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Some epidemiological aspects of liver cirrhosis and hepatocellular carcinoma in Sweden

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Some epidemiological aspects of liver cirrhosis and hepatocellular carcinoma in Sweden

Some epidemiological aspects of liver cirrhosis and hepatocellular carcinoma in Sweden

Juan Vaz, MD

LUND
UNIVERSITY

Thesis for the degree of Doctor of Philosophy

Supervisor: Prof. Patrik Midlöv
Co-supervisors: Prof. Ulf Strömberg, Dr. Berne Eriksson, Dr. David Buchebner

Faculty opponent: Assoc. Prof. Staffan Wahlin, Karolinska Institutet

To be publicly defended, with the permission of the Faculty of Medicine at Lund University,
in the Agardh lecture hall at the Department of Clinical Sciences, Malmö
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Abstract

Background: Contemporary epidemiological studies examining incidence rates (IR) of cirrhosis and hepatocellular carcinoma (HCC) in Swedish populations are scarce. Cirrhosis and HCC are associated with a significant burden of health inequity and stigma. The importance of socioeconomic status (SES) in cirrhosis survival has scarcely been studied in Sweden. The impact of SES on HCC incidence and prognosis had never been investigated in Sweden. **Aim:** The overall aim of this thesis was to describe the contemporary epidemiology of cirrhosis and HCC in Swedish settings. We also aimed to improve the understanding of the importance of sociodemographic and clinical characteristics for the clinical course and early identification of cirrhosis and HCC. **Methods:** We used population-based medical registries to identify adult patients diagnosed with cirrhosis in the region of Halland between 2011 and 2018. Annual crude IR of cirrhosis were calculated (Paper I). Patients were followed-up until date of liver transplantation, death, moving from Halland, or until December 31st, 2019; whichever occurred first. Cox regression models were employed to estimate unadjusted and adjusted hazard ratios (HR and aHR) for several clinical and sociodemograhic variables (Paper II). The nationwide quality register for liver cancer was used to identify all adult patients diagnosed with HCC in Sweden between 2012 and 2018. Poisson regression was used to estimate IRs of HCC across several populations of interest (Paper III). Data extracted from the quality register were cross-linked to data from other nationwide registers. Multivariable logistic regression models were employed to identify factors associated with an increased likelihood for having unrecognized cirrhosis, or late-stage HCC at diagnosis. Patients were followed-up until the date of death, emigration from Sweden, or until December 31st, 2020; whichever occurred first. Cox regression modelling was used for the estimation of HRs and aHRs for several clinical variables (Paper IV). IRs of HCC were estimated for the whole adult population of Sweden and stratified by HCC etiologies (Paper V). Patients were stratified into those with non-alcoholic fatty liver disease (NAFLD) associated HCC and those with non-NAFLD-HCC. Furthermore, those with NAFLD-HCC were divided into those with and without underlying cirrhosis. **Results:** We identified a total of 598 patients with cirrhosis. The IR of cirrhosis in adults in Halland was estimated at 30 per 100,000 person-years, 39 for men, and 22 for women (Paper I). Patients with a low SES, defined as a low occupational skill level, had more advanced cirrhosis at diagnosis, lower mean survival, and higher mortality risk when compared to patients with high SES (Paper II). A total of 3,473 adult patients with HCC were identified and 68% were diagnosed with a late-stage HCC. Sex, country of birth, and individual- and contextual level SES were associated with the IRs of HCC. Men with a low household income and/or living in the most deprived neighborhoods had the highest IR of HCC (Paper III). Among patients with HCC, 2670 (77%) had underlying cirrhosis. Cirrhosis was unrecognized in 39% of all patients with underlying cirrhosis. Unrecognized cirrhosis was associated with more advanced HCC at diagnosis and worse survival (Paper IV). Among the 3,473 patients with HCC, 21% had underlying NAFLD, which also was the second-leading cause of HCC and the fastest-increasing cause of HCC (Paper V). **Conclusions:** The IRs of cirrhosis may be higher than previously estimated. Low SES was associated with a worse prognosis in cirrhosis, higher IRs of HCC, and increased risk of unrecognized cirrhosis in HCC. NAFLD is an increasing cause of cirrhosis and has become a leading cause of HCC. NAFLD is also associated with an increased risk of cirrhosis unrecognition in HCC.

Keywords: liver cirrhosis, epidemiology, socioeconomic status, hepatocellular carcinoma, survival

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MADE IN SWEDEN

Manches sollte, manches nicht
Wir sehen, doch sind wir blind
Wir werfen Schatten ohne Licht

Nach uns wird es vorher geben
Aus der Jugend wird schon Not
Wir sterben weiter bis wir leben
Sterben lebend in den Tod

Dem Ende treiben wir entgegen
Keine Rast, nur vorwärts streben
Am Ufer winkt Unendlichkeit
Gefangen so im Fluss der Zeit

— Rammstein

Contents

List of publications

This thesis is based on the following scientific papers, which are referred to in the text by their Roman numerals.

I. Vaz J, Eriksson B, Strömberg U, Buchebner D, Midlöv P. Incidence, aetiology and related comorbidities of cirrhosis: a Swedish population-based cohort study. *BMC Gastronterol. 2020 Apr 3;20(1):84*.

II. Vaz J, Strömberg U, Eriksson B, Buchebner D, Midlöv P. Socioeconomic and marital status among liver cirrhosis patients and associations with mortality: a population-based cohort study in Sweden. *BMC Public Health. 2020 Nov 30;20(1):1820*.

III. Vaz J, Midlöv P, Eilard MS, Eriksson B, Buchebner D, Strömberg U. Targeting population groups with heavier burden of hepatocellular carcinoma incidence: A nationwide descriptive epidemiological study in Sweden. *Int J Cancer. 2022 Jul 15;151(2):229-239.*

IV. Vaz J, Strömberg U, Midlöv P, Eriksson B, Buchebner D, Hagström H. Unrecognized liver cirrhosis is common and associated with worse survival in hepatocellular carcinoma: A nationwide cohort study of 3473 patients. *J Intern Med. 2023 Feb;293(2):184-199.*

V. Vaz J, Jepsen P, Strömberg U, Midlöv P, Eriksson B, Buchebner D, Hagström H. Non-alcoholic fatty liver disease is the fastest growing cause of hepatocellular carcinoma in Sweden: A nationwide cohort study. *Manuscript*.

Populärvetenskaplig sammanfattning

Det är aldrig för sent att ge upp, så det kan vi lika gärna göra någon annan gång.

— Hans Rosling

Levern är kroppens största fasta invärtes organ och den är ansvarig för många livsviktiga funktioner. Den har också en unik återbildningsförmåga och en stor reservkapacitet. Av denna anledning kan det ta många år innan kroniska leversjukdomar gör sig till känna. Långvarig inflammation i levern kan leda till bildning av ärrvävnad (leverfibros) när leverceller som dör ersätts med bindväv. Om orsaken till inflammationen eller skadan inte försvinner, exempelvis genom behandling, kan leverfibros avancera till levercirros (skrumplever). Cirros är därmed slutstadiet för flertalet av de kroniska leversjukdomarna.

Hög alkoholkonsumtion och kronisk hepatit C-virus infektion är de främsta orsakerna till levercirros i Sverige. Icke alkohol-relaterad fettlever (non-alcoholic fatty liver disease [NAFLD] på engelska) är också en känd orsak till levercirros i västvärlden. NAFLD är dessutom världens vanligaste leversjukdom och drabbar 25-30 procent av världens befolkning. Det finns starka samband mellan NAFLD och andra folksjukdomar såsom typ 2 diabetes, fetma, höga blodfetter och kranskärlssjukdom. Internationella rapporter indikerar att NAFLD är den snabbast växande orsak till levercirros i världen. Eftersom cirros (gäller även levercancer) ofta associeras med riskfaktorer kopplade till osunda vanor och/eller missbruk anses personer med cirros vara mindre benägna att söka vård pga. stigmatiseringen kopplade till sjukdomen. Flertal studier from USA har också visat stora ojämlikheter från sjukvårdens sida vad det gäller omhändertagande av patienter med cirros jämfört patienter med andra kroniska sjukdomar.

Det tar lång tid att utveckla cirros, ofta 10 till 20 år. Medelålder vid cirrosdiagnos i Sverige är 60-65 år och män insjuknar i dubbel så stor utsträckning jämfört kvinnor. Man brukar dela in sjukdomsförloppet i två olika faser: kompenserad och dekompenserad cirros. Kompenserad cirros ger sällan symptom. Denna fas kan fortlöpa under flera årtionden och hos somliga fortskrider cirrosen till det mer avancerade stadiet dvs. den dekompenserade fasen. Det är först i denna fas, symptom relaterade till cirros gör sig till känna. Dessvärre har drygt hälften av patienterna cirrosrelaterade komplikationer redan vid diagnos. Ansamling av vätska i buken (ascites) är den vanligaste komplikationen och den är kopplad till sämre

prognos och påtaglig minskad livskvalitet. Blödning från åderbråck i matstrupen (esofagusvaricer), cirrosrelaterade hjärnpåverkan (hepatisk encefalopati) och ökad benägenhet för bakterieinfektioner är andra potentiellt livsfarliga komplikationer som kan finnas redan vid cirrosdiagnosen. Medellivslängden efter cirrosdiagnos är 9-12 år för patienter som upptäcks i den kompenserade fasen medan de som har dekompenserade sjukdom vid diagnos har en medellivslängd på cirka 2 år. Enligt Socialstyrelsens statistik dör årligen cirka 500-600 människor i Sverige till följd av cirros men risken för stora mörkertalen kan vara ansenlig.

En mycket fruktad komplikation till cirros är primär levercellscancer vilken också kallas hepatocellulär cancer (HCC). Cirros är den vanligaste riskfaktor for HCC och minst 2/3 av alla människor som diagnostiseras med HCC i Sverige har cirros. Varje år diagnostiseras cirka 500 människor med HCC i Sverige och medianålder vid diagnos är 69 år. Likt cirros, drabbar HCC män betydligt oftare och antal nya fall har ökat bland män i åldern 50-65 år. Medelöverlevnad efter HCC diagnos är beroende på om kirurgisk behandling kan erbjudas eller ej. Detta är i sin tur beroende av flertal olika faktorer såsom tumörstadiet, den samlade sjukdomsbördan (inklusive patientens allmäntillstånd) och den återstående leverfunktionen. Patienter vars HCC upptäcks tidigt och som kan vara mottagliga för potentiellt botande behandlingar har en femårsöverlevnad på 40-80 procent. Medelöverlevnad för patienter som får bromsande behandlingar varierar mellan 8 månader och 3 år. I de fallen där ingen behandling kan erbjudas är den relativa ettårsöverlevnaden mindre än 20 procent och den förväntade livslängden är ca 3-6 månader. I Sverige upptäcks mindre än 1/3 av fallen i tidiga skeden. I över 40 procent av samtliga fall av HCC som diagnostiseras i Sverige finns det ingen botande eller bromsande behandling att erbjudas. Eftersom det verkar finnas ett starkt samband mellan tidig diagnostik och ökad överlevnad i HCC rekommenderas att patienter med ökad risk för utveckling av HCC inkluderas i screeningsprogram. Detta innefattar i huvudsak patienter med känd cirros om sjukdomen är kompenserad eller om de skulle kunna bli aktuella för levertransplantation vid påvisad HCC i tidigt skede. Patienter vars HCC upptäcks i samband med screening kan erbjudas potentiellt botande behandlingar i cirka 62 procent av fallen. Trots detta är det fortfarande omdiskuterat om HCC screeningen hos patienter med cirros är samhällsekonomiskt försvarsvarbar då det vetenskapliga underlaget som stödjer HCC screening är relativt svagt.

Det övergripande syftet av detta avhandlingsarbete var att beskriva förekomsten av cirros (Halland) och HCC (Sverige). Först granskade vi patientjournaler för att hitta vuxna patienter bosatta i Halland som fick en diagnos av cirros för första gången mellan 2011 och 2018. Efter att ha granskat 2140 patientjournaler och 163 vävnadsprover identifierade vi 598 patienter (delarbete I). Vidare undersökte vi om det fanns några samband mellan socioekonomiska förutsättningar, medelöverlevnaden och dödsrisken bland 582 av de patienterna vi hade hittat (delarbete II). Vi definierade socioekonomisk status utifrån den svenska standarden för yrkesklassificeringar där mer kvalificerade yrken medförde högre

socioekonomiskt status och vice versa. I delarbetena III-V använde vi patientuppgifter samlade i det svenska kvalitetsregistret för levercancer vilka vi senare kopplade till uppgifter från flertal andra register från Socialstyrelsen och Statistikmyndigheten SCB. Vi identifierade 3473 vuxna patienter diagnostiserade med HCC i Sverige mellan 2012 och 2018. Vi beräknade förekomster av HCC bland olika samhällsgrupper definierade utifrån sex, födelseland, ålder, inkomst och bostadsområden (delarbete III). Bland de patienterna vi hittade i delarbete III selekterade vi 2670 patienter som bedömdes ha cirros. Vi uppskattade hur ofta man upptäckte cirros först i samband med HCC, hur detta påverkade prognosen av HCC och vilka patientgrupper som hade störst risk för oidentifierade cirros (delarbete IV). Slutligen tittade vi igen på samtliga 3473 patienter med HCC och beräknade förekomsten av olika orsaker till HCC där vi lade tyngden på patienter med NAFLD för att jämföra patientegenskaper mot patienter med andra orsaker till HCC.

I delarbete I beskrivs vår patientpopulation från Halland. Incidensen (antal nya fall) mellan 2011 och 2018 beräknades till 30 per 100 000 i den vuxna befolkningen i Halland. Incidensen av cirros bland vuxna män var 39 per 100 000 och 22 per 100 000 bland vuxna kvinnor. Dessa incidenssiffror var betydligt högre jämfört med tidigare svenska studier från Göteborg och Skåne. Vi fann också att medelålder vid diagnos var 66 år och cirka 2/3 av patienterna var män. Alkoholöverkonsumtion var den vanligaste orsaken till cirros (51 procent). Cirros av oidentifierad orsak (kryptonen cirros) hittades i ca 14 procent av fallen. Hepatit C fanns hos 13 procent av patienterna och 6 procent hade NAFLD som huvudorsak till cirros. Dekompenserad cirros hittades hos 49 procent vilket var i nivå med tidigare studier. Flertal patienter hade högt blodtryck (33 procent), typ 2 diabetes (29 procent) och fetma (24 procent). Ett överraskande fynd var att cirka 13 % av samtliga patienter fick HCC diagnos antingen i samband med att man diagnostiserade cirros eller inom sex månader efter det.

I delarbete II tittade vi vidare på patientuppgifter från de 582 patienterna som hade fått cirrosdiagnos före döden. Medelöverlevnaden var 4,4 år och bara 45 procent av patienterna levde vid sista uppföljningsdatum (2019-12-31). Gifta hade bättre medelöverlevnad än tidigare gifta (frånskilda eller änklingar). De med en anställning hade bättre medelöverlevnad än pensionärer eller förtidspensionerade. Det fanns starka samband mellan socioekonomisk status, cirrosstadiet vid diagnos, medelöverlevnad och dödsrisk. Patienter med lägsta socioekonomiska statusen (minst kvalificerade yrkena) hade betydligt oftare allvarliga komplikationer och tecken på dekompenserade cirros. Dessa hade också över 2 gånger kortare förväntad medelöverlevnad jämfört med patienter som tillhörde gruppen med de mest kvalificerade yrkena. Lägst socioekonomisk status var också associerad med en 3,4 gånger ökad risk för död jämfört patienter med de bästa socioekonomiska förutsägningarna.

I delarbete III beskrivs vår patientpopulation med vuxna patienter diagnostiserade med HCC i hela Sverige. Medelålder vid diagnos var 69 år och 76 procent av

patienterna var män. Majoriteten var födda i ett nordiskt land. Enbart 13 procent av patienterna hade en hög hushållsinkomst medan 41 procent hade en medel hushållsinkomst och 46 procent hade en låg hushållsinkomst. HCC diagnostiserades i ett tidigt skedde hos 1007 patienter (29 procent). Vi fann att män hade 4 gånger högre incidens av HCC jämfört med kvinnor. Incidensen av HCC ökade med fallande hushållsinkomstnivå och med stigande socioekonomisk utsatthet. Individer med medel eller låg hushållsinkomst hade cirka 2,1 respektive 4,7 gånger högre incidens av HCC jämfört dem med hög hushållsinkomst. Individer from de mest socioekonomiskt utsatta områdena hade cirka 1,5 gånger högre incidens av HCC jämfört individer från de minst socioekonomiskt utsatta områdena. Till exempel, individer med låg hushållsinkomst som bodde i de mest socioekonomiskt utsatta områdena hade cirka 7 gånger högre incidens av HCC jämfört med individer med hög hushållsinkomst som bodde i områdena med minst socioekonomisk utsatthet. Sammanfattningsvis visade vi att män som hade en låg hushållsinkomst och/eller män som bodde i de mest socioekonomiskt utsatta områdena hade den högsta incidensen av HCC i Sverige mellan 2012 och 2018.

I delarbete IV tittade vi på patienter med cirros bland de 3473 patienter med HCC som vi identifierade i delarbete III. Vi bedömde att 2670 patienter (77 procent) hade cirros vid HCC diagnos. Av dessa hade 1033 (39 procent) en tidigare oidentifierade cirros. Patienter med oidentifierade cirros var oftare män och äldre jämfört med patienter med tidigare känd cirros vars HCC hade hittats via screening. Större och fler antal tumörer samt spridd cancer utanför levern var också oftare funnet i patienter med tidigare oidentifierad cirros. Män, individer med en låg hushållsinkomst och individer med NAFLD hade ökad risk för att ha tidigare oidentifierade cirros. Jämfört patienter med känd cirros vars HCC upptäcktes via surveillance, hade patienter med tidigare oidentifierad cirros och HCC en 4 gånger ökad risk för avancerad cancer vid diagnos vilket också var förknippad med sämre överlevnad (0,9 år mot 3,8 år).

I delarbete V tittade vi på samtliga 3473 patienter med HCC och vi uppskattade antalet av dessa med underliggande NAFLD. Vi bedömde att 724 patienter (21 procent) hade NAFLD som huvudbidragande leversjukdom till HCC. Andelen patienter med HCC ökade från 18 till 24 procent mellan 2012 och 2018. NAFLD var den andra vanligaste leversjukdomen bland patienter med HCC sedan 2014 och den var också leversjukdomen som ökade snabbast (33 procent ökning) mellan 2012 och 2018. Denna ökning förklarades av en ökning av incidensen av NAFLD-relaterade HCC bland män och bland patienter med NAFLD och cirros. Jämfört med patienter med andra leversjukdomar som huvudorsak till HCC (icke-NAFLD) var patienter med NAFLD äldre vid HCC diagnos (75 år mot 67 år) och hade cirros i mindre utsträckning (58 mot 82 procent). Även om patienter med NAFLD hade oftare större tumörer och mer HCC spridning utanför levern diagnostiserades dessa i ett tidigt skede i likartad utsträckning som hos patienter med icke-NAFLD (27 mot 30 procent).

Abbreviations

ACLF	Acute-on-chronic liver failure
aHR	Adjusted hazard ratio
AIH	Autoimmune hepatitis
AKI	Acute kidney injury
aOR	Adjusted odds ratio
ArLD	Alcohol-related liver disease
ASIR	Age-standardized incidence rate
BCLC	Barcelona Clinic Liver Cancer
BSC	Best supportive care
CI	Confidence interval
CP	Child-Pugh
CT	Computed tomography
DAA	Direct-acting antiviral
DeSO	[Demografiska StatistikOmråden] in Swedish
EASL	European Association for the Study of the Liver
ESP	European Standard Population
FIB-4	Fibrosis-4
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HE	Hepatic encephalopathy
HR	Hazard ratio
HRS	Hepatorenal syndrome

ICD-10	International Classification of Diseases – 10th Edition
IMD	Index of multiple deprivation
IR	Incidence rate
IRR	Incidence rate ratio
MELD	Model for End-stage Liver Disease
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NPR	National Patient Register
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
SBP	Spontaneous bacterial peritonitis
SES	Socioeconomic status
SSYK 2012	Swedish Standard Classification of Occupations 2012
SweLiv	Swedish quality register for cancers found in the liver
T2D	Type 2 diabetes mellitus

Introduction

Even the greatest was once a beginner.
Don't be afraid to take that first step.

— Muhammad Ali

The liver

The liver is the largest internal solid organ of the body.[1, 2] The morphology of the liver is characterized by its two hepatic lobes (Fig. 1), but its functional anatomy is more complex and is comprised of eight liver segments.[2, 3]

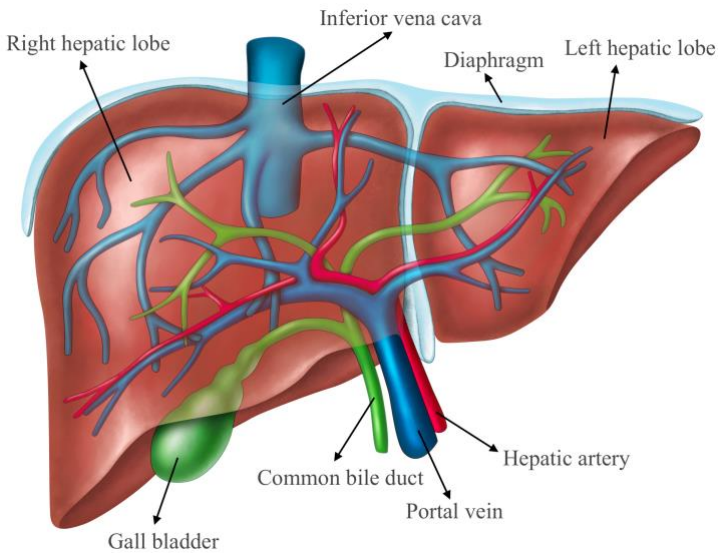

Fig.1. Liver anatomy, circulation and biliary tree. Illustration: adapted after iStock.com/Andreus.

Up to 25% of total cardiac output is received by the liver, which has a unique dual blood supply.[1, 2] The portal vein is responsible for 70-75% of the blood supply, while the hepatic artery contributes with the remaining 25-30% of it.[1, 2] Oxygenated blood supplied by the hepatic artery mixes in hepatic sinusoids with oxygen-deficient (but nutrient rich) blood from several abdominal organs (spleen, pancreas, stomach and intestines), received via the portal vein.[1] Afterwards, the blood is drained by hepatic veins into the systemic circulation through the inferior vena cava.[2]

The normal hepatic venous pressure gradient, which is the pressure difference between the portal vein and the inferior vena cava, is between 1 to 5 mmHg under physiological conditions.[4] The biliary system consists of multiple intrahepatic ducts that carry bile to the gallbladder and ultimately to the duodenum via the extrahepatic common bile duct.[1]

Hepatocytes are the main functional cell type of the liver.[2] These cells account for roughly 60% of all cells found in the liver and they constitute 90% of the liver volume.[2] Histologically, the liver is classically described by means of microscopic functional units called hepatic lobules. Hepatic lobules consist of hexagonal plates of hepatocytes arranged around a central vein (Fig. 2).[2]

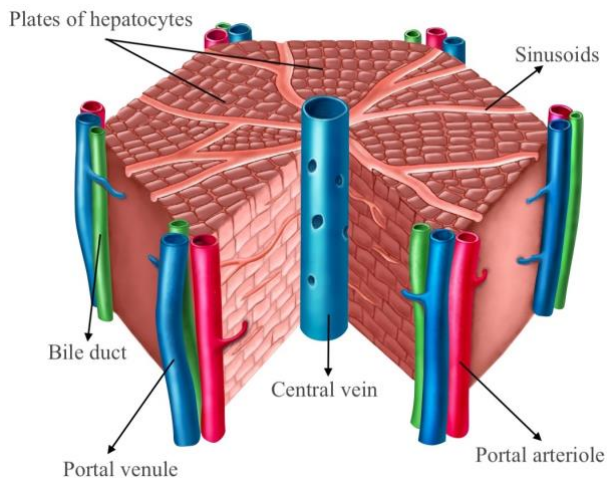

Fig. 2. Structure of the hepatic lobule. Illustration: adapted after iStock.com/Andreus.

The liver has also a unique regenerative ability and a large reserve capacity.[2, 5] Liver-to-bodyweight ratio is maintained within narrow limits, in order to achieve a liver size at 100% of what is needed for homeostasis.[2, 6] This characteristic is easily observed during pregnancy (increased liver size), and in cachexia, or severe loss of weight (decreased liver size).[6]

The mechanisms behind liver regeneration are complex and not fully understood, but they seem to involve all hepatic cell types.[6] The regenerative capacity of hepatocytes appears to be unlimited and beneficial in the healthy liver. However, chronic hepatocyte loss due to liver disease may be associated with liver fibrosis by compensatory activation of hepatic collagen-producing cells.[6] Chronic liver diseases may not only impair the regenerative capacity of the liver but also its most important functions, which can lead to devastating consequences, as described in the following sections.[7]

The liver is often depicted in media as the body's detoxing factory. However, the understanding and awareness of the importance of the liver in health and homeostasis seems to be limited in the general population, especially among individuals at the highest risk for severe liver diseases.[8-10] The liver plays an important role in almost every organ system of the body.[5] Hepatic functions, which mostly are performed by hepatocytes, can be classified as metabolic, synthetic, storage, catabolic, and excretory (Fig. 3).[2]

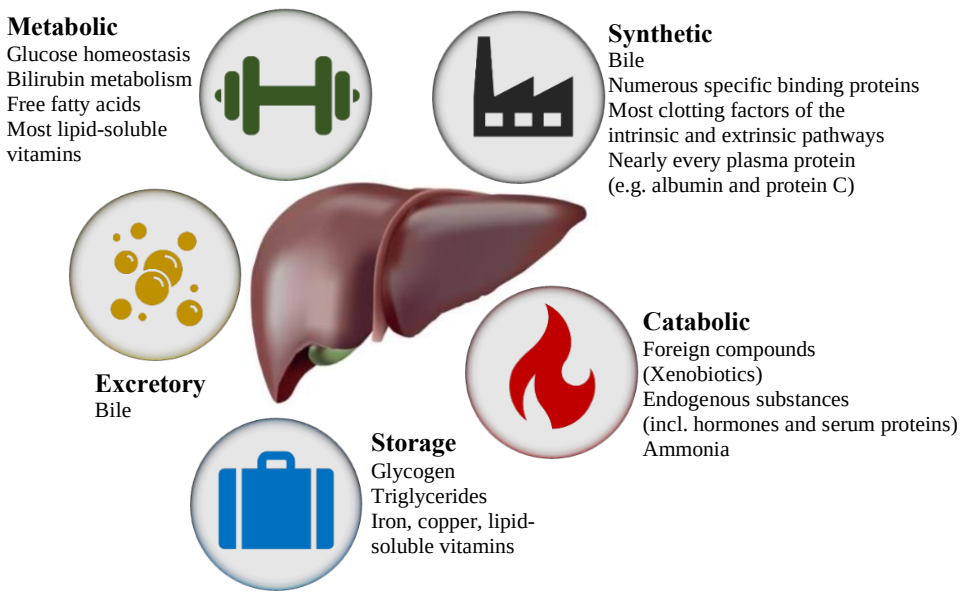

Fig. 3. Functions of the liver.

Liver cirrhosis

Common for chronic liver disease is the progression of liver injury, leading to hepatocyte damage and necrosis, thus resulting in changes in the micro architecture of the liver lobule, fibrosis.[2] If the cause of liver damage is not contained, normal liver tissue is replaced by regenerative hepatic nodules, causing liver cirrhosis, which is the end-stage of several chronic liver diseases (Fig. 4).[2, 7]

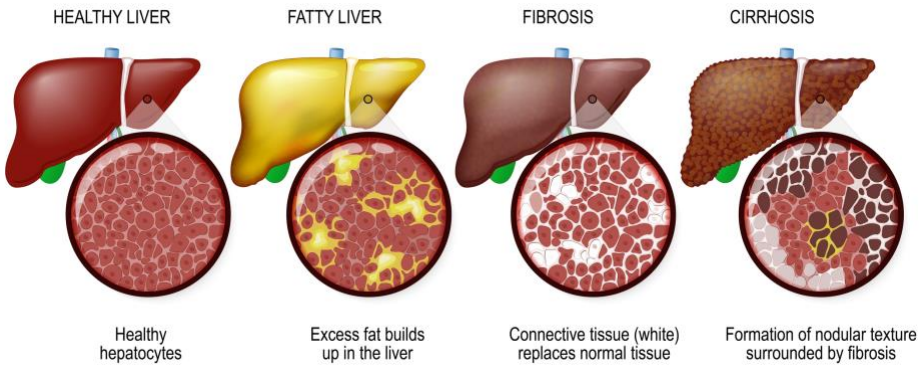

Fig. 4. Progression from healthy liver through cirrhosis. Illustration: iStock.com/ttsz

In clinical practice, the diagnosis of cirrhosis often requires a combination of diverse sources of data, such as physical examination findings, blood-based tests, diagnostic imaging, elastography, gastroscopy, and histology.

Physical examination findings

A large set of physical examination findings have been observed in patients with cirrhosis (Table 1).[11] The most common findings are usually noticed in patients with advanced disease.[12] The likelihood of cirrhosis is higher when ascites (likelihood ratio 7.2), or spider angiomas (likelihood ratio 4.2) are observed, but each of these findings have *per se* a low sensitivity for cirrhosis.[13, 14]

Blood-based tests and risk scores

Decreased platelet count is an early indicator of cirrhosis, while elevated prothrombin time test, decreased albumin level, or elevated bilirubin, are late signs of cirrhosis.[12, 15] Liver blood tests are frequently used for the prediction of incident liver fibrosis via non-invasive scores or serum markers.[12]

Fibrosis-4 (FIB-4) and alanine aspartate aminotransferase to platelet ratio index, are among the most widely used non-commercial scores for fibrosis risk stratification.[12, 16, 17]

The European Association for the Study of the Liver (EASL) recommends the use of alanine aminotransferase, alanine aspartate aminotransferase, and platelet count in routine investigations in primary care, when assessing the risk of fibrosis in patients with suspected liver disease.[12] The strength of non-invasive fibrosis scores is their high negative predictive value. Cirrhosis can thereby not be diagnosed by using fibrosis scores, and individuals at-risk of high-grade fibrosis need further investigation with diagnostic imaging, elastography, or liver biopsy.[12]

Table 1. Physical examination findings in patients with cirrhosis
Abdominal wall vascular collaterals (caput medusa)
Ascites
Asterixis (flapping hand tremor)
Clubbing and hypertrophic osteoarthropathy
Confusion or coma
Fetor hepaticus (hepatic halitosis)
Gynecomastia
Hepatomegaly
Jaundice
Muehrcke's nails (paired horizontal white bands)
Terry's nails (proximal two-thirds of nail white, distal third red)
Palmar erythema
Peripheral edema
Sarcopenia (muscle wasting, often of the limbs)
Splenomegaly
Testicular atrophy
Vascular spiders (spider telangiectasis, spider angiomas)

Diagnostic imaging

Ultrasound is a safe method, often performed as a first-line imaging examination in patients with suspected cirrhosis.[18] This method has a sensitivity of 52 to 69% and

a specificity of 74 to 89%, for cirrhosis diagnosis.[19, 20] Inter-observer variability is a major drawback of ultrasound-based diagnosis, and the usefulness of an ultrasound is limited in patients with obesity.[18, 19] Computed tomography (CT) has a sensitivity of 77 to 84% and a specificity of 53 to 68%.[20] CT allows a full cross-sectional visualization and signs of portal hypertension are very specific.[18, 19] Radiation exposure, increased cost compared to ultrasound, and risk for contrast-induced adverse events are well-known drawbacks related to CT.[18, 20] Magnetic resonance imaging (MRI) has sensitivity and specificity similar to CT without exposing patients to radiation.[18-20] MRI detects portal hypertension with a high specificity and cross-sectional visualization is superior to CT scans.[18] Major drawbacks of MRI are its higher cost and lower availability compared to CT.[18, 19]

Elastography

Elastography is a group of safe, non-invasive diagnostic methods for the assessment of liver stiffness.[21, 22] Transient elastography is the most widely used elastography method due to its applicability (>95%), time efficiency (requires only a few minutes to be performed), and real-time results.[12] Elastography has high sensitivity (>87%) and specificity (>90%) for cirrhosis in patients with different etiologies.[23-25] Major drawbacks include the requirement of a dedicated device for transient elastography and overestimation of liver stiffness under some conditions, such as in acute hepatitis or hepatic cholestasis, or after food intake, or in liver congestion.[12]

Gastroscopy and histology

Esophageal varices and portal hypertensive gastropathy are signs of cirrhosis detectable via gastroscopy. These findings have low sensitivity but a high specificity (89%) for cirrhosis.[26, 27] Liver biopsy - the gold standard - is an invasive and thereby not completely risk-free procedure. Its use has declined following improvements in other non-invasive methods. However, liver biopsy is still fundamental for the diagnosis of liver fibrosis and cirrhosis in selected patient categories.[12, 28]

Etiologies and causes

Etiologies are often referred as the main *causes* of cirrhosis. It must however be emphasized that, as for many chronic diseases and in cancer, a direct causal pathway between exposure and outcome can rarely be established due to the cumulative effect of confounding. The sufficient-component cause model is an alternative theoretical framework attaining increasing recognition in epidemiology.[29, 30] According to this model, a cause is not a single component but a minimal set of conditions or events that inexorably lead to the outcome.

Each component in a sufficient cause is called a *component cause* and component causes that must be present in every sufficient cause of a given outcome are referred to as a *necessary cause*.[29, 30] Chronic liver diseases should then be regarded as either *components of a sufficient cause* or *necessary causes* of cirrhosis, depending of the nature of the disease. Having these considerations in mind, we have chosen to increase the readability of this dissertation by using the terms *etiology* and *cause* as synonyms. Clinical guidelines from all major liver disease associations use similar simplifications.[31-33] Hence, etiologies referred to as *causes* in coming sections are strongly associated with cirrhosis (or liver cancer) but they may, or they may not, have direct causal pathways.

Specific etiologies

Viral hepatitis, alcohol, and non-alcoholic fatty liver disease (NAFLD) are the most common etiologies of cirrhosis.[7] Less commonly, cirrhosis can also be caused by other liver diseases, such as autoimmune liver disease, genetic liver disorders, or heart failure (Fig. 5).

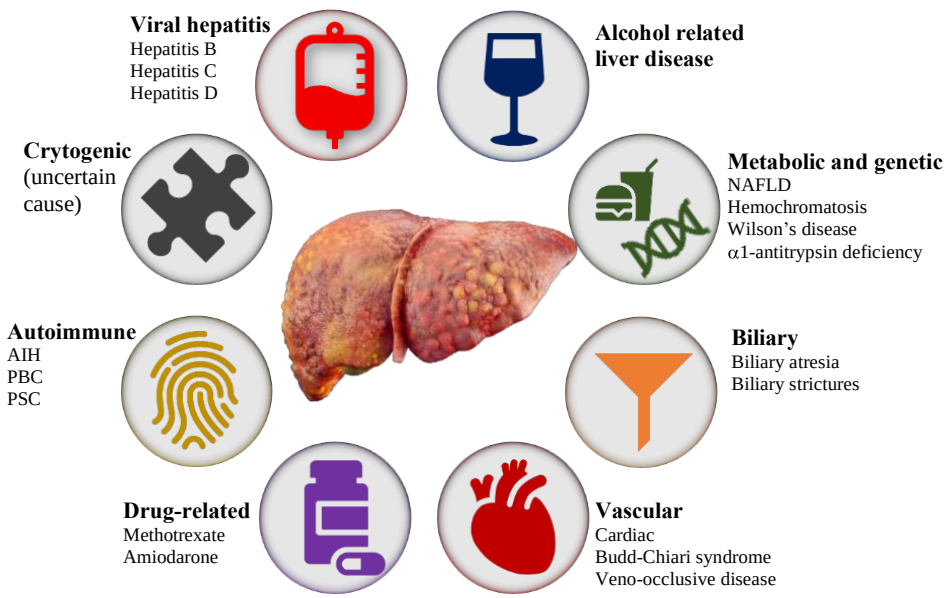

Fig. 5. Etiologies of cirrhosis. AIH: Autoimmune hepatitis; NAFLD: Non-alcoholic fatty liver disease; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

Viral hepatitis

Hepatitis B virus (HBV) is mainly transmitted perinatally or during early childhood exposure to HBV.[34] Horizontal transmission is caused by high-risk sexual behavior, and people who inject drugs are at higher risk for HBV infection.[34] The risk of chronic HBV is highly dependent on the age of the individual when the infection occurs.[34] Perinatal infections usually cause chronicity but infections in adults can frequently be controlled.[34] An important proportion of patients with chronic HBV develop cirrhosis.[34]

Hepatitis D virus (HDV) requires HBV for infection.[35, 36] Coinfection with HBV and HDV, observed in 5 to 13% of patients with HBV, is the most severe form of viral hepatitis.[35, 36] Compared to HBV-monoinfected, coinfected individuals have a substantially increased risk of fibrosis progression, and 50 to 70% develop cirrhosis within 5 to 10 years after diagnosis.[35, 36]

Hepatitis C virus (HCV) is transmitted through exposure to infected blood via intravenous drug use, blood transfusions, and healthcare-related parental administrations and surgical procedures (iatrogenic transmission).[37] Chronic infection develops in 75 to 80% of individuals after exposure to HCV.[37] HCV transmission due to sexual intercourse is uncommon.[37] The risk for mother-to-infant transmission is about 6%.[37]

Alcohol

Ethanol is primarily metabolized by the liver.[38, 39] Alcohol overconsumption has well-documented associations with the development of chronic liver disease.[39] Increasing amounts of consumed alcohol correlate with the incidence of cirrhosis.[38, 40] Women are more susceptible than men to alcohol abuse but they normally develop cirrhosis to a lesser extent as men tend to consume larger amounts of alcohol.[38, 40]

Alcohol-related liver disease (ArLD) is suspected in individuals with clinical or biological signs of liver injury when a regular alcohol consumption of >20 g per day in women, or >30 g per day in men is observed.[41, 42] The definition of risk consumption varies however across different countries.[43] *Standard drink* is a terminology often used in campaigns against alcohol-related illness. A standard drink is defined by a pre-defined quantity of pure ethanol, although, once again, the quantity of ethanol permitted in a standard drink differs across nations.[43] Examples of the Swedish standard drink are shown in Figure 6.[44]

Fig. 6. The Swedish standard drink of alcohol contains 12 grams of pure ethanol.

NAFLD

The term NAFLD covers a broad spectrum of histological conditions but is classically regarded as the collective designation of non-alcoholic fatty liver, or isolated steatosis, and non-alcoholic steatohepatitis (NASH).[45] NASH represents a more severe stage, hence being considered the leading cause of progression to cirrhosis in NAFLD.[45] It has though been shown that the grade of fibrosis, independent of the presence of NASH, is the most important prognostic factor for cirrhosis development and liver-related mortality in NAFLD.[46, 47] Therefore, isolated steatosis can progress to cirrhosis without NASH.[47]

About 5% of individuals with NAFLD may develop cirrhosis.[48] NAFLD is generally regarded as the hepatic manifestation of metabolic syndrome.[45] The associations between NAFLD and metabolic comorbidity, e.g. arterial hypertension, obesity, hypercholesterolemia, and type 2 diabetes (T2D), are well-documented.[45] Globally, over 55% of individuals with T2D are believed to have NAFLD.[49] Despite its strong link to obesity, NAFLD may also affect a substantial proportion of lean and non-obese individuals.[50, 51]

Autoimmune liver diseases

Autoimmune hepatitis (AIH) is a severe disease that can manifest at any age and has a female predominance.[52] The clinical presentation varies from mild to fulminant hepatitis and AIH is usually treated with immunosuppressive drugs.[52-54] Around 14 to 30% of patients with AIH may have cirrhosis at the time of their diagnosis.[55, 56]

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease often associated with inflammatory bowel disease.[57] PSC is characterized by fibrosis and strictures of the intra- and extrahepatic bile ducts.[57, 58] The disease can manifest at any age and there is a male predominance.[57, 58] PSC is associated with an increased

risk of developing cirrhosis, portal hypertension, and patients with PSC have a considerable risk of developing cholangiocarcinoma during their lifetime.[58]

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by the predominance of middle-aged women among patients.[59] Compared to other chronic autoimmune liver diseases, PBC is often referred to as having a better prognosis, although individuals with PBC have a higher mortality risk compared to controls.[59, 60] The highest mortality risk for PBC is seen in young adults and men have a worse prognosis.[59] The cumulative 10-year incidence of cirrhosis in patients with PBC has been estimated at 40%.[61]

Other etiologies

Hemochromatosis is a disorder characterized by increased iron absorption from the intestines, which in turn can lead to progressive body iron accumulation, mostly in the liver.[62] If untreated, hemochromatosis can lead to liver fibrosis, cirrhosis, and liver cancer.[62, 63] Wilson's disease is an inherited disorder characterized by defective biliary excretion of copper, leading to copper accumulation in the liver and the brain.[64] Wilson's disease may present at any age, but the majority of patients are between 5 and 35 years old at diagnosis. Many patients may already have developed cirrhosis at the time of diagnosis, which also applies to children and adolescents.[64] Alpha-1-antitrypsin is a protein abundantly produced by the liver.[65] This protein protects the body from excessive tissue destruction during infection. The most common clinical presentation of alpha-1-antitrypsin deficiency is lung disease but abnormal deposition of un-secreted protein in hepatocytes can lead to cirrhosis and liver cancer.[65] Longstanding use of some medications, such as amiodarone and methotrexate, has been linked to an increased risk of cirrhosis.[66, 67]

Cryptogenic cirrhosis

In some cases, the causes of cirrhosis remain undetermined. Cryptogenic cirrhosis is by many considered to be equal to "burn-out" NASH.[68] NASH cirrhosis may progress to a more advanced state, losing the histological feature of steatosis.[68] These assumptions are however debated since cryptogenic cirrhosis could also be seen as "burn-out" hepatitis, or occult alcohol abuse.[69] Patients with NASH and patients with cryptogenic cirrhosis have similar demographics, but the latter appear to have a higher risk of liver-related clinical events.[70]

Epidemiology

Liver diseases are a major health concern that are responsible for two million deaths per year worldwide.[71] According to the Global Burden of Disease (available at: https://www.healthdata.org/gbd/2019) most of these deaths are related to cirrhosis and its complications.

The Global Burden of Disease estimated a total of 123 million prevalent cases of cirrhosis in 2017.[72] The age-standardized prevalence of cirrhosis in Europe has been estimated at 833 per 100,000 person-years.[73]

The worldwide burden of cirrhosis is directly related to the prevalence of its foremost etiologies. Viral hepatitis has an estimated global prevalence of 4.8%, with HBV accounting for 85% of it.[74, 75] Over 1.3 billion people may regularly consume harmful amounts of alcohol, and NAFLD is the most common liver disease, having an increasing estimated worldwide prevalence of 25 to 30%.[76, 77]

In a systematic review, viral hepatitis was reported as the most common underlying liver disease in patients with cirrhosis worldwide, although regional variations were considerable.[78] Limitations for this study included the unavailability of data from multiple etiologies, and data regarding NAFLD were very limited.[78]

The burden of HBV is highest in Western Pacific regions and in Africa.[74] Since the introduction of HBV vaccination, the prevalence of chronic HBV and rates of HBV-related death have declined globally.[74] However, opposite trends have also been observed in many countries, mostly due to population growth and aging.[74]

The prevalence of HCV is highest in eastern Europe and central Asia.[75] Since the introduction of direct-acting antiviral (DAA) therapies, HCV can be successfully cured in the vast majority of cases, and the number of global HCV-related deaths has been decreasing since 2015.[75, 79] However, forecasts indicate that the global HCV elimination target introduced by WHO might not be achieved by 2030.[80] In this scenario, the number of HCV-related deaths would instead increase by 2030.[75]

One-quarter of all global cirrhosis-related deaths registered in 2019 were associated with ArLD.[81] The global per-capita alcohol consumption rate has been increasing since 1990 and is projected to increase further by 2030.[82] The highest levels of alcohol consumption and the highest prevalence of heavy episodic drinking in the world are observed in Europe, which also is the region with the highest percentage of cirrhosis deaths associated with alcohol drinking (42%).[9, 73]

NAFLD has been reported as the most rapidly growing liver disease associated with cirrhosis mortality and morbidity.[83] The estimated global prevalence of NAFLD is highest in South America (36%), followed by North America (35%), Europe (31%), Asia (30%), and Africa (28%).[84]

Natural history and complications

Cirrhosis is a silent disease that often develops throughout decades, remaining asymptomatic until the overt manifestation of cirrhosis-related complications.[7] During the initial stages of cirrhosis, which is referred to as compensated cirrhosis, patients might rarely have one or more of the following unspecific symptoms: malaise, poor appetite, loss of muscle mass, nausea and vomiting, itching,

abdominal pain, bruising and spontaneous nose bleeding.[7] The progression of liver fibrosis may regress if the cause or causes of liver damage are removed.[85]

However, a regression from cirrhosis to normal liver architecture appears unlikely. Several pharmacological agents have been developed for the treatment of liver fibrosis, but no treatment has been approved.[85] To date, the only available curative treatment for cirrhosis is liver transplantation.

Decompensated cirrhosis, or symptomatic cirrhosis, is to be regarded as a multi-organ/system dysfunction.[86] Symptoms associated with decompensated cirrhosis are intrinsically linked to the development of clinically significant portal hypertension and impaired liver function.[7]

The pathophysiology of portal hypertension is complex.[31] As previously described, portal circulation drains blood from most of the organs of the abdominal cavity.[1] As fibrosis progresses, liver stiffness increases, causing higher intrahepatic vascular resistance.[7, 31] Intrahepatic vascular resistance is further aggravated by increased intrahepatic vascular tone, which is caused by endothelial dysfunction and decreased nitric oxide bioavailability.[87] In turn, splanchnic arterial vasodilatation is established via the increased production of nitric oxide by extrahepatic endothelial cells, which act in response to vascular shear stress.[7, 31] Bacterial translocation further exacerbates the production of nitric oxide.[7] These events result in an increased portal blood flow.[87, 88] High intrahepatic vascular resistance, combined with increased portal blood flow, leads inexorably to an elevated hepatic venous pressure gradient (>5 mmHg).

Clinically significant portal hypertension is defined as a hepatic venous pressure gradient ≥10 mmHg since the risk for varices and ascites increases markedly above this level.[87, 89] Patients with cirrhosis and esophageal, or gastric varices, are regarded as having compensated disease if no other clinical signs of decompensation are observed (Table 2).[90]

Ascites

Annually, 5 to 10% of patients with compensated cirrhosis develop ascites, which also is the most common sign of decompensation.[7, 31, 91] Increased abdominal circumference with abdominal discomfort is the most frequent manifestation of ascites in patients with cirrhosis.[7] Ascites is caused by extracellular fluid volume expansion, which in turn is caused by sodium retention due to the activation of vasoactive and anti-natriuretic factors.[31] Ascites can be graded as mild (only detectable by diagnostic imaging methods), moderate (moderate symmetrical distention of the abdomen), or severe (marked abdominal distension of the abdomen).[7, 31] Ascites can further be graded as uncomplicated and complicated. Complicated ascites means recurrent or refractory ascites, or when ascites is associated with bacterial infection, or with kidney disfunction.[7, 92] The treatment of ascites is dependent on its grade and is comprised of a low-sodium diet, diuretics,

paracentesis with albumin replacement, transjugular intrahepatic portosystemic shunts, and liver transplantation.[31, 92]

Table 2. Complications of cirrhosis
Acute-on-chronic liver failure
Ascites
Bacterial infections other than spontaneous bacterial peritonitis
Frailty and sarcopenia
Gastrointestinal bleeding
Hepatic encephalopathy
Hepatic hydrothorax
Hepatocellular carcinoma
Hepatopulmonary syndrome
Non-obstructive jaundice
Portal vein thrombosis
Portopulmonary hypertension
Renal impairment
Spontaneous bacterial peritonitis

Gastrointestinal bleeding

Gastrointestinal bleeding, especially variceal hemorrhage (70% of cases), is the second-leading complication in cirrhosis.[7, 31] About 8% of patients without varices detected at screening may develop *de novo* varices.[31] Gastroesophageal varices are classified as either small or large, the latter having the higher risk of bleeding but small varices can also cause life-threatening hemorrhage.[31] The estimated overall risk of variceal bleeding is 5% per year, but it increases markedly when liver dysfunction severity progresses.[31] Other cause of gastrointestinal bleeding in cirrhosis is portal hypertension-related gastropathy.[31] Esophageal varices are treated with non-selective beta-blockers and with endoscopic treatment (variceal ligation) when needed. In patients with uncontrolled bleeding, variceal hemorrhage is treated with controlled volume resuscitation, vasoconstrictor therapy, variceal ligation, and rescue transjugular intrahepatic portosystemic shunt.[7, 31]

Bacterial infections

Patients with cirrhosis are more susceptible to bacterial infections due to multiple factors, including portosystemic shunting, and increased bacterial translocation.[7, 31] The liver plays a major role in innate and acquired immunity and liver dysfunction is a key component of cirrhosis-related infections.[2, 31] Spontaneous bacterial peritonitis (SBP) is a common cause of infection in cirrhosis.[92]

SBP is defined as a bacterial infection of ascitic fluid in the absence of intra-abdominal surgically treatable causes of infection.[7, 31] Up to 10% of hospitalized patients with cirrhosis have SBP and the prevalence of SBP in outpatients is around 1.5 to 3.5%.[31] Clinical symptoms of SBP may include peritonitis, systemic inflammation, gastrointestinal bleeding, and shock.[7, 31] SBP may also be asymptomatic in one-third of cases.[31, 92] SBP is diagnosed by diagnostic paracentesis (neutrophil count $\geq 0.25\times10^9$/L), and it is treated with intravenous antibiotics and albumin.[31, 92]

Hepatic encephalopathy

Hepatic encephalopathy (HE) is defined as a potentially reversible brain dysfunction caused by liver dysfunction, portosystemic shunting, or both; independent of the cause of liver disease.[7, 93, 94] The pathophysiology of HE is not completely understood but increased levels of ammonia, caused by decreased clearance of gut-derived ammonia, seem to be fundamental for the development of HE.[7, 93, 94] Systemic and neuroinflammation, oxidative stress, and electrolyte imbalance are also important for the development of HE.[93, 94] HE ranges from covert to overt.[7] Covert HE is not clinically detectable and can only be diagnosed by neuropsychological or electrophysiological testing.[93, 94] Patients with covert HE have a reduced quality of life and are at risk of driving accidents.[93] Overt HE is defined by a wide spectrum of neuropsychiatric abnormalities, ranging from lethargy or apathy, to confusion, bizarre behaviors, and coma.[7]

Up to 45% of patients with cirrhosis develop signs of overt HE, which is also the complication related to most admission and readmissions to hospital.[7] Overt HE is often triggered by constipation and by cirrhosis-related complications such as infection and gastrointestinal bleeding.[93] Overt HE is treated with osmotic laxatives, which also are used for prophylaxis in patients with covert HE.[93] Rifaximin is an antimicrobial agent used for secondary prophylaxis.[94]

Acute kidney injury and hepatorenal syndrome

Patients with decompensated cirrhosis and ascites are very susceptible to acute kidney injury (AKI), which is observed in 30 to 50% of hospitalized patients with cirrhosis.[92] AKI is defined as a serum creatinine increment ≥ 26.5 μmol/L within 48 hours, or an increment $\geq 50\%$ from a known or assumed level, supposedly occurred within the preceding seven days.[7, 31, 92] AKI is further divided into different stages

depending on the level of the serum creatinine increment.[7, 92] The most common causes of AKI in patients with cirrhosis are hypovolemia, hepatorenal syndrome (HRS) AKI, and acute tubular necrosis.[92] Infections, diuretics, and gastrointestinal bleeding are the most common precipitating factors of AKI.[31]

HRS-AKI is a distinctive form of renal failure that develops in patients with advanced cirrhosis. HRS-AKI has no specific clinical symptoms, but is characterized by a marked reduction of glomerular filtration rate.[7, 92]

The pathophysiology of HRS-AKI is partly understood, and includes several factors, such as renal hypoperfusion, increasing circulating levels of pro-inflammatory agents, and severe cholestasis.[31] In clinical practice, it is difficult to differentiate HRS-AKI from acute tubular necrosis, thus the diagnosis of HRS-AKI is made based on consensus criteria.[92] The recommended treatment for HRS-AKI is vasoconstrictor therapy and volume expansion.[7, 31] Severe cases may require renal replacement therapy and, in selected cases, liver transplantation, or simultaneous liver-kidney transplantation may be considered.[92]

Acute-on-chronic liver failure

There is no consensus regarding the definition of acute-on-chronic liver failure (ACLF) across the major international liver associations.[95] Common for all definitions is that ACLF is considered a syndrome characterized by acute decompensation, rapid deterioration, multiple organ failure, and high short-term mortality rate.[31, 95] Among patients hospitalized due to cirrhosis decompensation, >30% have ACLF at admission, or they develop ACLF during hospitalization. ACLF may be precipitated by bacterial infections, alcohol intake or binge, HBV reactivation, gastrointestinal bleeding, or drug induced liver injury.[31, 95] Precipitating factors cannot be identified in some patients.[31, 95]

The pathophysiology of ACLF is not completely understood, but systemic inflammation seems to play a major role in the development and clinical course of ACLF.[95] Clinical management comprises treatments for acute precipitants and suitable organ support therapies.[96]

Prognosis and survival

Compensated and decompensated cirrhosis have respectively a 5- and 10-times higher risk of death compared to the general population.[7] Patients with compensated cirrhosis have a median survival of nine to 12 years from diagnosis, which falls to two years upon decompensation.[91]

In 2005, based on combined data from two prospective studies, four clinical stages of cirrhosis were defined at the Baveno IV consensus conference (Fig. 7).[90] Two additional stages have been proposed. Further decompensation after any first

decompensation event defines stage five, which may reach five-year mortality of 88%.[97] The sixth stage, late advanced decompensation, is reached upon clinically evident multi-organ dysfunction, and may have a one-year mortality of 60 to 80%.[97] Although the clinical stages defined are associated with mortality risk, the progression across stages does not happen in a predictable order.[97]

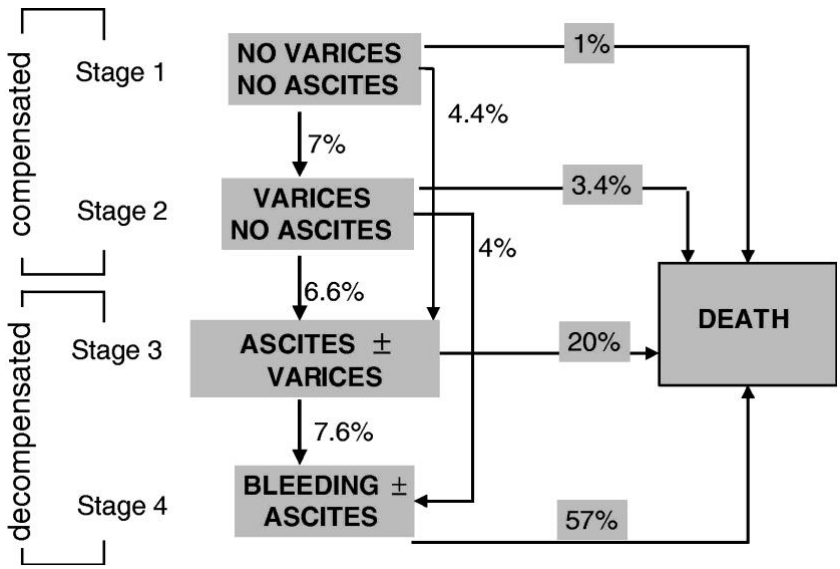

Fig. 7. Clinical course of cirrhosis and 1-year outcome probabilities according to clinical stages. Reprinted from "D'Amico G et al. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. *J Hepatol*. 2006 Jan;44(1):217-31",[91] with permission from Elsevier.

The median survival time in patients with cirrhosis is difficult to estimate due to variations between different studies, which may include patients at different cirrhosis stages and may lack adjustments for confounding. Other important limitations when comparing studies may be related to the etiology of cirrhosis, the prevalence of comorbidities, local clinical practices, and the general access to healthcare services. In a systemic review from 2006, the median survival time was calculated at 33 months, and the most commonly reported causes of death were liver failure, variceal hemorrhage, and liver cancer.[91] As the heterogenicity between study populations and confounding is large in the literature, the use of cirrhosis severity scores in the prognosis of cirrhosis is fundamental.

Severity scores

The most common cirrhosis severity scores are the Child-Pugh score (CP), and the Model for End-stage Liver Disease (MELD).[98, 99] CP is the oldest of the two scores,

and patients with cirrhosis are stratified into three different categories (Table 3). Although CP was originally created as a tool for the prediction of survival in surgery for patients with cirrhosis, the score has been validated in numerous studies.[100] A major drawback of CP is the inclusion of two variables sensitive for subjective assessment, ascites and HE. Patients with CP A, B, and C have estimated one-year cumulative survivals of 95%, 80%, and 45%, respectively.[91]

Table 3. Child-Pugh (CP) score for cirrhosis mortality

Variable	Points (in parentheses)
Hepatic encephalopathy	None (1), Grade 1-2 (2), Grade 3-4 (3)
Ascites	Absent (1), Slight (2), Moderate (3)
Bilirubin (μmol/L)	<34 (1), 34-51 (2), >51 (3)
Albumin (g/L)	>35 (1), 28-35 (2), <28 (3)
Prothrombin time	<1.7 (1), 1.7-2.3 (2), >2.3 (3)

CP A = 5-6 points, CP B = 7-9 points, CP C = 10-15 points.

MELD is an alternative score widely used in many countries when prioritizing patients for liver transplantation.[100] MELD-score was created in 2001, originally to predict short-term mortality in patients planned for a transjugular intrahepatic portosystemic shunts-procedure.[99] Contrary to CP, MELD-score only includes laboratory values (Table 4). Increasing MELD-score is associated with increased mortality.[99] MELD-score 20 to 29 has almost a 20% three-month mortality, while the three-month mortality in MELD >30 is 52 to 71%. MELD-score has been improved by including additional variables into the original model.[101, 102]

Table 4. Model for End-stage Liver Disease

Variables
Creatinine
Bilirubin
Prothrombin time
Dialysis[a] (yes/no)

[a] Twice a week, or 24 hours of continuous veno-venous hemodialysis, within a week prior to the serum creatinine test

Comorbidity

Survival in cirrhosis not only depends on the stage of the disease but also on the burden of prevalent comorbidities. Clinically significant comorbidities are diseases other than cirrhosis, which may affect the clinical course of cirrhosis, but that are neither a cause nor a consequence of cirrhosis.[103]

The total burden of comorbidity can be estimated by comorbidity scoring systems. The Charlson Comorbidity Index and the CirCom have been validated in cirrhosis.[104, 105] Among individual comorbidities, T2D is the most studied in cirrhosis.[106] Several studies have shown that T2D was associated with increased mortality in patients with cirrhosis.[107-109] Cardiovascular disease, chronic obstructive lung disease, and chronic kidney disease are other comorbidities associated with increased morbidity and mortality in patients with cirrhosis.[105, 106]

In a large cohort study of 35,361 patients with cirrhosis, those with compensated cirrhosis and concomitant chronic cardiometabolic comorbidities had higher mortality rates compared to patients with cirrhosis decompensation without comorbidity. Although these findings need to be validated in other cohorts, they underline the importance of comorbidity in cirrhosis survival.[110]

Hepatocellular carcinoma

Primary liver cancer is a major cause of mortality in patients with chronic liver diseases.[111-113] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, comprising almost 90% of cases globally.[111-113] Sustained inflammation can lead to fibrosis and cirrhosis, resulting in chronic hepatocyte necrosis and aberrant regeneration, hence stimulating the formation of dysplastic noduli.[111-113] These noduli can in turn become preneoplastic lesions, which after additional molecular alterations, can progress to full-blown primary liver cancer.[111, 113] For these reasons, 80 to 90% of patients with HCC have underlying cirrhosis, which together with HBV, constitute the main risk factors of HCC.[111]

Risk factors

Globally, HCC is rare among patients without underlying chronic liver disease.[111] Cirrhosis increases the risk of HCC independent of underlying etiology.[114] HCC can also arise in the absence of cirrhosis, or marked inflammation, e.g. in patients with non-cirrhotic NAFLD, HBV, or acute hepatic porphyria.[111, 112, 115, 116] Some well-documented risk factors of HCC are presented (Fig 8). Besides these risk factors, HCC is twice as common in men and tobacco smoking has been associated with an increased risk of HCC.[112, 117]

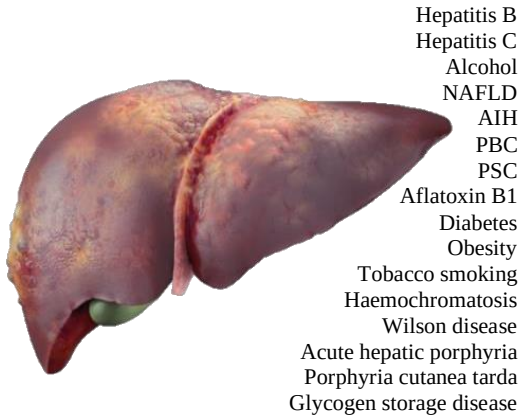

Fig. 8. Risk factors of hepatocellular carcinoma. AIH: autoimmune hepatitis; NAFLD: Non-alcoholic fatty liver disease; PBC: primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

Epidemiology

More than 900,000 people were diagnosed with primary liver cancer in 2020, making this malignancy the sixth most commonly diagnosed cancer worldwide.[118] Primary liver cancer, accounting for 830,000 deaths per year, has also become the third leading cause of cancer-related deaths worldwide.[119] In 2020, more than 553,000 deaths were registered among persons aged 30 to 69 years, making primary liver cancer the second-leading cause of premature death from cancer.[120]

The incidence of HCC is highly dependent on geographical region and ethnicity, which is explained by the varying prevalence of risk factors of HCC across the different regions of the world.[112] Both the incidence and mortality of HCC are highest in East Asia and Africa, but HCC has been reported as the fastest increasing cause of cancer-related death in the United States.[121] In Europe, liver cancer-related mortality increased by 70% from 1990 to 2019.[120] By 2040, a total of 1.3 million people are expected to die from liver cancer globally.[120] This is an increment of 55% compared to the number of deaths related to liver cancer registered in 2020.[120]

Viral hepatitis

Patients with viral hepatitis-related cirrhosis develop HCC more often than patients with cirrhosis due to ArLD, NAFLD, or autoimmune liver diseases.[122, 123] Globally, HBV and HCV are the most common underlying liver diseases in HCC, accounting for 56% and 20% of cases, respectively.[78, 124, 125] Over 60% of cases of HCC in Asia and Africa are attributable to HBV, while the corresponding percentage in western countries is 20%.[126] HCV is the most frequent liver disease in patients diagnosed with HCC in Japan, North America, and Europe.[126]

HBV-related HCC occurs predominantly in patients with underlying cirrhosis but the risk of HCC is also increased in the absence of cirrhosis. HCC risk in non-cirrhotic HBV is highest in men older than 40 years, in people with active HBV inflammation or who are exposed to aflatoxin B1, and in those with concomitant HCV or HDV co-infection.[34, 35, 37, 112] HCV-related HCC develops primarily in patients with underlying cirrhosis or bridging fibrosis.[112] The risk of HCC in HCV is reduced by 50 to 80% when a sustained virological response is achieved after treatment with DAAs.[127] However, if cirrhosis is already established before successful treatment of HCV infection, the risk of developing HCC persists even after sustained virological response (>2% per year).[128]

ArLD

Compared to viral hepatitis, the risk of HCC in ArLD is relatively low. Depending on the geographical location, ArLD accounts for 15 to 30% of all HCC cases.[112] The annual risk of HCC in ArLD cirrhosis differs between <1% to 2-3%, depending on the populations studied.[122, 129-134]

NAFLD

NAFLD has been reported as the fastest-growing cause of HCC in the United States, France, and the United Kingdom.[116] In patients with cirrhosis, the annual risk of HCC ranges from 0.5 to 2.6%.[116] Biopsy-proven NAFLD is associated with a 17-fold increased risk of HCC compared to controls.[135] Overall, up to 15% of all global cases of HCC may be secondary to NAFLD.[136] Compared to other etiologies, patients with NAFLD have less often underlying cirrhosis.[137] In a recent meta-analysis, it was found that nearly 40% of patients with NAFLD-related HCC did not have underlying cirrhosis.[136]

Other liver diseases

Cirrhosis is the main risk factor of HCC in patients with AIH, PBC, and PSC,[57, 138, 139] The risk for HCC development in these liver diseases is however relatively low compared to the risk reported for viral hepatitis.[123] Hereditary hemochromatosis has been associated with a 20-fold increased risk of HCC compared to the general population.[140]Acute hepatic porphyria has also been associated with a markedly increased risk of HCC when compared to matched controls.[115]

In summary, NAFLD and HBV are the most common underlying liver diseases in patients without cirrhosis diagnosed with HCC. Among patients with cirrhosis, the risk of HCC development varies by etiology.[123] In a large study of 15,215 individuals newly diagnosed with cirrhosis in Sweden between 2001 and 2016, men with viral hepatitis had the highest cumulative incidence of HCC at 10 years (27%), while women with ArLD had the lowest (4%).[123]

Diagnosis, prognosis and surveillance

In patients with underlying cirrhosis, HCC can be diagnosed with the use of validated diagnostic imaging methods. Small lesions (<1 cm in diameter) are very difficult to detect by ultrasound, or are seldom HCC. In these cases, a repeat ultrasound after three months is advised.[112] Lesions ≥ 1 cm in diameter detected during an ultrasound should be further examined by either quadruple-phase CT or by dynamic contrast enhanced MRI.[141-143] The radiological hallmark of HCC is *arterial enhancement and delayed washout*, which has a sensitivity of 89% and a specificity of 96% for HCC.[144] In cirrhosis, these radiological features are sufficient for the diagnosis of HCC.[141-143] According to EASL, diagnosis by liver histology is required in patients without underlying cirrhosis, or in patients with cirrhosis who had tumors lacking imaging hallmarks of HCC.[141] The use of contrast-enhanced ultrasound for HCC diagnosis is controversial.[145] According to Asian Pacific guidelines, this method is as sensitive as CT or MRI, while European guidelines consider it suitable for lesions ≥ 1 cm in cirrhosis, and American guidelines do not recommend the use of contrast-enhanced ultrasound for HCC diagnosis.[141-143]

Generally, patients with HCC have a very poor prognosis due to diagnosis at late- and terminal-stages.[146] Patients diagnosed at early-stages have an expected 5-year survival >70%, with a median survival time of 36 months.[111, 141, 147] Patients with preserved liver function that are diagnosed at intermediate- and advanced-stage HCC have median survivals of 16 and 6 months, respectively.[141, 143]

Several observational studies and a meta-analyses have shown that HCC surveillance is associated with earlier tumor detection, increased receipt of curative treatment, and better overall survival.[148] For these reasons, all major international liver associations advise bi-annual liver ultrasound in patients with cirrhosis (Table 5).[141-143]

Table 5. Liver cancer surveillance recommendations in patients with cirrhosis
American Association for the Study of Liver Diseases
Ultrasound every six months, alpha-fetoprotein optional
Asian Pacific Association for the Study of the Liver
Ultrasound and alpha-fetoprotein every six months
European Association for the Study of the Liver
Ultrasound every six months, alpha-fetoprotein not recommended

While American guidelines do not address the issue of HCC in patients without cirrhosis, European and Asian guidelines extend surveillance to specific non-cirrhotic high-risk groups.[145]

The implementation of HCC surveillance programs in patients with cirrhosis is widely accepted. The benefits and cost-effectiveness of HCC surveillance are however still debated.[149] Results from observational studies in HCC surveillance are highly vulnerable to lead-time and length-time bias.[149] Additionally, in a matched case control from the United States, HCC surveillance by ultrasound, alpha-fetoprotein, or both, was not associated with decreased HCC-related mortality.[150] Ultimately, no randomized control trial evaluating the benefit and cost-effectiveness of HCC surveillance has been performed.[149]

Staging

Since HCC is a unique form of cancer that primarily affects patients with cirrhosis, its prognosis depends not only on tumor characteristics but also on underlying liver function level and physical status.[141, 151] All these components are incorporated into the Barcelona Clinic Liver Cancer (BCLC) algorithm (Fig. 9). The BCLC was first introduced in 1999 and nowadays is the most widely used staging system in clinical guidelines for the treatment of patients with HCC.[141-143, 147]

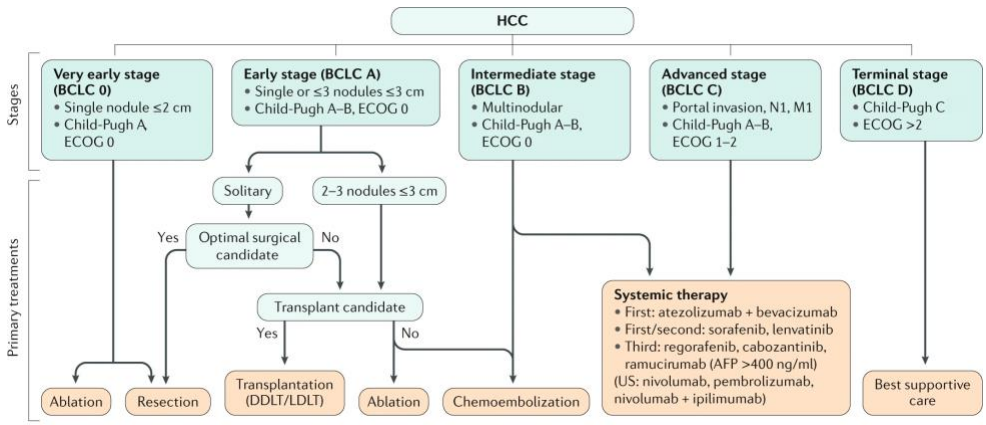

Fig. 9. The Barcelona Clinic Liver Cancer (BCLC) staging system. AFP: alpha-fetoprotein; DDLT: deceased-donor liver transplant; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; LDLT: living-donor liver transplant; M1: distant metastasis; N1: lymph node metastasis; OS: overall survival. Reprinted and adapted from "Llovet et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021 Jan; 7(6)",[112] with permission from Springer Nature.

The BCLC has been updated regularly with the latest update published in 2022.[151] Important tumor characteristics associated with survival in HCC are tumor size, number of tumors, portal invasion, and metastasis. Liver function can be assessed by CP-classification, or MELD-score. These estimates should however be refined by also taking consideration to alpha-fetoprotein levels and albumin-bilirubin score.[151]

Physical status, or performance status, is generally assessed using the Eastern Cooperative Oncology Group classification (Table 6).[152] Of note, according to BCLC, only tumor-related symptoms, and not baseline symptoms, should be considered when assessing performance status in patients with HCC.[151] This can be particularly challenging in clinical practice since patients diagnosed with HCC usually are >65 years at diagnosis, which *per se*, can be associated with a significant burden of comorbidity and worse baseline performance status.

Table 6. Eastern Cooperative Oncology Group performance status classification

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry on any work activities. Up and about more than 50% of working hours
3	Capable only of limited self-care, confined to bed or chair more than 50% of working hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Treatment

The main treatments with curative intent for patients with HCC are surgical.[112] Imaging-guided ablation is also considered a potentially curative treatment.[142] Intra-arterial therapies are regarded as a non-curative treatment options, often reserved for patients with intermediate-stage HCC.[141] These therapies can however be a part of neoadjuvant treatments prior to liver transplantation. In patients with advanced-stage HCC, systemic therapies may be the treatments of choice, but radiotherapies can also be considered an option in palliative settings.[112] Best supportive care (BSC), which comprises symptom-relieving treatments, is recommended to patients at terminal stages.

Liver transplantation

Liver transplantation is currently the best treatment option in patients with HCC and underlying cirrhosis as both conditions are treated by a single surgical procedure. Transplantation is however a very limited option due to the shortage of available organs. In order to be considered for transplantation, patients with HCC, besides lacking contraindications to surgery, need to have tumors within specific inclusion criteria (Table 7).[153, 154]

The post-transplantation five-year survival rate has been reported as 75 to 80% among patients with HCC.[153, 155-157] For most patients with HCC, the waiting time for liver transplantation is between six and nine months. During this waiting time, to avoid tumor progression, patients can be treated with bridging therapy, such as locoregional treatments. Locoregional treatments can also be used for downstaging (or downsizing) to reduce tumor mass to fulfill transplantation criteria.[112, 154, 158]

Table 7. Inclusion criteria for liver transplantation in HCC

Milan criteria
Single tumour ≤ 5 cm *OR* ≤ 3 tumors, none exceeding 3 cm *AND*
No extrahepatic spread *AND* no vascular invasion
University of California, San Francisco (UCSF) criteria
Single tumor ≤ 6.5 cm *OR* ≤ 3 tumors, none exceeding 4.5 cm, total tumor diameter ≤ 8 cm
AND No extrahepatic spread *AND* no vascular invasion

Locoregional therapies prior to liver transplantation have also shown a beneficial effect in reducing the risk of HCC recurrence after surgery.[154, 158] HCC recurrence rate after transplantation ranges from 10 to 20%.[159-161] Most cases of recurrence (70%) are diagnosed within the first two years of follow-up, and comprise typically extrahepatic spread.[160]

Liver resection

Liver resection is considered the first treatment option in patients without cirrhosis, who have a technically resectable tumor larger than 3 cm.[112, 151] Complete tumor resection and clear resection margins are the goals of this treatment. In patients with cirrhosis, this can be challenging due to the potential risk of post-surgical liver decompensation that can be caused by insufficient viable liver parenchyma after surgery.[112] Minimal invasive techniques are becoming the first option for resection in most centers worldwide, which in turn have increased short-term outcomes[162, 163]. Minimal invasive liver resection has also decreased the risk of decompensation in

patients with portal hypertension, or with advanced cirrhosis (CP-class B); which otherwise are considered patient groups not suitable for resection.[164, 165]

A recent meta-analysis of 110 studies reported an excellent post-resection one-year survival (about 90%), but a poor five-year survival of 55%.[166] HCC recurrence, observed in up to 80% of patients, is a main drawback of resection.[112]

Ablation

Patients with very-early and early-stage HCC (BCLC 0-A) that are not suitable for resection or transplantation, may be offered treatment with thermal ablation. Image-guided radiofrequency ablation is the most commonly used method for ablation used in HCC. Ablation is considered a potentially curative treatment for patients with tumors < 3 cm and most guidelines recommend this method as first-line therapy for single tumors < 2 cm.[112, 141, 142, 167] Patients receiving ablation as first-line treatment have an overall five-year survival ranging from 35 to 68%.[155, 168-170]

Intra-arterial therapies

Intra-arterial therapies are non-curative treatments recommended in patients with intermediate-stage HCC, or in those who may be suitable for liver transplantation after successful downsizing. The main goal is to cut off the blood supply to HCC tumors, which otherwise are hypervascular and derive most of their blood supply from the hepatic artery.[113] Transarterial chemoembolization is the most widely used method.[113] Patients treated with transarterial chemoembolization have a median overall survival of 26 to 30 months.[151, 171]

Systemic therapies

In patients with advanced-stage HCC, or in those with intermediate-stage who do not qualify for locoregional therapies; systemic therapy is recommended. Sorafenib, a multikinase-inhibitor, has been approved as monotherapy for unresectable HCC since 2007.[172] With a median survival of 10.7 months, the net survival benefit of sorafenib, compared to placebo, was modest (around three months). Lenvatinib is another multikinase inhibitor that was introduced as first-line therapy after showing non-inferiority compared to sorafenib.[173]

The combination atezolizumab-bevacizumab was the first treatment showing a significant survival benefit compared to sorafenib (19.2 vs 13.4 months).[174, 175] Patients treated with atezolizumab-bevacizumab have an increased risk of bleeding, and patients with portal hypertension need to be screened for varices.[175] Atezolizumab-bevacizumab is now considered the new standard of care in front-line treatment for patients with unresectable advanced-stage HCC.[151, 176, 177]

Best supportive care

A significant proportion of patients diagnosed with HCC are not eligible for any treatment, having a life expectancy of about three to six months.[147] At this stage, patients should receive adequate BSC, including management of pain, nutrition and psycho-oncological support.[141, 178] Since patients with HCC often have cirrhosis, adequate symptomatic treatment for cirrhosis-related complications, especially ascites and HE, is also required.[178] BSC is not only important for patients diagnosed at terminal stages as a majority of patients initially treated with potentially curative treatments may sooner or later present with HCC recurrence and progression to late- and terminal stages. Even patients firstly diagnosed at intermediate- or advanced stages may progress towards terminal stages within a few months.[178]

Knowledge gaps

As our circle of knowledge expands, so does the circumference of darkness surrounding it.

— Albert Einstein

Epidemiology of cirrhosis in Sweden

According to data from the Global Health Observatory provided by WHO (available at https://apps.who.int/gho/data/view.main.53420), Sweden has one of the lowest age-standardized mortality rates of cirrhosis in Europe: 8.4 per 100,000 person-years for men, and 4.2 for women. Sweden is also considered to have a stable low incidence of cirrhosis.[73] In general, Nordic studies examining the all-cause incidence of cirrhosis are scarce (Table 8).[179-185]

Table 8. Studies assessing incidence of cirrhosis in Nordic populations

Country	Location	Study period	N patients	Incidence rate[a]
Iceland	Nationwide[180]	1994-2003	98	3.3 (O)
Iceland	Nationwide[183]	2010-2015	157	9.5 (O), 12.6 (M), 6.6 (F)
Norway	Oslo (Aker Hospital)[181]	1999-2004	194	13.4 (O)
Finland[b]	Nationwide[184]	1996-2012	11,873	14.6 (M), 4.2 (F)
Sweden	Gothenburg[180]	1994-2003	918	15.3 (O)
Sweden	Region Skåne[179]	2001-2010	1,317	14.1 (O), 19.1 (M), 9.4 (F)
Denmark[b]	Nationwide[186]	1988-2005	16,745	26.5 (M), 11.8 (F)
Denmark	Funen[182]	1996-2006	1,369	33 (O), 46 (M), 21 (F)
Denmark[b,c]	Nationwide[187]	2009-2018	13,609	46.5 (O), 64.1 (M), 28.9 (F)

[a] Estimated per 100,000 person-years. [b] Only patients with cirrhosis due to alcohol-related liver disease. [c] Estimated for people aged 30 to 69 years. F: female sex; M: male sex; O: overall.

The main etiology of cirrhosis in Nordic populations seems to be ArLD, with Denmark and Finland having the highest proportions of patients with alcohol-related cirrhosis.[184, 185] These two countries have also the highest reported per-capita consumption of alcohol across the Nordic nations.[188]

At the time of publication of Papers I and II, which are presented later in this dissertation, there were only two epidemiological studies estimating the incidence of cirrhosis in Swedish populations. [179, 180] The first study was published in 2009 and was based on data from the second largest city of the country, Gothenburg (located in the southwest of Sweden, Region Västra Götaland).[180] The annual crude incidence rate (IR) of cirrhosis, between 1994 and 2003, was estimated at 15.3 per 100,000 person-years. In the second Swedish study, which was published in 2016, the annual crude IR of cirrhosis in Region Skåne (located in southern Sweden), between 2001 and 2010, was estimated at 14.1 per 100,000 person-years; 19.1 for men and 9.4 for women.[179] The crude prevalence of cirrhosis among adults was estimated at 67 per 100,000 inhabitants, 87 for men, and 48 for women.[179] Consistent with other Nordic studies, ArLD was reported as the main etiology of cirrhosis (≈50%), followed by HCV, alone or combined with ArLD.[179] Roughly half of the patients were diagnosed at a decompensated stage (Baveno IV, stage 3 or 4), and the overall 10-year survival probability was estimated at 27%.[179] Survival probabilities were largely dependent on the underlying cause of cirrhosis.[189]

Since 2014, IRs and prevalence of HCV have been declining in Sweden.[190] In 2018, the IR of HCV was estimated at 15.8 per 100,000 person-years, and the prevalence ranged from 196 to 295 per 100,000 person-years.[190] All inhabitants in Sweden have free access to highly effective DAAs, and the prevalence of HCV in the country is expected to reduce markedly by the next decade.[191] The per-capita alcohol consumption has shifted during the last two decades in Sweden, and was reported at 8.8 liters of pure alcohol in 2018 (Fig. 10).[192]

The prevalence of overweight and obesity (defined as a body mass index $\geq$ 25 Kg/m^2) has been increasing in Sweden since 2004 (Fig. 11).[193] In 2018, 58% of men and 46% of women in the age span 16 to 84 years, were either overweight or obese. In the same year, 62% of the Swedish population in the age span 45 to 64 years was either overweight or obese.[193]

The prevalence of T2D is also increasing in Sweden. It has been predicted the prevalence of T2D will continue to rise, from 6.8% in 2013 to 10.4% by the year 2050.[194]

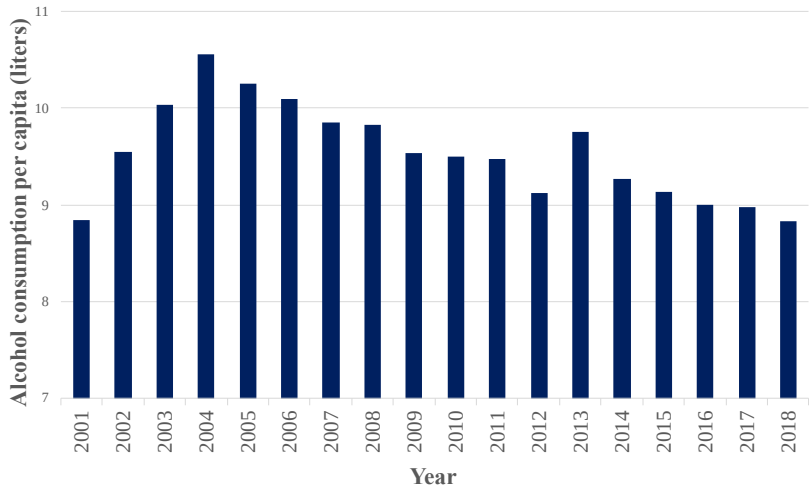

Fig. 10. Annual per capita consumption of alcohol among people aged 16 to 84 years living in Sweden.

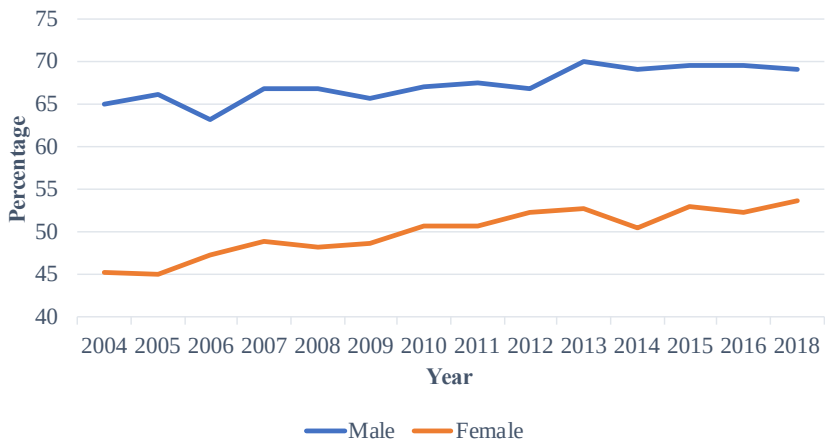

Fig. 11. Percentage of inhabitants of Sweden (2004-2018), aged 45 to 64 years, with a body mass index ≥ 25 kg/m^2 (overweight or obese).

In summary, the incidence and prevalence of several determinants of cirrhosis, and thereby of HCC, have been shifting during the last decade in Sweden. This changing setting across etiological factors in Sweden has made contemporary epidemiological studies highly needed; not only to confirm, or disregard prior results, but also to identify current challenges and improvement opportunities in the early diagnosis, treatment recommendations, and prognosis of patients with cirrhosis and HCC.

Epidemiology of HCC in Sweden

In Sweden, HCC comprises about 75% of all primary liver cancer cases.[195] The overall IR of HCC in Sweden has been estimated at five per 100,000 person-years.[195] During the last decade, the IR of HCC has been increasing among men in the age span 50 to 69 years.[195]

The IR of HCC in individuals with cirrhosis in Sweden has been estimated at 23 per 1,000 person-years, 29 in men, and 14 in women.[123] Men with viral hepatitis have the highest 10-year cumulative incidence of HCC (27%) among individuals with cirrhosis in Sweden.[123]

HCV has been reported as the most common liver disease associated with HCC in Sweden, accounting for almost 30% of cases.[157] A nationwide study of 3,376 patients diagnosed with HCC in Sweden (2009-2016) found that ArLD was the second-leading cause of HCC (25%).[157] The median age at diagnosis was 68 years, 60% had underlying cirrhosis, and 75% of patients were men.[157] About one-third of patients received potentially curative treatments and 39% were diagnosed at terminal stages.[157] The five-year survival rate was 71% after liver transplantation, 64% after resection, and 38% after ablation.[196] The estimated median survival rate for patients receiving palliative treatment was 1.5 years for transarterial chemoembolization, and 0.5 years for sorafenib.[157] BSC was associated with a median survival rate of 0.3 years.[157]

A study from Stockholm showed that among patients diagnosed with NAFLD-HCC (n = 225) between 2004 and 2017, 37% did not have underlying cirrhosis.[137] Additionally, a recent study reported NAFLD as the second-leading liver disease associated with HCC in Stockholm between 2003 and 2018 (n = 2,245).[155] In this study, nearly half of the patients received BSC. Also in Stockholm, data from 616 patients diagnosed with HCC between 2005 and 2015, showed that only 22% of HCC cases were diagnosed by surveillance.[197] Importantly, in one-third of all HCC cases surveillance was missed in patients that otherwise should have been surveilled.[197] Underdiagnosed liver disease and doctors' failure to order surveillance were the main causes of missed surveillance.[197]

Cirrhosis underdiagnosis has been reported in 22 to 50% of patients diagnosed with HCC in the United States.[198-202] Overall, less than 25% of patients with cirrhosis in the United States may receive consistent HCC surveillance.[203] The proportion of HCC surveilled among individuals with cirrhosis that belong to socioeconomically deprived groups, or to ethnic minorities, may be even lower thus reflecting the importance of health inequity in cirrhosis and HCC.[204]

Liver diseases and inequality

Social and health inequalities are intertwined with liver disease. Being one of the main contributors to liver disease, inequality is not only associated with etiological factors but also with access to proper medical and social resources.[9, 205] Liver diseases are often overrepresented in socially disadvantaged groups and underserved communities.[205] The reasons for these associations are multifactorial and include exposure to unhealthy physical, social, and economic environments; and use of food, drugs, or alcohol as response mechanisms to psychological stress.[9] Liver disease prevention, diagnosis, care, treatment and palliation, are all affected by inequality.[205]

Sex

Differences between sexes and their association with specific outcomes, e.g. IRs, expected survival, and liver transplant receipt; are arguably the most studied determinants of health inequality in cirrhosis and HCC. As previously described, IRs of cirrhosis in men are two-fold higher compared to those in women.[179, 182, 183] Men are also more frequently diagnosed with cirrhosis at decompensated stages and have worse survival.[179, 206] IRs of HCC are also two-fold higher in men compared to women.[123] Overall, men have a two to four-fold higher risk for HCC.[207, 208] On the other hand, women have poorer outcomes at every stage of the liver transplantation process.[209, 210] For instance, women are 14% less likely to receive a transplant compared with men, and they have also a 9% higher risk of death while in the waiting list for a transplant.[211]

Race and ethnicity

Racial disparities in cirrhosis- or HCC-related healthcare outcomes have been reported in numerous studies from the United States, but race is rarely used as a determinant of health inequality in Europe.[212-219] On the other hand, some ethnicities, such as those represented by immigrants from non-western countries, have been associated with an increased risk for liver cancer in European populations.[220, 221]

Marital status

Marital status is another factor regularly studied in health inequality.[222-227] In Denmark, patients with cirrhosis who were married had better five-year survival than patients who never married, or who were divorced.[228] In Hungary, the risk of cirrhosis was found to be increased in people separated or divorced, compared to

controls.[229] In South Korea, being married has been associated with better health-related quality of life in patients with chronic liver disease.[230] Several studies in HCC have shown that married patients had better survival compared to unmarried ones.[231-234]

Socioeconomic status

In public health studies, socioeconomic status (SES) is among the most commonly used determinants of inequality. Lower SES often predicts worse health and outcomes.[235] An individual's position in society is often described by his/hers SES, the latter being a combination of several factors, such as education, occupation, housing, and income.[236, 237] The different indicators of SES may not be entirely interchangeable, but they usually are intertwined to each other.[238, 239] For example, higher income is generally linked to the most qualified occupations, which in turn, often require a higher educational level.[238]

In a study from Denmark including 17,473 patients diagnosed with ArLD (78% cirrhosis), educational level and employment status were strongly associated with IRs of ArLD in people aged 30 to 69 years.[187] In the age span of 30 to 39 years, low educational level was associated with an IR of ArLD 9.8-fold higher than the IR estimated for individuals with a high level of education.[187] People with the lowest educational level had the highest cirrhosis-related mortality rate in Barcelona, Spain.[240] In the United States, the prevalence of cirrhosis was higher in people with a shorter formal education.[241] Health inequalities related to occupation, employment status, and income level, have previously been reported in patients with cirrhosis.[187, 213, 214, 228, 229, 241, 242]

In some cases, individual-level SES data may be unavailable, or misleading, when considering an individual's position in society. For instance, non-working housewives/househusbands, living in an otherwise wealthy household, may equivocally be regarded as having a low SES if defined by employment or individual income. These limitations could be overcome by using contextual-level SES indicators, such as indices of multiple deprivation (IMD).[243] IMDs are widely used in the United Kingdom but several European nations have developed their own IMDs.[244-250] IMDs at the small-area level, neighborhood deprivation level, may be useful for geographically targeted interventions, such as primary prevention initiatives against chronic diseases, or cancer screening programs in high-risk areas.[251, 252]

The importance of inequality in liver diseases in Europe was recently highlighted by the EASL-Lancet Liver Commission.[9] A recent review of 303 papers addressing health inequalities in liver disease (published between 1996 and June 2022), found that most of the studies (84%) were conducted in North American populations, of which almost 98% included data solely from the United States.[205] Only 10% of the

articles found were led by European institutions or conducted in European populations.[205] At the time of publication of Paper II, there were no contemporary studies from Sweden examining the role of marital status, employment status, and occupation in cirrhosis survival. The associations between SES, ethnicity, and liver cancer in European populations had been studied in cohorts from Germany, England, France, Finland, Norway, and Sweden.[253-260]

To the best of our knowledge, prior to Paper III, no other nationwide study from Europe had included both individual- and contextual-level SES indicators when estimating IRs of HCC.

Liver diseases and stigma

Liver diseases are often associated with a significant burden of stigma, which may be reflected by stereotypes (public stigma), negative labelling nomenclature or less access to healthcare (structural stigma), and discrimination and stereotyping by healthcare professionals.[9]

Public and structural stigma, together with stigma in health settings, can lead to self-stigma, resulting in lower disease awareness and healthcare avoidance.[9] This ultimately can result in late diagnosis and worse outcomes. As previously described, underdiagnosed cirrhosis has been reported in a substantial proportion of patients diagnosed with HCC in the United States.[200] At the time of publication of Paper IV, no other nationwide study from Europe had described the burden of unrecognized cirrhosis in HCC prognosis.

Aims

I was taught that the way of progress is neither swift nor easy.

— Marie Curie

The overall aim of this thesis was to describe the contemporary epidemiology of cirrhosis and HCC in Swedish settings. We aimed also to improve the understanding of the importance of sociodemographic characteristics and comorbidity for the clinical course and early identification of cirrhosis and HCC.

Our specific aims were:

I. To calculate IRs of cirrhosis, and to describe etiology, severity and burden of comorbidity and liver-related complications in cirrhosis (Paper I)

II. To study the importance of various sociodemographic characteristics on cirrhosis survival and mortality risk (Paper II)

III. To target population groups with heavier burden of HCC by assessing associations of individual-level sociodemographic variables and neighborhood deprivation, with all-stage and stage-specific IRs of HCC (Paper III)

IV. To determine the proportion of patients with unrecognized cirrhosis among patients diagnosed with HCC, and to describe patient characteristics, survival, and mortality risk associated with cirrhosis under-recognition (Paper IV)

V. To determine the extent to which NAFLD is an increasing cause of HCC, and to determine clinical characteristics associated with underlying NAFLD-HCC (Paper V)

Ethical considerations

Consciences keep silence more often than they should,
that's why laws were created.

— José Saramago

All studies presented in this dissertation have ethical approval from the Central Ethical Review in Sweden: decision numbers 2018-1177 (Papers I and II), 2019-05067 (Paper II), and 2020-04430 (Papers III, IV, and V). Due to the retrospective nature of these studies, no formal patient consent was required.

Although all individual patient data were pseudonymized and results were presented as group-level strata, epidemiological studies like ours may infer some indirect risks. First, liver diseases, especially those associated with alcohol or drug use, often are stigmatizing and the integrity of the included patients must carefully be taken into account.[9] Second, to identify specific at-risk populations for liver diseases in society, e.g. the poorest, immigrants, or the less formally educated; may increase the risk of stereotype dissemination. Third, some of our results may raise feelings of "social injustice" among patients with liver diseases, or among their relatives. However, this is an inevitable consequence of healthcare inequality research.

While I am aware of these risks, I believe that the potential benefit of the presented studies overcomes hypothetical harms. I believe that a first step against liver disease unawareness and stigma could be the identification of sociodemographic and clinical patient characteristics linked to an increased risk of disease progression and worse prognosis. Even if our studies do not infer a direct benefit to included patients, we attempted to elucidate several challenges found in cirrhosis and HCC in Sweden, aiming to increase our knowledge of liver diseases to provide tools that could be useful for the improvement of current preventive initiatives, screening methods, and management strategies.

Patients and Methods

Without data, you're just another person with an opinion.

— William Edwards Deming

Personal identity number

The Swedish personal identity number consists of a unique 12-digit code provided by the Swedish Tax Agency, to everyone registered in the Swedish Population Register.[261] This identification number is permanent throughout life, meaning that, with very few exceptions, a person has the same number despite changes in country of residency, marital state, or legal sex. Most registers in Sweden use personal identity numbers, allowing linkages between different registers.[261]

Data sources

Region Halland (Papers I and II)

The computerized medical record system in Halland is currently used by all primary and secondary care centers of the region. Through this electronic system, larger amounts of patient data can be retrieved. These data comprise medical records from in- and outpatient visits, remote healthcare visits, radiology reports, histology reports, laboratory values, prescribed medications, and scanned legal documents, such as certificates of fitness, sick leave certificates, and death certificates. All diagnoses made are registered using International Classification of Diseases – 10th Edition (ICD-10) coding.

Statistics Sweden (Papers III, IV, and V)

Statistics Sweden is a government agency operating under the Ministry of Finance. Statistics Sweden has established, maintained, monitored, and updated numerous population registers for many decades.

The Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies is a widely used database that, among other data, includes demographics, education, employment, income, social insurance, and family.[262, 263] Statistics Sweden also produces a large range of reports and maintains open-source databases (available at https://www.scb.se/en/services/open-data-api/).

Quality register (Papers III, IV and V)

The Swedish quality register for cancers found in the liver (SweLiv) was first established in 2008, and was in 2014 validated for HCC against the Swedish Cancer Register.[157, 195] Since its creation, SweLiv contains patient data from >95% of all known cases of primary liver cancer reported in Sweden (available at http://statistik.incanet.se/SweLiv/).[157, 195] At the time of the design of the presented studies, SweLiv consisted of four different modules (Table 9).

Table 9. Modules of SweLiv

Module 1 – Registration and treatment recommendations[a]
Diagnostic pathway; pre-surgical staging
Diagnosis: type of cancer (ICD-10), diagnostic imaging criteria, histology
Cirrhosis status, etiology, laboratory values including AFP, ascites, hepatic encephalopathy
Care plan: surgery, TACE, systemic treatment, other treatment, BSC (including reason for decision)
Module 2 – Surgery
Type of intervention, further intervention planned?
Comorbidity (ASA classification), performance status, staging
Cirrhosis status, steatosis?
Module 3 – Complications, post-operative 30-day follow-up, histology, care plan
Complications within 30-days after surgery
Performance status
Diagnosis (based on histology), histology report
Tumor burden 30-days after surgery
Planned adjuvant or palliative treatment
Module 4 – Two-year follow-up
Tumor status: recurrence, time to recurrence after primary treatment, local for recurrence

AFP: alpha-fetoprotein; ASA: American Society of Anesthesiologists; BSC: best supportive care; ICD-10: International Classification of Diseases – 10th Edition; SweLiv: Swedish quality register for cancers found in the liver, gallbladder, and bile ducts; TACE: Transarterial chemoembolization. [a] Treatment decision made at a multidisciplinary team conference.

Swedish National Board of Health and Welfare (Papers IV and V)

The National Patient Register (NPR) was first established in 1964 and has had national coverage since 1987.[264, 265] Diagnoses are registered using ICD-codes. NPR data does not include primary care visits but instead in- and outpatient (since 2001) visits to specialized care.[264] Surgical procedures are also reported to the NPR.

The Prescribed Drug Register was established in 2005 and contains since July 2005 nationwide data from prescribed medications distributed at any pharmacy in Sweden.[264] This register does not include data from prescription-free medications, or from drugs administrated to patients during in- or outpatient visits.

The Cause of Death Register was established in 1961 and is currently >99% complete. It contains ICD-based codes provided by physicians to classify the main and contributing causes of death.[264] Physicians must report a person's death within 48 hours and it is also compulsory for the reporting physician to provide a more detailed report, with the known or assumed cause of death, within three weeks.

Paper I

Study population

In 2014, Halland had a total of 310,665 inhabitants. In order to identify patients residing in Halland, who received a diagnosis of cirrhosis between January 1st, 2011, and December 31st, 2018, we searched the regional computerized healthcare system for ICD-10 codes associated with liver disease. The ICD-10 codes used were B18.0-9, C22.0-9, I85.0-9, I98.2-3, JJA20, K70.0-4, K71.7, K73.2-9, K74.3-6, K75.4, K76.0-6, K83, TJJ00, Z94.4. Furthermore, the regional pathology register was searched for Systemic Nomenclature of Medicine codes for liver (T-56), cirrhosis (M-495), and HCC (M-817).[179]

The search was carried out at all hospitals in Halland, together referred to as Halland Hospital, which are comprised of two midsize hospitals and a smaller one. The following data were retrieved from medical records: date of birth, date of diagnosis, sex, weight, length, diagnostic work-up, complications and comorbidity at cirrhosis diagnosis, use of warfarin, and laboratory values. Results from imaging examinations were also reviewed in order to verify the findings described in medical records.

Study I included patients aged ≥ 18 years. Patients who were not residents in Halland at cirrhosis diagnosis, or who already had a cirrhosis diagnosis prior to January 1st, 2011, or who were diagnosed with cirrhosis after December 31st, 2018; were excluded. Patients without cirrhosis (see next section) were also excluded.

Definitions

Histology data from liver biopsies were considered the gold standard for cirrhosis diagnosis. Patients lacking this kind of data were regarded as having cirrhosis based on clinical grounds (combination of clinical, laboratory, and imaging data). In order to increase the specificity of cirrhosis diagnosis, patients without diagnostic imaging or findings from a gastroscopy showing signs of cirrhosis were regarded as not having cirrhosis, independent of the presence of clinical, or laboratory data suggesting a diagnosis of cirrhosis. Seven different etiologies were defined: ArLD, HCV, NAFLD, cryptogenic cirrhosis, AIH, PBC, and "Other causes". HCV was given a higher priority than ArLD meaning that patients with both HCV and ArLD were only included in the HCV group. Arterial hypertension, T2D, chronic heart failure, ischemic heart disease, and obesity (body mass index $\geq$ 30 kg/m^2) were registered as comorbidities. Complications were defined as described in Table 10.

Table 10. Complications of cirrhosis - definitions

Ascites
Detected by clinical examination *AND/OR*
Detected and quantified by diagnostic imaging (ultrasound, CT, MRI)
Esophageal varices
Detected by gastroscopy, diagnostic imaging (CT), or autopsy
Variceal bleeding
Signs of bleeding such as hematemesis, or melena *OR*
Transfusion requirement of ≥ 2 units of blood according to the Baveno IV classification[90]
Portal vein thrombosis
Diagnosed by doppler ultrasound, CT, or MRI
Hepatic encephalopathy
If described by the treating physician, independent of grading
Spontaneous bacterial peritonitis
Positive bacterial culture of ascites *AND/OR*
Polymorphonuclear leukocyte count ≥ 0.25×10^9/L in ascites fluid *AND*
No other identified cause of peritonitis
Hepatocellular carcinoma
Diagnosed by histology, or by diagnostic imaging; within six months after cirrhosis diagnosis

CT: computed tomography; MRI: Magnetic resonance imaging.

The severity of cirrhosis at diagnosis was assessed by CP-class and MELD-score.[98, 100] Cirrhosis stages were defined as compensated, or decompensated, according to the Baveno IV stages of cirrhosis classification.[90]

Statistics

Variables describing patient characteristics were expressed as medians and percentiles, or as numbers and percentages, dependent on the type of data presented. Missing data were presented as percentages.

Population data from Halland for the study period (2011-2018) were retrieved from Statistics Sweden's open-source database (available at www.scb.se). Annual crude IRs were calculated per 100,000 person-years and stratified by year of diagnosis, sex, and five-year age group. Age-standardized incidence rates (ASIR) were calculated using the European standard population (ESP) from 1976, and the Revised ESP from 2013.[266] IR estimates were presented with corresponding 95% confidence intervals (CI).

Paper II

Study population

Study II included all previously identified adult patients diagnosed with cirrhosis in Halland between 2011 and 2018 (Paper I). Patients diagnosed with cirrhosis post-mortem (n = 16) were excluded. In addition to the previously retrieved data from medical records, we obtained sociodemographic data, comprising marital status, employment status, and occupational skill level.

Definitions

Etiologies, comorbidities, complications, cirrhosis severity, and stages at diagnosis were defined as described in Study I. Marital status at the time of cirrhosis diagnosis was defined as: married (or cohabiting), previously married (separated, divorced, or widowed), and never married.

Employment status was defined as employed (main income from employment, or own business), pensioner (main income from pension), disability retiree (main income from disability pension), or unemployed (only social security contributions or no income).

Individual-level SES was assessed by occupational skill level. Data regarding income or educational level were not available. Occupational skill level was defined according to the Swedish Standard Classification of Occupations 2012 (SSYK 2012), which is mainly based on the International Standard Classification of Occupations 2008 (Table 11).[267, 268] Occupations defined by prior Swedish classifications, such as SSYK 96, were converted to occupations registered in SSYK 2012, using a conversion key available at Statistics Sweden's website (available at www.scb.se). Patients were stratified into one of the four different occupational skill level groups defined by SSYK 2012. Patients with several occupations registered during work-life were included in the SSYK 2012 category representing the main source of income. If simultaneous occupations were registered, a patient was stratified based on self-reports, or by the main occupation registered by healthcare professionals.

Pensioners and retired people due disability were classified according to main occupations during their work life. Unemployed were classified as having occupational skill level I (lowest) when longstanding (10 to 15 years) unemployment was recorded, or if no prior occupation was self-reported, or registered by healthcare professionals.

Table 11. Associations between ISCO-08 and SSYK 2012

ISCO-08 Occupational skill level	SSYK 2012
I	Elementary occupations
II	Administration and customer service clerks
	Service, care and shop sales workers
	Agricultural, horticultural, forestry and fishery workers
	Building and manufacturing workers
	Mechanical manufacturing and transport workers, etc.
	Other ranks (privates, etc.)
III	Non-commissioned officers
	Operation managers in service industries
	Occupations requiring higher education qualifications
IV	Managers
	Commissioned officers
	Occupations requiring advanced level of higher education

ISCO-08: International Standard Classification of Occupations 2008; SSYK 2012: Swedish Standard Classification of Occupations 2012. Adapted and reprinted with permission from Springer Nature.

Outcomes

Each patient was followed-up until the date of liver transplantation, or death, or moving from Halland, whichever occurred first. The follow-up time ended on December 31st, 2019. Data regarding date of liver transplantation, or moving from Halland were retrieved from medical records. Date of death is automatically linked to the medical record system via the Swedish Civil Registration System. For deceased patients, the cause of death was retrieved from Death Certificates scanned in medical records or, if missing, from the Cause of Death Register.

Statistics

Variables describing patient characteristics were expressed as medians and percentiles, or as numbers and percentages, dependent on the type of data, continuous, or categorical, presented. Missing data were presented as percentages. When comparing proportions of patient characteristics (categorical) between different sociodemographic groups, Chi-square test, or Fisher's test, was used. For continuous variables, comparisons of median values between sociodemographic groups were done using the Kruskal-Wallis test.[269]

We primarily considered transplant-free survival; thus the follow-up time was censured for patients that had undergone a transplant. Similarly, patient follow-up time was censured if moving from Halland, or if alive at the end of follow-up (December 31st, 2019). Median and mean survival were determined using Kaplan-Meier estimated with Greenwood 95% CI.[270] The log-rank test was used when comparing survival curves.

Unadjusted and adjusted hazard ratios (HR and aHR) were determined using univariable and multivariable Cox regression models. For categorical variables with >2 categories, a reference category was chosen and HRs and aHRs for each other category, compared to the reference, were estimated. HRs and aHRs were presented with corresponding 95% CIs. The final multivariable Cox model (model I) included the following variables: sex (female, male), age (18-44, 45-49,…, 75-79, 80+), marital status (married, never married, previously married), employment status (employed, pensioner, disability retiree, unemployed), occupational skill level (IV, III, II, I), etiology (ArLD, cryptogenic, HCV, PBC, NAFLD, AIH, Other causes), MELD-score (<10, 10-14, ≥15), and CP-class (A, B, C). An alternative multivariable Cox model (model II) was constructed by replacing the tetrachotomous variable occupational skill level in Cox model I, with a dichotomous occupational skill level variable composed by the aggregate of groups III and IV (reference) vs the aggregate of groups I and II.

Paper III

Study population

All patients ≥18 years registered in SweLiv with a diagnosis of HCC (ICD-10 code C22.0) between January 1st, 2012, and December 31st, 2018, were included. The beginning of the study period took into consideration the launching of the Swedish national treatment program for HCC.[157, 195] Patient data were retrieved from the different modules in SweLiv.[157] Swedish personal identity numbers were used for data linkage between patients registered in SweLiv and data from national population registers maintained by Statistics Sweden (see next section).[261] Sociodemographic data for each patient, when available, were delivered by Statistics Sweden, which also delivered corresponding population size data for the incidence estimations described later.

Definitions

Country of birth was defined as Nordic for patients born in Sweden, Denmark, Norway, Finland, or Iceland; or as non-Nordic otherwise. However, patients born in a non-Nordic country were classified as Nordic if both parents had a Nordic origin. Individual-level SES was assessed by disposable income per household per consumption unit, referred to here as household income, registered at the Swedish Tax Office. Household income is a variable dependent on the composition of the examined household, with scales described in Table 12.

Table 12. Disposable income per household per consumption unit (Sweden)

Consumption unit	Scale
Single or living alone	1.00
Cohabiting people	1.51
Additional adult	0.60
First child 0-19 years	0.52
Second and subsequent children 0-19 years	0.42

Disposable income is the sum of all taxable and tax-free income minus taxes and negative transfers. Disposable income is divided by the weight of consumption of the household. The scale is determined by Statistics Sweden and is based, among other things, on budget calculations carried out by the Swedish Consumer Agency and the basis for assessing a basic consumption that can be calculated for different household types. Source: Statistics Sweden (available at https://www.scb.se/hitta-statistik/artiklar/2016/Att-jamfora-inkomster-for-hushall/)

A patient was regarded as having a low (first quartile [poorest]), medium (second or third quartiles), or high income (fourth quartile [wealthiest]); according to the distribution of household income for all household in Sweden.[245]

Contextual-level SES for each patient was assessed by residential neighborhood at the year of HCC diagnosis. In 2018, Statistics Sweden launched a novel geographic division called DeSO ("Demografiska StatistikOmråden" in Swedish), which can be used for monitoring the influence of neighborhood deprivation. A novel IMD for Sweden was created in 2021, by taking into account four single deprivation indicators (Table 13) with extracted DeSO-level data.[245] Using this IMD and the residential DeSO, each patient was assigned to a neighborhood deprivation quintile, from Q1 (least deprived) to Q5 (most deprived).[245]

Table 13. Swedish index of multiple deprivation by Strömberg *et al*.[245]

Single deprivation indicators	
Economic standard	Proportion of inhabitants with a low economic standard[a]
Educational level	Proportion of inhabitants aged 25-64 years with ≤ 12 years of schooling
Employment status	Proportion of inhabitants aged 16-64 years without paid employment
Type of housing	Proportion of inhabitants who live in a rented apartment/house

[a] Inhabitants belonging to a household with a disposable income per consumption unit in the lowest quartile of all households in Sweden.

Patients were classified as having either an early-stage or a late-stage HCC. Taking into account the Swedish treatment algorithm for HCC (Fig. 12), an early-stage HCC was defined as BCLC stage 0 or A, while all other patients were regarded as having a late-stage HCC (BCLC stage B, C, or D).[195] An important difference between the original BCLC staging system and the Swedish treatment algorithm is that the latter evaluates a patient's baseline performance status, hence taking into account symptoms related to comorbidity, while the original BCLC evaluates performance status based only on symptoms related to HCC.[151, 195]

Statistics

Variables describing patient characteristics were expressed as means and percentiles, or as numbers and percentages, dependent on the type of data, continuous, or categorical, presented. Missing data were presented as percentages. When comparing proportions of patient characteristics (categorical) between different groups, we used Chi-square test or Fisher's test. For continuous variables,

comparisons of mean values were done by using the t-test or, when comparing >2 groups, one-way ANOVA.

The underlying at-risk population was stratified by sex (male, female), calendar year (2012-2018), age group (15-19, 20-24, …, 85-89, 90+), country of birth (Nordic, non-Nordic), household income (low, medium, high), and neighborhood (DeSO). Multivariable Poisson regression models were employed for the estimation of HCC incidence variations for the total, early-stage, and late-stage; with regard to the IMD (Q1 to Q5) assigned to each neighborhood and the other explanatory variables listed above. The natural logarithm of the population size in each group was integrated into the models as an offset term.

IRs with 95% CIs, were estimated per 100,000 person-years by corresponding marginal means. Group comparisons were done by incidence rate ratios (IRR) with 95% CIs.

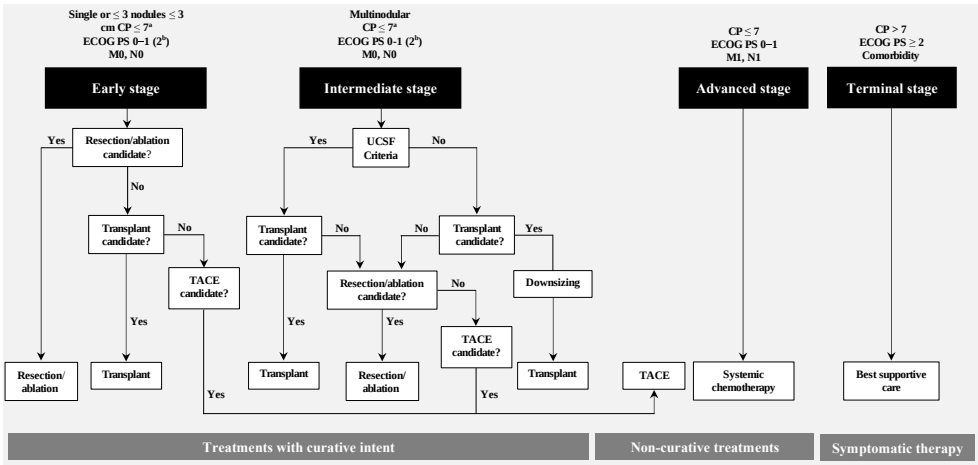

Fig. 12. The Swedish treatment algorithm for hepatocellular carcinoma (HCC). Adapted and translated after the Swedish national treatment program for patients with HCC.[195] CP: Child-Pugh; ECOG PS: Eastern Cooperative Oncology Group performace status; M: distant metastasis; N: regional lymph node metastasis; TACE: transarterial chemoembolization; UCSF: University of California San Francisco. [a] CP non-relevant for liver transplant candidates. [b] Selected patients with ECOG PS = 2 may become candidate for treatment with curative intent after individual evaluation at multidisciplinary conferences. Illustration reprinted with permission from Wiley.

Paper IV

Study population

Study IV was based on the patient population of patients with HCC identified in Study III (Paper III). Patients without cirrhosis (see next section) were excluded. Additional patient data were retrieved from the different modules in SweLiv. Swedish personal identity numbers were used for data linkage between patients registered in SweLiv and data from national population registers maintained by Statistics Sweden and from the NPR, the Prescribed Drug Register, and the Cause of Death Register.[261-265]

Definitions

Country of birth, household income, and HCC stage were defined as described for Study III. Diagnostic pathways and treatment recommendations were defined as shown in Table 14.

Table 14. Diagnostic pathways and treatment recommendations

Diagnostic pathways	
Surveillance	Patients with known liver disease and included in a surveillance program for HCC
Clinical	Diagnosed with HCC during a clinical work-up related to liver disease- or HCC-related symptoms
Incidental	HCC diagnosis in surgery or radiology in a patient without clinical symptoms related to HCC
Treatment recommendations	
Liver transplantation	Liver tranplanted patients, independent of prior treatment
Liver resection	If performed before ablation
Ablation	If performed before resection
TACE	If performed as palliative treatment, no prior surgical treatment
Systemic therapy	If given without prior surgical treatment or TACE
Best supportive care	No antitumoral treatment received

HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization

Patients were regarded as having cirrhosis if at least one ICD-10 cirrhosis-related code was registered in the NPR, or if registered as cirrhotic in SweLiv. We attempted to increase the sensitivity of our definition of cirrhosis by including patients with liver disease-related ICD-10 codes in the NPR, when a prescription for one of the following medications was found in the Prescribed Drug Register: non-selective betablockers, spironolactone, lactulose, or rifaximin.

Cirrhosis at the time of HCC was defined in patients fulfilling at least one of the following criteria: i) registered in SweLiv as having cirrhosis, or ii) one or more ICD-10 cirrhosis-related codes registered in the NPR up to 180 days after the date of HCC diagnosis. A patient was regarded as having unrecognized cirrhosis at the time of HCC diagnosis when at least one of the following criteria was fulfilled:

a) Cirrhosis according to SweLiv but no cirrhosis registered in the NPR (as described above) between 1997 and 30 days before the date of HCC diagnosis

b) No cirrhosis according to SweLiv but cirrhosis registered in the NPR (as described above) between 30 days before and 180 days after the date of HCC diagnosis

All patients classified as having cirrhosis at the time of HCC diagnosis but who did not fulfill criteria a) or b), were regarded as having recognized cirrhosis.

The etiologies of cirrhosis were retrieved from SweLiv or established through data from the NPR, the Prescribed Drug Register, or the Cause of Death Register. Cirrhosis decompensation was defined as ascites, HE, jaundice (bilirubin ≥52μmol/L), or hypoalbuminemia (<28g/L).

Comorbidities (arterial hypertension, T2D, coronary artery disease) were defined by ICD-10 codes, or by data from the Prescribed Drug Register. The number of visits registered in the NPR within a year prior to HCC diagnosis was calculated by subtracting the number of visits registered with an ICD-10 code HCC (or other suspicious tumor of the liver), from the total number of visits registered during the same period of time.

Outcomes

Each patient was followed-up until the date of death, or emigration, or the end of the study period (December 31st, 2020). Date of death was retrieved from SweLiv, or from the Cause of Death Register.

Statistics

Variables describing patient characteristics were expressed as medians and interquartile ranges, or as numbers and percentages, dependent on the type of data, continuous or categorical, presented. Missing data were presented as percentages. When comparing proportions of patient characteristics (categorical) between different groups, we used Chi-square test or Fisher's test. For continuous variables, comparisons of median values were done by using the Mann-Whitney U test. Results from two-tailed tests were considered significant when p-value $\leq 5\%$.

Logistic regression models were constructed to identify patient characteristics associated with the likelihood of unrecognized cirrhosis, and late-stage HCC at diagnosis. Clinically relevant variables were chosen when constructing the multivariable logistic regression models. The adjusted models included the following variables: sex (female, male), age (continuous variable), arterial hypertension, T2D, coronary artery disease, and decompensation.

Median and mean survival were determined using Kaplan-Meier estimated with Greenwood 95% CIs.[270] The log-rank test was used when comparing survival curves. HRs and aHRs were determined using univariable and multivariable Cox regression models. For categorical variables with >2 categories, a reference category was chosen and HRs and aHRs for each other category - compared to the reference - were estimated. HRs and aHRs were presented with corresponding 95% CIs. The final multivariable Cox model included the following variables: age (continuous variable), country of birth, household income, cirrhosis recognition status, etiology, number of visits registered in the NPR (continuous variable), arterial hypertension, T2D, coronary artery disease, and decompensation.

Paper V

Study population

Study V was based on the patient population of patients with HCC identified in Study III (Paper III). Additional patient data were retrieved from the different modules in SweLiv and from Statistics Sweden, the NPR and the Prescribed Drug Register.[261-265]

Definitions

Country of birth, household income, HCC stage, comorbidities, and treatment recommendations were defined as described for studies III and IV. Cirrhosis was defined upon specific criteria described for Study IV.

The etiologies of HCC were defined as viral hepatitis (both HBV and HBV), ArLD, NAFLD, "Other causes", and patients without diagnosed prior liver disease. Patients with concomitant ArLD and viral hepatitis were solely included in the latter group.

NAFLD was regarded as the main etiology in patients without other known liver diseases who fulfilled at least one of the following criteria: biopsy-proven NAFLD, prior diagnosis of NAFLD in the NPR, T2D, obesity, or NASH/NAFLD according to SweLiv. All patients were stratified into two major groups: NAFLD-HCC and non-NAFLD-HCC. Patients with NAFLD-HCC were further stratified into two groups: cirrhotic- and non-cirrhotic NAFLD-HCC.

Statistics

Variables describing patient characteristics were expressed as medians and interquartile ranges, or as numbers and percentages, dependent on the type of data presented - continuous or categorical. Missing data were presented as percentages. When comparing proportions of patient characteristics (categorical), we used Chi-square test or Fisher's test. For continuous variables, comparisons of median values were done by using the Mann-Whitney U test. Results from two-tailed tests were considered significant when the p-value was $\leq 5\%$.

Population data from Sweden for the study period (2012-2018) were retrieved from Statistics Sweden's open-source database. Annual crude IRs of HCC in the adult general population were calculated per 100,000 person-years and stratified by etiology, year of diagnosis, sex, and five-year age group. ASIRs were calculated using the Revised ESP from 2013.[266] IR estimates were presented with corresponding 95% CIs.

Results

It's not the numbers that are interesting.
It's what they tell us about the lives
behind the numbers.

— Hans Rosling

Paper I

Study population

We identified 598 patients diagnosed with cirrhosis in the region of Halland between 2011 and 2018 (Fig 13).

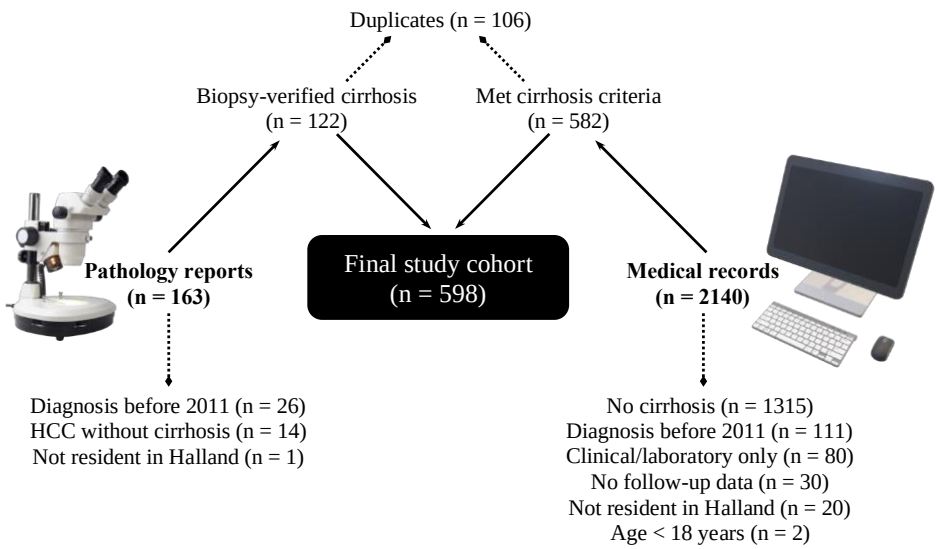

Fig.13. Identification of adult patients with cirrhosis in Halland (2011-2018). HCC: hepatocellular carcinoma.

The median age at diagnosis was 66 years and there was a male predominance (64%). ArLD was the most common etiology of cirrhosis (51%). Metabolic comorbidities were frequent and about half of the patients were diagnosed at decompensated cirrhosis stages (Table 15).

Table 15. Baseline characteristics at the time of cirrhosis diagnosis in Halland (2011-2018)

		Overall	Male	Female
Total, n (%)		598 (100)	380 (64)	218 (36)
Median age, years		66 (50-81)	66 (50-80)	67 (52-84)
Etiology, n (%)	ArLD	302 (51)	212 (56)	90 (41)
	Cryptogenic	87 (14)	59 (16)	28 (13)
	Hepatitis C	80 (13)	55 (14)	25 (12)
	NAFLD	34 (6)	19 (5)	15 (7)
	Primary biliary cholangitis	31 (5)	5 (1)	26 (12)
	Autoimmune hepatitis	30 (5)	6 (2)	24 (11)
	Other causes	34 (6)	24 (6)	10 (4)
Comorbidity, n (%)	Arterial hypertension	196 (33)	120 (32)	76 (35)
	Type 2 diabetes	171 (29)	124 (33)	47 (22)
	Obesity	143 (24)	94 (25)	49 (22)
	Coronary artery disease	114 (19)	90 (24)	24 (11)
	Chronic heart failure	86 (14)	63 (17)	23 (11)
CP-class, n (%)	A	217 (36)	126 (33)	91 (42)
	B	228 (38)	145 (38)	83 (40)
	C	122 (20)	86 (23)	36 (17)
MELD-score	Median	11	13	10
	<10	216 (36)	117 (31)	99 (45)
	10-14	142 (24)	95 (25)	47 (22)
	≥15	210 (35)	145 (38)	65 (30)
Baveno IV stage, n (%)	1-2	305 (51)	181 (48)	124 (57)
	3-4	292 (49)	199 (52)	94 (43)
Complications, n (%)	Ascites	280 (47)	193 (51)	87 (40)
	Esophageal varices	215 (36)	145 (38)	70 (32)
	Variceal bleeding	32 (5)	18 (5)	14 (6)
	Hepatic encephalopathy	43 (7)	31 (8)	12 (6)
	SBP	8 (1)	5 (1)	3 (1)
	Hepatocellular carcinoma	75 (13)	59 (16)	16 (7)

ArLD: Alcohol-related liver disease; CP: Child-Pugh; MELD: Model for End-stage Liver Disease; NAFLD: Non-alcoholic fatty liver disease; SBP: Spontaneous bacterial peritonitis. Median age presented with 10 and 90 percentiles in parentheses.

Incidence

The overall annual crude IR of cirrhosis in adults, between 2011-2018 was 30 per 100,000 person-years (95% CI 28-33). The overall ASIR during the same period was 17 per 100,000 person-years (95% CI 16-19) according to the ESP from 1976, and 23 per 100,000 person-years (95% CI 19-25) according to the Revised ESP from 2013. Generally, men had >1.7-fold higher IRs of cirrhosis compared to women (Table 16).

Table 16. Incidence rates of cirrhosis per 100,000 person-years

	Overall	Male	Female
Annual crude IR (95% CI)	24 (22-26)	30 (27-34)	17 (15-20)
Annual crude IR among adults (95% CI)	30 (28-33)	39 (35-42)	22 (19-25)
ASIR, ESP (1976)	17 (16-19)	23 (20-25)	12 (10-14)
ASIR, Revised ESP (2013)	23 (21-25)	31 (28-34)	16 (14-19)

ASIR: age-standardized incidence rate; CI: confidence interval; ESP: European Standard Population; IR: incidence rate. Adults: age ≥18 years

The highest IRs of cirrhosis were estimated for people in the age span 60 to 69 years, independent of sex (Fig. 14).

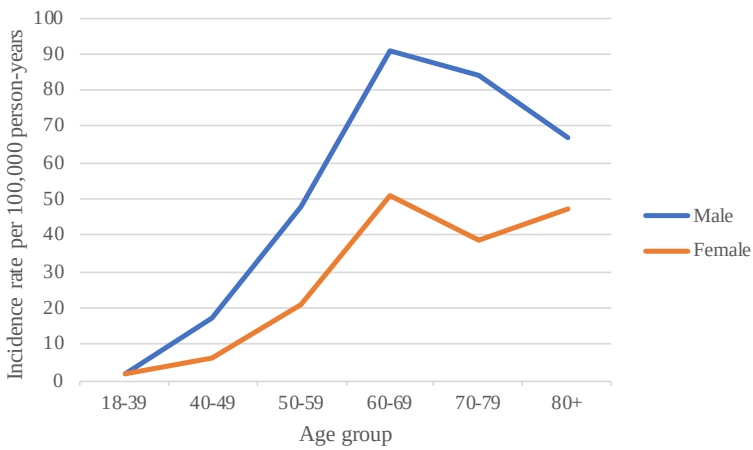

Fig. 14. Incidence rates of cirrhosis per 100,000 person-years, stratified by sex and age group.

Paper II

Study population

A total of 582 patients diagnosed with cirrhosis in Halland between 2011-2018 were included (Table 17).

Table 17. Baseline characteristics of 582 patients with cirrhosis, Halland (2011-2018)

	Occupational skill level					
	I	II	III	IV	I & II	III & IV
Total, n (%)	115 (20)	348 (60)	64 (11)	55 (9)	463 (80)	119 (20)
Male sex, n (%)	63 (55)	230 (66)	31 (48)	44 (80)	295 (64)	75 (63)
Median age, years	63	67	67	66	66	66
(10-90 percentile)	(46-84)	(53-80)	(52-82)	(49-77)	(50-82)	(51-80)
Marital status						
Married	46 (40)	208 (60)	43 (67)	42 (76)	254 (55)	85 (71)
Never married	38 (33)	86 (25)	9 (14)	8 (15)	124 (27)	17 (14)
Previously married	31 (27)	54 (15)	12 (19)	5 (9)	85 (18)	17 (14)
Employment status						
Employed	2 (2)	116 (33)	26 (41)	27 (49)	118 (25)	53 (45)
Pensioner	38 (33)	175 (50)	34 (53)	26 (47)	213 (46)	60 (50)
Disability retiree	30 (26)	57 (16)	4 (6)	2 (4)	87 (19)	6 (5)
Unemployed	45 (39)	0 (0)	0 (0)	0 (0)	45 (10)	0 (0)
Etiology, n (%)						
ArLD	44 (38)	187 (54)	36 (56)	28 (51)	231 (50)	64 (54)
Cryptogenic	14 (12)	53 (15)	11 (17)	5 (9)	67 (14)	16 (14)
Hepatitis C	34 (30)	36 (10)	3 (5)	7 (13)	70 (15)	10 (8)
NAFLD	5 (4)	19 (6)	3 (5)	2 (4)	24 (5)	5 (4)
Primary biliary cholangitis	3 (3)	24 (7)	1 (1)	3 (5)	27 (6)	4 (3)
Autoimmune hepatitis	5 (4)	14 (4)	7 (11)	4 (7)	19 (4)	11 (9)
Other causes	10 (9)	15 (4)	3 (5)	6 (11)	25 (4)	9 (8)
Comorbidity, n (%)						
Arterial hypertension	18 (16)	126 (36)	24 (38)	20 (36)	144 (31)	44 (37)
Type 2 diabetes	27 (24)	106 (31)	19 (30)	15 (27)	133 (29)	34 (29)
Coronary artery disease	15 (13)	75 (22)	11 (17)	4 (7)	90 (19)	15 (13)
Complications, n (%)						
Ascites	65 (57)	159 (46)	32 (50)	19 (35)	224 (48)	51 (43)
Variceal bleeding	9 (8)	19 (6)	4 (6)	0 (0)	28 (6)	4 (3)
Encephalopathy	14 (12)	27 (8)	1 (1)	1 (2)	41 (9)	2 (2)
Hepatocellular carcinoma	19 (17)	46 (13)	7 (11)	2 (4)	65 (14)	9 (8)

ArLD: Alcohol-related liver disease; NAFLD: Non-alcoholic fatty liver disease.

Most patients were married (58%). When considering employment status, pensioners were the predominant group (47%). Only 20% of patients belonged to the highest occupational skill levels (III or IV).

The severity of cirrhosis at diagnosis decreased with increasing occupational skill level (Fig. 15).

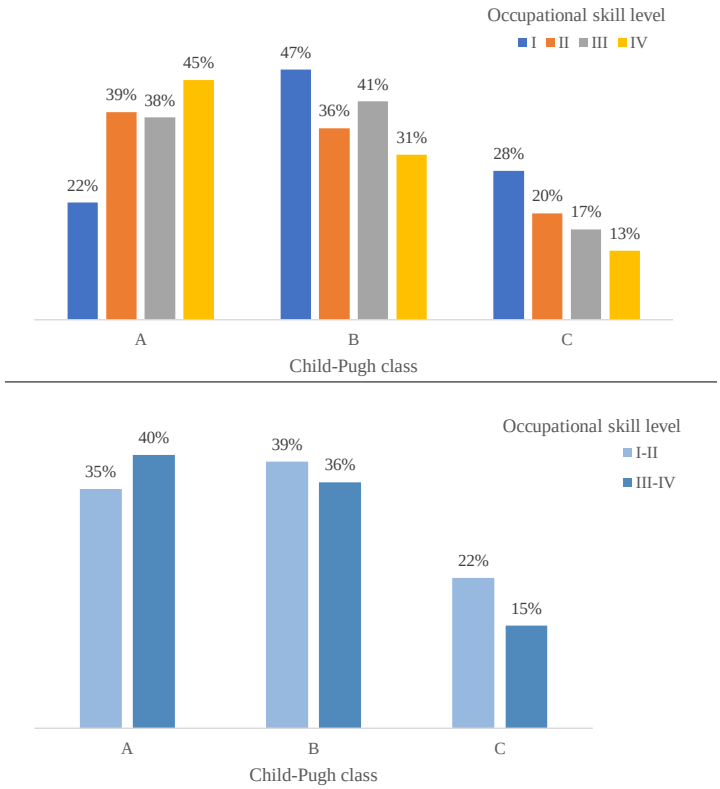

Fig. 15. Child-Pugh class at the time of cirrhosis diagnosis, stratified by occupational skill level

Transplant-free survival analysis

A total of 18 patients underwent a liver transplant during the follow-up time. The accumulated follow-up time for the entire cohort was 1,684 person-years, and a total of 319 patients (55%) died, including one of the patients who had previously undergone a transplant. The overall mean survival was 4.18 years (95% CI 3.86-4.50). Women had better mean survival compared to men. Previously married

patients had worse mean survival compared to married ones. Employed patients had the highest mean survival across employment status subgroups. Increasing occupational skill level was associated with better survival and patients in group IV (highest skill level) had the best mean survival (Table 18). Similarly, patients in the aggregated occupational skill level groups III-V had better survival compared to patients in the aggregated occupational skill level groups I-II (Fig. 16 and 17).

Table 18. Mean survival and survival probabilities of 582 patients diagnosed with cirrhosis

	Mean survival in years (95% CI)	1-year survival probability (95% CI)	5-year survival probability (95% CI)
Overall	4.18 (3.86-4.50)	0.67 (0.62-0.70)	0.42 (0.37-0.46)
Sex			
Female	4.82 (4.29-5.35)	0.73 (0.67-0.79)	0.50 (0.42-0.57)
Male	3.81 (3.42-4.20)	0.63 (0.58-0.67)	0.37 (0.32-0.43)
Marital status			
Married	4.56 (4.14-4.98)	0.71 (0.66-0.76)	0.46 (0.40-0.52)
Never married	3.97 (3.31-4.63)	0.60 (0.52-0.68)	0.41 (0.31-0.49)
Previously married	3.35 (2.69-4.01)	0.60 (0.50-0.69)	0.31 (0.22-0.41)
Employment status			
Employed	5.74 (5.17-6.32)	0.81 (0.74-0.86)	0.59 (0.51-0.67)
Pensioner	3.28 (2.85-3.70)	0.57 (0.53-0.64)	0.32 (0.26-0.39)
Disability retiree	3.63 (2.91-4.35)	0.62 (0.52-0.71)	0.37 (0.26-0.48)
Unemployed	4.30 (3.15-5.45)	0.71 (0.55-0.82)	0.40 (0.23-0.56)
Occupational skill level			
IV (highest)	6.39 (5.54-7.23)	0.91 (0.80-0.96)	0.67 (0.52-0.79)
III	4.78 (3.93-5.67)	0.83 (0.71-0.90)	0.48 (0.33-0.62)
II	4.04 (3.64-4.45)	0.66 (0.61-0.70)	0.40 (0.34-0.46)
I (lowest)	3.00 (2.33-3.67)	0.49 (0.39-0.57)	0.30 (0.22-0.40)
III-IV (aggregated)	5.64 (5.00-6.28)	0.87 (0.79-0.92)	0.58 (0.47-0.67)
I-II (aggregated)	3.79 (3.44-4.14)	0.62 (0.57-0.66)	0.38 (0.33-0.42)

CI: confidence interval.

In univariable analyses, previously married patients had increased HR compared to married ones. Similarly, pensioners, disability retirees, and unemployed patients had increased HRs compared to employed patients. However, these associations were not statistically significant in multivariable models. On the other hand, occupational skill level was strongly associated with increased HRs and aHRs. In the multivariable model, the aHR for occupational skill level I was 3.43 (95% CI, 1.89-6.23), compared to occupational skill level IV (Table 19). The aHR for occupational skill level I-II, compared to level III-IV, was 1.85 (95% CI 1.32-2.61).

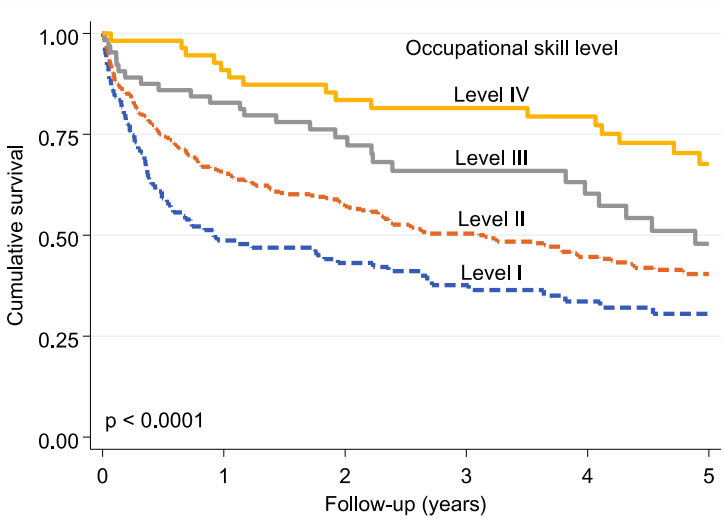

Fig. 16. Kaplan-Meier survival curves in a cohort of 582 patients diagnosed with cirrhosis in Halland (2011-2018). Compared by occupational skill level (lowest [I] through highest [IV]). The follow-up time was limited to five years.

Table 19. Univariable and multivariable estimates for mortality in cirrhosis, Halland (2011-2018)

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**aHR (95% CI)**	**p-value**
Cox regression model 1				
Occupational skill level				
IV (highest)	1.0 (ref)		1.0 (ref)	
III	1.72 (0.98-3.03)	0.060	1.87 (1.00-3.46)	0.062
II	2.42 (1.53-3.84)	<0.001	2.48 (1.48-4.12)	<0.001
I (lowest)	3.50 (2,14-5.73)	<0.001	3.43 (1.89-6.23)	<0.001
Cox regression model 2				
Occupational skill level				
III-IV (aggregated)	1.0 (ref)		1.0 (ref)	
I-II (aggregated)	1.98 (1.47-2.68)	<0.001	1.85 (1.32-2.61)	<0.001

Cox regression models were used to calculate hazard ratios (HR) and adjusted HRs (aHR). Each patient was followed-up from the date of cirrhosis diagnosis until date of liver transplantation, death, moving from Halland, or until 31st December 2019, whichever occurred first. The multivariable models were adjusted for sex, age, marital status, employment status, etiology, Model for End-stage Liver Disease, and Child-Pugh class. CI: confidence interval.

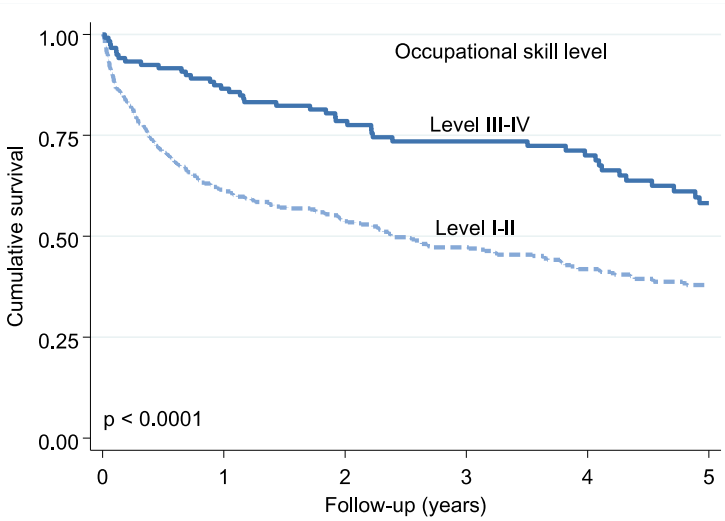

Fig. 17. Kaplan-Meier survival curves in a cohort of 582 patients diagnosed with cirrhosis in Halland (2011-2018). Compared by occupational skill level (level III-IV vs I-II). The follow-up time was limited to five years.

Paper III

Study population

We included 3,473 adult patients diagnosed with HCC in Sweden between 2011 and 2018. The mean age at diagnosis was 69 years and there was a male predominance (76%). A low household income was registered in 46% of cases, which also was the individual-level SES group with the highest proportion of patients born in a non-Nordic country and living in the most deprived neighborhoods (Table 20). A total of 2,372 patients (68%) were diagnosed with a late-stage HCC.

Incidence

Age and calendar year adjusted IRR estimates from the final multivariable model, which included the variables sex, country of birth, household income, and neighborhood deprivation, are presented in Table 21. Men had a pronouncedly elevated incidence of HCC compared to women. Low household income was associated with 5.5 times higher IR of late-stage HCC, compared to high household income.

Table 20. Baseline characteristics of adult patients diagnosed with HCC in Sweden (2012-2018)

	Household income			
	Low	**Medium**	**High**	**Total**
Total, n (%)	1598 (46)	1439 (41)	436 (13)	3473 (100)
Sex (male)	1157 (72)	1124 (78)	355 (81)	2636 (76)
Mean age (years) ± SD	68 ± 11	69 ± 10	66 ± 9	69 ± 10
Country of birth, n (%)				
Nordic	1292 (81)	1277 (89)	408 (94)	2977 (86)
Non-Nordic	306 (19)	162 (11)	28 (6)	496 (14)
Neighborhood deprivation, n (%)				
Q1 (least deprived)	104 (6)	207 (14)	121 (28)	432 (12)
Q2	202 (13)	286 (20)	110 (25)	598 (17)
Q3	283 (18)	300 (21)	80 (18)	663 (19)
Q4	395 (25)	326 (23)	69 (16)	790 (23)
Q5 (most deprived)	614 (38)	320 (22)	56 (13)	990 (19)
BCLC-stage, n (%)				
0-A	390 (24)	454 (32)	163 (37)	1007 (29)
B-D	1168 (73)	940 (65)	264 (61)	2372 (68)
Missing	40 (3)	45 (3)	9 (2)	94 (3)

Neighborhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5).[245] Nordic country of birth: Sweden, Denmark, Finland, Iceland and Norway. Household income defined as disposable income per household per consumption unit. BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma; SD: standard deviation.

Among people with a low household income, increasing neighborhood deprivation was associated with higher IRs of all-stage HCC. For instance, people with a low household income living in the most deprived neighborhoods (IR 3.90, 95% CI 3.28-4.64), had a seven times higher IR, as compared to people with a high household income living in the least deprived neighborhoods (IR 0.58, 95% CI 0.46.0.74) (Fig. 18).

Neighborhood deprivation was also associated with increased IRs, independent of other covariates; and living in the most deprived neighborhoods was associated with 1.5 times higher IR of all-stage HCC, compared to those living in the wealthiest neighborhoods (Table 21).

Table 21. Age- and calendar year incidence rate ratios of HCC in Sweden (2012-2018)

	Incidence rate ratio (95% CI)		
	All-stage	**Early-stage**	**Late-stage**
Sex			
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	3.85 (3.56-4.17)	3.14 (2.73-3.62)	4.26 (3.87-4.70)
Country of birth			
Nordic	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Nordic	1.01 (0.92-1.12)	1.36 (1.15-1.62)	0.90 (0.79-1.02)
Household income			
High	1.0 (ref)	1.0 (ref)	1.0 (ref)
Medium	2.06 (1.85-2.30)	1.86 (1.55-2.24)	2.16 (1.88-2.49)
Low	4.71 (4.20-5.28)	3.30 (2.71-4.03)	5.51 (4.78-6.36)
Neighborhood deprivation			
Q1 (least deprived)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2	1.07 (0.94-1.21)	1.15 (0.93-1.44)	1.02 (0.87-1.18)
Q3	1.06 (0.94-1.20)	0.98 (0.78-1.23)	1.10 (0.95-1.27)
Q4	1.19 (1.06-1.35)	1.06 (0.85-1.32)	1.22 (1.05-1.40)
Q5 (most deprived)	1.48 (1.31-1.66)	1.48 (1.20-1.84)	1.44 (1.25-1.67)

Neighborhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5).[245] Nordic country of birth: Sweden, Denmark, Finland, Iceland and Norway. Household income was defined as disposable income per household per consumption unit. CI: confidence interval; HCC: hepatocellular carcinoma.

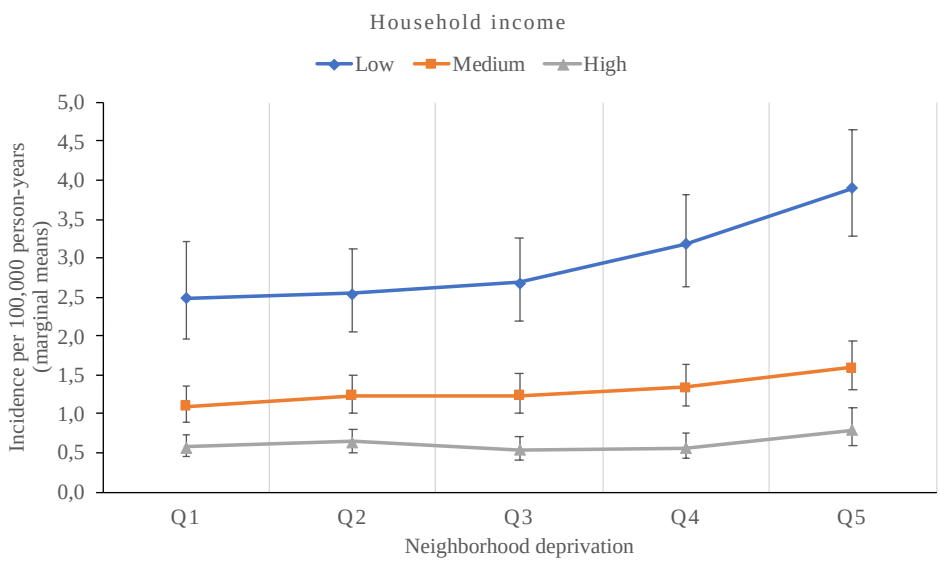

Fig. 18. Age- and calendar year incidence of all-stage hepatocellular carcinoma in Sweden (2012-2018) by neighborhood deprivation and household income.

The IRs of all-stage HCC increased with age and peaked in men aged 70 to 74 years, and women aged 75 to 79 years (Fig. 19). Among people with low household income, aged 60 to 79 years, the IR of HCC reached 30 per 100,000 person-years. In the same age group, living in the most deprived neighborhoods was associated with an IR of 20 per 100,000 person-years, regardless of household income.

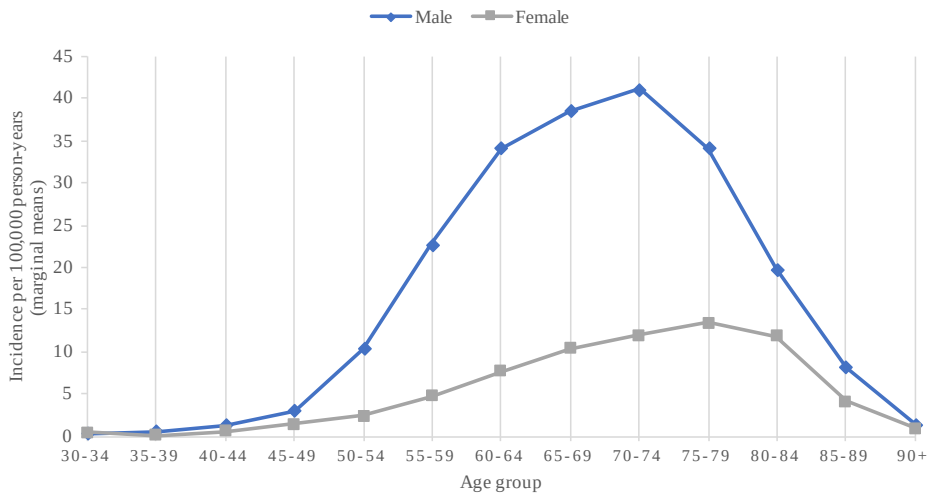

Fig. 19. Incidence of hepatocellular carcinoma in Sweden (2012-2018) by age group and sex.

Paper IV

Study population

We included 3,473 patients diagnosed with HCC in Sweden between 2012 and 2018. Of these, a total of 2,670 patients (77%) were considered to have cirrhosis at the time of HCC diagnosis. Among patients with cirrhosis, 39% were judged to have previously unrecognized cirrhosis at the time of HCC diagnosis. Among those with previously recognized cirrhosis, 55% were diagnosed with HCC while under surveillance. Baseline characteristics of the cohort are presented in Table 22.

NAFLD was the main underlying etiology in patients with unrecognized cirrhosis. Patients with unrecognized cirrhosis were older, had larger tumors (median size 55 vs 29 mm; $p < 0.001$), more multinodular cancers (18 vs 10%; $p < 0.001$), and extrahepatic metastasis (22 vs 4%; $p < 0.001$); compared to patients diagnosed while under surveillance.

Unrecognized cirrhosis was also associated with a higher proportion of late-stage HCC at diagnosis (79 vs 46%; $p < 0.001$), and less receipt of treatment with curative intention (23 vs 64%; $p < 0.001$); compared to surveilled patients.

Table 22. Baseline characteristics of patients with cirrhosis diagnosed with HCC in Sweden (2012-2018)

	Surveillance	No surveillance	Cirrhosis Unrecognized	Total
Total, n (%)	901 (34)	736 (27)	1033 (39)	2670 (100)
Sex (male)	684 (76)	543 (74)	855 (83)	2082 (78)
Median age, years	65 (59-71)	68 (61-74)	69 (62-76)	67 (61-74)
Country of birth, n (%)				
Nordic	740 (82)	636 (86)	867 (84)	2243 (84)
Non-Nordic	161 (18)	100 (14)	166 (16)	427 (16)
Household income, n (%)				
High	140 (16)	99 (14)	122 (12)	361 (14)
Medium	379 (42)	268 (36)	406 (39)	1053 (39)
Low	382 (42)	369 (50)	505 (49)	1256 (47)
Etiology, n (%)				
Viral hepatitis	233 (26)	117 (16)	200 (20)	550 (21)
Viral hepatitis + ArLD	258 (29)	167 (22)	161 (15)	586 (22)
ArLD	176 (19)	196 (27)	223 (22)	595 (22)
NAFLD	87 (10)	108 (15)	225 (22)	420 (16)
Other	105 (12)	111 (15)	63 (6)	279 (10)
Cryptogenic	42 (4)	37 (5)	161 (15)	240 (9)
Decompensation[a], n (%)	225 (25)	417 (57)	374 (36)	1016 (38)
Comorbidity, n (%)				
Arterial hypertension	484 (54)	421 (57)	585 (57)	1490 (56)
Type 2 diabetes	338 (38)	331 (45)	421 (41)	1090 (41)
Coronary artery disease	93 (10)	130 (18)	184 (18)	407 (15)
Number of visits in NPR[b]	3 (2-7)	4 (2-7)	2 (1-4)	3 (1-6)
BCLC-stage, n (%)				
0-A	456 (51)	144 (20)	195 (20)	795 (30)
B-D	414 (46)	583 (79)	821 (79)	1818 (68)
Missing	31 (3)	9 (1)	17 (2)	57 (2)

Nordic country of birth: Sweden, Denmark, Finland, Iceland, and Norway. Household income is defined as disposable income per household per consumption unit. ArLD: alcohol-related liver disease; BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty-liver disease; NPR: National Patient Register. Median age presented with corresponding interquartile range in parentheses. [a] Decompensated cirrhosis is defined as ascites or hepatic encephalopaty or ≥ 52 µmol/L or albumin < 28 g/L. [b] Registered within 365 days before HCC diagnosis

Logistic regression

In multivariable regression models, patients with unrecognized cirrhosis were more likely male (adjusted odds ratio [aOR] 1.80, 95% CI 1.45-2.25), and had more likely a low household income (aOR 1.39, 95% CI 1.06-1.83), NAFLD (aOR 1.94, 95% CI 1.45-2.60), or cryptogenic cirrhosis (aOR 2.77, 95% CI 1.95-3.93). Country of birth, decompensation, and comorbidity (arterial hypertension, T2D, coronary artery disease), were not associated with an increased likelihood of cirrhosis unrecognition in the multivariable model.

Multivariable regression models were also performed to ascertain the effect of different variables on the likelihood of a late-stage HCC at diagnosis. Compared to surveilled patients, patients with unrecognized cirrhosis had a noticeably increased likelihood of late-stage HCC, aOR 3.96 (95% CI 3.18-4.94). Other variables associated with higher likelihood were male sex, age, and household income (Table 23).

Table 23. Different factors and their association with the likelihood of late-stage HCC diagnosis in Sweden (2012-2018)

	Univariable		Multivariable	
	OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex				
Female	1.0 (ref)		1.0 (ref)	
Male	1.25 (1.03-1.52)	0.026	1.36 (1.09-1.71)	0.008
Age (years)	1.04 (1.03-1.05)	<0.001	1.03 (1.02-1.04)	<0.001
Country of birth				
Nordic	1.0 (ref)		1.0 (ref)	
Non-Nordic	0.63 (0.50-0.78)	<0.001	0.66 (0.51-0.85)	0.002
Household income				
High	1.0 (ref)		1.0 (ref)	
Medium	1.38 (1.07-1.77)	0.012	1.40 (1.07-1.84)	0.015
Low	1.85 (1.44-2.37)	<0.001	1.89 (1.43-2.52)	<0.001
Cirrhosis				
Recognized (surveillance)	1.0 (ref)		1.0 (ref)	
Recognized (non-surveillance)	4.46 (3.56-5.59)	<0.001	4.19 (3.32-5.29)	<0.001
Unrecognized	4.64 (3.78-5.69)	<0.001	3.96 (3.18-4.94)	<0.001
Comorbidity				
Arterial hypertension	0.81 (0.68-0.96)	0.013	0.61 (0.50-0.75)	<0.001
Type 2 diabetes	1.07 (0.91-1.27)	0.420	1.17 (0.94-1.47)	0.157
Coronary artery disease	1.72 (1.33-2.22)	<0.001	1.32 (0.99-1.74)	0.058

The multivariable model included all shown variables plus etiologies, and number of visits registered in the National Patient Register within 365 days before hepatocellular carcinoma (HCC) diagnosis. HCC stage was classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system as early-stage (BCLC 0-A) and late-stage (BCLC B-D). CI: confidence interval; OR: odds ratio.

Compared to viral hepatitis, only cryptogenic cirrhosis was associated with a statistically significant increased likelihood of late-stage HCC (aOR 1.97, 95% CI 1.26-3.01). Other etiologies were not associated with increased or decreased likelihood of a late-stage HCC at diagnosis, in the multivariable model.

Survival analysis

The accumulated follow-up time for the entire cohort was 5,847 person-years, and a total of 1,974 patients (74%) died, with the follow-up being censored for 696 patients. The median survival time was 1.48 years (95% CI 1.36-1.60). The median survival among surveilled patients was 3.79 years (95% CI 3.19-4.39), which was considerably higher compared to the median survival of patients with unrecognized cirrhosis (0.89 years, 95% CI 0.78-1.01) (Fig. 20).

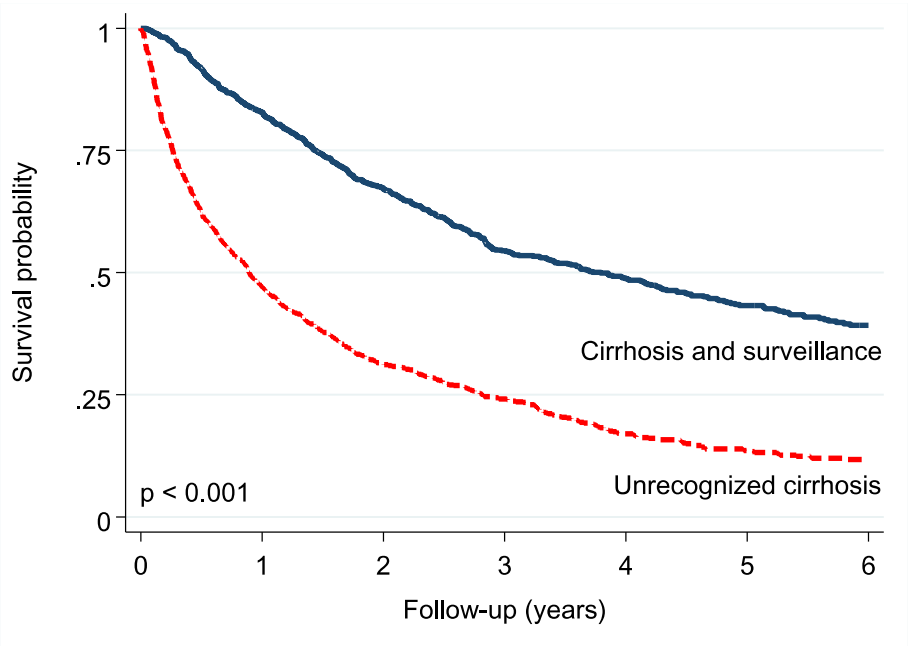

Fig. 20. Kaplan-Meier curves in a cohort of patients with cirrhosis diagnosed with hepatocellular carcinoma (HCC) in Sweden (2012-2018). Survival probabilities were compared between patients with previously recognized cirrhosis and diagnosed with HCC while under surveillance, and patients with unrecognized cirrhosis prior to HCC diagnosis. Time after HCC diagnosis was limited to six years.

Results from univariable and multivariable Cox regression models are presented in Table 24. Compared to patients diagnosed while under surveillance, patients with unrecognized cirrhosis had HR 2.59 (95% CI 2.32-2.90), and aHR 2.36 (95% CI 2.09-2.66).

Table 24. Univariable and multivariable estimates of mortality in 2,670 patients with cirrhosis diagnosed with HCC in Sweden, 2012-2018

	Univariable		Multivariable	
	HR (95% CI)	p-value	aHR (95% CI)	p-value
Sex				
Female	1.0 (ref)			
Male	1.00 (0.90-1.12)	0.972		
Age (years)	1.03 (1.02-1.03)	<0.001	1.01 (1.00-1.02)	<0.001
Country of birth				
Nordic	1.0 (ref)		1.0 (ref)	
Non-Nordic	0.77 (0.68-0.87)	<0.001	0.79 (0.63-0.84)	<0.001
Household income				
High	1.0 (ref)		1.0 (ref)	
Medium	1.29 (1.11-1.50)	<0.001	1.13 (0.97-1.32)	0.115
Low	1.54 (1.34-1.78)	<0.001	1.35 (1.16-1.58)	<0.001
Cirrhosis				
Recognized (surveillance)	1.0 (ref)		1.0 (ref)	
Recognized (non-surveillance)	2.64 (2.34-2.98)	<0.001	2.18 (1.92-2.48)	<0.001
Unrecognized	2.59 (2.32-2.90)	<0.001	2.36 (2.09-2.66)	<0.001
Etiology				
Viral hepatitis	1.0 (ref)		1.0 (ref)	
Viral hepatitis + ArLD	1.06 (0.93-1.23)	0.395	0.91 (0.78-1.07)	0.254
ArLD	1.32 (1.15-1.52)	<0.001	0.97 (0.83-1.13)	0.687
NAFLD	1.60 (1.38-1.86)	<0.001	1.09 (0.90-1.31)	0.389
Other	1.25 (1.05-1.48)	0.011	0.99 (0.82-1.20)	0.954
Cryptogenic	2.06 (1.74-2.44)	<0.001	1.25 (1.02-1.53)	0.030
Decompensation	2.38 (2.17-2.61)	<0.001	2.33 (2.11-2.57)	<0.001
Comorbidity				
Arterial hypertension	0.88 (0.80-0.96)	0.005	0.75 (0.68-0.83)	<0.001
Type 2 diabetes	1.05 (0.96-1.14)	0.325	1.02 (0.91-1.15)	0.756
Coronary artery disease	1.35 (1.20-1.51)	<0.001	1.13 (0.99-1.29)	0.069

Cox regression models were used to calculate hazard ratios (HR) and adjusted HRs (aHR). Each patient was followed-up from the date of hepatocellular carcinoma (HCC) diagnosis until date of death, emigration from Sweden, or until 31st December 2020, whichever occurred first. The multivariable models were adjusted for all variables shown. ArLD: alcohol-related liver disease; CI: confidence interval; NAFLD: non-alcoholic fatty liver disease.

Paper V

Study population

We included all adult patients with a diagnosis of HCC registered in SweLiv between 2012 and 2018 (n = 3,473). Vital hepatitis, alone and combined with ArLD, was the most common etiology associated with HCC (33%), followed by NAFLD (21%), and ArLD alone (18%) (Fig. 21). The proportion of patients with NAFLD-HCC increased during the study period, and NAFLD was since 2014 the second-leading cause of HCC. With a 33% increment between 2012 and 2018, NAFLD was also the fastest-growing cause of HCC. At the same time, the proportion of patients with underlying viral hepatitis, or other "causes" decreased by 13% and 35%, respectively.

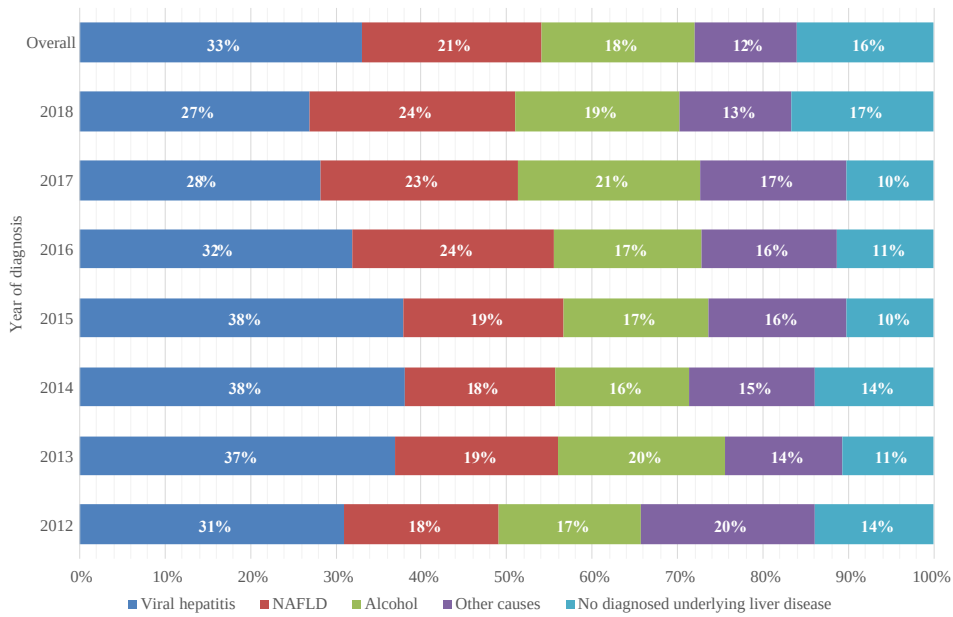

Fig. 21. Liver diseases associated with hepatocellular carcinoma in 3,473 adult patients diagnosed in Sweden (2012-2018). Viral hepatitis comprised both hepatitis B and C. NAFLD: non-alcoholic fatty liver disease. $p_{trend} = 0.012$

The proportion of patients with underlying viral hepatitis was highest in men, individuals born in a non-Nordic country, and individuals with a low household income. ArLD was also more common in men, but contrary to viral hepatitis,

individuals born in a Nordic country, and those with a high household income had the highest proportions of ArLD (Fig. 22-24).

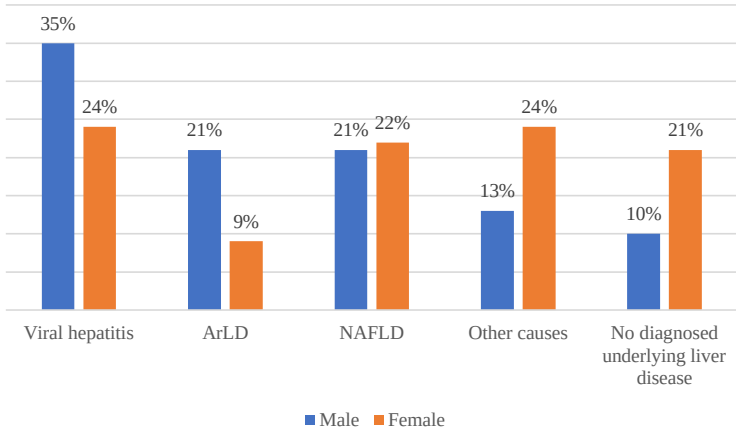

Fig. 22. Underlying etiologies in 3473 patients diagnosed with hepatocellular carcinoma in Sweden (2012-2018), stratified by sex. ArLD: alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease.

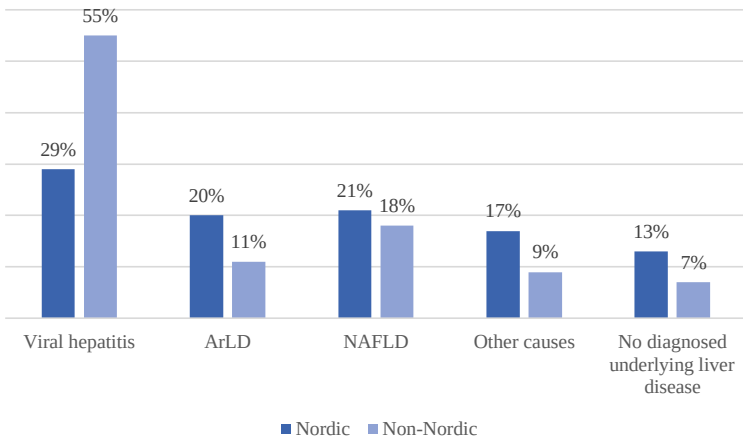

Fig. 23. Underlying etiologies in 3473 patients diagnosed with hepatocellular carcinoma in Sweden (2012-2018), stratified by country of birth. Nordic: Sweden, Denmark, Norway, Finland, and Iceland. ArLD: alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease.

Compared to patients with non-NAFLD-HCC, those with NAFLD-HCC were older (median 75 vs 67 years; $p < 0.001$), had less cirrhosis (58 vs 82%; $p < 0.001$), and they had metabolic disease in higher proportions (Table 25).

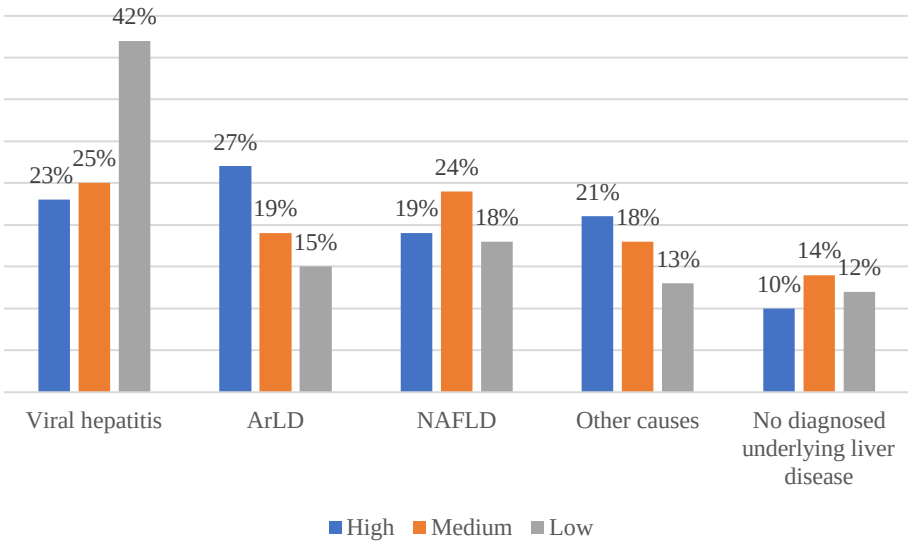

Fig. 24. Underlying etiologies in 3473 patients diagnosed with hepatocellular carcinoma in Sweden (2012-2018), stratified by household income. ArLD: alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease.

Table 25. Baseline characteristics of 3,473 patients diagnosed with HCC in Sweden, 2012-2018

	NAFLD-HCC	Non-NAFLD-HCC
Total, n (%)	724 (21)	2749 (79)
Male sex, n (%)	542 (75)	2094 (76)
Median age, years (IQR)	75 (70-80)	67 (60-74)
Country of birth, n (%)		
Nordic	633 (87)	2344 (85)
Non-Nordic	91 (13)	405 (15)
Household income, n (%)		
High	84 (12)	352 (13)
Medium	348 (48)	1091 (40)
Low	292 (40)	1306 (47)
Cirrhosis, n (%)	420 (58)	2250 (82)
Comorbidity, n (%)		
Arterial hypertension	594 (82)	1426 (52)
Type 2 diabetes	696 (96)	719 (26)
Coronary artery disease	242 (33)	377 (14)

HCC: hepatocellular carcinoma; IQR: interquartile range; NAFLD: non-alcoholic fatty liver disease.

NAFLD-HCC was also associated with larger tumors (median 55 vs 43 mm; $p < 0.001$), and more extrahepatic metastasis (22 vs 16%; $p < 0.001$). However, the proportion of patients diagnosed at an early stage did not significantly differ between patients with and without NAFLD-HCC (BCLC 0-A, 27 vs 30%; $p = 0.129$).

Incidence

The annual crude IR of NAFLD-HCC in adults, during the study period 2012-2018, was 1.3 per 100,000 person-years (95% CI 1.2-1.4); 1.9 for men (95% CI 1.7-2.1), and 0.6 for women (95% CI 0.5-0.7).

The overall ASIR of NAFLD-HCC increased by 71% between 2012 and 2018, from 0.7 per 100,000 person-years (95% CI 0.6-0.9) in 2012, to 1.2 (95% CI 1.8-2.3) in 2018. The ASIR of NAFLD-HCC for men increased by 53%, from 1.5 per 100,000 person-years (95% CI 1.1-1.8) in 2012, to 2.3 (95% CI 1.9-2.7) in 2018. At the same time, the ASIR of cirrhotic NAFLD-HCC doubled, from 0.4 per 100,000 person-years (95% CI 0.2-0.5) in 2012, to 0.8 (95% CI 0.6-1.0) in 2018.

Discussion

There is no book so bad…
that it does not have something good in it.

— Miguel de Cervantes Saavedra

Paper I

In this study, we report IR estimates considerably higher than those reported in previous Swedish epidemiological studies.[179, 180] In line with prior studies, IRs for men were twice as high than IRs for women; ArLD was the most common etiology; and roughly half of all patients had already developed signs of decompensation before cirrhosis diagnosis.[179, 180]

Our results indicate that the incidence of cirrhosis in Sweden may be noticeably higher than expected. Comparisons to prior findings are however challenging since different periods of time were studied. Despite the geographical proximity between Gothenburg, Halland, and Skåne, the distribution of risk determinants of cirrhosis may vary considerably across the three different populations. For example, Halland had the highest mean alcohol consumption per capita between 2002 and 2016: 10.8 liters vs. 9.2 liters (Skåne) and 10.2 liters (Gothenburg).[271] As the proportion of patients having ArLD did not meaningfully differ between our and prior studies, the higher IRs of cirrhosis in Halland cannot be explained by higher alcohol consumption.

On the other hand, between 2012 and 2018, the mean IR of HCV in Halland was 10.2 per 100,000 person-years, while the corresponding IRs in Gothenburg and Skåne were 15.8 and 14.7, respectively. The lower IR of HCV in Halland should infer a lower prevalence of HCV, thus explaining why the proportion of patients with HCV-cirrhosis in Halland (13%) was considerably lower compared to those reported for Gothenburg and Skåne (21% each).[179, 180] Generally, patients with HCV-related cirrhosis are younger at diagnosis, while patients with NAFLD or cryptogenic cirrhosis are often diagnosed at older ages.[179] This may explain why the median age at cirrhosis diagnosis was higher in Halland compared to those reported in other Swedish populations.[179, 180, 272]

Nonetheless, it is unclear if our IR estimates reflect one or several of the following:

i. a higher IR of cirrhosis in Halland when compared to its two closest neighboring regions
ii. a prior underestimation of the IR of cirrhosis in other regions
iii. a real increment of IRs of cirrhosis in Sweden during the last decades
iv. a combination of the alternatives listed above

Nationwide data from the NPR - recently presented at the 2022 EASL Liver Congress in London - indicates that IRs of cirrhosis increased in Sweden between 2005 and 2019.[273] There were also significant disparities across geographical regions.[273] The IR of ArLD in adults in Sweden was estimated at 13.1 per 100,000 person-years in 2019.[273] Since 50% of all cirrhosis cases in Halland were associated with ArLD, our IR estimates, 30 per 100,000 in adults for all-cause cirrhosis, are largely in-line with nationwide data.

We have also shown that NAFLD has become an important etiology of cirrhosis in Swedish populations. NAFLD was found in 6% of patients with cirrhosis, which at the time of publication was the highest proportion reported in a Swedish population. In 2021, Hagström et al. reported a higher proportion of NAFLD (9.6%) among patients diagnosed with cirrhosis in Stockholm.[272] When the same definition of NAFLD is used in our cohort, 10% of all patients diagnosed with cirrhosis in Halland between 2011 and 2018 may have had NAFLD.[274]

Strengths and limitations

Strengths of our study include the implementation of reliable and extensive patient data retrieved from computerized medical records. We also reviewed all liver-related histopathological samples registered in Halland during the study period. The healthcare of patients with cirrhosis was centralized to three public hospitals, thus minimizing the risk of selection bias as all adult patients were included disregarding etiology, cirrhosis stage, comorbidity, or expected survival.

Most limitations of this study were related to its retrospective nature. Some patients may have been excluded or included erroneously since neither the sensitivity nor the specificity of diagnostic imaging methods used were perfect. By excluding patients without results from diagnostic imaging or histology, we may have increased the specificity of our cirrhosis criteria at the cost of lower sensitivity, thus excluding some 80 patients with suspected cirrhosis. This may have affected our IR estimates. Only a minor proportion of patients were diagnosed by biopsy and we were not able to report the proportion of NASH among patients with suspected NAFLD. Likewise, some patients with ArLD or NAFLD may have been misclassified as having cryptogenic cirrhosis and *vice versa*.

Paper II

In this study, we report strong associations between individual-level SES, survival and mortality risk in patients diagnosed with cirrhosis in Halland between 2011 and 2018. Lower SES was associated with more severe cirrhosis at diagnosis. Marital and employment status were also associated with survival but there were no statistically significant associations with mortality risk in multivariable analyses.

In the United States, several studies have shown associations between lower SES and worse prognosis in cirrhosis cases.[213, 214, 241] Despite this, associations between SES and survival in patients with cirrhosis have scarcely been described in European populations.[228, 240] In contrast to the United States, healthcare services in Sweden are mainly tax-based in order to provide equal access to the whole population of the country. This may infer that our results are much less prone to selection bias related to economic disadvantages, compared to similar studies from nations without free universal access to healthcare services.

The Nordic countries share several characteristics, including similar healthcare systems and a comprehensive array of social safety nets.[275] In Denmark, personal income was not associated with survival in patients with cirrhosis, but patients who were disability retirees had worse five-year survival compared to those who were either employed or unemployed. Although we did not have access to income data, we found also that patients who were employed had better survival compared to disability retirees.[228] However, it must be remembered that our cohort comprised older patients thus making employment status a less suitable indicator of SES.

We found that patients with the highest occupational skill level were either employed or pensioners, which also comprise the groups with higher income compared to unemployed and disability retirees. Like in Denmark, we found that patients who were married had better survival rates than those who were previously married, but mortality risks were similar for the different marital statuses in our multivariable models.[228] Patients with the highest occupational skill level were more often married compared to patients with the lowest level. In Sweden, the most qualified occupations are associated with a higher educational level and better personal income.[276] Thus, the associations between occupational skill level, survival, and mortality risk described by us, may be multifactorial. Patients with the highest occupational skill level may have several favorable prognostic factors, such as higher economic (income and employment status) and social (marital status) safety. These patients may also be more prone to seek medical attention earlier, either by having a higher awareness of liver diseases and risk factors or by incitement from family members and employers.

Strengths and limitations

Strengths of this study include access to reliable baseline and follow-up data, and the implementation of well-defined statistical methods. We defined occupational skill level upon standardized definitions based on international recommendations. We included patients from all etiologies and with different stages of cirrhosis. To the best of our knowledge, our study was the first examining the importance of marital status, employment status, and individual-level SES on cirrhosis survival in a Swedish population.

The main limitation of the present study was the use of self-reported patient data regarding marital status, employment status, and occupation. Despite this limitation, we had access to a large number of scanned reports, including sick-leave certificates and disability certificates. Marital status and housing are usually documented in medical charts to evaluate a patient's need of social support or housing. In some cases, multiple simultaneous occupations were reported, but most of these occupations were within the same occupational skill level, thus having no effect in group-level analyses. As described before, we do not have access to income and education, which otherwise, like occupation, are indicators of individual-level SES widely used in epidemiology.

Paper III

In this study, we report that men had four times higher IRs of HCC than women, which is in line with prior findings from Sweden and the United Kingdom.[195, 277] Both individual- and contextual-level SES were associated with higher IRs of HCC, being most pronounced in men with a low household income, or living in the most socioeconomically deprived neighborhoods, or both. Non-Nordic inhabitants had similar IRs of all-stage HCC, but the IRs at early stages were higher compared to inhabitants born in a Nordic nation.

Low educational level and occupations associated with high alcohol consumption and/or smoking have historically been linked to a higher risk for primary liver cancer in Sweden.[258, 259] Our results are in line with prior observations. Low individual-level SES has been associated with a higher prevalence of several risk factors of HCC. Intravenous drug use is the main transmission route of HCV in Sweden and individuals belonging to low socioeconomic index groups are at the highest risk for both intravenous drug use and HCV.[278] The risk of HCC in ArLD is low compared to the risk associated with viral hepatitis.[123, 279] However, ArLD is the main etiology of cirrhosis in Sweden.[179] Low SES has been linked with a disproportionate burden of ArLD, considering that individuals with a high SES are believed to consume similar quantities of alcohol as those with a lower SES.[280] In

Sweden, the incidence and mortality of ArLD are also higher in groups with a low SES.[281, 282]

In western countries, the prevalence of NAFLD seems to be higher in individuals with a low SES, which also have higher proportions of advanced fibrosis compared to groups with a higher SES.[283]

Low SES at a contextual level has also been associated with an increased risk of liver cancer in other European populations.[253-255, 284] In England, the IR of HCC among individuals living in the most deprived areas was almost 2.5 times higher than the IR for those living in the least deprived areas.[284] This finding is similar to our results although more pronounced. In the United States, contextual-level socioeconomic deprivation was associated with an increased risk of HCC incidence, but this association was not statistically significant after adjustments for individual-level SES.[285] Here, we have shown that individual- and contextual-level SES reduced the effect of each other in multivariable models, but both remained statistically significant after adjustments. This motivates the inclusion of both determinants of SES (if possible) in studies describing the epidemiology of cancer.[237]

Patients born in a non-Nordic country were younger and more often diagnosed with an early-stage HCC, compared to patients with a Nordic origin. These findings are consistent with prior studies from Sweden and Norway.[286, 287] Another study has suggested that immigrants from high-endemic areas of viral hepatitis have a higher awareness of liver cancer, thus seeking medical attention earlier.[287] Physicians may also be more attentive to viral hepatitis, and thereby an increased risk of HCC, in ethnical minorities.[287] In Sweden, immigrants and refugees from high-endemic areas are offered screening for viral hepatitis soon after their arrival to the country. This may eventually lead to earlier cirrhosis identification and inclusion into HCC surveillance programs.

Strengths and limitations

Strengths of this study include the use of high-quality nationwide data retrieved from SweLiv, which has been validated for HCC. We were able to stratify HCC stage into three groups of interest (all-stage, early-stage, late-stage), with only 3% missing data. There were no missing data for ethnicity, individual-level, or contextual-level SES. To the best of our knowledge, this was the first nationwide study from Europe including both individual- and contextual-level SES indicators when estimating IRs of HCC.

The design of this study did not allow for causal interference, which was a limitation. Due to the lack of even more granular data, patients were regarded as having an early- or a late-stage HCC at diagnosis, meaning that IRs for each individual BCLC-stage could not be estimated. As the country of birth was defined

as either Nordic or non-Nordic, we could not estimate IRs for individual countries. Studies examining associations between SES and cancer IR often use educational level, or social class as the main indicator of individual-level SES. Strömberg et al. have pointed out that, although educational level has predominantly been used as a proxy of SES in the Scandinavian countries (categorizing patients into "low" [primary school], "intermediate" [gymnasium/pre-university level] and "high" [university level] SES), developments of education systems in these (and several other) countries have resulted in gradual shifts from lower to higher educational level in younger generations, raising concerns about the use of educational level as a direct measure of SES.[288]

Educational level is rather an indirect measure of SES; and standardization by calendar year, age, and sex should be considered. Data regarding educational level is also less reliable for immigrants, compared to economic data. According to Statistics Sweden (https://www.scb.se/en/), in 2017, data regarding educational level was missing for 7.5% of immigrants and 0.4% for people born in Sweden. Similarly, data regarding occupational social class might be less reliable for immigrants, especially for refugees (the main group of immigrants to Sweden), who are more frequently unemployed compared to people born in Sweden (19% vs 5%, 2020). Instead, household income is based on complete data (no missing data were registered for household income in patients diagnosed with HCC in Sweden 2012-2018, independent of country of birth).

Paper IV

In this study, we found that 77% of all adult patients diagnosed with HCC in Sweden between 2012 and 2018 had underlying cirrhosis. In patients with cirrhosis, cirrhosis was unrecognized before HCC diagnosis in 39% of cases. Among patients with previously recognized cirrhosis, HCC was diagnosed while under surveillance in 55% of cases. Unrecognized cirrhosis was associated with a four times higher likelihood of presenting with a late-stage HCC, compared to patients diagnosed while under surveillance. Larger tumors, more multinodular tumors, and more extrahepatic metastasis were all more frequent in patients with unrecognized cirrhosis, which were diagnosed at a late-stage HCC in 79% of cases. Consequently, patients with unrecognized cirrhosis had substantially worse survival and considerably increased mortality risk, compared to surveilled patients. These findings are consistent with studies from the United States.[198-202]

Male sex and a low household income were each associated with a higher likelihood of unrecognized cirrhosis. As we showed in Study III, these populations had also the highest IRs of late-stage HCC, suggesting important health inequalities in

Sweden, regarding the early identification of cirrhosis in the most socioeconomically deprived groups, and in men.

Compared to viral hepatitis, NAFLD was associated with an increased likelihood of cirrhosis unrecognition, which also has been observed in a prior study from Stockholm, and in studies from the United States.[197, 200, 201] Moreover, NAFLD was the most common liver disease observed in patients with unrecognized cirrhosis. This finding is of particular concern since NAFLD is becoming an increasing cause of cirrhosis and HCC in Sweden.[137, 155, 272] It has been shown in Sweden that patients with biopsy-proven NAFLD had a 17-fold higher rate of developing HCC compared with controls.[135] Here, we showed that NAFLD-related comorbidities were very common in patients with unrecognized cirrhosis, which otherwise had a median of two non-HCC-related visits registered in the NPR within a year before HCC diagnosis. These findings suggest the existence of health inequalities in cirrhosis detection in patients with NAFLD, and an urgent need for increased liver disease awareness among healthcare professionals.

Globally, NAFLD is the most common liver disease.[84, 116] NAFLD is also the main cause of HCC among Medicare users in the United States.[289] Patients with NAFLD and cirrhosis should be surveilled for HCC according to international guidelines.[141, 167] Despite this, NAFLD-related cirrhosis is mainly diagnosed incidentally and not seldom after the development of HCC.[290] The early diagnosis of HCC in patients with NAFLD is considerably more challenging that in patients with viral hepatitis, as cirrhosis is absent in an important proportion of patients with NAFLD-HCC.[136] For example, 37% of patients diagnosed with NAFLD-HCC in Stockholm between 2004 and 2017, did not have cirrhosis.[137]

We found that only 26% of patients were diagnosed with HCC while under surveillance. Similar proportions have been reported in populations from Stockholm, the United States, and even in a recent meta-analysis.[197, 203, 291] Although we reported that the 55% of patients with previously recognized cirrhosis were diagnosed with HCC while under surveillance, our findings indicate that surveillance strategies can be improved. In 28% of patients with previously recognized cirrhosis who we diagnosed after developing symptoms, HCC diagnoses should have been made while under surveillance but were not.

Strengths and limitations

Strengths of this study include the use of high-quality register data. By combining data from SweLiv, the NPR and the Prescribed Drug Register, we were able to identify a higher proportion of patients with cirrhosis, compared to a prior study based on data exclusively from SweLiv.[157] We were also able to identify patients with cirrhosis decompensation and most patients could be classified as having either

early- or late-stage HCC. The risk of selection bias in this study is lower than in prior studies from the United States, as all inhabitants in Sweden have free access to healthcare services.

The main limitations of this study are related to the lack of data from primary care visits in the NPR. We defined unrecognized cirrhosis based on data from SweLiv and the NPR, and some patients diagnosed with cirrhosis through primary care givers may erroneously have been classified as having unrecognized cirrhosis. The risk of misclassification is however modest as most patients diagnosed with cirrhosis in Sweden's primary care centers are normally referred to as secondary or tertiary care centers. Our results indicate that HCC surveillance is associated with better survival in patients with cirrhosis, later diagnosed with HCC. Nevertheless, it must be stated that the main aim of our study was not to evaluate the effect of HCC surveillance on survival. Our results regarding survival benefit must thereby be interpreted with caution and taking into consideration the potential effect of length and lead time bias.[149, 292, 293]

While similar results may be found in countries with similar healthcare systems, and proportions of risk factors for cirrhosis and HCC; validation studies are needed before our results can be applied in clinical practice. Our results validate in turn prior studies from the United States, indicating that free access to healthcare services may not be sufficient to identify patients with cirrhosis before HCC diagnosis.

Paper V

In this study, we found that 21% of all patients diagnosed with HCC in Sweden between 2012 and 2018 had underlying NAFLD. We have shown that the incidence of NAFLD increased by 33% during the study period, and that since 2014 NAFLD was the second-leading cause of liver disease in patients with HCC. Patients with NAFLD-HCC were more often older and had metabolic comorbidities, larger tumors, and extrahepatic metastasis, to a higher extent than patients with non-NAFLD-HCC. On the other hand, patients with NAFLD-HCC had less cirrhosis and there were no statistically significant differences regarding the proportion of patients diagnosed at an early-stage HCC, between those with and without NAFLD-HCC. These findings are consistent with prior reports from Stockholm, and with a recent meta-analysis.[136, 137, 155]

Since NAFLD is an increasing cause of cirrhosis in Sweden, and the prevalence of T2D, overweight and obesity are rising in the country, our findings are somewhat anticipated.[194, 272, 274, 294] The increment of NAFLD-HCC observed between 2012 and 2018 was mostly caused by an increase among men and in cirrhosis NAFLD-HCC, which are findings that had not been reported previously in Sweden.

Strengths and limitations

Similar to in studies III and IV, we used data from validated nationwide registers, with low risk for selection bias. Our definitions of NAFLD have previously been validated in a Swedish population, achieving positive and negative predictive values of 83% and 91%, respectively.[155] These definitions of NAFLD were also concordant with recommendations from an expert panel consensus statement.[295] We were also able to identify important metabolic comorbidities, and patients with underlying cirrhosis. To the best of our knowledge, this was the largest study of its kind using nationwide data from a Nordic country.

Our study is limited by its retrospective nature and the lack of even more granular data. As stated before, the NPR does not include data from primary care visits. Despite using validated definitions of NAFLD, it is possible that some patients may have been classified as having NAFLD-HCC erroneously. On the other hand, since the use of ICD codes for obesity and fatty liver is low in Sweden, it is possible that some patients classified as not having a previously identified liver disease had de facto NAFLD, thus affecting our incidence estimates.

Conclusions

Of all the forms of inequality,
injustice in health is the most shocking and inhuman

— Martin Luther King Jr.

Paper I

The annual crude IR of cirrhosis in adults, between 2011-2018, was 30 per 100,000 person-years (95% CI 28-33) in Halland. The ASIR during the same study period, was 23 per 100,000 person-years (95% CI 19-25). ArLD was the most common etiology. There was a high prevalence of metabolic comorbidities in patients with cirrhosis. Roughly 50% of patients newly diagnosed with cirrhosis were at decompensated stages, mostly due to the high proportion of patients with ascites. HCC was found in 12.5% of patients, either at cirrhosis diagnosis or within six months after cirrhosis diagnosis.

Paper II

Sex, marital status, employment, and occupational skill level, were all associated with mean survival in patients diagnosed with cirrhosis in Halland between 2011 and 2018. Low individual-level SES, defined by occupational skill level, was strongly associated with more severe cirrhosis at diagnosis, worse survival, and higher mortality risk.

Paper III

Men with a low household income, or living in the most deprived neighborhoods had the highest IRs of HCC in Sweden between 2012 and 2018.

Paper IV

Cirrhosis was found in 77% of patients diagnosed with HCC in Sweden between 2012 and 2018. Unrecognized cirrhosis was very common (39% of all cirrhosis cases in HCC) and associated with more advanced HCC at diagnosis and a worse overall survival rate.

Paper V

NAFLD has become the second-leading liver disease associated with HCC in Sweden. Patients with NAFLD-HCC had cirrhosis to a lesser extent, but they had a similar proportion of early-stage HCC at diagnosis, compared to patients without NAFLD-HCC.

Future perspectives

Time has taught me not to lose hope,
yet not to trust too much in hope either

— Carlos Ruiz Zafón

There is increasing evidence indicating a changing spectrum of liver diseases in Sweden. Similar to other Nordic countries, ArLD prevails as the most common cause of cirrhosis in Sweden. However, there may be considerable regional variations, which was evident in our findings regarding the proportion of HCV in cirrhosis.[179, 180, 272, 273] We found that only 14% of all cases of cirrhosis in Halland (2011-2018) were related to HCV, while the corresponding percentage reported for Stockholm (2004-2017) was 40%.[272] Several factors could explain this discrepancy. The incidence of HCV in Stockholm is much higher than in Halland.[190] Additionally, the prevalence of individuals at-risk of HCV, e.g. people who inject drugs, and immigrants from high-endemic areas, is also higher in Stockholm.[296] Despite these evident differences between Halland and Stockholm, NAFLD had become an important cause of cirrhosis in both regions.[274] Interventions against risk factor of cirrhosis may however have a divergent impact in different regions of Sweden. For instance, novel policies for the prevention of ArLD and/or NAFLD may have a uniformly distributed benefit across the country, while interventions against viral hepatitis, e.g. needle-exchange programs, screening of risk groups, and DAAs may have greater benefit in the largest cities of Sweden.

In line with the changing spectrum of cirrhosis, we have shown that the incidence of NAFLD-HCC is increasing while the incidence of HCV-HCC is decreasing in Sweden. Combined with the rising prevalence of risk factors of NAFLD, and the low risk of HCC reported in patients with ArLD, it is reasonable to postulate that NAFLD will become the most common liver disease associated with HCC in forthcoming decades.[123, 129, 132] NAFLD becoming the main cause of HCC is a major health concern as a high proportion of patients with NAFLD-HCC do not have underlying cirrhosis.[136, 137] Additionally, cirrhosis is often diagnosed incidentally in individuals with NAFLD.[290] Lack of awareness is a major challenge in the early diagnosis of NAFLD.[297] In Swedish primary care centers, the awareness of NAFLD in patients with T2D is low and liver disease is seldom followed-up as recommended by national and international guidelines.[298-300]

There are several non-invasive diagnostic and staging methods in NAFLD.[301] In a prospective study from the United Kingdom, a two-step pathway using established blood tests in primary care settings reduced unnecessary referrals by 80%, and improved the detection of cirrhosis three-fold.[302] This study was however limited by the use of a commercial biomarker panel, which was more expensive and less available than other serum-based fibrosis markers, such as FIB-4.[301, 302] The diagnostic accuracy of serum-based algorithms in liver steatosis diagnosis is however insufficient. Additionally, the use of repeated FIB-4 measurements for monitoring patients with known NAFLD may not be indicated due to the weak associations between changes in FIB-4 scores and disease progression.[301, 303] Nonetheless, the early identification of individuals with NAFLD through non-invasive methods is an area of extensive research. NAFLD is not only associated with an increased risk for liver outcomes but also with extrahepatic diseases.[304] Compared to the general population, individuals with NAFLD have an increased risk of cardiovascular disease, and colorectal cancer.[304]

Since all inhabitants in Sweden have access to free healthcare services and there are numerous safety nets against health inequality, our findings linking low SES to the following are particularly worrying: i) more advanced cirrhosis stages at diagnosis; ii) worse survival and higher mortality risk in cirrhosis; iii) higher incidence of HCC; iv) higher likelihood of unrecognized cirrhosis in HCC; and v) worse survival and higher mortality risk in cirrhotic HCC. These findings illustrate the burden of health inequality and stigma in liver diseases. Future studies examining the effect of preventive interventions and screening strategies in Sweden should focus on the most economically deprived groups, such as individuals (particularly men) with a low income, or living in socioeconomically deprived areas.

In summary, NAFLD has become a main cause of end-stage liver disease and liver cancer in Sweden. The burden of health inequality in liver diseases in Sweden is substantial. Current public health policies and health care strategies seem to be insufficient to increase the awareness of liver diseases in groups at high risk and to minimize stigma. Cirrhosis and NAFLD unawareness and stigma among healthcare professionals may also contribute to health inequality. Primary and secondary preventive interventions, liver disease awareness campaigns, patient education programs, cross-specialty collaboration, and more publicly funded liver disease research may all be highly needed to stand a chance against current and future challenges associated with cirrhosis, HCC, and health inequality in Sweden.

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References

1. Abdel-Misih SR, Bloomston M. Liver anatomy. *Surg Clin North Am* 2010;**90**: 643-53.
2. Rubin E, Reisner HM. *Principles of Rubin's pathology*, Seventh edition. ed. Philadelphia: Wolters Kluwer, 2019. xiii, 938 pages.
3. Sibulesky L. Normal liver anatomy. *Clinical Liver Disease* 2013;**2**: S1-S3.
4. Bosch J, Abraldes JG, Berzigotti A, et al. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol* 2009;**6**: 573-82.
5. Kalra A, Yetiskul E, Wehrle CJ, et al. Physiology, Liver *StatPearls*ed. Treasure Island (FL), 2022.
6. Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. *Nat Rev Gastroenterol Hepatol* 2021;**18**: 40-55.
7. Gines P, Krag A, Abraldes JG, et al. Liver cirrhosis. *Lancet* 2021;**398**: 1359-76.
8. Wahlin S, Andersson J. Liver health literacy and social stigma of liver disease: A general population e-survey. *Clin Res Hepatol Gastroenterol* 2021;**45**: 101750.
9. Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 2022;**399**: 61-116.
10. Alqahtani SA, Paik JM, Biswas R, et al. Poor Awareness of Liver Disease Among Adults With NAFLD in the United States. *Hepatol Commun* 2021;**5**: 1833-47.
11. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician* 2006;**74**: 756-62.
12. EASL. Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021;**75**: 659-89.
13. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? *Jama* 2012;**307**: 832-42.
14. de Bruyn G, Graviss EA. A systematic review of the diagnostic accuracy of physical examination for the detection of cirrhosis. *BMC Med Inform Decis Mak* 2001;**1**: 6.
15. Sharma P. Value of Liver Function Tests in Cirrhosis. *J Clin Exp Hepatol* 2022;**12**: 948-64.
16. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;**43**: 1317-25.
17. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;**38**: 518-26.

18. Procopet B, Berzigotti A. Diagnosis of cirrhosis and portal hypertension: imaging, non-invasive markers of fibrosis and liver biopsy. *Gastroenterol Rep (Oxf)* 2017;**5**: 79-89.

19. Huber A, Ebner L, Heverhagen JT, et al. State-of-the-art imaging of liver fibrosis and cirrhosis: A comprehensive review of current applications and future perspectives. *Eur J Radiol Open* 2015;**2**: 90-100.

20. Kudo M, Zheng RQ, Kim SR, et al. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. A multicenter collaborative study. *Intervirology* 2008;**51 Suppl 1**: 17-26.

21. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011;**54**: 650-9.

22. Friedrich-Rust M, Poynard T, Castera L. Critical comparison of elastography methods to assess chronic liver disease. *Nat Rev Gastroenterol Hepatol* 2016;**13**: 402-11.

23. Thanapirom K, Suksawatamnuay S, Tanpowpong N, et al. Non-invasive tests for liver fibrosis assessment in patients with chronic liver diseases: a prospective study. *Sci Rep* 2022;**12**: 4913.

24. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. *Gastroenterology* 2016;**150**: 123-33.

25. Jiang W, Huang S, Teng H, et al. Diagnostic accuracy of point shear wave elastography and transient elastography for staging hepatic fibrosis in patients with non-alcoholic fatty liver disease: a meta-analysis. *BMJ Open* 2018;**8**: e021787.

26. Kovalak M, Lake J, Mattek N, et al. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. *Gastrointest Endosc* 2007;**65**: 82-8.

27. Oberti F, Burtin P, Maiga M, et al. Gastroesophageal endoscopic signs of cirrhosis: independent diagnostic accuracy, interassociation, and relationship to etiology and hepatic dysfunction. *Gastrointest Endosc* 1998;**48**: 148-57.

28. Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut* 2020;**69**: 1382-403.

29. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *Am J Public Health* 2005;**95 Suppl 1**: S144-50.

30. Alrawahi AH. New approaches to disease causation research based on the sufficient-component cause model. *J Public Health Res* 2020;**9**: 1726.

31. EASL. Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;**69**: 406-60.

32. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021;**74**: 1014-48.

33. Yoshiji H, Nagoshi S, Akahane T, et al. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. *J Gastroenterol* 2021;**56**: 593-619.

34. Seto WK, Lo YR, Pawlotsky JM, et al. Chronic hepatitis B virus infection. *Lancet* 2018;**392**: 2313-24.
35. Urban S, Neumann-Haefelin C, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. *Gut* 2021;**70**: 1782-94.
36. Burm R, Maravelia P, Ahlen G, et al. Novel prime-boost immune-based therapy inhibiting both hepatitis B and D virus infections. *Gut* 2022.
37. Spearman CW, Dusheiko GM, Hellard M, et al. Hepatitis C. *Lancet* 2019;**394**: 1451-66.
38. O'Shea RS, Dasarathy S, McCullough AJ, et al. Alcoholic liver disease. *Hepatology* 2010;**51**: 307-28.
39. Fuster D, Samet JH. Alcohol Use in Patients with Chronic Liver Disease. *N Engl J Med* 2018;**379**: 1251-61.
40. Askgaard G, Grønbæk M, Kjær MS, et al. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. *J Hepatol* 2015;**62**: 1061-7.
41. EASL. Clinical Practice Guidelines: Management of alcohol-related liver disease. *J Hepatol* 2018;**69**: 154-81.
42. Singal AK, Bataller R, Ahn J, et al. ACG Clinical Guideline: Alcoholic Liver Disease. *Official journal of the American College of Gastroenterology | ACG* 2018;**113**: 175-94.
43. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**: 1513-23.
44. Swedish National Board of Health and Welfare. National Guidelines for Methods of Preventing Disease. [online]; 2018 [cited 7 Nov 2022]. Available at: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2018-6-24.pdf.
45. Lazarus JV, Mark HE, Anstee QM, et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol* 2022;**19**: 60-78.
46. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015;**149**: 389-97.e10.
47. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol* 2017;**67**: 1265-73.
48. Rinella M, Charlton M. The globalization of nonalcoholic fatty liver disease: Prevalence and impact on world health. *Hepatology* 2016;**64**: 19-22.
49. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019;**71**: 793-801.
50. Francque S, Wong VW-S. NAFLD in lean individuals: not a benign disease. *Gut* 2022;**71**: 234-6.

51. Hagstrom H, Nasr P, Ekstedt M, et al. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: A long-term follow-up study. *Hepatol Commun* 2018;**2**: 48-57.

52. Trivedi PJ, Hubscher SG, Heneghan M, et al. Grand round: Autoimmune hepatitis. *J Hepatol* 2019;**70**: 773-84.

53. Mack CL, Adams D, Assis DN, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology* 2020;**72**: 671-722.

54. Wahlin S, Efe C. Both tacrolimus and mycophenylate mophetil should be considered second-line therapy for autoimmune hepatitis. *J Hepatol* 2021;**74**: 753-5.

55. Grønbæk L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* 2014;**60**: 612-7.

56. Sharma R, Verna EC, Söderling J, et al. Increased Mortality Risk in Autoimmune Hepatitis: A Nationwide Population-Based Cohort Study With Histopathology. *Clin Gastroenterol Hepatol* 2021;**19**: 2636-47.e13.

57. EASL. Clinical Practice Guidelines on sclerosing cholangitis. *J Hepatol* 2022;**77**: 761-806.

58. Dyson JK, Beuers U, Jones DEJ, et al. Primary sclerosing cholangitis. *Lancet* 2018;**391**: 2547-59.

59. Marschall HU, Henriksson I, Lindberg S, et al. Incidence, prevalence, and outcome of primary biliary cholangitis in a nationwide Swedish population-based cohort. *Sci Rep* 2019;**9**: 11525.

60. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and Management of Primary Biliary Cholangitis. *Am J Gastroenterol* 2019;**114**: 48-63.

61. Trivedi PJ, Hirschfield GM. Primary biliary cirrhosis: Renaming primary biliary cirrhosis-clarity or confusion? *Nat Rev Gastroenterol Hepatol* 2015;**12**: 678-9.

62. EASL. Clinical Practice Guidelines on haemochromatosis. *J Hepatol* 2022;**77**: 479-502.

63. Hagstrom H, Ndegwa N, Jalmeus M, et al. Morbidity, risk of cancer and mortality in 3645 HFE mutations carriers. *Liver Int* 2021;**41**: 545-53.

64. EASL. Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012;**56**: 671-85.

65. Narayanan P, Mistry PK. Update on Alpha-1 Antitrypsin Deficiency in Liver Disease. *Clinical Liver Disease* 2020;**15**: 228-35.

66. Lewis JH, Ranard RC, Caruso A, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology* 1989;**9**: 679-85.

67. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. *Am J Med* 1991;**90**: 711-6.

68. Caldwell S, Marchesini G. Cryptogenic vs. NASH-cirrhosis: The rose exists well before its name. *J Hepatol* 2018;**68**: 391-2.

69. Thuluvath PJ, Kantsevoy S, Thuluvath AJ, et al. Is cryptogenic cirrhosis different from NASH cirrhosis? *J Hepatol* 2018;**68**: 519-25.

70. Younossi Z, Stepanova M, Sanyal AJ, et al. The conundrum of cryptogenic cirrhosis: Adverse outcomes without treatment options. *J Hepatol* 2018;**69**: 1365-70.

71. Asrani SK, Devarbhavi H, Eaton J, et al. Burden of liver diseases in the world. *J Hepatol* 2019;**70**: 151-71.

72. Collaborators GBDC. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020;**5**: 245-66.

73. Pimpin L, Cortez-Pinto H, Negro F, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. *J Hepatol* 2018;**69**: 718-35.

74. Collaborators GBDHB. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol* 2022;**7**: 796-829.

75. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. *Lancet Gastroenterol Hepatol* 2022;**7**: 396-415.

76. Collaborators GBDA. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet* 2022;**400**: 185-235.

77. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2022;**7**: 851-61.

78. Alberts CJ, Clifford GM, Georges D, et al. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. *Lancet Gastroenterol Hepatol* 2022;**7**: 724-35.

79. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. *Nat Rev Gastroenterol Hepatol* 2022;**19**: 533-50.

80. World Health Organization. (2016). Combating hepatitis B and C to reach elimination by 2030: advocacy brief. World Health Organization. Available at https://apps.who.int/iris/handle/10665/206453.

81. Huang DQ, Mathurin P, Cortez-Pinto H, et al. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. *Nat Rev Gastroenterol Hepatol* 2022.

82. Manthey J, Shield KD, Rylett M, et al. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *Lancet* 2019;**393**: 2493-502.

83. Paik JM, Golabi P, Younossi Y, et al. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. *Hepatology* 2020;**72**: 1605-16.

84. Le MH, Yeo YH, Li X, et al. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2021.

85. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol* 2021;**18**: 151-66.

86. Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015;**63**: 1272-84.

87. Garcia-Pagan JC, Gracia-Sancho J, Bosch J. Functional aspects on the pathophysiology of portal hypertension in cirrhosis. *J Hepatol* 2012;**57**: 458-61.

88. Aithal GP, Palaniyappan N, China L, et al. Guidelines on the management of ascites in cirrhosis. *Gut* 2021;**70**: 9-29.

89. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007;**133**: 481-8.

90. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;**43**: 167-76.

91. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;**44**: 217-31.

92. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021;**74**: 1014-48.

93. Rose CF, Amodio P, Bajaj JS, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. *J Hepatol* 2020;**73**: 1526-47.

94. EASL. Clinical Practice Guidelines on the management of hepatic encephalopathy. *J Hepatol* 2022;**77**: 807-24.

95. Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers* 2016;**2**: 16041.

96. Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment. *JHEP Rep* 2021;**3**: 100176.

97. D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. *J Hepatol* 2018;**68**: 563-76.

98. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**: 646-9.

99. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;**33**: 464-70.

100. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol* 2005;**42 Suppl**: S100-7.

101. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008;**359**: 1018-26.

102. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era. *Gastroenterology* 2021;**161**: 1887-95 e4.

103. Ording AG, Sørensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clin Epidemiol* 2013;**5**: 199-203.

104. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**: 373-83.

105. Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology* 2014;**146**: 147-56; quiz e15-6.

106. Jepsen P. Comorbidity in cirrhosis. *World J Gastroenterol* 2014;**20**: 7223-30.

107. Elkrief L, Chouinard P, Bendersky N, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. *Hepatology* 2014;**60**: 823-31.

108. Wild SH, Morling JR, McAllister DA, et al. Type 2 diabetes and risk of hospital admission or death for chronic liver diseases. *J Hepatol* 2016;**64**: 1358-64.

109. Ahn SB, Powell EE, Russell A, et al. Type 2 Diabetes: A Risk Factor for Hospital Readmissions and Mortality in Australian Patients With Cirrhosis. *Hepatology Communications* 2020;**4**: 1279-92.

110. Asrani SK, Hall L, Reddy V, et al. Comorbid Chronic Diseases and Survival in Compensated and Decompensated Cirrhosis: A Population-Based Study. *Am J Gastroenterol* 2022;**117**: 2009-16.

111. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med* 2019;**380**: 1450-62.

112. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nature Reviews Disease Primers* 2021;**7**: 6.

113. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. *Lancet* 2022;**400**: 1345-62.

114. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;**127**: S35-50.

115. Lissing M, Vassiliou D, Floderus Y, et al. Risk of primary liver cancer in acute hepatic porphyria patients: A matched cohort study of 1244 individuals. *J Intern Med* 2022;**291**: 824-36.

116. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021;**18**: 223-38.

117. Lee YC, Cohet C, Yang YC, et al. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol* 2009;**38**: 1497-511.

118. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;**71**: 209-49.

119. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians* 2022;**72**: 7-33.

120. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol* 2022;**77**: 1598-606.

121. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;**74**: 2913-21.

122. West J, Card TR, Aithal GP, et al. Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: a population-based cohort study. *Aliment Pharmacol Ther* 2017;**45**: 983-90.

123. Bengtsson B, Widman L, Wahlin S, et al. The risk of hepatocellular carcinoma in cirrhosis differs by etiology, age and sex: A Swedish nationwide population-based cohort study. *United European Gastroenterol J* 2022.

124. Maucort-Boulch D, de Martel C, Franceschi S, et al. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer* 2018;**142**: 2471-7.

125. de Martel C, Maucort-Boulch D, Plummer M, et al. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology* 2015;**62**: 1190-200.

126. Akinyemiju T, Abera S, Ahmed M, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncol* 2017;**3**: 1683-91.

127. Kanwal F, Kramer J, Asch SM, et al. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology* 2017;**153**: 996-1005 e1.

128. Ioannou GN, Beste LA, Green PK, et al. Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. *Gastroenterology* 2019;**157**: 1264-78.e4.

129. Jepsen P, Ott P, Andersen PK, et al. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med* 2012;**156**: 841-7, W295.

130. Jepsen P, Kraglund F, West J, et al. Risk of hepatocellular carcinoma in Danish outpatients with alcohol-related cirrhosis. *J Hepatol* 2020;**73**: 1030-6.

131. Mancebo A, González-Diéguez ML, Cadahía V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. *Clin Gastroenterol Hepatol* 2013;**11**: 95-101.

132. Hagstrom H, Thiele M, Sharma R, et al. Risk of Cancer in Biopsy-Proven Alcohol-Related Liver Disease: A Population-Based Cohort Study of 3410 Persons. *Clin Gastroenterol Hepatol* 2022;**20**: 918-29 e8.

133. Ganne-Carrie N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. *J Hepatol* 2019;**70**: 284-93.

134. Ganne-Carrie N, Chaffaut C, Bourcier V, et al. Estimate of hepatocellular carcinoma incidence in patients with alcoholic cirrhosis. *J Hepatol* 2018;**69**: 1274-83.

135. Simon TG, Roelstraete B, Sharma R, et al. Cancer Risk in Patients With Biopsy-Confirmed Nonalcoholic Fatty Liver Disease: A Population-Based Cohort Study. *Hepatology* 2021;**74**: 2410-23.

136. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol* 2022;**23**: 521-30.

137. Bengtsson B, Stål P, Wahlin S, et al. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. *Liver Int* 2019;**39**: 1098-108.

138. Tansel A, Katz LH, El-Serag HB, et al. Incidence and Determinants of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2017;**15**: 1207-17 e4.

139. Natarajan Y, Tansel A, Patel P, et al. Incidence of Hepatocellular Carcinoma in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2021;**66**: 2439-51.

140. Elmberg M, Hultcrantz R, Ekbom A, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003;**125**: 1733-41.

141. EASL. Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;**69**: 182-236.

142. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017;**11**: 317-70.

143. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;**68**: 723-50.

144. van der Pol CB, Lim CS, Sirlin CB, et al. Accuracy of the Liver Imaging Reporting and Data System in Computed Tomography and Magnetic Resonance Image Analysis of Hepatocellular Carcinoma or Overall Malignancy-A Systematic Review. *Gastroenterology* 2019;**156**: 976-86.

145. Foerster F, Galle PR. Comparison of the current international guidelines on the management of HCC. *JHEP Rep* 2019;**1**: 114-9.

146. Kudo M. Management of Hepatocellular Carcinoma in Japan as a World-Leading Model. *Liver Cancer* 2018;**7**: 134-47.

147. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;**19**: 329-38.

148. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. *J Hepatol* 2022.

149. Jepsen P, West J. We need stronger evidence for (or against) hepatocellular carcinoma surveillance. *J Hepatol* 2021;**74**: 1234-9.

150. Moon AM, Weiss NS, Beste LA, et al. No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis. *Gastroenterology* 2018;**155**: 1128-39.e6.

151. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022;**76**: 681-93.

152. West HJ, Jin JO. JAMA Oncology Patient Page. Performance Status in Patients With Cancer. *JAMA Oncol* 2015;**1**: 998.

153. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;**334**: 693-9.

154. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;**33**: 1394-403.

155. Noren S, Bengtsson B, Hagstrom H, et al. Hepatocellular carcinoma in Stockholm, Sweden 2003-2018: a population-based cohort study. *Scand J Gastroenterol* 2022;**57**: 1080-8.

156. Pommergaard HC, Rostved AA, Adam R, et al. Vascular invasion and survival after liver transplantation for hepatocellular carcinoma: a study from the European Liver Transplant Registry. *HPB (Oxford)* 2018;**20**: 768-75.

157. Henriksson M, Bjornsson B, Sternby Eilard M, et al. Treatment patterns and survival in patients with hepatocellular carcinoma in the Swedish national registry SweLiv. *BJS Open* 2020;**4**: 109-17.

158. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology* 2018;**67**: 381-400.

159. de'Angelis N, Landi F, Carra MC, et al. Managements of recurrent hepatocellular carcinoma after liver transplantation: A systematic review. *World J Gastroenterol* 2015;**21**: 11185-98.

160. Sapisochin G, Goldaracena N, Astete S, et al. Benefit of Treating Hepatocellular Carcinoma Recurrence after Liver Transplantation and Analysis of Prognostic Factors for Survival in a Large Euro-American Series. *Ann Surg Oncol* 2015;**22**: 2286-94.

161. Roayaie S, Schwartz JD, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. *Liver Transpl* 2004;**10**: 534-40.

162. Kabir T, Tan ZZ, Syn NL, et al. Laparoscopic versus open resection of hepatocellular carcinoma in patients with cirrhosis: meta-analysis. *Br J Surg* 2021;**109**: 21-9.

163. Ivanics T, Claasen MP, Patel MS, et al. Long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma: A propensity score matched analysis of a high-volume North American center. *Surgery* 2022;**171**: 982-91.

164. Azoulay D, Ramos E, Casellas-Robert M, et al. Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension. *JHEP Rep* 2021;**3**: 100190.

165. Berardi G, Morise Z, Sposito C, et al. Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in Child-Pugh B cirrhosis. *J Hepatol* 2020;**72**: 75-84.

166. Reveron-Thornton RF, Teng MLP, Lee EY, et al. Global and regional long-term survival following resection for HCC in the recent decade: A meta-analysis of 110 studies. *Hepatology Communications* 2022;**6**: 1813-26.

167. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;**67**: 358-80.

168. Yang W, Yan K, Goldberg SN, et al. Ten-year survival of hepatocellular carcinoma patients undergoing radiofrequency ablation as a first-line treatment. *World J Gastroenterol* 2016;**22**: 2993-3005.

169. Bai X-M, Cui M, Yang W, et al. The 10-year Survival Analysis of Radiofrequency Ablation for Solitary Hepatocellular Carcinoma 5 cm or Smaller: Primary versus Recurrent HCC. *Radiology* 2021;**300**: 458-69.

170. Lee DH, Lee JM, Lee JY, et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology* 2014;**270**: 900-9.

171. Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021;**18**: 293-313.

172. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**: 378-90.

173. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;**391**: 1163-73.

174. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020;**382**: 1894-905.

175. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;**76**: 862-73.

176. Vogel A, Martinelli E, clinicalguidelines@esmo.org EGCEa, et al. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol* 2021;**32**: 801-5.

177. Bruix J, Chan SL, Galle PR, et al. Systemic treatment of hepatocellular carcinoma: An EASL position paper. *J Hepatol* 2021;**75**: 960-74.

178. Laube R, Sabih AH, Strasser SI, et al. Palliative care in hepatocellular carcinoma. *J Gastroenterol Hepatol* 2021;**36**: 618-28.

179. Nilsson E, Anderson H, Sargenti K, et al. Incidence, clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study. *Aliment Pharmacol Ther* 2016;**43**: 1330-9.

180. Gunnarsdottir SA, Olsson R, Olafsson S, et al. Liver cirrhosis in Iceland and Sweden: incidence, aetiology and outcomes. *Scand J Gastroenterol* 2009;**44**: 984-93.

181. Haukeland JW, Lorgen I, Schreiner LT, et al. Incidence rates and causes of cirrhosis in a Norwegian population. *Scand J Gastroenterol* 2007;**42**: 1501-8.

182. Dam Fialla A, Schaffalitzky de Muckadell OB, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: a population-based cohort study. *Scand J Gastroenterol* 2012;**47**: 702-9.

183. Olafsson S, Rognvaldsson S, Bergmann OM, et al. A nationwide population-based prospective study of cirrhosis in Iceland. *JHEP Rep* 2021;**3**: 100282.

184. Sahlman P, Nissinen M, Pukkala E, et al. Incidence, survival and cause-specific mortality in alcoholic liver disease: a population-based cohort study. *Scand J Gastroenterol* 2016;**51**: 961-6.

185. Jepsen P, Vilstrup H, Sorensen HT. Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study. *BMC Gastroenterol* 2008;**8**: 3.

186. Jepsen P, Lash TL, Vilstrup H. The clinical course of alcoholic cirrhosis: development of comorbid diseases. A Danish nationwide cohort study. *Liver Int* 2016;**36**: 1696-703.

187. Askgaard G, Fleming KM, Crooks C, et al. Socioeconomic inequalities in the incidence of alcohol-related liver disease: A nationwide Danish study. *Lancet Reg Health Eur* 2021;**8**: 100172.

188. Häkkinen E. Information on the Nordic alcohol market 2021. *Alko Inc* 2021.

189. Nilsson E, Anderson H, Sargenti K, et al. Clinical course and mortality by etiology of liver cirrhosis in Sweden: a population based, long-term follow-up study of 1317 patients. *Aliment Pharmacol Ther* 2019;**49**: 1421-30.

190. Hälsofrämjande och förebyggande arbete med hepatiter i Sverige. Public Health Agency of Sweden. [Accessed 2022 Dec 8]. Report in Swedish. Available from: https://www.folkhalsomyndigheten.se/contentassets/bd55953042c2430a88b4a9f47915dcd6/halsoframjande-forebyggande-arbete-hepatiter-sverige-2019.pdf 2019.

191. Blach S, Blome M, Duberg AS, et al. Hepatitis C elimination in Sweden: Progress, challenges and opportunities for growth in the time of COVID-19. *Liver Int* 2021;**41**: 2024-31.

192. Trolldal B, [Alcohol consumption in Sweden 2018. Report 184]. Centralförbundet för alkohol- och narkotikaupplysning, 2019.

193. [Hälsa på lika vilkor] Public Health Agency of Sweden [accessed 2022 Dec 8. Report in Swedish. Available at https://www.folkhalsomyndigheten.se/livsvillkor-levnadsvanor/fysisk-aktivitet-och-matvanor/overvikt-och-fetma/] 2022.

194. Andersson T, Ahlbom A, Carlsson S. Diabetes Prevalence in Sweden at Present and Projections for Year 2050. *PLoS One* 2015;**10**: e0143084.

195. Swedish national treatment program for hepatocellular carcinoma. 2022 (available at https://kunskapsbanken.cancercentrum.se/diagnoser/levercellscancer/vardprogram/).

196. Eilard MS, Naredi P, Helmersson M, et al. Survival and prognostic factors after transplantation, resection and ablation in a national cohort of early hepatocellular carcinoma. *HPB (Oxford)* 2021;**23**: 394-403.

197. Edenvik P, Davidsdottir L, Oksanen A, et al. Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice? *Liver Int* 2015;**35**: 1862-71.

198. Stravitz RT, Heuman DM, Chand N, et al. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. *Am J Med* 2008;**121**: 119-26.

199. Singal AG, Yopp AC, Gupta S, et al. Failure rates in the hepatocellular carcinoma surveillance process. *Cancer Prev Res (Phila)* 2012;**5**: 1124-30.

200. Walker M, El-Serag HB, Sada Y, et al. Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. *Aliment Pharmacol Ther* 2016;**43**: 621-30.

201. Yang JD, Ahmed Mohammed H, Harmsen WS, et al. Recent Trends in the Epidemiology of Hepatocellular Carcinoma in Olmsted County, Minnesota: A US Population-based Study. *J Clin Gastroenterol* 2017;**51**: 742-8.

202. Guss D, Sherigar J, Mohanty SR. Missed Diagnosis of Liver Cirrhosis Leads to Disparities in Care for Older Patients. *Gastroenterology Res* 2018;**11**: 333-9.

203. Wolf E, Rich NE, Marrero JA, et al. Use of Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis: A Systematic Review and Meta-Analysis. *Hepatology* 2021;**73**: 713-25.

204. Singal AG, Li X, Tiro J, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. *Am J Med* 2015;**128**: 90 e1-7.

205. Ventura-Cots M, Bataller R, Lazarus JV, et al. Applying an equity lens to liver health and research in Europe. *J Hepatol* 2022;**77**: 1699-710.

206. Rubin JB, Sundaram V, Lai JC. Gender Differences Among Patients Hospitalized With Cirrhosis in the United States. *J Clin Gastroenterol* 2020;**54**: 83-9.

207. Petrick JL, Florio AA, Znaor A, et al. International trends in hepatocellular carcinoma incidence, 1978-2012. *Int J Cancer* 2020;**147**: 317-30.

208. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. *Hepatology* 2021;**73 Suppl 1**: 4-13.

209. Singh N, Watt KD, Bhanji RA. The fundamentals of sex-based disparity in liver transplantation: Understanding can lead to change. *Liver Transplantation* 2022;**28**: 1367-75.

210. Oloruntoba OO, Moylan CA. Gender-based disparities in access to and outcomes of liver transplantation. *World J Hepatol* 2015;**7**: 460-7.

211. Locke JE, Shelton BA, Olthoff KM, et al. Quantifying Sex-Based Disparities in Liver Allocation. *JAMA Surg* 2020;**155**: e201129.

212. Nguyen GC, Thuluvath PJ. Racial disparity in liver disease: Biological, cultural, or socioeconomic factors. *Hepatology* 2008;**47**: 1058-66.

213. Singh GK, Hoyert DL. Social epidemiology of chronic liver disease and cirrhosis mortality in the United States, 1935-1997: trends and differentials by ethnicity, socioeconomic status, and alcohol consumption. *Hum Biol* 2000;**72**: 801-20.

214. Singh GK, Jemal A. Socioeconomic and Racial/Ethnic Disparities in Cancer Mortality, Incidence, and Survival in the United States, 1950-2014: Over Six Decades of Changing Patterns and Widening Inequalities. *J Environ Public Health* 2017;**2017**: 2819372.

215. Mathur AK, Schaubel DE, Zhang H, et al. Disparities in liver transplantation: the association between donor quality and recipient race/ethnicity and sex. *Transplantation* 2014;**97**: 862-9.

216. Ganesh S, Rogal SS, Yadav D, et al. Risk factors for frequent readmissions and barriers to transplantation in patients with cirrhosis. *PLoS One* 2013;**8**: e55140.

217. Nephew LD, Aitcheson G, Iyengar M. The Impact of Racial Disparities on Liver Disease Access and Outcomes. *Current Treatment Options in Gastroenterology* 2022;**20**: 279-94.

218. Taefi A, Spiewak T, Patel S, et al. Racial Disparities in Cirrhosis-Related Healthcare Outcomes Among Hospitalized Patients: 1129. *Official journal of the American College of Gastroenterology | ACG* 2018;**113**.

219. Spiewak T, Taefi A, Patel S, et al. Racial disparities of Black Americans hospitalized for decompensated liver cirrhosis. *BMC Gastroenterology* 2020;**20**: 245.

220. Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. *Eur J Cancer* 2010;**46**: 2647-59.

221. Mihor A, Tomsic S, Zagar T, et al. Socioeconomic inequalities in cancer incidence in Europe: a comprehensive review of population-based epidemiological studies. *Radiol Oncol* 2020;**54**: 1-13.

222. Lennartsson C, Lundberg O. 'What's marital status got to do with it?': gender inequalities in economic resources, health and functional abilities among older adults. In: Fritzell J, Lundberg O. *Health Inequalities and Welfare Resources: Continuity and Change in Sweden*ed.: Bristol University Press, 2006: 179-98.

223. Hank K, Steinbach A. Families and Health: A Review. In: Doblhammer G, Gumà J. *A Demographic Perspective on Gender, Family and Health in Europe*ed. Cham: Springer International Publishing, 2018: 23-39.

224. Liang Y, Wu X, Lu C, et al. Impact of marital status on the prognosis of liver cancer patients without surgery and the critical window. *Annals of Palliative Medicine* 2021;**10**: 2990-9.

225. Chen F, Wu Y, Xu He, et al. Impact of marital status on overall survival in patients with early-stage hepatocellular carcinoma. *Scientific Reports* 2022;**12**: 19923.

226. Zueras P, Rutigliano R, Trias-Llimós S. Marital status, living arrangements, and mortality in middle and older age in Europe. *International Journal of Public Health* 2020;**65**: 627-36.

227. Robards J, Evandrou M, Falkingham J, et al. Marital status, health and mortality. *Maturitas* 2012;**73**: 295-9.

228. Jepsen P, Vilstrup H, Andersen PK, et al. Socioeconomic status and survival of cirrhosis patients: a Danish nationwide cohort study. *BMC Gastroenterol* 2009;**9**: 35.

229. Petrovski BE, Szeles G, Melles M, et al. Behaviour does not fully explain the high risk of chronic liver disease in less educated men in Hungary. *Eur J Public Health* 2011;**21**: 662-6.

230. Kim HJ, Chu H, Lee S. Factors influencing on health-related quality of life in South Korean with chronic liver disease. *Health and Quality of Life Outcomes* 2018;**16**: 142.

231. Wu C, Chen P, Qian J-J, et al. Effect of marital status on the survival of patients with hepatocellular carcinoma treated with surgical resection: an analysis of 13,408 patients in the surveillance, epidemiology, and end results (SEER) database. *Oncotarget* 2016;**7**.

232. He XK, Lin ZH, Qian Y, et al. Marital status and survival in patients with primary liver cancer. *Oncotarget* 2017;**8**: 64954-63.

233. Wu W, Fang D, Shi D, et al. Effects of marital status on survival of hepatocellular carcinoma by race/ethnicity and gender. *Cancer Manag Res* 2018;**10**: 23-32.

234. Zhang W, Wang X, Huang R, et al. Prognostic value of marital status on stage at diagnosis in hepatocellular carcinoma. *Scientific Reports* 2017;**7**: 41695.

235. Glymour MM, Avendano M, Kawachi I. 17Socioeconomic Status and Health. In: Berkman LF, Kawachi I, Glymour MM. *Social Epidemiology*ed.: Oxford University Press, 2014: 0.

236. Blakely T, Hales S, Woodward A. Assessing the Distribution of Health Risks by Socioeconomic Position at National and Local Levels. World Health Organization 2004.

237. Conway D, McMahon A, Brown D, et al. Measuring socioeconomic status and inequalities. In: Vaccarella S, Lortet-Tieulent J, Saracci R, et al., editors. Reducing social inequalities in cancer: evidence and priorities for research. Lyon (FR): International Agency for Research on Cancer; 2019. (IARC Scientific Publications, No. 168.) Chapter 4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK566205/.

238. Zajacova A, Lawrence EM. The Relationship Between Education and Health: Reducing Disparities Through a Contextual Approach. *Annu Rev Public Health* 2018;**39**: 273-89.

239. Yngwe MA, Diderichsen F, Whitehead M, et al. The role of income differences in explaining social inequalities in self rated health in Sweden and Britain. *J Epidemiol Community Health* 2001;**55**: 556-61.

240. Dalmau-Bueno A, Garcia-Altes A, Mari-Dell'olmo M, et al. Trends in socioeconomic inequalities in cirrhosis mortality in an urban area of Southern Europe: a multilevel approach. *J Epidemiol Community Health* 2010;**64**: 720-7.

241. Scaglione S, Kliethermes S, Cao G, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. *J Clin Gastroenterol* 2015;**49**: 690-6.

242. Najman JM, Williams GM, Room R. Increasing socioeconomic inequalities in male cirrhosis of the liver mortality: Australia 1981-2002. *Drug Alcohol Rev* 2007;**26**: 273-8.

243. Allik M, Leyland A, Travassos Ichihara MY, et al. Creating small-area deprivation indices: a guide for stages and options. *J Epidemiol Community Health* 2020;**74**: 20-5.

244. Ministry of Housing, Communities & Local Government. English indices of deprivation., 2019.

245. Stromberg U, Baigi A, Holmen A, et al. A comparison of small-area deprivation indicators for public-health surveillance in Sweden. *Scand J Public Health* 2021: 14034948211030353.

246. Meijer M, Engholm G, Grittner U, et al. A socioeconomic deprivation index for small areas in Denmark. *Scand J Public Health* 2013;**41**: 560-9.

247. Havard S, Deguen S, Bodin J, et al. A small-area index of socioeconomic deprivation to capture health inequalities in France. *Soc Sci Med* 2008;**67**: 2007-16.

248. Sundquist K, Malmstrom M, Johansson SE. Neighbourhood deprivation and incidence of coronary heart disease: a multilevel study of 2.6 million women and men in Sweden. *J Epidemiol Community Health* 2004;**58**: 71-7.

249. Slachtová H, Tomásková H, Splíchalová A, et al. Czech socio-economic deprivation index and its correlation with mortality data. *Int J Public Health* 2009;**54**: 267-73.

250. Lillini R, Quaglia A, Vercelli M. [Building of a local deprivation index to measure the health status in the Liguria Region]. *Epidemiol Prev* 2012;**36**: 180-7.

251. Stromberg U. How can precision prevention be approached from a general population perspective within the field of cancer epidemiology? *Acta Oncol* 2021;**60**: 1272-4.

252. Kimenai DM, Pirondini L, Gregson J, et al. Socioeconomic Deprivation: An Important, Largely Unrecognized Risk Factor in Primary Prevention of Cardiovascular Disease. *Circulation* 2022;**146**: 240-8.

253. Hoebel J, Kroll LE, Fiebig J, et al. Socioeconomic Inequalities in Total and Site-Specific Cancer Incidence in Germany: A Population-Based Registry Study. *Front Oncol* 2018;**8**: 402.

254. Bryere J, Dejardin O, Bouvier V, et al. Socioeconomic environment and cancer incidence: a French population-based study in Normandy. *BMC Cancer* 2014;**14**: 87.

255. Bryere J, Dejardin O, Launay L, et al. Socioeconomic status and site-specific cancer incidence, a Bayesian approach in a French Cancer Registries Network study. *Eur J Cancer Prev* 2018;**27**: 391-8.

256. Weiderpass E, Pukkala E. Time trends in socioeconomic differences in incidence rates of cancers of gastro-intestinal tract in Finland. *BMC Gastroenterol* 2006;**6**: 41.

257. Hjerkind KV, Qureshi SA, Moller B, et al. Ethnic differences in the incidence of cancer in Norway. *Int J Cancer* 2017;**140**: 1770-80.

258. Ji J, Hemminki K. Variation in the risk for liver and gallbladder cancers in socioeconomic and occupational groups in Sweden with etiological implications. *Int Arch Occup Environ Health* 2005;**78**: 641-9.

259. Hemminki K, Li X. Level of education and the risk of cancer in Sweden. *Cancer Epidemiol Biomarkers Prev* 2003;**12**: 796-802.

260. Hemminki K, Mousavi SM, Brandt A, et al. Liver and gallbladder cancer in immigrants to Sweden. *Eur J Cancer* 2010;**46**: 926-31.

261. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**: 659-67.

262. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;**31**: 125-36.

263. Ludvigsson JF, Svedberg P, Olén O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European Journal of Epidemiology* 2019;**34**: 423-37.

264. Bengtsson B, Askling J, Ludvigsson JF, et al. Validity of administrative codes associated with cirrhosis in Sweden. *Scand J Gastroenterol* 2020;**55**: 1205-10.

265. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**: 450.

266. *European Commission. Revision of the European Standard Population — Report of Eurostat's task force. ISBN 978-92-79-31094-2*ed., 2013.

267. The Swedish Standard Classification of Occupations 2012 (SSYK 2012). *Statistics Sweden* 2012.

268. International Standard Classification of Occupations 2008 (ISCO-08): Structure, group definitions and correspondence tables. *International Labour Office* 2012.

269. Kruskal WH, Wallis WA. Use of Ranks in One-Criterion Variance Analysis. *Journal of the American Statistical Association* 1952;**47**: 583-621.

270. Miettinen OS. Survival analysis: up from Kaplan-Meier-Greenwood. *Eur J Epidemiol* 2008;**23**: 585-92.

271. Trolldal B, Guttormsson U, Leifman H. Registered and unregistered alcohol in the counties of Sweden 2001-2016. Rapport 165. Centralförbundet för alkohol- och narkotikaupplysning. 2017.

272. Hagstrom H, Lindfors A, Holmer M, et al. Etiologies and outcomes of cirrhosis in a large contemporary cohort. *Scand J Gastroenterol* 2021;**56**: 727-32.

273. Nasr P, Ndegwa N, von Seth E, et al.: Incidence, prevalence and mortality of chronic liver diseases in Sweden between 2005 and 2019 *The International Liver Congress 2022* 2022; 77:S82-S.

274. Vaz J. NAFLD cirrhosis in Sweden. *Scand J Gastroenterol* 2021;**56**: 940-1.

275. Mackenbach JP, Stirbu I, Roskam AJ, et al. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 2008;**358**: 2468-81.

276. Darin-Mattsson A, Fors S, Kareholt I. Different indicators of socioeconomic status and their relative importance as determinants of health in old age. *Int J Equity Health* 2017;**16**: 173.

277. Burton A, Balachandrakumar VK, Driver RJ, et al. Regional variations in hepatocellular carcinoma incidence, routes to diagnosis, treatment and survival in England. *Br J Cancer* 2022;**126**: 804-14.

278. Stenbacka M, Allebeck P, Brandt L, et al. Intravenous drug abuse in young men: risk factors assessed in a longitudinal perspective. *Scand J Soc Med* 1992;**20**: 94-101.

279. Hagström H, Thiele M, Sharma R, et al. Risk of Cancer in Biopsy-Proven Alcohol-Related Liver Disease: A Population-Based Cohort Study of 3410 Persons. *Clin Gastroenterol Hepatol* 2022;**20**: 918-29.e8.

280. Collins SE. Associations Between Socioeconomic Factors and Alcohol Outcomes. *Alcohol Res* 2016;**38**: 83-94.

281. Hemmingsson T, Lundberg I, Romelsjo A, et al. Alcoholism in social classes and occupations in Sweden. *Int J Epidemiol* 1997;**26**: 584-91.

282. Norstrom T, Romelsjo A. Social class, drinking and alcohol-related mortality. *J Subst Abuse* 1998;**10**: 385-95.

283. Talens M, Tumas N, Lazarus JV, et al. What Do We Know about Inequalities in NAFLD Distribution and Outcomes? A Scoping Review. *J Clin Med* 2021;**10**.

284. Konfortion J, Coupland VH, Kocher HM, et al. Time and deprivation trends in incidence of primary liver cancer subtypes in England. *J Eval Clin Pract* 2014;**20**: 498-504.

285. Major JM, Sargent JD, Graubard BI, et al. Local geographic variation in chronic liver disease and hepatocellular carcinoma: contributions of socioeconomic deprivation, alcohol retail outlets, and lifestyle. *Ann Epidemiol* 2014;**24**: 104-10.

286. Taflin H, Hafstrom L, Holmberg E, et al. The impact of increased immigration to Sweden on the incidence and treatment of patients with HCC and underlying liver disease. *Scand J Gastroenterol* 2019;**54**: 746-52.

287. Thøgersen H, Møller B, Robsahm TE, et al. Comparison of cancer stage distribution in the immigrant and host populations of Norway, 1990-2014. *Int J Cancer* 2017;**141**: 52-61.

288. Stromberg U, Parkes BL, Baigi A, et al. Small-area data on socioeconomic status and immigrant groups for evaluating equity of early cancer detection and care. *Acta Oncol* 2021;**60**: 347-52.

289. Karim MA, Singal AG, Kum HC, et al. Clinical Characteristics and Outcomes of Nonalcoholic Fatty Liver Disease-Associated Hepatocellular Carcinoma in the United States. *Clin Gastroenterol Hepatol* 2022.

290. Bertot LC, Jeffrey GP, Wallace M, et al. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. *Hepatol Commun* 2017;**1**: 53-60.

291. Marquardt P, Liu PH, Immergluck J, et al. Hepatocellular Carcinoma Screening Process Failures in Patients with Cirrhosis. *Hepatol Commun* 2021;**5**: 1481-9.

292. Cucchetti A, Garuti F, Pinna AD, et al. Length time bias in surveillance for hepatocellular carcinoma and how to avoid it. *Hepatol Res* 2016;**46**: 1275-80.

293. Cucchetti A, Trevisani F, Pecorelli A, et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *J Hepatol* 2014;**61**: 333-41.

294. Hemmingsson E, Ekblom O, Kallings LV, et al. Prevalence and time trends of overweight, obesity and severe obesity in 447,925 Swedish adults, 1995-2017. *Scand J Public Health* 2021;**49**: 377-83.

295. Hagstrom H, Adams LA, Allen AM, et al. Administrative Coding in Electronic Health Care Record-Based Research of NAFLD: An Expert Panel Consensus Statement. *Hepatology* 2021;**74**: 474-82.

296. Narcotis use in Sweden. Public Health Agency of Sweden. 2010.

297. Arrese M. Nonalcoholic fatty liver disease: liver disease: an overlooked complication of diabetes mellitus. *Nat Rev Endocrinol* 2010;**6**: 660-1.

298. Bergram M, Nasr P, Iredahl F, et al. Low awareness of non-alcoholic fatty liver disease in patients with type 2 diabetes in Swedish Primary Health Care. *Scand J Gastroenterol* 2022;**57**: 60-9.

299. Blond E, Disse E, Cuerq C, et al. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral? *Diabetologia* 2017;**60**: 1218-22.

300. Hagstrom H, Marschall HU, Ekstedt M. Investigation and management of fatty liver disease. Swedish National guidelines. 2020.

301. Kechagias S, Ekstedt M, Simonsson C, et al. Non-invasive diagnosis and staging of non-alcoholic fatty liver disease. *Hormones (Athens)* 2022;**21**: 349-68.

302. Srivastava A, Gailer R, Tanwar S, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol* 2019;**71**: 371-8.

303. Balkhed W, Aberg FO, Nasr P, et al. Repeated measurements of non-invasive fibrosis tests to monitor the progression of non-alcoholic fatty liver disease: A long-term follow-up study. *Liver Int* 2022;**42**: 1545-56.

304. Hagstrom H, Kechagias S, Ekstedt M. Risk for hepatic and extra-hepatic outcomes in nonalcoholic fatty liver disease. *J Intern Med* 2022;**292**: 177-89.

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