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Cirrhosis is Under-recognized in Patients Subsequently Diagnosed with Hepatocellular Cancer

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Abstract

Background—Most clinical practice guidelines recommend screening for HCC in patients with cirrhosis. However, patients with compensated cirrhosis are often asymptomatic and may remain unrecognized for years.

Aims—To determine the extent to which cirrhosis is unrecognized in a US Veteran population with HCC and to evaluate the association between lack of cirrhosis recognition and stage of HCC at diagnosis.

Methods—We reviewed the electronic medical records of a random sample of HCC cases diagnosed in the national Veterans Affairs system between 2005 and 2011. We conducted multivariable analyses adjusting for patients' demographics, comorbidity, etiology of underlying disease, and healthcare utilization including HCC surveillance.

Results—Of 1201 patients with HCC and cirrhosis, 24.6% had unrecognized cirrhosis prior to HCC diagnosis. Older patients (>65yr, odds ratio [OR] 2.32), African Americans (OR 1.93), patients with alcoholic or NAFLD liver disease (OR 1.69 and 4.77 respectively), HIV (OR 3.02), and fewer comorbidities (Deyo 0 *vs*. 3, OR 2.42) had significantly higher odds of having unrecognized cirrhosis than comparison groups. Furthermore, patients with unrecognized cirrhosis were 6.5 times more likely to have advanced stage HCC at diagnosis. The effect of cirrhosis

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recognition on HCC stage remained significant after adjusting for pre-specified covariates (OR 3.37).

Conclusions—In one fourth of patients, cirrhosis was unrecognized prior to HCC diagnosis, and this group was significantly more likely to have advanced stage HCC. These findings emphasize the importance of timely evaluation for cirrhosis in at-risk populations as a critical step to improving outcomes for HCC patients.

Keywords

liver; cirrhosis; hepatocellular carcinoma; stage; detection; veterans

Background

Hepatocellular carcinoma (HCC) is a rapidly increasing, highly fatal cancer. Survival in HCC is stage dependent, with 5-year survival exceeding 50% in patients who are diagnosed at an early stage and undergo potentially curative treatments.[1–4] However, most HCC cases in the U.S. are diagnosed at an advanced stage.[4,5] Thus, despite recent advances in HCC treatment, the overall prognosis of patients with HCC remains dismal.[6]

Cirrhosis is the precursor lesion for most HCCs cases.[7,8] Presence of a defined at-risk group and the long latent period from cirrhosis to HCC offers an opportunity for healthcare providers to screen for HCC and possibly detect cancer at an early stage. However, cirrhosis may be asymptomatic and hence unidentified in some cases. Systematic screening for cirrhosis in those with risk factors is not a routine practice. More commonly, patients are diagnosed with cirrhosis after the onset of cirrhosis related complications such as ascites, gastroesophageal varices, or hepatic encephalopathy that occur late in the course of disease. This suggests that some patients with cirrhosis, particularly those who are likely to benefit from preventive and surveillance efforts targeting early detection of HCC, are un-diagnosed.

Using a geographically diverse large sample of patients with confirmed HCC, we sought to determine the extent to which cirrhosis was unrecognized prior to patients' HCC diagnosis as well as the association between failure to identify presence of cirrhosis and HCC stage at diagnosis. The findings from the study may suggest that under-recognition of cirrhosis might, at least in part, explain the disconnect between the expected and observed benefits associated with HCC screening practices in the U.S.

Methods

Study Population

We identified a national cohort of 1500 patients who had a confirmed HCC diagnosis at any of the Veterans Administration (VA) facilities between October 2005 and December 2011. These patients were initially identified based on the presence of ICD-9 CM code 155.0 (malignant neoplasm of liver) in the absence of code 155.1 (intrahepatic cholangiocarcinoma) from the VA administrative data. A structured review of the electronic medical record (EMR) was conducted to verify HCC diagnosis based on a combination of radiological and histological criteria.[9] We obtained detailed VA EMR information by

accessing the Compensation and Pension Records Interchange (CAPRI), which is a VA application that provides access to the EMR found in the Computerized Patient Record System (CPRS) at any VA facility nationwide. We included only patients who were active users of the VA healthcare system (at least 1 inpatient or outpatient encounter within 1 year prior to HCC diagnosis) to ensure that patients were in regular care prior to HCC diagnosis. The 1 year cut-off is consistent with other studies of VA patients [10].

Some HCC cases may occur in the absence of cirrhosis. Because the purpose of this study was to examine cirrhosis recognition (among those with clinical and/or histological evidence of cirrhosis), we limited our sample to patients for whom we could confirm presence of underlying cirrhosis based on standardized EMR review. We defined confirmed cirrhosis based on liver biopsy results at any time before or at the time of diagnosis of HCC, features suggestive of cirrhosis on abdominal imaging, clinical complications of cirrhosis (ascites, hepatic encephalopathy, varices), or laboratory evidence consisting of abnormal values on two of three laboratory tests (albumin <3.0g/l, platelets <200,000/microliter, INR >1.1 between 6 months before and 4 weeks after HCC diagnosis) or an APRI (AST to platelet ratio index) score >2.0.

Study variables

Our primary outcome variables were recognition of cirrhosis in clinical practice prior to HCC diagnosis and stage of HCC at the time of diagnosis. A study investigator reviewed clinical progress notes for evidence of provider recognition of cirrhosis from the 3 years prior to the day before the date of HCC diagnosis. Recognition of cirrhosis was defined as entry of a diagnostic code for cirrhosis *or* any mention of cirrhosis (or related term such as Child score) pertaining to the patient in a physician progress note.

We defined stage of HCC at diagnosis based on the Barcelona Clinic Liver Cancer (BCLC) scoring system.[11] We obtained size and number of lesions from imaging reports and used information in the providers' progress notes to derive patients' performance status. We classified BCLC stage 0 or A as early stage HCC and stages B, C, and D as advanced HCC.

We ascertained several factors that might be associated with our outcome variables (*i.e.*, recognition of cirrhosis in clinical practice, and HCC stage at diagnosis). These factors included patient demographics including age, gender, race/ethnicity, geography and urban vs. rural residence. We also analyzed medical comorbidities including HIV, Deyo comorbidity index, psychosis, and post-traumatic stress disorder (PTSD). The Deyo comorbidity index is a scoring system assigning points to various comorbidities by ICD 9 code. Conditions such as myocardial infarction, congestive heart failure, COPD, uncomplicated diabetes mellitus (DM) and mild liver disease are designated 1 point each. Complicated DM, paralysis and renal disease are assigned 2 points, moderate to severe liver disease 3 points and AIDS 6 points. Liver disease related factors included the stage (Child Pugh or Model of End stage Liver disease [MELD]) and etiology of liver disease (hepatitis C virus [HCV] infection, hepatitis B virus [HBV] infection, alcohol, nonalcoholic fatty liver disease [NAFLD], other etiologies). We defined HCV based on ≥ 1 positive anti-HCV or HCV ribonucleic acid (RNA) tests, HBV based on ≥ 1 HBV positive surface antigen, alcohol related liver disease based on as history of 3 or more drinks a day, documentation of

alcoholism/alcohol abuse in a physician progress notes, enrollment in a substance abuse treatment program, or diagnosis of alcoholic hepatitis, and NAFLD by features of hepatic steatosis on the histopathology when available, or in the absence of liver biopsy, by the presence of metabolic syndrome in the *absence* of other causes of chronic liver disease prior to HCC diagnosis. We used the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines to define metabolic syndrome.[9,12] Other etiologies of liver disease included hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency or autoimmune hepatitis defined based on positive laboratory tests results or documented diagnoses in the problem list or progress notes.

We also assessed several healthcare utilization factors. We defined HCC surveillance as receipt of liver ultrasound, computed tomography or magnetic resonance imaging or serum α-fetoprotein level performed within the 3 years prior to HCC diagnosis, as previously described [10]. Regular healthcare utilization was defined as at least one annual visit to the VA in each of the 3 years prior to HCC diagnosis. We also examined the number of hospitalizations and outpatient visits, as well as the types of clinics in which the patients were seen (primary care, gastroenterology, oncology, infectious diseases) during the 1 year prior to HCC diagnosis. We chose to evaluate oncology visits prior to HCC diagnosis as some patients in our population already had known other malignancies such as lung or prostate cancer. In addition, some patients were referred to oncology for evaluation of a liver mass that had not yet been conclusively diagnosed.

Last, because of more widespread use of noninvasive markers of liver fibrosis over time, we assessed the year of HCC diagnosis to adjust for these time trends.

All information was abstracted manually from the EMR.

Data Analysis

The analyses were limited to patients with cirrhosis prior to their HCC diagnosis that was confirmed by EMR review. We examined and compared patient demographic, comorbidity, liver disease severity, liver disease etiology, and healthcare utilization characteristics for patients with unrecognized *vs.* recognized cirrhosis in clinical practice using chi-square analysis for categorical variables and t-tests for continuous variables. We subsequently conducted multivariable logistic regression analyses to identify the subgroups of patients with cirrhosis that were at highest risk for having unrecognized cirrhosis in clinical practice. The dependent variable was unrecognized (*vs*. recognized) cirrhosis and independent variables were as described above. In addition to considering clinical grounds when choosing variables to enter in this model, model building followed a forward selection approach in which we included variables that were associated with the outcomes at a p-value <0.20. We conducted sensitivity analyses using MELD score *in lieu* of Child class as a marker of liver disease severity and by limiting the sample to patients with evidence of annual visits to the VA in the 3 years prior to HCC diagnosis.

We used separate multivariable logistic regression models to examine the association between unrecognized cirrhosis in clinical practice and stage of HCC at time of diagnosis while adjusting for pre-specified variables (see above). The dependent variable was

advanced stage HCC (*vs*. early stage HCC). We used a similar model building approach as described above. Because the effect of cirrhosis recognition on the stage of HCC was likely mediated by receipt of HCC surveillance, we explicated this relationship by evaluating the association between cirrhosis recognition and receipt of HCC surveillance and then adding HCC surveillance variable in the multivariable model that examined the relationship between cirrhosis recognition and stage of HCC.

All analyses were performed using SAS version 9.1.

Results

Of the 1500 patients with HCC, 1201 (80.1%) had cirrhosis that was confirmed based on our review of the clinical, biochemical, radiological or histological criteria recorded in the EMR. These patients comprised the final study group. Almost all of the patients (99.8%) were male, the majority was younger than 65 years (69.8 %), 59.2% were white, and 21.1% lived in rural areas. Approximately 42% had a Deyo comorbidity index of 3 or higher within a year prior to HCC diagnosis, 18.8% had PTSD and 3% had HIV. HCV was the most common cause of underlying liver disease (72.2%), followed by alcohol (17.2%), NAFLD (5.8%), and HBV (2.4%). Most patients had either Child class A (37.7%) or B (46.1%) cirrhosis, and most (66.8%) had annual visits to the VA in each of the 3 years prior to HCC diagnosis. Patients on average had 23.1 outpatient visits and 0.76 hospitalizations in the year prior to HCC diagnosis. Almost all patients were seen by their primary care providers (PCP) (n=1113, 92.6%) and 60.2% were also seen by a gastroenterologist in the one year prior to HCC diagnosis.

Extent and determinants of failure to recognize cirrhosis in clinical practice

Of the 1201 patients with confirmed evidence of cirrhosis, 296 (24.6%) did not have any mention of cirrhosis by healthcare providers prior to HCC diagnosis. There were significant differences in the demographic, clinical and healthcare utilization characteristics between patients with unrecognized compared to those with recognized cirrhosis (Table 1). Patients with unrecognized cirrhosis were older (>65 years 49.3% *vs*. 23.9%), more likely to be African American (32.1% *vs*. 22.8%), or live in the Central U.S. (21.9% *vs*. 14.8%). They were less likely to have significant medical comorbidity (Deyo score ≥3, 27.7% *vs*. 47.1%) yet more likely to have HIV compared to patients with recognized cirrhosis (4.73% *vs*. 2.54%, respectively). Significantly greater proportions of patients with unrecognized cirrhosis had Child class A and alcohol or NAFLD related liver disease as the underlying etiology than those with recognized cirrhosis.

Patients with unrecognized cirrhosis had fewer visits in the year prior to their HCC diagnosis compared to those with recognized cirrhosis (32.4% vs. 45.7% with > 20 outpatient encounters, $p<0.001$) (Table 1). There were also significant differences in the types of providers seen. A total of 24% of patients with unrecognized cirrhosis saw a gastroenterologist within one year prior to HCC diagnosis compared to 72% of patients who had recognized cirrhosis ($p<0.001$). There was also a smaller but significant difference in proportion of patients who visited their PCP (89.5% vs. 93.7% in the unrecognized vs. recognized group, respectively; $p= 0.016$). There were no differences between the groups in

the proportion of patients who saw an oncologist or infections disease physician in the year prior to HCC diagnosis. Most of these findings persisted in the multivariable logistic regression models predicting unrecognized cirrhosis (Table 2). Older patients, African Americans, patients with alcohol or NAFLD related liver disease, HIV, and those with less comorbidity had significantly higher odds of having unrecognized cirrhosis than the comparison groups.

Rate of cirrhosis recognition also varied by geography; the odds of being undetected were slightly higher for patients seen in the Central U.S compared to those seen in the West. There was no significant difference in cirrhosis recognition between urban versus rural patients. HCC patients who were diagnosed in the latter years of the study period had significantly lower odds of being unrecognized than those diagnosed in the earlier years. Patients who saw gastroenterologists were least likely to remain unrecognized as having cirrhosis (OR 0.15, 95% CI 0.10–0.21).

Using MELD score *in lieu* of Child class and limiting to patients with continuous care prior to HCC diagnosis did not significantly change the magnitude and direction of the results (data not shown).

We also looked for the particular evidence of cirrhosis that was missed in the group of patients with unrecognized cirrhosis. The most commonly overlooked evidence was imaging findings (56.1%), followed by laboratory evidence (22.3%), and clinical evidence (small ascites or varices, 15.5%). We analyzed which patients carried ICD-9 diagnosis codes for etiologies of liver disease prior to the time of HCC diagnosis, though cirrhosis was not recognized. We found that 69.9% of patients carried at least one diagnosis code indicating known chronic liver disease (HCV and HBV infection, alcoholic liver disease, unspecified non-alcoholic liver disease, hepatitis, hemochromatosis, autoimmune hepatitis and sclerosing cholangitis) prior to the time of HCC diagnosis.

Association between cirrhosis recognition in clinical practice and stage of HCC

Of the 1201 patients with cirrhosis, a total of 177 (14.7%) were diagnosed at an early stage HCC (defined as BCLC stage 0 or A), while the remaining patients had advanced HCC at the time of diagnosis. The failure to recognize cirrhosis was strongly associated with advanced stage at the time of HCC diagnosis. Specifically, 96.6% of patients with unrecognized cirrhosis had advanced stage HCC compared to 81.5% of patients with recognized cirrhosis. The association between lack of cirrhosis recognition and HCC stage did not change after adjusting for demographic, clinical and healthcare utilization variables. Overall, HCC patients with unrecognized cirrhosis had ~6.47 times higher odds of being diagnosed at an advanced stage compared to patients who had their cirrhosis recognized. When accounting for the above variables using our multivariable regression model, the results remained significant with an adjusted odds ratio of 3.37 (95% CI=1.69–6.70) (Table 3). Using MELD score *in lieu* of Child class did not affect the magnitude or direction of the effect of cirrhosis recognition or other variables.

A total of 61.4% of patients with recognized cirrhosis received at-least one HCC surveillance test performed within the 3 years prior to HCC diagnosis compared to 18.5% of

patients with unrecognized cirrhosis who had evaluation that would have served as HCC surveillance. We repeated the multivariable regression model that predicted advanced HCC after including HCC surveillance (Appendix Table). The association between lack of cirrhosis recognition and advanced stage HCC was attenuated but remained statistically significant in this analysis (OR=2.95, 95% CI=1.47–5.93).

Discussion

In this large national cohort of patients, we found that cirrhosis was not identified prior to HCC diagnosis in about one fourth of patients with HCC. Recognition of cirrhosis in clinical practice was the strongest predictor of the stage of HCC at the time of diagnosis. Specifically, we found that the odds of having advanced HCC were about 6.5 fold higher in patients with previously unrecognized cirrhosis than in patients with diagnosed cirrhosis. The association between unrecognized cirrhosis and HCC stage persisted after adjusting for several confounders.

This gap in cirrhosis recognition in clinical practice is not unique to the current study. In an audit of patients diagnosed with HCC at a large safety-net hospital, Singal *et al*. found that 39% of patients had unrecognized cirrhosis.[13] However, this study was limited to a single center and did not have the ability to examine a range of patient factors. Our multicenter study largely confirmed these data (although we found a somewhat lower rate of unrecognized cirrhosis) and extended the reach of the findings to show a direct relationship between unrecognized cirrhosis and advanced stage HCC – an endpoint strongly associated with survival in HCC. These data suggest timely recognition of cirrhosis is a key process to improve patient outcomes.

We also identified patient subgroups at particular risk for poor recognition of cirrhosis; some of these subgroups might indeed be the ones most likely to benefit from early detection of HCC. For example, we found that patients with less medical comorbidity or those with alcohol or NAFLD related cirrhosis were more likely to be missed compared to those with HCV related cirrhosis. However, NAFLD has now surpassed HCV as the most common chronic liver disease in the U.S. and has been linked to HCC.[14] Although carcinogenesis can occur in NAFLD in the absence of cirrhosis, [15, 16] data show that the majority of patients with NAFLD related HCC have underlying cirrhosis.[17] With the advent of highly effective treatment for HCV, other established (such as alcohol) and emerging (such as NAFLD) risk factors will become important precursors for HCC. Given these epidemiological trends, our data identifying these risk groups are concerning.

We also found evidence suggesting racial and geographic disparities in cirrhosis recognition prior to HCC diagnosis. African American patients with cirrhosis had ~1.93 fold higher odds of being unrecognized than Whites—although this may in part be explained by the lower degree of liver disease severity in African Americans than Whites (Child class C in 10.9% *vs*. 14.1%, respectively). We investigated and found no evidence to suggest that the geographic variation stemmed from low rates of cirrhosis recognition at one or few facilities. Future studies should examine the underlying explanations of the geographic variation in cirrhosis recognition that we observed in this study.

Our data have important implications for the present and future of HCC surveillance. Our results show that surveillance practice for the early detection of HCC might be missing an important subgroup of patients at risk for HCC. It is plausible that current HCC surveillance efforts might be targeting patients who are too late in the underlying disease process and thus unlikely to benefit from potentially curative treatments for HCC (if and when it develops). Currently surgical resection can only be offered to patients with solitary tumors <5cm who have Child's A liver disease, without evidence of portal hypertension and preserved synthetic function. For patients with more advanced disease, transplant is a potential curative option, but again strict criteria must be met. Adherence to the Milan criteria has resulted in worldwide improved survival outcomes up to 75% at 5 years, and thus far any proposed relaxation of the criteria has failed to produce similar results [18]. Patients who are not candidates for resection or transplant may be able to undergo potentially curative alcohol or radiofrequency ablation (RFA). However, the best reported 5 year survival in ablation is 50% [4]. This data again underscore the importance of early diagnosis of HCC. The under-recognition of cirrhosis might, at least in part, explain the disconnect between expected and observed mortality benefit associated with HCC screening practices in the U.S.[19,20] Success of HCC screening programs is strongly hinged on recognition of cirrhosis as all practice guidelines recommend to offer HCC screening once patients develop cirrhosis.[21] One positive association identified in our study was the increased recognition of cirrhosis in patients seen by a gastroenterologist compared to primary care physicians or other specialists. However, only 60.1% of all patients were seen by gastroenterologists in the year prior to HCC. Without systematic efforts to expand the pool of patients eligible for HCC screening, particularly targeting those groups identified as more likely to have unidentified cirrhosis in this study, the impact of HCC surveillance may continue to be limited.

Our results identified that in most cases of unrecognized cirrhosis, laboratory or imaging evidence were present that could have prompted providers to identify cirrhosis. Traditional methods of diagnosing cirrhosis have relied on recognition of cirrhosis-related complications (such as ascites, gastroesophageal varices, or hepatic encephalopathy) that occur too late in the course of disease. Alternatively liver biopsy, as the gold standard for assessing the presence of cirrhosis in patients without these complications, has inherent risks which are often unacceptable to patients and providers. Consequently, non-invasive laboratory test-based indices have been developed and validated to identify cirrhosis from different etiologies. [22, 23] Many of these markers rely on laboratory tests that are relatively inexpensive, well standardized, and widely employed in routine practice. Overall, laboratory based markers have a high negative predictive value, so can exclude advanced fibrosis, but are less useful in detecting early stage disease [24, 25]. The imaging modality, transient elastography (TE) (eg Fibroscan), has been widely used to assess stage of fibrosis, especially in HCV patients. More recently MRI elastography (MRE) has been introduced, which can assess the entire liver, and performs better than TE and laboratory based fibrosis makers. Imaging based modalities although noninvasive, are expensive, and have limited applicability as screening tools, especially when applied to large groups of patients at risk for cirrhosis. Thus, the best option may be sequential testing that combines use of laboratory based markers as the screening tools followed by use of imaging modalities to confirm

presence of cirrhosis [26]. With the wide implementation of electronic medical records, such non-invasive evaluations can be readily automated and when applied to patients at risk for chronic liver disease (such as those known to have HCV, HBV, or NAFLD) may serve as a potential tool to identify cirrhosis on the larger system-wide scale and thus improve the downstream care processes (including HCC surveillance). Development and use of these markers in clinical practice might indeed explain the improvement in the rate of cirrhosis recognition over time seen in our study.

Our study is limited by the observational retrospective nature of its design. However, large prospective studies of patients with diagnosed and undiagnosed cirrhosis with sufficient long term follow up to document HCC related outcomes are not likely to be conducted due to ethical and feasibility issues. Regardless, the clear temporal sequence between the exposure (failure to identify cirrhosis) and endpoint (stage of HCC) combined with the consistency of our results in primary and sensitivity analyses, as well as the biologically plausible mechanism of effect (through use of HCC surveillance) collectively suggest that sub-optimal cirrhosis recognition is causally linked with a higher risk of advanced stage HCC. We did not have information regarding patient compliance (or non-compliance) with recommended evaluation and follow up. However, previous evaluations of this topic by Singal, et al. have shown that patient non-compliance accounted for less than 10% cases in which HCC surveillance was not performed [27]. In our study we adjusted for the frequency of healthcare use as a surrogate for compliance in our models. Our cut-offs to define being in regular care and HCC surveillance were somewhat arbitrary. However, we selected these to ensure that comorbidity and treatment data would be as complete as possible and patients were receiving a majority of their care at the VA. Our time frame to define HCC surveillance is consistent with previous studies evaluating surveillance in the VA population.[10] Despite this broad definition, only 51% patients in our study cohort received any HCC surveillance prior to HCC diagnosis. Unfortunately, we did not have information on the extent to which HCC surveillance met the established guidelines. However, in our previous studies, we have found low rates of adherence to HCC screening guidelines.[28] Lastly, we did not examine the association between cirrhosis recognition and HCC related mortality in this study although we do not expect the results to be different given the strong association between stage and patient outcomes in HCC.[1,29]

Our results were derived from diagnosed HCC patients who sought care in the VA healthcare system and generalizing these data to individuals outside the VA may not be possible. The VA is an equal access system with a long history of a system-wide screening program for HCV and a culture of continuous quality monitoring and improvement. On the other hand, most of the HCV infected individuals in the U.S. are still undiagnosed and many lack a regular source of care.[30] It is therefore probable that cirrhosis recognition is actually lower outside of the VA setting—the few available data from other healthcare systems support this contention.[31]

In summary, we found that cirrhosis was not recognized in clinical practice prior to HCC diagnosis in about one fourth of patients with cirrhosis and HCC. Patients with unidentified cirrhosis were more likely to have advanced stage HCC at the time of diagnosis. Evaluation by a gastroenterologist was associated with lower odds that cirrhosis would be

unrecognized; however 39.9% of patients were not seen by a gastroenterologist in the year prior to HCC diagnosis. Cirrhosis patients who were older, African American, had non-viral risk factors, and comorbid HIV were at highest risk of being unrecognized. Our results emphasize that optimizing outcomes in HCC depends on timely identification of cirrhosis, particularly in these at-risk groups, in order to implement adequate screening and diagnose cancer at an early enough stage that patients can benefit from potentially curative treatments.

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Abbreviations used in this paper

HCC	hepatocellular carcinoma
VA	Veterans Affairs
EMR	electronic medical record
ICD-9	International Classification of Diseases, 9th Revision
MELD	model for end-stage liver disease
BCLC stage	Barcelona clinic liver cancer stage
APRI	AST to platelet ratio index
DM	diabetes mellitus
HIV	human immunodeficiency virus
HCV	hepatitis C virus
HBV	hepatitis B virus
NAFLD	non-alcoholic fatty liver disease
COPD	chronic obstructive pulmonary disease
PTSD	post-traumatic stress disorder
AIDS	acquired immune deficiency syndrome
RNA	ribonucleic acid
GI	gastrointestinal
PCP	primary care provider
ID	infectious disease

OR	odds ratio
CI	confidence interval
CPR	clinical prediction rule
FIB-4	fibrosis 4
TE	transient elastography
MRE	magnetic resonance elastography
RFA	radiofrequency ablation

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Table 1

Characteristics of cirrhosis patients diagnosed with hepatocellular cancer in the VA healthcare system from 2005–2011.

	Recognized cirrhosis (n =905)	Unrecognized cirrhosis (n=296)	
Variables, %			**P-value**
Age in years			<0.0001
<65	76.13	50.68	
>65	23.87	49.32	
Male gender	99.89	99.66	0.432
Race			0.002
White	60.99	53.72	
African American	22.76	32.09	
Hispanic	14.25	10.47	
Other/Unknown	1.99	3.72	
Geographic Region			0.002
Central	14.81	21.96	
East	23.65	20.61	
South	36.57	40.2	
West	24.97	17.23	
Rural status	20.44	22.97	0.354
Deyo index			<0.0001
0	16.8	35.47	
1–2	36.13	36.82	
3+	47.07	27.7	
HIV	2.54	4.73	0.059
Post-traumatic stress disorder	20.99	12.16	0.001
Psychosis	8.29	7.09	0.511
Child class			0.0002
A	36.57	41.22	
B	44.64	50.68	
C	14.7	5.41	
Missing	4.09	2.7	
MELD			0.012
<10	32.6	42.23	
10–19	53.37	42.91	
20+	5.86	5.74	
Missing	8.18	9.12	
Etiology of cirrhosis			<0.0001
HCV	77.46	56.08	
Alcohol	15.47	22.64	
NAFLD	3.2	13.85	
HBV	2.21	3.04	

	Recognized cirrhosis (n =905)	Unrecognized cirrhosis (n=296)	
Variables, %			**P-value**
Other	1.66	4.39	
Annual visit [1]	65.75	70.27	0.151
Number of outpatient visits [2]			<0.0001
0–10	23.9	39.9	
10–20	30.4	27.7	
>20	45.7	32.4	
Hospitalization [2]	43.5	49.0	0.102
Type of provider seen [2]			
PCP	93.7	89.5	0.017
GI	71.9	24.0	<0.0001
Oncology	11.7	12.2	0.835
ID	8.4	6.4	0.274
Year HCC diagnosis			<0.0001
2005–2007	30.72	47.97	
2008–2011	69.28	52.03	

[1] At least one annual visit to the VA in each of the 3 years prior to HCC diagnosis.

[2] Variables evaluated during the 1 year prior to HCC diagnosis.

Abbreviations: HIV, human immunodeficiency virus; MELD, model for end-stage liver disease; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; PCP, primary care provider; GI, gastroenterology; ID infectious disease

Table 2

Factors associated with failure to recognize cirrhosis in clinical practice prior to HCC diagnosis. Results of multivariable logistic regression models presented as adjusted odds ratio and 95% confidence intervals.

Characteristics	Odds Ratio	95% Confidence Interval
Age in years		
<65	1.0	--
>65	2.32	1.56 – 3.45
Race		
White	1.0	--
African American	1.93	1.29 – 2.89
Hispanic	0.63	0.37 – 1.09
Other	2.72	0.98 – 7.54
Region		
West	1.0	--
Central	1.76	1.04 – 2.96
East	1.02	0.61 – 1.73
South	1.15	0.73 – 1.81
Rural status		
No	1.0	--
Yes	1.37	0.92 – 2.05
Child class		
C	1.0	--
B	3.77	1.97 – 7.18
A	4.54	2.34 – 8.80
Etiology of cirrhosis		
HCV	1.0	--
Alcohol	1.69	1.06 – 2.67
NAFLD	4.77	2.43 – 9.34
HBV	1.17	0.40 – 3.48
Other	4.63	1.78 – 12.07
Deyo score		
3+	1.0	
1–2	1.49	0.99 – 2.23
0	2.42	1.53 – 3.83
HIV		
No	1.0	--
Yes	3.02	1.11 – 8.16
Posttraumatic stress disorder		
No	1.0	--
Yes	0.78	0.49 – 1.26
Number of outpatient visits [1]		
0–10	1.0	--

Characteristics	Odds Ratio	95% Confidence Interval
11–20	1.05	0.67 – 1.64
>20	1.01	0.63 – 1.63
Type of provider seen [1]		
PCP	0.93	0.51 – 1.70
GI	0.15	0.10 – 0.21
Oncology	0.97	0.58 – 1.63
ID	0.71	0.35 – 1.46
Year of HCC diagnosis		
2005–2007	1.0	--
2008–2012	0.66	0.47 – 0.92

[1] Variables evaluated during the 1 year prior to HCC diagnosis.

Abbreviations: HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; PCP, primary care provider; GI, gastroenterology; ID infectious disease

Table 3

Factors associated with advanced stage at the time of HCC diagnosis. Results of multivariable logistic regression models presented as adjusted odds ratio and 95% confidence intervals

Characteristics	Odds Ratio	95% Confidence Interval
Cirrhosis		
Recognized	1.0	--
Unrecognized	3.37	1.69 – 6.70
Etiology of cirrhosis		
HCV	1.0	--
Alcohol	2.40	1.35 – 4.26
NAFLD	1.85	0.70 – 4.91
HBV	2.84	0.65 – 12.45
Other	2.30	0.51 – 10.29
HIV		
No	1.0	--
Yes	2.46	0.50 – 11.95
Number of outpatient visits [1]		
0–10	1.0	--
11–20	0.76	0.45 – 1.29
>20	0.82	0.49 – 1.39
Type of provider seen [1]		
PCP	0.58	0.22 – 1.53
GI	0.36	0.22 – 0.58
Oncology	1.20	0.69 – 2.09
ID	1.11	0.55 – 2.25
Rural status		
No	1.0	--
Yes	1.32	0.85 – 2.05
Year HCC diagnosis		
2005–2007	1.0	--
2008–2012	0.67	0.45 – 0.98

[1] Variables evaluated during the 1 year prior to HCC diagnosis.

Abbreviations: HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; PCP, primary care provider; GI, gastroenterology; ID infectious disease

Appendix Table

Sensitivity Analysis

Factors associated with advanced stage cancer at the time of hepatocellular cancer (HCC) diagnosis including receipt of HCC surveillance

Characteristics	Odds Ratio	95% Confidence Interval
Cirrhosis		
Recognized	1.0	--
Unrecognized	2.95	1.47 – 5.93
HCC surveillance		
No	1.0	--
Yes	0.62	0.42 – 0.91
Etiology of cirrhosis		
HCV	1.0	--
Alcohol	2.18	1.22 – 3.89
NAFLD	1.54	0.57 – 4.14
HBV	2.67	0.61 – 11.74
Other	1.84	0.40 – 8.36
HIV		
No	1.0	--
Yes	2.33	0.48 – 11.37
Number of outpatient visits [1]		
0–10	1.0	--
11–20	0.77	0.46 – 1.30
>20	0.83	0.49 – 1.40
Type of provider seen [1]		
PCP	0.59	0.22 – 1.56
GI	0.40	0.24 – 0.65
Oncology	1.24	0.71 – 2.18
ID	1.17	0.58 – 2.36
Year HCC diagnosis		
2005–2007	1.0	--
2008–2012	0.70	0.47 – 1.03

[1] Variables evaluated during the 1 year prior to HCC diagnosis.

Abbreviations: HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; PCP, primary care provider; GI, gastroenterology; ID infectious disease