Hip fracture risk in patients with alcoholic cirrhosis: a population-based study using English and Danish data.

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Contributors

JW, KMF, and PJ conceived the study and planned it with HO and TD. HO and TD carried out the analysis. HO, TD, KMF, TC, AGP, PJ and JW contributed to the interpretation of data. OH, JW, and KMF drafted the article. HO, TD, KMF, TC, AGP, PJ and JW revised the article for important intellectual content. All authors gave final approval of the version to be published. JW is the guarantor.

Key words: Hip fracture, alcoholic liver disease, cirrhosis, mortality, epidemiology.

What is already known about the subject?

- Cirrhosis is on the rise with little proven treatment that affects its natural history or mortality
- The risk of hip fracture is increased among some groups of people with cirrhosis
- Hip fracture confers a large morbidity and mortality effect immediately following the event
- There is lack of evidence on the absolute and relative hip fracture risk specifically in patients with alcoholic cirrhosis, taking into account competing risk of death.

What are the new findings?

- Hip fracture risk is raised by at least 5 fold in an alcoholic cirrhosis population compared to population controls of similar age and sex
- The increased risks of hip fracture is higher in younger adults
- The cumulative incidence of hip fracture (having taken account of the competing risk of death) is greater than that of hepatocellular carcinoma (HCC) in this population.

How might it impact on clinical practice in the foreseeable future?

- Hip fracture is, via several interventions, potentially preventable. Given that the reported risk of hip fracture in people with cirrhosis is higher than that of HCC for which there is national surveillance, our findings support the need for more effort towards fracture prevention in this population as it could benefit both the individual and society burden.

Abstract

Background & aims: Cirrhosis is a risk factor for osteoporosis and fractures. However, little is known of the actual risk of hip fractures in patients with alcoholic cirrhosis. Using linked primary and secondary care data from the English and Danish nationwide registries, we quantified the hip fracture risk in two national cohorts of patients with alcoholic cirrhosis.

Methods: We followed 3,706 English and 17,779 Danish patients with a diagnosis of alcoholic cirrhosis, and we identified matched controls from the general populations. We estimated hazard ratios (HR) of hip fracture for patients versus controls, adjusted for age, sex and comorbidity.

Results: The 5-year hip fracture risk was raised both in England (2.9% vs 0.8% for controls) and Denmark (4.6% vs 0.9% for controls). With confounder adjustment, patients with cirrhosis had 5-fold (adjusted HR 5.5 (95% CI 4.3-6.9)), and 10-fold (adjusted HR 9.9 (95% CI 8.9-11.0)) increased rates. This association between alcoholic cirrhosis and risk of hip fracture showed significant interaction with age ($p<0.001$), being stronger in younger age groups (under 45 years HR: 17.9 and 16.6 respectively for English, Danish) than in patients over 75 years (HR 2.1 and 2.9 respectively). In patients with alcoholic cirrhosis, 30-day mortality following a hip fracture was 11.1% in England and 10.0% in Denmark, giving age-adjusted post-fracture mortality rate ratios of 2.8(95% CI 1.9-3.9) and 2.0(95% CI 1.5-2.7), respectively.

Conclusions: Patients with alcoholic cirrhosis have a markedly increased risk of hip fracture and post-hip fracture mortality compared with the general population.

Keywords: cirrhosis; epidemiology; fracture

Introduction

An important and often studied complication of chronic liver disease is osteoporosis (1–5). Osteoporosis may be asymptomatic, but increases the risk that minor accidents result in bone fractures, particularly of the distal radius and proximal femur (1,2). Hip fractures in particular have a significant impact on health, productivity and life expectancy (6,7), and the 30-day mortality is estimated to be up to 10% (8,9). In patients specifically with alcoholic cirrhosis, the risk of these fractures may be further increased due to the direct effect of high levels of alcohol use (10), or minimal hepatic encephalopathy (11). However, due to a dearth of studies that have actually quantified the incidence of fractures in chronic liver disease, the absolute risk of hip fractures in people with alcoholic cirrhosis is unknown.

Available estimates on the occurence of fractures in hepatic disorders originate from small studies on hetergenous populations that were carried out almost 10 years ago. Only two recent studies have addressed the risk of fractures in alcoholic liver disease specifically (5,12), but – like previous studies (13,14) – they studied relative risks, not absolute risks and did not do a comprehensive analysis by fracture type, so estimates of hip fracture specifically are unavailable. Clinical practitioners and policy makers would be better placed to inform and guide patients regarding prevention strategies if their actual risk of serious injury, such as hip fracture, was known. Indeed, while the relative risk of a hip fracture is useful in terms of identifying a group in which targeted intervention could be valuable, without absolute risks it is impossible to judge the risks and benefits of potential interventions. In a cirrhosis population it is crucial also when quantifying risk to take account of the fact that there is a high mortality (15,16). Only by accounting for this competing risk and demonstrating the cumulative risk of hip fracture can we accurately quantify the problem. We therefore have performed a large study using two national cohorts in England and Denmark to examine the absolute and relative risk of incident hip fracture in patients with alcoholic cirrhosis compared

with the general population, and to compare and contrast our findings given the differences in the populations of the two countries.

Methods

Data sources

English data was obtained from the linked Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES) database (17,18), while Danish data was obtained from The Danish National Patient Registry (NPR) (19) and the Danish civil registration system (20).

Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES)

The CPRD consists of computerised general practice records for over 15 million patients in the UK of which 4.4 million are active, alive and currently registered. With a coverage of 4.4 million, it covers approximately 6% of the UK population. Recorded data includes patient demography, diagnoses and test results entered during general practice appointments or following communication from secondary care. These data are coded electronically using the hierarchical Read coding system (21) and are subjected to regular data quality checks and audits to ensure 95% inclusion of prescribing and morbidity events. Since 1997, the CPRD has an established linkage to the HES database, which contains information on all admissions to the state-funded National Health Service (NHS) hospitals in England; including secondary care diagnoses coded using the International Classification of Disease (ICD) edition 10 (ICD-10). Approval for use of this linked data for this study was given by the Scientific and Ethical Committee of the CPRD (15_073RAR).

National Patient Registry (NPR)

The Danish NPR is a nationwide registry that holds data on all admissions to non-psychiatric hospitals since 1977 and from outpatient and emergency room visits since 1995 in Denmark. The data includes dates and diagnoses coded in accordance with the ICD-10 from 1994 and ICD-8 before that. The Danish Central Office of Civil Registration (CPR) monitors the vital

status of all Danish citizens (population 5.6 million) continuously and issues a unique personal identifier to everyone at birth or migration to Denmark. This number enables individual-level linkage with the NPR.

Study population

All adults (>18 years) with a first time diagnosis of alcoholic cirrhosis between 1997 and 2014 were identified. Alcoholic cirrhosis was defined by the presence of a diagnostic code (Read or ICD-10 code) for alcoholic cirrhosis. Our code lists were adapted from previously validated definitions (22,23). We defined the 'index date' of each patient as the first date of a recorded diagnostic code for alcoholic cirrhosis. Among the patients identified within the English data, we excluded those with an index date within 1 year of registration with a general practice in order to avoid prevalent cases. For each included patient, we identified up to 10 general population controls frequency-matched on sex, age (within 5 years) and by registration at the same general practice, (general practice matching was for patients identified in England only). The matched controls had to be alive and without a diagnostic or therapeutic code for cirrhosis, oesophageal varices and/or portal hypertension within their own general practice or hospital record.

Controls identified for the English cohort were assigned an index date, which was a randomly generated date from 1 year after the start of the linked dataset (1997) up to the date they left their general practice or died. For the Danish cohort, controls were assigned the same index date as the cirrhosis patient they were matched to. Patients with a diagnosis of a hip fracture (as defined below) before the index date were excluded from both cohorts.

Study period

Each patient and control was followed from the index date to a diagnosis for a hip fracture, date of death, date of moving out of their general practice (for English data only), or end of follow-up (31/12/2014).

Study definitions

Primary outcome

The primary outcome was time to first diagnosis for any hip fracture (ICD-10 S720-S729; Read codes 820 A, 820 B, 8210, S30..00, S30..11, S302.00, S30y.00, S30y.11, S30z.00) as recorded on the general practice, hospital, or patient registry records (24).

Severity of cirrhosis

Patients with alcoholic cirrhosis were classified as being in a compensated or decompensated disease state according to the Baveno clinical staging classification that takes into account the absence or presence of variceal bleed, and ascites (but specifically does not include hepatic encephalopathy) (25) . Variceal bleed or ascites was defined if there was a relevant diagnostic code (ICD-10 code: R18, I850, K920, K921, K922, I859, I864, I982) or procedure code (OPCS4 code: T461, T462, G104, G108, G109, G144, G174, G437) up to 1 year before the date of diagnosis of alcoholic cirrhosis; cirrhosis patients without such codes were defined as having compensated disease. We specifically identified evidence of hepatic encephalopathy by searching patient records for relevant diagnostic codes (ICD 10: E51.2, G31.2, K70.4, K72.1).

Other cirrhosis aetiologies

We reported whether our patients with alcoholic cirrhosis also had cirrhosis of other etiology including viral hepatitis, autoimmune liver disease (primary biliary cholangitis, primary sclerosing cholangitis and autoimmune hepatitis), haemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency at any time prior to alcoholic cirrhosis diagnosis using methods described previously(22).

Comorbidity

For each cirrhosis patient and population control, we used secondary care data recorded within two years before the index date to compute their Charlson Comorbidity Index (CCI)

(26). The CCI is a weighted comorbidity score that is defined for use in the ICD-10. It includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, mild liver disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, diabetes with or without complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, cancer, metastatic cancer, and HIV/AIDS. Diagnoses related to liver disease were excluded when calculating the CCI for this study. For clarity of presentation, we summarized the CCI in three categories: no comorbidity (CCI = 0), moderate comorbidity (CCI = 1), and multiple or severe comorbidity (CCI≥ 2).

Potential confounders

We extracted data on patients with an osteoporosis diagnosis. In addition, where available, we extracted data on drug exposure to oral and injected steroids, antidepressants, opiates and bisphosphonates. These drugs were chosen because they have been previously shown to be associated with fracture or are used as a treatment for osteoporosis(27). A density parameter for each subject was defined as the number of prescriptions received (with a maximum of 1 prescription per day per drug category permitted) per follow-up time as defined below. This prescription density was then categorised, for each drug category, into none, some and many of the specific prescriptions. The categorisation of some and many was made, for each drug, as ‘less than or equal to’ or ‘greater than’ the median density of prescriptions (having excluded those with zero prescriptions).

Statistical analyses

We calculated the rate of first hip fracture in alcoholic cirrhosis patients and population controls. Using Cox regression, we estimated the hazard ratio (HR) for a hip fracture in the alcoholic cirrhosis cohort compared with the control population. All standard Cox regression models were *a priori* adjusted for age, sex and comorbidity at baseline (Charlson comorbidity

index, 0,1 or 2). We computed HRs for subgroups defined by age group, sex and cirrhosis severity (compensated or decompensated cirrhosis) and examined effect modification by age with the likehood ratio test and graphically using a Schoenfeld residuals plot. We computed the 1- and 5- year cumulative risk of a hip fracture after alcoholic cirrhosis diagnosis using the cumulative incidence function with death without hip fracture as the competing risk (using age as the timescale). Proportional hazards assumptions were confirmed using Schoenfeld residuals and log-log plots. Finally, we identified all deaths occuring within 30 days after hip fracture diagnosis and estimated 30-day mortality and mortality risk for cirrhosis patients versus the control population.

Additional analyses

We repeated our analyses on disease severity to include patients who had a clinical diagnosis of hepatic encephalopathy in the decompensated group. This enabled us to examine the effect of hepatic encephalopathy on the association between disease severity and fracture rates. We also stratified fracture estimates by the presence or absence of osteoporosis and bisphosphonate use, as these are on the causal pathway between cirrhosis and fractures and adjusting for them in our models would have been inappropriate. We assessed the effect of drug exposure using English data where prescription records are available. Drug exposure (oral and injected steroids, antidepressants, opiates) was modelled as a categorical variable and included in the *a priori* adusted cox regression model if it conferred a 10% adjustment in the hazard ratios seen (Supplementary tables 1 and 2). Finally, to examine the role of comorbidity on fracture rates, we re-estimated the 5-year cumulative incidence of fracture in only those patients with a Charlson comorbidity score of 0 (Supplementary figure 1) i.e. no recorded comorbididy.

All statistical analyses were conducted using Stata version 13.0 (StataCorp, College Station, TX).

Results

Demographic and clinical characteristics

In the English data, we included 3,706 alcoholic cirrhosis patients and 36,859 matched population controls. The median age at diagnosis was 56 years, 68.0% of patients were men, and 49.8% had decompensated cirrhosis at their diagnosis. At inclusion, cirrhosis patients had more comorbidity than population controls and the prevalence of a CCI score of 1 or more was 37.7% in cirrhosis patients and 7.1% in population controls (Table 1).

In the Danish data, we included 17,779 cirrhosis patients and 80,815 population controls. They were slightly older than the English cirrhosis patients (median age 57 years), but their gender composition was similar to English cirrhosis patients (66.8% were men). The prevalence of decompensated cirrhosis at the diagnosis for cirrhosis was 30% and Danish cirrhosis patients also had more comorbidity than population controls; the prevalence of a CCI score of 1 or more was 36.6% in cirrhosis patients and 5.4% in population controls (Table 1). In both England and Denmark, the majority of patients [English (88.8%) and Danish (94.6%)] had an alcohol-only cirrhosis aetiology (taking into account medical records before alcoholic cirrhosis diagnosis). Evidence of osteoporosis was found in 6.3% and 3.1% of English and Danish patients respectively.

Fracture analysis

We followed up the English population for a total of 177,717 person years, during which 485 hip fractures occurred (108 fractures in cirrhosis patients, 377 fractures in controls). The absolute hip fracture rate for patients with cirrhosis was 11.4 fractures (95% CI: 9.4-13.8) per 1000 person years but the rate among controls was much lower at 2.2 (95% CI: 2.0-2.5) per 1000 person years (Table 2). In effect, there was an excess of 9.2 fractures per 1000 person years in English cirrhosis patients. The adjusted hip fracture hazard ratio for cirrhosis patients vs. controls was 5.5 (95% CI: 4.3-6.9) (Table 2).

The corresponding numbers for the Danish population were 753,797 person years of follow-up and 2,491 fractures (977 fractures in cirrhosis patients and 1,514 fractures in controls). Similarly, the absolute hip fracture rate for Danish cirrhosis patients was higher than that of controls, at 16.0 (95% CI: 15.0-17.0) per 1000 person years compared to 2.2 (95% CI 2.1-2.3) per 1000 person years (Table 2). Thus, there was an excess of 13.8 fractures per 1000 person years in Danish cirrhosis patients over controls. The adjusted hip fracture hazard ratio for Danish cirrhosis patients vs. controls was 8.5 (95% CI: 7.8–9.3).

Fracture rate analysis by subgroups

In both countries the association between cirrhosis and hip fracture rate was stronger in younger age groups (aged < 45 years) than in older age (p value for interaction with age <0.001). The hazard ratio of a hip fracture in those aged 45-54 years was 14.7 (95% CI 8.6-24.9) and 13.1 (95% CI 10.9-15.7) in England and Denmark respectively, whereas for those aged 75 years and over it was 2.1 (95% CI 1.1-3.9) (England) and 3.0 (95% CI 2.1–4.2) (Denmark) (Table 2 and Figure 1). In Denmark, the association between cirrhosis and hip fracture rate was slightly stronger in men (HR 9.0, 95% CI 8.0–10.1) than in women (HR 7.9 ,95% CI 6.9–9.0) but in England it was stronger in women (HR 7.1 (95% 5.0- 9.9)) than in men (HR 4.4 (95% 3.2 – 6.1)). Disease severity had no remarkable effect on absolute fracture rate in Demark, but in England, absolute fracture rates were higher in patients with decompensated disease than in compensated disease (14.2 vs. 9.4 per 1,000 person years). Including hepatic encephalopathy in the definition of disease severity had a minimal effect on the association between disease severity and fracture rates.

1-year and 5-year cumulative incidence analysis

After 1-year of follow-up, the cumulative hip fracture risk in English cirrhosis patients was 1.0% (95% CI: 0.7–1.4) compared to 0.2% (95% CI: 0.1–0.3) for population controls. The

corresponding 5-year risks were also higher for cirrhosis patients than for controls at 2.9% (95% CI 2.3-3.6) vs. 0.8% (95% CI 0.7-0.9). Likewise, in the Danish cohort, the 1-year hip fracture risk for cirrhosis patients was higher than that of controls at 1.4% (95% CI: 1.2–1.6) vs 0.2% (95% CI: 0.1–0.2). The corresponding 5-year risks were 4.6% (95% CI: 4.3–5.0) and 0.9% (95% CI: 0.8–0.9) respectively.

In both countries, the 5-year risks of hip fracture increased with increasing age and was higher for each cirrhosis age group than for the matched controls (Figure 2, Table 3). The cumulative risk among the young controls (less than 45 years) was very low, but the risk in young cirrhosis patients was remarkably high hence the increase in risk relative to the control population was greater in younger cirrhosis patients than in those over 75 years (Figure 2). We found no variation in hip fracture risk by disease severity (Table 3).

30-day mortality estimate

By 30 days post hip fracture, 11.1% (12/108) of English cirrhosis patients and 10.0% (98/977) of Danish cirrhosis patients had died compared to 5.0% (England) and 6.6% (Denmark) for the control populations (Table 4). The adjusted mortality risk ratio comparing deaths in cirrhosis patients to controls was 2.8 (95% CI: 1.9-3.9) and 2.0 (95% CI: 1.5–2.7), for England and Denmark respectively.

Additional analyses on drug use

Supplementary Table 1 provides information on drug usage for the English cirrhosis and control cohort. Patients with cirrhosis were more likely than controls to have had a prescription of opiates (42.2% vs 32.7%) and antidepresessants (14.2% vs 11.1%), but as

likely to have had a prescription for oral or injected corticosteroids(13.9% vs. 14.7%) . As shown in supplementary table 2, there was only minimal confounding identified following adjustment for prescription drug use.

Discussion

Using data from two national cohorts, we have shown an increased rate of hip fracture for people with alcoholic cirrhosis of between 5-fold to nearly 10-fold compared with the general population. The 5-year risk of hip fracture was 2.9% for cirrhosis patients in the England and 4.6% for patients in Denmark. In both countries, younger patients had the largest risk difference when comparing cirrhosis patients with controls. This association was due to the combination of a very low risk of hip fractures among young control patients and the contrasting high risk in young patients with alcoholic cirrhosis. We found a higher 30-day post-fracture mortality in cirrhosis patients of between 2 to 3 fold compared to population controls. Our study therefore indicates that interventions to prevent hip fracture in this population could have a significant benefit.

We chose to combine two national cohorts for this analysis so that we could compare and contrast our findings, and explore some of the differences. There were many similarities between the alcoholic cirrhosis cohorts in both countries. The age and sex profiles were very similar and the relative risks of fracture again were reasonably similar. Importantly the interaction with age showed the same pattern of relative and cumulative risks in both countries indicating its likely veracity. Our conclusions were the same irrespective of the severity of alcoholic cirrhosis suggesting that the 20% difference in the prevalence of decompensation between both cohorts was not crucial to the interpretation of our analysis.

Strengths and limitations

This is the first study to report the incidence of hip fracture in patients with alcoholic cirrhosis using prospectively collected data from two large national cohorts, with access to a suitable control population. Other strengths are its large size, competing risk adjustment, and population-based setting which means we have been able to estimate both the absolute and relative risks of hip fractures with reasonable precision and accuracy, and that these estimates are generalizable to the general populations of the two nations and possibly given the similarity between the results, to others as well. In addition, we were able to stratify estimates by age and sex, and by so doing have assessed for variation by these variables. Information on some other potential confounding factors (28,29) were either missing for some patients or absent in totality, e.g. weight bearing exercise, meaning that we could not assess their potential effect on our estimates. Our estimates were also not adjusted for alcohol use because heavy alcohol intake is an inherent part of having alcoholic cirrhosis and it would therefore be inappropriate to adjust for. Obviously, this means we do not know how much alcoholic individuals drank post-cirrhosis diagnosis nor how this might alter to their fracture risk. However, the presence of an increased risk of fracture in non-alcoholic groups with liver injury(4) argues that alcohol cannot entirely account for the relationship shown in our study.

The data sources used for this study have previously been validated and quality assured both for the diagnosis of cirrhosis (23,30) and for hip fracture (31,32). A validation of the severity of disease, as measured through decompensation, has not however been possible and as such, we may have missclassified some patients between stages of disease. Nevertheless, our previous work(33) has shown that the Baveno method of classifying decompensation accurately predicts mortality and as such appears a reasonably sound approach. Finally, while these results have important implications for fracture prevention in people with cirrhosis, this analysis does not consider the mechanism of fractures, thus it is not possible to explicitly attribute the increased risk of fractures to, for example, osteoporosis, trauma, both or some other risk factors. Although we found 6.3% (England)

and 3.1% (Denmark) of patients with evidence of osteoporosis, these should be interpreted with caution as recording of osteoporosis diagnosis within our data is presumed to be incomplete and therefore underestimated.

Comparison with previous literature

Previous publications on the association between osteoporosis, fractures and alcholic liver disease have been with small heterogenous populations and thus far, only relative risks have been presented. In 2014, Bang et al reported a relative fracture risk in people with alcoholic cirrhosis of 2.4, but this was based on a small subgroup of patients identified within a larger cohort of patients with either chronic pancreatitis or cirrhosis (5). In another meta-analysis from the same group in 2015, based on six studies (34–39), a lower relative increase in fracture risk of 1.9 was found among people with alcoholic liver disease of mixed severity (12). Several other data for comparison originate from studies based on other chronic liver diseases. Tsai et al, estimated the risk of fractures in 3,764 patients with cirrhosis (most likely to be predominantly hepatitis-B related) compared to non-cirrhotic controls, and found a 4-fold increase in skull fracture risk in cirrhosis patients with hepatic encephalopathy (HE), and a 1.6- to 1.8-fold increase in spine, trunk and upper limb fracture risk in cirrhosis patients without HE (40). In two other studies using the same UK primary care database as our study, high relative increases in hip and wrist fracture rates of between 1.9 and 4.0 were found in patients with primary biliary cholangitis (PBC) or any chronic liver disease (4,14).

In our analysis accounting for death as a competing risk, we found no difference in the cumulative risk of fractures between patients with compensated and decompensated disease. These findings are consistent with two smaller studies on other advanced liver disease (PBC) which found no association between the occurrence of fractures and severity of liver disease (4,41).

Clinical implications and conclusion

Overall, our study has shown that hip fracture is an important clinical outcome in patients with alcoholic cirrhosis due to its frequent occurrence and severe consequence. The cumulative risk of fracture, having accounted for the competing risk of death, in these patients is approximately 1% per annum and there is more than two fold higher post fracture 30-day mortality in people with cirrhosis than in the general population. Currently, great emphasis is placed on Hepatocellular carcinoma (HCC) as an important, potentially preventable, cause of mortality in cirrhosis with several guidelines proposing national HCC surveillance to enhance detection and thus early treatment (42,43). Given that our study has shown that the cumulative incidence of hip fractures in alcoholic cirrhosis is higher than that of HCC (15,44), hip fractures may be an even more important cause of death and morbidity among people with alcoholic cirrhosis. To these facts can be added the knowledge that effective pharmacotherapy exists to treat osteoporosis and is proven to reduce hip fracture risk(45–48).

Therefore, prophylaxis to reduce hip fracture occurrence in people with alcoholic cirrhosis (48–51), may have greater potential for benefit than does the currently common practice of surveillance for HCC, and certainly warrants consideration alongside it.

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Table 1. Demographic characteristics of alcoholic cirrhosis cohort and population controls in Denmark and England.

	UK		*Denmark*	
	Cirrhosis patients N=3,706	**Controls N=36,854**	**Cirrhosis patients N=17,779**	**Controls N=80,815**
***Age at diagnosis** (%)*				
≤44	645 (17.4)	7,426 (20.1)	2,117 (11.9)	10,033 (12.4)
45–54	1,089(29.4)	10,227(27.8)	5,379 (30.3)	24,950 (30.9)
55–64	1,109 (29.9)	10,439(28.3)	6,308 (35.5)	28,604 (35.4)
65–74	623 (16.8)	6,181 (16.8)	3,221 (18.1)	14,113 (18.1)
≥75	240 (6.5)	2,581 (7.0)	754 (4.2)	3,115 (3.9)
Median(IQR) age at diagnosis (years)	56 (47-64)	55(47-64)	57 (50–64)	57 (50–64)
Sex (%)				
Males	2,520 (68.0)	25,074 (68.0)	11,687 (66.8)	52,633 (65.1)
Female	1,186 (32.0)	11,780 (32.0)	5,912 (33.3)	28,182 (34.9)
Smoking status				
Smoker	1,673(45.1)	7,638(20.7)		
Ex-smoker	647(17.5)	6,589(17.9)		
Never smoked	791(21.3)	13,231(35.9)		
No available data	595(16.1)	9,396(25.5)		
Disease stage[a]				
Compensated	1,859 (50.2)	-	12,484 (70.2)	
Decompensated	1,847 (49.8)	-	5,295 (29.8)	
Charlson comorbidity score (%)				
0	2,310 (62.3)	34,262 (92.7)	11,276 (63.4)	76,403 (94.5)
1	793 (21.4)	1,358 (3.7)	3,043 (17.1)	2,347 (2.9)
2	603 (16.3)	1,234 (3.4)	3,460 (19.5)	2,065 (2.6)
Evidence of osteoporosis				
Diagnostic code +/- bisphosphonate prescription	234(6.3)	1133(3.1)	547 (3.1)	1,366 (1.7)
Previous densitometry scan	3(0.01)	6(0.16)	16(0.09)	30(0.04)
Other cirrhosis aetiology[b]				
Autoimmune disease	30(0.8)	-	44 (0.25)	-
Metabolic disease	157(4.2)	-	303 (1.7)	-
Viral hepatitis	243(6.6)	-	627 (3.5)	-
Only alcohol-related	3,290(88.8)	-	16,824 (94.6)	-

[a]Baveno classification [b]patients can have more than one other aetiology in addition to alcohol

Table 2: Hip fracture rates and hazard ratios (HR) for alcoholic cirrhosis patients and population controls in the Danish and UK sample according to sub-groups defined by age, gender, and decompensation status with 95% confidence intervals

	English Cirrhosis patients				*Danish Cirrhosis patients*			
	No. of hip fracture events	**Person years**	**Rate per 1,000 person years**	**Adjusted HR[1] (95% CI)**	**No. of hip fracture events**	**Person-years**	**Rate per 1,000 person years**	**Adjusted HR[1] (95% CI)**
Overall	108	9,483	11.4 [9.4 - 13.8]	5.5[4.3 - 6.9]	977	61,122	16.0[15.0, 17.0]	8.5[7.8–9.3]
Min-44	14	1,822	7.7 [4.6 - 12.9]	17.9 [7.8 - 40.8]	77	10,546	7.3 [5.8–9.1]	16.4 [11.4–23.6]
45–54	31	3,099	10.0 [7.0 - 14.2]	14.7[8.6 - 24.9]	297	21,712	13.7 [12.2–15.3]	13.1 [10.9–15.7]
55–64	33	2,958	11.2[7.9 - 15.7]	6.2[3.9 - 9.5]	363	20,360	17.8 [16.0–19.8]	9.8 [8.4–11.4]
65–74	19	1,226	15.5 [9.9 - 24.3]	3.2[1.9 - 5.4]	193	7361	26.2 [22.7–30.2]	5.9 [4.9–7.1]
75+	11	378	29.1[16.1 - 52.6]	2.1[1.1 - 2.2]	47	1,143	41.1 [30.2–54.7]	3.0 [2.1–4.2]
Men	59	6,259	9.4 [7.3 - 12.2]	4.4[3.2 - 6.1]	571	38,638	14.8 [13.7–16.0]	9.0 [8.0–10.1]
Women	49	3,224	15.2 [11.5 - 20.1]	7.1[5.0 - 9.9]	406	22,484	18.1 [16.3–19.9]	7.9 [6.9–9.0]
Compensated	53	5,621	9.4 [7.2 -12.3]	-	665	42,480	15.7 [14.5–16.9]	-
Decompensated	55	3,862	14.2 [10.9 -18.5]	-	312	18,642	16.7 [14.9–18.7]	-
Decompensated and/or HE[2]	61	4,367	13.9[10.9-17.9]	-	418	24,382	17.1 [15.5–18.9]	-
Evidence of osteoporosis	26	837	31.0[21.1-45.6]	-	44	1,245	35.3 [25.7–47.4]	-
None	82	8,646	9.5[7.6-11.8]	-	503	59,877	15.6 [14.6–16.6]	-

[1] HR adjusted for age, sex and comorbidity for cirrhosis patients vs. population controls

[2] *HE-Hepatic Encephalopathy, (includes alcoholic encephalopathy and Wernicke's syndrome)*

Table 3: Cirrhosis patients and population controls' 5-year risk of a hip fracture by age group at inclusion, gender and compensation status with 95% confidence intervals (CI's)

	England		Denmark	
	Cirrhosis patients	**Population controls**	**Cirrhosis patients**	**Population controls**
Overall	2.9[2.3-3.6]	0.8[0.7-0.9]	4.6 (4.3–5.0]	0.9 [0.8–0.9]
Age group				
Min-44	2.2 [0.9 - 4.4]	0.2 [0.1 - 0.5]	2.5 [1.9–3.3]	0.1 [0.1–0.2]
45–54	2.3 [1.4 - 3.4]	0.4 [0.3 - 0.6]	4.3 [3.8–4.9]	0.4 [0.3–0.5]
55–64	2.7 [1.8 - 3.9]	0.7 [0.6 - 0.9]	5.0 [4.4–5.6]	0.7 [0.6–0.8]
65–74	2.0 [1.1 - 3.2]	1.2 [1.1 - 3.1]	5.9 [5.1–6.8]	1.6 [1.4–1.6]
75–	3.8 [1.9 - 6.7]	2.6 [2.1 - 3.1]	5.9 [4.3–8.0]	5.5 [4.7–6.5]
Sex				
Male	2.4 [1.8 - 3.3]	0.8 [0.7 - 1.0]	4.2 [3.9–4.6]	0.7 [0.7–0.8]
Female	4.3 [3.1 - 5.8]	1.2 [1.0 - 1.6]	5.5 [4.9–6.1]	1.1 [1.0–1.2]
Disease severity				
Compensated	3.1 [2.3 - 4.1]	-	4.7 [4.3–5.1]	-
Decompensated	3.1 [2.3 - 4.2]	-	4.6 [4.0–5.2]	-

Table 4: Alcoholic cirrhosis patients and population controls' 30-day mortality risk (%) after a hip fracture with 95% confidence intervals (CI's)

	Alcholic cirrhosis patients			Population controls			Age adjusted Mortality risk ratio (95% CI)
	No. of deaths	**No at risk**	**Mortality risk**	**No of deaths**	**No. at risk**	**Mortality risk**	
English cohort	12	108	11.1[6.9-19.8]	19	377	5.0[3.4-8.2]	2.8 (1.9-3.9)
Danish cohort	98	977	10.0 [8.3–12.1]	1,411	100	6.6 [5.5–8.0]	2.0 (1.5-2.7)