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ORIGINAL RESEARCH

Cardiometabolic Comorbidities in Patients With Chronic Hepatitis B and Impact on Incidence of Liver Complications. A Danish Nationwide Cohort Study

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Purpose: To evaluate liver complications in patients with chronic hepatitis B, both with and without cardiometabolic comorbidities, and to compare the incidence of cardiometabolic comorbidities in these patients with that of the general population.

Study Population and Methods: This nationwide registry-based cohort study included data from 2002–2020. In the primary analysis, we used multivariate Poisson regression to estimate the incidence rate and incidence rate ratio of liver complications in patients with chronic hepatitis B, stratified by the presence of cardiometabolic comorbidities. In the secondary analysis, we compared the incidence rate of developing cardiometabolic comorbidities in patients with chronic hepatitis B to those of the general population. Both analyses were adjusted for sex, age, and country of origin, while the primary analysis was additionally adjusted for time since cardiometabolic comorbidity diagnosis and calendar year.

Results: The primary analysis included 4731 patients with chronic hepatitis B, of whom 532 (11%) had at least one cardiometabolic comorbidity. The unadjusted overall incidence rate of liver complications in patients with cardiometabolic comorbidities was 1.0 per 100 person-years (95% confidence intervals: 0.84–1.30) compared to 0.4 per 100 person-years (95% confidence intervals: 0.30–0.42) in those without. The incidence rate ratio for liver complications was highest in the first year following the diagnosis of cardiometabolic comorbidity. The incidence rate ratio for developing cardiometabolic comorbidities in the chronic hepatitis B cohort compared to the general population, was 1.10 (95% confidence intervals: 1.02–1.19). Sensitivity analyses revealed a higher incidence rate ratio for type 2 diabetes and hypertension but a lower incidence rate ratio for hypercholesterolemia.

Conclusion: Patients with chronic hepatitis B and cardiometabolic comorbidities exhibit a higher incidence of liver complications, particularly in the first year following comorbidity diagnosis compared to those without comorbidities. Furthermore, patients with chronic hepatitis B have a higher incidence of cardiometabolic comorbidities than the general population.

Keywords: chronic hepatitis B, DANHEP, comorbidity, type 2 diabetes, hypertension, hypercholesterolemia, liver disease

Introduction

Worldwide, more than 300 million people have chronic hepatitis B (CHB), defined as hepatitis B surface antigen (HBsAg) in the blood for longer than six months.[1] In Denmark, the estimated prevalence of CHB is about 14,500 representing 0.3% of the total population. However, only around 50% have been referred to secondary care in hospital departments.[2]

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The hepatitis B virus (HBV) resides and replicates in the liver, which can lead to chronic inflammation, and an increased risk of liver complications such as fibrosis, cirrhosis, liver decompensation and hepatocellular carcinoma (HCC).[3,4] Although there is no cure for CHB, antiviral therapy can suppress virus replication, thereby reducing HBV-related morbidity and mortality by mitigating the progression of liver fibrosis.[5,6]

Globally, the incidence of cardiometabolic diseases is increasing at a rapid pace.[7,8] The liver plays a crucial role in the development of insulin resistance, which is associated with cardiometabolic conditions such as central obesity, metabolic syndrome, type 2 diabetes (T2D), hypertension, hypercholesterolemia, and metabolic dysfunction–associated steatotic liver disease (MASLD).[9,10] The mechanism involves hepatic fat accumulation because of altered lipid metabolism, inflammatory signals, and mitochondrial dysfunction.[11] In patients with CHB and cardiometabolic comorbidity there is a higher risk of liver fibrosis progression.[12] Furthermore, patients with CHB and cardiometabolic comorbidity exhibit a higher relative risk of HCC and liver-related mortality compared to those without comorbidities.[13] On an individual level, T2D was a risk factor for the development of HCC in patients with CHB, but the evidence was heterogeneous in this meta-analysis, and very few studies have been conducted in European CHB populations.[14]

Studies have shown that individuals with T2D are at a higher risk of having CHB,[15] MASLD and metabolic dysfunction-associated steatohepatitis (MASH).[16] Additionally, central obesity and low levels of high-density lipoprotein (HDL), which together with T2D are risk factors in the definition of "the metabolic syndrome", are risk factors for the progression of liver fibrosis.[12,17]

The pathophysiological interaction between CHB and cardiometabolic diseases is not well understood. Conflicting results have been observed in two larger Asian cohort studies, which reported both lower and higher prevalence of cardiometabolic comorbidities compared to the general population.[18,19]

Currently, there are no specific clinical guidelines for managing patients with CHB and concurrent cardiometabolic conditions, and none of the established HBV-related HCC risk scores incorporate cardiometabolic comorbidities.[6] Only for patients with CHB and renal transplants receiving antiviral treatment, it is recommended that T2D and hypertension should be optimally managed.[20] In the Danish national guidelines for CHB management, it is recommended that patients should be screened for metabolic liver disease, but there is no discussion of the impact of cardiometabolic conditions in the CHB population or guidance on the follow-up of patients with both CHB and cardiometabolic diseases. This indicates a significant gap in the knowledge and evidence regarding the interaction between CHB and cardiometabolic disease.

The primary purpose of this study was to estimate the incidence of liver complications in patients with CHB, both with and without cardiometabolic comorbidities. The secondary purpose was to investigate whether patients with CHB have a higher incidence of cardiometabolic comorbidities compared to the general population in Denmark.

Materials and Methods

This nationwide, registry-based, cohort study utilised data from multiple Danish registries covering the period from January 1, 2002, to December 31, 2020.

Data Sources

The Civil Registration System (CRS)

The Danish Civil Registration System (CRS) assigns a unique ten-digit personal identification number (PIN) to all residents of Denmark for administrative purposes.[21] This PIN is recorded each time an individual receives care in public or private healthcare institutions, enabling the comprehensive linkage of data across all nationwide Danish registries.

The Danish Database for Hepatitis B and C (DANHEP)

Established in 2002, DANHEP is a nationwide observational, prospective cohort study that includes patients aged 16 years or older with CHB or chronic hepatitis C (CHC). Patients are enrolled if they are admitted to hospital departments or outpatient clinics specialising in infectious diseases or gastroenterology. The database is estimated to capture approximately 30% of the CHB population in Denmark.[2] Outpatient follow-up visits are generally planned every 3, 6, or 12 months, depending on the severity of the disease.[22] DANHEP collects detailed demographic and clinical data, including sex, age at entry, country of origin, mode of transmission, laboratory results (for CHB: HBsAg, HBV- deoxyribonucleic acid (DNA), HBV-genotype, Hepatitis B e Antigen

(HBeAg)), measurement of liver fibrosis, and diagnosis of cirrhosis (via transient elastography (TE) or liver biopsy), treatment initiation date and regimen, hepatitis C virus (HCV) or human immunodeficiency virus (HIV) co-infection, and alcohol use. Data from DANHEP was limited to three of the five Danish regions from November 1, 2020, to December 31, 2020.

The National Patient Registry (NPR)

The NPR, established in 1976, contains data on dates of admission and discharge, ICD-10 diagnoses, treatment, examinations, and surgical procedures for all in- and out-patient hospital contacts in Danish hospitals.[23]

The Cause of Death Registry (CDR)

Established in 1943, the CDR includes all death certificates issued by medical doctors in Denmark, including the assessed cause of death diagnosis given by a certifying physician.[24]

The Registry of Pharmaceutical Sales (RPS)

The RPS, established in 1994, contains information on all prescribed medications sold or dispensed to the Danish population by pharmacies, medical practitioners, and hospitals. Drugs are classified using the Anatomical Therapeutic Chemical (ATC) classification system.[25]

The Danish Diabetes Registry (DDR)

Established in 2020, the DDR includes data on nearly all individuals diagnosed with diabetes in Denmark since 1990. For the purpose of this study, the registry was utilised to identify individuals with T2D. T2D cases were defined based on a hospital ICD-10 code of T2D, use of antidiabetic medicine recorded in the RPS, or follow-up with relevant healthcare providers (eg podiatrists, dieticians, ophthalmologists) as documented in the Danish Adult Diabetes Database (DADD), NPR, the Danish Clinical Quality Assurance Database for Screening of Diabetic Retinopathy and Maculopathy (DiaBase) using an algorithm developed by Carstensen et al.[26]

Definitions

Study Population

The study included all patients with CHB registered in DANHEP, aged 16 years or older from January 1, 2002, to December 31, 2020. To minimise the potential confounding effects of co-infections on cardiometabolic health, individuals co-infected with HCV and/or HIV were excluded. Additionally, for the primary analysis, patients with pre-existing liver complications were also excluded.

The inclusion criteria for the general population were age >16 and a valid PIN. The exclusion criteria included HCV or HIV.

Demographics

The Danish Civil Registration System was utilised to obtain demographic information, including sex, date of birth, date of death, country of origin, immigration- and emigration status. For patients with CHB, the country of origin was primarily based on self-reported data from DANHEP; for those with missing data and for the general population, the country of origin data was extracted from the Civil Registration System. Countries of origin were grouped into the following regions: Denmark, the Middle East, Asia, Africa, Europe, and All Other Countries. The latter category included individuals from Australia and the Americas, grouped due to their small sample size. The Middle East was defined as Western Asian countries according to the United Nations Statistics Division M49/revision 4 standard[27] (Appendix 2).

Clinical Characteristics

We used DANHEP to extract data for CHB patients regarding age at entry in DANHEP, mode of HBV transmission, laboratory results (HBsAg, HBeAg), and TE score. Excessive alcohol use was defined according to The Danish National Board of Health guidelines as consumption of >21 units per week for men and >14 units per week for women).

Outcomes

Cardiometabolic Comorbidities

Cardiometabolic comorbidities were defined as having been treated for one or more of the following conditions: T2D,

hypertension, or hypercholesterolemia. These conditions were chosen due to their common association with cardiovascular risk and their modifiability through medical or lifestyle interventions.

T2D was defined by the DDR algorithm.[26]

Hypertension was defined by the presence of at least two filled prescriptions for antihypertensive medication in the RPS, including ATC codes: C02 (antihypertensive agents), C03 (diuretic agents), C07 (beta-blocking agents), C08 (calcium channel blockers), C09 (agents acting on the renin-angiotensin system).

Hypercholesterolemia was defined by at least two filled prescriptions for cholesterol-lowering medication in the RPS including ATC code: C10 (lipid modifying agents).

The use of prescription records as indicators of hypertension and hypercholesterolemia was considered more reliable than hospital records, as these conditions are predominantly managed in primary healthcare facilities, and thus may not be consistently recorded in the NPR.

Liver Complications

Liver complications were defined as a diagnosis of cirrhosis, liver decompensation (eg, esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, or hepatic coma), HCC, liver transplantation, or liver-related mortality as recorded in DANHEP, CDR or NPR. Cirrhosis was further defined in DANHEP by one of the following criteria: Registration of a cirrhosis diagnosis, a transient elastography (TE)-score of >17 kilopascal (kPa) in the absence of elevated alanine aminotransferase (ALT) (ALT less than ten times higher than the upper limit of normal), or a Metavir score of F4 based on histological liver biopsy findings (see Appendix 3 for further details).

Statistical Analyses

Patient characteristics are presented as numbers (percentages) for categorical variables or medians (interquartile range (IQR)) for continuous variables. In the primary analysis, we calculated the incidence rate (IR) and incidence rate ratio (IRR) of liver complications in CHB patients with and without cardiometabolic comorbidities. A multistate model, constructed using Lexis objects, included the following states: CHB, CHB with cardiometabolic comorbidity, CHB with liver complications and CHB with both cardiometabolic comorbidities and liver complications (Supplementary Figure 1). The entry date for the primary analysis was the date of inclusion in DANHEP. Participants were followed until death, emigration, or December 31, 2020, whichever occurred first. Poisson regression was used to calculate transition rates between states. Age, time from cardiometabolic comorbidity, and calendar year were included as time scales with three-month intervals. Individuals could contribute risk time across multiple states. We adjusted for sex and country of origin.

In three sensitivity analyses, T2D, hypertension, and hypercholesterolemia were assessed as individual exposures, rather than as part of a composite cardiometabolic comorbidity measure, using the same modelling approach.

In the secondary analysis, we compared the incidence rate of cardiometabolic comorbidities between patients with CHB and the general population, using similar methods as described above. Follow-up began on January 1, 2002, the individual's 16th birthday, or the date of immigration to Denmark, whichever occurred later. The follow-up period ended on December 31, 2020, or at the time of death or emigration, whichever came first. This model was adjusted for sex, age, and country of origin. As with the primary analysis three sensitivity analyses were conducted with T2D, hypertension and hypercholesterolemia evaluated as individual outcomes.

Data management was performed using STATA version 16 (StataCorp). Statistical analyses were conducted in R version 4.2.2 utilising the Epi package version 2.47.1 for multistate models with Lexis objects.[28]

Results

Patient Characteristics

We identified 5256 patients with CHB enrolled in the DANHEP cohort from 2002–2020. A total of 525 patients were excluded due to co-infection with HCV (n = 204), HIV (n = 197), or the presence of liver complications before inclusion in the study (n = 124). After exclusion, 4731 patients with CHB were included in the primary analysis, contributing a total follow-up time of 42,887 person-years (PY). Demographic characteristics of the CHB cohort at baseline are presented in Table 1. Of the 532

Table 1 Demographic Characteristics of 4731 Patients With Chronic Hepatitis B, Comparing Those With Cardiometabolic Comorbidity at Baseline to Those Without. Patients Were, Included in The Danish Database for Hepatitis B and C (DANHEP) From January 1, 2002, to December 31, 2020

	All	Cardiometabolic Comorbidity	No Cardiometabolic Comorbidity
Number of CHB patients, n	4731	532	4199
Age at entering DANHEP (years (median, IQR))	34 (27–44)	53 (45–61)	32 (26–40)
Sex (female, n (%))	2504 (53)	261 (49)	2243 (53)
Country of origin, n (%)			
Denmark	599 (13)	142 (27)	457 (11)
Asia	1712 (36)	120 (23)	1592 (38)
Europe + other	848 (18)	82 (15)	766 (18)
Africa	730 (15)	56 (11)	674 (16)
Middle East	842 (18)	132 (25)	710 (17)
Transmission of hepatitis B, n (%)			
Vertical	1457 (31)	107 (20)	1.350 (32)
Sexual transmission, tattoo/piercing, blood, needle injury, or other	380 (8)	47 (9)	333 (8)
Intravenous drug use	107 (2)	15 (3)	92 (2)
Unknown	2787 (59)	363 (68)	2424 (58)
Antiviral treatment ever, n (%)	680 (14)	93 (17)	587 (14)
HBeAg status at baseline, n (%)			
Positive	831 (18)	66 (12)	765 (18)
Negative	3635 (77)	434 (82)	3201 (76)
Unknown	265 (6)	32 (6)	233 (32)
TE score – highest measured (kPa), median (IQR)	5.7 (4.7–7.2)	6.7 (5.1–8.9)	5.7 (4.7–7.0)
Alcohol overconsumption when entering DANHEP (>21 units/ week for men and >14 units/week for women)			
Yes, n (%)	146 (3)	23 (4)	123 (3)
No, n (%)	2528 (53)	271 (51)	2257 (54)
Unknown, n (%)	2057 (43)	238 (45)	1819 (43)
Cardiometabolic comorbidity at baseline, n (%)	532 (11)		
T2D, n (%)	129 (3)	129 (24)	
Hypertension, n (%)	445 (9)	445 (84)	
Hypercholesterolemia, n (%)	179 (4)	179 (34)	

Abbreviations: CHB, chronic hepatitis B; DANHEP, the Danish Database for Hepatitis B and C; HBeAg; hepatitis B e antigen; IDU, intravenous drug use; IQR, interquartile range; T2D, type 2 diabetes; TE, Transient elastography.

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patients with baseline cardiometabolic comorbidities, 56 (11%) had all three comorbidities, 29 (5%) had T2D only, 296 (56%) had hypertension only, and 42 (8%) had hypercholesterolemia only. The patients with CHB and cardiometabolic comorbidities were older, with a median age of 53 years (IQR: 45–6) compared to 32 years (IQR: 26–40) in those without cardiometabolic comorbidities. Additionally, the comorbidity included a higher proportion of men (51% vs 47%), and a higher percentage of individuals having Denmark as their country of origin (27% vs 11%). The median TE score was also higher in the comorbidity group (6.7 kPa, IQR 5.1 kPa – 8.9 kPa) compared to those without comorbidities (5.7 kPa IQR: 4.7 kPa-7.0 kPa). Vertical transmission was more prevalent in the non-comorbidity group (32% vs 20%), and more patients were HBeAg positive at inclusion (18% vs 12%), indicating a higher HBV DNA replication at study entry. Reported excessive alcohol use was low in both groups (4% vs 3%).

Occurrence of Liver Complications in CHB Patients With and Without Cardiometabolic Comorbidities

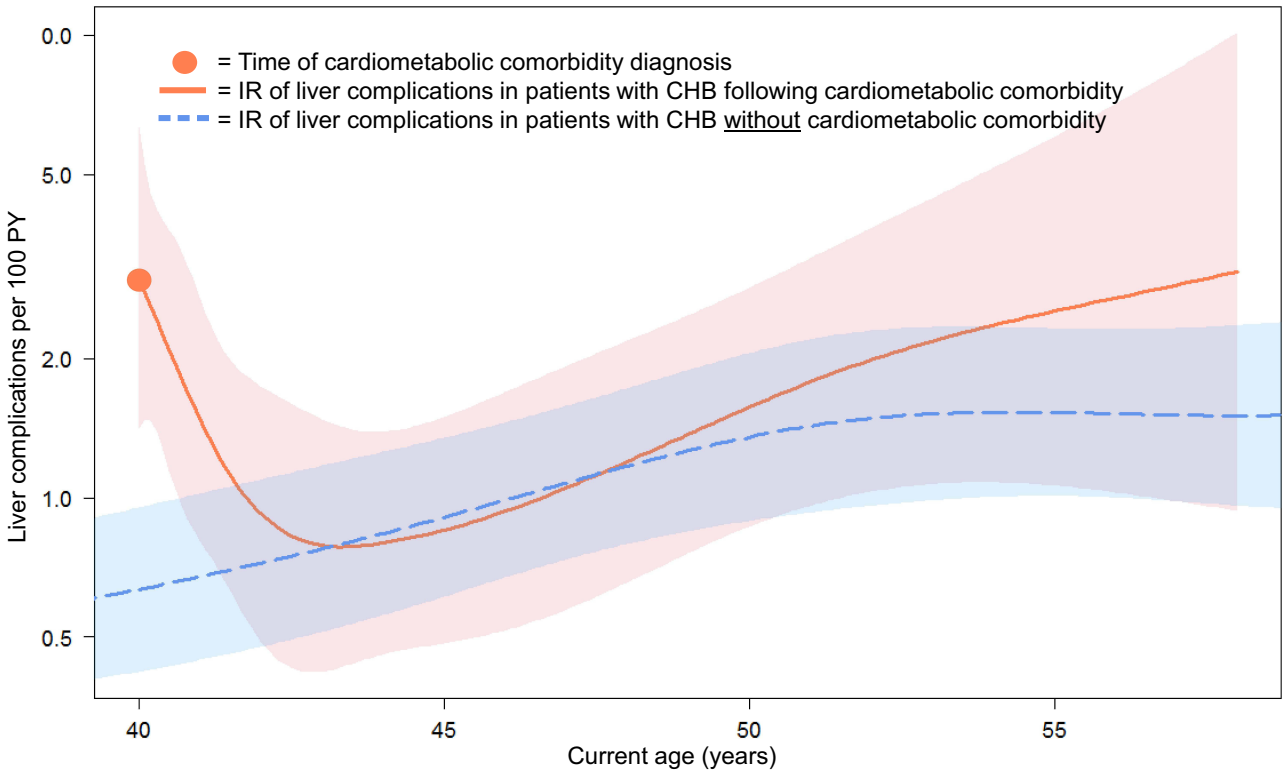
In patients with CHB and cardiometabolic comorbidities, 80 (7.3%) developed liver complications corresponding to an unadjusted IR: 1.0/100 person-years (PY). This rate was higher than observed in the non-comorbidity group, where 121 (2.9%) developed liver complications with an unadjusted IR: 0.4/100 PY (Table 2 and Supplementary Figure 1). The unadjusted IRR was 3.0 (95% CI: 2.2–3.9), and the adjusted IRR was 4.2 (95% CI: 2.1–8.5). The cumulative incidence over 18 years is 18% in CHB patients with cardiometabolic comorbidities, compared to 7% in those without (Supplementary Figure 4), indicating an absolute risk difference of 11%. The Poisson model was used to predict IRs and IRRs for varying strata determined by sex, age, country of origin, calendar year, and time from diagnosis of a cardiometabolic comorbidity.

As an example, we plotted the predicted IRs for a 40-year-old man from the Middle East (Figure 1) with a cardiometabolic comorbidity diagnosis at age 40 compared to a similar individual without a comorbidity diagnosis. The predicted IR is initially higher following the diagnosis of the cardiometabolic comorbidity, declining with a significant difference from the IR of a similar individual without comorbidity until 1.3 year. (Towards the end of the observation period, there is a trend of increasing IR (Figure 1). This tendency was observed for all population subgroups according to sex, age, country of origin, and calendar

Table 2 Rate of Liver Complications in Patients With Chronic Hepatitis B With -Versus Without Cardiometabolic Comorbidity

	Liver Complications, n	Unadjusted IRR per 100 PY (95% CI)	Adjusted IRR per 100 PY (95% CI)^
CHB	121	1 (Reference to below)	1 (Reference to below)
CHB and cardiometabolic comorbidity*	80	3.0. (2.2–3.9)	4.2 (2.1–8.5)
Sensitivity analysis			
Type 2 diabetes (T2D) as exposure			
CHB	172	1 (Reference to below)	1 (Reference to below)
CHB and T2D	29	3.2 (2.2–4.7)	6.4 (2.5–16.0)
Hypertension (HT) as exposure			
CHB	134	1 (Reference to below)	1 (Reference to below)
CHB and HT	67	2.8 (2.1–3.7)	3.9 (1.8–8.6)
Hypercholesterolemia (HC) as exposure			
CHB	176	1 (Reference to below)	1 (Reference to below)
CHB and HC	25	2.1 (1.4–3.2)	2.1 (0.6 −7.1)

Notes: *Cardiometabolic comorbidity= Type 2 diabetes, hypertension, and hypercholesterolemia, ^ adjusted for sex, age, time from cardiometabolic comorbidity diagnosis, calendar year and country of origin.
Abbreviations: CHB, chronic hepatitis B; CI, confidence intervals; IR, incidence rate; IRR, incidence rate ratio; PY, person-years; T2D, type 2 diabetes.



Cardiometabolic comorbidity	Time from cardiometabolic comorbidity (year)	IR (95 % CI) /100 PY	IRR (95 % CI)
No	NA	0.6 (0.4 – 1.0)	1 (reference to below)
Yes	0.1	2.7 (1.3 – 5.8)	4.2 (1.8 – 10.1)
Yes	1.3	1.2 (0.7 – 2.2)	2.0 (1.0 – 4.0)
Yes	3	0.8 (0.4 – 1.5)	1.2 (0.6 – 2.6)

Figure 1 Predicted incidence rates of liver complications per 100 person-years by current age in patients with chronic hepatitis B, stratified by presence (red) or absence (blue) of cardiometabolic comorbidity. Incidence rates are predicted from a Poisson model, assuming a male patient from the Middle East in 2010, with diagnosed cardiometabolic comorbidity at age 40.
Abbreviations: CI, confidence intervals; IR, incidence rate; IRR, incidence rate ratio; PY, person-years.

year (Supplementary Tables 1–4); This is also presented in Supplementary Figure 2, where the shape of the curve is similar across age groups. We observed that increasing age and male sex were associated with a higher IR of liver complications (Supplementary Tables 1 and 2). Additionally, the IR varied significantly based on the country of origin, with the highest rates observed in patients from Asia, followed by those from the Middle East, All Other Countries, Africa, and the lowest rates observed in patients from Denmark (Asia > Middle East > All Other Countries > Africa > Denmark; Supplementary Table 3 and Supplementary Figure 3). Additionally, higher IRs of liver complications were observed in earlier calendar years (2005 > 2007 > 2010 > 2015; Supplementary Table 4 and Supplementary Figure 3).

Sensitivity Analysis of Specific Cardiometabolic Comorbidities

When assessing T2D as a solitary exposure, the IRR for liver complications was significantly higher (IRR = 6.4, 95% CI: 2.5–16.0) compared to patients with CHB without T2D. Analysis of hypertension as a solitary exposure revealed an initially higher IR of liver complications following diagnosis, but the rate declined over time and became comparable to that of patients with CHB without hypertension within one year. For hypercholesterolemia, no difference in IR was observed (IRR = 2.1, 95% CI: 0.6–7.1), and there was no effect of time from hypercholesterolemia diagnosis on the incidence of liver complications. All IRs and IRRs are presented in Table 2.

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Incidence of Cardiometabolic Comorbidities in Patients With CHB Compared With the General Population

The IR of cardiometabolic comorbidities in patients with CHB was 1.9/100 PY, which was lower than the rate observed in the general population (2.5/100 PY), corresponding to an unadjusted IRR of 0.8 (95% CI: 0.7–0.9). However, after adjusting for sex, age, and country of origin, the IRR was elevated to 1.1 (95% CI: 1.0–1.2), indicating a higher incidence of cardiometabolic comorbidities in the CHB population (Table 3).

When using T2D as the sole outcome, the adjusted IRR was 1.3 (95% CI: 1.1–1.4), suggesting a significantly higher incidence of T2D in the CHB cohort. The same trend was observed for hypertension (IRR of 1.1, 95% CI: 1.0–1.2). Conversely, the incidence of hypercholesterolemia was significantly lower in the CHB cohort (IRR of 0.8, 95% CI: 0.7–0.9) compared to the general population (Table 3).

Discussion

In this nationwide, registry-based cohort study, we found that patients with CHB and cardiometabolic comorbidity had a higher IR of liver complications compared to those without such comorbidities. The difference was observed within approximately 1.3 years following the diagnosis of cardiometabolic comorbidity, varying by sex, age, country of origin and calendar year. Sensitivity analyses indicated that patients with CHB and T2D or hypertension exhibited higher IR of liver complications, whereas hypercholesterolemia did not show a significant association.

Our findings suggest that the critical point of being diagnosed with liver complications for patients with CHB typically occurs shortly after being diagnosed with cardiometabolic comorbidity. This may be attributed to detection bias, as patients with newly diagnosed cardiometabolic disease often undergo more frequent and extensive medical evaluations, increasing the

Table 3 Rate of Cardiometabolic Comorbidity in Patients With Chronic Hepatitis B Compared With the General Population in Denmark Based on Data From January 1, 2002, to December 31, 2020

Population	Cardiometabolic Comorbidities*, n	Unadjusted IR per 100 PY (95% CI)	Unadjusted IRR per 100 PY (95% CI)	Adjusted IRR per 100 PY (95% CI)^
General population	1,438,895	2.5 (2.5–2.5)	1 (Reference to below)	1 (Reference to below)
CHB	668	1.9 (1.8–2.1)	0.8 (0.7–0.9)	1.1 (1.0–1.2)
Sensitivity analysis				
Sensitivity analysis, type 2 diabetes (T2D) as the outcome				
	T2D, n			
General population	354,980	0.5 (0.5–0.5)	1 (Reference to below)	1 (Reference to below)
CHB	276	0.7 (0.6–0.8)	1.5 (1.3–1.7)	1.3 (1.1–1.4)
Sensitivity analysis, hypertension as the outcome				
	Hypertension, n			
General population	1,273,362	2.1 (2.1–2.1)	1 (Reference to below)	1 (Reference to below)
CHB	541	1.50 (1.4–1.6)	0.7 (0.7–0.8)	1.1 (1.0–1.2)
Sensitivity analysis, hypercholesterolemia as the outcome				
	Hypercholesterolemia, n			
General population	983,130	1.4 (1.4–1.4)	1 (Reference to below)	1 (Reference to below)
CHB	299	0.7 (0.7–0.8)	0.5 (0.5–0.6)	0.8 (0.7–0.9)

Notes: *Cardiometabolic comorbidity includes T2D, hypertension and hypercholesterolemia, ^ adjusted for sex, age, and country of origin.
Abbreviations: CHB, chronic hepatitis B; CI, confidence intervals; IR, incidence rate; IRR, incidence rate ratio; PY, person-years; T2D, type 2 diabetes.

likelihood of discovering liver disease. Previous studies, such as that by Bruijn et al, reported a threefold increase in cancer diagnoses within the first three months following T2D diagnosis.[29] Additionally, patients diagnosed with T2D generally receive more intensive treatment for hypertension and hyperlipidaemia compared to those without T2D or prediabetes, potentially lowering their risk of liver complications.[30,31] The observed trend of increasing risk during the later part of the follow-up period (Figure 1) indicates that patients with CHB with cardiometabolic disease do have an increased long-term risk of liver complications.

Our results highlight that the CHB population with cardiometabolic comorbidities is at higher risk of liver complications. Given the escalating global prevalence of obesity and T2D within the general population, patients with CHB may also be at increased risk of developing obesity, consequently leading to MASLD and thereby increasing hepatic inflammation.[32] Unfortunately, our study lacked registry data on MASLD. A study by Kim et al found that patients with CHB or CHC and MASLD, who also had T2D, had a higher risk of developing HCC, and improvements in blood sugar levels were associated with a lower risk of HCC.[33] A study by Huang et al, including 4084 patients with CHB, indicated that MASLD was associated with higher rates of HBsAg seroclearance compared to those without MASLD.[34] This is consistent with other studies showing higher HBsAg seroclearance rates in patients with MASLD[35] and an inverse correlation between hepatic steatosis and both HBeAg and HBV-DNA levels.[36] The underlying mechanisms for these associations remain poorly understood, but may involve steatosis-induced mitochondrial dysfunction[37] and endoplasmic reticulum stress in the hepatocytes, hindering HBsAg and HBV-DNA secretion, as demonstrated in mouse models.[38] Additionally, upregulation of Toll-like receptors and CD8+ T cells and natural killer cells may enhance immune responses, leading to increased seroclearance.[39,40]

Our findings indicate that patients with CHB and T2D have a higher IR of liver complications compared with CHB alone. A meta-analysis from 2015, found that patients with advanced liver disease stages such as cirrhosis were at higher risk of developing T2D,[41] underscoring the importance of considering the stage of liver disease in the CHB population. The increased risk may partly result from the insulin resistance associated with severe liver disease.[42] A meta-analysis by Zhou et al showed that metformin use is linked to a lower incidence of HCC, while use of insulin is associated with an increased risk.[31] It is worth noting that metformin is typically first-line treatment for T2D, while insulin is generally prescribed later in the treatment algorithm for those with more advanced T2D. Furthermore, a Turkish cohort study showed a correlation between elevated Hemoglobin A1c (HbA1c) levels and increased HBV-DNA levels.[32] Unfortunately, we could not investigate this relationship in our study due to limited access to HbA1c data. Given the evidence linking CHB and cardiometabolic comorbidities to increased liver complications, we recommend closer monitoring and more intensive management of cardiometabolic comorbidities in this population to reduce the risk of liver complications.

Our findings indicate that patients with CHB and hypertension have a higher IR of liver complications compared with CHB alone. Few studies have investigated the association between chronic viral hepatitis and hypertension. A Nepalese study involving 154 participants with either CHB or CHC, who were free from obesity and T2D suggested that the patients with essential hypertension exhibited higher cumulative survival rates and lower levels of inflammation in the liver compared to those with chronic viral hepatitis alone.[43] The authors concluded that these findings may be attributable to an unknown effect of antihypertensive medication. This may reflect the specific effect of individual antihypertensive medications. One study found that in patients with MASLD, treatment with Angiotensin-converting enzyme inhibitors was associated with a reduction in liver complications, whereas angiotensin receptor blockers did not show a significant difference in liver complications compared to MASLD patients who were not receiving antihypertensive treatment.[44]

In our study, we did not identify a significantly higher incidence of liver complications among patients with CHB and hypercholesterolemia. Since we used statin treatment use as an indicator of hypercholesterolemia, these results may reflect well-managed hypercholesterolemia and balanced lipid profiles. Previous research has shown that statin use is associated with a reduced risk of liver complications in individuals without CHB,[45,46] potentially due to mechanisms such as decreased oxidative stress and the inhibition of pro-inflammatory cytokines.[47] Furthermore, a prospective nationwide study from Sweden including 15,104 patients with CHB demonstrated a lower risk of HCC among statin users compared to those not treated with statins, suggesting a potential beneficial effect of statin use in CHB populations.[48] An important question is the interaction of antiviral treatment within the CHB population. The nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF) has been linked to an unfavourable effect on lipid profiles,

notably increasing the risk of hypercholesterolemia.[49] Conversely, other studies have reported that treatment with Tenofovir disoproxil (TDF) may lower the occurrence of hypercholesterolemia.[50] However, a study from Turkey including 165 patients with CHB receiving antiviral therapy found no significant difference in dyslipidaemia among the four compared antiviral treatments assessed,[51] although, it did report lower HDL, low-density lipoprotein (LDL), and total cholesterol in treated patients compared to those who were untreated.[51]

For liver complications in patients with CHB the adjusted IRR of 4.2 (95% CI: 2.1–8.5) suggests that patients with CHB and cardiometabolic comorbidities have over four times the rate of liver complications compared to CHB patients without comorbidities. However, focusing on the IRR alone may overestimate the clinical impact. The absolute risk difference is 13% after 18 years of follow-up (18% in CHB patients with cardiometabolic comorbidities, compared to 5% in those without; Supplementary Figure 4). However, we would like to highlight that this analysis is not adjusted for key variables such as age, sex, country of origin, and calendar year. As a result, the observed differences may partly reflect the fact that patients without cardiometabolic comorbidities are generally younger and, therefore, at a lower risk for both developing comorbidities and experiencing liver complications.

In our secondary analysis we observed a higher IR of cardiometabolic comorbidities in patients with CHB compared to the general population. This difference was primarily driven by T2D and hypertension, while hypercholesterolemia appeared to have the opposite effect, leading to a lower incidence in patients with CHB. These findings may suggest different pathophysiological pathways underlying the development of these comorbidities, indicating that using T2D, hypertension and hypercholesterolemia as a composite endpoint may be inappropriate for understanding the association between these conditions and CHB. In contrast, other studies have reported a lower occurrence of cardiometabolic comorbidities in patients with CHB compared to the general population. For example, an American registry study found that patients with CHB exhibited higher levels of HDL, lower waist circumference, and lower fasting glucose than those in the general population.[52] Interestingly, an inverse correlation has been noted between HBV-DNA levels and HDL.[53] A Chinese cohort study involving nearly 8000 patients with CHB also demonstrated lower rates of hypercholesterolemia despite a higher prevalence of abdominal obesity and a higher BMI.[54] Additionally, this study found that men with CHB had a lower rate of hypertension compared to those in the general population, although no such difference was observed in women.[54] The lower incidence of cardiometabolic comorbidity in CHB patients relative to the general population may also be attributed to more frequent interactions with the healthcare system, which include regular outpatient visits and management of comorbidities. Therefore, when comparing patients with CHB to the general population, it is essential to match groups according to sex, age, BMI, waist circumference and glucose tolerance -all critical factors influencing the risk of developing cardiometabolic diseases.

Our sensitivity analysis of the secondary analysis further indicated that the patients with CHB had a statistically significant 26% higher incidence of T2D compared with the general population, after adjusting for age, sex, and country of origin. These findings are supported by other research; a large, prospective cohort study from China reported an increase in T2D among 55,520 patients with CHB compared to the general population, yielding an adjusted hazard ratio (HR) of 1.2 (95% CI 1.0–1.4).[55] Similarly, a study from Korea found comparable results in a cohort of 8694 patients with CHB with an adjusted HR of 1.2 (95% CI: 1.1–1.4).[56]

Strengths and Limitations

This study has notable strengths, including its foundation on validated nationwide registries that can be linked through the unique PIN assigned to all individuals in the Danish Civil Registration System. Consequently, loss to follow-up was minimal, as individuals not emigrating remain continuously registered in the healthcare system. However, a key limitation is that the nationwide DANHEP registry is estimated to include only 30% of the total CHB population in Denmark,[2] primarily due to low referral rates from primary to specialised care.[57] However, this subset likely represents individuals more severely affected by their condition.

Moreover, the diagnosis of liver complications may be underestimated; to address this, we combined clinical data from DANHEP with the National Patient Registry. Nonetheless, some cases of liver complications may go undiagnosed, if not followed as intended in the specialised departments. Moreover, the cause of death may be inaccurate, given that autopsies are infrequently performed. A previous study indicates that discrepancies in cause-of-death classifications in up

to 30% of cases following autopsy.[58] However, we expect that possible underestimation of liver complications affects the group with and without cardio-metabolic comorbidities equally.

For hypertension and hypercholesterolemia diagnoses, we sought to minimise inaccuracies by using the Registry of Pharmaceutical Sales, only including patients who filled prescriptions for antihypertensive or lipid-lowering medications at least twice. Nevertheless, some individuals may not purchase their prescribed medications or purchase the medication but never administer it, leading to potential underestimation of these conditions. Access to clinical measurements, such as blood pressure and lipid profiles, could have enhanced diagnostic accuracy, but we lacked this data. While the Registry of Pharmaceutical Sales's accuracy is generally high due to automatic registration at Danish pharmacies, it may not capture patients obtaining medications online or abroad. On the other hand, it is a limitation that some of the patients might use these prescribed drugs to treat other medical diseases than hypertension or hypercholesterolemia, although we expect this number to be low.

Regarding the T2D diagnosis, a recent study investigating the validity of the Danish Diabetes Registry reported a high level of accuracy and completeness.[59] However, this study has never been published in a scientific journal. Thus, given the multi-source approach to diabetes diagnosis identification used in the DDR, we believe that the misclassification is minimal. Another limitation of this study is the lack of detailed adjustment for confounding factors. Although we aimed to account for variables, factors such as socioeconomic status, alcohol use, and smoking, that are likely relevant, were not available in our dataset. Where factors such as BMI, waist-to-hip ratio or MASDL were considered mediators, these factors could play a crucial role in the complex interplay between chronic hepatitis B and cardiometabolic comorbidities, potentially influencing our findings. Their absence may limit the interpretation of the results. Future studies should strive to incorporate these variables to provide a more comprehensive understanding of the relationships between chronic hepatitis B and associated health issues.

Our study is based on a nationwide registry and includes individuals from diverse countries of origin, with only 27% of patients being of Danish descent, thus reflecting a heterogeneous population. It is important to note that all individuals in the DANHEP cohort reside in Denmark and are predominantly expected to follow a European lifestyle and have access to Denmark's free of cost healthcare system. Consequently, while our findings may be broadly applicable to similar populations in other high-income countries with comprehensive healthcare systems, caution should be exercised when extrapolating the results to populations in different socioeconomic and healthcare contexts.

Conclusion

This study found a higher IR of liver complications in patients with CHB and with versus without cardiometabolic comorbidities. Notably, this elevated risk was driven by T2D and hypertension, while hypercholesterolemia did not contribute to the higher IR. This study also showed a significantly higher IR of developing cardiometabolic comorbidities among patients with CHB compared with the general population in Denmark. In a sensitivity analysis, this was shown to be mostly driven by T2D and hypertension, while the opposite was observed for hypercholesterolemia. The results are in line with previous findings and warrant that future clinical guidelines include a more comprehensive approach to cardiometabolic care in the CHB population. Future investigations should focus on elucidating the pathophysiological mechanisms underlying the higher incidence of T2D and hypertension in CHB patients, which could provide further insight into optimised preventive and therapeutic strategies. The findings of this study emphasize the need for heightened clinical vigilance and proactive management of cardiometabolic comorbidities in patients with CHB, specifically T2D and hypertension, to potentially mitigate the risk of liver complications.

Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CRS, the Danish Civil Registration System; DADD, the Danish Adult Diabetes Database; DANHEP, the Danish Database for Hepatitis B & C; DNA, deoxyribonucleic acid; CDR, the Danish Cause of Death Registry; DDR, the Danish Diabetes Registry; DiaBase, the Danish Clinical Quality Assurance Database for Screening of Diabetic Retinopathy and Maculopathy; HbA1c, hemoglobin A1c; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL, high-density-lipoprotein; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, intravenous drug use; IQR, interquartile range; IR, incidence rate; IRR, incidence rate ratios; kPa, kilo Pascal; LDL, low-density-lipoprotein; NPR, the National Patient

Registry; RPS, the Registry of Pharmaceutical Sales; T2D, type 2 diabetes; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; TE, transient elastography.

Data Sharing Statement

Data in this study from the public healthcare registries may be requested through an application to the Danish health data authorities. Data from DANHEP may be requested by application to the DANHEP steering group and must be approved by the Danish health data authorities.

Ethics Approval

Individual written informed consent was given from all participants in DANHEP to have their data collected prospectively. The study was approved by the Danish Data Protection Agency (P-2019-829). According to Danish law, nationwide registry data used in research studies is pseudo-anonymized and needs no individual consent and no approval from ethical committees.

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Disclosure

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