Extra-hepatic mMorbidity and mMortality in aAlcohol-related lLiver dDisease: Systematic rReview and mMeta-analysis

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Figure S1 PRISMA flow chart.

Figure S2 (A) rate of fatal extra-hepatic events in ALD in studies rated low risk of bias. (B) rates of fatal extra-hepatic events in ALD compared to control groups and persons with alcohol use disorder in studies rated low risk of bias.

Figure S3 (A) risk of fatal extra-hepatic events compared to control groups without a diagnosis of ALD in studies rated low risk of bias. (B) risk of fatal extra-hepatic events in groups with alcohol use disorder or ALD in studies rated low risk of bias.

Figure S4 Risk difference of liver vs. non-liver related mortality by method diagnosis.

Figure S5 Comparison of liver vs. non-liver mortality in histological steatohepatitis and clinical alcoholic hepatitis, risk difference calculated with random-effect meta-analysis.

Figure S6 Comparison of liver vs. non-liver mortality by source of data in included studies.

Figure S7 Meta-regression to illustrate trends in relative risk of liver vs. non liver related mortality over time.

Table S1 Characteristics of included studies of persons with alcohol use disorder (identified from systematic reviews by Roerecke, Adbdul-Rahman and Laramee.[5–7])

TABLE S2 Characteristics of included studies of ALD.

TABLE S3 Assessment of bias in included studies.

TABLE S4 Rates of outcomes when only studies at low risk of bias are included in meta-analysis.

TABLE S5 Risk of outcomes when only studies at low risk of bias are included in meta-analysis.

Abstract

Background

Alcohol use increases the risk of many conditions in addition to liver disease; patients with alcohol-related liver disease (ALD) are therefore at risk from both extra-hepatic and hepatic disease.

Aims

This review synthesises information about non-liver-related mortality in persons with ALD.

Methods

A systematic literature review was performed to identify studies describing non-liver outcomes in ALD. Information about overall non-liver mortality was extracted from included studies and sub-categorised into major causes: cardiovascular disease (CVD), non-liver cancer and infection. Single-proportion meta-analysis was done to calculate incidence rates (events/1,000 patient-years) and relative risks (RR) compared ~~to~~ with control populations.

Results

Thirty-seven studies describing 50,302 individuals with 155,820 patient-years of follow-up were included. Diabetes, CVD and obesity were highly prevalent amongst included patients (5.4%,

10.4% and 20.8% respectively). Outcomes varied across the spectrum of ALD: in alcohol-related fatty liver the rate of non-liver mortality was 43.4/1,000 patient-years, whereas in alcoholic hepatitis the rate of non-liver mortality was 22.5/1,000 patient-years. The risk of all studied outcomes was higher in ALD compared to with control populations: The RR of death from CVD was 2.4 (1.6–3.8), from non-hepatic cancer 2.2 (1.6–2.9) and from infection 8.2 (4.7–14.3).

Conclusion

Persons with ALD are at high risk of death from non-liver causes such as cardiovascular disease and non-hepatic cancer.

Keywords

Alcohol-related liver disease

Meta-analyses

Outcomes research

Epidemiology

Cirrhosis

Study highlights

What is known?

- Alcohol-related liver disease is a leading cause of liver-related morbidity and mortality.
- Excess alcohol consumption increases the risk of a wide variety of ill health.

What is new here?

- A systematic review and meta-analysis of non-liver ill health in persons with ALD.
- Comorbidity is common in ALD, with high rates of obesity, diabetes and cardiovascular disease.
- The risk of cardiovascular disease and malignancy are increased in ALD, compared to control groups without ALD and groups with alcohol use disorder.

ABBREVIATIONS

ALD	Alcohol-related liver disease
CVD	cardiovascular disease
RR	relative risk
AFLD	alcohol-related fatty liver
ASH	alcohol-related steatohepatitis
AH	alcohol-related hepatitis
HCC	hepatocellular carcinoma
AUD	alcohol use disorder
ALD-C	compensated cirrhosis

ALD-DC d~~D~~ecompensated cirrhosis

1. INTRODUCTION

Alcohol-related liver disease (ALD) is common worldwide and a frequent cause of ill health and premature mortality. ALD causes a spectrum of liver disease ranging histologically from hepatic steatosis (alcohol-related fatty liver, AFLD), steatohepatitis (alcohol-related steatohepatitis, ASH) to cirrhosis.[1] Alcohol-related hepatitis (AH) is an acute manifestation of ALD that is usually diagnosed clinically~~,~~ and is typified by jaundice and liver failure.[2] Hazardous alcohol intake is associated with many medical conditions[3] and consequently patients with ALD are at risk of other causes of morbidity and mortality in addition to liver disease.

Our group recently described the natural history of ALD based on published studies of histologically proven disease, where we considered progression of disease and mortality.[4] The information from these biopsy-based studies allowed us only to describe mortality in broad categories of 'liver-related' and 'non-liver-related'. Extra-hepatic disease in patients with ALD has not been systematically reviewed. The purpose of this analysis was to synthesise the available evidence regarding the rate and risk of extra-hepatic mortality from specific major causes in ALD.

2. METHODS

A systematic literature review was performed in PubMed and Ovid (including OvidMedline + EMBASE classic), searching title and abstract using the search terms: morbidity OR mortality OR surviv* OR outcome* OR "natural history" OR prognos* AND "~~"~~liver disease"~~"~~ OR "liver fibrosis" OR cirrho* OR hepatitis* OR decompensat* AND alcohol* OR alcohol-related.

Search terms were formed through discussion between MDT and RP of key terms found in the current literature. Included were manuscripts published in English from 1948 until the date of

the literature search, limited to human studies with the full text available. The literature search was performed on the 6th of April 2020 and updated 28th June 2022. The titles of the manuscripts identified by the literature search were reviewed for relevance by MDT and those which appeared suitable were reviewed in detail. The second review was performed by MDT and RP. Manuscripts were included if they described a cohort of patients with any stage of ALD with a follow-up period of at least one year, and included information on the incidence and cause of mortality. The reference lists and citing literature of each included paper were reviewed to identify other relevant papers not found by the initial search.

After review of outcomes reported in included studies, major causes of non-liver mortality that were considered were: cardiovascular disease, extra-hepatic cancer (i.e., non-HCC or cholangiocarcinoma) and infection. In addition the totality of non-hepatic mortality was noted. For the purposes of this review, hepatocellular carcinoma (HCC) and cholangiocarcinoma were considered a liver-related event. Control groups described in included studies were used to compare rates and risks between ALD and non-ALD populations. To compare rates of disease between ALD and alcohol use disorder (AUD), recent comprehensive meta-analyses of physical outcomes in AUD were used as a source of relevant studies[5–7] (supplementary Table S1), and data extracted from individual studies that were included in these meta-analyses.

Data were manually extracted into a spreadsheet. Extracted data included: time period of study, source of data (registry, multi-centre or single centre), method of diagnosis, subtype of liver disease included, years of follow-up, fatal and non-fatal events, liver-related events, events in control populations, biochemical and anthropometric data at baseline. Information regarding explicit exclusion of other liver diseases through patient history and blood testing was noted. Information about control populations, when present, was also extracted to allow them to be described. Two authors (RP, MDT) extracted data and inconsistencies were resolved by consensus. Where standardised mortality rates or standardised incidence rates were reported in comparison with control groups, absolute numbers were calculated from this ratio using a cohort of the same size as the corresponding cohort with ALD. Several papers identified patients from the same databases but were all included as they reported different outcomes, or outcomes from different eras.

ALD was defined as per original authors and the means of diagnosis (biopsy or clinical) recorded. ALD was considered as a single entity encompassing the whole spectrum of disease if described as such in original papers, and where possible sub-groups of ALD were considered: AFLD, AH, cirrhosis (ALD-C) and decompensated cirrhosis (ALD-DC). AH was defined primarily as a clinical entity rather than defined on histological grounds. The presence of ascites or bleeding varices were considered to represent decompensated cirrhosis based on the description of the natural history of cirrhosis by D'Amico and colleagues.[8]

Random effect meta-analysis using logit transformation to calculate an overall proportion was done for the following measures:

1. prevalence of extra-hepatic diseases at the beginning of follow-up
2. relative risk (RR) of liver-related versus non-liver-related mortality within groups with ALD
3. Mortality rate from extra-hepatic causes during follow-up calculated as events per 1,000 patient-years
4. relative risk of extra-hepatic mortality between ALD and control populations

Meta-analysis was performed using the 'meta' package in R. Sensitivity analysis for each outcome was done using only papers at a low risk of bias (see below). Additional subgroup analyses were undertaken to examine risk of liver vs. non-liver mortality between cohorts where all participants underwent biopsy and cohorts that relied on clinical or radiological information and between histological steatohepatitis and patients with the clinical syndrome of AH, and to assess differences over time between cohorts using the decade of the end of follow-up to define era of study. Data are presented as summary forest plots to allow for comparison between stages of liver disease and between ALD, AUD and control groups.

The risk of bias in included studies was assessed with the Newcastle–Ottawa tool for cohort studies.[9] Two authors (RP, MDT) scored each study and papers were rated as being at high or low risk of bias. A cut-off of seven, and scoring within each of the domains, indicated studies at low risk of bias. This systematic review was registered with the PROSPERO database (reference

CRD42019141607). All authors had access to the study data and reviewed and approved the final manuscript.

3. RESULTS

The literature search identified 116 papers of which 37 papers were included[10–46] (supplementary Figure S1). The included papers described outcomes in 50,302 patients with ALD with a total of 155,820 patient-years of follow-up (supplementary Table S2). The risk of bias of each study, assessed with the Newcastle–Ottawa tool, are shown in supplementary Table S3. Thirteen studies were considered to be at low risk of bias.

3.1. Case and control definition

Of the 37 included studies, seven (including 15,204 participants) reported outcomes in AFLD, five studies (2,541 participants) described outcomes in AH,[10, 18, 27, 33, 35] Thirteen studies (15,302 participants) described outcomes in cirrhosis,[21–24, 29, 31, 34, 36, 38, 39, 42, 43, 45] four studies (635 participants) described outcomes in decompensated cirrhosis[11–13, 25] and a further 11 studies (18,866 participants) reported outcomes for ALD as a single entity.[14, 17, 21, 26, 28, 30, 32, 34, 37, 40, 44] Sixteen studies (6,265 participants)[16, 18–21, 26–30, 36, 37, 41, 45–47] defined subgroups of ALD through biopsy, six studies (1,642 participants) used a combination of biopsy and clinical diagnosis,[12, 14, 31, 32, 34, 43] and 15 studies (42,395 participants) reported outcomes in patients diagnosed clinically.[11, 13, 15, 17, 22–25, 33, 35, 38–40, 42, 44] Two further studies reported on patients with histological steatohepatitis (169 participants), but not necessarily the clinical syndrome of AH[19, 41] and were considered separately. The median of reported age ranges of included studies was 52 years (range of medians 39.5–59 years), the median gender distribution was 74% male (45–100%).

Four studies described specific outcomes in control groups that included a total of 33,563 individuals.[21, 39, 42, 44] Two of these studies[21, 44] described a specific control group and two[39, 42] referred to a control population to calculate standardisedstandardized mortality rate (SMR) or

standardisedstandardized incident ratio (SIR). Explicit screening for and removal of patients with liver disease from the control group was only done in one study[44] where direct patient information was available, other studies relied on information from medical records to exclude other causes of liver disease. Limited data were reported about characteristics of studied populations. The median of reported average age in control groups was 45 years (range of reported medians 40 – 49) and 52% were male.

3.2. Prevalence of extra-hepatic morbidity at baseline

Ten studies[11, 12, 16, 17, 19–21, 37, 43, 44] described the presence of extra-hepatic co-morbidity at the beginning of follow-up. Co-morbidity due to diabetes, cardiovascular disease or obesity was common: 5.4% of studied individuals had diabetes, 10.4% had cardiovascular disease, and 20.8% were classified as obese (body mass index greater than 30 kg/m^2). The study by Chang et al[15] used a lower cut-off for obesity of 25 kg/m^2 and was excluded from this analysis; including this study increased the apparent prevalence of obesity to 61.1%. Extra-hepatic cancer was present at baseline in 8.3% of individuals in reported cohorts. The prevalence of comorbidity did not vary across types of liver disease except in diabetes where higher rates were seen in cohorts with cirrhosis. In comparison to with control groups or groups of persons with AUD, cohorts of ALD had higher rates of diabetes and cardiovascular disease, whereas the prevalence of extra-hepatic cancer and obesity were comparable to control groups.

3.3. Extra-hepatic mortality

3.3.1. Hepatic versus extra-hepatic mortality

In total, 21,376 deaths were reported across the included studies. Overall, 54.7% of deaths in included studies were due to liver disease (7,037 deaths in 33 studies). Non-hepatic causes of death (5,410 deaths in 30 studies) were recorded as: an average of 6.6% of deaths due to cardiovascular disease (2,321 deaths in 30 studies), 5.7% due to cancer (2013 deaths in 33 studies), and 1.9% due to infection (521 deaths reported in 18 studies). The cause of death varied considerably across the spectrum of liver disease: in AFLD, liver-related mortality accounted for 23.8% of deaths, whereas in ALD-DC 70.8% of deaths were liver-related (fFigure

1A). As a point of clarification, the reported mortality rates are specific to the group of studies that report each outcome as opposed to the total across all the studies.

In patients with AFLD the risk of liver mortality was lower than that of non-liver-related mortality (RR 0.25, 95% CI 0.16–0.38, p = <0.01). All other subtypes of ALD had a higher risk of liver-related deaths compared with non-liver-related mortality: AH RR 5.27 (95% CI 1.96–14.14, p < 0.01), ALD-C RR 1.78 (95% CI 1.31–2.42, p < 0.01), ALD-DC RR 2.38 (95% CI 2.00–2.82, p < 0.01). For studies that considered ALD as a whole, there was no statistically significant difference in risk between liver and non-liver mortality: RR 1.14 (95% CI 0.56–2.32, p = 0.722). These risks were in excess of AUD cohorts where the RR for liver vs. non-liver mortality was 0.14 (95% CI 0.10–0.19, p < 0.01) (Figure 1B).

3.4. Rate of extra-hepatic mortality

The rate of non-liver and liver-related mortality derived from meta-analysis are shown in Table 1. The rate of non-liver mortality was higher in all stages of ALD than in control groups (overall rate of non-liver-related mortality in ALD 34.3 events/1000 patient-years vs. 20 events/1000 patient-years). The overall rate of cardiovascular mortality in ALD was 8.4 events/1000 patient-years, overall rate of cancer-related mortality was 12.1 events/1000 patient-years, and overall rate of infection-related mortality was 10.5 events/1000 patient-years (Figure 2A). The rates of all types of mortality were numerically higher in ALD compared with control groups or AUD (Figure 2B). This was statistically significant when considering rates of cancer-related or infection-related deaths. When only studies considered to be at low risk of bias were included, the overall pattern of results remained but statistical significance between stages of liver disease was lost (supplementary Figure S2), but the increased rate of cancer and infection-related mortality in ALD compared with control groups or groups with AUD remained statistically significant.

3.5. Risk of extra-hepatic mortality

Studies that reported on mortality in ALD and control groups[21, 24, 33, 38–40, 42, 44] were analysed to describe the relative risks of non-liver mortality in ALD compared ~~to~~ with control populations. Persons with ALD had a higher risk of all studied outcomes compared ~~to~~ with control populations (T~~t~~able 2, F~~f~~igure 2C). The risk of cardiovascular- and cancer--related deaths in ALD was in excess of populations with AUD (F~~f~~igure 2D). There was insufficient data to analyse the relative risk of infection-related events. Limiting this analysis to only studies at low risk of bias produced the same pattern of results but with insufficient data to reach statistical significance (supplementary F~~f~~igure S3).

3.6. Sensitivity and subgroup analyses

Sixteen studies including 6~~,~~054 participants selected only patients with biopsy-confirmed disease and reported on cause of mortality: no differences were seen in the risk of liver versus non-liver--related mortality when considering the method of diagnosis (supplementary ~~f~~Figure S4). Five studies (including 2~~,~~541 participants) reporting patients with clinical AH[10, 18, 27, 33, 35] were compared to two studies (169 participants) reporting histological steatohepatitis.[19, 41] The risk of liver-related mortality was greater in patients with clinically diagnosed AH (RD 0.32, 95% CI 0.15–~~–~~0.50, p < ~~0~~.01), but no difference in risk was seen in patients with histological steatohepatitis (RD liver vs. non-liver mortality, –~~-~~0.32, –~~-~~0.75 – 0.~~10~~ 10, p = ~~0~~.14) (supplementary Figure S5). Studies were compared in terms of the source of their data: single centre, multi-centre or registry. Single-centre studies tended to report a greater risk of liver-related mortality (RD 0.17, 95% CI 0.03–~~–~~0.30, p = ~~0~~.02) compared ~~to~~ with multi-centre (RD ~~-~~–0.10, –~~-~~0.46~~–~~–0.27, p = ~~0~~.60) or registry studies (RD –~~-~~0.07, –~~-~~0.02~~–~~–0.16, p = ~~0~~.14) (supplementary F~~f~~igure S6). Meta-regression to analyse changes in the risk of liver versus non-liver mortality over time did not show any significant changes over five decades (estimate 0.0092, p -= ~~0~~.244) (supplementary F~~f~~igure S7).

4. DISCUSSION

Hazardous alcohol intake increases the risk of many adverse health events in addition to liver disease. Holistic management of patients with any stage of ALD should be underpinned by an

understanding of these risks. This systematic review is the first synthesis of all the available data to describe the risks of extrahepatic mortality in ALD. Our results confirm that liver-related mortality is the main cause of death in ALD, and also show that the risk of major fatal causes of ill health such as cardiovascular disease and non-HCC cancer are increased in persons with ALD. This risk is in excess of persons with AUD or control populations without ALD.

As might be expected, the rate of liver-related ill health increases across the spectrum of liver disease. Interestingly the risk of significant ill health from non-liver causes also increases for example, in people with AFLD the relative risk of death due to cardiovascular disease compared to with control populations was 1.4 (1.1 1.7), whereas in AH the relative risk was 5.0 (2.7 9.7) and in people with cirrhosis the relative risk was 2.5 (1.4 4.6) (Ttable 2). These differences may reflect other factors such as increasing age or more significant alcohol excessexcess, but it is possible that the presence of liver disease is a risk for excess mortality and morbidity from extrahepatic disease. The increased risk of health problems in AFLD, although numerically smaller than other subtypes of ALD, is important as this group is the most prevalent subgroup of ALD and are more likely to be seen in primary care or non-liver/gastroenterology clinics. The increased risk may not be recognised if the focus of management is solely on exclusion of serious liver disease.

Alcohol consumption is known to be associated with both cardiovascular disease and cancer[3] and therefore the excess risk associated with ALD compared to with control populations is likely largely attributable to alcohol rather than liver disease per se. However, excess risk was seen in ALD compared to groups with AUD, further raising the possibility of the presence of liver disease contributing to the development of extrahepatic ill-health. There are biological changes that occur in ALD both within the liver and outside it that will increase cardiovascular risk, for example impaired glucose metabolism and altered lipid profiles.[48] Moderate alcohol use has been associated with a decreased risk of cardiovascular disease[49] but the populations studied here drink at levels beyond protective consumption. Clarity about the additional risk that ALD may confer in excess of hazardous alcohol use will require a careful prospective study of heavy drinkers with and without liver disease.

This meta-analysis is based on a robust search of the available literature and reflects the current state of understanding of extra-hepatic mortality in ALD. However, there are conspicuous shortcomings in the literature: Data are scarce or entirely lacking for several of the areas addressed in this paper especially regarding non-cirrhotic disease, or non-fatal events. This latter point is important as many papers report on cause of death but not on important and common causes of non-fatal ill health. Furthermore, cause of death is often not an exact science. Acquiring accurate and consistent mortality data across the studies is challenging and likely to introduce an element of reporting bias that may influence the conclusions that can be drawn. For example, a patient with spontaneous bacterial peritonitis may have a cause of death listed as either infection or decompensated liver disease. The effect of abstinence, which is an important predictor of liver-related outcomes in ALD, is also not explored in sufficient detail to attempt quantitative analysis on the effect of extra-hepatic outcomes. Other important factors for cardiovascular disease or malignancy such as smoking are not addressed in sufficient detail to examine their effects. The majority of the studies included in this meta-analysis used cases of ALD that had been diagnosed in secondary care, and many of them used biopsy to confirm a diagnosis. The data from meta-analysis are therefore directly relevant to individuals who are managed from secondary care, and generalising the risks presented here to the wider population of hazardous drinkers should be done with a degree of caution.

The Newcastle–Ottawa tool is validated in the assessment of risk of bias for cohort studies[50] and was used to eliminate the studies with greatest risk of bias. The Newcastle–Ottawa tool is however a crude method of assessing quality and it is acknowledged that some bias will inevitably still be present in the remaining studies. In a meta-analysis such as this, when including such a broad range of data sets there is an inherent risk of bias, namely reporting bias, that is hard to account for statistically. Therefore each of the included studies, with a Newcastle-Ottawa rating of 'Good', were reviewed for bias that had not yet been addressed. Particular attention was focused on two main studies, Chang et al[15] (n = 13,890) and Sahlman et al.[40] (n = 11,873), as these accounted for 68% of all included patients in studies rated as 'Good'. Several studies including the study by Sahlman et al[40] obtained data from hospitalised inpatients, effectively excluding the 'healthy liver disease' population in the community and this

lack of heterogeneity between the groups inherently creates a selection bias. Sahlman et al[40] reported on 11,873 patients who were followed up for a total of 8468 patient-years. Though the follow-up period was up to five years, the average follow-up was less than one year which does raise questions about selection bias. This may have significant bearing on the reported standardised mortality. The study by Chang et al[15] is also at risk of selection bias as the cohort was a ~~self selecting~~self-selecting group of people who had undergone a comprehensive health exam and therefore not representative of the population. They are more likely to be from a higher socio-economic group and thus be afforded the associated health privileges this brings.[51] In addition, this cohort used a self-administered questionnaire which leaves the study vulnerable to reporting bias.

However, despite the methodological weaknesses identified, it must be acknowledged that there are inherent limitations to performing large population analyses, with restrictions on datasets available as well as resources assigned to conduct the study. Information on certain outcomes, such as reporting on HCC is limited in some studies. There is a lack of good-quality studies with a low risk of bias, particularly with a focus on alcohol-related hepatitis and decompensated cirrhosis. As a result, there is a continuing need for good-quality natural history studies, however, the challenges of performing these are recognised. Despite the overall lack of studies with a low risk of bias, in this analysis, the majority of the patients were derived from studies that were assessed to be at a low risk of bias via the Newcastle-Ottawa tool. Over 50,000 patients were assessed in this meta-analysis, of which 75% were obtained from 13 studies with a low risk of bias. Any bias within an individual study is therefore likely to be, at least in part, mitigated by the meta-analysis.

Our findings add to the existing literature as the first systematic synthesis of published outcome data. Our findings are consistent with a large study of mortality in chronic liver disease that was not suitable for inclusion in this meta-analysis: Kim et al examined trends in mortality in various types of chronic liver disease using data from the US National Vital Statistics System.[52] Cardiovascular disease and cancer were frequent causes of death, but outweighed by liver-related mortality in this cohort of patients diagnosed with ALD in secondary care settings. Recent work from our group used meta-analysis to examine rates of mortality in histologically-

proven disease.[4] This previous work did not examine causes of mortality or morbidity beyond broad categories of 'liver' and 'non-liver' and as such the data presented here adds to the previous analysis by illustrating specific causes of ill health in ALD. There was insufficient information to consider differential effects of abstinence on liver and non-liver-related ill health although this information would be of value to clinicians and to patients.

This systematic review and meta-analysis shows that the risk of non-liver mortality as well as major morbidity such as cardiovascular disease and cancer are increased in persons with ALD. This review also highlighted deficiencies in the available literature regarding outcomes in ALD and emphasises the urgent need for high-quality natural history studies in ALD to address these shortcomings. These data confirm that excess mortality and morbidity in ALD are driven not only by liver disease but also by other non-communicable diseases and will support appropriate holistic care of individuals with all stages of ALD.

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CONFLICT OF INTEREST STATEMENT~~Conflicts of interest~~

MDT has no conflicts of interest to declare. GA has no conflicts of interest to declare. MA has no conflicts of interest to declare. MB has no conflicts of interest to declare. EF has no conflicts of interest to declare. HH's institution has received research grants from AstraZeneca, EchoSens, Intercept, Gilead, MSD and Pfizer for unrelated work. HH has served as a board advisory member

for Gilead and Bristol Myers-Squibb. SJ has no conflicts of interest to declare. AK has no conflicts of interest to declare. AL has no conflicts of interest to declare. SM has no conflicts of interest to declare. AM has no conflicts of interest to declare. NR has no conflicts of interest to declare. MT has received speaker's fees from Echosens, Norgine and Siemens Healthcare. Advisory fee from GE Healthcare. IAR has no conflicts of interest to declare. RP has received speaking fees from Norgine, Siemens and Shionogi, and consulting fees from DURECT.

CONSENT

No patient consent was necessary for this meta-analysis.

ETHICS STATEMENT

No ethical approval was necessary for this meta-analysis.

GUARANTOR OF THE ARTICLE

Dr R Parker is the guarantor of this article.

PERMISSIONS

All data and images included are original material.

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FIGURE 1 (A) Overall cause of death in ALD and by differing stages of ALD, compared ~~to~~ with persons with alcohol use disorder. (B) Relative risk of liver versus non-liver mortality in differing stages of ALD.

FIGURE 2 (A) R~~r~~ate of fatal extra-hepatic events in ALD. (B) R~~r~~ates of fatal extra-hepatic events in ALD compared ~~to~~ with control groups and persons with alcohol use disorder. (C) ~~r~~Risk of fatal extra-hepatic events compared ~~to~~ with control groups without a diagnosis of ALD. (D) R~~r~~isk of fatal extra-hepatic events in groups with alcohol use disorder or ALD.

TABLE 1 Rates of non-liver and liver-related mortality (events/1000 patient-years).

	Mortality rate (deaths per 1000 patient-years)											
	Cardiovascular		Cancer		Infection		All non-liver		Liver		Total mortality	
	rate	95% CI	rate	95% CI	rate	95% CI	rate	95% CI	rate	95% CI	rate	95% CI
Overall	**8.9**	6.3–12.3	**10.9**	8.2–14.5	**7.6**	4.9–12.0	**35.7**	27.9–45.7	**47.5**	32.6–69.2	**101.7**	78.5–131.8
Fatty liver	**11.4**	6.8–19.0	**10.2**	6.9–15.1	**1.6**	0.7–3.8	**43.4**	30.1–62.7	**11.5**	6.1–21.6	**55.6**	37.0–83.5
Alcoholic hepatitis	**6.2**	4.9–7.8	**5.8**	2.6–13.0	**18.3**	14.5–23.1	**22.5**	12.4–41.0	**109.5**	74.0–160.5	**135.2**	111.3–164.2
Cirrhosis	**12.8**	7.3–22.3	**13.0**	7.5–22.6	**4.5**	2.0–10.5	**41.2**	25.7–66.0	**79.1**	53.1–117.6	**120.3**	84.8–170.7

Decompensated cirrhosis	**3.5**	1.7–7.3	**8.3**	5.6–12.3	**10.1**	5.7–17.9	**35.9**	18.4–70.1	**99.4**	55.9–176.9	**135.6**	76.7–240.0
All ALD[a]	**8.4**	3.7–19.0	**12.1**	6.6–22.5	**10.5**	4.8–22.8	**33.4**	18.5–60.3	**30.0**	13.0–69.0	**92.5**	45.3–188.7

[a]All ALD refers to studies that reported outcomes for alcohol-related liver disease as a whole without describing the stage of disease.

TABLE 2 Relative risk of non-liver and liver-related mortality in persons with alcohol-related liver disease.

	Relative risk of mortality (compared ~~to~~ with control populations)													
	Cardiovascular			Cancer			Infection			All non-liver			Liver	
	RR	95% CI	*p*	RR	95% CI	*p*	RR	95% CI	*p*	RR	95% CI	*p*	RR	95% CI	*p*
Overall	2.4	1.6–3.8	<~~0~~.01	2.2	1.6–2.9	<~~0~~.01	8.2	4.7–14.3	<~~0~~.01	2.2	1.6–3.1	<~~0~~.01	74.1	14.3–384.8	<~~0~~.01
Fatty liver	1.4	1.1–1.7	~~0~~.02	1.2	0.8–1.6	~~0~~.38				1.5	1.3–1.7	<~~0~~.01	53.3	27.1–	<~~0~~.01

														104.8	
Alcoholic hepatitis	5.0	2.7–9.7	<0.01	2.3	1.2–4.3	<0.01									
Cirrhosis	2.5	1.4–4.6	<0.01	2.3	1.5–3.7	<0.01	7.8	5.8–10.5	<0.01	3.0	1.8–5.0	<0.01	90.0	7.4–1099.6	<0.01
Decompensated Cirrhosis	4.0	3.6–4.5	<0.01	2.2	1.7–2.9	<0.01	31.5	11.7–85.1	<0.01	2.9	2.6–3.3	<0.01	162.7	77.5–341.6	<0.01
All ALD[a]	1.8	0.4–7.7	0.46	2.4	1.0–3.7	0.05				1.3	1.1–.6	0.02	40.3	14.3–384.8	<0.01

[a]All ALD refers to studies that reported outcomes for alcohol-related liver disease as a whole without describing the stage of disease.