ORIGINAL ARTICLE

Risk of infections and their role on subsequent mortality in biopsy-proven alcohol-related liver disease

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Abstract

Background and Aims: The risk for infection in alcohol-related liver disease (ALD) has rarely been investigated at a population level, nor if the underlying liver histopathology is associated with infection risk. We examined the rate of hospital-based infections in a nationwide cohort of biopsy-proven ALD, and the subsequent risk of death.

Methods: Population-based cohort study in Sweden comparing 4028 individuals with an international classification of disease (ICD) code for ALD and a liver biopsy from 1969 to 2017 with 19,296 matched general population individuals. Swedish national registers were used to ascertain incident infections in secondary or tertiary care and subsequent mortality until 2019. We used Cox regression, adjusted for sex, age, education, country of birth, diabetes, and number of hospitalizations in the year preceding liver biopsy date, to estimate hazard ratios (HRs) in ALD and histopathological subgroups compared to reference individuals.

Results: Median age at ALD diagnosis was 59 years, 65% were men and 59% had cirrhosis at baseline. Infections were more common in patients with ALD (84 cases/1000 person-years [PY]) compared to reference individuals (29/1000 PYs; adjusted hazard ratio [aHR] 3.06, 95% CI = 2.85–3.29). This excess risk corresponded to one additional infection per 18 ALD patients each year.

The rate of infections was particularly high in individuals with cirrhosis (aHR = 3.46) and in those with decompensation (aHR = 5.20). Restricting our data to those with an infection, ALD (aHR = 3.63, 95%CI = 3.36–3.93), and especially ALD cirrhosis (aHR = 4.31, 95%CI = 3.89–4.78) were linked to subsequent death.

Conclusions: Individuals with biopsy-proven ALD have a three-fold increased rate of infections compared with the general population. The risk of death after an infection is also considerably higher in individuals with ALD.

KEYWORDS

alcoholic liver disease, cirrhosis, death, epidemiology, ethanol, infection, prognosis

INTRODUCTION

Alcohol consumption can lead to alcohol-related liver disease (ALD) including cirrhosis.[1,2] In cirrhosis, the immune system is often compromised.[3] Additionally, alcohol per se has negative effects on the immune system, including on innate and adaptive response to infections.[4] Therefore, patients with ALD cirrhosis frequently experience infections, and these are a commonly linked to further deterioration in liver function and death.[5–8] A review on the subject found that patients with cirrhosis in general have a four-fold increased odds for death if they experience an infection compared to non-infected patients with cirrhosis.[9]

International guidelines stress the risk of bacterial infections in ALD-cirrhosis,[10] but do not elucidate several important topics. Since much evidence stems from specialized centers examining prevalent infections in hospitalized ALD patients,[10] there is risk of selection bias. For instance, studies from tertiary-centers have reported that spontaneous bacterial peritonitis (SBP) is the most common infection in patients with cirrhosis.[11] This has not always been replicated in prospective trials, for instance in the PRE-DESCI trial where SBP was a rare event.[8] It is further unclear if the risk of infections is increased also in non-cirrhotic ALD, and to what extent an infection increases the risk of death in average ALD patients. There are no studies examining the risk of death after an infection in patients with ALD compared to non-ALD patients with a similar infection. Finally, detailed information as to whether the risk of infections varies according to liver histopathology stage may be operative for treatment and surveillance decisions in ALD.[12]

Here, we investigated the risk for bacterial or opportunistic infections in all patients with biopsy-verified ALD 1969–2017 in Sweden, and their subsequent risk for mortality.

Key summary

Summarize the established knowledge on this subject

- Patients with alcohol-related liver disease (ALD) tend to develop infections.
- Infections often result in death.
- The risk for infections has mostly been examined in patients with cirrhosis.
- Risk estimates often stem from highly specialized centers.

What are the significant and/or new findings of this study?

- In a population-wide cohort with liver biopsy data, patients with ALD had a more than three-fold increased risk for infections compared to matched general population reference individuals.
- Patients without cirrhosis were also at an increased risk.
- After an infection, patients with ALD were at a higher risk for death compared to reference individuals who also had an infection.
- Clinicians should be aware of the high risk of infections also in non-cirrhotic patients with ALD.

MATERIAL AND METHODS

This was a national, population-based cohort study. We used the Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) cohort to identify all patients in Sweden with an ALD diagnosis.[13] Briefly, between 2015 and 2017, all pathology

departments in Sweden (n = 28) were contacted and asked to share histopathology record data from liver biopsies performed 1965–2017. Local IT personnel retrieved data on the date of histopathology and morphology, defined according to SnoMed codes[14] assigned by the reporting pathologist at the time of the original reading of the slide. Individuals with ALD and available 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). Data on the patient's personal identity number, unique to all Swedish residents, were also obtained.[15] The personal identity number allowed linkages to Swedish National Healthcare Registers. Briefly, these registers contain international classification of disease (ICD) codes for hospitalizations, causes of death and since 2001 hospital-based outpatient visits.[15–17] The Swedish National Patient Register has a positive predictive value of 85%–95% for most diagnoses, and 93% for ALD cirrhosis.[18] This register was used to obtain data on comorbidities, and relevant ICD-codes for ALD in combination with pathology data, were required for our definition of ALD.[16]

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: 571,00 and 571,01, Table S1) in the National Patient Register starting in 1969 when ICD-8 was introduced in Sweden, ending the inclusion period as of 31 Dec 2017. To reduce the risk for immortal time bias, the ALD exposure was defined when patients had *both* undergone a biopsy and received a medical discharge diagnosis of ALD. Thus, a person could first have a code for ALD, and later a liver biopsy, and vice versa, to be defined as exposed. We further used a grace period of 5 days after baseline to define the start of follow-up (index date). This was done to not include patients likely to have an undiagnosed infection at baseline.

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 Table S2. 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 Table S3) at or before the index date (Figure S1). Thus, no patient with ALD nor any reference individual had a diagnosis of another liver disease at or before baseline.

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,[19] we used the highest attained level of education in the individual registered after the index date for those starting follow-up before 1990. We also collected data on relevant co-morbidities at or before baseline, including diabetes and chronic obstructive pulmonary disease (COPD). As patients with decompensated liver disease might constitute a subgroup with a particularly high risk, we specifically investigated infection rates and mortality risk after an infection in patients with an ICD-code corresponding to decompensation prior to baseline. The definitions of these co-morbidities are shown in Table S1.

Follow-up and mortality outcomes

Follow-up time was determined through the Total Population Register,[20] the National Patient Register[16] and the Cause of Death Register.[17] The Total Population Register contains demographic data (e.g., emigration and date of death) on the Swedish population. The National Patient Register holds data on all hospitalizations since 1964, including outpatient visits in specialized care since 2001. However, primary care data is not registered. 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. Coverage for incident mortality is >99%.[17]

Follow-up ended at first incident infection, death, liver transplantation, emigration, or end of follow-up (31 December 2019), whichever occurred first. We further censored any reference individuals who were diagnosed with ALD after the index date.

Our main outcome measure was hospital-based infections requiring hospitalization or contact with specialized outpatient care, including emergency room visits. Secondary outcomes included pre-specified infection outcomes: sepsis; ear-nose-throat (ENT) or respiratory tract; gastrointestinal except for peritonitis; bacterial peritonitis (including but not exclusive to SBP); urogenital; musculoskeletal, skin and soft tissue; and other infection outcomes. In our secondary analyses, we did not censor for other infections than the infection of interest. For instance, in our analysis of later bacterial peritonitis, we did not consider if the patient had a record of other infections such as pneumonia or a skin infection (definitions in Table S4). We used both the inpatient and outpatient part of the National Patient Register and considered both primary and contributing infectious disease diagnoses.

Sensitivity analyses

Several sensitivity analyses were performed. First, we calculated the "E-value" approach outlined by VanderWeele et al.[21] This estimates the effect an unmeasured confounder needs to have to reduce an observed risk to 1.

Next, we further adjusted the final model for cirrhosis as a time-dependent covariate. This was done to estimate if progression to cirrhosis would account for some of any excess risk of infections in non-cirrhotic patients.

To account for smoking as a confounder, we adjusted the final model also for baseline COPD (reflecting heavy smoking). This was only done in the population with an index date as of 1 January 1987 as there were no specific ICD-codes for COPD prior to that and was further restricted to individuals aged 40 or older (since COPD diagnosed prior to that age may have low specificity and represent other aetiologies than smoking).

As an ongoing infection may predispose to another infection, we excluded all participants with any infection ≤90 days *before* baseline.

Finally, to explore the specificity of our findings, we examined the risk of infection in ALD compared with biopsy-proven non-alcoholic fatty liver diseases (NAFLD). The NAFLD cohort has been described in detail elsewhere.[22–24] This analysis was adjusted for the same confounders as the main model described below, but also for baseline cirrhosis.

Statistical analysis

We first calculated incidence rates per 1000 person-years of follow-up. Our primary objective was to evaluate the etiological association between ALD and infections, hence we used Cox regression to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for total and cause-specific mortality.

We calculated aHRs using two models: Model one was conditioned on matching factors (age, sex, county of residence, and calendar year of biopsy); in this model no additional adjustment was performed. In model two ("final model") we further adjusted for education, baseline diabetes, and number of hospitalizations in the year preceding the index date.

To account for the high competing risk of death, which was previously calculated to 41% 5 years after baseline in this cohort,[25] and to better investigate the cumulative incidence of infections, we also performed a competing risk regression, considering non-infection-related death and liver transplantation as the competing risks.[26,27] The cumulative incidences for the primary outcome are presented using cumulative incidence function curves.

Then, we restricted the cohort to study participants (ALD and reference individuals) who all had an infection, where patients with ALD were re-matched with up to five reference individuals on age, sex, county and calendar year of infection. We then investigated risk for overall mortality using Cox regression,

using the same final model as for the infection outcome. Analyses were performed using SAS statistical software v9.4 and STATA v15.1.

Ethical considerations

The study was approved by the Stockholm Ethics Review Board (No. 2014/1287-31/4). Because this is a register-based study using anonymized data and no patient contact, the Ethics Review Board waived informed consent.[28]

RESULTS

We identified 4028 adults with ALD and 19,296 matched reference individuals from the general population in the final analyses (flowchart in Figure S1). The median age at first ALD diagnosis was 59 years (IQR: 51–66) and 66% (n = 2643) were men. At a subgroup level, 89 individuals (2.2%) had a normal liver on biopsy, 489 (12.1%) simple steatosis, 461 (11.4%) fibrosis or steatohepatitis, 2370 (58.8%) cirrhosis and 619 (15.4%) had other findings. Participant characteristics at baseline are presented in Table 1. In total, 1236 patients with ALD (30.7%) had an ICD-code corresponding to decompensated liver disease prior to baseline.

Incident infections

Median follow-up was 2.6 years (IQR 0.5–7.8) in individuals with ALD and 12.5 years (IQR 6.3–19.5) in reference individuals. A total of 1807 (44.9%) individuals with ALD and 7531 (39.0%) reference individuals were diagnosed with or died from an infection during follow-up. The rate of infection development was considerably higher in patients with ALD (84.0 cases per 1000 person-years [PY]) compared to reference individuals (28.7/1000 Pys). This translated to an HR of 4.01 (95%CI = 3.75–4.28) in the model only conditioned on matching factors, and 3.06 (95% CI = 2.85–3.29) in the fully adjusted model. The rate of infection was comparable across several subgroups, such as in men (aHR = 3.12) and women (aHR = 2.97) and calendar period (ranging from aHR 2.96 to 4.33). Infection rate was highest in the year after ALD diagnosis (aHR = 4.59) compared to after 5 years of follow-up (aHR = 2.46).

Infection risk increased across histopathological subgroups, with the highest risk seen in individuals with cirrhosis (aHR = 3.46, 95%CI = 3.13–3.81), although infection risk was still substantial in individuals with ALD and normal liver (aHR = 1.87, 95%CI = 1.14–3.05), steatosis (aHR = 2.49, 95%CI = 2.07–2.99), fibrosis (aHR = 3.01, 95%CI = 2.48–3.65) and other findings (aHR = 2.73, 95%CI = 2.27–3.28). The estimates for infection risk

T A B L E 1 Baseline characteristics of the full alcohol-related liver disease (ALD) population, also stratified on histological subgroups, and matched reference individuals

Characteristic	Reference population (n = 19,296)	ALD overall (n = 4028)	Normal liver (n = 89)	Steatosis (n = 489)	Fibrosis (n = 461)	Cirrhosis (n = 2370)	Other (n = 619)
Sex, n (%)							
Women	6694 (34.7%)	1385 (34.4%)	37 (41.6%)	174 (35.6%)	170 (36.9%)	797 (33.6%)	207 (33.4%)
Men	12,602 (65.3%)	2643 (65.6%)	52 (58.4%)	315 (64.4%)	291 (63.1%)	1573 (66.4%)	412 (66.6%)
Age							
Mean (SD)	58.0 (11.5)	58.2 (11.6)	55.9 (15.0)	53.6 (11.7)	56.5 (11.0)	59.2 (10.7)	59.8 (13.2)
Median (IQR)	58.8 (50.6–66.2)	59.0 (50.8–66.6)	57.6 (44.6–66.9)	54.4 (45.1–63.1)	57.7 (49.9–63.9)	59.9 (52.3–66.9)	60.8 (51.9–69.3)
Range, min-max	18.2–88.6	18.0–88.3	22.0–83.9	19.0–81.1	22.1–82.5	18.0–84.9	18.6–88.3
Categories, no. (%)							
18–<40 years	1419 (7.4%)	290 (7.2%)	16 (18.0%)	65 (13.3%)	37 (8.0%)	114 (4.8%)	58 (9.4%)
40–<60 years	9075 (47.0%)	1860 (46.2%)	34 (38.2%)	268 (54.8%)	241 (52.3%)	1081 (45.6%)	236 (38.1%)
≥60 years	8802 (45.6%)	1878 (46.6%)	39 (43.8%)	156 (31.9%)	183 (39.7%)	1175 (49.6%)	325 (52.5%)
Country of birth, n (%)							
Nordic country	17,771 (92.1%)	3763 (93.4%)	86 (96.6%)	447 (91.4%)	418 (90.7%)	2234 (94.3%)	578 (93.4%)
Other	1523 (7.9%)	265 (6.6%)	3 (3.4%)	42 (8.6%)	43 (9.3%)	136 (5.7%)	41 (6.6%)
Missing	2 (0.0%)	0	0	0	0	0	0
Level of education using highest level of education in parents when missing, n (%)							
≤9 years	6962 (36.1%)	1540 (38.2%)	22 (24.7%)	187 (38.2%)	165 (35.8%)	916 (38.6%)	250 (40.4%)
10–12 years	7364 (38.2%)	1613 (40.0%)	46 (51.7%)	218 (44.6%)	205 (44.5%)	896 (37.8%)	248 (40.1%)
>12 years	4367 (22.6%)	528 (13.1%)	15 (16.9%)	66 (13.5%)	80 (17.4%)	288 (12.2%)	79 (12.8%)
Missing	603 (3.1%)	347 (8.6%)	6 (6.7%)	18 (3.7%)	11 (2.4%)	270 (11.4%)	42 (6.8%)
Start year of follow-up							
1969–1980	489 (2.5%)	99 (2.5%)	4 (4.5%)	7 (1.4%)	2 (0.4%)	82 (3.5%)	4 (0.6%)
1981–1990	3454 (17.9%)	709 (17.6%)	21 (23.6%)	101 (20.7%)	46 (10.0%)	452 (19.1%)	89 (14.4%)
1991–2000	6770 (35.1%)	1403 (34.8%)	28 (31.5%)	199 (40.7%)	131 (28.4%)	807 (34.1%)	238 (38.4%)
2001–2010	6237 (32.3%)	1313 (32.6%)	30 (33.7%)	136 (27.8%)	195 (42.3%)	735 (31.0%)	217 (35.1%)
2011–2017	2346 (12.2%)	504 (12.5%)	6 (6.7%)	46 (9.4%)	87 (18.9%)	294 (12.4%)	71 (11.5%)
Disease history ever before start of follow-up, n (%)							
COPD	210 (1.1%)	170 (4.2%)	4 (4.5%)	19 (3.9%)	27 (5.9%)	84 (3.5%)	36 (5.8%)
Diabetes	717 (3.7%)	811 (20.1%)	13 (14.6%)	71 (14.5%)	88 (19.1%)	512 (21.6%)	127 (20.5%)
Time to register-based definition of ALD onset (time in years between first ALD diagnosis and biopsy)							
Median (IQR)		0.3 (0.0–3.1)	1.7 (0.1–9.5)	0.3 (0.0–5.0)	0.5 (0.0–4.0)	0.2 (0.0–1.7)	2.1 (0.1–7.2)

Abbreviations: ALD, alcohol-related liver disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PY, person-years; SD, standard deviation.

across histological subgroups are presented in Table 2 for the full ALD population and the cumulative incidence of any infection is presented in Figure 1. Notably, patients with previous decompensation had rates of infection similar to patients with cirrhosis (aHR = 3.35, 95%CI = 2.89–3.89).

Specific infection rates

3300 incident infections were recorded in 1807 ALD individuals, as an individual could have several different infections during follow-up. The most frequent infections in the full ALD population after baseline

TABLE 2 Rates of any infection overall and by subgroups in patients with alcohol-related liver disease (ALD) and matched general population comparators

| Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)	HR** (95%CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators		
Overall	4028 (100%)	19,296 (100%)	1807 (44.9%)	7531 (39.0%)	84.0 (80.1–87.8)	28.7 (28.1–29.4)	4.01 (3.75–4.28)	3.06 (2.85–3.29)
Follow-up								
<1 year	4028 (100%)	19,296 (100%)	506 (12.6%)	464 (2.4%)	164.1 (149.8–178.4)	24.5 (22.3–26.8)	7.00 (6.10–8.04)	4.59 (3.93–5.36)
1–<5 years	2687 (66.7%)	18,582 (96.3%)	613 (22.8%)	1616 (8.7%)	78.3 (72.1–84.5)	23.5 (22.4–24.7)	3.98 (3.57–4.45)	3.08 (2.73–3.47)
5–<10 years	1459 (36.2%)	15,564 (80.7%)	340 (23.3%)	1737 (11.2%)	63.6 (56.9–70.4)	25.7 (24.5–26.9)	3.09 (2.67–3.57)	2.46 (2.11–2.88)
≥10 years	761 (18.9%)	11,478 (59.5%)	348 (45.7%)	3714 (32.4%)	66.0 (59.1–73.0)	34.7 (33.6–35.8)	2.78 (2.40–3.22)	2.51 (2.15–2.93)
≥1 year	2687 (66.7%)	18,582 (96.3%)	1301 (48.4%)	7067 (38.0%)	70.6 (66.7–74.4)	29.0 (28.4–29.7)	3.38 (3.13–3.64)	2.75 (2.53–2.98)
Sex								
Women	1385 (34.4%)	6694 (34.7%)	706 (51.0%)	2588 (38.7%)	85.5 (79.2–91.8)	27.4 (26.4–28.5)	3.82 (3.44–4.23)	2.97 (2.65–3.33)
Men	2643 (65.6%)	12,602 (65.3%)	1101 (41.7%)	4943 (39.2%)	83.0 (78.1–87.9)	29.4 (28.6–30.3)	4.14 (3.80–4.51)	3.12 (2.85–3.43)
Age								
18–<40 years	290 (7.2%)	1419 (7.4%)	120 (41.4%)	394 (27.8%)	33.4 (27.5–39.4)	13.4 (12.1–14.8)	2.75 (2.18–3.47)	2.27 (1.75–2.94)
40–<60 years	1860 (46.2%)	9075 (47.0%)	906 (48.7%)	3220 (35.5%)	77.9 (72.8–83.0)	22.1 (21.3–22.8)	4.77 (4.33–5.25)	3.77 (3.39–4.19)
≥60 years	1878 (46.6%)	8802 (45.6%)	781 (41.6%)	3917 (44.5%)	123.9 (115.3–132.6)	45.0 (43.6–46.4)	3.55 (3.21–3.92)	2.61 (2.34–2.90)
ALD subgroup								
Normal liver	89 (2.2%)	413 (2.1%)	35 (39.3%)	165 (40.0%)	51.2 (34.2–68.1)	27.7 (23.5–32.0)	2.27 (1.47–3.50)	1.87 (1.14–3.05)
Steatosis	489 (12.1%)	2336 (12.1%)	246 (50.3%)	857 (36.7%)	57.3 (50.2–64.5)	23.5 (22.0–25.1)	3.11 (2.62–3.68)	2.49 (2.07–2.99)
Fibrosis	461 (11.4%)	2184 (11.3%)	238 (51.6%)	748 (34.2%)	87.8 (76.7–99.0)	27.2 (25.2–29.1)	3.75 (3.13–4.48)	3.01 (2.48–3.65)
Cirrhosis	2370 (58.8%)	11,441 (59.3%)	1037 (43.8%)	4583 (40.1%)	96.3 (90.5–102.2)	29.6 (28.7–30.4)	4.63 (4.24–5.07)	3.46 (3.13–3.81)
Other	619 (15.4%)	2922 (15.1%)	251 (40.5%)	1178 (40.3%)	81.8 (71.6–91.9)	31.5 (29.7–33.3)	3.55 (2.99–4.22)	2.73 (2.27–3.28)
Liver decompensation[a]	1236 (30.7%)	5890 (30.5%)	501 (40.5%)	2224 (37.8%)	122.8 (112.1–133.6)	31.7 (30.4–33.0)	4.96 (4.36–5.66)	3.35 (2.89–3.89)
Year—infection during the first 5 years of follow-up								
1969–1980	99 (2.5%)	489 (2.5%)	16 (16.2%)	17 (3.5%)	40.2 (20.5–59.9)	7.3 (3.8–10.8)	5.88 (2.83–12.23)	5.56 (2.44–12.69)
1981–1990	709 (17.6%)	3454 (17.9%)	120 (16.9%)	183 (5.3%)	56.6 (46.5–66.7)	11.3 (9.7–13.0)	5.99 (4.56–7.85)	4.36 (3.25–5.84)
1991–2000	1403 (34.8%)	6770 (35.1%)	328 (23.4%)	597 (8.8%)	82.9 (74.0–91.9)	19.0 (17.5–20.6)	5.44 (4.63–6.40)	4.08 (3.43–4.85)
2001–2010	1313 (32.6%)	6237 (32.3%)	470 (35.8%)	895 (14.3%)	141.5 (128.7–154.2)	32.0 (29.9–34.1)	4.64 (4.07–5.29)	3.30 (2.85–3.82)
2011–2014	354 (8.8%)	1662 (8.6%)	132 (37.3%)	289 (17.4%)	157.4 (130.6–184.3)	39.4 (34.8–43.9)	4.42 (3.46–5.65)	3.07 (2.34–4.03)
2011–2017	504 (12.5%)	2346 (12.2%)	205 (40.7%)	486 (20.7%)	158.9 (137.2–180.7)	39.4 (35.9–42.9)	4.38 (3.59–5.33)	3.14 (2.52–3.91)

(Continues)

TABLE 2 (Continued)

Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)	HR** (95%CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators		
Country of birth								
Nordic	3763 (93.4%)	17,771 (92.1%)	1678 (44.6%)	7008 (39.4%)	83.9 (79.9–88.0)	28.7 (28.1–29.4)	4.00 (3.73–4.29)	3.04 (2.81–3.27)
Other	265 (6.6%)	1523 (7.9%)	129 (48.7%)	523 (34.3%)	84.3 (69.8–98.9)	28.2 (25.8–30.6)	5.20 (2.76–9.80)	3.08 (1.54–6.19)
Education								
≤9 years	1540 (38.2%)	6962 (36.1%)	733 (47.6%)	3118 (44.8%)	85.7 (79.5–91.9)	32.9 (31.8–34.1)	3.87 (3.35–4.48)	3.04 (2.61–3.55)
10–12 years	1613 (40.0%)	7364 (38.2%)	757 (46.9%)	2807 (38.1%)	84.3 (78.3–90.3)	27.4 (26.4–28.4)	4.12 (3.59–4.74)	3.19 (2.75–3.71)
>12 years	528 (13.1%)	4367 (22.6%)	246 (46.6%)	1432 (32.8%)	76.1 (66.6–85.6)	23.3 (22.1–24.6)	3.93 (2.94–5.25)	2.84 (2.08–3.89)
Comorbidity								
COPD	170 (4.2%)	210 (1.1%)	84 (49.4%)	121 (57.6%)	195.3 (153.5–237.0)	125.2 (102.9–147.5)	1.45 (0.44–4.83)	0.50 (0.07–3.45)
Diabetes	811 (20.1%)	717 (3.7%)	387 (47.7%)	365 (50.9%)	155.4 (139.9–170.8)	75.1 (67.4–82.8)	3.04 (1.88–4.92)	2.33 (1.37–3.96)
ALD diagnosis/biopsy timing								
Biopsy after diagnosis	2381 (59.1%)	11,621 (60.2%)	1037 (43.6%)	4577 (39.4%)	74.2 (69.7–78.7)	27.5 (26.7–28.3)	3.83 (3.52–4.17)	3.08 (2.81–3.37)
Diagnosis after biopsy	1591 (39.5%)	7399 (38.3%)	744 (46.8%)	2844 (38.4%)	105.2 (97.6–112.7)	31.1 (29.9–32.2)	4.33 (3.89–4.81)	3.02 (2.68–3.40)

Abbreviations: ALD, alcohol-related liver disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PY, person-years; SD, standard deviation.

[a]Note that "Liver decompensation" could be included in other subgroups.

*Conditioned on matching set (age, sex, county, and calendar period).

**Conditioned on matching set and further adjusted for education, baseline diabetes, and number of hospitalizations in the year preceding the index date.
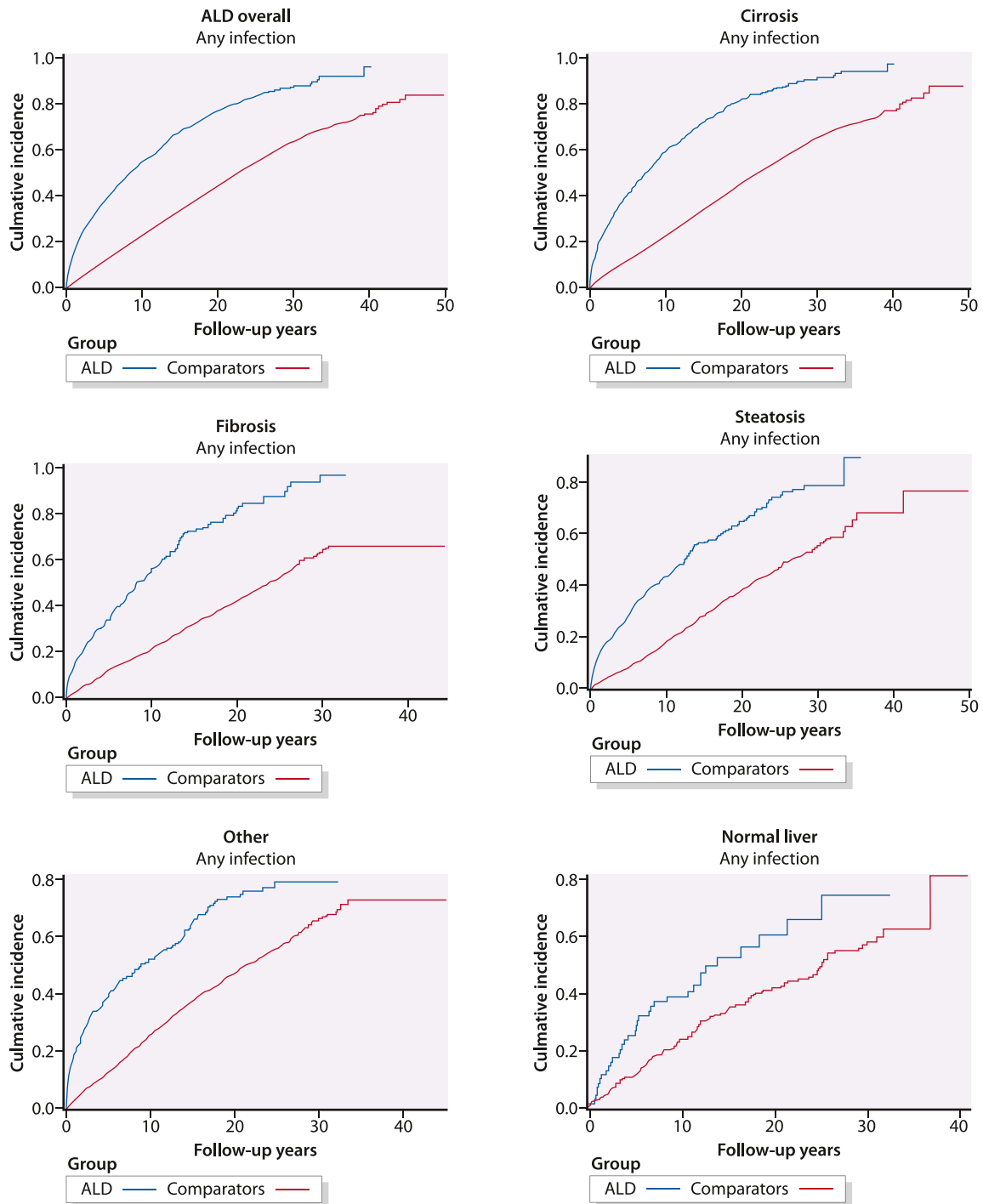
FIGURE 1 Cumulative incidence curves of time to any infection in patients with alcohol-related liver disease (ALD) and matched reference individuals from the general population

were, in order, ENT and respiratory tract infections (n = 859, 21.3%); urogenital (n = 637, 15.8%); musculoskeletal, skin or soft tissue (n = 431, 10.7%); sepsis (427%, 10.6%); gastrointestinal (n = 230, 5.7%) and peritonitis including spontaneous bacterial peritonitis (SBP, n = 122, 3.0%). Infections classified as "other subtype" were seen in 594 ALD patients (14.7%). In relative terms, the highest risk compared to the reference individuals were for peritonitis including SBP (aHR = 10.3, 95%CI = 6.9–15.3). This was roughly comparable across histological subgroups. Table 3 lists risk for specific infections

in the full ALD population, and Table S5a-S5e lists this in the ALD subgroups.

Risk of death after infection

Of the 1807 patients with ALD and an infection, 1779 (98.5%) could be re-matched with up to five reference individuals also with a first infection (n = 8625). Characteristics of this sub-population at the

TABLE 3 Rates of specific infections in all patients with alcohol-related liver disease (ALD) and matched general population comparators
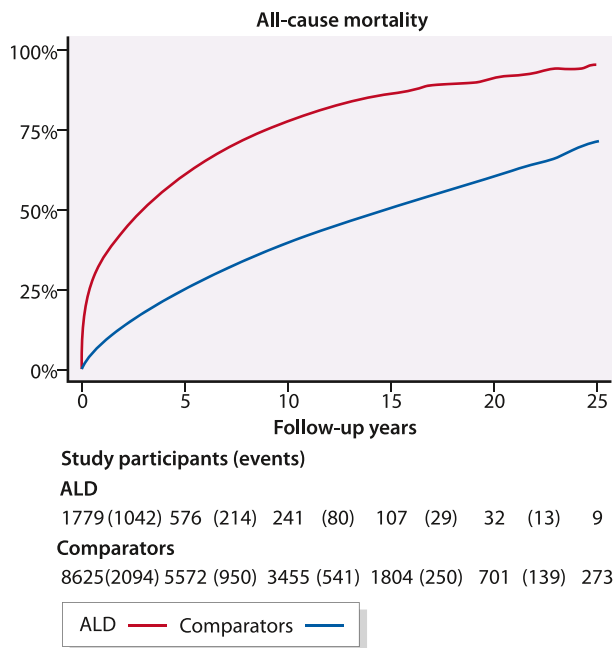
	N events		Incidence rate (95% CI) per 1000 PY			
Infection	ALD	Comparators	ALD	Comparators	HR* (95%CI)	HR** (95%CI)
Any (first) infection	1807 (44.9%)	7531 (39.0%)	84.0 (80.1–87.8)	28.7 (28.1–29.4)	4.01 (3.75–4.28)	3.06 (2.85–3.29)
Sepsis	427 (10.6%)	1070 (5.5%)	15.1 (13.6–16.5)	3.5 (3.3–3.7)	7.30 (6.23–8.54)	5.28 (4.45–6.25)
ENT and respiratory tract	859 (21.3%)	3850 (20.0%)	33.2 (31.0–35.4)	13.3 (12.9–13.7)	3.45 (3.15–3.78)	2.64 (2.40–2.92)
GI	230 (5.7%)	751 (3.9%)	8.0 (7.0–9.1)	2.5 (2.3–2.6)	4.18 (3.48–5.02)	2.91 (2.38–3.57)
Peritonitis including SBP	122 (3.0%)	125 (0.6%)	4.2 (3.4–4.9)	0.4 (0.3–0.5)	13.07 (9.16–18.64)	10.30 (6.93–15.30)
Urogenital	637 (15.8%)	2868 (14.9%)	23.5 (21.7–25.4)	9.7 (9.3–10.1)	3.78 (3.39–4.22)	2.77 (2.46–3.12)
Musculoskeletal, skin and soft tissue	431 (10.7%)	1540 (8.0%)	15.6 (14.1–17.1)	5.1 (4.9–5.4)	4.17 (3.65–4.77)	3.25 (2.81–3.76)
Other	594 (14.7%)	2475 (12.8%)	21.6 (19.9–23.4)	8.3 (8.0–8.6)	4.03 (3.59–4.51)	2.99 (2.64–3.38)

Note: Table S5a-S5e lists risks across ALD subgroups.

Abbreviations: ALD, alcohol-related liver disease; ENT, ear-throat-nose; HR, hazard ratio; IQR, interquartile range; PY, person-years; SBP, spontaneous bacterial peritonitis.

*Conditioned on matching set (age, sex, county, and calendar period).

**Conditioned on matching set and further adjusted for education, baseline diabetes, and number of hospitalizations in the year preceding the index date.

All-cause mortality

Study participants (events)
ALD
1779 (1042) 576 (214) 241 (80) 107 (29) 32 (13) 9
Comparators
8625 (2094) 5572 (950) 3455 (541) 1804 (250) 701 (139) 273

FIGURE 2 Kaplan-Meier failure curves for time to all-cause mortality from time of infection in patients with alcohol-related liver disease (ALD) and matched reference individuals, with an infection, from the general population

time of first infection are presented in Table S6. Mortality rate in patient with ALD after infection was 177.9 deaths per 1000 person-years (95%CI = 168.5–187.3), and in reference individuals 51.4/1000 Pys (95%CI = 49.8–53.0). Cumulative mortality in ALD patients after 1, 5, and 10 years was 34%, 59%, and 71%, respectively. This was considerably higher than in the reference population (8.6%, 24%, and 35%; Figure 2).

After adjustments, this translated to a more than three-fold risk for overall mortality after an infection in ALD patients versus (aHR = 3.63, 95%CI = 3.36–3.93). Estimates from this analysis across subgroups are presented in Table 4. Notably, the highest risk was seen in patients with cirrhosis (aHR = 4.31, 95%CI = 3.89–4.78) and in patients with previous decompensation before the infection event (n = 745, aHR = 5.20, 95%CI = 4.58–5.90).

Sensitivity analyses

When comparing the rate of infections to that of patients with NAFLD, we found that after adjustments, patients with ALD had a 55% increased rate of infections (aHR = 1.55, 95%CI = 1.45–1.65). Table S9 describes baseline characteristics of patients with NAFLD, and Table S10 presents infection estimates for patients with ALD compared to patients with NAFLD. The cumulative incidence of infections is presented in Figure S2. Estimates from the other sensitivity analyses were largely in accordance with results from the main model and are presented in the Appendix.

DISCUSSION

In this nationwide, population-based cohort study of all patients in Sweden with a biopsy-based diagnosis of ALD, we found a three-fold increased rate of developing an infection requiring hospitalization or contact with outpatient specialized care compared to the general population. The rate was highest in patients with cirrhosis, in particular those with decompensation, but also comparably high in patients with non-cirrhotic biopsy findings with an almost two-fold increased risk in ALD patients with normal liver histopathology.

TABLE 4 Risk of all-cause mortality overall and by subgroups in patients with alcohol-related liver disease (ALD) and matched general population comparators after an infection event

Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)	HR** (95%CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators		
Overall	1779 (100%)	8625 (100%)	1380 (77.6%)	4060 (47.1%)	177.9 (168.5–187.3)	51.4 (49.8–53.0)	3.71 (3.44–4.00)	3.63 (3.36–3.93)
Follow-up								
<1 year	1779 (100%)	8625 (100%)	598 (33.6%)	738 (8.6%)	458.4 (421.6–495.1)	91.0 (84.5–97.6)	5.12 (4.56–5.76)	5.39 (4.75–6.11)
1–<5 years	1131 (63.6%)	7727 (89.6%)	444 (39.3%)	1356 (17.5%)	137.2 (124.4–149.9)	51.5 (48.7–54.2)	2.90 (2.56–3.28)	2.84 (2.49–3.23)
5–<10 years	576 (32.4%)	5572 (64.6%)	214 (37.2%)	950 (17.0%)	111.1 (96.2–126.0)	42.6 (39.9–45.3)	3.18 (2.61–3.88)	3.01 (2.46–3.69)
≥10 years	241 (13.5%)	3455 (40.1%)	124 (51.5%)	1016 (29.4%)	96.1 (79.2–113.0)	45.7 (42.9–48.5)	2.72 (2.04–3.61)	2.52 (1.88–3.37)
≥1 year	1131 (63.6%)	7727 (89.6%)	782 (69.1%)	3322 (43.0%)	121.2 (112.7–129.7)	46.9 (45.3–48.5)	2.94 (2.67–3.25)	2.82 (2.54–3.12)
Sex								
Women	696 (39.1%)	3375 (39.1%)	520 (74.7%)	1400 (41.5%)	154.6 (141.3–167.8)	42.9 (40.6–45.1)	3.77 (3.33–4.26)	3.62 (3.18–4.11)
Men	1083 (60.9%)	5250 (60.9%)	860 (79.4%)	2660 (50.7%)	195.8 (182.7–208.8)	57.4 (55.3–59.6)	3.67 (3.34–4.04)	3.63 (3.29–4.01)
Age								
18–<40 years	49 (2.8%)	184 (2.1%)	23 (46.9%)	9 (4.9%)	51.2 (30.3–72.2)	3.1 (1.1–5.1)	36.90 (8.57–158.88)	44.57 (5.55–357.75)
40–<60 years	614 (34.5%)	2905 (33.7%)	430 (70.0%)	919 (31.6%)	117.9 (106.7–129.0)	25.2 (23.6–26.9)	5.48 (4.72–6.36)	5.13 (4.39–5.99)
≥60 years	1116 (62.7%)	5536 (64.2%)	927 (83.1%)	3132 (56.6%)	253.2 (236.9–269.5)	79.0 (76.3–81.8)	3.15 (2.88–3.44)	3.12 (2.84–3.42)
ALD subgroup								
Normal liver	33 (1.9%)	157 (1.8%)	26 (78.8%)	87 (55.4%)	108.2 (66.6–149.8)	55.0 (43.5–66.6)	2.39 (1.39–4.12)	2.75 (1.53–4.94)
Steatosis	224 (12.6%)	1086 (12.6%)	154 (68.8%)	469 (43.2%)	108.2 (91.1–125.3)	46.1 (41.9–50.2)	2.36 (1.91–2.91)	2.29 (1.84–2.85)
Fibrosis	221 (12.4%)	1084 (12.6%)	151 (68.3%)	416 (38.4%)	145.8 (122.6–169.1)	45.0 (40.7–49.4)	3.39 (2.72–4.22)	3.25 (2.59–4.08)
Cirrhosis	1067 (60.0%)	5161 (59.8%)	885 (82.9%)	2576 (49.9%)	225.9 (211.0–240.8)	54.4 (52.3–56.5)	4.41 (4.00–4.86)	4.31 (3.89–4.78)
Other	234 (13.2%)	1137 (13.2%)	164 (70.1%)	512 (45.0%)	143.7 (121.7–165.6)	48.3 (44.1–52.5)	3.06 (2.48–3.78)	3.07 (2.47–3.83)
Liver decompensation[a]	745 (41.9%)	3623 (42.0%)	612 (82.1%)	1595 (44.0%)	272.4 (250.8–294.0)	50.0 (47.6–52.5)	5.28 (4.68–5.96)	5.20 (4.58–5.90)
Year								
1969–1980	10 (0.6%)	37 (0.4%)	10 (100.0%)	36 (97.3%)	127.5 (48.5–206.5)	54.6 (36.8–72.4)	3.98 (1.55–10.22)	5.34 (1.88–15.17)
1981–1990	97 (5.5%)	413 (4.8%)	91 (93.8%)	355 (86.0%)	155.7 (123.7–187.7)	55.7 (49.9–61.4)	3.21 (2.36–4.35)	3.39 (2.47–4.64)
1991–2000	383 (21.5%)	1745 (20.2%)	349 (91.1%)	1208 (69.2%)	176.4 (157.9–194.9)	54.7 (51.6–57.8)	3.63 (3.11–4.23)	3.49 (2.98–4.08)
2001–2010	803 (45.1%)	4006 (46.4%)	661 (82.3%)	1876 (46.8%)	173.3 (160.1–186.5)	47.4 (45.3–49.6)	3.89 (3.49–4.34)	3.81 (3.40–4.27)
2011–2017	486 (27.3%)	2424 (28.1%)	269 (55.3%)	585 (24.1%)	206.7 (182.0–231.4)	56.8 (52.2–61.4)	3.58 (3.03–4.21)	3.59 (3.02–4.26)

(Continues)

TABLE 4 (Continued)

Group	N (%)		N events		Incidence rate (95% CI) per 1000 PY		HR* (95%CI)	HR** (95%CI)
	ALD	Comparators	ALD	Comparators	ALD	Comparators		
Year—mortality during the first 5 years of follow-up								
1969–1980	10 (0.6%)	37 (0.4%)	5 (50.0%)	5 (13.5%)	117.1 (14.5–219.7)	30.8 (3.8–57.8)	4.78 (1.28–17.92)	140.15 (0.95–20,632.5)
1981–1990	97 (5.5%)	413 (4.8%)	63 (64.9%)	114 (27.6%)	255.3 (192.2–318.3)	66.8 (54.5–79.0)	3.78 (2.63–5.43)	4.18 (2.85–6.12)
1991–2000	383 (21.5%)	1745 (20.2%)	238 (62.1%)	514 (29.5%)	243.3 (212.4–274.2)	71.9 (65.7–78.2)	3.89 (3.25–4.66)	3.90 (3.23–4.70)
2001–2010	803 (45.1%)	4006 (46.4%)	486 (60.5%)	974 (24.3%)	226.9 (206.7–247.1)	57.0 (53.5–60.6)	4.12 (3.64–4.67)	4.09 (3.59–4.67)
2011–2014	265 (14.9%)	1319 (15.3%)	151 (57.0%)	305 (23.1%)	202.9 (170.6–235.3)	53.9 (47.9–59.9)	3.84 (3.09–4.79)	3.70 (2.95–4.64)
Country of birth								
Nordic	1652 (92.9%)	7861 (91.1%)	1292 (78.2%)	3784 (48.1%)	181.5 (171.6–191.4)	52.7 (51.0–54.3)	3.59 (3.32–3.89)	3.50 (3.22–3.80)
Other	127 (7.1%)	764 (8.9%)	88 (69.3%)	276 (36.1%)	137.9 (109.1–166.8)	38.7 (34.1–43.3)	4.28 (2.02–9.05)	3.88 (1.77–8.52)
Education								
≤9 years	715 (40.2%)	3227 (37.4%)	585 (81.8%)	1900 (58.9%)	190.3 (174.9–205.8)	66.6 (63.6–69.6)	3.17 (2.74–3.68)	3.10 (2.66–3.60)
10–12 years	756 (42.5%)	3407 (39.5%)	562 (74.3%)	1414 (41.5%)	165.1 (151.4–178.7)	44.0 (41.7–46.3)	4.51 (3.82–5.33)	4.81 (4.03–5.75)
>12 years	245 (13.8%)	1747 (20.3%)	171 (69.8%)	538 (30.8%)	152.8 (129.9–175.7)	31.2 (28.6–33.9)	8.66 (5.35–14.01)	8.63 (5.22–14.27)
Comorbidity								
COPD	165 (9.3%)	784 (9.1%)	138 (83.6%)	578 (73.7%)	263.0 (219.1–306.9)	137.6 (126.4–148.8)	1.55 (0.99–2.43)	1.41 (0.88–2.27)
Diabetes	584 (32.8%)	1327 (15.4%)	476 (81.5%)	825 (62.2%)	231.6 (210.8–252.5)	97.0 (90.4–103.7)	3.16 (2.49–4.02)	3.40 (2.65–4.37)

Abbreviations: ALD, alcohol-related liver disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PY, person-years.

[a]Note that "Liver decompensation" could be included in other subgroups.

* Conditioned on matching set (age, sex, county, and calendar year for infection).

** Conditioned on matching set and further adjusted for education, baseline diabetes, and number of hospitalizations in the year preceding the index date.

The most commonly occurring infections were respiratory tract and urogenital infections, but the highest increase in *relative* risk compared to the general population was for peritonitis (including SBP). This was also true for the cirrhotic subgroup, where only 3.5% had an episode of peritonitis. This finding contrasts with international guidelines, where SBP is reported to be the most commonly occurring infection.[10] That SBP was not the most common infection in our Swedish ALD cohort could possibly be explained by our population-based cohort being less likely to have ascites at baseline, as biopsy is rarely performed in patients with ascites.[5,10] This perhaps unexpectedly low incidence of SBP is also in accordance with results from the recent PREDESCI trial, where only 3% of 201 patients developed SBP during 37 months.[8] In the same trial, bacterial infections were also associated with decompensation and subsequent mortality.[8] Furthermore, earlier studies have often originated from highly specialized centers, which risks selection bias by only including more severe cases[10,11,29,30]

We found an excess rate of infections, and subsequent mortality, also in individuals without cirrhosis. 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. An increased vigilance is also supported by a recent study of primarily non-cirrhotic ALD patients, where 31% were hospitalized for an infection after a median time of 49 months, although correlations between histology and infections were not reported.[31] It is not clear why the rate of infections was elevated also in patients without cirrhosis. Possible explanations could be progression to cirrhosis, but also unmeasured confounding such as low socio-economic status and a higher exposure to pathogenic environments. This would also be supported by our comparison to patients with NAFLD. Even after adjustment for cirrhosis, patients with ALD had a higher rate of infections, suggesting that alcohol use per se contributes to the increased risk.

The current study has several strengths. It compared the rate of hospital-based infection and subsequent mortality rates to a matched reference population, enabling capture of a large cohort and the calculation of precise relative and absolute risk estimates that might improve patient communication. We had access to a nationwide population-based sample of more than 4000 ALD patients exceeding 1800 infections, yielding substantial statistical power for several important subgroup analyses. Due to the nature of the high-quality registries, loss to follow-up was minimal and the duration of follow-up the longest hitherto described.

Earlier validation has suggested a high specificity for hospital-based infections,[32] and conditioning ALD on having both a relevant ICD code plus a liver biopsy, and then excluding individuals with differential diagnoses and conditions (Table S3), should yield a high specificity also for our exposure. Finally, estimates were robust across several pre-defined sensitivity analyses.

Epidemiological studies are prone to inherent limitations. We were limited by low granularity, as we had no access to clinical parameters such as Child-Pugh or MELD scores, body mass index, and data on treatment or prophylactic antibiotics. While we also lacked data on smoking, our HRs were similar after adjustment for the heavy smoking proxy COPD, and furthermore our E-value calculations suggested that only an unmeasured confounder with a >5-fold association with both ALD and infection could explain away the positive association in our study.

Our population consisted mainly of cirrhosis patients, why the estimates for normal liver, steatosis and inflammation or fibrosis are wider. Further, requiring a biopsy for ALD diagnosis may lead to selection bias. However, prior to the last 10–15 years, before the occurrence of accurate non-invasive fibrosis biomarkers, biopsy was a far more common method to stage fibrosis.

We could only examine infections diagnosed during hospitalization or in specialized outpatient care. However, these are likely to be of greater clinical importance and have a higher specificity than infections treated in primary care. Nevertheless, the cumulative incidence of *any* infection will be higher than that presented in our study.

Thanks to the large sample size, our effect size estimates for infection are probably more reliable than most previous data in ALD. While we cannot rule out that some reference individuals had undiagnosed ALD, such misclassification would push our estimates towards the null, why the true effect of ALD on infection risk might in fact be even higher. However severe ALD among reference individuals is uncommon, and unlikely to have affected our risk estimates more than marginally. In a recent study, the lifetime prevalence of any alcohol-related disorders and disease (independent of liver biopsy) requiring hospital contact was <2% in Sweden.[33]

Additionally, we excluded patients with other liver diseases (e.g., hepatitis C) before baseline. This approach increases the specificity of our exposure but results in fewer patients for analysis.

Our results highlight the high rate of infections in biopsy-proven ALD, an increased post-infectious mortality, and stress the detrimental role of cirrhosis. The finding that SBP was in relative terms rare also in cirrhotic patients calls for further studies on this topic and should be verified in other similar cohorts. These data can be helpful to inform patients on risk for infections and their role in prognosis, but also be helpful in sample size calculations for future clinical trials.

CONCLUSION

Individuals with biopsy-proven ALD are at a three-fold higher rate of infections compared with reference individuals and die more often after infection than the general population. Also, individuals *without* cirrhosis seem to be at substantially increased risk for infections, suggesting the need for increased vigilance and watchful surveillance of ALD patients across the histological spectrum.

CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work. Other conflict of interest are listed below. Hannes Hagström: consulting fees from Novo Nordisk and Gilead. Research grants to institution from Gilead, Astra Zeneca, Intercept, EchoSens, Pfizer, MSD. Advisory Board at Bristol-Myers Squibb and Gilead. Unrelated to current work. Maja Thiele: Speaker's fee from EchoSens, Siemens Healthcare, Norgine. Consulting fee from GE Healthcare. Unrelated to current work. Jonas F Ludvigsson: coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen Corporation. Unrelated to current work. Rajani Sharma: Speaker for Takeda. Unrelated to current work. Jonas Söderling, Bjorn Roelstraete, Tracey G Simon, Anna Röckert Tjernberg: nothing to disclose.

ETHICS APPROVAL

The study was approved by the Regional Ethics Committee in Stockholm (2014/1287-31/4).

AUTHOR CONTRIBUTIONS

Study conception and design: All. Acquisition of data: Jonas F Ludvigsson. Statistical analysis: Jonas Söderling. Analysis and interpretation of data: All. Drafting of the manuscript: Hannes Hagström. Critical revision: All. Guarantor of the article: Jonas F Ludvigsson. All authors approved the final version of the article, including the authorship list. Writing Assistance: None.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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