Atrial fibrillation, liver cirrhosis, thrombosis, and bleeding

A Danish population-based cohort study

Riahi, Emil B.; Adelborg, Kasper; Pedersen, Lars; Kristensen, Søren R.; Hansen, Anette T.; Sørensen, Henrik T.

Published in:
Research and Practice in Thrombosis and Haemostasis

DOI (link to publication from Publisher):
10.1002/rth2.12668

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Received: 5 July 2021 | Revised: 28 December 2021 | Accepted: 5 January 2022

DOI: 10.1002/rth2.12668

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

Atrial fibrillation, liver cirrhosis, thrombosis, and bleeding: A Danish population-based cohort study

Emil B. Riahi MD[1,2] | Kasper Adelborg MD, PhD[1,3] | Lars Pedersen MSc, PhD[1] | Søren R. Kristensen MD, PhD, DMSc[4,5] | Anette T. Hansen MD, PhD[1] | Henrik T. Sørensen MD, PhD, DMSc[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

[2]Department of Surgery, Randers Regional Hospital, Randers, Denmark

[3]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

[4]The Atrial Fibrillation Study Group, Aalborg University Hospital, Aalborg, Denmark

[5]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark

Correspondence
Emil B. Riahi, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark.
Email: emilriahi@gmail.com

Funding information
This study was partly funded by a grant from the Obel Family Foundation to the Atrial Fibrillation Study Group, Aalborg University Hospital. All other expenses were covered by Department of Clinical Epidemiology, Aarhus University Hospital.

Handling Editor: Dr Suzanne Cannegieter

Abstract

Objectives: We examined the impact of liver cirrhosis on the risk of thromboembolic events and bleeding complications in patients with atrial fibrillation or flutter (AFF).

Methods: This population-based cohort study used data from Danish health registries. We identified all patients with a first-time diagnosis of AFF during 1995 to 2015, and followed them from their AFF diagnosis until the end of 2016. Patients were categorized according to the presence or absence of liver cirrhosis. We computed incidence rates per 1000 person-years and hazard ratios (HRs) with 95% confidence intervals (CIs) based on Cox regression analyses, adjusting for age, CHA_2DS_2VASc score, and Charlson Comorbidity Index score.

Results: We identified 273 225 patients with AFF. Of these, 1463 (0.54%) had liver cirrhosis. During 0 to 5 years of follow-up, compared to patients without liver cirrhosis, patients with liver cirrhosis had higher incidence rates and hazards of ischemic stroke (29.7 vs 21.6; HR, 1.3; 95% CI, 1.1-1.6), venous thromboembolism (9.2 vs 5.5; HR, 1.5; 95% CI, 1.2-2.3), but not myocardial infarction (10.2 vs 11.2; HR, 0.9; 95% CI, 0.7–1.2). Patients with liver cirrhosis also had higher rates of hemorrhagic stroke (5.8 vs 3.3; HR, 1.7; 95% CI, 1.1-2.6), subdural hemorrhage (5.3 vs 1.6; HR, 3.2; 95% CI, 2.1-4.9), hemorrhage of the lung or urinary tract (24.6 vs 15.2; HR, 1.6; 95% CI, 1.3–2.0), and gastrointestinal hemorrhage (34.5 vs 10.4; HR, 3.3; 95% CI, 2.7–3.9).

Conclusion: In patients with AFF, liver cirrhosis was associated with an elevated risk of ischemic stroke, venous thromboembolism, and all evaluated bleeding complications.

KEYWORDS
atrial fibrillation, cohort study, hemorrhagic stroke, ischemic stroke, liver cirrhosis, venous thromboembolism

Essentials

- Research shows that liver cirrhosis is associated with bleeding and thromboembolism.
- We examined the risk of vascular events in patients with liver cirrhosis and atrial fibrillation.
- Liver cirrhosis was associated with an increased risk of stroke and venous thromboembolism.
- Liver cirrhosis was associated with an increased risk of bleeding.

1 | INTRODUCTION

Atrial fibrillation and atrial flutter (AFF) are the most common cardiac arrhythmias, and the incidence and prevalence of AFF continues to increase.[1,2] AFF are important risk factors for ischemic stroke, peripheral arterial embolism, heart failure, and premature death.[3,4] The CHA_2DS_2VASc score is used for risk stratification and as a tool to determine whether patients should receive oral anticoagulants to reduce their risk of ischemic stroke.[5-7] Comorbidities such as diabetes and chronic kidney disease are known to increase the risk of thromboembolic events in patients with AFF,[8,9] but whether liver cirrhosis affects the thromboembolic risk in patients with AFF is sparsely investigated.

Patients with liver cirrhosis have been considered to be "auto"-anticoagulated due to a clinical bleeding tendency, low levels of procoagulant factors, and reduced platelet function.[10,11] However, several studies have suggested that patients with liver cirrhosis have a 1.5-fold increased risk of venous thromboembolic events compared to patients without liver cirrhosis.[10,12-15]

Six studies have investigated the risk of thromboembolic and bleeding complications in patients with AFF and a history of liver cirrhosis.[16-21] Only two of these studies investigated how liver cirrhosis affects the risk of thromboembolic and bleeding complications in AFF, compared to patients with no liver disease.[17,19] However, these two studies were based on Asian populations only.[17,19] Although one study included nearly 290 000 patients with AFF, only few potential events such as systemic thromboembolism and bleeding complications were included.[17] Another study was limited by a small study population of 3923 patients.[19] Therefore, it is still unclear how liver cirrhosis affects the risk of thromboembolic events and bleeding complications in patients with AFF.

We therefore examined if liver cirrhosis was associated with an elevated risk of thromboembolic events and bleeding complications among patients with AFF in a large, Danish population-based cohort.

2 | METHODS

2.1 | Setting and design

We conducted a population-based cohort study from January 1, 1995, to December 31, 2015. The study was based on prospectively collected routine health care data retrieved from the Danish National Patient Registry (DNPR), which covers all Danish hospitals; the Danish National Prescription Registry, including all Danish pharmacies; and the Civil Registration System.[22-24] The Danish national healthcare service is tax funded, which ensures equal access to health services to the entire population.[25] All Danish inhabitants are assigned a unique civil registration number at birth or upon immigration.[24] This civil registration number enables the linkage of valid, anonymized, individual-level data between registries.[24]

According to Danish legislation, registry-based studies do not require approval from an ethics committee or informed consent from patients.

2.2 | Data sources

The DNPR holds records of all inpatient admissions to Danish hospitals since 1977, and records of all outpatient clinics, emergency rooms, and psychiatric admissions since 1995. The information contained in the registry includes one primary discharge diagnosis and up to 19 secondary diagnoses, the setting (ie, hospital, outpatient clinic, or emergency room), and the admission and discharge dates. The diagnoses in the DNPR were classified according to the International Classification of Diseases (ICD), Eighth Revision, from 1977 to 1993, and according to the ICD, Tenth Revision (ICD-10) thereafter.[22] The ICD, Ninth Revision (ICD-9) has never been implemented and used in Denmark.

The Danish National Prescription Registry holds records on all redeemed prescriptions filled from outpatient or municipality-based pharmacies, starting from 1995.[23] Information recorded in the registry includes the drug dispensed, the dispensation date, and the defined daily dosages. Dispensed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system codes.

2.3 | Study cohort

We searched the DNPR to identify all patients with a first-time inpatient or outpatient clinic diagnosis of AFF, recorded between January 1, 1995, and December 31, 2015. The patients were identified with ICD-10 codes. Patients who were diagnosed with AFF before January 1, 1995, were identified in the DNPR and excluded from the study.[22] We did not exclude patients with a prevalent diagnosis of thromboembolic or bleeding events. The positive predictive value for AFF diagnosis in the DNPR is ≈95%, with the medical record as the gold standard.[26]

We divided the cohort of patients with AFF into two groups according to the presence or absence of a diagnosis of liver cirrhosis

recorded any time before the diagnosis of AFF. The positive predictive value of an ICD code of liver cirrhosis has been validated in a subset of the DNPR in Jutland. The positive predictive value of liver cirrhosis was ≈85%, using medical records and/or histopathological findings as the gold standard.[27]

The Danish National Prescription Registry was used to classify patients as either users or nonusers of oral anticoagulant treatment, based on ATC codes.[23] Users of oral anticoagulant treatment were defined as those who filled at least one redeemed prescription of either vitamin K antagonists or a direct oral anticoagulant (DOAC) within 90 days after a first-time AFF diagnosis. Nonusers of oral anticoagulant treatment were defined as those who did not fill a prescription of either vitamin K antagonists or DOAC within the first 90 days of a first-time AFF diagnosis. To avoid immortal time bias, the index date was defined as 90 days after the AFF diagnosis for all patients.[28]

2.4 | Outcomes

Thromboembolic outcomes included ischemic stroke, myocardial infarction, and venous thromboembolism. Ischemic stroke diagnoses comprised both specified ischemic stroke and unspecified stroke, because two-thirds of unspecified strokes in the DNPR are known to be ischemic in origin.[29]

Bleeding outcomes included hemorrhagic stroke, subdural hemorrhage, bleeding in the lung or urinary tract, and gastrointestinal hemorrhage. Bleeding from the respiratory system or urinary tract was considered one combined outcome. Outcomes were identified in the DNPR and based on ICD-10 codes for primary and secondary diagnoses given at inpatient and outpatient visits. If a bleeding or thromboembolic event occurred more than once in a patient, only the first event (for each type) was included. Recorded cardiovascular outcomes have high validity in the DNPR, with validation studies reporting a positive predictive value of 97% for each of ischemic stroke and myocardial infarction, 88% for first-time venous thromboembolism, and 74% for intracranial hemorrhage.[22,26,29]

2.5 | Covariates

The DNPR was accessed to retrieve the medical history of all patients before the index date. Based on all inpatient and outpatient discharge diagnoses, we extracted information on the comorbidities of the study population. We recorded diabetes, chronic pulmonary diagnoses, and hypertension using a combination of ICD and ATC codes. The comorbidities were used to calculate the CHA_2DS_2VASc score for each patient.[7] We calculated a modified Charlson Comorbidity Index score for each patient, which included only the comorbidities that were not included in the CHA_2DS_2VASc score; that is, we did not include a history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, or diabetes. Neither did we include liver disease in our modified Charlson Comorbidity Index score.[30]

For the CHA_2DS_2VASc score, we grouped the scores into categories of 0 to 1, 2 to 3, and >3. For the Charlson Comorbidity Index score, we grouped the scores into categories of 0 to 1 and >1.

We used the Prescription Registry to extract information on medications. We defined medications as medications filled for at least one redeemed prescription and recorded within 90 days before the index date. The ICD and ATC codes used in the study are provided in Tables S1 through S6.

2.6 | Statistical analysis

We followed patients from their index date until death, emigration, end of study, or December 31, 2016 (to ensure at least 9 months of follow-up), whichever came first. When patients experienced one thromboembolic or bleeding outcome, they remained at risk for other thromboembolic or bleeding outcomes. For example, any patient who experienced a venous thromboembolism remained at risk of an ischemic stroke and vice versa.

In our main analysis, we compared patients with AFF without liver cirrhosis to patients with AFF with liver cirrhosis. We calculated incidence rates per 1000 person-years during the first year (0-1 year), the second and third year (1-3 years), the fourth and fifth year (3-5 years), and during the first 5 years of follow-up (0-5 years).

As a measure of relative risks, we conducted a Cox regression analysis to compute hazard ratios (HRs) with 95% confidence intervals (CIs) to evaluate the risk of a thromboembolic or bleeding event during the same time periods. We adjusted for age, CHA_2DS_2VASc score, and the modified Charlson Comorbidity Index score. We did not adjust for sex separately because it was included in the CHA_2DS_2VASc score. With log-log plots, we assessed the assumption of proportional hazards and found them valid in the follow-up periods.

To further explore the effects of covariates on the risk of thromboembolic and bleeding complications, we performed a stratified analysis during 0 to 1 year of follow-up. We stratified by oral anticoagulation, the CHA_2DS_2VASc score, and the modified Charlson Comorbidity Index score, and calculated the incidence rates per 1000 person-years and computed crude and adjusted HRs.

We used Stata version 15.1 for all data management and statistical computations.[31] The Danish Data Protection Agency approved the study (record number: 707026).

3 | RESULTS

We identified 273 225 patients who received a hospital-based diagnosis of AFF during 1995 to 2015. A total of 1463 (0.5%) patients had a concomitant diagnosis of liver cirrhosis (Table 1). Patients with liver cirrhosis had a lower median age (68 vs 74 years), were more likely to be men (63.8% vs 54.0%), and had a lower CHA_2DS_2VASc score

TABLE 1 Characteristics of patients with atrial fibrillation or flutter, with or without liver cirrhosis, in Denmark from 1995 through 2015

Characteristic	Patients without liver cirrhosis, N (%)	Patients with liver cirrhosis, N (%)
	271 762 (99.5)	1463 (0.5)
Sex		
Male	146 700 (54.0)	933 (63.8)
Age, y		
Median (IQR)	74 (65-82)	68 (61-75)
CHA_2DS_2VASc score		
0-1	77 202 (28.4)	525 (35.9)
2-3	13 ,558 (51.4)	658 (45.0)
>3	55,002 (20.2)	280 (19.1)
Modified Charlson Comorbidity Index score		
0-1	238 100 (87.6)	1140 (77.9)
>1	33 662 (12.4)	323 (22.1)

Note: Values are the number (%), unless otherwise specified.
Abbreviation: IQR, interquartile range.

than patients without liver cirrhosis. A smaller proportion of patients with liver cirrhosis had a Charlson Comorbidity Index score of ≤1 compared to patients without liver cirrhosis (77.9% vs 87.6%, respectively). The prevalence of comorbidities and comedications are shown in Table S7. The prevalence of previous ischemic stroke, hemorrhagic stroke, and ischemic heart diseases were similar between patients with and without liver cirrhosis. However, patients with liver cirrhosis had a higher prevalence of hypertension (41.6% vs 34.8%), diabetes (20.5% vs 10.0%), and chronic pulmonary diseases (36.1% vs 25.4%), compared to those without liver cirrhosis, respectively.

3.1 | Incidence of thromboembolic complications

During the 0- to 1-year follow-up period, patients with and without a history of liver cirrhosis, respectively, had somewhat similar incidence rates of ischemic stroke (34.1 vs 28.5 per 1000 person-years), myocardial infarction (14.2 vs 14.3 per 1000 person-years), and venous thromboembolism (7.8 vs 7.1 per 1000 person-years) (Table 2). During the 1- to 3-year follow-up period, patients with a history of liver cirrhosis had elevated incidence rates of venous thromboembolism compared to patients without liver cirrhosis (10.3 vs 5.1 per 1000 person-years). During 3 to 5 years of follow-up, patients with liver cirrhosis had increased incidence rates of ischemic stroke (30.2 vs 18.3 per 1000 person-years) and venous thromboembolism (9.1 vs 4.5 per 1000 person-years), compared to those without liver cirrhosis, respectively.

During 0 to 5 years of follow-up, patients with liver cirrhosis had higher incidence rates of ischemic stroke (29.7 vs 21.6 per 1000 person-years) and venous thromboembolism (9.2 vs 5.5 per 1000 person-years), compared to those without liver cirrhosis, respectively. We found no difference in the rates of myocardial infarction between patients with and without liver cirrhosis, during the 3- to 5-year and 0- to 5-year follow-up periods.

3.2 | Relative risks of thromboembolic complications

During the 0- to 1-year follow-up period, liver cirrhosis was associated with an increased risk of ischemic stroke (adjusted HR [aHR], 1.5; 95% CI, 1.1–2.0) (Figure 1). No association was observed with myocardial infarction (aHR, 1.1; 95% CI, 0.7–1.8) or venous thromboembolism (aHR, 1.2; 95% CI, 0.6–2.2). During the 1- to 3-year follow-up period, liver cirrhosis was associated with an increased risk of ischemic stroke (aHR, 1.6; 95% CI, 1.2–2.2) and venous thromboembolism (aHR, 2.2; 95% CI, 1.3-3.5). We found no association between liver cirrhosis and myocardial infarction (aHR, 0.8; 95% CI, 0.5-1.5). Similar observations were found during 3 to5 years of follow-up.

During the 0- to5-year follow-up period, liver cirrhosis was associated with an increased risk of ischemic stroke (aHR, 1.6; 95% CI, 1.4-2.0) and venous thromboembolism (aHR, 1.7; 95% CI, 1.2-2.4). No association was observed between liver cirrhosis and myocardial infarction (aHR, 1.0; 95% CI, 0.7-1.4).

3.3 | Incidence of bleeding complications

During the 0- to 1-year follow-up period, patients with liver cirrhosis had higher incidence rates of hemorrhagic stroke (9.4 vs 4.1 per 1000 person-years), subdural hemorrhage (7.8 vs 1.9 per 1000 person-years), and gastrointestinal hemorrhage (43.7 vs 12.2 per 1000 person-years). We found no differences in the rates of hemorrhage in the lung or urinary tract (23.0 vs 17.6; Table 2). During the 1- to 3-year follow-up period, patients with liver cirrhosis had higher incidence rates of hemorrhagic stroke (6.0 vs 3.1 per 1000 person-years), subdural hemorrhage (4.2 vs 1.6 per 1000 person-years), hemorrhage of the lung or urinary tract (22.9 vs 14.4 per 1000 person-years), and gastrointestinal hemorrhage (34.3 vs 9.8 per 1000 person-years). During the 3- to 5-year follow-up, we were not able to assess the incidence rates of hemorrhagic stroke and subdural hemorrhage in patients with liver cirrhosis due to a low number of cases. However, patients with liver cirrhosis continued to have higher incidence rates of hemorrhage of the lung or urinary tract and gastrointestinal hemorrhage.

Patients with liver cirrhosis had higher rates of hemorrhagic stroke (5.8 vs 3.3), subdural hemorrhage (5.3 vs 1.6), hemorrhage of the lung or urinary tract (24.6 vs 15.2), and gastrointestinal hemorrhage (34.5 vs 10.4) throughout the 0- to 5-year follow-up interval.

3.4 | Relative risks of bleeding complications

During the 0- to 1-year follow-up period, liver cirrhosis was associated with an increased risk of hemorrhagic stroke (aHR, 2.6; 95% CI, 1.5-4.6), subdural hemorrhage (aHR, 4.9; 95% CI, 2.6-9.2),

TABLE 2 Incidence rates and number of events of thromboembolic and bleeding complications after the index date in patients with atrial fibrillation or flutter, with and without liver cirrhosis, in Denmark from 1995 through 2016

	Number of events	Incidence rate (95% CI)			
	0-5 years	0-1 year	1–3 years	3-5 years	0-5 years
Ischemic stroke					
Without liver cirrhosis	19 344	28.5 (27.8-29.2)	19.6 (19.1-20.0)	18.3 (17.8-18.8)	21.6 (21.3-21.9)
With liver cirrhosis	111	34.1 (25.2-46.1)	25.9 (19.1-35.2)	30.2 (20.8-43.7)	29.7 (24.6-35.7)
Myocardial infarction					
Without liver cirrhosis	10 340	14.3 (13.8-14.8)	10.6 (10.2-10.9)	9.4 (9.1-9.8)	11.2 (11.0-11.4)
With liver cirrhosis	40	14.2 (8.9-22.5)	7.9 (4.6-13.6)	9.1 (4.7-17.4)	10.2 (7.5-13.9)
Venous thromboembolism					
Without liver cirrhosis	5131	7.1 (6.8-7.4)	5.1 (4.9-5.3)	4.5 (4.3-4.8)	5.5 (5.3-5.6)
With liver cirrhosis	36	7.8 (4.2-14.6)	10.3 (6.4-16.6)	9.1 (4.7-17.4)	9.2 (6.6-12.7)
Hemorrhagic stroke					
Without liver cirrhosis	3169	4.1 (3.8-4.3)	3.1 (2.9-3.2)	3.1 (2.9-3.3)	3.3 (3.2-3.4)
With liver cirrhosis	>22[a]	9.4 (5.3-16.5)	6.0 (3.2-11.1)	NA	5.8 (3.8-8.7)
Subdural hemorrhage					
Without liver cirrhosis	1568	1.9 (1.7-2.1)	1.6 (1.5-1.7)	1.5 (1.4-1.7)	1.6 (1.6-1.7)
With liver cirrhosis	>17[a]	7.8 (4.2-14.4)	4.2 (2.0-8.8)	NA	5.3 (3.4-8.1)
Hemorrhage of the lung or urinary tract					
Without liver cirrhosis	13,976	17.6 (17.1-18.2)	14.4 (14.0-14.8)	14.0 (13.6-14.5)	15.2 (14.9-15.4)
With liver cirrhosis	94	23.0 (16.0-33.1)	22.9 (16.6-31.7)	29.5 (20.4-42.8)	24.6 (20.1-30.1)
Gastrointestinal hemorrhage					
Without liver cirrhosis	9718	12.2 (11.8-12.6)	9.8 (9.5-10.1)	9.6 (9.3-10.0)	10.4 (10.2-10.6)
With liver cirrhosis	129	43.7 (33.5-57.0)	34.3 (26.3-44.8)	22.6 (14.7-34.6)	34.5 (29.0-41.0)

Note: Index date was defined as 90 days after the AFF diagnosis for all patients.

Abbreviations: AFF, atrial fibrillation or flutter; CI, confidence interval, NA, not applicable due to the number of events being <5.

[a]Due to Danish data regulations, we could not state the exact number.

hemorrhage of the lung or urinary tract (aHR, 1.4; 95% CI, 1.0-2.0), and gastrointestinal hemorrhage (aHR, 4.2; 95% CI, 3.2–5.5) (Figure 1). During the 1- to 3-year follow-up period, we found similar associations between liver cirrhosis and bleeding complications. During 3 to 5 years of follow-up, we found no association between liver cirrhosis and hemorrhagic stroke (aHR, 0.4; 95% CI, 0.1-2.6). However, patients with liver cirrhosis remained at an increased risk of all other bleeding complications during 3 to 5 years of follow-up.

During 0 to 5 years of follow-up, liver cirrhosis was associated with an increased risk of hemorrhagic stroke (aHR, 2.0; 95% CI, 1.3-3.0), subdural hemorrhage (aHR, 3.8; 95% CI, 2.5-5.9), hemorrhage of the lung or urinary tract (aHR, 1.7; 95% CI, 1.4-2.1), and gastrointestinal hemorrhage (aHR, 3.9; 95% CI, 3.3-4.6).

3.5 | Subgroup analyses

Stratifying by anticoagulation use, CHA_2DS_2VASc score, and Charlson Comorbidity Index score showed no substantial variation in the HR estimates of ischemic stroke, myocardial infarction, venous thromboembolism, hemorrhagic stroke, or hemorrhage of the lung or urinary tract (Table 3).

In particular, stratification by anticoagulation use showed similar HRs in both strata across all outcomes except for myocardial infarction, but the number of events was small.

However, in the stratum of patients with a CHA_2DS_2VASc score of 0 to 1, patients with liver cirrhosis had a markedly increased crude and adjusted HR of subdural hemorrhage (aHR, 19.1; 95% CI, 9.1-39.8) and gastrointestinal hemorrhage (aHR, 10.3; 95% CI, 6.9-15.2), compared to patients without liver cirrhosis (Table 3).

4 | DISCUSSION

4.1 | Main findings

In this large, population-based cohort study of patients with AFF, we found that during 0 to 5 years of follow-up, patients with liver cirrhosis had higher incidence rates of all thromboembolic outcomes except myocardial infarction. Patients with liver cirrhosis also had

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Ischemic stroke		
0-1 year	1.2 (0.9-1.6)	1.5 (1.1-2.0)
1-3 years	1.3 (1.0-1.8)	1.6 (1.2-2.2)
3-5 years	1.7 (1.1-2.4)	2.0 (1.4-2.9)
0-5 years	1.3 (1.1-1.6)	1.6 (1.4-2.0)
Myocardial infarction		
0-1 year	1.0 (0.6-1.6)	1.1 (0.7-1.8)
1-3 years	0.8 (0.4-1.3)	0.8 (0.5-1.5)
3-5 years	1.0 (0.5-1.9)	1.1 (0.6-2.1)
0-5 years	0.9 (0.7-1.2)	1.0 (0.7-1.4)
Venous thromboembolism		
0-1 year	1.1 (0.6-2.1)	1.2 (0.6-2.2)
1-3 years	2.0 (1.3-3.3)	2.2 (1.3-3.5)
3-5 years	2.0 (1.0-3.9)	2.1 (1.1-4.1)
0-5 years	1.6 (1.2-2.3)	1.7 (1.2-2.4)
Hemorrhagic stroke		
0-1 year	2.3 (1.3-4.1)	2.6 (1.5-4.6)
1-3 years	2.0 (1.1-3.6)	2.3 (1.2-4.2)
3-5 years	0.3 (0.1-2.3)	0.4 (0.1-2.6)
0-5 years	1.7 (1.1-2.6)	2.0 (1.3-3.0)
Subdural hemorrhage		
0-1 year	4.1 (2.2-7.7)	4.9 (2.6-9.2)
1-3 years	2.6 (1.3-5.6)	3.2 (1.5-6.8)
3-5 years	2.7 (1.0-7.1)	3.2 (1.2-8.4)
0-5 years	3.2 (2.1-4.9)	3.8 (2.5-5.9)
Hemorrhage of the lung or urinary tract		
0-1 year	1.3 (0.9-1.9)	1.4 (1.0-2.0)
1-3 years	1.6 (1.2-2.2)	1.7 (1.2-2.3)
3-5 years	2.1 (1.5-3.1)	2.2 (1.6-3.3)
0-5 years	1.6 (1.3-2.0)	1.7 (1.4-2.1)
Gastrointestinal hemorrhage		
0-1 year	3.6 (2.7-4.7)	4.2 (3.2-5.5)
1-3 years	3.5 (2.7-4.6)	4.1 (3.2-5.4)
3-5 years	2.4 (1.5-3.6)	2.8 (1.8-4.3)
0-5 years	3.3 (2.7-3.9)	3.9 (3.3-4.6)

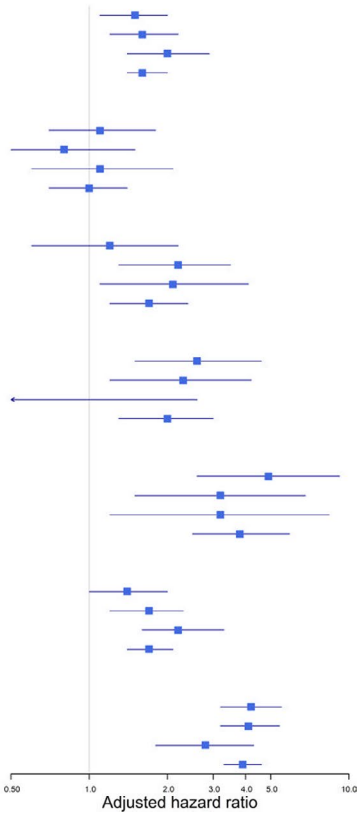

FIGURE 1 Risk of thromboembolic and bleeding events. CI, confidence interval; HR, hazard ratio

higher incidence rates of all bleeding complications during 0 to 5 years of follow-up.

4.2 | Implications

Our findings and those of Lee et al showed an association with an increased risk of thromboembolic and bleeding complications.[16,17] There is thus evidence that clinicians should be aware of the simultaneously increased risk of thromboembolic and bleeding complications in patients with AFF and liver cirrhosis, although lack of clinical detail prevents us from suggesting specific guidelines. Of note, our subgroup analysis among patients with CHA_2DS_2VASc score of 0 to 1 showed that liver cirrhosis was associated with ischemic stroke. This could indicate that liver cirrhosis should be considered as an independent risk factor for stroke in patients with AFF. However, the same patients also had an increased risk of bleeding, making the decision of anticoagulation difficult.

4.3 | Possible mechanisms

Liver cirrhosis has long been recognized as a condition associated with an increased risk of bleeding.[32] Bleeding associated with liver cirrhosis is thought to be caused by reduced synthesis of procoagulant factors, thrombocytopenia, impaired platelet function, and hemodynamic abnormalities, including portal hypertension.[10,12,32,33] However, within the past decades, a number of studies have suggested that liver cirrhosis is also a prothrombotic state.[13,34] This prothrombotic state is thought to be caused by the simultaneous reduction in anticoagulant factor synthesis and the reduction in von Willebrand factor clearance.[10,12,35] These considerations may explain why we observed an increase in the risks of both thrombotic and bleeding complications in our study.

It is worth noting that we did not find an increased risk of venous thromboembolism during the first year of follow-up, but we did find it in all other follow-up intervals. A possible explanation could be that liver cirrhosis may worsen after the initial diagnosis, and therefore these complications will not occur immediately after diagnosis.

4.4 | Contribution to the literature

Our findings of an increased risk of ischemic stroke and bleeding complications in patients with liver cirrhosis and AFF are supported by a small number of studies reported in the literature.[17,19]

In a Taiwanese setting, Kuo et al[17] studied 289 559 patients with AFF. Of those patients, 10 336 had a history of liver cirrhosis. Patients with and without a history of liver cirrhosis were compared and stratified by stroke prevention strategies (ie, no treatment, treatment with antiplatelet agents, or treatment with warfarin). Similar to our findings, Kuo et al reported an increased risk of ischemic stroke

TABLE 3 Incidence rates, number of events, and adjusted hazard ratios of thromboembolic and bleeding complications, during 0-1 year of follow-up, stratified by baseline values, in patients with atrial fibrillation or flutter

	Without liver cirrhosis		With liver cirrhosis			
	Number of events	IR (95% CI)	Number of events	IR (95% CI)	HR of each event (95% CI)	aHR of each event (95% CI)
Ischemic stroke						
Anticoagulation status						
Users	2535	23.2 (22.4-24.2)	10	28.5 (15.3-53.0)	1.2 (0.7-2.3)	1.3 (0.7-2.5)
Nonusers	4383	32.8 (31.8-33.8)	32	36.3 (25.6-51.3)	1.1 (0.8-1.6)	1.5 (1.0-2.1)
CHA_2DS_2VASc score						
0-1	989	13.5 (12.7-14.4)	11	23.8 (13.2-43.0)	1.7 (1.0-3.1)	1.8 (1.0-3.2)
2-3	3864	31.3 (30.3-32.3)	24	44.2 (29.6-66.0)	1.4 (0.9-2.1)	1.8 (1.2-2.6)
>3	2065	44.7 (42.8-46.6)	7	30.6 (14.6-64.2)	0.7 (0.3-1.4)	0.8 (0.4-1.6)
CCI score						
0-1	5910	27.5 (26.8-28.2)	28	28.7 (19.8-41.5)	1.0 (0.7-1.5)	1.3 (0.9-1.9)
>1	1008	35.9 (33.7-38.2)	14	54.5 (32.3-92.0)	1.5 (0.9-2.6)	1.7 (1.0-3.0)
Myocardial infarction						
Anticoagulation status						
Users	1289	11.5 (10.9-12.1)	7	19.1 (9.1-40.1)	1.7 (0.8-3.5)	1.7 (0.8-3.5)
Nonusers	2254	16.7 (16.0-17.4)	11	12.2 (6.7-22.0)	0.7 (0.4-1.3)	0.9 (0.5-1.6)
CHA_2DS_2VASc score						
0-1	521	7.0 (6.5-7.7)	<5	NA	0.6 (0.2-2.4)	0.6 (0.1-2.3)
2-3	1794	14.2 (13.6-14.9)	11	19.6 (10.9-35.4)	1.4 (0.8-2.5)	1.5 (0.8-2.8)
>3	1228	26.0 (24.6-27.5)	5	21.4 (8.9-51.5)	0.8 (0.3-2.0)	0.8 (0.3-2.0)
CCI score						
0-1	2933	13.4 (12.9-13.9)	8	7.9 (4.0-15.9)	0.6 (0.3-1.2)	0.7 (0.4-1.4)
>1	610	21.6 (19.9-23.3)	10	38.1 (20.5-70.8)	1.8 (0.9-3.3)	1.9 (1.0-3.6)
Venous thromboembolism						
Anticoagulation status						
Users	694	6.2 (5.7-6.6)	<5	NA	1.3 (0.4-4.1)	1.3 (0.4-4.1)
Nonusers	1083	7.8 (7.4-8.3)	7	7.7 (3.7-16.1)	1.0 (0.5-2.1)	1.1 (0.5-2.2)
CHA_2DS_2VASc score						
0-1	367	4.9 (4.4-5.4)	<5	NA	0.9 (0.2-3.4)	0.8 (0.2-3.2)
2-3	907	7.1 (6.7-7.6)	6	10.7 (4.8-23.8)	1.5 (0.7-3.3)	1.6 (0.7-3.6)
>3	503	10.3 (9.5-11.3)	<5	NA	0.8 (0.2-3.2)	0.8 (0.2-3.1)
CCI score						
0-1	1423	6.4 (6.1-6.7)	8	7.9 (4.0-15.9)	1.2 (0.6-2.5)	1.4 (0.7-2.8)
>1	354	12.2 (11.0-13.6)	<5	NA	0.6 (0.2-2.4)	0.6 (0.2-2.5)
Hemorrhagic stroke						
Anticoagulation status						
Users	507	4.4 (4.1- 4.8)	5	13.5 (5.6-32.3)	3.0 (1.3-7.3)	3.3 (1.4-7.9)
Nonusers	521	3.7 (3.4-4.1)	7	7.7 (3.7-16.1)	2.1 (1.0-4.3)	2.4 (1.1-5.0)
CHA_2DS_2VASc score						
0-1	187	2.5 (2.2-2.9)	<5	NA	3.4 (1.3-9.1)	3.3 (1.2-8.9)
2-3	590	4.6 (4.2-5.0)	7	12.2 (5.8-25.7)	2.7 (1.3-5.7)	3.0 (1.4-6.4)
>3	251	5.1 (4.5-5.8)	<5	NA	0.8 (0.1-5.9)	0.8 (0.1-5.7)

(Continues)

TABLE 3 (Continued)

	Without liver cirrhosis		With liver cirrhosis			
	Number of events	IR (95% CI)	Number of events	IR (95% CI)	HR of each event (95% CI)	aHR of each event (95% CI)
CCI score						
0-1	872	3.9 (3.6-4.2)	10	9.9 (5.3-18.3)	2.5 (1.4-4.7)	3.0 (1.6-5.6)
>1	156	5.3 (4.5-6.2)	<5	NA	1.4 (0.4-5.7)	1.5 (0.4-5.9)
Subdural hemorrhage						
Anticoagulation status						
Users	257	2.2 (2.0-2.5)	<5	NA	3.6 (1.2-11.2)	4.1 (1.3-12.9)
Nonusers	223	1.6 (1.4-1.8)	7	7.6 (3.6-16.0)	4.8 (2.2-10.1)	5.7 (2.7-12.2)
CHA_2DS_2VASc score						
0-1	67	0.9 (0.7-1.1)	8	16.8 (8.4-33.7)	19.0 (9.2-39.6)	19.1 (9.1-39.8)
2-3	293	2.3 (2.0-2.5)	<5	NA	1.5 (0.4-6.2)	1.9 (0.5-7.5)
>3	120	2.4 (2.0-2.9)	<5	NA	NA	NA
CCI score						
0-1	404	1.8 (1.6-2.0)	10	9.8 (5.3-18.2)	5.5 (2.9-10.2)	6.7 (3.6-12.6)
>1	76	2.6 (2.1-3.2)	<5	NA	NA	NA
Hemorrhage of the lung or urinary tract						
Anticoagulation status						
Users	2380	21.2 (20.3-22.0)	9	24.8 (12.9-47.7)	1.2 (0.6-2.3)	1.3 (0.7-2.4)
Nonusers	2026	14.7 (14.1-15.4)	20	22.3 (14.4-34.5)	1.5 (1.0-2.3)	1.6 (1.0-2.5)
CHA_2DS_2VASc score						
0-1	1010	13.6 (12.8-14.4)	11	23.6 (13.1-42.6)	1.7 (1.0-3.1)	1.7 (0.9-3.1)
2-3	2448	19.3 (18.5 –20.1)	15	26.9 (16.2-44.6)	1.4 (0.8-2.3)	1.5 (0.9-2.4)
>3	948	19.5 (18.3-20.8)	<5	NA	0.7 (0.2-2.0)	0.6 (0.2-1.9)
CCI score						
0-1	3695	16.7 (16.2-17.3)	23	23.1 (15.3-34.8)	1.4 (0.9-2.1)	1.5 (1.0-2.3)
>1	711	24.8 (23.0-26.7)	6	22.7 (10.2-50.4)	0.9 (0.4-2.0)	1.0 (0.4-2.1)
Gastrointestinal hemorrhage						
Anticoagulation status						
Users	1289	11.4 (10.7-12.0)	17	47.1 (29.3-75.8)	4.1 (2.6-6.7)	4.2 (2.6-6.8)
Nonusers	1768	12.9 (12.3-13.5)	37	42.3 (30.6-58.3)	3.3 (2.4-4.5)	4.1 (3.0-5.7)
CHA_2DS_2VASc score						
0-1	389	5.2 (4.7-5.7)	25	55.7 (37.6-82.4)	10.7 (7.1-16.0)	10.3 (6.9-15.2)
2-3	1777	13.9 (13.3-14.6)	22	39.8 (26.2-60.4)	2.9 (1.9-4.3)	3.4 (2.2-5.2)
>3	891	18.3 (17.2-19.6)	7	29.9 (14.3-62.8)	1.6 (0.8-3.4)	1.7 (0.8-3.5)
CCI score						
0-1	2435	10.9 (10.5-11.4)	43	43.8 (32.5-59.1)	4.0 (3.0-5.4)	5.0 (3.7-6.8)
>1	622	21.7 (20.1-23.5)	11	43.1 (23.9-77.9)	2.0 (1.1-3.6)	2.2 (1.2-4.0)

Note: In the adjusted analysis we adjusted for: age, CHA_2DS_2VASc score, and CCI score. When stratifying by a variable, we did not adjust for it.
Abbreviations: aHR, adjusted hazard ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NA, not applicable due to the number of events being <5.

among untreated patients with AFF and liver cirrhosis (HR, 1.10; 95% CI, 1.00-1.20).[17] However, Kuo et al reported that among patients treated with warfarin, those with liver cirrhosis were not at increased risk of ischemic stroke (HR, 0.89; 95% CI, 0.71-1.12) or intracranial hemorrhage (HR, 1.17; 95% CI, 0.81–1.68), compared to patients without liver cirrhosis.

In another Taiwanese study, Lai et al[19] compared 3490 patients without liver disease to 433 patients with chronic liver disease. They reported an increased risk of ischemic stroke among patients with chronic liver disease, compared to no history of chronic liver disease (HR, 1.50; 95% CI, 1.21-1.87),[19] but no increased risk of cerebral hemorrhage.

Jepsen et al[36] investigated the risk of arterial and venous thromboembolic events in patients with liver cirrhosis. They compared patients with liver cirrhosis to a general population cohort. They found that patients with liver cirrhosis had an increased risk of ischemic stroke (aHR, 1.7; 95% CI, 1.3-2.3) and venous thromboembolism (aHR, 2.0; 95% CI, 1.5-2.6), but not myocardial infarction (aHR, 0.7; 95% CI, 0.5-0.9). Similar findings on the lack of association between liver cirrhosis and myocardial infarction are described by Deleuran et al.[37]

Søgaard et al[13] investigated the risk of venous thromboembolism in patients with liver cirrhosis, compared to the general population. They conducted a case-control study and found that liver cirrhosis was associated with an elevated risk of venous thromboembolism (odds ratio, 1.74; 95% CI, 1.54-1.95).

Grønbæk et al[38] investigated the risk of intracerebral hemorrhage in patients with liver cirrhosis compared to the general population control. They found that liver cirrhosis was associated with intracerebral hemorrhage (adjusted odds ratio, 5.1; 95% CI, 3.1-8.5).

Thus, there are a number of studies showing an association between liver cirrhosis and thromboembolic events. However, Kuo et al.,[17] who also focused on AFF and liver cirrhosis, did not find an association between liver cirrhosis and intracranial hemorrhage.

4.5 | Strengths and limitations

The main strength of our study was the inclusion of all eligible patients via a national database that ensured virtually complete follow-up. Thus, the risk of selection bias was minimal. Further, we had a large cohort of >270 000 patients and the ability to follow the patients for >20 years. Our access to the complete medical history of each patient and the ability to link each patient to the prescription registry allowed us to account for a range of potential confounders.

Our study also had limitations. Although the entire AFF cohort was large, only few patients had liver cirrhosis, which reduced the statistical precision of our estimates. We did not assess our exposures as time-varying variables. Indeed, patients without liver cirrhosis could develop liver cirrhosis during the study period, and the inability to track these changes could cause a misclassification bias. However, such differential misclassification would likely cause an underestimation of the results. Similarly, both users and nonusers of oral anticoagulants could potentially terminate or initiate treatment with oral anticoagulants during the study period. We had no detailed information on the severity of liver cirrhosis and no clinical scores of disease severity, such as the Child-Pugh score or the Model of End-Stage Liver Disease score.

There was also a risk of uncontrolled confounding. For example, it was possible that only patients with the lowest clinical bleeding risk were treated with oral anticoagulants. This selective treatment could have led to an underestimation of the risk of bleeding complications among users of oral anticoagulants.[39] We could not control for smoking. The increased risk of ischemic stroke in patients with liver cirrhosis might partly have been mediated by lifestyle factors, such as smoking and obesity, rather than by the history of liver cirrhosis. However, we did not observe any association between a history of liver cirrhosis and myocardial infarction during the 0- to 1-year and 0- to 5-year follow-up periods. Because ischemic stroke and myocardial infarction share risk factors, we believe that a potential confounding of the association between liver cirrhosis and ischemic stroke would also impact the association between liver cirrhosis and myocardial infarction. The impact of these potential confounders was likely minor.[40,41]

5 | CONCLUSION

We found that a history of liver cirrhosis in patients with AFF was associated with an increased risk of ischemic stroke throughout all follow-up periods, and was associated with venous thromboembolism during 0 to 5 years of follow-up. Additionally, a history of liver cirrhosis was also associated with all evaluated bleeding complications during 0 to 5 years of follow-up.

RELATIONSHIP DISCLOSURE

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

EBR conceived the study idea, wrote the protocol, conducted all data management and statistical analyses, and wrote the first draft of the manuscript. KA assisted in conceiving the study idea and design, supervised the process of writing the protocol, reviewed all drafts of the manuscript, and aided in writing the manuscript. LP supervised and aided in the process of data management and statistical analyses. SRK assisted in conceiving the study idea and reviewed the manuscript. ATH assisted in conceiving the study idea and reviewed the protocol and manuscript drafts. HTS assisted in conceiving the study idea and design and reviewed the protocol and manuscript drafts.

ORCID

Emil B. Riahi https://orcid.org/0000-0002-6733-4019
Kasper Adelborg https://orcid.org/0000-0001-5639-7252
Søren R. Kristensen https://orcid.org/0000-0002-2649-506X
Henrik T. Sørensen https://orcid.org/0000-0003-4299-7040

TWITTER

Emil Riahi @ERiahi1
Henrik T. Sørensen @ToftSorensen

REFERENCES

1. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154-162.
2. Frost L, Vestergaard P, Mosekilde L, Mortensen LS. Trends in incidence and mortality in the hospital diagnosis of atrial fibrillation or flutter in Denmark, 1980–1999. *Int J Cardiol*. 2005;103:78-84.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
4. Sundbøll J, Hováth-Puhó E, Adelborg K, et al. Risk of arterial and venous thromboembolism in patients with atrial fibrillation or

flutter: a nationwide population-based cohort study. *Int J Cardiol*. 2017;241:182-187.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857-867.
6. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1:175-179.
7. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
8. Olesen JB, Lip GYH, Kamper A-L, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625-635.
9. The Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology*. 2007;69:546-554.
10. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011;365:147-156.
11. Vinholt PJ, Hvas A-M, Nielsen C, et al. Reduced platelet activation and platelet aggregation in patients with alcoholic liver cirrhosis. *Platelets*. 2018;29:520-527.
12. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood*. 2010;116:878-885.
13. Søgaard KK, Horváth-Puhó 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.
14. Lisman T, Violi F. Cirrhosis as a risk factor for venous thrombosis. *Thromb Haemost*. 2017;117:3-5.
15. Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis: a systematic review and meta-analysis. *Thromb Haemost*. 2016;117:139-148.
16. Lee S-J, Uhm J-S, Kim J-Y, Pak H-N, Lee M-H, Joung B. The safety and efficacy of vitamin K antagonist in patients with atrial fibrillation and liver cirrhosis. *Int J Cardiol*. 2015;180:185-191.
17. Kuo L, Chao T-F, Liu C-J, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc*. 2017;6:e005307.
18. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. *Eur J Haematol*. 2017;98:393-397.
19. Lai H-C, Chien W-C, Chung C-H, et al. Atrial fibrillation, liver disease, antithrombotics and risk of cerebrovascular events: a population-based cohort study. *Int J Cardiol*. 2016;223:829-837.
20. Choi J, Kim J, Shim JH, Kim M, Nam G-B. Risks versus benefits of anticoagulation for atrial fibrillation in cirrhotic patients. *J Cardiovasc Pharmacol*. 2017;70:255-262.
21. Mwalitsa JP, Maimone S, Filomia R, et al. Atrial fibrillation in patients with cirrhosis. *Liver Int*. 2016;36:395-400.
22. Schmidt M, Schmidt SAJ, 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.
23. 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.
24. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol Dordr*. 2014;29:541-549.
25. Schmidt M, Sørensen HT. The Danish health care system and epidemiological research: from healthcare contacts to database records. *Clin Epidemiol*. 2019;11;563-591.
26. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832.
27. 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.
28. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol*. 2008;167:492-499.
29. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a national register of patients. *Neuroepidemiology*. 2007;28:150-154.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
31. StataCorp. *Stata Statistical Software: Release 15*. StataCorp LLC; 2017.
32. Jairath V, Burroughs AK. Anticoagulation in patients with liver cirrhosis: complication or therapeutic opportunity? *Gut*. 2013;62:479-482.
33. Pradella P, Bonetto S, Turchetto S, et al. Platelet production and destruction in liver cirrhosis. *J Hepatol*. 2011;54:894-900.
34. Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol*. 2010;8:800-805.e1.
35. Lisman T, Hernandez-Gea V, Magnusson M, et al. The concept of rebalanced hemostasis in patients with liver disease: communication from the ISTH SSC working group on hemostatic management of patients with liver disease. *J Thromb Haemost*. 2021;19:1116-1122.
36. Jepsen P, Tapper EB, Deleuran T, et al. Risk and outcome of venous and arterial thrombosis in patients with cirrhosis: a Danish nationwide cohort study. *Hepatology*. 2021;74(5):2725-2734.
37. 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;50:e13205.
38. Grønbæk H, Johnsen SP, Jepsen P, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population-based case-control study. *BMC Gastroenterol*. 2008;8:16.
39. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2:221-228.
40. Boehme AK, Esenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. *Circ Res*. 2017;120:472-495.
41. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837-1847.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Riahi EB, Adelborg K, Pedersen L, Kristensen SR, Hansen AT, Sørensen HT. Atrial fibrillation, liver cirrhosis, thrombosis, and bleeding: A Danish population-based cohort study. *Res Pract Thromb Haemost*. 2022;6:e12668. doi:10.1002/rth2.12668