein thrombosis during the period (3 patients had instead thrombosis of the splenic or mesenteric vein) [22].

Our study included information on several covariates used both for matching and confounder adjustment. The validity of diagnoses of cancer and comorbidities, as well as the surgical procedures examined in our study, has been shown to be consistently high (overall 98%) [23, 24]. Still, a study limitation is the lack of clinical information allowing us to assess the degree of thrombosis, severity of underlying diseases, or presence of prothrombotic disorders.

In conclusion, we found that SVT was associated with increased short- and long-term mortality. The clinical implications of our study are not entirely clear. The members of the SVT cohort were diverse, and some patients with chronic diseases at high risk of death may not have benefited from extended diagnostic work-up or treatment.

Addendum

K.K. Søgaard and H.T. Sørensen conceived the study idea. K.K. Søgaard and H.T. Sørensen designed the study and directed the analyses, which were carried out by B. Darvalics and E. Horváth-Puhó. K.K. Søgaard reviewed the literature, organized the writing, and wrote the initial drafts. All authors critically revised the manuscript and approved the final version for submission to JTH.

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Disclosures

None of the authors received any fees, honoraria, grants or consultancies that would constitute a conflict of interest with the current study. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of the company-funded studies have any relation to the present study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Diagnostic coding according to International Classification of Diseases 8th (ICD-8) and 10th revision (ICD-10) and Danish Procedure Coding.

Table 1 Characteristics for patients with SVT and for the general population comparison cohort

	SVT cohort n = 1,915, n(%)	Comparison cohort n = 18,267, n(%)
Age categories (y)		
<40	271 (14.1)	2,633 (14.4)
40–64	777 (40.6)	7,345 (40.2)
65+	867 (45.3)	8,289 (45.4)
Calendar period		
1994-1999	270 (14.1)	2,605 (14.3)
2000-2005	445 (23.2)	4,297 (23.5)
2006-2013	1,200 (62.7)	11,365 (62.2)
Matching factors		
Liver cirrhosis	216 (11.3)	1,671 (9.2)
Pancreatitis	206 (10.8)	1,821 (10.0)
Liver cancer	32 (1.7)	107 (0.6)
Pancreatic cancer	41 (2.1)	270 (1.5)
Other gastrointestinal cancer	104 (5.4)	970 (5.3)
Myeloproliferative neoplasm	23 (1.2)	179 (1.0)
Extra-intestinal cancer	200 (10.4)	1,818 (10.0)
Atrial fibrillation or flutter	173 (9.0)	1,545 (8.5)
Venous thromboembolism	132 (6.9)	1,069 (5.9)
Congestive heart failure	169 (8.8)	1,479 (8.1)
Other alcohol-related disease	194 (10.1)	1,667 (9.1)
Inflammatory bowel disease	69 (3.6)	588 (3.2)
Comorbid conditions		
Myocardial infarction	140 (7.3)	982 (5.4)
Peripheral vascular disease	173 (9.0)	809 (4.4)
Cerebrovascular disease	200 (10.4)	1,451 (7.9)
Dementia	33 (1.7)	239 (1.3)
Chronic pulmonary disease	208 (10.9)	1,479 (8.1)
Connective tissue disease	90 (4.7)	545 (3.0)
Ulcer disease	220 (11.5)	1,074 (5.9)
Mild liver disease	266 (13.9)	1,909 (10.5)
Diabetes	278 (14.5)	1,314 (7.2)
Diabetes with end-organ failure	129 (6.7)	628 (3.4)
Hemiplegia	8 (0.4)	54 (0.3)
Moderate to severe renal disease	86 (4.5)	391 (2.1)
AIDS	6 (0.3)	19 (0.1)
Other covariates		
Pregnancy or childbirth within 90 days	6 (0.3)	37 (0.2)
Surgical procedures within 90 days	763 (39.8)	1,668 (9.1)
Abdominal ultrasound/CT/MR/angiography*	1,181 (77.1)	-

* Examined 30 days before or after the SVT-related hospital contact [including only SVT patients diagnosed from 2002 on (n=1,532)].

Table 2 Mortality risk among patients with SVT and members of the general population comparison cohort, by subgroup and follow-up period

	Mortality risk (%) and 95% CI		
	30 days	**31-364 days**	**1-5 years**
Comparison cohort	0.7 (0.6-0.8)	4.7 (4.4-5.0)	17.7 (17.0-18.4)
SVT cohort	20.6 (18.8-22.5)	21.7 (19.7-23.9)	25.4 (22.6-28.6)
Portal vein	15.6 (13.9-17.5)	23.1 (20.9-25.6)	27.2 (23.9-30.7)
Hepatic vein	13.2 (9.3-18.7)	16.5 (11.7-22.8)	20.9 (14.8-29.1)
Mesenteric vein	63.1 (56.6-69.5)	10.8 (5.5-20.4)	7.4 (2.4-21.5)
Subgroups			
Liver cancer			
Comparison cohort	4.0 (1.5-10.4)	35.2 (26.0-46.5)	69.4 (41.8-92.5)
SVT cohort	3.1 (0.5-20.2)	66.5 (49.4-82.7)	12.5 (1.9-61.3)
Pancreatic cancer			
Comparison cohort	8.5 (5.7-12.5)	33.9 (28.1-40.6)	48.3 (38.7-59.0)
SVT cohort	22.0 (12.1-37.9)	47.8 (31.4-67.4)	31.6 (13.2-64.1)
Other gastrointestinal cancer			
Comparison cohort	1.2 (0.7-2.2)	9.3 (7.5-11.4)	26.5 (22.9-30.5)
SVT cohort	27.9 (20.3-37.6)	27.7 (18.6-40.1)	33.3 (20.4-51.5)
Myeloproliferative neoplasms			
Comparison cohort	0.6 (0.1-3.9)	4.8 (2.4-9.3)	18.3 (12.4-26.5)
SVT cohort	17.4 (6.9-39.9)	10.5 (2.7-35.9)	39.9 (18.5-71.8)
Extra-intestinal cancer			
Comparison cohort	1.0 (0.6-1.6)	9.7 (8.4-11.2)	24.8 (22.4-27.5)
SVT cohort	31.5 (25.6-38.4)	35.8 (28.2-44.6)	48.6 (36.2-62.6)
Liver cirrhosis			
Comparison cohort	1.6 (1.1-2.3)	8.8 (7.5-10.4)	34.2 (31.2-37.4)
SVT cohort	17.1 (12.7-22.9)	42.3 (35.3-50.2)	41.3 (29.7-55.4)
Pancreatitis			
Comparison cohort	0.5 (0.3-1.0)	3.5 (2.7-4.5)	16.6 (14.5-19.0)
SVT cohort	12.3 (8.5-17.7)	18.8 (13.7-25.6)	32.4 (23.8-43.2)
Atrial fibrillation or flutter			
Comparison cohort	1.4 (0.9-2.2)	11.1 (9.6-12.9)	39.9 (36.7-43.3)
SVT cohort	42.8 (35.8-50.6)	42.2 (32.8-53.0)	52.3 (37.7-68.5)
Congestive heart failure			
Comparison cohort	1.4 (0.9-2.2)	12.9 (11.2-14.8)	47.9 (44.7-51.2)
SVT cohort	36.1 (29.4-43.8)	42.0 (33.0-52.2)	65.7 (52.2-78.8)
Venous thromboembolism			
Comparison cohort	0.4 (0.1-1.0)	5.6 (4.4-7.2)	22.5 (19.7-25.7)
SVT cohort	18.2 (12.6-25.9)	25.5 (18.1-35.1)	28.1 (18.1-42.0)
Other alcohol-related disease			
Comparison cohort	0.8 (0.5-1.4)	7.0 (5.8-8.4)	27.5 (24.7-30.4)
SVT cohort	21.7 (16.6-28.2)	25.7 (19.3-33.7)	43.6 (32.7-56.3)
Inflammatory bowel disease			
Comparison cohort	0.3 (0.1-1.4)	2.4 (1.4-4.0)	8.8 (6.4-12.0)
SVT cohort	16.0 (9.2-27.1)	14.6 (7.6-27.0)	14.2 (6.1-31.4)

CI, confidence interval

Table 3 Mortality after SVT compared with the general population comparison cohort

	Mortality rate ratio and 95% CI		
	30 days	**31-364 days**	**1-5 years**
Comparison cohort	1.00	1.00	1.00
Splanchnic vein thrombosis	40.7 (32.4-51.1)	7.4 (6.4-8.6)	2.4 (2.1-2.8)
Portal vein	26.9 (20.8-34.7)	7.4 (6.3-8.8)	2.6 (2.2-3.1)
Hepatic vein	32.6 (14.8-71.8)	7.6 (4.6-12.6)	2.4 (1.5-3.7)
Mesenteric vein	435.0 (138.8-1369.3)	6.1 (2.4-15.5)	0.6 (0.2-1.9)
Subgroups			
Liver cancer	1.7 (0.2-15.6)	3.3 (1.5-7.0)	0.4 (0.1-3.6)
Pancreatic cancer	3.7 (1.6-8.2)	2.2 (1.1-4.3)	0.9 (0.2-3.1)
Other gastrointestinal cancer	39.0 (17.0-89.4)	3.7 (2.1-6.4)	1.8 (0.9-3.3)
Myeloproliferative neoplasm	20.0 (1.8-220.5)	2.4 (0.5-11.2)	1.8 (0.5-6.5)
Extra-intestinal cancer	37.9 (21.5-66.9)	6.0 (4.1-8.8)	3.1 (2.0-4.8)
Liver cirrhosis	12.4 (7.3-21.0)	7.3 (5.1-10.4)	1.5 (0.9-2.4)
Pancreatitis	25.9 (11.5-58.3)	7.8 (4.8-12.9)	2.5 (1.6-3.8)
Atrial fibrillation or flutter	60.1 (32.7-110.8)	5.8 (3.7-9.2)	2.8 (1.7-4.6)
Congestive heart failure	47.8 (25.7-89.0)	5.8 (3.8-8.8)	2.8 (1.8-4.2)
Venous thromboembolism	40.4 (13.7-119.4)	6.3 (3.6-10.8)	1.4 (0.8-2.7)
Other alcohol-related disease	29.4 (15.3-56.3)	5.0 (3.3-7.7)	2.4 (1.6-3.7)
Inflammatory bowel disease	41.0 (9.0-187.6)	4.4 (1.5-13.3)	2.4 (0.8-7.4)

CI, confidence interval

Supplementary Table 1. Mortality after SVT compared with the general population comparison cohort, adjusted for surgery within 90 days

	Mortality rate ratio and 95% CI		
	30 days	**31-364 days**	**1-5 years**
Comparison cohort	1.00	1.00	1.00
Splanchnic vein thrombosis	36.4 (28.9-45.9)	6.3 (5.4-7.4)	2.3 (1.9-2.7)
Portal vein	23.4 (18.0-30.3)	6.3 (5.4-7.5)	2.4 (2.0-2.9)
Hepatic vein	29.4 (12.4-69.9)	6.6 (3.9-11.1)	2.0 (1.2-3.2)
Mesenteric vein	469.0 (143.4-1534.1)	4.6 (1.8-12.1)	0.6 (0.2-1.9)

CI, confidence interval

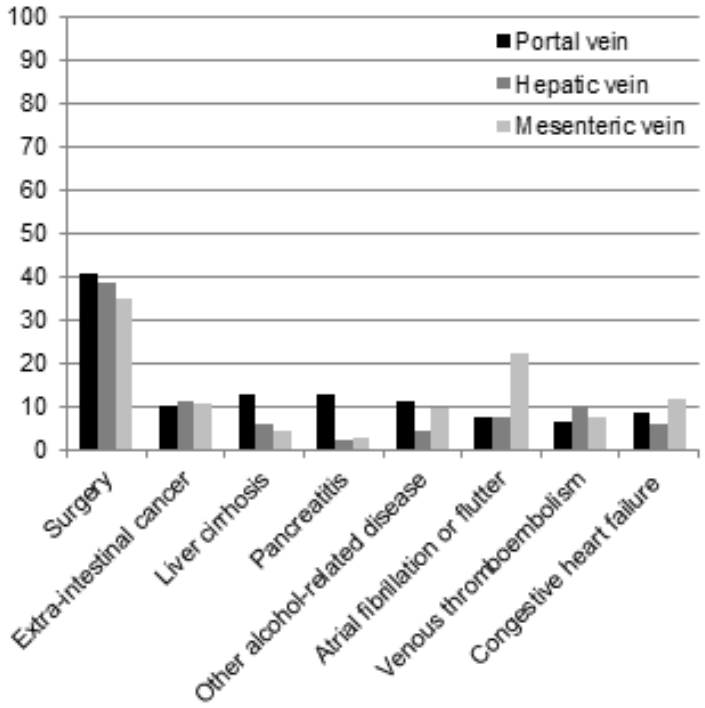


Figure 1

Figure 1. Frequencies (%) of selected comorbidities and conditions by type of thrombosis

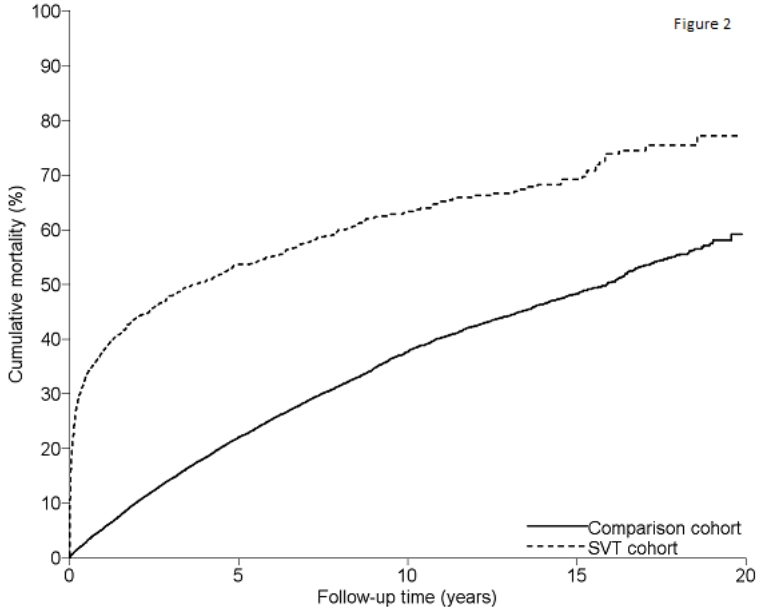
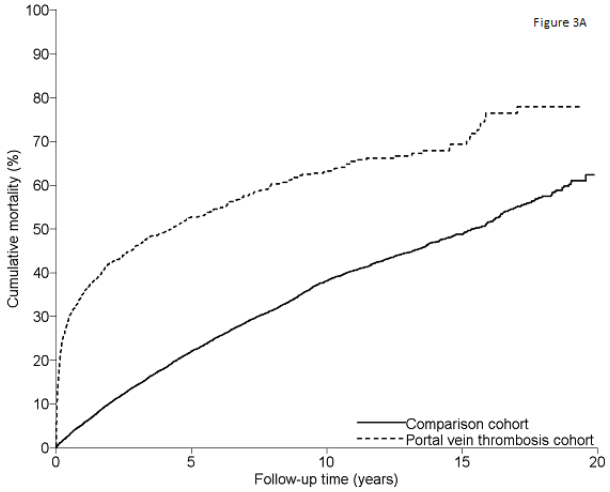
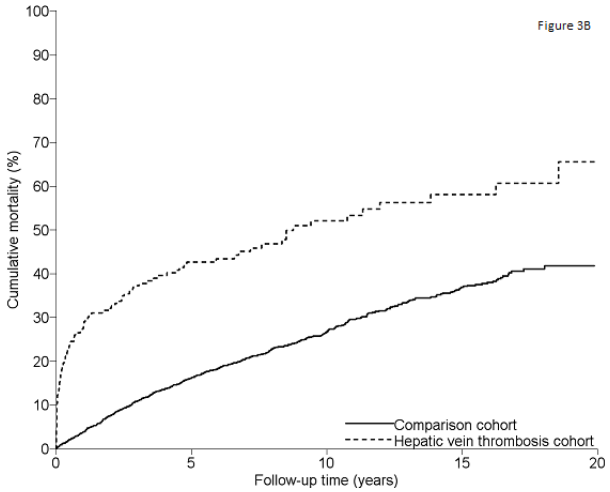


Figure 2. 20-year mortality among SVT patients and the matched comparison cohort from the general population





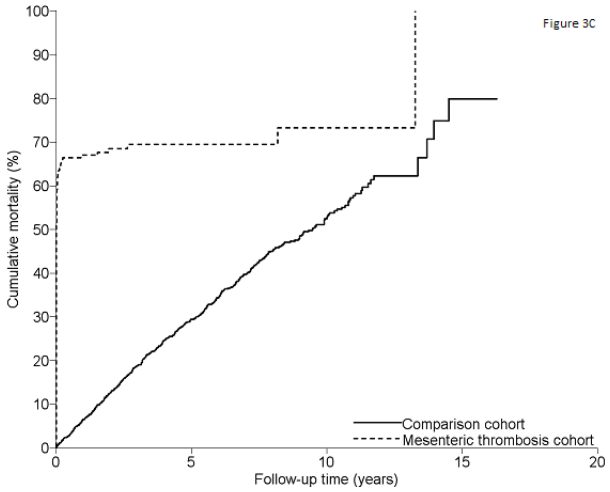


Figure 3. 20-year mortality for SVT subtypes

Survival curves for patients with a diagnosis of portal vein thrombosis (A), hepatic vein thrombosis (B) and mesenteric vein thrombosis (C), and their matched comparison cohorts.

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Appendix*:* ICD-8 and ICD-10 codes used in the study

	ICD-8	ICD-10
Splanchnic vein thrombosis		
Portal vein thrombosis	452.99	I81.9
Hepatic vein thrombosis	453.01	I82.0
Mesenteric thrombosis	444.29	K55.0H
Splenic vein thrombosis	289.44, 453.03	-
Matching factors		
Liver cancer	155, 156.10, 156.11, 156.18, 156.19	C22.0, C22.1, C22.7, C22.9
Pancreatic cancer	157	C25
Other gastrointestinal cancer	150-154, 156.09, 156.29,156.99, 158-159	C15-C21, C23-C24, C26
Myeloproliferative neoplasms	208.99, 209.00, 287.29	D45.9, D47.4A, D47.3, D75.2
Other cancer	140-149, 160-209	C00-C14, C27-C96
Liver cirrhosis	571.09, 571.90-571.92, 571.99	K70.3, K71.7, K73.2E, K74.3, K74.4, K74.5, K74.6
Pancreatitis	57700, 57701, 57704-57719	K85, K86.0, K86.1
Atrial fibrillation or flutter	427.93, 427.94	I48
Venous thromboembolism	450.99, 451.00	I26.0, I26.9, I80.1–3
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Other alcohol-related disease	291.00-291.99, 303.00-303.99, 571.10	E24.4, E52.9A, F10.1, F10.2–10.9, G31.2, G62.1, G72.1, I42.6, K29.2, T50.0A, Z50.2, Z71.4, Z72.1
Inflammatory bowel disease	563.01, 563.19, 569.04	K50, K51
Other covariates		
Pregnancy or childbirth	630–680	O00–O99
Ultrasonography, CT-/MR-scan, angiography of pelvis and abdomen	-	UXUD, UXCD, UXMD, UXAD
Ischemic colitis or infarction	-	K55.0 (minus K55.0H)

Procedure codes	**1979-1995**	**ICD-10**
Recent surgical procedure	0000-9999	KA-KZ
Gastrointestinal endoscopies	91000, 91010, 91020, 91055, 91060, 91065, 91070, 91080, 91090, 91123, 92260, 92280, 92300, 92320, 92340, 92360	KUJ
Charlson Comorbidity Index	**ICD-8**	**ICD-10**
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430–438	I60–I69; G45; G46
Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30
Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531–534	K22.1; K25–K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0
Diabetes without end-organ damage	249.00; 249.06; 249.07; 249.09; 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Diabetes with end-organ damage	249.01–249.05; 249.08; 250.01–250.05; 250.08	E10.2–E10.8, E11.2–E11.8
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00–456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic cancer	195–198; 199	C76–C80
AIDS	079.83	B21–B24

Cause of death	**ICD-10 codes**
Circulatory system disease	I00-I99
Splanchnic venous thrombosis	I819, I820, K550
Venous thromboembolism	I26, I80
Liver disease	K70-K77
Cancer	C00-C96
Bleeding	I60, I61, I62, I850, K250, K522, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K922, N421, N93, R040, R041, R042, R048, R049, R589, D629
Respiratory system	J00-J99

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