Incidence of hepatocellular carcinoma in a community-based Taiwanese population without chronic HBV/HCV infection

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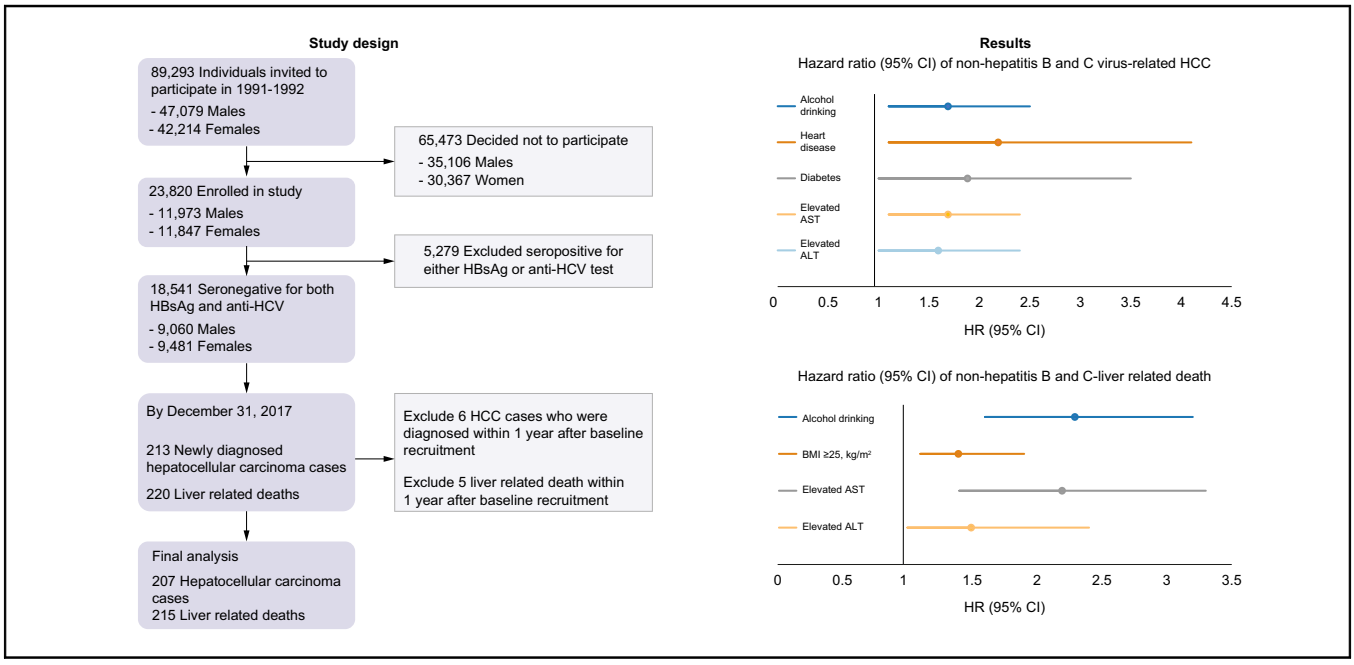
Graphical abstract



Highlights

- Alcohol drinking increases risks of NonB/C-HCC and liver-related death.
- Both heart disease and diabetes are associated with the risk of NonB/C-HCC.
- Elevated AST and ALT are major risk factors for NonB/C-HCC and liver-related death.
- Prevention and treatment of diabetes and heart disease are critical for NonB/C-HCC.

Lay summary

We followed up individuals with no chronic HBV or HCV infection and described the risk of hepatocellular carcinoma (HCC, the most common form of primary liver cancer) and mortality from liver-related disease by modifiable risk factors. This study estimated the incidence rate of HCC by selected lifestyle risk factors and chronic diseases conditions. Alcohol consumption, heart disease, diabetes, and abnormal blood liver function tests showed a strong association with HCC risk and mortality.

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Research article

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Incidence of hepatocellular carcinoma in a community-based Taiwanese population without chronic HBV/HCV infection

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Background & Aims: In addition to HBV/HCV causing hepatocellular carcinoma (HCC), other risk factors including obesity and alcohol drinking also increase risk. We describe the cumulative risk of HCC and mortality from liver-related disease by selected modifiable risk factors among a non-hepatitis virus-infected population.

Methods: For a community-based cohort, residents aged 30–65 years living in 7 townships in Taiwan were recruited, and have been followed up since 1991. A total of 18,541 individuals were seronegative for markers of chronic infection of HBV/HCV and with no history of HCC at baseline. New non-HBV/HCV HCC cases and liver-related deaths were ascertained through data linkage to the National Cancer Registry and Death Certification System from 1 January 1991 through 31 December 2017.

Results: There were 207 HCC cases and 215 liver-related deaths identified. The incidence rate of non-HBV/HCV HCC was 47.2 per 100,000 person-years. The mortality rate of liver-related death was 49.0 per 100,000 person-years. Baseline information on alcohol consumption, heart disease, diabetes, elevated aspartate aminotransferase, and alanine aminotransferase predicted higher risks of HCC, with hazard ratios (HRs) (95% CIs) of 1.7 (1.1–2.5), 2.2 (1.1–4.1), 1.9 (1.0–3.5), 1.7 (1.1–2.4), and 1.6 (1.0–2.4), respectively. The HRs (95% CIs) of liver-related death were 2.3 (1.6–3.2) for alcohol consumption, 1.4 (1.1–1.9) for BMI ≥25 kg/m^2, 2.2 (1.4–3.3) for elevated aspartate aminotransferase, and 1.5 (1.0–2.4) for elevated alanine aminotransferase. The HR (95% CI) was 8.1 (3.6–18.5) for those with diabetes and elevated aspartate aminotransferase.

Conclusions: Individuals with elevated liver enzymes are at high risk of liver disease. Prevention and treatment of diabetes and heart disease are critical for non-hepatitis B, non-hepatitis C (NonB/C)-HCC.

Lay summary: We followed up individuals with no chronic HBV or HCV infection and described the risk of hepatocellular carcinoma (HCC, the most common form of primary liver cancer) and mortality from liver-related disease by modifiable risk factors. This study estimated the incidence rate of HCC by selected lifestyle risk factors and chronic diseases conditions. Alcohol consumption, heart disease, diabetes, and abnormal blood liver function tests showed a strong association with HCC risk and mortality.

Introduction

Chronic liver diseases (CLDs) represent an important public health issue because of poor long-term clinical outcome, including premature death from liver cirrhosis and hepatocellular carcinoma (HCC).[1] CLDs rank 23rd among the leading causes of the global burden of disease.[1] HCC, the major type of liver cancer, is one of the few cancers showing upward trends worldwide[2] and is the third leading cause of cancer-related death.[3] Although HBV/HCV contributes a large proportion of HCCs globally,[4] mortality from CLDs and HCC associated with infection is decreasing because of the implementation of HBV vaccination programmes[5] and the efficacy of antiviral treatments.[6,7] In contrast, the burden of non-hepatitis B, non-hepatitis C (NonB/C)-HCC is increasing and largely is attribute to the unabated obesity/metabolic syndrome epidemic as well as heavy alcohol use.[8–10]

Current clinical guidelines recommend biannual HCC screening using ultrasonography only in high-risk populations, mainly individuals with liver cirrhosis.[11] However, NonB/C-HCCs

Keywords: Alcohol drinking; Cumulative incidence; Diabetes; Epidemiology; Hepatocellular carcinoma; Liver-related death; Non-hepatitis B, non-hepatitis C HCC; Non-viral HCC; Obesity; Smoking.

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are often diagnosed at a more advanced stage and are less likely to have periodic intensive medical assessments than are viral-related HCCs.[12–14] The median survival is lower in NonB/C-HCC cases than in viral-related cases (2.3 *vs.* 1.7 years of follow-up, p <0.001).[14] Examining the characteristic of patients with NonB/C-HCC, a study in China found that 64% of patients did not have evidence of cirrhosis.[15] The AASLD recommends offering surveillance when the risk of HCC is at least 1.5% per year.[16] A detailed understanding of the cumulative risk of HCC by different modifiable risk factors will be useful to identify people at risk, thus enhancing HCC surveillance.

Using information from a community-based Cancer Screening Program (CSP) cohort, we had previously reported the natural history of HBV/HCV-related HCC among participants who were seropositive for the HBsAg or antibodies against HCV (anti-HCV).[17,18] In the present population-based, long-term prospective study, we followed up a total of 18,541 individuals who were seronegative for HBsAg and anti-HCV at study entry. The goals were to describe the cumulative risk of NonB/C-HCC and NonB/C-liver-related death (LRD) among the general population who were negative for seromarkers of chronic infection with HBV and HCV in Taiwan, an endemic area of chronic HBV.

Patients and methods

Study population and design

Participants were from the CSP cohort recruited in Taiwan. The cohort characteristics and methods of screening and follow-up have been described in detail previously.[17] Briefly, individuals who were between 30 and 65 years old and lived in 7 townships in Taiwan were recruited between 1991 and 1992. A total of 11,973 males and 11,847 females agreed to participate in this study and provided written informed consent for the questionnaire interview, biospecimen collection, health examinations, and computerised data linkage of health status with the national cancer registry and death certification system. Strict quality controls and safeguards were used to protect confidentiality.

This prospective study used information from a total of 18,541 participants who were seronegative for the HBsAg and anti-HCV at study entry. All study participants were without HCC at enrolment. Participants were followed up through 31 December 2017 for HCC status and LRD. This study was approved by Columbia University's Institutional Review Board as well as the Research Ethics Committee of the College of Public Health, National Taiwan University. Fig. S1 shows the flow of participants from the CSP cohort.

Interview and biospecimen collection at recruitment

During the recruitment, all participants were interviewed in person using a structured questionnaire, administered by well-trained public health nurses to collect epidemiological information including cigarette smoking, alcohol drinking, and self-report on medical condition including diabetes, hypertension, and heart disease. Habitual cigarette smoking and alcohol drinking were defined as smoking and/or drinking alcohol containing products >4 days/week for at least 6 months. Anthropometric measurements including height, weight, hip, and waist were recorded using standardised protocols during the interview. Using standard sterile techniques, we collected a 10-ml blood sample from each participant and stored it at -80°C after processing. A spot urine sample was also collected and stored at -80°C.

Blood samples were tested for serological markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), α-foetoprotein (AFP), total cholesterol, triglycerides, serum uric acid, creatinine, HBsAg, and anti-HCV. HBsAg, anti-HCV, and AFP were tested by enzyme immunoassay using commercial kits (Abbott Laboratories, North Chicago, IL, USA). Both ALT and AST levels were determined with a serum chemistry autoanalyser (Hitachi Model 736; Hitachi Co., Tokyo, Japan) using commercial reagents (Biomerieux, Mercy I'Etoile, France). Urine samples were tested for ketones, glucose, urinary protein, pH level, and haematuria using dipstick paper (Siemens Labstix SG Reagent Strips 2181, Tarrytown, NY).

Ascertainment of HCC and LRD

Newly developed HCCs were ascertained by computerised data linkage with the National Cancer Registry and the National Death Certification System from 1 January 1991 through 31 December 2017. New LRDs were ascertained by computerised data linkage with the National Death Certification System from 1 January 1991 through 31 December 2017. Ascertainment of newly developed HCC and deaths were considered complete and accurate. International Classification of Diseases, 9th Revision and 10th Revision (ICD-9 and ICD-10, respectively), codes were used to define outcomes. In total, we identified 213 incident HCC cases (ICD-9 codes: 155; ICD-10 code: C22.0) and 220 LRDs (ICD-9 codes: 155, 571, 456, 570, and 572; ICD-10 code: C22, K70, K71, K74, K75, K76, and I85) occurring during the follow-up period. We excluded 6 HCC cases and 5 LRDs that occurred within 1 year after recruitment (see Fig. S1). The overall follow-up rate is 98%. We included 207 HCCs and 215 LRDs in the final data analysis.

Statistical methods

Incidence rates for outcomes per 100,000 person-years and 95% CIs were calculated as the number of outcomes (NonB/C-HCC and NonB/C-LRD) divided by the person-years at risk of the underlying population. Any 2 rates with CIs that did not overlap were considered significantly different. For NonB/C-HCC, follow-up (in years) was considered as the time interval between the study entry and the earliest of these endpoints: date of NonB/C-HCC diagnosis, date of death, or end of follow-up in the absence of NonB/C-HCC development (31 December 2017), whichever came first. For NonB/C-LRD, analysis time (in years) was the time interval between the study entry and the date of NonB/C-LRD, date of death other than NonB/C-LRD, or the end of follow-up (31 December 2017), whichever came first. To estimate the effect of various variables on the hazard of outcomes including NonB/C-HCC and NonB/C-LRD, we used Cox proportional hazards regression models to calculate hazard ratios (HRs) and their 95% CIs. We used follow-up time as the time scale and Schoenfeld's global test to test the assumption of proportional hazards. Variables that were significantly associated with outcomes in the age- and sex-adjusted model defined as p <0.25 were considered as the potential risk factors. We then used stepwise regression analysis to determine whether covariates were included in the multivariable models, beginning with all potential risk factors and retain covariates with p <0.25. We omitted cases with missing data and analysed the remaining data. This approach is

Table 1. Baseline demographic and clinical characteristics of the study population.

	Population at risk N = 18,541 n(%)	NonB/C-HCC cases N = 207 n (%)	NonB/C-LRD N = 215 n (%)
Sex			
Female	9,481 (51.1)	88 (42.5)	75 (34.9)
Male	9,060 (48.9)	119 (57.5)	140 (65.1)
Age at recruitment (years)			
Mean (SD) (years)	47.3 (10.0)	54.1 (8.2)	53.3 (8.9)
<40	5,582 (30.1)	16 (7.7)	27 (12.6)
40–50	4,811 (26.0)	37 (17.9)	37 (17.2)
50–60	5,666 (30.6)	96 (46.4)	92 (42.8)
60–70	2,482 (13.4)	58 (28.0)	59 (27.4)
Educational level			
Illiterate	3,967 (21.4)	70 (33.8)	63 (29.3)
Elementary	7,712 (41.6)	90 (43.5)	98 (45.6)
Middle, high school	5,308 (28.6)	38 (18.4)	44 (20.5)
Undergraduate	1,544 (8.3)	9 (4.4)	10 (4.6)
Missing	10	0	0
Cigarette smoking			
No	13,270 (71.7)	129 (62.6)	121 (56.5)
Yes	5,236 (28.3)	77 (37.4)	93 (43.5)
Missing	35	1	1
Alcohol consumption			
No	16,544 (89.4)	167 (81.1)	158 (73.8)
Yes	1,953 (10.6)	39 (18.9)	56 (26.2)
Missing	44	1	1
BMI (kg/m^2)			
Mean (SD) (kg/m^2)	24.0 (3.4)	24.7 (3.5)	25.1 (3.7)
<18.5	583 (3.2)	9 (4.4)	7 (3.2)
18.5–22.9	6,846 (37.0)	60 (29.0)	60 (27.9)
23–24.9	4,385 (23.7)	42 (20.3)	40 (18.6)
25–29.9	5,795 (31.3)	81 (39.1)	87 (40.5)
≥30	887 (4.8)	15 (7.2)	21 (9.6)
Missing	45	0	0
BMI (kg/m^2)			
<25	11,814 (63.8)	111 (53.6)	107 (49.8)
≥25	6,682 (36.1)	96 (46.4)	108 (50.2)
Central obesity*			
No	12,812 (69.3)	116 (56.0)	111 (51.6)
Yes	5,676 (30.7)	91 (44.0)	104 (48.4)
Missing	53	0	0
Abdominal obesity†			
No	9,945 (53.8)	83 (40.1)	74 (34.4)
Yes	8,540 (46.2)	124 (59.9)	141 (65.6)
Missing	56	0	0
Self-report heart disease			
No	18,142 (98.2)	196 (95.2)	206 (96.3)
Yes	342 (1.8)	10 (4.8)	8 (3.7)
Missing	57	1	1
Self-report hypertension			
No	17,360 (93.9)	183 (88.8)	189 (88.3)
Yes	1,124 (6.1)	23 (11.2)	25 (11.7)
Missing	57	1	1
Self-report diabetes			
No	18,034 (97.5)	193 (93.7)	202 (94.4)
Yes	454 (2.5)	13 (6.3)	12 (5.6)
Missing	53	1	1
Elevated serum AST‡ at recruitment (IU/L)			
No	16,376 (88.6)	157 (76.6)	158 (74.2)
Yes	2,099 (11.4)	48 (23.4)	55 (25.8)
Missing	66	2	2
Elevated serum ALT§ at recruitment (IU/L)			
No	16,542 (89.5)	161 (78.5)	164 (77.4)
Yes	1,934 (10.5)	44 (21.5)	48 (22.6)
Missing	65	2	3
AST/ALT ratio at recruitment			
<1	4,578 (24.8)	59 (28.8)	53 (25.0)
≥1	13,874 (75.2)	146 (71.2)	159 (75.0)
Missing	89	2	3
AFP at recruitment (ng/ml)			
<5	15,502 (83.7)	161 (78.2)	165 (77.5)
5+	3,022 (16.3)	45 (21.8)	48 (22.5)
Missing	17	1	2
Serum triglyceride at recruitment (mg/dl)			
<200	15,389 (83.0)	156 (74.4)	160 (74.4)
≥200	3,152 (17.0)	51 (24.6)	55 (25.6)
Serum cholesterol at recruitment (mg/dl)			
<240	16,715 (90.2)	177 (85.5)	184 (85.6)
≥240	1,826 (9.8)	30 (14.5)	31 (14.4)
Hyperuricaemia# at recruitment			
No	15,199 (82.0)	165 (79.7)	161 (74.9)
Yes	3,342 (18.0)	42 (20.3)	54 (25.1)
Elevated serum creatinine¶ at recruitment			
No	16,537 (89.2)	187 (90.3)	198 (92.1)
Yes	2,004 (10.8)	20 (9.7)	17 (7.9)
Urine ketone at recruitment (mg/dl)			
Negative	17,868 (97.3)	198 (97.1)	207 (97.6)
≥5	499 (2.7)	6 (2.9)	5 (2.4)
Missing	174	3	3
Urine glucose at recruitment (mg/dl)			
Negative	17,757 (96.7)	195 (95.6)	202 (95.3)
≥100	609 (3.3)	9 (4.4)	10 (4.7)
Missing	175	3	3
Blood in urine at recruitment			
Negative	16,921 (92.1)	187 (91.7)	197 (92.9)
Positive	1,445 (7.9)	17 (8.3)	15 (7.1)
Missing	175	3	3
Urine pH at recruitment			
5	3,661 (19.9)	38 (18.6)	36 (17.0)
6, 7	13,049 (71.4)	151 (74.0)	156 (73.6)
8, 9	1,658 (9.0)	15 (7.4)	20 (9.4)
Missing	173	3	3
Urinary protein (mg/dl)			
Negative	15,212 (82.8)	164 (80.4)	164 (77.4)
≥15	3,156 (17.2)	40 (19.6)	48 (22.6)
Missing	173	3	3

AFP, α-foetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma; NonB/C-LRD, non-hepatitis B, non-hepatitis C liver-related death.

* Central obesity as a waist circumference >90 cm for males and >80 cm for females.

† Abdominal obesity as a waist–hip ratio above 0.90 for males and above 0.80 for females.

‡ Elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females.

§ Elevated ALT as ALT ≥30 IU/L for males and ≥19 IU/L for females.

Hyperuricaemia as serum uric acid level >7.0 mg/dl in men and >6 mg/dl in women.

¶ Abnormal serum creatinine as creatinine ≥1.1 mg/dl in women and ≥1.3 mg/dl in men.

known as the complete cases (or available case) analysis or listwise deletion.

We defined central obesity as a waist circumference >90 cm for men and >80 cm for women. We used the current World Health Organization (WHO) BMI cut-off points for Asian populations to categorise BMI (kg/m^2) into underweight (<18.5),

Table 2. Estimated incidence rate and HR of selected variables at baseline for NonB/C-HCC.

	HCC cases N = 207	Person-years (438,494)	Incidence rate, per 100,000 (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)[¶¶]
Sex					
Female	88	231,465	38.0 (30.5–46.8)	1.0	1.0
Male	119	207,029	57.5 (47.6–68.8)	1.6 (1.2–2.1)	1.4 (1.0–1.8)
Age at recruitment (years)					
<40	16	141,881	11.3 (6.4–18.3)	1.0	
40–50	37	119,044	31.1 (21.9–42.8)	2.8 (1.6–5.0)	
50–60	96	129,325	74.2 (60.1–90.7)	7.0 (4.1–11.9)	
60–70	58	48,243	120.2 (91.3–155.4)	12.5 (7.2–21.8)	
Educational level					
Illiterate	70	89,220	78.5 (61.6–98.5)	1.0	1.0
Elementary	90	180,229	50.0 (40.4–61.1)	0.6 (0.5–0.9)	0.9 (0.7–1.3)
Middle, high school	38	130,188	29.3 (21.0–39.7)	0.4 (0.2–0.5)	0.9 (0.6–1.3)
Undergraduate	9	38,640	23.3 (11.4–42.7)	0.3 (0.1–0.6)	0.7 (0.3–1.4)
Cigarette smoking					
No	129	321,424	40.1 (33.6–47.5)	1.0	1.0
Yes	77	116,267	66.2 (52.6–82.3)	1.7 (1.3–2.3)	1.5 (1.2–2.0)[¤¤]
Alcohol consumption					
No	167	394,384	42.3 (36.2–49.3)	1.0	1.0
Yes	39	43,115	90.5 (64.3–123.7)	2.2 (1.6–3.1)	2.0 (1.4–2.9)[¤¤]
BMI (kg/m^2)					
<18.5	9	13,238	68.0 (33.2–124.8)	1.9 (0.9–3.8)	2.2 (1.1–4.5)[¤¤]
18.5–22.9	60	164,031	36.6 (28.2–46.8)	1.0	1.0
23–24.9	42	104,850	40.1 (29.2–53.6)	1.1 (0.7–1.6)	1.0 (0.7–1.4)
25–29.9	81	135,260	59.9 (47.9–74.4)	1.7 (1.2–2.3)	1.4 (1.0–1.9)[¤¤]
≥30	15	20,081	74.7 (43.4–120.4)	2.1 (1.2–3.7)	1.7 (0.9–3.0)
BMI (kg/m^2)					
<25	111	282,119	39.4 (32.4–47.4)	1.0	1.0
≥25	96	155,342	61.8 (50.1–75.5)	1.6 (1.2–2.1)	1.4 (1.0–1.8)[¤¤]
Central obesity[*]					
No	116	307,446	37.7 (31.2–45.3)	1.0	1.0
Yes	91	129,834	70.1 (56.4–86.1)	1.9 (1.5–2.5)	1.3 (0.9–1.7)
Abdominal obesity[†]					
No	83	240,922	34.5 (27.4–42.7)	1.0	1.0
Yes	124	196,279	63.2 (52.6–75.3)	1.9 (1.4–2.5)	1.2 (0.9–1.7)
Self-report heart disease					
No	196	430,121	45.6 (39.4–52.4)	1.0	1.0
Yes	10	7,083	141.2 (67.6–259.6)	3.3 (1.7–6.2)	2.4 (1.3–4.6)[¤¤]
Self-report hypertension					
No	183	413,898	44.2 (38.0–51.1)	1.0	1.0
Yes	23	23,305	98.7 (62.5–148.1)	2.4 (1.5–3.7)	1.4 (0.9–2.2)
Self-report diabetes					
No	193	429,142	45.0 (38.9–51.8)	1.0	1.0
Yes	13	8,130	160.0 (85.1–273.4)	4.1 (2.3–7.2)	2.5 (1.4–4.3)[¤¤]
Elevated serum AST[‡] at recruitment (IU/L)					
No	157	388,500	40.4 (34.3–47.3)	1.0	1.0
Yes	48	48,449	99.1 (73.0–131.4)	2.5 (1.8–3.5)	2.0 (1.5–2.8)[¤¤]
Elevated serum ALT[§] at recruitment (IU/L)					
No	161	392,244	41.1 (35.0–47.9)	1.0	1.0
Yes	44	44,743	98.3 (71.5–132.0)	2.4 (1.8–3.4)	2.2 (1.6–3.1)[¤¤]
AST/ALT ratio					
<1	59	107,084	55.1 (41.9–71.1)	1.0	1.0
≥1	146	329,294	44.3 (37.4–52.1)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
AFP at recruitment (ng/ml)					
0–5	161	369,113	43.6 (37.1–50.9)	1.0	1.0
5+	45	69,020	65.2 (47.6–87.2)	1.5 (1.1–2.1)	1.4 (0.9–1.9)
Serum triglyceride at recruitment (mg/dl)					
<200	156	367,577	42.4 (36.0–49.7)	1.0	1.0
≥200	51	70,917	71.9 (53.5–94.6)	1.7 (1.3–2.4)	1.4 (1.0–2.0)[¤¤]
Serum cholesterol at recruitment (mg/dl)					
<240	177	397,406	44.5 (38.2–51.6)	1.0	1.0
≥240	30	41,087	73.0 (49.3–104.2)	**1.7 (1.1–2.5)**	1.2 (0.8–1.8)

(*continued on next page*)

Table 2 (*continued*)

	HCC cases N = 207	Person-years (438,494)	Incidence rate, per 100,000 (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)††
Hyperuricaemia¶ at recruitment					
No	165	362,276	45.6 (38.9–53.1)	1.0	1.0
Yes	42	76,218	55.1 (39.7–74.5)	1.2 (0.9–1.7)	1.1 (0.8–1.5)
Elevated serum creatinine** at recruitment					
No	187	394,020	47.5 (40.9–54.8)	1.0	1.0
Yes	20	44,474	45.0 (27.5–69.5)	1.0 (0.6–1.55)	0.8 (0.5–1.2)
Urine ketone at recruitment (mg/dl)					
Negative	198	422,546	46.9 (40.6–53.9)	1.0	1.0
≥5	6	11,927	50.3 (18.4–109.5)	1.1 (0.5–2.4)	1.5 (0.7–3.3)
Urine glucose at recruitment (mg/dl)					
Negative	195	423,215	46.1 (39.8–53.0)	1.0	1.0
≥100	9	11,242	80.1 (36.5–152.0)	**2.0 (1.1–3.9)**	1.4 (0.7–2.7)
Blood in urine at recruitment					
Negative	187	400,875	46.7 (40.2–53.8)	1.0	1.0
Positive	17	33,583	50.6 (19.5–81.1)	1.1 (0.7–1.8)	1.0 (0.6–1.7)
Urine pH at recruitment					
6, 7	151	307,998	49.0 (41.7–57.3)	1.0	1.0
5	38	87,755	43.3 (38.5–58.8)	0.9 (0.6–1.2)	1.0 (0.7–1.4)
8, 9	15	38,754	38.7 (22.5–62.4)	0.8 (0.5–1.4)	0.8 (0.5–1.4)
Urinary protein (mg/dl)					
Negative	164	362,926	45.2 (39.7–53.7)	1.0	1.0
≥15	40	71,584	55.9 (40.0–76.5)	1.3 (0.9–1.8)	1.1 (0.8–1.6)

Numbers in bold indicate p <0.25. AFP, α-foetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HR, hazard ratio; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma.
* Central obesity as a waist circumference >90 cm for men and >80 cm for women.
† Abdominal obesity as a waist–hip ratio above 0.90 for males and above 0.80 for females.
‡ Elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females.
§ Elevated ALT as ALT ≥30 IU/L for males and ≥19 IU/L for females.
¶ Hyperuricaemia as serum uric acid level >7.0 mg/dl in men and >6 mg/dl in women.
** Abnormal serum creatinine as creatinine ≥1.1 mg/dl in women and ≥1.3 mg/dl in men.
†† Age (continuous value)-adjusted Cox proportional hazards regression model.
‡‡ Level of significance: p <0.25.

normal (18.5–22.9), overweight (23–24.9), obese (25–29.9), and extremely obese (≥30).[19] We defined abdominal obesity as a waist–hip ratio above 0.90 for males and above 0.80 for females. We defined elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females with the same definition for elevated ALT as suggested by the American College of Gastroenterology Clinical Gudeline.[20] Hyperuricaemia was defined as serum uric acid level >7.0 mg/dl in men and >6 mg/dl in women. The abnormal creatinine was defined as >1.1 mg/dl in women and >1.3 mg/dl in men.

To estimate the proportion of NonB/C-HCC and NonB/C-LRD that may have been avoided by selected risk factors, we calculated population attribute risk percentage (PAR%) using the following formula: PAR% = $(I_{total} - I_{nonexposed})/I_{total}$, where I_{total} is the incidence of the outcome in the population and $I_{nonexposed}$ is the incidence of the outcome in the nonexposed population. We set the significance level 2-sided p value at <0.05. All analyses were performed with SAS software 9.4 (SAS Institute, Cary, NC, USA).

Results

Table 1 presents the baseline characteristics for the total population at risk and by NonB/C-HCC cases and NonB/C-LRD. The mean ages were 47.3, 54.1, and 53.3 years for the total population at risk, NonB/C-HCC, and NonB/C-LRD, respectively. Among NonB/C-HCC, 37% were cigarette smokers, and 19% had a habit of alcohol drinking. Among NonB/C-LRD, 44% and 26% had a history of cigarette smoking and alcohol drinking, respectively. The prevalence of cigarette smoking and alcohol drinking was 28% and 11%, respectively, among the total population at risk. BMI above 25 kg/m^2 was found in 46% of NonB/C-HCC, 50% of NonB/C-LRD, and 36% of the total population at risk. Self-reported diabetes was documented in 6% of NonB/C-HCC and NonB/C-LRD and only 3% of the total population at risk. The prevalence of elevated AST and ALT at baseline was about 11% in the population. Among NonB/C-HCC, the prevalence at baseline was 23% for elevated AST and 22% for elevated ALT. Among NonB/C-LRD, the prevalence was 26% and 23% for elevated AST and ALT, respectively.

Incidence rates of NonB/C-HCC and mortality rates of NonB/C-LRD

During a total of 438,494 person-years of follow-up, 207 NonB/C-HCC were identified (incidence rate: 47.2 per 100,000 person-years), whereas during 438,886 person-years of follow-up, 215 NonB/C-LRD occurred (mortality rate: 49.0 per 100,000 person-years). Tables 2 and 3 present the incidence rates of NonB/C-HCC and the mortality rates of NonB/C-LRD by selected risk factors, respectively. Alcohol drinking was associated with higher incidence rates per 100,000 person-years of NonB/C-HCC (90.5 *vs.* 42.3) and NonB/C-LRD (129.7 *vs.* 40.0), compared with

Table 3. Estimated mortality rate and HR of selected variables at baseline for NonB/C-LRD.

	LRD N = 215	Person-years (438,886)	Incidence rate, per 100,000 (95% CI)	Crude HR (95% CI)	Age-adjusted HR (95% CI)[††]
Sex					
Female	75	231,676	32.3 (25.5–40.6)	1.0	1.0
Male	140	207,210	67.6 (56.8–79.7)	2.1 (1.6, 2.8)	1.9 (1.5, 2.6)[‡‡]
Age at recruitment (years)					
<40	27	141,913	19.0 (12.8–27.3)	1.0	
40–50	37	119,132	31.9 (22.9–43.3)	1.7 (1.0, 2.7)	
50–60	92	129,490	71.8 (58.3–87.6)	3.9 (2.6, 6.0)	
60–70	59	48,351	128.4 (99.3–163.5)	7.3 (4.6, 11.6)	
Educational level					
Illiterate	63	89,336	70.5 (54.7–89.6)	1.0	1.0
Elementary	98	180,426	54.3 (44.3–65.9)	0.8 (0.6, 1.0)	1.1 (0.8, 1.4)
Middle, high school	44	130,249	31.6 (22.2–42.0)	0.5 (0.3, 0.7)	1.1 (0.7, 1.6)
Undergraduate	10	38,657	25.9 (13.1–46.1)	0.4 (0.2, 0.7)	0.8 (0.4, 1.6)
Cigarette smoking					
No	121	321,683	37.6 (31.4–44.8)	1.0	1.0
Yes	93	116,395	79.9 (64.9–97.4)	2.2 (1.7, 2.9)	2.0 (1.5, 2.6)[*]
Alcohol consumption					
No	158	394,711	40.0 (34.0–46.8)	1.0	1.0
Yes	56	43,176	129.7 (98.0–168.4)	3.3 (2.5–4.5)	3.1 (2.3–4.2)[‡‡]
BMI (kg/m^2)					
<18.5	7	13,250	52.8 (23.1–104.5)	1.5 (0.7–3.2)	1.7 (0.8–3.7)
18.5–22.9	60	164,137	36.6 (28.1–46.7)	1.0	1.0
23–24.9	40	104,937	38.1 (27.6–51.4)	1.0 (0.7–1.6)	0.9 (0.6–1.4)
25–29.9	87	135,416	64.3 (51.8–78.9)	1.8 (1.3–2.5)	1.5 (1.1–2.1)[‡‡]
≥30	21	20,113	104.4 (66.4–156.9)	2.9 (1.8–4.9)	2.4 (1.5–3.9)[‡‡]
BMI (kg/m^2)					
<25	107	282,324	37.9 (31.1–45.8)	1.0	1.0
≥25	108	155,529	69.4 (57.0–83.8)	1.9 (1.4–2.4)	1.6 (1.2–2.1)[‡‡]
Central obesity[*]					
No	111	307,656	36.1 (29.7–44.5)	1.0	1.0
Yes	104	130,017	80.0 (65.4–96.9)	2.2 (1.7–3.0)	1.6 (1.2–2.1)[‡‡]
Abdominal obesity[†]					
No	74	241,107	30.7 (24.1–38.5)	1.0	1.0
Yes	141	196,488	71.8 (60.4–84.6)	2.4 (1.8–3.2)	1.7 (1.3–2.2)[‡‡]
Self-report heart disease					
No	206	430,490	47.9 (41.5–54.9)	1.0	1.0
Yes	8	7,106	112.6 (48.5–221.8)	2.5 (1.2–5.0)	1.9 (0.9–3.8)
Self-report hypertension					
No	189	414,257	45.6 (39.4–52.6)	1.0	1.0
Yes	25	23,338	107.1 (69.3–158.1)	2.5 (1.6–3.8)	1.6 (1.0–2.4)[‡‡]
Self-report diabetes					
No	202	429,515	47.0 (40.8–54.0)	1.0	1.0
Yes	12	8,149	147.3 (76.0–257.2)	3.5 (2.0–6.3)	2.2 (1.2–4.0)[‡‡]
Elevated serum AST[‡] at recruitment (IU/L)					
No	158	388,766	40.6 (34.6–47.5)	1.0	1.0
Yes	55	48,563	113.3 (85.3–147.4)	2.8 (2.1–3.8)	2.4 (1.7–3.2)[‡‡]
Elevated serum ALT[§] at recruitment (IU/L)					
No	164	392,554	41.8 (35.6–48.7)	1.0	1.0
Yes	48	44,815	107.1 (79.0–142.0)	2.6 (1.9–3.6)	2.4 (1.7–3.3)[‡‡]
AST/ALT ratio					
<1	53	107,197	49.4 (37.0–64.7)	1.0	1.0
≥1	159	329,564	48.3 (41.0–56.4)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
AFP at recruitment (IU/L)					
0–5	165	369,404	44.7 (38.1–52.0)	1.0	1.0
5+	48	69,123	69.4 (51.2–92.1)	1.6 (1.1–2.2)	1.4 (1.0–2.0)[‡‡]
Serum triglyceride at recruitment (mg/dl)					
<200	160	367,877	43.5 (37.0–50.8)	1.0	1.0
≥200	55	71,009	77.5 (58.4–100.8)	1.8 (1.3–2.5)	1.5 (1.1–2.1)[‡‡]
Serum cholesterol at recruitment (mg/dl)					
<240	184	397,745	46.3 (39.8–53.5)	1.0	1.0
≥240	31	41,141	75.4 (51.2–107.0)	1.7 (1.1–2.4)	1.3 (0.9–1.8)
Hyperuricaemia[¶] at recruitment					
No	161	362,588	44.4 (37.8–51.8)	1.0	1.0
Yes	54	76,298	70.8 (53.2–92.4)	1.6 (1.2–2.2)	1.5 (1.1–2.0)[‡‡]

(*continued on next page*)

Table 3 (*continued*)

	LRD N = 215	Person-years (438,886)	Incidence rate, per 100,000 (95% CI)	Crude HR (95% CI)	Age-adjusted HR (95% CI)[††]
Elevated serum creatinine[**] are recruitment					
No	198	394,349	50.2 (4.53–57.7)	1.0	1.0
Yes	17	44,537	38.2 (22.2–61.2)	0.8 (0.5–1.3)	0.6 (0.4–1.0)
Urine ketone at recruitment (mg/dl)					
Negative	207	422,924	48.9 (42.5–56.1)	1.0	1.0
≥5	5	11,933	41.9 (13.5–97.8)	0.9 (0.4–2.0)	1.1 (0.5–2.8)
Urine glucose at recruitment (mg/dl)					
Negative	202	423,588	48.4 (42.1–55.4)	1.0	1.0
≥100	10	11,254	107.1 (58.0–182.1)	**2.1 (1.1–3.9)**	1.5 (0.8–2.9)
Blood in urine at recruitment					
Negative	197	401,233	49.1 (42.5–56.5)	1.0	1.0
Positive	15	33,610	44.6 (25.0–73.6)	0.9 (0.5–1.6)	0.8 (0.5–1.4)
Urine pH at recruitment					
6, 7	156	308,307	50.6 (43.1–59.0)	1.0	1.0
5	36	87,801	41.0 (29.2–56.2)	0.8 (0.6–1.2)	0.9 (0.6–1.3)
8, 9	20	38,786	51.6 (32.4–78.2)	1.0 (0.6–1.6)	1.0 (0.6–1.6)
Urinary protein (mg/dl)					
Negative	164	363,234	45.2 (38.5–52.6)	1.0	1.0
≥15	48	71,661	67.0 (49.4–88.8)	**1.5 (1.1–2.1)**	1.4 (0.9–1.9)

Numbers in bold indicate p <0.25. AFP, α-foetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; LRD, liver-related death; NonB/C-LRD, non-hepatitis B, non-hepatitis C liver-related death.
[*] Central obesity as a waist circumference >90 cm for males and >80 cm for females.
[†] Abdominal obesity as a waist–hip ratio above 0.90 for males and above 0.80 for females.
[‡] Elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females.
[§] Elevated ALT as ALT ≥30 IU/L for males and ≥19 IU/L for females.
[¶] Hyperuricaemia as serum uric acid level >7.0 mg/dl in men and >6 mg/dl in women.
[**] Abnormal serum creatinine as creatinine ≥1.1 mg/dl in women and ≥1.3 mg/dl in men.
[††] Age (continuous value)-adjusted Cox proportional hazards regression model.
[‡‡] Level of significance: p <0.25.

non-drinkers. Among individuals with BMI ≥25 kg/m^2, 96 developed NonB/C-HCC during a follow-up of 155,342 person-years (incidence rate: 61.8 per 100,000 person-years), whereas 108 NonB/C-LRD occurred during a follow-up of 155,529 person-years (mortality rate: 69.4 per 100,000 person-years). The incidence rates (95% CIs) per 100,000 person-years of NonB/C-HCC were 160.0 (85.1–273.4) for individuals with self-reported diabetes. The mortality rates per 100,000 person-years of NonB/C-LRD were 147.3 for self-reported diabetes and 107 for self-reported hypertension. Compared with normal AST, elevated AST was associated with higher incidence rates per 100,000 person-years of NonB/C-HCC (99.1 *vs.* 40.4) and NonB/C-LRD

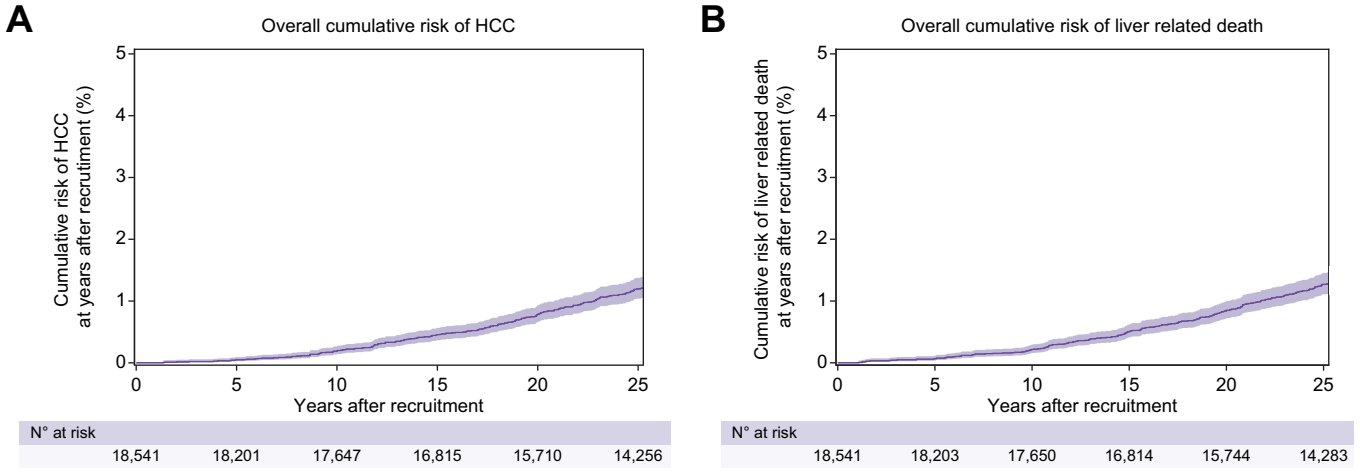


Fig. 1. The cumulative risk with 95% CIs of NonB/C-HCC and LRDs among individuals without chronic HBC/HCV infection. (A) The cumulative risk with 95% CIs (1.31%, 1.14–1.51%) of NonB/C-HCC among individuals without chronic HBC/HCV infection during 1991 to 1992 and a follow-up period that ended in December 2017. (B) The cumulative risk with 95% CIs (1.37%, 1.19–1.58%) of LRDs among individuals without chronic HBC/HCV infection during 1991 to 1992 and a follow-up period that ended in December 2017. HCC, hepatocellular carcinoma; LRD, liver-related death; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma.

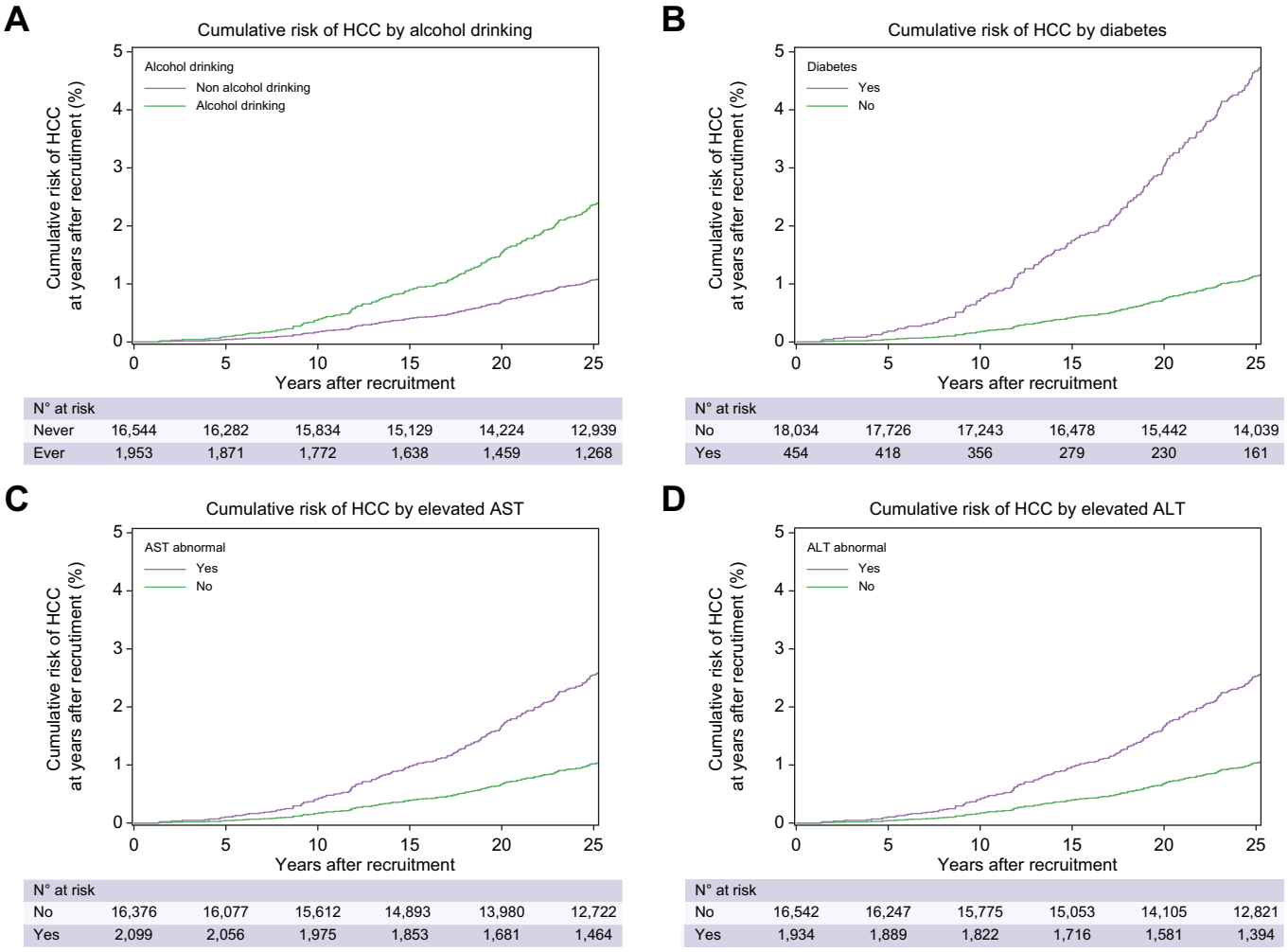


Fig 2. The cumulative risk of NonB/C-HCC by selected risk factors among individuals without chronic HBV/HCV infection. (A) The cumulative risks (95% CIs) for alcohol drinking status were 2.60% (1.90–3.57%) for ever drinker and 1.18% (1.01–1.37%) for never drinker. (B) The cumulative risks (95% CIs) for diabetes (yes *vs.* no) were 5.14% (2.98–8.87%) and 1.25% (1.08–1.44%). (C) The cumulative risks (95% CIs) for elevated AST (yes *vs.* no) were 2.80% (2.11–3.73%) and 1.12% (0.96–1.32%). (D) The cumulative risks (95% CIs) for elevated ALT (yes *vs.* no) were 2.79% (2.07–3.75%) and 1.14% (0.98–1.33%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma.

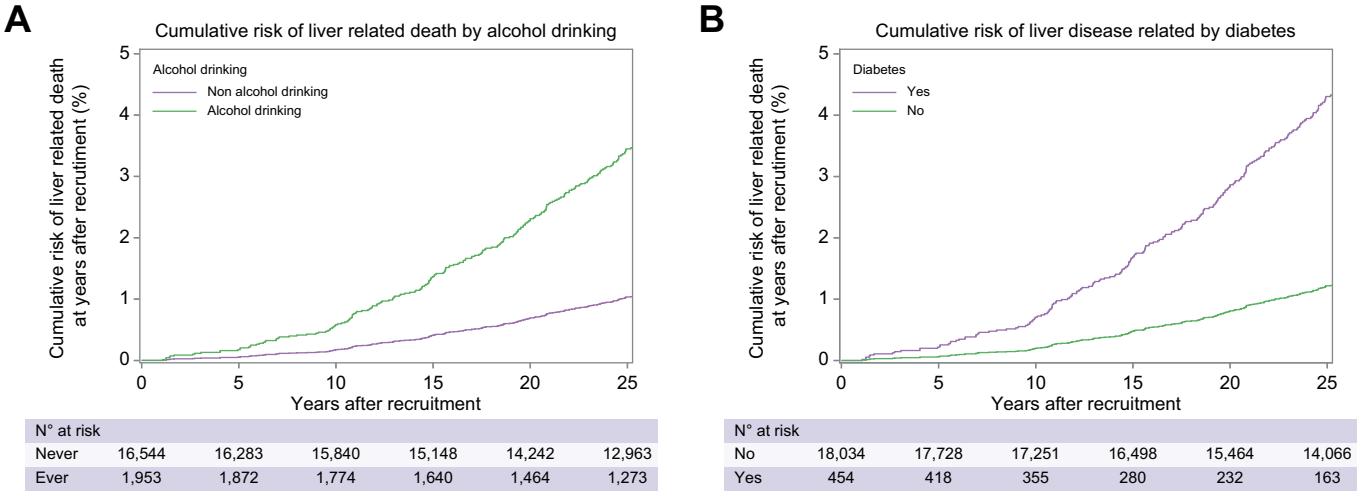
(113.3 *vs.* 40.6). Similarly, individuals with elevated ALT had higher incidence rates for both NonB/C-HCC (98.3 *vs.* 41.1 per 100,000 person-years) and NonB/C-LRD (107.1 *vs.* 41.8 per 100,000 person-years) than those without.

Cumulative incidences

The overall cumulative risk (95% CI) was 1.31% (1.14–1.51%) at the end of 26 years of follow-up for NonB/C-HCC and 1.37% (1.19, 1.58%) for NonB/C-LRD (Fig. 1). Figs. 2 and 3, respectively, present the cumulative incidence of NonB/C-HCC and NonB/C-LRD associated with alcohol drinking, diabetes, and liver enzymes. The cumulative incidence of NonB/C-HCC was positively associated with alcohol drinking (2.60%, 95% CI 1.90–3.57%) compared with no alcohol drinking (1.18%, 95% CI 1.01–1.37%; Fig. 2A). The cumulative risks (95% CIs) of diabetes for NonB/C-HCC and NonB/C-LRD were 5.14% (2.98–8.87%) and 4.66% (2.64–8.24%), respectively, compared with 1.25% (1.08–1.44%) and 1.32% (1.14–1.52%) for non-diabetic individuals (Figs. 2B and 3B). The cumulative incidence of NonB/C-HCC was positively associated with elevated AST (2.80 *vs.* 1.12%) and ALT (2.79 *vs.* 1.14%) (Fig. 2C and D). There was an increasing cumulative risk of NonB/C-LRD for elevated AST (3.21%, 95% CI 2.46–4.19%) and ALT (3.04%, 95% CI 2.28–4.05%) compared with normal AST (1.14%, 95% CI 0.97–1.33%) and ALT (1.17%, 95% CI 1.00–1.37%) (Fig. 3C and D). Figs. 2 and 3 present selected risk factors including smoking, obesity, heart disease, hypertension, elevated AFP, triglyceride, and cholesterol.

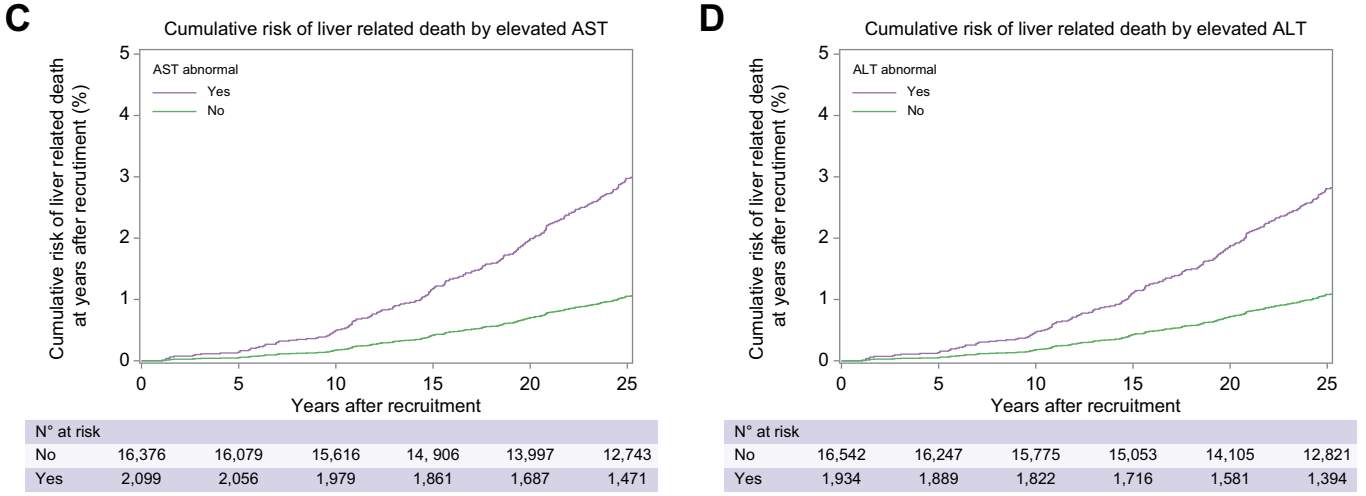
Age-adjusted HRs

Table 2 presents the age-adjusted relative risk (95% CI) of NonB/C-HCC by risk factors. Male sex (HR 1.4, 95% CI 1.0–1.8), cigarette smoking (HR 1.5, 95% CI 1.2–2.0), alcohol drinking (HR 2.0, 95% CI



N° at risk						
Never	16,544	16,283	15,840	15,148	14,242	12,963
Ever	1,953	1,872	1,774	1,640	1,464	1,273

N° at risk						
No	18,034	17,728	17,251	16,498	15,464	14,066
Yes	454	418	355	280	232	163



N° at risk						
No	16,376	16,079	15,616	14, 906	13,997	12,743
Yes	2,099	2,056	1,979	1,861	1,687	1,471

N° at risk						
No	16,542	16,247	15,775	15,053	14,105	12,821
Yes	1,934	1,889	1,822	1,716	1,581	1,394

Fig. 3. The cumulative risk of NonB/C-LRDs by selected risk factors among individuals without chronic HBV/HCV infection. (A) The cumulative risks (95% CIs) for alcohol drinking status were 3.73% (2.86–4.87%) for ever drinker and 1.12% (0.95–1.32%) for never drinker. (B) The cumulative risks (95% CIs) for diabetes (yes *vs.* no) were 4.66% (2.64–8.24%) and 1.32% (1.14–1.52%). (C) The cumulative risks (95% CIs) for elevated AST (yes vs. no) were 3.21% (2.46–4.19%) and 1.14% (0.97–1.33%). (D) The cumulative risks (95% CIs) for elevated ALT (yes ***vs***. no) were 3.04% (2.28–4.05%) and 1.17% (1.00–1.37%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; LRD, liver-related death; NonB/C-LRD, non-hepatitis B, non-hepatitis C liver-related death.

1.4–2.9), BMI ≥25 kg/m^2 (HR 1.4, 95% CI 1.0–1.8), self-reported heart disease (HR 2.4, 95% CI 1.3–4.6), diabetes (HR 2.5, 95% CI 1.4–4.3), elevated AST level (HR 2.0, 95% CI 1.5–2.8), elevated ALT level (HR 2.2, 95% CI 1.6–3.1), and triglyceride ≥200 mg/dl (HR 1.4, 95% CI 1.0–2.0) were significantly associated with NonB/C-HCC and were adjusted for in further multiple regression analyses.

Table 3 presents the age-adjusted relative risk (95% CI) of NonB/C-LRD by risk factors. Similar to the results for NonB/C-HCC risk, male sex (HR 1.9, 95% CI 1.5–2.6), cigarette smoking (HR 2.0, 95% CI 1.5–2.6), alcohol drinking (HR 3.1, 95% CI 2.3–4.2), BMI ≥25 kg/m^2 (HR 1.6, 95% CI 1.2–2.1), self-reported hypertension (HR 1.6, 95% CI 1.0–2.4), self-reported diabetes (HR 2.2, 95% CI 1.2–4.0), elevated AST level (HR 2.4, 95% CI 1.7–3.2), and elevated ALT level (HR 2.4, 95% CI 1.7–3.3) were significantly associated with NonB/C-LRD. In addition, higher levels of selected blood markers were associated with NonB/C-LRD. The HRs (95% CIs) were 1.4 (1.0–2.0) for AFP (≥5 *vs.* <5 ng/ml), 1.5 (1.1–2.1) for triglyceride (≥200 *vs.* <200 mg/dl), and 1.5 (1.1–2.0) for hyperuricaemia.

Multivariable-adjusted HRs

In the multivariable-adjusted model, alcohol drinking (HR 1.7, 95% CI 1.1–2.5), self-reported heart disease (HR 2.2, 95% CI 1.1–4.1), self-reported diabetes (HR 1.9, 95% CI 1.0–3.5), elevated AST (HR 1.7, 95% CI 1.1–2.4), and elevated ALT (HR 1.6, 95% CI 1.0–2.4) remained significantly associated with NonB/C-HCC risk (Table 4). Alcohol drinking (HR 2.3, 95% CI 1.6–3.2), obesity (HR 1.4, 95% CI 1.1–1.9, for BMI ≥25 *vs.* <25 kg/m^2), elevated AST (HR 2.2, 95% CI 1.4–3.3), and elevated ALT (HR 1.5, 95% CI 1.0–2.4) remained significantly associated with NonB/C-LRD (Table 4). Both central obesity and abdominal obesity were also associated with LRD (Tables S1 and S2).

PAR%

We estimated that the PAR% of alcohol drinking was 10.1% for NonB/C-HCC risk and 18.1% for NonB/C-LRD. For NonB/C-HCC, 3.3% and 4.5% were attributed to heart disease and diabetes, respectively. The PAR% of elevated AST and ALT for NonB/C-HCC was 13.9% and 12.5%, respectively. The corresponding PAR% for

Table 4. HRs (95% CIs) for NonB/C-HCC and NonB/C-LRD in a multivariable model and estimated PAR%.

	Multivariable model[§]	*p* value	PAR%
HCC			
Cigarette smoking (yes *vs.* no)	1.4 (0.9–2.0)	0.12	
Alcohol consumption (yes *vs.* no)	1.7 (1.1–2.5)	0.01[¶]	10.1 (4.8–16.7)
BMI (kg/m^2) (≥25 *vs.* <25)	1.2 (0.9–1.6)	0.20	
Heart disease (yes *vs.* no)	2.2 (1.1–4.1)	0.02[¶]	3.3 (1.0–7.3)
Diabetes (yes *vs.* no)	1.9 (1.0–3.5)	0.03[¶]	4.5 (1.9–8.9)
Elevated AST (IU/L)[*]	1.7 (1.1–2.4)	0.01[¶]	13.9 (7.9–20.9)
Elevated ALT (IU/L)[†]	1.6 (1.0–2.4)	0.04[¶]	12.5 (6.8–19.4)
Serum triglyceride (mg/dl) (≥200 *vs.* <200)	1.1 (0.8–1.6)	0.60	
LRD			
Cigarette smoking (yes *vs.* no)	1.4 (0.9–2.0)	0.07	
Alcohol consumption (yes *vs.* no)	2.3 (1.6–3.2)	<0.0001[¶]	18.1 (12.1–25.1)
BMI (kg/m^2) (≥25 *vs.* <25)	1.4 (1.1–1.9)	0.01[¶]	22.8 (12.5–33.1)
Hypertension (yes *vs.* no)	1.2 (0.7–1.8)	0.48	
Diabetes (yes *vs.* no)	1.7 (0.9–3.1)	0.11	
Elevated AST (IU/L)[*]	2.2 (1.4–3.3)	<0.0001[¶]	16.6 (10.5–23.6)
Elevated ALT (IU/L)[†]	1.5 (1.0–2.4)	0.04[¶]	13.8 (8.1–20.6)
AFP (ng/ml) (≥5 *vs.* <5)	1.0 (0.7–1.5)	0.79	
Serum triglyceride (mg/dl) (≥200 *vs.* <200)	1.1 (0.8–1.5)	0.69	
Hyperuricaemia[‡] (yes *vs.* no)	1.1 (0.7–1.4)	0.76	

AFP, α-foetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HR, hazard ratio; LRD, liver-related death; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma; NonB/C-LRD, non-hepatitis B, non-hepatitis C liver-related death; PAR%, population attribute risk percentage.
[*] Elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females.
[†] Elevated ALT as ALT ≥30 IU/L for males and ≥19 IU/L for females.
[‡] Hyperuricaemia as serum uric acid level >7.0 mg/dl in men and >6 mg/dl in women.
[§] Multivariable cox proportional hazards regression model.
[¶] Level of significance: p <0.05.

Table 5. The combined effects of alcohol consumption, diabetes, and elevated liver enzyme on NonB/C-HCC risk.

Liver enzyme	Variable	Age- and sex-adjusted HR[‡] (95% CI)
Elevated AST[*]	Alcohol consumption	
No	No	1.0
No	Yes	1.7 (1.1–2.6)[§]
Yes	No	2.2 (1.5–3.2)[§]
Yes	Yes	4.8 (2.4–9.6)[§]
Elevated AST[*]	Diabetes	
No	No	1.0
No	Yes	1.8 (0.8–3.8)
Yes	No	2.2 (1.6–3.2)[§]
Yes	Yes	8.1 (3.6–18.5)[§]
Elevated AST[*]	Heart disease	
No	No	1.0
No	Yes	2.6 (1.3–5.3)[§]
Yes	No	2.4 (1.7–3.4)[§]
Yes	Yes	3.9 (0.9–15.7)
Elevated ALT[‡]	Alcohol consumption	
No	No	1.0
No	Yes	1.7 (1.1–2.6)[§]
Yes	No	2.1 (1.4–3.1)[§]
Yes	Yes	5.3 (2.7–10.3)[§]
Elevated ALT[‡]	Diabetes	
No	No	1.0
No	Yes	1.3 (0.5–3.2)
Yes	No	2.1 (1.4–3.0)[§]
Yes	Yes	8.5 (4.2–17.4)[§]
Elevated ALT[‡]	Heart disease	
No	No	1.0
No	Yes	1.9 (0.9–4.4)
Yes	No	2.3 (1.6–3.2)[§]
Yes	Yes	7.1 (2.6–19.1)[§]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; NonB/C-HCC, non-hepatitis B, non-hepatitis C hepatocellular carcinoma.
[*] Elevated AST as AST ≥30 IU/L for males and ≥19 IU/L for females.
[†] Elevated ALT as ALT ≥30 IU/L for males and ≥19 IU/L for females.
[‡] Age (continuous value)- and sex-adjusted Cox proportional hazards regression model.
[§] Level of significance: p <0.05.

NonB/C-LRD was 16.6% and 13.8% for elevated AST and ALT, respectively. The PAR% of BMI ≥25 kg/m^2 was 22.8%.

Interaction effect

Table 5 presents the interaction effect of elevated AST with alcohol consumption and diabetes. The HRs (95% CIs) were 4.8 (2.4–9.6) for individuals with alcohol consumption and elevated AST and 8.1 (3.5–18.5) for diabetes and elevated AST.

Discussion

Examining the temporal trend of HCC across 3 decades in Singapore where HBV infection is high, Goh *et al.*[10] observed that non-viral aetiology increased over time, while the percentage of HBV-related HCC decreased. This observation suggests changes in the distribution of risk factors. A detailed understanding of the epidemiology, molecular mechanisms, and prognosis associated with NonB/C-HCC could improve our screening and therapy for this disease. Consistent with other studies,[21,22] our study highlights the importance of alcohol consumption and metabolic risk factors, possibly through fatty liver disease in NonB/C-HCC. In addition, our study shows that the incidence of NonB/C-HCC and mortality from NonB/C-LRD are considerably high even among individuals without chronic HBV or HCV infection but with elevated levels of blood liver function tests.

Using information from the Taiwan Liver Cancer Network, Huang *et al.*[21] reported that diabetes was associated with non-viral HCC, especially for patients without alcoholism. We observed about a 2-fold increased risk of NonB/C-HCC associated with diabetes using information collected from participants by questionnaire during recruitment. Nearly a quarter of people with diabetes are unaware of their diabetes condition in the general Taiwanese population,[23] suggesting the association might be an underestimation. In our study, the reason that the association of being overweight with risk of NonB/C-HCC

disappeared in the multivariable model might be attributable to the strong relationship between increased BMI and prevalence of diabetes.[24]

We found alcohol consumption contributed to about 10% of NonB/C-HCC. In our study, the majority of alcohol drinkers (77%) had consumed alcohol regularly for more than 10 years. This suggests that our observation might be related to long-term alcohol consumption. We did not collect more detail information regarding drinking patterns or daily consumption amount and thus were not able to further explore the dose–response relationship.

Elevated ALT or AST is associated with liver-related mortality[25] and HCC risk.[26,27] Several risk stratification models include AST/ALT to rationalise HCC surveillance decisions.[27,28] Some fibrosis scores use blood markers including AST/ALT to identify advanced fibrosis in patients with CLDs.[29] These observations suggest that serum levels of AST and ALT are important seromarkers in clinical management for identifying a subgroup of individuals without chronic HBV/HCV infection who need to be monitored periodically for end-stage liver disease.[30] We did not collect liver cirrhosis information from the questionnaire, or blood markers. Several non-invasive liver fibrosis tests have been developed to evaluate liver steatosis and fibrosis. However, we did not measure platelets, which is the key blood measurement for fibrosis-4 (FIB-4), and non-alcohol fatty liver disease fibrosis score.[31]

To our knowledge, our study is the longest follow-up study to assess the incidence of NonB/C-HCC and LRD across different host factors, history of medical conditions and clinical blood tests from a community setting; understanding the natural history of HCC among a community-based population with no hepatitis virus infection will help identify at-risk populations for HCC surveillance. However, the results of our study need to be interpreted with caution owing to some limitations. First, similar to other studies,[21] we cannot rule out the effect of past or current HBV infection in HCC risk. Prior HBV infection is relatively common in Taiwan. Before a national HBV vaccination programme was implemented in 1984, the prevalence of chronic HBV infection in the general population in Taiwan was up to 20%.[32] Anti-hepatitis B core (HBc) positivity was reportedly associated with an increased risk of HCC among HBsAg-negative individuals with CLD.[33,34] In our ongoing work, we measured hepatitis B core-related antigen (HBcrAg) in a subset of our cohort participants who were seronegative for both HBsAg and anti-HCV (129 HCC and 520 controls). We observed that the prevalence of HBcrAg levels >600 U/ml were 18% and 2% in cases and controls, respectively (HI Yang *et al.*, manuscript in preparation). Similarly, we were not able to rule out the effect of ongoing HCV infection as we did not have information other than anti-HCV.

Another limitation is medical history was self-reported, and we cannot exclude the possibility of underestimation of risk ratio results from non-differential misclassification. Both blood and urine tests associated with metabolic factors were based on one-time measurement. Given the long-term follow-up, it is likely that many variables/risk factors that played a major role in disease progression might change during the study. Examining the trajectories of blood tests is required to better understand the utility of blood tests for clinical management of end-stage liver diseases. However, in our subgroup data analysis based on years of follow-up, the effect of history of heart disease, diabetes, and alcohol consumption was consistently positively associated with NonB/C-HCC. These observations suggest that these risk factors might be involved in cancer initiation and progression. Lastly, although this study, to our knowledge, is the largest population study examining the epidemiology of end-stage liver disease among a population with low risk of HCC, the modest sample size still limits the power to estimate the potential interaction effects across different risk factors.

Given that the burden of CLD is expected to rise owing to increasing rates of alcoholism and obesity-related fatty liver disease, it is expected that the incidence of HCC will increase in the foreseeable future even among individuals without chronic infection of HBV/HCV. Our results suggest risk factors including diabetes and alcohol drinking are important to determine the risk for both HCC and LRD among individuals without HBV/HCV infection. Currently, routine screening for HCC in the population without HBV/HCV infection and cirrhosis is not typically recommended owing to the limitations of diagnostic tools. Concerted strategies need to be developed for HCC surveillance in at-risk populations. Prevention and treatment of diabetes and heart disease are critical for NonB/C-HCC.

Abbreviations

AFP, α-foetoprotein; ALT, alanine aminotransferase; anti-HCV, antibodies against HCV; AST, aspartate aminotransferase; CLD, chronic liver disease; CSP, Cancer Screening Program; FIB-4, fibrosis-4; HBc, hepatitis B core; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD-9, International Classification of Disease 9th Revision; ICD-10, International Classification of Diseases 10th Revision; LRD, liver-related death; NonB/C-HCC, non-hepatitits B, non-hepatitis C-hepatocellular carcinoma; NonB/C-LRD, non-hepatitis B, non-hepatitis C virus liver-related death; PAR%, population attribute risk percentage; WHO, World Health Organization.

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Conflicts of interest

The authors report no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Designed the study and collected data: HCW, HIY, CJC
Maintained the primary database and data linkage to tumour registry: MHP, CJC, HIY
Mainly conducted data analyses and wrote the manuscript: HCW
Reviewed and edited the manuscript: HCW, WJJ, MHP, YCH, SNL, CJC, HIY
Shared the corresponding authorship: HCW, HIY. All authors contributed substantially to the interpretation of data and the drafting or critical revision of the manuscript for important intellectual content. All authors assume full responsibility for analyses and interpretation of these data. The corresponding author attests that all listed authors meet authorship criteria and that those not meeting the criteria have been omitted.

Data availability statement

Contact the corresponding author at hiyang@gate.sinica.edu.tw for any inquiries regarding data or analytical code. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

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Supplementary data

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Author names in bold designate shared co-first authorship

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