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Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark

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Abstract

Mortality from cirrhosis of the liver has been examined in few long-term follow-up studies. In the Danish National Registry of Patients, 1982–1989, we identified a cohort of 10,154 patients with liver cirrhosis and divided them according to the etiology of their liver disease. Causes of death were identified in the Danish Death Registry, 1982–1993. We estimated relative survival and standardized mortality ratios by comparing with the mortality in the general population. The 10-year relative survival was worse in patients with alcoholic cirrhosis (34%) or nonspecified cirrhosis (32%) than in patients with primary biliary cirrhosis (58%) or chronic hepatitis (66%). The standardized mortality ratio for all causes of death combined was 12-fold increased, 5-fold excluding cirrhosis-related causes. Mortality in all disease categories was increased, even in those not traditionally related to cirrhosis. In conclusion, patients with cirrhosis of the liver face reduced life expectancy due to several causes of death.

Keywords: Liver cirrhosis; Epidemiology; Mortality; Prognosis; Cause-specific; Survival

1. Introduction

Liver cirrhosis and its complications are major clinical problems that carry a considerable risk of disability and death. There is no curative treatment for liver cirrhosis, so prevention and treatment of complications such as variceal hemorrhage, ascites, and encephalopathy are keystones for the clinical care of these patients. Because the liver plays an important role for many vital functions (eg, immunity, metabolism, and coagulation), the range of cirrhotic complications is broad. Consequently, understanding the disease process, making appropriate risk stratification, and implementing tertiary prevention requires valid and precise understanding of outcomes such as mortality patterns. The short-term prognosis of liver cirrhosis is relatively well described within the framework of randomized controlled trials, but population-based reports of long-term follow-up in causes of death are few and limited in size [1–13].

To clarify the clinical course of patients with liver cirrhosis, we determined the survival and causes of death of a large cohort of such patients, using population-based data from the Danish National Registry of Patients (NRP) and the Danish Death Registry.

2. Materials and methods

The study cohort was identified in the NRP, which contains information on all hospital admissions in Denmark (population 5.2 million) since 1977 [14]. Each admission record includes a date of admission, a date of discharge, up to 20 discharge diagnoses, and a civil registry number assigned to all Danes at birth, incorporating date of birth and sex. Diagnoses were classified according to the Danish version of the International Classification of Diseases, 8th edition (ICD-8) during the study period [14]. Patients were eligible for the study if they had been discharged with a diagnosis of alcoholic cirrhosis (ICD-8 = 571.09), primary biliary cirrhosis (571.90), nonspecified cirrhosis (571.92), chronic hepatitis (571.93), or "other types of cirrhosis, alcoholism not indicated" (571.99). Including all cases thus identified would have led to the inclusion of prevalent and

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incident cases because the patients could have been hospitalized with liver cirrhosis before the registry was established in 1977 [15]. To focus on incident cases, we restricted the cohort to patients whose first discharge diagnosis of liver cirrhosis was between 1982 and 1989. Patients younger than 15 years of age were excluded because most liver diseases in childhood are due to congenital malformations [16].

The cohort of patients with cirrhosis was considered as a whole and also as four sub-cohorts. The sub-cohorts were defined according to ICD-8 discharge diagnosis codes for alcoholic cirrhosis (571.09), primary biliary cirrhosis (571.90), chronic hepatitis (571.93), and nonspecified cirrhosis (571.92) plus cirrhosis, alcoholism not indicated (571.99) considered together as nonspecified cirrhosis. From 1977 to 1989, 12% of the cohort was diagnosed with more than one type of cirrhosis. These patients were assigned to a sub-cohort based on the following hierarchy: (1) alcoholic cirrhosis, (2) primary biliary cirrhosis, (3) chronic hepatitis, and (4) nonspecified cirrhosis. In addition, cirrhotic patients with a diagnosis of alcoholism (ICD-8 = 303) at any time from 1977 to 1989 were categorized as having alcoholic liver cirrhosis, regardless of the type of cirrhosis registered. On this background, we transferred 16% from the cohorts of primary biliary cirrhosis, chronic hepatitis, and nonspecified cirrhosis to the sub-cohort of alcoholic liver cirrhosis.

We obtained information on the vital status of cohort members from the Danish Civil Registration System, which, since 1968, has kept electronic records of all changes in vital status, such as emigration and death. Patients who died during the first hospital admission were included in the study. The cohort from the NRP was linked to the National Registry of Death (NRD) by the civil registry number. The NRD contains information on all death certificates since 1943, also coded in ICD-8 during the study period. We used the underlying cause of death reported on the death certificate in the analysis. A grouping into 50 categories based on ICD-8 as defined by the Danish National Board of Health [17] was applied in the main analyses. The different groups of death causes were merged into larger groups in the analysis of the sub-cohorts of liver cirrhosis. Cirrhosis-related death consisted of liver cirrhosis (ICD-8, 571), esophageal varices (ICD-8, 456), and hepatic coma (ICD-8, 473).

2.1. Statistical analysis

The number of person-years under observation was calculated from the date of first discharge with a diagnosis of liver cirrhosis until death, emigration, or the end of follow-up on 31 December 1993, whichever occurred first.

The relative survival was calculated as the ratio of the observed survival proportion to that expected for persons of the same age and sex in the general population. The expected survival proportions after every full year of follow-up time were computed from national mortality rates and were subsequently used to calculate a continuous expected rate [18]. We reported the 10-year relative survival because only a few patients were followed for all 12 years.

National sex-specific mortality rates in 5-year age groups and 5-year calendar periods were multiplied by person-years under observation to yield the number of deaths that would be expected if patients with liver cirrhosis had the same risk of death as the general population. The standardized mortality ratio (SMR) is the ratio of observed to expected number of deaths, based on the assumption that the observed number of cases in a specific category follows a Poisson distribution. We reported the SMR after 12 years of follow-up, and this was also divided into a 1-year SMR and a 2- to 12-year SMR. Confidence intervals (95% CI) for SMRs were calculated from an accurate asymptomatic approximation; exact limits were used when the observed number was less than 10 [19].

3. Results

We identified 10,154 patients with liver cirrhosis during the study period; 6374 (63%) were men, and 3780 (37%) were women. The mean age at entry into the study cohort was 56.9 years. The median and mean follow-up were 2.8 years and 3.7 years, respectively; the total number of person-years at risk was 37.382 years. Alcoholic cirrhosis was the largest of the four sub-cohorts (61% of all patients), whereas primary biliary cirrhosis accounted for only 2%. The sub-cohorts of primary biliary cirrhosis and chronic hepatitis had the longest mean follow-up period. In the alcoholic cirrhosis group, 71% of the patients were men, whereas 80% of patients with primary biliary cirrhosis were women (Table 1).

Table 1
Characteristics of 10,154 patients with different types of liver cirrhosis in Denmark, 1982–1989.

	Type of liver cirrhosis				
Patient characteristic	Alcoholic	PBC	Chronic hepatitis	Nonspecified	Total
Number of patients	6139	223	992	2800	10,154
Proportion of total, %	60.5	2.2	9.8	27.6	100
Male:female ratio	4353:1786	45:178	455:537	1521:1279	6374:3780
Mean age at entry into the study, y	56.3	60.1	52.2	59.6	56.9
Mean follow-up time, y	3.8	5.3	5.8	2.5	3.7
Total number of person-years at risk	23,518	1186	5780	6898	37,382
Number of deaths in the follow-up period	4230	104	404	2241	6979

Abbreviation: PBC = primary biliary cirrhosis.

Fig. 1. Deaths in patients (n = 6979) with liver cirrhosis, grouped in three follow-up periods according to cirrhosis-related death and other causes of death.

3.1. Survival

Of the 10,154 patients, 3863 (38%) died within the first year of follow-up; 56% died of a cirrhosis-related disease (eg, liver cirrhosis, esophageal varices, or hepatic coma), and 44% died of other causes. Beyond the first year of follow-up, other causes of death became relatively more frequent than death from liver cirrhosis (Fig. 1). During the 12-year follow-up period, 6979 (69%) died; 51% died from a cirrhosis-related disease, and 49% died from other causes.

The 10-year relative survival was 0.34 (95% CI 0.32–0.36) for alcoholic cirrhosis and 0.32 (95% CI 0.28–0.35) for nonspecified cirrhosis. Primary biliary cirrhosis and chronic hepatitis had a much better prognosis: a 10-year relative survival of 0.59 (95% CI 0.47–0.71) and 0.66 (95% CI 0.61–0.71), respectively (Figure 2).

The poorest prognosis was found in patients aged 60 years or more at diagnosis, with a relative 1-year survival rate of 0.67 (95% CI 0.66–0.69) and a 10-year relative survival rate of 0.25 (95% CI 0.22–0.28).

3.2. Causes of death

The mortality in cirrhotic patients for noncirrhotic causes of death was increased 5-fold compared with the general population. Mortality was increased for all disease categories, including for accidents and suicides. There was a 5- to 22-fold increased risk of dying from various infectious diseases and an 8- to 14-fold increased risk of dying from disorders of the digestive system. Nonetheless, ischemic heart diseases contributed the largest excess of deaths (Table 2). There were 398 deaths from gastrointestinal cancer, of which 202 were deaths from primary liver cancer. The overall risk of mortality from gastrointestinal cancer was more than 8-fold increased (SMR 8.3, 95% CI 7.5–9.2) compared with the general population. The increase in overall mortality was most pronounced during the first year of follow-up.

Mortality varied according to the underlying liver disease but was increased for all types of cirrhosis. There was a 5-fold increased mortality in alcoholic cirrhosis and a 7-fold increased mortality in nonalcoholic cirrhosis after subtracting the cirrhosis-related deaths; mortality was increased 2- to 3-fold in primary biliary cirrhosis and chronic hepatitis. The risk of dying from infections was most pronounced for nonspecified cirrhosis, chronic hepatitis, and alcoholic cirrhosis, but heart disease mortality was increased for all four sub-cohorts. A significantly increased risk of death from suicide was found among patients with alcoholic and nonspecified cirrhosis (Table 3).

4. Discussion

This analysis of more than 10,000 patients with liver cirrhosis and complete nationwide long-term follow-up showed that patients with liver cirrhosis have a high mortality, even for causes of death not usually associated with chronic liver

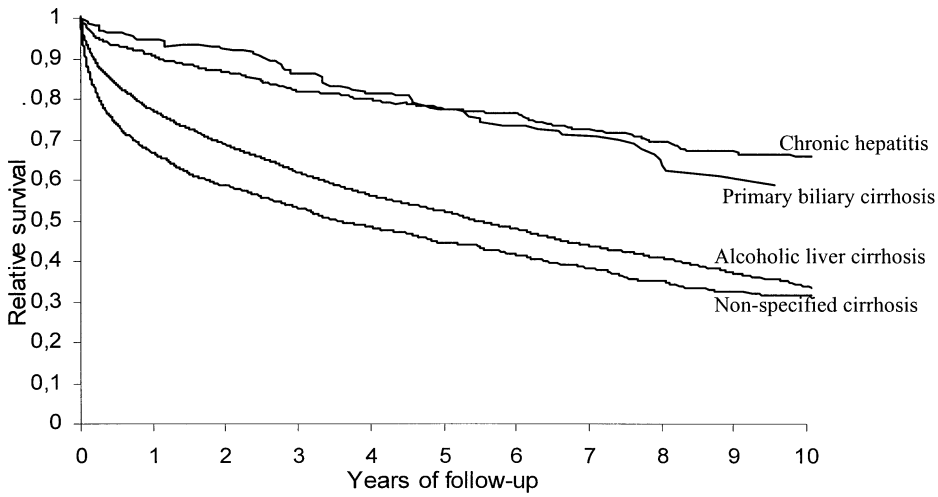

Fig. 2. Relative survival curves for 10,154 patients with liver cirrhosis, grouped in four sub-cohorts during a 10-year follow-up period.

Table 2
Observed (OBS) and expected (EXP) number of deaths and cause-specific standardized mortality ratio (SMR) for all patients with liver cirrhosis during the 12-year, 1-year, 2- to 12-year follow-up

	12-year follow-up			1-year follow-up			2- to 12-year follow-up		
Causes of death (ICD-8)	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All causes	6979	10.5	10.3–10.8	3863	32.3	31.3–33.4	3116	5.7	5.5–5.9
Liver cirrhosis-related disease	3536			2156			1380		
All causes without cirrhosis-related disease	3443		5.1–5.4	1707	14.3	13.6–15.0	1736	3.3	3.2–3.5
Heart diseases									
Ischemic heart disease (410–413)	621	3.7	3.3–3.9	353	10.5	9.4–11.6	268	1.9	1.7–2.2
Other forms of heart disease (420–429)	180	7.6	6.5-8.8	94	24.9	20.1–30.4	86	4.3	3.4–5.3
Vascular disease									
Circulatory system (440–445, 450–458, 400–404)	107	3.8	3.1–4.6	53	12.9	9.7–16.1	54	2.3	1.7–3.0
Cerebrovascular (430–438)	198	3.8	3.3–4.3	87	9.3	7.4–11.4	111	2.6	2.1–3.1
Infectious diseases									
Infective and parasitic diseases (009, 035–038, 044, 070–079)	63	21.9	16.9–28.1	24	62.4	40.0–92.9	39	15.6	11.1–21.3
Tuberculosis (011–019)	10	14.5	6.9–26.6	6	42.3	15.4–92.0	4	7.4	2.0–19.0
Pneumonia and acute respiratory infections (481–486, 466, 471)	64	4.9	3.8–6.3	38	15.2	10.8–20.7	26	2.5	1.6–3.6
Respiratory system									
Bronchitis, emphysema, and asthma (491–493)	151	4.9	4.1–5.9	83	15.6	12.6–23.0	68	2.6	2.1–3.3
Other diseases of the respiratory system (510–519)	36	12.2	8.5–16.9	18	35.1	20.8–55.4	18	7.2	4.3–11.4
Malignant neoplasm of larynx, trachea, lung, and pleura (161–163)	181	3.5	3.0–4.1	73	8.1	6.3–10.1	108	2.5	2.1–3.1
Digestive system disease									
Diseases of the oral cavity, oesophagus, and stomach (530–535)	71	13.6	10.7–17.2	46	54.0	39.5–72.0	25	5.8	3.8–8.6
Digestive diseases (540–577)	97	13.6	11.0–16.6	65	52.7	40.7–67.2	32	5.3	3.7–7.5
Malignant neoplasm of buccal cavity and pharynx (141–150)	84	11.5	9.2–14.3	20	16.2	9.9–25.0	64	3.8	2.9–4.8
Gastrointestinal cancer (151–154, 155–157)	398	8.3	7.5–9.2	251	17.5	15.3–19.7	147	5.2	3.2–6.1
Endocrine disorders									
Diabetes mellitus (249–250)	67	6.5	5.1–8.3	29	16.1	10.8–23.1	38	4.5	4.3–6.0
Other endocrine disorders (242, 245, 268, 270, 273, 276, 277)	38	14.1	10.0–19.4	23	51.0	32.3–76.6	15	6.9	3.8–11.4
Renal disease									
Nephritis and other kidney infections (580–584,590–592)	33	11.4	7.8–16.0	17	24.3	14.1–38.9	16	7.6	4.4–12.4
Other categories									
Mental disorder (290–304)	128	17.7	14.8–21.1	42	41.1	29.6–55.5	86	13.4	10.8–16.8
Other diseases	677	5.1	4.8–5.6	308	9.9	8.9–11.1	369	3.7	3.3–4.1
Non-disease related death									
Accidents (812–819, 826–940)	166	8.5	7.3–9.9	50	14.3	13.5–24.5	116	7.2	6.0–8.7
Suicide (950–958)	73	4.6	3.6–5.8	27	8.6	5.7–12.6	46	3.7	2.7–5.0

*EXP and SMR for cirrhosis-related death are not reported because a liver cirrhosis-related death requires a diagnosis of liver cirrhosis.

disease. Survival was particularly poor within the first year after the initial hospitalization for cirrhosis and in patients with alcoholic and nonspecified cirrhosis.

Our study has important strengths and limitations. We used nationwide, population-based registries from a uniformly organized health care system with complete long-term follow-up data. This large population-based study was well defined and had a considerable advantage in statistical precision over previous long-term follow-up studies [5]. Furthermore, unlike most previous investigators, we were able to adjust for the expected survival in the general population [5]. The limitations of the study included lack of clinical details in the registries, the relatively broad classification of cirrhosis, and lack of data on lifestyle factors that may have contributed to the poor prognosis. This lack of clinical details prevented us from further subdivision of the sub-cohorts.

An additional limitation of our investigation is the use of administrative discharge data. It is well known that diagnoses at discharge are not entirely accurate [20], and liver cirrhosis may have been misclassified in 5% to 10% of the cases listed in the NRP [21]. This lack of specificity may have led us to underestimate the mortality associated with liver cirrhosis because most of the misclassified cases were likely to have had a more benign liver disease than cirrhosis. It is well known that the diagnosis on the death certificate might not be entirely correct [22]. It is thus possible that doctors who filled in the certificates might be biased because they know that the patients have liver cirrhosis. Therefore, liver cirrhosis as cause of death has possibly been overestimated compared with other causes.

An important clinical finding of our study was that the mortality of patients with liver cirrhosis was very high in the first year of follow-up, after which it declined but remained substantially higher than that of the general population. This was true for deaths from cirrhosis-related causes and for death from other causes. This demonstrates that patients with liver cirrhosis are seriously ill at the time of diagnosis and that immediate intensive care is crucial. Death from variceal bleeding is likely to be responsible for a large part of the increased immediate mortality from cirrhosis-related causes, and Sharara et al have proposed a classifica-

Table 3
Observed (OBS) and expected (EXP) number of deaths and cause-specific standardized mortality ratio (SMR) for categories of causes of death according to type of liver cirrhosis during the 12 year follow-up period

	Alcoholic cirrhosis			Primary biliary cirrhosis			Chronic hepatitis			Nonspecified cirrhosis		
Causes of death	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All causes	4230	12.3	11.9–12.7	104	3.8	3.1–4.7	404	4.4	4.0–4.9	2241	11.1	10.7–11.6
All causes without cirrhosis-related disease	1675	5.0	4.8–5.2	59	2.2	1.7–2.8	290	3.2	2.9–3.6	1419	7.1	6.8–7.5
Heart disease	301	3.1	2.7–3.4	19	2.4	1.5–3.8	42	1.6	1.2–2.2	439	6.7	6.1–7.4
Vascular disease	126	3.5	3.0–4.2	8	2.1	0.9–4.1	23	1.9	1.2–2.8	148	5.1	4.3–6.0
Infections	67	8.4	6.5–10.4	1	1.1	0.1–6.2	39	12.6	8.9–17.2	59	8.3	6.3–10.7
Respiratory disease	98	5.4	4.4–6.5	2	1.5	0.2–5.6	11	2.4	1.2–4.4	70	6.9	5.4–8.8
Digestive system disease	83	14.6	11.6–18.1	3	5.0	1.0–14.6	15	7.9	4.4–13.0	67	16.0	12.4–20.3
Endocrine disorders	43	6.1	4.5–8.3	0			10	5.7	2.7–10.2	52	14.4	10.8–18.9
Renal disease	18	13.8	8.2–21.9	1	10.0	0.3–55.7	3	7.5	1.6–21.9	11	11.0	5.5–19.7
All cancers	565	4.9	3.9–4.7	19	2.7	1.6–4.2	77	3.0	2.4–3.8	418	8.8	8.0–9.7
Mental disorders	110	29.5	24.2–35.5	0			5	4.9	1.6–11.5	13	5.9	3.2–10.1
Other diseases	389	8.4	8.2–9.8	9	1.7	0.8–9.5	97	7.8	6.2–9.5	271	8.1	7.2–9.2
Accidents	102	10.5	8.6–12.8	2	2.8	0.3–10.3	25	8.0	5.2–11.9	37	6.2	4.3–8.5
Suicide	57	5.1	4.2–7.1	0			7	2.1	0.8–4.2	9	3.1	1.4–5.9

tion of liver cirrhosis according to the presence of varices [23]. Concerning death from other causes, the increased immediate mortality shows the liver's importance for normal function of other organs and the immune system.

Our findings were consistent with Saunder's 20-year-old study of 512 patients in Birmingham, UK [5]. It showed a 1-year survival rate of 40% to 80% depending on the type of cirrhosis, patients with cryptogenic cirrhosis having the worst prognosis and those with chronic active hepatitis having the best [5]. Our data are not completely new due to lack of updating of the Danish Registry of Death. There are some indications that during the last years the outcome of esophageal varices may have been slightly improved [24,25].

It is well known that the type of liver cirrhosis affects short-term prognosis [26]. This is not only because of differences in the clinical course, but also because of differences in lifestyle and risk factors for liver cirrhosis. Although we do not have the data to examine this, it is likely that some of the excess mortality, particularly the pattern of excess mortality from cardiovascular and respiratory diseases, diabetes, accidents, and suicide, is explained by smoking, alcohol, poor nutrition, and psychiatric diseases. The limitations of our data and the observational nature of our study prevent us from giving detailed guidelines to the clinical care of patients with liver cirrhosis. Probably a multi-disciplinary approach is needed. However, few data exist on the benefit of preventive care of patients with liver cirrhosis [27]. Screening for varices and treatment with nonselective beta-blockers reduce the risk of first variceal bleeding [25]. Liver patients are at increased risk of liver and other types of cancer [28]. However, screening for hepatocellular cancer with AFP and ultrasound and prophylaxis against spontaneous bacterial peritonitis remain controversial [29,30].

In conclusion, our data showed that the prognosis of patients with liver cirrhosis is poor. There was a substantial excess mortality in all types of cirrhosis due to the underlying liver disease and lifestyle factors. Intensive multi-organ care for patients with newly diagnosed liver cirrhosis is crucial.

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