FACULTY OF HEALTH SCIENCES, UNIVERSITY OF AARHUS, DENMARK

Prognosis for Danish patients with liver cirrhosis

The impact of complications, comorbidity, socioeconomic status, and galactose elimination capacity

PhD thesis Peter Jepsen



Departments of Clinical Epidemiology and Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, and Department of Biostatistics, Institute of Public Health, University of Copenhagen, Denmark.

SUPERVISORS

Henrik Toft Sørensen, Professor Department of Clinical Epidemiology Aarhus University Hospital

Hendrik Vilstrup, Professor Department of Medicine V (Hepatology and Gastroenterology) Aarhus University Hospital

Per Kragh Andersen, Professor Department of Biostatistics, Institute of Public Health University of Copenhagen

PREFACE

It is now more than eight years since I first set my foot in the Department of Clinical Epidemiology. So much has happened between then and now, but it remains a wonderful place to learn and practice clinical epidemiology at the highest international level. I wish to thank my everexpanding cohort of coworkers for that, and a particularly warm thank you to our Professor, Henrik Toft Sørensen, who works day and night to make all this possible.

Henrik should also be thanked for getting me interested in hepato-epidemiology, as we now call it, by setting me up with Professor Hendrik Vilstrup at the Department of Medicine V (Hepatology and Gastroenterology) at Aarhus University Hospital. Henrik and Hendrik are truly a dynamic duo, and Hendrik's clinical expertise and enthusiasm have been – and will be – constant motivation to do better. My third supervisor, Professor Per Kragh Andersen at the Department of Biostatistics, Institute of Public Health, University of Copenhagen, has been an excellent supplement owing to his vast knowledge of the biostatistical methods that I have used in my studies. Perhaps more importantly, he has the gift of understanding my questions even when I don't, and of answering them in a way that makes sense to a non-statistician like me. I have learned so much, and I hope that I can make good use of it in the years to come.

Finally, my warmest thanks to my wonderful wife, Britta, and our beloved children, Simon, Anne, and Tobias, for always being there to celebrate with me when my studies were successful, and to cheer me up when they were not.

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- I. Jepsen P, Vilstrup H, Andersen PK, Ott P, Sørensen HT. The clinical course of alcoholic liver cirrhosis: A Danish population-based study. *In manuscript*.
- II. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study. Hepatology 2008;48:214-20.
- III. Jepsen P, Vilstrup H, Andersen PK, Sørensen HT. Socioeconomic status and mortality among cirrhosis patients: A Danish nationwide cohort study. *Submitted*.
- IV. Jepsen P, Vilstrup H, Ott P, Keiding S, Andersen PK, Tygstrup N. The galactose elimination capacity and mortality in 781 Danish patients with newly-diagnosed liver cirrhosis: A cohort study. *Submitted*.

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1 INTRODUCTION

The aim of this thesis is to examine selected aspects of the prognosis for Danish patients with liver cirrhosis based on four clinical epidemiological studies. Study I examines the clinical course of alcoholic cirrhosis. Studies II, III, and IV examine the impacts of comorbidity, socioeconomic status, and galactose elimination capacity on the mortality of cirrhosis patients. This introductory section defines prognosis and cirrhosis.

1.1 Prognosis

Prognosis (from the Greek *pro-gnosis*, meaning 'foreknowledge') is a prediction of the future course of a disease following its onset (Figure 1), and it can be described as a natural history or a clinical course of a disease.⁴¹ The natural history of a disease is its prognosis from onset to resolution without medical intervention,^{41,56,137} whereas the clinical course of a disease is its prognosis after the patient has come under medical care.⁴¹

Figure 1 Risk and prognosis. Risk factors are characteristics associated with an increased risk of developing cirrhosis; prognostic factors are characteristics associated with a particular outcome of cirrhosis.⁴¹



Prognosis can be described with respect to different outcomes, and an outcome is a clinical event such as death, disease, discomfort, disability, or dissatisfaction.⁴² The prognosis is usually described in terms of patients' probability of experiencing an outcome, less often in terms of the rate at which patients experience an outcome. This thesis is mostly concerned with death as an outcome and uses the following terms:

- *Mortality* describes cirrhosis patients' probability of death before a particular time after the diagnosis of cirrhosis. Thus, mortality is used as a synonym for 'cumulative mortality', 'cumulative incidence of death', or 'mortality risk'.⁷⁶
- *Risk of an outcome* is used in the same way as 'mortality' but for outcomes other than death.

Prognostic factors are characteristics associated with a particular disease outcome,⁴¹ and they help identify groups of patients with the same disease but different prognoses.⁴¹ Figure 1 (page 2) presents the prognostic factors examined in this thesis; Figure 2 presents a comprehensive model of prognostic factors.¹⁰⁸

Figure 2 Determinants of the outcome of illness.¹⁰⁸



1.1.1 Why study prognosis?

Clinicians study prognosis to **predict**, **understand**, and **change** the outcomes of disease.⁴² However, prognostic studies are important not only to clinicians but also to patients who wish to know their prognosis and how it can be improved. Additionally, healthcare policy makers would like to understand how they can change prognoses by changing the organization of healthcare, and clinical epidemiologists would like to know the prognosis and prognostic factors so they can design, analyze, and interpret epidemiological studies.^{4,63,139}

1.2 Cirrhosis

Any liver disease may result in liver fibrosis as part of the inflammatory process and its resolution.¹¹⁶ Cirrhosis is an advanced stage of liver fibrosis defined as the histological development of regeneration nodules surrounded by fibrous tissue, and it results in a loss of liver function and a syndrome of metabolic and hemodynamic disturbances.^{7,116}

In Northern Europe, the majority of cirrhosis patients have alcoholic liver disease,^{3,61,110} while the rest of the patients have other chronic liver diseases, such as viral hepatitis; autoimmune, biliary, genetic, or toxic liver disease; venous outflow obstruction; or obesity-related liver disease.^{3,7,64,65,96,126}

We recently showed that, in Denmark from 2001 to 2005, the incidence rate of alcoholic cirrhosis was 265 per 1,000,000 men per year and 118 per 1,000,000 women per year based on hospitalization data.⁶⁶ The average prevalence during the same period was 1,326 per 1,000,000 men and 701 per 1,000,000 women.⁶⁶ The incidence and prevalence of non-alcoholic cirrhosis in Denmark have not been examined recently, but from 1981 to 1985 the incidence rate for men and women was 110 and 82 per 1,000,000 per year, respectively.³

2 BACKGROUND

This section presents the background for the thesis' four studies, including definitions and a review of the relevant literature followed by a discussion of the limitations of the existing literature.

2.1 Study I - The Clinical Course Study

The 10-year mortality of 6,139 patients with a hospital diagnosis of alcoholic cirrhosis between 1982 and 1989 was three times as high as that of persons of the same gender and age in the general population.¹²⁴ This finding highlights the poor clinical course of patients with alcoholic cirrhosis, but more can be learned by studying the complications of cirrhosis.

2.1.1 Pathogenesis of cirrhosis complications

A complication of cirrhosis can be defined as a second disease, or another event associated with a decrease in health, that develops in a cirrhosis patient and may or may not be caused by cirrhosis.¹²⁷ Ascites, variceal bleeding, and hepatic encephalopathy are the only cirrhosis complications considered in this thesis.

Ascites and variceal bleeding

In cirrhosis, changes in the intrahepatic vasculature contribute to an elevated sinusoidal hydrostatic pressure,^{112,116} which results in an increased production of splanchnic lymph. When lymph production exceeds the reabsorption capacity of the lymphatics, lymph spills into the peritoneal cavity, eventually causing clinically evident ascites.¹¹²

The increased intrahepatic vascular resistance and, possibly, an increased splanchnic blood flow result in portal hypertension, defined as a portal pressure exceeding 5 mmHg.¹¹² Nature

decompresses the portal vein by diverting the portal flow back to the heart through collaterals which are often located at the gastroesophageal junction.¹¹² These collaterals enlarge in response to the increased flow and may present as gastric or esophageal varices if the portal pressure exceeds 10 mmHg.¹¹² Such gastroesophageal varices are asymptomatic at first, but they will grow if the portal pressure increases further.¹²⁸ If the portal pressure reaches 12 mmHg, the varices can rupture and bleed.^{112,128}

Hepatic encephalopathy

Hepatic encephalopathy is a reversible condition caused by cerebral effects of toxins accumulating in the blood of patients with acute or chronic liver failure.⁸⁹ The condition manifests in many ways which may be divided into 'overt' or 'minimal', meaning not clinically detectable without psychometric tests.⁸⁹ Despite its name, even minimal hepatic encephalopathy is severely debilitating.^{8,120} The development of hepatic encephalopathy is usually triggered by exposure to one or more of these risk factors: bacterial infection, gastrointestinal bleeding, dehydration, constipation, insertion of a transjugular intrahepatic portosystemic shunt, psychoactive drugs, surgery, or anesthesia.¹³

2.1.2 Describing the clinical course of cirrhosis

The occurrence of complications is often used to describe the course of cirrhosis. This clinical practice has been consolidated with the 4th Baveno Consensus Meeting's 2006 publication of a clinical course model based on ascites and bleeding or non-bleeding varices (Figure 3, page 7).^{27,45} The model is intended as a framework for future epidemiological studies of cirrhosis patients, and it is recommended that prognostic studies include only patients in the same stage of cirrhosis.⁴⁵



Figure 3 The Baveno model of the clinical course of cirrhosis.²⁷

2.1.3 Existing literature

Prevalence of complications at cirrhosis diagnosis

I searched for population-based or hospital-based (population-based: all hospitalized patients within a population are included; hospital-based: all patients hospitalized in one or more hospitals are included)^{50,93} studies on the prevalence of ascites, variceal bleeding, and hepatic encephalopathy at hospital diagnosis of alcoholic cirrhosis. I used this Medline query:

("Ascites"[Mesh] OR "Esophageal and Gastric Varices"[Mesh] OR "Hepatic Encephalopathy"[Mesh]) AND "Prevalence"[Mesh] AND "Liver cirrhosis"[Mesh]

Similar queries were performed in Scopus and Web of Science, but the search produced no relevant results. However, I was aware of some relevant articles and also examined these articles' references, the articles that cited them, and the articles that were related to them by citing the same references.

Table 1Summary of studies on the prevalence of ascites, variceal bleeding (or gastrointestinal
bleeding), and hepatic encephalopathy at the time of hospital diagnosis of alcoholic
cirrhosis. The studies are ordered by the number of patients included.

Author	Ν	Country	Years of diagnosis	Population	Prevalence
Ratnoff ¹⁰¹	386	USA	1916-1938	5 general hospitals	Ascites: 28% Gastrointestinal bleeding: 10% Hepatic encephalopathy: ?
Powell ⁹⁷	283	USA	1951-1963	1 department of hepatology	Ascites: 31% Gastrointestinal bleeding: 6% Hepatic encephalopathy: ?
Saunders ¹¹⁵	242	Britain	1959-1976	1 general hospital	Ascites: 43% Gastrointestinal bleeding: 9% Hepatic encephalopathy: 10%
Chedid ²¹	149	USA	?	VA hospital(s)	Ascites: 46% Variceal bleeding: ? Hepatic encephalopathy: 53%
Pessione ⁹⁴	122	France	1991	1 department of hepatology	Ascites: ? Variceal bleeding: 15% Hepatic encephalopathy: ?
Bell ⁹	100	Norway	1984-1988	1 medical department	Ascites: 67% Variceal bleeding: 34% Hepatic encephalopathy: ?
Stone ¹²²	52	Britain	1959-1964	1 general hospital	Ascites: 39% Gastrointestinal bleeding: 13% Hepatic encephalopathy: 23%

With the exception of a Norwegian study,⁹ the prevalence of ascites and variceal/gastrointestinal bleeding at the time of cirrhosis diagnosis varied little between studies (Table 1). It is not clear from the description of the Norwegian study why the prevalence of cirrhosis complications was twice as high as in other studies and the authors could not explain it either.⁹ The prevalence of hepatic encephalopathy has been examined in only three studies, and the patients studied by Stone et al. were also included in the study by Saunders et al.^{115,122} The difference in the prevalence of hepatic encephalopathy between the two studies is therefore striking, and Saunders et al. reported that the prevalence in 1959-1964 was in fact 11%, not 23% as originally reported by Stone et al.^{115,122} This discrepancy may be due to changes in the definition of hepatic encephalopathy. The

53% prevalence of hepatic encephalopathy published in 1991 by Chedid et al. is astonishing,²¹ and no other study has found a prevalence of hepatic encephalopathy exceeding the prevalence of ascites. Chedid et al. did not present their criteria for the diagnosis of hepatic encephalopathy, but it is possible that they counted both minimal and overt hepatic encephalopathy (see page 6).

Incidence of complications

I searched for studies of alcoholic cirrhosis patients' risk of developing ascites, variceal bleeding, or hepatic encephalopathy with this Medline query:

("Ascites"[Mesh] OR "Esophageal and Gastric Varices"[Mesh] OR "Hepatic Encephalopathy"[Mesh]) AND ("Risk"[Mesh] OR "Prognosis"[Mesh]) AND "Cohort studies"[Mesh] AND "Liver cirrhosis"[Mesh]

Similar queries were performed in Scopus and Web of Science, but no studies were found that were restricted to patients with alcoholic cirrhosis. However, eight studies followed cirrhosis patients from diagnosis and examined their risk of ascites, variceal bleeding, or hepatic encephalopathy. Expanding the search as described above yielded seven more studies but still none that were restricted to patients with alcoholic cirrhosis. Table 2Summary of studies on the risk of ascites, variceal bleeding, or hepatic
encephalopathy (HE) among cirrhosis patients. Compensated cirrhosis is defined as
the absence of ascites, variceal bleeding, hepatic encephalopathy, and jaundice. The
studies are ordered by the proportion of alcoholic cirrhosis patients included.

Author	Ν	Country	Follow-up	Inclusion criteria	Etiology	Risk of complications	Mortality
Ginès ⁴⁹	283	Spain	1968-1980	Compensated	42% alcohol 8% HBV 50% cryptogenic	Ascites: 5 years = 35% Bleeding: 5 years = 25% HE: 5 years = 20% Decomp: 7% per year	5 years = 30%
Kim ⁷⁰	351	Korea	1991-1999	Compensated	26% alcohol 58% HBV 11% HCV 2% HBV+HCV 3% cryptogenic	Decomp: 5 years = 44%	5 years = 26%
D'Amico ²⁵	435	Italy	1974-1981	Compensated	21% alcohol 20% HBV 59% ?	Decomp: 10% per year	6 years = 46%
Turnes ¹²⁸	71	Spain	1994-2002	Non-bleeding varices	21% alcohol 79% ?	Ascites: 8 years = 55% Bleeding: 8 years = 39% HE: 8 years = 49%	8 years = 48%
Merli ⁸⁵	206	Italy	1994-1999	No (55%) or small (45%) esophageal varices	16% alcohol 84% HBV/HCV	Bleeding: 5 years = 10%	5 years = 15%
Benvegnù ¹⁰	312	Italy	1986-2001	HBV or HCV Child-Pugh A	14% HBV 81% HCV 5% HBV/HCV (15% also alcohol)	Ascites: 5 years = 7.5% Bleeding: 5 years = 0% HE: 5 years = 0%	?
Fattovich ³⁵	317	Europe	1973-1991	HBV Compensated	100% HBV	Decomp: 5 years = 23%	?
Fattovich ³⁸	161	Europe	1987-1997	HBV Compensated	100% HBV	Decomp: 5 years = 16%	5 years = 14%
Gentilini ⁴⁷	405	Italy	1976-1991	HBV/HCV No portal hypertension	21% HBV 79% HCV	Ascites: 5 years = 25% Bleeding: 5 years = 5% HE: 5 years = 9%	?
Fattovich37	384	Europe	1982-1993	HCV	100% HCV	Decomp: 5 years = 18%	5 years = 9%
Fattovich ³⁶	329	Europe	1982-1993	HCV Compensated High ALAT/ASAT	100% HCV	Decomp: 5 years = 26%	?
Sangiovanni ¹¹¹	214	Italy	1982-2001	HCV Child-Pugh A	100% HCV	Ascites: 5 years = 15% Bleeding: 5 years = 3% HE: 5 years = 0%	5 years = 10%
Fattovich ³⁸	136	Europe	1987-1997	HCV Compensated	100% HCV	Decomp: 5 years = 28%	5 years = 16%
Serfaty ¹¹⁷	103	France	1989-1995	HCV Compensated	100% HCV	Decomp: 4 years = 11.5%	4 years = 16%
Hashizume ⁶⁰	110	Japan	1972-1981	Not alcoholic or biliary cirrhosis Esophageal varices	?	Bleeding: 5 years = 25%	5 years = 54%

Only one study has included more than 100 alcoholic cirrhosis patients (Table 2),⁴⁹ but it appears that the risk of decompensation (a combined endpoint combining ascites, variceal bleeding,

hepatic encephalopathy, and jaundice) was higher in the studies that included both alcoholic and non-alcoholic cirrhosis patients, approximately 7-10% per year vs. 3-5% per year in the studies that included only non-alcoholic cirrhosis patients (Table 2). However, it must also be considered that the risk estimates from the studies in Table 2 overestimated the true risks because they were computed with methods for a single outcome though they examined several outcomes (death and one or more complications).¹¹³ The single-outcome method that has been used has yielded results like in this figure:^{26,47,49}

Figure 4 Risk of selected cirrhosis complications with respect to time since cirrhosis diagnosis, as presented in a review article by Talwalkar and Kamath.¹²⁵



It is not clear how to interpret Figure 4, a problem that is particularly evident from around seven years onwards because the sum of the outcome-specific risks exceeds 100%, even without considering death as an outcome.

Mortality of patients with or without complications

I searched for population-based or hospital-based studies of mortality of alcoholic cirrhosis patients by presence or absence of ascites, variceal bleeding, and hepatic encephalopathy. I used this Medline query:

("Ascites"[Mesh] OR "Esophageal and Gastric Varices"[Mesh] OR "Hepatic Encephalopathy"[Mesh]) AND "Survival rate"[Mesh] AND "Liver cirrhosis"[Mesh]

The search was expanded as described above and returned a total of five studies.

Table 3	Summary of studies on the mortality of alcoholic cirrhosis patients with ascites.						
	variceal bleeding, hepatic encephalopathy, or none of these complications. The studies						
	are ordered by calendar year.						

	Author	Ν	Country	Follow-up	Mortality
Ascites	- 101				
	Ratnoff	296	USA	1916-1938	1 year = 68% 5 years = 93%
	Powell ⁹⁷	182	USA	1951-1963	5 years = 60%
	Saunders ¹¹⁵	103	Britain	1959-1976	1 year = 60% 5 years = 80%
Variceal bleeding					
	Ratnoff ¹⁰¹	106	USA	1916-1938	1 month = 40% 1 year = 70% 5 years = 80%
	Powell ⁹⁷	69	USA	1951-1963	5 years = 75%
	Saunders ¹¹⁵	21	Britain	1959-1976	1 year = 80% 5 years = 100%
	Pessione ⁹⁴	122	France	1991	1 year = 40% 5 years = 77%
	Krige ⁷²	287	South Africa	1984-2001	1 year = 33% 5 years = 74%
Hepatic encephalopathy					
	Saunders ¹¹⁵	25	Britain	1959-1976	1 year = 80% 5 years = 100%
No complications					
	Powell ⁹⁷	45	USA	1951-1963	5 years = 25%
	Saunders ¹¹⁵	90	Britain	1959-1976	1 year = 20% 5 years = 45%

The 1-year mortality of patients with variceal bleeding has decreased in recent decades, which is consistent with studies that were not restricted to patients with alcoholic cirrhosis,^{16,34,121} but there is little evidence for reductions in the mortality of other alcoholic cirrhosis patients (Table 3). This conclusion is consistent with an English registry-based study reporting that the standardized mortality ratio⁷⁵ for alcoholic cirrhosis patients vs. the general population did not change between 1968 and 1998.¹⁰⁴

2.1.4 Limitations of the existing literature

Alcoholic cirrhosis patients' risk of developing ascites, variceal bleeding, and hepatic encephalopathy, and their prognosis after these complications develop, is largely unknown. However, this information would help clinicians predict a patient's clinical course and update this prediction when complications develop. It might also help clinicians understand the clinical course of alcoholic cirrhosis.

2.2 Study II – The Comorbidity Study

Study II examines comorbidity as a prognostic factor for cirrhosis patients.

2.2.1 Definition of comorbidity

A comorbidity is defined as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study".³⁹ Hall describes comorbidities as "diseases, disorders, or illnesses – excluding the disease of interest – that might influence prognosis. In clinical practice this is the past history, the review of systems, and the list of current medications."⁵⁸ Thus, the prognostic importance of comorbidities is well recognized by clinicians and taken into consideration in patient management.^{39,58}

2.2.2 The Charlson comorbidity index

A comorbidity index is a tool to reduce the information on a patient's comorbidities to a single numeric score.⁵⁸ It is reasonable to simply count a patient's comorbidities, but they are usually given weights reflecting their impact on mortality.^{30,74} Several weighted comorbidity scoring systems exist, but the Charlson comorbidity index (CCI) is the most widely used (Figure 5, page 15).^{30,58} The development of the CCI was motivated by the observation that many experimental studies on treatments excluded patients with comorbidity because an imbalance in the prevalence of comorbidities between treatment arms might bias efficacy estimates.²⁰ The CCI was developed to predict the 1-year mortality of 604 patients admitted to the medical service at New York Hospital during one month in 1984 on the basis of the diseases recorded in their medical records.²⁰

Table 3. Wei	ghted index of comorbidity
Assigned weights for diseases	Conditions
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease
2	Diabetes Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3 6	Moderate or severe liver disease Metastatic solid tumor AIDS

Figure 5 Diseases in the Charlson comorbidity index (from Charlson et al).²⁰

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) =total score (3).

The CCI's ability to discriminate survivors from non-survivors has been confirmed repeatedly since its publication in 1987,^{18-20,90} and translations of the index from written diagnoses to diagnosis codes in healthcare registries have been found to retain this ability.^{90,100} However, the CCI also has some weaknesses. First, the CCI was not designed for use with a particular index disease; therefore, the disease weights are not optimized to any particular disease,¹³⁶ and some of the diseases may have to be excluded because they do not fulfill the definition of comorbidity. Second, the CCI was developed on the basis of a small number of patients, and rare diseases may not have been considered for inclusion in the CCI. Psychiatric diseases, for example, were not encountered in the 604 patients on whom the CCI was based.²⁰

2.2.3 Existing literature

I searched Medline for relevant literature with this query, but it gave no results:

"Comorbidity" [Mesh] AND "Liver Cirrhosis" [Mesh] AND "prognosis" [Mesh]

Instead, the articles cited by D'Amico et al. in their review of prognostic factors in cirrhosis were examined.²⁷ According to that review, hypothyroxinemia (low T_4),¹⁷ smoking,⁹⁴ diabetes,^{12,47,88} and HIV infection⁹⁵ have been associated with a poor prognosis for cirrhosis patients.

2.2.4 *Limitations of existing literature*

The impact of comorbidity on the mortality of cirrhosis patients is largely unknown, but comorbidities are likely to be prevalent among cirrhosis patients because of their age – most of them are in their fifties or older at the time of diagnosis⁶⁶ – and because cirrhosis shares risk factors with other chronic diseases. For example, alcoholism is also a risk factor for cancer and stroke.^{14,54,55,102} It is important to examine whether comorbidity is associated with mortality of cirrhosis patients because such prognostic information would help clinicians to predict which patients have a worse prognosis and to understand why. Furthermore, many comorbidities can be treated or prevented, and therefore clinicians might also use this information to change the prognosis for cirrhosis patients.

2.3 Study III – The SES Study

Study III examines socioeconomic status as a prognostic factor for cirrhosis patients.

2.3.1 Measures of socioeconomic status

A person's socioeconomic status describes his or her position in society, usually by combining measures of income, education, and occupation.^{75,138} Study III deviated from the usual approach

by considering marital status instead of education, because data on education were missing for a substantial proportion of patients. Furthermore, we used only three categories per socioeconomic measure and did not integrate the three measures into one measure of socioeconomic status.

2.3.2 Existing literature

I searched Medline for relevant literature with this query, but no relevant studies were identified:

("Marital Status"[Mesh] OR "Employment"[Mesh] OR "Income"[Mesh] OR "Socioeconomic Factors"[Mesh]) AND "Liver Cirrhosis"[Mesh] AND "Prognosis"[Mesh]

It has been found, however, that populations in deprived regions – based on housing density, car ownership, male unemployment and the head of the household's social class – have higher cirrhosis mortality rates (computed as the number of patients who die from cirrhosis divided by the population size⁴¹) than populations in less deprived regions,⁷⁸ but this finding does not clarify whether deprivation is associated with an increased risk of developing cirrhosis, an increased mortality of cirrhosis patients, or both. Additionally, several indicators of low socioeconomic status have been associated with a poor prognosis for patients with alcoholism,⁷⁷ cancer,^{28,71} heart failure,²⁹ stroke,⁷³ or myocardial infarction.^{62,87}

2.3.3 Limitations of the existing literature

The association between socioeconomic status and mortality of cirrhosis patients is essentially unknown, but it is important to examine this association because it may help clinicians predict which patients will have a worse prognosis.

2.4 Study IV – The GEC study

Study IV examines galactose elimination capacity (GEC) as a prognostic factor for cirrhosis patients.

2.4.1 The GEC test

There is no simple definition of 'metabolic liver function' because the liver has a multitude of functions involved in metabolism.⁸⁶ One function that can be measured is the metabolism of galactose into glucose by galactokinase in the cytosol of hepatocytes, and the liver's capacity to perform these processes is a measure of the functioning metabolic liver mass, i.e. the mass of active hepatocytes.^{86,133}

The galactose elimination capacity (GEC) test is conducted as follows: A galactose solution is injected intravenously over the course of 5 minutes. From 20 to 45 minutes, arterialized capillary blood is drawn at intervals of 5 minutes to measure the galactose concentration, and urine is collected for 4 hours to measure the urinary excretion of galactose. The GEC can then be calculated with the formula^{131,132}

$$GEC = \frac{Infused - Excreted}{t_{\sigma=0} + 7} mmol/min$$

In the formula, $t_{c=0}$ is the time from infusion until the blood galactose concentration reaches zero based on a linear extrapolation of the measurements of galactose concentration in capillary blood.

2.4.2 Existing literature

I searched for studies of GEC as a prognostic factor for cirrhosis patients by querying Medline for articles with the words "galactose" and "cirrhosis" in the title. These articles' references and articles citing them were also identified and included if relevant.

Author	N	Aim	Inclusion criteria	Country	Outcome	Follow-up	GEC associated with mortality in crude analysis?	Variables in final prediction rule
Salerno ¹⁰⁹	194	Prediction	Liver transplant candidates No comorbidities	Italy	Death (N=62) Death from liver failure (N=20)	2 years	Yes, 2 categories	Child-Pugh score GEC
Zoli ¹⁴²	100	Prediction	No ascites	Italy	Death (N=54)	5.9 years	Yes, 2 categories	Albumin Bilirubin Cholesterol Liver volume
Merkel ⁸³	78	Prediction	No comorbidities	Italy	Death (N=27)	3.2 years	Yes, 3 categories	Child-Pugh score GEC
Merkel ⁸²	61	Prediction	Non-bleeding varices No comorbidities	Italy	Death (N=22)	3.3 years	Yes, 2 categories	Albumin Bilirubin Encephalopathy Varices
Merkel ⁸²	61	Prediction	Non-bleeding varices No comorbidities	Italy	Death from liver failure (N=15)	3.3 years	Yes, 2 categories	Bilirubin Albumin Ascites GEC
Albers ²	47	Prediction	Unselected	Germany	Death (N=22)	5.2 years	Yes, 3 categories	Child-Pugh score Age Sex History of upper GI bleed Alkaline phosphatase
Garello ⁴⁶	47	Prediction	Unselected	Italy	Death (N=20)	2 years	Yes, 2 categories	Pseudocholinesterase
Merkel ⁸⁴	45	?	Selection based on follow-up data Alcohol abuse No comorbidities	Italy	Death from liver failure (N=13)	4 years	Yes, 2 categories	
Lindskov ⁷⁹	44	?	Unselected	Denmark	Death from liver failure (N=17)	7.1 years	Yes, 2 categories	
Addario ¹	35	Prediction	Viral cirrhosis No comorbidities	Italy	Death (N=8)	2 years	Yes, 2 categories	Child-Pugh score

Table 4Summary of studies in which GEC has been examined as a prognostic factor for
cirrhosis patients.

2.4.3 *Limitations of the existing literature*

The aim of the existing studies was to examine whether clinicians can improve their predictions of cirrhosis patients' prognoses with respect to death or death from liver failure by adding data on GEC to data on standard liver chemistry tests (e.g., bilirubin and INR).^{1,2,46,52,82,83,109,142} Thus, their clinical questions were about predicting death and not about understanding what caused it, and a variable's inclusion in or exclusion from a clinical prediction rule⁵⁷ cannot be taken as evidence

that the variable does or does not cause the outcome.¹⁰⁷ Thus it remains unclear whether GEC is causally associated with mortality, but this information is important to clinicians who want to understand the clinical course of cirrhosis and the importance of liver function.

3 AIMS

The aim of this thesis was to answer the following questions:

- What is the prevalence of complications when alcoholic cirrhosis is diagnosed? What are the risks of complications and death after diagnosis, and how do they depend on the presence of complications? In which sequence do complications develop? (Study I – The Clinical Course Study)
- Is the presence of comorbidity at cirrhosis diagnosis associated with mortality of cirrhosis patients? (Study II – The Comorbidity Study)
- Is marital status, employment, or personal income at cirrhosis diagnosis associated with mortality of cirrhosis patients? (Study III – The SES Study)
- Is GEC at cirrhosis diagnosis associated with mortality of cirrhosis patients? (Study IV The GEC Study)

4 METHODS

4.1 Data sources

The studies for this thesis relied on data from several sources that will be described here.

4.1.1 Medical records

Study I used data from the medical records of all Danish hospitals in which the included patients had been hospitalized during the study period.

4.1.2 Administrative registries

Denmark has a host of registries that were established for administrative purposes but are also valuable for scientific use.¹²³ These registries are population-based,⁹³ and individual-level data can be linked across registries by the unique personal identifier issued to all Danish citizens.⁴⁴ Studies II and III were based exclusively on registry data.

The National Patient Registry

All four studies used data from the National Patient Registry, which contains data from all inpatient admissions to Denmark's non-psychiatric hospitals since 1977 and from outpatient and emergency room visits since 1995.⁶ Each hospital contact is represented by one discharge record describing service dates, which were the dates of admission and discharge for inpatients, dates of first and last visit for outpatients, and date of visit for emergency room patients; one primary diagnosis and up to twenty secondary diagnoses; and surgical procedures performed. Diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10), but before 1994 they were coded according to the 8th revision (ICD-8). The diagnosis codes are

specified by a physician; for inpatients they are given at hospital discharge, for outpatients they are given at the last visit in a series of outpatient visits.

The Cause of Death Registry

Study II used data from the Cause of Death Registry, which was established in 1943.⁶⁷ When a Danish citizen dies, the medical doctor in charge of treatment must report the cause of death and a chain of events leading to death can be described by specifying up to four diagnoses. In the Cause of Death Registry, these diagnoses are translated to ICD-10 diagnosis codes.

The Integrated Database for Labor Market Research (IDA)

Study III used data from the IDA database, established in 1990 and administered by Statistics Denmark. The database consists of more than 200 variables describing the Danish population, the population's attachment to the labor market, and the labor market. All Danish citizens are described by data on their family and household, education, employment, and income, and the data are supplied by tax authorities, educational institutions and employment services. The IDA database is updated annually.¹¹⁹

The Civil Registration System

All studies used data from the Civil Registration System, which was established in 1968 and continuously updates Danish citizens' vital status.⁴⁴ Place of residence and dates of birth, death, and emigration can be obtained from this registry.

4.1.3 The GEC database

Denmark has two tertiary referral centers for liver disease, at Aarhus University Hospital and Rigshospitalet. In these centers, all patients undergo a GEC test if cirrhosis is suspected. Both centers record the results of the GEC tests they perform, and the results from the two centers were combined in one database for Study IV.

4.2 Variable definitions

4.2.1 Cirrhosis

In Study I, we relied on the information in the medical records, so the diagnosis of cirrhosis was based on the criteria used by the hospital physicians. In Studies II, III, and IV, we defined cirrhosis with the diagnosis codes for alcoholic or unspecified cirrhosis (ICD-8 571.09, 571.92, 571.99 and ICD-10 K70.3, K74.6).

4.2.2 Comorbidity

Comorbidity was scored with the CCI. Comorbidities were defined by the ICD-10 codes provided by Quan et al.¹⁰⁰ and by ICD-8 codes that matched the ICD-10 codes as closely as possible.

4.2.3 Socioeconomic status

The IDA database has one variable defining marital status, and we combined variables describing employment status and unemployment grade to define employment. Taxable personal income was recorded as such in the IDA database, but we used publicly available data from Statistics Denmark to scale personal income to a percentage of the average income for all Danish citizens of the same gender and age during the same calendar year.

4.2.4 GEC

All GEC tests were performed as described on page 18. The average GEC values for men and women without suspected liver disease are 2.7 (95% CI 1.7-3.6) and 2.4 (95% CI 1.4-3.4) mmol/min, respectively.¹³⁰

4.2.5 Other variables

In Study II, we defined alcoholism on the basis of diagnosis codes in the National Patient Registry. In Study III, we used the National Patient Registry to define the presence of variceal bleeding, ascites, liver failure, or bacterial infection at the time of cirrhosis diagnosis. We also ascertained whether the patient was being seen as an inpatient or outpatient at the time of cirrhosis diagnosis and whether cirrhosis was registered as the primary or secondary diagnosis. Furthermore, we counted each patient's hospital diagnoses of alcohol abuse in the five years prior to cirrhosis diagnosis, and we examined whether patients had received a hospital diagnosis of psychiatric disease or substance abuse, other than alcohol abuse, during the same period.

4.3 Study design

4.3.1 Study populations

All studies were cohort studies, and the cohorts consisted of patients with newly-diagnosed cirrhosis. Study I included all patients who had cirrhosis due, in part or in full, to alcohol abuse and were diagnosed between 1 January 1993 and 31 August 2005; lived in the hospital catchment area that includes the city of Aarhus when the hospital workup for suspected cirrhosis began; and had not previously been examined for suspected cirrhosis in any hospital. Study II was nationwide and included all patients with a first hospital diagnosis of cirrhosis between 1 January 1995 and 31 August 2006. Study III was also nationwide and included all patients with a first hospital and included all patients with a first study 1999 and 31 December 2001 who were 45-59 years of age at that time. Study IV included cirrhosis patients who underwent a GEC test in one of the two Danish tertiary referral centers for liver disease between 1 August 1992 and 31 December 2005 and had a first hospital diagnosis of cirrhosis less than 90 days before the GEC test.

4.3.2 Prognostic factors of interest

In Study I, ascites, variceal bleeding, and hepatic encephalopathy were the prognostic factors of interest; a patient described as having 'no complications' may have had other complications than these three. In Study II, comorbidity was the prognostic factor of interest (in four categories: CCI=0, 1, 2, or \geq 3). In Study III, we were interested in three prognostic factors, each with three categories: marital status (never married, divorced, or married), employment (employed, disability pensioner, or unemployed), and personal income (0-49, 50-99, or \geq 100 percent of the national average). In Study IV, the prognostic factor of interest was GEC; the range of GEC values was divided into 10 categories with an equal number of patients, i.e. into deciles of GEC.

4.3.3 Outcomes

In Study I, the outcomes were first-time ascites, first-time variceal bleeding, first-time hepatic encephalopathy, and death. In Study II, the outcome was death, though we also conducted an analysis with death from cirrhosis and death from other causes as outcomes. In Studies III and IV, the outcome was death.

4.3.4 Follow-up

In Studies I, II, and III, patients were followed from cirrhosis diagnosis, whereas in Study IV patients were followed from their first GEC test. In all studies follow-up ended at death, or patients were censored upon emigration or on an end-of-study date.

In Study I, we counted follow-up time as the time from cirrhosis diagnosis to the first complication, then from the first to the second complication, then from the second to the third complication, and finally from the third complication to death.⁹⁹ In Studies II, III, and IV, follow-up time was simply counted from the beginning to the end of follow-up.

4.4 Statistical analyses

4.4.1 Mortality and risk of outcomes other than death

In analyses with a single outcome, the mortality was computed by the Kaplan-Meier estimator, and the median survival time was defined as the duration until mortality reached 50%. In analyses with competing outcomes (Studies I and II), the mortality and risk of outcomes other than death were computed by a method that allows for competing outcomes.^{81,113}

In Study I, patients might have experienced an outcome more than once during follow-up. The Aalen-Johansen estimator pieces together the risk of the next outcome, i.e. computes conditional risks,^{5,114} and it was used to compute the distribution of outcomes after 1 and 5 years. Possible outcomes were: Alive without additional complications, alive with additional complications, dead without additional complications, or dead with additional complications.

In Study II, we computed directly adjusted mortality curves.^{48,141} These curves resemble Kaplan-Meier curves but use standardization to control for confounding, in this case for confounding by gender, age, calendar year, and alcoholism.

In Study IV, each GEC-decile's median GEC was plotted against its 30-day, 1-year, and 5-year mortality; lowess smoothing was used to facilitate the visual interpretation of the association between GEC and mortality.²³

4.4.2 Cox proportional hazards regression

We used Cox proportional hazards regression to estimate hazard ratios for the prognostic factors of interest whilst controlling for potential confounders. The hazard ratio can be interpreted as a relative risk, the ratio of two risks at a particular follow-up time, but only in qualitative terms, not quantitative. For example, a hazard ratio of 1.50 implies that exposure increases mortality

('increase' being a qualitative term), but not that it increases it by 50% ('50%' being a quantitative term). Cox proportional hazards regression is based on the assumption that the hazard ratio is constant throughout follow-up, an assumption that was found to be tenable in all analyses.

In Study II, we estimated the hazard ratio for comorbidity, controlling for gender, age, calendar year, and alcoholism. In Study III, we estimated the hazard ratio for marital status, employment, and personal income, each of them controlled for the other two factors and cirrhosis severity, which encompassed variceal bleeding, ascites, liver failure, bacterial infection, inpatient status at time of cirrhosis diagnosis, and cirrhosis as the primary diagnosis; gender; age; substance abuse, encompassing the number of hospital diagnoses of alcohol abuse and other substance abuse; and comorbidity, encompassing CCI, psychiatric disease, and the number of inpatient hospitalizations. The first analysis was based on socioeconomic data for the calendar year preceding the cirrhosis diagnosis, but in subsequent analyses we substituted these data for data from earlier calendar years or the year of cirrhosis diagnosis. In Study IV, we estimated the hazard ratio associated with the GEC-decile (included as a categorical variable), controlling for gender, age, and CCI.

4.4.3 Regression on the risk of a particular outcome

In analyses with competing outcomes, a Cox model's hazard ratio for a prognostic factor with respect to a particular outcome cannot be interpreted as a relative risk, not even in qualitative terms.^{11,32} Therefore, in the analysis of cirrhosis-related mortality for Study II, we used a regression method designed to compare the risks of a particular outcome when other outcomes are also possible. The resulting 'subdistribution hazard ratio' can be interpreted as a relative risk of that particular outcome, though still only in qualitative, not quantitative, terms.^{11,40}

4.4.4 Interaction risk

Biological interaction is defined as a causal interaction between prognostic factors in producing a particular disease outcome,⁷⁵ meaning that the outcome would have occurred later (or earlier) if the patient had not possessed all of the interacting prognostic factors.¹⁰⁵ Biological interaction is a special case of statistical interaction, which is defined as the need for a product term in a regression model.⁷⁵

The interaction risk has been proposed as a measure of the amount of biological interaction between two prognostic factors, and it yields the risk of death from mechanisms that involve both factors.¹⁰⁵ In Study II, we included a group of 10 matched non-cirrhosis patients from the general population per cirrhosis patient to compute the interaction risk for cirrhosis and comorbidity in causing death within 1 year after cirrhosis diagnosis.

4.4.5 Sensitivity analysis

A sensitivity analysis is a means of quantifying the influence of bias or unknown confounders on estimates of association.⁵³ In Study II, we used a sensitivity analysis to examine how reductions in the positive predictive value of cirrhosis diagnoses recorded in the National Patient Registry (i.e., the probability that a person with a diagnosis of cirrhosis recorded in the National Patient Registry does in fact have cirrhosis⁷⁵) might affect the estimated effect of comorbidity (CCI \geq 3 vs. CCI=0) on the 1-year mortality.⁵³ We considered two likely causes of a reduced positive predictive value:¹⁴⁰

• Typos in the personal identification number or the diagnosis code; the person who was mistakenly recorded as having cirrhosis could be anybody, but was not likely a cirrhosis patient because of the low prevalence of cirrhosis.
Misinterpretation of a patient's signs and symptoms as being caused by cirrhosis; those
who were mistakenly recorded as having cirrhosis were correctly recorded with respect to
CCI. Such errors were more likely for patients with a CCI≥3 because they had more
symptoms.

Estimates of the 1-year mortality of those who were mistakenly registered as cirrhosis patients were obtained from the group of matched non-cirrhosis patients from the general population.

5 Results

5.1 Study I - The Clinical Course Study

We included 466 patients (71% men). At diagnosis, their median age was 53 years (range: 27-84 years), and there was no gender or age difference between patients with or without complications.

What is the prevalence of complications when alcoholic cirrhosis is diagnosed?

Of the 466 patients included in the study, 114 (24%) had no complications at the time of cirrhosis diagnosis, 254 (55%) had ascites alone, 29 (6%) had variceal bleeding alone, 20 (4%) had ascites and variceal bleeding, and 49 (11%) had hepatic encephalopathy alone or in combination with other complications.

What are the risks of complications and death after diagnosis?

The median survival time for the 114 patients who presented without complications was 48 months. After 1 year, 22% had developed complications (Figure 6, page 33), and 17% were dead (Table 5, page 34). After 5 years, 48% had developed complications (Figure 6, page 33), 58% were dead, and 28% were alive and still without complications (Table 5, page 34).

The median survival time for the 287 patients with ascites alone was 37 months. After 1 year, 27% had developed more complications (Figure 6, page 33), and 29% were dead (Table 5, page 34). After 5 years, 42% had developed more complications (Figure 6, page 33), 59% were dead, and 32% were still alive and without more complications (Table 5, page 34).

The median survival time for the 45 patients with variceal bleeding alone was 48 months. During the first month, these patients had a higher mortality than patients without complications (10% vs. 4%), but their outcomes after 1 year were comparable (Table 5, page 34). After 5 years, 54% had

developed more complications (Figure 6, page 33), 64% were dead, and 27% were still alive and without more complications (Table 5, page 34).

The median survival time for the 94 patients with ascites and variceal bleeding was 13 months. After 1 year, 22% had developed hepatic encephalopathy (Figure 6, page 33), and 49% were dead (Table 5, page 34). After 5 years, 44% had developed hepatic encephalopathy (Figure 6, page 33), 80% were dead, and 17% were still alive and without hepatic encephalopathy (Table 5, page 34).

The median survival time for the 169 patients who had hepatic encephalopathy alone or in combination was 2.4 months. Forty-five percent of the patients (95% CI 39-51) died within 1 month. After 1 year, 64% were dead, and after 5 years, 85% (Table 5, page 34).

In which sequence do complications develop?

Patients without complications at the time of diagnosis were likely to develop ascites first (Figure 6, page 33), but the complications did not develop in a specific sequence. Thus, any complication could be the first to develop, and even after the first complication developed, the two other complications had nearly equal probability of coming next (Figure 6, page 33).

Figure 6 Risk of the development of more cirrhosis complications and mortality with the current complications. Risk estimates are followed by a 95% confidence interval in parentheses.



5-year risk: 7% (3-13)

Table 5Outcome of alcoholic cirrhosis 1 year (top) and 5 years (bottom) after onset of complications (for patients without complications:
1 and 5 years after cirrhosis diagnosis). Cells contain the risk of a particular outcome followed by a 95% confidence interval in
parentheses.

1-year outcome	No complications	Ascites	Variceal bleeding	Ascites + variceal bleeding	Hepatic encephalopathy alone or in combination
Alive	83% (78-89)	71% (67-75)	80% (71-89)	51% (43-59)	36% (31-42)
Alive without more complications	68% (62-75)	59% (55-64)	64% (54-76)	47% (39-54)	-
Alive with more complications	15% (10-20)	12% (9-15)	16% (7-23)	4% (2-7)	-
Ascites alone	5% (2-8)	-	-	-	-
Variceal bleeding alone	4% (1-7)	-	-	-	-
Ascites + variceal bleeding	4% (1-6)	7% (4-9)	11% (3-18)	-	-
Hepatic encephalopathy	2% (0-3)	5% (3-7)	4% (0-8)	4% (2-7)	-
Dead	17% (11-22)	29% (25-33)	20% (11-29)	49% (41-57)	64% (58-69)
Dead without more complications	10% (5-14)	15% (12-18)	11% (4-18)	31% (24-38)	-
Dead after developing more complications	7% (4-11)	14% (11-17)	9% (3-15)	18% (12-24)	-
Total	100% (N=114)	100% (N=287)	100% (N=45)	100% (N=94)	100% (N=169)

5-year outcome	No complications	Ascites	Variceal bleeding	Ascites + variceal bleeding	Hepatic encephalopathy
Alive	42% (34-50)	41% (36-46)	35% (23-48)	20% (13-27)	15% (10-19)
Alive without more complications	28% (21-35)	32% (28-37)	27% (15-39)	17% (10-23)	-
Alive with more complications	13% (8-19)	9% (5-11)	8% (0-16)	4% (0-6)	-
Ascites alone	8% (3-12)	-	-	-	-
Variceal bleeding alone	5% (0-8)	-	-	-	-
Ascites + variceal bleeding	1% (0-3)	4% (2-6)	0	-	-
Hepatic encephalopathy	0	4% (2-6)	8% (0-16)	4% (0-6)	-
Dead	58% (50-66)	59% (54-64)	64% (52-77)	80% (73-87)	85% (81-90)
Dead without more complications	22% (17-29)	25% (21-29)	18% (9-26)	44% (35-51)	-
Dead after developing more complications	35% (28-43)	33% (29-38)	45% (32-59)	36% (29-45)	-
Total	100% (N=114)	100% (N=287)	100% (N=45)	100% (N=94)	100% (N=169)

5.2 Study II - The Comorbidity Study

This study included 14,976 cirrhosis patients, of whom 9,391 (63%) died during a total of 42,524 years of follow-up; 62% had a CCI of 0, 21% CCI=1, 10% CCI=2, and 7% CCI \geq 3.

5.2.1 All-cause mortality

Mortality depended markedly on CCI (Figure 7). Compared with patients who had a CCI of 0, the adjusted hazard rate was increased 1.17-fold for patients with a CCI of 1 (95% CI 1.11-1.23), 1.51-fold increased for patients with a CCI of 2 (95% CI 1.42-1.62), and 2.00-fold increased for patients with a CCI greater than or equal to 3 (95% CI 1.85-2.15).

Figure 7 Mortality of 14,976 cirrhosis patients adjusted (black) or not adjusted for (gray) confounding by gender, age, calendar time, and alcoholism.



Years after cirrhosis diagnosis

5.2.2 Cirrhosis-related mortality

Seventy-three percent of deaths were cirrhosis-related, meaning that cirrhosis, liver failure, portal hypertension, hepatorenal syndrome, or gastroesophageal varices were recorded as a cause of death. Mortality from both cirrhosis-related and other causes increased with the comorbidity level (Figure 8), also after adjustment for confounders.



Figure 8 Mortality from cirrhosis and other causes.

5.2.3 Interaction risk

In the first year after cirrhosis diagnosis, 14.0% (95% CI 10.4-17.4) of cirrhosis patients with comorbidity died from a biological interaction between cirrhosis and comorbidity.

5.2.4 Sensitivity analysis

The 1-year mortality was 29.0% for cirrhosis patients with a CCI=0 and 61.0% for cirrhosis patients with a CCI \geq 3 (Figure 7, page 35); thus, the relative 1-year mortality for a CCI \geq 3 vs. CCI=0 was 2.10. This association could not be explained by a low positive predictive value for recorded cirrhosis diagnoses, even in the unlikely event that typos were not random (Table 6).

Table 6Effect of reductions in the positive predictive value (PPV) of cirrhosis diagnoses
recorded in the National Patient Registry on the relative 1-year mortality of cirrhosis
patients with a CCI≥3 vs. a CCI=0.

PPV among CCI≥3	PPV among CCI=0	True relative mortality				
Errors were caused by typos						
100	100	2.10				
90	90	2.11				
85^{\dagger}	85^{\dagger}	2.11				
78^{\dagger}	78^{\dagger}	2.12				
70	70	2.12				
100	90	1.90				
100	85^{\dagger}	1.80				
100	78^{\dagger}	1.67				
100	70	1.50				
Errors were caused by misinterpretation of signs and symptoms						
100	100	2.10				
90	90	2.04				
85^{\dagger}	85^{\dagger}	2.01				
78^{\dagger}	78^{\dagger}	1.97				
70	70	1.92				
90	100	2.27				
85^{\dagger}	100	2.36				
78^\dagger	100	2.53				
70	100	2.73				

[†] Estimates from validation studies.^{66,135}

5.3 Study III - The SES study

We included 1,765 cirrhosis patients, of whom 68% were men. During a total follow-up time of 3,855 years, 877 patients (50%) died. Forty-one percent of the patients were married, 40% were divorced, less than one-third were employed, two-thirds had a personal income less than half the national average, and only 6% had an income above the national average.

Compared with married patients, divorced or never-married patients were more likely to be disability pensioners, have a low income, and abuse alcohol. Employed patients were more likely than others to be married, have a higher income, and not abuse alcohol, whereas disability pensioners were more likely to be divorced, abuse alcohol, and have comorbidities. Cirrhosis severity was unrelated to socioeconomic status.

5.3.1 Mortality

Mortality was higher for divorced and never-married patients than married patients, and it was higher for disability pensioners than employed or unemployed patients. Personal income had no clear association with mortality (Figure 9).

Figure 9 Mortality with respect to time (years) after cirrhosis diagnosis by marital status, employment, and personal income.



5.3.2 Adjustment for other characteristics

Adjusting for other socioeconomic factors, cirrhosis severity, gender, age, substance abuse, and comorbidity attenuated the prognostic impact of marital status, but the prognosis remained worse for divorced patients than married patients (hazard ratio for divorced vs. married = 1.22, 95% CI 1.05-1.42). Likewise, the impact of employment was reduced, but being a disability pensioner was still associated with a poorer prognosis (hazard ratio for disability pensioner vs. employed = 1.35, 95% CI 1.10-1.66; hazard ratio for disability pensioner vs. unemployed = 1.39, 95% CI 1.18-1.65). These associations were essentially the same if socioeconomic information from earlier calendar years or from the year of cirrhosis diagnosis was used.

5.4 Study IV - The GEC Study

We included 781 patients, of whom 421 (54%) died during a total of 2,617 years of follow-up. The GEC ranged from 0.59 to 3.97 mmol/min with a median value of 1.48 mmol/min. Men had a higher GEC than women (median GEC 1.54 mmol/min vs. 1.40 mmol/min), and the 29% of patients with a CCI of 1 or greater had a higher GEC than the other patients (median GEC 1.57 mmol/min vs. 1.45 mmol/min).

5.4.1 Mortality

In the total cohort, the 30-day mortality was 10% (95% CI 8-13), the 1-year mortality was 27% (95% CI 24-31), and the 5-year mortality was 55% (95% CI 51-59). The association between GEC and mortality was strong among patients with a GEC less than 1.75 mmol/min, but weak among patients with a higher GEC (Figure 10, page 40); confounding was negligible. The same pattern was found among the cirrhosis patients with comorbidities.

Figure 10 Association between GEC and 30-day, 1-year, and 5-year mortality. Gray lines connect each GEC-decile's median GEC with its observed mortality. Black lines are lowess smoothings of the gray lines.²³



6 LIMITATIONS

This section discusses the methodological limitations of the studies. In Study I, absolute risk estimates were presented, and the methodological concern was whether these estimates were biased. In Studies II, III, and IV, we quantified associations, and the methodological concern was whether the associations were affected by bias, confounding, or chance.⁴³ The precision of the estimates of association was described by the 95% confidence intervals in the Results section, and will not be discussed further. Dates of death will also not be discussed; registration in the Central Office of Civil Registration can be assumed to be without error.⁴⁴

6.1 Study I - The Clinical Course Study

The clinical course predicted for alcoholic cirrhosis patients could be biased if the patients included did in fact not have cirrhosis, or they did in fact not have the complications they were thought to have. Thus, the lack of standardized diagnostic criteria in the study is a limitation, but cirrhosis diagnoses based on clinical observations alone have a high positive predictive value among alcohol abusers.⁵⁹ Therefore, all patients probably had cirrhosis. Also, it is plausible that all first-time episodes of ascites, variceal bleeding, and hepatic encephalopathy were recorded in the medical records because these complications are well-known and often dramatic,¹⁴⁰ and because 92% of medical records have been found to contain information about a patient's chief complaint.¹⁴⁰ Nonetheless, a recorded variceal bleeding may in fact have been an ulcer bleeding, and a recorded episode of hepatic encephalopathy could in fact have been dementia or septic shock. If so, the effects of cirrhosis complications may have been underestimated, but this bias is expected to be negligible.

The study was population-based and had complete follow-up, making it more likely that the risk estimates can be generalized to other settings.¹³⁴ However, more detailed information about the patients and other prognostic factors in Figure 2 (page 3) would have made it easier for others to make this judgment.^{42,139}

6.2 Study II - The Comorbidity Study

6.2.1 Selection bias

This study was based on a comparison of patients with or without comorbidity *within* a cohort of cirrhosis patients. Such internal comparisons without loss to follow-up are generally unlikely to be affected by selection bias,^{24,92} and our sensitivity analysis clarified that even substantial reductions in the positive predictive value of recorded cirrhosis diagnoses introduced only weak selection bias (Table 6, page 37).

6.2.2 Information bias

Diagnoses of myocardial infarction, cancer, and diabetes recorded in the National Patient Registry have a high positive predictive value,⁹¹ and a yet unpublished study found that this was true of all diagnoses included in the CCI (Thygesen S, personal communication). Some comorbidities may not have been recorded in the National Patient Registry, but we may still have correctly classified patients with respect to the CCI categories used, and the dose-response relationship between CCI and mortality indicates that very few patients were misclassified.

Our analysis of cirrhosis-related death relied on death certificate data, which has been found to have a low reproducibility.⁵¹ This limitation weakens the conclusion that comorbidity increased

cirrhosis mortality, but the same conclusion was reached in the interaction risk analysis, which did not rely on death certificates.

6.2.3 Confounding

Comorbidity alone does not determine the prognosis for cirrhosis patients (Figure 2, page 3), and other prognostic factors may have contributed to our findings.

Liver function at the time of cirrhosis diagnosis, for example, could have been worse for patients with comorbidity than for patients without. If so, the apparent effect of comorbidity could in fact have been an effect of poor liver function. However, this was an unlikely possibility. First, patients with chronic diseases are seen regularly in a hospital, so they have a higher probability of having cirrhosis diagnosed early in the course of the disease than do patients who are rarely hospitalized. Second, cirrhosis patients with comorbidity had a higher GEC at the time of the cirrhosis diagnosis than other patients in Study IV. Therefore, the diagnostic procedures (cf. Figure 2, page 3) may in fact have led us to *under*estimate the impact of comorbidity on mortality.

Lifestyle factors also affect the prognosis for cirrhosis patients. Alcohol abuse is a risk factor for developing cirrhosis, and if it continues after cirrhosis diagnosis it also increases mortality.^{9,68,94,118} Smoking and obesity may also increase mortality of cirrhosis patients,^{64,65,94} and alcohol abuse, smoking, and obesity are likely to be more prevalent among patients with comorbidities. Our analyses were adjusted for alcoholism, but it is possible that the adjustment was incomplete due to failure to record alcoholism diagnoses in the National Patient Registry or to differences in alcohol consumption among alcohol abusers.¹⁵ Thus, confounding by lifestyle factors may have led us to overestimate the true impact of comorbidity on the mortality of

cirrhosis patients; however, the impact was so strong that confounding could not realistically be the full explanation.

6.3 Study III - The SES Study

6.3.1 Selection bias

Similar to Study II, this study was based on an internal comparison within a cohort of cirrhosis patients without loss to follow-up, so selection bias was unlikely to have a substantial impact on our findings.^{24,92}

6.3.2 Information bias

The socioeconomic information used in this study is likely to have been recorded without error, but it was updated only once per calendar year. This could raise concerns that the available data did not reflect the socioeconomic status on the date of cirrhosis diagnosis, or that the socioeconomic status deteriorated after cirrhosis diagnosis so that, for example, those who were employed at the time of cirrhosis diagnosis were in fact disability pensioners during the majority of the follow-up period. Both of these scenarios would introduce a misclassification of socioeconomic status into our data, but we showed that it was not important for our findings whether we used socioeconomic data from the year before or the year after cirrhosis diagnosis (page 39). This observation speaks against the possibility of substantial misclassification of socioeconomic status.

6.3.3 Confounding

Marital status and employment were associated with mortality, but their effect might be explained by other factors (Figure 2, page 3). Most of these other factors should be thought of as explanations, rather than confounders, of the association between socioeconomic status and mortality because they can be regarded as a component of socioeconomic status and therefore violate confounder criteria.¹⁰⁶ Our analyses indicated that we did not have the data to fully explain why divorced or disabled cirrhosis patients had a worse prognosis than other cirrhosis patients.

6.4 Study IV - The GEC Study

6.4.1 Selection bias

Again, this study was an internal comparison within a cohort of cirrhosis patients who were hospitalized in a tertiary referral center and had undergone a GEC test. Because there was no loss to follow-up, selection bias was also unlikely in this study.^{24,92}

6.4.2 Information bias

It is unlikely that the accuracy of the GEC measurements – the extent to which the GEC test measures the true GEC^{75} – depended on patient characteristics, and its precision – the extent to which repeated GEC tests give the same result^{75,129} – is within 10%. Therefore, it is unlikely that our findings were notably affected by bias in the GEC test itself.

6.4.3 Confounding

We adjusted for confounding by gender, age, and comorbidity and were not aware of other factors associated with GEC and mortality, but even if such factors existed, the association between GEC and mortality was so strong that confounding could not possibly be the full explanation.

7 MAIN CONCLUSIONS

This section presents the answers to the research questions presented on page 21.

7.1 Study I – The Clinical Course Study

We found that 24% of our alcoholic cirrhosis patients had no complications at the time of cirrhosis diagnosis, 55% had ascites alone, 6% had variceal bleeding alone, 4% had both ascites and variceal bleeding, and 11% had hepatic encephalopathy alone or in combination. All patients had an approximate 25% risk of developing more complications within 1 year, but their 1-year mortality depended strongly on the presence of complications: hepatic encephalopathy (1-year mortality = 64%) > ascites and variceal bleeding (49%) > ascites alone (29%) > variceal bleeding alone (20% [1-month mortality = 10%]) > no complications (17% [1-month mortality = 4%]). The 5-year risk of developing more complications: Patients with hepatic encephalopathy or the combination of ascites and variceal bleeding had a 5-year mortality of 80-85% compared with approximately 60% for other patients. Most patients developed ascites first, but complications did not develop in a specific sequence.

7.2 Study II – The Comorbidity Study

Comorbidity present at the time of cirrhosis diagnosis increased mortality. This association was due, in part, to a higher risk of cirrhosis-related death for patients with comorbidity during the first year after cirrhosis diagnosis.

7.3 Study III – The SES Study

Marital status and employment at the time of cirrhosis diagnosis were associated with mortality. Specifically, divorced cirrhosis patients had a higher mortality than married cirrhosis patients, and cirrhosis patients who were disability pensioners had a higher mortality than employed or unemployed cirrhosis patients. These associations could not be explained by differences in other socioeconomic factors, cirrhosis severity, gender, age, substance abuse, or comorbidity. Personal income was not associated with mortality.

7.4 Study IV – the GEC study

GEC at the time of cirrhosis diagnosis was inversely associated with short- and long-term mortality, particularly among cirrhosis patients with a GEC less than 1.75 mmol/min. This association was also seen among cirrhosis patients with comorbidity.

8 **DISCUSSION AND PERSPECTIVES**

This section contains a discussion of the studies' main conclusions in relation to the existing literature and provides a perspective on questions raised by the studies that should be answered in order to further improve clinicians' ability to predict, understand, and change the prognosis for cirrhosis patients (cf. paragraph 1.1.1, page 3).

8.1 Study I – The Clinical Course Study

8.1.1 Discussion

The prevalence of ascites at cirrhosis diagnosis was higher in our study than in most previous studies (compare Table 1, page 8), but it did not exceed the 67% prevalence in the Norwegian study.⁹

The risk of cirrhosis complications was higher in our study than in earlier studies, but this was expected because all of our patients had alcoholic cirrhosis (page 9). Specifically, we found a 2-3 fold higher 1-year risk (22%) than the 7-10% per year reported in previous studies (Table 2, page 10), but the 5-year risk for our patients (49%) did not exceed this. Two likely explanations are that a large proportion of our patients died before complications developed and that previous risk estimates were biased upwards (page 11).

The mortality of patients without complications was higher in our study than in the two previous studies (Table 3, page 12), whereas the mortality of patients with complications was lower in our study than in previous studies (Table 3, page 12). These observations suggest that the negative prognostic impact of complications has decreased during recent decades, and such a decrease has been found for patients with variceal bleeding (page 12).^{16,121}

Ascites, variceal bleeding, and hepatic encephalopathy did not develop in a specific sequence, but ascites had the highest prevalence at the time of cirrhosis diagnosis, and patients without complications were likely to develop ascites first. These findings are consistent with the existing literature (Table 1, page 8; Table 2, page 10), so there is strong evidence that ascites develops before variceal bleeding and hepatic encephalopathy in most cirrhosis patients.

8.1.2 Perspectives

Clinicians may use our findings to predict alcoholic cirrhosis patients' clinical course and to update their prediction when complications develop. There is, however, large variation in patients' risk of complications or death, and future prediction studies could improve upon ours by using standardized diagnostic criteria and including more clinical data. The continuous collection of this data in a nationwide clinical database would be an attractive way of securing a valuable data source for future studies.

Clinicians should predict that cirrhosis patients will develop ascites before variceal bleeding or hepatic encephalopathy, but such a prediction is not founded on a deep understanding of the link between hemodynamic, biochemical, and clinical signs of complicated cirrhosis.^{69,103} Further studies are necessary to foster our understanding of why a large minority develops variceal bleeding or hepatic encephalopathy first.

8.2 Study II – The Comorbidity Study

Our findings indicate that the prediction of mortality of cirrhosis patients might be improved by including comorbidity in the prediction rules. In this regard, it is interesting that comorbidity was not considered for inclusion in any of the prediction rules currently in routine use: the Child-Pugh, MELD, and Mayo systems.^{31,80,98} These prediction rules are almost exclusively based on

indicators of liver function or portal hypertension, and comorbidity may improve the accuracy of mortality predictions because they hold prognostic information that is not described by these indicators.²²

Our finding that comorbidity increased cirrhosis-related mortality helps us understand why comorbidity increases mortality of cirrhosis patients; some comorbid diseases, such as congestive heart failure, may reduce the body's ability to compensate for the circulatory consequences of a cirrhotic liver, and others may contraindicate treatments for cirrhosis. However, further studies are needed to clarify the mechanisms involved.

As many as 38% of cirrhosis patients had comorbidities, thus the prevention and treatment of comorbidities may have great potential for improving the prognosis for cirrhosis patients, and it should be emphasized that successful elimination of comorbidity would have prevented *all* deaths attributable to comorbidity, including those resulting from a biological interaction with cirrhosis. This emphasizes that hepatologists caring for cirrhosis patients should also assume responsibility for the patients' comorbidities.

8.3 Study III – The SES Study

Our results were consistent with studies of patients with other diseases (page 17). Based on our study, it can be predicted that divorced or disabled cirrhosis patients will have a worse prognosis than other cirrhosis patients; therefore, they may benefit from closer follow-up and screening for other factors that could explain their poor prognosis.

A sensible starting point for future studies would be to examine whether divorced or disabled cirrhosis patients have increased cirrhosis-related mortality. Such an association might be explained by differences in clinical performance (Figure 2, page 3), as suggested by a recent

Swedish study of mortality among women with breast cancer. The Swedish study compared diagnostic procedures and treatment offers between women of high and low socioeconomic status,³³ and it showed that women of low socioeconomic status were less likely to be offered a complete examination and appropriate treatment.

8.4 Study IV – The GEC Study

Our finding of an association between GEC and mortality is consistent with existing studies, but our study expands upon them by creating strong arguments that the association is causal, presenting a near-continuous relationship between GEC and short- and long-term mortality and showing that the GEC-mortality association also exists among cirrhosis patients with comorbidities. Our study contributes to the understanding of the clinical course of cirrhosis by confirming the basic assumption that residual organ function is a determinant of prognosis (Figure 2, page 3). This affirmation should motivate the development of physiological liver function tests that are easier to perform than the GEC test. Currently, the GEC test is too invasive, tedious, and labor-intensive for widespread clinical use, but the inherent robustness of a physiological test similar to the GEC test may be desirable in complex situations, for example, when treating cirrhosis patients with comorbidities that affect standard liver chemistry tests.⁵²

8.5 Conclusion

The aim of this thesis was to examine selected aspects of the prognosis for Danish cirrhosis patients. This goal has been reached; the clinical course of alcoholic cirrhosis has been examined, and comorbidity, marital status, employment, and GEC have been identified as prognostic factors for cirrhosis patients. Hopefully, these findings will contribute to continuous improvements in the ability to predict, understand, and change the prognosis for cirrhosis patients.

9 SUMMARY

Patients with cirrhosis, an advanced stage of chronic liver disease, have a high mortality, but the prognosis and factors that determine prognosis are otherwise poorly elucidated. Ascites, variceal bleeding, and hepatic encephalopathy are cirrhosis complications that are widely used to describe the course of cirrhosis, so information about patients' risk of developing these complications would not only improve our ability to predict the prognosis, but might also help us understand it. The impact of comorbidity and socioeconomic status on the mortality of cirrhosis patients has not previously been examined, and the impact of galactose elimination capacity (GEC), a measure of liver function, is not clear from the existing literature; therefore, studies of these prognosis for cirrhosis patients. On this background, the aims of this thesis were to examine the prevalence of complications when alcoholic cirrhosis is diagnosed, the risks of complications and death after diagnosis, and the sequence in which complications develop (Study I), as well as the impacts of comorbidity (Study II), marital status, employment, income (Study III), and GEC (Study IV) on mortality of cirrhosis patients.

Study I used data from medical records, whereas the other studies relied on data from Danish nationwide administrative registries. The GEC measurements were obtained from hospital databases. All studies were cohort studies following cirrhosis patients from hospital diagnosis to death.

In Study I, 24% of alcoholic cirrhosis patients had no complications at the time of cirrhosis diagnosis, 55% had ascites alone, 6% had variceal bleeding alone, 4% had ascites and variceal bleeding, and 11% had hepatic encephalopathy alone or in combination. All patients had an

approximate 25% risk of developing more complications within 1 year, but 1-year mortality depended strongly on the presence of complications: hepatic encephalopathy (64%) > ascites and variceal bleeding (49%) > ascites alone (29%) > variceal bleeding alone (20%) [1-month mortality = 10%) > no complications (17% [1-month mortality = 4%]). The 5-year risk of developing more complications was about 50% for all patients, and 5-year mortality depended less on complications: 80-85% for patients with hepatic encephalopathy or with both ascites and variceal bleeding compared with about 60% for other patients. Most patients developed ascites first, but complications did not develop in a specific sequence. In Study II, comorbidity present at the time of cirrhosis diagnosis increased mortality. This association was due, in part, to a higher risk of cirrhosis-related death for patients with comorbidities during the first year after cirrhosis diagnosis. In Study III, cirrhosis patients who were divorced at the time of cirrhosis diagnosis had a higher mortality than married cirrhosis patients, and cirrhosis patients who were disability pensioners had a higher mortality than employed or unemployed cirrhosis patients. Personal income was not associated with mortality. In Study IV, GEC at cirrhosis diagnosis was inversely associated with short- and long-term mortality of cirrhosis patients, particularly among those with a GEC less than 1.75 mmol/min. In summary, the findings in this thesis contribute to our ability to predict and understand the prognosis for cirrhosis patients, and they may also be important for our ability to change it.

10 DANSK RESUME

Patienter med levercirrose, et fremskredet stadie af kronisk leversygdom, har høj dødelighed, men deres prognose og de faktorer, der bestemmer prognosen, er derudover dårligt belyst. Ascites, variceblødning og hepatisk encefalopati er cirrosekomplikationer, som hyppigt anvendes til at beskrive forløbet af cirrose, og information om cirrosepatienters risiko for at udvikle disse komplikationer vil derfor ikke blot forbedre vores evne til at forudsige prognosen, men måske også hjælpe os til at forstå den. Betydningen af comorbiditet og socioøkonomisk status for cirrosepatienters dødelighed er ikke tidligere blevet undersøgt, og betydningen af galaktose-eliminations-kapacitet (GEC), et mål for leverfunktionen, er ikke blevet klarlagt af den eksisterende litteratur, så studier af disse prognosen for cirrosepatienter. Formålene med denne afhandling var derfor at undersøge prævalensen af ascites, variceblødning og hepatisk encefalopati blandt patienter med nydiagnosticeret alkoholisk cirrose, risikoen for komplikationer og død, samt rækkefølgen hvori komplikationer udvikles (Studie I); endvidere undersøgtes betydningen af comorbiditet (Studie II), civilstand, beskæftigelse, indkomst (Studie III) og GEC (Studie IV) for cirrosepatienters dødelighed.

Studie I var baseret på data fra sygehusjournaler, hvorimod de andre studier var baseret på data fra landsdækkende administrative registre. GEC-målingerne blev udtrukket fra hospitalsdatabaser. Alle studierne var kohortestudier, som fulgte cirrosepatienter fra diagnose til død.

I Studie I fandt vi, at 24% af patienter med alkoholisk cirrose ikke havde komplikationer, da de fik stillet diagnosen cirrose, 55% havde ascites som eneste kompliation, 6% havde variceblødning som eneste komplikation, 4% havde både ascites og variceblødning og 11% havde hepatisk encefalopati. Alle patienter havde en ca. 25% risiko for at udvikle flere komplikationer inden for 1 år, men 1-års dødeligheden var stærkt afhængig af tilstedeværelsen af kompliationer: hepatisk encefalopati (64%) > ascites og variceblødning (49%) > ascites alene (29%) > variceblødning alene (20% [1-måneds dødelighed = 10%]) > ingen komplikationer (17% [1-måneds dødelighed = 4%]). Risikoen for at udvikle flere komplikationer inden for 5 år var omkring 50% for alle patienter, og 5-års dødeligheden var mindre afhængig af tilstedeværelsen af komplikationer: Den var 80-85% for patienter med hepatisk encefalopati eller både ascites og variceblødning mod ca. 60% for andre patienter. De fleste patienter udviklede ascites først, men komplikationerne udvikledes ikke i en fast rækkefølge. I Studie II fandt vi, at comorbiditet på tidspunktet for cirrosediagnosen øgede dødeligheden. Denne sammenhæng skyldtes delvist, at cirrosepatienter med comorbiditet havde en højere risiko for at dø af cirrose inden for det første år. I Studie III fandt vi, at cirrosepatienter, der var fraskilt, da de fik stillet diagnosen cirrose, havde højere dødelighed end gifte cirrosepatienter, og at cirrosepatienter, som var invalidepensionister, havde højere dødelighed end cirrosepatienter med eller uden job. Indkomst havde ingen betydning for cirrosepatienters dødelighed. I Studie IV fandt vi, at GEC på tidspunktet for cirrosediagnosen var omvendt associeret med kort- og langtidsdødelighed for cirrosepatienter, specielt blandt dem med GEC under 1.75 mmol/min. Samlet set har fundene i denne afhandling bidraget til vores evne til at forudsige og forstå prognosen for cirrosepatienter, og de kan også vise sig at være vigtige for vores evne til at ændre den.

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The clinical course of alcoholic liver cirrhosis: A Danish population-based study

Peter Jepsen (1)

Hendrik Vilstrup (2)

Per Kragh Andersen (3)

Peter Ott (2)

Henrik Toft Sørensen (1)

- 1. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
- Department of Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, Aarhus, Denmark.
- Department of Biostatistics, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark.
ABSTRACT

Patients with alcoholic cirrhosis have a high mortality, but their clinical course is otherwise largely unknown. We aimed to answer the following questions based on observations of the cirrhosis complications ascites, variceal bleeding, and hepatic encephalopathy: What is the prevalence of complications at cirrhosis diagnosis? What are the risks of complications and death after diagnosis? In which sequence do complications develop? What is the prevalence of complications after diagnosis? Our study followed a population-based cohort of 466 Danish alcoholic cirrhosis patients diagnosed in 1993-2005 from hospital diagnosis to death. Data were from medical records. We computed the prevalence and incidence of complications and mortality with or without complications. At cirrhosis diagnosis, 24% had no complications, 55% had ascites alone, 6% had variceal bleeding alone, 4% had ascites and variceal bleeding, and 11% had hepatic encephalopathy. All patients had an approximate 25% risk of developing more complications within 1 year, but 1year mortality depended strongly on the presence of complications: hepatic encephalopathy (64%) > ascites and variceal bleeding (49%) > ascites alone (29%) > variceal bleeding alone (20% [1month mortality = 10%]) > no complications (17% [1-month mortality = 4%]). The 5-year risk of developing more complications was roughly 50% for all patients, and 5-year mortality depended less on complications: 80-85% for patients with hepatic encephalopathy or with both ascites and variceal bleeding compared with approximately 60% for other patients. Most patients developed ascites first, but complications did not develop in a specific sequence. The prevalence of complications increased from 76% at cirrhosis diagnosis to 81% five years later. Conclusion: Our alcoholic cirrhosis patients were characterized by a high prevalence of complications and a high mortality.

INTRODUCTION

We have recently shown that each year 1 in 2000 Danish citizens aged 45-64 years is diagnosed with alcoholic cirrhosis (1). Not much is known about their clinical course after being diagnosed: Mortality is high (2, 3), but we found no studies of the risk of developing ascites, variceal bleeding, or hepatic encephalopathy, which are complications of cirrhosis that are often used to describe the clinical course (4, 5). Studies including both patients with alcoholic and non-alcoholic cirrhosis found that the risk of developing one of these complications was 7-10% per year (6-9), but patients with alcoholic cirrhosis have a higher risk of cirrhosis-related death (2), so their risk of complications may also be higher. Studies of the prevalence of complications and the mortality of alcoholic cirrhosis patients with them have been hospital-based as opposed to population-based (3, 10-15), and they have included 100 or fewer patients (12, 13) or included only patients diagnosed before 1980, at which time clinical management was different (3, 10-12). Therefore we did not expect findings from existing studies to apply to a contemporary population-based cohort of alcoholic cirrhosis patients. On this background we designed a study to answer these questions: What is the prevalence of ascites, variceal bleeding, and hepatic encephalopathy when alcoholic cirrhosis is diagnosed? What are the risks of complications and death after diagnosis, and how do they depend on the presence of complications? In which sequence do complications develop? What is the prevalence of complications after diagnosis? The study included 466 Danish alcoholic cirrhosis patients diagnosed in 1993-2005.

MATERIAL AND METHODS

This study was set in the hospital catchment area that includes the city of Aarhus, Denmark. The catchment area has a population of 365,000, and the largest hospital is Aarhus University Hospital which has a specialist department of hepatology to which all cirrhosis patients are referred upon

diagnosis. There are no private acute-care hospitals in Denmark, and all citizens have free, unlimited access to general practitioners and public hospitals.

Study cohort

We used data from two administrative registries to identify possible cirrhosis patients in the catchment area: The Danish National Patient Registry, which stores discharge diagnoses from all admissions to public and private Danish hospitals after 1977 and from all outpatient and emergency room visits after 1995 (16), and the Danish Pathology Registry, which stores diagnoses from all histological examinations conducted in Danish hospitals after 1997. Our search criteria are given in Appendix 1, and we retrieved the medical records of all relevant patients. We included all who had cirrhosis due in part or in full to alcohol abuse according to their medical record, were diagnosed between 1 January 1993 and 31 August 2005, lived in the catchment area when hospital workup for suspected cirrhosis began, and had not previously been examined for suspected cirrhosis in any hospital. Patients were included in the cohort on the date that they were first described in their medical record as having cirrhosis. In patients who presented with ascites, variceal bleeding, or hepatic encephalopathy, this date was usually the date of hospital admission; in the remaining patients it was usually the date of a subsequent liver biopsy or ultrasound examination.

Patient data

Using the medical records we recorded when patients presented with ascites, variceal bleeding, and hepatic encephalopathy. Ascites was defined as clinically detectable ascites, i.e. no ultrasound examination required; variceal bleeding as clinically significant bleeding (patient presenting with a heart rate >100 beats per minute and a systolic blood pressure <100 mmHg, or requiring blood transfusion) presumed by the hospital physicians to be from esophageal or gastric varices; hepatic encephalopathy as clinically detectable hepatic encephalopathy, i.e. minimal hepatic encephalopathy was excluded (17). All complications were assumed to be diagnosed without delay

and to persist throughout follow-up. Hereafter, "complications" refers to ascites, variceal bleeding, and hepatic encephalopathy, exclusively.

Dates of death were obtained from the Danish Civil Registration System, a continuously updated source of dates of birth, death, and emigration for the Danish population (18). The cornerstone of registration is a unique personal identifier issued to Danish citizens at birth or immigration which permitted us to link individual-level data from all data sources.

Study design

Patients were followed from inclusion into the study cohort to death, or they were censored at emigration from Denmark or on 31 August 2006. We counted follow-up time as time from inclusion to onset of the next complication, and once the next complication developed follow-up time was counted from onset of that complication to the next complication, and so on. This design implied the following assumption: Whether a complication is present at the time of cirrhosis diagnosis or develops later, the prognosis from the time it is diagnosed is the same. We found this assumption to be tenable based on our clinical experience.

Statistical analysis

We computed cumulative mortality as the complement of the Kaplan-Meier estimate of survival probability, and the median survival time was defined as the time to reach a cumulative mortality of 50%. Competing risks methods were used to compute the cumulative incidence (i.e., risk) of ascites, variceal bleeding, hepatic encephalopathy, and death (19, 20), and we used the Aalen-Johansen estimator to piece together these cumulative incidences (21, 22) and compute the distribution of cirrhosis outcomes 1 and 5 years after onset of the current complications; possible outcomes were: Alive without more complications, alive with more complications, dead without more complications, and dead with more complications. Ninety-five percent confidence intervals were bootstrapped.

5

RESULTS

We included 466 patients (71% men) at the time of cirrhosis diagnosis. At inclusion, the median age was 53 years (range: 27-84), and there was no gender or age difference between patients with or without complications. Nearly all patients (96%) were seen in the specialized department of hepatology. During a total observation time of 1,611 years 299 patients died (Table 1).

What is the prevalence of complications when alcoholic cirrhosis is diagnosed?

Of the 466 patients included, 114 (24%) presented without complications, 254 (55%) with ascites alone, 29 (6%) with variceal bleeding alone, 20 (4%) with ascites and variceal bleeding, and 49 (11%) with hepatic encephalopathy alone or in combination with other complications (Table 1).

What are the risks of complications and death after diagnosis?

Figure 1 illustrates the association between complications and mortality, and Table 2 adds information about the risk of having developed more complications during a 1- or 5-year period. Figure 2 presents the risk of each of the clinical events that might come next; for example, patients with newly developed ascites have, during the first year, a 12% risk of developing variceal bleeding as the next complication plus a 15% risk of developing hepatic encephalopathy as the next complication. Thus, they have a total 27% risk of developing another complication within 1 year, but Figure 2 also shows that there is an additional 15% risk that they will die before doing so. It follows that they have a 100 - $(27 + 15) \approx 59\%$ chance of being alive and still only with ascites after 1 year (cf. Table 2).

No complications

The median survival time for our 114 patients without complications was 48 months from cirrhosis diagnosis (Figure 1). After 1 year, 22% had developed complications (Figure 2) – 15% were still alive, and 7% had died after developing complications (Table 2) – 10% had died without complications, and 68% were alive and still without complications (Table 2). After 5 years, 49%

had developed complications (Figure 2) -13% were still alive, and 35% had died after developing complications (Table 2) -22% had died without complications, and 28% were alive and still without complications (Table 2).

Ascites

While 254 patients were included with ascites as the only complication, an additional 33 entered this category after inclusion (Table 1). The median survival time for these 287 patients was 37 months from onset of ascites (Figure 1). During the first month they had a higher mortality than patients without complications (10% vs. 4%, Figure 1), but their outcome after 5 years was nearly identical (Table 2 and Figure 1). After 1 year, 26% of them had developed more complications (Figure 2) – 12% were still alive, and 14% had died after developing complications (Table 2) – while 15% had died without developing more complications, and 59% were alive and had not developed more complications. After 5 years, 42% had developed more complications (Figure 2) – 9% were still alive, and 33% had died after developing more complications (Table 2) – 25% had died without developing more complications, and 32% were alive and had not developed more complications (Table 2).

Variceal bleeding

At inclusion, 29 patients presented with bleeding varices alone and 16 additional patients entered this category after inclusion (Table 1). These 45 patients had a median survival time of 48 months from onset of variceal bleeding (Figure 1). During the first month they had a higher mortality than patients without complications (10% vs. 4%, Figure 1), but their outcome after 1 year was comparable (Table 2 and Figure 1). Thus, after 1 year, 24% of patients presenting with variceal bleeding had developed more complications (Figure 2) – 16% were still alive, and 9% had died after developing more complications (Table 2) – 11% had died without developing more complications, and 64% were alive and had not developed more complications. After 5 years, 54%

had developed more complications (Figure 2) – 8% were still alive, and 45% had died after developing more complications (Table 2) – 18% had died without developing more complications, and 27% were alive and had not developed more complications (Table 2).

Both ascites and variceal bleeding

While 20 patients had both ascites and variceal bleeding at inclusion, an additional 74 entered this category after inclusion (Table 1). These 94 patients had a median survival time of 13 months from onset of the last of the two complications (Figure 1). After 1 year, 22% of them had developed hepatic encephalopathy (Figure 2) – 4% were still alive, and 18% had died after developing hepatic encephalopathy (Table 2) – 31% had died without developing hepatic encephalopathy, and 47% percent were alive and had not developed hepatic encephalopathy. After 5 years, 39% had developed hepatic encephalopathy (Figure 2) – 4% were still alive, and 36% had died after developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2) – 44% had died without developing hepatic encephalopathy (Table 2).

Hepatic encephalopathy

At inclusion 49 patients had hepatic encephalopathy, and 9 patients without complications, 66 patients with ascites alone, 10 patients with variceal bleeding alone, and 35 patients with both ascites and variceal bleeding developed hepatic encephalopathy after inclusion (Table 1). All these 169 patients had a similar mortality from the onset of hepatic encephalopathy and were therefore considered as one group. Their median survival time was 2.4 months, and 45% (95% CI 39-51) died within 1 month (Figure 1). After 1 year 64% were dead, and after 5 years 85% (Table 2).

In which sequence do the complications develop?

Patients without complications were likely to develop ascites first (Figure 1), but the development of complications did not follow a specific sequence. Thus, any complication could be the first to

develop, and even after the first complication developed, the two other complications had nearly equal probability of coming next (Figure 1).

What is the prevalence of complications after diagnosis?

At inclusion, 352 (76%) of the 466 patients had one or more complications. On the basis of mortality and risk estimates for our cohort, 292 patients would be alive after 1 year including 206 who had complications at diagnosis and 17 patients who had developed complications during the first year. Hence the prevalence of complications would be $206 + 17 / 292 \approx 77\%$. After 5 years, 148 patients would remain alive, and the prevalence of complications would have increased to 105 $+ 15 / 148 \approx 81\%$.

DISCUSSION

We found that 24% of our alcoholic cirrhosis patients had no complications at the time of cirrhosis diagnosis, 55% had ascites alone, 6% had variceal bleeding alone, 4% had both ascites and variceal bleeding, and 11% had hepatic encephalopathy alone or in combination. All patients had an approximate 25% risk of developing more complications within 1 year, but 1-year mortality depended strongly on the presence of complications: hepatic encephalopathy (1-year mortality = 64%) > ascites and variceal bleeding (49%) > ascites alone (29%) > variceal bleeding alone (20% [1-month mortality = 10%]) > no complications (17% [1-month mortality = 4%]). The 5-year risk of developing more complications: hepatic encephalopathy or the combination of ascites and variceal bleeding had a 5-year mortality of 80-85% compared with roughly 60% for other patients. Most patients developed ascites first, but complications did not develop in a specific sequence. Only 32% of patients survived 5 years from cirrhosis diagnosis, and the prevalence of complications increased slightly, from 76% at cirrhosis diagnosis to 81% five years later.

Our study has limitations. Although we had complete follow-up, our findings could be biased if the patients we included did in fact not have cirrhosis, or they did in fact not have the complications we thought they had. The lack of standardized diagnostic criteria is therefore a limitation, but cirrhosis diagnoses based on clinical observations alone have a high positive predictive value among alcohol abusers (23). Therefore all patients probably had cirrhosis, and it is also plausible that all first-time episodes of ascites, variceal bleeding, and hepatic encephalopathy were recorded in the medical records since nearly all patients were seen in a specialized department of hepatology.

The prevalence of ascites, but not of variceal bleeding or hepatic encephalopathy, was higher in our study than in most previous studies, in which ascites had a prevalence of 30-40% at diagnosis of alcoholic cirrhosis (3, 10, 11, 14). However, a Norwegian study based on 100 patients seen in one medical department in 1984-1988 reported a 67% prevalence of ascites and a 34% prevalence of variceal bleeding, but no explanation for these high prevalences was offered (13).

Previous studies, the largest including 122 patients with alcoholic cirrhosis and 171 patients with non-alcoholic cirrhosis (6), have reported that cirrhosis patients have a 7-10% per year risk of developing ascites, variceal bleeding, or hepatic encephalopathy (6-9). We found a 2-3 fold higher 1-year risk (22%), but our 5-year risk (49%) did not exceed 10% per year. Two likely explanations are that many of our patients died before complications developed, and that previous risk estimates were biased upwards because they were based on statistical methods to compute the risk of a single outcome of cirrhosis, i.e. death, though in fact two or more outcomes of cirrhosis were possible in the analysis, i.e. death or development of complications (6-9, 24). Thus it remains likely that the risk of complications is higher for patients with alcoholic cirrhosis than for other cirrhosis patients.

The proportion of our patients who died without ever developing complications was twice as high as in studies of patients with non-alcoholic cirrhosis (4), and in fact the mortality of our patients without complications was higher than in the two previous studies of alcoholic cirrhosis patients, although these studies followed patients diagnosed between 1951 and 1976 (3, 10, 11, 14). The reasons are unclear, and we do not know why our patients were hospitalized. Among patients with complications, by contrast, mortality was lower in our study than in previous studies (3, 10, 11, 14, 25). This indicates that the negative prognostic impact of complications has decreased during recent decades, and such a decrease has been found for patients with variceal bleeding (26), but not for patients with ascites or hepatic encephalopathy.

The higher mortality after development of complications is consistent with the existing literature (4) and therefore unlikely to be a result of uncontrolled confounding in our study. The development of complications marked the beginning of a brief period of highly increased mortality, a fact that emphasizes that clinicians should monitor patients closely after they develop complications. Our finding that ascites usually developed before variceal bleeding and hepatic encephalopathy is also consistent with the existing literature (4, 6).

The slightly increasing prevalence of complications after cirrhosis diagnosis might indicate that the burden of cirrhosis complications on the hospital system increases over time, and that is consistent with our finding that the number of hospitalizations per Danish alcoholic cirrhosis patient per year increased during 1996-2005 (1).

Although hemodynamic, biochemical, and clinical signs of complicated cirrhosis are imperfectly correlated (27, 28), the presence or absence of three clinical complications was enough to divide our patients in categories with different clinical courses over 5 years. Our findings could therefore be used to define clinical stages of cirrhosis, like those proposed by the 2005 Baveno International Consensus Workshop on the basis of data from the 1970-80s (4). We chose not to adopt the Baveno staging system because it overestimates the prognostic importance of variceal bleeding (29), does

not consider hepatic encephalopathy, and uses non-bleeding varices to distinguish stage 2 from stage 1, meaning that some patients are in an unknown clinical stage until an upper endoscopy has been made (4).

Our risk estimates may generalize to alcoholic cirrhosis patients in other settings because they were based on a population-based patient sample under contemporary care and with complete follow-up. Arguably, data on prognostic factors such as alcohol use during follow-up, comorbid diseases (30), and treatment received would have made it easier for clinicians to judge the generalizability of our estimates (31), but such data were not available to us. Nonetheless, our findings should assist clinicians in making treatment decisions, e.g. it appears to always be relevant to consider whether a patient who has had both ascites and variceal bleeding should be transplant-listed. Our findings are also highly relevant as patient information, and they may be helpful to researchers who design experimental studies because they provide the information required to determine an appropriate study size (32, 33).

In conclusion, we have examined the clinical course of alcoholic cirrhosis. Our findings demonstrated that patients with alcoholic cirrhosis have a high prevalence of complications and a high mortality.

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Appendix 1

We retrieved the medical records of all patients with a liver biopsy showing cirrhosis, defined as a SNOMED (Systematized Nomenclature of Medicine) code of M495xx or M496xx, or with one or more of the diagnoses listed below from a hospital in the catchment area that includes the city of Aarhus between 1 January 1993 and 31 August 2005. Diagnoses codes were coded with reference to the 8th edition of the International Classification of Diseases (ICD8) through 1993, and with reference to the 10th edition (ICD10) thereafter.

	ICD8	ICD10
Alcoholic cirrhosis or fibrosis	571.09	K70.2, K70.3, K70.4
Primary or secondary biliary cirrhosis	571.90, 571.91	K74.3, K74.4, K74.5
Chronic hepatitis	571.93	B18.x, K73.x
Unspecified cirrhosis	571.92, 571.99	K74.6
Primary sclerosing cholangitis	575.04	K83.0
Toxic hepatitis	-	K71.7
Alcoholic hepatitis	570.0x	K70.1
Chronic liver insufficiency	-	K72.1
Gastroesophageal varices	456.0x	I85.x, I86.4, I98.2
Hepatorenal syndrome	-	K76.7
Hepatocellular carcinoma	155.09	C22.0
Peritonitis	567.xx	K65.x
Ascites	785.39	R18.9
Icterus	785.29	R17.9
Alcohol dependency	303.19, 303.20, 303.28, 303.29, 303.91	F10.2, F10.7, F10.8, F10.9
Alcohol poisoning	980.xx	T51.x

Table 1Observed development of cirrhosis complications among 466 alcoholic cirrhosis patients. Each row represents a category
of cirrhosis complications, and the cells contain the number of patients who developed a specific cirrhosis complication
and thus moved from one category to another.

				At inclusion				То				Censored alive	Dead	Total	Total observation time
	Ascites				+	-	-	+	+	-	+				
		Bleeding			-	+	-	+	-	+	+				
			Hep. enc.		-	-	+	-	+	+	+				
	-	-	-	114	33	16	9	•	•	•	•	32	24	114	308 years
	+	-	-	254	•	•	•	62	66	•	•	81	78	287	761 years
	-	+	-	29	•	•	•	12	•	10	•	15	8	45	112 years
m	-	-	+	19	•	•	•	•	8	2	•	3	15	28	44 years
Fro	+	+	-	20	•		•	•	•	•	35	19	40	94	171 years
	+	-	+	23	•		•	•	•		11	11	75	97	128 years
	-	+	+	2	•		•	•	•		2	2	10	14	21 years
	+	+	+	5			•			•		4	49	53	66 years
			Total	466									299		1611 years

Table 2Outcome of alcoholic cirrhosis 1 year (top) and 5 years (bottom) after onset of complications (for patients without complications: 1
and 5 years after cirrhosis diagnosis). Cells contain the risk of a particular outcome followed by a 95% confidence interval in
parentheses.

1-year outcome	No complications	Ascites Variceal bleeding		Ascites + variceal bleeding	Hepatic encephalopathy alone or in combination
Alive	83% (78-89)	71% (67-75)	80% (71-89)	51% (43-59)	36% (31-42)
Alive without more complications	68% (62-75)	59% (55-64)	64% (54-76)	47% (39-54)	-
Alive with more complications	15% (10-20)	12% (9-15)	16% (7-23)	4% (2-7)	-
Ascites alone	5% (2-8)	-	-	-	-
Variceal bleeding alone	4% (1-7)	-	-	-	-
Ascites + variceal bleeding	4% (1-6)	7% (4-9)	11% (3-18)	-	-
Hepatic encephalopathy	2% (0-3)	5% (3-7)	4% (0-8)	4% (2-7)	-
Dead	17% (11-22)	29% (25-33)	20% (11-29)	49% (41-57)	64% (58-69)
Dead without more complications	10% (5-14)	15% (12-18)	11% (4-18)	31% (24-38)	-
Dead after developing more complications	7% (4-11)	14% (11-17)	9% (3-15)	18% (12-24)	-
Total	100% (N=114)	100% (N=287)	100% (N=45)	100% (N=94)	100% (N=169)

5-year outcome	No complications Ascites		Variceal bleeding	Ascites + variceal bleeding	Hepatic encephalopathy alone or in combination
Alive	42% (34-50)	41% (36-46)	35% (23-48)	20% (13-27)	15% (10-19)
Alive without more complications	28% (21-35)	32% (28-37)	27% (15-39)	17% (10-23)	-
Alive with more complications	13% (8-19)	9% (5-11)	8% (0-16)	4% (0-6)	-
Ascites alone	8% (3-12)	-	-	-	-
Variceal bleeding alone	5% (0-8)	-	-	-	-
Ascites + variceal bleeding	1% (0-3)	4% (2-6)	0	-	-
Hepatic encephalopathy	0	4% (2-6)	8% (0-16)	4% (0-6)	-
Dead	58% (50-66)	59% (54-64)	64% (52-77)	80% (73-87)	85% (81-90)
Dead without more complications	22% (17-29)	25% (21-29)	18% (9-26)	44% (35-51)	-
Dead after developing more complications	35% (28-43)	33% (29-38)	45% (32-59)	36% (29-45)	-
Total	100% (N=114)	100% (N=287)	100% (N=45)	100% (N=94)	100% (N=169)

Figure 1 Mortality with respect to time after onset of complications (for patients without complications: time after cirrhosis diagnosis).



Years after onset of complications

Figure 2 Risk of the development of more cirrhosis complications and mortality with the current complications. Risk estimates are followed by a 95% confidence interval in parentheses.



5-year risk: 7% (3-13)

Comorbidity and Survival of Danish Cirrhosis Patients: A Nationwide Population-Based Cohort Study

Peter Jepsen,¹ Hendrik Vilstrup,² Per Kragh Andersen,³ Timothy L. Lash,^{1,4} and Henrik Toft Sørensen^{1,2}

Patients with liver cirrhosis have a high mortality, not just from cirrhosis-related causes, but also from other causes. This observation indicates that many patients with cirrhosis have other chronic diseases, yet the prognostic impact of comorbidities has not been examined. Using data from a nationwide Danish population-based hospital registry, we identified patients who were diagnosed with cirrhosis between 1995 and 2006 and computed their burden of comorbidity using the Charlson comorbidity index. We compared survival between comorbidity groups, adjusting for alcoholism, sex, age, and calendar period. We also examined the risks of cirrhosis-related and non-cirrhosis-related death using data from death certificates and identified a matched comparison cohort without cirrhosis from the Danish population. We included 14,976 cirrhosis patients, 38% of whom had one or more comorbidities. The overall 1-year survival probability was 65.5%; the 10-year survival probability was 21.5%. Compared with patients with a Charlson comorbidity index of 0, the mortality rate was increased 1.17-fold in patients with an index of 1 [95% confidence interval (CI), 1.11-1.23], 1.51-fold in patients with an index of 2 (95% CI, 1.42-1.62), and two-fold in patients with an index of 3 or higher (95% CI, 1.85-2.15). In the first year of follow-up, but not later, comorbidity increased the risk of cirrhosis-related death, and this was consistent with an apparent synergy between the cirrhosis and comorbidity effects on mortality in the same period. Conclusion: Our findings demonstrate that comorbidity is an important prognostic factor for patients with cirrhosis. Successful treatment of comorbid diseases in the first year after diagnosis may substantially reduce the mortality rate. (HEPATOLOGY 2008;48:214-220.)

iver cirrhosis is a life-threatening chronic disorder with an incidence rate of more than 190/ 1,000,000 per year in Denmark.¹ Most patients with cirrhosis are in their fifties or older at the time of diagnosis,¹ so many may have other diseases that are unrelated to cirrhosis, i.e., comorbidities² and hence an increased mortality from several chronic diseases.³ Furthermore, cirrhosis shares risk factors with other

Potential conflict of interest: Nothing to report.

chronic diseases, such as alcoholism, smoking, malnutrition, and obesity.4-6 For example, alcoholism, the most prevalent cirrhosis risk factor in Denmark,⁷ is also a risk factor for cancer and stroke.⁸⁻¹⁰ Improvements in prophylaxis and treatment of cirrhosis complications have decreased the risk of dying from cirrhosis,11 but this reduction inevitably increases the risk of dying from other causes. Nonetheless, the prognostic importance of comorbidity in cirrhosis patients is largely unknown.^{12,13} Accurate data on prognosis and prognostic factors are important for clinical decision making and patient counseling, for understanding the clinical course of cirrhosis, for the design and analysis of epidemiologic studies of patients with cirrhosis, and for health care policy making.14,15 We examined the prognostic impact of comorbidity in a large nationwide population-based study of cirrhosis patients followed for as many as 12 years.

Patients and Methods

Data were prospectively collected from a Danish nationwide population-based hospital registry.¹⁶ Denmark

Abbreviation: CCI, Charlson comorbidity index; CI, confidence interval; ICD, International Classification of Diseases.

From the Departments of ¹Clinical Epidemiology and ²Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, Aarhus, Denmark; ³Department of Biostatistics, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark; and ⁴Department of Epidemiology, Boston University School of Public Health, Boston, MA.

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Address reprint requests to: Peter Jepsen, Department of Clinical Epidemiology, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark. E-mail: pj@dce.au.dk; fax: (45)-89-42-48-01.

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has 5.3 million inhabitants, and the National Health Service provides free tax-supported health care for all.

Data Sources

The National Patient Registry contains data from hospital contacts. It was established in 1977, and data from all inpatient admissions to a nonpsychiatric hospital in Denmark have been recorded since then.¹⁷ Data from outpatient visits have been recorded since 1995. Each record includes the dates of admission and discharge (outpatients: first and last visit) and up to 20 diagnoses, one of which is designated as the primary diagnosis. All diagnoses were coded according to International Classification of Diseases (ICD) 8 until 1993 and ICD10 from 1994 onward. Diagnosis codes are recorded at discharge by the physician who discharges the patient.

The Cause of Death Registry was established in 1943. Whenever a Danish citizen dies, the attending physician must report the cause of death, and a chain of events leading to death can be described by specifying up to four diagnoses. In the Cause of Death Registry, causes of death are translated into ICD10 diagnoses. Registration is currently complete through 2001.

Denmark's Civil Registration System updates the vital status of all Danish citizens on a daily basis, including date of death or emigration. Individual-level data from the National Patient Registry, the Cause of Death Registry, and the Civil Registration System can be linked through the unique personal identification number,¹⁶ which embeds information on birth date and sex.

Information on Patients with Cirrhosis

We included all patients who received their first hospital diagnosis, whether primary or secondary, of alcoholic or unspecified cirrhosis (ICD8: 571.09, 571.92, 571.99; ICD10: K70.3, K74.6) during an inpatient admission or an outpatient visit between January 1, 1995, and August 31, 2006.

Comorbidity. We used the cirrhosis patients' primary and secondary diagnoses from all inpatient hospitalizations in the 10 years preceding their first diagnosis to identify comorbidities. The severity of comorbidity was based on the widely used Charlson comorbidity index (CCI), which was originally developed to predict 1-year mortality in hospitalized medical patients.¹⁸ This scoring system assigns between 1 and 6 points to a range of diseases (1 point for myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes without organ damage; 2 points for diabetes with organ damage, hemiplegia, severe renal disease, and nonmetastatic cancer; 3 points for severe liver disease; 6 points for metastatic cancer and human immunodeficiency virus infection), and the sum of points serves as a measure of the burden of comorbidity. We defined the comorbid diseases according to the ICD10 codes provided by Quan et al.¹⁹ and to the ICD8 codes that matched the ICD10 codes as closely as possible. All patients had liver disease, so mild liver disease and severe liver disease were not counted as comorbidities. Hepatocellular carcinoma, on the other hand, was counted as a comorbid cancer.

Alcoholism is a risk factor for several of the diseases in the CCI, and it is also a prognostic factor among cirrhosis patients.^{20,21} Therefore, we identified those patients who had been given a diagnosis suggesting chronic alcohol abuse (ICD8: 291.xx, 303.xx except 303.90, 571.09, 571.10; ICD10: F10.x except F10.0 and F10.1, G31.2, K70.x) after an inpatient hospitalization in the decade preceding their cirrhosis diagnosis.

Cause of Death. Based on data from the Cause of Death Registry, deaths were classified as cirrhosis-related or non-cirrhosis-related. Cirrhosis-related deaths were those with at least one of the following listed as the cause of death or as part of the events leading to death: cirrhosis (K70.3, K74.6), liver failure (K70.4, K72.x), portal hypertension (K76.6), hepatorenal syndrome (K76.7), or esophageal or gastric varices (I85.x, I86.x). All other deaths were classified as non-cirrhosis-related.

Statistical Analysis

All-Cause Mortality. Cirrhosis patients were followed from when they were first discharged from hospital with a diagnosis of cirrhosis until death or censorship at emigration or on December 31, 2006. The outcome was time to death.

We classified patients according to CCI (0, 1, 2, or \geq 3), and computed the survival probability for each comorbidity group using the Kaplan-Meier estimator. This estimator does not control for confounding, however, so we also computed direct adjusted survival curves to control for sex, age at diagnosis, calendar period of diagnosis (1995–1998, 1999– 2002, or 2003–2006), and alcoholism.^{22,23}

We used Cox proportional hazards regression to estimate the association between comorbidity group and mortality rate (specifically, the hazard rate), adjusting for sex, age at diagnosis, calendar period of diagnosis, and alcoholism. Our preliminary analyses indicated that the hazard rates for men and women were nonproportional, as were the rates for alcohol abusers and individuals who did not abuse alcohol. However, a regression model stratified by sex and alcoholism and with adjustment for age and calendar period yielded almost exactly the same association between CCI and mortality rate as did a regression model with adjustment for all four variables. Therefore, we used the model without stratification. Furthermore, we found that substituting current age, as a time-dependent variable, for age at diagnosis did not affect the results of the regression model. CCI and calendar period were included in the regression model using indicator variables. Age was included in the regression model as a continuous variable, and we used the procedure described by Royston et al. to examine whether a first- or second-degree fractional polynomial transformation of age would yield a better-fitting regression model and thus reduce residual confounding.²⁴ In a supplementary analysis, we substituted the individual comorbidities for the comorbidity groups in the final regression model.

We examined whether the association between comorbidity group and mortality rate was constant over calendar time and patient characteristics. This examination was done by repeating the regression model for patients included in each of the three calendar periods of diagnosis separately, for men and women separately, and for alcohol abusers and those who did not abuse alcohol separately.

Cirrhosis-Related and Non–Cirrhosis-Related Mor-tality. In this analysis cirrhosis patients were censored on December 31, 2001, because cause of death registration was incomplete after 2001, and deaths were classified as cirrhosis-related or from other causes. We computed the cumulative incidence of cirrhosis-related death and death from other causes, taking into account that these were competing risks.²⁵

We used competing risks regression to estimate the associations between comorbidity group and cumulative incidence of cirrhosis-related death and of not cirrhosis-related death.²⁶ Our preliminary analyses indicated that the associations were stronger shortly after cirrhosis diagnosis than later, so we computed separate estimates of association (specifically, subdistribution hazard ratios) for the first year after cirrhosis diagnosis and for the remainder of follow-up. The estimates were controlled for gender, age, calendar period, and alcoholism, coded and included as they were in the analysis of all-cause mortality.

Synergy Between Cirrhosis and Comorbidity Effects. We identified a comparison cohort without cirrhosis through the Danish Civil Registration System. This cohort consisted of 10 Danish citizens per cirrhosis patient, matched for sex and birth year but otherwise random, who were alive and without cirrhosis when their matching cirrhosis patient was included. Like the cirrhosis patients, these persons were classified using the CCI with liver diseases ignored and followed until death or censorship at emigration or on December 31, 2006. However, they were also censored in the event of a cirrhosis diagnosis during follow-up. Using both cohorts, we estimated the synergy between the prognostic effects of cirrhosis and comorbidity. The synergy was computed as the interaction risk,²⁷ with a bootstrap 95% confidence interval (CI),²⁸ on 1-year cumulative mortality and on 5-year cumulative mortality among 1-year survivors. Cumulative mortality was based on the Kaplan-Meier estimator.

Results

We included 14,976 cirrhosis patients in the study, 9391 (63%) of whom died during follow-up. The median age at inclusion was 56 years, and 66% were men. Sixtytwo percent had a CCI of 0, 21% had an index of 1, 10% had an index of 2, and 7% had an index of 3 or higher (Table 1). Older patients had more comorbidities than younger patients, men had more comorbidities than women, and patients diagnosed late in the study period had more comorbidities than patients diagnosed early in the study period (Table 1). The most common comorbidities were ulcer disease [n = 1869 (12%)], diabetes [n = 1524 (10%)], and cancer [n = 1016 (7%)]. Approximately half of the patients with a CCI of 3 or higher had cancer (Table 1).

All-Cause Mortality. The overall survival probability was 65.5% after 1 year (95% CI, 64.7%-66.2%), 37.5% after 5 years (95% CI, 36.7%-38.4%), and 21.5% after 10 years (95% CI, 20.5%-22.5%). Survival depended markedly on CCI, although the differences in survival were attenuated by adjusting for sex, age at diagnosis cubed, calendar period, and alcoholism (Fig. 1). Compared with patients with a CCI of 0, the adjusted mortality rate was increased 1.17-fold for patients with an index of 1 (95% CI, 1.11-1.23), 1.51-fold for patients with an index of 2 (95% CI, 1.42-1.62), and two-fold for patients with an index of 3 or higher (95% CI, 1.85-2.15) (Table 2). Male sex increased the mortality rate 1.23-fold (95% CI, 1.18-1.29) and alcoholism 1.36-fold (95% CI, 1.29-1.42), whereas calendar period had no effect. The mortality rate increased with age, but the fractional polynomial analysis indicated that age cubed yielded a betterfitting regression model. This better fit implied that a 10-year age difference was more important for the risk of death among elderly patients than among younger patients. The association between comorbidity and mortality was constant over calendar time and patient characteristics (Table 2). The analysis of individual comorbidities showed that most comorbidities in the CCI were associated with mortality, and that the 2-point comorbidities were more strongly associated with mortality than the 1-point comorbidities, but not as strongly as the 6-point comorbidities (Supplementary Table 1).

	CCI :	= 0	CCI =	= 1	CCI =	= 2	CCI =	: 3+	Total	
Characteristics	n	%	n	%	n	%	n	%	n	%
Age at cirrhosis diagnosis										
0-49	3,209	35	707	22	213	14	90	9	4,219	28
50-59	3,283	35	1,052	33	467	31	232	23	5,034	34
60-69	1,888	20	898	28	472	31	351	34	3,609	24
70-79	706	8	427	13	265	18	270	26	1,668	11
80+	168	2	113	4	85	6	80	8	446	3
Sex										
Women	3,196	35	1,040	33	498	33	291	28	5,025	34
Men	6,058	65	2,157	67	1,004	67	732	72	9,951	66
Year of cirrhosis diagnosis										
1995-1998	3,131	34	974	30	464	31	271	26	4,840	32
1999-2002	3,121	34	1,101	34	499	33	341	33	5,062	34
2003-2006	3,002	32	1,122	35	539	36	411	40	5,074	34
Comorbidity not in CCI*										
Alcoholism	6,353	69	2,310	72	993	66	637	62	10,293	69
Comorbidities in CCI*										
Ulcer disease	0	0	1,145	36	360	24	364	36	1,869	12
Diabetes	0	0	651	20	422	28	451	44	1,524	10
Diabetes without organ damage	0	0	651	20	298	20	260	25	1,209	8
Diabetes with organ damage	0	0	0	0	124	8	191	19	315	2
Cancer	0	0	0	0	518	34	498	49	1,016	7
Nonmetastatic cancer	0	0	0	0	458	30	327	32	785	5
Metastatic cancer	0	0	0	0	0	0	108	11	108	1
Chronic pulmonary disease	0	0	440	14	237	16	258	25	935	6
Congestive heart failure	0	0	276	9	222	15	309	30	807	5
Cerebrovascular disease	0	0	345	11	172	11	241	24	758	5
Myocardial infarction	0	0	120	4	101	7	168	16	389	3
Peripheral arterial disease	0	0	106	3	77	5	158	15	341	2
Severe renal disease	0	0	0	0	75	5	142	14	217	1
Dementia	0	0	58	2	55	4	52	5	165	1
Connective tissue disease	0	0	56	2	32	2	31	3	119	1
Hemiplegia	0	0	0	0	8	1	20	2	28	0.2
HIV infection	0	0	0	0	0	0	20	2	20	0.1
Total	9,254	100	3,197	100	1,502	100	1,023	100	14,976	100

Table 1. Characteristics of 14,976 Cirrhosis Patients

Patients are categorized by the Charlson comorbidity index (CCI) at the time of cirrhosis diagnosis. HIV indicates human immunodeficiency virus. *Only the number and percentage of patients with the comorbidity are shown.

Cirrhosis-Related and Non–Cirrhosis-Related Mortality. We included 8599 cirrhosis patients diagnosed before December 31, 2001, 4298 (50%) of whom died during follow-up. Seventy-three percent of the deaths were cirrhosis-related, and the cumulative incidence of cirrhosis-related death exceeded the cumulative incidence of death from other causes in all comorbidity groups at all times. As would be expected, the risk of death from causes other than cirrhosis increased with the comorbidity level, but so did the risk of death from cirrhosis, albeit less clearly and only shortly after diagnosis (Fig. 2). After adjustment for confounders, the cumulative incidence of cirrhosis-related death increased with the comorbidity level during the first year of follow-up [subdistribution hazard ratio for CCI of 1, 1.04 (95% CI, 0.93-1.16); for index of 2, 1.20 (95% CI, 1.05-1.38); for index of 3 or higher, 1.37 (95% CI, 1.17-1.62)], but not later. The cumulative incidence of death from other causes increased with the comorbidity level throughout the follow-up period, although more so during the first year after cirrhosis diagnosis.

Synergy Between Cirrhosis and Comorbidity Effects. Of the 149,760 members of the matched cohort without cirrhosis, 87% had a CCI of 0, 7% had an index of 1, 4% had an index of 2, and 2% had an index of 3 or higher. In the first year after cirrhosis diagnosis, but not later, the prognostic effects of cirrhosis and comorbidity were synergistic (that is, the joint effects of cirrhosis and comorbidity exceeded the sum of their individual effects on mortality); 14% (95% CI, 10.4%-17.4%) of cirrhosis patients with a CCI of 3 or higher died from this synergy (Table 3).

Discussion

In this nationwide population-based study, we followed nearly 15,000 cirrhosis patients from diagnosis and found



Fig. 1. Survival by CCI for the 14,976 included cirrhosis patients. Survival probabilities are shown as Kaplan-Meier survival curves (gray), which are not adjusted for confounding, and direct adjusted survival curves (black), which are adjusted for confounding by sex, age cubed, calendar period, and alcohol abuse.

that the burden of comorbidity at the time of cirrhosis diagnosis was strongly associated with mortality. This association was due in part to a higher risk of cirrhosis-related death for patients with comorbidities in the first year after cirrhosis diagnosis, a finding corroborated by the synergy between the effects of cirrhosis and comorbidity. These findings suggest that treatment of comorbidities should be considered an integral part of clinical care for newly diagnosed cirrhosis patients. Successful treatment of comorbidity would reduce the mortality attributable to comorbidity itself, and also the mortality attributable to the synergy between comorbidity and cirrhosis. The biological mechanisms of the cirrhosis-comorbidity synergy are unknown. We speculate that some comorbidities, such as congestive heart failure and renal disease, may reduce the body's ability to compensate for the circulatory consequences of a cirrhotic liver, and others may contraindicate treatments: chronic pulmonary disease may contraindicate β -blockers, heart failure may contraindicate insertion of a transjugular intrahepatic portosystemic shunt, and any severe comorbidity may contraindicate liver transplantation.¹³

The major strengths of our study were its size, its complete and long-term follow-up, and its 10 years of hospital-diagnosed comorbidities for each cirrhosis patient. The validity of the recorded diagnoses, including cirrhosis, is crucial for our findings. It appears that 15% of those we included may not have fulfilled diagnostic criteria for cirrhosis,²⁹ but regardless of what is assumed about these patients' prognosis and comorbidity level, they could not have produced the dose-response relationship between comorbidity level and prognosis that we found if no such relationship existed.

We only included patients with a hospital diagnosis of alcoholic cirrhosis or unspecified cirrhosis. We did so because the ICD8 and ICD10 do not have separate codes for the histological stages of other chronic liver diseases, such as primary biliary cirrhosis and chronic viral hepatitis, of which cirrhosis is the end stage. For example, had we included patients at their first hospital diagnosis of primary biliary cirrhosis, we would have included many patients without cirrhosis. As it is, we fail to include some patients with nonalcoholic cirrhosis. However, alcoholism is the most common cause of cirrhosis in Denmark,⁷ and we showed that the association between comorbidity and mortality was essentially the same for cirrhosis patients with and without alcoholism; therefore, the association may be independent of the cause of cirrhosis.

			CCI = 0		CCI = 1		CCI = 2	CCI = 3+	
	n	MRR	95% CI	MRR	95% CI	MRR	95% CI	MRR	95% CI
Year of diagnosis									
1995-1998	4,840	1.0	_	1.15	(1.06-1.25)	1.45	(1.31-1.62)	1.93	(1.69-2.21)
1999-2002	5,062	1.0	_	1.14	(1.05 - 1.24)	1.57	(1.41-1.75)	2.07	(1.83-2.34)
2003-2006	5,074	1.0	_	1.26	(1.14-1.39)	1.53	(1.35 - 1.74)	1.99	(1.74-2.28)
Sex									
Women	5,025	1.0	_	1.20	(1.09-1.31)	1.49	(1.32-1.68)	2.05	(1.78-2.36)
Men	9,951	1.0	_	1.16	(1.09-1.23)	1.52	(1.41 - 1.65)	1.98	(1.81-2.17)
Alcoholism									
No	4,683	1.0	_	1.20	(1.09-1.33)	1.58	(1.41 - 1.77)	2.31	(2.04-2.62)
Yes	10,293	1.0	_	1.16	(1.09-1.23)	1.49	(1.38-1.62)	1.86	(1.69-2.05)
Total	14,976	1.0	-	1.17	(1.11-1.23)	1.51	(1.42-1.62)	2.00	(1.85-2.15)

Table 2. Association Between CCI and Mortality Rate Within Patient Groups

The strength of association is expressed as the MRR with the associated 95% CI obtained from a Cox regression model adjusted for sex, age cubed, calendar period, and alcohol abuse. MRR indicates mortality rate ratio.



Fig. 2. Cumulative incidence of death from cirrhosis and from other causes by CCI for the 8599 cirrhosis patients diagnosed before December 31, 2001.

The validity is not known for all the comorbidity diagnoses. Myocardial infarction, cancer, and diabetes have a very high validity,³⁰ but even if a patient has several wrong or missing diagnoses, we may have classified him or her correctly with respect to the CCI categories that we used. Even if we misclassified some patients, the doseresponse relationship between comorbidity level and prognosis indicates that few patients were misclassified.

We had no information on lifestyle factors other than alcohol abuse (for example, malnutrition and smoking), but they probably contributed to the higher comorbidity prevalence in cirrhosis patients than in the general population. They are also prognostic factors among cirrhosis patients^{4,5} and could therefore have confounded our findings if they were more prevalent among patients with comorbidities. However, it is unlikely that malnutrition would completely explain our findings, because it should not be considered a confounder if it is caused by a comorbidity (for example, cancer).³¹

It was a limitation of our study that we did not have information on the cirrhosis stage at the time of diagnosis, but both the risk of cirrhosis-related and non-cirrhosis-related death increased with the comorbidity level. This pattern implies that many patients with severe comorbidity did not die from cirrhosis-related causes, so it is unlikely that they were in a more advanced cirrhosis stage at diagnosis than patients with less comorbidity. Also, patients who present at the hospital regularly for something other than cirrhosis may have a greater chance of having cirrhosis diagnosed in an early stage.

We hope that our findings contribute to both an understanding of the clinical course of cirrhosis and to clinical decision making.^{14,15} The former goal might be achieved by studying the mechanisms of the cirrhosis-comorbidity synergy, the latter by

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	No Cirrhosis, No Comorbidity	Cirrhosis, No Comorbidity	Comorbidity Definition	No Cirrhosis, Comorbidity	Cirrhosis, Comorbidity	Interaction Risk* (95% Cl)		
1-Year follow-up	0.7%	29.0%	CCI = 1	3.9%	37.0%	4.9% (2.9% to 6.7%)		
	0.7%	29.0%	CCI = 2	7.8%	47.1%	11.0% (8.2% to 13.7%)		
	0.7%	29.0%	CCI = 3 +	18.8%	61.0%	14.0% (10.4% to 17.4%)		
5-Year follow-up†	4.7%	39.1%	CCI = 1	18.2%	46.4%	-6.2% (-9.3% to -3.2%)		
	4.7%	39.1%	CCI = 2	25.4%	56.4%	-3.5% (-8.3% to 1.0%)		
	4.7%	39.1%	CCI = 3 +	41.9%	69.3%	-7.0% ($-13.5%$ to $-0.2%$)		

Table 3. Synergy Between Cirrhosis and Comorbidity Effects

Each row shows the cumulative mortality in the four combinations of \pm cirrhosis and \pm comorbidity, but the definition of comorbidity differs between rows. The far right column shows the interaction risk (that is, the percentage of patients whose death was attributable to interaction between cirrhosis and comorbidity).

*Among cirrhosis patients with a CCl of 2, in the first year of follow-up, an estimated 28.3% (29.0-0.7) died from cirrhosis, 7.1% (7.8-0.7) died from comorbidity, and 11.0% (47.1-28.3-7.1-0.7) died from the synergy between cirrhosis and comorbidity.

+Conditional on being alive at 1-year follow-up.

including comorbidities in prognostic scoring systems for cirrhosis patients. To this end, it should be emphasized that the CCI was developed for unselected medical patients and would probably be even more strongly associated with prognosis if modified to be specific to cirrhosis patients.¹³ Another point to note is that comorbidity was not considered for inclusion in the Child-Pugh, Model for End-Stage Liver Disease, or Mayo systems,³²⁻³⁴ whereas it has long been recognized as an important prognostic factor in patients with upper gastrointestinal bleeding.^{35,36} Comorbidity was therefore included in the widely used Rockall prognostic scoring system for upper gastrointestinal bleeding.^{37,38}

In conclusion, we have shown that comorbidity is strongly associated with mortality in patients with cirrhosis, and it appears that treatment of comorbidities should be a priority among newly diagnosed cirrhosis patients.

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Socioeconomic status and mortality among cirrhosis patients: A Danish nationwide cohort study

Peter Jepsen,¹ Hendrik Vilstrup,² Per Kragh Andersen,³ Henrik Toft Sørensen^{1,2}

- 1. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
- Department of Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, Aarhus, Denmark.
- Department of Biostatistics, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark.

Corresponding author: Peter Jepsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark. E-mail: pj@dce.au.dk. Fax: +45 8942 4801. Telephone: +45 8942 4800.

E-mail-addresses:

PJ:	pj@dce.au.dk
HV:	hvils@as.aaa.dk
PKA:	pka@biostat.ku.dk
HTS:	hts@dce.au.dk

ABSTRACT

Background: Low socioeconomic status is a risk factor for liver cirrhosis, but it is unknown whether it is a prognostic factor after cirrhosis diagnosis. We examined whether marital status, employment, and personal income were associated with survival for cirrhosis patients.

Methods: Using registry-data we conducted a population-based cohort study with five-year followup of 1,765 Danish cirrhosis patients diagnosed in 1999-2001 at age 45-59. With Cox regression we examined the associations between marital status (never married, divorced, married), employment (employed, disability pensioner, unemployed), personal income (0-49, 50-99, 100+ percent of the national average) and survival, controlling for potential confounders.

Results: Five-year survival was higher for married patients (48%) than for patients who never married (40%) or were divorced (34%), but after adjustment only divorced patients had poorer survival than married patients (adjusted hazard ratio for divorced vs. married = 1.22, 95% CI 1.05-1.42). Five-year survival was lower for disability pensioners (31%) than for employed (46%) or unemployed patients (48%), also after adjustment (adjusted hazard ratio for disability pensioners vs. employed = 1.22, 95% CI 1.05-1.42). Personal income was not associated with survival.

Conclusions: Marital status and employment were prognostic factors for cirrhosis patients, whereas personal income was not.

BACKGROUND

Liver cirrhosis is a chronic disease with a median survival time of about three years following diagnosis in Denmark [1]. In the white U.S. population aged 45-54 cirrhosis was the 5th-leading cause of death after cancer, heart disease, accidents, and suicide in 2004 [2]. Studies have found an association between low socioeconomic status and increased cirrhosis incidence [3-6], but it remains unclear whether low socioeconomic status is also associated with a worse prognosis after cirrhosis diagnosis. There is evidence in favor of such an association from studies of patients with alcoholism [5], cancer [7, 8], heart failure [9], stroke [10], or myocardial infarction [11, 12], but this topic has not been addressed among cirrhosis patients [13]. Accurate information on prognostic factors for cirrhosis patients may improve our understanding of the clinical course of the disease and may also lead to the identification of patients who require special interventions. We therefore examined whether marital status, employment, and personal income, all of which are markers of socioeconomic status, were associated with survival for Danish cirrhosis patients.

METHODS

Denmark's 5.3 million inhabitants have access to free tax-supported healthcare, and there are no acute-care private hospitals. The unemployment rate is low, around five percent of the workforce aged 45-59 years in 1999-2001 [14], and economic support is provided to low-income groups. The Danish welfare system aims to reduce socioeconomic inequalities in health [15], but there are no economic benefits associated with the diagnosis of a chronic disease, such as cirrhosis.

Data sources

Integrated Database for Labour Market Research (IDA)

The IDA database, established in 1990 and administered by the government agency Statistics Denmark, contains socioeconomic information at the individual level for each Danish citizen. The data are primarily supplied by tax authorities, educational institutions and employment services. The IDA database is updated annually on 31 December [16].

National Patient Registry

The National Patient Registry contains data from all inpatient admissions to public and private nonpsychiatric hospitals in Denmark since 1977 and from outpatient and emergency room visits since 1995 [17]. Each discharge record includes service dates (dates of admission and discharge for inpatients, dates of first and last visit for a given condition for outpatients, and date of visit for emergency room patients), one primary diagnosis and up to twenty secondary diagnoses, and surgical procedures performed. Diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10), but before 1994 they were coded according to the 8th revision (ICD-8). Diagnosis codes are specified by a physician; for inpatients they are given at hospital discharge, for outpatients they are given at the last visit in a series of outpatient visits. Procedure codes are coded according to the Nordic Classification of Surgical Procedures. Unless otherwise noted, we defined diseases using hospital diagnoses from inpatient hospitalizations, outpatient visits, and emergency room visits.

Civil Registration System

Denmark's Civil Registration System records dates of birth, death, and emigration for all Danish citizens and is updated daily. It also assigns a personal identification number to each citizen, and this identifier was used to link individual-level data from the IDA database, the National Patient Registry, and the Civil Registration System [18].

Information on cirrhosis patients

We identified all patients with a diagnosis of cirrhosis (ICD-8 codes 571.09, 571.92, and 571.99; ICD-10 codes: K70.3 or K74.6) made during an inpatient hospitalization or outpatient visit between 1 January 1977 and 31 December 2001. Eligibility criteria were a first cirrhosis diagnosis during the years 1999 through 2001 and age 45-59 years at that time. The calendar year and age restrictions ensured that study patients were of working age and reduced differences in living conditions.

Information on the severity of the study patients' cirrhosis was based on other hospital diagnoses given at the time of cirrhosis diagnosis. We identified the presence/absence of variceal bleeding (diagnosis code I85.0), ascites (diagnosis code R18.9 or procedure code TJA10), liver failure (diagnosis code K72.x), and bacterial infections (diagnoses codes K65.x [spontaneous bacterial peritonitis], J13.x-J18.x [pneumonia], N10.x [pyelonephritis], N30.x [cystitis], A46.x [erysipelas], I33.x [endocarditis], and A40.x-A41.x [septicemia]) [19]. We also ascertained whether the patient was an inpatient or outpatient at the time of diagnosis, and whether cirrhosis was the primary diagnosis or a secondary diagnosis.

Socioeconomic status

We obtained information on three markers of socioeconomic status: marital status (never married, divorced/widowed, or married/cohabiting) on 31 December of the year of cirrhosis diagnosis and on 31 December of each of the five preceding calendar years; employment (employed, disability pensioner, or unemployed) during the majority of the calendar year in which cirrhosis was diagnosed and during each of the five preceding calendar years; and taxable personal income (0-49 percent, 50-99 percent, or 100+ percent of the average income for all Danish citizens of the same gender and age in the same calendar year) during the calendar year of cirrhosis diagnosis and during each of the five preceding the calendar year of cirrhosis diagnosis and during each of the five preceding the calendar year of cirrhosis diagnosis and during each of the five preceding the calendar year of cirrhosis diagnosis and during each of the five preceding the calendar year of cirrhosis diagnosis and during each of the five preceding the calendar year of cirrhosis diagnosis and during each of the five preceding calendar years. Information on marital status and personal income for the

year of cirrhosis diagnosis was missing for patients who died in that year, so we assumed that they were the same as in the previous year.

Substance abuse

For each patient we counted the number of diagnoses of alcohol abuse (diagnosis codes F10.x [except F10.0 and F10.1], G31.2, K70.x, and K86.0) in the five years before cirrhosis diagnosis (in categories of 0, 1-4, 5-9, or 10+ diagnoses), and we ascertained whether the patient had received a diagnosis of substance abuse other than alcohol abuse during the same period (diagnosis code F1x.x, except F10.x).

Comorbidity

We measured comorbidity using the patients' diagnoses in the five years preceding their cirrhosis diagnosis. The Charlson comorbidity index (in categories of 0, 1, 2, or 3+) served as an overall measure [20], and comorbid diseases were defined according to Quan et al [21]. The index includes mild and severe liver disease, but they were not counted as comorbidities; however, hepatocellular carcinoma counted as a comorbid cancer. Additional comorbidity measures were the presence or absence of hospital diagnoses for psychiatric disease (diagnosis codes Fxx.x, except F1x.x) and the number of inpatient hospitalizations in the five years before the cirrhosis diagnosis (in categories of 0-1, 2-4, 5-9, or 10+).

Statistical analysis

Patients whose first cirrhosis diagnosis originated from an inpatient hospitalization were followed from the discharge date of that hospitalization, and patients whose first cirrhosis diagnosis originated from an outpatient visit were followed from the last visit in that series of outpatient visits. All patients were followed until death or emigration, or were censored on 31 December 2003, whichever came first. The study outcome was survival time. Patients who died during the hospitalization associated with their first cirrhosis diagnosis were given a survival time of 0.5 days. Analyses were based on socioeconomic data for the calendar year preceding the cirrhosis diagnosis, unless otherwise specified.

We computed survival probabilities using the Kaplan-Meier method and used Cox proportional hazards regression to estimate hazard ratios. First, we computed the crude hazard ratios for marital status, employment, and personal income. Second, we included all three markers of socioeconomic status in one Cox model together with cirrhosis severity (encompassing variceal bleeding, ascites, liver failure, bacterial infection, inpatient status at time of cirrhosis diagnosis, and cirrhosis as the primary diagnosis), gender, age at cirrhosis diagnosis, substance abuse (encompassing number of diagnoses for alcohol abuse and other substance abuse), and comorbidity (encompassing Charlson comorbidity index, psychiatric disease, and number of inpatient hospitalizations). Using Schoenfeld residuals, we determined that hazard ratios were constant over follow-up time.

We examined whether the timing of the socioeconomic status measurement affected the hazard ratios for the three markers of socioeconomic status. This was done by substituting the marital status, employment, and income data used in the fully adjusted Cox regression model with the same information for the year of cirrhosis diagnosis and for earlier calendar years.

RESULTS

We included 1,765 cirrhosis patients, of whom 68 percent were men. During a total follow-up time of 3,855 years, 877 patients (50 percent) died; none received a liver transplant. Forty-one percent were married, 40 percent were divorced, less than one-third were employed, two-thirds had a personal income less than fifty percent of the national average, and six percent had an income above the national average (Table 1). Eighty-five percent of all cirrhosis patients had one or more
diagnoses of alcohol abuse (Table 1), and 17 percent were divorced disability pensioners earning less than half the national average.

Compared with married patients, divorced or never-married patients were more likely to be disability pensioners, to have a low income and to abuse alcohol. Employed patients were more likely than others to be married, have a higher income, and not abuse alcohol, whereas disability pensioners were more likely to be divorced, abuse alcohol, and have comorbidities. Patients in the highest income category were more likely than others to be employed, female, and old. Cirrhosis severity was unrelated to socioeconomic status (Table 1).

Five-year survival was lower for divorced (34 percent, 95% CI 28-40) and never-married patients (40 percent, 95% CI 32-48) than for married patients (48 percent, 95% CI 43-53), and it was clearly lower for disability pensioners (31 percent, 95% CI 25-37) than for employed (46 percent, 95% CI 39-52) or unemployed (48 percent, 95% CI 42-54) patients. By contrast, patients earning less than half the national average had only slightly lower five-year survival (38 percent, 95% CI 34-43) than those with higher earnings (45 percent for both categories) (Figure 1). These survival probabilities were consistent with the crude hazard ratios (Table 2).

Adjustment for other patient characteristics attenuated the prognostic impact of marital status, but the prognosis remained better for the married than for the divorced (HR = 1.22, 95% CI 1.05-1.42) (Table 2). Likewise, the impact of employment was reduced, but being a disability pensioner remained associated with a poorer prognosis (HR for disability pensioner vs. employed = 1.35, 95%CI 1.10-1.66; HR for disability pensioner vs. unemployed = 1.39, 95% CI 1.18-1.65). The prognosis appeared to be worse for those who earned more than the national average, but not by a significant amount (Table 2).

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The socioeconomic status of the cirrhosis patients deteriorated over the five years preceding their cirrhosis diagnosis. Notably, 27 percent of patients were disability pensioners five years before their cirrhosis diagnosis, and this proportion rose to 39 percent by the end of the year preceding diagnosis. Of the 713 divorced patients, 112 (16 percent) were divorced during the five years preceding their cirrhosis diagnosis. Of the 695 disability pensioners, 577 (83 percent) had not been employed in the five preceding years. This was true of 211 out of a total of 516 unemployed patients (41 percent). Still, substituting socioeconomic information from earlier calendar years or from the year of cirrhosis diagnosis had only a small effect on our findings: the hazard ratios for divorced vs. married patients ranged from 1.21 to 1.31, and those for disability pensioners vs.

DISCUSSION

In this nationwide population-based study of 1,765 cirrhosis patients, we found that marital status and employment were prognostic factors for cirrhosis patients, whereas personal income was not.

The major strengths of our study were access to data from a tax-funded healthcare system with equal access to hospital care and complete follow-up. Use of routinely collected nationwide administrative data on socioeconomic status and hospitalization history ensured that data collection was independent of the study, greatly reducing the risk of bias due to differential data validity. At the same time, hospital diagnoses in the National Patient Registry data are not all of high validity [22]. Of particular concern was the validity of cirrhosis diagnoses. A 1985-1990 study of hospital diagnoses of cirrhosis indicated that 15 percent did not fulfill diagnostic criteria for cirrhosis [23]. It is possible that this 15 percent of patients had a relatively good prognosis and a relatively high socioeconomic status. They were *suspected* of having cirrhosis, however, which indicates that they may have had a similar socioeconomic status as those who did in fact have cirrhosis. While invalid

cirrhosis diagnoses could lead to overestimation of the benefit of high socioeconomic status, it is unlikely that such a bias substantially affected our findings. The lack of data on socioeconomic status at the time of cirrhosis diagnosis is another weakness because the socioeconomic information from the calendar year before cirrhosis diagnosis might have been affected by an already established cirrhosis, or it might have predated the cirrhosis by up to one year. However, we showed that our conclusions were not sensitive to these scenarios. In fact, the consistency of our results indicated that the prognostic impacts of marital status and employment were not caused by changes in them during the five years before cirrhosis diagnosis.

The mechanisms behind our findings are unclear. Cirrhosis severity, substance abuse, and comorbidity are likely to both affect and reflect socioeconomic status, and also the three markers of socioeconomic status affect one another. Nonetheless, our findings indicate that marital status and employment were in fact prognostic factors, and that the poor survival for those who never married could be explained by these patients' high prevalence of disability and alcohol abuse, whereas the same characteristics could not fully explain the poor survival for the divorced. Similarly, the poor survival for the disabled could only partially be explained by their high prevalence of divorce, substance abuse, and comorbidity. Therefore we can only speculate on the mechanism. One possibility is that the divorced and the disabled were less compliant with doctors' advice to abstain from alcohol, but a range of behavioral, psychological, social and biological mechanisms may be involved [24]. Importantly, more severe cirrhosis at the time of cirrhosis diagnosis or a lower income did not contribute to the poor prognosis for the divorced or disabled. This might be attributed to the Danish welfare system [15], in which case our findings may not generalize to other countries.

The prognostic impact of socioeconomic status among cirrhosis patients has not previously been examined [13], but survival among Danish cancer patients has been shown to be associated with several markers of socioeconomic status, including marital status, employment, and income [7]. It is not clear why high income was associated with longer survival for Danish cancer patients and not cirrhosis patients, but in our data an effect of income could be explained by other patient characteristics; in the cancer study, only gender, age, calendar year, and educational level were considered as possible explanations [7]. The better prognosis for married cirrhosis patients than for divorced cirrhosis patients is also consistent with findings among alcoholic men [5], cancer patients [8], and patients with myocardial infarction [11, 12]. However, a recent study of more than 3,000 patients with myocardial infarction failed to find an association between social support, employment, or income and prognosis, after extensive adjustment for preexisting cardiovascular conditions [25]. This might indicate that we could have explained the prognostic impact of divorce and disability in our study with such patients' alcohol abuse and comorbidity if only our data had been sufficiently detailed. Although we cannot rule out this possibility, the unmeasured effects of alcohol abuse and comorbidity would have to be at least as strong as their measured effects to fully explain our findings, and that is unlikely.

Our data might have clinical implications. Interventions against alcohol abuse and comorbidities are important to reduce the higher mortality for those who are not married and for the disability pensioners. In addition to standard care, psychosocial therapy may be beneficial, as it has been shown to reduce alcohol dependence and improve social support and quality of life [26, 27], but its effect among cirrhosis patients is unknown. Our findings also indicate that other relevant intervention points remain to be identified.

CONCLUSIONS

In conclusion, we have shown that marital status and employment were prognostic factors for cirrhosis patients, whereas personal income was not.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

PJ and HTS conceived and designed the study. PJ and PKA analyzed the data, and all authors interpreted the data. PJ drafted the manuscript, and HV, PKA, and HTS revised it. All authors read and approved the final manuscript.

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FIGURE LEGEND

Figure 1 Survival with respect to time (years) after cirrhosis diagnosis by marital status, employment, and personal income (in percent of the national average income for citizens of same age and gender).



Table 1. Characteristics of the 1,765 cirrhosis patients included in the study. The data on socioeconomic status pertain to the calendar year before cirrhosis diagnosis. The number and percentage of patients in each of the three categories of marital status, employment, and personal income, as well as for the total cohort, are provided in the columns.

		Marital status			Employment			Personal income			Total
		Never married	Divorced	Married	Disability pensioner	Unemployed	Employed	0-49	50-99	100 +	
		327 (19)	713 (40)	725 (41)	695 (39)	516 (29)	554 (31)	1180 (67)	482 (27)	103 (6)	1765 (100)
Socioeconomic status											
	Marital status										
	Never married	-	-	-	156 (22)	93 (18)	78 (14)	254 (22)	65 (13)	8 (8)	327 (19)
	Divorced	-	-	-	346 (50)	204 (40)	163 (29)	498 (42)	174 (36)	41 (40)	713 (40)
	Married	-	-	-	193 (28)	219 (42)	313 (57)	428 (36)	243 (50)	54 (52)	725 (41)
	Employment										
	Disability pensioner	156 (48)	346 (49)	193 (27)	-	-	-	613 (52)	72 (15)	10(10)	695 (39)
	Unemployed	93 (28)	204 (29)	219 (30)	-	-	-	400 (34)	105 (22)	11(11)	516 (29)
	Employed	78 (24)	163 (23)	313 (43)	-	-	-	167 (14)	305 (63)	82 (80)	554 (31)
	Income (% of national average)	. ,	· /						· · ·	. ,	
	0-49	254 (78)	498 (70)	428 (59)	613 (88)	400 (78)	167 (30)	-	-	-	1180 (67)
	50-99	65 (20)	174 (24)	243 (34)	72 (10)	105 (20)	305 (55)	-	-	-	482 (27)
	100+	8 (2)	41 (6)	54 (7)	10(1)	11 (2)	82 (15)	-	-	-	103 (6)
Cirrhosis severity											
	Variceal bleeding	24 (7)	35 (5)	54 (7)	32 (5)	30 (6)	51 (9)	73 (6)	33 (7)	7 (7)	113 (6)
	Ascites	64 (20)	146 (20)	121 (17)	136 (20)	100 (19)	95 (17)	231 (20)	86 (18)	14 (14)	331 (19)
	Liver failure	12 (4)	30 (4)	17 (2)	26 (4)	14 (3)	19 (3)	40 (3)	15 (3)	4 (4)	59 (3)
	Bacterial infection	29 (9)	54 (8)	54 (7)	61 (9)	44 (9)	32 (6)	101 (9)	30 (6)	6 (6)	137 (8)
	Inpatient at cirrhosis diagnosis	278 (85)	563 (79)	551 (76)	579 (83)	411 (80)	402 (73)	951 (81)	368 (76)	73 (71)	1392 (79)
	Cirrhosis is primary diagnosis	184 (56)	437 (61)	436 (60)	399 (57)	318 (62)	340 (61)	693 (59)	306 (63)	58 (56)	1057 (60)
Demographics	r y g	- ()					(- /				
0 1	Men	274 (84)	459 (64)	467 (64)	457 (66)	337 (65)	406 (73)	889 (74)	262 (54)	49 (48)	1200 (68)
	Age at diagnosis								. ,	~ /	. ,
	45-49 years	158 (48)	193 (27)	159 (22)	197 (28)	162 (31)	151 (27)	360 (31)	128 (27)	22 (21)	510 (29)
	50-54 years	101 (31)	239 (34)	266 (37)	239 (34)	164 (32)	203 (37)	408 (35)	158 (33)	40 (39)	606 (34)
	55-59 years	68 (21)	281 (39)	300 (41)	259 (37)	190 (37)	200 (36)	412 (35)	196 (41)	41 (80)	649 (37)
Substance abuse	2								. ,	~ /	· · /
	Alcohol diagnoses										
	10+	34 (10)	104 (15)	41 (6)	120 (17)	37 (7)	22 (4)	132 (11)	36(7)	11(11)	69 (4)
	5-9	52 (16)	125 (18)	97 (13)	127 (18)	94 (18)	53 (10)	199 (17)	66 (14)	9 (9)	174 (10)
	1-4	201 (61)	402 (56)	445 (61)	364 (52)	324 (63)	360 (65)	690 (58)	297 (62)	61 (59)	1258 (71)
	0	40 (12)	82 (12)	142 (20)	84 (12)	61 (12)	119 (21)	159 (13)	83 (17)	22 (21)	264 (15)
	Other substance abuse	6(2)	8(1)	6(1)	17 (2)	2 (0.4)	1 (0.2)	18 (2)	1 (0.2)	1(1)	20(1)
Comorbidity						· · ·	· · ·				
2	Charlson comorbidity index										
	3+	14 (4)	29 (4)	25 (3)	42 (6)	11 (2)	15 (3)	49 (4)	16(3)	3 (3)	68 (4)
	2	29 (9)	58 (8)	62 (9)	79 (11)	34 (7)	36(7)	103 (9)	38 (8)	8 (8)	149 (8)
	1	75 (23)	160 (22)	145 (20)	177 (25)	95 (18)	108 (19)	269 (23)	94 (20)	17 (17)	380 (22)
	0	209 (64)	466 (65)	493 (68)	397 (57)	376 (73)	395 (71)	759 (64)	334 (69)	75 (73)	1168 (66)
	Psychiatric disease	17 (5)	48 (7)	25 (3)	63 (9)	18 (3)	9 (2)	69 (6)	18 (4)	3 (3)	90 (5)
	Hospitalizations in last five years										
	10+	16 (5)	52 (7)	26 (4)	67 (10)	14 (3)	13 (2)	70 (6)	22 (5)	2 (2)	94 (5)
	5-9	53 (16)	123 (17)	109 (15)	158 (23)	72 (14)	55 (10)	204 (17)	64 (13)	17 (17)	285 (16)
	2-4	140 (43)	305 (43)	289 (40)	295 (42)	219 (42)	220 (40)	494 (42)	204 (42)	36 (35)	734 (42)
	0-1	118 (36)	233 (33)	301 (42)	175 (25)	211 (41)	266 (48)	412 (35)	192 (40)	48 (47)	652 (37)

Table 2.The associations of marital status, employment, and personal income with survival for
cirrhosis patients. Associations are expressed as hazard ratios (HR) with associated
95% confidence intervals.

	Crude	Adjusted ^{\dagger}
	HR (95% CI)	HR (95% CI)
Marital status		
Never married	1.26 (1.05-1.52)	1.05 (0.86-1.29)
Divorced	1.40 (1.21-1.62)	1.22 (1.05-1.43)
Married	1.00 [reference]	1.00 [reference]
Employment		
Disability pensioner	1.60 (1.37-1.88)	1.35 (1.10-1.67)
Unemployed	1.00 (0.83-1.20)	0.97 (0.79-1.20)
Employed	1.00 [reference]	1.00 [reference]
Income (% of national average)		
0-49	1.12 (0.84-1.50)	0.80 (0.58-1.11)
50-99	0.88 (0.65-1.20)	0.81 (0.59-1.12)
100+	1.00 [reference]	1.00 [reference]

[†] Adjusted for the other two markers of socioeconomic status, cirrhosis severity, gender, age,

substance abuse, and comorbidity.

The galactose elimination capacity and mortality in 781 Danish patients with newly-diagnosed liver cirrhosis: a cohort study

Peter Jepsen (1), Hendrik Vilstrup (2), Peter Ott (2), Susanne Keiding (2), Per Kragh Andersen (3), Niels Tygstrup (4)

- 1. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
- Department of Medicine V (hepatology and gastroenterology), Aarhus University Hospital, Aarhus, Denmark.
- Department of Biostatistics, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark.
- 4. The Liver Unit, Rigshospitalet, Copenhagen, Denmark.

Corresponding author: Peter Jepsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark. E-mail: pj@dce.au.dk. Fax: +45 8942 4801. Telephone: +45 8942 4800.

E-mail-addresses:

pj@dce.au.dk
hvils@as.aaa.dk
peott@as.aaa.dk
susanne@keiding.dk
pka@biostat.ku.dk
tygstrup@mail.dk

Abstract

Background: We hypothesized that the function of the liver is important for survival of patients with chronic liver disease. The galactose elimination capacity (GEC) is a physiological measure of the total metabolic capacity of the liver. Thus, we examined whether GEC was associated with mortality among newly-diagnosed cirrhosis patients.

Methods: Combining data from a GEC database with data from healthcare registries we identified cirrhosis patients with a GEC test at the time of cirrhosis diagnosis after August 1st 1992. They were followed until death or December 31st 2005. We divided the patients into 10 equal-sized groups according to GEC and calculated the mortality after 30 days, 1 year, and 5 years for each group. Cox regression was used to adjust for age, gender and comorbidity. We repeated the analyses for the group of cirrhosis patients with comorbidity.

Results: We included 781 patients, 454 (58%) of whom died during 2,617 years of follow-up. GEC was markedly associated with short- and long-term mortality, most strongly so among the 75% of patients with a GEC below the normal range. The GEC-mortality association was unaffected by confounding, and it was also found among patients with comorbidity.

Conclusions: GEC was associated with both short- and long-term mortality for newlydiagnosed cirrhosis patients. The association was strongest among cirrhosis patients with GEC below 1.75 mmol/min.

Background

Cirrhosis is a chronic liver disease with high mortality [1]. The condition implies loss of liver function, and it is a fundamental assumption that this is important for survival. Still little is known about the association between the prognosis of the patients and their liver function. When other organs are sick or failing such an association is evident, e.g. the ejection fraction in heart failure and the glomerular filtration rate in renal failure. A similar generally accepted way to estimate the extent of lost liver function is missing. This is likely due to the fact that the liver has multiple and diverse functions, and it is not known which of them are essential for health and survival [2]. In this situation clinicians, therefore, have to rely on scores based on standard blood tests and symptoms of the liver disease, e.g. the Child-Pugh score and the MELD-score, as prognostic indicators [3]. However, such scores must be considered as surrogate markers because of their indirect relationship to the liver disease and because of their dependence on treatments.

Although the liver may change the priority of its functions when challenged by disease it is reasonable to assume that a declining total function of the liver during chronic liver disease will reduce the possibility of survival of the individual. The liver's capacity to metabolize galactose can be taken to reflect the liver's total metabolic capacity to serve the homeostasis of the organism by functions that are essential for health and survival [4]. Thus, galactose is metabolized only in the liver and by enzymes that are phylogenetically old, constitutive, and non-inducible. During the test these enzymes are substrate saturated and working at maximum velocity, i.e. at their capacity, even at low galactose concentrations that are feasible for clinical use. This is the basis for the galactose elimination capacity (GEC) test [2, 4] as a physiological quantitative measure of the metabolic capacity of the liver. We hypothesized

that assessment of the metabolic capacity of the liver by use of the GEC is related to mortality in cirrhosis patients.

A number of studies support this hypothesis. Thus, a prognostic value of the test has been documented in patients with acute liver failure [5]. Also, it has been reported that the GEC adds prognostic information beyond that obtained by standard blood tests [6-9]. These studies, however, included only selected cirrhosis patients, comprised an insufficient number of patients (between 61 and 194), and had relatively short observation time. Other smaller studies identified no prognostic value of the GEC [10, 11].

To test the hypothesis a large number of patients and long observation time is needed, and a number of other factors influencing the course of the disease have to be taken into account. The GEC has been reported to decline with age and to be higher in men than in women [12-14], but the prognostic interference between GEC and comorbidity [15] is not known. The relationship between cirrhosis patients' prognosis and their GEC has not been studied in standardized patient populations or after adjustment for such possible confounders. Thus, the concept of the prognostic importance of liver function in cirrhosis remains unexplored.

The purpose of this work, therefore, was to study the association between mortality and GEC measured at diagnosis of cirrhosis in a large group of patients followed for up to 13 years. Age, sex, and comorbidity were taken into account in the analyses.

Methods

Study population

This study was based on GEC tests done between August 1st 1992 and December 31st 2005 in the two Danish tertiary referral centers for liver disease. All tests were performed as

previously described [16, 17], and the average GEC values in men and women without suspected liver disease are 2.7 (95% CI 1.7-3.6) and 2.4 (95% CI 1.4-3.4) mmol/min, respectively [14]. We identified 3388 patients with a GEC test, among whom 781 had been diagnosed with cirrhosis less than 90 days before their first test. Hospital discharge diagnoses from the Danish National Patient Registry were used to identify the patients discharged with a cirrhosis diagnosis. This registry records individual-level information from all admissions to Danish hospitals since 1977, and from all outpatient visits since 1995 [18]. The information includes primary and secondary discharge diagnoses coded according to ICD8 (before 1994) or ICD10 (from 1994), and we defined cirrhosis by the following codes: 571.09, 571.92, 571.99, K70.3, and K74.6. Comorbid diseases were identified in the same registry and defined by the Charlson comorbidity index, based on 19 common chronic diseases, as previously described [15, 19].

Statistical analysis

The patients were followed from the date of their first GEC test until death or December 31st 2005. Dates of death were obtained from the Danish Civil Registration System [20]. The cumulative mortality was estimated as 1 minus the Kaplan-Meier estimate of survival probability. The association between GEC and mortality was examined by dividing the patients into 10 equal-sized groups according to GEC (i.e., GEC-deciles) and plotting each decile's median GEC against its 30-day, 1-year, and 5-year mortality. We used lowess smoothing to facilitate the visual interpretation of these plots [21]. The impact of confounding by gender, age at GEC test, and comorbidity (defined by a Charlson comorbidity index of 1 or higher) on the association between GEC-decile and mortality was examined by Cox regression. Finally, the analyses were repeated but restricted to cirrhosis patients with comorbidity.

Results

Among the 781 patients, 454 (58%) died during follow-up. The total observation time was 2,617 years with a median of 2.5 years per patient. The median age at inclusion was 52 years and 65% were men. GEC ranged from 0.59 to 3.97 mmol/min (median 1.48 mmol/min). It was higher in men than in women (median GEC 1.54 vs. 1.40 mmol/min) but it was not associated with age.

GEC was markedly associated with short- and long-term mortality (Fig. 1), most strongly so among the 75% of patients with a GEC below 1.75 mmol/min. For example, patients with a GEC of 1.0 mmol/min had a mortality of 30% within the first 30 days after the test, 45% within one year, and 70% within 5 years. For newly-diagnosed cirrhosis patients with a GEC within the normal range, i.e. >1.75 mmol/min, the mortalities were <5%, 15% and 45%, respectively (Fig. 1). The GEC-mortality association was the same whether adjusted for potential confounders or not, and was also present among the 29% of patients with comorbidity.

Discussion

In this study of newly-diagnosed cirrhosis patients with long-term follow-up we found that the mortality was markedly associated with the GEC, an effect present even beyond 5 years and after adjustment for the effects of potential confounders.

Our findings are consistent with the existing studies of GEC and mortality for cirrhosis patients [6-11, 22-24], but our study extends them by being sufficiently large to examine subgroups, by having complete long-term follow-up, and by presenting a near-continuous relationship between GEC and short- and long-term mortality and by showing that gender,

age and comorbidity only marginally affected the relation between GEC and survival.

It is possible that some cirrhosis patients died before they had a GEC test, but our failure to include these patients would only affect our conclusions if they had a high GEC, and that is unlikely. We may also have included some patients without cirrhosis, since about 15% of cirrhosis diagnoses in the National Patient Registry are wrong [25]. However, this proportion should be lower in our study because it is unlikely that patients without cirrhosis had a GEC test performed in our referral centers for liver disease. The risk of selection bias in our study is, therefore, negligible.

In our analyses we adjusted for gender, age, and comorbidity, but we cannot rule out that other confounders may have contributed to the GEC-mortality association. However, no confounder could realistically explain the full extent of the association.

Our study confirmed the existence of a significant association between GEC at cirrhosis diagnosis and short- and long-term mortality. This is in accordance with the basic assumption that total metabolic capacity of the liver determines the clinical course, also in chronic liver disease. Nevertheless, the GEC test has not gained widespread use in clinical hepatology because it is invasive, tedious and labor-expensive. Therefore, our demonstration of the prognostic value of GEC is largely of pathophysiological importance and of interest for academic hepatology. Still, regarded as proof-of-concept, our result should prompt the development of easy-to-perform physiological liver function tests. The non-physiological scores such as Child-Pugh and MELD may be sufficient for many clinical decisions, but in complex situations, e.g., when treating cirrhosis patients with comorbidities, the inherent

robustness of a physiological test is desirable. At present, the GEC remains useful in specialized centers.

Conclusions

A decrease in GEC was markedly associated with short- and long-term mortality among cirrhosis patients.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: PJ, HV, and NT conceived and designed the study. PJ and PKA analyzed the data, and all authors interpreted the data. PJ and HV drafted the manuscript, and PO, SK, PKA, and NT revised it. All authors read and approved the final manuscript.

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Figure legend

Figure 1 Association between GEC and 30-day, 1-year, and 5-year mortality. The gray lines connect each GEC-decile's median GEC with its observed mortality, and the black lines are lowess smoothings of the gray lines.



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