Frequency and Outcomes of Abnormal Imaging in Patients With Cirrhosis Enrolled in a Hepatocellular Carcinoma Surveillance Program

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There are limited data on the downstream effects of hepatocellular carcinoma (HCC) surveillance, including the frequency of false-positive results. We aimed to quantify the incidence of indeterminate nodules (INs) and the follow-up testing needed to resolve these findings among patients enrolled in a structured HCC surveillance program. We retrospectively analyzed adult patients with cirrhosis enrolled in a structured HCC surveillance program in a large tertiary care center. Outcomes included surveillance benefits, defined as early HCC detection, and harm, defined as INs prompting additional diagnostic evaluation. Among 999 patients followed for a median of 2.2 years, HCC surveillance imaging was consistently completed every 6, 9, and 12 months in 46%, 51%, and 68% of patients, respectively. Of 256 (25.6%) patients with abnormal imaging, 69 (27.0%) were diagnosed with HCC and 187 (73.0%) with INs. Most HCC (n = 54, 78.3%) were found within Milan criteria. Among those with an IN, 78.1% returned to ultrasound surveillance after a median of 2 (interquartile range [IQR], 1-3) negative computed tomography (CT)/magnetic resonance imaging (MRI) scans, and 21.9% continued CT/MRI imaging (median, 1; IQR, 1-2). Eleven patients underwent diagnostic liver biopsy. Hypoalbuminemia, thrombocytopenia, and larger nodule size were independently associated with HCC diagnosis. In conclusion, 1 in 4 patients enrolled in an HCC surveillance program had abnormal surveillance imaging, but three-fourths of the lesions were INs, resulting in downstream harm. Improved risk-stratification tools are needed to identify nodules that are benign to reduce follow-up diagnostic evaluation.

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide.[1,2] In the United States, the annual incidence and mortality of HCC are increasing, largely because of a peak in hepatitis C virus (HCV)–related complications and the emergence of nonalcoholic fatty liver disease (NAFLD) as a rapidly growing cause of chronic liver disease.[3] This high HCC-related mortality is due to a significant proportion of patients presenting with late-stage tumors, which only have palliative treatment options.[4,5] Accordingly, several professional society guidelines recommend HCC surveillance using ultrasound (US) ± alpha-fetoprotein (AFP) in patients with cirrhosis to improve early tumor detection and curative treatment receipt.[6-8]

The value of a cancer-screening program must weigh any benefits against potential harm of the screening tests. The benefit of HCC surveillance is dependent on adherence to the surveillance program and its effectiveness.[9] Prior studies suggest that adherence to HCC surveillance in real-world clinical

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IN, indeterminate nodule; INR, international normalized ratio; IQR, interquartile range; LI-RADS, Liver Imaging Reporting and Data System; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; US, ultrasound.

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practice is low at 15%-20% for 1-time screening and 5%-10% for biannual surveillance, highlighting a need for interventions to increase surveillance utilization.[10-13] Similarly, studies have suggested variability in sensitivity to detect HCC at an early stage with high rates of surveillance failure even in high-volume academic centers.[14] Conversely, finding nodules during US surveillance that do not have the characteristic features of HCC on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) nor typical features of benign lesions, ie, indeterminate nodules (INs), can result in physical harm (eg, radiation exposure, contrast nephropathy, and biopsy complications), financial harm (eg, copays or lost wages), and/or psychological harm (eg, worries about cancer), particularly if the nature of these nodules cannot be resolved after initial cross-sectional imaging.[15-17] Excess diagnostic testing is well established as a physical harm in patients undergoing colon, breast, and prostate cancer screening. However, this has been underexplored in patients undergoing HCC surveillance.[18-20] A randomized trial comparing 3- and 6-month surveillance using US found that 70% of focal lesions that were detected on US were not HCC. However, the downstream harm to those patients with INs was not characterized.[21] Similarly, a recent study from a safety-net hospital suggested that up to 27.5% of patients may experience physical harm related to false-positive findings. However, data in other practice settings are limited.[22]

The aims of this study were to determine the following:

1. The incidence of abnormal imaging results in a large cohort of cirrhosis patients enrolled in a structured HCC surveillance program at a high-volume academic liver center.
2. The frequency in which the nodule(s) detected on US were indeterminate and the number of cross-sectional imaging scans needed to resolve the benign versus malignant nature of these nodules.
3. The factors predictive of HCC among patients with abnormal imaging.

Patients and Methods

PATIENT POPULATION AND HCC SURVEILLANCE PROGRAM

All adult patients (age ≥18 years) with cirrhosis followed in outpatient hepatology clinics at the University of Michigan between January 2010 and December 2015 were prospectively enrolled in a chronic disease management program. Enrollment in this program was previously shown to increase 1-time screening after implementation.[23] The diagnosis of cirrhosis for entry into the chronic disease management program was based clinically on histology, transient elastography, or imaging showing a nodular liver with or without associated signs of portal hypertension. The chronic disease management program included serial tracking of all laboratory and imaging results, including HCC surveillance, with a capacity to generate reminders at designated intervals. Clinic nurses contacted patients to complete any necessary surveillance testing at recommended intervals. According to the American Association for the Study of Liver Diseases (AASLD) guideline recommendations during the study period, abdominal imaging was required for completion of HCC surveillance, whereas AFP testing was optional and its measurement was provider dependent, although 94% of patients in the cohort had at least 1 AFP measurement.[8] The program captured outside imaging if results were scanned into the electronic medical record and patients were logged into the reminder system. Abdominal imaging done for nonsurveillance purposes was also logged, given this satisfies

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the need for surveillance testing. For this study, included patients were required to have had at least 1 surveillance US without IN or HCC at baseline. We excluded patients with a history of liver transplantation and those who exclusively received MRI/CT–based surveillance. Given that our aim was to quantify incidents of HCC and INs, we also excluded patients who had any history of HCC or any INs at baseline. Abnormal imaging was defined as any imaging with a nodule that required follow-up multiphasic cross-sectional imaging. An IN was defined as any solid lesion >1 cm in diameter that could not be categorized as definitely benign (ie, cyst or hemangioma) and did not meet diagnostic criteria for HCC on cross-sectional imaging. The recently adopted Liver Imaging Reporting and Data System (LI-RADS) imaging criteria were not available during the study period. However, most of the INs in this study would likely be classified as LI-RADS3 or LI-RADS4 lesions.

DATA COLLECTION AND DEFINITION OF OUTCOMES

Baseline demographics (age, sex, race, and ethnicity), etiology of cirrhosis, body mass index (BMI), and laboratory values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, albumin, total bilirubin, AFP, creatinine, international normalized ratio [INR], and platelet count) at the time of enrollment were abstracted from electronic medical records. Complete records were available for all reviewed patients. Dates and results of all liver imaging (US and multiphasic contrast-enhanced CT or MRI) during the study period were recorded. For each imaging study, the presence of any suspicious lesions was documented, and the number and size of the lesions were recorded when available. For CT/MRI, diagnostic characteristics for HCC as defined by AASLD guidelines were noted, including arterial enhancement and delayed washout.[24] A small proportion of patients (n = 6) were treated for HCC based on liver tumor board review and recommendations, despite not meeting all imaging criteria for HCC. Data were collected from enrollment in the surveillance program until the end of the study period (December 2015), last outpatient clinic visit, or development of HCC.

To evaluate the effectiveness of the surveillance program, we measured the proportion of patients who underwent imaging at 6-, 9-, and 12-month intervals.

STATISTICAL ANALYSIS

The primary outcome of interest was surveillance harm, defined as the proportion of patients with INs who underwent subsequent follow-up testing (eg, 4-phase CT, contrast-enhanced MRI, or biopsy).[16,25] Diagnostic testing for INs was defined as physical harm consistent with the definition adopted in the screening literature for other malignancies (eg, breast cancer[26] and prostate cancer[27]). We further stratified patients by mild harm (1-3 multiphasic cross-sectional imaging tests without a diagnosis of HCC) and severe harm (≥4 multiphasic cross-sectional imaging tests without a diagnosis of HCC or performance of a liver biopsy).

We also measured the surveillance benefits, defined as early-stage HCC detection. Early-stage HCC was defined as being within Milan criteria, the most common criteria for liver transplantation in the United States. Bivariate analyses were performed to assess frequencies of INs and HCC and patient-level factors associated with each outcome. Chi-square tests and Fisher's exact tests were used for categorical variables, and *t* tests were used for continuous variables. Variables with distributions that deviated from normality were reported by median and interquartile range (IQR) rather than by conventional mean ± standard deviation and were compared using the Kruskal-Wallis test. A multivariate analysis was conducted to identify factors associated with HCC and INs in the entire cohort. We used prespecified cutoffs for continuous variables, including platelet count, albumin, and nodule size. An additional multivariate analysis was conducted for correlates of HCC in patients with abnormal imaging. We included variables from the univariate analysis (ie, baseline characteristics) with *P* values <0.1 in our multivariate analyses, for which *P* values <0.05 were considered statistically significant. All analyses were performed in STATA, version 14 (StataCorp, College Station, TX). This study was approved a priori by the University of Michigan institutional review board.

Results

BASELINE CHARACTERISTICS

A total of 999 patients met inclusion criteria (Table 1). The cohort consisted primarily of middle-aged (median

TABLE 1. Baseline Characteristics of Patients With or Without Abnormal Imaging

	Overall (n = 999)	Normal Imaging (No IN or HCC; n = 743)	Abnormal Imaging (IN or HCC; n = 256)	*P* Value
Baseline clinical characteristics				
Age, years	58.0 (52.2-64.7)	57.9 (51.8-64.5)	58.7 (52.7-65.2)	0.32
Sex, male	535 (53.6)	383 (51.5)	152 (59.4)	0.03
Race				0.32
White	849 (85.0)	630 (84.7)	219 (85.5)	
Black	42 (4.2)	30 (4.0)	12 (4.7)	
Asian	29 (2.9)	19 (2.6)	10 (3.9)	
Hispanic/Latino (n = 974)	24 (2.5)	16 (2.2)	8 (3.1)	0.41
Etiology of cirrhosis				0.01
HCV	356 (35.6)	248 (33.4)	108 (42.2)	
Alcoholic cirrhosis	175 (17.5)	143 (19.2)	32 (12.5)	
NASH/NAFLD*	165 (16.5)	124 (16.7)	41 (16.0)	
PBC/PSC	73 (7.3)	60 (8.1)	13 (5.1)	
HBV	47 (4.7)	30 (4.0)	17 (6.6)	
Other	182 (18.2)	137 (18.4)	45 (17.6)	
BMI, kg/m^2	29 (25-35)	29 (25-35)	29 (25-35)	0.84
Follow-up duration, years	2.2 (0.9-3.9)	1.9 (0.8-3.7)	2.9 (1.4-4.0)	<0.001
Baseline laboratory values				
MELD	7 (6-10)	6 (6-10)	7 (7-10)	0.24
Platelet count, K/μL	104 (74-147)	108.5 (75-156)	97 (67-125)	<0.001
AFP, ng/mL	3.4 (2.1-6.4)	3.1 (2-5.8)	4.4 (2.7-8.4)	<0.001
AST, IU/L	49 (34-75)	47 (33-73)	58 (34-75)	<0.001
ALT, IU/L	37 (25-61)	35 (24-57)	45 (28-79)	0.001
Total bilirubin, mg/dL	1.0 (0.7-1.7)	1.0 (0.7-1.7)	1.1 (0.8-1.8)	0.03
Alkaline phosphatase, IU/L	116 (87-163)	115 (87-167)	117 (89-160)	1.0
Albumin, g/dL	3.8 (3.3-4.2)	3.8 (3.3-4.2)	3.7 (3.2-4.2)	0.36
INR	1.1 (1.0-1.3)	1.1 (1-1.2)	1.2 (1.1-1.3)	0.01
Imaging, median (IQR; range)				
Total US	4 (2-7; 1-19)	4 (2-6; 1-19)	5 (3-7; 1-14)	<0.001
Total CT/MRI	1 (0-2; 0-12)	0 (0-1; 0-12)	2 (1-3; 0-12)	<0.001
Outcomes				
HCC or empiric treatment for HCC	69 (6.9)	0	69 (27.0)	<0.001
Hepatic decompensation	532 (53.3)	394 (53.0)	138 (53.9)	0.87
Variceal bleeding	112 (11.2)	87 (11.7)	25 (9.8)	
Ascites	319 (31.9)	227 (30.6)	92 (35.9)	
Hepatic encephalopathy	99 (9.9)	79 (10.6)	20 (7.8)	

NOTE: Data are given as median (IQR) and n (%) unless otherwise noted.
*Includes 22 patients with cryptogenic cirrhosis.

age, 58 years; IQR, 52.2-64.7 years), white (90.7%) individuals. Sex was evenly distributed (53.6% males), and the majority were overweight or obese (median baseline BMI, 29 kg/m^2; IQR, 25-35 kg/m^2). The etiology of cirrhosis was diverse (HCV, 35.6%; alcohol, 17.5%; NAFLD, 16.5%), and the median baseline Model for End-Stage Liver Disease (MELD) score was 7 (IQR, 6-10).

RECEIPT OF HCC SURVEILLANCE

During the study period (median follow-up, 2.2 years; IQR, 0.9-3.9 years), HCC surveillance imaging was consistently completed every 6, 9, and 12 months in 46%, 51%, and 68% of patients, respectively. Of the patients who did not complete surveillance every 6 months, nearly half (44%) only missed 1 surveillance

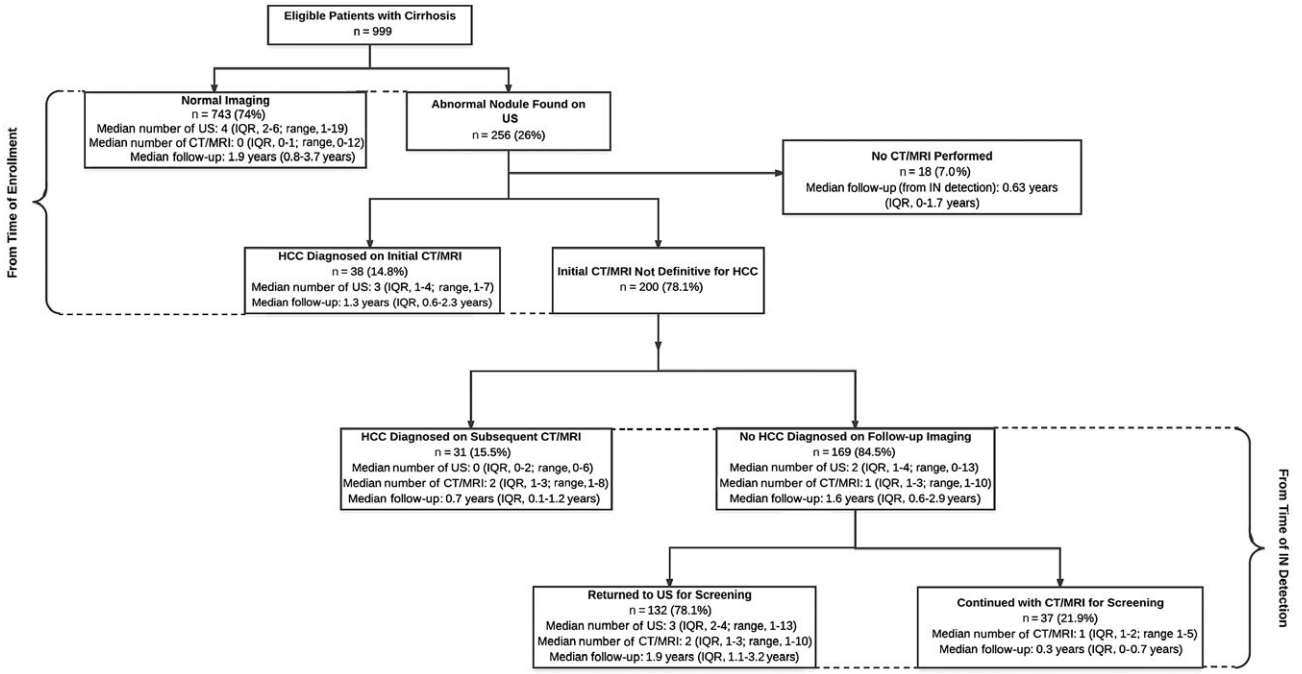

FIG. 1. A summary of imaging findings and subsequent evaluation.

imaging appointment during follow-up, one-third (30%) missed 2, and 26% missed 3 or more imaging appointments.

In the overall cohort, the median number of US conducted was 4 (IQR, 2-7; range, 1-19), and the median number of CT/MRIs was 1 (IQR, 0-2; range, 0-12). Among all imaging studies performed for HCC surveillance or for clinical reasons other than follow-up of INs, 89.6% were conducted as an outpatient, 7.4% as an inpatient, and 2.9% in the emergency department. The indication for most imaging studies was primarily for HCC surveillance in 81.5%, diagnostic purposes in 18%, and unspecified in 0.5%.

PROPORTION OF PATIENTS WITH INS AND HCC

A summary of surveillance results and follow-up evaluation is depicted in Fig. 1. A suspicious nodule was detected in 256 (26%) patients during US surveillance over a median period of 2.2 years (IQR, 0.9-3.9 years). The median number of nodules seen on US was 1 (IQR, 1-2), and the median size was 1.7 cm (IQR, 1.2-2.5 cm). HCC was diagnosed in 69 (6.9%) patients, of whom 78% were within Milan criteria or less. Specifically, 14 had T1 tumor burden; 36 had T2; and 3 with advanced HCC (metastatic disease). Of these patients, 38 were diagnosed on initial CT/MRI after abnormal US, and 31 patients required multiple CT/MRIs (median, 2, IQR, 1-3; range, 1-12) after an abnormal US to make a diagnosis of HCC during a median follow-up time of 0.7 years (IQR, 0.1-1.2 years) after IN was detected (Fig. 2A,B). A total of 10 patients had missed lesions with HCC diagnosed on initial CT/MRI in the setting of a normal US. There was a median time of 18 days (IQR, 3-163 days) from the normal US to HCC diagnosis in these 10 patients. In these patients, cross-sectional imaging was prompted by elevated AFP in 1 patient, poor US quality in 2 patients, reasons other than surveillance in 2 patients, and unclear reasons in 5 patients. These patients had similar clinical and demographic characteristics when compared with the remainder of the cohort with similar age (60.0 versus 58.0 years), BMI (29 versus 29 kg/m^2), and similar liver function (all nonsignificant).

Among the 187 patients with an IN on US but without HCC during the study period, 18 (9.6%) had not undergone CT/MRI for diagnostic evaluation after a median follow-up of 0.63 years (IQR, 0-1.7). Of the 169 patients who had further evaluation with CT/MRI, 132 (78.1%) were determined to

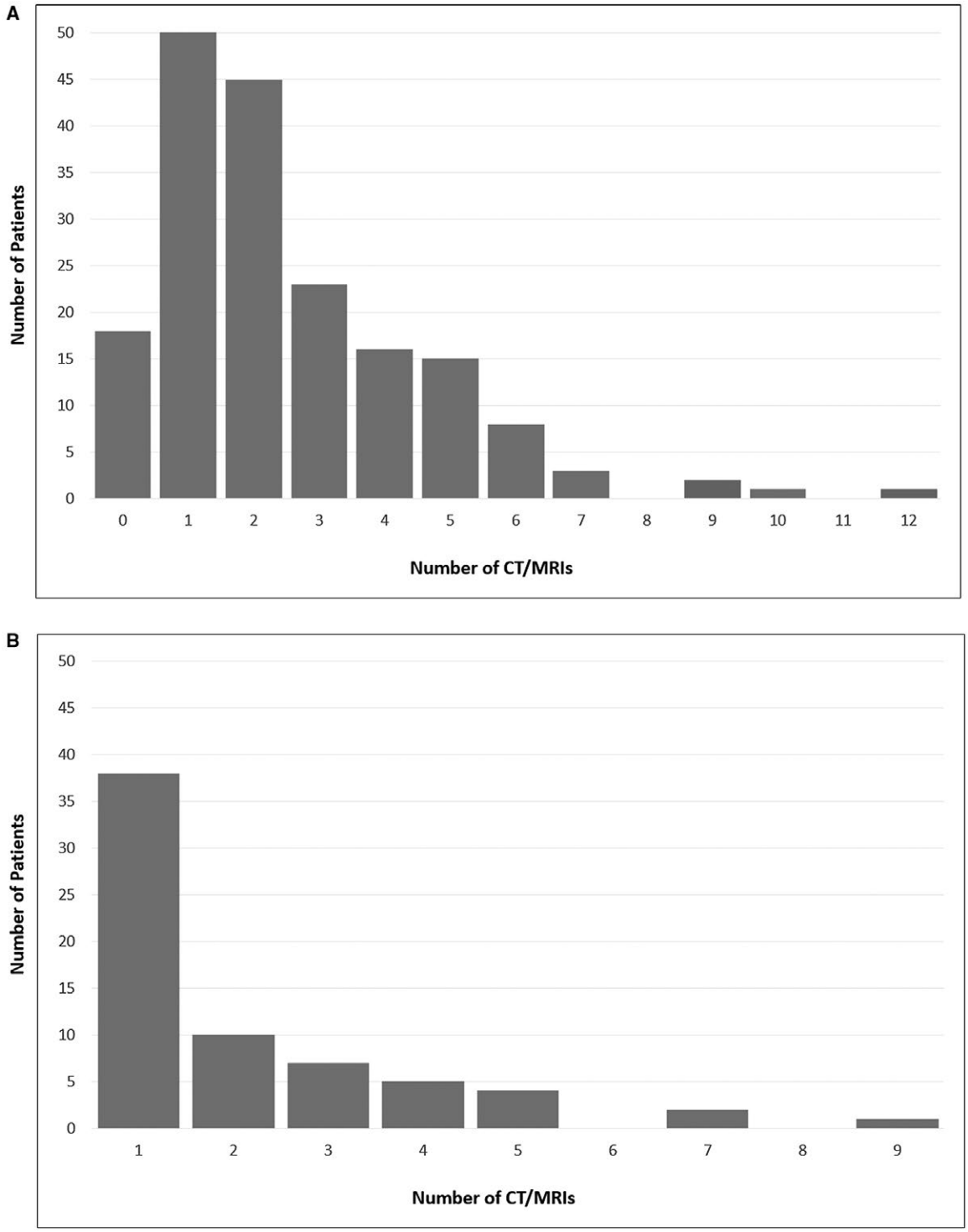

FIG. 2. CT/MRI utilization among patients with abnormal imaging (A) without and (B) with diagnosis of HCC.

be false-positive results and returned to surveillance US after a median of 2 CT/MRIs (IQR, 1-3; range, 1-10) during a median follow-up of 1.9 years (IQR, 1.1-3.2 years) after the IN was detected. Among these patients, 49.5% had 1 CT/MRI, 18.0% had 2, 13.6% had 3, and 18.9% had ≥4 CT/MRIs after IN

detection. The remaining 37 (21.9%) patients were still categorized as indeterminate and undergoing CT/MRI imaging (median, 1; IQR, 1-2; range, 1-5) at the end of the study period after a median follow-up of 0.3 years (IQR, 0.1-0.7 years) following IN detection on US. Among these patients, 62.2% had 1 CT/MRI, 18.9% had 2, 10.8% had 3, and 8.1% had ≥4 CT/MRI after IN detection.

Percutaneous liver biopsy was performed in 11 patients with IN, of whom 6 were diagnosed with HCC and 5 were benign. One patient, who had a benign lesion on biopsy, experienced a biopsy-related complication of abdominal pain, which required an emergency department visit without the need for a transfusion or hospitalization. Overall, 17.1% of patients with INs on US experienced severe harm with either ≥4 cross-sectional imaging tests or a liver biopsy with no diagnosis of HCC.

CHARACTERISTICS ASSOCIATED WITH IN AND HCC

Characteristics of patients with normal imaging compared with those with abnormal imaging (IN or HCC) are displayed in Table 1. Patients with abnormal imaging were more commonly male, more likely to have HCV cirrhosis, had lower platelet count, and higher AFP, AST, ALT, total bilirubin, and INR. However, there was no difference in the presence of any hepatic decompensation, including ascites, hepatic

TABLE 2. Characteristics of Patients With Abnormal Imaging Without or With Subsequent HCC Diagnosis

Baseline Clinical Characteristics	Abnormal Imaging Without HCC (n = 187)	Abnormal Imaging With HCC (n = 69)	*P* Value
Age, years	58.2 (52.2-65.9)	61.1 (55.4-64.6)	0.12
Sex, male	105 (56.1)	47 (68.1)	0.08
Race			0.74
White	162 (90.5)	57 (87.7)	
Black	8 (4.4)	4 (6.1)	
Asian	7 (3.9)	3 (4.6)	
Hispanic/Latino	6 (3.2)	2 (2.9)	0.90
Etiology of liver disease			0.76
HCV	75 (40.1)	33 (47.8)	
Alcoholic cirrhosis	23 (12.3)	9 (13.0)	
NASH/NAFLD	33 (17.6)	8 (11.6)	
PBC/PSC	10 (5.3)	3 (4.3)	
HBV	14 (7.5)	4 (5.8)	
Other	32 (17.1)	13 (18.8)	
BMI, kg/m^2	29 (25-35)	30 (25-32)	0.74
Follow-up duration, years	3.3 (1.9-4.2)	1.8 (1.1-2.9)	<0.001
Baseline laboratory values			
MELD	7 (6-10)	8 (6-11)	0.02
Platelet count, K/μL	103 (75-132)	77 (52-106)	<0.001
AFP, ng/mL	4 (2.3-7.3)	6.0 (3.5-12.1)	0.003
AST, IU/L	55 (39-88)	61 (45-103)	0.07
ALT, IU/L	45 (27.5-80)	46 (32-77)	0.88
Total bilirubin, mg/dL	1 (0.7-1.65)	1.3 (0.9-2)	0.02
Alkaline phosphatase, IU/L	111.5 (88-151.5)	140 (95-174)	0.01
Albumin, g/dL	3.8 (3.4-4.25)	3.3 (3.1-3.9)	<0.001
INR	1.1 (1.1-1.2)	1.2 (1.1-1.3)	<0.001
Imaging/diagnostics, median (IQR; range)			
Total US	5 (4-8; 1-14)	3 (2-5; 1-10)	<0.001
Total CT/MRI	2 (1-3; 0-12)	1 (1-3; 1-9)	0.19
Number of nodules on US	1 (1-2)	1 (1-3)	0.36
Size of largest nodule on US, cm	1.4 (1.1-2.0)	2.3 (1.8-2.8)	<0.001

NOTE: Data are given as median (IQR) and n (%) unless otherwise noted.

TABLE 3. Multivariate Analysis of Predictors of HCC Diagnosis

	OR	95% CI	*P* Value
Within overall cohort			
Age, year	1.01	0.97-1.04	0.51
Sex, male	1.56	0.82-2.99	0.17
Baseline MELD	0.98	0.91-1.06	0.74
Baseline low platelets (<100 K/μL)	2.75	1.37-5.53	0.004
Baseline AFP	1.00	0.99-1.02	0.37
Baseline albumin (<3.4 g/dL)	2.77	1.43-5.35	0.002
Patients with abnormal imaging			
Age, year	1.00	0.96-1.04	0.83
Sex, male	1.02	0.43-2.41	0.06
Baseline MELD	0.92	0.81-1.05	0.23
Baseline thrombocytopenia (<100 K/μL)	3.67	1.46-9.23	0.006
Baseline AFP	1.02	0.99-1.05	0.15
Baseline hypoalbuminemia (<3.4 g/dL)	4.07	1.56-10.63	0.004
Maximum nodule size (≥2.0 cm)	8.63	3.55-20.92	<0.001

encephalopathy, or variceal bleeding. Compared with those with IN, patients with HCC had significantly higher MELD scores, alkaline phosphatase, and AFP; lower platelet count and albumin; larger nodule size; and were more likely to have hepatic decompensation (Table 2).

In a multivariate analysis of the overall cohort, no factors were independently associated with IN. However, baseline platelet count approached significance (Supporting Table 1). Thrombocytopenia (odds ratio [OR], 2.75; 95% confidence interval [CI], 1.37-5.53) and hypoalbuminemia (OR, 2.77; 95% CI, 1.43-5.35) were independently associated with HCC diagnosis (Table 3). In a subgroup multivariate analysis among those patients with abnormal imaging, thrombocytopenia (OR, 3.67; 95% CI, 1.46-9.23) and hypoalbuminemia (OR, 4.07; 95% CI, 1.56-10.63) continued to be associated with HCC diagnosis. Larger nodule size on US (≥2 cm) was also associated with diagnosis of HCC (OR, 8.63; 95% CI, 3.55-20.92; Table 3).

Discussion

Our study is one of the first to quantify the benefits and harm of a structured US-based HCC surveillance program in a large cohort of cirrhosis patients followed in an academic tertiary care center. The structured surveillance program was able to achieve consistent surveillance completion in nearly half of all patients over a 2.2-year median follow-up and detected over 75% of HCC patients at an early stage. However, these benefits were accompanied by physical harm, including nearly 20% of patients having an IN requiring additional diagnostic evaluation.

Our study builds upon our prior results demonstrating the benefits of a structured surveillance program.[23] Our program using electronic medical record reminders achieved consistent HCC surveillance every 6 months in 46% of enrolled cirrhosis patients over a median of 2.2 years. Furthermore, most patients without consistent surveillance only missed 1 or 2 surveillance examinations. These results are notable because most prior studies in the United States reported consistent surveillance rates of only 5%-10% when assessed over extended study periods.[11] For example, a study investigating the effectiveness of a mailed outreach program doubled 1-time HCC screening (47%) compared with usual care, but longitudinal surveillance was only 5% over an 18-month period.[28] A review of hepatology provider orders noted that nearly all (>95%) patients enrolled in the program had orders for HCC surveillance at 6-month intervals. Therefore, this structured program addresses provider oversight as a source of surveillance failure, which has been reported as the most common failure in the HCC screening process.[29] A potential contributing factor to suboptimal surveillance completion rates is that outside imaging reports may not have been accurately captured. To circumvent this issue, we now try to schedule imaging the same day as patients' clinic visits. Further research to optimize this multistep process and achieve higher rates of HCC surveillance completion is needed to improve early HCC detection. Increased HCC surveillance completion was associated with early HCC detection because over 75% of HCC patients in our surveillance program were detected at an early stage. Ten patients were diagnosed in the setting of a normal US. However, the reasons for subsequent cross-sectional imaging varied, and we could not find any age or BMI differences to explain the false-negative US results.

The benefits of an HCC surveillance program must be weighed against observed HCC surveillance harm.[30] Over 15% of patients in our cohort had an IN that was determined to be benign or remains indeterminate and continues to undergo diagnostic evaluation. Our results are similar to a study from a safety-net health system, in which 22.7% of cirrhosis patients

underwent "unnecessary" imaging due to indeterminate or false-positive surveillance tests.[25] Most surveillance-related "harm" in the study by Atiq et al.[25] was limited to a single CT or MRI diagnostic examination, although some patients experienced moderate to severe harm, defined as repeated cross-sectional imaging or invasive evaluation with biopsy or angiogram. In our study, over half of patients with INs also underwent repeated cross-sectional imaging or invasive evaluation with biopsy. We were able to quantify the number of cross-sectional examinations in all patients with INs, adding further granularity to the data on harm related to HCC surveillance. However, notably, there were 31 patients who required multiple cross-sectional imaging tests and 6 patients who required biopsy to diagnose HCC, highlighting the fact that it can be difficult to define what is "excessive" or "unnecessary" diagnostic evaluation at the time.

There is a clear need for better risk-stratification tools to differentiate HCC from benign lesions to reduce unnecessary imaging. Unfortunately, we did not identify any demographic or clinical factors correlated with IN. Thus, we failed to identify subgroups who may benefit from alternate modalities of surveillance. However, other studies suggest US false-positive and indeterminate results may be more likely in obese patients, those with alcohol- or NASH-related cirrhosis, and those with more advanced liver dysfunction.[25,31,32] Controversy still surrounds the use of AFP in surveillance,[33] and although AFP levels were statistically significantly higher in those patients with HCC when compared with those patients with IN in our cohort, this difference was not clinically significant. Accurate risk stratification for HCC development remains a challenging task with most studies only able to achieve modest predictive accuracy.[34,35] A study of 494 hepatitis B virus (HBV)–infected patients with INs noted that age, nodule size, arterial enhancement, albumin, and AFP levels were independently predictive of HCC progression. The associated predictive model had an area under the curve of 0.88 and 0.92 for 3- and 5-year risk prediction.[36] This model still requires external validation because it is unclear how the model would perform in heterogeneous patient populations with different etiologies of liver disease. In our study, we found thrombocytopenia and hypoalbuminemia were independently predictive of HCC development among the overall cohort. In addition to these factors, nodule size was also associated with HCC in the subset of patients with abnormal imaging.

There are several notable limitations with our study. The study was performed at a single center, so it is unknown if our results can be generalized to other centers. However, our data are consistent with what has been reported in the literature.[25] As demonstrated in Table 1, our patient population is relatively homogeneous in terms of race and ethnicity, which has been associated with variable incidence rates of HCC. However, we did have diverse etiologies of chronic liver disease, which represents a strength over much of the existing literature that focuses on HCC risk within disease-specific groups (ie, HBV or HCV). Additionally, our center does not routinely perform contrast-enhanced US which could be included as part of a diagnostic algorithm for IN where available and could be effective in reducing the number of CT/MRIs performed. Second, some patients with abnormal imaging were still in the process of evaluation, and we may have overestimated the IN rate because some of these patients could have been diagnosed with HCC after the data collection had been completed. We mitigated this by excluding patients who had not yet received multiphasic cross-sectional imaging after IN detection in calculating the IN rate. Patients with nodules on cross-sectional imaging are at increased risk of eventually developing HCC. However, continued surveillance of nodules until they meet diagnostic criteria for HCC can be prolonged, incurring costs and causing patient anxiety. The optimal timing of when to return to US surveillance remains an open question. Third, given the study design, we did not capture the psychological harm of surveillance for HCC and the psychological burden of having an IN. Fourth, the study spanned the introduction of LI-RADS radiographic criteria for HCC and nodule diagnosis on cross-sectional imaging, so the LI-RADS classification for the INs was not readily available for this analysis. Although the LI-RADS classification is an important tool in classifying nodules seen on dynamic imaging, it lacks thorough validation. Importantly, there is little guidance on the management and follow-up for indeterminate (LI-RADS3 and LI-RADS4) lesions, especially ones that are identified on serial imaging.[37] Thus, we believe these data in INs are relevant even without LI-RADS classification of the INs. Lastly, as a retrospective analysis, there are inherent limitations in determining indications for imaging studies and the possibility of provider bias influencing which patients received cross-sectional imaging, whether liver tumor board review was conducted, and their follow-up.

In conclusion, a structured HCC surveillance program effectively promoted HCC surveillance completion and detected over 75% of HCC at an early stage. However, over 15% of patients in the surveillance program had suspicious nodules prompting CT/MRI evaluation that did not lead to HCC diagnosis. This information is critically important when counseling patients on the risks and benefits upon entering an HCC surveillance program. Improved risk-stratification tools are needed to better predict HCC risk as well as better differentiate benign from malignant nodules to maximize the value of HCC surveillance in patients with cirrhosis.

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