Original research

Mortality in biopsy-proven alcohol-related liver disease: a population-based nationwide cohort study of 3453 patients

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ABSTRACT

Objective Patients with alcohol-related liver disease (ALD) are at increased risk of death, but studies have rarely investigated the significance of histological severity or estimated relative risks compared with a general population. We examined mortality in a nationwide cohort of biopsy-proven ALD.

Design Population-based cohort study in Sweden comparing 3453 individuals with an International Classification of Disease (ICD) code for ALD and a liver biopsy from 1969 to 2017 with 16 535 matched general population individuals. Swedish national registers were used to ascertain overall and disease-specific mortality, starting follow-up at the latest of first ICD diagnosis or liver biopsy plus 3 months. Cox regression adjusted for relevant confounders was used to estimate HRs in ALD and histopathological subgroups.

Results Median age at diagnosis was 58 years, 65% were men and 52% had cirrhosis at baseline. Five-year cumulative mortality was 40.9% in patients with ALD compared with 5.8% in reference individuals. The risk for overall mortality was significantly increased (adjusted HR (aHR)=4.70, 95% CI 4.35 to 5.08). The risk of liver-related death was particularly high (43% of all deaths, aHR=167.6, 95% CI 101.7 to 276.3). Mortality was significantly increased also in patients with ALD without cirrhosis and was highest in the first year after baseline but persisted after ≥10 years of follow-up (aHR=2.74, 95% CI 2.37 to 3.16).

Conclusion Individuals with biopsy-proven ALD have a near fivefold increased risk of death compared with the general population. Individuals with ALD without cirrhosis were also at increased risk of death, reaffirming the need to increase vigilance in the management of these individuals.

Significance of this study

What is already known on this subject?

- Patients with alcohol-related liver disease (ALD) have a high mortality, but comparisons against healthy controls is lacking.
- Mortality in histological subgroups of patients with ALD is also lacking.

What are the new findings?

- In a population-based study of all Swedish individuals with ALD and a liver biopsy, overall mortality was near fivefold as high as general population reference individuals.
- The highest risk was found for liver-related mortality and in patients with cirrhosis. However, also non-liver mortality was significantly higher than in reference individuals and in patients without cirrhosis.

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

- Results can be used to inform patients on precise risk estimates for disease-specific mortality.
- Clinicians should be aware of the increased risk also in patients previously thought to have a benign course of disease.

INTRODUCTION

Alcohol-related liver disease (ALD) is the leading cause of cirrhosis, accounting for about 50% of all cases of liver-related mortality worldwide.[1 2] The gold standard for diagnosing and staging ALD is liver biopsy.[3] Before decompensated liver disease occurs, fibrosis stage appears to be the best predictor of liver-related and overall survival, but because three of four patients ith ALD present with decompensated disease,[4] little is known about mortality in early ALD. Most studies are either population based without histological characterisation or originate from smaller cohorts, usually prone to selection bias with limited follow-up time and ascertainment of outcomes.[5] Recently, a systematic review and meta-analysis of 37 studies on the natural history of biopsy-proven ALD was published, presenting mortality outcomes from 23 studies with 2753 patients.[6] The authors found an increased mortality across all subtypes of ALD, but provided incomplete evidence on disease-specific mortality, as only 39% of the 240 fatal events could be defined as either liver related or non-liver related. Furthermore, in that study the non-liver-related causes of death were not possible to investigate in detail because of missing data.[6] A recent population-based study on US data showed that liver-related deaths in ALD accounted for >80% of overall mortality, but the definition of ALD

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was solely based on administrative coding without subgrouping across histopathological subgroups.[7] Finally, most studies have not compared individuals with ALD with a reference population free of ALD, which is vital in order to make correct inferences and recommendations, and when communicating the risk of ALD with patients and policy-makers.

To our knowledge, there are no population-based cohort studies on liver-related and non-liver-related mortality in biopsy-proven ALD compared with general population reference individuals, and in which the impact of underlying histopathology has been explored. Indeed, the most recent guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver on ALD do not list any studies in which mortality is reported directly comparing patients with ALD with a general population comparison group.[8 9]

We, therefore, examined the risk of mortality in more than 3000 patients with biopsy-proven ALD diagnosed between 1969 and 2017 in Sweden.[10] Our primary aim was to examine long-term mortality in biopsy-verified ALD compared with matched reference individuals in order to make inferences of mortality in biopsy-verified ALD compared with the general population. A secondary aim was to explore whether underlying liver histopathology impacts mortality.

MATERIAL AND METHODS

This was a national, population-based cohort study. We used the Epidemiology Strengthened by Histopathology Reports in Sweden cohort to identify all patients in Sweden with an ALD diagnosis. A detailed cohort description is available elsewhere.[10] Briefly, between 2015 and 2017, all pathology departments in Sweden (n=28) were contacted and asked to procure histopathology record data from the liver for biopsies performed between 1969 and 2017. For each individual, local IT personnel retrieved data on the date of histopathology and morphology, defined according to SnoMed codes[11] assigned by the reporting pathologist at the time of the original reading of the slide. The SnoMed system was applied to classify biopsies during the entire follow-up period in Sweden. Individuals with ALD and with histopathology data were matched with up to five reference individuals from the general population on age, sex, county of residence and calendar year of biopsy in the ALD patient. Of note, there was no liver biopsies performed in the reference individuals. Data on the patient's personal identity number (PIN), unique to all Swedish residents, were also obtained.[12] The PIN allowed linkages to Swedish National Healthcare Registers. Briefly, the registers contain International Classification of Disease (ICD) codes of hospitalisations, causes of death and since 2001 hospital-based outpatient visits.[12–14] The Swedish National Patient Register has a positive predictive value (PPV) of 85%–95% for most diagnoses. This register was used to obtain data on comorbidities but also partly to define ALD.[13]

Study population

We included patients with a liver biopsy and ALD defined according to ICD codes (ICD-10: K70x, ICD-9: 571.0–3, ICD-8: 57 100 and 57 101) in the National Patient Register starting in 1969 when ICD-8 was introduced in Sweden. We are unaware of any validation study of ALD, but an earlier validation of ICD codes for chronic liver disease in the registers showed a PPV of 85%–88%.[13]

To reduce the risk for immortal time bias, which is common in studies of survival outcome, start of follow-up (index date) began on the date when patients had both undergone a biopsy and received a medical diagnosis of ALD. Thus, a person could first have a liver biopsy and later receive a code for ALD and vice versa, to be defined as an exposed. Because the aim of this study was to investigate long-term mortality and because we could not ascertain whether the reason for the liver biopsy was due to suspicion of ALD or for other concurrent diseases (such as part of a cancer evaluation in patients with ALD or investigating patients with terminal disease), we chose to start follow-up 3 months after the index date, excluding individuals who died during that period.

A priori, we defined six histopathological subgroups based on the liver biopsy. However, because one of the predefined subgroups ('alcoholic hepatitis') was small (n=24), it was due to a lack of power for any outcome combined with the 'fibrosis' subgroup into 'fibrosis or steatohepatitis' leaving five subgroups for the remaining analyses (normal liver, simple steatosis, fibrosis or steatohepatitis, cirrhosis and other). The definitions of these subgroups, based on ICD and SnoMed coding, are presented in the online supplementary appendix. Of note, the 'normal liver' group still had an ICD-code for ALD, but the histopathological findings were classified as normal.

We excluded all individuals with any other liver disease (definitions in online supplementary etable 1) at or before the index date. A flow chart of participant inclusion/exclusion is presented in figure 1).

Variables at baseline

Parameters collected at the index date included age, sex, highest achieved education (≤9, 10–12, >12 years) and country of birth (Nordic vs other). Because the length of education was available per year only from 1990,[15] we used the highest attained level of education in the individual registered after the index date for those starting follow-up before 1990. For individuals with no registered education, we used the highest attained education of the parents (if available) as a proxy. We also collected data on relevant comorbidities at or before baseline, including cardiovascular disease (CVD), diabetes and extrahepatic malignancies. The definition of these comorbidities is shown in online supplementary etable 2.

Follow-up and mortality outcomes

Follow-up time was determined through the Total Population Register[16] and Cause of Death Register.[14] Briefly, the Total Population Register contains demographic data (eg, emigration and date of death) on the Swedish population. Since 1952, the Cause of Death Register contains data on causes of mortality, as reported by the responsible physician at the time of an individual's death. It is legally mandatory for physicians to report to this register. Coverage for incident mortality is >99%.[14]

Follow-up was until either death, liver transplantation, emigration or end of follow-up (31 December 2017 for overall mortality recorded from the Total Population Register and 31 December 2016 for cause-specific mortality as the Cause of Death Register has a lag period), whichever occurred first. Our main outcome measure was overall mortality. However, because liver transplantation significantly changes the natural history of all chronic liver diseases,[17] we defined mortality as either death or liver transplantation. Secondary outcomes were cause-specific mortality (defined as either liver related, including hepatocellular carcinoma (HCC) or liver transplantation, malignancies other than HCC, CVD and other causes of death). We used

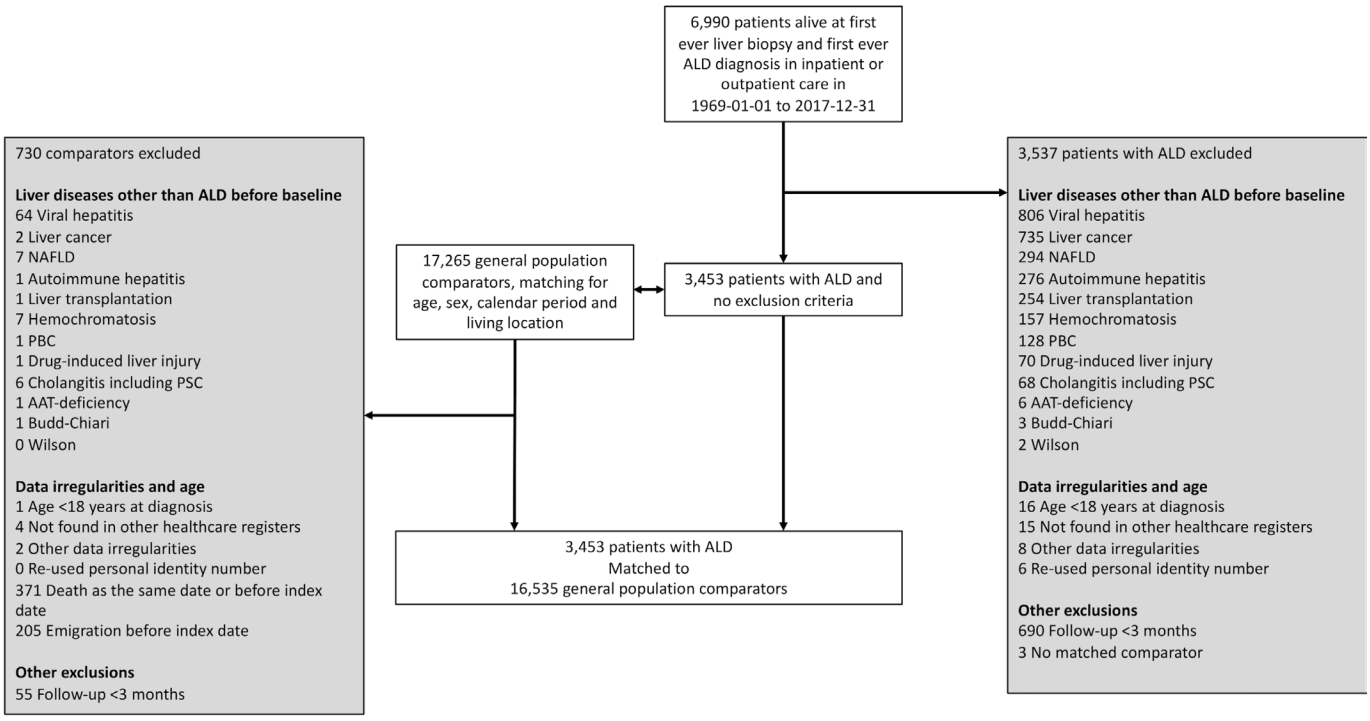

Figure 1 Flow chart of participant inclusion. AAT, alpha-1-antitrypsin; ALD, alcohol-related liver disease; NAFLD, non-alcoholic fatty liver disease; pBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

relevant ICD codes in the Cause of Death Register[14] to define outcomes (online supplementary etable 3).

Because heavy drinking is a major predictor of adverse outcomes in ALD,[5] we investigated the importance of heavy drinking at any time during the study period. We used an alcohol use disorder (AUD) diagnosis as a proxy for heavy drinking (coding definitions in online supplementary etable 3) and compared mortality in patients with ALD that received an AUD diagnosis at any time with those that did not.

Sensitivity analyses

A number of sensitivity analyses were performed.

First, we restricted our reference population to individuals without a record of AUD or ALD prior to study entry and censored reference individuals who were diagnosed with AUD or ALD after baseline, using the model not additionally adjusted for AUD. This was done to get better inference on the risk of mortality for patients with ALD compared with a reference population without persons diagnosed with ALD/AUD.

Second, we also examined mortality in ALD adjusting for the number of last-year hospital admissions that we unrelated to liver disease.

Third, smoking could be a confounder that we could not measure directly. Instead, we adjusted our final model for having a diagnosis of chronic obstructive pulmonary disease (COPD) as a proxy for heavy smoking. This analysis was restricted to persons with a first diagnosis of COPD after the age of 40 years and analysed as a time-dependent covariate (see online supplementary appendix for relevant ICD codes). Using an age-cut at 40 years for COPD is common in Swedish register-based research.[18] Fourth, we also included the 690 individuals with a follow-up <3 months in the analysis.

Fifth, we also considered a stricter definition of cirrhosis, requiring a SnoMed code for cirrhosis and an ICD-code for cirrhosis within 3 months of each other.

As there might be cases with non-alcoholic fatty liver disease (NAFLD) wrongly classified as ALD, we excluded individuals with a medical diagnosis of NAFLD at baseline and censored follow-up at first NAFLD diagnosis after baseline to further reduce the risk of misclassification.

We also calculated an 'e-value'.[19] In brief, this is a method to estimate the effect an unmeasured confounder, such as smoking, would need to have to completely obviate the findings of an association.

Statistical analysis

We first calculated mortality rates per 1000 person-years of follow-up. We used Cox regression to estimate adjusted HRs (aHRs) and 95% CIs for total and cause-specific mortality. The cumulative incidences for both main and secondary outcomes are presented using Kaplan-Meier curves.

We calculated aHRs using three models: model 1 was conditioned on matching factors (age, sex, county of residence, calendar year of biopsy); in this model no additional adjustmet was performed. In model 2, we further adjusted for education and baseline comorbidities (CVD, extrahepatic cancer, diabetes). Model 3 included AUD as a time-dependent covariate. Missing indicator was used as a category for analyses including education in the regression model. Analyses were performed using SAS statistical software V. 9.4 and STATA V.15.1. Statistical significance was set to $p<0.05$.

Ethical considerations

This is a register-based study using anonymized data and no patient contact, the Ethics Review Board waived informed consent.[20]

Patient and public involvement

No patients or members of the public were involved in the development of research questions, the design of the study or

Table 1 Baseline characteristics of the ALD population and matched reference individuals

Characteristic	Reference population	ALD population					
	Overall (n=16 535)	Full ALD population (n=3 453)	Normal liver (n=91)	Steatosis (n=504)	Fibrosis (n=482)	Cirrhosis (n=1780)	Other (n=596)
Sex, n (%)							
Women	5898 (35.7)	1219 (35.3)	41 (45.1)	179 (35.5)	175 (36.3)	614 (34.5)	210 (35.2)
Men	10 637 (64.3)	2 234 (64.7)	50 (54.9)	325 (64.5)	307 (63.7)	1 166 (65.5)	386 (64.8)
Age							
Mean (SD)	56.8 (11.4)	57.1 (11.5)	54.4 (13.5)	53.7 (11.7)	56.4 (10.8)	58.2 (10.6)	57.5 (13.1)
Median (IQR)	57.9 (49.5–64.9)	58.2 (49.8–65.2)	55.3 (44.8–65.1)	54.4 (45.1–63.0)	57.7 (49.7–63.5)	59.0 (51.4–65.6)	58.6 (48.6–66.8)
Range, minimum-maximum	18.2–88.6	18.0–88.3	22.0–81.8	19.0–81.1	22.1–82.5	18.0–84.5	18.6–88.3
Categories, n (%)							
18 to <40 years	1416 (8.6)	288 (8.3)	16 (17.6)	63 (12.5)	38 (7.9)	104 (5.8)	67 (11.2)
40 to <60 years	8224 (49.7)	1690 (48.9)	42 (46.2)	280 (55.6)	254 (52.7)	851 (47.8)	263 (44.1)
≥60 years	6895 (41.7)	1475 (42.7)	33 (36.3)	161 (31.9)	190 (39.4)	825 (46.3)	266 (44.6)
Country of birth, n (%)							
Nordic country	15 197 (91.9)	3211 (93.0)	87 (95.6)	461 (91.5)	438 (90.9)	1670 (93.8)	555 (93.1)
Other	1336 (8.1)	242 (7.0)	4 (4.4)	43 (8.5)	44 (9.1)	110 (6.2)	41 (6.9)
Missing	2 (0.0)	0	0	0	0	0	0
Level of education, n (%)							
≤9 years	5812 (35.1)	1270 (36.8)	25 (27.5)	197 (39.1)	178 (36.9)	637 (35.8)	233 (39.1)
10–12 years	6403 (38.7)	1426 (41.3)	43 (47.3)	218 (43.3)	205 (42.5)	712 (40.0)	248 (41.6)
>12 years	3836 (23.2)	476 (13.8)	17 (18.7)	67 (13.3)	79 (16.4)	243 (13.7)	70 (11.7)
Missing	484 (2.9)	281 (8.1)	6 (6.6)	22 (4.4)	20 (4.1)	188 (10.6)	45 (7.6)
Level of education using highest level of education in parents when missing, n (%)							
≤9 years	5819 (35.2)	1270 (36.8)	25 (27.5)	197 (39.1)	178 (36.9)	637 (35.8)	233 (39.1)
10–12 years	6413 (38.8)	1427 (41.3)	44 (48.4)	218 (43.3)	205 (42.5)	712 (40.0)	248 (41.6)
>12 years	3840 (23.2)	476 (13.8)	17 (18.7)	67 (13.3)	79 (16.4)	243 (13.7)	70 (11.7)
Missing	463 (2.8)	280 (8.1)	5 (5.5)	22 (4.4)	20 (4.1)	188 (10.6)	45 (7.6)
Start year of follow-up							
1969–1980	484 (2.9)	98 (2.8)	4 (4.4)	7 (1.4)	2 (0.4)	81 (4.6)	4 (0.7)
1981–1990	2990 (18.1)	615 (17.8)	25 (27.5)	110 (21.8)	56 (11.6)	307 (17.2)	117 (19.6)
1991–2000	5772 (34.9)	1 197 (34.7)	30 (33.0)	214 (42.5)	163 (33.8)	534 (30.0)	256 (43.0)
2001–2010	5379 (32.5)	1 133 (32.8)	27 (29.7)	131 (26.0)	183 (38.0)	616 (34.6)	176 (29.5)
2011–2017	1910 (11.6)	410 (11.9)	5 (5.5)	42 (8.3)	78 (16.2)	242 (13.6)	43 (7.2)
Disease history ever before start of follow-up, n (%)							
CVD	1217 (7.4)	359 (10.4)	7 (7.7)	54 (10.7)	44 (9.1)	180 (10.1)	74 (12.4)
Extrahepatic cancer	1450 (8.8)	585 (16.9)	22 (24.2)	61 (12.1)	94 (19.5)	279 (15.7)	129 (21.6)
Diabetes	554 (3.4)	651 (18.9)	10 (11.0)	68 (13.5)	87 (18.0)	373 (21.0)	113 (19.0)
AUD	480 (2.9)	1 215 (35.2)	33 (36.3)	164 (32.5)	167 (34.6)	624 (35.1)	227 (38.1)
Time in years between first ALD diagnosis and biopsy							
Mean (SD)		2.5 (4.7)	4.8 (7.2)	3.1 (5.4)	2.7 (4.8)	1.7 (3.5)	3.9 (6.1)
Median (IQR)		0.3 (0.0–2.9)	0.6 (0.0–6.3)	0.2 (0.0–4.3)	0.3 (0.0–3.1)	0.2 (0.0–1.7)	0.8 (0.0–5.6)
Range, minimum-maximum		0.0–32.9	0.0–28.0	0.0–29.3	0.0–31.3	0.0–32.9	0.0–32.0

ALD, alcohol-related liver disease; AUD, alcohol use disorder; CVD, cardiovascular disease.

selecting our outcome measure. No patient was asked to advise on interpretation or writing up of results. We plan to disseminate the results of our research to the relevant patient community.

RESULTS

We identified 3453 adults with ALD and 16 535 matched reference individuals from the general population in the final analyses (flowchart in figure 1). The median age in the ALD population at baseline was 58.2 years (64.7% were men). On a subgroup level, 91 individuals (2.6%) had a normal liver on biopsy, 504 (14.6%) simple steatosis, 482 (14.0%) fibrosis or steatohepatitis, 1780 (51.5%) cirrhosis and 596 (17.3%) had other findings. The most common findings in the "other" subgroup were unspecified or chronic inflammation, not meeting the criteria for alcoholic hepatitis, or too little material for a reading. The median time between an ICD-based ALD code and the liver biopsy was 0.3 years (IQR 0.0–2.9 years). Of the 3453 adults with ALD, 35.2% had had an ICD code corresponding to AUD before or at the index date. Participant characteristics at baseline appear in table 1.

Table 2 Outcome events during follow-up in patients with ALD and matched reference individuals

Characteristic	Overall	Normal liver	Steatosis	Fibrosis	Cirrhosis	Other
ALD population						
N	3453	91	504	482	1780	596
Inpatient or outpatient visits related to AUD during follow-up, n (%)	1213 (35.1)	29 (31.9)	225 (44.6)	173 (35.9)	609 (34.2)	177 (29.7)
Liver transplantation during follow-up, n (%)	78 (2.3)	3 (3.3)	5 (1.0)	8 (1.7)	52 (2.9)	10 (1.7)
Follow-up (years)						
Mean (SD)	8.2 (7.6)	11.0 (8.8)	11.6 (8.9)	8.2 (6.9)	6.9 (7.0)	8.5 (7.7)
Median (IQR)	5.7 (2.1–12.3)	10.1 (2.6–16.8)	9.8 (3.6–18.7)	6.2 (2.9–12.1)	4.6 (1.7–9.9)	5.9 (1.9–14.2)
Range, minimum-maximum	0.3–47.1	0.3–30.5	0.3–35.6	0.3–30.9	0.3–47.1	0.3–37.2
Deaths or liver transplantation						
Within 1 year after index date	436 (12.6%)	12 (13.2%)	26 (5.2%)	41 (8.5%)	263 (14.8%)	94 (15.8%)
Within 5 years after index date	1413 (40.9%)	25 (27.5%)	137 (27.2%)	165 (34.2%)	831 (46.7%)	255 (42.8%)
Within 10 years after index date	1979 (57.3%)	35 (38.5%)	211 (41.9%)	245 (50.8%)	1 136 (63.8%)	352 (59.1%)
All follow-up time	2557 (74.1%)	57 (62.6%)	314 (62.3%)	316 (65.6%)	1427 (80.2%)	443 (74.3%)
Incidence rate by 1000 PY	90.9 (87.3–94.4)	56.7 (42.0–71.4)	53.5 (47.6–59.5)	80.0 (71.2–88.8)	116.2 (110.2–122.3)	87.8 (79.6–96.0)
Reference population						
N	16 535	427	2418	286	8572	2832
Inpatient or outpatient visits related to AUD during follow-up, n (%)	598 (3.6)	16 (3.7)	87 (3.6)	79 (3.5)	303 (3.5)	113 (4.0)
Liver transplantation during follow-up, n (%)	1 (0.0)	0	0	0	1 (0.0)	0
Follow-up (years)						
Mean (SD)	15.3 (8.8)	17.1 (8.3)	17.0 (8.4)	14.2 (7.9)	14.9 (9.2)	15.8 (8.3)
Median (IQR)	14.7 (8.2–21.4)	16.8 (10.9–23.2)	17.1 (10.6–23.7)	14.1 (7.7–20.3)	13.9 (7.5–20.7)	15.7 (9.3–22.2)
Range, minimum-maximum	0.3–48.0	0.3–38.9	0.3–48.0	0.3–42.2	0.3–47.3	0.3–43.0
Deaths or liver transplantation						
Within 1 year after index date	147 (0.9%)	5 (1.2%)	12 (0.5%)	10 (0.4%)	92 (1.1%)	28 (1.0%)
Within 5 years after index date	954 (5.8%)	21 (4.9%)	87 (3.6%)	109 (4.8%)	546 (6.4%)	191 (6.7%)
Within 10 years after index date	2027 (12.3%)	46 (10.8%)	226 (9.3%)	215 (9.4%)	1 125 (13.1%)	415 (14.7%)
All follow-up time	5 107 (30.9%)	136 (31.9%)	670 (27.7%)	527 (23.1%)	2 759 (32.2%)	1 015 (35.8%)
Incidence rate by 1000 PY	20.1 (19.6–20.7)	18.6 (15.5–21.7)	16.3 (15.0–17.5)	16.2 (14.8–17.6)	21.6 (20.8–22.4)	22.7 (21.3–24.1)

ALD, alcohol-related liver disease; AUD, alcohol use disorder; PY, person-years.

Overall mortality

Median follow-up was 5.7 years (IQR 2.1–12.3, range 0.3–47.1) in individuals with ALD and 14.7 years (IQR 8.2–21.4, range 0.3–48.0) in reference individuals. A total of 2557 (74%) individuals with ALD and 5107 (31%) reference individuals died or underwent liver transplantation during follow-up, of which 78 with ALD (2.3%) and 1 reference individual (<0.1%) were transplanted. Mortality data are summarised in table 2. During the first year of follow-up, in those surviving for ≥3 months, mortality was 12.6% in individuals with ALD and 0.9% in reference individuals. This figure differed between subgroups of individuals with ALD (for simple steatosis, 5.2% vs 0.5% in matched reference individuals and for cirrhosis, 14.8% vs 1.1%). During the first 5 years of follow-up, overall mortality was 40.9% (n=1413) in the ALD population compared with 5.8% (n=954) in the reference population.

The overall mortality rate during the full study period was 90.9 (95% CI 87.3 to 94.4) per 1000 person-years in individuals with ALD compared with 20.1 (19.6 to 20.7) in reference individuals, corresponding to an aHR of 4.70 (95% CI 4.35 to 5.08), with the highest aHRs observed in the first year after baseline (aHR=13.00, 95% CI 9.96 to 16.97). Overall mortality was similar in men (aHR=4.67) and women (aHR=4.79). Mortality risk increased across histopathological subgroups, with the highest risk observed in individuals with cirrhosis (aHR=6.07, 95% CI 5.43 to 6.77) and the lowest in individuals with steatosis (aHR=2.72, 95% CI 2.20 to 3.36) as compared against their respective reference individuals.

Overall mortality is further described in table 3 and figure 2 (all individuals with ALD and reference individuals) and for subgroups in online supplementary etable 4a–e.

Disease-specific mortality

Liver disease was the most common cause of death, accounting for 43.3% of all deaths in the ALD population, which can be compared with 1.5% in the reference population. These rates corresponded to an aHR of 167.6 (95% CI 101.7 to 276.3). The risk of liver-related mortality was significantly increased in all ALD subgroups compared with their respective reference individuals, except for in the normal liver subgroup (online supplementary etable 5a–e). A substantially increased risk of liver-related death was noted soon after diagnosis while the relative risk plateaued after 5–10 years but remained significantly increased even after ≥10 years of follow-up (aHR=2.74, 95% CI 2.37 to 3.16).

The risk of non-liver-related causes of death also increased. The mortality aHR for CVD was 2.20 in ALD (95% CI 1.87 to 2.59) (data in table 4 for the full ALD cohort and stratified for subgroups inonline supplementary etable 5a–e). Individuals

Table 3 Risk of overall mortality and by histopathological subgroups in all patients with ALD and matched general population comparators

Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95% CI)	HR† (95% CI)	HR†* (95% CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators			
Overall	3453 (100)	16 535 (100)	2557 (74.1)	5107 (30.9)	90.9 (87.3 to 94.4)	20.1 (19.6 to 20.7)	7.53 (7.06 to 8.04)	6.45 (6.02 to 6.91)	4.70 (4.35 to 5.08)
Follow-up									
3 months to <1 year	3453 (100)	16 535 (100)	436 (12.6)	147 (0.9)	133.3 (120.8 to 145.8)	8.9 (7.5– to 10.4)	15.63 (12.85 to 19.01)	15.81 (12.45 to 20.08)	13.00 (9.96 to 16.97)
1 to <5 years	3006 (87.1)	16 329 (98.8)	977 (32.5)	807 (4.9)	104.2 (97.7 to 110.7)	13.1 (12.2 to 14.0)	9.55 (8.55 to 10.67)	7.88 (6.99 to 8.89)	5.99 (5.22 to 6.86)
5 to <10 years	1856 (53.8)	14 339 (86.7)	566 (30.5)	1073 (7.5)	79.0 (72.5 to 85.5)	16.7 (15.7 to 17.7)	6.37 (5.59 to 7.27)	5.69 (4.95 to 6.54)	3.70 (3.14 to 4.35)
≥10 years	1095 (31.7)	11 381 (68.8)	578 (52.8)	3080 (27.1)	69.4 (63.7 to 75.0)	27.7 (26.7 to 28.7)	4.46 (3.94 to 5.04)	4.03 (3.55 to 4.58)	2.74 (2.37 to 3.16)
≥1 year	3006 (87.1)	16 329 (98.8)	2 121 (70.6)	4960 (30.4)	85.3 (81.6 to 88.9)	20.9 (20.3 to 21.5)	6.75 (6.30 to 7.23)	5.83 (5.42 to 6.27)	4.14 (3.81 to 4.50)
Sex									
Women	1219 (35.3)	5898 (35.7)	848 (69.6)	1526 (25.9)	76.8 (71.6 to 81.9)	16.4 (15.6 to 17.2)	7.09 (6.35 to 7.91)	6.25 (5.57 to 7.02)	4.79 (4.18 to 5.50)
Men	2234 (64.7)	10 637 (64.3)	1 709 (76.5)	3581 (33.7)	100.0 (95.2 to 104.7)	22.3 (21.6 to 23.0)	7.78 (7.17 to 8.43)	6.55 (6.01 to 7.14)	4.67 (4.24 to 5.14)
Age at diagnosis									
18 to <40 years	288 (8.3)	1416 (8.6)	130 (45.1)	95 (6.7)	29.2 (24.2 to 34.2)	3.1 (2.5 to 3.7)	12.19 (8.74 to 17.00)	9.48 (6.56 to 13.70)	5.33 (3.41 to 8.34)
40 to <60 years	1690 (48.9)	8224 (49.7)	1 212 (71.7)	1835 (22.3)	77.6 (73.3 to 82.0)	12.8 (12.2 to 13.4)	9.22 (8.35 to 10.18)	7.85 (7.06 to 8.72)	5.03 (4.45 to 5.69)
≥60 years	1475 (42.7)	6895 (41.7)	1215 (82.4)	3177 (46.1)	150.4 (142.0 to 158.9)	40.0 (38.6 to 41.4)	6.07 (5.55 to 6.65)	5.23 (4.76 to 5.76)	4.32 (3.89 to 4.80)
Mortality during the first 5 years of follow-up									
1969–1980	98 (2.8)	484 (2.9)	21 (21.4)	36 (7.4)	47.8 (27.3 to 68.2)	15.5 (10.4 ot 20.5)	2.92 (1.70 to 5.04)	0.77 (0.32 to 1.87)	0.78 (0.30 to 2.00)
1981–1990	615(17.8)	2990 (18.1)	227 (36.9)	177 (5.9)	97.2 (84.5 to 109.8)	12.2 (10.4 to 14.0)	11.42 (8.97 to 14.52)	4.23 (3.00 to 5.96)	3.70 (2.46 to 5.56)
1991–2000	1197 (34.7)	5772 (34.9)	495 (41.4)	343 (5.9)	109.4 (99.7 to 119.0)	12.3 (11.0 to 13.6)	10.56 (8.99 to 12.40)	9.42 (7.94 to 11.17)	7.59 (6.29 to 9.16)
2001–2010	1133 (32.8)	5379 (32.5)	518 (45.7)	324 (6.0)	125.8 (114.9 to 136.6)	12.5 (11.1 to 13.8)	11.61 (9.86 to 13.66)	10.10 (8.49 to 12.00)	7.54 (6.17 to 9.21)
2011–2012‡	164 (4.7)	766 (4.6)	69 (42.1)	37 (4.8)	110.5 (84.4 to 136.6)	9.9 (6.7 to 13.1)	10.73 (6.94 to 16.58)	12.56 (7.57 to 20.85)	8.36 (4.75 to 14.71)
Country of birth									
Nordic	3211 (93.0)	15 197 (91.9)	2399 (74.7)	4831 (3.8%)	91.9 (88.2 to 95.6)	20.5 (19.9 to 21.1)	7.44 (6.95 to 7.97)	6.24 (5.81 to 6.72)	4.60 (4.23 to 4.99)
Other	242 (7.0)	1336 (8.1)	158 (65.3)	276 (2.7)	77.5 (65.4 to 89.6)	15.2 (13.4 to 17.0)	9.36 (4.48 to 19.57)	8.30 (3.88 to 17.74)	6.15 (2.57 to 14.71)
Education									
≤9 years	1270 (36.8)	5819 (35.2)	984 (77.5)	2519 (43.3)	87.7 (82.3 to 93.2)	27.3 (26.2 to 28.3)	6.59 (5.72 to 7.58)	5.93 (5.13 to 6.85)	4.70 (4.02 to 5.51)
10–12 years	1427 (41.3)	6413 (38.8)	1003 (70.3)	1570 (24.5)	84.6 (79.3 to 89.8)	15.8 (15.0 to 16.6)	8.95 (7.63 to 10.49)	8.04 (6.84 to 9.46)	5.40 (4.51 to 6.46)
>12 years	476 (13.8)	3840 (23.2)	296 (62.2)	654 (17.0)	73.0 (64.7 to 81.3)	11.2 (10.4 to 12.1)	13.00 (8.48 to 19.94)	12.30 (7.89 to 19.18)	8.02 (4.85 to 13.26)
Missing	280 (8.1)	463 (2.8)	274 (97.9)	364 (78.6)	270.5 (238.4 o to 302.5)	99.0 (88.8 to109.1)	2.09 (1.53 to 2.86)	1.90 (1.35 to 2.66)	1.82 (1.25 to 2.66)
Comorbidity before start of follow-up									
CVD	359 (10.4)	1217 (7.4)	294 (81.9)	626 (51.4)	148.9 (131.9 to 166.0)	53.3 (49.1 to 57.5)	4.99 (3.37 to 7.40)	4.14 (2.76 to 6.21)	3.55 (2.29 to 5.50)
Extrahepatic cancer	585 (16.9)	1450 (8.8)	464 (79.3)	561 (38.7)	130.8 (118.9 to 142.7)	32.1 (29.5 to 34.8)	4.16 (3.04 to 5.70)	3.96 (2.83 to 5.52)	3.32 (2.28 to 4.83)
Diabetes	651 (18.9)	554 (3.4)	536 (82.3)	256 (46.2)	154.3 (141.3 to 167.4)	52.3 (45.9 to 58.7)	4.90 (2.97 to 8.07)	4.66 (2.66 to 8.17)	3.50 (1.89 to 6.48)
ALD									
Biopsy after diagnosis	2078 (60.2)	10 114 (61.2)	1549 (74.5)	3200 (31.6)	84.5 (80.3 to 88.7)	19.5 (18.8 to 20.1)	7.06 (6.51 to 7.67)	6.07 (5.57 to 6.61)	4.25 (3.85 to 4.69)
Diagnosis after biopsy	1325 (38.4)	6174 (37.3)	972 (73.4)	1812 (29.3)	105.6 (99.0 to 112.3)	21.4 (20.4 to 22.4)	8.57 (7.68 to 9.57)	7.40 (6.57 to 8.33)	5.53 (4.85 to 6.31)

*Conditioned on matching set (age, sex, county of residence, calendar year of biopsy).
†Conditioned on matching set and further adjusted for education and baseline comorbidities (CVD, extrahepatic cancer, diabetes).
‡Not using data from 2013 to 2017 to allow for at least 5 years of follow-up in all individuals in this analysis.
§Conditioned on matching set and further adjusted for education, baseline comorbidities (CVD, extrahepatic cancer, diabetes) and time-dependent adjustment for AUD.
ALD, alcohol-related liver disease; CVD, cardiovascular disease; PY, person-years.

with ALD were at a 3.18-fold increased risk of death from extrahepatic malignancies, with similar risk estimates across histopathological subgroups. A similar pattern was also observed for other causes of death (online supplementary etable 5a–e). Kaplan-Meier failure curves for disease-specific mortality in the full ALD cohort are depicted in figure 3 and subgroups in online supplementary efigure 1a–e.

Impact of AUD

More than 35% of individuals with ALD had a diagnosis of AUD during the follow-up, most commonly those with steatosis (44.6% vs 3.6% of reference individuals). The median time between baseline and the first AUD event was 1.6 years (IQR 0.3–5.0) in individuals with ALD who were diagnosed with AUD. Having a diagnosis of AUD was associated with excess overall mortality across ALD subgroups, with an aHR of 1.30 (95% CI 1.21 to 1.41) in the full ALD cohort compared with individuals with ALD without an AUD diagnosis. Overall mortality associated with AUD was higher in ALD subgroups without cirrhosis (aHR=1.85, 95% CI 1.03 to 3.33) for the normal liver subgroup compared with an aHR of 1.10 (95% CI 0.99 to 1.22) in the cirrhosis subgroup. Estimates for overall mortality attributed to AUD are listed in detail in online supplementary etable 6.

Sensitivity analyses

Excluding reference individuals with an earlier record of AUD or ALD before baseline and censoring reference individuals diagnosed with AUD or ALD after baseline, the risk for mortality was somewhat higher (n.b. second model without adjustment for AUD was used; aHR=7.13, 95% CI 6.64 to 7.66) compared with the original model (aHR=6.45, 95% CI 6.02 to 6.91).

When adjusting for number of hospital admissions in the last year before study entry, the risk of mortality was slightly lower (aHR=4.28; 95% CI 3.95 to 4.64) as compared with those of the original final model (aHR=4.70, 95% CI 4.35 to 5.08. Adjusting for a diagnosis of COPD did not affect the estimates (aHR=4.62, 95% CI 4.26 to 5.00). Using a stricter definition of cirrhosis (coding for cirrhosis according to pathology and ICD within 3 months) yielded a slightly higher estimate for overall

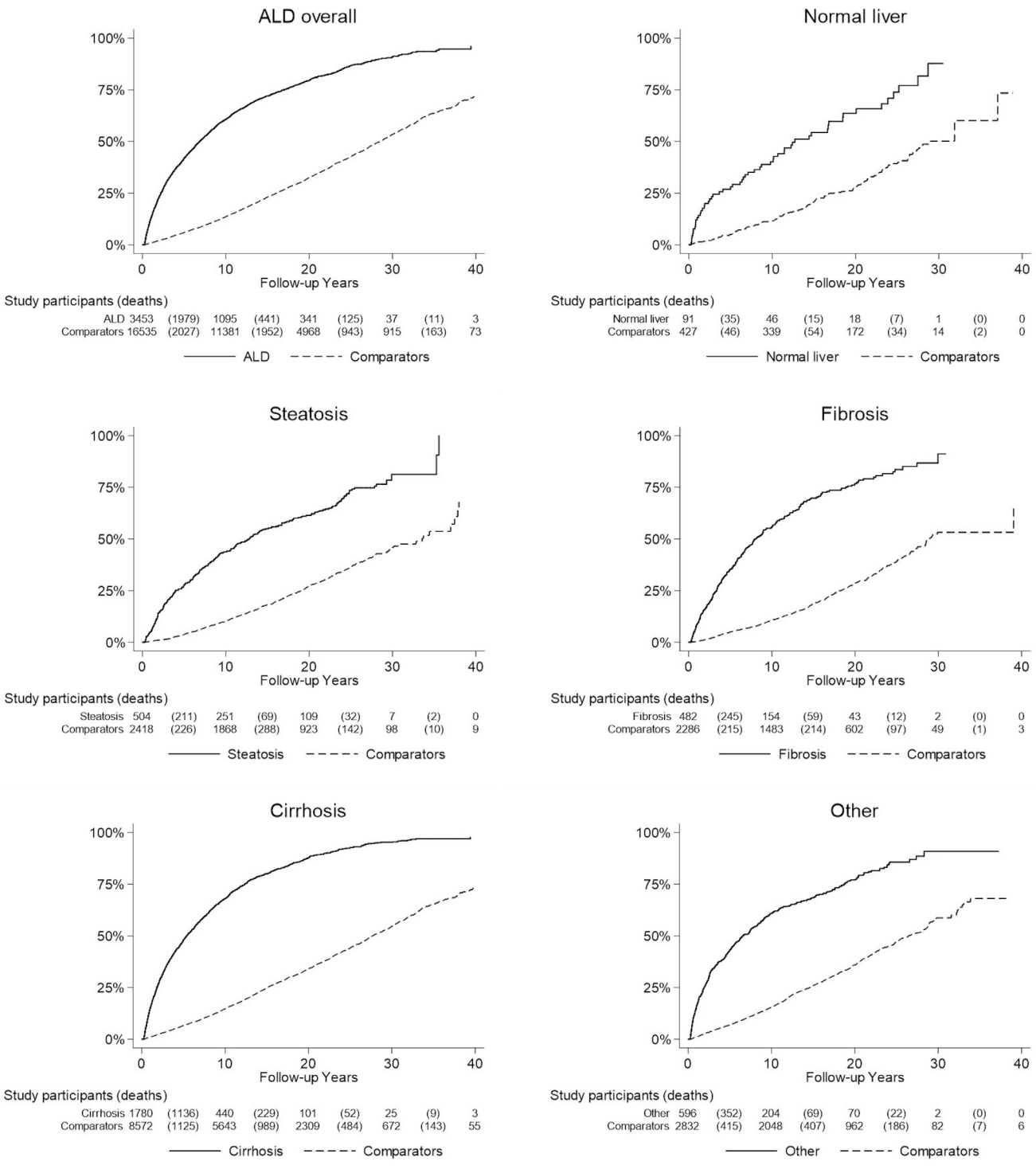

Figure 2 Kaplan-Meier failure curves of overall mortality (including liver transplantation) in patients with ALD and across histopathological subgroups compared with reference individuals. ALD, alcohol-related liver disease.

mortality (aHR=7.34, 95% CI 6.35 to 8.48) compared with aHR 6.45 in the original analysis.

When including the 690 persons with follow-up <3 months, the risk for overall mortality was slightly higher (aHR=5.95, 95% CI 5.54 to 6.39), likely an effect by including severely ill patients with ALD.

Excluding study subjects with NAFLD at or before baseline and censoring anyone diagnosed with NAFLD during the follow-up did not change the estimates (aHR=4.64, 95% CI 4.29 to 5.02).

Using the e-value approach, we found that an unmeasured confounder would have to have a magnitude of HR 8.9 to fully explain the increased mortality independent of ALD.

DISCUSSION

In this nationwide, population-based cohort study of 3453 patients with biopsy-verified ALD and 16 535 matched reference individuals from the general population, we found a 4.7

Table 4 Risk of cause-specific mortality in all patients with ALD and matched general population comparators

Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95% CI)	HR† (95% CI)	HR† (95% CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators			
Liver-specific mortality (including HCC)	3438	16 464	1043 (30.3%)	71 (0.4%)	38.3 (35.9 to 40.6)	0.3 (0.2 to 0.4)	261.24 (163.92 to 416.34)	234.35 (143.13 to 383.69)	167.59 (101.67 to 276.26)
CVD mortality	3438	16 464	413 (12.0%)	1919 (11.7%)	15.2 (13.7 to 16.6)	7.9 (7.6 to 8.3)	3.18 (2.79 to 3.63)	2.76 (2.40 to 3.18)	2.20 (1.87 to 2.59)
Death from malignancies other than HCC	3438	16 464	445 (12.9%)	1 366 (8.3%)	16.3 (14.8 to 17.8)	5.6 (5.3 to 5.9)	4.19 (3.67 to 4.79)	3.41 (2.95 to 3.95)	3.18 (2.69 to 3.76)
Other cause of death	3438	16 464	507 (14.7%)	1447 (8.8%)	18.6 (17.0 to 20.2)	6.0 (5.7 to 6.3)	5.11 (4.48 to 5.83)	4.34 (3.78 to 4.99)	2.72 (2.32 to 3.20)

The number of patients in this analysis is slightly lower than in the main analysis; this is because of a 1-year shorter follow-up period due to lag in the causes of death register.
*Conditioned on matching set (age, sex, county of residence, calendar period).
†Conditioned on matching set and further adjusted for education and baseline comorbidities (CVD, extrahepatic cancer, diabetes).
‡Conditioned on matching set and further adjusted for education, baseline comorbidities (CVD, extrahepatic cancer, diabetes), and time-dependent adjustment for AUD.
ALD, alcohol-related liver disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; PY, person-years.

times higher overall mortality and 168 times higher liver-related mortality in ALD. Patients with ALD within the full spectrum of histological lesions had high excess overall mortality, not just restricted to patients with cirrhosis. This is consistent with other population-based studies.[21] Furthermore, time-dependent analyses showed that the risk of liver-specific mortality was non-linear, with extremely high relative risks in the first year after liver biopsy, decreasing aHRs from year 1 to 10, and then stabilising at a continued, substantial elevation of aHR 2.7 after 10 years or more. We also observed excess risk of extrahepatic mortality, but with a more linear pattern over time. AUD was an important contributor to the excess overall mortality, again stressing the importance of achieving abstinence in individuals with ALD. Of note, the relative risk of overall mortality associated with AUD was highest in patients without cirrhosis at baseline, suggesting that the survival benefit of achieving abstinence may be particularly high in individuals with non-cirrhotic liver disease (fibrosis stages 1–3) but not yet stage 4 (cirrhosis).

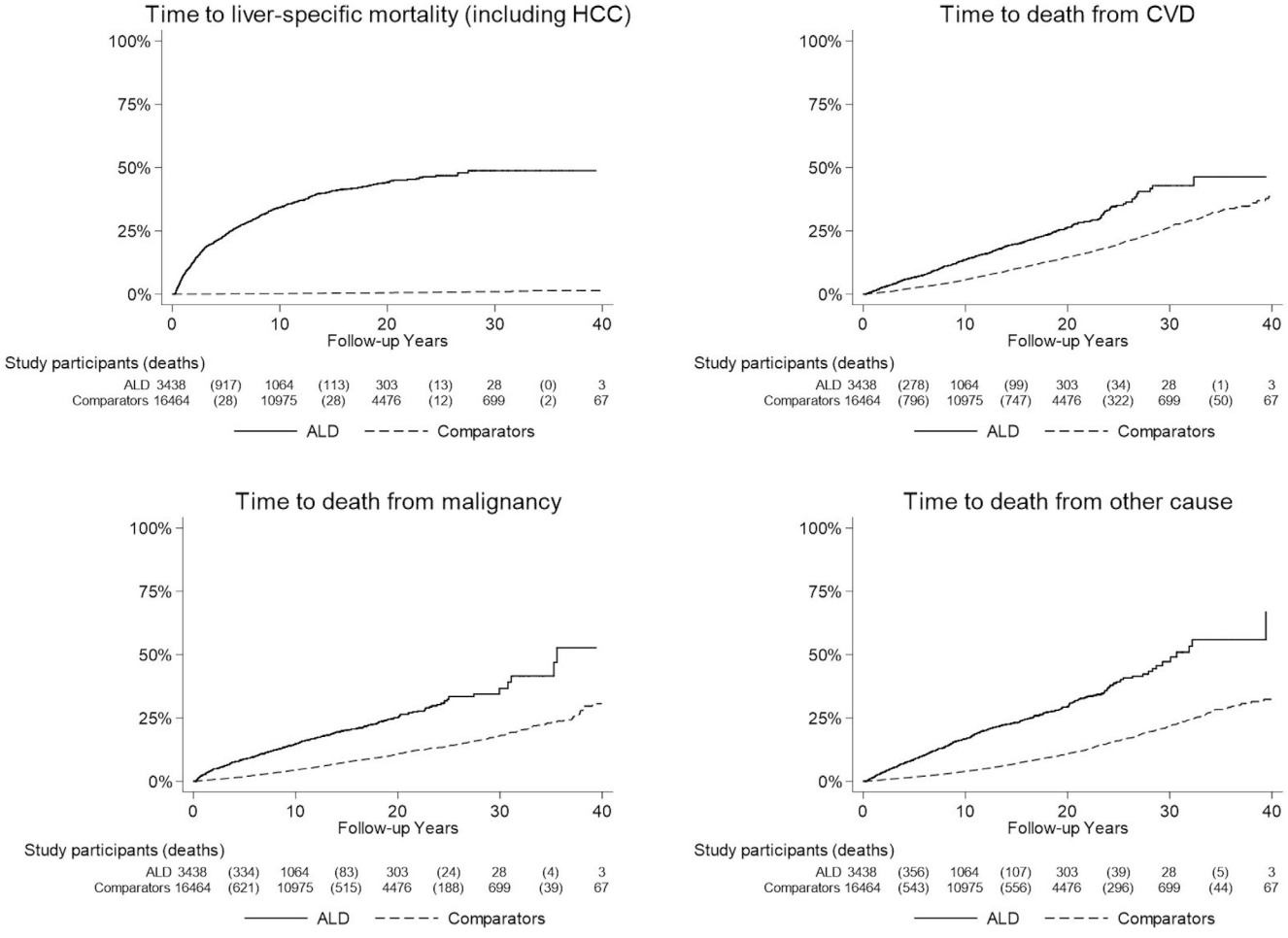

Figure 3 Kaplan-Meier failure curves of time to cause-specific mortality in all patients with ALD and matched comparators. ALD, alcohol-related liver disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma.

Our data are consistent with recent a meta-analysis.[6] In this study, annual mortality in individuals with steatosis was 6.0%, closely resembling the 5.3% incidence rate in our study. However, we found a higher overall mortality of 116 deaths per 1000 person-years in individuals with cirrhosis, as compared with 80 in the meta-analysis.[6] Our data might be more reliable as our cohort is larger than all the combined studies in the meta-analysis, and consist of population-wide, registry data, in contrast to primarily single-centre studies, that are susceptible to selection bias and lost to follow-up. Importantly, we also compared our mortality rates with those of a matched reference population, enabling the calculation of precise relative risk estimated that enable patient communication. Our estimates were robust across several post hoc sensitivity analyses.

We found excess overall mortality in individuals classified as having a 'normal' liver biopsy and in individuals with simple steatosis. This finding is important given that many hepatologists today might be prone to abstain from following up such individuals. Instead, we suggest increased vigilance for the progression of disease, especially in the shorter term. We found that AUD diagnoses were particularly common in the simple steatosis group, suggestive of continued heavy drinking as the main driver of disease progression. Our findings also indicate that clinicians should pay attention to the risk of increased mortality from extrahepatic comorbidities, which may contribute to the excess mortality in patients with ALD, regardless of liver histopathology.

Epidemiological studies are prone to inherent limitations. We were limited by low level of detail, as we had no access to clinical parameters such as the Child-Pugh or MELD score, body mass index and data on actual drinking pattern or amounts of alcohol consumed during the follow-up. However, thanks to the large sample size, our effect estimates are probably more reliable than most previous data for large groups of individuals with ALD. For persistent heavy drinking, we captured individuals diagnosed with AUD at a hospital contact, but not those who continued heavy drinking without contact to the secondary healthcare system. Accordingly, we likely underestimate the occurrence of continued heavy drinking, which threatens external validity. There might also be reference individuals with undiagnosed ALD. This would mean our estimates would be diluted towards the null, why the true effect of ALD on mortality might in fact be higher than presented here. We acknowledge the lack of data on smoking and ethnicity. By law ethnicity must not be recorded in any Swedish register. For smoking, we used a diagnosis of COPD as a proxy for heavy smoking. This did not impact on our findings. Additionally, the e-value approach indicated that an unmeasured confounder, such as smoking, would need to have a very high impact on mortality to fully nullify our findings. Finally, there were missing data on education, however, infrequent (8.1%) in patients with ALD.

We restricted our cohort to individuals with ALD with a liver biopsy to increase specificity. Liver biopsy is only performed in a minority of individuals with ALD because of its invasiveness. Moreover, the reason for performing biopsies has changed over time. For example, in the subgroup that underwent biopsy in 2011–2017, 31% had cirrhosis compared with 25% of those that underwent biopsy in 1981–1990, indicating a change in indication over time. Furthermore, a biopsy is generally performed in gastroenterology/hepatology units, which likely favours the more complicated cases. Meanwhile, the requirement of a liver biopsy is likely to increase specificity, not only because it is likely to rule out other liver diseases with non-ALD origin but also because it eliminates administrative coding error where an ALD ICD code is unrelated to the liver. Additionally, we excluded patients with other liver diseases (eg, hepatitis C) before baseline. This approach increases the specificity of our estimates but results in fewer patients for analysis. While we were able to identify 3453 individuals with ALD and liver biopsy, it has been estimated that 3%–4% of excess drinkers in a primary care population have cirrhosis[22 23] and up to 19% have elevated liver stiffness as an indicator of fibrosis.[24] In the Swedish population (>8 M adults), where an estimated 4% of adults exhibit a harmful use of alcohol,[25] this equals approximately 12 000 individuals at a given time. In consequence, we only capture a minority of the total ALD population. However, the high mortality observed in this study is comparable with that seen in non-biopsy-proven patients with ALD in Sweden.[26] Additionally, we found a significantly increased mortality, even in individuals with a normal liver on biopsy.

The SnoMed system has been used unaltered in Sweden during the entire follow-up period and we used broad categories of codes to reduce potential misclassification bias. Alcoholic hepatitis as per our predefined classification was rare and we cannot rule out that some cases of alcoholic hepatitis were categorised as 'other'. Indeed, the most common SnoMed coding in the 'other' subgroup was unspecified or chronic inflammation. While this did not meet our criteria for alcoholic hepatitis, it might be an effect of suboptimal coding. This possibility might partly explain the high excess liver-related mortality in this group.

Our results highlight the dismal prognosis in biopsy-proven ALD and are important in the recognition that individuals with 'pure' steatosis or normal liver biopsies are at an increased risk of mortality, especially immediately after diagnosis and in case of continued heavy drinking. A new finding is the particularly high risk of mortality in the short term relative to the long term. Increased risks of CVD and cancer mortality were also obvious in our data. Identifying CVD risk factors, including smoking and the metabolic syndrome, and making sure extrahepatic comorbidities are treated and followed up appropriately, should be emphasised to reduce overall mortality.[8 9]

CONCLUSION

Individuals with biopsy-proven ALD are at a 4.7-fold higher risk of death compared with reference individuals, with the highest risks soon after diagnosis and related to liver-specific death. Individuals without cirrhosis are also at substantially increased risk of death, suggesting the need for increased vigilance and watchful surveillance of patients with ALD across the histological spectrum.

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Patient consent for publication Not required.

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