All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study

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Abstract

Background: Mortality due to cirrhosis has tripled over the last 30 years in the UK. However, we lack adequate, contemporary, population-based estimates of the excess mortality patients who are at risk compared with the general population. Aim: To determine the overall survival in patients with cirrhosis compared with the general population taking into account the effects of severity and aetiology of disease and comorbidity. Methods: In a cohort study, we identified 4537 people with cirrhosis and a control cohort of 44 403 patients, matched by age, sex and general practice from the UK General Practice Research Database between June 1987 and April 2002. Results: Patients with compensated cirrhosis had a nearly five-fold [hazard ratio (HR) 4.7, 95% confidence interval (CI) 4.4–5.0] increased risk of death, while those with decompensated cirrhosis had a near 10-fold (HR 9.7, 95% CI 8.9–10.6) increased risk compared with the general population. Alcoholic cirrhosis conferred a worse prognosis than non-alcohol-related cirrhosis both in the first year following diagnosis and subsequently. Conclusion: Having a diagnosis of cirrhosis confers a substantial increased mortality risk compared with the general population, even for those with compensated disease, with 5-year survival between that seen for breast and colorectal cancer.
Cirrhosis mortality

We categorised age as 25–44, 45–64 and 65+ for cirrhosis patients or date of pseudo-diagnosis for decompensated disease state with all other cases classified before the date of diagnosis. Cases with a code for ascites or gastrointestinal bleed or a prescription for spironolactone at or within this database are recorded through direct entry during general practice appointments and following communication from secondary care. Data are coded based on both the Oxmis and Read medical coding dictionaries. The GPRD has previously been shown to be broadly representative of the population of the UK (8). Approval was given by the Scientific and Ethical Committee of the GPRD for this study.

Study population

We obtained all records of patients with a diagnostic code for any liver disease within the GPRD between June 1987 and April 2002. Patients aged 25 and over were selected based on the presence of a diagnostic or therapeutic code for cirrhosis, oesophageal varices and/or portal hypertension to represent a cohort of adult-diagnosed cirrhosis. This age cut-off was designed to avoid including patients who may have had the onset of cirrhosis under the age of 18. Each patient was assigned a date of diagnosis of cirrhosis as the date of the first record of any of these codes.

For each subject with liver disease, up to 10 general population controls were identified, matched by registration at the same general practice, by sex and age (within 5 years). Controls had to be alive and contributing data to the GPRD on the subject’s date of diagnosis of liver disease. We excluded controls who subsequently had any diagnostic or therapeutic code for cirrhosis, oesophageal varices and/or portal hypertension within their own general practice record and those who were no longer alive at their matched subject’s time of diagnosis with cirrhosis. The date of diagnosis of cirrhosis was taken as the date of ‘pseudo-diagnosis’ for controls.

Definitions

Patients with cirrhosis were classified as being in a compensated or decompensated disease state at the date of diagnosis. Cases with a code for ascites or gastrointestinal bleed or a prescription for spironolactone at or before the date of diagnosis were classified as being in a decompensated disease state with all other cases classified as compensated.

Age was defined as age at date of diagnosis of cirrhosis for cirrhosis patients or date of pseudo-diagnosis for controls. We categorised age as 25–44, 45–64 and 65+ years. Alcohol intake before diagnosis was defined as either teetotal, drinker or problem drinker based on Read and Oxmis codes. Comorbidity was defined using the Charlson index, a weighted score shown to be strongly related to mortality (9). Weighted scores for mild or severe liver disease were not included within this analysis. Patients’ records were examined for comorbidities before the date of diagnosis or pseudo-diagnosis and then an individual Charlson score was calculated. Scores were categorised as 0, 1 or 2+ for the purposes of analysis. Body mass index (BMI, kg/m²) was defined using data on height, weight and/or BMI recorded at least 1 year before diagnosis or pseudo-diagnosis. This cut-off was used to try and ensure that weight loss because of undiagnosed disease did not change the initial BMI categorisation of subjects. Presumed aetiology of cirrhosis of either alcoholic-related, viral hepatitis, autoimmune liver disease, metabolic liver disease or other unspecified causes of cirrhosis was defined as described previously (2). Liver transplant was defined as a code for liver transplant subsequent to diagnosis of cirrhosis. To define death, we used a combination of the patient’s registration status within the GPRD and medical codes for death, with the earliest date of these being assigned as the date of death.

Statistical analyses

Using Cox proportional hazards regression, we modelled the hazard of death in the cirrhosis cohort compared with the control cohort using an historical matched cohort study design. Subjects with cirrhosis and controls entered the analysis period at the date of diagnosis or pseudo-diagnosis, respectively, and exited at the earliest of either date of death, date of moving out of their general practice or 30 April 2002, the last date of available data at the time of extraction. We classified subjects with cirrhosis as either compensated at entry or decompensated at entry and subsequently modelled compensation as a time-varying covariate. All models were adjusted, a priori, for age and sex. Additional potential confounders (alcohol intake and comorbidity) were modelled as categorical variables (with a separate category for missing data) and included if they conferred a 10% adjustment in the hazard ratios (HRs) seen. Following results from previous studies, we planned to stratify by comorbidity at the design stage. We split follow-up time at 1 year and modelled HRs during the first year following diagnosis and after 1 year. We then split the population of cases into those with alcoholic cirrhosis and those with non-alcoholic-related cirrhosis (all other causes and unspecified) and examined the mortality rates and adjusted HRs compared with their matched controls for these two aetiologic groups.

To minimise the potential for survival bias, we ran the principal analysis again comparing mortality between compensated and decompensated cases and controls using only incident cases [as described previously (2)] and their matched controls. To try to account for potential attrition bias, the principal analysis was repeated using the earliest of date of death, deregistration or last recorded appointment in the GPRD as the exit point for the analysis.

Proportional hazards assumptions were checked using Schoenfeld residuals and log–log plots. Stata version 9.2 SE was used for all statistical analyses.
Results

A total of 4537 patients aged 25 and over with a diagnosis of cirrhosis were identified, with a control cohort of 44403 patients, matched by age, sex and general practice. Median age at diagnosis was 56 years and 58% of subjects were males. Selected demographic, lifestyle and clinical characteristics of the study population are described in Table 1. Subjects with cirrhosis had more recorded comorbidity than the control cohort, but the majority of patients in both cohorts had no recorded comorbidity illness (77.7% of patients with cirrhosis; 83.5% of control cohort). Substantially, more subjects with cirrhosis than control subjects were recorded as being known problem drinkers before diagnosis/pseudo-diagnosis (30 vs. 2% respectively).

The presumed aetiology of cirrhosis (taking into account medical records before and after diagnosis of cirrhosis) was recorded as alcoholic in just over half of our study population (50.9%). Nearly two-fifths of our cirrhosis cohort had no specified aetiology (38.1%). The majority of the patients with cirrhosis were identified at an early stage of cirrhosis with 68.9% being classified as compensated at entry. Only 2.3% of patients with cirrhosis went on to subsequently have a liver transplant recorded.

Survival analysis

In a total of 226412 person-years of follow-up (median length of follow-up 3.5 years), there were 1759 deaths in our cirrhosis cohort (38.8%) and 4033 deaths in the control cohort (9.1%). Only a priori confounders of age and sex remained in the Cox regression model alongside the time-varying covariate to represent compensation/decompensation. Overall, patients with cirrhosis had a HR for death (adjusted for age at diagnosis and sex) of 5.8 [95% confidence interval (CI) 5.5, 6.1] compared with the general population cohort. A higher HR for death was observed for patients with decompensated cirrhosis compared with the general population with a HR of 9.7 (95% CI 8.9, 10.6) (Table 2), but a significantly higher hazard of death was still seen for patients with compensated cirrhosis (HR 4.7, 95% CI 4.4, 5.0) compared with the general population.

Overall survival at 1 and 5 years was 87.3% (95% CI 86.1, 88.4) and 66.5% (95% CI 64.5, 68.5), respectively, in patients with compensated disease (Fig. 1). This contrasts with the much lower figures for patients with decompensated disease being 75.0% at 1 year (95% CI 72.5, 77.3) and at 5 years 45.4% (95% CI 42.1, 48.7).

Mortality was higher during the first year than follow-up as shown in Table 3, but also remained substantial beyond 1 year. Stratification by comorbidity showed that although the absolute mortality rates in those with no comorbidity were not as high as those with a large amount of comorbidity (Charlson score 2 or more), the adjusted HRs for death were highest in this group.

Table 1. Demographic, lifestyle and clinical characteristics of cirrhosis cohort and general population cohort

| Demographics/lifestyle factors | Cirrhosis cohort (n = 4537) | Control cohort (n = 44403) |
|-------------------------------|----------------------------|--------------------------|
| Age at diagnosis (years)      |                            |                          |
| 25–44                         | 943 (20.8)                 | 9403 (21.2)              |
| 45–64                         | 2256 (49.7)                | 22219 (50.0)             |
| 65+                           | 1338 (29.5)                | 12781 (28.8)             |
| Sex                           |                            |                          |
| Male                          | 2612 (57.6)                | 25599 (57.7)             |
| Female                        | 1925 (42.4)                | 18804 (42.3)             |
| Comorbidity*                  |                            |                          |
| Charlson 0                    | 3525 (77.7)                | 37085 (83.5)             |
| Charlson 1                    | 534 (11.8)                 | 3704 (8.3)               |
| Charlson 2+                   | 478 (10.5)                 | 3614 (8.1)               |
| BMI                           |                            |                          |
| Median BMI [IQR] (kg/m²)      | 25.5 [22.5, 28.7]          | 25.3 [23.0, 28.2]        |
| No recorded BMI               | 3624 (80.0)                | 33294 (75.0)             |
| Alcohol status (before diagnosis) |                        |                          |
| Teetotal                      | 2 (< 0.1)                  | 10 (< 0.1)               |
| Drinker                       | 170 (3.7)                  | 1007 (2.3)               |
| Problem drinker               | 1378 (30.4)                | 740 (1.7)                |
| No record                     | 2987 (65.8)                | 42646 (96.0)             |
| Presumed aetiology†           |                            |                          |
| Alcoholic cirrhosis           | 2307 (50.8)                |                          |
| Viral hepatitis               | 238 (5.2)                  |                          |
| Autoimmune LD                | 48 (1.1)                   |                          |
| Metabolic LD                 | 354 (7.8)                  |                          |
| Not classified                | 1730 (38.1)                |                          |
| Disease state at entry        |                            |                          |
| Compensated                   | 3126 (68.9)                |                          |
| Decompensated                 | 1411 (31.1)                |                          |
| Liver transplant (following diagnosis of cirrhosis) | 106 (2.3) | 2 (< 0.1) |

*Charlson index as per methods excluding liver disease. Absence of coding for disease assumed to represent disease not present.
†As subjects were able to have more than one presumed aetiology, numbers in the table do not add up to 4537.

Table 2. Mortality rates and hazard ratios overall compared with the general population

| Events | Person-years | Mortality rate (per 1000 person-years) | Adjusted hazard ratio [95% CI]* |
|--------|--------------|----------------------------------------|--------------------------------|
| Population controls | 4033 | 209555 | 19.2 [18.7, 19.8] | 1 |
| All cirrhosis | 1759 | 16858 | 104.3 [99.6, 109.3] | 5.8 [5.5, 6.1] |
| Compensated | 1115 | 13317 | 83.7 [79.0, 88.8] | 4.7 [4.4, 5.0] |
| Decompensated | 644 | 3541 | 181.9 [168.4, 196.5] | 9.7 [8.9, 10.6] |

*Adjusted for age and sex.
This high relative risk of death was most noticeable in the first year following diagnosis with HRs of 8.3 for the compensated cohort compared with the general population and 18.0 for the decompensated cohort.

The absolute mortality rates of subjects with non-alcohol-related cirrhosis was higher than that of subjects with alcoholic cirrhosis in the first year following diagnosis (Table 4). Subsequent to the first year absolute mortality was similar in both groups. However, the adjusted HRs for mortality were much higher in the subjects with alcoholic cirrhosis compared with those with non-alcohol-related cirrhosis both during the first year following diagnosis and subsequently. This is a result of the absolute mortality rates seen in the control populations with the matched controls of subjects with alcoholic cirrhosis having a considerably lower mortality than the matched controls of subjects with non-alcohol-related cirrhosis. This is principally mediated by the age matching of controls. Patients with alcoholic cirrhosis had a significantly lower age at diagnosis (median age 52 years) than those with non-alcohol-related cirrhosis (median age 63 years).

Sensitivity analyses

Running the analyses using slightly different cohort definitions led to no substantial differences in the adjusted HRs for mortality either during the first year following diagnosis or subsequently.

Discussion

We have shown that patients with cirrhosis including those not necessarily admitted to hospital have a substantially reduced survival. Overall, patients with compensated cirrhosis have a nearly five-fold increased risk of death compared with the general population and those with decompensated disease a nearly 10-fold increased risk. The considerable excess mortality we found is not explained by comorbidity in our cirrhotic cohort as even in those with no recorded comorbidity, the HRs for mortality are markedly increased compared with similarly matched general population controls. Mortality relative to similar age- and sex-matched control cohorts was substantially greater for those subjects with alcoholic cirrhosis compared with subjects with non-alcohol-related cirrhosis both in the first year following diagnosis and subsequently.

By virtue of the electronic primary care data from a broad sample of primary care physicians at our disposal, we have constructed a large, representative, population-based cohort of patients with cirrhosis with an appropriate general population comparison cohort. These cohorts were identified reasonably recently (1987–2002) and therefore the results we have obtained reflect the natural history of cirrhosis during this period. As this is a population-based cohort, it is unlikely to have been affected by the variation in referrals and follow-ups seen in cohorts selected from secondary care. The size of the dataset we have used has allowed us to estimate mortality

![Kaplan–Meier survival estimates](image)

**Fig. 1.** Survival estimates for controls, subjects with compensated cirrhosis and subjects with decompensated cirrhosis.

| Table 3. Mortality rates and hazard ratios during the first year and subsequently compared with the general population stratified by Charlson index and adjusted for age and sex |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Mortality rate (per 1000 person-years) | Adjusted hazard ratio |
| Control cohort | Compensated cohort | Decompensated cohort | Compensated cohort | Decompensated cohort |
|----------------|---------------------|----------------------|---------------------|----------------------|
| **During first year** | | | | |
| Overall | 20.1 | 141.7 | 304.8 | 7.2 [6.4, 8.2] | 15.1 [13.3, 17.2] |
| Charlson score | 0 | 16.5 | 132.9 | 295.0 | 8.3 [7.2, 9.6] | 18.0 [15.4, 21.0] |
| | 1 | 28.6 | 152.9 | 266.1 | 5.7 [4.0, 8.3] | 10.7 [7.4, 15.5] |
| | 2+ | 49.5 | 215.4 | 396.6 | 4.4 [3.2, 6.1] | 8.2 [6.1, 11.1] |
| **Following first year** | | | | |
| Overall | 19.0 | 69.2 | 129.1 | 4.0 [3.7, 4.3] | 7.5 [6.7, 8.5] |
| Charlson score | 0 | 16.4 | 65.8 | 121.7 | 4.4 [4.0, 4.8] | 8.1 [7.0, 9.3] |
| | 1 | 32.8 | 89.6 | 116.0 | 3.1 [2.4, 3.9] | 5.0 [3.7, 6.9] |
| | 2+ | 43.0 | 90.5 | 201.6 | 2.3 [1.7, 3.0] | 5.9 [4.4, 7.9] |
rates and adjusted HRs for death stratifying by severity of disease, follow-up time and comorbidity. We are confident based upon our previous validation study (2) (which showed the vast majority of patients with a recorded code for cirrhosis had available extra evidence from secondary care) that for the diagnosis of cirrhosis in general, this coding within primary care is good. The additional clinical signs and symptoms of decompensation may not always be recorded as accurate, however, unless they are of obvious clinical relevance to the GP. Hence, ascites is probably symptomatic and therefore likely to be moderate to large volume, clinically significant ascites (rather than that only identified by ultrasound). It could be argued that the inclusion of both incident and prevalent cases in the cirrhosis cohort might lead to the introduction of survival bias as those cases that are prevalent and have, by definition, already survived a particular period of time to be still included in the analysis. However, estimates from the sensitivity analyses, including only incident cases, remained within the 95% CI of the principal analysis. The results obtained including all incident and prevalent cases probably more accurately reflect the real world of clinical practice within the general population and allows for the communication of results that are directly valid to the patients being seen in primary care.

Though the data available have allowed for an appropriate individually matched adjustment for some confounders (age and sex), it was not possible to examine the potential associations or modifying effects of other variables either because they were not available in the version of the GPRD used for this analysis, e.g. socio-economic status, or because there was such a high proportion of missing data, e.g. BMI. Data were also missing for alcohol status before diagnosis in over 90% of our cohort (66% of those with cirrhosis, 96% of control cohort). There is a potential bias in the recording of alcohol status with a GP perhaps more likely to record the knowledge of a patient drinking heavily as this may affect their health, but conversely a patient may not be recorded as being teetotal unless they actually suffered from a condition that may be considered to be associated with alcohol use. With such a high proportion of missing data, it was not practical to model the survival analyses including only patients with available data. When including missing data as a separate category alcohol status did not remain within the multivariable model.

Our mortality analysis is perhaps best compared in detail with the two large studies on this subject and the most relevant previous study from the UK. In 1981, Saunders et al. (10) described the survival of 512 people admitted to hospital with cirrhosis in the West Midlands region of the UK between 1959 and 1976. Our 5-year survival estimates for compensated and decompensated cirrhosis are higher than theirs. This suggests that as expected, some improvements that impact on death in the management of cirrhosis have occurred in the intervening 20 years or so, although some ascertainment bias in the earlier study with the most severe (and frequently hospitalised) cases being over represented is possible. Our findings are analogous to the case fatality rates and standardised mortality ratios (SMR) reported from the Oxford region of the UK between 1968 and 1999 in people who had an admission to hospital with either chronic liver disease or cirrhosis (6). The 1-year SMR of 16.3 is substantially higher than the 1-year adjusted HRs we have reported for patients with either compensated or decompensated disease. Five-year survival was not calculated in their study. In comparison with the large Danish cohort study, we again report better 1- and 5-year survival

### Table 4. Mortality rates and hazard ratios during the first year and subsequently compared with the general population stratified by aetiology and adjusted for age and sex

|                         | Events | Person-years | Mortality rate (per 1000 person-years) | Adjusted hazard ratio [95% CI]* |
|-------------------------|--------|--------------|----------------------------------------|---------------------------------|
| **During first year**   |        |              |                                        |                                 |
| Alcoholic cirrhosis     |        |              |                                        |                                 |
| Controls                | 271    | 20,344       | 13.3 [11.8, 15.0]                      | –                               |
| Compensated cirrhosis   | 174    | 1282         | 135.8 [117.0, 157.5]                   | 10.5 [8.7, 12.7]                 |
| Decompensated cirrhosis | 153    | 631          | 242.6 [207.1, 284.3]                   | 17.7 [14.5, 21.6]               |
| Non-alcohol-related cirrhosis | 525 | 19,257       | 27.3 [25.0, 29.7]                      | –                               |
| Controls                | 204    | 1385         | 147.3 [128.4, 168.9]                   | 5.7 [4.8, 6.7]                  |
| Compensated cirrhosis   | 171    | 432          | 395.5 [340.5, 459.5]                   | 13.7 [11.5, 16.3]               |
| Following first year    |        |              |                                        |                                 |
| Alcoholic cirrhosis     |        |              |                                        |                                 |
| Controls                | 1181   | 90,469       | 13.1 [12.3, 13.8]                      | –                               |
| Compensated cirrhosis   | 398    | 5285         | 75.3 [68.3, 83.1]                      | 6.0 [5.4, 6.8]                  |
| Decompensated cirrhosis | 190    | 1501         | 126.6 [109.8, 146.0]                   | 11.0 [9.4, 12.8]                |
| Non-alcohol-related cirrhosis | 2056 | 79,485       | 25.9 [24.8, 27.0]                      | –                               |
| Controls                | 339    | 5365         | 63.2 [56.8, 70.3]                      | 2.9 [2.6, 3.2]                  |
| Decompensated cirrhosis | 130    | 977          | 133.0 [112.0, 158.0]                   | 5.2 [4.4, 6.2]                  |

*Adjusted for age and sex.
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The poorer survival estimates seen in these previous studies are unsurprising considering the hospital-based nature of the patients selected. Our results are perhaps more widely generalisable to patients diagnosed with cirrhosis including those ambulatory patients who have not been admitted to hospital. A similar difference in survival rates between patients with compensated and decompensated disease is seen when comparing our results to that of the widely quoted figures from D’Amico et al. (11) of 6-year survival of 54 and 21%, respectively. It is possible that the improvements in survival seen in our data are a reflection of improved management and outcomes of the complications of cirrhosis in the intervening decades or indeed that the high prevalence of hepatitis B virus in the Sicilian population means that we are comparing the mortality experiences from different aetiologies of cirrhosis in the two populations. While other recent studies have reported on a variety of the outcomes, we also examine here, the differences in design and populations used, particularly the absence of ambulatory patients, render comparisons of limited use (12–14).

In summary, our study has described the mortality associated with a diagnosis of cirrhosis in contemporary clinical practice. We have shown that overall mortality from cirrhosis remains high with a 5-year survival of around 60%, which, while better than that observed over 20 years ago, is between the figures observed in people with colorectal and breast cancer (15). The comparison with the general population puts our findings in wider context, demonstrating that even those with no recorded comorbidity and compensated disease have about a five-fold increased risk of death, and we have been able to show that an alcoholic aetiology remains a particularly bad prognostic indicator. We conclude that our results in conjunction with the previously observed increasing incidence of cirrhosis emphasise the growing threat of liver disease to public health.

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