

ORIGINAL CONTRIBUTION

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Increasing co-morbidities in chronic hepatitis B patients: experience in primary care and referral practices during 2000–2015

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Abstract

Objectives: Data on liver and non-liver co-morbidities in chronic hepatitis B (CHB) patients are limited. This study analyzes the prevalence of co-morbidities in a multicenter CHB cohort evaluated over 15 years.

Methods: This study included 2734 consecutive adult American CHB patients from a university medical center and several community primary care clinics. Data were analyzed by time periods (patients in each time period were unique without overlapping): 2000–2005 ($n = 885$), 2006–2010 ($n = 888$), and 2011–2015 ($n = 961$). Patients were identified via electronic query using diagnosis code with data confirmed and extracted via individual chart review. Most patients were male (57.9%) and Asian (89.6%).

Results: Mean age increased significantly from 43.3 ± 13.4 years during 2000–2005 to 49.1 ± 14.4 during 2011–2015 ($p < 0.001$). Between 2000–2005 and 2011–2015, fatty liver disease among new CHB patients increased from 1.6 to 6.8% ($p < 0.001$). Advanced liver diseases also increased ($p < 0.001$): cirrhosis (12.6–24.6%), hepatic decompensation (1.1–7.9%), and hepatocellular carcinoma (HCC) (4.9–9.1%). Similar trends were observed for non-liver co-morbidities ($p < 0.001$). Specifically, diabetes increased almost fivefold (4.9–22.9%), hypertension increased threefold (12.3–36.1%) and chronic kidney disease increased 4.5-fold (4.4–19.7%). Prevalence of osteopenia and osteoporosis also increased in CHB patients: 5.4–13.4% ($p < 0.001$) and 2.9–8.7% ($p < 0.001$), respectively. These trends were observed in both liver clinics and primary care clinics (except for advanced liver disease), treated and untreated patients, and for both sexes.

Conclusions: The CHB patient population is aging and now presents with significantly more co-morbidities. Early diagnosis and linkage to care is needed to prevent and mitigate liver as well as non-liver co-morbidities.

Introduction

There are 1.25 million individuals in North America¹ and 248 million individuals globally² who have chronic hepatitis B (CHB)³. The estimated number of patients with CHB-related cirrhosis, hepatic decompensation, and deaths was 341,400 in 2005 and 371,100 in 2015⁴. HCC

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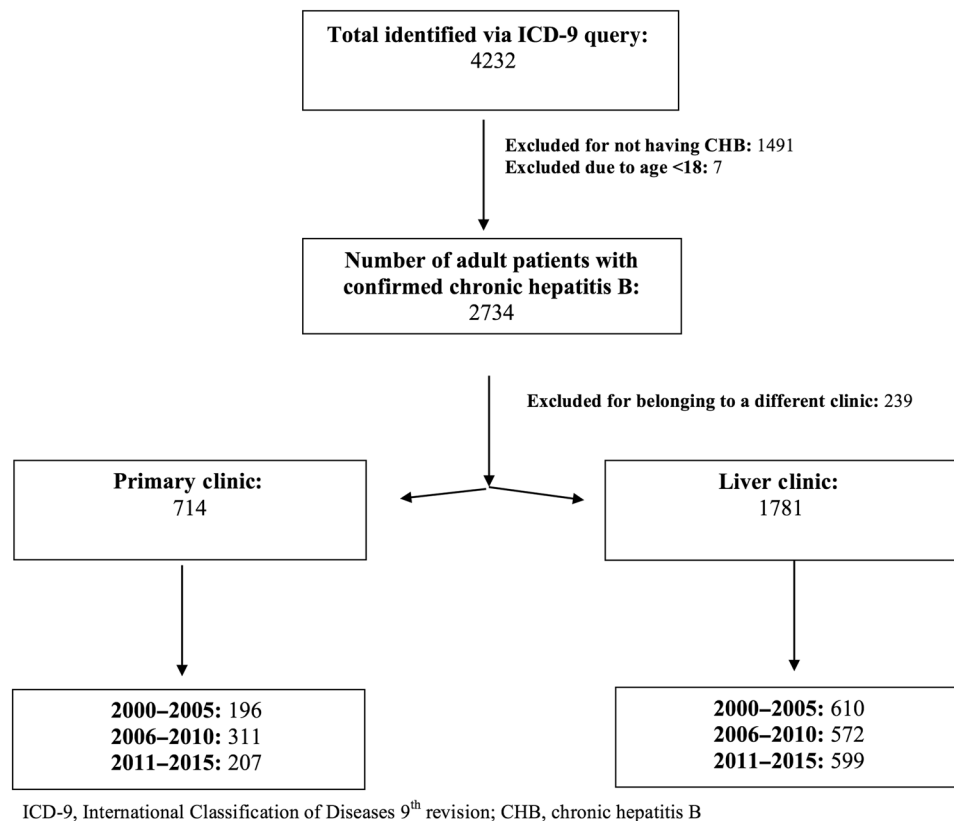


Fig. 1 Flow chart. Displays the numbers of patients included in the study analyses

deaths related to CHB were estimated to be 263,100 in 2005 and 265,300 in 2015⁴.

In addition to liver complications, CHB patients may also suffer morbidity and mortality from non-liver medical illnesses. A Thai pilot study in 2016 studied kidney and bone disorders in CHB patients. Over 1.5 years, 20 patients showed an annual reduction in estimated glomerular filtration rate (eGFR) and an osteopenia prevalence of 45%⁵. Subsequently, a systematic review reported possible eGFR reduction in CHB patients⁶. In addition, a cross-sectional study of the National Taiwan Insurance Database showed that CHB patients aged ≥ 65 years have more than 13 times increased risk of osteoporosis compared to uninfected controls ($p < 0.001$, 95% CI: 11.8–14.9)⁷. Another study showed that bone mineral density was lower in 25 out of 43 patients (58%) with chronic hepatitis B or C⁸. Furthermore, a retrospective study on 8237 Taiwanese CHB patients with 10-year follow-up concluded that new-onset diabetes is an independent predictor for cirrhosis and hepatic decompensations in CHB patients⁹. These data suggest the need for increased awareness, screening, and appropriate management of non-liver co-morbidities in CHB patients as this will help improve overall clinical outcomes for CHB patients.

The aim of this study is to characterize the trends in clinical presentation among patients with CHB in the

current practice environment. We do so by describing the demographics and clinical characteristics including liver and non-liver co-morbidities of patients with CHB in a large multicenter American patient cohort that includes patients in both university and community settings, referral as well as primary care practices. We hypothesize that there is an increase in liver and non-liver co-morbidities when comparing patients presenting in 2000–2005 to those presenting in 2011–2015.

Methods

Study design and population

We performed a retrospective, observational study enrolling consecutive CHB patients meeting study inclusion criteria at Stanford University Medical Center in Palo Alto, California, Chinese Hospital and Clinics (inclusive of several primary care clinics throughout the San Francisco Bay area) and two community private primary care clinics in San Francisco from 2000 to 2015. The study was approved by the Institutional Review Board at Stanford University (Stanford, California, USA).

Patient inclusion criteria

Inclusion criteria included adult CHB patients identified by International Classification of Diseases, 9th revision, Clinical

Modification diagnostic codes 070.2× or 070.3×. A total of 4232 patients were identified. Individual medical records were reviewed and confirmed 2734 adult (≥ 18 years) patients with CHB (positive hepatitis B surface Ag or HBV DNA) who were included in the study analysis (Fig. 1). A case report form was created specifically for this study and was used to carry out a thorough chart review and data extraction of the electronic medical records for each individual patient.

Patients were divided into three 5-year study periods: 2000–2005, 2006–2010, and 2011–2015 according to the year of the patient's first presentation to each medical center. For the latter periods (2006–2010 and 2011–2015), only patients not previously included in analyses of the previous time periods (2000–2005 or 2000–2010, respectively) were included. Therefore, patients in each time period were unique patients without repeating or overlapping among the time periods. To avoid observational, time-related biases, for all study periods, study index date for each patient was the date of first presentation to care at each medical center whether that visit was related to HBV care or not¹⁰. Each center in this study had a self-contained medical record system that was not linked to other medical or administrative systems. Subanalyses were performed for clinic setting (primary care vs. liver clinics), by treatment status, and sex.

Study variables

Liver-related morbidities/co-morbidities included fatty liver, liver cirrhosis, hepatic decompensations, and HCC. Fatty liver was determined by pathology, ultrasound, magnetic resonance imaging, or previously noted history of fatty liver in physician notes. Liver cirrhosis was determined by liver histology or clinical, radiologic, or endoscopic evidence of portal hypertension (nodular contour on imaging, thrombocytopenia with platelets < 120 , splenomegaly, presence of varices, or clinical hepatic decompensation) or physician clinical notes. Hepatic decompensation was determined by imaging and/or clinic notes documenting symptoms of decompensation such as ascites, hepatic encephalopathy, hepatic hydrothorax, spontaneous bacterial peritonitis, variceal bleeding, hepatorenal syndrome, or Child-Turcotte Pugh score of 7 or higher. HCC was determined by cytology, pathology, or non-invasive criteria by the American Association for the Study of Liver Diseases^{11,12}.

Non-liver-related chronic medical conditions included metabolic disorders (diabetes, hypertension, hyperlipidemia, obesity, overweight), chronic kidney disease (CKD), and bone disorders (osteopenia, osteoporosis, vitamin D deficiency). These medical conditions were defined by ICD-9 codes and/or noted in the physician notes. The BMI cutoff was 23 kg/m^2 for overweight and 25 kg/m^2 for obesity as the majority of the patients were Asian. This cutoff has been proposed for use in the Asia-Oceania Region and noted by

the World Health Organization¹³. Vitamin D deficiency was defined as $< 20 \text{ ng/mL}$. In addition, subcategories included: vitamin D 0–11 ng/mL as deficient, 12–20 ng/mL as insufficient and $> 20 \text{ ng/mL}$ as sufficient.

Regarding renal disease, serum creatinine and eGFR were also examined. The Cockcroft–Gault Formula, which takes into consideration sex, age, serum creatinine, and weight, was calculated to obtain the eGFR¹⁴.

History of alcohol use included patients who had occasional, moderate, or heavy use of alcohol. Heavy alcohol use was from physician note documentation of at least six standard drinks, equivalent to 60 g, per day over a period of at least 6 months. Information was also collected on whether the patient quit and the duration of alcohol usage in years. This also applies for history of tobacco use.

On the basis of the index date described above, liver-related morbidities and non-liver co-morbidities were recorded if they were known to be present at the index date or within 6 months from the index date^{10,15}.

Statistical analysis

The proportions of patients in different age groups and with various co-morbidities were analyzed by time periods: 2000–2005, 2006–2010, and 2011–2016. Descriptive statistics were reported as proportion (%) for categorical variables, and mean \pm standard deviation (SD) or median (range) for continuous variables. Categorical variables were evaluated using the χ^2 -test. For continuous variables, the one-way ANOVA test was applied if a normal distribution was observed; otherwise, the Kruskal–Wallis H test was used. Multivariate logistic regression analysis was utilized to determine predictors for renal and bone-related disorders. Statistical significance was defined as a two-tailed p -value of 0.05 or less. All statistical analyses were carried out using Stata 14.2 (Stata Corporation, College Station, TX, USA).

Results

General characteristics

In total, there were 885 patients during 2000–2005, 888 patients during 2006–2010 and 961 patients during 2011–2015. The average patient age was 46 years ± 14.3 with the majority being male (57.9%) and Asian—predominantly Chinese and Vietnamese (89.6%) and foreign born (89.4%). There were significant changes in the proportions of patients who were foreign born: 90.9% from 2000–2005, 91.1% from 2006–2010, and 86.1% from 2011–2015 ($p = 0.016$). Table 1 shows the clinical characteristics of CHB patients at time of presentation to the clinics, which were similar with the exception of age and ethnicity. Mean age increased significantly and consistently from 2000–2005 to 2011–2015 ($p < 0.001$). Figure 2a shows that the proportion of patients presenting with CHB at age > 50 has almost doubled when comparing 2000–2010 to

Table 1 Patient characteristics in patients with chronic hepatitis B at time of presentation to clinic (n = 2734)

	2000–2005 (n = 885)	2006–2010 (n = 888)	2011–2015 (n = 961)	p-value
Age	43.3 ± 13.4	46.6 ± 14.4	49.1 ± 14.4	<0.001
Male	58.3%	56.2%	59.0%	0.451
Ethnicity				
Asian	90.9%	91.4%	85.6%	0.001
White	4.3%	4.0%	5.3%	
Black	0.7%	1.1%	2.5%	
Hispanic	0.2%	0.7%	1.1%	
Other	3.9%	2.8%	5.4%	
Family history of HBV	40.1%	35.7%	35.2%	0.091
Family history of liver cancer	15.9%	13.1%	13.5%	0.142
Family history of liver disease	9.8%	6.8%	8.5%	0.093
Family history of liver-related death	9.8%	6.8%	8.5%	0.093
History of tobacco use	22.9%	24.3%	24.6%	0.762
History of alcohol use	24.7%	26.5%	29.8%	0.069

HBV Hepatitis B virus

The bolded p-values are statistically significant (< 0.05).

2011–2015. Figure 2b for primary care clinics and Fig. 2c for liver clinics show a similar pattern.

In regard to laboratory profiles over time, the patients had similar ALT levels when they first presented to care with CHB, though Hepatitis B virus (HBV) DNA levels decreased from 4.2 ± 2.6 log₁₀ IU/mL to 3.3 ± 2.3 log₁₀ IU/mL ($p < 0.001$). From 2000–2005, 57.4% of patients had an HBV DNA level <2000 IU/mL, in comparison to 2006–2010 at 55.1% and to 2011–2015 at 47.6% ($p = 0.001$). The proportions of HBeAg-positive patients decreased from 26.4 to 15.8% ($p < 0.001$) between 2000–2005 to 2011–2015, respectively. Hepatitis C virus co-infection increased from 0.8% to 0.2% to 3.7% ($p < 0.001$).

Liver morbidities

All four liver morbidities that were evaluated had increasing prevalence over the time periods between 2000 and 2015 (Fig. 3). For fatty liver, the prevalence increased from 1.6 to 6.8%. Liver cirrhosis increased from 12.6 to 24.6%. Hepatic decompensations increased from 1.1 to 7.9%. HCC increased from 4.9 to 9.1%.

Non-liver co-morbidities

Figure 4 shows hypertension increasing from 12.3 to 36.1%, hyperlipidemia from 8.4 to 39.4%, diabetes mellitus from 4.9 to 22.9%, osteoporosis from 2.9 to 8.7%, and osteopenia from 5.4 to 13.4% ($p < 0.001$) in the time period from 2000–2005 to 2011–2015. In addition, not shown in the figure, cerebrovascular disease increased from 3.6 to 13.2% ($p < 0.001$).

The prevalence of CKD with eGFR <60 has also increased significantly in the 2011–2015 cohort, from 4.4 up to 19.7% (Fig. 5). A similar trend was observed when renal impairment was analyzed using creatinine cutoff >1.2 and 1.4 mg/dL ($p < 0.001$).

Practice setting differences

On further sub-analysis of patients presenting to primary care clinic or liver clinic, 239 patients were excluded for not belonging to either clinic. There were 714 patients presenting to primary care clinic and 1781 patients presenting to liver clinic (Fig. 1).

Mean age increased in both primary clinic and liver clinic patients over time. Supplementary Table 1a shows that age ($p < 0.001$) and HBV DNA levels ($p = 0.014$) were noted to change significantly over the three time periods for primary care clinic. Notably, platelets declined significantly from 2000–2005 to 2011–2016 ($p = 0.0096$). Supplementary Table 1b generally shows similar changes over time for liver clinic patients.

In regards to liver morbidities, there were clearly much higher rates for cirrhosis and HCC in liver clinic patients compared to primary care patients for each of the time periods (16.6 vs. 1.1%, 17.5 vs. 2.3%, 28.0 vs. 5.3% for cirrhosis and 6.8 vs. 0%, 7.4 vs. 0%, and 13.3 vs. 0% for HCC during 2000–2005, 2006–2010, and 2011–2015, respectively, $p < 0.001$ for all comparisons). Within each clinic population, as shown in Supplementary Tables 2a and 2b, there were significantly higher proportions of patients presenting with fatty liver, cirrhosis, hepatic

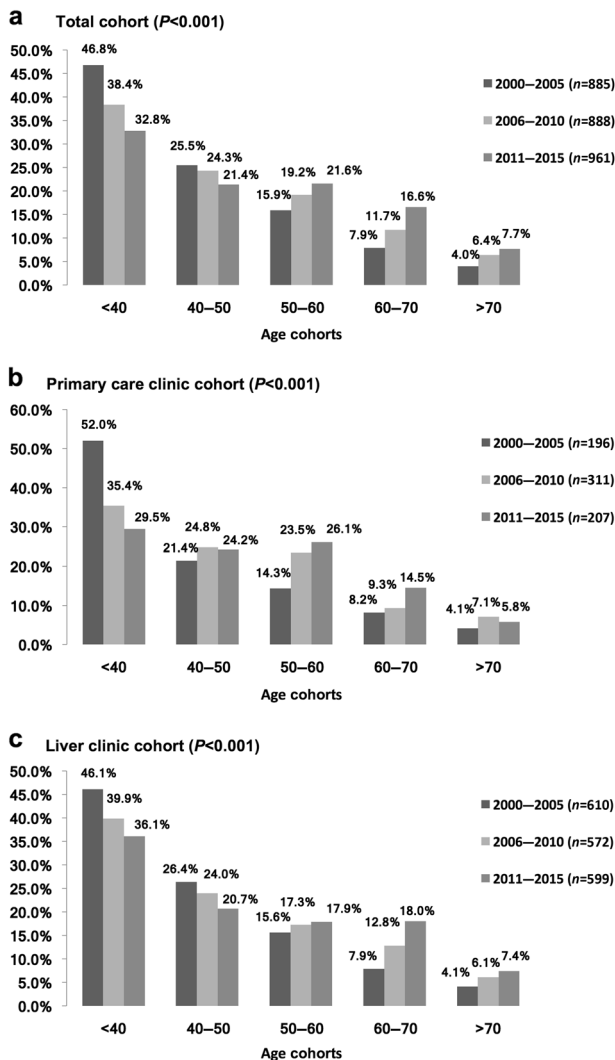


Fig. 2 Chronic hepatitis B patients are presenting at older ages. **a** Total cohort ($p < 0.001$). **b** Primary care clinic cohort ($p < 0.001$). **c** Liver clinic cohort ($p < 0.001$).

decompensation, and HCC over time for the liver clinic population ($p < 0.001$ for each morbidity) but not the primary clinic group, though there was a trend for increasing rate of cirrhosis (1.1% in 2000–2005, 2.3% in 2006–2010, and 5.3% in 2011–2015, $p = 0.085$).

For non-liver co-morbidities, besides obesity and vitamin D deficiency, there were significantly higher proportions of CHB patients with other metabolic disorders (hypertension, hyperlipidemia, diabetes) and bone disorders (osteopenia and osteoporosis) for both primary care and liver clinics ($p < 0.001$ for each co-morbidity and for each clinic population) (Supplementary Tables 3a and 3b).

Supplementary Tables 4a and 4b describe proportions of patients with CKD (overall and by stages 1, 2, vs. 3–5) in different time periods for the total cohort, primary clinic cohort and liver clinic cohort. Similarly, significant

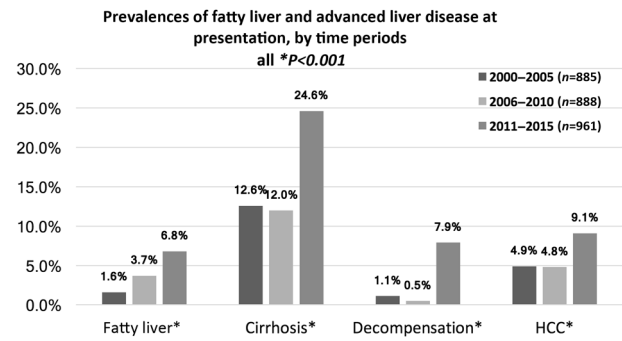


Fig. 3 The proportion of chronic hepatitis B patients with liver morbidities significantly increased between 2000 and 2015 (χ^2 test $p < 0.001$).

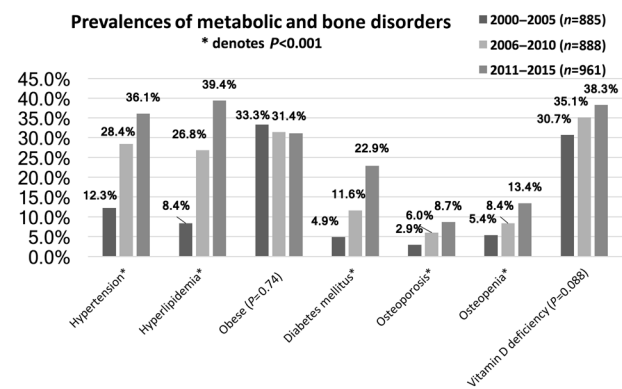


Fig. 4 The proportion of chronic hepatitis B patients with metabolic and bone-related co-morbidities significantly increased between 2000 and 2015 (χ^2 test $p < 0.001$).

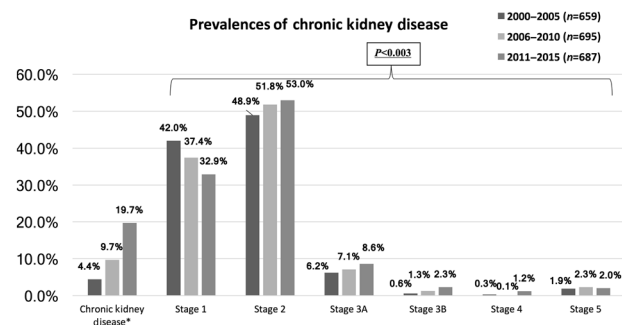


Fig. 5 The proportion of CHB patients with chronic kidney disease significantly increased between 2000 and 2015 (χ^2 test $p < 0.001$).

increase in proportions of CHB patients with CKD was seen in both liver clinic and primary care clinic settings. On further sub-analysis of the different stages of CKD, there were a trend for higher proportions of CHB patients with CKD stage 2 or 3–5 over time in both primary care clinic ($p = 0.069$) and liver clinic ($p = 0.086$) settings.

Treatment differences

Overall, a total of 1229 (44.9% of 2734) patients received antiviral therapy: 46.1% of 885 patients in 2000–2005, 41.6% of 888 patients in 2006–2010, and 47.0% of 961 patients in 2011–2015 ($p = 0.057$). In 2000–2005, 17% of patients started antiviral therapy within 6 months of presentation with the following treatment regimens: 71.2% on lamivudine, 17.0% on adefovir, 7.6% on entecavir, and 4.2% on other treatment. In 2006–2010, 28.6% of patients started antiviral therapy within 6 months of presentation with the following treatment regimens: 14.2% on lamivudine, 12.9% on adefovir, 51.1% on entecavir, 14.7% on tenofovir, 2.2% on telbivudine, and 5.7% on other treatment. In 2011–2015, 35.3% of patients started antiviral therapy within 6 months of presentation with the following treatment regimens: 1.3% on lamivudine, 0.7% on adefovir, 32.7% on entecavir, 59.8% on tenofovir, 0.7% on telbivudine, and 4.8% on other treatment.

There was no significant difference of CKD in untreated vs. treated with 10.3% of the untreated and 11.9% of the treated group having eGFR <60 mL/min ($p = 0.27$). Similarly, there were no significant differences in the proportions of patients with eGFR <60 mL/min between the treated and untreated group for each of the time periods ($p = 0.24$ – 0.94). The proportions of patients with osteopenia, osteoporosis, and/or vitamin D deficiency were not significantly different between the untreated and treated patient groups overall (29.7% vs. 26.2%, $p = 0.066$). However, from 2000–2005 to 2006–2010 and 2010–2016, the proportions of patients with CKD increased significantly in both treated (3.7%, 9.0%, 19.8%, respectively, $p = 0.029$) and untreated patients (4.5%, 9.5%, 23.4%, respectively, $p < 0.001$). Over the three respective time periods, mean age increased from 43.3 ± 12.9 to 46.6 ± 14.5 and 50.9 ± 14.6 in treated patients and 43.3 ± 13.9 to 46.5 ± 14.1 and 47.5 ± 14.3 , respectively, all $p < 0.001$, as well as other co-morbidities such as hypertension, hyperlipidemia, osteoporosis, and osteopenia ($p < 0.001$ for all comparisons in treated patients and 0.02 to <0.001 for untreated patients). There were also more advanced liver diseases in both treated and untreated patients over time: 14.3 to 31.2% for cirrhosis, 0.7 to 12.5% for hepatic decompensation, and 5.4 to 16.5% for HCC, respectively, all $p < 0.001$ for treated patients and 11.2 to 18.0% for cirrhosis ($p = 0.008$), 1.4 to 7.1% for hepatic decompensation ($p < 0.001$), and 4.6 to 6.4% for HCC ($p = 0.2$) for untreated patients.

Sex differences

Overall, at the initial clinic visit with CHB, more women presented with an age <40 (43.7 vs. 35.8%) and overall were younger compared to men. Women also tended to have significantly less tobacco use (10.0 vs. 30.7%) and

alcohol use (15.4 vs. 35.6%) ($p < 0.001$). Compared to men, liver-related complications tend to be lower in women. At baseline, fatty liver was found to be lower by 1.8-fold (2.5 vs. 4.7%), cirrhosis by 2.5-fold (8.7 vs. 22.2%), hepatic decompensation by 2.5-fold (1.7 vs. 4.5%), and hepatocellular carcinoma by 2.5-fold (3.3 vs. 8.6%). Women also had lower rates of non-liver co-morbidities compared to men: diabetes mellitus (10.8 vs. 15.4%, $p = 0.001$), hypertension (22 vs. 28.7%, $p < 0.001$), and chronic kidney disease (10.1 to 13.2%, $p = 0.02$). On the other hand, osteopenia and osteoporosis were significantly higher in women compared to men. In 2000–2005, there was a fourfold higher rate of osteopenia (10.0 vs. 2.4%, $p < 0.001$) and a ninefold higher rate of osteoporosis (6.4 vs. 0.7%, $p < 0.001$) in women compared to men. Over time, the proportions of CHB with osteopenia and osteoporosis increased significantly in women: 12.2, 17.7, and 26.5% in 2000–2005, 2006–2010, and 2011–2015, respectively ($p < 0.001$), as well as in men: 2.6, 6.6, and 13.0%, respectively ($p < 0.001$).

Discussion

In this large study of CHB patients from both university referral and community primary care settings, we found that CHB patients are presenting at older ages, with more advanced liver disease and medical co-morbidities. Specifically, we found that there was more than a 50% increase in patients over age 50 when comparing the 2000–2005 and the 2011–2015 cohorts. There were also changes with decreasing proportions of patients who were foreign born over the time periods, which many suggest changes in immigration of patients served at participating clinical centers. However, this cannot be generalizable to the whole CHB populations in the Bay area as our study cohort was not a population-based sample. In addition, patients presented with a twofold increase in cirrhosis, sevenfold increase in liver decompensations, and twofold increase in HCC. The data on non-liver-related co-morbidities are equally staggering with a fivefold increase for diabetes, threefold for hypertension, 4.5-fold for hyperlipidemia, and 4.5-fold for CKD ($p < 0.001$). With only few exceptions, this increasing trend in age, in liver morbidities, and in non-liver co-morbidities were consistently discovered for patients seen at university liver clinics as well as community primary care clinic patients, men as well as women, and treated as well as untreated patients.

Although we found significant increasing trends in various liver and non-liver co-morbidities among both treated and untreated patients, we did not find significant differences in the proportions of patients with bone disorders and renal insufficiency between untreated patients and patients on antiviral therapies for CHB. Although some of the currently available oral anti-HBV medications

have been reported to associate with renal and/or bone disease^{16–19}, this effect is likely to be time-dependent and our analysis is based on the presence of disease at the time of initial presentation to clinics. The effect of antiviral therapies on renal and bone function requires additional studies with longitudinal follow-up of treated patients.

On the other hand, we found significant differences in men and women, with men having more advanced liver disease such as HCC, a finding previously described in other studies, and other non-liver co-morbidities except for osteopenia and osteoporosis, which were more common in women²⁰. However, within each sex, the proportions of CHB patients with CKD or bone disorders increased significantly over time, suggesting that these trends exist in both sexes.

Several factors likely contribute to the rising age of CHB patients and the increase in co-morbidities that are likely associated with the rising age. Gaps in the care cascade for CHB patients have been well documented²¹. Decrease awareness leads to delayed diagnoses and more advanced disease at presentation. In a recent study, only 2–3% of individuals who attended local fairs over 2 years took advantage of free HBV and hepatitis C virus education and screening²². Perhaps many people may not be aware if they have a family history of HBV. In our study, HBV family history was only 35–40%, suggesting possible lack of awareness and/or underreporting. Therefore, the need for patient education about HBV and its associated risks cannot be understated. Even individuals diagnosed with CHB often undergo suboptimal evaluation and treatment despite meeting criteria for therapy^{23–26}. According to the World Health Organization, only 9% of all HBV infections globally were diagnosed in 2015. Worse, only 8% of those diagnosed with HBV infection (1.7 million people out of the total 248 million people with CHB) were on treatment²⁷. The older age of CHB patients presenting to both primary care clinics and liver clinics suggest that the finding of our study is not just due to delayed referral to subspecialty or university clinics but also a delay in linkage to care at a community primary care level. The fact that we found increasing trends in advanced liver disease such as cirrhosis and hepatic decompensation in untreated patients is also particularly concerning with 18% of them presenting with cirrhosis, 7.1% with hepatic decompensation, and 6.4% with HCC in 2011–2015. Furthermore, the proportion of patients who were started on treatment within 6 months of presentation did increase from 17% in 2000–2005 to 35.3% in 2010–2015. There was a shift from lamivudine to tenofovir as the most commonly prescribed drug at initiation.

Also, notable in our finding is the increase in the proportion of CHB patients with concurrent fatty liver disease over the study periods from 1.6% in 2000–2005 to 6.8% in 2011–2015. However, this is still lower than the

US prevalence of 30% for non-alcoholic fatty liver disease based on the most recent population-based data from the 1999–2012 National Health and Nutrition Examination Survey^{28,29}. Asians were under-represented in the National Health and Nutrition Examination Survey but the prevalence of non-alcoholic fatty liver disease is also estimated to be about 25% by a recent non-alcoholic fatty liver disease management guideline by the Asia Pacific Association for the Study of Liver Diseases³⁰. Under-reporting and/or under-coding for fatty liver may be a problem here as physicians may perceive CHB as the primary disease and overlook a concomitant liver process.

There were some inherent limitations to the study due to the retrospective and observational design. Though we included consecutive patients with CHB who presented at the study centers, referral of sicker patients to the university center may have generated some selection bias. We attempted to mitigate this by including community centers and primary care clinics. The increasing trends in co-morbidities were similar in both clinic settings except for analysis of advanced liver disease, though there was also a trend for increasing proportions of patients with cirrhosis and significant decline in platelet values among primary care clinic patients. Another limitation to consider is the screening and surveillance bias, which may occur when a patient diagnosed with one chronic illness such as CHB receives more screening and/or surveillance for other illnesses by care providers leading to earlier and more diagnosis of other diseases³¹. As patients become older, they can have more illnesses. They may also be monitored more closely by their physicians with more and earlier diagnoses made as a result. However, this surveillance bias is unlikely to change over the three study periods as there were no significant changes to screening recommendation for CKD, diabetes, hypertension, and osteoporosis to our knowledge. Since the Institute of Medicine published a national report defining vitamin D deficiency as 25(OH)D <20 ng/mL in 2011, there may have been an increase in vitamin D screening¹⁹. There is a 70.8% rate of vitamin D deficiency in patients attended in primary care clinics during 2011–2015 compared to the 22.6% rate in patients seen in liver clinics, suggesting that this non-liver co-morbidity may be underdiagnosed or underreported in liver clinics. In addition, although the overall proportion of patients with vitamin D deficiency increased over time in our CHB patients (30.7% to 35.1% to 38.3%), this rise did not reach statistical significance ($p = 0.088$). As for renal function, the Chronic Kidney Disease Epidemiology Collaboration equation is more accurate than the Modification of Diet in Renal Disease study equation, and both are more accurate than the Cockcroft–Gault equation. Only data from the Cockcroft–Gault equation were available and used in this study, which may be an overestimate of creatinine

clearance. However, the same equation was used for all study periods and this limitation should not have affected the changes in renal function over time as seen in our study. In addition, we have also avoided potential observational time-related biases by noting the presence of liver and non-liver co-morbidities only if they were present at or within 6 months of the index date, which was the patient's initial presentation to any service (HBV-related or not) at each study center. Each of these centers also had its own medical record system unlinked to external medical or administrative systems and thus preventing observational bias in patients with longer observational windows.

In conclusion, between 2000 and 2015, the median age of patients and the proportion of CHB patients with co-morbidities increased significantly. We found that these changes occurred in both primary care clinic and liver clinic settings, in both men and women, and in both treated and untreated patients. The facts that more patients are presenting with more advanced liver disease even in primary care clinics and more patients with advanced liver disease presented without prior treatment are disturbing. Further efforts are urgently needed to diagnose CHB earlier and to link CHB patients to appropriate care before age advancement and the development of advanced liver disease and other co-morbidities complicate CHB management.

Study Highlights

What is current knowledge

- Many patients with chronic hepatitis B are asymptomatic.
- Chronic hepatitis B patients have high morbidity and mortality rates.
- Data on liver and non-liver co-morbidities in chronic hepatitis B patients are limited.

What is new here

- Chronic hepatitis B patients are presenting to care at more advanced ages.
- Over the last 15 years, more patients are presenting with advanced liver disease without prior treatment.
- Further efforts are urgently needed to diagnose chronic hepatitis B earlier and to link these patients to appropriate care.

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Conflict of interest

Guarantor of the article: Mindie H. Nguyen, MD, MAS.

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Supplementary information

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