Causes of death in people with liver cirrhosis in England compared to the general population: a population-based cohort study

A competing risks analysis

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List of Abbreviations: ONS-Office for National Statistics, CPRD-Clinical Practice Research Datalink, HES-Hospital Episode Statistics; ICD-International Classification of Disease; AI-autoimmune

ABSTRACT

Introduction Liver cirrhosis is increasing worldwide and associated with high mortality. Precise estimates of cause-specific mortality compared to the general population, by underlying aetiology, are lacking. Such information may demonstrate areas where therapeutic interventions can be targeted.

Method We identified from the linked Clinical Practice Research Datalink (CPRD) and English Hospital Episode Statistics adults with an incident diagnosis of liver cirrhosis linked to the Office for National Statistics between 1998 and 2009. Age-matched controls from the CPRD general population were selected. We calculated the cumulative incidence (adjusting for competing risks) and excess risk of death by 5-years from diagnosis for different causes of death, stratified by aetiology and stage of disease.

Results 5118 patients with cirrhosis were matched to 152,903 controls. Amongst compensated patients, the 5-year excess risk of liver-related death was higher than that of any other cause of death for all patients except those of unspecified aetiology. For example, those of alcohol aetiology had 30.8% excess risk of liver-related death (95%CI 27.9%, 33.1%) compared to 9.9% excess risk of non-liver related death. However, patients of unspecified aetiology had a higher excess risk of non-liver related compared to liver-related death (10.7% vs. 6.7%). This was due to a high excess risk of non-liver neoplasm death (7.7%, 95%CI 5.9%, 9.5%). All decompensated patients had a higher excess of liver-related mortality than any other cause.

Conclusion In order to reduce associated mortality amongst people with liver cirrhosis, patients' care pathways need to be tailored depending on aetiology and stage of disease.

Study Highlights

What is the current knowledge

- Liver cirrhosis is increasing in the UK more than the top 4 diagnosed cancers and is associated with comparable poor survival.

- Contemporary knowledge about the excess cause of death in patients with liver cirrhosis compared to the general population and how this varies by aetiology is lacking.

- No previous study on the subject has adjusted for competing risks which may lead to overestimates of cause-specific mortality.

What is new here

- Five-year excess risk of liver-related death is higher than that of any other cause of death for all compensated patients except those of unspecified aetiology.

- Of all compensated patients, those with alcoholic cirrhosis have the highest excess risk of liver-related death.

- Compensated patients of unspecified aetiology have a higher excess of non-liver neoplastic death than that of any other cause of death, by 5-years post diagnosis.

INTRODUCTION

Cirrhosis of the liver is increasing worldwide at an alarming rate.[1] In the UK the increase is faster than the four most common diagnosed cancers (breast, bowel, lung, prostate).[2] Mortality in people with cirrhosis is high, with 5-year survival rates reported to be similar to that of bowel cancer.[3] However, contemporary knowledge of what people with cirrhosis die from and how this varies by aetiology of their cirrhosis is lacking. Such information can be important to demonstrate areas where premature mortality could be reduced and guide evidence-based practice in patient follow-up. For example, a recent matched cohort study of patients experiencing a gastrointestinal (GI) bleed showed that over half the excess risk of death (i.e. the risk of death in cases compared to that of controls) was due to non-GI comorbidity, warranting non-GI assessment after a bleeding episode.[4] To date, the excess cause of death of patients with liver cirrhosis of all aetiologies estimated from a population-based study has not been determined. Studies previously attempting to describe this have been either uncontrolled [5-7] or limited to reporting the relative mortality compared to an external comparator.[8-9]

Current evidence in the UK, based on studies which commenced over 20 years ago, suggests that over half of people with cirrhosis die due to liver-related causes and those of alcohol aetiology are at higher risk of dying from liver-related death compared to those of non-alcohol aetiology.[6,8] However, the main limitation of previous papers is their hospital-based setting that can lead to an overestimate of mortality. This is because these patients are likely to have more severe disease than patients with cirrhosis who are ambulatory. In addition, none of the authors have adjusted for competing risks (i.e. taken into account that patients may die due to other causes before dying from the cause of death of interest). This can lead to an overestimate of risk of death for each specific cause of death investigated.[10]

There is consequently a need for unbiased estimates of cause-specific mortality by aetiology of disease that can be used in a clinical setting to allow appropriate allocation of resource and ensure optimal patient care. The aim of this study is to use nationwide linked electronic routine healthcare data from primary and secondary care alongside national death registry data to report such estimates.

METHODS

Study design

We used population-based routinely collected electronic healthcare data from primary and secondary care registries in England to identify newly diagnosed cases of cirrhosis and linked Office for National Statistics (ONS) death registry data to determine cause and date of death.

Primary care data

The Clinical Practice Research Datalink (CPRD) is a longitudinal electronic database consisting of anonymised primary care records for over 10 million patients in the UK, collected since 1987. Data are coded using the Read code system.[11] Participating practices are assigned an up to standard (UTS) date on completion of regular audits confirming data quality and completeness; patient-level data are also assessed.[12] The CPRD has previously been shown to be representative of the population of the UK.[13]

Secondary care data

The Hospital Episodes Statistics (HES) database comprises statutory records of all admissions (excluding outpatients) conducted in NHS hospitals and independent treatment centres in England, since 1989. For each period of time under the care of a consultant, a patient is assigned a primary diagnosis and up to 19 secondary diagnoses, coded using the ICD-10 (International Classification of Diseases, tenth revision), and/or up to 24 recorded procedures coded using the OPCS4 (Office of Population, Censuses and Surveys' classification of surgical operations and procedures, fourth revision). Linked HES data are available for patients registered at consenting CPRD practices in England. Characteristics of patients in linked practices do not differ from those in non-linked practices.[14]

Death registry data

The ONS provides death registry data for CPRD practices that are linked to the HES. The data consist of date of death and underlying cause of death obtained from death certification and completed according to World Health Organisation guidelines,[15] coded using International Classification of Diseases versions 9 (ICD-9) and 10 (ICD-10).

Study population

We have described the study population in detail previously.[2] In brief, we defined cirrhosis in primary care if a person had a record containing a Read code for cirrhosis, oesophageal varices and/or portal hypertension in the CPRD. This code list has been previously validated using medical notes.[16] We developed code lists for cirrhosis diagnosis in secondary care from ICD-10 and OPCS4 codes. More than 90% of patients with a diagnosis in secondary care were reported to have supportive evidence of liver cirrhosis, either on their death certificate, in their primary care records or in the free text section of their primary care records.[2] For each patient we assigned the date of diagnosis as the first date associated with a Read or ICD-10/OPCS4 code for cirrhosis. Incident diagnoses in either CPRD or HES for patients (≥18years) were identified between January 1998 and December 2009.

Aetiology

For each patient, we searched all medical records for evidence of viral hepatitis, autoimmune and metabolic diseases. We have described the diagnostic codes used for each aetiology in detail previously.[2] Aetiology was ascribed in an hierarchical fashion of viral hepatitis, autoimmune or metabolic disease and alcoholic cirrhosis. All remaining patients with no recorded aetiology were defined as having unspecified aetiology. Although

patients may have a record of more than one type of underlying disease, using four mutually exclusive groups minimises the loss of power in the analysis of these subgroups.

Stage of disease

We defined stages of disease, within one year from diagnosis, as agreed at the Baveno IV consensus conference.[17] For the analyses in this paper we grouped stages 1 and 2 (cirrhosis with or without non-bleeding oesophageal varices, with no ascites) as compensated cirrhosis and stages 3 and 4 (cirrhosis with ascites and/or bleeding oesophageal varices) as decompensated cirrhosis.

Causes of death

We used the underlying cause of death code provided by the ONS, derived using standardised guidelines from the information available on death certificates.[18] Where necessary we mapped ICD-9 codes to ICD-10 codes; if mapping was not possible the cause of death was considered missing. Causes of death were categorised using the main ICD-10 chapter headings as follows: liver (K70-K77,) which include alcoholic liver disease, toxic liver disease, hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver, other inflammatory liver diseases, other diseases of liver and liver disorders in diseases classified elsewhere; additionally malignant neoplasm of liver and intrahepatic bile ducts C22 which includes hepatocellular carcinoma (C22.0),, oesophageal and gastric varices (I85, I864 and I982); non-liver neoplasm (C00-D48 excluding C22);circulatory (I00-I99, excluding: I85, I864, I982) and respiratory (J00-J99). All other causes of deaths or missing ICD codes were categorised as ‘Other’.

Comparison group

Controls were selected from the general population (patients from CPRD practices who did not have a liver cirrhosis diagnosis). We calculated a random pseudo-diagnosis date during the incident study period by selecting a random date between the registration start and end dates. Age was then calculated at this date and controls aged 18 years and onwards at the time of pseudo-diagnosis were included. Thirty controls were frequency matched to each case by age at diagnosis within 5 year age bands.

Statistical analysis

We excluded patients whose diagnosis of cirrhosis occurred on the same day as death. We described patient characteristics by aetiology (exposure) and used chi-squared tests for significance testing. The five grouped causes of death were the principal outcomes.

Crude mortality rates

Person-time at risk commenced at diagnosis of cirrhosis or pseudo-diagnosis date and ended at date of death or censoring of the patient record (earliest of date patient left the practice or last data collection date: 30th December 2010 or liver transplant date). Cause-specific mortality rates were calculated by dividing the number of deaths due to each cause by the total person years of follow-up. Rates were calculated for each major subgroup, and hepatocellular carcinoma specifically, for both cases and those without liver cirrhosis.

Adjusted analysis

As stated previously, conventional survival analysis provides probabilities of surviving a particular cause of death, say cancer, in the hypothetical world where it is not possible to die from anything else, say myocardial infarction. [19,20]. In contrast, competing risks theory

allows us to calculate real world probabilities where a patient is not only at risk of dying from a specific cause but also from any other cause of death. To adjust for this bias, we determined the cumulative incidence function (i.e. the predicted cumulative risk of death) by 5 years from diagnosis for each specific cause of death. The 5-year cut-off point was used as the majority of deaths had occurred by then. The cumulative incidence function adjusts for competing risks by calculating the cumulative probability of dying from a specific cause at each time point having survived to that time without a death from any other cause. We derived the cumulative incidence from baseline survival functions and estimates of instantaneous hazards from cause-specific Cox proportional regression models, a well-established approach.[10,21,22] The models were adjusted for age and sex, as we considered these to be a priori confounders. We stratified the cumulative incidence of death by aetiology and whether patients were compensated or decompensated at diagnosis.

We calculated the excess risk of death for each specific cause as the difference between the cumulative incidence of death for cases and the cumulative incidence of death for those without liver cirrhosis; 95% confidence intervals were calculated by bootstrapping (50 iterations). The cumulative incidence of death, and excess risk, for each cause of death was plotted using stacked graphs by aetiology sub-group. Stata version 12/MP4 was used for all statistical analyses.

Subgroup analysis

We identified patients' last smoking record as the latest but not closer than 6 months before diagnosis (pseudo-diagnosis date for those without liver cirrhosis). Smoking status was classified as 'ever-smoker' (current/ex-smoker), 'non-smoker' or 'missing'. We then determined whether the excess risk of death differed between ever-smokers and non-smokers.

RESULTS

Study population

Our cohort consists of 5118 patients with an incident diagnosis of liver cirrhosis frequency matched on age to 152,903 people without liver cirrhosis. The median follow-up was 1.88 [IQR 0.40, 4.27] and 3.13 [IQR 1.38, 6.14] years for those with and without liver cirrhosis, respectively. Age, sex, and stage of disease varied significantly by aetiology subgroup, $p<0.001$, (Table 1). Particularly decompensation around diagnosis was more prevalent amongst patients of alcohol and unspecified aetiology (48.2% and 45.4% respectively) than amongst the other aetiology subgroups (autoimmune/metabolic 27.1%; viral hepatitis 32.6%).

The comparison group had a smaller proportion of men and a smaller proportion of ever-smokers than the study cohort. The proportion of ever-smokers amongst those without liver cirrhosis was similar to that of the unspecified aetiology subgroup (Table 1).

Crude mortality rates

Table 2 shows the crude mortality rates for those with and without liver cirrhosis. Overall, for people with cirrhosis, there were 2546 (49.7%) deaths during 13,938 person-years of follow-up, and the overall mortality rate was 18.3 (17.6, 19) per 100 person-years. Of all deaths, approximately half were liver-related (n=1293, (50.8%)). Just under two-thirds of all deaths occurred within one year of diagnosis (n=1513, 59.4%), and again around half were liver-related (n=819, 54.1%). Overall, liver-related deaths were greater at all time points than any other single cause of death. Mortality in the comparison group was a fifth of that in people with cirrhosis, 2.98 (95% CI 2.94, 3.03) per 100 person-years with the most common cause of death being circulatory (32.7%) followed by non-liver neoplasm (29.4%), other (24.8%),

respiratory (12.5%) and liver (0.7%), the latter being fifty times less than that of people with cirrhosis.

Table 3 shows crude mortality rates stratified by aetiology. For all specified aetiologies, liver-related death was the most common cause of death. Non-liver neoplastic death was the main cause of death amongst patients of unspecified aetiology and the rate was higher than that seen in the other aetiology subgroups.

We have looked at the specific type of liver-related deaths by aetiology. The main difference was a significantly higher proportion of people dying due to alcoholic liver disease (ICD-10 code K709) in the alcohol subgroup compared to the other subgroups. The proportion of liver-related deaths due to alcoholic liver disease were 20.2% (n=24), 9.6% (n=10), 42.1% (n=384) and 2.5% (n=4) in viral hepatitis, AI/metabolic, alcohol and unspecified aetiology groups respectively, ($p<0.01$).

Hepatocellular carcinoma as cause of death

Of all cases who died, 96 (3.8%) deaths were due to hepatocellular carcinoma (mortality rate = 0.68 (95%CI 0.56, 0.84) per 100 person-years), this varied by aetiology ranging from 0.5 per 100 person-years to 1.5, for patients of alcohol and viral hepatitis aetiology respectively (see Table 3). The equivalent hepatocellular carcinoma rate amongst controls was 0.003 (95%CI 0.002, 0.004).

Amongst those who died due to a liver-related cause, hepatocellular carcinoma was the underlying cause of death for 7.4% (96 out of 1302) and 13.5% (17 out of 126) in those with and without liver cirrhosis, respectively. In compensated and decompensated patients, the proportion of liver-related deaths attributed to hepatocellular carcinoma was 13.3% and 3.2% respectively.

Risk of mortality adjusted for competing events

Table 4 shows the cumulative incidence and excess risk of death by 5 years after diagnosis; after adjusting for competing risks, age and sex, and stratified by stage of disease. As the pattern for cumulative incidence and excess risk are similar we have focused on the latter. In compensated patients, the excess risk of death due to liver-related death was higher than non-liver causes of death combined for all aetiologies (apart from unspecified), with those of alcoholic aetiology representing the highest excess risk of 30.8% (95%CI [27.9, 33.1]). This compares to an excess risk of all non-liver related deaths combined of only 9.9% in patients with alcoholic cirrhosis. In people with cirrhosis of unspecified aetiology, the excess risk of non-liver death was 10.7% (of which 7.7% was attributed to non-liver neoplasm death) and that of liver-related mortality was 6.7%. For patients of unspecified aetiology, the three most common types of the 181 non-liver related neoplastic deaths were pancreatic (n=32, 17.7%), primary site unspecified (n=25, 13.8%) and lung (n=17, 9.4%).

Figure 1 displays the excess risk of death compared to those without liver cirrhosis, in compensated patients, at every time point up to 5 years, for each aetiology subgroup. The figure highlights clearly that at every time point, liver-related death is associated with the highest excess risk in those with viral hepatitis, autoimmune/metabolic and alcohol aetiology. Whereas those of unspecified aetiology have a higher excess risk of non-liver causes of death combined throughout the five years post diagnosis, than that of liver-related cause of death.

In decompensated patients, the excess risk of death due to liver-related reasons was higher than any other cause of death, for all aetiologies and all 95% confidence intervals for liver-related excess mortality excluded zero (Table 4).

Figure 1: Excess risk of mortality following diagnosis in compensated patients by aetiology, adjusting for age, sex and competing events.

a: Viral hepatitis

b: Autoimmune/metabolic disease

C: Alcoholic cirrhosis

d: Unspecified cirrhosis

Legend: Cause of death by ICD-10

Subgroup analysis: smoking status

Supplementary Tables 1 and 2 show the cumulative incidence and excess mortality by aetiology for ever-smokers and non-smokers respectively. There was a similar pattern to that without stratification by smoking status. For example in compensated patients, the highest excess of non-liver neoplasm death was seen in patients of unspecified aetiology, in both ever-smokers (9.24%, 95%CI [7.67, 10.81]) and non-smokers (5.87%, 95%CI [4.68, 7.05]).

DISCUSSION

Main findings

We have demonstrated how cause of death in people with cirrhosis varies by the underlying aetiology of liver disease and stage of disease. After adjusting for competing risks, people with compensated and decompensated cirrhosis of alcohol, viral hepatitis and autoimmune/metabolic aetiology, were more likely to die from liver-related causes than any other cause of death, when compared to the general population. In particular, people of alcohol aetiology had the highest 5-year excess risk of liver-related death compared to any other compensated aetiology subgroup. Importantly however, people with unspecified cirrhosis who were compensated at diagnosis had a higher excess risk of non-liver death than liver-related death.

Most of the non-liver related deaths in compensated unspecified cirrhosis patients were due to non-liver neoplastic deaths that occurred independently of smoking status. Knowledge of the risk of non-liver neoplasm (particularly pancreatic) during an early stage of disease should provide an opportunity for clinicians to be vigilant when reviewing these patients.

Strengths/Limitations

Our study has the advantages of its large size, general population setting, adjustment for competing risks and a design which minimizes selection bias. An important limitation to consider is the potential of misclassification with respect to identifying patients' aetiology which is crucial to discuss given that it is our primary exposure variable. It is possible, for example, that we have underreported, to some degree, the number of people with alcohol aetiology both owing to our imposed hierarchy of aetiologies and as reporting of alcohol consumption in medical notes is known not to reflect true alcohol consumption.[21]

However, we are confident that using a combination of both primary and secondary care healthcare records has provided us with as much information as would be obtained if we were to conduct a case-note review. For the aetiologies which are diseases we expect these to have a high specificity as a recent study has reported high validation for the diagnosis of autoimmune hepatitis in the CPRD [24] and additionally a systematic review showed that the validation of many other diagnoses recorded in the CPRD was high.[25] Compared to other published studies in the UK [6,8,16] it would appear that our coverage of aetiology (i.e. the proportion of each type of subgroup) is as good, if not better, probably because we are the first study to use linked databases and hence multiple healthcare records. Despite the large size of our cohort, we were unable to carry out subgroup analyses among those with multiple aetiologies for example viral hepatitis and alcohol. Had we used more than four subgroups this would have resulted in lack of power and imprecision due to small numbers of events (deaths). In addition, it is likely that there would be some misclassification of the joint aetiologies and that coupled with the small numbers of events would mean that we would be unable to accurately assess the relationships with cause-specific deaths. The main limitation of having four mutually exclusive categories is that the liver-related mortality rates we have provided in our viral hepatitis and AI/metabolic aetiology subgroups may be overestimates of the true risk in those with a single aetiology.

Another limitation is potential ascertainment bias. It is possible that there is a recording bias with doctors filling in death certificates more likely to record liver disease as the cause of death in patients known to have liver cirrhosis compared to those without cirrhosis. Furthermore, it is well documented that cause of death information taken from death certificates is often lacking in accuracy and completeness. Diagnostic and coding errors often occur and multiple disease processes can mask the true underlying causes of

death.[26] However, ONS data based on WHO guidelines is the most pragmatic and only feasible method to ascertain cause of death in a standardised way for such a large study population. In addition, a recent study has shown that misclassification of cause of death may only bias estimates in patients older than 85, a small proportion of our study cohort (n=183, 3.6%).[21] Finally, underlying cause of death was used to avoid the possible effect of changes in coding requirements over time.[27]

There may be some misclassification with respect to stage of disease. In the UK, once a patient is diagnosed with cirrhosis they do not necessarily always receive surveillance therefore assigning stage of disease around diagnosis is imprecise. It is possible that we have underestimated the number of people diagnosed with decompensated cirrhosis, however we have minimized this as best we can by identifying the first clinical symptom up to one year before the diagnosis date; thus taking into account that diagnosis date may not be when the person first became symptomatic. Finally, by calculating cumulative incidence, and therefore adjusting for competing events, we have minimized the likelihood of over estimating the risk of death for each specific cause.

Comparison with other studies

Our study is probably best compared with a large Danish nationwide cohort study which identified 10,154 patients with liver cirrhosis admitted to hospital during the period 1982-1989.[9] Of the 69% of patients who died by 1993, 51% of deaths were attributed to causes related to cirrhosis (similar to this current study).

Also, similar, the non-specified cirrhosis group had a greater excess risk of cancer-related death (Standardized Mortality Ratio (SMR) of 8.8), than the alcoholic cirrhosis group (SMR of only 4.9). When comparing the cause-specific risks of death with the general population the authors have not reported absolute risk of death which limits the practical translation of

their figures into the clinical arena. One further limitation, as mentioned by the authors, is lack of lifestyle data such as smoking status which they have not been able to adjust for.

A commonly referenced study describing the cause-specific mortality in patients with cirrhosis in the UK is the afore-mentioned paper by Roberts et al. which used data from hospital discharge statistics in the Oxford region during 1968 to 1999.[8] The authors included patients admitted for any chronic liver disease (ICD-10 K70, K73, K74, K76.0) a much broader case definition than our specific measure of cirrhosis diagnosis including patients who do not necessarily have cirrhosis, for example people with alcoholic liver disease (K70.9). After following patients up to one year, they found that liver disease was the certified underlying cause of death for 51% of patients who died, similar to our study (53.8%). Cause-specific SMRs by aetiology were determined and, also similar to our findings, the unspecified cirrhosis subgroup had a higher relative risk of death from neoplastic causes (SMR 9.6) than the alcoholic subgroup (3.2), and all other aetiology subgroups. Those people with cirrhosis of alcoholic aetiology had a higher SMR for liver-related mortality compared to all other aetiology subgroups. However unlike our findings, the SMR for liver-related death was higher than non-liver related deaths combined for the unspecified group. The authors did not have access to clinical or demographic data therefore they were unable to categorise patients by severity of cirrhosis or smoking status, as has been done in the present study, and therefore we cannot make a direct comparison with some of the figures we have displayed.

We found that 3.8% of all deaths were due to hepatocellular carcinoma and rates varied from 0.5 per 100 person- years to 1.5, for patients of alcohol and viral hepatitis aetiology respectively. In 2012 Jepsen et al. conducted a registry-based study similar to ours and reported an annual hepatocellular carcinoma incidence rate of 0.4% (95% CI 0.34% to 0.47%) in patients exclusively with alcoholic cirrhosis, diagnosed between 1993 and 2005 in Denmark.[28] Sorensen et al determined hepatocellular carcinoma risks among people with

cirrhosis in Denmark between 1977 and 1989.[29] Their rates of hepatocellular carcinoma were slightly lower than ours (0.34 and 0.25 per 100 person years for alcohol and unspecified cirrhosis respectively). Other studies from Europe, Japan and America report substantially higher rates of hepatocellular carcinoma.[30-34] Our rates therefore are not that dissimilar from equivalent database epidemiological studies from Denmark to which our work is probably best compared.

Clinical implications

Predicting future mortality rates is important as such knowledge may enable improved planning of health services and prioritization of limited public health resources. For example, the finding that the alcohol aetiology group had the highest excess risk of liver-related death compared to the other subgroups, when diagnosed at early stage of disease, and given the rise in the occurrence of alcohol-related cirrhosis previously reported,[1,2] implies that the planning of future services should allow for the number of people requiring liver services in England and other countries. Given that the most common liver-related death amongst those with alcohol cirrhosis is alcoholic liver disease, this highlights the importance of attempting to reduce alcohol consumption and the development of other interventions in this regard. For example, including alcohol consumption in the Quality Outcomes Framework may lead to better recording of alcohol in the UK (as in the case of smoking,[35]) and ultimately the identification of patients at high risk of liver disease and interventions to reduce future cirrhosis development

We have determined that compensated patients of unspecified aetiology had an excess risk of non-liver related neoplasm compared to the general population. There are several possible reasons for this excess mortality. Firstly, whilst we have shown that the excess is not due to differences in distributions of age, sex and smoking status between people with cirrhosis and those without the disease; the excess non-liver neoplasm mortality between these two groups could be due to residual confounding. For example, social deprivation has recently been associated with cancer mortality.[36] With respect to the association between the incidence of cirrhosis and socio-economic class, the current literature is limited, but if a positive relationship does exist then differences in deprivation between those with and without cirrhosis could explain some of the excess we report. Future research is required to investigate the effect of deprivation on excess mortality.

Secondly, as patients with cirrhosis of unspecified aetiology undergo several tests (similar to those used to detect cancer) these patients are consequently likely to have more incidental findings, of say non-specific and pancreatic cancer, compared to those without cirrhosis. Ascertainment bias, therefore, may explain why people with unspecified cirrhosis are at higher risk of dying from cancer compared to the general population.

Thirdly, patients with cirrhosis are known to have comorbidities which may influence excess mortality.[37] However, statistically, we cannot adjust for particular comorbidities as they are part of the final common pathway to the specific causes of death. For example, myocardial infarction and congestive heart failure are comorbidities that are necessary for the outcome of circulatory death and therefore should not be treated as confounders in the context of our study.

It is biologically plausible that people with unspecified cirrhosis may truly be of higher risk of non-liver neoplasm than those without the disease of similar age and sex. It has long been reported that cryptogenic cirrhosis (analogous to our unspecified group) is associated with

non-alcohol fatty liver disease[38] which in turn is related to obesity, and there are several prospective epidemiological studies which have demonstrated a direct association between being overweight and risk of cancer.[39,40] It has been estimated that about 20% of cancers are caused by excess weight.[40] Therefore the excess neoplastic death we find in compensated unspecified patients may be explained by a higher level of obesity present in those with unspecified cirrhosis than those without the disease of similar age and sex. However, we cannot test for this inference statistically as it may be misleading to adjust for patients' weight, as timing of measurement may be influenced by disease stage. For example, patients are likely to have been first weighted with cirrhosis at their presentation or decompensation and therefore could be overweight due to having ascites or those with cancer could lose weight dramatically due to cancer cachexia or the effects of chemotherapy.

Conclusion

In summary, our study has described the cause-specific mortality of a comprehensive and heterogeneous population of people with cirrhosis in England. The causes of excess death in people with liver cirrhosis vary by underlying cause of liver disease and stage of disease. Patients of alcoholic cirrhosis, chronic viral hepatitis and autoimmune/metabolic aetiology are at higher risk of liver-related death than any other cause of death, and compensated unspecified patients are at higher risk of non-liver neoplastic death, when compared to the general population, up to five years post-diagnosis. In order to reduce premature mortality amongst people with liver cirrhosis, patients' care pathways need to be tailored depending on aetiology and stage of disease.

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