DR. PETER JEPSEN (Orcid ID : 0000-0002-6641-1430)

DR. THOMAS DELEURAN (Orcid ID : 0000-0001-7319-975X)

Author Manuscript

Article type : Original

Risk and outcome of venous and arterial thrombosis in patients with cirrhosis: a Danish nationwide cohort study

Peter Jepsen (1, 2), pj@clin.au.dk

Elliot B. Tapper (3), etapper@med.umich.edu

Thomas Deleuran (1), thomas.deleuran@clin.au.dk

Konstantin Kazankov (1, 4), konskaza@rm.dk

Gro Askgaard (1), gask@dadlnet.dk

Henrik Toft Sørensen (2), hts@clin.au.dk

Hendrik Vilstrup (1), vilstrup@clin.au.dk

Joe West (5, 6), joe.west@nottingham.ac.uk

1. Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
2. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.32019

This article is protected by copyright. All rights reserved

3. Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor USA
4. Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom
5. Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom
6. NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom

Key words: Epidemiology; hepatology; cardiovascular disease; coagulation

Contact information: Peter Jepsen, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark. E-mail: pj@clin.au.dk. Telephone: +45 2425 2944.

Financial support: Peter Jepsen was supported by a grant from the Novo Nordisk Foundation (NNF18OC0054612). Elliot Tapper receives funding from the National Institutes of Health - NIDDK (K23DK117055). The funding organizations were not involved in the design and conduct of the study, or in the decision to submit the manuscript for publication.

Authors' contributions: Peter Jepsen conceived the study, conducted the analysis, and drafted the manuscript. All authors have contributed to the interpretation of the results and revised the manuscript for important intellectual content.

Author Manuscript

ABSTRACT

Background & 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 & Results:** We used nationwide Danish healthcare registries to identify outpatients with cirrhosis and a sex- and age-matched comparison cohort without cirrhosis from the general population. Patients with cirrhosis and

This article is protected by copyright. All rights reserved

comparators were followed until they had a venous thromboembolism, acute myocardial infarction, ischemic stroke, or died. We computed absolute risks and hazard ratios of thrombosis, and compared outcomes after thrombosis. We included 5,854 patients with cirrhosis (median MELD score 9, IQR 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 venous thromboembolism (adjusted hazard ratio [HR] 2.0, 95% CI 1.5–2.6) or ischemic stroke (adjusted HR 1.7, 95% CI 1.3–2.3), but not myocardial infarction (adjusted HR 0.7, 95% CI 0.5–0.9). Among patients with cirrhosis, decompensation increased the risk of acute myocardial infarction but not the other thromboses. Following thrombosis, patients with cirrhosis had higher 90-day mortality than comparators (after venous thromboembolism: 17% vs. 7%; after acute myocardial infarction: 27% vs. 5%; after ischemic stroke: 10% vs. 7%) and were less likely to receive antithrombotic treatment. **Conclusions:** Patients with cirrhosis had an increased risk of venous thromboembolism and ischemic stroke, but not acute myocardial infarction. Among patients with cirrhosis, decompensation increased the risk of myocardial infarction, 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.

Patients with cirrhosis are at increased risk of venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism (1-5), possibly due to an imbalance in procoagulant and anticoagulant factors (5-7). Although existing studies provide estimates of the relative risk of venous thrombosis for patients with cirrhosis, we do not know the absolute risk which is a key metric for informing the need for intervention.

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 (9). In addition, a recent meta-analysis found no apparent association between cirrhosis and risk of ischemic stroke, but all five meta-analyzed studies were from Asia, and relative risks ranged from 0.32 to 1.22 (10). Thus, the risks of acute myocardial infarction and ischemic stroke in patients with cirrhosis remain poorly defined.

The clinical implications of thrombotic events are heightened for patients with cirrhosis. Indeed, cirrhosis is associated with higher mortality after both venous thromboembolism and acute myocardial infarction (11, 12), partly explained by a lower chance of receiving

This article is protected by copyright. All rights reserved

Author Manuscript

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.

METHODS

We conducted this population-based cohort study using pseudonymized data from Danish healthcare registries (15). We did not have access to the 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 healthcare (15). We used data from the Danish National Patient Registry, which covers all Danish hospitals. This registry includes data from inpatient 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 twenty secondary diagnoses, coded according to the International Classification of Diseases, 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 individual-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 (18 years or older) who received their first primary or secondary diagnosis of cirrhosis after 1 January 1996, whether from an inpatient, outpatient, or emergency room visit. We then defined the 'index date' as the date

This article is protected by copyright. All rights reserved

Author Manuscript

1 year after this first diagnosis. Thus, the earliest possible index date was 1 January 1997. To join the cohort, patients had to be outpatients followed for cirrhosis on their index date. Finally, we excluded patients who before the index date had received a diagnosis code for venous thromboembolism, acute myocardial infarction, or ischemic stroke, 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 Supplementary Table 1.

We identified a sex-, age-, and birthyear-matched comparison cohort from the general population. This comparison cohort consisted of five persons without cirrhosis for each patient with cirrhosis. Matching occurred on the date of the first cirrhosis diagnosis of the cirrhosis patient 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 venous thromboembolism (deep vein thrombosis or pulmonary embolism, but not portal vein thrombosis), acute myocardial infarction, or ischemic stroke, whichever occurred first. The admission date defined the date of these outcomes. Ischemic stroke included diagnoses of both ischemic and unspecified stroke since 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 1 November 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, or in censoring after 90 days.

Potential confounding factors

Cancer, diabetes, renal failure, smoking, arterial hypertension, atrial fibrillation 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, earliest diabetes diagnosis, earliest renal failure diagnosis, earliest smoking indicator, and earliest diagnosis of atrial

This article is protected by copyright. All rights reserved

Author Manuscript

fibrillation 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 arterial hypertension was the earliest of these: a hospital diagnosis for arterial hypertension, or a filled prescription for a drug to treat arterial hypertension (thiazides, calcium channel blockers, ACE 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, each spell lasting 90 days from the date of hospital admission.

Characteristics of patients with cirrhosis

Patients with alcohol-related cirrhosis had a diagnosis code for alcohol-related 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 hepatic encephalopathy does not have a specific diagnosis code). Patients could not re-compensate after they had decompensated, but we divided patients with decompensated cirrhosis in two: Those with a 'recent banding or drainage' and those without. Patients with decompensated cirrhosis 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.

Author Manuscript

This article is protected by copyright. All rights reserved

Statistical analysis

To characterize the cirrhosis cohort, we described the subset of patients with cirrhosis who had data available on serum biochemistry (albumin and MELD score, based on INR, bilirubin, creatinine, and sodium) (26). These data were available across most of Denmark from 2015 onwards (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 vs. comparators without cirrhosis

We used the cumulative incidence function to compute the risks of venous thromboembolism, acute myocardial infarction, and ischemic stroke. Death without thrombosis was treated as a competing risk.

We used stratified Cox regression to examine the hazard ratio of each outcome event. Each cirrhosis patient and his or her comparators constituted one stratum. We adjusted for confounding from cancer, diabetes, renal failure, smoking, arterial hypertension, atrial fibrillation or flutter, surgery, and trauma, and these were included as time-dependent variables. We repeated the Cox regression analysis within strata defined by alcohol-related or nonalcoholic cirrhosis; by gender; and by compensated or decompensated cirrhosis on the index date.

Cirrhosis severity as a risk factor for thrombosis among patients with cirrhosis

We examined whether decompensation was associated with the hazard ratio of thrombosis among patients with cirrhosis. We adjusted for confounding by sex, age, cirrhosis etiology (alcohol-related or nonalcoholic), cancer, diabetes, renal failure, smoking, arterial hypertension, atrial fibrillation 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 onwards, 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 upper gastrointestinal bleeding within 90 days from first thrombosis.

This article is protected by copyright. All rights reserved

Author Manuscript

Death without upper gastrointestinal bleeding was a competing risk event in these analyses. The date of upper gastrointestinal bleeding was defined as the admission date of a hospital contact eliciting a procedure code for an upper endoscopy and a diagnosis code for upper gastrointestinal bleeding or bleeding from gastroesophageal varices (27).

RESULTS

Clinical Characteristics

We included 5,854 patients with cirrhosis and 23,870 matched comparators. The patients' median age was 57 years (IQR 50–64 years), 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-related cirrhosis. A MELD score was available on the index date for 1,826 patients with cirrhosis (31% of the total cohort). The 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 or lower. The median serum albumin was 36 g/L (IQR 32–40 g/L).

Outcomes

The 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 (Supplementary Figure 1).

The number of new users of antithrombotic drugs per year of follow-up without thrombosis, *i.e.*, the 'new user rate', was higher for patients with cirrhosis than for the comparators (Table 1). The same was seen 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).

Author Manuscript

This article is protected by copyright. All rights reserved

Thrombosis incidence

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

Patients with cirrhosis were more likely than comparators to have a venous thromboembolism (10-year risk = 2.5% vs. 1.7%), and the adjusted hazard ratio was 2.0 (95% CI 1.5 to 2.6). This association between cirrhosis and venous thromboembolism was stronger for alcohol-related cirrhosis than for nonalcoholic cirrhosis, and stronger for women than for men. The risk of acute myocardial infarction was lower for patients with cirrhosis than comparators (10-year risk = 1.3% vs. 2.3%), and the hazard rate was decreased (adjusted hazard ratio = 0.7, 95% CI 0.5 to 0.9). The risk of ischemic stroke was higher for patients with cirrhosis than for comparators (10-year risk = 2.5% vs. 1.7%, adjusted hazard ratio = 1.7, 95% CI 1.3 to 2.3), entirely because of a strong association between alcohol-related cirrhosis and ischemic stroke (adjusted hazard ratio = 2.1, 95% CI 1.6 to 2.7) (Table 2 and Supplementary Table 2).

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 decompensated patients were in hospital at least once to undergo variceal banding or ascites drainage. Relative to patients with compensated cirrhosis, patients with decompensated cirrhosis who within the previous 90 days had been in hospital for variceal banding or ascites drainage had an adjusted hazard ratio of acute myocardial infarction of 8.7 (95% CI 2.7–28.3). The hazard ratio for other decompensated patients was 1.6 (95% CI 0.7 to 3.9). By contrast, decompensation, with or without a recent banding or drainage, was not a risk factor for venous thromboembolism or ischemic stroke (Table 3).

Outcomes after thrombosis

Ninety-day mortality was higher for patients with cirrhosis than for comparators after venous thromboembolism (17% vs. 7%) and acute myocardial infarction (30% vs. 5%), whereas the difference was small after ischemic stroke (10% vs. 7%) (Table 4).

Author Manuscript

This article is protected by copyright. All rights reserved

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 or bypass surgery after acute myocardial infarction. The 90-day risk of upper gastrointestinal bleeding was 2.2% for the patients with cirrhosis and zero for the matched comparators (Table 4). Among the patients with cirrhosis, it was marginally higher for those who had decompensated, 2.3% vs. 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 venous thromboembolism and ischemic stroke but a reduced risk of acute myocardial infarction. Among patients with cirrhosis, however, decompensation was a risk factor for acute myocardial infarction but not for venous thromboembolism or ischemic stroke. 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 venous thromboembolism (17% vs. 7%) and after acute myocardial infarction (30% vs. 5%). The risk of upper gastrointestinal bleeding following thrombosis was 2.2% for the patients with cirrhosis, zero for the comparators.

Our patients with cirrhosis were at increased risk of venous thromboembolism, 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 due to increased levels of factor VIII and decreased levels of protein C (28), or other factors contribute. We did not examine the risk of portal vein thrombosis 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 acute myocardial infarction. 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 acute myocardial infarction. We also extend our previous study by highlighting that acute myocardial infarction is highly fatal in patients with cirrhosis. It is striking that our patients with cirrhosis were more

Author Manuscript

This article is protected by copyright. All rights reserved

likely to receive antithrombotic treatment as prophylaxis, yet much less likely to receive antithrombotic treatment after thrombosis. In their study of United States patients with acute myocardial infarction, Hillerson et al. found, like us, that patients with cirrhosis received less antithrombotic treatment and had higher mortality (11). A later United States study reported that, among patients with cirrhosis, the use of percutaneous coronary intervention after myocardial infarction increased between 2003 and 2016, but the excess mortality persisted (31). Concerns over bleeding risk should not discourage antithrombotic treatment after thrombosis, and after myocardial infarction in particular. We found a 90-day bleeding risk of only 5% after acute myocardial infarction. Hillerson et al. reported that the risk of bleeding after acute myocardial infarction was 12.3% in patients with cirrhosis vs. 7.1% in matched comparators (11).

The strong association of ischemic stroke with alcohol-related cirrhosis but not with nonalcoholic cirrhosis was notable. Others have found that cirrhosis is associated with ischemic stroke (32), but that was in an older population (mean age 74 years versus 57 in our cohort) with a higher absolute risk of ischemic stroke. In that study no difference in risk was found between patients with alcohol-related 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 due to residual confounding from smoking, although smoking is more prevalent in both alcohol-related and nonalcoholic cirrhosis than in people without cirrhosis (33). Another possibility is that, among patients with alcohol-related cirrhosis, relatively many of the unspecified strokes were in fact hemorrhagic strokes.

It is unclear why alcohol-related cirrhosis is a risk factor for ischemic stroke and not for acute myocardial infarction, 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 acute myocardial infarction but is not a risk factor for ischemic stroke or venous thromboembolism. 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 acute myocardial infarction (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 hospital. The 79% prevalence of decompensation

This article is protected by copyright. All rights reserved

Author Manuscript

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, the prevalence of decompensation was 75% and 76%, respectively. The 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 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 positive predictive value of a first-time diagnosis code is 86% for deep venous thrombosis, 90% for first-time pulmonary embolism, and 97% for first-time myocardial infarction (20). The diagnosis code for ischemic stroke has a positive predictive value 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 whilst maintaining a positive predictive value of 70%. The others are 7% intracranial bleedings, 7% unspecified strokes, and 15% other diseases (22). It remains possible that the association between alcohol-related cirrhosis and ischemic stroke is due to a larger proportion of incorrect diagnoses of ischemic stroke 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, acute myocardial infarction, and venous thrombosis have not been assessed for completeness. We speculate that completeness of registration is very high for a usually symptomatic event like acute myocardial infarction. We are more concerned for venous thromboembolism 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 venous thromboembolism and ischemic stroke. Cirrhotic decompensation events seem to be causally linked with acute myocardial infarction, 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

This article is protected by copyright. All rights reserved

Author Manuscript

antithrombotic treatment at inclusion—yet the combined risks of the thrombosis types we considered was approximately 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 venous thromboembolism and ischemic stroke, but not acute myocardial infarction. Among patients with cirrhosis, decompensation events increased the risk of acute myocardial infarction, but did not affect the risk of venous thromboembolism or ischemic stroke. Relative to matched comparators, our patients with cirrhosis were treated less intensely after thrombosis and had a higher mortality.

REFERENCES

1. Ali M, Ananthakrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: A nationwide analysis. Dig Dis Sci 2011;56:2152-2159.
2. Ambrosino P, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, et al. The risk of venous thromboembolism in patients with cirrhosis: A systematic review and meta-analysis. Thromb Haemost 2017;117:139-148.
3. Violi F, Ferro D. Clotting activation and hyperfibrinolysis in cirrhosis: Implication for bleeding and thrombosis. Semin Thromb Hemost 2013;39:426-433.
4. Søgaard KK, Adelborg K, Darvalics B, Horvath-Puho E, Beyer-Westendorf J, Ageno W, et al. Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: A population-based cohort study. Lancet Haematol 2018;5:e441-e449.
5. Søgaard KK, Horvath-Puho E, Grønbæk H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Am J Gastroenterol 2009;104:96-101.
6. Northup PG, Caldwell SH. Coagulation in liver disease: A guide for the clinician. Clin Gastroenterol Hepatol 2013;11:1064-1074.

Author Manuscript

This article is protected by copyright. All rights reserved

7. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147-156.
8. Kazankov K, Munk K, Øvrehus KA, Jensen JM, Siggaard CB, Grønbæk H, et al. High burden of coronary atherosclerosis in patients with cirrhosis. Eur J Clin Invest 2017;47:565-573.
9. Deleuran T, Schmidt M, Vilstrup H, Jepsen P. Time-dependent incidence and risk for myocardial infarction in patients with alcoholic cirrhosis. Eur J Clin Invest 2020:e13205.
10. Zheng K, Yoshida EM, Tacke F, Li Y, Guo X, Qi X. Risk of stroke in liver cirrhosis: A systematic review and meta-analysis. J Clin Gastroenterol 2020;54:96-105.
11. Hillerson D, Ogunbayo GO, Salih M, Misumida N, Abdel-Latif A, Smyth SS, et al. Outcomes and characteristics of myocardial infarction in patients with cirrhosis. J Invasive Cardiol 2019;31:E162-E169.
12. Søgaard KK, Horvath-Puho E, Montomoli J, Vilstrup H, Sørensen HT. Cirrhosis is associated with an increased 30-day mortality after venous thromboembolism. Clin Transl Gastroenterol 2015;6.
13. Schmidt M, Horvath-Puho E, Ording AG, Bøtker HE, Lash TL, Sørensen HT. The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: A nationwide cohort study. Int J Cardiol 2020;308:1-8.
14. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study. Hepatology 2008;48:214-220.
15. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: From healthcare contacts to database records. Clin Epidemiol 2019;11:563-591.
16. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish national patient registry: A review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-490.
17. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish national prescription registry. Int J Epidemiol 2017;46:798-798f.
18. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, Adelborg K. Existing data sources in clinical epidemiology: Laboratory information system databases in Denmark. Clin Epidemiol 2020;12:469-475.

This article is protected by copyright. All rights reserved

Author Manuscript

19. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. Eur J Epidemiol 2014;29:541-549.
20. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish national patient registry: A validation study. BMJ Open 2016;6:e012832.
21. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in the Danish national registry of patients. J Clin Epidemiol 2002;55:602-607.
22. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a national register of patients. Neuroepidemiology 2007;28:150-154.
23. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016;388:3060-3073.
24. Campbell BCV, Khatri P. Stroke. Lancet 2020;396:129-142.
25. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-1305.
26. United Network for Organ Sharing. Clerical changes for implementation of adding serum sodium to the MELD score. https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf (accessed on 8 April 2020).
27. Valkhoff VE, Coloma PM, Masclee GM, Gini R, Innocenti F, Lapi F, et al. Validation study in four health-care databases: Upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk. J Clin Epidemiol 2014;67:921-931.
28. Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137:2105-2111.
29. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: Results of a longitudinal study. Hepatology 2015;61:660-667.
30. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: A systematic review and meta-analysis. Gastroenterology 2017;153:480-487.e481.

Author Manuscript

This article is protected by copyright. All rights reserved

31. Alqahtani F, Balla S, AlHajji M, Chaudhary F, Albeiruti R, Kawsara A, et al. Temporal trends in the utilization and outcomes of percutaneous coronary interventions in patients with liver cirrhosis. Catheter Cardiovasc Interv 2020;96:802-810.
32. Parikh NS, Navi BB, Schneider Y, Jesudian A, Kamel H. Association between cirrhosis and stroke in a nationally representative cohort. JAMA Neurol 2017;74:927-932.
33. Dam MK, Flensborg-Madsen T, Eliasen M, Becker U, Tolstrup JS. Smoking and risk of liver cirrhosis: A population-based cohort study. Scand J Gastroenterol 2013;48:585-591.
34. Danielsen KV, Wiese S, Hove J, Bendtsen F, Møller S. Pronounced coronary arteriosclerosis in cirrhosis: Influence on cardiac function and survival? Dig Dis Sci 2018;63:1355-1362.
35. Krag A, Bendtsen F, Henriksen JH, Moller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut 2010;59:105-110.
36. Krag A, Wiest R, Albillos A, Gluud LL. The window hypothesis: Haemodynamic and non-haemodynamic effects of beta-blockers improve survival of patients with cirrhosis during a window in the disease. Gut 2012;61:967-969.
37. Dam Fialla A, Schaffalitzky de Muckadell OB, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: A population-based cohort study. Scand J Gastroenterol 2012;47:702-709.
38. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: A Danish population-based cohort study. Hepatology 2010;51:1675-1682.
39. Vestberg K, Thulstrup AM, Sørensen HT, Ottesen P, Sabroe S, Vilstrup H. Data quality of administratively collected hospital discharge data for liver cirrhosis epidemiology. J Med Syst 1997;21:11-20.
40. Jepsen P, Vilstrup H, Sørensen HT. Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: A descriptive cohort study. BMC Gastroenterol 2008;8:3.
41. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253-1260 e1254.

This article is protected by copyright. All rights reserved

Author Manuscript

42. Dhar A, Mullish BH, Thursz MR. Anticoagulation in chronic liver disease. J Hepatol 2017;66:1313-1326.

Author Manuscript

This article is protected by copyright. All rights reserved

Table 1. Characteristics of patients with cirrhosis and comparison cohort at study inclusion matched on sex, age, and birthyear. The incidence rates of new drug users are presented per 1000 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.

		Cirrhosis	Comparison cohort
Number 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%)
Arterial hypertension		2,566 (44%)	5,523 (23%)
Atrial fibrillation 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

† Proportion of follow-up time spent less than 90 days after surgery or trauma.

Author Manuscript

This article is protected by copyright. All rights reserved

Table 2. Effect of cirrhosis on the risks and hazard rates of thrombosis events and on death without thrombosis. The cumulative risks are presented as the risk for cirrhosis patients *vs.* the risk for matched comparators. The hazard ratios are for cirrhosis patients vs. sex- and age-matched comparators, with and without adjustment for confounding from cancer, diabetes, renal failure, smoking, arterial hypertension, atrial fibrillation or flutter, surgery, and trauma (see also Supplementary Table 2)..

	Venous thromboembolism	Acute myocardial infarction	Ischemic stroke	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 hazard ratio	2.4 (1.9–3.1)	0.9 (0.6–1.2)	2.2 (1.8–2.9)	17 (15–18)
Adjusted hazard ratio	2.0 (1.5–2.6)	0.7 (0.5–0.9)	1.7 (1.3–2.3)	15 (14–17)
Stratified analyses, adj. hazard ratio				
Alcohol-related 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)
Compensated cirrhosis†	2.5 (1.4–4.6)	0.7 (0.3–1.5)	1.0 (0.5–1.9)	10 (8–13)
Decompensated cirrhosis†	1.9 (1.4–2.6)	0.7 (0.5–1.0)	2.0 (1.5–2.7)	17 (15–19)

Author Manuscript

This article is protected by copyright. All rights reserved

† Patients with compensated/decompensated cirrhosis at inclusion vs. their comparators.

Author Manuscript

Table 3. Hazard ratios associated with decompensation and with potential confounders. This analysis includes only patients with cirrhosis. We conducted separate regression models for each of the outcomes under consideration.

	Venous thromboembolism	Acute myocardial infarction	Ischemic stroke	Death without thrombosis
Number 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-related 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)
Arterial hypertension	1.5 (1.0–2.3)	1.1 (0.6–2.0)	0.8 (0.6–1.2)	0.9 (0.8–1.0)
Atrial fibrillation 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 article is protected by copyright. All rights reserved

Author Manuscript

This article is protected by copyright. All rights reserved

Table 4. Antithrombotic treatment and mortality following thrombosis. The numbers of patients and proportions are presented as cirrhosis patients vs. comparators.

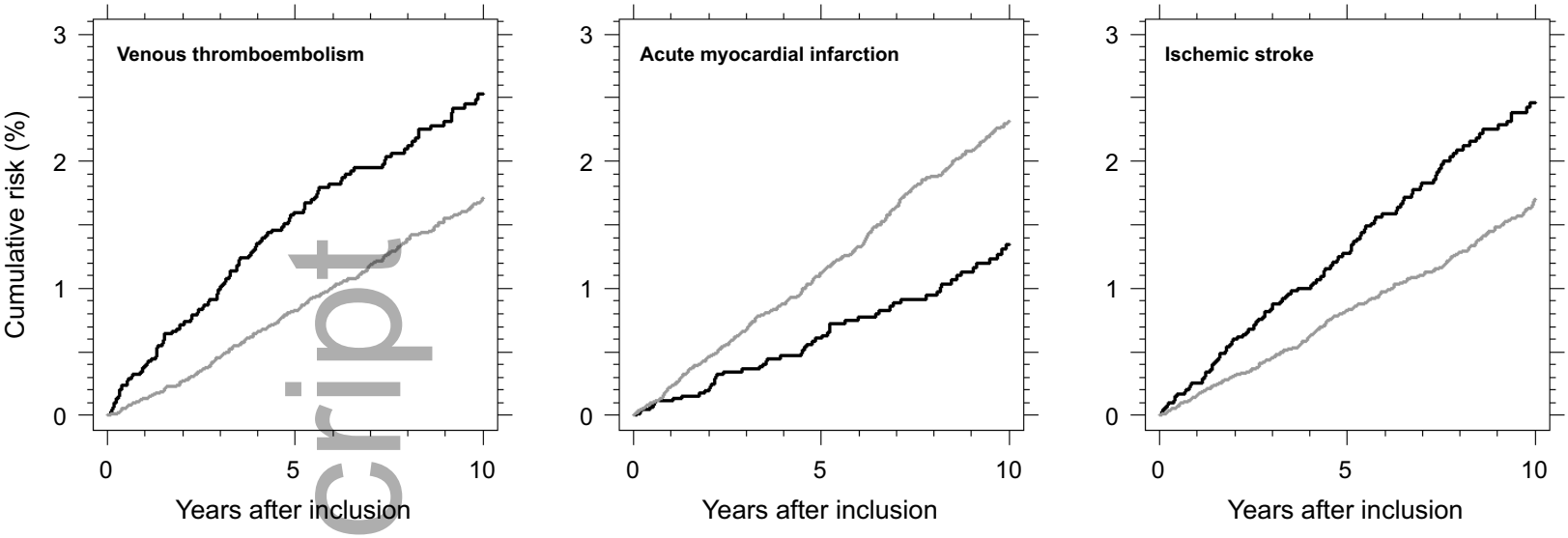
	Venous thromboembolism	**Acute myocardial infarction**	**Ischemic stroke**
Numbers of patients and comparators	115 vs. 304	56 vs. 416	108 vs. 300
Filled prescription for antithrombotic drug	37% vs. 77%	62% vs. 93%	69% vs. 90%
Most frequently prescribed antithrombotic drug(s)	Warfarin (16% vs. 39%), rivaroxaban (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 upper gastrointestinal bleeding	2% vs. 0	5% vs. 0	1% vs. 0
90-day all-cause mortality	17% vs. 7%	30% vs. 5%	10% vs. 7%

Author Manuscript

FIGURE LEGENDS

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

This article is protected by copyright. All rights reserved



hep_32019_f1.eps

Author Manuscript

This article is protected by copyright. All rights reserved