

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

Jonathan Montomoli, Rune Erichsen, Kirstine Kobberøe Søgaard, Dóra Körmendiné Farkas, Anna-Marie Bloch Münster, Henrik Toft Sørensen

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Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Correspondence to
Dr Jonathan Montomoli;
jonathan.montomoli@gmail.com

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.

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}

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.

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

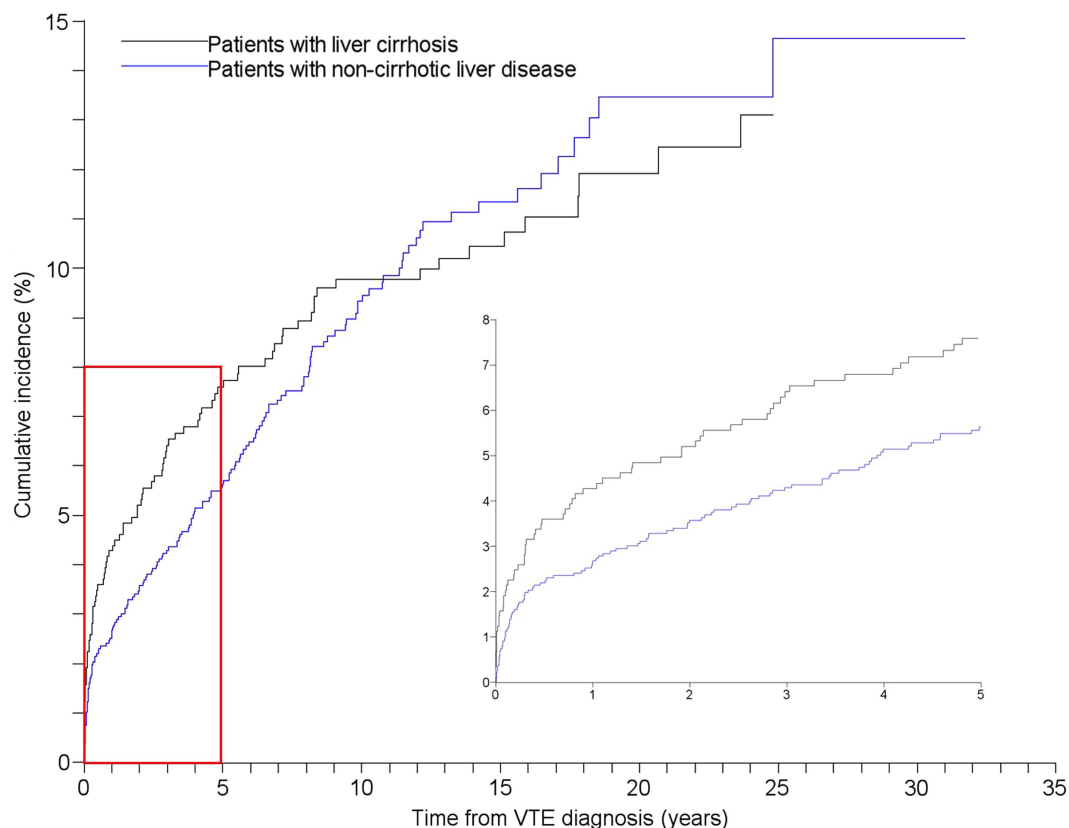


Figure 1 Cumulative incidence for all cancers among patients with liver disease following venous thromboembolism (VTE).

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)	20	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 diseases³¹ and comorbidity³² 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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REFERENCES

- Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012;379:1835–46.
- Lee AY. Thrombosis in cancer: an update on prevention, treatment, and survival benefits of anticoagulants. *Hematology Am Soc Hematol Educ Program* 2010;2010:144–9.
- Sorensen HT, Mellekjaer L, Steffensen FH, et al. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998;338:1169–73.
- Murchison JT, Wylie L, Stockton DL. Excess risk of cancer in patients with primary venous thromboembolism: a national, population-based cohort study. *Br J Cancer* 2004;91:92–5.
- Sorensen HT, Svaerke C, Farkas DK, et al. Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer. *Eur J Cancer* 2012;48:586–93.
- Baron JA, Gridley G, Weiderpass E, et al. Venous thromboembolism and cancer. *Lancet* 1998;351:1077–80.
- Buresi M, Hull R, Coffin CS. Venous thromboembolism in cirrhosis: a review of the literature. *Can J Gastroenterol* 2012;26:905–8.
- Huerta C, Johansson S, Wallander MA, et al. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med* 2007;167:935–43.
- Gulley D, Teal E, Suvannasankha A, et al. Deep vein thrombosis and pulmonary embolism in cirrhosis patients. *Dig Dis Sci* 2008;53:3012–17.
- Sogaard KK, Horvath-Puho E, Gronbaek H, et al. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol* 2009;104:96–101.
- Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol* 2010;8:800–5.
- Sorensen HT, Thulstrup AM, Mellekjaer L, et al. Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. *J Clin Epidemiol* 2003;56:88–93.
- Sorensen HT, Friis S, Olsen JH, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* 1998;28:921–5.
- Berman K, Tandra S, Vuppalanchi R, et al. Hepatic and extrahepatic cancer in cirrhosis: a longitudinal cohort study. *Am J Gastroenterol* 2011;106:899–906.
- Goldacre MJ, Wotton CJ, Yeates D, et al. Liver cirrhosis, other liver diseases, pancreatitis and subsequent cancer: record linkage study. *Eur J Gastroenterol Hepatol* 2008;20:384–92.
- Kalaitzakis E, Gunnarsdottir SA, Josefsson A, et al. Increased risk for malignant neoplasms among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011;9:168–74.
- Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398–9.
- Andersen TF, Madsen M, Jorgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.
- Severinsen MT, Kristensen SR, Overvad K, et al. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol* 2010;63:223–8.
- Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol* 2005;162:975–82.
- Storm HH, Michelsen EV, Clemmensen IH, et al. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull* 1997;44:535–9.
- Breslow NE, Day NE. *Statistical methods in cancer research. Volume II. The design and analysis of cohort studies*. IARC Scientific Publications, 1987;69–72.
- Sogaard KK, Erichsen R, Lund JL, et al. Cholangitis and subsequent gastrointestinal cancer risk: a Danish population-based cohort study. *Gut* 2013;63:356–61.
- Sorensen HT, Mellekjaer L, Jepsen P, et al. Risk of cancer in patients hospitalized with fatty liver: a Danish cohort study. *J Clin Gastroenterol* 2003;36:356–9.
- Steffensen FH, Sorensen HT, Brock A, et al. Alcohol consumption and serum liver-derived enzymes in a Danish population aged 30–50 years. *Int J Epidemiol* 1997;26:92–9.
- Shaboodien R, Stansby G, Hunt BJ, et al. Unprovoked venous thromboembolism: assess for cancer. *Lancet Oncol* 2012;13:973–4.
- Piccoli A, Lensing AW, Prins MH, et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. *J Thromb Haemost* 2004;2:884–9.
- Sorensen HT, Mellekjaer L, Olsen JH, et al. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000;343:1846–50.
- Carrier M, Le Gal G, Wells PS, et al. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? *Ann Intern Med* 2008;149:323–33.
- Jepsen P, Ott P, Andersen PK, et al. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med* 2012;156:841–7.
- Vestberg K, Thulstrup AM, Sorensen HT, et al. Data quality of administratively collected hospital discharge data for liver cirrhosis epidemiology. *J Med Syst* 1997;21:11–20.
- Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.
- Greenland S, Rothman KJ, Lash T. Measures of effect and measures of association. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern epidemiology*. Philadelphia: Lippincott Williams & Wilkins, 2008:51–70.