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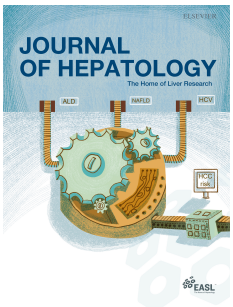

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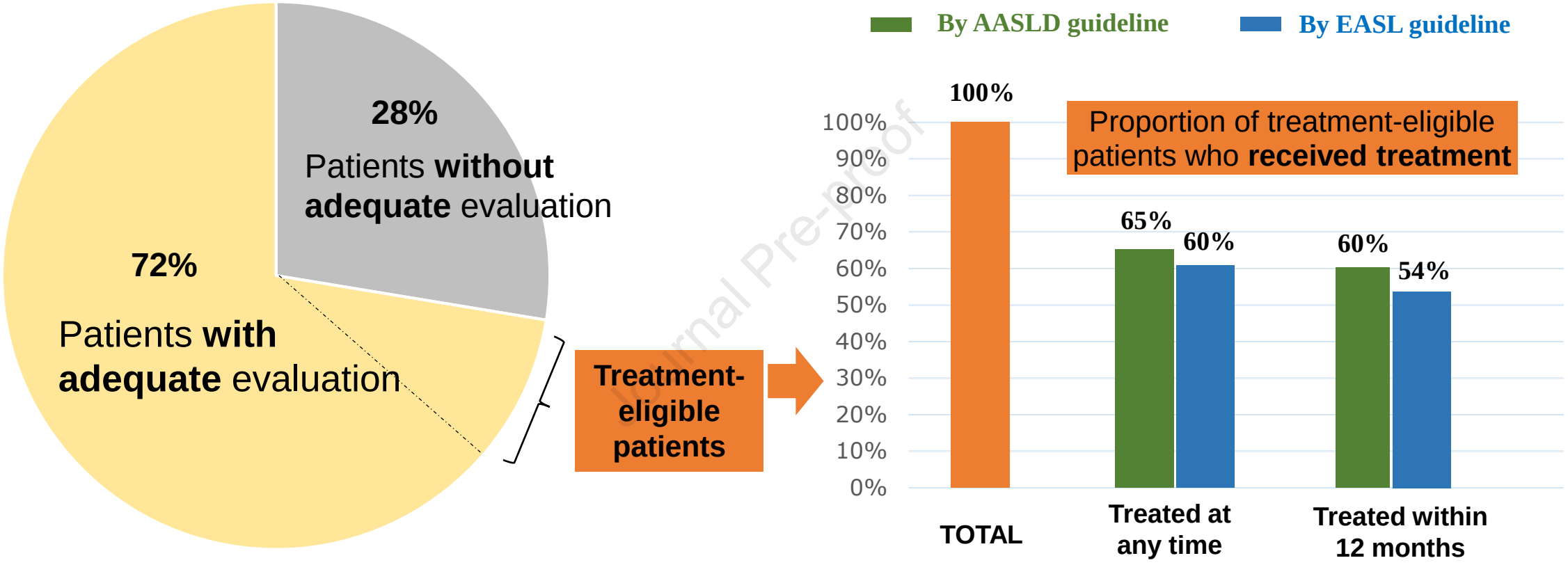
Chronic HBV infection in the United States 2003-2019, N=12,608



Substantial gaps in evaluation and treatment of patients with hepatitis B in the US

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All other authors have nothing to disclose.

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Specific author contributions:

Study design: Qing Ye, Leslie Y. Kam, Yee Hui Yeo, Ramsey C. Cheung, Mindie H. Nguyen

Data analysis: Leslie Y. Kam, Nolan Dang, Mindie H. Nguyen

Manuscript drafting: Qing Ye, Leslie Y. Kam, Ramsey C. Cheung, Mindie H. Nguyen

Data interpretation and review and revision of the manuscript: All authors

Study concept and study supervision: Mindie H. Nguyen

Abstract (274/275)

Background and Aims:

HBV associated liver complication is reduced by antiviral therapy. Prior studies using local institutional cohorts have suggested suboptimal evaluation and treatment. We aimed to determine the proportion of patients with chronic HBV infection who received adequate evaluation, were treatment eligible, and received antiviral treatment using a large, nationwide cohort.

Methods:

This retrospective analysis utlized claims data of approximately 73 million enrollees across the US from Optum's de-identified Clinformatics® Data Mart Database, 2003-2019. Adults with chronic HBV infection observed for ≥ 6 months before and after index chronic HBV infection diagnosis were identified via ICD-9/ICD-10 codes and confirmed by positive HBsAg, HBeAg or HBV DNA PCR.

Results:

We included 12,608 eligible patients in the study analysis (mean age 45.7 years, 52.1% male, 54.6% Asian, 18.1% Caucasian, 10.5% African American). About half of the cohort (n=6,559, 52.3%) did not have a complete laboratory evaluation (defined as having HBeAg, HBV DNA, and ALT tests) and only 72.4% (n=9,129) had an "adequate" evaluation (at least HBV DNA and ALT) during the entire study period. Of those with an adequate evaluation, 11.2% were treatment eligible by AASLD criteria and 13.9% by EASL criteria; and of these, 60.4% of AASLD eligible patients

and 54.3% of EASL eligible patients received treatment within 12 months from becoming eligible.

Conclusions:

Half of chronic HBV infection patients in the US with private insurance did not have a complete laboratory assessment. Over one third of treatment-eligible patients did not receive antiviral therapy. Patients who visited a GI/ID specialist had a higher chance of receiving adequate evaluation and treatment. Urgent intervention is needed to identify and address the barriers for these care gaps.

Lay summary

In this study, we used a national database that includes laboratory data in addition to medical and pharmacy claims data to assess the current real-world situation of chronic HBV infection care in the US. Among the 12,608 patients with chronic HBV infection included in our study, 52.3% never had a complete laboratory and only 73% had adequate evaluation. Among those who were treatment eligible by AASLD or EASL guidelines, only 60.4% and 54.3% received treatment within 12 months, respectively.

Introduction

Chronic hepatitis B (CHB) is a global public health problem affecting about 290 million people and is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). [1, 2] In the United States (US), recent estimates suggest that up to 1.59 million have CHB and the majority were foreign-born. [3, 4] While a cure is not yet available, well tolerated oral antiviral medications have been available since 1998 and have been shown to be highly effective in suppressing viral replication and preventing the progression of liver disease to cirrhosis, hepatic failure, and HCC. [5]

However, global estimates suggest that only about 10% of persons with CHB have been diagnosed, and only 5% of those who are eligible for treatment have received treatment. [1] In the US, population-based data found that only about 20% among a cohort of about 250 persons with CHB were aware of having a liver disease. [3] Claims data from about 138 million Americans with private insurance (which is generally considered to be a better insurance type than government-sponsored insurance) also estimated a CHB diagnosis rate of only about 20%.[6] Though large, this study was limited by the lack of laboratory data and clinical data to determine the quality of patient evaluation, the proportion of patients meeting guideline criteria for antiviral therapy, and the treatment rate among those who were treatment eligible. Nevertheless, this study of over 500,000 CHB patients found a treatment rate among patients with liver cirrhosis and HCC of only about 30% and 50%, respectively, suggesting significant under-treatment. [6]

In the past decade, there have also been studies conducted at either a single clinical center or a few clinical centers to answer these important questions regarding the linkage to care for CHB in the US, [7-9] but these studies were limited by either small sample sizes and/or selection bias of patients presenting at clinical centers well experienced with CHB care. This lack of data was recently further highlighted by a systematic review and meta-analysis conducted by investigators at the World Health Organization (WHO) who found very few studies reporting the proportion of treatment-eligible patients with CHB, with only two for the American Association for the Study of Liver Diseases (AASLD) guideline and insufficient data for analysis of the treatment rate among the treatment-eligible population. [10]

Therefore, our goal was to assess the current real-world situation of CHB care in the U.S. using a national database that includes laboratory data in addition to medical and pharmacy claims data. Specifically, we aimed to first estimate the proportion of chronic HBV infection patients who had an adequate laboratory evaluation for treatment eligibility; then among those with an adequate evaluation data, the proportion of chronic HBV infection patients meeting the 2018 AASLD criteria for antiviral therapy, [11] and lastly the proportion of treatment-eligible chronic HBV infection patients who received treatment.

Materials and Methods

Study design and study population

This is a retrospective study of a national sample of patients with chronic HBV infection without mentioning of hepatitis D infection who were assessed for relevant laboratory evaluation and treatment for chronic HBV infection. The data for this study were derived from Optum's Clinformatics® Data Mart (CDM) Database through the Population Health Science Center at Stanford University, Stanford, California, US. CDM is a de-identified administrative health claims database for beneficiaries of commercial and Medicare Advantage health plans. This claims database provides both medical and prescription drug coverage as well as laboratory test results from contracted national reference laboratory vendors of approximately 15-18 million patients. [12] The study was approved by the Institutional Review Board at Stanford University, Stanford, California, US.

For this study, we first searched the CDM from January 1, 2003 to June 30, 2019 for patients with chronic HBV infection using the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM or ICD-10-CM) codes of 070.22, 070.32, and B18.1. We then confirmed HBV infection with either a positive hepatitis B surface antigen (HBsAg), a positive hepatitis B envelope antigen (HBeAg), or a positive HBV DNA PCR test. Eligible patients were adult patients (aged ≥ 18 years) with confirmed HBV infection as above, with laboratory data for at least 6 months before and 6 months after the index chronic HBV infection diagnosis, and pharmacy claims data. We excluded patients who were organ transplant recipients or co-infected with hepatitis C or human immunodeficiency virus

(Fig.1). We followed the identified patients and the care received over the time of this study.

Study variables

Baseline demographics, clinical characteristics, and laboratory parameters were all obtained within six months of index chronic HBV infection diagnosis. Demographic factors included age, sex, race/ethnicity, and geographic region. Socioeconomic factors included educational level, occupation, and household income. Geographic location was categorized by US region as defined by the US Census Bureau in the 2010 Census Regions and Divisions of the United States. [13] Patients with visits to a specialist (either gastroenterologist/hepatologist [GI] or infectious disease [ID] specialist) were categorized in the group with GI/ID specialist visits and those without any GI/ID visits were categorized in the non-GI/ID group. Patients were also categorized into groups with and without advanced care provider visits such as nurse practitioners or physician assistants (NP/PA). Since NP/PA providers usually see patients with a supervisory physician, patients with NP/PA visits were further categorized whether they were seen by the NP/PA with a GI/ID specialist or without a GI/ID physician.

Clinical characteristics included presence of cirrhosis or HCC as identified by ICD9-CM or ICD-10 CM codes (571.2, 571.5, 571.6, K70.30, K74.0, K74.60, K74.69, K74.3, K74.4, K74.5, 572.3, 789.2, 456.1, 456.21, K76.6, R16.1, I85.00, I85.10, 155.0, C22.0, C22.2, C22.7, C22.8) at index chronic HBV infection diagnosis.

Laboratory parameters included in the study analysis were HBV DNA, HBeAg, HBsAg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, albumin (ALB), platelets (PLT), international normalized ratio (INR), hematocrit (HCT), and creatinine. Fibrosis-4 (FIB-4) index was also calculated to assess for fibrosis with advanced fibrosis defined with FIB-4 ≥ 3.25. [14]

Cascade of care

We assessed the cascade of care for chronic hepatitis B virus infected patients by calculating the proportion of chronic HBV infection patients who had adequate evaluation for treatment, the proportion of chronic HBV infection patients who were eligible for treatment, and of the treatment eligible chronic HBV infection patients the proportion who received treatment.

Since the 2018 AASLD treatment guidance as well as earlier versions (as well as EASL guidelines) were all largely based on HBeAg status, HBV DNA, and ALT levels, [11, 15-17] we considered patients to have had a "complete" evaluation if all three of these tests were completed within 12 months of each other at any time during the entire study period. However, many patients did not have HBeAg test. Therefore, as noted in guideline treatment criteria, if the HBV DNA threshold was > 20,000 IU/mL, patients met treatment eligibility regardless of the status of HBeAg. As such, we considered patients to have had a partial evaluation if they only had HBV DNA PCR and ALT tests within 12 months of each other at any time during the entire study

period. Finally, for the purpose of this study, we considered patients to have had an "adequate" evaluation if either a complete or partial evaluation (as defined above) was completed. We divided the number of patients with a complete or adequate laboratory evaluation by the total number of chronic hepatitis B virus infected patients in the study cohort to obtain the proportion of patients with complete or adequate treatment evaluation (**Fig.1**). In addition, to determine if the evaluation was timely or delayed, we calculated the proportions of patients having had an adequate evaluation within the first 12 months of index chronic HBV infection diagnosis or at any time within the study period.

Among the sub-cohort of patients with an adequate laboratory evaluation, we identified patients who were treatment eligible and divided the number of treatment eligible patients by the total number of patients with adequate laboratory evaluation to obtain the proportion of treatment eligible patients (**Fig.1**). Treatment eligibility was defined using the "standard" treatment indications by either AASLD or EASL guidelines corresponding to the appropriate year each guideline was updated.[11, 15-17] In patients without cirrhosis, treatment eligibility was defined by HBeAg status, ALT, and HBV DNA levels. According to AASLD, it was the presence of HBeAg, HBV DNA > 20,000 IU/mL and ALT > 2x the upper limit of normal (ULN), which was 40 U/L for both men and women for the 2001 guideline, 30 U/L for men and 19 U/L for women for the 2007, 2009, and 2015 guideline, and 35 U/L for men and 25 U/L for women in the 2018 guideline. Patients without cirrhosis and absent HBeAg were also considered treatment eligible with ALT > 2x ULN and HBV DNA > 20,000 IU/mL

until 2009 when the HBV DNA level was changed to > 2,000 IU/mL. Patients with cirrhosis were considered treatment eligible if accompanied with HBV DNA levels > 20,000 IU/mL in 2001; compensated cirrhosis with HBV DNA > 2,000 IU/mL or decompensated cirrhosis with detectable levels of HBV DNA in 2007, 2009, and 2015 guidelines; and either compensated or decompensated cirrhosis with detectable HBV DNA in 2018 guidelines.[16,17] The EASL treatment eligibility guidelines were similar, except the ALT ULN was 40 U/L for both men and women. Those without cirrhosis required HBV DNA > 20,000 IU/mL and either ALT >1xULN with present HBeAg or ALT >2xULN with absent HBeAg in 2002. Later on, patients without cirrhosis required either ALT > 1x ULN and HBV DNA > 2,000 IU/mL for HBeAg-negative or ALT >2x ULN and HBV DNA > 20,000 IU/mL for HBeAg-positive in the 2009, 2012, and 2017 guidelines. Patients with cirrhosis either required HBV DNA > 2,000 IU/mL in 2002 or any detectable HBV DNA in 2009, 2012, and 2017 guidelines. In patients missing HBeAg status, we used the higher HBV DNA threshold for HBeAg-positive as proxy for treatment eligibility.

Among the subcohort of treatment eligible patients, we identified treated patients using the National Drug Codes (NDC) for HBV medications (adefovir, entecavir, lamivudine, interferon alpha, pegylated interferon, telbivudine, tenofovir disoproxil, emtricitabine and tenofovir disoproxil fumarate, and tenofovir alafenamide). Patients were considered “treated” if they received at least one HBV medication prescription during the entire study period. We divided the number of treated patients by the total number of treatment eligible patients to obtain the proportion of treatment eligible

patients who received treatment (**Fig.1**). To determine the proportion of patients who received more timely treatment, we determined the proportion of treated patients who received treatment within 12 months of meeting treatment eligibility. We also calculated the proportion of those who initiated treatment and stayed on treatment for at least one year which was defined as filling 4 or more prescriptions within 12 months of treatment initiation date.

Statistical analysis

For the descriptive analysis, categorical variables were reported as counts and percentages while continuous variables were reported either as mean and standard deviation (SD) or median and interquartile range (IQR). Comparison between subgroups used the Pearson chi-squared test for categorical variables and the student t-test of variance or Wilcoxon rank-sum test for continuous variables.

To assess for possible changes in patient characteristics, treatment evaluation, and treatment rate of treatment eligible patients in the past decade (2010 and after) compared to earlier time, we also performed a sub-analysis by year of index of chronic HBV infection diagnosis, before versus 2010 and after.

To identify factors associated with adequate treatment evaluation for chronic HBV infection and treatment for treatment-eligible chronic HBV infection patients, we performed univariate and multivariate logistic regressions to estimate odds ratios (ORs) relating patient demographic, socioeconomic, and clinical factors to evaluation and treatment outcomes. Variables with potential association with outcomes by prior

knowledge or with univariate OR < 0.10 were included in the multivariate models. ORs were reported with 95% confidence intervals (95% CI).

As a sensitivity analysis, we evaluated the proportion of treatment eligible patients and treatment rate among treatment eligible patients for the subgroup of patients with complete laboratory evaluation (as defined by having all 3 tests: HBeAg, HBV DNA, and ALT).

All analysis was conducted using R statistical software (version 3.5.1), *and P*-values < 0.05 were considered significant.

Results

Study population

In total, we identified 19,132 patients with a chronic HBV infection diagnosis code and a positive HBsAg or HBeAg or HBV DNA test within 6 months from the index chronic HBV infection diagnosis date. After applying the exclusion criteria, 12,608 adult chronic HBV infection patients without viral coinfection or prior organ transplantation were included in this study **(Fig.1)**.

Overall, at the index chronic HBV infection diagnosis, the cohort mean age was 45.7 ± 14.6 years, 52.1% were males, 8.5% had cirrhosis, and 1.1% had HCC **(Table 1)**. Over half (54.6%) were Asian, 18.1% were Caucasian, 10.5% were African American, 5.7% were Hispanic, and 11.1% were of other unspecified race/ethnicities.

The majority of patients (58.2%) had at least one visit to a GI/ID specialist. One-fifth (20.1%) had at least one NP/PA visit, but only 4.0% were a NP/PA visit from GI/ID specialist practice. About half of the patients (46.5%) received care in the South, with 28.7% in the West and 18.5% in the Northeast. Almost all patients (99.0%) completed at least a high school education, about half (46.5%) had a bachelor's degree, and close to one-third (30.1%) had some level of graduate education, reflecting a fairly educated population. In addition, about one-third (29.3%) were business owners or had managerial or professional positions, while another one-third (35.1%) were white collar, health or civil or military workers. Annual household incomes were more than $100,000 for close of half of the cohort (42.5%), $60,000-100,000 for about one-quarter (26.7%), reflecting a population with household income well above the poverty line.

Compared to those with an index chronic HBV infection prior to 2010, those after 2010 were significantly older (42.1±11.8 vs. 50.5±15 years, $P<0.001$) though the median birth year for both groups was 1966, more likely to receive care in the West or Northeast, more likely to have cirrhosis or HCC, and less likely to receive care by GI/ID specialists (67.1% vs 55.2%, $P<0.001$). There were also significant differences among the different geographic regions (**Supplemental Table 1**).

Chronic HBV infection patients with adequate treatment evaluation

Of the total cohort of 12,608 chronic HBV infection patients who were observed for at least 6 months before and 6 months after the index chronic HBV infection

diagnosis date, 6,449 (51.2%) received adequate evaluation within 12 months of index chronic HBV infection diagnosis date (4,288 [66.5%] with complete evaluation, 2,161 [33.5%] with partial evaluation). **(Fig.1 and Fig.2A)**. Over the course of the study follow-up (mean/SD=3.0 ± 3.2 years), a slightly higher number and percentage of patients had an adequate evaluation (n=9,129 [72.4%]; 6,009 [65.8%] with complete evaluation and 3,120 [34.2%] with partial evaluation). Encouragingly, both the proportions of patients with an adequate evaluation within 12 months of index chronic HBV infection date as well as at any time during follow-up increased significantly after 2010 versus before 2010 (32.6% vs.58.8% and 65.6 vs. 75.2%, respectively, both $P<0.001$) **(Fig.2B)**.

Among the 9,129 (72.4%) patients with adequate laboratory evaluation at any time during the study follow-up, as noted in **Table 2,** the majority of patients had a HBV DNA < 2,000 IU/mL (84.0%) and an ALT < 2x ULN (86.9%) while 9.1% had a HBV DNA ≥ 2,000-20,000 IU/mL, 6.9% had a HBV DNA ≥ 20,000 IU/mL, and 13.1% had ALT > 2x ULN. The median level of albumin was 4.4 g/dL, total bilirubin was 0.5 mg/dL, complete platelet level was 223.1 x 10^3/μL, and creatinine level was 0.9 mg/dL. Data were available for FIB-4 calculation for only 564 patients. Of these, 78.5% had high likelihood of no or minimal fibrosis, while 4.8% had high likelihood of advanced fibrosis. Post-2010 patients and pre-2010 patients had fairly similar HBV DNA distribution, but post-2010 patients had lower median ALT (24 U/L vs. 29 U/L) and less likely to have ALT ≥ 2 x ULN (11.9% vs. 17.7%), both $P<0.001$.

On multivariate logistics regression adjusting for age, sex, race/ethnicity, GI/ID specialist care, NP/PA visit, education, income, and occupation **(Table 3)**, only race/ethnicity, care region, and GI/ID care were independently associated with adequate evaluation. African Americans, Caucasian, and Hispanic patients were all about 50-60% less likely to receive adequate evaluation than their Asian counterparts, with similar findings in patients from the Midwest, Northeast, and the South as compared to the West (all $P \leq 0.001$). In addition, having at least one GI or ID specialist encounter was independently associated with 46% higher likelihood of receiving adequate evaluation (P=0.02), but not NP/PA visit.

Treatment eligible patients and their treatment rates

Of the 9,129 chronic HBV infection patients with adequate evaluation at any time during study follow-up (**Fig.1**), 1,024 (11.2%) met AASLD treatment criteria and 1,275 (13.9%) met EASL treatment criteria. Data on characteristics of those not meeting treatment criteria were described in **Supplemental Tables 2 and 3**.

Of the 1,024 treatment-eligible patients who met the AASLD treatment criteria, 618 patients (60.4%) were treated within 12 months of becoming treatment-eligible and 50 (4.9%) were treated one year after becoming treatment-eligible **(Fig.3A)**. In total, 668 (65.2%) of treatment-eligible patients received treatment. The proportions of treatment eligible patients who received treatment within 12 months before 2010 and after 2010 were not significantly different (62.0 vs. 60.0 %, P=0.60) (**Fig.3B**).

Of the 1,275 treatment-eligible patients who met the EASL treatment criteria, 692 patients (54.3%) were treated within 12 months of becoming treatment-eligible and 67 (5.3%) were treated one year after becoming treatment-eligible **(Fig.3C)**. In total, 759 (59.5%) of treatment-eligible patients received treatment. The proportions of treatment eligible patients who received treatment within 12 months before 2010 and after 2010 were not significantly different (53.2 vs. 54.6 %, *P*=0.65) (**Fig.3D**).

The vast majority of treatment-eligible patients by either guideline who initiated therapy received either entecavir or tenofovir based therapies with only 3.4% received pegylated interferon (none received conventional interferon) or lamivudine or telbivudine. (**Supplemental Table 4**). Of the patients who were eligible for treatment according to AASLD and EASL guidelines, 518 (77.5%) and 583 (76.8%) stayed on treatment, respectively. In analysis of both guidelines, the treatment rates at any time during study period were similar among treatment-eligible patients with cirrhosis compared to treatment-eligible patients without cirrhosis (AASLD: 63.3% vs. 65.9%, *P*=0.44; EASL: 61.0% vs. 59.4%, *P*=0.75, respectively).

Tables 4A and 4B present logistic regression data for potential factors associated with treatment among treatment eligible patients. On univariate analysis, the only factor significantly associated with AASLD treatment was having at least one GI/ID specialist visit (OR=1.42, *P*=0.02), though this association was no longer statistically significant in multivariate analysis. None of the demographic and socioeconomic factors such age, sex, race/ethnicity, NP/PA visit, care region, educational level

household income, or occupation was associated with treatment in univariate or multivariate analysis.

Sensitivity analysis

We performed a sensitivity analysis for the subcohort of 6,009 patients with a complete evaluation (HBeAg, HBV DNA PCR, and ALT). We found a similar proportion of treatment-eligible patients (AASLD 798 [13.3%]; EASL 895 [14.9%]) as well as a similar total proportion of treatment eligible patients who received treatment (AASLD 526, [65.9%]; EASL 559, [62.5%]) as those with an adequate evaluation.

Discussion

In this nationwide US study of chronic HBV infection evaluation and treatment, we found severe gaps in the linkage to care for insured chronic HBV infection patients. Only half of the chronic HBV infection patients in our study received complete evaluation (defined by measurement of ALT, HBV DNA and HBeAg), and only three-quarters received an adequate evaluation (defined by measurement of only ALT and HBV DNA). Among patients with an adequate evaluation to determine treatment eligibility, we found 11.2% and. 13.9% to be treatment eligible according to the AASLD and the EASL guidelines, respectively. However, only 65.2% and 59.5% respectively of the treatment-eligible patients by AASLD and EASL guideline in our study received antiviral therapy. The treatment rates were notably not higher for

patients with cirrhosis. These data are particularly sobering when the study population are likely better insured, better educated, and with higher household income than the general US population and our definition of adequate evaluation and treatment were based liberally on having only basic laboratory tests and on having only one hepatitis B prescription for our analysis of adequate evaluation and treatment rate, respectively.

We also found that Caucasian, Hispanic, and African American chronic HBV infection patients were less than twice as likely to receive adequate evaluation for chronic HBV infection compared to Asians, after adjusting for a comprehensive range of demographic and socioeconomic factors. This finding may be related to heightened disease awareness among the Asian communities as a result of public health campaigns and education efforts targeting both Asian patients and care providers to increase their knowledge about their high risk for chronic HBV infection. [18] The same reason may also explain the independent association between care region and adequate evaluation since both the Western region of the US which includes California and the Pacific Northwest states are well known to house a large immigrant population from the Western Pacific region. [19, 20]

These findings are highly significant for two reasons. First, they highlight a racial/ethnic disparity that should be addressed and corrected. Second, they suggest that public campaign and education efforts are beneficial. As such, additional public health campaigns including community outreach programs and provider education efforts should be developed and implemented among other areas in which chronic

HBV infection is known to be prevalent while also maintain the current community interventions within the Asian communities.

Another important independent factor associated with better treatment evaluation was a care encounter with GI/ID specialists. In fact, having at least one encounter with a GI/ID specialist was associated with 46% higher chance of receiving an adequate evaluation. This can be due to GI/ID specialists being more familiar with guideline recommendations for chronic HBV infection care as well as having more time to focus on chronic HBV infection during the patient visit compared to general practice providers who need to provide more comprehensive care. On the other hand, it may also be due to patient selection, as patients seen by specialists may either be more likely to have advanced disease and/or higher motivation to seek additional care.

In fact, among patients with adequate evaluation meeting treatment eligibility criteria, having a GI/ID visit was the only significant factor associated with a higher chance of receiving treatment for treatment eligible patients in univariate analysis, though it was no longer significant in multivariate analysis. The reason for this as well as lack of association between other factors and treatment can be due to a smaller sample size in this group as well as a possible selection bias; as by default, patients who received adequate evaluation were more likely “similar” and the cohort of treatment eligible patients were more likely “homogeneous”, making it difficult to discern the different associations without a large patient sample size.

Nevertheless, while specialist care can add more direct cost which could be the reason for the observed lower proportion of patients with GI/ID visit in the latter time period with the general increasing trend of more restricted managed care by insurance payors and the higher indirect cost because patients may need to take additional time off work for healthcare visits, we advocate for chronic HBV infection patients to have at least one consultative visit with care providers specialized in and/or familiar with chronic HBV infection care. As evidenced by the presence of multiple chronic HBV infection treatment guidelines and revisions in the US and overseas, [11, 15-17, 21-27] chronic HBV infection management is complex and may be difficult for many general practitioners, especially those not having many chronic HBV infection patients in their practice, to keep up to date with recent advances and guideline recommendations for chronic HBV infection patients; and physician lack of knowledge has been reported as a barrier to optimal chronic HBV infection care. [28, 29]

Another important point to note is the lack of association between NP/PA care with more optimal care. This was a surprising finding as prior reports have shown better adherence to practice guidelines in other liver diseases when care has been delivered by advanced practice providers such as NP/PA, particularly when working with GI/hepatologists, as well as improved quality of care, 30-day readmission, and mortality rates of patients with cirrhosis. [30] However, the lack of similar benefits with NP/PA care in our study may be due to a combination of the small proportion of patients with a NP/PA visit (only one in five) with the vast majority of patients receiving their care in a non-GI/ID specialist practice. Therefore, further investigation

is needed to evaluate whether advanced care provider engagement can help improve the quality of care of chronic HBV infection patients as already seen in examples of other liver disease.

The severe care gaps seen in our study population, all of whom had private health insurance with the majority having at least a college degree education and/or a household income of $60,000 or higher, strongly suggest that the barriers of chronic HBV infection cascade of care involve more than just general patient literacy, lack of financial resource or access to care. Indeed, prior studies have reported a variety of patient factors as barriers to chronic HBV infection care to include chronic HBV infection-associated stigma, chronic HBV infection-specific health literacy, and patients' diverse cultural belief systems. [31-34] These prior findings should be incorporated and specifically addressed when developing community outreach programs for the diverse communities affected by chronic HBV infection. It is also important to note, that when compared to HCV treatment rates, as reported in the literature, HBV treatment rates appear to be better with HCV treatment rate of only 18.7% in the interferon era. However, while HBV treatment update did not change significantly over time as shown in the current study, the advent of well tolerated and highly efficacious direct acting antiviral therapy has revolutionized HCV management. A most recent study found that approximately 50-60% of patients with HCV in the United States are aware of their infection with a median of 74% attending a follow-up clinic and of those a median of 39% received treatment (21.5%-76.1%).[35,36] Therefore, continued effort to develop well tolerated and effective HBV

cure with finite treatment duration can improve HBV treatment and is urgently needed.

The strength of our study is the larger sample size, the diverse racial/ethnic composition of the cohort, the representation of patients from different regions of the US as opposed to studies based on data from local institutional cohorts and the availability of several important socioeconomic factors that were missing in prior studies, which together make our findings more generalizable. Indeed, the treatment eligibility rates in our study (11.2% for AASLD and 13.9% for EASL) are more in line with the pooled rate for prior community based studies rather than the rate for those from clinic settings (12% vs. 25% respectively) as reported by a recent meta-analysis.[10] In addition, as treatment eligibility data from this recent meta-analysis were derived from original studies that used different treatment guidelines with few on updated AASLD or EASL guidelines (4 AASLD all before AASLD 2018 guideline, 8 EASL 2012, 2 EASL 2017, 2 WHO, and 16 other), our current study fills in this knowledge gap with a large nationwide data set using guidelines contemporary to the date of patient evaluation including the updated AASLD 2018 and EASL 2017 guidelines. The current study also evaluates the chronic HBV infection care cascade in a comprehensive manner, starting with the proportion of patients receiving adequate evaluation (within 12 months or delayed), the proportion of patients meeting treatment criteria, and the proportion of treatment eligible patients who received treatment (within 12 months or delayed). We also identified factors associated with adequate evaluation and treatment that may be modifiable such as GI/ID care and the

racial/ethnic disparity for further public health intervention. Our study filled in several important knowledge gaps that were identified by a recent systematic review and meta-analysis by the WHO investigators on chronic HBV infection treatment eligibility and treatment of this population. [10]

Therefore, we advocate for a simplified test set (ALT, HBeAg and HBV DNA) such as those used in this study or similar should be incorporated in diverse community practices for races/ethnicities. We also strongly suggest that at least a one-time referral to a GI/ID specialist or other providers familiar with chronic HBV infection care should be considered for all chronic HBV infection patients. Finally, it is important that additional patient engagement/perspectives should be sought out, investigated, and incorporated into the chronic HBV infection management paradigm.

We acknowledge the following limitations. Our study cohort was derived from a database of commercially insured persons, leading to a possible selection bias for patients with better access to care and more educated patients, but this would only bias our results towards higher proportions of patients with adequate evaluation and treatment. Therefore, the care gaps seen in the general chronic HBV infection population, many of whom have less or no health insurance coverage, are likely even worse, further highlighting the importance of the current study message. Our definition of “adequate” or “complete” evaluation is also fairly liberal because there are several other recommended evaluations such as liver ultrasound, assessment for liver fibrosis, etc. [11] However, as shown by the small number of patients with adequate labs to calculate Fib-4 (564 out of the total cohort of 9,129 patients, 6.2%),

the proportion of patients having any additional tests would be very small. Consequently, results based on this simplified approach are underestimates of the current care gaps and further highlight the magnitude of the problem. Similarly, our requirement of having only one prescription of chronic HBV infection medication to be considered "treated" likely overestimates the true treatment rate, because receipt of a prescription does not mean the patient actually took the medication and using one prescription does not mean the patient would stay on the medication long-term, which would be required for the vast majority of chronic HBV infection patients. Due to inadequate evaluation, HBeAg status was not available for many patients, and hence treatment eligibility in non-cirrhotic patients was determined based on a more stringent threshold of HBV DNA >20,000 IU/mL for those with missing HBeAg who may have been HBeAg negative. Therefore, our estimate for the proportion of treatment-eligible patients may be an underestimate. However, this strengthens our argument for urgent measures to improve treatment evaluation and treatment of treatment eligible patients. In addition, large databases such as the one used in this study can be subjected to miscoding, so we have attempted to confirm the chronic HBV infection diagnosis by adding the requirement of having at least one positive HBsAg, HBeAg or HBV DNA PCR test. The database also lacks certain laboratory data such as quantitative HBsAg level though this is currently not currently used as a criterion for treatment initiation. Finally, while our data are likely to be representative of patients with chronic HBV infection with private insurance seen in routine practice in the U.S., our data may not be generalizable to other countries.

Conclusions

In summary, though slightly improved after 2010, the care cascade of chronic HBV infection care in the US remains poor. Even among a cohort of well insured, educated and well-to-do patients, one in three patients with chronic hepatitis B infection did not have the minimum evaluation needed to determine treatment eligibility and only one in three treatment eligible patients received antiviral treatment within 12 months from meeting treatment criteria. Efforts must continue to address the multilayered (patients, care givers, communities and society) barriers to care. More simplified and more "user-friendly" guidelines may also help improve adherence and the overall care of patients with chronic HBV infection. Further studies are also needed to assess adherence to long-term monitoring and the evolution of chronic HBV disease activity over time.

Abbreviations

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; WHO, World Health Organization; AASLD, American Association for the Study of Liver Diseases; CDM, Clinformatics® Data Mart; ICD, International Classification of Diseases; GI, Gastroenterologist; ID, Infectious Disease; PA, Physician's Assistant; NP, Nurse Practitioner; ALT, alanine transaminase; AST, Aspartate aminotransferase; INR, international normalized ratio; FIB-4, fibrosis 4 score

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Substantial gaps in evaluation and treatment of patients with hepatitis B in the US

Main Tables

Table 1. Characteristics of patients with chronic HBV infection

Characteristics	Overall n=12,608	Before 2010 n=3,667	2010 and after n=8,941	*P-value*
Age	45.7 ± 14.6	42.1 ± 11.8	50.5 ± 15	< 0.001
Male	6,569 (52.1)	1,956 (53.3)	4,613 (51.6)	0.07
Race/Ethnicity				
Asian	6,887 (54.6)	2,006 (54.7)	4,881 (54.6)	<0.001
African American	1,321 (10.5)	342 (9.3)	979 (10.9)	
Caucasian	2,284 (18.1)	721 (19.7)	1,563 (17.5)	
Hispanic	720 (5.7)	175 (4.8)	545 (6.1)	
Other	1,396 (11.1)	423 (11.5)	973 (10.9)	
Care Region (n=12,541; 3,644; 8,897)				
West	3,603 (28.7)	785 (21.5)	2,818 (31.7)	<0.001
Midwest	784 (6.3)	288 (7.9)	496 (5.6)	
Northeast	2,324 (18.5)	589 (16.2)	1,735 (19.5)	
South	5,830 (46.5)	1,982 (54.4)	3,848 (43.3)	
Care provider				
GI/ID providers*	7,400 (58.2)	2,461 (67.1)	4,939 (55.2)	<0.001
Without GI/ID providers	5,308 (41.8)	1,206 (32.9)	4,002 (44.8)	
NP/PA Visit* (n=2,528; 550; 1,978)				
With GI/ID providers	102 (4.0)	23 (4.2)	79 (4.0)	0.84
Without GI/ID providers	2,426 (96)	527 (95.8)	1,899 (96)	
Education Level (n=11,486; 3,667; 8,166)				
< 12th grade	113 (1.0)	37 (1.0)	76 (0.9)	<0.001
High school	2,577 (22.4)	688 (18.8)	1,889 (23.1)	
Bachelor degree	5,342 (46.5)	1511 (41.2)	3,831 (46.9)	
> Bachelor degree	3,454 (30.1)	1,084 (29.6)	2,370 (29)	
Annual Household Income (n=8,984; 2,344; 6,640)				
< $40,000	1,523 (17.0)	276 (11.8)	1,247 (18.8)	<0.001
$40,000- <60,000	1,252 (13.9)	312 (13.3)	940 (14.2)	
$60,000-100,000	2,395 (26.7)	598 (25.5)	1,797 (27.1)	
>$100,000	3,814 (42.5)	1158 (49.4)	2,656 (40.0)	

Occupation (n=1,160; 368; 792)				
Manager/Owner/Professional	340 (29.3)	111 (30.2)	229 (28.9)	0.07
White collar/Health/ Civil Service/ Military	407 (35.1)	134 (36.4)	273 (34.5)	
Blue Collar	265 (22.8)	90 (24.5)	175 (22.1)	
Homemaker/ Retired	148 (12.8)	33 (9)	115 (14.5)	
Cirrhosis**	1,071 (8.5)	270 (7.4)	801 (9)	0.004
Hepatocellular carcinoma**	136 (1.1)	28 (0.8)	108 (1.2)	0.03
Alcoholism	290 (2.3)	32 (0.9)	258 (2.9)	<0.001
Hypertension	4010 (31.8)	772 (21.1)	3238 (36.2)	<0.001
Diabetes mellitus	2133 (16.9)	356 (9.7)	1777 (19.9)	<0.001
Dyslipidemia	4501 (35.7)	957 (26.1)	3544 (39.6)	<0.001
Chronic kidney disease	661 (5.2)	41 (1.1)	620 (6.9)	<0.001
Osteoporosis	825 (6.5)	110 (3)	715 (8)	<0.001
Osteoarthritis	1718 (13.6)	266 (7.3)	1452 (16.2)	<0.001

*At least one visit with GI/ID specialist or with NP/PA, respectively.
**Cirrhosis and HCC, from any time before CHB diagnosis to 6 months after index CHB diagnosis.
GI, Gastroenterologist; ID, Infectious Disease; PA, Physician's Assistant; NP, Nurse Practitioner.
Values as mean (standard deviation) or (%).
P-values derived from chi-square test, t-test, or Wilcoxon rank sum test as applicable and compare before 2010 vs. 2010 and after.
2010 income in US dollars per U.S. Census Bureau (https://data.census.gov/cedsci/table?q=United%20States&t=Income%20and%20Poverty&y=2010&tid=ACSST1Y2010.S1901, accessed 5/30/21): <50,000, 49.9%; 50,000-74,999, 18.3%; 75,000-99,999, 11.8%; ≥100,000, 19.9%.

Table 2. Characteristics of patients with adequate* laboratory evaluation for patients with chronic hepatitis B

	Overall n=9,129	**Before 2010** n=2,405	**2010 and after** n=6,724	***P-value***
HBV DNA (n=6,285; 1,157; 5,128)	1.0 (0-456)	0.4 (0-248.2)	2.0 (0-499)	<0.001
<2,000 IU/mL	5,282 (84)	976 (84.4)	4,306 (84)	0.01
2,000-20,000 IU/mL	569 (9.1)	116 (10)	453 (8.8)	
20,000-200,000 IU/mL	238 (3.8)	46 (4)	192 (3.7)	
≥200,000 IU/mL	196 (3.1)	19 (1.6)	177 (3.5)	
Positive HBeAg (n=4,023; 915; 3,108)	753 (18.7)	256 (28)	497 (16)	<0.001
ALT (U/L) (n= 6,991; 1,469; 5,522)	25 (18-40)	29 (20-51)	24 (17-38)	0.01
<1x ULN	4,284 (61.3)	750 (51.1)	3,534 (64)	<0.001
1-2x ULN	1,790 (25.6)	459 (31.2)	1,331 (24.1)	
>2x ULN	917 (13.1)	260 (17.7)	657 (11.9)	
AST (U/L) (n=6,971; 1,469; 5,522)	24 (19-32)	26 (20-38)	23 (19-31)	<0.001
Alkaline phosphatase (U/L) (n=6,896; 1,412; 5,484)	66 (54-81)	67 (54-82.3)	65 (54-80)	<0.001
Total bilirubin (mg/dL) (n=6,855; 1,397; 5,614)	0.5 (0.4-0.7)	0.6 (0.4-0.8)	0.5 (0.4-0.7)	0.01
Albumin (g/dL) (n=7,041; 1,427; 6,257)	4.4 (4.2-4.6)	4.4 (4.1-4.6)	4.4 (4.2-4.6)	<0.001
Platelet (10^3/uL) (n=572; 544; 28)	223 (185-263.5)	223 (184.3-261.8)	241 (196-270)	0.21
INR (n=1,549; 364; 1,185)	1 (1-1.1)	1 (1-1.1)	1 (1-1.1)	0.78
Hematocrit (%) (n=6,004; 1,195; 4,809)	42.1 (39.1-45)	42.1 (39-45)	42.1 (39.1-44.9)	0.83
Creatinine (mg/dL) (n=6,351; 1,156; 5,195)	0.9 (0.7-1)	0.9 (0.8-1)	0.8 (0.7-1)	<0.001
FIB-4 (n=564; 536; 28)				
<1.25	443 (78.5)	417 (77.8)	-	0.15
1.25 – 3.25	94 (16.7)	92 (17.2)	-	
≥3.25	27 (4.8)	27 (5)	-	
Phases of the natural history of HBV (AASLD)** (n= 4,648; 905; 3,743)				
Indeterminate	2,729 (58.7)	601 (66.4)	2,128 (56.9)	<0.001
Inactive	1,709 (36.8)	276 (30.5)	1,433 (38.3)	
Immune Tolerant	17 (0.4)	-	16 (0.4)	
Immune Active	193 (4.2)	-	166 (4.4)	
Phases of the natural history of HBV (EASL) ** (n= 4,379; 864; 3,515)				
Indeterminate	2,016 (46)	454 (52.5)	1,562 (44.4)	0.001
HBeAg(+) Chronic Infection	11 (0.3)	0 (0)	11 (0.3)	
HBeAg(+) Chronic Hepatitis	135 (3.1)	30 (3.5)	105 (3)	
HBeAg(-) Chronic Infection	2,056 (47)	355 (41.1)	1,701 (48.4)	
HBeAg(-) Chronic Hepatitis	161 (3.7)	25 (2.9)	136 (3.9)	

* Adequate evaluation refers to HBV DNA + ALT ± HBeAg tests within one year of each other.
ALT, alanine transaminase; AST, Aspartate aminotransferase; INR, international normalized ratio; FIB-4, fibrosis 4 score.
**Patients with missing HBeAg data were classified as indeterminate phase of the natural history of HBV.

-Data for individual rows not shown as per Stanford Center for Population Health Sciences requirement for data cells with < 11 patients.
Values as mean ± SD or median (IQR) or (%). *P*-values derived from chi-square test, t-test, or Wilcoxon rank sum test as applicable and compare before 2010 vs. 2010 and after.

Table 3. Factors associated with adequate evaluation* of chronic hepatitis B infection

Characteristics	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age	1.01 (1.01 - 1.01)	<0.001	1.01 (1.00 - 1.02)	0.20
Sex				
Male	Referent	-	Referent	-
Female	0.88 (0.81 - 0.95)	0.001	1.05 (0.78 - 1.4)	0.74
Race/Ethnicity				
Asian	Referent	-	Referent	-
African American	0.48 (0.42 - 0.54)	<0.001	0.40 (0.25 - 0.64)	<0.001
Caucasian	0.48 (0.44 - 0.53)	<0.001	0.49 (0.34 - 0.7)	<0.001
Hispanic	0.48 (0.41 - 0.57)	<0.001	0.38 (0.22 - 0.64)	<0.001
Other	0.59 (0.52 - 0.67)	<0.001	0.85 (0.32 - 2.72)	0.77
Care Provider				
Without GI/ID providers	Referent	-	Referent	-
GI/ID providers**	1.29 (1.19 - 1.4)	<0.001	1.46 (1.07 - 1.98)	0.02
NP/PA Visit**				
No NP/PA visit	Referent	-	Referent	-
NP/PA visit with GI/ID providers	1.02 (0.67 - 1.62)	0.92	0.84 (0.25 - 3.09)	0.78
NP/PA visit without GI/ID providers	0.84 (0.76 - 0.93)	< 0.001	1.12 (0.79 - 1.59)	0.54
Care Region				
West	Referent	-	Referent	-
Midwest	0.28 (0.24 - 0.32)	<0.001	0.22 (0.12 - 0.4)	<0.001
Northeast	0.84 (0.74 - 0.95)	0.005	0.44 (0.27 - 0.72)	0.001
South	0.65 (0.59 - 0.72)	<0.001	0.57 (0.39 - 0.82)	0.003
Education Level				
Less than 12th grade	Referent	-	Referent	-
High school	0.89 (0.58 - 1.35)	0.60	1.61 (0.06 - 41.94)	0.74
Bachelor degree	1.04 (0.68 - 1.56)	0.85	1.52 (0.06 - 39.57)	0.77
Bachelor degree and higher	1.05 (0.68 - 1.58)	0.82	1.46 (0.06 - 38.51)	0.79
Annual Household Income				
< $40,000	Referent	-	Referent	-
$40,000-60,000	1.43 (1.21 - 1.7)	<0.001	1.24 (0.72 - 2.15)	0.44
$60,000-100,000	1.42 (1.23 - 1.64)	< 0.001	1.00 (0.63 - 1.57)	0.99
>$100,000	1.46 (1.28 - 1.66)	<0.001	1.23 (0.76 - 1.99)	0.39
Occupation				
Manager/Owner/Professional	Referent	-	Referent	-
White collar/Health/Civil Service/Military	1.32 (0.96 - 1.82)	0.09	1.34 (0.93 - 1.94)	0.11
Blue Collar	1.21 (0.85 - 1.72)	0.30	1.09 (0.72 - 1.66)	0.69
Homemaker/ Retired	0.99 (0.65 - 1.5)	0.95	1.19 (0.73 - 1.95)	0.49
Cirrhosis	0.94 (0.82 - 1.08)	0.37	1.91 (1.14 - 3.3)	0.02

* Adequate evaluation refers to HBV DNA + ALT ± HBeAg tests within one year of each other.

**At least one visit with GI/ID providers or NP/PA. GI, Gastroenterologist; ID, Infectious Disease; PA, Physician's Assistant; NP, Nurse Practitioner.

Values as mean (standard deviation) or (%). *P*-values derived from Cox regression.
2010 income in US dollars per U.S. Census Bureau (https://data.census.gov/cedsci/table?q=United%20States&t=Income%20and%20Poverty&y=2010&tid=ACSST1Y2010.S1901, accessed 5/30/21): <50,000, 49.9%; 50,000-74,999, 18.3%; 75,000-99,999, 11.8%; ≥100,000, 19.9.

Table 4. Factors associated with treatment in treatment-eligible chronic hepatitis B patients

A. By AASLD guideline

Characteristics	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age	1.00 (0.99 - 1.01)	0.58	0.99 (0.95 - 1.03)	0.60
Sex				
Male	Referent	-	Referent	-
Female	0.85 (0.65 - 1.11)	0.22	0.82 (0.27 - 2.48)	0.73
Race/Ethnicity				
Asian	Referent	-	Referent	-
African American	0.76 (0.49 - 1.19)	0.23	1.47 (0.22 - 11.3)	0.70
Caucasian	0.80 (0.58 - 1.11)	0.18	0.42 (0.08 - 1.91)	0.27
Hispanic	0.74 (0.40 - 1.38)	0.32	0.09 (0.001 - 2.62)	0.17
Other	0.60 (0.37 - 0.97)	0.04	-	-
Care Provider				
Without GI/ID providers	Referent	-	Referent	-
GI/ID providers*	1.42 (1.06 - 1.91)	0.02	1.71 (0.46 - 6.45)	0.42
NP/PA Visit*				
No NP/PA visit	Referent	-	Referent	-
NP/PA visit with GI/ID providers	0.75 (0.31 - 1.94)	0.54	15.12 (0.17 - 1954.91)	0.23
NP/PA visit without GI/ID providers	1.13 (0.83 - 1.55)	0.45	0.61 (0.16 - 2.30)	0.46
Care Region				
West	Referent	-	Referent	-
Midwest	1.40 (0.72 - 2.88)	0.33	1.4 (0.09 - 29.08)	0.81
Northeast	0.99 (0.66 - 1.47)	0.95	0.22 (0.03 - 1.19)	0.09
South	1.17 (0.85 - 1.59)	0.54	0.90 (0.18 - 4.46)	0.90
Education Level				
Less than 12th grade	Referent	-	Referent	-
High school	0.78 (0.11 - 3.49)	0.77	-	-
Bachelor degree	0.65 (0.09 - 2.85)	0.60	0.76 (0.15 - 3.49)	0.72
Bachelor degree and higher	0.71 (0.10 - 3.14)	0.67	0.17 (0.02 - 1.05)	0.06
Annual Household Income				
< $40,000	Referent	-	Referent	-
$40,000-60,000	1.53 (0.90 - 2.62)	0.12	0.18 (0.02 - 1.31)	0.10
$60,000-100,000	1.41 (0.89 - 2.24)	0.14	0.94 (0.13 - 6.62)	0.95
>$100,000	1.36 (0.89 - 2.08)	0.15	1.21 (0.17 - 8.20)	0.84
Occupation				
Manager/Owner/Professional	Referent	-	Referent	-
White collar/Health/Civil Service/Military	1.56 (0.59 - 4.15)	0.37	3.06 (0.77 - 13.37)	0.12
Blue Collar	3.03 (0.84 - 12.83)	0.10	4.12 (0.73 - 28.65)	0.12
Homemaker/ Retired	3.11 (0.77 - 16.07)	0.13	5.77 (0.84 - 54.42)	0.09
Cirrhosis	0.81 (0.60 - 1.08)	0.15	0.69 (0.17 - 2.73)	0.59

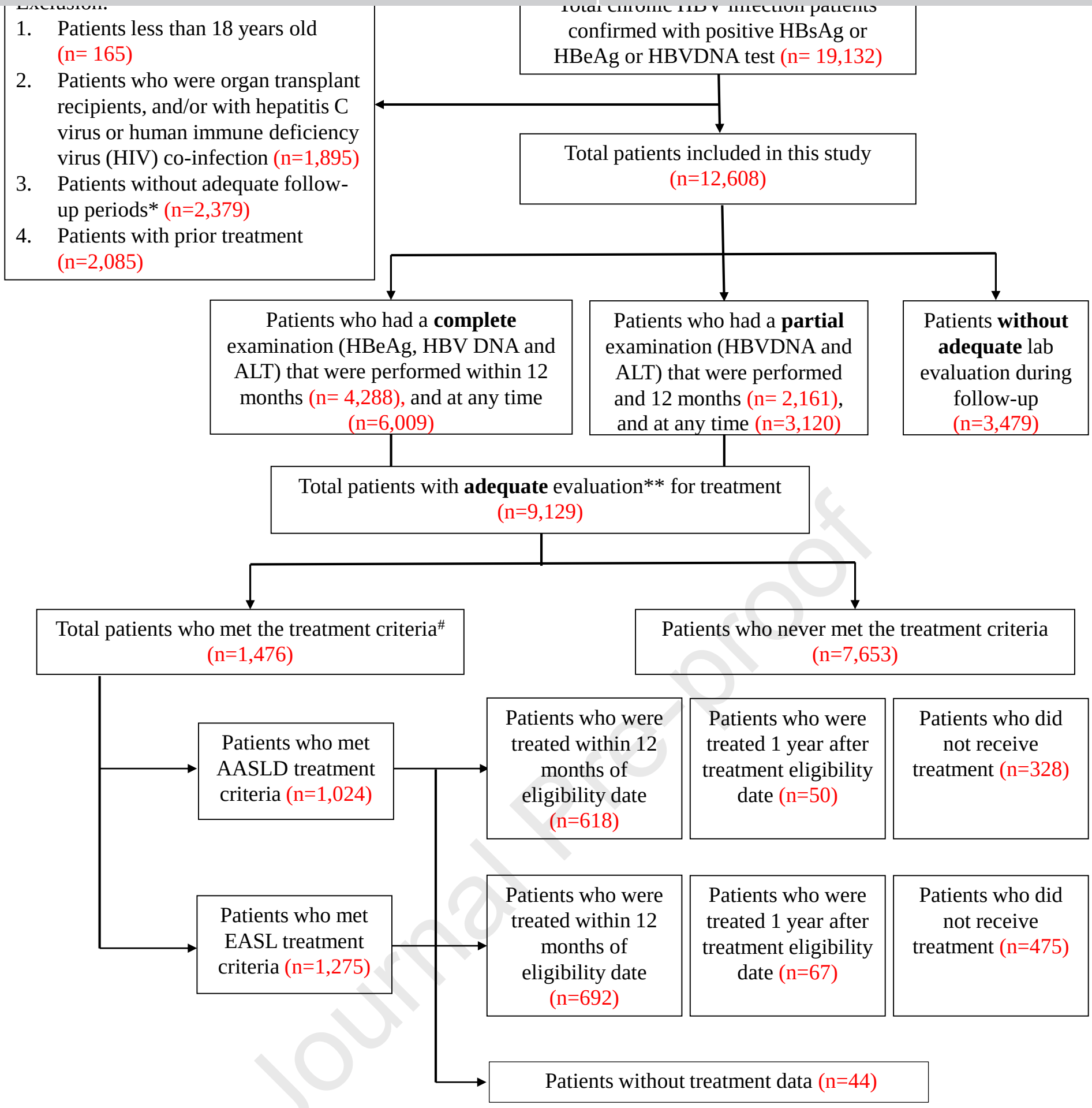
**At least one visit with GI/ID or NP/PA. GI, Gastroenterologist; ID, Infectious Disease; PA, Physician's Assistant; NP, Nurse Practitioner.Values as mean (standard deviation) or (%). *P*-values derived from Cox regression.
2010 income in US dollars per U.S. Census Bureau (https://data.census.gov/cedsci/table?q=United%20States&t=Income%20and%20Poverty&y=2010&tid=ACSST1Y2010.S1901, accessed 5/30/21): <50,000, 49.9%; 50,000-74,999, 18.3%; 75,000-99,999, 11.8%; ≥100,000, 19.9%

B. By EASL guideline

Characteristics	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age	0.99 (0.99 – 1.00)	0.14	0.98 (0.94 - 1.02)	0.27
Sex				
Male	Referent	-	Referent	-
Female	1.13 (0.89 - 1.44)	0.31	0.86 (0.32 - 2.31)	0.77
Race/Ethnicity				
Asian	Referent	-	Referent	-
African American	1.30 (0.85 - 2.01)	0.23	0.81 (0.13 - 5.18)	0.82
Caucasian	0.89 (0.66 - 1.21)	0.47	0.95 (0.28 - 3.2)	0.20
Hispanic	0.71 (0.43 - 1.2)	0.19	0.47 (0.03 - 13.96)	0.60
Other	0.60 (0.40 - 0.91)	0.02	-	-
Care Provider				
Without GI/ID providers	Referent	-	Referent	-
GI/ID providers*	1.65 (1.29 - 2.11)	<0.001	1.16 (0.42 - 3.28)	0.77
NP/PA Visit*				
No NP/PA visit	Referent	-	Referent	-
NP/PA visit with GI/ID providers	0.33 (0.07 - 1.24)	0.11	-	-
NP/PA visit without GI/ID providers	1.33 (0.98 - 1.82)	0.07	0.98 (0.30 - 3.22)	0.97
Care Region				
West	Referent	-	Referent	-
Midwest	1.51 (0.84 - 2.82)	0.18	2.22 (0.12 - 80.85)	0.61
Northeast	1.05 (0.75 - 1.47)	0.78	0.23 (0.05 - 0.95)	0.05
South	1.43 (1.10 - 1.87)	0.01	0.83 (0.22 - 3.09)	0.78
Education Level				
Less than 12th grade	Referent	-	Referent	-
High school	1.45 (0.41 - 4.94)	0.54	-	-
Bachelor degree	1.39 (0.40 - 4.66)	0.59	2.14 (0.58 - 8.28)	0.26
Bachelor degree and higher	1.31 (0.37 - 4.44)	0.66	0.51 (0.09 - 2.58)	0.42
Annual Household Income				
< $40,000	Referent	-	Referent	-
$40,000-60,000	1.51 (0.93 - 2.46)	0.10	0.51 (0.09 - 2.86)	0.45
$60,000-100,000	1.41 (0.92 - 2.14)	0.11	1.20 (0.23 - 5.89)	0.83
>$100,000	1.16 (0.79 - 1.70)	0.45	0.90 (0.16 - 4.92)	0.91
Occupation				
Manager/Owner/Professional	Referent	-	Referent	-
White collar/Health/Civil Service/Military	1.24 (0.49 - 3.11)	0.65	1.47 (0.44 - 5.03)	0.53
Blue Collar	1.97 (0.65 - 6.36)	0.24	3.05 (0.52 - 21.56)	0.23
Homemaker/ Retired	1.06 (0.32 - 3.50)	0.92	1.85 (0.39 - 9.48)	0.44
Cirrhosis	0.98 (0.65 - 1.50)	0.91	0.61 (0.10 - 3.31)	0.57

**At least one visit with GI/ID providers or NP/PA, respectively.

GI, Gastroenterologist; ID, Infectious Disease; PA, Physician's Assistant; NP, Nurse Practitioner.
Values as mean (standard deviation) or (%). *P*-values derived from Cox regression.
2010 income in US dollars per U.S. Census Bureau (https://data.census.gov/cedsci/table?q=United%20States&t=Income%20and%20Poverty&y=2010&tid=ACSST1Y2010.S1901, accessed 5/30/21): <50,000, 49.9%; 50,000-74,999, 18.3%; 75,000-99,999, 11.8%; ⩾100,000, 19.9%.



*Adequate follow-up periods = at least 6 months after index date
**Adequate evaluation refers to having HBV DNA + ALT ± HBeAg tests within one year of each other
Patients with missing HBeAg data but HBV DNA≥20,000IU/mL were considered treatment eligible

Fig.1. Flow chart of study patient selection, Optum™ 2003-2019 database

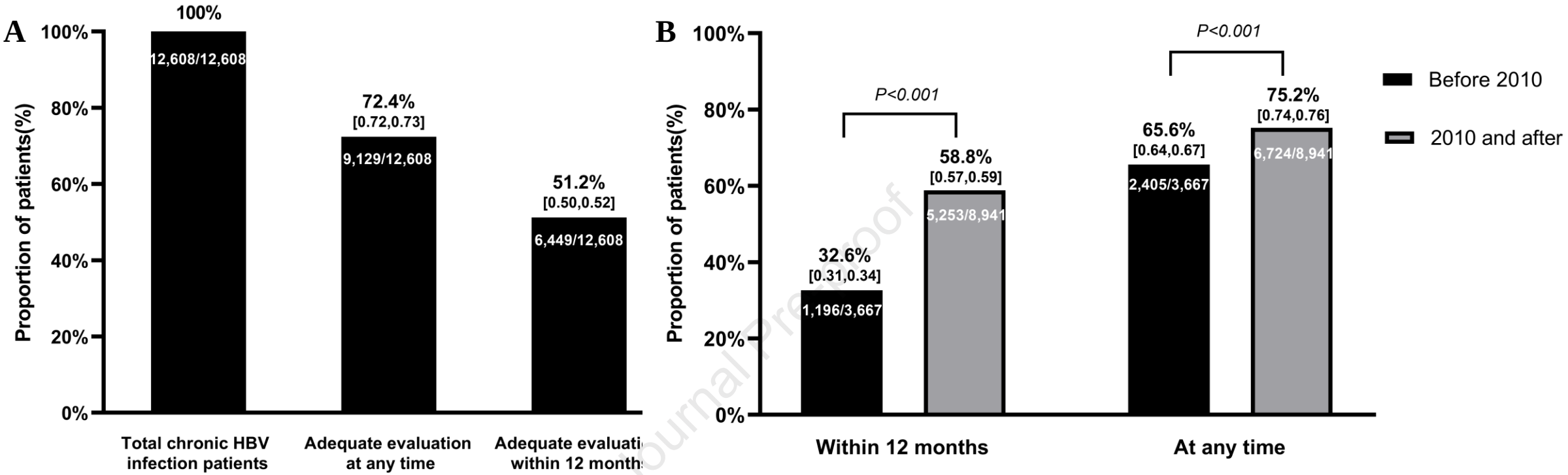


Fig.2. Proportion of chronic HBV infected patients who received adequate evaluation

(A) by timing of evaluation and (B) by year of index chronic hepatitis B diagnosis, before 2010 vs. 2010 and after

(* Adequate evaluation refers to HBV DNA + ALT ± HBeAg tests within one year of each other)

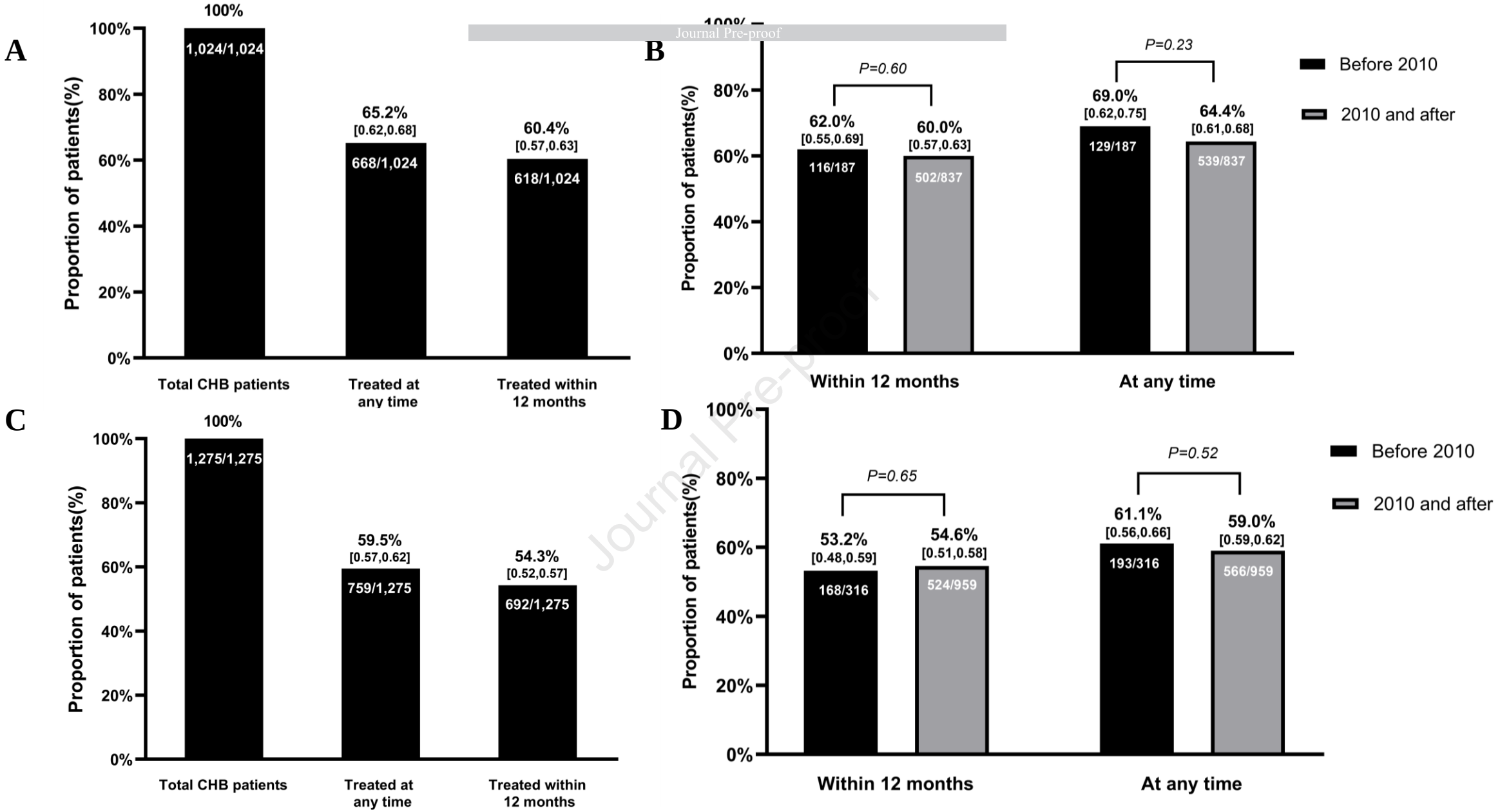


Fig.3. Proportion of treatment eligible CHB patients who received treatment (A) according to AASLD guideline by timing of evaluation and (B) according to AASLD guideline by year of index chronic hepatitis B diagnosis, before 2010 vs. 2010 and after (C) according to EASL guideline by timing of evaluation and (D) according to EASL guideline by year of index chronic hepatitis B diagnosis, before 2010 vs. 2010 and after

Highlights

- We assessed the proportion of patients who had complete (ALT, HBV DNA, and HBeAg tests) adequate laboratory evaluation (ALT, HBV DNA with or without HBeAg tests) for treatment eligibility, and of those the proportion of patients meeting treatment criteria, and lastly among treatment-eligible patients the proportion of patients who received treatment.

- Among the 12,608 patients with chronic HBV infection included in our study, 52.3% never had a complete laboratory and only 73% had adequate evaluation.

- In the 9,129 patients who had an "adequate" evaluation, 11.2% and 13.9% of included patients were treatment-eligible by the AASLD or EASL criteria, respectively.

- Among those who were treatment eligible by AASLD or EASL guidelines, only 60.4% and 54.3% received treatment within 12 months, respectively.