

# 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.<sup>1</sup> By contrast, portal vein thrombosis (PVT) is less common, but a potential serious condition with 30-day mortality varying from ~3 to 50%.<sup>2</sup> 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.<sup>1</sup> 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.<sup>1</sup> Among patients with PVT, prevalent cancer or cirrhosis are predictors of increased mortality.<sup>2,3</sup>

Patients with cirrhosis are at increased risk of DVT and PE compared with the general population.<sup>2,4–6</sup> 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)<sup>7,8</sup> and intrinsic factors (disturbance of the coagulation system and increased estrogen levels).<sup>7–9</sup> 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.<sup>10,11</sup> 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.<sup>12</sup> Recorded information includes civil registration number (unique personal identifier assigned to all Danish citizens),<sup>13</sup> 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,<sup>14</sup> 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.<sup>15</sup>

We used the Danish Register of Causes of Death<sup>16</sup> 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.<sup>17</sup> Patients diagnosed only in emergency departments were excluded ( $n=12,184$ ) owing to the expected low positive predictive value of diagnoses in this setting.<sup>18</sup> 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).<sup>19</sup> 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).<sup>20,21</sup>

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.<sup>22–25</sup> Patients with cirrhosis are prone to infections because of their compromised immune system,<sup>26</sup> and prevalent infections have a strong impact on prognosis.<sup>27</sup> 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<sup>13</sup> and the specific immediate cause of death from the Danish Register of Causes of Death.<sup>16</sup> 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  $\chi^2$ -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  $\pm$  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). Corres-

pondingly, 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).

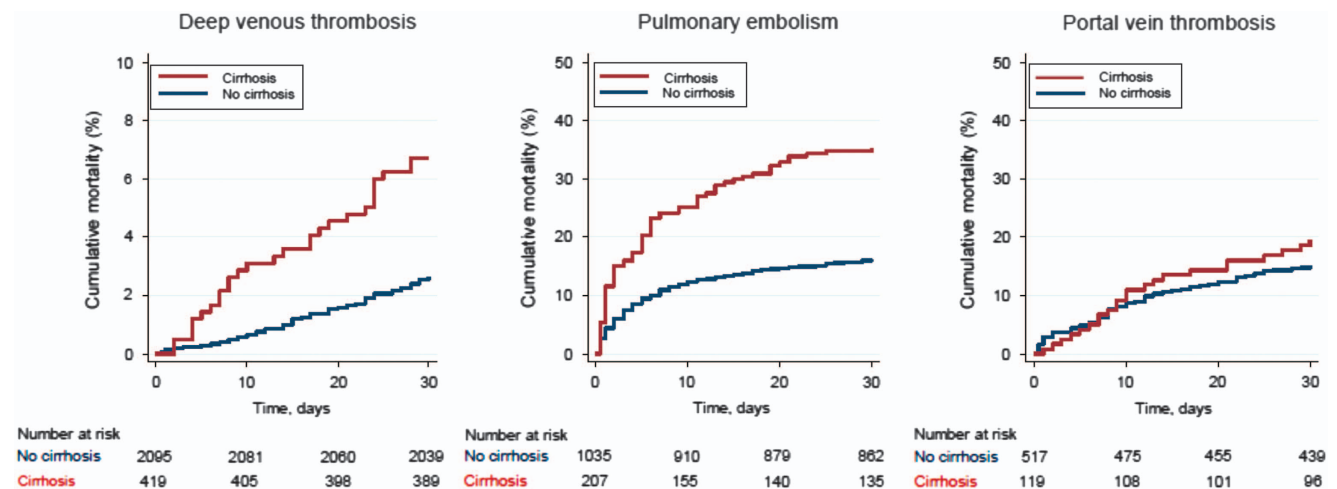
**Table 1** Characteristics of 4392 patients with a first-time diagnosis of venous thromboembolism

	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 <sup>a</sup>	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 <sup>b</sup>						
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.

<sup>a</sup>Liver cancer accounted for 11 of the cancer cases among cirrhosis patients.

<sup>b</sup>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 <sup>a</sup> (95% CI)	Adjusted MRR <sup>b</sup> (95% CI)
<i>Deep venous thrombosis</i>	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 <sup>c</sup>	22	2	9 (2–32)	3.24 (0.78–13.41)	2.80 (0.67–11.75)
Other or non-specified <sup>d</sup>	77	8	10 (5–20)	3.22 (1.51–6.86)	2.36 (1.06–5.22)
<i>Pulmonary embolism</i>	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 <sup>c</sup>	18	4	22 (9–49)	1.25 (0.46–3.40)	1.00 (0.36–2.75)
Other or non-specified <sup>d</sup>	47	18	38 (26–54)	2.54 (1.55–4.14)	2.30 (1.40–3.78)
<i>Portal vein thrombosis</i>	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 <sup>c</sup>	8	1	13 (2–61)	0.85 (0.12–6.21)	0.57 (0.08–4.30)
Other or non-specified <sup>d</sup>	36	6	17 (8–33)	1.05 (0.46–2.42)	1.17 (0.50–2.72)

CI, confidence interval; MRR, mortality rate ratio.

<sup>a</sup>Adjusted for matching factors by study design (gender, age, calendar period).

<sup>b</sup>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.

<sup>c</sup>Biliary cirrhosis includes primary, secondary, and other or non-specified biliary cirrhosis.

<sup>d</sup>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)
<i>Comorbidity<sup>a</sup></i>			
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)
<i>Cancer<sup>b</sup></i>			
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.

<sup>a</sup>Adjusted for matching factors by study design (gender, age, calendar period), fracture/trauma, surgery, alcoholism-related disease, and infection.

<sup>b</sup>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.<sup>28</sup> 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)
<i>Liver disease (including complications) (21)</i>
Cirrhosis (7)
Bleeding esophageal varices (6)
Hepatorenal syndrome (3)
Alcoholic hepatitis (1)
Alcoholic liver disease (1)
Liver failure (2)
Alcoholic cardiomyopathy (1)
<i>Other gastrointestinal disease (9)</i>
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)
<i>Other diseases (6)</i>
Stroke (2)
Renal insufficiency (2)
Fracture (1)
Anemia (1)
Gangrene (1)
Dehydration (1)
Unknown cause of death (2)

from the general population.<sup>1</sup> 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.<sup>1</sup> In general, patients with cirrhosis have a substantial excess short-term mortality.<sup>27,29–31</sup> This increased mortality likely stems from a high comorbidity burden,<sup>11</sup> increased susceptibility to bacterial infections,<sup>32,33</sup> and complications of cirrhosis.<sup>34</sup> 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,<sup>35–38</sup> 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.<sup>39</sup> 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.<sup>17,39</sup> 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<sup>18</sup> 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<sup>40</sup> or through comparison with medical charts.<sup>41</sup> In regard to confounder control, the positive predictive values of other diseases<sup>41</sup> and surgical procedures<sup>42,43</sup> 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.<sup>44</sup>

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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