Risk of hepatocellular carcinoma in Danish outpatients with alcoholic cirrhosis: a nationwide cohort study

Peter Jepsen (1, 2), Frederik Kraglund (1), Joe West (3,4), Gerda E. Villadsen (1), Henrik Toft Sørensen (2), Hendrik Vilstrup (1)

1. Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark.
2. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
3. Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom.
4. NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom.

Corresponding author: Peter Jepsen, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark. E-mail: pj@clin.au.dk. Telephone: +45 2425 2944.

Keywords: Liver cirrhosis; primary liver cancer; prognosis; screening; epidemiology.

Conflicts of interest: None.

Electronic word count: 5994 (including abstract, references, tables, and figure legends)

Numbers of figures and tables: 3 figures, 2 tables.

Conflict of interest statement: None.

Financial support statement: Peter Jepsen was supported by grants from the Novo Nordisk Foundation (NNF18OC0054612) and the Danish Cancer Society (R208-A12410). The funding organizations were not involved in the design and conduct of the study, or in the decision to submit the manuscript for publication.

Authors contributions: Peter Jepsen conceived the study, conducted the analysis, and drafted the manuscript. All authors have contributed to the interpretation of the results and revised the manuscript for important intellectual content.

ABSTRACT

Background and aims: Accurate estimates of the risk of hepatocellular carcinoma (HCC) in patients with cirrhosis are important for clinical decisions about HCC surveillance. We described HCC risk among outpatients with alcoholic cirrhosis and contrasted the risk of death from HCC with the risk of death from variceal bleeding or trauma.

Methods: This was a nationwide, registry-based historical cohort study between 2006 and 2018. We included all Danish outpatients with a hospital diagnosis of alcoholic cirrhosis, except those with cancer, those with chronic viral hepatitis or autoimmune liver disease, and those older than 80 years. We followed them through 2018 and described the cumulative risk of HCC and the cumulative risk of death from HCC, variceal bleeding, or trauma.

Results: Of the 4553 included patients, 181 developed HCC and 2274 died. The cumulative risk of HCC was 0.9% (95% confidence interval [CI] 0.7 to 1.3) after 1 year, 3.6% (95% CI 3.0 to 4.2) after 5 years, and 6.0% (95% CI 5.1 to 7.0) after 10 years, or approximately 0.7% per year. Male gender, older age, and decompensated cirrhosis predicted a higher HCC risk. After 10 years, 6.9% of deaths in the cohort could be attributed to HCC, whereas 6.5% could be attributed to variceal bleeding, and 5.0% to trauma.

Conclusions: In 2006–2018, Danish outpatients with alcoholic cirrhosis had an HCC risk of 0.7% per year, and they were nearly as likely to die from variceal bleeding or from trauma as from HCC. The implications are that many potentially harmful examinations are required for every HCC found through surveillance, so interventions targeting the prevention of other causes of death might be more cost-effective.

LAY SUMMARY

We described the risk of hepatocellular carcinoma (HCC, the commonest form of liver cancer originating in the liver) in Danish outpatients with liver cirrhosis due to harmful alcohol consumption. Accurate data on that risk are important for patient counselling and decisions about screening for HCC. The risk was about 0.7% per year, which is lower than might be expected and suggests that many potentially harmful screening examinations are required for every HCC found through surveillance.

INTRODUCTION

Alcoholic cirrhosis is a strong risk factor for hepatocellular carcinoma (HCC), and current United States and European guidelines recommend that patients with alcoholic cirrhosis be offered surveillance with an ultrasound examination every 6 months.[1,2] The recommendation rests on observational studies and simulations that have identified a lower limit of 1.5% risk per year for cost-effective HCC surveillance.[2] It is therefore unfortunate that studies of HCC risk continue to rely on the Kaplan-Meier method to describe HCC risk,[3] despite the fact that it overestimates HCC risk substantially.[4]

We have previously reported that the HCC risk was as low as 0.25% per year for Danish patients diagnosed with alcoholic cirrhosis in 1993–2005 and followed through 2009.[5] In England it was even lower.[6] HCC incidence has risen in the Danish general population since 2009,[7] and it was a limitation of our former study that we did not consider cirrhosis severity; current HCC guidelines note that patients with the most severe cirrhosis (Child-Pugh class C) should not be offered surveillance.[1,2] Given this background, we described the risk of HCC for patients with alcoholic cirrhosis who would be candidates for HCC surveillance. Our aim was to provide accurate up-to-date information and context for informed decisions about HCC surveillance.

PATIENTS AND METHODS

Data sources

We used data from nationwide Danish healthcare databases.[8] The National Patient Registry includes data from inpatient and outpatient hospital contacts. For every contact, the treating physician specifies one primary diagnosis and up to twenty secondary diagnoses, coded according to the International Classification of Diseases, Tenth Revision (ICD-10). The National Patient Registry also contains records of all surgical procedures and imaging examinations.[9] In addition, we used

data from the Cancer Registry,[10] the Cause of Death Registry,[11] the National Prescription Registry,[12] and the Civil Registration System.[13] Together, the registries provided individual-level data on diagnoses, surgical and endoscopic procedures, imaging examinations, prescription drug use, and dates and causes of death. The Cancer Registry records HCC stage according to the TNM staging system. According to Danish law, studies based entirely on data from registries require neither ethical approval nor patient consent.

Study cohort

We included all Danish citizens who 1) were followed as outpatients for alcoholic cirrhosis between 1 January 2006 and 31 December 2017, 2) had received their first diagnosis of alcoholic cirrhosis exactly 6 months previously, 3) had not previously been diagnosed with any cancer, 4) had not within the previous 5 years received a diagnosis code for autoimmune liver disease or chronic viral hepatitis, and 5) were younger than 80 years. These patients were followed from the index date which was 6 months after the date of their first diagnosis of alcoholic cirrhosis.

We categorized the patients as compensated or decompensated. Patients categorized as having decompensated cirrhosis had one or more of the following before or on the index date: a diagnosis code for ascites, variceal bleeding, or hepatorenal syndrome; a procedure code for banding ligation/sclerotherapy of varices or for ascites puncture or drainage; or redemption of a prescription for spironolactone and furosemide, or for nonselective beta-blockers. The remaining patients were categorized as having compensated cirrhosis. All codes used in the study are shown in Supplementary Table 1.

We identified all patients' ultrasound, CT, or MRI examinations of the liver, upper abdomen, or entire abdomen. Finally, we extracted information about HCC treatments given with curative intent, defined as resection, ablation, or transplantation.

Study design

Patients were followed from the index date until death or censoring on 31 December 2018. Other reasons for ending follow-up were defined by multistate models.[4] Our first model had four states: 'Alive' (literally, alive without HCC and without liver transplantation), 'Liver transplant', 'HCC', and 'Dead' (Supplementary Figure 1A). We used it to compute the risk of HCC (literally, risk of HCC before liver transplantation) in the full cohort. We defined HCC as a primary diagnosis code of HCC (C22.0) in the National Patient Registry or in the Cancer Registry. The earlier of the two registry records was the HCC diagnosis date.

Our second model had five states because it divided the 'Alive' state in two by cirrhosis severity (compensated or decompensated) (Supplementary Figure 1B). Patients were moved from the compensated to the decompensated state on the earliest date they fulfilled the criteria for decompensated cirrhosis given above, and they could not re-compensate. Thus, the risk of HCC for patients with compensated cirrhosis was literally 'the risk of developing HCC without having decompensated and before liver transplantation', which is clinically relevant if HCC surveillance is restricted to patients with compensated cirrhosis.

The multistate model shown in Supplementary Figure 2 was used in an analysis contrasting the risk of death from HCC with the risk of death from other causes. By our definition, all decedents who had been diagnosed with HCC died from HCC. For comparison, we identified deaths less than 30 days after hospitalization for variceal bleeding or trauma as being attributable to those causes.

We used the multistate model shown in Supplementary Figure 3 in an analysis describing the proportion of surviving patients who had had a liver imaging examination (ultrasound, CT, or MRI) within the previous 6 months. We had no data on the indication for the examination, but HCC surveillance was not recommended by Danish guidelines during the period of the study.[14] Patients

were in the 'Alive with recent liver imaging' for 6 months after a liver imaging examination, and then they transited to 'Alive without recent liver imaging' and stayed there until their next examination.

Statistical analysis

Our goals were description and prediction, not causal inference.[15] We aimed to describe the risk of HCC in the total cohort and within strata defined by key characteristics: gender, age, cirrhosis severity, and calendar year. In our analyses of multistate disease models, we used the cumulative incidence function to compute the risk of making a specific transition from one disease state to the next. We used the Aalen-Johansen method to compute the probability of being in a specific state at a specific time during the follow-up.[4,16] The Kaplan-Meier estimator was used in analyses of all-cause mortality. We computed HCC incidence rates and rates of liver imaging examinations (separately for ultrasound and CT/MRI) for every calendar year of the study period to examine time trends. In this analysis, patients could have multiple imaging examinations during the follow-up, but examinations conducted on the same day counted as one examination. We computed the risk of HCC per year as the cumulative risk of HCC after x years divided by x. This is not a formal statistical procedure, but we used it to facilitate comparison with international guidelines.[1,2]

We estimated predicted probabilities of HCC for patients of varying gender, age, and cirrhosis severity. These predictions were based on a Fine & Gray regression model including gender, current age, current cirrhosis severity, and current calendar year as predictors of the subdistribution hazard ratio for HCC. Age, cirrhosis severity, and calendar year were time-dependent variables, and age and calendar year were included as linear variables. Predictions were subsequently computed as described by Therneau.[17]

Sensitivity analysis

We expanded our definition of HCC to explore how our estimates of HCC risk could have been affected by the possibility that some HCCs had been overlooked or diagnosed but miscoded. We added the following: 1) HCCs coded as a secondary diagnosis in the National Patient Registry; 2) cancers with a diagnosis code of C22.9 (unspecified primary liver cancer) in the Cancer Registry or as a primary or secondary diagnosis in the National Patient Registry; and 3) HCCs or unspecified primary liver cancers recorded only in the Cause of Death Registry. In this last case we used the date of death as the date of HCC diagnosis.

We used multistate modeling to explore the extent to which we underestimated HCC risk by assuming that an HCC did not exist before it was diagnosed. With this approach, the data are thought to represent snapshots of an underlying disease process that progresses through clinically defined states,[18] here from 'alive, no HCC' to 'death' with the possibility of transitioning through an intermediate 'alive with HCC' state. The snapshots were the dates of imaging examinations, HCC diagnosis, and death. We assumed the following: HCCs might have developed before they were diagnosed; patients who died or were censored might have developed an undiagnosed HCC; dates of death were exact; patients might have HCC on the date of a CT or MRI examination, or on the date of an ultrasound examination that was followed within 14 days by a CT or MRI examination; and patients did not have HCC on the date of other ultrasound examinations. This approach must yield higher estimates of HCC risk than our primary analysis because it allowed for undiagnosed HCCs. We modeled the effects of gender, age, cirrhosis severity, and calendar year on the transition rates using the 'msm' package for R,[18] and we used them to compute predicted probabilities of HCC development for various patient characteristics.

We conducted our primary analysis restricting it to patients who at inclusion were followed at either of Denmark's two departments specialized in hepatology (Copenhagen, department code 130115;

Aarhus, department codes 700336 and 662036), and who had also received their first diagnosis of alcoholic cirrhosis at the same departments. The purpose of this analysis was to examine whether patients followed by specialists were more likely to be diagnosed with HCC.

Finally, we repeated our primary analysis excluding variceal bleeding as a criterion defining decompensation. Patients with variceal bleeding alone have a lower mortality than patients with ascites or hepatic encephalopathy,[19] so it may be more appropriate to consider them as being part of the population who should be under surveillance Specifically, for this purpose, we removed variceal bleeding, banding ligation/sclerotherapy, and nonselective beta-blockers from the criteria defining decompensation.

RESULTS

We included 4553 patients. Their median age was 59.3 years at inclusion (interquartile range 52.5–65.2), 67% were men, and 22% had compensated cirrhosis (Table 1). Men below the age of 60 years constituted 36% percent of the cohort. During 18,384 person-years of follow-up, 2274 patients died (mortality rate = 124 per 1000 person-years). All-cause mortality was 12% after 1 year, 46% after 5 years, and 71% after 10 years. It was higher for those who were decompensated as opposed to compensated at inclusion: 13% vs. 9% after 1 year, 48% vs. 39% after 5 years, and 74% vs. 62% after 10 years (Supplementary Figure 4).

During the follow-up 41 patients received a liver transplant, and 181 were diagnosed with HCC. Of those 181 patients, 19 had compensated cirrhosis and 162 had decompensated cirrhosis, including 20 patients who presented with compensated cirrhosis but decompensated during follow-up and were diagnosed with HCC after that. The cumulative risk of HCC was 0.9% (95% confidence interval [CI] 0.7 to 1.3) after 1 year, 3.6% (95% CI 3.0 to 4.2) after 5 years, and 6.0% (95% CI 5.1 to 7.0) after 10 years. Thus, the average risk per year was around 0.7%, slightly higher in the first 5

years, slightly lower thereafter (Figure 1, left). HCC risk was much higher for men than for women (5-year risk = 4.6% [95% CI 3.8 to 5.5] vs. 1.4% [95% CI 0.9 to 2.2], Figure 1, left), and lower for patients with compensated cirrhosis (5-year risk = 2.2% [95% CI 1.3 to 3.4] vs. 3.5% [95% CI 2.8 to 4.1], Figure 1, right). The 3-year outcomes of the 980 patients with compensated cirrhosis were: 1.4% developed HCC, 0.1% was transplanted, 33.4% decompensated, 12.9% died without HCC, and 52.2% did not experience any event.

In the full cohort of 4553 patients, deaths from HCC accounted for 5.5% of all deaths after 5 years, and for 6.9% of all deaths after 10 years. Deaths after variceal bleeding (6.5% of deaths after 10 years) or after trauma (5.0%) were nearly as frequent (Figure 2). Among men, the proportion of all deaths attributable to HCC was 8.6% after 10 years, while among women this proportion was 3.0%. The registered causes of death are presented in Supplementary Table 2.

Of the 19 patients with compensated cirrhosis who developed HCC, only 5 (26%) were treated with curative intent, all with tumor ablation. Of those 5 patients, 3 had T1 or T2 HCC, and 2 did not have the TNM stage recorded. Of the other 14 patients, 2 had T4 HCC and extrahepatic spread, 2 had T3 HCC, 5 had T1 or T2 HCC, and 5 did not have the TNM stage recorded. Supplementary Figure 5 shows the imaging examinations done from the beginning of follow-up to the date of HCC diagnosis.

The proportion of surviving patients with a liver imaging examination within the previous 6 months was 63% at the beginning of follow-up, and then rapidly declined to 24% after 1 year to decline more slowly to 20% after 5 years and 16% after 10 years (Supplementary Figure 6). It increased during the study period, from less than 10% in 2007 to 25% by the end of 2018 (Supplementary Figure 7). Of the 402 patients who had their first variceal bleeding during the follow-up, 73% had a liver imaging examination less than 6 months before or after that bleeding episode. Of the 2137

patients who died without having been diagnosed with HCC, 64% had had a liver imaging examination less than 6 months before death.

Time-trends in HCC incidence

The incidence rate of HCC was 10.0 per 1000 person-years (95% CI 8.6 to 11.5), with an increasing trend during the 2008–2013 period followed by stabilization. The rates of ultrasound and CT/MRI examinations of the liver rose continuously, reaching a combined rate of nearly 1000 per 1000 person-years in 2018, i.e., 1 examination per patient per year (Figure 3).

Predicted HCC risks

Male gender (subdistribution hazard ratio [sHR] = 3.08, 95% CI 2.02 to 4.70), older age (sHR = 1.06 per year, 95% CI 1.04 to 1.08), and later calendar year (sHR = 1.06 per year, 95% CI 1.01 to 1.11) were risk factors for HCC. Decompensated cirrhosis also predicted a higher risk of HCC, but this association did not reach statistical significance (sHR = 1.51, 95% CI 0.94 to 2.43). For women, all predicted risks were below 1% per year. Only men aged 70 years or older had a predicted HCC risk reaching 1.5% per year (Table 2).

Sensitivity analysis

Via our expanded definition of HCC we identified 33 possible HCCs, bringing the total to 214. With this expanded HCC definition, the cumulative risk of HCC was 1.2% (95% CI 0.9 to 1.6) after 1 year, 4.2% (95% CI 3.6 to 4.9) after 5 years, and 7.0% (95% CI 5.9 to 8.2) after 10 years. When instead we used the snapshot approach allowing for undiagnosed HCCs, we found that the cumulative risk of HCC was 1.0% (95% CI 0.9 to 1.3) after 1 year, 4.3% (95% CI 3.5 to 5.1) after 5 years, and 6.7% (95% CI 5.6 to 8.1) after 10 years. With this approach, younger men (60 years or older) had a predicted risk of HCC approaching 1.5% per year, but still no women did

(Supplementary Table 3). Restricting the analysis to patients followed by hepatologists, the 5-year risk of HCC was 4.6% (95% CI 3.1 to 6.5) vs. 3.6% (95% CI 3.0 to 4.2) in the primary analysis, and the mortality rate was 133 per 1000 person-years vs. 124 per 1000 person-years in the primary analysis. When we excluded variceal bleeding from the definition of decompensation, the 5-year risk of HCC among those with compensated alcoholic cirrhosis rose from 2.2% (95% CI 1.3 to 3.4) to 3.2% (95% CI 2.3 to 4.3), and the predicted 5-year risk of HCC for a 60-year old man with compensated alcoholic cirrhosis in the year 2018 rose from 3.7% (95% CI 1.8 to 5.5) to 5.4% (95% CI 3.4 to 7.4).

DISCUSSION

We described HCC risk and found that Danish outpatients with alcoholic cirrhosis had a low risk of HCC (0.7% per year). We predicted HCC risks for patients of varying gender, age, and cirrhosis severity and found that only men aged 70 years or older can be expected to have an HCC risk of 1.5% per year or higher. Sensitivity analyses including possible or undiagnosed HCCs yielded HCC risks around 0.9% per year and indicated that also men aged 60 years could potentially have an HCC risk of 1.5% per year. After 10 years, 6.9% of deaths in this population could be attributed to HCC, 6.5% to variceal bleeding, and 5.0% to trauma.

Current recommendations about HCC surveillance rely on estimates of HCC risk. We may have underestimated the true HCC risk if our patients did in fact not have cirrhosis, or if we failed to identify HCCs. The reported positive predictive value for a registry diagnosis code for alcoholic cirrhosis is around 80%,[20-22] but it was likely higher in this study because we included only patients who were given the diagnosis code twice. Moreover, most of our patients had additional codes for diagnoses, procedures, or medical treatments that corroborated the cirrhosis diagnosis. It remains possible that some patients did in fact have alcoholic hepatitis without cirrhosis, and therefore a

lower risk of HCC, but we are confident that the vast majority of our patients in fact had alcoholic cirrhosis. The completeness of the Cancer Registry ensured that all diagnosed HCCs were captured, and we supplemented Cancer Registry data with primary diagnosis codes from the National Patient Registry. Adding possible or undiagnosed HCCs, or restricting the analysis to patients followed by specialists, raised the estimates of HCC risk, but did not change the conclusion that only men, and only the older of them, have an HCC risk above 1.5% per year.

We categorized patients as compensated or decompensated and found that 79% had decompensated before study inclusion. This high proportion is similar to what we found in our 2010 study based on data from patients' medical charts (76%),[19] indicating that our definition was valid. Nonetheless, it is a limitation of our study that we could not categorize patients by Child-Pugh class, which is the categorization used in current HCC guidelines. It is an additional limitation that we could not determine whether patients were fit to receive HCC surveillance although in truth this is not easy to determine without individualized assessment.

Our patients with compensated cirrhosis had nearly as high all-cause mortality as those with decompensated cirrhosis. A recent regional study from Sweden found the same, an all-cause mortality hazard ratio for patients presenting with decompensated vs. compensated cirrhosis of only 1.13 (95% CI 0.95 to 1.35).[23] Probably, many patients who present with compensated alcoholic cirrhosis decompensate early despite the clinical care they receive. In our Danish study using data from medical records,[19] we found virtually the same mortality hazard ratio, 1.16 (95% CI 0.88 to 1.52), and within 1 year 22% of compensated patients decompensated while 10% died without having decompensated. At 5 years the numbers were 49% and 22%, respectively. Such a poor prognosis resonates with what we find here for patients with compensated alcoholic cirrhosis: within 3 years 33.4% of patients decompensated, and 12.9% died without HCC. Moreover, only 5 of 19 patients with compensated cirrhosis could be offered curative treatment for HCC. Why so

few? Although only 12 of the 19 patients had data on TNM stage, we could show that some had too advanced HCC (4 patients had T3 or T4 HCC), while others must have had too advanced cirrhosis or comorbidities (5 patients had T1 or T2 HCC yet were not treated with curative intent). These observations indicate that even our patients with compensated cirrhosis had severely reduced liver function.

The HCC risks presented here are lower than those reported by Ganne-Carrie et al. for a French cohort with Child-Pugh class A alcoholic cirrhosis.[24] In the French study, the HCC incidence rate was 29 per 1000 person-years and the HCC risk was approximately 2.6% per year. A key difference is that we included all Danish patients meeting our inclusion criteria, whereas patients in the Ganne-Carrie study were recruited from 28 specialist centers. This raises the question of selection bias. First, the French patients included in the study could have had a higher HCC risk than French patients who met the same inclusion criteria but were not included. Second, 23.5% of the patients in the French study were lost to follow-up. Assumptions about these patients' mortality and HCC risk have a strong effect on estimates of HCC risk: If in fact they died soon after dropping out, HCC risk would have been considerably lower than what was reported. Estimates of HCC risk can be severely upward-biased if deaths without HCC are not identified, as in the study from France, or if they are not accounted for in the analysis, as in the study from Spain by Mancebo et al. or the study from the United States by Ioannou et al.[3,4,25] The above-mentioned Swedish study did not have any of those shortcomings.[26] In that cohort the incidence rate of HCC was 15 per 1000 person-years (Harald Anderson, personal communication), which is higher than the 10 per 1000 person-years in our cohort, but random variation might explain this difference in HCC incidence rate between Sweden and Denmark.

It is conceivable that there is true geographic variation in HCC incidence, attributable to differences in the prevalence of HCC risk factors. The PNPLA3 gene is the strongest known genetic risk factor

for HCC development, but there are no data on geographic differences in its prevalence in patients with alcoholic cirrhosis. However, a recent review indicated that the prevalence of the risk variant is very similar throughout Europe and in the United States.[27] Environmental risk factors for HCC, like aflatoxin exposure, also cannot explain the differences between low-risk countries like Denmark, Sweden, and England and high-risk countries like France, Spain, and the United States.[28] Differences in the prevalence of comorbidity, primarily diabetes,[3] of chemopreventive drugs like statins and metformin, and of coffee consumption or tobacco smoking may have contributed.[29]

Our study showed that HCC incidence increased in parallel with liver imaging examinations until around 2013. We speculate that some HCCs were overlooked before that, but identification is now more complete, as indicated by the flattening of the HCC incidence rate curve despite the increasing use of liver imaging examinations. The structural change underlying these trends was the introduction of a Cancer Patient Pathway for primary liver cancer in 2009.[30,31] That pathway allows general practitioners to refer patients with cirrhosis and a focal liver lesion to urgent workup led by HCC specialists. Pathways for other cancers have been introduced, and although they do not affect the true incidence of HCC, they increase the number of imaging examinations that are being done, and it probably means that fewer HCCs are overlooked. We showed that the proportion of patients under surveillance increased during the study period, but in our clinical experience imaging examinations are primarily done in patients with perceived high risk of HCC. We acknowledge that a substantial proportion of our cohort did not have imaging examinations during the follow-up, and that it remains possible that we underestimated the incidence of HCC. Autopsy is very rarely conducted, and the incomplete examination of patients remains a limitation of our study.

We see four candidate explanations to the relatively low HCC risk in our population: First, it could be explained by the high mortality among patients with compensated alcoholic cirrhosis, which itself might be a Northern European characteristic. Second, it could be explained by our failure to

diagnose HCCs. However, we believe that our findings are a reasonably pragmatic reflection of the natural history of HCC development and clinical presentation in alcoholic cirrhosis. With complete ascertainment of HCCs we would inevitably have HCC overdiagnosis, i.e., we would have diagnosed HCCs that would not have had any impact on the patient's quality or quantity of life had it not been diagnosed.[32] Third, it could be explained by true geographic variation in HCC incidence. Fourth, it could be an artifact, the result of differences in data availability and analysis. We speculate that this fourth possibility explains the majority of the apparent geographical variation.

Does HCC surveillance provide value for money? Assume that for 3 years we offer HCC surveillance to 1000 patients with compensated alcoholic cirrhosis. Based on our findings, 14 will be diagnosed with HCC, 1 will be transplanted, 334 will decompensate and thus leave the surveillance program, and 129 will die without HCC. Of the 14 patients with HCC, 26% would receive curative treatment under our current standard of care, so 74% of patients with HCC benefit from surveillance, assuming optimistically that ultrasound screening has 100% sensitivity for small HCCs. More realistically, the sensitivity is 47%,[33] so we estimate that 14*0.74*0.47 = 5 patients benefit per 1000 offered HCC surveillance for 3 years. The base costs are 522 patients * 2 examinations per patient per year * 3 years + 478 patients * 2 examinations per patient per year * 1.5 years = 4566 ultrasound examinations, assuming that those who experience an event do so halfway through the surveillance period. Atiq et al. followed 523 cirrhosis patients who were offered HCC surveillance for 3 years and received at least one ultrasound examination; 119 (23%) of them experienced harm, primarily due to diagnostic CT and MRI scans for false-positive or indeterminate screening results.[34] We may consequently assume that at least 230 of our hypothetical 1000-patient cohort will experience harm, thus adding costs and potentially reducing quality of life. An analysis such as this is by no means definitive, but it is consistent with a recent review which estimated that 400 patients with cirrhosis must be surveilled to prevent one death,[35] and it provides

an argument for restricting HCC surveillance to high-risk populations.[33] We found that male gender, older age, and severity of portal hypertension predicted a higher risk of HCC development, and that is consistent with two recent North American studies.[3,36] Now further studies are needed to determine the efficacy and cost-effectiveness of offering HCC surveillance to older men with decompensated alcoholic cirrhosis, who also have a high mortality from non-HCC causes.

We speculate that other interventions could provide better value for money than HCC surveillance. One possibility is to provide wider access to early insertion of a transjugular intrahepatic portosystemic shunt to manage acute variceal bleeding.[37,38] Another possibility is to improve the treatment of alcohol use disorders. It could potentially prevent both trauma and variceal bleeding, and improve quality of life, too, but we recognize that the evidence in this field is limited.[39]

In conclusion, we found that HCC plays a relatively small role in the clinical course of alcoholic cirrhosis, particularly among female patients. The resources spent on HCC surveillance might be better spent on other interventions to improve quantity and quality of life.

REFERENCES

[1] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-380.

[2] European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.

[3] Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019;71:523-533.

[4] Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology 2015;62:292-302.

[5] Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: A Danish nationwide cohort study. Ann Intern Med 2012;156:841-847.

[6] West J, Card TR, Aithal GP, Fleming KM. Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: A population-based cohort study. Aliment Pharmacol Ther 2017;45:983-990.

[7] Jepsen P, Andersen MW, Villadsen GE, Ott P, Vilstrup H. Time-trends in incidence and prognosis of hepatocellular carcinoma in Denmark: A nationwide register-based cohort study. Liver Int 2017;37:871-878.

[8] Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: From healthcare contacts to database records. Clin Epidemiol 2019;11:563-591.

[9] Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish national patient registry: A review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-490.

[10] Gjerstorff ML. The Danish cancer registry. Scand J Public Health 2011;39:42-45.

[11] Helweg-Larsen K. The Danish register of causes of death. Scand J Public Health 2011;39:26-29.

[12] Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish national prescription registry. Int J Epidemiol 2017;46:798-798f.

[13] Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. Eur J Epidemiol 2014;29:541-549.

[14] Danish Society for Gastroenterology and Hepatology. Hepatocellulært carcinom ved levercirrose: Screening, udredning og behandling [in Danish]. Accessed 25-11-2019. Available from: https://dsgh.dk/images/Guidelines/pdf/hcc.pdf

[15] Hernán MA, Hsu J, Healy B. A second chance to get causal inference right: A classification of data science tasks. Chance 2019;32:42-49.

[16] Ferguson N, Datta S, Brock G. msSurv: An R package for nonparametric estimation of multistate models. J Stat Softw 2012;50:1-24.

[17] Therneau T, Crowson C, Atkinson E. Multi-state models and competing risks. Accessed 04-07-2019. Available from: https://cran.r-project.org/web/packages/survival/vignettes/compete.pdf

[18] Jackson CH. Multi-state models for panel data: The msm package for R. J Stat Softw 2011;38:1-28.

[19] Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: A Danish population-based cohort study. Hepatology 2010;51:1675-1682.

[20] Vestberg K, Thulstrup AM, Sørensen HT, Ottesen P, Sabroe S, Vilstrup H. Data quality of administratively collected hospital discharge data for liver cirrhosis epidemiology. J Med Syst 1997;21:11-20.

[21] 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;47:702-709.

[22] Jepsen P, Vilstrup H, Sørensen 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.

[23] Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. Clinical course and mortality by etiology of liver cirrhosis in Sweden: A population based, long-term follow-up study of 1317 patients. Aliment Pharmacol Ther 2019;49:1421-1430.

[24] Ganne-Carrie N, Chaffaut C, Bourcier V, Archambeaud I, Perarnau JM, Oberti F, et al. Estimate of hepatocellular carcinoma incidence in patients with alcoholic cirrhosis. J Hepatol 2018;69:1274-1283.

[25] Mancebo A, González-Diéguez ML, Cadahía V, Varela M, Pérez R, Navascués CA, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. Clin Gastroenterol Hepatol 2013;11:95-101.

[26] Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. Risk and outcome of hepatocellular carcinoma in liver cirrhosis in southern Sweden: A population-based study. Scand J Gastroenterol 2019;54:1027-1032.

[27] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.

[28] Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 2004;127:S72-78.

[29] Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018.

[30] Probst HB, Hussain ZB, Andersen O. Cancer patient pathways in Denmark as a joint effort between bureaucrats, health professionals and politicians - a national Danish project. Health Policy 2012;105:65-70.

[31] Villadsen GE, Simonsen K, Ott P, Vilstrup H, Grønbæk H. Effects of implementation of a national fast track clinical pathway for hepatocellular carcinoma in Western Denmark. J Gastrointestin Liver Dis 2019;28:83-88.

[32] Rich NE, Parikh ND, Singal AG. Overdiagnosis: An understudied issue in hepatocellular carcinoma surveillance. Semin Liver Dis 2017;37:296-304.

[33] Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: Current best practice and future direction. Gastroenterology 2019;157:54-64.

[34] Atiq O, Tiro J, Yopp AC, Muffler A, Marrero JA, Parikh ND, et al. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. Hepatology 2017;65:1196-1205.

[35] Roskilly A, Rowe IA. Surveillance for hepatocellular cancer. Clin Med (Lond) 2018;18:s66-s69.

[36] Sharma SA, Kowgier M, Hansen BE, Brouwer WP, Maan R, Wong D, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol 2017;68:92-99.

[37] European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460.

[38] García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362:2370-2379.

[39] Rogal S, Youk A, Zhang H, Gellad WF, Fine MJ, Good CB, et al. Impact of alcohol use disorder treatment on clinical outcomes among patients with cirrhosis. Hepatology 2019.

Table 1. Characteristics of the study population.

	Compensated	Decompensated	All
Number of patients	980	3573	4553
Gender			
Men	667 (68%)	2405 (67%)	3072 (67%)
Women	313 (32%)	1168 (33%)	1481 (33%)
Age			
<50	182 (19%)	603 (17%)	785 (17%)
50–59	350 (36%)	1312 (37%)	1662 (37%)
60–69	355 (36%)	1300 (36%)	1655 (36%)
70–79	93 (9%)	358 (10%)	451 (10%)
Median age (IQR)	59.2 (52.1 – 65.5)	59.3 (52.5 – 65.1)	59.2 (52.4 – 65.0)
Outcomes (first event only)			
Decompensation	390	-	390
HCC[*]	19	142	161
Liver transplantation[†]	1	29	30
Death[‡]	170	1765	1935
No event	400	1637	2037
Follow-up time, total (to first event)	3024 years	14,039 years	17,063 years

[*] 20 patients had compensated cirrhosis initially and were diagnosed with HCC after having decompensated.

[†] 7 patients had compensated cirrhosis initially and underwent liver transplantation after having decompensated.

[‡] 339 patients died after having experienced one or more events.

Table 2. Predicted risks of HCC. All are predictions for 2018, the last year of our study period and the most relevant year for future decisions about HCC surveillance. Predictions for earlier years are lower.

Cirrhosis severity	Gender	Age	1-year risk	5-year risk	10-year risk
Compensated	Woman	50	0.2% (0.1 – 0.3)	0.7% (0.2 – 1.1)	1.0% (0.3 – 1.7)
Compensated	Woman	60	0.3% (0.1 – 0.6)	1.2% (0.5 – 1.9)	1.9% (0.7 – 3.0)
Compensated	Woman	70	0.6% (0.2 – 1.1)	2.2% (0.9 – 3.5)	3.4% (1.4 – 5.4)
Compensated	Man	50	0.6% (0.2 – 0.9)	2.0% (0.9 – 3.2)	3.1% (1.3 – 4.9)
Compensated	Man	60	1.1% (0.5 – 1.7)	3.7% (1.8 – 5.5)	5.7% (2.8 – 8.4)
Compensated	Man	70	1.9% (0.9 – 3.0)	6.7% (3.4 – 9.8)	10.2% (5.3 – 14.8)
Decompensated	Woman	50	0.3% (0.1 – 0.5)	1.0% (0.5 – 1.5)	1.5% (0.7 – 2.3)
Decompensated	Woman	60	0.5% (0.2 – 0.8)	1.8% (1.0 – 2.6)	2.8% (1.6 – 4.0)
Decompensated	Woman	70	1.0% (0.5 – 1.5)	3.3% (1.8 – 4.8)	5.1% (2.9 – 7.3)
Decompensated	Man	50	0.9% (0.5 – 1.3)	3.0% (1.9 – 4.2)	4.7% (2.9 – 6.4)
Decompensated	Man	60	1.6% (1.0 – 2.2)	5.5% (4.0 – 7.1)	8.4% (6.2 – 10.6)
Decompensated	Man	70	2.9% (1.8 – 4.0)	9.9% (7.2 – 12.5)	14.9% (11.4 – 18.4)

FIGURE LEGENDS

Fig. 1. Cumulative risk of HCC in the cohort of 4553 outpatients with alcoholic cirrhosis. The risk is shown by gender (left) and by compensated or decompensated cirrhosis at inclusion (right). For patients with compensated cirrhosis, the risk of HCC presented in the figure is literally 'the risk of developing HCC without having decompensated and before liver transplantation'.

Fig. 2. Cumulative mortality in the cohort of 4553 outpatients with alcoholic cirrhosis. The color indicates cause of death.

Fig. 3. **Incidence rates of HCC (red) and of liver imaging (blue and green, right-side y axis).** The actual annual rates are shown in the thin, brighter lines. The thick, darker lines are lowess smoothing plots to facilitate the visual interpretation of time trends.