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Original article

# Time-trends in disease characteristics and comorbidities in patients with chronic hepatitis B in the period 1980–2020

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ABSTRACT

*Background & aims:* The incidence of chronic hepatitis B (CHB) is declining due to successful implementation of vaccination programs and widespread use of antiviral therapy. We aimed to study time-trends in disease characteristics and comorbidities in newly referred CHB patients.

*Methods:* We collected information on hepatitis B virus (HBV) related disease characteristics (including hepatitis B e-antigen (HBeAg) status, viremia, stage of liver fibrosis and indication for treatment and/or hepatocellular carcinoma (HCC) surveillance) and presence of comorbidities in all CHB patients referred to our center from 1980 through 2020. Patient characteristics were compared according to referral date (before 2000, between 2000 and 2010 and after 2010).

*Results:* We identified 1515 eligible patients. Patients referred after 2010 were older (36 versus 34 years, $p < 0.001$), more often non-Caucasian (82.3% versus 55.0%, $p < 0.001$) and more frequently HBeAg negative (81.5% versus 49.8%, $p < 0.001$) when compared to patients referred before 2000. Adjusted for ethnicity, sex and age, patients referred after 2010 were less likely to have significant fibrosis (adjusted odds ratio [aOR]:0.178, $p < 0.001$) or indication for antiviral therapy (aOR:0.342, $p < 0.001$) but were more likely to be affected by the metabolic syndrome (aOR:1.985, $p = 0.013$), hepatic steatosis (aOR:1.727, $p < 0.001$) and metabolic dysfunction associated fatty liver disease (MAFLD) (aOR:1.438, $p = 0.013$).

*Conclusions:* The characteristics of the CHB populations are changing. Newly referred patients are older, have less active HBV related liver disease but are more likely to be co-affected by MAFLD. These findings provide guidance for adequate allocation of resources to cope with the changing characteristics of the CHB population.

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## 1. Introduction

Chronic hepatitis B (CHB) virus infection is a major global health concern due to its association with development of end-stage liver disease and hepatocellular carcinoma (HCC). Studies estimate a worldwide prevalence of 3.6% with a distinct geographical distribution [1]. In western countries the prevalence is low (<2%) whereas in some Asian and African countries a prevalence ≥8% has been reported [1]. Between 1990 and 2010 deaths due to HBV-associated HCC have increased with 62.4% [2].

Fortunately, in endemic and even in non-endemic countries, the incidence of CHB has declined over the past decades, probably due to widespread implementation of global vaccination programs [3]. In addition, new potent antiviral therapies such as entecavir and tenofovir achieve complete viral suppression in nearly all CHB patients [4], decreasing the risk of horizontal and vertical transmission. As a result, the characteristics of the CHB population across the globe are changing [5–11], with newly referred patients being older and potentially more often afflicted by various comorbidities including the metabolic syndrome. This may be very relevant as increasing age and the presence of metabolic comorbidities have been associated with an increased risk of

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**Abbreviations**

| | |
|---|---|
| AASLD | the American Association for the Study of Liver Diseases |
| ALT | alanine aminotransferase |
| BMI | Body-mass index |
| CHB | chronic hepatitis B |
| DM | diabetes mellitus |
| EASL | European Association for the Study of the Liver |
| eGFR | estimated glomerular filtration rate |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HDL | high-density lipoprotein |
| HIV | human immunodeficiency virus |
| IQR | interquartile range |
| MAFLD | metabolic associated fatty liver disease |
| OR | odds ratio |
| PBC | primary biliary cholangitis |
| PSC | primary sclerosing cholangitis |
| SD | standard deviation |
| ULN | upper limit of normal |

adverse clinical outcomes in patients with CHB [12,13].

With this study we therefore aimed to analyse the changes in patient and disease characteristics over time in our CHB population.

## 2. Materials and methods

### 2.1. Study design and patient selection

This is a single-center retrospective study conducted in the Erasmus MC University Medical Center in Rotterdam, the Netherlands. All consecutive adults with a positive HBsAg test were identified through a search of our electronic data storage system and were then individually assessed for eligibility through chart review. Laboratory results have been retrospectively added to the electronic database system since its inception, with the first patient eligible for this study identified in 1984.

All subjects with chronic hepatitis B (defined as HBsAg positivity for at least 6 months) were eligible for this study. Exclusion criteria were: [1] presence of other liver disease (i.e., auto-immune hepatitis, alcoholic liver disease (>60 g of alcohol per day), PBC, PSC, hemochromatosis and Wilson's disease) [2] concomitant infection with hepatitis C or D virus or the human immunodeficiency virus, and [3] insufficient data for assessment of liver disease severity (defined as lack of histological or radiological assessment of the liver). Patients were characterized according to the findings obtained at the time of the first patient visit.

### 2.2. Data collection

Patient charts were individually reviewed by the investigators. Data were collected on patient demographics (date of birth, sex, ethnicity),

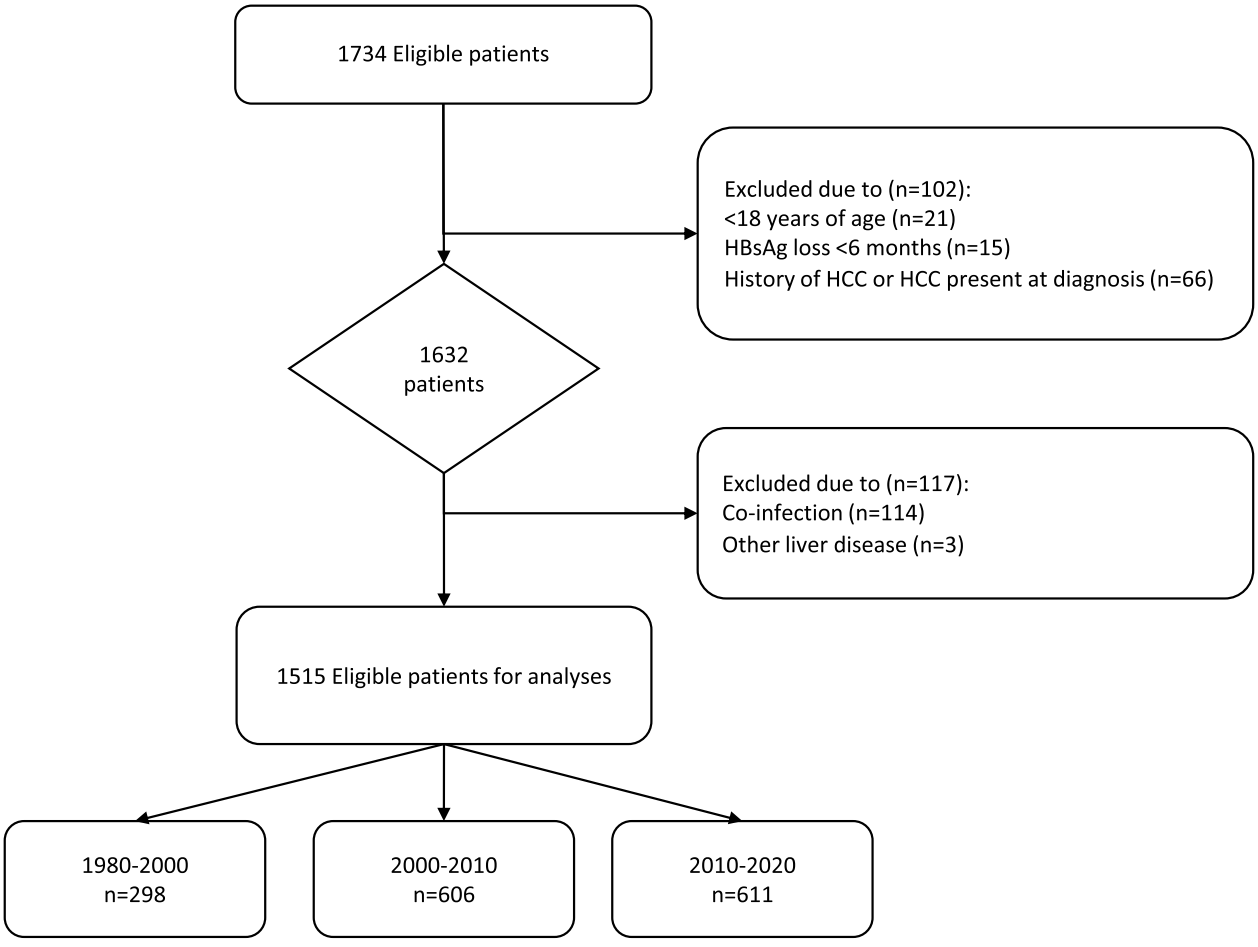


**Fig. 1.** Patient disposition. HCC, hepatocellular carcinoma.

**Table 1**
Cohort characteristics.

| Characteristics | 1980-2000 $n = 298$ | 2000-2010 $n = 606$ | 2010-2020 $n = 611$ | *p* |
|---|---|---|---|---|
| Age, median (IQR) | 34 (27-44) | 34 (26-44) | 36 (29-48) | <0.001 |
| Male, n (%) | 196 (65.8%) | 390 (64.4%) | 309 (50.6%) | <0.001 |
| Ethnicity, n (%) | | | | <0.001 |
| Caucasian | 134 (45.0%) | 139 (22.9%) | 108 (17.7%) | |
| Asian | 64 (21.5%) | 194 (32.0%) | 196 (32.1%) | |
| Black | 43 (14.4%) | 123 (20.8%) | 136 (22.3%) | |
| North African/ Middle East | 57 (19.1%) | 150 (24.8%) | 171 (28.0%) | |
| HBeAg-positive, n/N (%) | 148/295 (50.2%) | 225/605 (37.2%) | 112/606 (18.5%) | <0.001 |
| HBV DNA (log), median (IQR) | 5.13 (2.81-7.10) | 4.73 (2.69-7.15) | 3.47 (2.52-5.25) | <0.001 |
| ALT above ULN, n/N (%) | 190/298 (63.8%) | 445/605 (73.6%) | 311/610 (51.0%) | <0.001 |
| Treatment indication, n (%) | 141 (47.3%) | 244 (40.3%) | 107 (17.5%) | <0.001 |
| Indication for HCC Surveillance, n (%) | 78 (26.2%) | 191 (31.5%) | 232 (38.0%) | 0.001 |
| Any fibrosis, n/N (%) | 230/285 (80.7) | 345/538 (64.1) | 148/551 (26.9) | <0.001 |
| Cirrhosis, n/N (%) | 31/298(10.4) | 33/606 (5.4) | 30/611 (4.9) | 0.003 |
| Metabolic Syndrome[#] | 12 (4.0) | 15 (2.5) | 48 (7.9) | <0.001 |
| Overweight, n/N (%) | 133/279 (47.7%) | 294/527 (55.8%) | 297/486 (61.1%) | 0.001 |
| Hypertension, n (%) | 20 (6.7%) | 33 (5.4%) | 82 (13.4%) | <0.001 |
| Dyslipidaemia, n (%) | 21 (7.0%) | 31 (5.1%) | 78 (12.8%) | <0.001 |
| Diabetes Mellitus, n (%) | 24 (8.1%) | 23 (3.8%) | 37 (6.1%) | 0.024 |
| Steatosis, n/N (%) | 64/297 (21.5%) | 152/604 (25.2%) | 201/610 (33.0%) | <0.001 |
| MAFLD, n/N (%) | 51/297 (17.2%) | 122/604 (20.2%) | 148/610 (24.3%) | 0.036 |
| GFR (CKD-EPI), median (IQR) | 112 (99-124) | 114 (102-124) | 111 (97-123) | 0.081 |
| Renal dysfunction[*], n/N (%) | 1/174 (0.6%) | 5/484 (1.0%) | 18/579 (3.1%) | 0.019 |

ULN, upper limit of normal. HCC, hepatocellular carcinoma.
Indication for antiviral therapy was based on presence of (1) HBV DNA ≥2,000 IU /mL with ALT > ULN and at least F2 fibrosis (2) HBV DNA ≥20,000 IU/mL and ALT > 2x ULN regardless of degree of fibrosis or (3) presence of cirrhosis with detectable HBV DNA.
HCC surveillance was based on Asian males ≥40 years, Asian females ≥50 years, Sub-Saharan African patients ≥20 years, all patients with cirrhosis and patients with a positive family history of HCC.
[#] Metabolic syndrome was based on presence of any 3 of the following: overweight, hypertension, reduced HDL cholesterol, elevated triglycerides or diabetes mellitus.MAFLD was based on combined presence of hepatic steatosis with overweight or diabetes mellitus or hypertension and dyslipidaemia.
[*] Renal dysfunction = eGFR < 60 mL/min.

anthropometric measurements (length and weight), liver and renal biochemistry and virology. Information on presence of liver steatosis, fibrosis and/or cirrhosis was obtained from ultrasound reports, liver stiffness and controlled attenuation parameter assessment and/or histology whenever available. Data was also collected on presence of relevant comorbidities.

### 2.3. Key study variables

Biochemistry and virology obtained within 6 months of the first positive HBsAg test were used for analysis. Eligibility for antiviral therapy was assessed using the EASL criteria; the following patients were considered eligible for antiviral therapy: [1] HBV DNA ≥2,000 IU /mL with ALT > ULN and at least F2 fibrosis [2] HBV DNA ≥20,000 IU/mL and ALT > 2x ULN regardless of fibrosis [3] and presence of cirrhosis with detectable HBV DNA [14]. In case of missing HBV DNA levels, HBeAg positive patients were considered to have HBV DNA levels above the treatment threshold.

Eligibility for HCC surveillance was based on the following criteria as set forth in the Dutch HCC guideline (and are in line with international guidance): Asian males ≥40 years, Asian females ≥50 years, Sub-Saharan African patients ≥20 years, all patients with cirrhosis and patients with a family history of HCC [15].

Cirrhosis was based on histology, or on liver stiffness > 12.2 kPa [16]. In patients without available data on histology or liver stiffness, cirrhosis could be ruled in based on ultrasound findings compatible with cirrhosis and/or portal hypertension. Significant fibrosis was based on histology (METAVIR ≥F2), or a liver stiffness measurements >7.2 kPa [16]. In patients without information on histology and liver stiffness, and without signs of cirrhosis on ultrasound, presence of significant fibrosis was considered unknown. Hepatic steatosis was based on histology, a controlled attenuation parameter >248 dB/m [17], or ultrasound (e.g. hyperechoic liver parenchyma).

Overweight was defined as BMI ≥25 kg/m$^2$ for non-Asians and ≥23 kg/m$^2$ for Asians. Presence of hypertension was based on the medical history or use of antihypertensives. Dyslipidaemia was based on the medical history, or on presence of triglycerides ≥1.7 mmol/L or HDL <1.03 mmol/L for males and <1.30 mmol/L for females or use of cholesterol lowering agents. Diabetes mellitus was based on medical history or use of antidiabetic medication. Conditions were considered present when the above-mentioned criteria were met at the time of or within one year after the first positive HBsAg test result.

Metabolic syndrome was defined as presence of ≥3 of the following: overweight, hypertension, reduced HDL cholesterol, elevated triglycerides or diabetes mellitus.

MAFLD was defined as presence of hepatic steatosis in combination with either overweight, diabetes mellitus or two minor metabolic health criteria such as hypertension and dyslipidaemia [18].

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min [19].

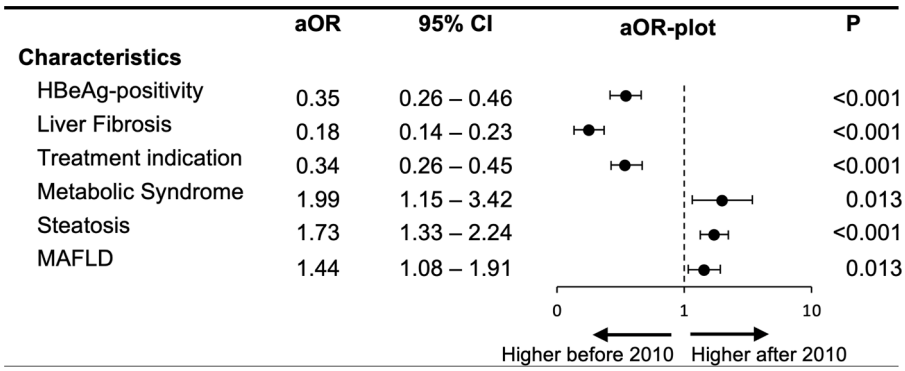


**Fig. 2.** Association between referral date and patient characteristics.Adjusted odds ratios (aORs) for HBeAg positivity, presence of significant liver fibrosis, treatment indication, metabolic syndrome, hepatic steatosis and MAFLD for patients referred to before or after 2010. Analyses adjusted for ethnicity, age and sex. Odds-ratios with 95% confidence intervals for multivariable analyses. aOR, adjusted Odds-ratio.MAFLD, metabolic dysfunction associated fatty liver disease.

### *2.4. Statistical analysis*

Descriptive data of demographic and anthropometric measurements were given as mean +/- SD or if not-normally distributed with median and interquartile range (IQR). The study population was categorized based on referral date into the following time cohorts: 1980-2000, 2000-2010 and 2010-2020. Characteristics of patients were compared across these timeframes using the Chi-square test or Fisher's exact test and one-way ANOVA or the Kruskal Wallis test where applicable. As part of this aetiological study we also performed multivariable logistic regression analysis, comparing patients referred in the most recent timeframe (i.e., 2010-2020) versus those referred before 2010, adjusting for potential confounders age, sex and ethnicity. P-values <0.05 (two-tailed) were considered statistically significant. All statistical analyses were performed with IBM SPSS statistics 25.

### *2.5. Ethics*

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. Patients were not subjected to additional medical interventions. The study protocol was reviewed by the Erasmus MC Medical Ethical Committee (MEC-2020-0699).

## 3. Results

We identified 1,734 eligible CHB patients with the first visit between 1980 and 2020. Of these patients, 221 were excluded (Fig. 1).

The overall study population consisted of 1,515 patients of whom 895 (59.1%) were male. The median age of our population was 35 (IQR 27-45) years, with the majority being Asian (30%), Caucasian (25%) or from Northern Africa or the Middle East (25%).

### *3.1. Time-trends in patient demographics*

The median age of our study population increased from 34 to 36 years ($p < 0.001$). Before 2000, the most common patient ethnicity was Caucasian (45.0%) which shifted to mostly Asian (32.1%) and North-African / Middle Eastern (28.0%) for patients referred between 2010 and 2020 ($p < 0.001$; Table 1).

### *3.2. Time-trends in HBV related disease characteristics*

While the majority of patients were HBeAg positive before 2000, more recently referred patients were almost exclusively HBeAg negative (Table 1, Fig. 2, Fig. A1). HBV DNA levels at the time of presentation were significantly lower in the most recent era (3.47 versus 5.13 log IU/mL, $p < 0.001$). The number of patients with elevated ALT at presentation declined from 63.4% to 51.0% ($p < 0.001$). While the majority of patients (80.7%) had signs of liver fibrosis in the 1980-2000 subset, fibrosis was present in a minority in the 2010-2020 era (26.9%; $p < 0.001$). Similar trends were observed for cirrhosis. The proportion of patients eligible for antiviral therapy at the time of referral also declined from 45.0% to 19.0% ($p < 0.001$), whereas the number of patients eligible for HCC surveillance increased substantially (from 26.8 to 38.3%, $p = 0.001$). Multivariable analysis adjusting for differences in ethnicity, age and sex distributions showed consistent results: patients referred after 2010 were less likely to have significant fibrosis, or to require antiviral therapy (Fig. 2). No multivariable analyses were performed for HCC surveillance indications given its collinearity with age and ethnicity.

### *3.3. Time-trends in comorbidities*

The number of patients affected by (components of) the metabolic syndrome increased over time from 4.0% to 7.9% ($p < 0.001$; Fig. 2, Fig. A1), which was mirrored by an increase in the proportion of patients with hepatic steatosis (21.5% to 33.0%, $p < 0.001$). The number of CHB patients with MAFLD increased from 17.2% to 24.3% ($p = 0.036$). Multivariable analysis adjusting for differences in ethnicity, age and sex distributions showed consistent results: patients referred after 2010 were significantly more likely to be affected by the metabolic syndrome, hepatic steatosis and MAFLD (Fig. 2).

## 4. Discussion

In this large cross-sectional study spanning 3 decades, we observed significant changes in the characteristics of our CHB patients. Newly referred patients were older, more often of Asian or of Northern African / Middle Eastern ethnicity and presented with less severe HBV specific disease characteristics. In contrast, the number of patients eligible for HCC surveillance increased substantially. Furthermore, newly referred patients were more likely to have metabolic dysfunction associated comorbidities and renal dysfunction.

The current study reveals important changes in patient demographics and disease specific characteristics in the CHB population in the Netherlands. First, the population is ageing, which is likely due to both a reduction in novel CHB cases as a result of vaccination and treatment-associated reductions in the risk of vertical and horizontal transmission. Our findings are in line with other recent observations (Table A1) [5–11]. Interestingly, the mean age in these cohorts was significantly higher than in our cohort. The differences could potentially be accounted for by the fact that nearly all of these studies used data from insurance systems, which may limit external validity, and by differences in screening and referral policies across countries. Finally, it is important to note that this is the first study on this topic from Europe.

Another interesting observation is the change in patient ethnicities. While the majority of CHB patients referred before 2000 were of Caucasian ethnicity, this changed substantially to a predominantly Asian and Northern African / Middle Eastern population. The reduction in the number of new Caucasian patients is likely to be attributable to several interventions aimed at risk groups, such as people who inject drugs and men who have sex with men, as well as implementation of prenatal HBV screening programs (combined with initiation of antiviral therapy in selected cases) in the Netherlands. The increase in the number of patients with Asian and Northern African / Middle Eastern ethnicity reflects migration trends over the last decades [20].

In addition to changes in patient demographics we also observed major shifts in HBV-specific disease characteristics. While the majority of patients in the first era were HBeAg positive with high viral load and often elevated ALT, more recently referred patients are usually HBeAg negative with low viral load and normal ALT. In part, this change reflects the change in ethnicity; patients from Northern African and the Middle East are often infected with genotype D which is most likely to present in a HBeAg negative state [21]. Interestingly, these findings are mirrored by a decrease in the number of patients presenting with significant fibrosis or cirrhosis. Whereas the majority of patients had fibrosis during the era before 2000, this has dwindled to less than 30% in recent years. Some of this may be explained by more widespread access to liver test assessment, resulting in identification of asymptomatic patients with chronic liver disease who may otherwise not have been identified until they had developed advanced liver disease. This is nicely illustrated by studies showing a reduced number of HBV cases diagnosed during the COVID-19 pandemic [22]. These changes in patient characteristics have a major influence on the number of patients eligible for antiviral therapy. In the current study more than 40% of patients presenting before 2000 had an indication for antiviral therapy, which declined to 19% in the most recent cohort. Our estimate for the most recently referred patients is lower than that reported by a recent meta-analysis, which showed a pooled estimate for treatment eligibility of 25% in clinic settings [23]. However, it is important to note that the estimates for treatment eligibility in the individual studies that were used for this meta-analysis varied widely, and that these studies were conducted over a wide timeframe. Based on the findings reported in the current study, future meta-analyses should focus on the most recently performed studies. This may result in estimates which are more valid for the current timeframe.

Another important consequence of aging and transition to a predominantly Asian population is that the number of patients considered eligible for HCC surveillance is rapidly increasing. Almost 39% of newly referred patients are eligible for HCC surveillance, which increases the already considerable burden placed on ultrasonography programs.

Finally, we observed a strong increase in the proportion of CHB patients co-affected by metabolic comorbidities. The number of patients with overweight increased to over 61%, and 24.3% of the CHB patients now also complied with the recently introduced MAFLD criteria. The high prevalence of metabolic comorbidities in this population is in line with other reports [5–11] and is particularly worrisome as a recent study from our group indicates that presence of MAFLD is an independent predictor of adverse outcome in patients with CHB [24]. The increasing proportion of patients co-affected by MAFLD should therefore be taken into account, especially since there are currently no effective treatment options for MAFLD. Furthermore, since subcutaneous and liver fat complicates ultrasonography surveillance, the current findings highlight the importance of investing in alternative surveillance methods such as MRI.

Although this is one of the largest non-insurance claims-based studies on time-trends in CHB, there are some limitations. Firstly, given the retrospective design and long time period that is included in this study, missing data are unavoidable. This could have especially led to underreporting of metabolic comorbidities. However, the same trend that was observed for metabolic comorbidities was also seen for steatosis (<1% missing), supporting the robustness of the findings. Furthermore, diagnostic modalities have changed over time, with liver biopsy being most frequently used to ascertain fibrosis and steatosis before 2000, changing to transient elastography in the most recent era. Also, access to liver test assessment and liver ultrasound has improved significantly in the recent era when compared to the 1980's. Such changes in use and access to diagnostic modalities could potentially lead to time bias. However, transient elastography has an excellent diagnostic accuracy for assessing liver cirrhosis, suggesting that a change from liver biopsy to liver stiffness assessment is unlikely to have influenced our findings regarding changes in the prevalence of significant liver fibrosis [25]. Furthermore, our findings were consistent when we limited them to only biopsied patients or patients with transient elastography (data not shown). Additionally, we performed multiple sensitivity analyses where we either in- or excluded viral co-infections and/or considered incident cases of DM, hypertension and dyslipidemia within 5 years after referral as being present at the time of study enrolment. Findings were consistent in these analyses (data not shown). Additionally, since viral load assessment was not always available during the first era of our study, some patients had missing information on HBV DNA levels. To circumvent this, we considered all HBeAg positive patients as having a viral load above the treatment threshold, as this is the case in the vast majority of these patients. Furthermore, a small number of patients ($n$=28) had received antiviral therapy at other hospitals before referral to our center. Exclusion of these patients from the analyses had no influence on the reported findings. Additionally, although we excluded patients with known alcohol abuse from this analysis, this may have been underreported causing potential misclassification. At last, external validity could potentially be a concern when using data from a tertiary center, although we feel this is unlikely to be a significant issue for our study for several reasons. First, management of CHB patients in the Netherlands is not limited to academic sites. In fact, there are dozens of licensed viral hepatitis treatment centers across the nation. Of course, patients requiring liver transplant would be referred to academic sites, but this concerns a very small minority of the patients (e.g., only 6.2% of the patients had cirrhosis in this cohort). Patient ethnicity, presence of metabolic comorbidities or fatty liver disease and/or need for HCC surveillance would not be a reason to refer patients to our center. On top of that, only a few patients had a history of antiviral therapy at another center, further underscoring that this is not a highly selected tertiary patient population. Nevertheless, external validation of our findings in other, preferably non-academic, centers is important to confirm the robustness of our findings.

In conclusion, our study, conducted in a low-prevalence country,

shows that newly referred patients with CHB are older, more likely to be Asian, have less active CHB related liver disease but are more likely to meet criteria for HCC surveillance and to be affected by metabolic comorbidities. The findings provide guidance for adequate allocation of resources to cope with the changing characteristics of the CHB population.

## Role of the funding source

The study was sponsored by the Foundation for Liver and Gastrointestinal Research (SLO), Rotterdam, the Netherlands. The project was financially supported by Gilead under grant number IN-NL-988-5952. Neither the SLO nor Gilead had influence on study design, data acquisition or analysis, nor the decision to submit for publication.

## Disclosures & Conflicts of interest

M.J.S. received speaker's fees and research support from Gilead and Fujirebio.

S.M.B. received research support from Gilead.

Rd.M. received speaker's fees from Falk and Cook.

Rd.K. is a speaker for Echosens, consultant for AbbVie and received grants from Abbvie, Gilead and Janssen. The other authors report no conflicts.

## Author contributions

Study design, collection of data, data analysis, writing of the manuscript and approval of final version: D.v.d.S., W.K.K., Lv.K., S.M.B., A.v.d.M., M.J.S.

Study design, data interpretation, critical review of the manuscript and approval of final version: all authors.

M.J.S. is guarantor of the article.

## Data availability statement

Individual patient data cannot be shared.

## Lay Summary

Newly referred patients with chronic hepatitis B (CHB) are more likely to be Asian, are older, have less active CHB, but more metabolic comorbidities. Given the association between metabolic dysfunction and adverse outcomes in CHB, our findings further underscore the need for thorough assessment of metabolic health in the CHB population.

## Appendix

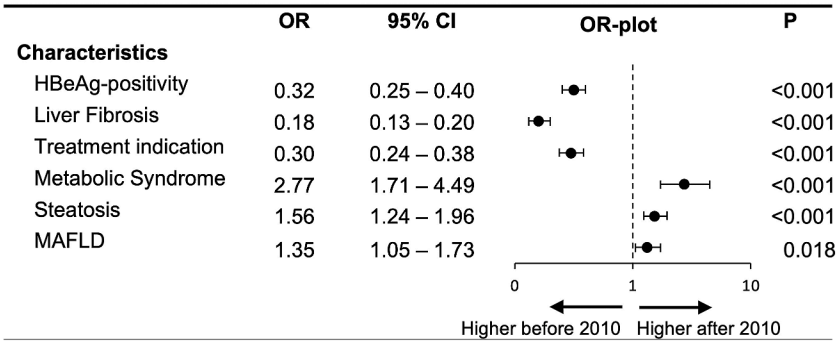


**Fig. A1.** Association between referral date and patient characteristics. Odds ratios (ORs) for HBeAg positivity, presence of significant liver fibrosis, treatment indication, metabolic syndrome, hepatic steatosis and MAFLD for patients referred to before or after 2010. Odds ratios with 95% confidence intervals.MAFLD, metabolic dysfunction associated fatty liver disease.

**Table A1**
Results of recent studies into the changing characteristics of the CHB population.

| Studies | Subjects (n) | Country | Timeframe | Age (years) | HBeAg (%) | Diabetes (%) | Hypertension (%) | Obesity (%) | NAFLD (%) |
|---|---|---|---|---|---|---|---|---|---|
| Liu et al. 2018 (11) | 2734 | United States | 2000-2015 | **43.3→49.1** | **26.4→15.8** | **4.9→22.9** | **12.3→36.1** | 33.3→31.4 | **1.6→6.8** |
| Nguyen et al. 2019 (5) | 12,913 | United States | 2006-2015 | **48.1→51.8** | - | **10.1→15.3** | **18.5→32.0** | **0.6→10.8** | - |
| | 3703 | United States | 2006-2015 | **44.1→50.2** | | **18.2→27.2** | **31.6→58.7** | **3.7→19.8** | |
| Oh et al. 2020 (6) | 991,346 | South Korea | 2007-2016 | **46.9→52.3** | - | **18.0→19.7** | **23.8→29.4** | - | - |
| Sanai et al. 2019 (9) | 765 | Saudi Arabia | 2010-2015 | **42.0→46.9** | - | - | - | -* | 25→32 |
| Tseng et al. 2021 (7) | 693,167 | Taiwan | 2001-2011 | **45.4→52.3** | - | **11.8→24.3** | **20.8→35.2** | - | - |
| Wong et al. 2020 (10) | 135,395 | Hong Kong | 2000-2017 | **40.8→54.5** | **39.3→22.0** | **10.6→20.1** | **25.5→28.6** | - | - |
| Yotsuyanagi et al. 2022 (8) | 11,125 | Japan | 2012-2016 | **62.0→65.2** | - | **27.7→35.6** | **35.2→39.1** | 0.31→0.35 | 3.7→4.1 |

*Sanai et al did not report on obesity, but showed a significant increase in BMI between 2010 and 2015. BMI, Body-mass index. NAFLD, Non-alcoholic fatty liver disease.

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