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The risk of hepatocellular carcinoma in cirrhosis differs by etiology, age and sex: A Swedish nationwide population-based cohort study

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Abstract

Background: Current risk estimates for hepatocellular carcinoma (HCC) in individuals with cirrhosis vary between studies. The risk has mostly been evaluated for single etiologies separately.

Objectives: We examined the risk of HCC in Swedish outpatients with a new diagnosis of cirrhosis, aiming to identify subgroups with a particularly high risk for incident HCC.

Methods: All patients with a first diagnosis of cirrhosis in the National Outpatient Register for whom the etiology of cirrhosis could be estimated were identified. Incident cases of HCC were ascertained until the end of 2016 using record linkage to national registers. The cumulative incidence of HCC across etiologies of cirrhosis, sex and age was calculated considering non-HCC death as a competing risk.

Results: We identified 15,215 individuals with cirrhosis. The incidence rate for HCC in cirrhosis was 23/1000 person-years (95%CI = 22–24). Stratified on gender, it was 29/1000 person-years (95%CI = 27–31) in men versus 14/1000 person-years (95% CI = 13–16) in women. The cumulative incidence of HCC in cirrhosis was 8.3% (95% CI = 7.8–8.8) at 5 years and 12.2% (95%CI = 11.6–13.0) at 10 years. At 10 years, the lowest cumulative incidence was seen in women with alcohol-related liver disease (4.3%) and the highest in men with viral hepatitis (26.6%). These figures also varied by age.

Conclusions: The risk of HCC differs extensively across subgroups of etiologies of cirrhosis, age and sex, suggesting that initiation of HCC surveillance could be individually tailored.

KEYWORDS

cumulative incidence, epidemiology, liver cancer, liver cirrhosis, subgroup analysis

INTRODUCTION

Liver cirrhosis is the major risk factor of hepatocellular carcinoma development. It has been shown that 80%–90% of individuals with HCC have cirrhosis.[1] Screening with liver ultrasound every 6 months (HCC surveillance) in high-risk individuals is recommended to identify HCC early when curative treatment is feasible.[2] Swedish guidelines stress the importance of regular HCC surveillance in all patients with liver cirrhosis.[3]

For HCC surveillance to be cost-effective, an annual HCC incidence of ≥1.5% is usually proposed.[4] However, both lower and higher HCC incidence thresholds have been suggested.[5,6] Estimates of HCC risk vary substantially, with several studies reporting incidence rates of HCC in cirrhosis ranging from 0.7 to 26.0 per 1000 person-years.[7–9]

The high variation in risk estimates can be attributed to different HCC risks in various cirrhosis etiologies. In cirrhosis due to viral hepatitis, the risk is higher than in autoimmune liver disease and alcohol-related liver disease (ALD).[10,11] Another reason could be the lack of population-based studies evaluating HCC risk in multiple etiologies of cirrhosis in the same population. With a few exceptions (e.g.),[8,12,13] most studies report HCC risk estimates that derive from tertiary liver centers, which might be more likely to select individuals with a higher HCC risk or estimates obtained from studies that examine single etiologies of cirrhosis separately (e.g.).[14,15] A direct comparison of HCC incidence between cirrhosis etiologies from different studies is therefore problematic because the background population in single-etiology studies often differs.[10,14–17] Likewise, age and sex can affect the risk of HCC,[11,18,19] but estimates are seldom reported for these subgroups, often due to a lack of statistical power for meaningful analyses. Additionally, the competing risk of non-HCC death (death without having been diagnosed with HCC) differs across etiologies of cirrhosis, with a particularly high risk of death in alcohol-related cirrhosis,[20] which affects the cumulative incidence of HCC as fewer patients live long enough to develop cancer.[11] In all, there is a lack of cohort studies large enough to enable comparisons between different subgroups.

This study aimed to investigate the risk and cumulative incidence of HCC in cirrhosis patients in a nationwide population-based cohort study where comparison of risk in various etiologies and subgroups within the same setting is feasible. We hypothesized that the cumulative incidence of HCC in persons with cirrhosis is lower than previously considered.

Key Summary

- Cirrhosis is a major risk factor of hepatocellular carcinoma (HCC), but this risk varies and some patients might need more or less active surveillance.
- We investigated HCC risk across subgroups in all newly diagnosed Swedish outpatients with cirrhosis between 2001 and 2016.
- The lowest cumulative incidence of HCC at 10 years was seen in women with alcohol-related liver disease (4.3%) and the highest in men with viral hepatitis (26.6%).
- These findings support individual decision-making when considering initiation or continuation of HCC surveillance.

METHODS

Data sources

Cross-linked data from four Swedish registries were used. The Swedish National Patient Register was started in 1964 and contains the International Classification of Diseases (ICD) codes from inpatient care with national coverage from 1987. Since 2001, the National Patient Register also includes visits in specialized outpatient care from private and public caregivers.[21]

The Swedish Cancer Register was established in 1958. The Cancer Register is based on physicians' mandatory reporting of newly detected cancer and an independent mandatory reporting by pathologists on every cancer diagnosis made from pathological specimens. The completeness differs depending on the type of cancer but is overall high (about 96%).[22] However, HCC is often diagnosed by non-invasive methods without histology and the completeness is reported to be lower than for other types of cancer.[23] Consequently, capturing HCC diagnoses outside of the Cancer Register is recommended.[23] Our method to capture incident HCC is described below.

The National Causes of Death Register comprises data on all deaths in Sweden through a two-step process. First, a death certificate in which a physician confirms the death is sent to the Swedish tax office for registration. The death certificate must be completed before a burial can be authorized. The second step entails a report of the cause of death filled in by a physician and sent to the National Board of Health and Welfare within 3 weeks.[24]

Finally, the Total Population Register, frequently used to link study participants to matched reference individuals for comparison, contains data on date of birth, migration and death as well as other parameters.[25]

Study population

First, all individuals with an ICD code potentially associated with cirrhosis registered in the outpatient part of the National Patient Register in Sweden from 2001 to 2016 were included. ICD codes and definitions are listed in eTable 1.

Exclusion criteria were HCC and liver transplant before or at start of follow-up. Persons with coding for diagnoses associated with cirrhosis (e.g., liver failure or ascites), but where the diagnosis of cirrhosis was uncertain (e.g., patients with a diagnosis of ascites but without coding for cirrhosis or a specific liver disease) were also

excluded as such cases cannot reliably be defined as having cirrhosis.[26] Up to 10 reference individuals matched for age, sex, county and calendar year of cirrhosis diagnosis were *randomly selected from the Total Population Register* for each patient with cirrhosis. A flowchart of the inclusion process is illustrated in Figure 1. The definitions of all variables are explained in detail in eMethods.

Follow-up

Start of follow up started 6 months after the first diagnosis of cirrhosis in the outpatient register. The 6 months was used to define etiologies, but also to exclude individuals liver transplanted, diagnosed with HCC and individuals that died or emigrated during the first 6 month after the cirrhosis diagnosis. By doing this, the risk of capturing HCC: s already present at baseline is lower and it allows for a more accurate definition of cirrhosis etiologies. The drawback is a somewhat shorter follow-up period and losing patients that died during this time. However, such patients often are excluded from HCC surveillance due to a poor prognosis. End of follow-up was defined as the first diagnosis of HCC or censoring, whichever came first. Censoring was defined as emigration, liver transplantation, non-HCC death or end of the study period (31 December 2016). Reference individuals diagnosed with cirrhosis during follow-up were censored at such time and thereafter considered as exposed.

Statistical analysis

Continuous data are presented as medians with interquartile ranges (IQR) and categorical variables as total numbers and percentages. Incidence rates of HCC were calculated as the number of new cases per 1000 person-years of follow-up. When investigating the risk of HCC in individuals with cirrhosis, the high competing risk of death in cirrhosis is important to consider. Kaplan-Maier analyses systematically overestimate the risk of HCC[27] and we therefore performed a competing risk regression using Fine and Gray's sub hazards model to graphically study the cumulative incidence function (STATA commands stcrreg and stcurve).[28] Cumulative incidence of HCC at five and 10 years was calculated (STATA command stcompet). Cox proportional-hazards models were used for the time-to-event analysis where the rate of events was compared to reference individuals. This complements the competing risk regression by focusing on the different way of censoring and is preferred when the research questions focus on etiological questions, such as if the strength of the association is larger in a particular group of patients.[29] The proportional-hazards assumptions were verified with the use of Schoenfeld residuals. We conditioned the model on the matching factors (age, sex, county and year of diagnosis). A second model also adjusted for diabetes as time-varying covariate, defined by ICD-codes corresponding to type 1 or type 2 diabetes (listed in eTable 2) since diabetes has consistently been found to be an independent risk factor for HCC development. We investigated risk of HCC in all individuals with cirrhosis and stratified on etiology of cirrhosis, sex, and age (categorized as <50, 50–65 and >65 at baseline). Finally, we examined risk of HCC stratified on presence of liver decompensation at or before baseline. Statistical analysis was performed using STATA version 16.1 and R version 3.6.2. A two-tailed *p*-value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the regional ethical committee in Stockholm (reg no 2017/1019-31/1). Because of the retrospective nature of the data collection process and because there was no direct contact with any of the individuals, the need for informed consent was waived by the ethical committee.

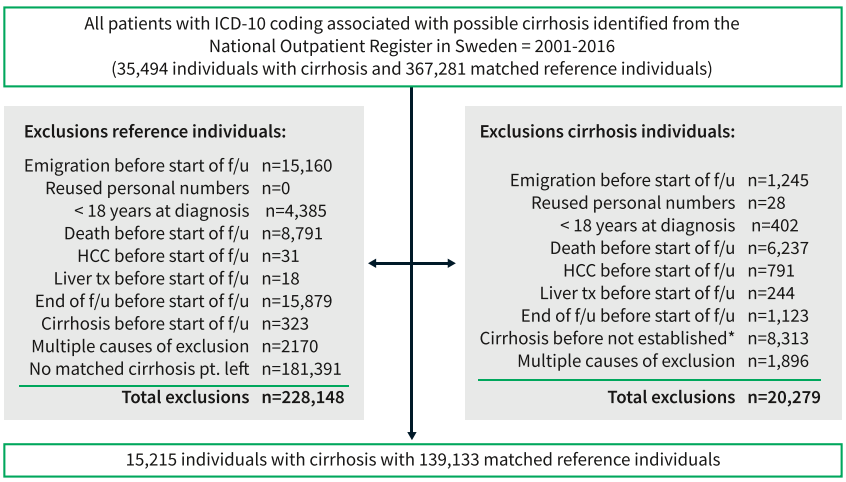

FIGURE 1 Flowchart of inclusion and exclusion criteria: *For example, a code for ascites but no code for etiology of cirrhosis. Abbreviations: Tx, transplant. Pt, patient. F/u, follow-up. Reused personal number refers to when the same personal number exists for several individuals over time. One example is when one individual who immigrates receive the same personal number as an individual that has emigrated

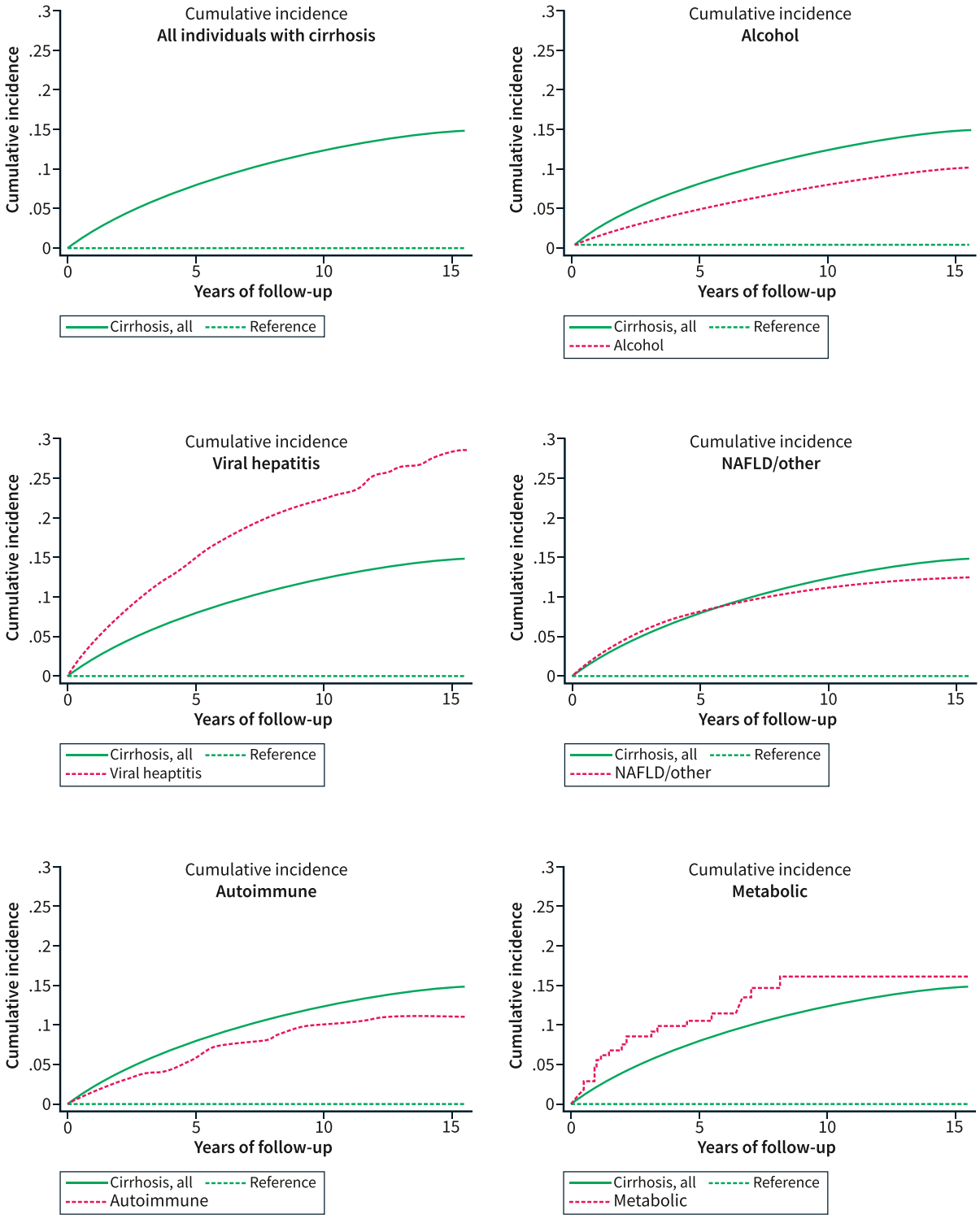

FIGURE 2 Cumulative incidences of HCC for all individuals with cirrhosis and matched reference individuals and further stratified by etiologies with a reference line denoting all individuals with cirrhosis for comparison

RESULTS

We identified 15,215 individuals with cirrhosis between 2001 and 2016. Median age was 61 years (IQR = 15) and 63% were men. Characteristics of the study population are further described in Table 1. The distribution of the etiologies of cirrhosis was as follows: ALD 7485 (49%), viral hepatitis 4084 (27%), NAFLD or other liver diseases 2446 (16%), autoimmune liver diseases 1010 (7%) and metabolic liver disease other than NAFLD 190 (1%). A hospitalization event associated with cirrhosis at or before baseline was present in 50% (7664). Median follow-up for individuals with cirrhosis was 2.5 years compared to 5.6 in the reference population. During follow-

TABLE 1 Descriptive characteristics of individuals with cirrhosis at baseline or at start of follow up as appropriate

	Individuals with cirrhosis						
	All	Alcohol	Viral hepatitis	NAFLD/ Other	Auto-immune	Metabolic	Reference individuals
Included individuals, *n* (% of all)	15,215 (100%)	7485 (49%)	4084 (27%)	2446 (16%)	1010 (7%)	190 (1%)	139,133 (100%)
Follow-up years, sum	55,781	28,366	13,963	9077	3675	700	885,767
Median (IQR) follow-up year/person	2.5 (4.3)	2.6 (4.6)	2.4 (3.8)	2.5 (4.3)	2.4 (4.3)	2.2 (4.9)	5.6 (7.5)
Sex, men *n* (%)	9564 (62.9%)	5165 (69.0%)	2750 (67.3%)	1193 (48.8%)	330 (32.7%)	126 (66.3%)	86,989 (62.5%)
Age at diagnosis, years median (IQR)	61 (15)	61 (13)	55 (13)	68 (15)	65 (19)	65 (13)	60 (15)
Period of first cirrhosis diagnosis (n/% etiology per period)							
2001–2004	3349 (100%)	1818 (54.3%)	682 (20.4%)	598 (17.9%)	209 (6.2%)	42 (1.3%)	30,764 (100%)
2005–2008	3205 (100%)	1704 (53.2%)	772 (24.1%)	463 (14.4%)	228 (7.1%)	38 (1.2%)	29,411 (100%)
2009–2012	3961 (100%)	1870 (47.2%)	1167 (29.5%)	606 (15.3%)	264 (6.7%)	54 (1.4%)	36,194 (100%)
2013–2016	4700 (100%)	2093 (44.5%)	1463 (31.1%)	779 (16.6%)	309 (6.6%)	56 (1.2%)	42,764 (100%)
Country of birth							
Nordic (n/%)	13,383 (88.0%)	6987 (93.3%)	3147 (77.1%)	2138 (87.4%)	935 (92.6%)	176 (92.6%)	124,608 (89.6%)
Other (n/%)	1832 (12.0%)	498 (6.7%)	937 (22.9%)	308 (12.6%)	75 (7.4%)	14 (7.4%)	14,525 (10.4%)
Comorbidity at/before cirrhosis diagnosis							
Decompensation[a], *n* (%)	7664 (50.4%)	4421 (59.1%)	1561 (38.2%)	931 (38.1%)	667 (66.0%)	84 (44.2%)	22 (0.02%)
Diabetes, *n* (%)	3218 (21.2%)	1488 (19.9%)	683 (16.7%)	844 (34.5%)	160 (15.8%)	43 (22.6%)	7653 (5.5%)

Abbreviations: IQR, interquartile range. NAFLD, non-alcoholic fatty liver disease.

[a]Decompensation is defined as having an ICD-10 code of R18.9 (ascites), I85.0/I85.9/I98.2/I98.3 (esophageal varices) and/or K76.7 (hepatorenal syndrome) at or before cirrhosis diagnosis in the National Patient Register.

up, 42.7% (6491) of individuals with cirrhosis died compared to 10.6% (14,684) in the reference group.

Incidence of HCC in patients with cirrhosis

The incidence rate for HCC in all individuals with cirrhosis was 23/1000 person-years (95%CI = 22–24), ranging from 15/1000 person-years (95%CI = 13–16) in ALD and 17/1000 person-years in autoimmune liver disease (95%CI = 13–22) to 41/1000 person-years (95%CI = 38–45) in viral hepatitis. The incidence rate of HCC in the reference population was 0.16/1000 person-years (95%CI = 0.14–0.19). Incidence differed depending on age and sex. For instance, the incidence rate of HCC in all men with cirrhosis was 29/1000 person-years (95% CI = 27–31) versus 14/1000 person-years (95%CI = 13–16) in women. The cumulative incidence for cirrhosis in the full cohort was 8.3% (95%CI = 7.8–8.8) at 5 years and 12.2% (95%CI = 11.6–13.0) at 10 years. At 10 years, the lowest cumulative incidence was seen in women with alcohol-related liver disease (4.3%) and the highest in men with viral hepatitis (26.6%). The overall incidence of HCC for all subgroups is presented in Table 2 while the cumulative incidence at five and 10 years after start of follow up is listed in Table 3. The cumulative incidence in different etiologies is plotted in Figure 2.

Impact of decompensation

A total of 7664 (50,4%) patients had a diagnosis of decompensation at or before baseline. In this population, 606 (7.9%) developed HCC during follow-up. The incidence rate was 22/1000 person-years (95% CI = 21–24) in those with prior decompensation, in contrast to 24/1000 (95%CI = 22–25) in those with presumed compensated cirrhosis. The cumulative incidence of HCC at five and 10 years was 7.5% (95%CI = 6.8–8.2) and 10.8% (95%CI = 10.0–11.7) in those with decompensation. In those with compensated cirrhosis, this was 9.1% (95%CI = 8.4–9.9) and 13.9% (95%CI = 12.8–15.0).

Rate of HCC compared to reference individuals

During follow-up, 1275 (8.4%) persons with cirrhosis and 143 (0.1%) in the reference group were diagnosed with HCC. The rate of HCC in individuals with cirrhosis was higher compared to the reference group (HR = 162, 95%CI = 127–207). However, this differed depending on the etiology of liver disease, sex and age (estimates are presented in Table 2). Lower age and female sex were consistently associated with a lower rate of HCC compared to older individuals and male sex.

TABLE 2 Absolute numbers and percentages of incident cases of HCC during follow-up in cirrhosis and reference individuals

	Number of individuals (%)		Number of events (%)		Incidence rate (95% CI) per 1000 person-years			
	All individuals with cirrhosis	Ref. Individuals	All individuals with cirrhosis	Ref. Individuals	All individuals with cirrhosis	Ref. Individuals	HR (crude)(95%CI)	HR (adjusted)[a](95%CI)
Overall	15,215	139,133	1275 (8.4%)	143 (0.1%)	22.9 (21.6–24.1)	0.16 (0.14–0.19)	162.2 (127.1–207.0)	144.6 (113.1–184.9)
Decomp-ensation	7664 (50.4%)	22 (0.02%)	606 (7.9%)	0	22.2 (20.5–24.0)	0	---	---
No decomp-ensation	7551 (49.6%)	139,111 (99.98%)	669 (8.9%)	143 (0.1%)	23.5 (21.8–25.3)	0.16 (0.14–0.19)	186.8 (130.3–267.8)	167.6 (116.5–241.1)
Sex								
Women	5651 (37.1%)	52,144 (37.5%)	320 (5.7%)	50 (0.1%)	14.3 (12.8–16.0)	0.15 (0.11–0.20)	104.0 (70.2–154.1)	91.8 (61.7–136.7)
Men	9564 (62.9%)	86,989 (62.5%)	955 (10.0%)	93 (0.1%)	28.6 (26.8–30.5)	0.17 (0.14–0.21)	200.5 (146.7–274.1)	182.9 (133.1–251.5)
Age								
<50	2497 (16.4%)	23,281 (16.7%)	151 (6.1%)	5 (<0.1%)	13.1 (11.2–15.4)	0.03 (0.01–0.07)	272.4 (111.8–664.2)	252.9 (103.6–617.2)
50–65	7784 (51.2%)	71,734 (51.6%)	710 (9.1%)	60 (<0.1%)	23.9 (22.2–25.8)	0.12 (0.10–0.16)	272.4 (179.8–412.6)	238.9 (157.1–363.4)
>65	4934 (32.4%)	44,118 (31.7%)	414 (8.4%)	78 (0.2%)	28.4 (25.8–31.3)	0.33 (0.26–0.41)	85.3 (61.6–118.0)	77.0 (55.5–106.9)
	Viral	**Ref. Individuals**	**Viral**	**Ref. Individuals**	**Viral**	**Ref. Individuals**	**HR (crude)(95%CI)**	**HR (adjusted)[a](95%CI)**
Overall	4084	36,399	575 (14.1%)	21 (<0.1%)	41.2 (37.9–44.7)	0.10 (0.06–0.15)	556.0 (287.8–1074.2)	521.4 (268.4–1013.0)
Sex								
Women	1334 (32.7%)	12,033 (33.1%)	134 (10.0%)	<5 (<0.1%)	27.8 (23.4–32.9)	0.04 (0.01–0.13)	1183.0 (165.4–8460.9)	1525.9 (163.8–14,216)
Men	2750 (67.3%)	24,366 (66.9%)	441 (16.0%)	18 (<0.1%)	48.3 (44.0–53.0)	0.13 (0.08–0.20)	477.6 (237.3–961.2)	440.1 (218.3–887.4)
Age								
<50	1046 (25.6%)	9609 (26,4%)	110 (10.5%)	<5 (<0.1%)	25.4 (21.1–30.6)	0.05 (0.01–0.14)	328.9 (104.4–1035.7)	305.1 (96.7–962.1)
50–65	2446 (59.9%)	21,941 (60.3%)	374 (15.3%)	15 (<0.1%)	46.8 (42.3–51.8)	0.12 (0.07–0.20)	656.3 (271.5–1586.1)	618.7 (251.6–1521.2)
>65	592 (14.5%)	4849 (13.3%)	91 (15.4%)	<5 (<0.1%)	55.6 (45.3–68.3)	0.13 (0.04–0.39)	735.6 (102.5–5280.7)	785.4 (99.9–6177.1)
	Alcohol	**Ref. Individuals**	**Alcohol**	**Ref. Individuals**	**Alcohol**	**Ref. Individuals**	**HR (crude)(95%CI)**	**HR (adjusted)[a](95%CI)**
Overall	7485	69,104	419 (5.6%)	70 (0.1%)	14.8 (13.4–16.3)	0.15 (0.12–0.19)	102.8 (72.8–145.3)	91.4 (64.4–129.9)
Sex								
Women	2320 (31.0%)	21,606 (31.3%)	70 (3.0%)	18 (<0.1%)	7.2 (5.7–9.1)	0.12 (0.08–0.19)	60.1 (31.0–116.8)	51.1 (26.1–100.3)
Men	5165 (69.0%)	47,498 (68.7%)	349 (6.8%)	52 (0.1%)	18.7 (16.8–20.8)	0.17 (0.13–0.22)	119.9 (79.9–180.0)	109.1 (72.0–165.4)

TABLE 2 (Continued)

	Alcohol	Ref. Individuals	Alcohol	Ref. Individuals	Alcohol	Ref. Individuals	HR (crude)(95%CI)	HR (adjusted)[a](95%CI)
Age								
<50	970 (13.0%)	9151 (13.2%)	28 (2.9%)	<5 (<0.1%)	6.1 (4.2–8.8)	0.03 (0.01–0.11)	129.2 (30.8–542.5)	118.1 (28.0–498.3)
50–65	4147 (55.4%)	38,624 (55.9%)	230 (5.6%)	28(<0.1%)	13.9 (12.2–15.8)	0.10 (0.07–0.15)	156.8 (89.7–274.3)	135.7 (77.4–237.9)
>65	2368 (31.6%)	21,329 (30.9%)	161 (6.8%)	40 (0.2%)	22.5 (19.2–26.2)	0.34 (0.25–0.47)	65.3 (41.0–104.1)	60.5 (37.2–98.2)
	NAFLD/other	**Ref. Individuals**	**NAFLD/Other**	**Ref. Individuals**	**NAFLD/Other**	**Ref. Individuals**	**HR (crude)(95%CI)**	**HR (adjusted)[a](95%CI)**
Overall	2446	22,818	196 (8.0%)	34 (0.2%)	21.6 (18.8–24.8)	0.25 (0.18–0.34)	113.8 (67.3–192.5)	88.7 (52.0–151.4)
Sex								
Women	1253 (51.2%)	11,768 (51.6%)	70 (5.6%)	20 (0.2%)	14.1 (11.1–17.8)	0.28 (0.18–0.43)	70.4 (35.1–140.9)	52.1 (25.1–108.1)
Men	1193 (48.8%)	11,050 (48.4%)	126 (10.6%)	14 (0.1%)	30.7 (25.8–36.6)	0.21 (0.13–0.36)	178.7 (78.8–405.6)	144.4 (63.2–329.7)
Age								
<50	245 (10.0%)	2309 (10.1%)	5 (2.0%)	0 (0%)	3.26 (1.4–7.8)	---	---	---
50–65	787 (32.2%)	7408 (32.5%)	72 (9.2%)	8 (0.1%)	21.1 (16.7–26.5)	0.16 (0.08–0.31)	318.5 (78.1–1298.5)	214.8 (47.9–963.7)
>65	1414 (57.8%)	13,101 (57.4%)	119 (8.4%)	26 (0.2%)	28.9 (24.1–34.5)	0.38 (0.26–0.55)	78.9 (44.5–140.1)	66.4 (37.2–118.6)
	Autoimmune	**Ref. Individuals**	**Autoimmune**	**Ref. Individuals**	**Autoimmune**	**Ref. Individuals**	**HR (crude)(95%CI)**	**HR (adjusted)[a](95%CI)**
Overall	1010	9109	63 (6.2%)	16 (0.2%)	17.1 (13.4–21.9)	0.28 (0.17–0.45)	59.8 (29.7–120.4)	57.0 (28.2–115.1)
Sex								
Women	680 (67.3%)	6159 (67.6%)	41 (6.0%)	9 (0.2%)	15.5 (11.4–21.0)	0.23 (0.12–0.44)	50.4 (22.6–112.6)	47.4 (21.0–107.3)
Men	330 (32.7%)	2950 (32.4%)	22 (6.7%)	7 (0.2%)	21.5 (14.2–32.6)	0.38 (0.18–0.81)	92.7 (21.7–395.2)	105.6 (23.1–483.4)
Age								
<50	214 (21.2%)	2006 (22.0%)	8 (3.7%)	0 (0%)	9.1 (4.5–18.1)	---	---	---
50–65	326 (32.3%)	3026 (33.2%)	24 (7.4%)	7 (0.2%)	17.3 (11.6–25.7)	0.32 (0.15–0.66)	72.5 (21.8–240.9)	108.4 (23.6–498.7)
>65	470 (46.5%)	4077 (44.8%)	31 (6.6%)	9 (0.2%)	22.1 (15.6–31.5)	0.40 (0.21–0.76)	41.5 (17.3–99.8)	44.8 (17.4–115.4)
	Metabolic	**Ref. Individuals**	**Metabolic**	**Ref. Individuals**	**Metabolic**	**Ref. Individuals**	**HR (crude)(95%CI)**	**HR (adjusted)[a](95%CI)**
Overall	190	1703	22 (11.6%)	<5 (0.1%)	31.4 (20.7–47.7)	0.19 (0.05–0.77)	---	---
Sex								
Women	64 (33.7%)	578 (33.9%)	5 (7.8%)	0 (0%)	22.1 (9.19–53.1)	---	---	---
Men	126 (66.3%)	1125 (66.1%)	17 (13.5%)	<5 (0.2%)	35.9 (22.3–57.7)	0.28 (0.07–1.14)	---	---

(Continues)

TABLE 2 (Continued)

	Metabolic	Ref. Individuals	Metabolic	Ref. Individuals	Metabolic	Ref. Individuals	HR (crude)(95%CI)	HR (adjusted)[a](95%CI)
Age								
<50	22 (11.6%)	206 (12.1%)	0 (0%)	0 (0%)	---	---	---	---
50–65	78 (41.1%)	735 (43.2%)	10 (12.8%)	<5 (0.3%)	33.1 (17.8–61.6)	0.42 (0.11–1.69)	---	---
>65	90 (47.4%)	762 (44.7%)	12 (13.3%)	0 (0%)	47.3 (26.8–83.2)	---	---	---

Note: Incidence rates and hazard ratios for HCC compared to reference individuals by cirrhosis etiology, age and sex.

Abbreviations: HR, Hazard Ratio; NAFLD, non-alcoholic fatty liver disease.

[a]Model adjusted for diabetes type 1 or 2 as a time-varying covariate.

Impact of diabetes

In a model further adjusted for diabetes as a time-varying covariate the rate of HCC was slightly attenuated (HR 145, 95%CI = 113–185) compared to HR 162 (95%CI = 127–207) in the crude analysis. Diabetes was an independent risk factor for HCC development in this analysis (HR 3.1, 95%CI = 2.1–4.4). This finding was consistent for all subgroups, except for autoimmune liver disease, where no meaningful difference was noted and for metabolic liver disease where few events were observed. The HRs for this adjusted model are summarized in Table 2.

DISCUSSION

In this nationwide population-based cohort study we found that the rate of HCC in all outpatients in Sweden diagnosed with cirrhosis, was about 23 cases per 1000 person-years. The high competing risk of death translated into a cumulative HCC incidence of 12.2% at 10 years. This figure varied significantly between etiologies of cirrhosis, from 7.9% in ALD to 23.1% in viral hepatitis and age, sex, previous decompensation and diabetes were significant contributors to the different risks of HCC. Together, our findings highlight the large variation in the absolute risk of HCC in individuals with cirrhosis according to these factors, supporting individualized decision making on if and when to initiate HCC surveillance.

Our findings can be compared to those reported in previous studies in this field. In two recently published studies, including Swedish individuals with biopsy-proven cirrhosis, the incidence rate of HCC in NAFLD was 6.2/1000 person-years[30] and in ALD 8.6/1000 person-years.[31] The cumulative incidence after 10 years in ALD cirrhosis was 5%.[31] We report higher estimates than the studies examining risk in biopsy-proven patients,[33,34] possibly explained by the selection bias introduced when including only individuals who have undergone a biopsy, as these individuals might be healthier. Patients with cirrhosis and comorbidities might not be eligible for biopsy, as well as patients with symptoms from cirrhosis where biopsy will not add any additional data on diagnosis or prognosis. A longer median survival time, at least in the ALD study,[31] than in the current study suggests that those studies included healthier cohorts.

The authors of a Danish register study of more than 4000 outpatients with ALD[11] reported a cumulative HCC risk at 5 and 10 years of 4.2% and 7.0%, respectively, and an incidence rate of 10.0/1000 person-years. Most of the individuals (78%) in this study were decompensated at baseline versus 59% of the individuals with ALD cirrhosis in our cohort. Despite a slightly different definition of decompensation between the studies, this difference might impact the risk of developing HCC as individuals who are more severely ill from liver cirrhosis have a higher risk of dying before being diagnosed with HCC.

We report a high risk of HCC in viral hepatitis and a lower risk in ALD and autoimmune liver disease consistent with

TABLE 3 Cumulative incidence of HCC at five and 10 years in cirrhosis by etiology, sex and age at diagnosis

	Number of exposed	Cumulative incidence at 5 years (95%CI)	Cumulative incidence at 10 years (95%CI)
All individuals with cirrhosis	15,215 (100%)	8.3 (7.8–8.8)	12.2 (11.6–13.0)
Decompensation	7664 (50.4%)	7.5 (6.8–8.2)	10.8 (10.0–11.7)
No decompensation	7551 (49.6%)	9.1 (8.4–9.9)	13.9 (12.8–15.0)
Women	5651 (37.1%)	5.3 (4.6–6.0)	8.2 (7.3–9.2)
Men	9564 (62.9%)	10.0 (9.4–10.7)	14.7 (13.8–15.7)
Age <50	2497 (16.4%)	5.1 (4.1–6.2)	9.7 (8.1–11.5)
Age 50–65	7784 (51.2%)	8.9 (8.2–9.7)	13.3 (12.3–14.3)
Age >65	4934 (32.4%)	8.9 (8.0–9.8)	11.9 (10.8–13.1)
Viral	4084 (26.8%)	15.6 (14.3–17.0)	23.1 (21.1–25.0)
Women	1334 (32.7%)	11.0 (9.0–13.2)	15.9 (13.1–18.8)
Men	2750 (67.3%)	17.9 (16.2–19.7)	26.6 (24.1–29.2)
Age <50	1046 (25.6%)	9.6 (7.6–11.9)	17.6 (14.3–21.3)
Age 50–65	2446 (59.9%)	17.7 (15.9–19.6)	25.2 (22.6–28.0)
Age >65	592 (14.5%)	18.8 (15.0–23.0)	24.6 (19.8–29.6)
Alcohol	7485 (49.2%)	4.9 (4.3–5.4)	7.9 (7.1–8.7)
Women	2320 (31.0%)	2.4 (1.8–3.2)	4.3 (3.3–5.4)
Men	5165 (69.0%)	5.9 (5.3–6.7)	9.6 (8.6–10.6)
Age <50	970 (13.0%)	2.2 (1.3–3.4)	4.6 (3.0–6.8)
Age 50–65	4147 (55.4%)	4.4 (3.7–5.2)	7.7 (6.7–8.8)
Age >65	2368 (31.6%)	6.9 (5.8–8.2)	9.9 (8.4–11.5)
NAFLD/Other	2446 (16.1%)	8.4 (7.2–9.7)	11.3 (9.8–13.0)
Women	1253 (51.2%)	5.3 (4.0–6.8)	8.1 (6.3–10.2)
Men	1193 (48.8%)	11.7 (9.7–13.9)	14.7 (12.3–17.4)
Age <50	245 (10.0%)	1.8 (0.5–4.8)	--
Age 50–65	787 (32.2%)	9.3 (7.1–11.8)	13.7 (10.6–17.1)
Age >65	1414 (57.8%)	9.2 (7.6–11.0)	--
Autoimmune	1010 (6.6%)	6.4 (4.7–8.4)	10.3 (7.8–13.2)
Women	680 (67.3%)	5.4 (3.7–7.7)	9.6 (6.8–13.0)
Men	330 (32.7%)	9.4 (5.8–14.0)	---
Age <50	214 (21.2%)	5.3 (1.9–11.5)	---
Age 50–65	326 (32.3%)	7.6 (4.6–11.6)	---
Age >65	470 (46.5%)	6.9 (4.6–9.8)	9.4 (6.2–13.3)
Metabolic	190 (1.2%)	12.2 (7.6–18.0)	---
Women	64 (33.7%)	11.0 (3.6–23.0)	---
Men	126 (66.3%)	14.3 (8.3–21.8)	---
Age <50	22 (11.6%)	---	---
Age 50–65	78 (41.1%)	15.2 (7.3–25.7)	---
Age >65	90 (47.4%)	12.8 (6.5–21.3)	---

Note: ---, Not possible to estimate because of few outcomes.

Abbreviation: NAFLD, non-alcoholic fatty liver disease.

previous findings.[9,11,15,32] A Canadian study from a single hepatology center in Toronto[10] found that HCC occurred most often in individuals with viral hepatitis (incidence rate 23/1000 person-years). Their 5- and 10-year cumulative incidences were in line with our results.[10]

Diabetes was found to be an independent predictor of HCC in individuals with cirrhosis. This finding has been reported in several other studies,[33,34] further underscoring that those with cirrhosis and diabetes constitute a high-risk group for HCC development.

Strengths and limitations

The nationwide inclusion of all individuals in Sweden with cirrhosis meeting our inclusion criteria is an important strength. In previous research the focus has often been the risk of HCC within a specific disease etiology. Our results can thus be used to put the risk of HCC into context between etiologies of cirrhosis. Moreover, the registers enable a long follow-up, virtually without loss to follow-up except for emigration. The registers are considered of high quality, and we have previously confirmed a high positive predictive value of both our main exposure (cirrhosis) and outcome (HCC) in the National Patient Register.[26] Another strength is that we compared the risk of HCC to that of matched reference individuals, which has rarely been done in a population-based register study including multiple etiologies of cirrhosis. Finally, we have a large sample size, enabling meaningful subgroup analyses (e.g., age and sex) of important risk factors for HCC.

There are also limitations. The main limitation is the compromises needed to identify and distinguish individuals with different diagnoses of cirrhosis. Our algorithm detects cirrhosis cases with a certain etiology and cases where a definite etiology could not be ascertained. For example, an individual with undefined cirrhosis but with no code for etiology was defined as having NAFLD/other causes, which has implications on interpreting the estimates for HCC in the NAFLD/other group. Another limitation related to the use of ICD-codes to define exposure and outcome status is the risk of incorrect coding. However, the ICD codes used in this study have been validated and found to be highly accurate.[26] Nevertheless, a remaining risk for selection bias and some degree of misclassification bias cannot be excluded.

We did not include patients where the diagnosis of HCC and cirrhosis was made at the same time. This is a common clinical scenario, but classifying the date of cirrhosis diagnosis in such patients is not possible. Further, we did not examine HCC risk in patients with chronic liver disease but without cirrhosis. Even if such patients might have a higher risk for HCC than the background population,[35] the absolute risk for HCC is low, and these patients are currently not eligible for HCC surveillance.

The relatively few outcomes in individuals with autoimmune and metabolic liver disease imply that the estimates for HCC risk in these subgroups should be interpreted cautiously. Additionally, HCC was rare in the reference population why the estimates from these analyses yielded wide confidence intervals. Finally, we lack granular data on important factors such as smoking, body mass index, ethnicity, lifestyle modifications such as alcohol cessation and laboratory data to calculate liver disease severity.

Implications

An annual incidence of HCC of at least 1.5% is considered a requirement for HCC surveillance to be cost-effective.[4] While we found an incidence of 23/1000 person-years, the high competing risk of death in cirrhosis strongly affects the cumulative incidence and led to a lower-than-expected HCC risk at 10 years. We identify several risk groups with a particularly high risk of HCC in whom surveillance might be most effective. In contrast, the 5-year cumulative incidence of HCC in individuals <50 years old was low for most etiologies except viral hepatitis, suggesting that any surveillance could be postponed until after that age, at least in non-viral cirrhosis. Stratification based on age, sex, etiology and diabetes could take the different risks into account when deciding whether to initiate HCC surveillance in patients with cirrhosis.

Conclusion

The cumulative incidence of HCC in Swedish outpatients with cirrhosis is approximately 12% 10 years after diagnosis, but varies greatly according to cirrhosis etiology and severity, sex and age. The rates of HCC development in several subgroups do not reach the threshold for when HCC surveillance is considered cost-effective. In total, our data support individualized decision making regarding if and when HCC surveillance should be initiated.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Study conception and design: Hannes Hagström. Acquisition of data: Hannes Hagström. Statistical analysis: Linnea Widman, Hannes Hagström. Analysis and interpretation of data: Bonnie Bengtsson, Hannes Hagström. Drafting of manuscript: Bonnie Bengtsson, Hannes Hagström. Critical revision: All. Guarantor of article: Hannes Hagström. All authors approved the final version of the article, including the authorship list. Writing Assistance: None.

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Data Transparency Statement: Data not available due to Swedish regulations.

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