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Risk and Outcome of Venous and Arterial Thrombosis in Patients With Cirrhosis: A Danish Nation-wide Cohort Study

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BACKGROUND AND AIMS: Cirrhosis affects hemostasis, but its effects across the spectrum of thromboses remain poorly understood. We examined risks and outcomes of venous and arterial thrombosis.

APPROACH AND RESULTS: We used nation-wide Danish health care registries to identify outpatients with cirrhosis and a sex- and age-matched comparison cohort without cirrhosis from the general population. Patients with cirrhosis and comparators were followed until they had a venous thromboembolism (VTE), acute myocardial infarction (AMI), or ischemic stroke (IS) or died. We computed absolute risks and HRs of thrombosis and compared outcomes after thrombosis. We included 5,854 patients with cirrhosis (median Model for End-Stage Liver Disease score, 9; interquartile range, 7-13), and their risk of any of the thrombotic events was 0.8% after 1 year and 6.3% after 10 years. They were more likely than the 23,870 matched comparators to have a VTE (adjusted hazard ratio [aHR], 2.0; 95% CI, 1.5-2.6) or IS (aHR, 1.7; 95% CI, 1.3-2.3), but not AMI (aHR, 0.7; 95% CI, 0.5-0.9). Among patients with cirrhosis, decompensation increased the risk of AMI, but not the other thromboses. Following thrombosis, patients with cirrhosis had higher 90-day mortality than comparators (after VTE: 17% vs. 7%; after AMI: 27% vs. 5%; after IS: 10% vs. 7%) and were less likely to receive antithrombotic treatment.

CONCLUSIONS: Patients with cirrhosis had an increased risk of VTE and IS, but not AMI. Among patients with cirrhosis, decompensation increased the risk of AMI, exclusively. Mortality after thrombosis was higher in patients with cirrhosis than in other patients. These findings are relevant for decisions about antithrombotic prophylaxis in patients with cirrhosis. (Hepatology 2021;74:2725-2734).

Patients with cirrhosis are at increased risk of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE),[1-5] possibly attributable to an imbalance in pro- and anticoagulant factors.[5-7] Although existing studies provide estimates of the relative risk of venous thrombosis for patients with cirrhosis, the absolute risk, which is a key metric for informing the need for intervention, is open for study.

We have found that patients with cirrhosis have more severe and extensive coronary artery disease than controls,[8] yet they do not have an increased risk of acute myocardial infarction (AMI).[9] In addition, a recent meta-analysis found no apparent association between cirrhosis and risk of ischemic stroke (IS), but all five meta-analyzed studies were from Asia,

Abbreviations: AF, atrial fibrillation; AH, arterial hypertension; aHR, adjusted hazard ratio; AMI, acute myocardial infarction; CC, compensated cirrhosis; DC, decompensated cirrhosis; DVT, deep venous thrombosis; ICD, International Classification of Diseases; IQR, interquartile range; IS, ischemic stroke; MELD, Model for End-Stage Liver Disease; PE, pulmonary embolism; PPV, positive predictive value; UGIB, upper gastrointestinal bleeding; VTE, venous thromboembolism.

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and relative risks ranged from 0.32 to 1.22.[10] Thus, risks of AMI and IS in patients with cirrhosis remain poorly defined.

Clinical implications of thrombotic events are heightened for patients with cirrhosis. Indeed, cirrhosis is associated with higher mortality after both VTE and AMI,[11,12] partly explained by a lower chance of receiving revascularization or anticoagulation therapy[11,12] and possibly also by their higher prevalence of comorbidity.[13,14]

Valid information about the risk and impact of venous and arterial thrombosis is important for clinical decision making and patient counseling. Given this background, we examined the risks and outcomes of venous and arterial thrombosis in Danish patients with cirrhosis and in a matched comparison cohort from the general population.

Patients and Methods

We conducted this population-based cohort study using pseudonymized data from Danish health care registries.[15] We did not have access to patients' medical charts or to the patients themselves, so we did not need permission from an ethics committee to conduct the study, according to Danish law.

DATA SOURCES

Denmark has free tax-supported health care.[15] We used data from the Danish National Patient Registry, which covers all Danish hospitals. This registry includes data from in- and outpatient hospital contacts since 1995, as well as inpatient data going back to 1977. For every contact, the treating physician specifies one primary diagnosis and up to 20 secondary diagnoses, coded according to the International Classification of Diseases (ICD), Tenth Revision (ICD-10). In 1977-1993, coding was according to the ICD-8, and the ICD-9 has never been used in Denmark. The National Patient Registry also contains records of all procedures and examinations.[16] In addition, we used data from the National Prescription Registry, which contains data on all prescriptions filled at community pharmacies in Denmark since 1995[17]; from the Register of Laboratory Results for Research[18]; and from the Civil Registration System.[19] Together, the registries provided person-level data on diagnoses, in-hospital and outpatient treatments, prescription drugs, serum biochemistry, and dates of death.

STUDY COHORTS AND OUTCOMES

We included a cohort of outpatients who had cirrhosis and were not using anticoagulants. We first identified a cohort of all adult patients (aged ≥18 years) who received their first primary or secondary diagnosis of cirrhosis after January 1, 1996, whether from an inpatient, outpatient, or emergency room visit. We then defined the "index date" as the date 1 year after this first diagnosis. Thus, the earliest possible index date was January 1, 1997. To join the cohort, patients had to be outpatients followed for cirrhosis on their index date. Finally, we excluded patients who

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before the index date had received a diagnosis code for VTE, AMI, or IS, using previously validated diagnosis codes.[20,21] Also excluded were patients who before the index date had filled a prescription for an antithrombotic agent. The remaining patients constituted the cirrhosis cohort. All codes are provided in Supporting Table S1.

We identified a sex-, age-, and birth-year–matched comparison cohort from the general population. This comparison cohort consisted of 5 persons without cirrhosis for each patient with cirrhosis. Matching occurred on the date of the first cirrhosis diagnosis of the patient with cirrhosis to whom a comparator was matched. Follow-up of the comparators did not begin until the matched patient's index date, and we used the same exclusion criteria for the comparators as for the cirrhosis cohort. As a result, not all patients with cirrhosis were matched with five comparators on the index date, but all were matched with at least one.

Patients with cirrhosis and comparators were followed until they died or were diagnosed with VTE (DVT or PE, but not portal vein thrombosis [PVT]), AMI, or IS, whichever occurred first. The admission date defined the date of these outcomes. IS included diagnoses of both ischemic and unspecified stroke given that two thirds of unspecified stroke diagnoses are ischemic.[22] Patients and comparators who survived without thrombosis were censored after 10 years of follow-up, or on November 1, 2019 at the latest. In our analysis of outcomes of thrombosis, follow-up began on the date of a patient's first thrombosis and ended at death, at upper gastrointestinal bleeding (UGIB), or in censoring after 90 days.

POTENTIAL CONFOUNDING FACTORS

Cancer, diabetes, renal failure, smoking, arterial hypertension (AH), atrial fibrillation (AF) or flutter, surgical procedures, and trauma are risk factors for thrombosis,[23-25] and their prevalence likely differed between patients with cirrhosis and their comparators despite similar sex and age distributions.

We identified all participants' earliest cancer diagnosis, diabetes diagnosis, renal failure diagnosis, smoking indicator, and diagnosis of AF or flutter. The date of diabetes diagnosis was defined as the earlier of a hospital diagnosis of diabetes or a filled prescription for an antidiabetic drug. The date defining smoking was the earliest of the following: a hospital diagnosis of chronic obstructive pulmonary disease, or a filled prescription for a drug to treat chronic obstructive pulmonary disease, for a drug to treat nicotine addiction, or for medicinal oxygen. The date defining AH was the earliest of these: a hospital diagnosis for AH, or a filled prescription for a drug to treat AH (thiazides, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or cardioselective beta-blockers). Surgical procedures and trauma were defined by surgical and diagnosis codes, respectively. They could be experienced repeatedly, with each spell lasting 90 days from the date of hospital admission.

CHARACTERISTICS OF PATIENTS WITH CIRRHOSIS

Patients with alcohol-associated cirrhosis had a diagnosis code for alcohol-associated cirrhosis or a diagnosis code suggesting alcohol dependency on or before the index date. All other patients were assumed to have nonalcoholic cirrhosis.

We classified cirrhosis severity as compensated or decompensated on the basis of diagnosis codes, procedure codes, and prescriptions filled before the index date or during the follow-up period. The date of decompensation was defined as the earliest of these: a diagnosis code for ascites, variceal bleeding, or hepatorenal syndrome; a procedure code for banding ligation/sclerotherapy of varices or for ascites puncture or drainage; or redemption of a prescription for spironolactone, furosemide, nonselective beta-blockers, or lactulose (rifaximin could not be identified because it is handed out by hospitals, not prescribed, and HE does not have a specific diagnosis code). Patients could not recompensate after they had decompensated, but we divided patients with decompensated cirrhosis (DC) in two: those with a "recent banding or drainage" and those without. Patients with DC were in the recent banding or drainage subcategory for 90 days following banding ligation/sclerotherapy of varices or ascites puncture/drainage during an inpatient hospitalization. Such banding/drainage spells could be experienced repeatedly.

STATISTICAL ANALYSIS

To characterize the cirrhosis cohort, we described the subset of patients with cirrhosis who had data available on serum biochemistry (albumin and Model for End-Stage

Liver Disease [MELD] score, based on international normalized ratio, bilirubin, creatinine, and sodium).[26] These data were available across most of Denmark from 2015 onward.[18] We used the Kaplan-Meier method to compute all-cause mortality for patients with cirrhosis with or without data on serum biochemistry.

THROMBOSIS INCIDENCE FOR PATIENTS WITH CIRRHOSIS VERSUS COMPARATORS WITHOUT CIRRHOSIS

We used the cumulative incidence function to compute the risks of VTE, AMI, and IS. Death without thrombosis was treated as a competing risk.

We used stratified Cox regression to examine the HR of each outcome event. Each patient with cirrhosis and his or her comparators constituted one stratum. We adjusted for confounding from cancer, diabetes, renal failure, smoking, AH, AF or flutter, surgery, and trauma, and these were included as time-dependent variables. We repeated the Cox regression analysis within strata defined by alcohol-associated or nonalcoholic cirrhosis; by sex; and by compensated cirrhosis (CC) or DC on the index date.

CIRRHOSIS SEVERITY AS A RISK FACTOR FOR THROMBOSIS AMONG PATIENTS WITH CIRRHOSIS

We examined whether decompensation was associated with the HR of thrombosis among patients with cirrhosis. We adjusted for confounding by sex, age, cirrhosis etiology (alcohol-associated or nonalcoholic), cancer, diabetes, renal failure, smoking, AH, AF or flutter, surgery, and trauma. Decompensation and confounders were included in the analysis as time-dependent variables. Patients were compensated until their first decompensation event. From that time onward, they could transition back and forth between the "recent banding or drainage" and "no recent banding or drainage" subcategories of decompensation, as described above.

OUTCOMES AFTER THROMBOSIS

We used the Kaplan-Meier method to compute 90-day all-cause mortality after thrombosis for patients with cirrhosis and comparators, and we used the cumulative incidence function to compute the risk of UGIB within 90 days from first thrombosis. Death without UGIB was a competing risk event in these analyses. The date of UGIB was defined as the admission date of a hospital contact eliciting a procedure code for an upper endoscopy and a diagnosis code for UGIB or bleeding from gastroesophageal varices.[27]

Results

CLINICAL CHARACTERISTICS

We included 5,854 patients with cirrhosis and 23,870 matched comparators. Patients' median age was 57 years (interquartile range [IQR], 50-64), and 62% were men. They were more likely than comparators to have the chronic diseases we considered, and they were also more likely to be hospitalized for surgery or trauma (Table 1). Of the 5,854 patients with cirrhosis, 4,771 (82%) had alcohol-associated cirrhosis. A MELD score was available on the index date for 1,826 patients with cirrhosis (31% of the total cohort). Median MELD score was 9 (IQR, 7-13); 14% of patients had the minimum MELD score of 6, and 95% had a MELD score of ≤21. Median serum albumin was 36 g/L (IQR, 32-40).

OUTCOMES

Total duration of follow-up was 26,476 person-years for patients with cirrhosis (median, 3.7 years; maximum, 10 years) and 170,385 person-years for comparators. During the follow-up, 279 patients with cirrhosis experienced a thrombosis event, 3,003 patients died without such an event, and the remaining 2,572 patients survived event free until follow-up ended. Patients with data on MELD had the same risk of death or thrombosis as the other 69% of the cirrhosis cohort (Supporting Fig. S1).

The number of new users of antithrombotic drugs per year of follow-up without thrombosis, that is, the "new user rate," was higher for patients with cirrhosis than for comparators (Table 1). The same was noted for antianginals, but the pattern was different for statins: Patients with cirrhosis were more likely to use statins at inclusion and less likely to start taking them during follow-up (Table 1).

TABLE 1. Baseline Characteristics of Patients With Cirrhosis and Comparison Cohort Matched on Sex, Age, and Birth Year

		Cirrhosis	Comparison Cohort
No. of patients		5,854	23,870
Men		3,631 (62%)	14,477 (61%)
Age, median (IQR)		57 (50-64)	56 (49-62)
Cancer		574 (10%)	1319 (6%)
Diabetes		931 (16%)	920 (4%)
Renal failure		87 (1.5%)	56 (0.2%)
Smoking		1,725 (29%)	5,315 (22%)
AH		2,566 (44%)	5,523 (23%)
AF or flutter		105 (1.8%)	142 (0.6%)
Surgery*	Time spent, %	6.3	2.6
Trauma*	Time spent, %	1.4	0.2
Antithrombotic drugs	At inclusion	0	0
Acetylsalicylic acid	New user rate	14.8	13.4
Vitamin K antagonist	New user rate	4.6	2.2
Other antiplatelet drug	New user rate	4.3	3.7
Direct thrombin/Xa inhibitors	New user rate	3.3	2.8
Other anticoagulant	New user rate	2.8	0.6
Antianginals	At inclusion	171 (2.9%)	354 (1.5%)
	New user rate	5.9	3.6
Statins	At inclusion	584 (10.0%)	2,126 (8.9%)
	New user rate	14.5	22.7

The incidence rates of new drug users are presented per 1,000 person-years and computed as the number of persons who develop a given characteristic during the follow-up divided by the follow-up time. We excluded patients and comparison cohort members who were using antithrombotic drugs at inclusion.
*Proportion of follow-up time spent <90 days after surgery or trauma.

THROMBOSIS INCIDENCE

Risk of any thrombosis for patients with cirrhosis was 0.8% (95% CI, 0.6-1.0) after 1 year, 3.5% (95% CI, 3.0-4.0) after 5 years, and 6.3% (95% CI, 5.6-7.1) after 10 years. For the comparison cohort, those risks were lower: 0.5% (95% CI, 0.4-0.6) after 1 year; 2.8% (95% CI, 2.6-3.0) after 5 years, and 5.7% (95% CI, 5.4-6.1) after 10 years (Fig. 1; Table 2).

Patients with cirrhosis were more likely than comparators to have a VTE (10-year risk = 2.5% vs. 1.7%), and the adjusted hazard ratio (aHR) was 2.0 (95% CI, 1.5-2.6). This association between cirrhosis and VTE was stronger for alcohol-associated cirrhosis than for nonalcoholic cirrhosis, and stronger for women than for men. Risk of AMI was lower for patients with cirrhosis than comparators (10-year risk = 1.3% vs. 2.3%), and the hazard rate was decreased (aHR = 0.7; 95% CI, 0.5-0.9). Risk of IS was higher for patients with cirrhosis than for comparators (10-year risk = 2.5% vs. 1.7%; aHR = 1.7; 95% CI, 1.3-2.3), entirely because of a strong association between alcohol-associated cirrhosis and IS (aHR = 2.1; 95% CI, 1.6-2.7; Table 2 and Supporting Table S2).

CIRRHOSIS SEVERITY AS A RISK FACTOR FOR THROMBOSIS

Among the 5,854 patients with cirrhosis, 4,601 (79%) were decompensated when follow-up began. During the follow-up, 1,601 (35%) of those

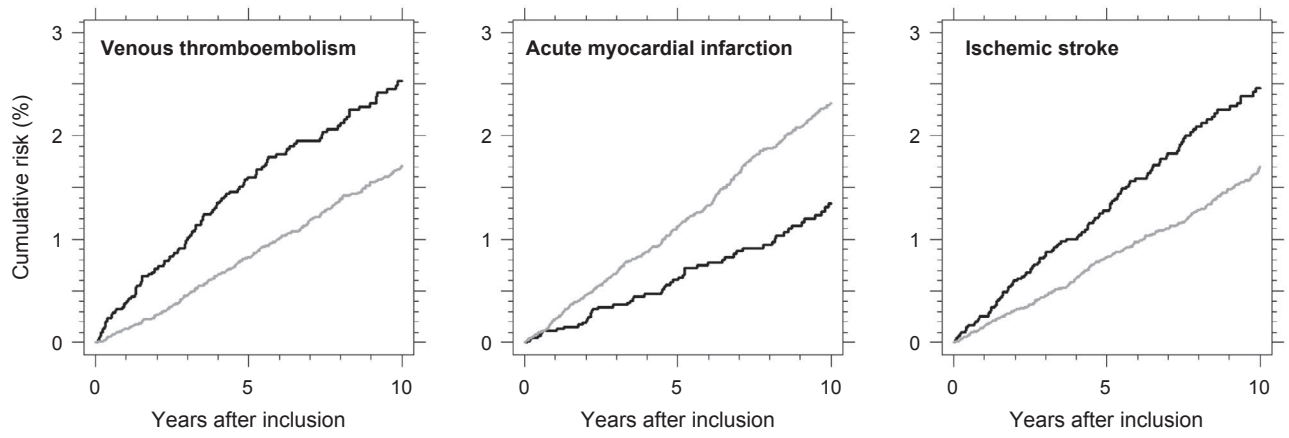

FIG. 1. Cumulative risks of each outcome event for patients with cirrhosis (black) and comparison cohort members matched on sex, age, and birth year (gray).

TABLE 2. Effect of Cirrhosis on the Risks and HRs of Thrombosis Events and on Death Without Thrombosis

	VTE	AMI	IS	Death Without Thrombosis
Cumulative risk (%)				
1 year	0.4 (0.3-0.6) vs. 0.1 (0.1-0.2)	0.1 (0.1-0.2) vs. 0.2 (0.2-0.3)	0.3 (0.2-0.4) vs. 0.2 (0.1-0.2)	11.1 (10.3-11.9) vs. 0.5 (0.4-0.6)
5 years	1.6 (1.3-2.0) vs. 0.8 (0.7-1.0)	0.6 (0.4-0.9) vs. 1.1 (1.0-1.3)	1.3 (1.0-1.6) vs. 0.8 (0.7-1.0)	43.2 (41.8-44.6) vs. 3.2 (2.9-3.4)
10 years	2.5 (2.1-3.0) vs. 1.7 (1.5-1.9)	1.3 (1.0-1.7) vs. 2.3 (2.1-2.5)	2.5 (2.0-3.0) vs. 1.7 (1.5-1.9)	64.1 (62.6-65.6) vs. 7.5 (7.1-7.9)
Unadjusted HR	2.4 (1.9-3.1)	0.9 (0.6-1.2)	2.2 (1.8-2.9)	17 (15-18)
aHR	2.0 (1.5-2.6)	0.7 (0.5-0.9)	1.7 (1.3-2.3)	15 (14-17)
Stratified analyses, aHR				
Alcohol-associated cirrhosis	2.2 (1.6-2.9)	0.7 (0.5-0.9)	2.1 (1.6-2.7)	18 (16-20)
Nonalcoholic cirrhosis	1.3 (0.7-2.6)	0.6 (0.3-1.3)	0.4 (0.2-1.2)	8 (6-10)
Men	1.6 (1.1-2.3)	0.7 (0.5-0.9)	1.6 (1.2-2.3)	15 (13-17)
Women	2.9 (1.9-4.5)	0.7 (0.4-1.4)	2.2 (1.4-3.6)	16 (14-19)
CC*	2.5 (1.4-4.6)	0.7 (0.3-1.5)	1.0 (0.5-1.9)	10 (8-13)
DC*	1.9 (1.4-2.6)	0.7 (0.5-1.0)	2.0 (1.5-2.7)	17 (15-19)

The cumulative risks are presented as the risk for patients with cirrhosis versus the risk for matched comparators. HRs are for patients with cirrhosis versus sex- and age-matched comparators, with and without adjustment for confounding from cancer, diabetes, renal failure, smoking, AH, AF or flutter, surgery, and trauma (see also Supporting Table S2).
*Patients with CC/DC at inclusion versus their comparators.

decompensated patients were in the hospital at least once to undergo variceal banding or ascites drainage. Relative to patients with CC, patients with DC who within the previous 90 days had been in the hospital for variceal banding or ascites drainage had an aHR of AMI of 8.7 (95% CI, 2.7-28.3). The HR for other decompensated patients was 1.6 (95% CI, 0.7-3.9). By contrast, decompensation, with or without a recent banding or drainage, was not a risk factor for VTE or IS (Table 3).

OUTCOMES AFTER THROMBOSIS

Ninety-day mortality was higher for patients with cirrhosis than for comparators after a VTE (17% vs. 7%) and AMI (30% vs. 5%), whereas the difference was small after IS (10% vs. 7%; Table 4).

Patients with cirrhosis were less likely than other patients to receive antithrombotic treatment after thrombosis. They were also less likely to undergo percutaneous coronary intervention (PCI) or bypass surgery after AMI. The 90-day risk of UGIB was 2.2% for patients with cirrhosis and zero for matched comparators (Table 4). Among patients with cirrhosis, it was marginally higher for those who had decompensated: 2.3% versus 1.6% for those who were still compensated.

Discussion

We found that, compared with matched comparators from the general population, patients with cirrhosis had an increased risk of a VTE and IS, but a reduced risk of AMI. Among patients with cirrhosis, however, decompensation was a risk factor for AMI, but not for a VTE or IS. The combined risk of the three types of thrombosis was increased for patients with cirrhosis (10-year risk = 6.3% vs. 5.7% for matched comparators), although they were slightly more likely to receive prophylactic antithrombotic treatment. Patients with cirrhosis were less likely than comparators to receive antithrombotic or other treatment after thrombosis, and they had a markedly higher 90-day mortality after a VTE (17% vs. 7%) and after AMI (30% vs. 5%). Risk of UGIB following thrombosis was 2.2% for patients with cirrhosis and zero for the comparators.

Our patients with cirrhosis were at increased risk of a VTE, consistent with previous studies.[5-7] We found that decompensation was a risk factor among patients with cirrhosis, but it remains unclear whether the effect of decompensation is mediated by hypercoagulability attributable to increased levels of factor VIII and decreased levels of protein C,[28] or other factors contribute. We did not examine the risk of

TABLE 3. HRs Associated With Decompensation and With Potential Confounders

	VTE	AMI	IS	Death Without Thrombosis
No. of outcomes observed	115	56	108	3,003
Decompensation				
Decompensated, with recent banding/drainage	0.9 (0.3-3.2)	8.7 (2.7-28.3)	0.8 (0.2-3.8)	28 (23-34)
Decompensated, without recent banding/drainage	1.0 (0.6-1.7)	1.6 (0.7-3.9)	1.2 (0.6-2.2)	3.0 (2.5-3.5)
Compensated	Ref.	Ref.	Ref.	Ref.
Sex, male vs. female	1.0 (0.7-1.5)	2.0 (1.1-3.7)	1.2 (0.8-1.8)	1.3 (1.2-1.4)
Age, per 10 years	1.2 (1.0-1.5)	1.3 (1.0-1.7)	1.6 (1.3-2.0)	1.2 (1.2-1.3)
Alcohol-associated cirrhosis	1.4 (0.8-2.3)	0.6 (0.3-1.2)	2.7 (1.3–5.4)	1.2 (1.1-1.4)
Cancer	1.7 (1.1-2.7)	0.5 (0.2-1.3)	0.9 (0.5-1.6)	2.1 (1.9-2.3)
Diabetes	0.9 (0.6-1.4)	1.0 (0.5-1.8)	1.3 (0.9-2.1)	1.0 (0.9-1.1)
Renal failure	1.9 (0.8-4.3)	1.8 (0.5-5.8)	2.6 (1.2-5.4)	1.2 (1.0-1.4)
Smoking, yes vs. no	1.2 (0.8-1.7)	1.1 (0.6-1.9)	1.4 (0.9-2.0)	1.1 (1.0-1.2)
AH	1.5 (1.0-2.3)	1.1 (0.6-2.0)	0.8 (0.6-1.2)	0.9 (0.8-1.0)
AF or flutter	0.9 (0.4-2.2)	2.3 (0.9-5.5)	1.5 (0.7-3.2)	1.3 (1.1-1.6)
Surgery	2.8 (1.7-4.7)	1.2 (0.5-2.9)	1.9 (1.1-3.4)	2.7 (2.4-4.9)
Trauma	1.3 (0.5-3.7)	4.6 (1.5-13.9)	3.9 (1.8-8.3)	2.2 (1.9-2.3)

This analysis includes only patients with cirrhosis. We conducted separate regression models for each of the outcomes under consideration.

TABLE 4. Antithrombotic Treatment and Mortality Following Thrombosis

	VTE	AMI	IS
Nos. of patients and comparators	115 vs. 304	56 vs. 416	108 vs. 300
Filled prescription for antithrombotic drug	37% vs. 77%	62% vs. 93%	69% vs. 90%
Most frequently prescribed antithrombotic drug(s)	Warfarin (16% vs. 39%), rivaroxaban (8% vs. 25%)	Acetylsalicylic acid (57% vs. 90%), clopidogrel (23% vs. 54%), ticagrelor (16% vs. 28%)	Clopidogrel (46% vs. 49%), acetylsalicylic acid (24% vs. 40%), dipyridamole (14% vs. 24%)
Cerebral thrombolysis/thrombectomy	—	—	1% vs. 1%
Thrombolysis	—	0% vs. 0.5%	5% vs. 9%
Percutaneous intervention	—	30% vs. 62%	—
Coronary bypass surgery	—	0% vs. 8%	—
90-day risk of UGIB	2% vs. 0%	5% vs. 0%	1% vs. 0%
90-day all-cause mortality	17% vs. 7%	30% vs. 5%	10% vs. 7%

The numbers of patients and proportions are presented as patients with cirrhosis vs. comparators.

PVT because it involves different causal mechanisms, such as portal hypertension slowing blood flow in the portal vein.[7,29,30]

We found that cirrhosis was not a risk factor for AMI. This finding is consistent with our previous study,[9] and here we show that—among patients with cirrhosis—decompensation was a strong risk factor for AMI. We also extend our previous study by highlighting that AMI is highly fatal in patients with cirrhosis. It is striking that our patients with cirrhosis were more likely to receive antithrombotic treatment as a prophylaxis, yet much less likely to receive antithrombotic treatment after thrombosis. In their study of USA patients with AMI, Hillerson et al. found, like us, that patients with cirrhosis received less antithrombotic treatment and had higher mortality.[11] A later USA study reported that, among patients with cirrhosis, the use of PCI after AMI increased between 2003 and 2016, but the excess mortality persisted.[31] Concerns over bleeding risk should not discourage antithrombotic treatment after thrombosis and after AMI in particular. We found a 90-day bleeding risk of only 5% after AMI. Hillerson et al. reported that risk of bleeding after AMI was 12.3% in patients with cirrhosis versus 7.1% in matched comparators.[11]

The strong association of IS with alcohol-associated cirrhosis, but not with nonalcoholic cirrhosis, was notable. Others have found that cirrhosis is associated with IS,[32] but that was in an older population (mean age, 74 years vs. 57 in our cohort) with a higher absolute risk of IS. In that study, no difference in risk was found between patients with alcohol-associated and nonalcoholic cirrhosis.[32] A recent meta-analysis found varying results with no clear pattern.[10] It is possible that the association we found was partly attributable to residual confounding from smoking, although smoking is more prevalent in both alcohol-associated and nonalcoholic cirrhosis than in persons without cirrhosis.[33] Another possibility is that, among patients with alcohol-associated cirrhosis, relatively many of the unspecified strokes were, in fact, hemorrhagic strokes.

It is unclear why alcohol-associated cirrhosis is a risk factor for IS and not for AMI, but it is likely that the causal mechanisms are different. This interpretation is corroborated by our observation that cirrhotic decompensation is a strong risk factor for AMI, but is not a risk factor for IS or VTE. One possibility is that cirrhosis reduces the heart's demand for oxygen,[8,34] until the circulatory changes and changes in cardiac output following decompensation events increase the risk of AMI.[35,36] Further research is needed to clarify the mechanisms involved.

Our findings must be interpreted in the context of the study design. First, we could only study patients diagnosed with cirrhosis in the hospital. The 79% prevalence of decompensation among our Danish patients with a hospital diagnosis of cirrhosis is high, but consistent with two previous Danish studies in which the diagnoses of cirrhosis and decompensation were based on record review.[37,38] In those studies, prevalence of decompensation was 75% and 76%, respectively. Prevalence of decompensation is lower among patients with cirrhosis who have not been hospitalized, and it is a limitation of our study that we could not follow such patients. As it is, we cannot know whether our findings generalize to patients who have only been seen in primary care or to countries where alcohol is not the dominant cause of cirrhosis.[37] Second, the validity of diagnosis codes for cirrhosis and thrombosis was crucial for this study. Previous studies have indicated that the positive predictive value (PPV) of diagnosis codes for cirrhosis is at least 80%.[37,39,40] We had the additional requirement that patients had to be followed as outpatients for cirrhosis, so we believe that at least 90% of our patients truly had this disease. The PPV of a first-time diagnosis code is 86% for DVT, 90% for first-time PE, and 97% for first-time AMI.[20] The diagnosis code for IS has a PPV of 87.6% and, more recently, 97%.[21,22] The completeness of stroke registration is merely 35%,[22] so we added diagnoses of unspecified stroke. This addition ensured essentially complete identification of diagnosed ischemic strokes while maintaining a PPV of 70%. The others are 7% intracranial bleedings, 7% unspecified strokes, and 15% other diseases.[22] It remains possible that the association between alcohol-associated cirrhosis and IS is attributable to a larger proportion of incorrect diagnoses of IS in these patients. Overall, we believe that the associations we found are valid, but it is a limitation of our study that the diagnosis codes we relied on to identify cirrhosis, AMI, and VTE have not been assessed for completeness. We speculate that completeness of registration is very high for a usually symptomatic event like AMI. We are more concerned for VTE that may present less acutely and with indistinct symptoms; we may have underestimated its true incidence.

Our findings are important for several reasons: (1) They emphasize that cirrhosis does not confer a natural anticoagulant state, but is a cause of VTE and IS. Cirrhotic decompensation events seem to be causally linked with AMI, specifically. (2) Our cirrhosis cohort was defined to have a perceived low risk of thrombosis—they could not have a history of thrombosis or be taking antithrombotic treatment at inclusion—yet the combined risks of the thrombosis types we considered were ~0.7% per year. (3) Patients with cirrhosis have high mortality following thrombosis, highlighting the need to consider more intensive prophylaxis and treatment of thrombosis. Studies indicate that anticoagulation in cirrhosis is safe, effective, and ameliorates liver fibrosis.[41,42] For now, we would encourage clinicians to ensure prophylaxis of thrombosis after surgery or trauma, as suggested.[42]

In conclusion, we found that cirrhosis was associated with an increased risk of VTE and IS, but not AMI. Among patients with cirrhosis, decompensation events increased the risk of AMI, but did not affect the risk of VTE or IS. Relative to matched comparators, our patients with cirrhosis were treated less intensely after thrombosis and had a higher mortality.

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