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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Retrospective Cohort Study

Adherence to guideline-directed hepatocellular carcinoma screening: A single-center US experience

William W King, Raymond Richhart, Tyler Culpepper, Maneola Mota, Debdeep Banerjee, Media Ismael, Joydeep Chakraborty, Michael Ladna, Walid Khan, Nicole Ruiz, Jake Wilson, Ellery Altshuler, Virginia Clark, Roniel Cabrera

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Abstract**BACKGROUND**

The American Association for the Study of Liver Disease recommends screening patients with cirrhosis for hepatocellular carcinoma (HCC) using imaging with or without alpha-fetoprotein every six months. Unfortunately, screening rates remain inadequate.

AIM

To assess root causes of screening failure in a subspecialty hepatology clinic.

METHODS

The authors identified patients with cirrhosis seen in a subspecialty hepatology clinic and determined whether they underwent appropriate screening, defined as two cross-sectional images between five and seven months apart. The authors characterized the primary driver of screening failure. Finally, other hepatologists were surveyed to determine provider perceptions of screening failure causes.

RESULTS

1034 patients were identified with an average age of 61 years and a mean MELD of 8.1 ± 3.8 . Hepatitis C virus was the most common cirrhosis etiology. 489 (47%) underwent appropriate screening. No demographic or clinical differences were detected between those who underwent appropriate screening and those who did

not. The most common etiologies of screening failure, in descending order, were: radiology unable to schedule timely imaging, provider did not order imaging, patient canceled follow up appointment, appointments scheduled too far apart, lost to follow up, no-show to radiology appointment, and provider canceled appointment. Hepatologists surveyed believed the most common cause of screening failure was no-show to radiology.

CONCLUSION

Rates of screening were poor even in a subspecialty hepatology clinic. Screening failure was mostly due to systemic factors such as radiology availability and time between hepatology appointments rather than individual error.

Key Words: Hepatocellular carcinoma; Cirrhosis; Health maintenance; Quality improvement; Screening; Hepatology

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Core Tip: This study reinforces existing knowledge that screening rates for Hepatocellular carcinoma are woefully inadequate, even in a subspecialty hepatology clinic. Unlike previous studies, ours identifies specific failure points, showing that screening failures are driven more by systemic issues than by physician or patient error.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the sixth leading cause of cancer and the third leading cause of cancer death worldwide[1]. The most common and important risk factor for HCC is cirrhosis [2]. Estimates of the annual incidence of HCC among patients with cirrhosis range from 1 to 8%[3,4]. The lifetime incidence in patients with cirrhosis may be as high as 32% and is increasing in the United States[3,5-7].

The American Association for the Study of Liver Disease (AASLD) recommends screening for HCC with abdominal ultrasound, computed tomography, or magnetic resonance imaging, with or without alpha-fetoprotein, every six months[8-10]. Adherence to AASLD guidelines correlates with improved survival, as demonstrated in a French cohort study of 1671 patients at 35 centers. Patients who adhered to semi-annual screening protocols had increased lead-time adjusted survival[11]. A theoretical model by Sarasin *et al*[12] predicted an increase in life expectancy among patients with Child-Turcot-Pugh A cirrhosis with HCC screening if the expected incidence of HCC is at least 1.5% per year. Unfortunately, predictive algorithms to stratify patients by HCC risk have failed external clinical validation[13]. Much research now focuses on blood-based biomarkers for simple and accessible point of care screening, but these strategies are not yet ready for clinical practice[14].

Unfortunately, adherence to screening guidelines remains poor[15-17]. A 2011 retrospective cohort study of 13002 patients with cirrhosis across 128 Veterans Affairs medical centers showed that only 12% had received appropriate screening[18]. A 2012 systematic review by Singal *et al*[15] found the surveillance rate among all patients with cirrhosis to be only 18.4%, although it was higher (51.7% *vs* 16.9%) among patients followed in subspecialty gastroenterology clinics. A subsequent retrospective cohort study performed by the same group found that only 2% of patients received consistent surveillance; 33% had inconsistent surveillance, and 65% had no surveillance over 3 years[19]. A qualitative study within the Veterans Health Administration similarly found that following with a subspecialist, whether gastroenterology or infectious disease, significantly increased HCC screening rates[20]. Poor knowledge and vigilance of screening protocols among primary care providers has been well-documented[21,22]. Other factors included distance to a screening site and lead time between screening order and screening date[20]. Socioeconomic factors also contribute to screening utilization [23,24]. Primary care-based clinical reminders have also been shown to improve screening rates[25]. Singal *et al*[26] showed that a mailed outreach program increases HCC screening rates.

Many previous studies examined patients diagnosed with HCC to identify factors related to lack of screening [18,27,28]. Our group sought to collect data on all patients at a subspecialty hepatology clinic to retrospectively identify risk factors for screening failure among all patients with cirrhosis, not just those with HCC. We hypothesized that there may be additional factors not previously identified that contribute to screening failure.

The purpose of this study was two-fold: (1) To determine the rate of appropriate HCC screening in patients with cirrhosis in a subspecialty practice in which screening guidelines are well known; and (2) to identify barriers at an institutional and provider level as well as the patient-related factors. The data will be used to improve adherence to guideline-directed screening protocols *via* future quality improvement initiatives.

MATERIALS AND METHODS

The electronic medical record was queried for billing codes from the 9th revision of the International Classification of Diseases (ICD-9) or ICD-10 to identify patients. Demographic, disease etiology, and laboratory data were collected. Inclusion criteria included patients with cirrhosis who were seen at least twice in the subspecialty hepatology clinic between August 2015 and August 2017. The charts were then manually reviewed to confirm that each patient was appropriate for screening based on AASLD guidelines. Exclusion criteria included prior liver transplantation and prior HCC.

Next, the authors determined whether the patients had been appropriately screened, defined as having undergone two imaging studies (abdominal ultrasonography, contrasted computed tomography, or magnetic resonance imaging) within 150 to 210 days of each other during the study period. Because the AASLD guidelines suggested an optional role for α -fetoprotein, the authors did not look for α -fetoprotein measurement. The charts of these patients were reviewed to determine the primary cause of screening failure. The reason for failure was categorized based on the screening barriers listed below. For patients with multifactorial screening failure, the first failed step in the screening process was counted as the primary reason for failure. For example, if a patient canceled a hepatology appointment and subsequently did not receive orders for imaging, the reason for screening failure was attributed to the clinic cancellation. The hierarchy of steps, in order, were: loss to follow-up, patient clinic appointment cancellation, physician clinic appointment cancellation, appointments more than 7 mo apart, failure to order imaging, failure to schedule imaging, or failure to present to radiology.

Finally, eight hepatologists in the clinic who were not involved in this study were anonymously surveyed on their perceptions of risk factors for screening failure.

Statistical significance was defined using $\alpha < 0.05$. Continuous variables were abnormally distributed according to Shapiro-Wilk testing. Therefore, comparisons were made using the Mann-Whitney *U* test. Categorical variables were compared using chi-square or Fisher's exact testing. The study protocol was reviewed and approved by our institutional IRB prior to any data collection and study procedures.

RESULTS

The authors identified 1276 patients who met the inclusion criteria. 242 were removed due to meeting exclusion criteria. Therefore, a total of 1034 patients were analyzed. The study population had an average age of 61 years, was 55% male, and was 83% White. Hepatitis C virus was the most common cirrhosis etiology, accounting for 51% of participants. The mean MELD score was 8.1 (SD 3.8). No statistically significant differences were detected in baseline characteristics between patients who underwent appropriate screening and those who did not (Table 1).

489 (47%) patients underwent appropriate screening during the study period. 410 (40%) underwent two imaging studies that were outside the time range criterion. Six percent of patients had only one imaging study, and 7% had none (Figure 1). The most common cause of HCC screening failure was delays in scheduling of imaging studies (Figure 2). Patient-centered factors, including appointment cancellations, no-shows, and loss to follow up accounted for 36% of screening failures. System failures were classified as delays in radiology and hepatology scheduling as well as physician cancellation of follow-up appointments. These accounted for 40% of screening failures. Lack of physician order accounted for 21%.

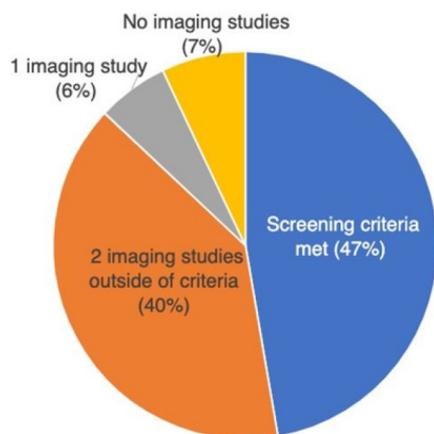
All of those who received their care exclusively within the public university medical system were referred to the radiology department within the institution. 35 patients who followed with community-based gastroenterologists and came to the institution for periodic subspecialty consultation elected to undergo HCC screening with local private radiologists.

All patients diagnosed with HCC experienced delays in screening. One was diagnosed at stage IVb and passed away due to HCC. One was lost to follow-up following discovery of a 3.1 cm nodule on an magnetic resonance imaging protocol for liver masses. Two underwent Y-90 transarterial radioembolization and partial surgical hepatectomy. One of these patients ultimately elected to transition to hospice and passed away due to worsening hepatic decompensation; the other is still alive.

Table 1 Baseline patient characteristics, *n* (%)

Baseline patient characteristic	Met screening criteria (<i>n</i> = 463)	Failed screening criteria (<i>n</i> = 545)	<i>P</i> value
Age	61.4 ± 10.7	60.2 ± 10.5	0.06
Gender			0.37
Male	261 (56)	292 (54)	
Female	202 (44)	253 (46)	
Race			0.85
White	385 (83)	452 (83)	
African-American	48 (10)	55 (10)	
Other	20 (4)	30 (6)	
Unknown	5 (1)	5 (1)	
County of residence			0.61
Same county as institution	115 (25)	143 (26)	
Different county than institution	348 (75)	402 (74)	
Etiology			0.64
NASH	144 (31)	157 (29)	
AIH	21 (5)	25 (5)	
PBC	34 (7)	37 (7)	
PSC	19 (4)	13 (2)	
HCV	229 (49)	283 (52)	
HBV	29 (6)	37 (7)	
AALD	44 (10)	63 (12)	
MELD	8.2 ± 3.8	8.1 ± 3.8	0.65

NASH: Non-alcoholic steatohepatitis; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AALD: Alcohol-associated liver disease.



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Figure 1 Rates of appropriate hepatocellular carcinoma screening in a sub-specialty hepatology clinic. HCC: Hepatocellular carcinoma.

In a poll, other hepatologists at the same institution believed the most common causes of screening failure, in order, to be: failure to present to radiology, patient clinic appointment cancellation, loss to follow up, and failure to order imaging. Human error and deferral to primary care provider (PCP) were the most cited reasons for failure to order screening.

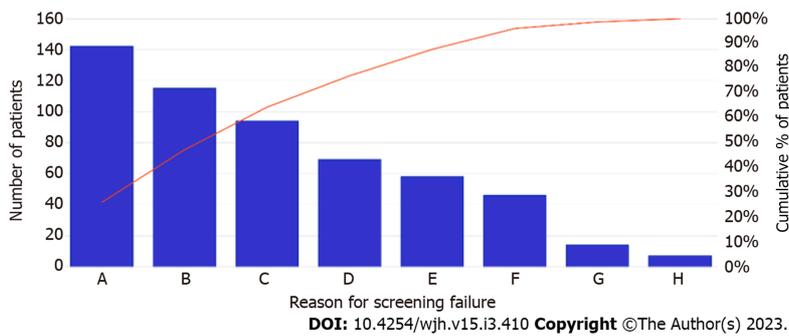


Figure 2 Pareto chart of root cause of screening failures. A: Radiology unable to schedule timely imaging; B: Physician/Provider did not order imaging; C: Patient canceled hepatology follow up appointment; D: Hepatology follow up appointments scheduled too far apart; E: Patient lost to follow up; F: Patient no show to radiology appointment; G-H: Physician/Provider canceled hepatology follow up appointment.

DISCUSSION

Despite guidelines that were well-known to the providers in the subspecialty hepatology practice, fewer than half of the patients in our cohort underwent appropriate screening during the study period. The findings are consistent with previous studies and add to the growing evidence that HCC screening rates are grossly insufficient.

However, our study illuminates some nuances in the reasons for screening failure. Most screening failures in our cohort were institutional rather than patient-driven or secondary to physician oversight. We were able to investigate what happened after the order was placed for screening to evaluate the system factors that contribute. Radiology scheduling failure, whether from inability to contact the patient or unavailability of timely imaging appointments, was the primary reason for lack of adherence. The multiple failure points both highlight the complexity of care coordination for cirrhosis patients in a subspecialty clinic and offer targets for intervention and improvement.

Failure to order screening was the second leading risk factor among subspecialty hepatologists in this cohort. Other investigators have demonstrated poor knowledge of screening protocols among primary care providers (PCPs), which can explain lack of adherence to guidelines. However, we do not believe a knowledge deficit was a major contributing factor in a subspecialty clinic. Many hepatologists cited deferral to PCP as a reason for not ordering screening, even though knowledge among PCPs remains poor. The authors also speculate that a busy, often overbooked clinic with competing priorities makes even the most diligent hepatologists forget to order screening. It is difficult to order abdominal imaging while counseling a patient that they will die from cirrhosis unless they overcome innumerable psychosocial barriers to abstain from alcohol for long enough to become a liver transplant candidate.

This study has several important limitations. Firstly, the window for “appropriate screening” in this study was 5 to 7 mo, which is narrower than the 4–8-mo window suggested by the AASLD, resulting in a positive bias toward ineffective screening. Secondly, patients who had two imaging studies 6 mo apart were considered “appropriately screened,” regardless of whether a third imaging study was completed on time. This data simplification may have resulted in an overestimation of the screening rate. Thirdly, the attribution of screening failure to a single step fails to capture the multifactorial nature of screening failure. For example, a patient for whom radiology did not schedule an imaging study because the physician did not order one because they missed their clinic appointment would be classified as “no show,” even though the provider could have ordered the screening even without the patient there. Finally, the logistical complexity of the screening process leaves room for interpretation variation between multiple investigators, even with rigorous standardization.

The debate over the proper length of screening is likely to continue, with many authors pointing out that longer intervals have not been studied. Some experts, including the National Cancer Institute, have opined that hepatologists ought to abandon screening protocols entirely due to a lack of survival benefit [29–32]. Furthermore, the World Gastroenterology Organization suggests that screening in low and middle-resource settings is appropriate only if the patient would have access to HCC treatments [33]. However, we contend that every effort be made to adhere to current practice guidelines when resources are available. Our findings demonstrate the need for future measures to address system and provider level improvements. We have implemented an automatic reminder in the electronic medical record for physicians and other healthcare professionals and targeted reminders *via* main or electronic media for patients. In addition, our findings highlight the need for serum biomarkers for HCC screening, which would eliminate the logistical delays with radiology [34].

CONCLUSION

In conclusion, the rate of appropriate HCC screening, though above the estimated national average, was inadequate in this patient population. The reasons for failure were multifactorial, but the primary driver was delays in radiology scheduling. These data immediately identify targets for future quality improvement initiatives.

ARTICLE HIGHLIGHTS

Research background

The American Association for the Study of Liver Disease recommends that patients with cirrhosis be screened for hepatocellular carcinoma (HCC) every six months. Other researchers have shown that adherence to these guidelines is poor, but little is known about the causes of this failure.

Research motivation

The authors noted that many patients in their own subspecialty hepatology practice did not undergo appropriate screening. They studied factors contributing to screening failure in order to develop a possible quality improvement initiative.

Research objectives

The authors sought to identify root causes of HCC screening failure among patients with cirrhosis in their subspecialty hepatology clinic.

Research methods

The authors identified patients with cirrhosis in their subspecialty hepatology clinic and determined whether they underwent appropriate screening. The authors reviewed the medical records of patients who did not undergo appropriate screening to identify the root causes of screening failure.

Research results

Among 1034 patients, only 489 underwent appropriate screening. The most common causes of screening failure, in descending order, were: radiology unable to schedule timely imaging, provider did not order imaging, patient canceled follow up appointment, appointments scheduled too far apart, lost to follow up, no-show to radiology appointment, and provider canceled appointment.

Research conclusions

Even in a subspecialty hepatology clinic in which providers strive to follow guideline-based HCC screening, rates of screening were still poor. Most of the barriers to appropriate screening were due to systemic factors such as radiology availability, rather than to individual error.

Research perspectives

HCC screening is vital to the comprehensive care of patients with cirrhosis, yet systemic and institutional barriers often prevent patients from receiving adequate care. The root causes identified in this article immediately suggest areas for possible quality improvement and provide guidance to those at other institutions.

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FOOTNOTES

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