Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998–2009: A large population study

Sonia Ratib[1,*], Kate M. Fleming[1], Colin J. Crooks[1], Guruprasad P. Aithal[2], Joe West[1]

[1]*Division of Epidemiology & Public Health, University of Nottingham, UK;* [2]*NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK*

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Background & Aims: Large, population-based studies that have included the full spectrum of cirrhosis estimating survival, taking into account time-at-risk are lacking. We aimed to report 1- and 5-year average survival rates for people with cirrhosis to be used in a clinical and healthcare policy setting.

Methods: We used the Clinical Practice Research Datalink and linked English Hospital Episode Statistics to identify adult cases of cirrhosis from January 1998 to December 2009. We estimated 1- and 5-year survival according to whether time-at-risk was ambulatory or followed an emergency hospital admission related to liver disease, stratified by age, sex, and aetiology to be used in a clinical setting. We used a multivariate Cox-proportional hazards model with a time-varying variable, adjusted for Baveno IV stage of cirrhosis at diagnosis, age, aetiology, and sex.

Results: We identified 5118 incident cases. Average survival probabilities at 1- and 5-years were 0.84 (95% CI 0.83–0.86) and 0.66 (95% CI 0.63–0.68) for the ambulatory group and 0.55 (95% CI 0.53–0.57) and 0.31 (95% CI 0.29–0.33) following hospitalisation, respectively. A hospital admission at diagnosis or subsequently for liver disease substantially impaired prognosis independent of stage of cirrhosis (HR = 2.78, 95% CI 2.53, 3.06).

Conclusions: Emergency hospitalisation for liver disease heralds a downturn in a patient's outlook independent of their stage of cirrhosis. Our results provide population-based clinically translatable estimates of prognosis for the purposes of healthcare delivery and planning and communication to patients.

Introduction

The prognosis of liver cirrhosis is only well described amongst non-representative groups of patients as previous studies were limited by geographical region [1–3], disease severity [4,5] or to a specific aetiology such as viral hepatitis B [6,7]. These studies are therefore of limited use in a clinical setting where patients with a range of aetiologies often ask about their prognosis, and they might also be misleading if used to advise how healthcare services should be tailored appropriately.

One common limitation of previous large epidemiological studies was a restriction to either primary or secondary healthcare records [8,9] preventing a truly non-selective population-based approach. Consequently, they have either not taken into account the large proportion of patients with cirrhosis who remain ambulatory, or alternatively the studies have failed to identify cirrhosis diagnosed during a fatal hospitalisation. Having an emergency hospital admission is not just associated with a deterioration in cirrhosis, but can be associated with and potentially be the cause of a number of fatal complications such as pulmonary embolism [10]. No previous study has quantified the difference in survival between patients with cirrhosis who are managed during ambulatory care, and those who are managed following an emergency hospitalisation. Without a comprehensive and heterogeneous population of people with cirrhosis that includes varying time-at-risk, it is impossible to quantify survival estimates, which can be used in a clinical setting and describe the effect of hospitalisation for the full spectrum of disease.

The recent linkage of the Clinical Practice Research Datalink with the Hospital Episode Statistics database and data from the Office for National Statistics has provided us with a novel opportunity to construct a study cohort that is representative of the whole population of people with cirrhosis in England.

The aim of this study is to determine 1- and 5-year average survival of people with cirrhosis and the independent effect of hospitalisation, while taking into account their age, sex, underlying aetiology and stage of disease.

Materials and methods

Primary care data

The Clinical Practice Research Datalink (CPRD) is a longitudinal electronic database consisting of anonymised primary care records of over 10 million patients in the UK. Data are coded using the Read code system. Participating practices are assigned an up to standard (UTS) date on completion of regular audits con-

Keywords: Cirrhosis; Survival; Aetiology; Population-based.
Received 15 February 2013; received in revised form 26 September 2013; accepted 30 September 2013; available online 12 October 2013
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2013.10.023.
* Corresponding author. Address: Division of Epidemiology & Public Health, University of Nottingham, Nottingham NG5 1PB, UK. Tel.: +44 (0)115 8231344; fax: +44 (0)115 8231946.
E-mail address: sonia.ratib@nottingham.ac.uk (S. Ratib).
Abbreviations: CPRD, Clinical Practise Research Datalink; HES, Hospital Episode Statistics; ONS, Office of National Statistics; ICD10, International Classification of Disease 10th version; OPCS4, Office of Population Censuses and Surveys' classification of interventions and procedures 4th version; UTS, up to standard.

firming data quality and completeness. The CPRD has previously been shown to be representative of the population of the UK [11].

Secondary care data

The Hospital Episodes Statistics (HES) database comprises statutory records of all admissions (excluding out-patients) conducted in NHS trust hospitals and independent treatment centres in England. 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 ICD10 (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 interventions and procedures, fourth revision).

Death registry data

The Office for National Statistics (ONS) provides death registry data for CPRD practices that are linked to the HES database. Date of death from CPRD records was used where ONS date of death was unavailable.

Study population

We had access to data from all 244 CPRD practices in England linked to HES between April 1997 and August 2010 and to the ONS between April 1998 and December 2010. 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. The Read code lists were adapted and updated from our previous externally validated definition [12] (Supplementary data, Appendix 1). We developed codes lists for cirrhosis diagnosis in secondary case from ICD10 (K70.3, K71.7, K72.1, K74.4, K74.5, K74.6, K76.6, I85.0, I85.9, I86.4, I98.2) and OPCS4 (J06.1, J06.2, T46.1, T46.2, G10.4, G10.8, G10.9, G14.4, G17.4, G43.7).

Observation period

The observation period commenced on the latest of (i) one year after the patient's current registration date or (ii) the practice's UTS date. The one year cut-off was used to avoid including potential prevalent cases, adapted from Lewis *et al.*'s methodology [13]. The period terminated on the earliest of (i) date of death, (ii) date the patient left the practice, or (iii) the practice's last data collection date. We identified incident diagnoses between 1st January 1998 and 31st December 2009.

Validating case definition

For people with a cirrhosis diagnosis recorded in primary care we established how many had a hospital admission related to liver disease (e.g., alcoholic liver disease) (Supplementary data, Appendix 2). We identified whether the admissions were elective or emergency defined as per the NHS Information Centre definition [14].

For patients identified with cirrhosis from secondary care records only, we searched for evidence of liver disease in their healthcare records (Supplementary data, Appendix 3) and anywhere on their death certificate (Supplementary data, Appendix 4). We excluded patients who had a record of cancer and an isolated procedure relating to ascites and no other evidence or death related to liver disease. For the remaining patients we examined their primary care free text data for terms related to cirrhosis.

Diagnosis date

For each patient we assigned the date of diagnosis as the first date associated with a Read or ICD10/OPCS4 code for cirrhosis within the observation period. Patients younger than 18 years at diagnosis were excluded.

Exposure of interest: Patient setting at diagnosis and in subsequent follow up

We categorised patients into three groups based on the patient setting:

(1) Ambulatory at first diagnosis. These were patients who had a first record of cirrhosis in primary care or an elective admission in secondary care records.
(2) Ambulatory with subsequent emergency hospital admission for liver disease: These were group (1) patients who had a subsequent emergency hospital admission related to liver disease.
(3) Hospitalised at first diagnosis: These were patients whose first record of cirrhosis occurred during an emergency hospital admission.

Aetiology

We searched the patient's medical records for evidence of viral hepatitis, autoimmune and metabolic diseases. We defined patients as having an underlying alcoholic aetiology if there was mention in their records of alcoholism for example alcohol abuse, addiction or dependence, 'problem drinking' or referral to alcohol cessation services, or if their weekly alcohol consumption in their primary care records exceeded the Chief Medical Officer's recommended amount (14 units for women, 21 units for men) [15]. Our Read code list for this was adapted from previous work [12] and our ICD10 code list was adapted from Statistics on Alcohol, England [16]. We also searched for evidence of viral hepatitis, autoimmune and metabolic diseases. Aetiology was ascribed in a hierarchical fashion of viral hepatitis, autoimmune or metabolic disease and alcoholic cirrhosis. If a patient had no recorded aetiology they were ascribed a cryptogenic aetiology.

Stage of disease

We defined stages of disease as agreed at the Baveno IV consensus conference [17]. Each of the four stages is defined by the presence or absence of certain clinical symptoms within one year of incident diagnosis. Stages 1 and 2 represent compensated cirrhosis and stages 3 and 4 decompensated cirrhosis.

Statistical analysis

We used death from any cause as the primary outcome in our study and excluded patients whose diagnosis date was concurrent with date of death. We tested for baseline differences between patient groups using chi-squared. In order to include deaths in the ambulatory time-at-risk period that were related to hospitalisation, discharge date of first subsequent emergency hospital admission for liver disease plus 30 days was considered a time-varying variable with follow-up split at this date to identify two groups based on time-at-risk:

(1) Patients in group 1 and group 2 (up to their emergency hospital discharge date plus 30 days) contributed time-at-risk to the ambulatory group.
(2) Patients in group 2 (followed-up from their emergency hospital discharge date plus 31 days) and group 3 contributed time-at-risk to the subsequent to hospitalisation group.

We plotted a Kaplan-Meier survival curve to show the difference in survival by time-at-risk and estimated survival probabilities (and 95% confidence intervals (CI)) overall and at 1- and 5-years stratified by sex, age, aetiology, and disease stage. In order to determine how survival differed between the two time-at-risk groups we used Cox regression to estimate hazard ratios (HR) adjusting for potential confounders of age, sex, aetiology, and stage of disease in our model. The proportional hazards assumption was checked using log-log plots. Clinically relevant interactions were tested with likelihood ratio tests. Stata version 12 MP4 was used for all statistical analyses and a p value <0.05 was taken as the cut-off for statistical significance.

Results

Incident cases

A total of 5247 people aged 18 and over were identified as incident cirrhosis cases between January 1998 and December 2009, 2965 from primary care records and an additional 2282 from secondary care. 129 (2.5%) patients whose date of diagnosis was concurrent with death were excluded, establishing an incident

study cohort of 5118 people diagnosed with cirrhosis during the observation period.

Validation of case definition

A total of 2975 cases were identified in primary care, 10 were excluded as they had a cirrhosis-related hospitalisation before 1998, 2721 (91.5%) were hospitalised during the observation period and 2230 (75%) had a diagnosis or procedure related to liver disease. Out of the 2282 patients with a record of cirrhosis in secondary care over 90.4% (n = 2062) either died, had additional evidence related to liver disease in their records, or a confirmation of a cirrhosis diagnosis in their free text.

Patient groups

2698 patients (52.7% of the incident cohort) were ambulatory at first diagnosis. Of these, 1677 (62.1%) remained ambulatory throughout the study period (group 1) and 1021 (37.8%) had a subsequent emergency hospital admission for liver disease (group 2). 2420 patients had a first diagnosis during an emergency admission (group 3, 47.3%).

Patient characteristics

The cohort of 5118 patients had a mean age of 59.3 (SD = 14.3) years and slightly more men (57.9%) than women; just over half of the population had an aetiology of alcoholic cirrhosis (53.9%) (Table 1). A higher proportion of men than women had alcoholic cirrhosis, 61.9% *vs.* 42.8% respectively ($\chi^2_{(3)} = 235.7$, $p < 0.001$). Just over half of the study population (56.3%) had compensated cirrhosis (Baveno IV stages 1 or 2) at diagnosis.

The distribution of age, sex, stage of disease, and aetiology varied between the ambulatory and hospitalised at first diagnosis groups: the former had a substantially lower proportion of people with alcoholic cirrhosis, almost twice the proportion of people with viral hepatitis ($\chi^2_{(3)} = 117.7$, $p < 0.001$), and a smaller proportion of men ($\chi^2_{(1)} = 6$, $p = 0.02$) compared to the latter. The hospitalised at first diagnosis group had a higher proportion of younger patients than the ambulatory at first diagnosis group ($\chi^2_{(4)} = 23$, $p < 0.001$). A lower proportion of the ambulatory at first diagnosis group had decompensated cirrhosis (24.2% *vs.* 66.3%, $\chi^2_{(3)} = 918$, $p < 0.001$) than the hospitalised at first diagnosis group. Supplementary Table 1 shows patient characteristics of those in group 2.

Survival

In a total of 14,437 person-years of follow-up (median length of follow-up 1.88 [IQR 0.40–4.27] years), there were 2565 (50.1%) deaths in our cohort. Overall the survival probabilities were 0.70 (95% CI 0.69–0.71) at 1-year and 0.47 (95% CI 0.45–0.48) at 5-years. For the ambulatory time-at-risk, survival probabilities at 1- and 5-years were 0.84 (95% CI 0.83, 0.86) and 0.66 (95% CI 0.63, 0.68), respectively and 0.55 (95% CI 0.53, 0.57) and 0.31

Table 1. Patient characteristics of the incident study cohort, 1998–2009.

Patient group	Men			Women		
	Ambulatory at first diagnosis n = 1520	Hospitalised at first diagnosis n = 1445	Overall n = 2965	Ambulatory at first diagnosis n = 1178	Hospitalised at first diagnosis n = 975	Overall n = 2153
Median f/up [IQR], yr*	2.39 [0.95, 4.76]	0.97 [0.12, 2.97]	1.69 [0.35, 3.98]	2.99 [1.27, 5.79]	1.12 [0.1, 3.3]	2.17 [0.51. 4.72]
No. deaths (%)¥	681 (44.8)	875 (60.6)	1556 (52.5)	438 (37.2)	571 (58.6)	1009 (46.9)
No. with aetiology (%)						
Alcohol	853 (56.1)	971 (67.2)	1834 (61.9)	426 (36.2)	496 (50.9)	922 (42.8)
Viral hepatitis	215 (14.1)	120 (8.3)	335 (11.3)	162 (13.8)	77 (7.9)	239 (11.1)
Autoimmune/metabolic disease	114 (7.5)	69 (4.8)	183 (6.2)	222 (18.8)	100 (10.3)	322 (15)
Cryptogenic	328 (21.6)	285 (19.7)	613 (20.7)	368 (31.2)	302 (31)	670 (31.1)
Mean age (sd) yr	58.5 (13)	58.6(14.6)	58.6 (13.8)	60.7 (14.6)	60.1 (15.1)	60.4 (14.8)
Age at diagnosis (%) yr:						
<45	203 (13.4)	242 (16.7)	445 (15)	156 (13.2)	143 (14.7)	299 (13.9)
45 to 54	356 (23.4)	340 (23.5)	696 (23.5)	231 (19.6)	214 (21.9)	445 (20.7)
55 to 64	459 (30.2)	336 (23.3)	795 (26.8)	283 (24)	231 (23.7)	514 (23.9)
65 to 74	305 (20.1)	277 (19.2)	582 (19.6)	263 (22.3)	178 (18.3)	441 (20.5)
75+	197 (13)	250 (17.3)	447 (15.1)	245 (20.8)	209 (21.4)	454 (21.1)
Baveno IV stage						
1	871 (57.3)	348 (24.1)	1219 (41.1)	694 (58.9)	252 (25.8)	946 (43.9)
2	284 (18.7)	148 (10.2)	432 (14.6)	218 (18.5)	68 (7)	286 (13.3)
3	215 (14.1)	609 (42.1)	824 (27.8)	179 (15.2)	438 (44.9)	617 (28.7)
4	150 (9.9)	340 (23.5)	490 (16.6)	87 (7.3)	217 (22.3)	304 (14.1)

*Follow-up from date of diagnosis to end of follow-up.
¥For group and not time-at-risk period.
IQR, Inter-quartile range.

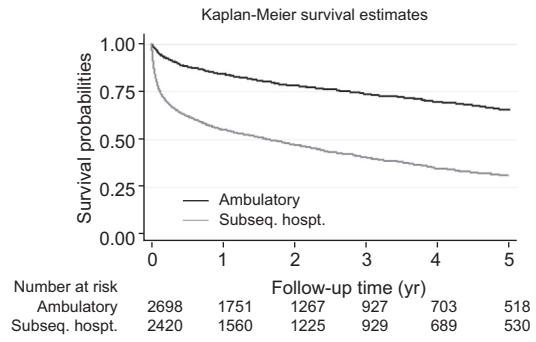

Fig. 1. Survival estimates within 5 years by time-at-risk period. Number at risk is calculated at each point by excluding previous deaths and censored events. Subseq.hospt, subsequent to hospitalisation.

(95% CI 0.29, 0.33), respectively for the subsequent to hospitalisation group (Fig. 1). The Kaplan-Meier curve was truncated at 5 years given that there was little follow-up time there onwards.

Table 2 shows the survival probabilities at 5-years stratified by sex, time-at-risk, aetiology, and age. They have been presented this way to provide prognostic information that could be applied easily in a clinical setting. Supplementary Table 2 shows the equivalent 1-year survival probabilities. In general, survival decreased with age, was better for women and overall did not differ substantially between the different aetiologies, apart from a few instances. Supplementary Table 3 provides clinical examples that demonstrate how the survival estimates vary dependent on patient factors and clinical setting. Tables 3A and B show the 5-year survival probabilities for compensated and decompensated patients separately, respectively. Supplementary Table 4A and B show the equivalent 1-year survival probabilities. These tables show that hospitalisation heralds a downturn irrespective of stage of disease at diagnosis.

Multivariate analysis

Adjusting for age, sex, aetiology and disease stage the risk of death was independently higher subsequent to hospitalisation compared to the ambulatory group (HR = 2.78, 95% CI 2.53, 3.06). The risk of death in those with decompensated cirrhosis

Table 2. Survival probabilities (95% CI) at 5-years by sex, time-at-risk, aetiology, and age.

Aetiology	Men		Women	
	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk
Alcoholic, n = 2756				
<45 yr	0.71 (0.57, 0.82)	0.46 (0.38, 0.54)	0.79 (0.62, 0.89)	0.51 (0.40, 0.61)
45 to 54	0.66 (0.56, 0.75)	0.39 (0.33, 0.45)	0.66 (0.52, 0.77)	0.34 (0.27, 0.42)
55 to 64	0.59 (0.51, 0.66)	0.33 (0.27, 0.39)	0.64 (0.49, 0.75)	0.37 (0.30, 0.44)
65 to 74	0.61 (0.51, 0.70)	0.21 (0.15, 0.28)	0.59 (0.42, 0.73)	0.27 (0.17, 0.38)
75+	0.29 (0.14, 0.45)	0.08 (0.04, 0.15)	0.51 (0.24, 0.73)	0.13 (0.05, 0.24)
Overall	0.60 (0.55, 0.64)	0.32 (0.29, 0.35)	0.65 (0.58, 0.71)	0.35 (0.31, 0.39)
Viral hepatitis, n = 574				
<45 yr	0.78 (0.61, 0.89)	0.35 (0.19, 0.51)	0.89 (0.58, 0.97)	0.46 (0.24, 0.66)
45 to 54	0.75 (0.58, 0.85)	0.37 (0.23, 0.52)	0.77 (0.55, 0.89)	0.48 (0.26, 0.66)
55 to 64	0.72 (0.53, 0.84)	0.45 (0.24, 0.63)	0.80 (0.54, 0.92)	0.38 (0.18, 0.58)
65 to 74	0.66 (0.18, 0.90)	0	0.80 (0.58, 0.92)	0.21 (0.05, 0.45)
75+	0.42 (0.10, 0.72)	0.10 (0.01, 0.30)	0.43 (0.23, 0.61)	0.22 (0.04, 0.49)
Overall	0.72 (0.63, 0.79)	0.32 (0.24, 0.40)	0.74 (0.64, 0.81)	0.37 (0.27, 0.47)
Autoimmune/metabolic disease, n = 505				
<45 yr	0.80 (0.20, 0.97)	0.51 (0.19, 0.76)	1	0.88 (0.39, 0.98)
45 to 54	0.94 (0.67, 0.99)	0.26 (0.07, 0.49)	1	0.42 (0.21, 0.63)
55 to 64	0.76 (0.47, 0.90)	0.25 (0.11, 0.41)	0.93 (0.81, 0.97)	0.65 (0.41, 0.82)
65 to 74	0.69 (0.40, 0.86)	0.42 (0.21, 0.63)	0.68 (0.49, 0.81)	0.21 (0.10, 0.34)
75+	0.51 (0.22, 0.74)	0	0.58 (0.33, 0.77)	0
Overall	0.73 (0.60, 0.83)	0.30 (0.21, 0.40)	0.80 (0.72, 0.86)	0.31 (0.23, 0.40)
Cryptogenic, n = 1283				
<45 yr	0.81 (0.44, 0.94)	0.72 (0.48, 0.87)	0.90 (0.76, 0.96)	0.81 (0.64, 0.90)
45 to 54	0.95 (0.81, 0.99)	0.49 (0.27, 0.68)	0.95 (0.82, 0.99)	0.42 (0.15, 0.67)
55 to 64	0.65 (0.48, 0.77)	0.16 (0.07, 0.29)	0.85 (0.70, 0.93)	0.47 (0.30, 0.62)
65 to 74	0.44 (0.30, 0.57)	0.20 (0.10, 0.32)	0.61 (0.47, 0.72)	0.26 (0.16, 0.37)
75+	0.35 (0.22, 0.49)	0.11 (0.07, 0.18)	0.53 (0.43, 0.63)	0.14 (0.08, 0.21)
Overall	0.55 (0.48, 0.62)	0.21 (0.16, 0.26)	0.70 (0.64, 0.75)	0.31 (0.26, 0.37)
Total	0.61 (0.58, 0.65)	0.30 (0.27, 0.32)	0.71 (0.67, 0.74)	0.33 (0.31, 0.36)

CI, confidence intervals.

Table 3. Survival probabilities (95% CI) at 5-years by sex, time-at-risk, aetiology, and age for COMPENSATED (A) and DECOMPENSATED (B) patients.

A	Men		Women	
Aetiology	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk
Alcoholic, n = 1428				
<45 yr	0.76 (0.56, 0.88)	0.57 (0.43, 0.69)	0.82 (0.63, 0.92)	0.61 (0.42, 0.75)
45 to 54	0.71 (0.59, 0.80)	0.40 (0.30, 0.50)	0.75 (0.58, 0.86)	0.35 (0.24, 0.47)
55 to 64	0.60 (0.52, 0.68)	0.31 (0.22, 0.40)	0.74 (0.57, 0.85)	0.31 (0.20, 0.43)
65 to 74	0.70 (0.60, 0.79)	0.19 (0.11, 0.29)	0.59 (0.37, 0.75)	0.29 (0.14, 0.45)
75+	0.32 (0.15, 0.50)	0.08 (0.02, 0.20)	0.50 (0.20, 0.74)	0.09 (0.01, 0.25)
Overall	0.64 (0.59, 0.69)	0.32 (0.27, 0.37)	0.71 (0.62, 0.77)	0.35 (0.29, 0.42)
Viral hepatitis, n = 387				
<45 yr	0.81 (0.62, 0.91)	0.44 (0.20, 0.66)	0.89 (0.43, 0.98)	0.86 (0.33, 0.98)
45 to 54	0.78 (0.61, 0.89)	0.35 (0.17, 0.54)	0.83 (0.55, 0.95)	0.55 (0.19, 0.81)
55 to 64	0.78 (0.58, 0.89)	0.35 (0.12, 0.60)	0.81 (0.51, 0.94)	0.32 (0.04, 0.66)
65 to 74	0.66 (0.18, 0.90)	0	0.82 (0.58, 0.93)	0.14 (0.01, 0.41)
75+	0.51 (0.12, 0.81)	0.18 (0.01, 0.50)	0.49 (0.25, 0.69)	0.38 (0.06, 0.72)
Overall	0.76 (0.66, 0.83)	0.28 (0.18, 0.38)	0.77 (0.66, 0.85)	0.45 (0.29, 0.60)
Autoimmune/metabolic, n = 368				
<45 yr	0.75 (0.13, 0.96)	0.51 (0.12, 0.81)	1.0	1.0
45 to 54	1.0	0.33 (0.01, 0.77)	1.0	0.33 (0.08, 0.62)
55 to 64	0.75 (0.42, 0.91)	0.30 (0.07, 0.58)	0.94 (0.82, 0.98)	0.78 (0.36, 0.94)
65 to 74	0.67 (0.36, 0.85)	0.57 (0.22, 0.81)	0.67 (0.48, 0.80)	0.22 (0.08, 0.41)
75+	0.54 (0.23, 0.77)	0.0	0.60 (0.31, 0.80)	.
Overall	0.73 (0.58, 0.83)	0.40 (0.24, 0.55)	0.81 (0.72, 0.87)	0.34 (0.22, 0.45)
Cryptogenic, n = 700				
<45 yr	0.91 (0.68, 0.98)	1.0	0.91 (0.68, 0.98)	0.80 (0.20, 0.97)
45 to 54	0.94 (0.77, 0.98)	0.43 (0.16, 0.67)	1.0	0.28 (0.01, 0.68)
55 to 64	0.64 (0.45, 0.78)	0.10 (0.01, 0.33)	0.87 (0.69, 0.95)	0.62 (0.33, 0.81)
65 to 74	0.49 (0.33, 0.64)	0.20 (0.06, 0.40)	0.69 (0.53, 0.80)	0.23 (0.36, 0.58)
75+	0.38 (0.22, 0.53)	0.17 (0.07, 0.30)	0.54 (0.42, 0.65)	0.27 (0.13, 0.42)
Overall	0.59 (0.51, 0.67)	0.25 (0.16, 0.35)	0.72 (0.65, 0.78)	0.36 (0.25, 0.47)
Total	0.65 (0.62, 0.69)	0.31 (0.27, 0.35)	0.74 (0.71, 0.78)	0.36 (0.31, 0.41)

(*continued on next page*)

was 1.3-fold that of patients with compensated cirrhosis (95% CI 1.24, 1.47) adjusting for confounders. The multivariate Cox regression model is shown in Supplementary Table 5. There was a statistically significant interaction between aetiology and age in the Cox regression model ($\chi^2_{(12)} = 28.4$, $p < 0.01$), adjusting for sex, stage of disease and time-at-risk group. Comparing the alcoholic with the cryptogenic patients there was approximately a two-fold risk of death in those younger than 45 years but no significant difference for patients older than 55 years. We report the adjusted hazard for each age-group by aetiology in Supplementary Table 5.

Discussion

Main findings

Our study is the first to use both primary and secondary healthcare linked data to establish a comprehensive cohort of people with incident cirrhosis in England and consequently to take into account the transition from ambulatory to hospitalised time-at-risk when calculating accurate survival estimates. Our findings show that patients who remain ambulatory have a 5-year survival of 66%, which is comparable to that seen for cancer of the bladder [18]. In contrast, once a patient is hospitalised for an emergency their survival drops markedly. Indeed our findings suggest that emergency hospitalisation for liver disease heralds a downturn in a patient's outlook independent of their stage of cirrhosis. This we believe is important both for policy makers but also for clinical practice as we provide precise estimates of survival derived from an unbiased population that represents the generality of patients with cirrhosis. These estimates, stratified by age, sex, and aetiology can help with healthcare service provision planning but equally they can be used to communicate prognosis to patients based on a clinical assessment of disease and the natural history it undergoes. In addition, using emergency hospitalisation as a risk factor is a pragmatic way of determining prognosis as it is objective and relatively easy to define.

Strengths and limitations

The largest potential limitation with a study trying to determine incidence from routinely collected data is confidence in case definition. Compared to previous studies, which have used broad

Table 3. (*continued*)

B Aetiology	Men		Women	
	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk	Ambulatory time-at-risk	Subsequent to hospitalisation time-at-risk
Alcoholic, N = 1328				
<45 yr	0.64 (0.38, 0.81)	0.40 (0.29, 0.50)	0.69 (0.25, 0.91)	0.43 (0.28, 0.57)
45 to 54	0.49 (0.27, 0.69)	0.39 (0.31, 0.46)	0.49 (0.26, 0.69)	0.34 (0.24, 0.43)
55 to 64	0.56 (0.40, 0.69)	0.35 (0.27, 0.43)	0.31 (0.07, 0.61)	0.42 (0.33, 0.51)
65 to 74	0.23 (0.05, 0.49)	0.24 (0.16, 0.33)	0.59 (0.29, 0.80)	0.27 (0.14, 0.41)
75+	.	0.09 (0.03, 0.18)	0.50 (0.06, 0.84)	0.18 (0.06, 0.35)
Overall	0.46 (0.35, 0.56)	0.33 (0.29, 0.37)	0.51 (0.36, 0.63)	0.36 (0.30, 0.41)
Viral hepatitis, n = 187				
<45 yr	0.60 (0.13, 0.88)	0.19 (0.03, 0.44)	0.83 (0.27, 0.97)	.
45 to 54	.	0.45 (0.21, 0.66)	0.56 (0.15, 0.84)	0.44 (0.19, 0.67)
55 to 64	.	0.58 (0.24, 0.81)	0.75 (0.13, 0.96)	0.44 (0.20, 0.65)
65 to 74	.	.	.	.
75+	.	.	.	0
Overall	0.37 (0.09, 0.67)	0.32 (0.17, 0.47)	0.62 (0.39, 0.79)	0.29 (0.17, 0.43)
Autoimmune/metabolic, n = 137				
<45 yr	1.0	0.50 (0.06, 0.84)	.	0.75 (0.13, 0.96)
45 to 54	0.50 (0.01, 0.91)	0.18 (0.02, 0.46)	1.0	0.51 (0.19, 0.76)
55 to 64	0.86 (0.33, 0.98)	0.20 (0.05, 0.42)	0.50 (0.01, 0.91)	0.53 (0.20, 0.78)
65 to 74	.	0.25 (0.33, 0.76)	.	.
75+	.	.	0.44 (0.07, 0.78)	0
Overall	0.78 (0.46, 0.93)	0.21 (0.11, 0.34)	0.72 (0.40, 0.89)	0.29 (0.16, 0.43)
Cryptogenic, n = 583				
<45 yr	.	0.60 (0.31, 0.80)	0.89 (0.64, 0.97)	0.81 (0.62, 0.91)
45 to 54	1	.	0.80 (0.41, 0.95)	0.57 (0.28, 0.78)
55 to 64	0.69 (0.41, 0.86)	0.20 (0.08, 0.37)	0.73 (0.37, 0.90)	0.39 (0.20, 0.57)
65 to 74	0.30 (0.10, 0.55)	0.20 (0.09, 0.35)	0.28 (0.06, 0.58)	0.27 (0.16, 0.40)
75+	0.19 (0.01, 0.52)	0.09 (0.04, 0.16)	0.53 (0.31, 0.70)	0.09 (0.04, 0.17)
Overall	0.43 (0.26, 0.58)	0.19 (0.13, 0.26)	0.62 (0.49, 0.73)	0.29 (0.23, 0.36)
Total	0.46 (0.38, 0.54)	0.29 (0.26, 0.33)	0.58 (0.50, 0.66)	0.32 (0.29, 0.36)

CI, confidence intervals. '.' means the number of events was very small.

ICD10 code lists including non-cirrhotic codes of K70.9 (alcoholic liver disease) and K74.3 (primary biliary cirrhosis) [19], our definition of cirrhosis was much more restrictive. The linked data have confirmed our case definitions by providing supporting evidence of liver disease among the various healthcare records and death registry, analogous to a chart review. Our current finding that a large proportion of patients diagnosed within the CPRD had a hospital admission related to liver disease (75%) emphasises the reliability of our case definition (given that we would not expect all cirrhotic patients to require a hospital admission). The finding falls in line with our previous external validation of primary care records where review of patients' paper records confirmed cirrhosis in the majority of patient records checked [12]. In two recent systematic reviews case validity for most chronic conditions was described as good using the CPRD [20,21].

In those presenting with cirrhosis in secondary care only, we found 90% had additional evidence of liver disease or death related to liver disease, or a mention of cirrhosis in their primary care written record. Kramer *et al.* [22] recently found ICD9 codes for cirrhosis had a 90% positive predictive value and 87% negative predictive value. Unlike the CPRD, HES data cannot be validated against medical records directly due to the anonymization process used. A recent government audit found 91% median accuracy [23] and our findings confirm accurate coding in the HES.

Overall we believe our case definition is as robust as previously reported in bespoke case studies of cirrhosis from secondary care. That our population was not drawn from an individual tertiary referral centre is on its own a strength of the present study as the population is more representative of the entire spectrum of disease and is drawn from a population, which is representative of the whole population of England [11].

Our group and others [24,25] have shown previously that survival differs by disease stage, i.e., compensated or decompensated cirrhosis. By splitting follow-up at 30 days plus emergency hospital discharge date to define our time-at-risk we have been able to add to our previous work, showing how those who initially present as ambulatory patients can have varied survival dependent on subsequent hospitalisation. Our study also highlights that irrespective of whether the patient had compensated or decompensated cirrhosis at first diagnosis, the key risk factor is having an emergency hospitalisation for liver disease. We cannot tease out from the data available what the exact cause of the hospital

admission is and therefore are not able to speculate as to whether it is the liver disease *per se* or an event, which occurs in hospital, which is affecting this difference in survival.

Several studies have used the Model for End-stage Liver Disease (MELD) or Child-Turcotte-Pugh scores [26,27] to prognosticate survival for patients with cirrhosis and determine whether transplantation is necessary. Although we have not reported these scores in our study, due to lack of laboratory data, the attraction of our method is its simplicity and independence of complete laboratory measurements in determining long-term prognostic information. For those we could determine a MELD score for (n = 1415, 27.6%) Baveno IV stage of disease was shown to be highly correlated (p <0.01). As information on this variable was available for the entirety of our study population we took the pragmatic approach of using Baveno IV stage of disease to present our survival estimates and adjust our mortality estimates for disease severity. It should be noted that Baveno IV stage here reflects what is known on patients in routine clinical practice around incident diagnosis; it is possible that there may be some misclassification error.

For the ambulatory time-at-risk we have included death during the first subsequent hospitalisation period plus 30 days following discharge to take into account the real life situation of cirrhotics who deteriorate in the community and are admitted to hospital to manage their death and/or are then discharged to die outside hospital. An alternative method of performing a competing risk analysis with hospitalization as a competing event would provide higher survival estimates for the ambulatory period, but would exclude deaths in patients admitted to hospital as part of their final deterioration.

Finally, although we have ascertained the date of diagnosis and excluded prevalent individuals, the exact onset of a chronic disease process such as cirrhosis can't be ascertained without a population-based screening programme. As there is no screening for cirrhosis in the National Health Service in England, it is generally only diagnosed clinically when people first present to a healthcare provider. We have identified incident diagnoses rather than incident cases. Our study therefore is relevant to the pragmatic approach that is the reality in clinical practice.

Other literature

Our mortality analysis can be compared in detail with two large hospital-based studies from England and Denmark. In 2005, Roberts *et al.* described the survival experience of 8192 people admitted to hospital with either chronic liver disease or cirrhosis in the Oxford region between 1968 and 1999. Our 1-year survival in the subsequent to hospitalisation group (55%) was lower than theirs (66.4%) and lower than that of the large Danish cohort study (65.5%) [3]. This is likely because our subsequent to hospitalisation group consisted of solely emergency admissions, whereas the other two studies combined in- and out-patients. The recent Danish study by Fialla *et al.* [2] separated in- and out-patients and reported 1-year survival for their out-patients as 76%, which was lower than that of our ambulatory group (84%), most likely due to the fact that their out-patient group excluded ambulatory patients, a limitation highlighted by the authors.

In comparison with our previous study [25], survival at 1-year in the ambulatory group was almost identical to those who had compensated cirrhosis according to their primary care records (87.3%), while survival at 1-year in the subsequent to hospitalisation group was worse than the survival of those who had decompensated cirrhosis (75%). This demonstrates how survival of severely ill patients is over estimated if only primary care records are used.

Most previous studies have found that those, who had alcoholic cirrhosis had a worse prognosis than those without [8,9]. We were also able to report how relative mortality between aetiology groups differs by age, information that has not previously been available. We showed aetiology affected prognosis in young patients but less so in older patients; comparing the alcoholic with the cryptogenic patients there was approximately a two-fold risk of death in those younger than 45 years but no significant difference for patients older than 55 years.

Conclusion

In summary we have established a comprehensive, contemporary cohort, representing the whole spectrum of people with cirrhosis in terms of their mode of presentation and aetiology of disease. We have determined survival estimates for patients with different presentations of the disease and taken into account the transition from being ambulatory to becoming hospitalised and subsequently. We have shown that an emergency hospitalisation predicts a poorer prognosis irrespective of disease stage, and conversely that patients have a relatively good outcome whilst ambulatory. This finding suggests that liver disease could be managed more intensively in an outpatient or day case setting, which might reduce emergency admission, with the hope of ultimately improving the survival experience of cirrhotic patients. Our results provide physicians as well as those planning health services with precise and unbiased estimates of survival, which should help to allow optimisation of the allocation of limited resources.

Financial support

University of Nottingham/National University Hospitals NHS Trust/National Institute for Health Research Senior Clinical Research Fellowship.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgements

J.W. had the original idea for the study and all authors contributed to its interpretation. S.R. was responsible for data management and performed the data analysis. S.R. and J.W. initially drafted the paper. K.M.F., C.J.C., and G.P.A. revised the paper critically and all authors approved the final version. The funders of this study had no role in the design, analysis or interpretation of the data. S.R. is funded by the Fellowship awarded to J.W. Approval was given by the Independent Scientific and Ethical Committee of the CPRD for this study (09_065RA_3).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.09.027.

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