Cause-specific mortality in patients with alcohol-related liver disease: a population-based study

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Abstract

Background

Knowledge of the causes of death is essential to prevent premature death in alcohol-related liver disease (ALD). We examined cause-specific mortality, including death due to specific cancers, in 15 years after diagnosis of ALD.

Methods

We used nationwide health registries to identify patients diagnosed with ALD from 2002 to 2017 in Denmark and followed them for the underlying cause of death through 2019. We estimated the cause-specific mortality and investigated whether the cause-specific mortality differed by sex, age (<50, 50-59, and ≥60 years), ALD severity at diagnosis (decompensated cirrhosis, compensated cirrhosis, steatosis, and alcoholic hepatitis), and presence of diabetes.

Findings

The study included 23,385 patients with incident ALD. Patients had a median age of 58 years, 15,819 (68%) were men, and 15,358 (66%) had cirrhosis. During 111,532 person-years of follow-up, 15,692 (67%) died. Liver disease was the leading cause of death. In the first five years after ALD diagnosis, liver disease caused more than half of all deaths, and the 5-year risk of death due to liver disease was 25·8% (95%CI: 25·3-26·4%). Beyond five years of ALD diagnosis, cancer, alcohol use disorder, and cardiovascular disease became more frequent. HCC was the dominant cause of cancer death, followed by lung cancer, with 10-year risks of 2·5% (95%CI: 2·3-2·7%) and 1·9% (95%CI: 1·7-2·1), respectively. The 10-year risk of death due to liver disease of 30% was similar for patients in all age groups and independent of sex and diabetes but three times higher for those with decompensated cirrhosis than steatosis.

Interpretation

Patients diagnosed with ALD were at high risk of dying from liver disease many years after diagnosis, irrespective of age and sex. Death due to specific cancers, including HCC, each contributed minimally to the total mortality in patients with ALD.

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Introduction

Alcohol-related liver disease (ALD) is a preventable disease that often develops over several years before it leads to symptoms and is eventually diagnosed. Worldwide, more than 26 million individuals have chronic ALD, with the highest prevalence of patients in Europe and lowest in the Eastern Mediterranean region.[1] Patients with ALD have a 1-year mortality risk of 25% despite their young median age of 60 years.[2] Knowledge of the causes of death in patients with ALD is essential in the prevention of these premature deaths. For example, if liver disease is the leading cause of death in the first years after ALD diagnosis, we may consider initiatives to detect ALD earlier. Moreover, knowledge of cause-specific cancer death in ALD patients is wanted. International guidelines propose that surveillance for specific cancers, such as hepatocellular carcinoma (HCC), may be relevant for selected patients with ALD.[3] According to good clinical practice, a cancer surveillance program is only relevant if it is expected to reduce cancer-specific mortality and is cost-effective. [4]

Previous literature has investigated the cause of death in ALD patients and found high liver-related mortality in patients with ALD.[5–11] Hagström et al.[7] investigated three causes of death until 40 years after biopsy-proven ALD in 3,453 patients and found that the increased risk of liver-related death plateaued after five-ten years. This indicates that cause-specific mortality in ALD patients should be investigated according to time since ALD diagnosis. Moreover, long-term follow-up is necessary to study cancer death.[12] Besides Hagström et al., no other studies have assessed cause-specific mortality according to time since ALD diagnosis with more than five years of follow-up.

Our study filled this literature gap with an investigation of ten causes of death from ALD until 15 years after diagnosis. The cohort was more extensive than earlier investigations with >20,000 ALD patients, which enabled stratification by sex, age, severity of ALD, and diabetes.

Methods

The study was a historical cohort study based on nationwide healthcare registries of patients with a first-time diagnosis of ALD from January 2002 to December 2017 in Denmark. Patients were followed for cause-specific mortality until December 2019, which provides all patients with at least two years of follow-up data.

Data sources

We obtained data from The Danish National Patient Registry[13], The Danish Cause of Death Registry[14], The Civil Registration System[15], and the Danish Cancer Registry.[16]

The Danish National Patient Registry

The Danish National Patient Registry was established in 1977 and contains data from all hospital admissions and, since 1995, outpatient hospital contacts and emergency room visits. The registry records diagnosis codes according to the International Classification of Diseases (ICD-8) before 1994 and ICD-10 from 1994.[13]

The Danish Cause of Death Registry

The Danish Cause of Death Registry holds data about the cause of death, date of death, place of death, manner of death, and autopsy information.[14] The causes of death are recorded as underlying, immediate, or contributory and coded according to WHO's tenth international classification (ICD-10). For all analyses, we used the underlying cause of death and grouped the causes as shown in Supplemental Table S1.[5,8,9] As an additional investigation; we extracted the contributory causes of death for each underlying cause of death category (Supplemental Table S6). We began the study period in 2002 because Denmark introduced the Automated Classification of Medical Entities (ACME) in the Danish Cause of Death Registry in 2002.[14] The ACME system selects an underlying cause of death from codes reported by the physician on the death certificate.[17] The underlying cause of death was missing in 66 (0·4 %) patients in our cohort, corresponding to the national number of cause-of-death registrations that are incomplete (0·3-0·6 %).[14]

Other registries

The Civil Registration System records all persons alive with permanent residence in Denmark since 1968, and the vital status is continuously updated. All persons in the Civil Registration System are assigned a unique identifier number, enabling individual-level data linkage across registries.[15] The Cancer Registry has recorded all new cancer cases in Denmark since 1943 and holds different tumour characteristics. For this study, we used the ICD-10 diagnosis of the tumour.[16]

Study population

We included all Danish patients with a first-time diagnosis of ALD from 1 January 2002 to 31 December 2017 in the Danish National Patient Registry. To identify patients, we used the ICD-10 code K70 (Alcoholic liver disease), which includes alcoholic fatty liver disease (ICD-10: K70.0), alcoholic hepatitis (ICD-10: K70.1), alcoholic fibrosis and sclerosis of the liver (ICD-10: K70.2), alcoholic cirrhosis (ICD-10: K70.3), alcoholic hepatic failure (ICD-10: K70.4), and alcoholic liver disease, unspecified (ICD-10: K70.9). Patients with a previous ALD diagnosis in ICD-8 (4560x, 5710x, 5718x, 5719x, 7853x) or ICD-10 from 1977-2001 were excluded.

The sex and age were obtained from the Civil Registration System at the time of ALD diagnosis, and we included patients aged 18 years or older. Based on diagnosis codes in the National Patient Registry, we defined the severity of liver disease at the time of ALD diagnosis. We divided patients into four groups: decompensated cirrhosis, compensated cirrhosis, alcoholic hepatitis, and steatosis/unspecified liver disease. The applied diagnosis codes are shown in Supplemental Figure S1. We defined the patients' comorbidity burden according to the Charlson comorbidity index score, excluding codes for liver disease. We obtained comorbidity burden five years before and until ALD diagnosis from the National Patient Registry.[18] We were able to collect information about comorbidity five years before ALD diagnosis for all patients. In addition, we obtained information on the presence of diabetes type 1 and 2 from the National Patient Registry (ICD-10: DE10-DE11 + DE14).

Cause-specific mortality

We followed patients with ALD for the following causes of death: liver disease, hepatocellular carcinoma (HCC), cancer other than HCC, alcohol use disorder, cardiovascular disease, infection, gastroenterological disease, respiratory disease, external causes, cerebrovascular disease, and other causes. See Supplemental Table S1 for the definition of groups.

Cancer-specific mortality

In addition, we followed patients with ALD for the following cancer deaths: HCC, oropharyngeal, lung, colorectal, breast, prostate, urological, and pancreas cancer. See Supplemental Table S2.

Statistical analyses

The primary outcome was the underlying cause of death. We followed patients from ALD diagnosis until death and censored survivors at emigration or the end of follow-up on 31 December 2019. First, we examined the distribution of causes of death according to time since ALD diagnosis (≤1 month, 1 month-1 year, 1-5 years, >5 years). Second, we used the Kaplan-Meier Method to estimate all-cause mortality. Third, we examined cause-specific mortality and used the cumulative incidence function, considering the competing risk of death from any other cause than the cause in question.[19] Fourth, we repeated the analyses in subgroups according to sex, age, the severity of ALD diagnosis, type of hospital care, and diabetes – assessed at the time of ALD diagnosis.

Finally, we did a sensitivity analysis in relation to cancer death, where we used diagnoses from the Danish Cancer Registry. If a patient had a diagnosis code in the Danish Cancer Registry, we changed the cause of death to this specific code. Thus, we repeated our calculation of cause-specific mortality with the modification that a cancer diagnosis in the Danish Cancer Registry overruled any other underlying cause of death in the Cause of Death Registry. We did this analysis to evaluate if a cancer diagnosis deviated from the underlying cause of death and, thereby, to evaluate if we underestimated the importance of cancer death. For all statistical analyses, we used the statistical software Stata 17.

Ethics

Our research was conducted using pseudo-anonymized data from the Danish health registries. Approval from an ethics committee or written consent from patients was unnecessary, according to the Danish Data Protection Agency laws.

Role of funding source

AK was supported by a grant from TrygFonden (152366). GA and PJ were supported by a grant from the Novo Nordisk Foundation (NNF18OC0054612). Both funders had no role in the study design, data collection, analysis, data interpretation, writing of the manuscript, or decision to publish. GA, AK, and PJ had access to the raw data.

Results

From 2002 to 2017, 23,385 patients were diagnosed with ALD in Denmark. The median age was 58 years (IQR 51-65). In the total cohort, 3,440 (15%) had decompensated cirrhosis, 11,918 (51%) had compensated cirrhosis, 6,474 (28%) had alcoholic steatosis, and 1,553 (7%) had alcoholic hepatitis at the time of diagnosis (Supplemental Table S5). In all, 802 (3%) of the patients had viral hepatitis, and 2,806 (12%) had diabetes. Patients were followed for 111,532 person-years, during which 15,692 (67%) died. The overall mortality rate was 14·1 per 100 person-years for the total cohort and 18·6 for both decompensated and compensated cirrhosis. The all-cause mortality risk was 11·5% (95%CI: 11·1-11·9%) at one month, 26·3% (95%CI: 25·7-26·9%) at one year, and 52·5% (95%CI: 51·8-53·1%) at five years for the total cohort.

Of the 15,692 patients who died during follow-up, 7,016 (45%) died from liver disease. Liver disease was the most frequent single cause of death at all time points until 15 years after ALD diagnosis (Figure 1). However, it was most dominant in the first years after ALD diagnosis. For example, liver disease was the cause of death in 1,728 (63%) patients who died during the first month after ALD diagnosis compared to 1,113 (29%) patients who died beyond five years after ALD diagnosis. In addition, death due to cancer, HCC, and other causes became more frequent over time, whereas death due to alcohol use disorder, cardiovascular disease, and infection did not differ much over time.

Liver disease was the leading cause of death in the first five years after ALD diagnosis, and other causes than liver disease were more likely beyond five years (Table 1, Figure 2). The 1-year risk of death due to liver disease was 15·0% (95%CI 14·5-15·4), and the 10-year risk was 31·4% (95%CI 30·8-32·1). In comparison, the 1-year risk of cancer-related death was 3·1% (95%CI 2·9-3·4), while the 10-year risk was 11·0% (95%CI 10·6-11·4). The risk of death due to cardiovascular disease or alcohol use disorder was lower, with 10-year risks of 4·5% (95%CI 4·3-4·9) for cardiovascular disease and 5·1% (95%CI 4·8-5·4) for alcohol use disorder. The 10-year risk of death from infection, gastroenterological disease, respiratory disease, external causes, and cerebrovascular disease was about 2%.

The three most common causes of cancer death after ten years of ALD diagnosis were HCC (10-year risk of 2·5 % [95%CI 2·3-2·7]), lung cancer (1·9% [95%CI 1·7-2·1]), and oropharyngeal cancer (1·0% [95%CI 0·9-1·1]) (Figure 3, Supplemental Table S3). The 10-year risk of death caused by HCC was 3·2% (95%CI 2·5-3·9) for decompensated cirrhosis and 0·7% (95%CI 0·5-1·0) for steatosis. Of all cancer deaths, 27 (1·1%) had cholangiocarcinoma as the underlying cause of death. The sensitivity analysis based on the Danish Cancer Registry showed similar 10-year risks compared to those based on the Cause of Death Registry (Supplemental Table S4).

The 10-year risk of death due to liver disease of approximately 30% was similar in men and women, for ages <50 years, 50-59 years, and ≥60 years, and irrespective of diabetes (Table 2). The risk of death due to liver disease increased gradually with increasing ALD severity from steatosis (10-year risk of 16%) to decompensated cirrhosis (10-year risk of 47%). The 10-year risk of death from extra-hepatic causes was high in patients with diabetes (10-year risk of 51%). This could not be explained solely by death due to cardiovascular disease; instead, it seemed that the extra-hepatic deaths were spread across all causes in patients with diabetes (Supplemental Figure S2, f). Patients diagnosed with ALD during admission were at higher risk of dying from liver disease than when diagnosed in outpatient clinics (10-year risk of 35% vs. 21%).

Liver disease was the most frequent, and alcohol use disorder was the second most frequent contributing cause of death (Supplemental Table S6). Alcohol use disorder was a contributing cause of death in 240 (46%) of patients with an external cause as their underlying cause of death, in 2,290 (33%) of patients with liver disease as the underlying cause of death, and in 260 (13%) of patients with cancer (other than HCC) as the underlying cause of death. Of the 7,016 patients with liver disease as the underlying cause of death, 63 (1%) had HCC recorded as a contributory cause of death.

Discussion

In this nationwide register-based study of 23,385 ALD patients, liver disease was identified as the leading cause of death. In the first five years after ALD diagnosis, liver disease caused more than half of all deaths, with a 5-year risk of 26%. This high risk was found to be similar across age, sex, and diabetes status. Beyond five years, extrahepatic causes dominated, with cancer, heart disease, and alcohol use disorder as the most common causes of death. The 10-year risk of death from cancer was 11%. HCC was the leading cancer cause, but no cancer caused more than 2.5% 10-year mortality.

Our study was consistent with previous literature, showing that liver disease was the most common cause of death in ALD patients.[5–11] Our mortality rate of 18·7 per 100 person-years for cirrhotic patients is identical to the mortality rate of 18·3 reported by Ratib et al. for 2,756 English cirrhosis patients.[8] Compared to our mortality rate for the total cohort of 14·1 per 100 person-years, Hagström et al.[7] found a lower rate of 9·1 per 100 person-years in 3,453 biopsy-proven ALD patients. The difference in the mortality rates is likely because biopsy-verified patients tend to have a better prognosis as they are healthy enough to undergo a biopsy. A biopsy is rarely needed for those with cirrhosis and is usually only used for those with an uncertain etiology. This means biopsy-proven ALD patients are a selected group compared to our nationwide patient cohort. Ratib et al. found a 5-year risk of liver-related death of 47%, extrahepatic malignancy of 5%, and cardiovascular death of 5 % in decompensated alcoholic cirrhotic patients, and these estimates align with our findings for ALD patients with decompensated cirrhosis. Hagström et al. found that the risk of liver death was high shortly after diagnosis and reached a plateau after five-ten years, which matches our findings.

Our study filled critical literature gaps. First, we had a longer follow-up of 15 years compared to prior studies and used the competing risk method, which is the proper statistical approach when considering cause-specific mortality.[19] Second, we gave estimates for more malignant and non-malignant causes of death than previously reported. Lastly, our estimates were more precise and generalizable than previous studies because of the large sample size and the inclusion of a broad spectrum of ALD patients.

A possible limitation of our study was the validity of the Danish Cause of Death Registry. Autopsy rates in Denmark are low (<10%), so the underlying cause of death relies on the ACME system and the physician's death certificate, which can be uncertain.[14,17] This could lead to misclassification of the cause of death, resulting in over- or under-recording. Jensen et al.[20] suggested an under-recording of deaths caused by chronic obstructive pulmonary disease in Denmark, while Madsen et al. [21] found no under-recording of deaths from myocardial infarction. This inconsistency suggests that some causes of death are more likely to be under-recorded than others. Validation studies of death due to liver disease are few. A Swiss study[22] found similar diagnosis codes for liver disease in the terminal hospitalization and the cause of death registry for 93% of 1367 patients who died in the hospital. In a Swedish study[23], 83% of 231 death cases with liver disease as the underlying cause of death had liver disease as the primary discharge diagnosis. Another Swedish study showed that the proportion of alcoholic liver cirrhosis deaths increased from 3% to 12% when information from medical records and autopsy reports were added to the Cause of Death Registry.[24] These studies indicate a minor under-recording of liver disease in the Cause of Death registry. In addition, our analyses of the contributory causes of death showed that liver disease was a contributory cause of death in about 30% of each extrahepatic underlying cause of death – except for alcohol use disorder (Supplemental Table S6). A broader definition of liver disease, including potential causes of death associated with liver disease, such as peritonitis and renal failure, increased the proportion of liver deaths by nearly a third (data not shown). The risk of liver death after five years was 15·0% (95% CI 14·5-15·4) in our original liver death definition and 17·7 (95% CI 17·2-18·2) in our broader definition. Therefore, we believe our results may slightly under-record liver-related mortality. On the contrary, our sensitivity analysis using the Danish Cancer Registry showed that cause-specific cancer death was not underestimated. We consider our results reliable.

Another potential limitation of the study includes the quality of the general data on ICD-10 codes used to identify ALD patients and define the disease severity. Previous studies have reported positive predictive values for the diagnostic code of liver disease between 78%-90% in Denmark.[25,26] Our 10-year all-cause mortality risk was considerably lower for non-cirrhotic

patients than cirrhotic patients but remained high at 55%. This may suggest that we mistakenly classified patients with cirrhosis as non-cirrhotic. However, it has previously been demonstrated that 6.9% of patients with biopsy-proven steatosis and 16.0% of patients with biopsy-proven steatohepatitis develop cirrhosis within five years.[27] Thus, our classification may be accurate. We were unable to include information regarding hepatic encephalopathy in the definition of decompensation due to a lack of ICD-10 codes for hepatic encephalopathy. Since hepatic encephalopathy is a rare stand-alone symptom of decompensation (i.e., without ascites or variceal bleeding), it is unlikely to change our results.[28] The registries in Denmark do not record data on alcohol consumption, obesity, or Child-Pugh score, which is a limitation of our study. We hope future studies can collect these data to understand better their contribution to ALD patients' cause of death.

To conclude, our study highlights many preventable deaths from liver- and alcohol-related diseases in patients with ALD. If patients were helped to abstain from alcohol consumption, many deaths would have been avoided. Observational data suggest that treatment of alcohol use disorder reduces the risk of decompensation and death.[29] Unfortunately, in Denmark, as in many other countries, there is a lack of structured strategies to treat alcohol use disorders across the health care system. As a result, patients with ALD are not systematically offered treatment for alcohol use disorders. Furthermore, various barriers, such as fear of stigma, may impede the patient's initiative to seek help.[30] Patients with ALD constitute a unique patient group, as they suffer from chronic liver disease and comorbidity of alcohol use disorder. We hope our findings will motivate further research into interventions to combat continued alcohol consumption in liver patients. In addition, our finding of a better prognosis in patients with less severe ALD should motivate studies of the impact of screening for liver disease on patients´ long-term prognosis.

Research in context

Evidence before this study

Prior to the commencement of this study, a systematic search of Pubmed was conducted using the search terms ("liver diseases, alcoholic"[MeSH Terms]) AND (“cause of death”[MeSH Terms]), which yielded 160 hits. All of these were screened, and full texts were read if they addressed the cause of death in ALD patients. In addition to this systematic search, free text searches were conducted on Pubmed and Google using the terms “alcohol-related liver disease”, “cause of death”, “cause-specific death”, “underlying cause of death”, and “mortality”. If studies cited other pertinent studies, they were also included. The studies revealed a high liver-related mortality rate in patients with ALD. One study demonstrated that the increased risk of liver-related death plateaued after five to ten years. Nevertheless, only two studies have investigated causes of death according to the time since ALD diagnosis, which is essential knowledge for designing preventive interventions or surveillance programs such as cancer surveillance.

Added value of this study

This register-based study of cause-specific mortality has extended the existing literature by providing comprehensive follow-up, estimates for more malignant and non-malignant causes of death, and more precise and generalizable estimates due to its large and unselected sample size (>20,000). Our findings suggest that extrahepatic causes of death, including cancer, may not be the primary concern in ALD patients. Rather, liver disease is the main contributor to death in ALD patients several years after diagnosis. Our findings provide important information about causes of death according to the severity of liver disease, which has not been previously investigated. When diagnosed with a severe stage of liver disease, the risk of death from liver disease is significantly higher than in a less severe stage. Finally, this study is the first to demonstrate that alcohol use disorder is a persistent contributor to the risk of death many years after diagnosis.

Implications of all the available research

Previous studies have indicated that treatment of alcohol use disorder in ALD can reduce the risk of mortality. Unfortunately, in Denmark, as in many other countries, there is a lack of structured strategies to treat alcohol use disorders across the health care system. As a result, patients with ALD are not systematically offered treatment for alcohol use disorders. We hope our findings will motivate further academic research into interventions to combat continued alcohol consumption in liver patients. In addition, our finding of a better prognosis in patients with less severe ALD should motivate studies of the impact of screening for liver disease on patients´ long-term prognosis.

Data statement

The data used in this register-based study will not be available in any way due to laws by The Danish Data Protection Agency.

Contributors statement

AK, GA, PJ, JW, and LM designed and conceptualized the study. AK and GA managed, accessed, and verified all underlying data. AK provided the data analysis and the first draft of the manuscript. AK, GA, PJ, JW, and LM contributed to critical revisions of the manuscript and contributed to the decision to submit.

Declaration of interest

We declare no competing interests.

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