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**Rate of decompensation and clinical progression of disease
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Rate of decompensation and clinical progression of **disease in people with cirrhosis: a cohort study**

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Running title: Cirrhosis progression

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Keywords: cirrhosis, decompensation, epidemiology, progression

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a National Institute for Health Research Clinician Scientist Fellowship awarded to JW.

Abstract

Background

We lack population-based estimates of the rate of decompensation in people with compensated cirrhosis as well as estimates of the manner in which the disease progresses once identified.

Aim

To determine the rate of decompensation and clinical progression of disease in patients with cirrhosis based upon clinical symptoms recorded electronically in general practice data.

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Methods

Using Cox proportional hazards regression we modelled the rate of decompensation for patients from the UK General Practice Research Database with a diagnosis of cirrhosis between 1987 and 2002. We determined the [clinical progression in the first year following diagnosis and subsequently](#) categorising patients through time according to a simple clinical staging system [agreed at the Baveno IV consensus conference](#).

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progression following diagnosis

Results

The rate of decompensation in patients with compensated cirrhosis was found to be 11% overall. The rate of decompensation was higher in [the first year \(at 31% compared with 7.3% afterwards\) and in](#) patients with an alcoholic aetiology. Patients with compensated cirrhosis had a one-year probability of proceeding directly to death of 7% compared with 20% in patients with decompensated cirrhosis.

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Conclusions

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Using data recorded in general practice records it has been possible to determine the rate of [decompensation and the clinical](#) progression of disease in people with cirrhosis.

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For Peer Review

Introduction

The natural history of cirrhosis has long been of interest to gastroenterologists and hepatologists [1] [2] [3] [4] [5] [6] [7] as knowledge of the progression of the disease allows planning of management and development of effective strategies for the primary prevention of complications and is of obvious interest to patients who wish to understand their risk of death, distressing symptoms and time to referral for consideration for transplantation. While in recent years advances have been made in the management of portal hypertension[8] with a consequent apparent improvement in some outcomes[9] we have surprisingly little information on the effect of these developments on the natural history of cirrhosis in a general population-based setting. The most commonly referenced studies have focussed on those patients who are admitted to hospital. In addition, while scoring systems such as Child-Pugh, MELD, UKELD enable the ranking of patients at an individual level and near the end stage of disease, we cannot at present provide useful absolute estimates of [the rate of decompensation, clinical](#) progression or mortality to patients in the earlier stages of disease.

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In a recent comprehensive systematic review of the natural history and prognostic indicators of survival in cirrhosis which included 118 pertinent publications[10] the authors reported a wide range of estimates of survival and factors that predicted death but many methodological difficulties were also described. Perhaps most saliently they provided for the first time one year outcome probabilities for cirrhosis according to the clinical stages of disease agreed at the Baveno IV consensus conference[11]. However, as their estimates were based on the experience in a sole hospital in Sicily in the late 1970s-early1980s they may not be widely generalisable. We therefore do not have contemporary estimates of the progression of disease in cirrhosis at a population level.

Increasingly people are being diagnosed with cirrhosis at earlier stages of the disease i.e. compensated rather than decompensated. We have consequently taken the opportunity presented by prospectively-recorded electronic primary care data from the UK to determine

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the rate of decompensation and the progression of disease in patients with cirrhosis based upon the Baveno IV stage of disease criteria.

For Peer Review

Methods

Description of GPRD

The General Practice Research Database (GPRD) is a longitudinal database consisting of anonymous computerised general practice records for over 13 million patients in the UK, including over 50 million patient-years of usable data. Practices are subjected to regular data quality checks and audits to maintain 95% inclusion of prescribing and morbidity events. Data contained 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[12] of which it represents approximately a 4-6% sample. Approval for this study was given by the Scientific and Ethical Committee of the GPRD.

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 or 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.

Definitions

We then categorised patients with cirrhosis through time following date of diagnosis according to the four stages of cirrhosis as agreed at the Baveno IV conference[11] – stage 1, uncomplicated cirrhosis i.e. cirrhosis in the absence of both oesophageal varices and ascites; stage 2, cirrhosis with oesophageal varices but without ascites and without bleeding; stage 3, cirrhosis with ascites, with or without oesophageal varices; and stage 4, cirrhosis

with GI bleeding, with or without ascites. Stages 1 and 2 together correspond to compensated cirrhosis with stages 3 and 4 together corresponding to decompensated cirrhosis. Each patient was assigned up to four dates corresponding to the earliest recording of the symptoms representing each stage. To minimise the potential for misclassification of patients with decompensated cirrhosis as patients with compensated disease we additionally looked for the recording of one or more prescriptions for spironolactone as evidence of decompensation.

Death was defined using 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.

Presumed aetiology of cirrhosis was defined as alcoholic, viral hepatitis, autoimmune liver disease or metabolic liver disease as previously reported.[13]. For the purposes of analyses all cases not defined as alcoholic, were classified as non-alcohol related cirrhosis.

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Deleted: All other cases of cirrhosis

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Statistical analyses

Using Cox proportional hazards we modelled the rate of decompensation in the group of patients with compensated disease. Subjects entered the analysis period at the date of earliest recorded code for stage 1 or 2 and exited at the earliest of date of earliest recorded code for stage 3 or 4, date of death, date of liver transplant, date of deregistration with their general practice or 30 April 2002 which was the last date of available data in this dataset.

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We examined the rate of decompensation for subjects with alcoholic cirrhosis and those with non-alcohol related cirrhosis. Follow-up time was split at 1 year and we modelled the rate of decompensation during the first year after diagnosis and subsequent to that first year again stratifying by presumed aetiology.

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We examined the probabilities of patients with cirrhosis progressing from an individual stage to a subsequent stage or death within one year and across the whole time period of their records with 95% confidence intervals being calculated assuming a binomial distribution.

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2 We again stratified the cohort into those with alcoholic cirrhosis and those with non-alcohol
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4 related cirrhosis.

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6 Stata version 9.2 SE was used for all statistical analyses.
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Results

A total of 4,537 patients were identified with cirrhosis. Table 1 shows selected clinical and demographic information about the study population. 56.1% entered the study cohort at stage 1, 12.8% at stage 2, 23.0% at stage 3 and 8.1% at stage 4. A total of 2307 (50.9%) of cirrhosis cases were classified as alcoholic cirrhosis with the remainder being assigned as non-alcohol related cirrhosis for the purposes of the subsequent analyses.

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Rate of decompensation

Overall, the rate of decompensation for those patients with compensated disease was 11.8% per year adjusted for age and sex (95%CI[11.2%, 12.5%]). This figure varied considerably both by length of follow-up and by presumed aetiology. A Kaplan-Meier survival curve showing the difference in rate of decompensation by presumed aetiology is shown in figure 1.

During the first year after diagnosis the rate of decompensation was 31.0% adjusted for age and sex (95%CI [28.8%, 33.4%]); for those patients with a presumed aetiology of alcoholic cirrhosis the rate of decompensation during the first year was 37.6% (95%CI [34.1%, 41.5%]) compared with 25.2% (95%CI [22.6%, 28.2%]) for those with non-alcohol related cirrhosis.

Following the first year the rate of decompensation did not vary much by presumed aetiology with a rate of 7.3% per year adjusted for age and sex (95%CI [6.5%, 8.2%]) for those with alcoholic cirrhosis compared with an adjusted rate of decompensation of 5.5% per year (95%CI [4.8%, 6.2%]) for those with non-alcohol related cirrhosis.

Progression

Outcome probabilities in the first year are shown in figure 2. Patients in stage 1 and 2 had a one-year probability of proceeding directly to death of around 7%. The probability of progression to death within 1 year was highest for patients within stage 3, rather than stage 4 (at 20.1% and 18.2% respectively) though this difference was not statistically significant.

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State progressions across the whole study period are shown in figure 3. Of note is the high proportion of people in the early stages of disease i.e. patients with compensated cirrhosis, who progressed directly to death without the recording of other clinical symptoms of decompensation. These results support the categorisation of stages 1 and 2 together as representing compensated disease and stages 3 and 4 together as representing decompensated disease.

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The probabilities of progressing both during the first year and state progressions subsequently for those with alcoholic cirrhosis and non alcohol-related cirrhosis are shown in table 2 and 3 respectively. Reading across the table shows the stage at which patients began their follow-up. The rows in the column represent the stage to which the patients directly progressed. For example looking at the first column we can see that alcoholics who began follow-up in stage 1 had a 64.6% chance of remaining in stage 1 during the first year, with 2.9% progressing directly to stage 2 (oesophageal varices), and so on. In the first year following diagnosis patients with alcoholic cirrhosis had a slightly higher probability of progressing to another stage of cirrhosis than those with non-alcohol related cirrhosis but a lower probability of progressing directly to death. Across the whole study period patients with a presumed aetiology of alcoholic cirrhosis were again more likely to progress to another later stage of cirrhosis than those with non-alcohol related cirrhosis. The differences in progression directly to death were not so marked across the whole time period, rather less patients with alcoholic cirrhosis remained in their entry stage with the exception of patients in stage 3.

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Discussion

Using the clinical observations recorded in primary care records of people with cirrhosis we have described the progression of disease as experienced by patients and as recorded by primary care physicians in the UK. Progression of disease is rapid with the rate of decompensation in patients with compensated cirrhosis being 11% per year, but is particularly rapid in the first year following diagnosis at 31% in this first year. We have used a relatively simple staging system, based on the presence or absence of symptoms rather than relying on laboratory tests, mimicking the Baveno IV consensus clinical staging system to classify patients with cirrhosis. The classification is useful in long-term planning of management of patients with cirrhosis. We have applied this classification to an ambulatory population from primary care to describe the natural history of this disease. For example, in those patients without recorded evidence of portal hypertension, i.e. those in stage 1 of disease, there was about a 11% probability of progressing to a more severe form of disease (development of ascites, varices or GI bleeding) within a year alongside an 7% likelihood of dying. In those patients with stage 2 disease, the chance of developing ascites or bleeding was approximately 24% in the following year alongside a 7% risk of death.

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. This cohort was identified reasonably recently (1987-2002) and therefore the results we have generated 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. We are confident based upon our own previous validation study (which showed the vast majority of patients with a recorded code for cirrhosis had available extra evidence from secondary care [13] 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

1
2 accurately however, unless they are of obvious clinical relevance to the GP. Hence ascites
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4 is probably symptomatic and hence, likely to be moderate to large-volume, clinically
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6 significant ascites (rather than that only identified by ultrasound). We acknowledge there
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8 may have been some misclassification between stages 1 and 2 as the recognition of
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10 development of oesophageal varices in the absence of bleeding depends on endoscopic
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12 surveillance which, for the period our data covers, was not necessarily uniform in the UK.
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14 We believe though that it is unlikely that much misclassification has occurred between the
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16 compensated and decompensated disease states nor between stages 3 and 4 as events
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18 such as bleeding oesophageal varices are of such importance that they are highly unlikely to
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20 be inaccurately recorded.

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22 For the purposes of predicting progression of disease and mortality we were unable to
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24 calculate the typically used Child-Pugh classification[14, 15] or the more recently derived
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26 model for end-stage liver disease (MELD)[16] as we had no measures of blood indices
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28 available. However, we argue that the strength of Baveno IV consensus clinical staging
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30 system is that it allows such a broad evaluation of the natural history of patients with
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32 cirrhosis without relying upon laboratory tests. In addition, unlike Child-Pugh and MELD
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34 scores which are of limited value in early stages of cirrhosis where specific laboratory tests
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36 are unaltered (e.g. Child-Pugh class A patients), the Baveno classification can be applied to
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38 both early and late stage disease. This not only allows us to describe disease progression,
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40 but also to do so in a way which is intelligible both to non-specialist clinicians, and to
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42 patients. Of course, the simplicity of the Baveno classification is also one of its weaknesses
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44 in that many other factors that are known to influence the progression of cirrhosis, such as
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46 the development of hepatocellular carcinoma, hepatic encephalopathy and nutritional status
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48 are not included within the criteria.

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50 We have included both incident and prevalent cases of cirrhosis by design as there is clear
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52 evidence that cirrhosis, as with most chronic diseases, has a wide heterogeneity of
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54 presentation. The results of our study therefore reflect the real world of clinical practice
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2 within the general population which is unlikely to be true of series collected from within
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4 secondary care centres with a particular interest in the disease. This may explain some of
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6 the discrepancies with previously reported data as discussed below.
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9 In comparison with historical studies of the natural history of cirrhosis[1] [2] [3] [4] [5] [6] [10]
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11 our work shows that even in the later stages of the 20th century progression of disease is
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13 rapid. Following our replication of D'Amico et al's [10] outcome model using the Baveno IV
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15 stage of disease system we found both similarities and differences with their reported
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17 findings. We found a similar clear demarcation of risk of death between compensated
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19 disease (stage 1 and stage 2) and decompensated disease (stage 3 and 4) although the
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21 probability of death within one year we observed for stage 1 and stage 2 disease was
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23 substantially higher than they reported. In contrast, we did not find a difference in the rate of
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25 progression to death for those patients with ascites rather than bleeding oesophageal
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27 varices. The explanation for these disparities most likely lies in the differences in
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29 methodology and population selection we have used. In the current study we have taken
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31 each individual's record and defined their progression of disease within 1 year, whereas
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33 D'Amico et al appears to report outcome probability estimates which were averaged risks
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35 from 10 years of follow up. In addition we have used a population-based approach to
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37 collection of cases rather than the single centre approach previously used. The great
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39 benefits of a population based approach i.e. avoiding bias and improving generalisability
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41 need no rehearsal, but in this case the potential for misclassification of minor degrees of
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43 decompensation consequent upon lack of direct access to cases may explain some of the
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45 difference in our results. It is likewise probable that much of the difference between our
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47 results is a consequence of the fact that the UK, with low levels of chronic viral hepatitis, has
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49 a different aetiological picture with respect to cirrhosis to that seen in Sicily (the setting from
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51 which the Baveno classification was derived). Finally some of the difference may be due to
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53 the era of data collection. Our finding that ascites is as severe a marker of poor prognosis as
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55 bleeding fits with the prevailing view that since the late 1970s widely available important
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2 improvements have been made in the management and outcomes of variceal bleeding [17]

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4 with improvements in the treatments for ascites broadly limited to the administration of
5 antibiotics in cases of spontaneous bacterial peritonitis which is a much less frequent
6 complication than bleeding.
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11 A recent paper from Denmark looking at only alcoholic cirrhosis has provided similarly
12 greater estimates for the 1-year progression directly to death in patients with no reported
13 complications of 10% and similar estimates for 1-year progression directly to death for
14 patients with clinical symptoms of ascites and variceal bleeding.[18] There are no such
15 comparable figures for patients with non-alcohol related cirrhosis available in current
16 published literature.
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24 In summary, our study has described the disease progression following a diagnosis of
25 cirrhosis in contemporary clinical practice using data recorded electronically in general
26 practice. Our reproduction of the use of a simple, internationally recognised, Baveno IV
27 consensus clinical staging system is practical, useful and relevant to patients with cirrhosis
28 and clinicians in the UK and beyond (within the limits of the assumptions underpinning its
29 design). Of particular interest is the overall rate of decompensation for all those with
30 cirrhosis as a contemporary estimate of this has not been readily available. Clearly further
31 validation of the approach we have used to stage disease in other datasets will be of value.
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33 We conclude that our results in conjunction with the previously observed increasing
34 incidence of cirrhosis emphasise the growing threat of liver disease to public health.
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Table 1. Selected demographic and clinical characteristics of study population

| <u>Demographics / lifestyle factors</u> | <u>Cirrhosis Cohort</u> <u>N=4537</u> <u>n (%)</u> |
|---|--|
|---|--|

Age at diagnosis(years)

| | |
|--------------|--------------------|
| <u>25-44</u> | <u>943 (20.8)</u> |
| <u>45-64</u> | <u>2256 (49.7)</u> |
| <u>65+</u> | <u>1338 (29.5)</u> |

Sex

| | |
|---------------|--------------------|
| <u>Male</u> | <u>2612 (57.6)</u> |
| <u>Female</u> | <u>1925 (42.4)</u> |

Presumed aetiology†

| | |
|----------------------------|--------------------|
| <u>Alcoholic cirrhosis</u> | <u>2307 (50.8)</u> |
| <u>Viral hepatitis</u> | <u>238 (5.2)</u> |
| <u>Autoimmune LD</u> | <u>48 (1.1)</u> |
| <u>Metabolic LD</u> | <u>354 (7.8)</u> |
| <u>Not classified</u> | <u>1730 (38.1)</u> |

Disease state at entry

| | |
|----------------------|--------------------|
| <u>Compensated</u> | <u>3126 (68.9)</u> |
| <u>Decompensated</u> | <u>1411 (31.1)</u> |

Liver Transplant

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|---|------------------|
| <u>(following diagnosis of cirrhosis)</u> | <u>106 (2.3)</u> |
|---|------------------|

Diagnosis of hepatocellular carcinoma

| | |
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| <u>Previous to diagnosis of cirrhosis</u> | <u>5 (0.1)</u> |
| <u>Following diagnosis of cirrhosis</u> | <u>59 (1.3)</u> |

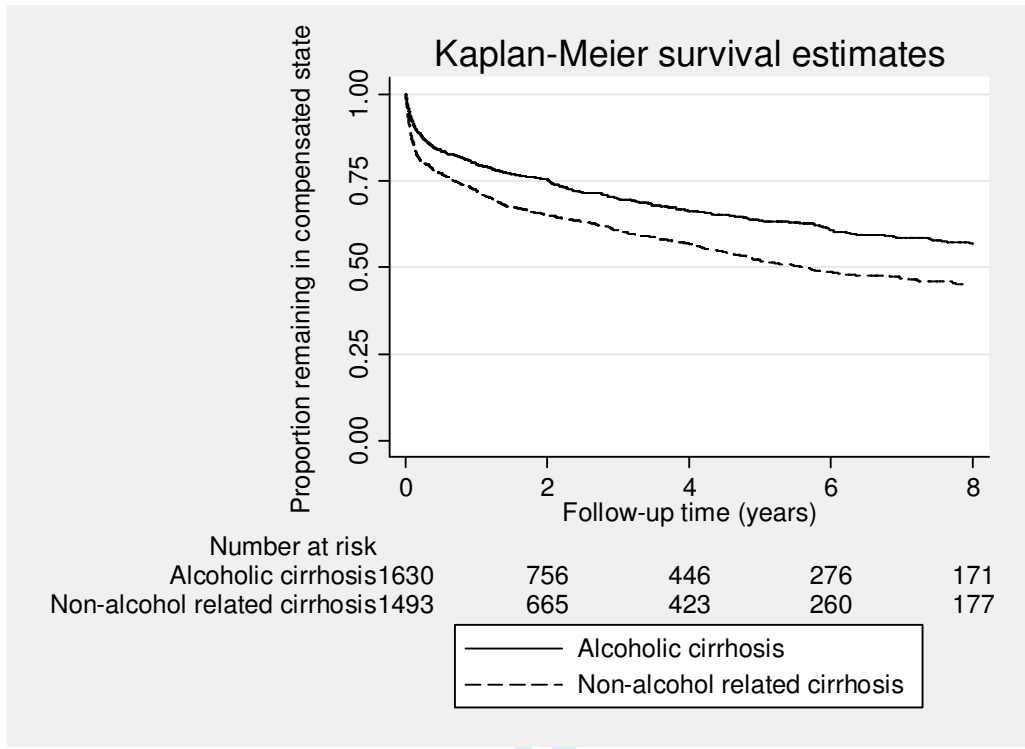
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Figure 1. Kaplan-Meier survival estimates for decompensation in subjects with compensated alcoholic and non-alcohol related cirrhosis

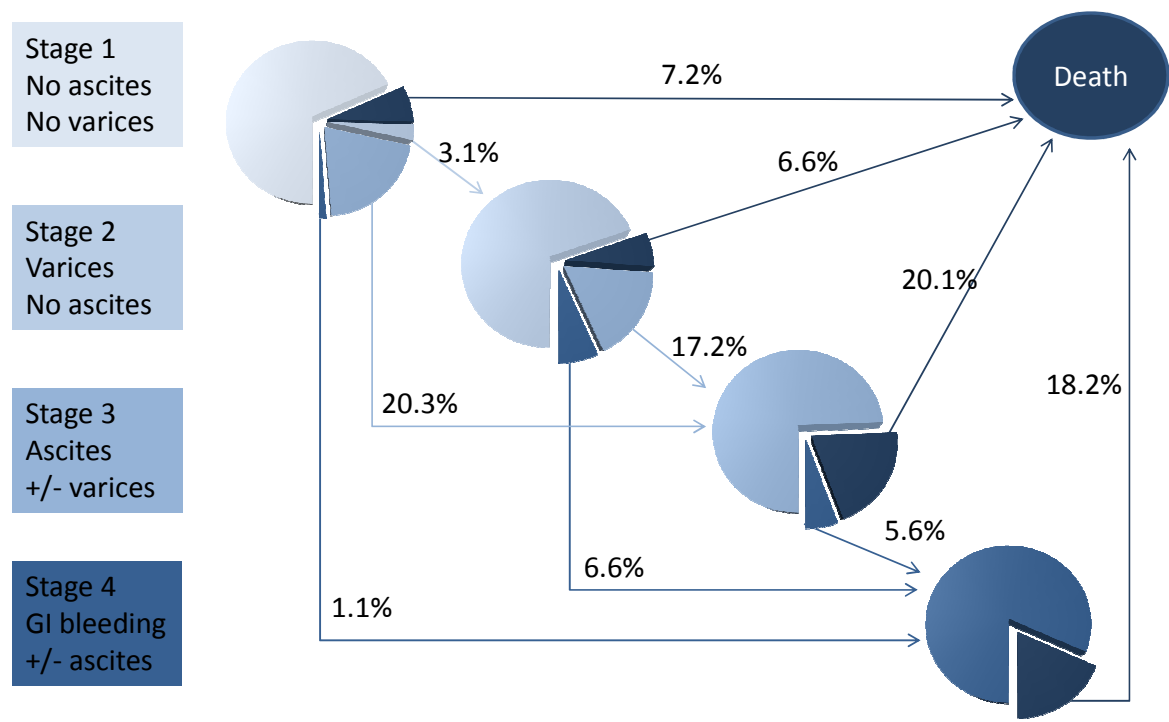


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Figure 2. Probabilities for progression within one year, all patients

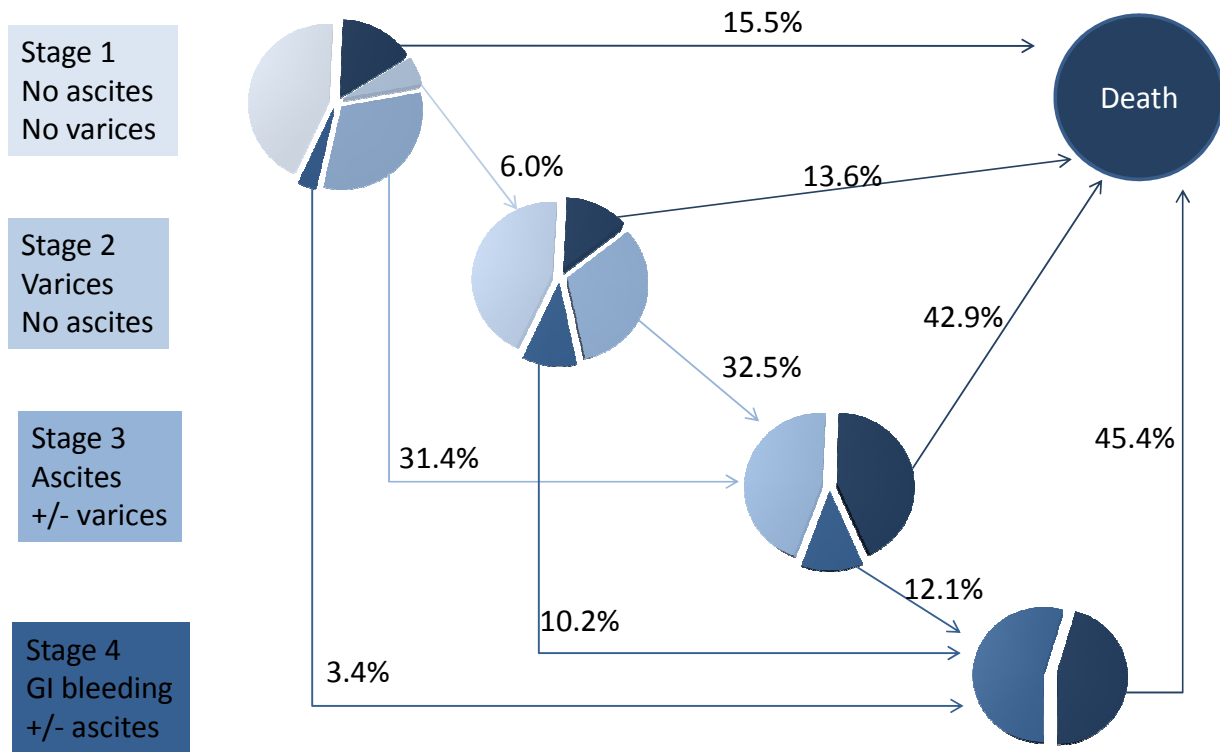


Figure 3. Probabilities for progression across whole record, all patients



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Table 2. Probability of progression in first year, patients with alcoholic and non-alcohol related cirrhosis

| | | Stage from | | | | | | | |
|---------------------------------------|---------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | | Stage 1 | | Stage 2 | | Stage 3 | | Stage 4 | |
| | | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related |
| Progression directly to / remained in | Stage 1 | 64.6 [61.9, 67.2] | 72.1 [69.5, 74.6] | - | - | - | - | - | - |
| | Stage 2 | 2.9 [2.1, 4.0] | 3.2 [2.3, 4.4] | 66.8 [60.7, 72.5] | 71.1 [66.8, 75.2] | - | - | - | - |
| | Stage 3 | 24.1 [21.8, 26.5] | 16.4 [14.4, 18.5] | 17.4 [13.0, 22.5] | 17.1 [13.8, 20.8] | 76.3 [73.8, 78.6] | 71.7 [68.6, 74.6] | - | - |
| | Stage 4 | 1.5 [0.9, 2.3] | 0.8 [0.4, 1.5] | 9.3 [6.0, 13.5] | 5.1 [3.3, 7.5] | 7.3 [5.9, 8.9] | 3.2 [2.1, 4.6] | 83.5 [79.5, 86.9] | 79.6 [74.8, 83.8] |
| | Death | 7.0 [5.7, 8.5] | 7.5 [6.1, 9.1] | 6.6 [3.9, 10.3] | 6.6 [4.5, 9.3] | 16.4 [14.3, 18.6] | 25.1 [22.3, 28.1] | 16.5 [13.1, 20.5] | 20.4 16.2, 25.2] |

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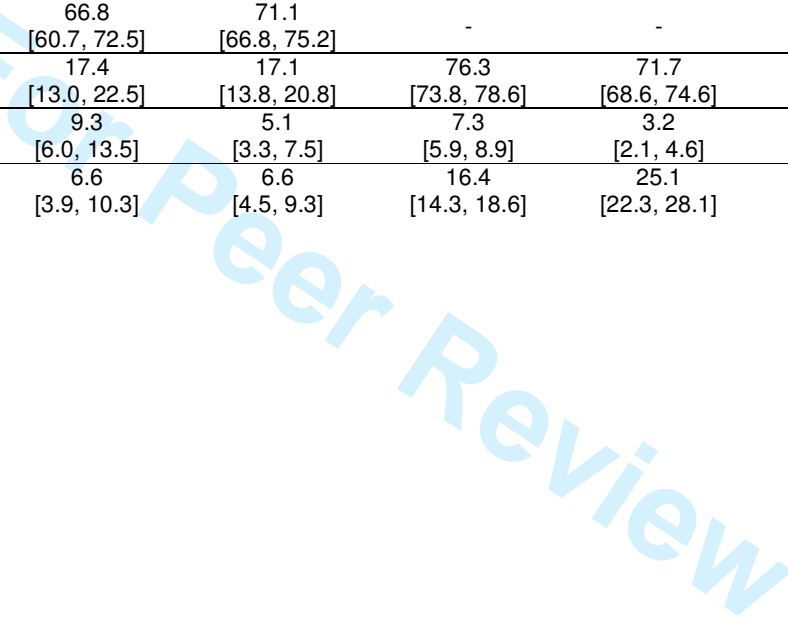


Table 3. State progression across whole record, patients with alcoholic and non-alcohol related cirrhosis

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| | | Stage from | | | | | | | |
|---------------------------------------|---------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | | Stage 1 | | Stage 2 | | Stage 3 | | Stage 4 | |
| | | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related | Alcoholic | Non-alcohol related |
| Progression directly to / remained in | Stage 1 | 37.6 [35.0, 40.3] | 50.2 [47.4, 53.1] | - | - | - | - | - | - |
| | Stage 2 | 5.6 [4.4, 7.0] | 6.4 [5.1, 7.9] | 35.5 [29.7, 41.7] | 48.3 [43.7, 52.9] | - | - | - | - |
| | Stage 3 | 37.4 [34.8, 40.1] | 25.0 [22.6, 27.5] | 36.3 [30.4, 42.5] | 30.3 [26.2, 34.7] | 47.8 [44.9, 50.7] | 41.1 [37.8, 44.4] | - | - |
| | Stage 4 | 3.7 [2.7, 4.8] | 3.1 [2.2, 4.3] | 13.5 [9.6, 18.3] | 8.3 [6.0, 11.2] | 14.0 [12.1, 16.1] | 9.4 [7.5, 11.5] | 54.7 [49.8, 59.5] | 54.5 [48.9, 60.0] |
| | Death | 15.7 [13.8, 17.8] | 15.2 [13.3, 17.4] | 14.7 [10.6, 19.6] | 13.0 [10.1, 16.4] | 38.2 [35.4, 41.0] | 49.5 [46.2, 52.9] | 45.3 [40.5, 50.2] | 45.5 [40.0, 51.1] |

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