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Hepatocellular Carcinoma Surveillance Rates in Commercially Insured Patients with Non-Cirrhotic Chronic Hepatitis B

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Abstract

AASLD and EASL guidelines recommend biannual hepatocellular carcinoma (HCC) screening for non-cirrhotic patients with chronic hepatitis B infection (HBV), yet there are no data estimating surveillance rates or factors associated with surveillance. We performed a retrospective cohort study of U.S. patients using the Truven Health Analytics databases from 2006-2010, and identified patients with non-cirrhotic chronic HBV. Surveillance patterns were characterized using categorical and continuous outcomes, with the continuous measure of the proportion of time “up-to-date” with surveillance (PUTDS), with the six-month interval following each ultrasound categorized as “up-to-date.” During a median follow-up of 26.0 (IQR: 16.2-40.0) months among 4,576 non-cirrhotic patients with chronic HBV (median age: 44 years, IQR: 36-52), only 306 (6.7%) had complete surveillance (one ultrasound every 6-month interval), 2,727 (59.6%) incomplete (1 ultrasound), and 1,543 (33.7%) none. The mean PUTDS was 0.34 ± 0.29 , and the median was 0.32 (IQR: 0.03-0.52). In multinomial logistic regression models, patients diagnosed by a non-gastroenterologist were significantly less likely to have complete surveillance ($p < 0.001$), as were those co-infected with HBV/HIV ($p < 0.001$). In linear regression models, non-gastroenterologist provider, health insurance subtype, HBV/HIV co-infection, rural status, and metabolic syndrome were independently associated with decreased surveillance. Patients with HIV had an absolute decrease in the PUTDS of 0.24, while patients in less populated rural areas had an absolute decrease of 0.10. HCC surveillance rates in non-cirrhotic patients with chronic HBV in the United States are poor, and lower than reported rates of HCC surveillance in cirrhotic patients.

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Disclosures

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Keywords

Ultrasound; surveillance; hepatocellular carcinoma; chronic hepatitis B

Introduction

The prevalence of chronic hepatitis B virus (HBV) in the United States (US) is increasing, attributable to increased number of immigrants from countries where HBV is endemic.^{1,2} It is estimated that 40-70% of people in the US with chronic HBV are foreign-born, with the total US prevalence of HBV potentially eclipsing 2 million individuals.^{1,2} HBV is a risk factor for the development of hepatocellular carcinoma (HCC), regardless of cirrhosis status.³⁻⁶ When diagnosed at an early stage, HCC has 5-year survival rates of greater than 70%.^{3,7,8} American Association for the Study of Liver Diseases' (AASLD) guidelines published in November 2005 recommended HCC surveillance with an abdominal ultrasound every 6 months, with or without testing for alpha fetoprotein (AFP), in patients with chronic HBV, with the age of onset of surveillance based on country of origin/racial background.³ By contrast, the newer European Association for the Study of the Liver (EASL) HCC surveillance guidelines published in 2012, also recommend biannual HCC surveillance in non-cirrhotic patients with chronic HBV, but do not use different age cutoffs for HCC surveillance as a function of race or country or origin.⁹

While there have been several studies evaluating HCC surveillance rates in cirrhotic patients in the US, only a small fraction of these patients had HBV.¹⁰⁻¹³ Furthermore, despite published recommendations for HCC surveillance in patients with chronic non-cirrhotic HBV in both the US and Europe, there has only been a single study of HCC surveillance rates in this population from either the US or Europe. Furthermore, this study included only Asian Americans with chronic HBV at a single hospital and its satellite clinics.¹⁴

Given that patients with non-cirrhotic HBV diagnosed with early-stage HCC are potentially eligible for curative treatment, including resection, without the need for liver transplantation, timely and routine surveillance is critical.¹⁰⁻¹³ Identification of surveillance rates and factors associated with surveillance are needed in order to develop targeted interventions to improve surveillance, and in turn, HCC-related survival among patients with non-cirrhotic HBV. As such, we sought to: 1) identify surveillance rates for HCC in a nationally representative commercially insured population with chronic non-cirrhotic HBV; and 2) evaluate patient, physician, and geographic factors associated with HCC surveillance.

METHODS

Data source

We used the Truven Health Analytics databases (Ann Arbor, MI, USA)¹⁵, which contain data from 100 large employers, health plans, and government and public organizations. The Truven database is an administrative, claims-based database collected from multiple different data sources, and includes data on inpatient hospitalizations, outpatient care, and prescription drug utilization,¹⁵ and has been used extensively in epidemiologic studies.^{15,16}

Study Period

The index period was from January 1, 2006 to December 31, 2009. The AASLD HCC surveillance guidelines were published in November 2005, thus the start date of January 1, 2006 provided a two-month period of dissemination of the guidelines. Any patient with HBV seen on or after January 1, 2006 would be eligible for an HCC surveillance protocol.

Study population

Eligible subjects were identified based on billing claims. We included all adults 18 years of age in the Truven Health Analytics database with diagnostic coding for HBV and a minimum of 18 months of continuous follow-up. Chronic non-cirrhotic HBV was defined as having at least two outpatient codes for hepatitis B (ICD-9-CM codes: 070.20, 070.21, 020.22, 070.23, 070.3, 070.31, 070.32, and/or 070.33), based on clinician face-to-face encounters using Current Procedural Terminology (CPT) codes with the first 3 digits of 992XX (e.g. 99215). The two codes were required to be at least 30 days apart in order to exclude patients with either acute HBV, and/or those seen by a clinician who was “ruling out” HBV. At least one of the claims must have been on or after January 1, 2006. Any patient with ICD-9-CM codes for cirrhosis (571.2: alcoholic cirrhosis; 571.5: cirrhosis of the liver without mention of alcohol; one inpatient or two outpatient codes) preceding the diagnosis of HBV or within 365 days of the diagnosis was excluded in order to create a cohort of patients with non-cirrhotic HBV, for whom enrollment in an HCC surveillance protocol was based on HBV, rather than cirrhosis. Inclusion did not distinguish between incident and prevalent diagnoses of HBV given that many incident diagnoses identify longstanding chronic infections, especially in foreign-born patients who acquired HBV through vertical transmission.

A minimum six-month baseline was required to exclude patients with HCC and/or other malignancies (other than non-melanoma skin cancer; NMSC), whom would not be eligible for an HCC surveillance protocol, and/or may have imaging for surveillance of that malignancy rather than to screen for HCC (Supplementary Table 1). At least 12 months of continuous follow-up after the index date without a diagnosis of HCC, malignancy other than NMSC, or liver transplant was also required so that all patients had at least two six-month HCC surveillance intervals. However, a sensitivity analysis included all patients diagnosed with HCC in the first 12 months who were excluded as instead having “complete” surveillance to assess the robustness of our results.

Study outcome

The primary outcome was performance of an ultrasound, identified using two CPT codes: 76700 (complete abdominal ultrasound) or 76705 (limited abdominal ultrasound). Any ultrasound was included for the primary outcome, given that regardless of the indication, any abdominal ultrasound would evaluate the liver and serve as a screening test for HCC.

Patient-level HCC surveillance was measured in two ways: 1) categorical variable, coded as complete, incomplete, and none; and 2) continuous variable, defined as the proportion of time a patient was up to date with surveillance (PUTDS), measured as the number of months a patient was “up-to-date” with surveillance divided by the total amount of follow-up time.

The categorical variable evaluated follow-up time in increments of six months as this variable did not discriminate based on the timing of the test within a given interval. Thus a patient with 20 months of follow-up would be evaluated over three, six-month intervals. Within each 6-month interval, a patient was categorized as having a screening ultrasound (yes/no), and then subsequently categorized as: a) complete; one ultrasound performed during each 6-month interval; b) incomplete; at least one ultrasound during follow-up but not in every interval; and c) none.¹⁰

The continuous measure of surveillance (PUTDS) was calculated for each patient based on his/her respective follow-up time. This novel continuous variable accounted for the timing of the test within a given interval, included all follow-up time, and considered performed within the baseline period, all of which were excluded by previous methods.¹⁰ The only tests performed during the baseline that could be included in this analysis were those performed during the six months prior to the index date, as each ultrasound test would only allow a patient to be “up-to-date” with surveillance for the six months following that test.

Secondary outcomes included other imaging tests which screen for HCC, but are not part of the AASLD guidelines: triple-phase abdominal CT scan (CPT-74160, 74170) or abdominal magnetic resonance imaging (MRI) with contrast (CPT-74181, 74183).

Study Variables

Several covariates were selected prior to initiating the analysis given their potential association with access to care, or likelihood of having HCC surveillance (Supplementary Table 2) using validated algorithms:^{10-13,17-19} The two geographic factors that were tested were geographic region, as defined in the Truven database, and the modified residential Rural Urban Commuting Area (mRUCA) code²⁰ which is a modification of the standard RUCA classification that accounts for both county and residential size. The association between provider subtype and surveillance was assessed by assigning each patient to a provider subtype using data from outpatient visits with an ICD-9 HBV billing code. A hierarchy of provider subtype was used for patients with multiple providers (Supplementary Table 3). Race and/or ethnicity data are not available in the Truven database.

Statistical Analysis

Multinomial logistic regression models were used to explore factors associated with surveillance using the categorical outcome variable. Complete surveillance served as the reference category as a way to specifically evaluate factors that were associated with either incomplete or no surveillance (ordinal regression models were also assessed but the null hypothesis of proportional odds assumption was violated). Linear regression models were fit with the continuous outcome of PUTDS, with the beta coefficient for a given variable representing the change in the PUTDS, compared to the reference category for that variable. We also examined whether there were changes in surveillance rates over time and association of number of physician visits with pattern of HCC surveillance using factorial ANOVA.

We performed sensitivity analyses that 1) limited follow-up to the first 12 months after the index date, the period at which the highest surveillance rates would be expected¹⁴; 2)

broadened the outcome to include any ultrasound and/or contrast-enhanced imaging modality (CT, MRI) as surveillance; and 3) restricting the cohort to patients ≥ 50 at the time of HBV diagnosis. The latter sensitivity analysis was performed because AASLD guidelines recommend HCC surveillance starting at age 50 in non-cirrhotic patients with HBV, with the exception of Asian males starting at age 40, and patients of African descent at age 20.

All the statistical analyses were conducted using SAS version 9.2.

Results

Among 50,511 patients in the Truven Health Analytics database identified as having at least 1 ICD-9-CM code for HBV from 2006-2010, 4,576 (9.1%) were eligible for analysis based on two outpatient ICD-9-CM codes for HBV at least 30 days apart, in the absence of ICD-9 codes for cirrhosis (Figure 1). The mean age was 44.2 (SD: 11.0) years, and 2,874 (62.8%) were male (Table 1). The majority were located in the South (1,736; 37.9%) or North West (1,427; 31.2%) regions of the U.S. Over 90% of patients were either insured through a preferred provider organization (PPO) or point-of-service (POS) plan ($n=3,039$, 66.4%) or a health maintenance organization (HMO; $n=1,174$, 25.7%). Only half (2,375; 51.9%) were diagnosed with HBV by a gastroenterologist.

Categorical surveillance outcome

During a median follow-up of 26.0 (IQR: 16.2-40.0) months, 306 (6.7%) non-cirrhotic HBV patients had complete surveillance, 2,727 (59.6%) had incomplete, and 1,543 (33.7%) had none. Inclusion of cross-sectional contrast-enhanced imaging (CT and MRI) only increased these values to 399 (8.7%), 2,849 (62.3%), and 1,328 (29.0%), respectively (Table 2). In analyses restricting follow-up to the first 12 months after the index date, only 604 (13.2%) had complete surveillance (Table 2). When the cohort was restricted to non-cirrhotic HBV patients ≥ 50 years of age at the index date (1,511 patients; 33.0% of HBV cohort), the proportion with complete, incomplete, and no surveillance was unchanged. When the 27 patients who developed HCC within the first 12 months who were excluded from the primary analysis were instead classified as having complete surveillance, the proportion of non-cirrhotic HBV patients with complete HBV surveillance overall and in the first 12 months were 7.2% and 13.8%, respectively.

There was no appreciable difference in the proportion of non-cirrhotic HBV patients receiving complete follow-up when patients were stratified by year of index date and follow-up restricted to the first 12 months after the index date in order to ensure uniform follow-up for all patients—the proportion with complete surveillance ranged from 12.6% (2006) to 14.9% (2009).

Continuous surveillance outcome

During follow-up, the mean PUTDS was 0.34 (SD: 0.29), and the median was 0.32 (IQR: 0.03-0.52). The mean PUTDS was unchanged when restricted to the first 12 months of follow-up or months 13-24 of those with at least two years of follow-up, while the median PUTDS increased when restricted to months 0-12 (Table 2). These results were unchanged when restricted to the cohort ≥ 50 years of age at inclusion (data not shown).

Physician visits and HCC surveillance

Patients with complete HCC surveillance had a significantly greater number of physician visits compared to patients with incomplete or no surveillance ($p < 0.001$). Specifically, patients with complete surveillance had mean of 1.76 (SD: 1.81) physician visits, compared to 1.18 (SD: 1.45) and 0.93 (SD: 1.39) for patients with incomplete or no surveillance.

Multinomial logistic regression model

In multinomial logistic regression models, with complete HCC surveillance as the reference, several variables were significantly associated with HCC surveillance patterns (Table 3). Patients co-infected with HIV were significantly more likely to have incomplete or no HCC surveillance, thus less likely to have complete surveillance (Table 3). Patients with chronic non-cirrhotic HBV diagnosed by a non-gastroenterologist were significantly more likely to have no HCC surveillance, in comparison to those diagnosed by a gastroenterologist. However, even among the subgroup of patients deemed 'low-risk' for incomplete surveillance due to the absence of any of the factors associated with incomplete or no surveillance (diagnosing provider, HIV status, rural/urban status, health insurance subtype, and metabolic syndrome), only 8.3% (40/487) had complete screening during all of follow-up, while 62.5% (303/487) had incomplete surveillance. When restricted to the first 12 months of follow-up, the proportion with complete surveillance increased from 13.2% in the entire cohort, to 16.7% (81/487) among patients deemed 'low-risk.'

Linear regression model for continuous outcome

When all follow-up time was evaluated, non-gastroenterologist provider subtype, non-PPO or POS commercial health insurance, HBV/HIV co-infection, rural status, and metabolic syndrome were each independently associated with decreased surveillance, defined as decreased PUTDS, in multivariable linear regression models (Table 4). The beta coefficients of the linear regression model represent the absolute decrease (or increase) in the PUTDS relative to the reference group for a specific category. For example, compared to a patient mono-infected with HBV alone, a patient co-infected with HIV and HBV would be expected to have an absolute decrease in the PUTDS of 0.242, or an absolute decrease in the percentage of time up-to-date with surveillance of 24.2%. For one year of follow-up, this would equate to 2.9 fewer months of being up-to-date, or 6.3 fewer months up-to-date for a patient with the median months of follow-up of 26.0 months. In addition to HIV, those factors associated with the largest decrease in PUTDS were population density (the absolute percentage of time up-to-date decreased by 9.3% and 10.1% in patients in mRUCa category 4 and 5 relative to mRUCa category 1, respectively), diagnosis by an internal medicine subspecialist (12.5% absolute decrease relative to diagnosis by a gastroenterologist), and comprehensive health insurance (8.8% absolute decrease relative to having a PPO or POS plan; Table 4).

Discussion

In this study we demonstrate that in a nationally-representative commercially insured cohort with non-cirrhotic chronic HBV in the United States, surveillance rates for HCC are poor despite formalized surveillance guidelines. Although prior US studies have evaluated HCC

surveillance rates in patients with cirrhosis, this is the first to specifically focus on non-cirrhotic patients with chronic HBV. Although these data may not generalize to the broader immigrant population in the US with HBV, the data do highlight the low surveillance rates in commercially insured patients with access to care, who might be expected to be more likely to have appropriate surveillance. While efforts have been made to improve HCC screening rates in cirrhotic patients, these data highlight that delivery of HCC screening is inadequate in the population of commercially insured non-cirrhotic patients with chronic HBV. With continued increases in immigrants from intermediate and high HBV endemic countries, chronic HBV is expected to be a growing public health problem¹. Such patients, who may be more likely to have poor access to healthcare due to language or other socio-demographic barriers, are likely to have even lower surveillance rates than observed in this study. Given that HCC arising in the setting of non-cirrhotic HBV can be curable with surgical resection if caught early, efforts to improve HCC screening in these patients are needed.

The only randomized controlled trial of HCC screening for at-risk patients was conducted in China in a cohort 18,000 patients with chronic HBV. This study demonstrated a 37% decreased risk of mortality in patients enrolled in a regular screening protocol, and included all patients with chronic HBV, independent of cirrhosis.⁶ However, nearly all previous HCC surveillance studies in the US have focused exclusively on patients with cirrhosis, with only a small fraction of such patients having HBV given the low prevalence of HBV-related cirrhosis in the U.S. The only published study of HCC surveillance practices in patients with HBV in the U.S. was from a single hospital in San Francisco and its “safety net clinics.”¹⁴ In the first year after diagnosis of chronic HBV, 42% of patients had at least one imaging test using any imaging modality (CT, MRI, and/or ultrasound; each with or without AFP), with this number decreasing to <25% for months 13-24.¹⁴ In the current study, we found a higher proportion of patients with non-cirrhotic HBV underwent at least one screening imaging test in months 0-12 (56.8%) or 13-24 (54.3%), which may in part be attributable to the fact that the previous data were derived from a “public health safety net system,”¹⁴ in contrast to a cohort with commercial health insurance. Thus the HCC surveillance rates seen in our cohort of patients with commercial health insurance likely overestimates the HCC surveillance rates in immigrant populations who have less access to healthcare. Even under the best-case scenario whereby a patient had none of the features associated with lower surveillance, rates of complete HCC surveillance were quite poor. This highlights the urgent need to initiate efforts to increase HCC surveillance rates in all patients at risk of developing HCC.

Previous work involving cirrhotic patients has identified that provider subtype is associated with HCC surveillance in cirrhotic patients¹³, while HBV specific data from San Francisco suggests that surveillance rates differ in patients based on severity of liver disease (i.e. cirrhosis or liver enzymes elevation) or attending a liver specialty clinic.¹⁴ Our data identify several additional and novel factors associated with HCC surveillance, including provider subtype (non-gastrointestinal), insurance type among those with commercial insurance, rural versus urban status, and HIV positivity (a severe comorbidity but not one that should preclude appropriate HCC surveillance), which are consistent with our a-priori hypotheses. These data can be used to help identify patients at greatest risk of not undergoing

recommended HCC surveillance, and can help guide targeted interventions to improve HCC surveillance rates. The cohort had a small fraction (3.2%) co-infected with HIV/HBV, with a fraction of those receiving care from an infectious disease specialist. Further work should identify a cohort enriched with patients co-infected with HIV and HBV in order to address specific questions related to HCC surveillance in this cohort.

This study raises several issues regarding surveillance in non-cirrhotic patients with chronic HBV. The nature of these administrative data do not allow for us to determine why surveillance was not performed, specifically whether it was due to patient and/or provider factors. Administrative data only account for tests that were performed. Thus some patients may have had the test ordered but not completed. Providers, particularly those without formal training in gastroenterology, may not be aware of recommendations for HCC surveillance in this patient population. The demonstrated rates of HCC surveillance did not differ based on a patient's age, which is notable as AASLD, unlike EASL, guidelines specifying different ages at which a patient should be enrolled in a surveillance program based on his/her racial/ethnic background. This differentiation by age is based on limited data, and our data suggest that even those providers who perform HCC surveillance in their patients with HBV do not change practices accordingly. Whether the complexity of the AASLD guidelines has been a deterrent to surveillance overall is unknown, but we hypothesize that simplification of guidelines may lead to improved compliance.

Although all patients had commercial insurance, socioeconomics may play a factor in terms of co-payments for imaging tests. Even under the Affordable Care Act, co-payments for HCC surveillance ultrasounds are not covered,²¹ which could contribute to the variability based on insurance subtype. Lastly, medical co-morbidities, notably HIV, were associated with significantly decreased surveillance, which may be a consequence of provider knowledge about the risk of HCC or surveillance ultrasounds being overlooked amidst complex medical care for co-infected patients. It will be necessary to further understand these potential mechanisms for low surveillance rates to develop effective quality improvement interventions.

This study has limitations. First, the retrospective administrative data only indicate whether an imaging study was performed, and does not capture the indication (i.e. was it for screening or to evaluate symptoms). This is unlikely to have biased the results since an abdominal imaging study, most importantly an abdominal ultrasound as recommended in the AASLD and EASL guidelines, investigates the liver, regardless of the indication for the study. Second, we identified patients using administrative data, and not laboratory testing. However, ICD-9 codes have been previously demonstrated to accurately identify patients with chronic HBV in administrative data.²² Third, we included all non-cirrhotic patients with chronic HBV, regardless of age, as we could not identify the race and ethnicity of patients in the database. While AASLD guidelines recommend different ages at which to initiate surveillance based on a patient's country of origin/racial background, EASL guidelines do not make such distinctions. Notably, although this study was conducted using US data, the results of the analyses using either the categorical or continuous outcomes were unchanged when restricted to the cohort to patients 50 years or older at inclusion. This is important, because even though patient ethnicity could not be identified, all patients with

chronic HBV over age 50 should undergo HCC surveillance; nevertheless, future work is needed to evaluate differences in HCC surveillance rates as a function of race/ethnicity. Furthermore, even by AASLD guidelines, which use age 50 as a cutoff for surveillance in non-Africans and non-Asian males, HCC surveillance rates are poor. Data on family history of HCC were not available in this database. To the extent that the population included a small percentage of patients with a family history of HCC, these patients would be more likely to have undergone screening and as such, we may have slightly overestimated the screening rate in average risk patients with HBV infection. Fourth, it is possible that patients with cirrhosis may have been included, despite using a validated algorithm with a high positive predictive value to exclude such patients. Any bias introduced by inclusion of cirrhotic patients would be expected to falsely increase our estimated HCC surveillance in patients with chronic HBV, thus making the true rates even lower. Finally, the administrative dataset did not include laboratory data (i.e., hepatitis B surface antigen and/or HBV DNA), thus we could not confirm the diagnosis of HBV using laboratory data, and/or evaluate surveillance rates based on levels of HBV surface antigen and/or DNA. While this should be explored in future studies, we feel confident we identified a cohort with chronic HBV based on previous studies validating HBV ICD-9-CM codes as a means to identify patients with chronic HBV.^{23,24} In order to create a cohort that would provide internal validity for the study question,²⁵ we used exclusions available in administrative data. The data thus likely provided the best-case scenario estimates of HCC surveillance rates, however we cannot say with certainty the impact of such exclusions.

In conclusion, HCC surveillance rates for commercially insured non-cirrhotic patients with chronic HBV in the United States remain inadequate despite formalized screening guidelines, and are much lower than national screening rates for other cancers in the general population. Rural status, insurance subtype, provider specialty, and HIV infection are associated with significantly lower rates of compliance with surveillance guidelines. Targeted interventions are needed to reduce morbidity and mortality from this curable disease in well-identified at risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

HBV	Hepatitis B virus
US	United States
HCC	Hepatocellular carcinoma
AASLD	American Association for the Study of Liver Diseases
AFP	Alpha fetoprotein
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
CPT	Current Procedural Terminology
NMSC	Non-melanoma skin cancer
PUTDS	Proportion of time a patient was up to date with surveillance
mRUCA	Modified residential Rural Urban Commuting Area
PPO	Preferred provider organization
POS	Point-of-service

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Figure 1.
Flow diagram of inclusion of subjects with non-cirrhotic hepatitis B in the Truven Health Analytics databases

Table 1

Baseline Demographic Characteristics, N=4,576

Characteristics	
Age	
Continuous in years	
Mean (SD)	44.2 (11.0)
Median (IQR)	44 (36-52)
Categorical, No. (%)	
18-44	2,356 (51.5)
45-64	2,104 (46.0)
65-74	98 (2.1)
75+	18 (0.4)
Male, No. (%)	2,874 (62.8)
Region of United States, No. (%)	
South Region	1,736 (37.9)
West Region	1,427 (31.2)
Northeast Region	792 (17.3)
North Central Region	609 (13.3)
Unknown Region	12 (0.3)
Insurance type, N (%)	
PPO/POS	3,039 (66.4)
HMO	1,174 (25.7)
Others	174 (3.8)
Comprehensive	101 (2.2)
Missing/Unknown	88 (1.9)
Provider specialty diagnosis hepatitis B [*]	
Gastroenterology	2,375 (51.9)
Any primary care	1,219 (26.6)
Internal Medicine sub-specialty	121 (2.6)
Others	861 (18.8)
Medical co-morbidities, No. (%)	
HIV	144 (3.2)
Metabolic syndrome	1,913 (41.8)
Median number of transplant centers within geographic region, IQR [†]	
Median (IQR)	3 (2-5)
Mean (SD)	3.6 (1.9)
County size based on mRUCA, No. (%) [‡]	
Group 1	2,323 (50.8)
Group 2	1,491 (32.6)
Group 3	483 (10.6)
Group 4	148 (3.2)

Characteristics	
Group 5	130 (2.8)
Median follow-up in months (IQR)	26.0 (16.2-40.0)

Abbreviations: PPO=preferred provider organization; POS=point of service CDHP=consumer directed health plan; EPO=exclusive provider organization; HDHP=high-deductible health plans; HMO=health maintenance organization; mRUCA=modified rural urban commuting area

* Provider specialty based on the provider subtype associated with the billing code used to diagnose the patient with cirrhosis, based on the hierarchy provided in eTable 3.

[†] Geographic region defined as the donor service area, or geographic unit of organ allocation within one of the 11 United Network for Organ Sharing (UNOS) regions

[‡] Category 1 and 2 includes counties of metro areas of 1 million population or more, with county population of ≥ 1 million population and < 1 million population respectively; category 3 and 4 includes counties in metro areas of 250,000 - 1,000,000 and $< 250,000$ population respectively, category 5 includes counties with urban and rural populations.²⁶

Table 2

Results of categorical and continuous measures of HCC surveillance among patients with chronic non-cirrhotic HBV

Follow-up period	Outcome				
	Categorical, No. (%) [*]			Continuous PTUDS [†]	
	Complete	Incomplete	None	Mean (SD)	Median (IQR)
All follow-up, n=4,576	306 (6.7)	2,727 (59.6)	1,543 (33.7)	0.34 (0.29)	0.32 (0.03-0.52)
Months 0-12, n=4,576	604 (13.2)	1,856 (40.6)	2,116 (46.2)	0.35 (0.32)	0.42 (0.00-0.50)
Month 13-24, n=2,446	276 (11.3)	946 (38.7)	1,224 (50.0)	0.31 (0.32)	0.29 (0.00-0.50)

* "Complete" defined as at least one ultrasound during every six-month interval, "incomplete" is defined as at least 1 screening ultrasound during at least one six-month interval, and "none" is defined as no screening during any of the six-month intervals.

[†] PTUDS= (the number of months a patient was "up-to-date" with surveillance) / (total amount of follow-up time)

Table 3

Multinomial logistic regression model evaluating HCC surveillance, with routine surveillance as the reference^{*}

Variable	Multivariable odds ratio (95% CI) for None	Multivariable odds ratio (95% CI) for Incomplete	P-value [†]
Age	0.98 (0.97-0.99)	0.99 (0.98-1.00)	<0.001
Liver centers per OPO	0.98 (0.90-1.07)	1.05 (0.97-1.14)	0.005
Prior Charlson index	0.89 (0.76-1.05)	0.93 (0.79-1.09)	0.3
Male sex	0.86 (0.65-1.13)	0.84 (0.64-1.09)	0.4
Modified RUCA category			
Category 1			<0.001
Category 2	1.19 (0.88-1.63)	1.07 (0.79-1.45)	
Category 3	1.89 (1.14-3.12)	1.20 (0.73-1.98)	
Category 4	2.26 (0.87-5.89)	1.22 (0.47-3.19)	
Category 5	3.21 (0.96-10.7)	2.20 (0.66-7.33)	
Provider type diagnosing chronic hepatitis B			<0.001
Gastrointestinal			
“Other” provider	1.21 (0.79-1.86)	1.09 (0.72-1.66)	
Primary care	1.69 (1.23-2.32)	1.22 (0.89-1.68)	
Internal medicine subspecialty	3.48 (1.06-11.5)	1.25 (0.37-4.25)	
Geographic region			0.008
South			
Northeast	0.82 (0.55-1.22)	1.12 (0.76-1.65)	
North Central	0.78 (0.45-1.22)	0.97 (0.63-1.51)	
West	0.63 (0.43-0.91)	0.92 (0.64-1.32)	
Unknown	0.62 (0.06-5.98)	0.34 (0.03-3.40)	
Insurance plan type			
PPO/POS			0.25
Comprehensive	3.63 (1.06-12.4)	2.19 (0.64-7.48)	
HMO	1.07 (0.76-1.50)	1.07 (0.77-1.49)	
“Other”	1.01 (0.55-1.84)	0.96 (0.53-1.72)	
HIV positive	32.1 (3.49-295.6)	7.94 (0.86-73.5)	<0.001
1 component metabolic syndrome	1.40 (1.05-1.88)	1.18 (0.88-1.56)	0.02
Follow-up [‡]	1.05 (1.03-1.07)	1.09 (1.07-1.11)	<0.001

Abbreviations: OPO=organ procurement organization; RUCA= rural urban commuting area PPO=preferred provider organization; POS=point of service; HMO=health maintenance organization

^{*} Model also adjusted for co-morbid medical conditions using the Charlson co-morbidity index, male gender (p-value=0.4), and year of index date (p=0.3)

[†] P-value for continuous variable, or for overall category of categorical variable. The p-value signifies whether there is a significant association between the covariate and the categorical outcome of complete, incomplete, or no surveillance, thus the p-value may be <0.05 even if the odds ratio for incomplete and/or none crosses 1.0 as this is not a pairwise comparison. For pairwise comparisons of the association between a covariate and only one specific outcome (complete vs incomplete or complete vs none), only those that do not cross 1.0 are considered significant (p<0.05) in a pairwise comparison.

[†]Increase in odds ratio for increase in one month of follow-up

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Table 4

Multivariable linear regression model evaluating HCC surveillance, with continuous outcome of proportion of time up to date with surveillance *

Variable	Beta coefficient (95% CI) [†]	P-value [‡]
Age	0.002 (0.001, 0.003)	<.0001
Liver centers per OPO	0.013 (0.002, 0.024)	0.002
Prior Charlson index	0.008 (0.003, 0.013)	0.02
Modified RUCA category		<.0001
Category 1	Reference	
Category 2	-0.017 (-0.038, 0.003)	
Category 3	-0.064 (-0.093, -0.035)	
Category 4	-0.093 (0.142, -0.044)	
Category 5	-0.101 (-0.153, -0.049)	
Provider type diagnosing chronic hepatitis B		<.0001
Gastrointestinal	Reference	
“Other” provider	-0.030 (-0.056, -0.003)	
Primary care	-0.065 (-0.086, -0.045)	
Internal medicine subspecialty	-0.125 (-0.180, -0.071)	
Geographic region		0.006
South		
Northeast	0.009 (-0.018, 0.036)	
North Central	0.036 (0.009, 0.063)	
West	0.042 (0.018, 0.067)	
Unknown	0.063 (-0.103, 0.229)	
Insurance plan type		0.005
PPO/POS		
Comprehensive	-0.088 (-0.147, -0.030)	
HMO	-0.024 (-0.045, -0.003)	
“Other”	-0.017 (-0.060, 0.026)	
HIV positive	-0.242 (-0.326, -0.158)	<.0001
1 component metabolic syndrome	-0.035 (-0.054, -0.016)	<.0001
Follow-up ^{**}	-0.001 (-0.002, 0.000)	0.046

Abbreviations: OPO=organ procurement organization; RUCA= rural urban commuting area PPO=preferred provider organization; POS=point of service; HMO=health maintenance organization

* Model also adjusted for male gender (p-value=0.4), and year of index date (p=0.05). Intercept for model was 0.2939.

[†] The beta coefficients of the linear regression model represent the absolute decrease (or increase) in the PUTDS relative to the reference group for a specific category. For example, compared to a patient mono-infected with HBV alone, a patient co-infected with HIV and HBV would be expected to have an absolute decrease in the PUTDS of 0.242, or an absolute decrease in the percentage of time up-to-date with surveillance of 24.2%. For one year of follow-up, this would equate to 2.9 fewer months of being up-to-date, or 6.3 fewer months up-to-date for a patient with the median months of follow-up of 26.0 months.

[‡] P-value for continuous variable, or for overall category of categorical variable

^{**} Increase in odds ratio for increase in one month of follow-up