Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study

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ABSTRACT

OBJECTIVE: 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 with four categories of liver disease: alcoholic liver cirrhosis, non-alcoholic liver cirrhosis, alcoholic non-cirrhotic liver disease, and non-alcoholic non-cirrhotic liver disease.

METHODS: We conducted a nationwide Danish case-control study of incident cases of venous thromboembolism from 1980-2005 using population-based data from the Danish National Registry of Patients, and from the Danish 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 99,464 patients with venous thromboembolism (53,576 with deep venous thrombosis and 45,888 with pulmonary embolism) and 496,979 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, 1.47-2.07) to 2.03 (95% CI, 1.86-2.21). In the analysis restricted to 69,481 patients with unprovoked venous thromboembolism and 318,782 population controls, we found slightly higher relative risks, varying from 1.96 (95% CI, 1.57-2.44) to 2.46 (95% CI, 2.05-2.95).

CONCLUSION: Patients with liver disease have a substantial increased risk of venous thromboembolism.

1. INTRODUCTION

Venous thrombosis and its complications (pulmonary embolism and post-thrombotic syndrome) is common (incidence = 1/1000 persons/year) and has 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 US case-control study, Heit *et al*. found a substantially reduced relative risk of 0.10 of VTE associated with serious liver disease (6). In contrast, a recent case-control study from Britain found a non-significant increased relative risk 1.65 of VTE associated with chronic liver disease (9). The studies were not designed specifically to examine the risk of VTE associated with liver diseases. Neither included a detailed analysis by type of liver disease.

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 haemostasis. 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**.**

2. MATERIAL AND METHODS

We conducted this Danish nationwide population-based case-control study using the Danish National Registry of Patients, which contains records on 99.4% of all hospital discharges since January 1, 1977 (12), and the Danish Civil Registration System. We made use of the civil registration number, a personal identifier assigned to all Danes at birth, to link records across registries.

2.1 Cases of venous thromboembolism

The Danish National Registry of Patients records patients' 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). One registered discharge diagnosis for each patient is recorded 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 I801-03 in ICD-10), and pulmonary embolism (code 450.99 in ICD-8 and code I26 in ICD-10) between January 1, 1980 and December 31, 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 identified 99,464 patients with a first recorded hospitalization for deep venous thrombosis in the lower limb or for a pulmonary embolism.

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 prior to the hospitalization for VTE (13).

2.2 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 April 1, 1968. The controls were selected using risk set sampling (14) 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 496,979 population controls were included in the study.

2.3 Liver diseases

Based on diagnoses in the Danish National Registry of Patients, we defined four subgroups according to expected severity of liver disease and alcohol involvement: (1) Alcoholic liver cirrhosis, (2) Non-alcoholic liver cirrhosis, (3) Alcoholic non-cirrhotic liver disease, and (4) Non-alcoholic non-cirrhotic liver disease. We included all discharge diagnoses of liver disease from January 1, 1977 until the date of VTE diagnosis among patients or the index date among controls. The diagnosis codes used in the study are provided in the Appendix.

2.4 Confounders

In order to classify patients as having primary or secondary VTE, we collected data on cancer, fractures, trauma, surgery and pregnancy from the Danish National Registry of Patients. We also collected data on former diagnoses of cardiovascular diseases (acute myocardial infection, heart

failure, and stroke) (2;15), chronic obstructive pulmonary disease (COPD) (2), diabetes (2;16), obesity (1;2;17-20), and psychiatric diseases (as a marker of antipsychotic drug use) (2;21;22). 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.

2.5 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 the contingency tables by gender and age category (≤54 years, 55-74 years and 75+ years)**,** and conducted a separate analysis on unprovoked VTE. We also fitted conditional logistic regression models that controlled for age category, cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, obesity, and psychiatric diseases. 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 (23;24).

3. RESULTS

3.1 Descriptive data

3.1.1 All patients with venous thromboembolism

For the overall case-control analysis, we identified 99,464 individuals with VTE (53,576 with deep venous thrombosis and 45,888 with pulmonary embolism) and 496,979 population controls. Among both cases and controls, there were slightly more females than males and one-third was older than 75 years. VTE patients had a higher prevalence of all comorbidities compared to controls (Table 1). In regard to liver disease, 0.32% of cases had alcoholic liver cirrhosis, 0.24% non-alcoholic liver cirrhosis, 0.20% alcoholic non-cirrhotic liver disease and 0.92% non-alcoholic non-cirrhotic liver disease, while the corresponding prevalence's among controls were 0.11%, 0.10%, 0.08% and 0.37%, respectively.

3.1.2 Patients with unprovoked venous thromboembolism

In the case-control analysis of unprovoked VTE, we identified 69,481 cases with VTE (37,738 with deep VTE and 31,743 with pulmonary embolism) and 318,782 population controls. Slightly more cases were females than males and one-third of both cases and controls was 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 2) compared to population controls. The highest prevalence of liver disease among patients with unprovoked VTE was in the category of non-alcoholic non-cirrhotic liver disease, with 629 (0.91%) cases compared to 1,011 (0.32%) controls.

3.2 Risk of venous thromboembolism

3.2.1 All patients with venous thromboembolism

Patients with all categories of liver disease had an approximately doubled adjusted risk of any type of VTE, varying from 1.74 (95% CI, 1.47-2.06) for patients with non-alcoholic liver cirrhosis to 2.03 (95% CI, 1.86-2.21) for patients with non-alcoholic non-cirrhotic liver disease (Table 3).

3.2.2 Patients with unprovoked venous thromboembolism

The relative risks of unprovoked VTE were approximately 10% higher than the risks of any VTE (Table 3), varying from 1.96 (95% CI, 1.57-2.44) in patients with alcoholic non-cirrhotic liver disease to 2.46 (95% CI, 2.05-2.95) in patients with alcoholic cirrhosis. The relative risks were slightly higher in men than women and in patients younger than 55 years. The adjusted relative risks varied from 2.64 (95% CI, 1.81-3.86) in patients aged under 55 years with alcoholic non-cirrhotic liver disease, to 4.04 (95% CI, 2.87-5.70) in patients in this age group with alcoholic cirrhosis (data not presented).

4. 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 factors.

Our findings differ from those of a case-control study of 625 VTE cases and 625 population controls conducted in Olmsted County in the US. In the US study hepatitis and liver cirrhosis were combined into one category. The study showed a substantial reduced risk, but with an imprecise relative risk estimate of 0.10 (95% CI, 0.01-0.71). While several confounding factors were taken into consideration, some residual confounding cannot be ruled out. In concert with the crude classification of liver diseases, such confounding may have influenced the study results (6). In a recent study based on data from the General Practice Research Database in Britain, including 6,550 VTE patients and 10,000 population controls, Huerta *et al*. reported a 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 chronic liver diseases. In addition, the study relied solely on VTE data from general practitioners' medical records. This might explain the slightly lower risk found in the study, compared to our risk estimates (9).

The validity of our findings depends on several factors. Our study's major strengths are its population-based design, large size, complete follow-up and nationwide coverage. It was conducted within the setting of a free tax supported national health service, which eliminates referral and diagnostic bias. Differential information bias was avoided by making use of computerized data collected for purposes independent of our study. Still, the accuracy of our findings depends on the quality of coding of VTE and liver disease. In healthcare databases, the predictive value of coding

has been reported to be 90% for pulmonary embolism (25) and slightly lower for venous thrombosis and liver diseases (25;26). However, any deficit in coding specificity would bias our risk estimates towards the null (27).

Data on confounding variables were derived from the Danish National Registry of Patients, which has a high validity (12). In accordance with the procedure used in another epidemiologic study (13), diagnoses of cancer, fractures, trauma, and pregnancy, together with surgical procedures, were used to define unprovoked VTE. While we did not have data on lifestyle factors such as smoking and alcohol intake, there is little evidence that these are risk factors for VTE (6;9). This makes major unmeasured or residual confounding unlikely.

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 play a role. Northup *et al*. recently showed that severity of liver disease, as reflected in low serum albumin, was a predictor for developing thromboembolic events (10). This may indicate that the liver is producing low levels of anticoagulants. Also, it is well-established that exogenous estrogens are a risk factor for venous thrombosis (28-30) and endogenous estrogen levels are elevated in cirrhosis (31;32). Recently, the metabolic syndrome has been implicated as a risk factor for VTE (33), and non-alcoholic fatty liver disease and to some extent cirrhosis of unknown etiology are considered hepatic manifestations of this syndrome (34;35).

It is also likely that the immobility associated with liver disease, secondary to or contributing to muscle weakness, increases the risk of VTE. Cirrhosis patients have a markedly increased

frequency of severe infective and haemorrhagic complications (36), and it is well known that critically ill patients have a substantially increased risk of deep venous thrombosis (37;38).

VTE is associated with significant short-term mortality (9), and liver disease is a relative contraindication for anticoagulation therapy, suggesting that non-pharmacological prevention is important. The lack of clinical detail in our data prevents us from providing guidelines on this important issue.

In conclusion, our data show that any liver disease is a strong risk factor for VTE, and that other risk factors for venous thrombosis supersede the decrease in coagulation associated with liver disease.

5. FUNDING

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TABLE 1

Characteristics of patients with venous thromboembolism and population controls.		
Variable	**VTE Cases (%)** **N=99,464**	**Controls (%)** **N=496,979**
Female	52,356 (52.6%)	261,535 (52.6%)
Male	47,108 (47.4%)	235,444 (47.4%)
≤54	23,835 (23.96%)	119,286 (24.00%)
55-74	41,880 (42.11%)	209,464 (42.15%)
≥75	33,749 (33.93%)	168,229 (33.85%)
Alcoholic liver cirrhosis	320 (0.32%)	562 (0.11%)
Non-alcoholic liver cirrhosis	236 (0.24%)	504 (0.10%)
Alcoholic non-cirrhotic liver disease	199 (0.20%)	392 (0.08%)
Non-alcoholic non-cirrhotic liver disease	919 (0.92%)	1,829 (0.37%)
Cancer	16,788 (16.88%)	31,018 (6.24%)
Fractures or trauma	9,612 (9.66%)	6,735 (1.36%)
Surgery	8,158 (8.20%)	9,119 (1.83%)
Pregnancy	840 (0.84%)	727 (0.15%)
Cardiovascular diseases	15,754 (15.84%)	40,707 (8.19%)
Chronic obstructive pulmonary disease	6,799 (6.84%)	14,750 (2.97%)
Diabetes	5,593 (5.62%)	15,003 (3.02%)
Psychiatric diseases	4,426 (4.45%)	9,731 (1.96%)
Obesity	3,452 (3.47%)	6,136 (1.23%)

TABLE 2

Characteristics of patients with unprovoked venous thromboembolism and population controls.		
Variable	**VTE Cases (%) N=69,481**	**Controls (%) N=318,782**
Female	35,513 (51.1%)	161,304 (50.1%)
Male	33,968 (48.9%)	157,478 (49.4%)
≤54	17,392 (25.03%)	83,633 (26.24%)
55-74	29,412 (42.33%)	136,190 (42.72%)
≥75	22,677 (32.64%)	98,959 (31.04%)
Alcoholic liver cirrhosis	217 (0.31%)	310 (0.11%)
Non-alcoholic liver cirrhosis	153 (0.22%)	279 (0.09%)
Alcoholic non-cirrhotic liver disease	139 (0.20%)	233 (0.07%)
Non-alcoholic non-cirrhotic liver disease	629 (0.91%)	1,011 (0.32%)

TABLE 3

Crude and adjusted relative risks (odds ratios) and 95% confidence intervals (95% CI) for venous thromboembolism.				
	All VTE		**Unprovoked VTE**	
Variable	**Crude RR**	**Adjusted* RR**	**Crude RR**	**Adjusted** RR**
Alcoholic liver cirrhosis	2.88 (2.51-3.30)	1.98 (1.70-2.31)	3.29 (2.76-3.91)	2.46 (2.05-2.95)
Non-alcoholic liver cirrhosis	2.35 (2.01-2.74)	1.74 (1.47-2.06)	2.51 (2.06-3.06)	2.07 (1.68-2.54)
Alcoholic non-cirrhotic liver disease	2.56 (2.16-3.04)	1.81 (1.50-2.19)	2.78 (2.25-3.44)	1.96 (1.57-2.44)
Non-alcoholic non-cirrhotic liver disease	2.53 (2.34-2.74)	2.03 (1.86-2.21)	2.86 (2.59-3.17)	2.31 (2.08-2.56)

- *Adjusted for cancer, fractures, trauma, surgery, pregnancy, cardiovascular diseases, COPD, diabetes, psychiatric diseases, and obesity.
- ** Adjusted for cardiovascular diseases, COPD, diabetes, psychiatric diseases, and obesity.

APPENDIX

ICD Codes

Outcome:

Deep venous thrombosis in the lower limb (ICD-8 451.00, ICD-10 I801-03)

Pulmonary embolism (ICD-8 450.99, ICD-10 I26)

Exposures:

Reference group: no liver disease

1) Alcoholic liver cirrhosis:

Cirrhosis hepatis, non-alcoholic (ICD-8: 571.09)

Alcoholic liver cirrhosis (ICD-10 K70.3)

2) Non-alcoholic liver cirrhosis:

Non-alcoholic liver cirrhosis (ICD-8 571.90-571.92, 571.99, ICD-10 K71.7, K74.3, K74.4, K74.5, K74.6)

3) Alcoholic non-cirrhotic liver disease

Steatosis hepatis alcoholica (ICD-8 571.10)

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

4) Non-alcoholic non-cirrhotic liver disease:

Non-alcoholic liver disease excl. cirrhosis (ICD-8 570.00-573.09 excl. 571.09, 571.10, 571.90-571.92, 571.99) (ICD-10 R74.0, K71.0-K77.8 excl. 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-8 800–999, ICD-10 S00–T14)

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

Cardiovascular disease:

- Stroke (ICD-8 431–435, ICD-10 I61, I63, I64, I65, I66)
- Myocardial infarction (ICD-8 410, ICD-10 I21)
- Heart failure (ICD-8 42709, 42710, 42711, ICD-10 I50)

Chronic obstructive pulmonary disease (ICD-8 491,492, ICD-10 J42 J43 J44)

Diabetes (ICD-8 249, 250, ICD-10 E10, E11)

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

Obesity (ICD-8 277.99, ICD-10 E66)

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