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Liver cirrhosis in southern Sweden

Liver cirrhosis in southern Sweden

Epidemiology and clinical course

Emma Nilsson



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DOCTORAL DISSERTATION

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Title and subtitle: Liver cirrhosis in southern Sweden: Epidemiology and clinical course		
Abstract <p>Background: Liver cirrhosis is the end-stage of many liver diseases. It is characterized by a silent phase until decompensation, defined by ascites, variceal bleeding, or hepatic encephalopathy. In Sweden, the most common cause is alcohol overconsumption, followed by hepatitis C (HCV). Recent Swedish data on the clinical characteristics and survival are scarce. Further, survival after decompensation is presumed to be the same once it has occurred, yet little data support this presumption. Liver cirrhosis is a risk factor for hepatocellular carcinoma (HCC), but the risk is not fully established in all etiologies.</p> <p>Aims: The aims of this thesis were to determine the incidence of cirrhosis, to describe the clinical presentation and clinical course, to study the pattern of survival and causes of death, and to study the risk and outcome of HCC by etiology of liver cirrhosis. We also aimed to study the impact of time of decompensation on the clinical course and survival.</p> <p>Methods: We used population-based medical registries to identify patients diagnosed with cirrhosis between 2001 and 2010, in the Scania region in southern Sweden. Medical records and histopathology data were reviewed to classify patients by etiology and to register clinical parameters. Patients were followed clinically until death, transplantation or December 2011 in Paper I and II with the addition of follow-up for death or transplantation until December 2014 in Paper II. In Paper III and IV, the follow-up period was prolonged until December 2017.</p> <p>Results: A total of 1,317 patients were identified. The crude annual incidence of cirrhosis was estimated at 14.1/100,000. The most common etiologies were alcohol overconsumption, with or without additional causes of cirrhosis, (58%), HCV (13%) and cryptogenic cirrhosis (12%). At diagnosis, 631 patients were decompensated, with ascites in 43%, variceal bleeding in 6% and hepatic encephalopathy in 4%. An additional 387 decompensated during follow-up until December 2017. The cumulative ten-year incidence of decompensation, with death and transplantation as competing risks, was 89% in alcoholic cirrhosis, 58% in HCV and 75% in cryptogenic cirrhosis. By December 2017, 991 patients had died and 91 were transplanted. The total one- and five-year transplantation-free survival were 78% and 43%. Patients with ascites as first complication showed worse survival than patients with ascites at diagnosis (HR 1.60; 95% CI 1.34-1.90). The lowest ten-year survival rates were seen in cryptogenic cirrhosis (11%), alcoholic cirrhosis (18%) and alcohol combined with HCV (12%). Decompensation at diagnosis was an important predictor for death in all etiologies except alcoholic cirrhosis. HCC developed in 200 patients, of which 75 were prevalent (within six months) at cirrhosis diagnosis. The annual incidence of HCC was 1.5% in alcoholic cirrhosis and 4.7% in HCV cirrhosis. The median survival after HCC diagnosis was 4.5 months in alcoholic cirrhosis, 11 months in HCV cirrhosis, and 9.3 months in cirrhosis of remaining causes.</p> <p>Conclusions: We found a low incidence of cirrhosis compared to other European countries. The clinical course and survival in cirrhosis varied by both etiology and disease severity at diagnosis. We also found an association between transplantation-free survival after decompensation and time of decompensation in liver cirrhosis, with better survival if decompensated at diagnosis. In patients with alcoholic cirrhosis, the annual incidence of HCC was 1.5%, supporting a continued need for surveillance. Survival after HCC diagnosis was worst in alcoholic cirrhosis.</p>		
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Liver cirrhosis in southern Sweden

Epidemiology and clinical course

Emma Nilsson



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List of papers

Paper I

Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. **“Incidence, Clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study”**. *Alimentary Pharmacology and Therapeutics*, 2016;43:1330-1339.

Paper II

Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. **“Patients with liver cirrhosis show worse survival if decompensation occurs later during course of disease than at diagnosis”**. *Scandinavian Journal of Gastroenterology*, 2018;53:475-481.

Paper III

Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. **“Clinical course and mortality by etiology of liver cirrhosis in Sweden: a population based, long-term follow-up study of 1317 patients”**. *Alimentary Pharmacology and Therapeutics*, 2019;1-10.

Paper IV

Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. **“Risk and outcome of HCC in cirrhosis in southern Sweden: a population-based study”**. *Scandinavian Journal of Gastroenterology*, Published online: 07 Aug 2019.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACLF	Acute on Chronic Liver Failure
AIH	Autoimmune Hepatitis
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AoCLF	Acute on Chronic Liver Failure
APRI	Aspartate aminotransferase to Platelet Ratio Index
AST	Aspartate Aminotransferase
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Interval
CO	Cardiac Output
CP	Child-Pugh
CT	Computed Tomography
DAA	Direct Acting Antiviral
DNA	Deoxyribonucleic Acid
EASL	European Association for the Study of the Liver
GGT	Gamma-Glutamyltransferase
HBV	Hepatitis B
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C
HE	Hepatic Encephalopathy
HR	Hazard Ratio
HRS	Hepatorenal Syndrome
MELD	Model for End-stage Liver Disease
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic Fatty Liver Disease

NASH	Non-alcoholic Steatohepatitis
PEth	Phosphatidylethanol
PSC	Primary Sclerosing Cholangitis
PBC	Primary Biliary Cholangitis
PIIINP	Procollagen-3 N-terminal peptide
PS	Performance Status
SBP	Spontaneous Bacterial Peritonitis
SVR	Sustained Virologic Response
TACE	Trans-Arterial Chemoembolization
TIMP-1	Tissue Inhibitor of Metalloproteinase
TIPS	Transjugular Intrahepatic Portosystemic Shunt
UCSF	University of California, San Francisco
WHO	World Health Organisation

Introduction

Background

Liver cirrhosis is defined by replacement of normal liver tissue by fibrosis and formation of regenerative noduli (1). Fibrosis develops in response to liver injury that causes apoptosis with subsequent regeneration of hepatocytes and activation of the hepatic stellate cells which transform into myofibroblasts generating large amounts of collagen and other extracellular matrix components. Additionally, Kupffer cells and sinusoidal endothelial cells contribute to the activation of hepatic stellate cells (2).

The clinical course in liver cirrhosis is characterized by two phases: the compensated (silent) phase and the decompensated phase. The silent phase can last several years. The decompensated phase is defined by the onset of ascites, variceal bleeding or hepatic encephalopathy (HE). Some authors also include bacterial infections or jaundice as decompensating events (3-5). As the liver disease progresses, the hepatic resistance to blood flow gradually increases due to morphological and molecular vascular changes, and the pressure in the portal vein increases. Splanchnic vasodilation occurs as an adaptive response and contributes to further increase in portal pressure. Decompensation occurs first when the portal pressure exceeds a clinically significant threshold of 10 mmHg. It has also been suggested that systemic inflammation, caused by translocation of bacterial components from the intestinal lumen to the systemic circulation, acute hepatic inflammation or systemic bacterial infections, is an important contributing factor in development of decompensation (6). Additional clinical consequences of liver cirrhosis are related to impaired liver function, including altered plasma protein synthesis, altered hormone metabolism and diminished bile excretion.

Cirrhosis is the end stage of many liver diseases. While the cirrhotic state was long considered to be irreversible, the modern view is that the fibrosis can regress following treatment of the underlying cause (7). Regression of fibrosis has been demonstrated in chronic viral hepatitis after anti-viral treatment, in non-alcoholic fatty liver disease after bariatric surgery, and in cardiac cirrhosis after heart transplantation (8). As of now, there is no treatment available that effectively targets

the cirrhotic process, but there are ongoing studies that approaches fibrogenesis. These studies aim to prevent the activation of the hepatic stellate cells or to stop the fibrogenic functions in the activated cells (7). Currently, the only curative treatment for liver cirrhosis is liver transplantation.

Diagnosis

In clinical practice, the diagnosis of cirrhosis is based on a combination of clinical findings, diagnostic imaging, elastography, laboratory test and histology. In most cases, cirrhosis can be diagnosed by findings on imaging together with impaired liver function. Basic diagnostic imaging modalities are ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Typical findings include an irregular and nodular liver, small and shrunken liver, hypertrophy of the caudate lobe and splenomegaly or varices indicating portal hypertension. In early stages, however, cirrhosis may be radiologically undetectable (9). In these cases, or to confirm the diagnosis, a liver biopsy is indicated, and the gold standard to assess fibrosis. Cirrhosis is histologically characterized by bridging fibrous septa delineating nodular structures of various size. An important limitation of liver biopsy, in addition to inter-observer and sampling variability, is the invasive nature of the procedure (10). This has led to the development of several non-invasive diagnostic tests, mainly based on measurement of liver stiffness or serum biomarkers of fibrosis. The most widely used method to assess liver stiffness is transient elastography (Fibroscan®), where pressure waves are transmitted through the liver and the measured wave velocity is used as a proxy for tissue stiffness. Fibrosis scores based on blood parameters combine factors measured routinely (*e.g.*, transaminases, platelet count, bilirubin) with or without addition of direct markers reflecting the extracellular matrix in the liver (*e.g.*, hyaluronan, procollagen-3 *N*-terminal peptide). The most widely used scores are aspartate aminotransferase to platelet ratio index (APRI) and the Fibrotest® (11). Additional available diagnostic tools are outlined in Figure 1.

Liver histology scores
<ul style="list-style-type: none"> • Batt-Ludwig (I to IV; cirrhosis = IV) • Ishak (1-6; cirrhosis = 5-6) • Metavir (1-4; cirrhosis = 4A-4C)
Imaging
<ul style="list-style-type: none"> • Ultrasound (including Doppler for portal and hepatic venous flow) • Computed tomography • MRI
Liver stiffness
<ul style="list-style-type: none"> • Fibroscan[®] (transient elastography) • ARFI (acoustic radiation force impulse) • SSWE (supersonic shear wave elastography) • MRI (resonance elastography)
Serum markers
<ul style="list-style-type: none"> • APRI (AST, platelets) • FIB-4 (platelets, AST, ALT, age) • ELF[®] (PIIINP, hyaluronate, TIMP-1) • Fibrotest[®] (haptoglobin, α2 macroglobulin, apolipoprotein A1, γGT, bilirubin) • Fibrometer[®] (platelets, prothrombine time, AST, α2 macroglobulin, hyaluronate, urea, age) • Hepascore[®] (bilirubin, γGT, hyaluronate, α2 macroglobulin, age, gender)

Figure 1: Diagnostic modalities for liver cirrhosis. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; AST aspartate aminotransferase; ALT, alanine aminotransferase; γ GT, gamma-glutamyltransferase; PIIINP, procollagen-3 N-terminal peptide; TIMP-1, tissue inhibitor of metalloproteinase.

Etiology

The main causes of cirrhosis are alcohol overconsumption, hepatitis B (HBV), hepatitis C (HCV), non-alcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and hemochromatosis. Cases with unknown cause of cirrhosis are called cryptogenic.

Alcohol-related liver disease

Alcohol overconsumption is the most common cause of cirrhosis in Europe. Alcohol-related liver disease is suspected in patients with regular alcohol consumption of > 20 g/d in females and > 30 g/d in males together with the presence of clinical and/or biological signs of liver injury. Over time, 10 to 35% of patients

with alcohol overconsumption develop cirrhosis. Factors that influence the risk of developing alcohol cirrhosis include the amount of alcohol consumed, smoking, obesity, and sequence variation in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene. With discontinued intake of alcohol, the early stages of alcohol-related liver disease, such as liver steatosis, are completely reversible, but also more advanced disease can benefit substantially from abstinence (12).

Hepatitis B

About 5 to 10% of individuals infected with hepatitis B are unable to clear the virus and become chronic virus carriers. Worldwide, more than 300 million people are chronically infected. Sweden is a low-endemic country with a prevalence of < 1%. About one third of patients with chronic hepatitis B develop long-term complications such as cirrhosis or HCC. The risk of liver complications is increased in patients showing elevated transaminases, high HBeAg DNA levels, and positive HBeAg status, which signals active virus replication. For patients with a high risk of liver complications, anti-viral treatment with nucleoside analogues or interferon is recommended in order to reduce fibrosis development and the risk of HCC (13).

Hepatitis C

Methods to detect hepatitis C became available in 1990. The estimated prevalence in Sweden is 0.5%. The spread of HCV culminated in the 1970s, most likely due to increased injection drug abuse. About 75% of patients become chronically infected and develop fibrosis that progresses to cirrhosis over the course of around 20 years. Treatment of hepatitis C was long limited to interferon-based regimens, which had poor response rates and significant side effects. In 2014, however, new treatments with direct acting antivirals (DAAs) became commercially available. These interferon-free regimens have transformed the treatment of hepatitis C by achieving sustained virological response (SVR) in more than 90% of patients and are available to most patients thanks to lower toxicity (14, 15).

Non-alcoholic steatohepatitis

NASH was recognized as a disease entity in the 1980s. Together with non-alcoholic fatty liver, it is included in the modern term non-alcoholic fatty liver disease (NAFLD), which refers to fat accumulation in the liver in combination with insulin resistance and associates with the metabolic syndrome. Because of increasing prevalence of obesity and diabetes, the incidence is rising world-wide. Diagnosing NAFLD, includes ruling out alcohol overconsumption. A diagnosis of the NASH subtype requires a liver biopsy showing typical histopathological features, including inflammation. The most important predictor of mortality among NAFLD patients is the degree of fibrosis (16). Several therapies have been evaluated, of which

pioglitazone and vitamin E may be of value in NASH, but there is no generally recommended treatment beside healthier lifestyle (17).

Primary biliary cholangitis

PBC is a rare chronic cholestatic liver disorder that primarily affects middle-aged women. Fatigue and pruritus are common symptoms, but most patients are initially asymptomatic. The diagnosis is based on elevated alkaline phosphatase, indicating cholestasis, combined with a positive test for anti-mitochondrial antibodies. Treatment with ursodeoxycholic acid slows disease progression (18).

Primary sclerosing cholangitis

PSC is a chronic cholestatic disease with male predominance. Approximately 80% of patients also have inflammatory bowel disease. It is diagnosed by typical findings on a cholangiogram with segmental strictures and dilatation of the bile ducts. Although treatment with ursodeoxycholic acid has not been proven effective on mortality, it may still be beneficial in a subset of patients that respond with improved liver tests (19). Apart from liver failure, PSC patients have an increased risk of cholangiocarcinoma, with an annual incidence of 2%. In Sweden, PSC is among the most common causes for liver transplantation (20).

Autoimmune hepatitis

AIH is a chronic autoimmune liver disease with female predominance, diagnosed by histological findings, including inflammation and necrosis of the interface between hepatocytes and portal tracts (“interface hepatitis”) and lymphoplasmacytic infiltration, together with autoantibodies (e.g., anti-nuclear antibodies, smooth muscle antibodies or liver kidney microsomal antibodies) and elevated immunoglobulin G. The initial clinical course ranges from mild to fulminant hepatitis. Anti-inflammatory treatment with steroids and/or azathioprine are given to induce and maintain remission (21).

Rare etiologies

Hemochromatosis, Wilson’s disease and alpha-1 antitrypsin deficiency are genetic metabolic liver diseases that can lead to cirrhosis. In hemochromatosis (*HFE* and other genes), increased absorption of iron leads to accumulation in the liver and other tissues, particularly in men and post-menopausal women. In Wilson’s disease (*ATP7B*), accumulation of copper, due to impaired biliary excretion, causes liver damage, sometimes together with neuropsychiatric manifestations. While most DNA sequence variants that cause alpha-1 antitrypsin deficiency (*SERPINA1*) do not associate with liver disease, homozygous carriers of the *SERPINA1* Z allele have an increased risk of cirrhosis. Cystic fibrosis and congestive hepatopathy, due to right heart failure, are other rare causes of cirrhosis (22-24).

Epidemiology

The etiology of cirrhosis varies geographically. In Europe, cirrhosis is mainly alcohol-related. In Asia and sub-Saharan Africa, more than half of the cases can be attributed to HBV and HCV (25). The predominant cause in Sweden is alcohol overconsumption followed by HCV (26). The mean age at diagnosis in Western countries is around 60 years and two thirds of patients are male. Cirrhosis causes more than one million deaths annually worldwide. According to the WHO mortality database, liver cirrhosis is responsible for 170,000 (1.8%) of all deaths per year in Europe (27). There is a large variation in cirrhosis mortality between different regions, with the highest mortality rates in south-eastern and north-eastern Europe (28). Cirrhosis mortality in Sweden is among the lowest in Europe (25). In 2016, the age-standardized, annual cirrhosis death rate (age > 15 years) in Sweden was 8.4/100,000 in males and 4.2/100,000 in females (27).

Incidence

Studies on incidence of cirrhosis in the Nordic countries are few. Modern studies in Sweden are limited to one from Gothenburg published 2009 with an estimated annual incidence of 15.3 per 100,000 (26). In a study from Denmark, markedly higher annual incidence of 33 per 100,000 was found (29). See Table 1 below for previous studies on incidences in Europe.

Table 1: Studies assessing incidences of cirrhosis in Europe

Country	Incidence per 100,000	Year	Method	Publication
Sweden	15.3	1994-2003	Database search with medical chart review in Gothenburg (600,000 inhabitants).	Gunnarsdottir, 2009 (26)
Denmark	22.5 in men and 11.8 in women	1988-2005	Nationwide hospital registry study on alcoholic cirrhosis.	Jepsen, 2010 (30)
Denmark	33	1996-2006	Database search with review of medical records at Funen (470,000 inhabitants).	Dam Fialla, 2012 (29)
Norway	13.4	1999-2004	Calculated from 93 identified patients with cirrhosis in Aker hospital catchment area.	Haukeland, 2007 (31)
United Kingdom	14.55	1992-2001	Search in UK General Practise Research Database for diagnosis codes.	Fleming, 2008 (32)
Finland	14.6 in men and 4.2 in women	2012	Alcoholic cirrhosis patients identified from Finnish National Inpatient Register.	Färkkilä, 2016 (33)

Prevalence

Using registry data from the United Kingdom, the prevalence of cirrhosis has been estimated at 76/100,000 (age > 25 years) in 2001 (32). However, the prevalence of cirrhosis is challenging to estimate as it is initially asymptomatic, leaving both patients and physicians unaware of its existence. To estimate the true prevalence of liver fibrosis and cirrhosis, screening studies of the general population have been carried out. Using transient elastography, the prevalence of fibrosis has been estimated at 2 to 7%, with cut-off values for liver stiffness from 8.0 kPa to 9.6 kPa (34). Further, two studies also estimated the prevalence of cirrhosis. A French study evaluating biomarkers for fibrosis estimated the prevalence of cirrhosis at 0.3% in a general population above 40 years of age (35). A Spanish study, employing transient elastography followed by liver biopsy for further confirmation, estimated the prevalence at 0.4% in a general population aged 18 to 75 years (34). In all screening studies, the most common cause of unknown fibrosis was NAFLD.

The prevalence of cirrhosis in the population varies between different geographic regions and mainly reflects the prevalence of the major risk factors. Europe has the highest per-capita consumption of alcohol in the world, with some European countries showing increasing consumptions (*e.g.*, Finland, Bulgaria), and others decreasing consumption (*e.g.*, France, Italy) (36). Another major risk factor is NAFLD. Both the prevalence of NAFLD and its long-term consequences increase globally in accordance with increased prevalence of obesity and diabetes. This was shown in an American study where the prevalence of NASH cirrhosis increased from 0.072% to 0.178% over a ten-year period (NASH cirrhosis defined by APRI > 2 and abnormal liver function tests combined with obesity, diabetes, insulin resistance or metabolic syndrome) (37). By contrast, analyses by the WHO indicate that the prevalence of HBV is decreasing (36). Thus, the current trend is an ongoing shift from viral etiologies towards NAFLD, while the role of alcohol remains essentially unchanged, as etiology for cirrhosis.

Natural history and complications

The natural history of cirrhosis is characterized by an asymptomatic state of varying length, followed by a symptomatic state when complications of portal hypertension and/or liver dysfunction occur (Figure 2). The first asymptomatic state without complications is referred to as compensated cirrhosis and the symptomatic state, with complications of variceal bleeding, ascites and/or HE, is referred to as decompensated cirrhosis. As the liver disease progresses, the portal pressure increases. Empirically, it has been found that a portal pressure of 10 mmHg or higher

associates with development of varices or ascites, and portal pressure above this threshold is therefore referred to as clinically significant portal hypertension. Conversely, decompensation usually does not occur below this level (38).

Ascites is the most common decompensating event. The pathophysiology of ascites is splanchnic vasodilation as the sinusoidal pressure increases, causing decreased arterial blood volume which in turn activates vasoconstrictive and anti-natriuretic factors, which leads to sodium and fluid retention. Ascites is clinically detectable at a volume of 1500 ml while smaller volumes can be detected radiologically (42). In about 10% of patients, the ascites does not respond to standard treatment with sodium restriction and diuretics and thus becomes refractory. Ascites is associated with a five-year mortality of approximately 50% (43). A complication to ascites is spontaneous bacterial peritonitis (SBP), defined by ascitic neutrophil count $\geq 0.25 \times 10^9/L$ or a positive ascitic fluid culture. SBP is associated with poor outcome. The in-hospital mortality in patients with SBP is almost 30% (44).

The rate of development of esophageal varices is about 7-8% per year (39). The risk of variceal bleeding after occurrence of varices is estimated to 5-15% per year (40). As the portal pressure increases, so does the risk of portal hypertensive gastrointestinal bleeding. Although the mortality rate with variceal bleeding has decreased over the last decades from 50% to 10-20% owing to better management with vasopressors, antibiotics and early endoscopy, variceal bleeding is still a critical condition. Comparing bleeding from varices and peptic ulcers in patients with liver cirrhosis, a recent study reported similar 45-day mortality rates in both groups (19% vs 17%), and the cause of death was mostly related to liver failure or comorbidities rather than uncontrolled bleeding (41).

Overt HE is the additional event, apart from ascites and variceal bleeding, that defines decompensation. HE is a brain dysfunction caused by liver insufficiency or portosystemic shunting. The pathogenesis is not completely understood, but a key factor is the accumulation of ammonia in the systemic circulation causing neuronal dysfunction. While there are additional contributory factors, such as inflammation and other neurotoxins, the mainstay treatment of HE is directed towards lowering systemic ammonia levels (45). The ammonia level correlates with the severity of HE and is an independent risk factor for short-term mortality (46). HE manifests with a wide spectrum of neurological or psychiatric abnormalities, ranging from covert, subclinical alterations (*e.g.*, slower reaction time in psychometric tests) to coma. Covert or minimal HE occurs in 20–80% of patients whereas overt HE typically occurs with advanced disease. During the clinical course of cirrhosis, overt HE develops in 30-40% of patients (47). HE is associated with a one- and three-year survival probability of 42% vs 23% (48).

With further decline of liver function, renal dysfunction is common. Traditionally, the diagnosis of renal dysfunction in cirrhosis is defined as a 50% increase in serum creatinine, but since smaller increases in serum creatinine have also been associated with an increased mortality, the term acute kidney injury (AKI) has been adapted. AKI is defined as a change in serum creatinine of $\geq 26.5 \mu\text{mol/L}$ in ≤ 48 h, or a 50% increase in serum creatinine from a known baseline level. AKI can be caused by prerenal, renal, and postrenal factors, and includes the hepatorenal syndrome (49). In addition to renal failure, infections are more common in advanced cirrhosis because of bacterial translocation from the intestinal lumen to the mesenteric lymph nodes or the systemic circulation (50). In 25-35% of patients with cirrhosis, infections are present at admission or develop during hospitalization. Bacterial infections are associated with a 3.75 times higher risk of death in patients with decompensated cirrhosis (51). Acute-on-Chronic Liver Failure (AoCLF) is a relatively new concept. The diagnostic criteria were set in the CANONIC study 2013, which defines AoCLF as an acute decompensation accompanied by one or more organ failures in patients with pre-existing liver disease. It is associated with high short-term mortality. The 28-day mortality ranges from 22 to 77% depending on the number of organ failures (52). The most common precipitating event is bacterial infections. AoCLF can occur at any time during the course of cirrhosis. Finally, a last complication of cirrhosis, especially in HCV cirrhosis, is hepatocellular cancer (HCC), which further adds to the rate of decompensation.

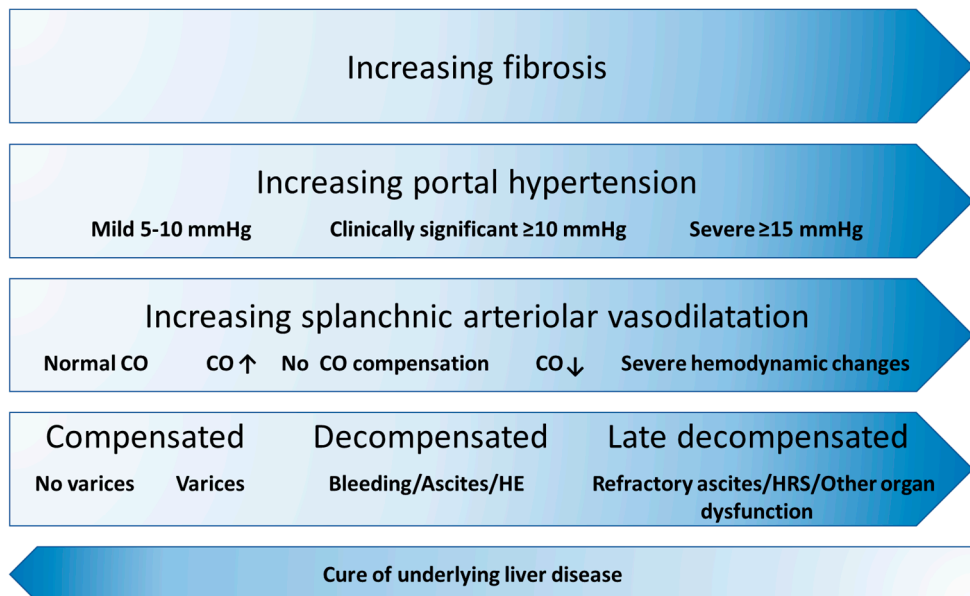


Figure 2: Schematic presentation of cirrhosis progression. CO, cardiac output.

Prognostic scores

To predict mortality, prognostic models have been proposed. The most common are the Child-Pugh (CP) and Model for End-stage Liver Disease (MELD) scores. The oldest model is the CP score (53) based on bilirubin level, prothrombin time, albumin and the presence and/or severity of ascites and HE. It divides patients by severity into three groups: mild (A=5-6), moderate (B=7-9), and severe (C=10-15). A drawback is that it requires subjective assessment of ascites and HE. When prioritizing patients for liver transplantation, objective evaluation is important. In this situation, the MELD score is widely used. This score was developed in 2001 as a predictor of short-term mortality among patients undergoing placement of transjugular intrahepatic portosystemic shunt (TIPS) (54). It is based on bilirubin, prothrombin time and creatinine, and is defined as $3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$. Increasing MELD associates with increased mortality (54). In a validation study, the accuracy of MELD to predict death within three months was 0.87 for hospitalized patients (vs 0.84 for CP score) (54). MELD also predicts survival in patients with cirrhosis who have infections, variceal bleeding, as well as in patients with fulminant hepatic failure and alcoholic hepatitis (55). Extensions of MELD have been proposed, such as adding plasma sodium level to further improve the predictive value (56).

Clinical states in cirrhosis

Clinical states in cirrhosis have been defined to enable stratification by mortality risk. The estimated median survival in patients with compensated cirrhosis is 12 years, but only two years in patients with decompensated cirrhosis. These estimates originate from two prospective studies from 1986 and 2001, totalling 1,649 patients. Based on these studies, four clinical states were defined at the Baveno IV consensus conference in 2006. State 1 represents compensated cirrhosis without varices. As long as patients remain in this stage, mortality rate is 1% per year. State 2 represents compensated cirrhosis with varices and has a mortality rate of 3.4% per year. State 3 and 4 are both decompensated cirrhosis where state 3 is defined as ascites with or without varices and state 4 as variceal bleeding with or without ascites (57). In these states, mortality rates are 20% and 57%, respectively. A fifth state has also been proposed, defined by the occurrence of any second decompensating event (5) with a five-year mortality of 88%. In late, advanced decompensation presenting with complications such as infections and kidney failure, a sixth state is reached. This state has a one-year mortality around 60-80%. While increasing Baveno IV state associates with increased mortality, there is no predictable sequence in which these states occur. They can therefore not be regarded as progressive disease states (6).

Survival

In 2006, a systematic review on the natural history of cirrhosis, based on a total of 118 studies, was published (57). The median survival time, calculated from 32 eligible studies, was 33 months, though the variation between different studies was wide. Among the problems associated with comparing survival estimates between studies, the authors identified inclusion of patients at different disease states without stratification by complications, and heterogeneity of the patient cohorts in terms of cirrhosis etiology. Further studies on survival are presented in Table 2 below.

Table 2: Studies assessing survival of cirrhosis

Country	Population (patients)	Etiology	Survival /Mortality	Publication
Denmark	466	100% Alcohol	17% one-year mortality in compensated cirrhosis vs 29% after development of ascites	Jepsen, 2010 (30)
Spain	165	100% Alcohol	61 months median survival in decompensated cirrhosis	Alvarez, 2011 (3)
England	4537	51% Alcohol 5.2% Viral	14% and 38% one-year mortality in compensated vs decompensated cirrhosis	Fleming, 2010 (58)
Denmark	1369	79% Alcohol 5% HCV	34% one-year mortality	Dam Fialla, 2012 (29)
Germany	632	56% Alcohol 44% Non-Alcohol	47 and 42 months mean survival in alcohol vs non-alcohol cirrhosis	Wiegand, 2012 (59)
Italy	455	30% Alcohol 41% HCV	16% one-year mortality in decompensated cirrhosis	Bruno, 2013 (60)
Cuba	402	100% HCV	1% one-year mortality in compensated cirrhosis	Gomez, 2013 (61)
Greece	552	31% Alcohol 41% HCV	115 and 55 months median survival in compensated vs decompensated cirrhosis	Samonikis, 2014 (62)
England	5118	54% Alcohol 11% Viral	30% one-year mortality	Ratib, 2014 (63)
Italy	494	3% Alcohol 16% Alcohol+ HCV 66% HCV	38% two-year mortality after development of ascites	DÁmico, 2014 (5)

Comorbidity

Comorbidities are the patient's other diseases apart from cirrhosis. While comorbidities neither cause, nor are consequences, of cirrhosis, they affect mortality and are therefore clinically important. Additionally, they can be confounding factors in epidemiologic studies. To measure the total comorbidity, various scoring systems have been developed. A commonly used system is the Charlson comorbidity index, which is calculated as the sum of the numeric scores from one to six according to their effect on mortality to 17 diseases. Another comorbidity scoring system is Circom, which is developed specifically for cirrhosis patients and is based on information about nine diseases (64, 65). Comorbidity increases the risk of cirrhosis-related death in the first year of follow-up, but not later (66).

Diabetes is the best studied comorbidity in cirrhosis. In cirrhosis, diabetes may be either underlying type 2 diabetes or a consequence of the liver disease, so called hepatogenous diabetes. Potential mechanisms for hepatogenous diabetes are peripheral insulin resistance due to HCV infection or NAFLD, decreased insulin clearance causing hyperinsulinemia, which can cause insulin resistance, and beta-cells dysfunction (67). In patients with diabetes, it is known that poor glycemic control increases development of diabetic micro- and macroangiopathy (68). However, in patients with cirrhosis the risk of cirrhosis complications seems to outweigh the diabetic complications (69, 70). Whether better glycemic control improves cirrhosis prognosis is hard to assess, yet it is shown that metformin treatment of diabetes may reduce the risk of developing HCC (71, 72). Diabetes has an impact on survival in liver cirrhosis. Most studies show that diabetes is associated with a lower survival (73, 74). In other studies, diabetes associates with complications such as SBP and HE (73, 75, 76).

Hepatocellular carcinoma

Globally, HCC is the fifth most common malignancy in men and the seventh most common malignancy in women. It causes more than 700,000 deaths annually (77). In 70-90% cases, HCC develop in patients with chronic liver disease (78). Liver cirrhosis of any cause is a risk factor for development of HCC. Apart from cirrhosis, risk factors for HCC include obesity, type 2 diabetes and smoking (79). HCC is twice as common in men as in women. The highest prevalence of HCC (80%) is seen in East Asia and sub-Saharan Africa where the dominant risk factor is chronic infection with HBV. In North America, Europe, and Japan, the main risk factor is HCV. In total, 54% and 31% of cases worldwide can be attributed to chronic HBV and HCV infection, respectively (80).

Apart from the geographical variation, which reflects variation in the spectrum of liver diseases, the risk of developing HCC depends on the underlying cirrhosis etiology (81-86). In compensated HBV cirrhosis, the annual HCC incidence ranges from 2.2 to 4.3%. Patients with chronic HBV, but without cirrhosis, also have an increased risk, estimated at 0.1 to 1.0% (78). In HCV cirrhosis, the annual incidence is estimated to 3-5%, though the risk is reduced in patients who show sustained virologic response (SVR) in response to treatment with either interferon-based regimens or DAAs (81). In a study on compensated HCV cirrhosis, the one-year HCC incidence was 2.1% in patients with SVR after DAA treatment, and 6.6% in patients not achieving SVR (87). In a prospective study on NASH cirrhosis, the yearly cumulative incidence of HCC was 2.6% (88). Alcoholic cirrhosis is another underlying cause of HCC, but the estimated risk varies in different studies (89). In a population-based record study in the United Kingdom, the one-year cumulative incidence was 0.3% whereas the annual incidence was 2.9% in a recent prospective study in France and Belgium of biopsy-proven alcoholic cirrhosis (90, 91). In cirrhosis due to AIH, the incidence is low compared to other etiologies, with an annual HCC incidence of 1.0% in a meta-analysis and 0.3% in a Swedish study (82, 92). A complicating factor in estimates of HCC incidence is missed cases in studies based on data from cancer registries due to underreporting when HCC is diagnosed using imaging techniques alone, excluding histopathology (89, 93).

Cancer surveillance aims to detect tumors early, when treatment with curative intent is possible. This is important in HCC as the outcome is poor, with a five-year survival of 18% (94). Surveillance for HCC is considered cost-effective in patients whose risk of HCC is 1.5% per year or higher (95). Although lower HCC incidences are seen with some cirrhosis etiologies, (e.g., AIH and PBC), patients with liver cirrhosis as a group have an annual HCC incidence of 2-4% (82, 96). Due to the high risk of HCC in cirrhosis, guidelines recommend surveillance in all patients, irrespective of etiology. However, patients with advanced liver disease or advanced comorbidity, who are not eligible for treatment with curative intent, are not surveyed. The current guidelines recommend HCC surveillance with ultrasound twice yearly in all patients with cirrhosis (EASL and AASLD) with or without alpha-fetoprotein (AASLD) (97, 98). The time interval is based on tumor doubling times and performed surveillance studies (99). Detection by surveillance associates with better survival, as ultrasonography allows diagnosis at an early stage (100). Surveillance in cirrhosis of most etiologies, such as HCV, HBV and NASH, is widely accepted, as the HCC risk is high in these groups. Yet, in alcoholic cirrhosis, representing a large group of surveyed patients, the value of HCC surveillance has been questioned by authors who have observed an annual incidence less than 1.5% in this group (89, 90).

In patients with cirrhosis, the diagnosis of HCC is based on non-invasive criteria and/or pathology, whereas histopathological confirmation is required in non-cirrhotic patients (98). The non-invasive criteria apply to nodules ≥ 1 cm and are based on imaging techniques with multiphase CT, dynamic contrast-enhanced MRI, or contrast-enhanced ultrasonography. Malignant lesions receive their blood supply via the hepatic artery whereas benign lesions are supplied by the portal system. This vascular shift in the malignant lesions makes it possible to distinguish them from benign lesions on imaging. In patients with nodules smaller than 1 cm, surveillance every 3 to 4 months is recommended.

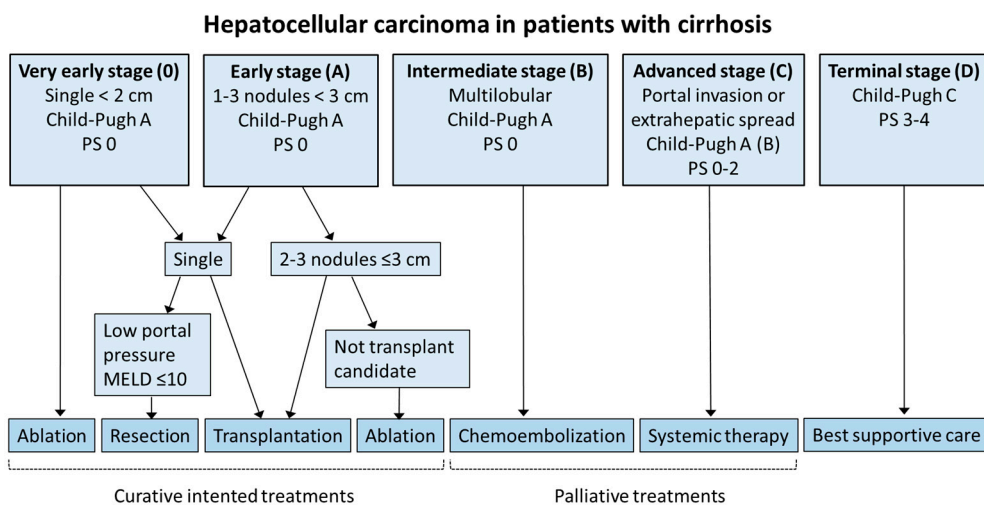


Figure 3: BCLC staging system and treatment strategy as presented in EASL clinical practical guidelines (98). Performance status (PS) 0 refers to asymptomatic patients, PS 1-2 to patients with cancer-related symptoms and 3-4 to patients confined to bed or chair $\geq 50\%$, in the WHO score.

To assess prognosis in patients with HCC, not only the tumor burden, but also liver function and performance status must be taken into account. The most common staging system that includes all of these factors is the Barcelona Clinic Liver Cancer (BCLC) system, which links the HCC stage to treatment strategy (Figure 3) (101). Treatment options in HCC are surgery (resection or liver transplantation), locoregional therapy (radiofrequency ablation or chemoembolization), and systemic therapy (sorafenib). Liver transplantation potentially cures both the underlying cirrhosis and the tumor but can only be considered if the tumor burden is limited. To select patients with favorable post-transplant survival, the Milan criteria (defined as a single nodule ≤ 5 cm or up to three nodules ≤ 3 cm, and no macrovascular invasion or extrahepatic spread) were proposed in 1996 and have been adopted by

transplant clinics since. Patients with tumors that meet the Milan criteria have a five-year survival after transplantation of 70% (102). Several expansions of the Milan criteria have been proposed, with similar survival rates. The best validated are the University of California San Francisco (UCSF) criteria, which are defined as a single nodule ≤ 6.5 cm or 2–3 nodules ≤ 4.5 cm with a total diameter ≤ 8 cm (103). The UCSF criteria are the suggested criteria in Swedish HCC therapy guidelines. The median overall survival after HCC diagnosis ranges from 5.7 to 40.6 months (104). Patients who are only eligible for best supportive care due to large tumor mass or poor liver function, have an estimated survival time of three months.

Aims

The aim of this thesis is to describe liver cirrhosis in a modern population-based cohort from southern Sweden. The specific aims are:

- To calculate the incidence and prevalence of liver cirrhosis.
- To describe the etiological spectrum and survival.
- To describe the clinical presentation at diagnosis and events during the clinical course.
- To understand how cirrhosis etiology impacts on clinical course, survival and mortality.
- To understand how mortality and cause of death depend on decompensation and etiology in liver cirrhosis.
- To understand how time of decompensation impacts on the clinical course.
- To determine HCC risk in patients with alcoholic cirrhosis compared to other cirrhosis etiologies.

Patients and methods

Study cohort

To identify patients residing in the Scania region who received a diagnosis of cirrhosis between January 1, 2001, and December 31, 2010, we searched the Patient Administrative System in Skåne (PASIS) for ICD-10 codes indicating liver disease. The ICD-10 codes used were K70.3, K74.6, B18.2G, B18.1, K76.0, K83.0, K73.2, K75.4, I85.0, I85.9, C22.0 and C22.9. To identify additional patients, we retrieved data on liver biopsy from the common pathology registry in the Scania region (SymPathy) using SNOMED codes for cirrhosis (T-code 56 for liver; M-code 495 for cirrhosis). The search was carried out at all hospitals in the Scania Region, including Skåne University Hospital in Lund and Malmö, two midsize hospitals, and six smaller hospitals. In 2005, the population in Scania region was 1,169,464. All patients ≥ 18 years of age who were diagnosed with cirrhosis for the first time during the study period were included. Clinical data were obtained from medical records. The registered parameters in all patients were etiology of cirrhosis, age, gender, date of diagnosis, and date of complications (ascites, varices, variceal bleeding, SBP, portal vein thrombosis, HCC), serum markers for calculation of MELD at diagnosis and at time of complication, comorbidities at diagnosis, date of transplantation and date of death. In paper IV, we retrieved additional information about tumor size, treatment of HCC, and information required to calculate CP score. Electronic records were available from 2003 at all hospitals and during the whole study period at all major hospitals. All residents in Sweden are provided with a unique personal identification number at birth or immigration which makes it possible to identify and follow patients in population-based registries. The study was approved by the regional Ethics Committee at Lund University, Sweden.

Definitions

Cirrhosis

Patients were regarded as having cirrhosis based on liver biopsy, radiological evidence (*e.g.*, signs of portal hypertension or irregular liver contour), or clinical findings. Serum biochemistry was never the sole diagnostic criterion for cirrhosis.

Etiology of cirrhosis

Patients were categorized into the following etiological subgroups: alcohol, HCV, cryptogenic, NASH, PBC, PSC, AIH and "others". If a patient had two causes of cirrhosis, both were registered. Patients were regarded as having alcoholic cirrhosis when alcohol overconsumption was stated in their medical records. Patients with HCV in combination with alcohol abuse made out a separate group. When alcohol overconsumption was combined with another etiology, alcohol was regarded as the dominant cause. In patients with PSC and AIH-overlap patients, AIH was regarded as the dominant cause and the patients were classified accordingly. Patients were categorized as having NASH when the clinicians used this diagnosis (including patients without histological verification), and patients were regarded as having cryptogenic cirrhosis when the etiology was unclear. Patients were grouped as "others" when a specific cause was known but the total number of patients with this etiology was low. For example, this term was used for patients with cirrhosis due to hepatitis B, hemochromatosis and alfa-1-antitrypsin deficiency.

Comorbidities

At time of cirrhosis diagnosis, concurrent diabetes mellitus, arterial hypertension, ischemic heart disease and history of cerebrovascular insults were registered.

Complications

The decompensating events that were registered were ascites, variceal bleeding and HE. Patients were regarded as having ascites when ascites was clinically diagnosed, but not when it was only detectable radiologically. Patients were regarded as having a variceal bleeding if there were overt signs of bleeding such as hematemesis or melena, or need for at least two units of blood transfusion according to the Baveno IV classification of significant bleeding (105). HE was registered when noted by the treating clinician. Only overt HE was included.

Spontaneous bacterial peritonitis

Patients were regarded as having SBP if a positive bacterial culture of ascites was obtained, or leukocyte count $> 0.35 \cdot 10^9/L$ was found in ascitic fluid.

Model for End-stage Liver Disease

MELD scores were calculated at diagnosis, at time of first complication, and at HCC diagnosis. The formula is: MELD Score = $10 * ((0.957 * \ln(\text{Creatinine})) + (0.378 * \ln(\text{Bilirubin})) + (1.12 * \ln(\text{INR}))) + 6.43$ (54).

Hepatocellular carcinoma

The diagnosis of HCC was defined by histological findings or radiologically using non-invasive criteria (97).

Surveillance

Patients with at least one radiological examination of the liver each year were regarded as in surveillance.

Follow-up

Dates of death and emigration were obtained from the Swedish Civil Registration System, which is linked to the patient administrative system in Skåne (PASiS), used by all participating hospitals. In Paper I and II, all patients were clinically followed until death, transplantation, emigration or end of follow-up until December 31, 2011, with overall survival determined at December 31, 2014, in Paper II. In Paper III and IV, follow-up was prolonged to December 31, 2017. Cause of death was obtained from the retrieved clinical records and, when information was missing in these, from the Causes of Death Register until December 31, 2014.

Statistics

Cirrhosis incidence was calculated per 100,000 person years stratified by year of diagnosis, gender and five-year age group (Paper I). Age-standardized incidence was calculated using the 1976 European standard population (10). Continuous and categorical baseline characteristics were compared between groups using two-sided rank sum and Fisher's exact tests, respectively (Paper II). Follow-up was censored at December 31, 2011 (Paper I); at December 31, 2011 for time to decompensation and at December 31, 2014 for time to death or transplantation (Paper II); and at December 31, 2017 for clinical data, death and transplantation (Paper III and IV). Thirteen patients moved outside the Scania Region within Sweden and were followed for vital status but not in clinical records (Paper I). In 24 cases, follow-up was censored at time of emigration (Paper III).

To estimate survival probabilities, we used Kaplan-Meier's method with Greenwood confidence intervals. To compare time from decompensation to death or transplantation for patients with first decompensating event at diagnosis vs during follow-up, we used log-rank tests, stratified for etiology (Paper II), and only patients with a single decompensating event were included. Cumulative incidence functions for time to decompensating events were estimated using transplantation and death as competing events. To compare cumulative incidence between patient groups, we used Gray's test. To estimate hazard ratios, we used Cox regression with and without adjustment for gender, age group, and prognostic factors at diagnosis, such as MELD, Baveno group, etiology and comorbidity. To test proportional hazards assumptions, we used log-log plots and tests based on Schoenfeld residuals.

To describe the clinical course in Paper III, we used a state occupancy model with the four states: compensated, decompensated, death before decompensation, and death after decompensation (21). In this model, patients who were decompensated at diagnosis are only allowed to transition to the state death after decompensation, and the state probabilities were thus determined by Kaplan-Meier estimates. The state probabilities for patients compensated at diagnosis were determined in steps. First, overall survival and being alive compensated were estimated by means of the Kaplan-Meier method, and the cumulative incidence of death before decompensation was determined with decompensation as competing risk. Then, the probability of death after decompensation was obtained as a difference of total death probability and probability of death before decompensation, and the probability of being alive decompensated was inferred by subtraction using the fact that all four state probabilities sum to 1. Finally, the state probabilities for the combined compensated and decompensated groups were determined by weighing the respective state probabilities with the proportions of compensated and decompensated at diagnosis.

Statistical analyses were done using STATA v12 and v14 (StataCorp LLC, College Station, TX). Gray's test was done using R (106) .

Results

Study cohort

We identified a total of 4,611 patients with liver disease and possible liver cirrhosis. After review of their medical charts, we found that 2,950 patients (mainly autoimmune liver disease (30%), NAFLD (26%) and HCV (17%)) had not reached a cirrhotic stage. Of remaining patients, 339 were excluded as they were diagnosed with cirrhosis before January 2001. Additionally, three were excluded because of lacking identification number necessary for follow-up in national registries, four due to emigration abroad with loss of follow-up, and two were under 18 years of age. In our cohort, we thus included 1,317 patients with cirrhosis of all etiological background, diagnosed between 2001 and 2010. This cohort was analysed in all four studies with different times for end of follow-up.

In most cases, cirrhosis was diagnosed by a combination of radiological and clinical signs, 812 patients in total. Further, 415 patients were diagnosed or verified as cirrhosis on liver biopsy findings and 90 patients were diagnosed only on clinical evidence of cirrhosis. The patients were stratified into nine groups according to the dominating etiology. In cases with several potential etiologies, alcohol was considered as the primary etiology, except for patients with alcohol and HCV who were sufficiently many to form a separate group. In our cohort, 30 patients had hepatitis B, 12 patients had hemochromatosis and 7 patients had alfa-1-antitrypsin deficiency, and they were included in the mixed group of “others”.

Among the 1,317 patients, 2/3 were males and 1/3 were females (Table 3). Median age at diagnosis was 60 years for men and 61 years for women. The most common etiology was alcohol overconsumption solely (49%), followed by HCV (13%), and cryptogenic cirrhosis (12%). Patients with cryptogenic cirrhosis were oldest at diagnosis whereas patients with PSC and HCV were younger than average.

In the total cohort, 53% were in Baveno IV, stages 1 or 2, at diagnosis, varying widely from 39% in alcoholic cirrhosis and 45% in cryptogenic cirrhosis to 82% in HCV cirrhosis and 83% in PSC cirrhosis (Table 3). In Paper III, patients were classified as compensated or decompensated, with decompensation including HE as

well as ascites and variceal bleeding. HE is not included in the Baveno IV classification. As a few patients had only HE at diagnosis, the number of compensated patients were slightly lower in Paper III (52% vs 53%). At diagnosis, 569 (43%) patients had ascites, 78 (6%) patients had variceal bleeding, and 51 (4%) had HE. Portal vein thrombosis was recorded in 32 (2.4%) patients. Median MELD score at diagnosis was 12.3 for the whole cohort. The highest MELD scores were seen in alcohol cirrhosis (14.8) (Table 3). A total of 605 (46%) patients had one or more comorbidities at cirrhosis diagnosis. The most common comorbidities were arterial hypertension (29%) and diabetes (25%).

Table 3. Characteristics of patients at diagnosis of liver cirrhosis in southern Sweden, 2001-2010

	N	Freq %	Gender (M/F)	Median age (10-90 percentile)	MELD (median)	Baveno IV, 1-2, N (%)	Baveno IV, 3-4, N (%)
Overall	1317	100	869/448	60 (46-76)	12.3	703 (53)	614 (47)
Alcohol	645	49	467/178	61 (49-73)	14.8	249 (39)	396 (61)
HCV	170	13	113/57	53 (42-72)	9.3	139 (82)	31 (18)
Alcohol and HCV	114	8.7	85/29	51 (44-60)	11.5	66 (58)	48 (42)
Cryptogenic	153	11.6	90/63	73 (57-83)	10.9	69 (45)	84 (55)
NASH	53	4	31/22	66 (53-76)	9.2	42 (79)	11 (21)
PBC	34	2.6	6/28	70 (56-83)	8.4	24 (71)	10 (29)
PSC	30	2.3	18/12	55 (25-73)	10.4	25 (83)	5 (17)
AIH	70	5.3	23/47	66 (34-78)	11.2	52 (74)	18 (26)
Other	48	3.6	36/12	56 (35-74)	10.7	37 (77)	11 (23)

Incidence and prevalence (Paper I)

Over our 10-year study period, the crude annual incidence of cirrhosis in southern Sweden was estimated at 14.1/100,000, 19.1 for men and 9.4 for women. The corresponding age-standardized incidences for men and women were 17.8 and 8.8 per 100,000 person-years. We observed no significant changes in incidence during the study period. The incidence was highest at ages 60-69 years in men and at ages 65-75 years in women (Figure 4). The Scania region population, aged 18 years or older, was 994,464 inhabitants yielding a crude prevalence “within 10-years cirrhosis” of 66.7 per 100,000 inhabitants. The prevalence was 80.1 per 100,000 for men and 43.8 for women.

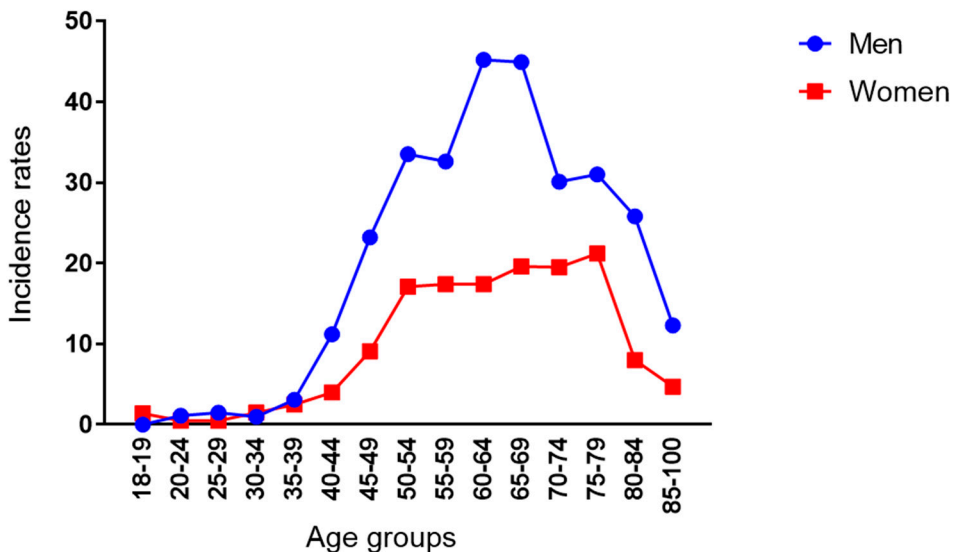
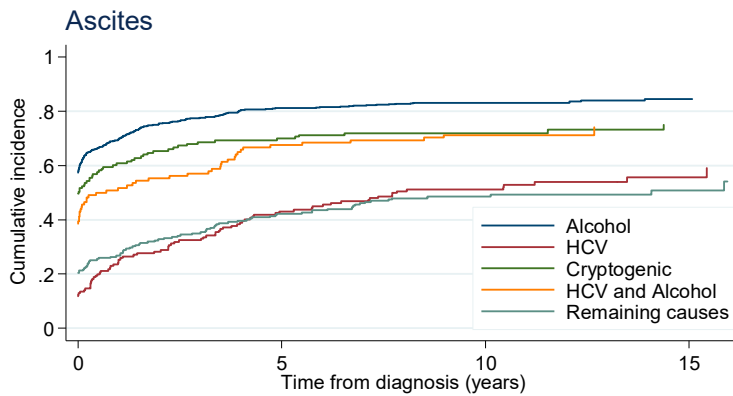


Figure 4: Incidence rates of cirrhosis per 100,000 person years for men and women plotted by age groups

Clinical course of cirrhosis (Paper II and III)

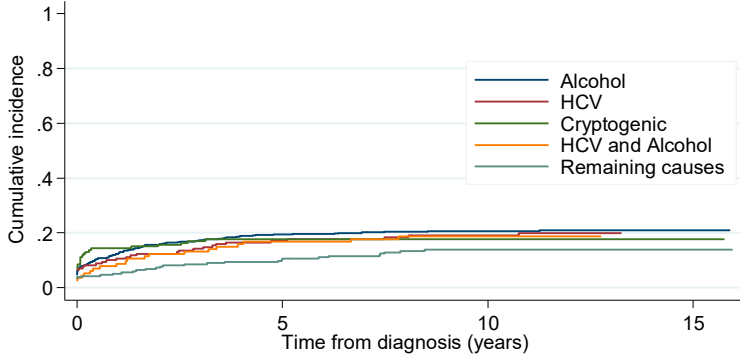
During the clinical course, a total of 938 patients (71%) developed ascites, 246 (19%) variceal bleeding, and 438 HE (33%). The cumulative incidences of decompensation, i. e. ascites, variceal bleeding and/or HE, with death and transplantation as competing risks at one and ten years of follow-up was 59% and 77%, respectively (Figure 5). Among the 688 patients initially compensated, a

further 387 (56%) patients decompensated until end of follow-up, December 2017. In the patients initially compensated, the cumulative incidences of ascites, variceal bleeding and HE after 10 years were 43%, 13% and 26%, respectively. At the end of December 2017, 991 patients had died. Among the 91 patients who received a liver transplant, 34 had died. The median follow-up for surviving patients was 10.8 years (range 0.27-17.0).



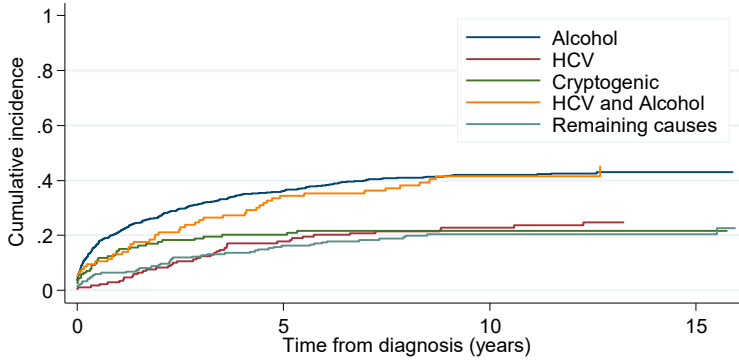
Alcohol	644	61	24	3
HCV	170	72	36	7
Cryptogenic	153	23	7	2
HCV&Alcohol	114	22	7	0
R.causes	235	102	41	11

Variceal bleeding



Alcohol	644	205	71	12
HCV	170	72	35	7
Cryptogenic	153	28	8	3
HCV&Alcohol	114	36	9	0
R.causes	235	124	52	12

HE

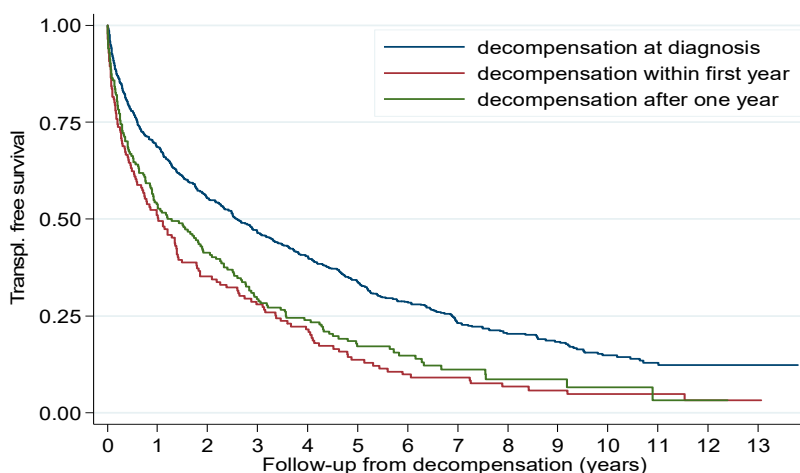


Alcohol	644	61	24	3
HCV	170	72	36	7
Cryptogenic	153	23	7	2
HCV&Alcohol	114	22	7	0
R.causes	235	102	41	11

Figure 5: Cumulative incidences of ascites, variceal bleeding and HE, with death and transplantation as competing risks. Remaining causes include AIH, PSC, PBC, NASH and others.

Decompensation at diagnosis vs during follow-up

In Paper II, we examined whether time to death/transplantation after decompensation differ if the patients were decompensated at the time of diagnosis or decompensated during follow-up. In all, 629 (48%) patients were decompensated (having ascites, variceal bleeding and/or HE) at diagnosis and 327 (48%) of initially compensated patients developed decompensation during follow-up until December 2011. Patient characteristics were compared between these groups at the time of decompensation. No differences were found in terms of gender, age, MELD scores, rates of comorbidities, or percentage of patients treated in university clinics, but HCC and portal vein thrombosis were more common in patients decompensating during follow-up (2.9% vs 14.7%, $p < 0.001$, 3.2% vs 8.3%, $p = 0.001$). The survival was better in patients who were decompensated at diagnosis. Their five- and ten-year transplantation-free survival rates were 34% and 15% whereas the survival rates, after decompensation, in patients who developed decompensation during follow-up were 16% and 6%, respectively (Figure 6).



Dx	629	344	251	143	87	36	8
<1 year	141	49	30	13	8	4	1
>1 year	184	76	42	17	7	2	1

Figure 6: Transplantation-free survival from time of decompensation in patients decompensated at diagnosis and with decompensation during follow-up.

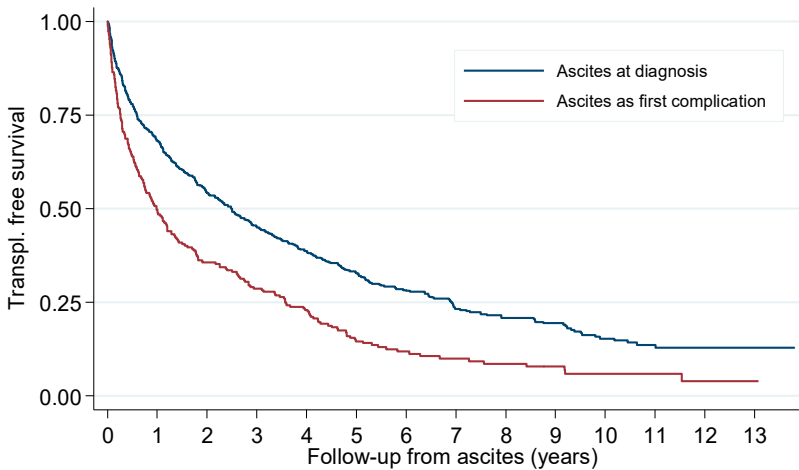
The adjusted hazard ratio (HR) for death/transplantation for patients who developed decompensation during follow-up was 1.57 (95% CI 1.35-1.83) compared with patients who were decompensated at cirrhosis diagnosis. The excess risk of death/transplantation remained after additional adjustment for MELD score, comorbidities, HCC and portal vein thrombosis (Table 4).

Table 4: Hazard ratio (95% CI) for first complication during follow-up vs at diagnosis. Analysis of time from first complication to death/transplantation. All analyses were stratified by etiology.

Type of first complication	Univariate HR	HR adjusted by age and sex	HR adjusted by age, sex, MELD, HCC and portal vein thrombosis.
Any complication (including ascites, variceal bleeding and/or HE) n=954	1.62 (1.39-1.88) p<0.001	1.57 (1.35-1.83) p<0.001	1.50 (1.28-1.77) p<0.001
Ascites n=732	1.60 (1.34-1.90) p<0.001	1.54 (1.29-1.83) p<0.001	1.38 (1.15-1.67) p=0.001
Variceal Bleeding n=83	2.27 (1.34-3.86) p=0.002	2.21 (1.29-3.79) p=0.004	1.90 (0.98-3.68) p=0.06
HE n=61	1.38 (0.71-2.70) p=0.35	1.27 (0.63-2.53) p=0.50	2.62 (1.15-5.96) p=0.02

Clinical course with ascites as first complication

Ascites was the most common complication. A total of 938 patients (66%) developed ascites by December 2017 (Table 3). Ascites as the only complication at diagnosis was found in 505 (38%) patients. With follow-up until December 2011, 102 (7.7%) of initially compensated developed ascites as first complication during the first year, 72 (5.5%) after one to three years and 54 (4.1%) later, in total 228 patients. In Paper II, we studied how time of first appearance of ascites during the clinical course influenced survival. We found better survival in patients with ascites as the sole complication at diagnosis than in those who developed ascites as first complication during follow-up with one- and five-year survival rates of 68% and 33% compared to 50% and 15% respectively (Figure 7).



Ascites at dx	505	270	193	112	70	30	8
Ascites later	227	81	51	19	11	4	1

Figure 7: Transplantation-free survival by ascites at diagnosis or as fist complication during follow-up

The HR for death or transplantation in patients developing ascites during follow-up was 1.60 (95% CI 1.34-1.90). Although HCC at first appearance of ascites was more frequent in patients with ascites during follow-up compared with patients with ascites at time of cirrhosis diagnosis (15.8% vs 3.2%, $p < 0.001$) the excess risk of death/transplantation persisted (HR 1.38 (CI 1.15-1.67)) after stratification and adjustments (Table 4).

Clinical course with variceal bleeding as first complication

A total of 246 patients ever experienced variceal bleeding until December 2017. In 44 (3.3%) patients, this was the initial complication at cirrhosis diagnosis and a further 39 (2.9%) patients had variceal bleeding as the first complication during follow-up until December 2011 (Table 3). As for ascites, we found better survival in patients with variceal bleeding as the sole complication at diagnosis than in those with variceal bleeding as the first complication during follow-up. The one- and five-year survival rates were 91% and 43% vs 66% and 21%, (Figure 8). The HR for death/transplantation was 1.9 (95% CI 0.98-3.68) after stratifications and adjustments (Table 4).

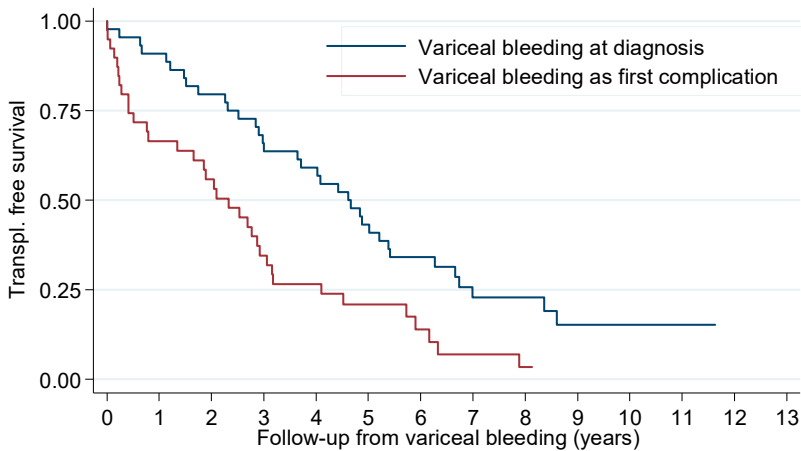


Figure 8: Transplantation-free survival by variceal bleeding (VB) at diagnosis or during follow-up. P-values determined by log-rank tests stratified by etiology

Clinical course with hepatic encephalopathy as first complication

In our cohort, a total of 438 patients developed HE until December 2017 (Table 3). Only 15 (1.1%) patients had HE as the sole complication at diagnosis and 46 (3.5%) developed HE as the first complication during follow-up by December 2011. The patients with HE had the highest MELD scores compared to patients with other decompensating events, representing a more advanced cirrhosis, but the MELD score did not differ between patients with HE at diagnosis and patients with HE developed during follow-up. One- and five-year survival rates, for patients with HE as the sole complication at diagnosis compared with HE as first event during follow-up, were 53% and 27% vs 43% and 15%, respectively.

Clinical course by etiology

In Paper III, we examined whether different etiology of cirrhosis influenced the clinical course. The largest group of patients were alcoholic cirrhosis, accounting for 49% of the total cohort. In these patients, the prevalence of ascites at diagnosis was 59%. The corresponding proportions were 50% in cryptogenic cirrhosis and less than 24% in patients with HCV, PSC, PBC, AIH and NASH cirrhosis (Table 5). In alcoholic cirrhosis, patients without ascites at diagnosis also developed ascites

more frequently during follow-up (cumulative incidence, with death and transplantation as competing risks, 55% after five years) than patients with HCV (35%), cryptogenic (40%), NASH (25%) and AIH (17%) cirrhosis.

In the total cohort, 6% had variceal bleeding at cirrhosis diagnosis (Table 5). The five-year cumulative incidence of variceal bleeding was 17%. In difference to ascites, we found no significant relation between etiology and prevalence of variceal bleeding at diagnosis. Slightly lower five-year cumulative incidences were seen in AIH (4.3%) and PSC cirrhosis (10%) compared to alcoholic cirrhosis (20%) and HCV cirrhosis (17%).

Few patients (3.9%) had HE as the only decompensation event at diagnosis, whereas 29% developed HE during follow-up (Table 5). In subgroup analysis, we observed a higher five-year cumulative incidence of HE in alcoholic cirrhosis, both with and without concomitant HCV (36% and 35%, respectively), compared to cirrhosis caused by HCV (18%), PSC (6.7%), or AIH (14%).

Table 5: Major outcome events at diagnosis and during follow-up until December 2017

	N	Ascites at diagnosis, N (%)	Ascites during follow-up, N (%)	Variceal bleeding at diagnosis, N (%)	Variceal bleeding during follow-up, N (%)	HE at diagnosis, N (%)	HE during follow-up, N (%)
Overall	1317	570 (43)	368 (28)	79 (6.0)	167 (13)	51 (3.9)	387 (29)
Alcohol	645	378 (59)	160 (25)	42 (6.5)	91 (14)	32 (5.0)	239 (37)
HCV	170	22 (13)	68 (40)	11 (6.5)	22 (13)	2 (1.2)	37 (22)
Alcohol and HCV	114	45 (39)	37 (32)	4 (3.5)	17 (15)	7 (6.1)	40 (35)
Cryptogenic	153	77 (50)	35 (23)	13 (8.5)	14 (9.2)	6 (3.9)	27 (18)
NASH	53	9 (17)	18 (34)	3 (5.7)	10 (19)	1 (1.9)	15 (28)
PBC	34	7 (21)	13 (38)	3 (8.8)	5 (15)	1 (2.9)	7 (21)
PSC	30	5 (17)	11 (37)	1 (3.3)	2 (6.6)	1 (3.3)	1 (3.3)
AIH	70	16 (23)	10 (14)	2 (2.9)	2 (2.9)	2 (2.9)	8 (11)
Other	48	11 (23)	16 (33)	0	4 (8.3)	0	12 (25)

Survival (Paper I and III)

In Paper I, overall survival was determined at December 2014 with mean follow-up of 4.3 years. At the end of follow-up, 903 patients had died and the five- and ten-year transplantation-free survival were 47% and 27%, respectively. In Paper III, with prolonged follow-up until December 2017, a total of 991 patients had died. The updated one-, five-, ten- and fifteen-year transplantation-free survival rates were 78%, 42%, 22% and 14%.

Survival was better among younger patients and women fared better than men. During the first year of follow-up, patients in Baveno IV stages 3-4 had worse survival compared with patients in Baveno IV stages 1-2, HR 2.62 (CI 2.03-3.38) after adjustment for gender and age. The excess death rate in Baveno IV stages 3-4 remained, but was less pronounced, after the first year of follow-up (HR 1.44; CI 1.23-1.68). The five- and ten-year survival probabilities in Baveno IV stages 3-4 were 36% and 18% compared to 57% and 34% in Baveno IV stages 1-2.

Patients with lower MELD scores had significantly better transplantation-free survival both with and without adjustment for gender and age. The excess death rate with higher MELD was particularly marked during the first year of follow-up. There was no significant difference in transplantation-free survival for patients with or without comorbidities at diagnosis after adjustment for gender and age.

Survival by etiology

In Paper III, we studied how the etiology of cirrhosis effected survival. The one- and ten-year survival rates were lower in alcoholic cirrhosis compared to HCV cirrhosis, 77% and 18% vs 85% and 31%, respectively (Table 6). In alcoholic cirrhosis with concomitant HCV, survival rates were similar to alcoholic cirrhosis. Cryptogenic cirrhosis showed the poorest unadjusted survival rates, 11% at ten years, whereas best survival rates were seen in AIH cirrhosis, 53% at ten years. The ten-year survival rate in NASH, PBC, and PSC and other causes averaged 30%.

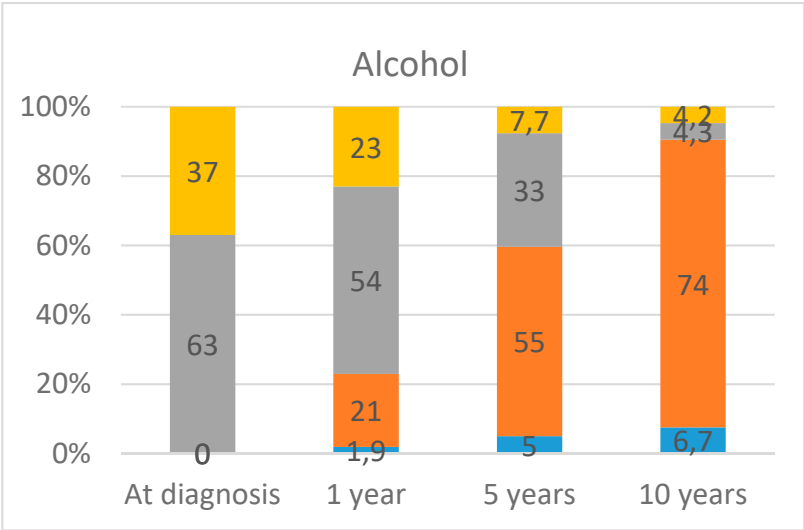
Table 6: One-, five-, ten- and fifteen-years survival by etiology of cirrhosis with follow-up until December 2017

	One-year survival	Five-years survival	Ten-years survival	Fifteen-years survival
Overall	0.78 (0.76-0.80)	0.42 (0.39-0.45)	0.22 (0.20-0.24)	0.14 (0.12-0.17)
Alcohol	0.77 (0.74-0.80)	0.39 (0.36-0.44)	0.18 (0.16-0.22)	0.11 (0.08-0.14)
HCV	0.85 (0.79-0.90)	0.51 (0.43-0.58)	0.31 (0.24-0.38)	0.23 (0.16-0.31)
Alcohol and HCV	0.79 (0.71-0.86)	0.38 (0.30-0.47)	0.12 (0.06-0.19)	.
Cryptogenic	0.63 (0.55-0.70)	0.22 (0.16-0.29)	0.11 (0.07-0.17)	0.08 (0.04-0.14)
NASH	0.89 (0.76-0.95)	0.57 (0.42-0.69)	0.29 (0.16-0.42)	0.12 (0.03-0.29)
PBC	0.82 (0.65-0.92)	0.47 (0.30-0.63)	0.27 (0.13-0.44)	0.14 (0.02-0.39)
PSC	0.80 (0.61-0.90)	0.57 (0.37-0.72)	0.31 (0.15-0.48)	0.31 (0.15-0.48)
AIH	0.85 (0.75-0.92)	0.65 (0.53-0.75)	0.53 (0.40-0.64)	0.42 (0.28-0.55)
Other	0.83 (0.69-0.91)	0.46 (0.31-0.59)	0.35 (0.22-0.48)	0.35 (0.22-0.48)

Survival in patients also differed by etiology, both in patients with and without decompensation at cirrhosis diagnosis. In general, survival was worse for patients decompensated at diagnosis. However, a strong interaction was found between decompensation and alcoholic cirrhosis. When considering only alcoholic cirrhosis, the HR for decompensation (adjusted for sex and age group) was 1.13 (95% CI 0.95-1.35; $p = 0.16$), i.e. the prognostic effect of decompensation in this group was very small. On the other hand, in non-alcoholic cirrhosis the adjusted HR was 1.95 (95% CI 1.54-2.39; $p < 0.001$). Further, time of decompensation during the clinical course affected survival in most etiologies, with worse survival after decompensation if it occurred during the course of disease rather than at diagnosis, particularly in alcoholic, HCV, PBC and AIH cirrhosis. In alcoholic cirrhosis, five-year survival rates were 40% vs 19% with decompensation at diagnosis vs during follow-up.

State occupancy probabilities (Paper III)

At any given time, each patient can be in either of the following four states: alive and compensated, alive and decompensated, dead or transplanted before decompensation, or dead or transplanted after decompensation. At diagnosis, one, five and ten years, we estimated the number patients in each of these four groups. The disease state probabilities were estimated for the whole cohort and by the four largest etiological groups. This allowed us to compare the occupancy states across the major etiologies. We observed a higher probability of death after decompensation in alcoholic cirrhosis than in HCV cirrhosis. On the contrary, the probability of death before decompensation was higher in HCV cirrhosis than in alcoholic cirrhosis (Figure 9). The probability of being alive without decompensation at five years was higher in HCV cirrhosis than in the other groups (38%). In cirrhosis due to alcohol and HCV, the disease state probabilities resembled those of alcohol cirrhosis more than those of HCV cirrhosis.



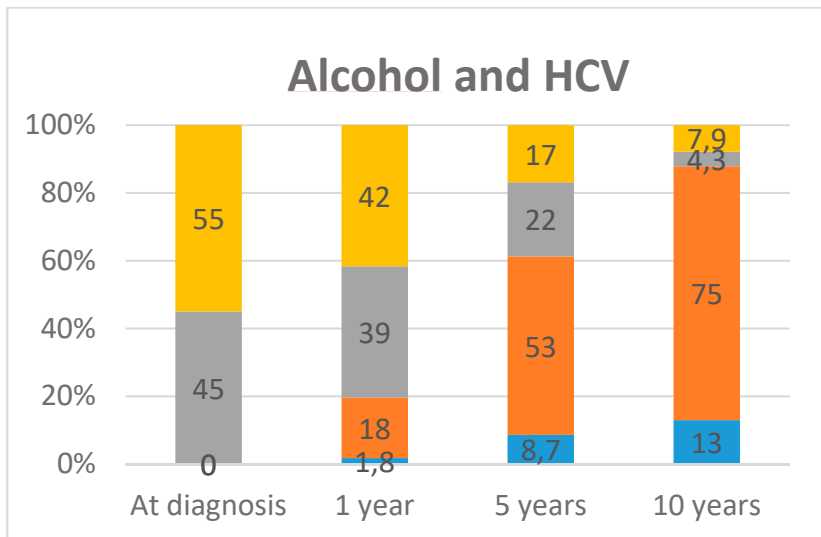
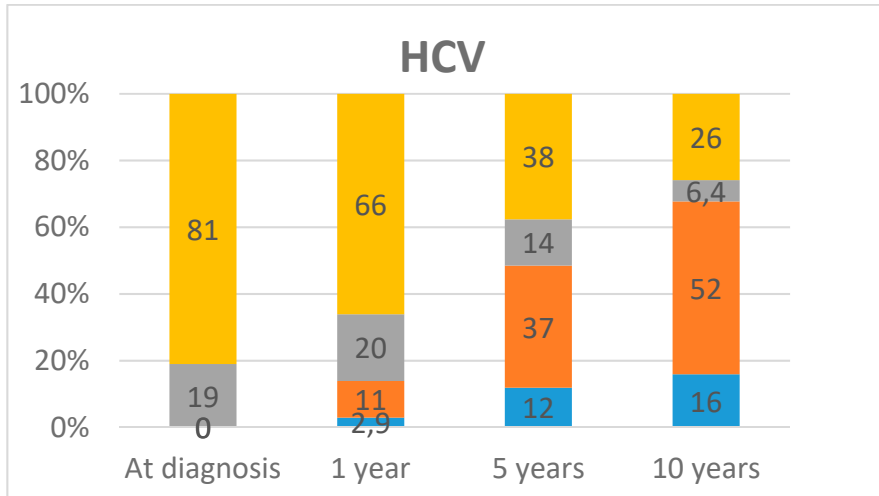


Figure 9: Disease state probabilities: alive compensated (yellow), alive decompensated (gray), dead or transplanted after decompensation (red) and dead or transplanted before decompensation (blue), at diagnosis and after 1, 5 and 10 years follow-up in cirrhosis due to alcohol, HCV and alcohol and HCV.

Mortality (Paper III)

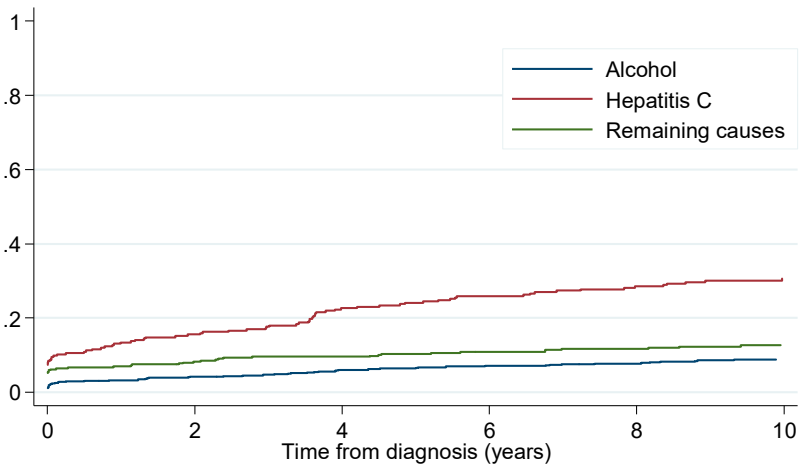
A total of 991 (75%) patients died during follow-up until December 2017. The most common cause of death was liver failure/complications to cirrhosis (49%) followed by HCC (15%) (Table 7). HCC was the cause of death in 45% of patients with HCV cirrhosis, 22% in alcoholic cirrhosis with concomitant HCV and 8.4% of patients with alcoholic cirrhosis. A higher proportion of non-liver related mortality was found in cryptogenic cirrhosis compared to other etiologies, 39% other causes or malignancies. However, these patients were older at cirrhosis diagnosis. In patients who died before decompensation, most deaths were non-liver related, 37%, or other malignancies, 16%.

Table 7: Cause of death by etiology of cirrhosis diagnosed 2001-2010, with follow-up until December 2017

	Deaths N (%)	Liver- related N (%)	HCC N (%)	Other malignancies N (%)	Infection N (%)	Other causes N (%)	Unknown N (%)
Overall	991	489 (49)	152 (15)	84 (8.5)	57 (5.7)	195 (20)	14 (1.4)
Alcohol-related	526	299 (57)	44 (8.4)	46 (8.8)	27 (5.1)	103 (20)	7 (1.1)
HCV	105	36 (34)	47 (45)	3 (2.9)	4 (3.8)	14 (13)	1 (0.9)
Alcohol and HCV	92	45 (49)	20 (22)	2 (2.2)	7 (7.6)	16 (17)	2 (2.2)
Cryptogenic	136	57 (42)	18 (13)	20 (15)	8 (5.9)	33 (24)	0
NASH	39	16 (41)	6 (15)	3 (7.7)	4 (10)	9 (23)	1 (2.6)
PBC	20	9 (45)	5 (25)	3 (15)	0	2 (10)	1 (3.8)
PSC	14	6 (43)	2 (14)	2 (14)	0	3 (21)	1 (7)
AIH	32	13 (41)	1 (3.1)	3 (9.4)	4 (13)	11 (34)	0
Other	27	8 (30)	9 (33)	2 (7.4)	3 (11)	4 (15)	1 (3.7)

HCC in cirrhosis (Paper IV)

In our cohort, 200 patients were diagnosed with HCC during follow-up until December 2017. In 75 of these patients, HCC was present at cirrhosis diagnosis or diagnosed within six months and thus regarded as already prevalent at cirrhosis diagnosis. The total annual HCC incidence, excluding the prevalent cases, was 2.2%. The annual incidences were 4.7% in HCV cirrhosis, 1.5% in alcoholic cirrhosis and 1.3% in cirrhosis due to remaining causes. The one- and ten-year cumulative incidences of HCC in alcoholic cirrhosis, with death and transplantation as competing risks, were 3.3% and 8.8%, respectively (Figure 10). In HCV cirrhosis, the cumulative incidences were 13% and 31%, respectively.



Alcohol	645	401	294	207	143	86
HCV	284	194	141	105	75	46
Remaining causes	388	241	189	138	99	63

Figure 10: Cumulative incidences of hepatocellular carcinoma, with death and transplantation as competing risks, in patients with liver cirrhosis in southern Sweden, diagnosed 2001-2010, and followed until December 31, 2017.

Compared to cirrhosis patients without HCC at diagnosis, patients with prevalent HCC were older (66 vs 60 years) and had a higher frequency of diabetes at cirrhosis diagnosis (41% vs 24%). MELD scores were similar (11.1 vs 12.4). In a multivariate analysis, the HCC risk was higher in patients with HCV cirrhosis (HR 3.74 (2.45-5.71) with alcoholic cirrhosis as reference, with diabetes (HR 1.52 (1.03-2.25), male gender (HR 1.67 (1.10-2.54) and with age (relative risk increase 2.7% per year).

Tumor characteristics

In prevalent HCC, most tumors were large and multinodular, and few fulfilled the Milan criteria (16 cases, 21%). In HCC diagnosed during follow-up, patients in the three etiological groups showed similar proportions of uninodular HCC (40-52%) and most tumors had a total size of 2-8 cm (48-60%). Less than half of cases met the Milan criteria (54 cases, 43%).

Patient characteristics, treatment and outcome

A majority of the 75 patients with prevalent HCC had advanced cirrhosis at the time of HCC diagnosis (Child class B+C=63%). Few patients received treatment with curative intention and median survival after HCC diagnosis was short (5.0 months).

In HCC diagnosed during follow-up, less than half of the 125 cases were diagnosed by surveillance (46 cases, 37%). Advanced cirrhosis or severe comorbidity partly accounted for the lack of surveillance. During follow-up, particularly patients with alcoholic cirrhosis had advanced disease at time of HCC diagnosis, only 28% in Child class A (Table 8). In the alcoholic cirrhosis group, 15 of 40 patients had tumors that fulfilled the Milan criteria and only three of these received treatment with curative intention. In HCV cirrhosis, 30 of 62 patients had tumors that fulfilled the Milan criteria and 21 of these received treatment with curative intent.

The total six-month and one-year survival after HCC diagnosis were 54% and 41%. The overall median survival after HCC diagnosis was 7.7 months (CI 5.0-11). Prevalent cases had worse survival compared to HCC diagnosed during follow-up, 5.0 vs 11 months (p=0.002). Survival also differed by etiology, with worse survival in patients with alcoholic cirrhosis (4.5 months (CI 2.5-10) compared to cirrhosis due to HCV (11 months (CI 6.4-20)) or remaining causes (9.3 months (CI 3.9-13)).

Table 8: Characteristics, treatment and outcome in patients with HCC after 6 months from cirrhosis diagnosis

	Alcohol N=40	HCV (with and without alcohol) N=62	Remaining causes N=23	Total N=125
Patient characteristics at HCC diagnosis				
Ever smoking (previous or active)	25 (63%)	41 (66%)	13 (57%)	79 (63%)
Other advanced disease	12 (30%)	8 (13%)	3 (13%)	23 (18%)
MELD, median	12.9	10.3	13.1	9.9
Child-Pugh score (A, B, C)	A=11 (28%) B=11 (28%) C=16 (40%)	A=33 (53%) B=23 (37%) C=6 (9.7%)	A=10 (44%) B=6 (26%) C=5 (22%)	A=54 (43%) B=40 (32%) C=27 (22%)
AFP median (25-75%) Missing data >200 (% of measured AFP)	60 (5-1942) 5 (13%) 15 (43%)	23 (10-1206) 10 (16%) 23 (44%)	46 (9-3216) 3 (13%) 8 (40%)	47 (7-1817) 18 (14%) 46 (43%)
Treatment				
Curative intention (RF, resection or TX)	3 (7.5%)	26 (42%)	6 (26%)	35 (28%)
Palliative treatment (chemotherapy or TACE)	7 (18%)	13 (21%)	5 (22%)	25 (20%)
Best supportive care	29 (72.5%)	23 (37%)	12 (52%)	64 (51%)
Follow-up				
Surveillance performed	9 (22.5%)	28 (45%)	9 (39%)	46 (37%)
Patients alive December 2017	6 (15%)	17 (27%)	7 (30%)	30 (24%)

Discussion

Epidemiology of liver cirrhosis in southern Sweden

Incidence

We found a crude annual incidence of cirrhosis of 14.1/100,000, which is on par with previous studies from Gothenburg, Norway and the United Kingdom (range 13.4 to 15.3/100,000) but half the incidence found in a Danish study from Funen (33/100,000) (26, 29, 31, 32). The difference in incidence with the latter study may be explained by the higher average alcohol consumption in Denmark compared to Sweden (11.3 liters compared to 6.6 liters adult consumption year 2005) (107). In line with the previous Swedish study from Gothenburg, we found no significant changes in incidence over time (26). However, in the United Kingdom the crude annual incidences increased from 12 to 17 cases per 100,000 between 1992 and 2001 (32, 108), including both alcoholic and non-alcoholic cirrhosis.

Prevalence

In Northern European countries, the age-adjusted prevalence of liver disease is lower than in Eastern and Southern European countries. Within Europe, the prevalences of chronic liver disease range from 447 in Iceland to 1,100 per 100,000 in Romania. In Sweden, the prevalence of liver disease is estimated to be almost as low as in Iceland. The relative contribution of different etiologies of liver disease in Europe varies geographically. Alcohol is the predominant cause in Western Europe, whereas viral hepatitis B and C are more prevalent in Eastern Europe (36). It seems reasonable to assume that the underlying etiology pattern and prevalence for different liver diseases in a given geographic region is reflected in the etiology patterns and prevalence among cirrhosis patients.

We found an estimated prevalence of cirrhosis year 2010 of 67/100,000 adults. In comparison, the prevalence in the United Kingdom was 76/100,000 individuals 25 years or older (32). Thus, the prevalence in our study was slightly lower, partly due to different age at inclusion, but our prevalence is also somewhat underestimated as patients who had lived with cirrhosis more than ten years escaped inclusion. However, prevalence is hard to estimate because of the initial asymptomatic phase when both patients and clinicians are unaware of the cirrhosis, and thus the real

prevalence could be substantially higher. This notion is supported by a French screening program in individuals 40 years and older from the general population, showing a prevalence of ~300/100,000 and a Spanish screening study in individuals aged 18 to 75 years old showing a prevalence of ~400/100,000 (34, 35).

Cirrhosis etiologies

The most common etiology of cirrhosis among the 1,317 patients in our cohort was alcohol (49%) followed by HCV (13%). The etiological spectrum was similar to that reported in studies from Sweden (Gothenburg) and Norway (26, 31). However, in a Danish study from Funen, the proportion of alcohol-related cirrhosis was higher, 79%, accounting for their higher total incidence of cirrhosis, as the incidence of HCV cirrhosis was comparable to ours (29). Relatively few patients in our study (12%) were classified as cryptogenic cirrhosis, compared to a British study where 40% of cases had unspecified etiology (58). However, the latter study was registry-based whereas we reviewed medical records for more thorough classification. We found a higher rate (4%) of NASH-cirrhosis in our study than in older studies, possibly reflecting increased awareness of NASH as a cirrhosis etiology and/or an increased prevalence of NAFLD. In the US, the prevalence of NASH cirrhosis has increased 2.5-fold from 1999-2002 to 2009-2012, with parallel increases in the prevalence of obesity, diabetes, and insulin resistance during the same period (37). To diagnose NASH correctly, a liver biopsy is needed. In our cohort, 58% of NASH cirrhosis were confirmed histologically while the remaining cases were diagnosed clinically on the basis of concurrent metabolic syndrome. Thus, some patients may have been misclassified as NASH but, on the other hand, some patients classified as cryptogenic cirrhosis may have been NASH patients. Additional patients may have been misclassified due to under-detection of alcohol overconsumption, as analysis of the alcohol marker B-PEth was not used during the entire study period.

Clinical course

The clinical presentation and course of cirrhosis in our cohort were comparable with previous descriptions (3, 26, 29, 58, 59). About half of the patients were decompensated at diagnosis, similar to the median decompensation rate of 56% described in the review of 118 studies (23 studies had information on decompensation at diagnosis) (57). A Danish study performed after this review found a 75% initial decompensation rate, but included varices and HRS, in addition to ascites and HE, as decompensating events (29). It is possible that the lower complication rate in our study results from less advanced disease at diagnosis, but the difference in definition of decompensation may also play a part. In accordance

with previous studies on the natural history of cirrhosis, ascites was the most common complication in our study (3, 5). By contrast, HE, which is regarded as a late decompensating event, was the sole complication at diagnosis in only 1.1% of patients but developed in 27% of patients within five years. This finding is in agreement with a study on decompensated alcoholic cirrhosis where HE was the initial decompensation in 2%, but responsible for 28% of readmissions (3). In our cohort, the five-year cumulative incidence of variceal bleeding was 17% (including 6% present at diagnosis), which probably is comparable to the five-year cumulative incidence of 10% in compensated patients previously reported (5). Unlike most of older studies, we applied competing risk analysis for death and transplantation to avoid overestimation of the risk of complications. This is important in cirrhosis since patients can enter several possible disease states (6).

Clinical course by etiology

Previous studies aimed at detecting etiology-associated differences in clinical course have been limited to comparing some patient subgroups, such as alcoholic *vs* non-alcoholic cirrhosis or HCV *vs* NASH (59, 109, 110). In our analysis of clinical course, we instead included all major etiologies. Similar to previous reports, we found the highest prevalence of complications at diagnosis in alcoholic cirrhosis, which also reflects the poor prognosis in this group. In the Danish study on alcoholic cirrhosis, the complication rate at diagnosis was even higher than in our patients with alcoholic cirrhosis, 76% *vs* 63% (30).

Cryptogenic cirrhosis is another subgroup with a poor prognosis. As for alcoholic cirrhosis, the majority of these patients were decompensated at diagnosis (56%). Sometimes cryptogenic cirrhosis is considered a NAFLD spectrum disease. In our study, cryptogenic cirrhosis patients were older than NASH cirrhosis patients, and exhibited a higher rate of decompensation, both at diagnosis and during follow-up. This is consistent with a recent study reporting a more aggressive course for compensated cryptogenic cirrhosis compared to NASH cirrhosis, especially regarding ascites development (111). Thus, NASH and cryptogenic cirrhosis may belong to the same spectrum of diseases but with the difference of more advanced disease progression in cryptogenic cirrhosis (111).

Survival

Liver cirrhosis is the 14th most common cause of death in the world but the fourth in Central Europe (112, 113). In general, the survival rates are low, in fact lower than for major cancers (colorectal, breast, stomach, liver and lung cancer included) (114). The differences in mortality between countries reflect the differences in alcohol consumption and the different rates of HCV and HBV infection (115). In Sweden, the liver-specific mortality is relatively low according to the WHO database (113). In our cohort, the overall five-year survival was 47%, identical to a British cohort (47%), but higher than in a Danish cohort (38%) (29, 63). The worse survival in the Danish cohort is probably due to a higher proportion of alcoholic cirrhosis (79% vs 58% in our cohort). Consistent with previous studies, we found better survival in younger patients, and women fared better than men. Furthermore, survival was better in patients who were compensated at diagnosis than in decompensated patients both with and without adjustment for gender and age (5, 29, 63). In contrast to previous reports, we found no significant difference in survival for patients with or without comorbidities. This may be due to the limited number of concurrent diseases registered in our cohort (65, 66).

The MELD score was initially developed 18 years ago as a more objective predictor of short-term mortality among cirrhosis patients undergoing TIPS placement. Nowadays, the MELD score is widely used to determine prognosis and is also used for organ allocation at transplantation centers (54, 55). As expected, patients with lower MELD scores at diagnosis showed better survival rates than those with higher scores. While the difference was higher the first year of follow-up, the survival rates remained better in patients with MELD scores below ten at diagnosis. Thus, we confirmed that the MELD score is useful for prediction of medium term survival as previously reported, but we also demonstrated that MELD score at diagnosis may predict even extended survival beyond one year (116).

Survival by etiology

In our analysis, cirrhosis etiology influenced overall survival. The shortest ten-year survival rates were observed in cryptogenic and alcoholic cirrhosis (11% to 18%), which is consistent with the higher complication rates in these groups. In accordance with previous reports, alcoholic cirrhosis with concomitant HCV also showed poor survival after adjustment for age and gender (117). We found that most patients with alcoholic cirrhosis were decompensated or dead, already at one year after diagnosis with only 7.7% of patients alive without decompensation at five years. The high and early mortality could explain why decompensation at diagnosis did not predict death in alcoholic cirrhosis, while doing it in all other etiologies.

The best ten-year survival was found in AIH cirrhosis (53%), possibly because of less progressive disease due to immunosuppressive treatment, or overestimation of the histopathological degree of fibrosis at diagnosis due to inflammation, thus accounting for a better prognosis. However, our mortality rates for AIH cirrhosis were similar to those of a recent nationwide Danish study (118).

In HCV cirrhosis, our observed one-year survival after decompensation at diagnosis (75%) was comparable with a previous study from 2004 (82%) (4). Recently, SVR after HCV treatment was found to associate with regression of hepatic fibrosis and reduced risk of cirrhosis-related complications, including HCC (119). In our study, data on HCV clearance were not collected. Furthermore, treatment with DAAs was only available during the latter part of follow-up. Thus, a probable lack of HCV clearance may have worsened survival for HCV cirrhosis in our study (109).

In all, our observations illustrate the importance of taking etiology into account when comparing survival between studies as cohort composition may vary between countries and hospital catchment areas.

Survival after decompensation

Currently, it is presumed that the survival after decompensation in patients with liver cirrhosis is the same, regardless of when in the clinical course the decompensation occurs (3, 5, 30, 58, 120). Our results challenge this view since they indicate that patients who are initially compensated, but decompensate during follow-up, have worse survival than patients who are already decompensated at diagnosis of cirrhosis. In patients who developed ascites during follow-up, the rate of death or transplantation was ~1.5 times higher than in patients who presented with ascites at diagnosis. There could be several explanations for the poor prognosis in patients with late decompensation, including higher age, higher portal pressure, more comorbidities, and sustained alcohol consumption despite a diagnosis of cirrhosis. Yet, we did not observe any differences in these parameters at the onset of decompensation. Other explanations include HCC and portal vein thrombosis. These two complications were more prevalent in patients with first decompensation during follow-up. However, the increased risk of death or transplantation remained after adjustment for these factors. Further, it is conceivable that patients decompensated at diagnosis may have had a temporary, superimposed alcoholic hepatitis at the time of diagnosis, whereas the underlying cirrhosis was perhaps less advanced. As a result, these patients may appear to be in a worse condition regarding their cirrhosis at diagnosis than they actually are, hence survival could be biased upwards. However, the differences in survival were observed in most etiologies, and not only in alcoholic cirrhosis. Finally, a healthier lifestyle, inspired by fear

elicited by the decompensation symptoms and diagnosis of cirrhosis at the same time, could also contribute to better survival.

At the time of our data collection, the ACLF criteria were not yet established. In the CANONIC study, which defined the ACLF criteria in 2013, the 28-day mortality probability was 1.9% in decompensated patients without evidence of ACLF (52). In our study, the 28-day mortality in patients with ascites at diagnosis was 5.2% and 11.4% after ascites development during follow-up. The higher mortality rates in our cohort suggest that ACLF was present among some of our patients and might have been more prevalent among those who developed ascites during follow-up.

Cause of death

In our cohort, 991 of the 1,317 patients had died by the end of 2017. Most deaths were related to cirrhosis (15% HCC and 53% other liver-related complications), which is similar to previous studies (26, 121, 122). In alcoholic cirrhosis, most deaths were liver-related (57%), and HCC dominated in HCV cirrhosis (45%), comparable to a prospective study on compensated HCV cirrhosis where HCC was main cause of death (123). As our patients with cryptogenic cirrhosis were older, they had a higher proportion of non-liver-related deaths compared to other etiologies. In all, the distribution of causes of death and number of patients who died before decompensation (13%) in our material were in line with previous observations. Thus, our cohort of cirrhosis patients in southern Sweden does not differ in large from other cohorts (58) (109).

HCC in cirrhosis

In alcoholic cirrhosis, we found a one-year incidence of HCC of 1.5%. This finding differs markedly from a previous Danish study, reporting a five-year incidence of 1%. Since the current view is that HCC surveillance is beneficial when the one-year incidence is 1.5% or greater, our finding prompts HCC surveillance in alcohol cirrhosis whereas the Danish result indicates the opposite (89). These conflicting results could be explained by differences in data collection methods. Previous studies, including the Danish one, usually rely on Cancer Registries to identify patients with HCC. However, registry validation studies have shown that up to 45% of HCC cases are not reported to Cancer Registries when HCC is diagnosed using imaging alone (89, 93), biasing the HCC incidence downwards. By contrast, our work is based on careful review of the medical records of all participants, which is

a more sensitive method for identifying patients the HCC. In our cohort, 55 out of 176 HCC cases were missing in the Cancer Registry data extracted for 2001 to 2013 (unpublished data), thus on par with previous estimations.

In line with previous reports, we found that high age, diabetes and male gender associate with increased HCC risk (124), and patients with HCV cirrhosis showed the largest HCC risk. Other authors have shown that HCC risk is reduced in patients who show sustained virologic response upon DAA treatment (81). However, DAAs were not commercially available until 2013. Our patients were included from 2001 to 2010 and followed until 2017, and only one patient achieved sustained virological response before HCC diagnosis.

While early detection of HCC associates with better outcome (125), few HCCs were detected early in our study. In alcoholic cirrhosis, 38% of HCC diagnosed during follow-up met the Milan criteria, compared to 34% of HCCs in an Italian study (126). In contrast, 77% of HCCs met the Milan criteria in a recent, prospective study from France and Belgium (20). To detect HCC early, guidelines recommend surveillance with ultrasound in all patients with cirrhosis. Yet, out of the alcoholic cirrhosis patients in our cohort who developed HCC, only one fourth had been subject to liver imaging at least once per year since they received their diagnosis of cirrhosis. In patients with advanced cirrhosis or advanced extrahepatic diseases, surveillance is not recommended due to poor survival irrespective of therapy. Although this partly explains the observed under-surveillance of alcoholic cirrhosis patients, a number of patients in our cohort who did not exhibit contraindications were not surveyed for HCC. Possible causes are unawareness of guidelines, or non-compliance due to alcohol abuse. Internationally, low rates of surveillance are a recognized problem. For example, registry-based studies in the United States suggest that less than 20% of cirrhosis patients are surveyed for HCC (127).

Surveillance is associated with early detection and longer survival (128, 129). Yet, survival analysis may be affected by different biases. For example, when HCC is detected by surveillance, there is a risk that the asymptomatic time period will be included in the survival time, leading to longer apparent survival compared to symptom-detected HCC (lead-time bias). Additionally, aggressive tumors are less likely to be detected by surveillance than tumors with slow progression (length-time bias). In a recent case-control study that took these factors into account, screening was not shown to be associated with a reduced risk of HCC-related mortality (130).

The Milan criteria, in addition to selecting HCC patients for liver transplantation, can also be used to assess if patients are candidates for other curative treatment. In our study, it is noteworthy that few alcoholic cirrhosis patients with HCC who

fulfilled the Milan criteria actually received treatment with curative intention. Similar low rates have been reported in two previous studies (91, 131). The low treatment rate in alcoholic cirrhosis, despite the fact that tumors were within Milan, may be due to liver-related complications possibly aggravated by the tumor, suspected lack of compliance or advanced extrahepatic comorbidity. In comparison, our HCV cirrhosis patients with HCC within Milan criteria were receiving treatment with curative intention to a larger extent. Further, HCV cirrhosis patients were more likely to have been HCC-surveyed, possibly due to better liver function. Finally, the tumors of HCV patients were less advanced at detection (both survey and non-survey detected), possibly due to an awareness of the risk of malignancy among HCV cirrhosis patients with both radiologists and treating clinicians.

We found a shorter one-year survival after HCC diagnosis (41%) compared to most previous studies (64% one-year survival in a French prospective study on alcoholic cirrhosis; 51% and 28% three-year survival in surveyed and non-surveyed patients, respectively, in a meta-analysis including 47 studies) (91, 126, 128). At the same time, results similar to ours were seen in a French study on 1,207 patients. In this study, the lead-time adjusted median survival was 5.7 vs 9.7 months in alcoholic and non-alcoholic cirrhosis, respectively, which compares to the median survival time of 5.0 vs 11 months in our study (131).

Strengths and limitations

Strengths of our studies include that they are based on a large cohort from a well-defined geographic region with a single-provider healthcare and that fact that our cohort was followed over a long period of time. Patients were included during the ten-year period 2001-2010 with follow-up through 2011 in Paper I and II and prolonged through 2017 in Paper III and IV. Thirdly, the drop-out rate was low, 24 out of 1,317 patients by the end of 2017. Fourthly, we considered all major etiologies to provide a more complete picture of the clinical reality.

Limitations include that most patients were diagnosed with cirrhosis by radiological techniques, primarily ultrasound, which has a diagnostic sensitivity of 85% (132), possibly leaving a portion of cirrhosis patients undiagnosed. Further, transient elastography was not implemented in clinical practice during the inclusion period which may add to the number of undiagnosed patients, as patients with transient elastography measures indicative of cirrhosis, are subjects to further investigation for confirmation. Other weaknesses include those inherent with a retrospective study, such as lack of protocol endoscopies and ultrasound examinations to detect esophageal varices and HCC, though guidelines for endoscopy and ultrasound

existed during the study period. Also, the retrieved information is limited to documentation in the medical journals. Portal pressure measurement has not been performed as it is not part of the local clinical praxis. Thus we could not perform risk assessment with measurement of portal pressure and not detect decreased portal pressure in response to treatment with non-selective betablockers which has shown to be beneficial on complication rate (133). In Paper IV were tumors characterized using radiological reports without re-evaluation of imaging. In this paper, the group “remaining causes” included etiologies with different HCC risks, as our sample size precluded robust subgroups analysis.

Conclusions

The main conclusions of my thesis are:

- Sweden has a low incidence of cirrhosis compared to other European countries. The crude annual incidence of cirrhosis in southern Sweden estimates at 14.1/100,000. The mortality varies with gender, etiology, and disease severity at diagnosis. Patients with alcoholic cirrhosis with or without concomitant HCV infection fare worst.
- The time when decompensation occurs, during course of cirrhosis, effects survival. Initially compensated patients who develop decompensation during follow-up show worse survival from time of decompensation compared to patients who were decompensated at diagnosis of cirrhosis. This difference exists with most etiologies of cirrhosis and remain after adjustment for HCC and portal vein thrombosis.
- The clinical course and survival differ by etiology of cirrhosis. Decompensation at diagnosis is an important predictor for death in all etiologies apart from alcoholic cirrhosis. Patients with alcoholic cirrhosis have the highest overall mortality and decompensation rate at diagnosis whereas AIH cirrhosis patients have the best survival rates.
- In southern Sweden, the annual incidence of HCC is 1.5% in alcoholic cirrhosis and 4.7% in HCV cirrhosis. The incidence in alcoholic cirrhosis reaches the threshold for surveillance of 1.5%. Alcoholic cirrhosis patients show the worst survival after HCC diagnosis due to more advanced stage at HCC diagnosis with few patients eligible for treatment.

Future perspectives

Is the spectrum of liver diseases changing?

While liver diseases continue to be an important cause of morbidity and mortality, the spectrum of liver diseases is changing. Chronic HBV infections decrease globally due to vaccination programs. Clearance of HCV is achieved more often after the introduction of DAAs resulting in reduced prevalence of HCV in global estimates, and demonstrated by a 30% decrease of patients with decompensated HCV cirrhosis on the liver transplant waitlist in the United States (134, 135). At the same time, NAFLD is increasing. Among NASH patients in the United States, the prevalence of compensated cirrhosis is expected to increase by 163% and the prevalence of decompensated cirrhosis by 180% during 2015-2030 because of increasing adult obesity and diabetes (136). Most likely, these trends for HCV and NAFLD also hold true for Sweden as treatment with DAAs is widely implemented and obesity and diabetes are becoming more common also in our country (137). In Europe, alcohol is still the main cause of liver-related morbidity and mortality. In Sweden and some other European countries, the alcohol consumption has remained stable low over the last decades, while a decreasing trend is seen in some countries that historically have had a high consumption, including France and Italy, and an increasing trend is seen in Eastern Europe (36). Globally, the total consumption is unchanged, though it appears to decrease in Western Europe while increasing in parts of Asia (138). The etiological spectrum is important for healthcare planning and disease prevention. Therefore, there will still be a need for studies on cirrhosis etiology in the future as the landscape is constantly changing.

Would it be valuable to screen for cirrhosis?

It is difficult but important to estimate the true prevalence of cirrhosis. With identification of subclinical cases, it is possible to initiate preventive measures to slow the clinical course. In screening studies of the general population, the most common cause of unknown fibrosis was NAFLD (34, 35). Thus, it is seemingly appropriate to target risk populations, such as diabetics or other patients with the metabolic syndrome, if screening is to be performed. In a French screening study

targeting patients with type 2 diabetes, 2.1% of 669 patients without known liver disease had cirrhosis (139). Without screening, many patients with cirrhosis are discovered in a decompensated phase. If diagnosed earlier, and possibly treated for the underlying cause of cirrhosis, this might slow disease progression. Screening is probably not practically feasible in Sweden, but a higher awareness of cirrhosis in risk populations, could possibly lead to earlier detection. For example, guidelines for patients with methotrexate-treated psoriasis are now recommending liver elastography when suspicion of liver fibrosis arises, although the main cause for liver damage may not be solely methotrexate but diabetes, obesity or unknown alcohol overconsumption (140).

Would registries and quality measures be valuable?

Our studies were performed retrospectively, and thus prospective studies could illuminate further the clinical course in cirrhosis. Potentially, creating a national cirrhosis registry to ensure both prospective data collection and higher inclusion, could help answering some of our outstanding questions, including what precisely explains the differences in survival after decompensation during follow-up *vs* at diagnosis (Paper II). Another potential advantage with national registries could be raised awareness of structured clinical follow-up and screening for varices and HCC, which could improve survival. Recent data suggest that quality measures, including specialist appointment within 12 months of cirrhosis diagnosis, surveillance for HCC and varices, follow-up after discharge within 30 days, and administration of antibiotics to patients with upper gastrointestinal bleeding, were all associated with lower all-cause mortality (141). Potentially, quality measures and increased awareness of factors influencing survival could encourage clinicians to be more active with recommending healthier lifestyle, treating alcohol abuse, and initiating surveillance. For variceal bleeding, the mortality rate has decreased from 50% to 10-20% with better management over the last decades (142). It is conceivable that better adherence to guidelines for surveillance and treatment of underlying cause of cirrhosis could improve survival after other complications as well. This is important as organs for liver transplantations are limited.

Can HCC surveillance guidelines be improved?

Patients with cirrhosis are at risk for HCC. The risk of HCC is expected to decrease because of HBV vaccination and increased HCV cure rates with DAAs. Yet, in the United States, the HCC incidence continues to rise, despite decreasing HCV, because of increasing obesity and subsequent NASH. By 2025, NASH is predicted to cause three times as many cases of HCC as HCV in the United States (143). In Sweden, the major HCC risk factors are still cirrhosis due to HCV and alcohol abuse. Congruent with the ongoing changes in etiology spectrum, NASH may become an increasingly important HCC risk factor in Sweden in the future.

Guidelines for HCC surveillance have existed since 2001, but they are sometimes not followed in practice, either because of poor patient compliance or because the treating clinician is not aware of them (144). Similar to other studies (145), we found that a significant fraction of all patients eligible for HCC surveillance were in fact not surveyed (Paper IV). Potentially, structured follow-up and quality registries could facilitate better selection of patients for surveillance. For example, one study in the United States suggests that the adherence can be improved by sending letters to patients offering surveillance (146). Further, a recent study on NAFLD and alcoholic cirrhosis developed a web-based predictor to assess HCC risk based on seven parameters (age, gender, diabetes, body mass index, platelet count, serum albumin and AST/ \sqrt ALT ratio) (147). This study reported a large variation in HCC risk within the alcoholic cirrhosis and NAFLD cirrhosis subgroups. Consistent with our data (Paper IV), male alcoholic cirrhosis patients with diabetes exhibited markedly higher HCC risk. Reasons to take risk factors into account are to precisely counsel patients on their individual need for surveillance, and to allow the healthcare system to prioritize patients for surveillance at a group level.

Populärvetenskaplig sammanfattning

Vid långvarig sjukdom eller skada i levern dör leverceller och ersätts av ärrvävnad. Denna strukturomvandling kallas levercirros (skrumplever), och är slutstadiet för många leversjukdomar. De vanligaste orsakerna till levercirros i Sverige är hög alkoholkonsumtion och kronisk hepatit C virus-infektion, men det finns även andra orsaker såsom fettlever och autoimmuna sjukdomar. Det tidiga symtomlösa stadiet kallas kompenserad cirros. När sjukdomen fortskrider övergår emellertid cirrosen i en dekompenenserad fas som kännetecknas av tillkomst av vätska i bukhålan (ascites), blödning från åderbräck i matstrupen (esofagusvaricer) eller leverorsakad hjärnpåverkan (hepatisk encefalopati).

Syftet med mitt avhandlingsarbete var att undersöka förekomsten av levercirros och beskriva sjukdomsförloppet. Vi använde patientregister vid tio olika sjukhus i Skåne för att hitta patienter som diagnostiserats med cirros från 2001 till 2010. Sammanlagt identifierades 1317 patienter. Från patienternas journaler inhämtade vi därefter uppgifter om bl a cirrosens grundorsak, komplikationer, död och levertransplantation. Uppgifterna analyserades statistiskt i fyra delarbeten.

I delarbete 1 beskrivs vårt patientmaterial. Vi undersökte förekomsten av cirros i Skåne. Medelåldern vid cirrosdiagnos var 60 år och två tredjedelar var män. De vanligaste orsakerna var alkoholöverkonsumtion (58%), hepatit C (13%) och cirros med oklar grundorsak (kryptogen cirros; 12%). Den vanligaste komplikationen vid diagnos var ascites (43%). Incidensen för cirros var 14,1/100000 vilket är lågt jämfört med många länder i Europa, men i nivå med England och en tidigare svensk studie. Män hade sämre överlevnad än kvinnor och överlevnaden försämrades med stigande ålder. Patienter med både alkoholöverkonsumtion och hepatit C som orsak till cirros hade sämst prognos.

I delarbete 2 studerades överlevnad efter dekompenensation. Vi jämförde patienter som var dekompenenserade redan vid diagnos (n=629) med patienter som utvecklade dekompenensation först under uppföljningstiden (n=327). Övåntat nog visade det sig att överlevnad, räknad från tidpunkt för dekompenensation, var bättre för de patienter som var dekompenenserade vid diagnos (33% vs 15% femårsöverlevnad). Komplikation med levercancer eller blodpropp i portavenen (ven som transporterar blod till levern från övriga bukorgan) leder ofta till ökad dekompenensation och

försämrar överlevnaden. Tillkomst av dessa komplikationer kan till viss del förklara varför överlevnaden var sämre för patienter som dekompensterade under uppföljningstiden, men merparten av skillnaden är fortfarande oförklarad. En spekulering är att patienter som upplever symptom kopplade till cirros när de insjuknar är mer benägna att förbättra sin livsstil på grund av rädsla för försämring.

I delarbete 3 studerade vi kopplingen mellan kliniskt förlopp och cirrosens grundorsak. I gruppen alkoholcirros hade 89% utvecklat dekomensation inom tio år från diagnos, medan motsvarande andel vid hepatit C-cirros och kryptogen cirros var 58% och 75%. Alkoholcirros och kryptogen cirros visade sig ha sämst överlevnad, 18% respektive 11% efter 10 år. Detta är i samklang med fler komplikationer i alkoholgruppen respektive högre genomsnittsålder vid kryptogen cirros. Vid uppföljningstidens slut, december 2017, hade 991 av totalt 1317 patienter avlidit. Leversvikt eller andra komplikationer till cirros var de vanligaste dödsorsakerna, totalt 49%. Bland patienter med hepatit C-cirros var emellertid levercancer den vanligaste dödsorsaken och stod för 45 % av dödsfallen. I gruppen cirros orsakad av autoimmun hepatit förelåg nästan inga lever-relaterade dödsfall och denna grupp uppvisade också bäst tio-årsöverlevnad.

I delarbete 4 studerades risken att utveckla levercancer till följd av cirros och överlevnaden efter detta. Det är känt att patienter med cirros har ökad risk för levercancer men risken varierar med cirrosens grundorsak. I tidigare studier har man funnit att patienter med hepatit C har en årlig risk på 2-4% och alkoholcirros 0,3-2,7%. I vårt material utvecklade 200 patienter levercancer. Hos 75 patienter fanns tumören redan vid cirrosdiagnos eller upptäcktes inom sex månader, d v s fanns troligen redan vid cirrosdiagnos. Det årliga insjuknandet i levercancer var 1,5% vid alkoholcirros och 4,7% vid hepatit C-cirros. Den genomsnittliga överlevnaden efter levercancerdiagnos var 4,5 månader hos patienter med alkoholcirros och 11 månader hos patienter med hepatit C-cirros. Orsaker var större tumörbörda och sämre leverfunktion vid diagnos hos patienter med alkoholcirros, vilket gjorde att färre blev aktuella för behandling syftande till bot. För att hitta tumörerna tidigt, d v s när botande behandling är möjlig, rekommenderas övervaknings-undersökningar med ultraljud av levern var sjätte månad. Detta anses kostnadseffektivt när den årliga risken för levercancer är 1,5 % eller högre. Vi fann att risken för levercancer var 1,5 % per år hos våra patienter med alkoholcirros. Våra resultat stödjer därmed fortsatt övervakning med ultraljud i den patientgruppen.

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