Shifting Demographics and Comorbidity Burden in Chinese Urban Patients With Chronic Hepatitis B, 2013 and 2016

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Abstract

Background: The long-term safety of anti-hepatitis B virus (HBV) therapies is critical to assess, particularly in the context of aging chronic hepatitis B (CHB) populations and accumulating comorbidities. HBV is common and clinically consequential in China; however, the demographics and comorbidity burden of this population have not been fully characterized.

Aim: To characterize changes in demographics and comorbidity burden of urban Chinese patients with CHB between 2013 and 2016.

Methods: The China Health Insurance Research Association (CHIRA) annual urban health insurance claims database from 2013 and 2016 was used to identify adults with ≥1 ICD-10 code for CHB. Descriptive analyses were conducted to compare age and comorbidities distributions between 2013 and 2016.

Results: Median age increased from 40 in 2013 (N=14,545) to 44 in 2016 (N=11,648) (*P*<0.001). The proportion of patients aged >45 years increased significantly from 40.3% in 2013 to 49% in 2016 (*P*<0.001). Significant increases in multiple comorbidities were observed, including hypertension (9.4% to 14.5%), hyperlipidemia (4.7% to 7.0%), and cardiovascular disease (5.7% to 10%) (*P*<0.001 for all comparisons). Increases were also observed in renal impairment (8.8% to 10.0%; *P*<0.001) and osteoporosis and/or pathologic nontraumatic bone fracture (3.8% to 7.3%; *P*<0.001).

Conclusions: Even over the short interval assessed in this study, there was a significant shift in the characteristics of urban CHB patients in China. Aging of the population was accompanied by significant increases in the percentage of patients having potentially concerning comorbidities. Careful selection of treatment options and comorbidity monitoring should be considered when managing Chinese patients with CHB.

Background

Worldwide estimates suggest that approximately 250 million individuals have chronic hepatitis B (CHB), and approximately 650,000 die of associated hepatic failure, liver cirrhosis, and/or hepatocellular carcinoma (HCC) each year.[1,2] Nearly one-third of the global population with CHB live in China, of whom 28 million require treatment and 7 million require immediate treatment due to the presence of advanced liver disease and a high risk for developing liver cancer.[3,4] The introduction of a universal vaccine program in China led to a gradual reduction in the prevalence of hepatitis B virus (HBV) carriers from 9.8% in 1992 to 6.1% in 2007 to 2013.[5,6] Nevertheless, CHB continues to be an epidemic in China, imposing the highest disease burden associated with a communicable disease in this country, with some estimates suggesting that about 10 million people living with CHB will die by 2030.[4,7]

Treatment for CHB, which is often long-term or even lifelong, is directed at improving quality of life and survival by maximally suppressing HBV replication in a sustained manner.[8] Appropriate treatment of CHB

has been shown to reduce hepatic inflammation and fibrosis, decrease risk for hepatic failure, slow progression of hepatic decompensation, and reduce the incidence of HCC. Treatment is evolving, and a number of therapies with a high genetic barrier to resistance have been introduced worldwide, including entecavir, available since 2006, and tenofovir disoproxil fumarate since 2008; in late 2018, tenofovir alafenamide, a novel, targeted prodrug of tenofovir, was approved by the China National Medical Products Administration.

In patients with CHB, infection and the resulting liver complications are superimposed over a range of liver-related and non-liver comorbidities that may be directly related, closely associated, or unrelated to the underlying infection, and—as in most chronic diseases—these comorbidities accumulate and worsen as patients age. These comorbidities, and the concomitant medications used to treat them, have the potential to complicate both the initial selection of appropriate nucleotide/nucleoside analog (NA) therapy as well as ongoing treatment for CHB, and it is thus important to understand the changing regional demographics and clinical characteristics of patients with CHB. It is clear from other studies conducted outside of China that the demographics of the CHB population are shifting substantially, becoming not only older overall, but also subject to a dramatically higher comorbidity burden over time.[9]

The characteristics of the Chinese population with HBV are important to understand, particularly because these populations are aging and accumulating comorbidities that may require concomitant treatment. The present study, which leverages data from the China Health Insurance Research Association (CHIRA) Annual Urban Claims Database to identify patients with CHB, is the first to provide an assessment of demographic and comorbidity trends in this important population.

Methods

Study objective

This was a retrospective, cross-sectional analysis of the CHIRA annual urban claims databases from 2013 and 2016. The primary objective was to describe the time trend of demographic characteristics and the comorbidity profile among CHB patients in China. The research protocol for this study was reviewed and approved by CHIRA.

Database description

The CHIRA annual claims database is generated yearly by randomly selecting 2% of urban worker and resident claimants living in national cities (including Beijing, Shanghai, Tianjin, and Chongqing) or provincial capital cities, and 5% of claimants living in regional cities in 32 Chinese provinces and extracting their claims records for the year. In total, data from 90 cities were included in this analysis. The created annual claims database consisted of 2 datasets: a general dataset that contained demographic information (age, sex, residence), insurance type (urban workers or residents), healthcare settings (hospital tier rank which ranges from I to III; the higher hospital rank, the larger hospital scale), diagnosis, and medical costs associated with claims and a transaction dataset that consisted of claims records for

drug prescriptions, laboratory tests, image tests, and other healthcare resources associated with each insurance claim. There are 3 types of public health insurances in China: the Urban Employee Basic Medical Insurance (UEBMI), the Urban Resident Basic Medical Insurance (URBMI), and the New Rural Cooperative Medical Insurance. The UEBMI covers urban employees and the URBMI covers those who are not employed (young children, students, and nonworking adult urban residents). Once an enrollee has been covered by the UEBMI for more than 15 years, they will be covered by the same medical insurance for their entire life (ie, the enrollee will continue to be covered by the UEBMI after retirement).

Identification of patients with CHB

The diagnosis information in the 2013 and 2016 CHIRA annual claims databases was recorded in Chinese. To facilitate the patient identification and the extraction of comorbidity information, this study pooled the diagnosis information contained in the 2 claims databases and removed the duplicated diagnosis names and Chinese medicine diagnosis names. The remaining diagnosis information was further standardized using International Classification of Diseases, Tenth Revision (ICD-10) codes. After conversion to ICD-10, diagnosis codes were assigned to the claimants to create diagnosis datasets for the calendar years of 2013 and 2016, respectively. The 2 diagnosis datasets were further used to identify patients with CHB using the ICD-10 code for CHB (B18.1). The 2 diagnosis datasets were also the data source used to identify the comorbidities associated with included CHB patients in this study. This analysis also excluded patients aged <18 years and patients who only had diagnosis information for CHB from pharmacy store claims records, which were deemed insufficiently accurate to determine diagnoses with confidence.

Data extraction

Claims records associated with CHB were extracted to create a study dataset that included patient demographics, converted ICD-10 diagnosis codes, and prescriptions for NAs for the 2013 and 2016 cohorts. Extracted diagnostic codes were cleaned by removing duplications and were categorized according to selected common comorbidities in patients with chronic HBV. Liver-related comorbidities were defined according to the ICD-10 codes for cirrhosis, decompensated liver failure, portal hypertension, esophageal varices, ascites, gastrointestinal bleeding, jaundice, HCC, and liver transplantation. Renal comorbidities were defined according to ICD-10 codes for chronic kidney disease, end-stage renal disease, dialysis, chronic pyelonephritis, glomerulonephritis, nephrolithiasis, nephropathy, renal osteodystrophy, proteinuria, and renal insufficiency. Diseases related to bone density were defined according to ICD-10 codes for osteoporosis, osteopenia, osteomalacia, bone fracture related to osteoporosis, and any ICD-10 codes indicating fracture but not falling into the injury-related fracture categories. Additional comorbidities assessed in this study are listed in Supplemental Table S1. The prescription records associated with the included CHB patients were screened using the generic names of NAs that were approved before 2017 in China for their NA treatment status. These NAs included lamivudine, adefovir, telbivudine, entecavir, and tenofovir disoproxil fumarate.

Statistical analyses

Continuous variables were summarized with means and standard deviations. Other patient demographic characteristics, comorbidities, NA treatments, and liver-related complications were summarized using percentages for distributions. Patient characteristics in the 2013 and 2016 datasets were compared for changes in demographics, comorbidities, NA treatments, and liver-related complications. Age group distribution (≥18 to <35 years, ≥35 to <45 years, ≥45 to <55 years, ≥55 to <65 years, and ≥65 years) was also evaluated. Analyses used each student's t-test for continuous variables and the chi-square test for categorical variables. The statistical significance in these comparisons was defined as a 2-sided *P* value <0.05. All analyses were conducted using the statistical software R.

Results

Study population

A total of 15,218 patients from the 2013 dataset and 11,757 patients from the 2016 dataset were identified based on an ICD-10 code indicating a diagnosis of CHB (**Figure 1**). After excluding claimants identified from pharmacy records as those aged <18 years or for whom an age was not recorded, there were 14,545 patients in the 2013 dataset and 11,648 in the 2016 dataset.

Demographics

Between 2013 and 2016, the mean age of urban Chinese patients with CHB increased from 42.4 ± 14.2 years to 45.6 ± 42.4 years (*P*<0.001). There was a significant increase in the proportion of patients aged ≥35 years (63.5% vs 73.9%; *P*<0.001) and ≥45 years (40.3% vs 49.0%; *P*<0.001) from 2013 to 2016 (**Figure 2**). Similar trends in mean age were observed for both male and female patients. The proportions of male patients increased significantly between 2013 and 2016 (15.0% vs 29.4%; *P*<0.001) (**Table 1**) and there were also increases in the percentage of patients living in national cities (15.0% vs 29.4%; *P*<0.001). The percentage of patients treated at top-ranked (Tier 3) hospitals declined significantly from 86.8% to 69.8% (*P*<0.001).

Comorbidities

Comorbidities were common in the study population. The proportion of patients with ≥1 comorbid condition increased from 54.1% in 2013 to 61.2% in 2016 (*P*<0.001). The percentage of patients with certain common comorbidities significantly increased between 2013 and 2016, including hypertension, non-alcoholic fatty liver disease (NAFLD), endocrine diseases, cardiovascular diseases, and hyperlipidemia (**Table 2**). A number of additional comorbidities also increased in prevalence, including renal impairment (8.8% to 10.0%; *P*<0.001) and osteoporosis and/or pathologic/nontraumatic bone fracture (3.8% vs 7.3%; *P*<0.001).

Liver-related complications

The percentage of patients with ≥1 liver-related complication increased from 16.4% in 2013 to 21.1% in 2016 (*P*<0.001). The percentage of patients with compensated cirrhosis (11.3% vs 15.8%; *P*<0.001) and

decompensated cirrhosis (6.4% vs 7.2%; *P*<0.001) also increased between 2013 and 2016. The distribution of liver-related complications is illustrated in **Figure 3**.

Distribution of nucleoside analogue therapy

The proportion of patients with ≥1 prescription record for any NA increased significantly from 39.5% in 2013 to 55.2% in 2016 (*P*<0.001) (**Table 3**). Thus, the proportion of untreated CHB patients in the 2013 claims database was significantly higher than that in the 2016 claims database (60.5% vs 44.8%, *P*<0.001). The proportion of patients receiving prescriptions for 4 of the 5 NAs evaluated increased, with the largest increase seen in entecavir prescriptions (22.8% to 39.6%; *P*<0.001) and only small, but statistically significant, increases seen for adefovir, telbivudine, and tenofovir disoproxil fumarate. Prescriptions of lamivudine fell significantly from 10.4% to 8.4% (*P*<0.001).

Discussion

This large, retrospective study of urban Chinese patients with CHB leveraged the only nationally representative database for urban workers and residents, and is the first study to characterize the demographics, comorbidity burden, and recent trends in NA treatment patterns in this population. The data revealed that the Chinese urban population with CHB is aging and that the comorbidity burden is increasing, even over the relatively short time span assessed in this analysis.

These results are consistent with data from multiple studies conducted across Asia that together show that the CHB population is rapidly aging and accumulating comorbidities.[10–13] A recent evaluation of CHB comorbidities in Hong Kong over an 18-year period spanning 2000 to 2017. In this study, the prevalence of hypertension (25.5–28.6%), diabetes (10.6–20.1%), cardiovascular disease (12.5–22.2%), and malignancies (7–23.6%) increased between the initial study period (2000 to 2004) and the latest data collection period (2014 to 2017). There was also a dramatic and statistically significant shift in the age of the HBV population, from 41 ± 15 in 2000–2004 to 55 ± 15 years in 2014–2017. A second study, conducted in a Korean population, identified a significant increase in age from 47 years in 2007 to 52 years in 2016. As in other studies, the comorbidity burden increased in parallel with age, with significant increases in the percentage of patients with hyperlipidemia, hypertension, diabetes, osteoporosis/bone fracture, and chronic kidney disease.[11] In Taiwan, a retrospective claims review of data from the National Health Insurance Research Database found that the Taiwanese CHB population had aged substantially between 2001 and 2011, at which point nearly 42% of patients were aged ≥ 55 years. Increases in the percentage of patients with clinically significant comorbidities, including chronic kidney disease, osteoporotic fractures, and metabolic syndrome, were also apparent, with the latter increasing almost 4-fold over the time period assessed in the analysis.[12] In Japan, an analysis of 13,639 patients that compared the demographics of the CHB population in 2011 and 2016 found that the average age of patients with CHB increased from 62 to 66 years across this brief time period and that the rates of key comorbidities and complications, including diabetes (from 8–14%), kidney disease (from 4–5%), bone fracture (from 5–9%), and NAFLD (from 14–16%), all increased significantly.[13]

Globally, a similar pattern appears. An analysis conducted in the United States compared demographics and comorbidities between 2000 to 2015 and found a similar shift in demographics.[9] Mean age in this US-based study increased from 43.3 years during the 2000–2005 assessment period to 49.1 during the 2011–2015 period. Also consistent with this analysis, the percentage of patients with non-liver comorbidities increased substantially: diabetes by almost 5-fold, hypertension by 3-fold, and chronic kidney disease by 4.5-fold. The prevalence of osteopenia and osteoporosis likewise increased by 3-fold and 2.5-fold, respectively, in the US analysis.

Although the time periods assessed in this study were separated by only 3 years, there was a small but significant increase in the percentage of renal disease that may be concerning, particularly in light of the fact that renal function decline may be associated with aging and antiviral treatments.[14] Further, some data suggest that patients with CHB may be fundamentally at greater risk for kidney and bone disease compared with non-CHB controls.[15] For these reasons, the most recent European Association for the Study of the Liver (EASL) guidelines indicate that all patients at risk for renal disease who are on antiviral therapy, as well as all patients treated with tenofovir disoproxil fumarate regardless of renal risk, should undergo baseline and periodic renal monitoring, including at least estimated glomerular filtration rate and serum phosphate levels.[14]

There was a larger and statistically significant increase in the percentage of patients with bone disease, which may also potentially be exacerbated by NA treatment and has also been raised as a concern in updated guidelines.[14] Given that aging is associated with reduced renal function and an increasing prevalence of bone disease, the superimposition of age- and treatment-related changes in renal function and bone health may represent a significant emerging clinical issue as CHB patients continue to age and the proportion of treated patients increases.

Another interesting finding was a striking increase in the percentage of patients with NAFLD over the time period of the study, consistent with recent analyses indicating that the prevalence of NAFLD is increasing globally.[16,17] This finding is concerning, as NAFLD associated with CHB may be associated with an increased risk for end-stage liver disease and death.[17] It is noteworthy that the prevalence of diabetes only increased from 3.2–3.6% in this study, yet this may be an underestimate as many physicians may not code comorbidities, such as diabetes, if the primary reason for the visit is CHB.

The percentage of patients with CHB-related liver complications, including cirrhosis and decompensated cirrhosis, increased significantly between 2013 and 2016. There was a small but significant decline in the rate of HCC in this population; however, it is important to note that this estimate may not by accurate due to the fact that cancer patients are not well captured in the CHIRA dataset.

An analysis of treatment trends found that the percentage of patients receiving any NA therapy increased by nearly 40% even over the relatively short span assessed in this study, from 39.5–55.2%. While promising, these data also show that more than half of Chinese patients with CHB remain untreated. Further, while much of this increase was driven by increased prescription of entecavir, an NA with a high

genetic barrier to resistance,[18] at least half of the treated patients included in this analysis were still receiving therapy with agents that have a low genetic barrier to resistance (eg, adefovir, lamivudine, telbivudine) as of 2016. Tenofovir alafenamide, along with entecavir, has particular utility in patients with or at risk for renal or bone disease and is recommended in these patients by the most recent iteration of the EASL guidelines.[14]

The trends observed in this study have several important implications for the future management of CHB in Chinese patients. Current Chinese clinical practice guidelines do not recommend routine screening of comorbidities in CHB patients.[8] Increasing age, a greater likelihood of comorbidities, and a consequent increase in the need for comedications raise potential safety risks. Additionally, the observed trends of rapid increases in the percentage of CHB patients with comorbid cardiovascular diseases, chronic renal diseases, NAFLD, and osteoporosis in this study clearly demonstrate the need to assess and manage these comorbidities to improve overall patient health outcomes. Routine screening for comorbidities is thus increasingly important to guide the selection of appropriate NA treatment and manage comorbidities in CHB patients. These data also point to the ongoing need for new CHB therapies with improved safety profiles and high genetic barriers to resistance.

The design of this study is accompanied by a number of inherent limitations. The study periods assessed in this study, 2013 and 2016, were separated by only 3 years. Thus, they provide only a limited snapshot of changes in demographics and comorbidities over a short period of time. Nevertheless, the changes observed for age and for many comorbidities were striking and significant and point toward the potential for major shifts in the clinical profile of CHB patients in China over longer assessment periods. Estimates of comorbidity burden may be low because clinicians may not code comorbidities if the primary reason for the visit was for CHB. This study also provides no information on the impact of treatment on renal function or bone disease, as it included a mixed population of treated and untreated patients. The use of the CHIRA annual claims database, which included only patients from the 2 major urban health insurance plans in China, as a data source may result in some degree of selection bias. Further, the data sources used do not track previous treatment history or accurately estimate the duration of CHB treatment. The design and available data sources precluded following patients longitudinally, pointing to the need for future studies to follow a real-world cohort of Chinese CHB patients with detailed clinical information to address the needs of screening and monitoring comorbidities in the current clinical management of CHB in China.

Conclusion

In summary, this study leveraged the CHIRA annual urban claims databases for 2 calendar years (2013 and 2016) and showed distinct and statistically significant shifts toward increased age and an increasing comorbidity burden in Chinese urban CHB patients. Further, these data show that a significant proportion of this patient population remains untreated for CHB, and of those who are treated, many still receive treatments with a low genetic barrier to resistance. As this patient population ages and comorbidities

accumulate, it will become even more important that comorbidities are carefully assessed, managed, and taken into account when selecting NA treatment.

Declarations

Ethics and consent to participate

The study was approved by CHIRA, which assessed the risk of ethics regarding the use of the urban claims data of CHIRA. The study was performed in compliance with the ethical principles of good clinical practice and according to the ICH Harmonised Tripartite Guideline.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from CHIRA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of CHIRA.

Competing interests

J. Hou has received research grants and a speaker honorarium from Gilead Sciences, Inc., Bristol-Myers Squibb, GSK, and Novartis; W. Chen is the founder of Normin Health, a consulting firm receiving industry funds to conduct health economics and outcomes research; H. Ying has served on advisory boards for Gilead Sciences, Inc., Bristol-Myers Squibb, GSK, Roche, AbbVie, Merck Sharpe & Dohme, Abbott, and Mylan; L. Wang has served on advisory boards for Gilead Sciences, Inc., and has been a speaker for Bristol-Myers Squibb, GSK, AbbVie, Merck Sharpe & Dohme, Mylan, and Roche; I. Lee and L. Hsu are employees of Gilead Sciences, Inc., and own stock in the company; D. Xie has received speaker honoraria from Gilead Sciences, Inc., Bristol-Myers Squibb, GSK, and Novartis; X. Yin has no conflict of interest to declare; F. Hou has no conflict of interest to declare; Y. Yang has received research grants from Gilead Sciences, Inc., and has received speaker honoraria from GSK and Gilead Sciences, Inc.

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Authors' contributions

WC and LH contributed to the study protocol, data extraction/clean, data analyses, results interpretation, and manuscript development. All other authors were involved with study protocol, results interpretation, and manuscript development. All authors have critically reviewed the manuscript and approved the

manuscript submission. Writing and editorial support was provided by Impact Communication Partners, Inc.

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Not applicable.

Abbreviations

CHB, chronic hepatitis B

CHIRA, China Health Insurance Research Association

EASL, European Association for the Study of the Liver

HBV, hepatitis B virus

HCC, hepatocellular carcinoma

ICD-10, International Classification of Diseases, Tenth Revision

NA, nucleoside analog

NAFLD, non-alcoholic fatty liver disease

UEBMI, Urban Employee Basic Medical Insurance

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Tables

Table 1.

	2013 Cohort (n=14,545)	2016 Cohort (n=11,648)	*P* Value
Mean age, years (SD)	42.4 (14.2)	45.6 (42.4)	<0.001
Male sex (%)	58.4%	63.2%	<0.001
Insurance plan			
Employee	86.8%	87.6%	0.077
Resident	13.2%	12.4%	0.077
Residence city level			
National	15.0%	29.4%	<0.001
Provincial	43.7%	38.4%	<0.001
Regional	41.3%	32.2%	<0.001
Medical setting			
Tier I hospital	10.1%	12.9%	<0.001
Tier II hospital	30.9%	36.9%	<0.001
Tier III hospital	86.8%	69.8%	<0.001
Community hospital	16.1%	25.3%	<0.001
Outpatient clinics	7.4%	6.6%	0.019
Pharmacy store	8.7%	12.8%	<0.001
Not reported	0.2%	12.0%	<0.001

Table 2.

	2013 Cohort (n=14,545)	2016 Cohort (n=11,648)	*P* Value
NAFLD	13.9%	17.0%	<0.001
Hypertension	9.4%	14.5%	<0.001
Endocrine disease	7.8%	11.1%	<0.001
Renal impairment	8.8%	10.0%	<0.001
Cardiovascular diseases	5.7%	10.0%	<0.001
Osteoporosis and/or pathologic/ nontraumatic bone fracture	3.8%	7.3%	<0.001
Hyperlipidemia	4.7%	7.0%	<0.001
Diabetes	3.2%	3.6%	<0.001

Table 3.

	2013 Cohort (n=14,545)		2016 Cohort (n=11,648)		*P* Value
	n	%	n	%	
Any NA*	5741	39.5	6424	55.2	<0.001
Entecavir	3319	22.8	4614	39.6	<0.001
Adefovir	1789	12.3	1519	13.0	<0.001
Lamivudine	1516	10.4	974	8.4	<0.001
Telbivudine	536	3.7	631	5.4	<0.001
Tenofovir	0	0.0	131	1.1	<0.001

Figures

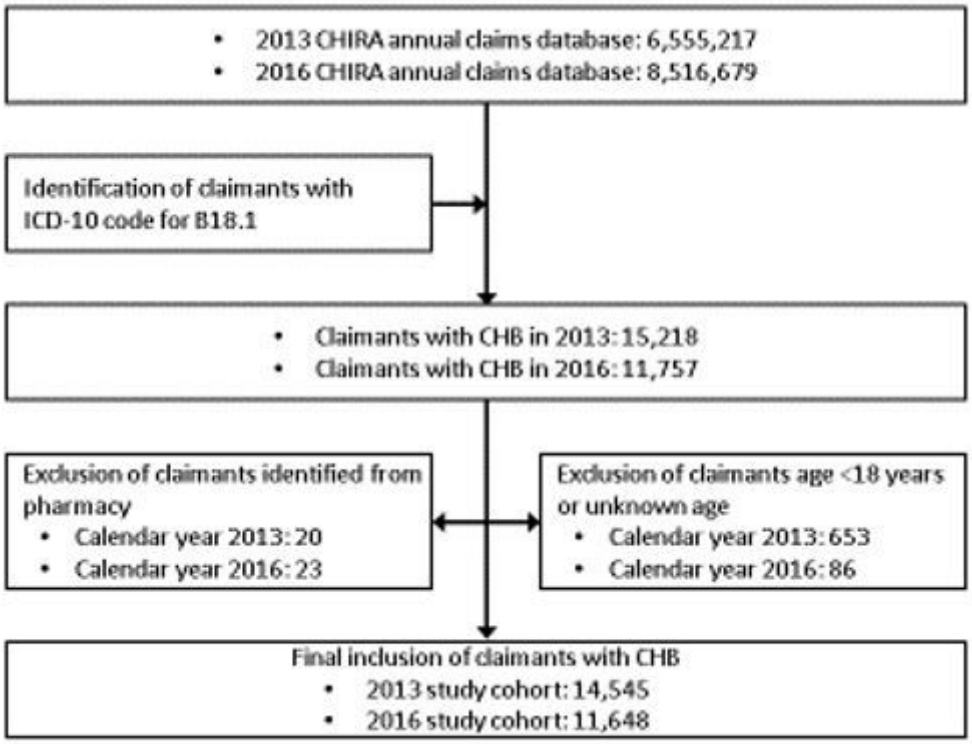

Figure 1

Derivation of the study populations for analysis.

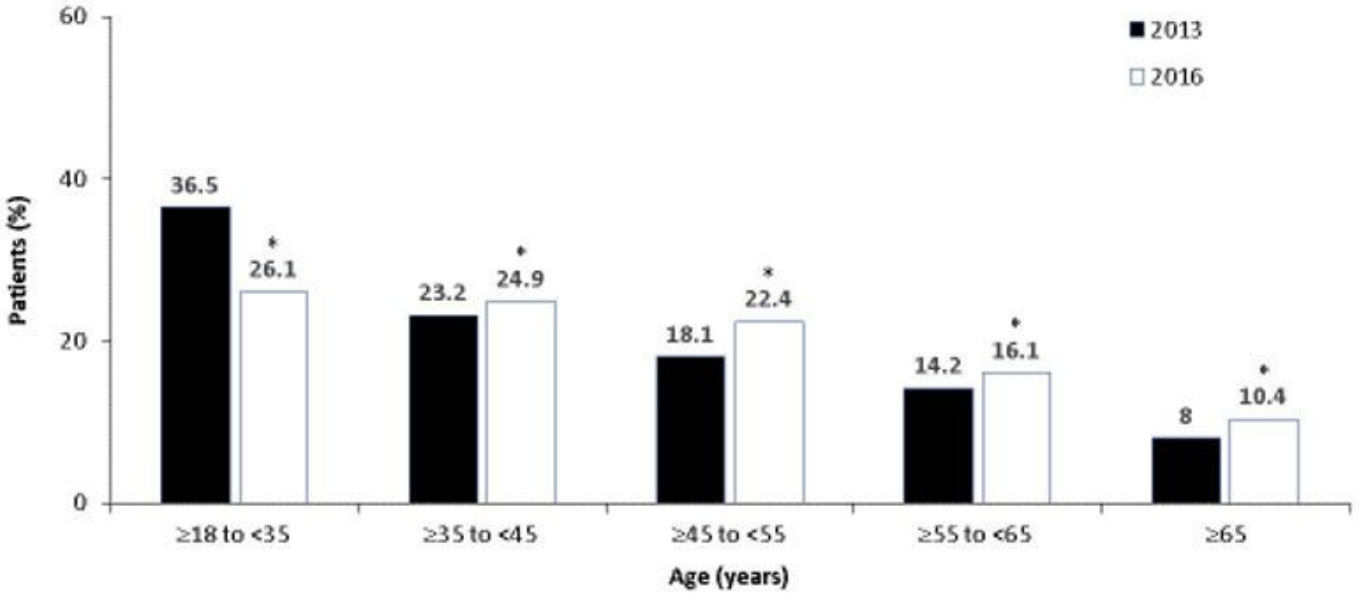

Figure 2

Distribution of age groups, 2013 vs 2016. *P<0.001.

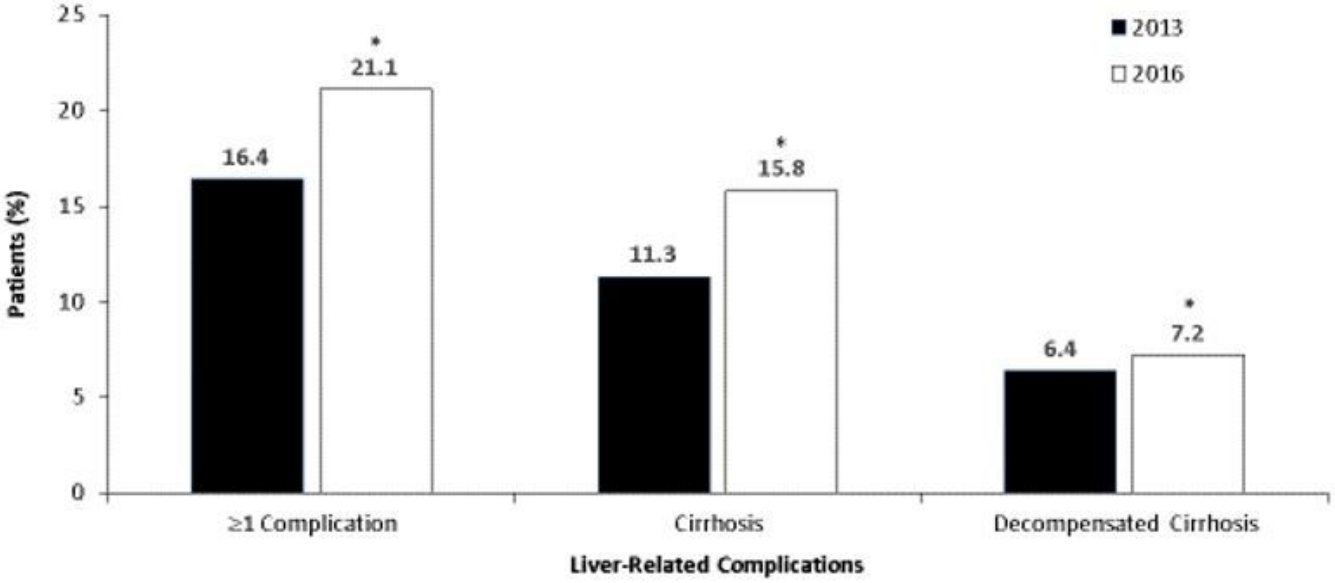

Figure 3

Distribution of liver-related complications, Chinese urban patients with CHB, 2013 and 2016. *P<0.001.