JIM Original Article

doi: 10.1111/joim.13624

Risk of fractures and postfracture mortality in 3980 people with primary biliary cholangitis: A population-based cohort study

Johanna Schönau[1], Axel Wester[2], Jörn M. Schattenberg[1] & Hannes Hagström[2,3]

From the [1]Department of Internal Medicine I, University Medical Center Mainz, Langenbeckstrasse, 1, Mainz, Rhineland-Palatinate, 55131, Germany; [2]Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; and [3]Unit of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden

Abstract. Schönau J, Wester A, Schattenberg JM, Hagström H. Risk of fractures and postfracture mortality in 3980 people with primary biliary cholangitis: A population-based cohort study. *J Intern Med*. 2023;**OO**:1–14.

Background. Morbidity in primary biliary cholangitis (PBC) is multifactorial. Osteoporosis related to cholestasis is an extrahepatic complication of PBC. It is not fully established to what extent people with PBC have an increased risk for fractures, and if mortality after a fracture is increased, compared to the general population.

Methods. All Swedish people with PBC diagnosed between 2001 and 2016 were identified from the National Swedish Patient Register using ICD-10 codes. Incident fractures were ascertained in the same register and compared to matched controls from the Swedish general population (1:10 for age, sex, and municipality). Cox regression was used to investigate the rates of fractures and postfracture mortality. The cumulative incidence of fractures was calculated while accounting for competing risks (death or liver transplantation).

Results. People with PBC ($n = 3980$) showed a higher risk of fractures at all-time points during follow-up compared to matched controls (n = 37,196), which was seen both in men and women. At 5 years of follow-up, the cumulative incidence of any fracture in people with PBC was 16.8% (95% confidence interval [CI] = 15.6–18.1), compared to 11.6% (95%CI = 11.3–12.0) in controls. The rate of osteoporotic fractures was particularly high (adjusted Hazard ratio [aHR] = 1.9; 95% = CI 1.7–2.0). The 30-day as well as the 1-year mortality after a fracture was significantly higher in people with PBC compared to controls that also experienced a fracture (aHR = 2.2; 95%CI = 1.5–3.2; aHR = 2.0; 95%CI 1.7–2.4).

Conclusion. People with PBC have a significantly higher risk of fractures and postfracture mortality compared to matched controls from the general population.

Keywords: bone fracture, cirrhosis, liver disease, mortality, osteoporosis, population-based register study

Background

Primary biliary cholangitis (PBC) is a rare cholestatic liver disease characterized by the progressive destruction of bile ducts, which in late stages leads to fibrosis and liver cirrhosis [1, 2]. Hepatic and extrahepatic symptoms including fatigue, pruritus, and bone disease lead to increased mortality and severely reduced quality of life. People affected by PBC carry an excessive extrahepatic morbidity that is partly related to decreased bone density supporting fractures from falls [3, 4]. The incidence of osteoporosis is three- to fourfold higher in people with PBC [5, 6]. The majority of people with PBC (80%–90%) are female [7]. The impaired absorption of fat-soluble vitamins in PBC appears to be a major factor in the development of bone disease. Vitamin D has a critical role in liver and bone metabolism [8], even beyond its role in bone mineralization. This is achieved through antiproliferative and antifibrotic

Jörn M. Schattenberg and Hannes Hagström are senior authors.

effects on hepatic stellate cells and liver fibrosis [7]. Seasonally adjusted mean vitamin D levels were shown to be not only significantly lower in people with PBC, but also correlate with advanced disease. Recent studies even suggest variations of the vitamin D receptor gene to influence susceptibility to develop chronic autoimmune liver diseases, such as PBC [7].

Cholestatic and autoimmune liver diseases such as PBC have complex etiologies, and the pathogenesis of extrahepatic manifestations is not fully understood [1]. Of special interest for therapeutic options is the assumption that the development of osteoporosis in liver disease is, as opposed to postmenopausal osteoporosis, driven by decreased bone formation rather than increased bone resorption. Despite these findings, most treatment strategies against bone loss in PBC are identical with the therapeutic approaches in postmenopausal osteoporosis [3]. The American Association for the Study of Liver disease recommends vitamin D, calcium, and alendronate as treatment options, although the quality of evidence on bisphosphonates in PBC is low [9]. PBC-specific therapies such as ursodeoxycholic acid (UDCA), obeticholic acid, and fibrates, which all significantly reduce alkaline phosphatase levels as a surrogate marker of disease activity in PBC, have not demonstrated to have any effect on osteopenia or osteoporosis [10–13].

To date, it is a matter of controversy to what extent people with PBC have an increased risk of developing osteoporotic fractures. Even the numbers concerning osteoporosis among people with PBC have shown great disparity over the past years [3, 14]. More recently, a positive association between PBC and bone disease with a three to four times increased risk of osteoporosis in PBC-cohorts compared to age and gender-matched controls has been reported [3, 14]. The prevalence of osteoporosis is increased in advanced stages of liver disease, which is augmented by sarcopenia, reduced physical activity, malnutrition, and infections [15], and reaches its peak in patients with cirrhosis on the liver transplant list. As the prevalence of PBC is growing, most likely due to improved diagnostics and awareness, the incidence and prevalence of PBC-related osteoporosis is assumed to rise as well [3]. As stated in a recent review dealing with prevalence, impact, and management challenges for osteoporosis in PBC, the incidence of fractures in PBC ranges from 0% to 14% over a 2-year period, whereas the prevalence ranges from 9% to 22% [3]. The incidence of fractures is highest in the first year after liver transplantation, at around 20%–40%. This is due to major bone loss in the first months after liver transplantation [3].

The symptom burden of fractures in people with PBC is high [16]. Data emphasizing to which extent people with PBC suffer from fractures are showing great discrepancies, and therapeutic options are lacking. This study aims to quantify the risk of fractures and resulting mortality in people with PBC compared to matched controls in a large-scaled, population-based study.

Materials and methods

The DELIVER (DEcoding the epidemiology of LIVER disease in Sweden) is a cohort linking different Swedish population-based registers with information on liver disease diagnoses made between 1964 and 2016. By matching every included patient with up to 10 reference individuals from the general population for age, sex, municipality, and calendar year of first liver disease diagnosis, the database allows researchers to explore the clinical course of several liver diseases and their risk of comorbidities and complications [17].

Herein, we used the DELIVER cohort to conduct a national, population-based, matched cohort study. We used the National Patient Register to identify all Swedish individuals with a diagnosis of PBC as a primary or contributing diagnosis at any time between 1 January 2001 and 31 December 2016. This register includes data on inpatient care since 1964 and specialty outpatient care since 2001. As most people with PBC are first diagnosed in outpatient care, we decided to start the study in 2001 to reduce selection bias related to different inclusion periods. The National Patient Register has been externally validated and found to be highly accurate [18].

Study population

We included people with PBC defined according to the International Classification of Disease (ICD-10) code of K74.3. A comprehensive list of all ICD-codes used to define exposure and outcomes is presented in Table S2. Anyone with a reused personal identity number, people that emigrated from Sweden before baseline or people that were registered as dead before baseline were excluded. Patients receiving liver transplantation before or at baseline

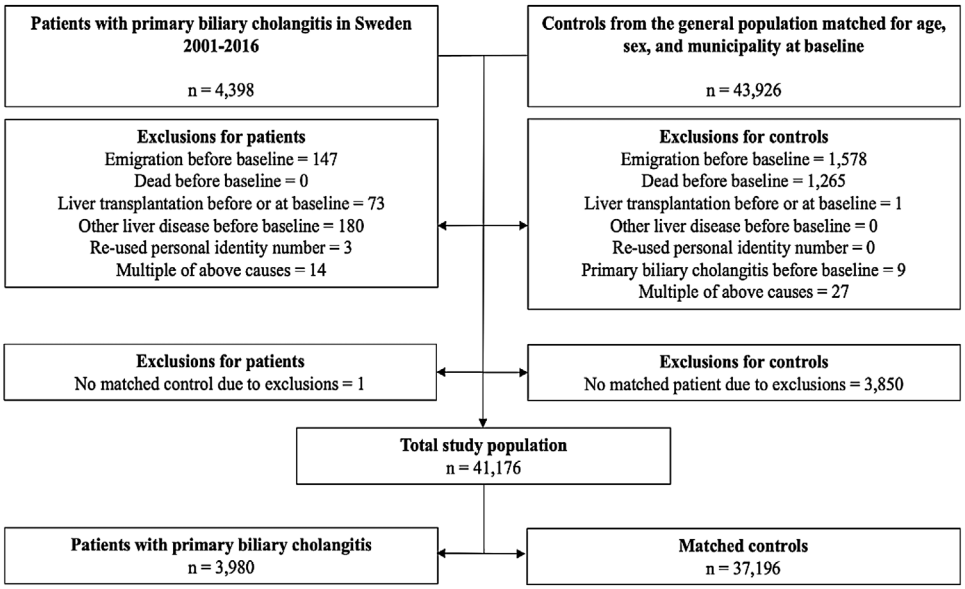

Fig. 1 *Consort chart on study population.*

were also excluded, as well as patients with ICD-coding for other liver diseases than PBC before or at baseline. Excepted from these were patients with autoimmune hepatitis based on a possible coexistence and patients with coding for primary sclerosing cholangitis in order to avoid misclassification of patients with PBC that at some time point received a code for PSC. This was done to ensure a higher sensitivity for the PBC diagnosis (Fig. 1). Each individual with PBC was compared with up to 10 reference individuals from the DELIVER dataset, applying identical inclusion and exclusion criteria.

Follow-up and outcomes

The start of follow-up (baseline) was the first time point of ICD-coding for PBC in the National Patient Register. Controls started the follow-up on the same date as their matched people with PBC. A time-to-event analysis was performed for the primary outcome "any fracture." The fractures were defined by ICD-10 codes (Table S2). We only considered the first fracture after baseline, as it would be unclear if additional diagnoses would represent new fractures, or clinical follow-up visits for the first fracture. As fracture risk might differ for different categories of people, we investigated the primary outcome stratified on the following parameters: sex, age group (<50 and ≥50 years old), disease severity (PBC with or without cirrhosis at baseline), osteoporosis before baseline and any previous fracture before baseline.

Secondary outcomes included subcategories of fractures, defined as either osteoporotic fractures, non-osteoporotic fractures, or specific fracture sites.

As common sites for osteoporotic fractures are vertebrae, pelvis, proximal humerus, distal radius/ulna, or the hip, we defined a fracture due to osteoporosis as an ICD-coded fracture in one of these sites or the ICD-10 code M80 ("osteoporosis with pathological fracture"), unless a code for high-energy trauma was present. This definition is aligned with the analysis in the literature [19]. All other ICD-10 coded fractures, including high-energy fractures, were categorized as non-osteoporotic fractures. The secondary outcome "fracture location" differentiated among all fracture sites, including skull, vertebral, shoulder, humerus, upper forearm, distal radius/ulna, hand, ribs/sternum, pelvis, proximal femur, femur shaft, lower leg, and foot (Table S2).

Separately, we investigated all-cause mortality within 30 days and 1 year after any fracture, comparing this to controls who also experienced a fracture. Mortality outcomes were ascertained from the

Total Population Register [18]. For this analysis, follow-up started at the date of the first fracture during the study period.

The end of follow-up was the occurrence of a primary or secondary outcome or a censoring event (emigration from Sweden, death, liver transplantation, or the end of the study period [31 December 2016]). When investigating the cumulative incidence of fractures, we considered death and liver transplantation as competing events, as the risk for these might differ between people with PBC and the general population. Data regarding the follow-up time were extracted from the Total Population Register, which contains demographic data like emigration and date of death of the Swedish citizens [20], and from the National Patient Register.

Variables at baseline

Parameters collected at the index date included sex, age, and country of birth. We further recorded established diagnoses at or before baseline for several comorbidities: cardiovascular disease (CVD), diabetes type 1 and 2, cirrhosis, dementia, chronic pulmonary obstructive disease (COPD), cancer (hepatocellular carcinoma or other cancers), chronic kidney disease, rheumatic disease, and osteoporosis. The definitions of these were based on ICD-codes listed in Table S1.

Statistical analysis

Incident fracture rates per 1000 person-years and the cumulative incidence of fractures at 1, 5, and 10 years, and after the full study period were calculated. For the cumulative incidences, we accounted for competing risks (death or liver transplantation) using the Aalen–Johansen estimator (Stata command *stcompet*) [21]. Descriptive statistics for continuous variables were expressed as median (IQR), and categorical variables were presented as absolute numbers (%). Cox regression was used to assess the rate of fractures in people with PBC compared to their reference individuals. We considered two separate models. The first model accounted for the matching factors (age, sex, municipality, and calendar year of diagnosis). In the adjusted model, the following covariates were included as possible confounders: CVD, diabetes type 1 and 2, dementia, COPD, cancer, chronic kidney disease, and rheumatic disease.

Cox regression was also used to compare postfracture all-cause mortality between people with PBC and controls adjusted for age, sex, municipality, and inclusion year. Here, study subjects were censored at the date of emigration, end of study period (31 December 2016), or date of liver transplantation. This analysis was done after the first date of any fracture and therefore only included people with PBC and controls who had a fracture during follow-up. The mortality rate was adjusted for the previous mentioned covariates as well.

The cumulative incidences for both main and secondary outcomes were presented in cumulative incidence curves. All-cause mortality was presented in Kaplan–Meier curves. Analyses were performed using Stata V.17.0.

Sensitivity analyses

Osteoporotic fractures might be coded only by their location and without a specific diagnosis of osteoporosis. The main analysis in this study defined a fracture due to osteoporosis as a fracture in one of the common sites for osteoporotic fractures. However, such fractures might also be non-osteoporotic. To account for this, we added a sensitivity analysis in which we redefined an osteoporotic fracture using the same coding as mentioned earlier, but in mandatory combination with a code for osteoporosis before, at or within 3 months after the date of fracture (Table S1). The timeframe of 3 months was introduced as osteoporosis might first have been suspected due to the incident of a fracture and be formally diagnosed at a later stage.

Patient and public involvement

As this study used anonymized, register-based data, no patient-contact was necessary. The Ethics Review Board waived informed consent. Patients were not involved in establishing the study design or in specific contents, neither were they asked to get involved in interpreting or typing any results. The results of this study will be revealed to patients by press release.

Ethical considerations

The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983 and approved by the Ethics Committee at Karolinska University Hospital, Stockholm, Sweden (registry no. 2017/1019-31/1).

Table 1. *Baseline characteristics of the primary biliary cholangitis (PBC) population and matched controls*

	PBC population	Control population
Included persons, *n*	3980	37,196
Follow-up (years) (median, IQR)	4.3 (1.5–9.1)	6.2 (2.7–11.6)
Sex, men *n* (%)	604 (15.2)	5553 (14.9)
Age at baseline, years (median, IQR)	64 (55–73)	64 (55–73)
Period of inclusion *n* (%)		
2001–2004	1651 (41.5)	15,236 (41.0)
2005–2008	682 (17.1)	6436 (17.3)
2009–2012	740 (18.6)	6956 (18.7)
2013–2016	907 (22.8)	8568 (23.0)
Country of birth *n* (%)		
Nordic	3672 (92.3)	34,214 (92.0)
Other	308 (7.7)	2982 (8.0)
Comorbidity at/before baseline *n* (%)		
CVD	516 (13.0)	3022 (8.1)
Diabetes (types 1 and 2)	336 (8.4)	1486 (4.0)
Cirrhosis	217 (5.5)	1 (0.0)
Dementia	18 (0.5)	354 (1.0)
COPD	120 (3.0)	599 (1.6)
Cancer		
HCC	15 (0.4)	4 (0.0)
Other cancer	310 (7.8)	2736 (7.4)
Chronic kidney disease	61 (1.5)	162 (0.4)
Rheumatic disease	107 (2.7)	512 (1.4)
Osteoporosis	133 (3.3)	532 (1.4)
Previous fracture	442 (11.1)	3586 (9.6)

Abbreviations: COPD, chronic pulmonary obstructive disease; CVD, cardiovascular disease.

Results

Baseline characteristics of the PBC and control cohorts

During 2001–2016, a total of 3980 people with PBC were identified. These were matched with 37,196 general population controls. Table 1 lists the baseline characteristics of the included participants. As a result of the matching process, both cohorts contained approximately 15% male individuals (people with PBC: 15.2%, controls: 14.9%). Median age at baseline was 64 years (IQR: 55–73), and most individuals were born in a Nordic country (people with PBC: 92.3%; controls: 92.0%). Participants were enrolled in the study between 2001 and 2016. We defined four separate periods to monitor the number of included individuals: Between 2001 and 2004, approximately 41% (people with PBC: 41.5; controls: 41.0) of all participants were included. The number of inclusion was highest in the first time period as it takes all people into account that were diagnosed before the study period, as well as newly diagnosed people. The second inclusion period was defined as 2005 until 2008 and accounted for approximately 17% (17.1; 17.3) participants. Between 2009 and 2012, for approximately 19% (18.6; 18.7), and between 2013 and 2016, approximately 23% (22.8; 23.0) of participants, were included. At baseline, most comorbidities were more common in people with PBC (Table 1). Cirrhosis was present in 5.5% of people with PBC and 0% of controls. Overall, 3.3% of the people with PBC and 1.4% of the control individuals had a diagnosis of osteoporosis. During follow-up, 136 people with PBC (3.4%) and 5 controls (0.0%) received a liver transplantation.

Rate and risk of fractures

Table 2 depicts the rate of fractures in people with PBC and in controls, distinguishing between osteoporotic and non-osteoporotic fractures as well as the fracture site.

Table 2. *Rate of fractures in people with primary biliary cholangitis (PBC) and matched controls*

	People with PBC (events, *n* [%])	Matched controls (events, *n* [%])	People with PBC (incidence rate/1000 PY [95%CI])	Matched controls (incidence rate/1000 PY [95%CI])	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Any fracture	938 (23.6)	7082 (19.0)	41.3 (38.8–44.0)	26.6 (25.9–27.2)	1.7 (1.6–1.8)	1.6 (1.5–1.7)
Presumed fracture mechanism						
Osteoporotic fracture	674 (16.9)	4651 (12.5)	28.1 (26.1–30.3)	16.6 (16.1–17.1)	1.9 (1.7–2.1)	1.9 (1.7–2.0)
Non-osteoporotic fracture	437 (11.0)	3655 (9.8)	17.6 (16.1–19.4)	12.9 (12.5–13.4)	1.4 (1.3–1.6)	1.4 (1.3–1.5)
Fracture site						
Skull	28 (0.7)	276 (0.7)	1.1 (0.7–1.5)	0.9 (0.8–1.0)	1.2 (0.8–1.9)	1.2 (0.8–1.8)
Vertebral	198 (5.0)	938 (2.5)	7.6 (6.6–8.7)	3.2 (3.0–3.4)	2.9 (2.5–3.4)	2.8 (2.4–3.3)
Shoulder	28 (0.7)	235 (0.6)	1.1 (0.7–1.5)	0.8 (0.7–0.9)	1.4 (1.0–2.1)	1.4 (0.9–2.1)
Humerus	146 (3.7)	1006 (2.7)	5.6 (4.8–6.6)	3.4 (3.2–3.6)	1.7 (1.5–2.1)	1.7 (1.4–2.0)
Upper forearm	63 (1.6)	421 (1.1)	2.4 (1.9–3.1)	1.4 (1.3–1.5)	1.9 (1.4–2.5)	1.8 (1.4–2.4)
Distal radius/ulna	202 (5.1)	1741 (4.7)	7.9 (6.9–9.0)	6.0 (5.7–6.3)	1.4 (1.2–1.6)	1.4 (1.2–1.6)
Hand	62 (1.6)	653 (1.8)	2.3 (1.8–3.0)	2.2 (2.0–2.4)	1.1 (0.9–1.5)	1.1 (0.8–1.4)
Ribs/sternum	87 (2.2)	436 (1.2)	3.3 (2.7–4.1)	1.5 (1.3–1.6)	2.7 (2.1–3.4)	2.7 (2.1–3.4)
Pelvis	65 (1.6)	372 (1.0)	2.4 (1.9–3.1)	1.2 (1.1–1.4)	2.4 (1.8–3.2)	2.3 (1.7–3.1)
Hip	217 (5.5)	1711 (4.6)	8.3 (7.3–9.5)	5.8 (5.5–6.1)	1.7 (1.5–2.0)	1.6 (1.4–1.9)
Femur shaft	21 (0.5)	171 (0.5)	0.8 (0.5–1.2)	0.6 (0.5–0.7)	1.6 (1.0–2.6)	1.4 (0.8–2.3)
Lower leg	110 (2.8)	1105 (3.0)	4.2 (3.5–5.1)	3.7 (3.5–4.0)	1.2 (0.9–1.4)	1.1 (0.9–1.3)
Foot	59 (1.5)	435 (1.2)	2.2 (1.7–2.9)	1.5 (1.3–1.6)	1.5 (1.1–2.0)	1.4 (1.1–1.9)

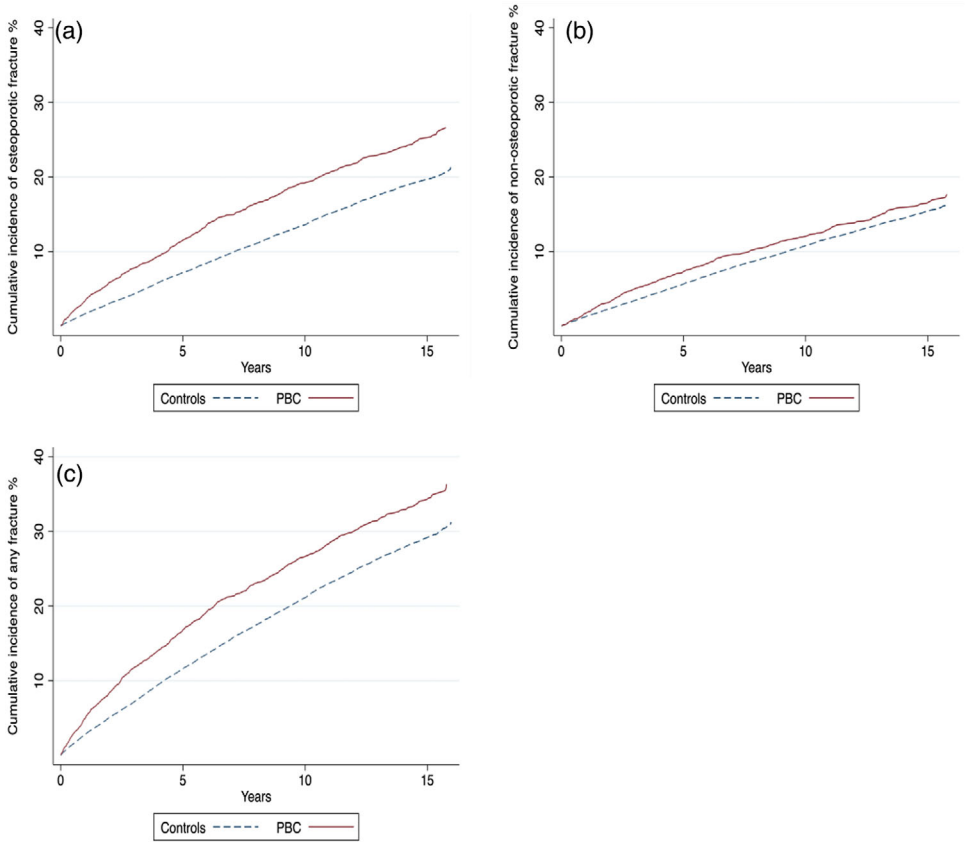

Fig. 2 *Cumulative incidence function curve of (a) osteoporotic fracture, (b) non-osteoporotic fracture, and (c) any fracture in people with primary biliary cholangitis (PBC) and reference individuals.*

Over a median of 4.3 years of follow-up, 938 incident fractures were reported among people with PBC (41.3/1000 person-years [PY], 95% confidence interval [CI] 38.8–44.0). Controls experienced 7082 fracture events (26.6/1000 PY, 95%CI 25.9–27.2) during 6.2 years of follow-up. This difference translated to a Hazard ratio (HR) of 1.7 (95%CI 1.6–1.8). After multivariable adjustment, people with PBC had a significant, 1.6-fold higher rate of any fracture compared to the controls (adjusted HR [aHR]: 1.6; 95%CI 1.5–1.7) (Fig. 2).

Considering the presumed fracture mechanism, people with PBC showed a higher rate of osteoporotic fractures (674 [16.9%], incidence rate/1000 PY 28.1 [95%CI = 26.1–30.0]) compared to the controls (4651 [12.5%], incidence rate/1000 PY 16.6 [95%CI = 16.1–17.1]). There was approximately a twofold increase in the rate of an osteoporotic fracture for the PBC-cohort compared with the controls (aHR 1.9; 95%CI = 1.7–2.0). For non-osteoporotic fractures, the difference in rate between people with PBC and controls was smaller, (aHR = 1.4; 95%CI = 1.3–1.5) (Fig. 2). When restricted to an analysis of the fracture site, some differences were noted. For instance, people with PBC showed a nearly threefold increase for vertebral fractures (aHR = 2.8; 95%CI = 2.4–3.3) compared with controls, a similar increase in the PBC-group was seen in rib/sternum fractures (aHR = 2.7; 95%CI = 2.1–3.4). Other fracture sites showed smaller differences in the fracture rate (Table 2).

Table 3 presents estimates for fractures in the prespecified subgroups, comparing people with PBC to their matched controls. PBC appeared to have a stronger effect on the fracture rate among men (aHR = 1.9; 95%CI = 1.5–2.4) compared with women (aHR = 1.6; 95%CI = 1.5–1.7), although this was not statistically significant ($p_{\text{interaction}} = 0.387$).

Table 3. *Rate of any fracture in subgroups of people with primary biliary cholangitis (PBC) and their matched controls*

	People with PBC (events, *n* [%])	Matched controls (events, *n* [%])	People with PBC (incidence rate/1000 PY [95%CI])	Matched controls (incidence rate/1000 PY [95%CI])	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Sex						
Men	91 (15.1)	665 (12.0)	30.9 (25.2–37.9)	17.8 (16.4–19.2)	1.9 (1.5–2.4)	1.9 (1.5–2.4)
Women	847 (25.1)	6417 (20.3)	42.9 (40.1–45.9)	28.0 (27.3–28.7)	1.7 (1.5–1.8)	1.6 (1.5–1.7)
Age group						
<50	60 (10.8)	410 (7.8)	15.9 (12.3–20.4)	10.1 (9.2–11.2)	1.6 (1.2–2.1)	1.5 (1.2–2.0)
≥50	878 (25.7)	6672 (20.9)	46.4 (43.4–49.6)	29.5 (28.8–30.2)	1.7 (1.6–1.8)	1.6 (1.5–1.8)
Baseline cirrhosis						
Yes	39 (17.9)	394 (19.8)	71.6 (52.3–98.0)	34.8 (31.5–38.4)	2.1 (1.4–3.0)	2.2 (1.5–3.2)
No	899 (23.9)	6688 (19.0)	40.6 (38.0–43.3)	26.2 (25.6–26.8)	1.7 (1.5–1.8)	1.6 (1.5–1.7)
Baseline osteoporosis						
Yes	53 (39.9)	303 (24.6)	119.3 (91.2–156.2)	41.3 (36.9–46.2)	3.6 (2.6–4.9)	3.4 (2.4–4.8)
No	885 (23.0)	6779 (18.9)	39.8 (37.2–42.5)	26.1 (25.5–26.8)	1.6 (1.5–1.7)	1.6 (1.5–1.7)
Previous fracture						
Yes	163 (36.9)	735 (17.9)	119.5 (102.5–139.3)	36.9 (34.3–39.7)	3.6 (3.0–4.3)	3.5 (2.9–4.2)
No	775 (21.9)	6347 (19.2)	36.3 (33.9–39.0)	25.7 (25.1–26.4)	1.5 (1.4–1.6)	1.5 (1.3–1.6)

There were no major differences in fracture rates depending on age at PBC diagnosis. Persons below 50 years had an adjusted HR of 1.5 (95%CI = 1.2–2.0), similar to those aged 50 or older (aHR = 1.6; 95%CI = 1.5–1.8) ($p_{interaction}$ = 0.983). When restricted to only those people with PBC who had a diagnosis of cirrhosis, the rate of any fracture was more than two times higher in the PBC-cohort compared to matched controls (aHR = 2.2; 95%CI = 1.5–3.2). People with PBC without a diagnosis of cirrhosis, on the other hand, had a 1.6-fold increase of any fractures compared to the control-group (95%CI = 1.5–1.7). When applying a more stringent sensitivity analysis accounting osteoporotic fracture only if a code for osteoporosis before, at or within 3 months after the date of fracture at one of the common sites for osteoporotic fractures was present (see methods), we observed for the subgroup with a diagnosis of osteoporosis a 3.4-fold higher rate of any fracture compared to matched controls (95%CI 2.9–4.2). In contrast, people with PBC without coding for osteoporosis had a less pronounced rate increase (aHR = 1.6, 95%CI 1.5–1.7) ($p_{interaction}$ = 0.069).

Finally, rates of any fractures were examined distinguishing between participants who had had previous fractures or not. People with PBC that did not suffer any fracture before baseline also showed an increased fracture rate (aHR = 1.5, 95%CI 1.3–1.6) compared to the controls.

Table 4 lists the cumulative incidence of any fracture during follow-up. At 1 year, people with PBC presented a cumulative incidence of 4.9% (95%CI = 4.3–5.6). At 5 years, the cumulative incidence was 16.8% (95%CI = 15.6–18.1) and at 10 years, 26.6% (95%CI = 25.0–28.3). At full follow-up, 36.3% (95%CI = 33.9–38.8) of the people with PBC had experienced a fracture, whereas the controls had a lower cumulative incidence of 31.2% (95%CI = 30.3–32.2). Considering subgroups, the cumulative incidence was higher in people with PBC compared to controls at all-time points during follow-up, as well. At full follow-up, men showed a cumulative incidence of any fracture of 21.6% (95%CI = 17.6–25.9) (controls: 20.4% [95%CI = 18.8–22.1]), women showed a cumulative incidence of 38.8% (95%CI = 36.1–41.5) (controls: 33.0% [95%CI = 31.9–34.1]). The age group ≥50 years had significantly more incidences of any fracture compared to participants <50 years old in people with and controls. For patients with cirrhosis, the high competing risk of non-fracture death led to a somewhat smaller cumulative incidence of fractures during the full follow-up period. Nevertheless, these patients still had higher risks of fractures during the first years after baseline. In people with PBC and baseline osteoporosis, the cumulative incidence of any fracture was 49.6% (95%CI = 39.2–59.2). Controls with a diagnosis of osteoporosis at baseline had a cumulative incidence for any fracture of 38.4% (95%CI = 34.6–42.1).

Overall mortality after fracture in PBC and controls

After a fracture event, people with PBC had a significantly higher 30-day as well as 1-year mortality rate compared to controls that also experienced a fracture. There were approximately twofold relative increases in the mortality after experiencing a fracture in people with PBC in the fully adjusted model. The 30-day mortality rate was more than twice as high in people with PBC (aHR 2.2; 95%CI = 1.5–3.2), which persisted during the first year after fracture (aHR 2.0; 95%CI = 1.7–2.4) (Table 5, Fig. 3).

Discussion

The current study quantifies the risk of fractures in people with PBC in a large population-based cohort with linked health-care data and explores overall mortality after a fracture. The 1-year mortality rate after experiencing a fracture was twofold higher in people with PBC compared to controls. People with PBC had a 1.6-fold increased rate of any fractures compared to controls, and this rate was even higher for osteoporotic fractures. Overall, the highest difference between the two groups was seen for vertebral fractures. With regard to liver function, patients with cirrhosis had the highest rate.

For the purpose of this analysis, we identified all Swedish individuals with an ICD-10 coded diagnosis of PBC in the National Outpatient Register. Registers were also used to explore fracture risk restricted to relevant subgroups, including sex, age, disease severity, osteoporosis, or previous fractures. In contrast to smaller and non-population based studies [22], the current analysis underlines the increased risk of fractures in both men and women. This was observed at all-time points during follow-up. With 38.8%, women had a particularly high risk of experiencing a fracture during follow-up, whereas the cumulative incidence was only 21.6% in men. An explanation could be that women have additional risk

Table 4. Cumulative incidence of any fracture during follow-up.

Group: Cumulative incidence (%), (95%-CI)	People with PBC at 1 year	Matched controls at 1 year	People with PBC at 5 years	Matched controls at 5 years	People with PBC at 10 years	Matched controls at 10 years	People with PBC full follow-up	Matched controls full follow-up
Overall	4.9 (4.3–5.6)	2.8 (2.7–3.0)	16.8 (15.6–18.1)	11.6 (11.3–12.0)	26.6 (25.0–28.3)	21.1 (20.6–21.6)	36.3 (33.9–38.8)	31.2 (30.3–32.2)
By subgroup								
Sex								
Men	3.3 (2.0–4.9)	1.8 (1.5–2.2)	11.8 (9.2–14.7)	7.5 (6.8–8.3)	17.7 (14.3–21.4)	13.7 (12.6–14.8)	21.6 (17.6–25.9)	20.4 (18.8–22.1)
Women	5.2 (4.5–6.0)	3.0 (2.8–3.2)	17.7 (16.3–19.1)	12.3 (11.9–12.7)	28.2 (26.4–30.0)	22.4 (21.8–22.9)	38.8 (36.1–41.5)	33.0 (31.9–34.1)
Age group								
<50	2.0 (1.1–3.5)	1.0 (0.7–1.3)	8.5 (6.2–11.3)	4.1 (3.5–4.7)	12.1 (9.0–15.7)	9.5 (8.5–10.6)	19.8 (14.6–25.7)	15.9 (14.1–17.7)
≥50	5.4 (4.6–6.2)	3.1 (2.9–3.3)	18.1 (16.8–19.5)	12.8 (12.4–13.2)	28.7 (26.9–30.5)	22.9 (22.3–23.4)	38.3 (35.7–40.8)	33.2 (32.1–34.2)
Baseline cirrhosis								
Yes	6.3 (3.5–10.2)	3.5 (2.7–4.4)	14.8 (10.1–20.3)	14.5 (12.8–16.3)	20.9 (14.9–27.6)	25.3 (22.9–27.7)	31.2 (22.9–39.9)	37.3 (33.2–41.5)
No	4.8 (4.2–5.6)	2.8 (2.6–3.0)	16.9 (15.7–18.2)	11.5 (11.1–11.8)	26.9 (25.3–28.6)	20.9 (20.4–21.4)	36.8 (34.3–39.3)	31.0 (30.0–32.0)
Baseline osteoporosis								
Yes	19.6 (13.2–26.9)	4.5 (3.4–5.8)	35.9 (27.3–44.5)	16.6 (14.4–19.0)	47.5 (37.5–56.9)	28.8 (25.7–31.8)	49.6 (39.2–59.2)	38.4 (34.6–42.1)
No	4.4 (3.8–5.1)	2.8 (2.6–2.9)	16.2 (14.9–17.5)	11.5 (11.1–11.8)	25.9 (24.3–27.6)	20.9 (20.4–21.4)	35.9 (33.4–38.4)	31.0 (30.0–32.0)
Previous fracture								
Yes	15.6 (12.3–19.2)	3.9 (3.3–4.5)	39.4 (34.2–44.6)	14.8 (13.6–16.1)	48.9 (42.7–54.7)	27.0 (25.1–28.9)	54.4 (46.3–61.7)	37.2 (34.2–40.3)
No	3.6 (3.0–4.3)	2.7 (2.5–2.9)	14.3 (13.0–15.5)	11.3 (10.9–11.6)	24.2 (22.6–25.9)	20.6 (20.1–21.1)	34.4 (31.9–37.0)	30.8 (30.0–31.8)

Abbreviation: PBS, primary biliary cholangitis.

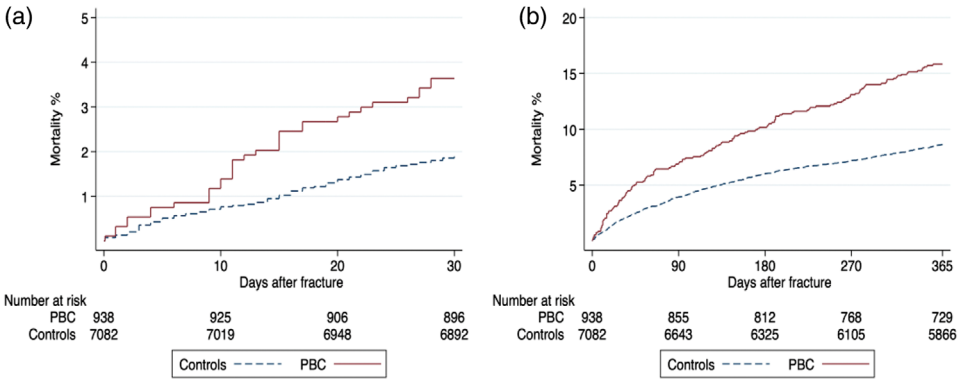

Fig. 3 *Kaplan–Meier curve of (a) 30-day and (b) 1-year mortality after any fracture in people with primary biliary cholangitis (PBC) and reference individuals.*

factors for bone illness leading to falls and fractures, such as postmenopausal osteoporosis [23]. Albeit a numerically higher HR in men compared to women, it was not statically significant in this analysis, suggesting that additional factors beyond postmenopausal osteoporosis affect the gender differences in PBC.

A number of studies and reviews have summarized the risk of fractures in people with PBC [3]. A cohort study from 2006 based on the General Practice Research Database in the United Kingdom with a comparable study design included 930 cases with PBC and observed an approximately twofold relative increase of fractures compared to matched controls from the same database [24]. The current analysis expands these findings by including risk factors for fractures in particular osteoporosis. In subgroup analysis, the presence of osteoporosis exaggerated the risk of fracture in PBC by 3.4-fold. In this group, vertebral fractures had the strongest association with PBC, followed by fractured ribs and sternum. In alignment with previous observations [24], the current analysis suggests an excess risk in individuals with cirrhosis. Interestingly, the absolute risk of experiencing a fracture was higher for people with PBC and cirrhosis only in the first year of follow-up. At 5 years, the cumulative incidence in the subgroup with cirrhosis at baseline was comparable between people with PBC and controls and after that the risk was even higher for the controls. This might be related to the incremental increase of fractures in older age when frailty and falls are the strongest contributors to fractures in general [25] but can also be an effect of a higher mortality in people with cirrhosis. When trying to assess disease activity in relation to fractures, it is important to note that cholestasis and in particular alkaline phosphatase levels are responsive to UDCA as first-line therapy [26], limiting the ability to link baseline values to the disease course over an extended time. Moreover, it seems unlikely that the approval of obeticholic acid by the FDA in 2016 as second line therapy in PBC had a relevant impact on our study results.

A central finding of our analysis was the increased mortality of people with PBC following fracture. The 1-year mortality rate was twofold higher in people with PBC compared to controls. Although we cannot provide a mechanism for this excess mortality, it can be speculated that cholestatic liver diseases impair wound healing and increase the risk of subsequent infections. This emphasizes the detrimental effect a fracture has on people with PBC and measures to prevent fractures in an aging PBC population will be of great importance to maintain the benefit of modern therapies. The study included patients diagnosed between 2001 and 2016. People with a previous diagnosis of PBC at study baseline were also included, why the proportion of people with PBC and controls was highest in the early study period.

The following strengths and limitations are acknowledged. This is one of the largest analyses, including 3980 Swedish individuals diagnosed with PBC during the study period. We assume that people diagnosed with PBC have been seen in specialized care settings at least once, thus minimizing the selection bias frequently seen in single or expert-center cohorts. The possibility to link cases to 37,196 matched general population controls allowed for an unbiased comparison. The

Table 5. Mortality rate in people with primary biliary cholangitis (PBC) and matched controls who had a fracture during follow-up.

	People with PBC (events, *n* [%])	Matched controls (events, *n* [%])	People with PBC (incidence rate/1000 PY [95%CI])	Matched controls (incidence rate/1000 PY [95%CI])	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
30-day mortality	34 (3.6)	135 (1.9)	452.6 (323.4–633.4)	235.5 (198.9–278.7)	2.1 (1.5–3.1)	2.2 (1.5–3.2)
1-year mortality	144 (15.4)	591 (8.4)	177.5 (150.7–208.9)	92.8 (85.6–100.6)	2.1 (1.8–2.5)	2.0 (1.7–2.4)

availability of linkage between Swedish national registers further allowed us to assess the overall mortality following fractures in PBC compared to controls that also experienced a fracture. Only a few cases were lost during follow-up, mostly related to emigration from Sweden. The Swedish National Patient Register has been shown to have high positive predictive values for most chronic diseases. Therefore, the risk of misclassification bias by using ICD-10 codes to determine disease status can be considered quite small, although some risk of this cannot be ruled out [20]. The analysis is limited by the lack of laboratory data or data on drug prescriptions, and thus, a granular analysis between responder or non-responder and disease severity—outside of the coding of cirrhosis—was not possible. It is anticipated that these factors will be explored in further studies. Another limitation of the current analysis is that osteoporosis remains an underdiagnosed disease. We observed a low prevalence of osteoporosis in both people with PBC as well as in controls. To avoid misclassification, we used fractures at common osteoporotic fracture sites as the main definition and included coding for osteoporosis within 3 months after the baseline in a corresponding sensitivity analysis.

In conclusion, this study is the first to compare fracture incidents in a large, population-based cohort study, including both male and female patients of all ages. We found that the incidence of fractures, especially osteoporotic fractures, is more than twofold higher in people with PBC compared with controls and after careful consideration of confounders. The overall mortality in people with PBC following a fracture event is significantly increased. These results call for a high clinical vigilance for the detection of osteoporosis in PBC to reduce the incidence of fractures and thereby postfracture mortality.

Author contributions

Interpretation of data; preparation of Figs./Tables; drafting of the manuscript: Johanna Schönau. *Analysis and interpretation of data; statistical analysis; revision of the manuscript*: Axel Wester. *Interpretation of data; revision of the manuscript*: Jörn M. Schattenberg. *Acquisition of data; analysis and interpretation of data; revision of the manuscript*: Hannes Hagström.

Acknowledgments

Open access funding enabled and organized by Projekt DEAL.

Conflicts of interest statement

JMS declares consultant honorary from BMS, Boehringer Ingelheim, Echosens, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Merck, Novartis, Pfizer, Roche, Sanofi, and Siemens Healthcare GmbH, JMS institution has received research funding from Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH, and speaker honorarium from Falk Foundation, Novo Nordisk, Madrigal. HH's institution has received research funding from Astra Zeneca, EchoSens, Gilead, Intercept, MSD and Pfizer. HH has served as a board advisory member for BMS and Gilead.

Funding information

Swedish Research Council and Region Stockholm (CIMED).

References

1 Gidwaney NG, Pawa S, Das KM. Pathogenesis and clinical spectrum of primary sclerosing cholangitis. *World J Gastroenterol.* 2017;**23**(14):2459–69.
2 KV LN, Nguyen LT. The role of vitamin d in primary biliary cirrhosis: possible genetic and cell signaling mechanisms. *Gastroenterol Res Pract.* 2013;**2013**:602321.
3 Trivedi HD, Danford CJ, Goyes D, Bonder A. Osteoporosis in primary biliary cholangitis: prevalence, impact and management challenges. *Clin Exp Gastroenterol.* 2020;**13**:17–24.
4 Nakchbandi IA. Osteoporosis and fractures in liver disease: relevance, pathogenesis and therapeutic implications. *World J Gastroenterol.* 2014;**20**(28):9427–38.
5 Guanabens N, Pares A, Ros I, Caballería L, Pons F, Vidal S, et al. Severity of cholestasis and advanced histological stage but not menopausal status are the major risk factors for osteoporosis in primary biliary cirrhosis. *J Hepatol.* 2005;**42**(4):573–7.
6 Guanabens N, Cerda D, Monegal A, Pons F, Caballería L, Peris P, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. *Gastroenterology.* 2010;**138**(7):2348–56.
7 Kempinska-Podhorodecka A, Adamowicz M, Chmielarz M, Janik MK, Milkiewicz P, Milkiewicz M. Vitamin-D receptor-gene polymorphisms affect quality of life in patients with autoimmune liver diseases. *Nutrients.* 2020;**12**(8):2244.
8 Agmon-Levin N, Kopilov R, Selmi C, Nussinovitch U, Sánchez-Castañón M, López-Hoyos M, et al. Vitamin D in primary biliary cirrhosis, a plausible marker of advanced disease. *Immunol Res.* 2015;**61**(1–2):141–6.
9 Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. *Hepatology.* 2021;**75**(4):1012–3.
10 Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med.* 2016;**375**(7):631–43.
11 Pares A, Caballeria L, Rodes J, Bruguera M, Rodrigo L, García-Plaza A, et al. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. *J Hepatol.* 2000;**32**(4):561–6.
12 Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. *Hepatology.* 1999;**29**(6):1668–71.
13 Levy C, Peter JA, Nelson DR, Keach J, Petz J, Cabrera R, et al. Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Aliment Pharmacol Ther.* 2011;**33**(2):235–42.
14 Liao CY, Chung CH, Chu P, Wei KY, Feng TM, Lin FH, et al. Increased risk of osteoporosis in patients with primary biliary cirrhosis. *PLoS One.* 2018;**13**(3):e0194418.
15 Danford CJ, Trivedi HD, Papamichael K, Tapper EB, Bonder A. Osteoporosis in primary biliary cholangitis. *World J Gastroenterol.* 2018;**24**(31):3513–20.
16 Kaps L, Grambihler A, Yemane B, et al. Symptom burden and treatment response in patients with primary biliary cholangitis (PBC). *Dig Dis Sci.* 2020;**65**(10):3006–13.
17 Hagstrom H, Shang Y, Wester A, Widman L. Cohort profile: decoding the epidemiology of liver disease in Sweden (DELIVER). *Scand J Gastroenterol.* 2022;**57**:978–83.
18 Simon TG, Roelstraete B, Hagstrom H, Sundstrom J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. *Gut.* 2021;**71**(9):1867–75.
19 Diamantopoulos AP, Rohde G, Johnsrud I, Skoie IM, Hochberg M, Haugeberg G. The epidemiology of low- and high-energy distal radius fracture in middle-aged and elderly men and women in Southern Norway. *PLoS One.* 2012;**7**(8):e43367.
20 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;**11**:450.
21 Boggess VCaM. Cumulative incidence estimation in the presence of competing risks. *Stata J.* 2004;**4**(2):103–12.
22 Boulton-Jones JR, Fenn RM, West J, Logan RF, Ryder SD. Fracture risk of women with primary biliary cirrhosis: no increase compared with general population controls. *Aliment Pharmacol Ther.* 2004;**20**(5):551–7.
23 Eastell R, O'Neill TW, Hofbauer LC, Langdahl B, Reid IR, Gold DT, et al. Postmenopausal osteoporosis. *Nat Rev Dis Primers.* 2016;**2**:16069.
24 Solaymani-Dodaran M, Card TR, Aithal GP, West J. Fracture risk in people with primary biliary cirrhosis: a population-based cohort study. *Gastroenterology.* 2006;**131**(6):1752–7.
25 Liang W, Chikritzhs T. The effect of age on fracture risk: a population-based cohort study. *J Aging Res.* 2016;**2016**:5071438.

26 Schattenberg JM, Pares A, Kowdley KV, Heneghan MA, Caldwell S, Pratt D, et al. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol.* 2021;**74**(6): 1344–54.

Correspondence: Jörn M. Schattenberg, Department of Internal Medicine, University Medical Center Mainz, Mainz, Rheinland-Pfalz, Germany.
Email: joern.schattenberg@unimedizin-mainz.de

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Table 1 ICD-10 codes used to define liver diseases and comorbidities
Supplementary Table 2 ICD-10 codes for fractures ■

