Review Article

Integrative review: patient and provider factors related to hepatocellular carcinoma surveillance in patients with liver cirrhosis

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and the fifth most prevalent cancer worldwide, with cirrhosis being the main risk factor for the development of HCC. The American Association for Study of Liver Disease (AASLD) recommends surveillance of patients with cirrhosis for HCC using ultrasound (US) of the abdomen every 6 months as a cost-effective intervention to reduce mortality and improve survival. However, it is widely known that surveillance is not consistently completed, and the rates of HCC surveillance are very low. The purpose of this integrative review was to evaluate and summarize the available data related to provider and patient factors that are associated with surveillance and missed surveillance for HCC in patients with cirrhosis of the liver, and to recommend interventions to improve these rates of surveillance and subsequently improving survival in patients with cirrhosis.

Keywords: Carcinoma; hepatocellular; liver cirrhosis; review

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Introduction

Cirrhosis of liver is an end stage of chronic liver disease whose prevalence is on the rise due mostly to viral hepatitis (particularly Hepatitis B & C), non-alcoholic fatty liver disease (NAFLD) and alcoholism (1). Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and the fifth most prevalent cancer worldwide, with rising prevalence seen in the United States (2). The major risk factor for the development of HCC is cirrhosis of the liver, with cirrhosis found in more than 80–90% of liver cancer patients (2). The American Association for Study of Liver Disease (AASLD) has recommended surveillance of patients with cirrhosis for HCC using ultrasound (US) of abdomen every 6-month interval as a cost-effective intervention to reduce mortality and improve survival. However, it is widely known that patients with cirrhosis are not being routinely screened, and surveillance rates range around 30–40% (3-5), though rates as low as 1.7–17.4% are seen when surveillance is defined as any imaging of abdomen within 6 months (6-10)

HCC, which is the most prevalent of liver cancers, has an increased incidence in all races in the birth cohort of persons born between 1945–1965 due to higher rates of hepatitis C in this group. The strongest predictor of HCC incidence is hepatitis C virus (HCV) infection, followed by hepatitis B virus (HBV) infection and alcohol related liver disease (11). HCC incidence has increased 2.5-fold, and HCC mortality has tripled since 2001 (12). The 5-year cumulative risk for development of HCC is 5–30% in patients with cirrhosis (2). The key to survival of HCC is early detection. HCC

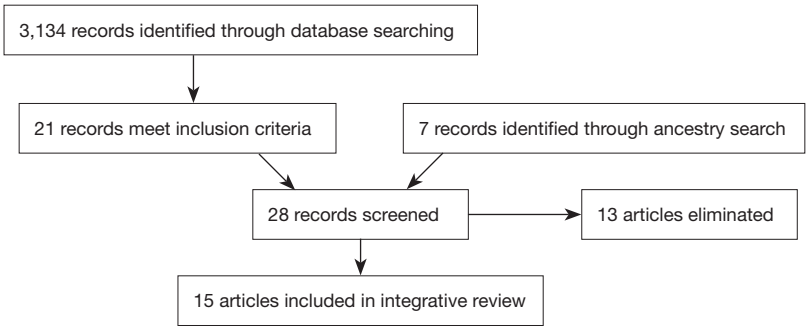

Figure 1 PRISMA diagram for integrative review.

detected early can achieve 5-year survival rates near 50–70% with resection and transplantation *vs*. 3-year survival of 8% if there are later signs of disease (13).

In a large robust randomized controlled study HCC surveillance (n=18,816) showed clear benefits, the patients in the surveillance arm had a 37% decrease in mortality despite less than optimal adherence to surveillance recommendations (14). Surveillance for HCC is the recommendation by all the major international liver associations including the AASLD in the United States (15), the Asian Pacific Association for the Study of Liver Disease (16), and the European Association for the Study of Liver (17). Most importantly, surveillance of HCC in high risk patients, including patients with cirrhosis, remains the standard of care.

Ultimately, the evaluation of the factors that are associated with surveillance of HCC in patients with cirrhosis is essential to clinical practice. The purpose of this integrative review is to evaluate the current state of the literature and to determine the factors associated with the surveillance of HCC in patients with cirrhosis, in order to understand the underlying variables and design interventions that influence surveillance behavior.

Methods

Literature search

An exhaustive review of the literature was completed to evaluate the factors related to lower rate of HCC surveillance in cirrhotic patients, to better understand the causes. Four electronic databases were searched, CINHAL, SCOPUS, Cochrane and PubMed using search terms cirrhosis, adherence, compliance, HCC, screening and surveillance restricted to articles from the United States since 2005, when the AASLD guidelines were formalized (15). Studies looking at patients from outside of the United States were excluded, as the unique characteristics of the United States insurance markets are not applicable to other countries and insurance and co-pay issues may influence surveillance behaviors. Only studies that considered causes of HCC surveillance in adults with cirrhosis in the outpatient setting were included. Excluded articles were those studies that discussed prevalence without examining cause, guidelines, inpatient studies, studies with patients less than 18 years old, or studies that looked at adherence to variceal surveillance guidelines, alfa-fetoprotein (AFP) surveillance alone, medication or diet adherence. Studies that evaluated patients after 2005 were included, as that is when the first AASLD guidelines recommending surveillance were initially issued (15), and the presence of guidelines should positively influence surveillance behavior. Of note, AASLD surveillance guidelines were established in 2005, recommending HCC surveillance with abdominal US every 6–12 months and subsequently changed in 2011, to recommend abdominal US for HCC surveillance every 6-month interval.

Search results

The initial database search identified 3,134 articles (*Figure 1*). After adjusting for duplicates, eliminating those studies that did not meet inclusion criteria, 21 articles remained. Hand searching references found an additional 7 articles, and all 28 articles were further screened. Seven studies were eliminated for not meeting inclusion criteria, including two studies that were published after 2005, but whose dates of study were before 2005 and thus did not meet inclusion criteria. The 15 publications that remained were evaluated for content, quality and relevance to clinical question. The research design, sample characteristics and factors related to HCC surveillance in patients with

cirrhosis were extracted. Secondary evaluation also was done to examine the rate of HCC surveillance in the studies (see *Table S1*).

Results

Synthesis of findings

Of the 15 studies selected, 4 were provider surveys, 2 were patient surveys, and 9 were retrospective chart reviews, of which 2 were quality improvement projects. Definitions of surveillance varied among studies, from the current standard of an US of abdomen every 6-month interval, to any imaging done over a patient's lifetime. Several factors were associated with surveillance for HCC, with provider type, setting of care and number of visits to a specialist provider being the finding most often established. Additional factors were etiology of liver disease, patient and provider related factors. Interventions to improve surveillance behaviors were also discussed. These are reported individually below.

Rates of surveillance for HCC

The definition of appropriate HCC surveillance intervals and included studies (i.e., US of abdomen or CT/MRI) varied with each study and impacted the reported surveillance rates. Type of study such as retrospective chart review, provider survey or if patients were enrolled in a clinical trial also affected the reported ranges of surveillance. When proper surveillance was defined as US of abdomen every 6 months, rates were very low, ranging from 1.7–17.4% (6-10,18).

Rates of surveillance for HCC using any imaging modality completed within a 12-month period were higher with a much wider range, with rates 13.4% to 76.4% (8-10,19-21). Rates of annual surveillance were slightly higher in patients enrolled in a clinical trial with 68.9% of patients having yearly US, and 31.3% having inconsistent adherence; of note, these patients were enrolled in a clinical trial with near perfect surveillance conditions, as patients were selected for compliance (21). Rates were also higher when the population was highly educated (63% with college degree or higher), with surveillance rates up to 76.4%. An outlier study which was a quality improvement program found 74% adherence to annual surveillance which increased to 93.2% post intervention (a reminder system for providers) (22). It is unclear how they achieved that rate, while others fell in the range below 80%. When these three studies are removed, the range falls between 13.4–51% of patients with annual surveillance (8-10,19)

Three studies defined surveillance as any imaging done within 15, 18 or 24 months, and rates of surveillance were also low, at 26% (5), 27.6% (23), and 20% (24) respectively.

The three studies that used data obtained from provider self-reported surveys reflected a higher rate of surveillance than the majority of studies, with self-reported rates of HCC surveillance ranging from 45% to 76.4% (6,25,26). However, in one of these surveys, the provider self-reported rates of every 6 months surveillance was still low, reported as 15% (6). An interesting finding in a study of VA providers was the difference in reported adherence to guidelines (70.9%) with actual adherence seen at 39.8% (26).

Factors associated with rates of HCC surveillance

Effect of type of provider, setting and visit frequency

Factors most associated with HCC surveillance was follow up with a specialist in gastroenterology or hepatology (5,7,19,24,26), increased number of visits to a specialist care provider per year (7-10), and care in an academic center (5,10). Fewer than one primary care or specialist care provider a year was negatively associated with surveillance (9). Patients followed by primary care providers for cirrhosis or diagnosis by a primary care provider were a cause of lower HCC surveillance rates (8). One study found that cirrhosis diagnosed by a surgeon to be negatively associated with surveillance (19). If the treatment site was able to refer for liver transplantation or had curative treatments available at their site, there was a higher chance of being screened for HCC (26). Care by nurse practitioners or physician assistants was associated with decreased rates of surveillance in one study (26), and higher rates (self-reported) of surveillance in another (6).

Effect of etiology of cirrhosis on adherence

Many studies linked the etiology of cirrhosis to levels of surveillance for HCC. Three studies found the highest rates of surveillance with the diagnosis of any viral hepatitis (5,8), or hepatitis C (18). The diagnosis with the lowest rates of surveillance was non-alcoholic steatohepatitis (NASH) (7,9,19). Non-viral, non-NASH cirrhosis was also associated with low adherence to surveillance guidelines (19). However, there was conflicting data related to alcoholic cirrhosis as a factor in surveillance with one study finding a positive association with surveillance (5) and one finding it negatively associated with surveillance (24).

Patient level factors

Patient declining surveillance or not going for ordered surveillance was not seen as a major factor in low surveillance rates, with patient's not going for ordered surveillance in 6% of patient's (23), and 14.3% (24). African American race was identified as a factor in decreased surveillance rates in two studies (7,9). Complete adherence to all follow up appointments was also associated with greater surveillance frequency (21).

Two studies directly surveyed patients regarding HCC surveillance facilitators and barriers with different populations—one looked at a predominantly Caucasian, well-educated population (20) and another in an urban safety net hospital (18). These surveys revealed that patient knowledge that cirrhosis was a risk factor for HCC was associated with higher HCC surveillance rates in one patient survey (18) and patient involvement in their care and decision making process was associated with increased surveillance, with surveillance rates increasing from 62.5% in patients who were not involved in their care, to 76.4% in patients involved in their care (20). Presence of patient perceived barriers was negatively associated with HCC surveillance (OR, 0.42; 95% CI, 0.25–0.70)—these included difficulty scheduling imaging (30.5%), costs of surveillance test (25.3%), uncertainty about where to get surveillance tests (19.6%) and difficulty with transportation (17.3%) in one study which utilized patient surveys (18).

Other patient factors were associated with HCC surveillance, though each of the following factors was seen in only one study and not across studies. Long distance (>35 miles) from home to place of care was seen as a factor in one study (7). Clinical factors that were positive predictors of surveillance included a history of a decompensation from a cirrhotic event, patients with at least one component of metabolic syndrome (8) and platelet count greater than 150,000/mm^3 (21). Medicare dual eligible insurance (5) and general insurance type (8) was associated with increased probability of surveillance. Gender's effect on surveillance rates had contradictory findings with female sex being associated with increase probability of surveillance (5) in one study, and male gender associated with higher rates in another (9). Lower rates of surveillance was associated with increasing age (5).

Provider related factors

Two surveys of primary care providers that managed cirrhotic patients reported they did not order surveillance because they were not aware of guidelines, feeling that they had more important issues to deal with than HCC surveillance, incorrect knowledge about proper surveillance, difficulty communicating with patients about surveillance, and to a lesser degree, uncertainty about benefits of guidelines and cost (6,25). Primary care providers reported in a survey that they were motivated to order surveillance because of the recommendations by medical societies and that the guidelines were supported by evidence, as well as fear of malpractice (25). Failure of the provider to recognize liver disease was also associated with non-adherence to surveillance guidelines (24).

Intervention level factors associated with improved HCC surveillance rates

Two studies that examined the effect of reminders in the medical record found that reminders to providers were a mechanism for improving surveillance rates (22,23). In the study by Aberra *et al*. (22), reminders were generated to alert nursing staff when a patient's surveillance was out of date, so they could facilitate ordering of US of abdomen, which increased the rates of surveillance from 74% to 93.2%. Alternatively, in the study by Beste *et al*. (23), alerts were displayed during visits that could be acted upon or ignored. This intervention increased surveillance rates by 51%.

Discussion

In most of the studies, HCC surveillance rates were low even with broad definitions of appropriate surveillance. Definitions of appropriate or consistent surveillance ranged from the current AASLD guidelines which recommends US of abdomen every 6 months, to defining surveillance as an US of abdomen in the preceding 15 months period (5). Many studies stratified surveillance as complete, incomplete and no surveillance in recognition of the low rates of surveillance. Discrepancies in the definition of appropriate surveillance, however, is often due to the change in AASLD guidelines from the 2005 version which advised US of abdomen at every 6–12 months interval with AFP, to the current guidelines updated in 2011 which recommend U/S every 6 months (15). Ultimately, despite varied definitions of adherence, any factors associated with consistent HCC surveillance are only associated with an increased chance of surveillance, since the rates of surveillance is astonishingly low, with the likelihood of surveillance decreasing with length of time after cirrhosis diagnosis (8). Though the cause of this was not clearly identified, low rates of HCC surveillance is likely related to a multitude of factors

including lack of knowledge by primary care providers regarding the importance or appropriate interval of HCC surveillance, the difficulty in following surveillance guidelines that require frequent follow up, and logistical issues in scheduling tests (18).

Specialist care (gastroenterologist or hepatologist) was strongly associated with increased surveillance rates (5,19,24,26), and this is clearly due to an ability to focus on the liver during visits, without ultimate responsibility to other organ systems. An increase in number of visits to a specialist provider is also closely related to increased HCC surveillance (8-10); after acute issues are resolved, more visits allow for preventative care to be emphasized, including ordering of surveillance tests. Primary care management of cirrhosis was also associated with lower surveillance rates (8). In a primary care environment, where the provider is responsible for the care of all organ systems and care coordination, there may not be a specific awareness of the need to screen for HCC at every 6 months, and even when there is this knowledge, it may not be prioritized. Not all geographic locations have easy availability of gastroenterologists or hepatologist, but in areas where there are ample specialists, it is important to refer cirrhotic patients to them for more consistent surveillance and care.

Studies that looked at patient related factors associated with low HCC surveillance rates mostly focused on demographic difference. Two studies found some influence of insurance type on HCC surveillance rates; one study found Medicare dual eligible insurance were associated with improved surveillance rates, and anther found insurance affected rates of HCC surveillance as well (5,8), though the effect was not explicit. In the United States insurance environment where may patients have high specialist co-pays and deductibles, this may prove to have some influence on attainment of specialty care and number of visits, which has been shown to influence surveillance rates. This may be an area that requires more attention.

Two studies showed rates of HCC surveillance lower amongst African American patients (7,9). This correlates with two previous influential studies that were excluded from this review, due to study dates prior to 2005, which showed race as an influence on HCC surveillance behaviors. In a large study of patients with HCC from the veterans administration (3), non-Caucasians had lower surveillance rates than Caucasians, particularly African Americans (4). A separate large study evaluating data from the SEER database also showed the lowest rates of HCC surveillance amongst African American patients (4).

An interesting finding by Singal (9) was that the failure of providers to recognize liver disease is related to lower surveillance behaviors. Failure to recognize cirrhosis is of course, linked to lower rates of surveillance. NASH cirrhosis was the diagnosis least likely to be screened (9,19), and this may be due to the difficulty diagnosing cirrhosis in this population. This points to the need to increase focus on patients with fatty liver, and identify those patients at greatest risk for NASH and cirrhosis and to follow them appropriately. As NASH overtakes viral hepatitis as the leading cause of cirrhosis in patients, this will prove to be more significant an issue moving forward.

Finally, studies found that reminders in the electronic health record increased surveillance rates (22,23), which points to the idea that increased organizational focus on surveillance cirrhotic patients for HCC, would likely increase the rates of surveillance in these patients. Offering financial incentives to providers such as those for colonoscopy and mammogram may have a positive effect on surveillance rates. From a patient perspective, lack of institutional support can also affect surveillance rates- barriers to surveillance such as cost of imaging, difficulty in scheduling imaging tests, and cost of imaging can influence surveillance rates (18). Further studies related to organizational supports and barriers that affect surveillance rates should be explored. Furthermore, patient engagement in their own care was associated with increased surveillance (20), raising the possibility that patients can influence their provider's behavior.

Limitations

The reasons for non-surveillance of HCC in patients are complex and difficult to ascertain. Though this study showed some clear data related to patient and provider characteristics that affect surveillance behavior, there is not a clear target for intervention. The studies included in this review include retrospective chart reviews and surveys, which each have distinct limitations. Retrospective chart review misses unmeasured confounders, and often has missing data such as imaging tests done and not captured. Surveys depend on self-report and are dependent on response rates, which are low in all included studies. In the one study that sought to validate provider reports against actual data, there was a large discrepancy between reported rates of surveillance and actual surveillance tests performed (26). Furthermore, due to the cross-sectional nature of most studies included in this review, there is limited information about surveillance behaviors over time. Finally, and perhaps

most importantly, the surveillance rates are generally low across studies and the reason for this was not clearly identified.

Implications for practice

The main finding of this study is that specialist care such as gastroenterologist and/or hepatologist, setting of care, and number of visits to a provider has the greatest influence of surveillance behaviors. However, specialty care is limited in many areas and primary care follows patients with cirrhosis in most cases, with only 20–40% of all cirrhotic patients followed by a specialist (4). Therefore, intervention in terms of increasing knowledge of current guidelines at the level of primary care is clearly warranted to improve surveillance rates. One compelling study pointed to the lack of cirrhosis diagnosis a significant risk factor for lack of surveillance, and increased education related to identification of cirrhotic patients should also be emphasized. Furthermore, the role of cost of healthcare as it affects surveillance behaviors has not been fully studied. In the current healthcare environment in the United States where patients often pay high co-pays and deductibles, this may have a role in surveillance behaviors as well, especially as it influences number of visits to a provider, and uptake of specialist care, which are known to influence surveillance behavior. In cases where providers were prompted to order screening by a reminder, rates were higher, pointing to the idea that organizational supports can influence surveillance rates positively. Finally, surveillance of patients with cirrhosis for HCC is low, irrespective of most factors, and a greater understanding of this phenomenon is clearly needed through further focused study.

Conclusions

The findings from the integrative review point to varied patient, provider and organizational factors that influence whether a patient with cirrhosis is screened for HCC or not. Early detection of HCC is important to improve survival in HCC, and surveillance rates are very low across studies. It is important that we continue to address factors that influence surveillance behaviors in providers to improve these rates of surveillance and ultimately, improve survival in patients with cirrhosis.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.03.80). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Description of studies included in integrative review

Reference	Type of study; methods; years of enrollment	Purpose of study	Sample size (demographics by age, race, ethnicity, population focus)	Results [percent (%) screened]	Results (factors related to screening or not screening patients with cirrhosis for HCC)	Strengths/limitations
Aberra, Essenmacher, Fisher & Volk, 2013	Quasi experimental (chart review); quality Improvement (QI) project-reminder generated to alert nursing staff if patient is due or overdue for screening; April 2010–May 2011 *vs*. control 2008–2009	To evaluate the effectiveness of implementing QI measures to increase HCC surveillance	Hepatology clinic, tertiary, academic; N=355 (>85% Caucasian, 58% male); mean age: 57 (21–89)	Surveillance increased from 74% to 93.2% post intervention (sending reminders) (P<0.001)	Reminders to providers associated with increased surveillance; endpoint: 1 ultrasound (US) a year	Pre-QI cohort self-selected because needed consent; no data collection tool information including process of determining causes of nonadherence
Beste *et al*., 2015	Quasi experimental; QI project; reminder generated when chart opened in any department, easy way to order US when seen (can opt out); Jan 2011–June 2012, numerous sites	To evaluate if primary care oriented, point of care clinical reminder in heath record will improve HCC surveillance rates	VA primary care providers; one site got reminder, other 7 aggregate data as control; N=2,884 (790 intervention, 2,094 control); mean age (intervention: 60.2, control: 61.0); race (intervention: 78.6% White, 10.1% Black, 3.4% Hispanic; control: 77.4% Caucasian, 1.9% Black, 2.6% Hispanic)	Surveillance increased by 51% (27.6% at intervention site *vs*. 17.5%); Baseline surveillance intervention site 18.2% *vs*. 16.1% control (P=0.23); after intervention: 27.6% *vs*. 17.5% at control (P<0.001)	Clinical reminders increased HCC surveillance; not factor for nonadherence: PT declines surveillance in only 6%; adequate imaging defined as imaging within 18 months	PT must go to an appointment to get reminder
Dalton-Fitzgerald *et al*., 2015	Web-based survey sent to all 131 PCP, 77 responded; August 2012–March 2013	Evaluation of factors associated with adherence to guidelines for HCC surveillance for PCPs	77 primary care providers at urban, safety net hospital (Parkland in Dallas); primary care sites: 12 clinics, hospital and outpatient based; majority of PTS uninsured, majority AA/Hispanic	Primary care providers reported annual surveillance rates of 65% of patients with cirrhosis; PCPs reported biannual surveillance rates of 15% of patients with cirrhosis	Causes of non-adherence (providers): (I) not up to date with guidelines (68%); (II) more important issues to manage (52%); (III) difficulty with effective communication with patients about surveillance 52%; (IV) incorrectly thought AFP alone (89%), LFTS (59%) or clinical exam (45%) was effective for surveillance	Study type survey is limitation (self-reported *vs*. actual practice may value)
El-Serag *et al*., 2013	Survey in VA (self-administered online); all providers caring for veterans with HCV invited to respond; November–December 2007; survey related to hepatitis C treatment, also asking who and when patients should be screened for HCC	2007 Survey to Assess Hepatitis C Care in Veterans Health Administration collected information regarding the care of patients with hepatitis C (HCV)	N=268 providers who treat hepatitis C (140 physicians, 65 nurse practitioners, 14 registered nurses, 11 physician assistants); 61% in gastroenterology & hepatology practices	70.9 % recommended HCC screening within guidelines; survey respondents reported 70.9% compliance with screening recommendations, but 2007 data showed 39.8% compliance with recommendations	Screening: (I) GI/hepatology or ID subspecialties providers (P=0.031); (II) providers that treat hepatitis c (P=0.001); (III) providers that referred for liver transplant (P=0.01); (IV) providers in facilities that had presence of any treatment modalities for HCC including RFA, resection, ethanol injection, chemoembolization, transplant referral; less adherence to screening among PA/NPs (P=0.002)	Surveys: reflect perceived rather than actual practice; survey only with providers that care for vets with hepatitis C- may be more familiar with guidelines for HCC screening than general pop; higher reported adherence to screening guidelines than generally seen, may reflect more specialist practice
Farvardin *et al*., 2016	Survey of patients- in person (convenience sample) or in phone (random sample). Then correlated with other patient demographics and clinical information in EMR; used Health Behavior Framework Theoretical Model; Parkland Health and Hospital System (safety net system of Dallas); August 2014–December 2015	Study patient attitudes, knowledge, and barriers to HCC screening	753 patients approached, 541 agreed to survey (71.8%), including 34 in person, 157 by telephone	Any imaging in study period: 356 (65.8%); imaging every 6 months: 2.8% (15); imaging specifically for surveillance only counted—91 additional patients were classified as having no surveillance, had non-surveillance imaging	Associated with any surveillance: hepatology specialty care (OR 2.65, 95% CI, 1.30–5.41); HCV etiology of cirrhosis: (OR 2.08, 95% CI, 1.19–3.63); patient knowledge that cirrhosis is high risk for HCC (OR 3.09, 95% CI, 1.25–7.62); not significantly associated with surveillance: attitudes that surveillance reduces HCC mortality or worry about HCC; patient reported barriers inversely associated with patient barriers (OR .47, 95% CI, 0.30–0.36) including: difficulty with scheduling (30.5%), cost of surveillance (25.3%), uncertainty about where to have US done (19.6%), transportation issues (17.3%)	
David S. Goldberg *et al*., 2016	Retrospective chart review; 2006–2010; database search (Truven Health Analytics database—from 100 plans)	Evaluation of Truven database to evaluate the proportion of time patients with cirrhosis are "up to date" with surveillance	8,916 cirrhotic patients with 18 months of continuous follow up included; mean age: 56; sex: male 58.1%; type of provider: GI 50.8%, PCP: 20.8%; insurance: PPO/POS: 66.6%, HMO: 15%	Adequate surveillance (any imaging every 6 months): 17.4%; incomplete surveillance: 61.1%; no surveillance: 21.5%; however, surveillance rates remained low, decreased with length of time after diagnosis	Decreased chance of screening: (I) diagnosis by non-gastroenterology (GI) provider (P<0.05). Increased surveillance: (I) history of hepatic decompensation event (P≤0.001); (II) presence of any component of metabolic syndrome (P=0.05); (III) diagnosis of hepatitis C (P<0.001); (IV) increased number of provider visits (P<0.001); (V) insurance type (P=0.03); (VI) provider specialty (P<0.001)	Strength: only includes patients after American association for the study of liver diseases (AASLD) guidelines established in 2005; no analysis of race; no comment on race of patients evaluated
David S. Goldberg *et al*., 2016	Retrospective chart review; Utilization of dataset Veterans Outcomes and Costs Associated with Liver Disease-ID of subset of patients with first diagnosis of cirrhosis from Jan 2008–Dec 2010	Utilization of data to ID rates of HCC surveillance and factors related to insufficient test ordering and completion and evaluate association of geography and adherence with HCC surveillance guidelines	26,577 veterans with cirrhosis; PTS all from Veterans Health Administration; median age 60 yrs; demographics not clear	Percent of time up to date with HCC surveillance every 6 months: 37.3% (9,904) no abdominal US at all; 27.4% (7,289) no abdominal imaging (any imaging) at all; of 62.7% that had US for HCC surveillance: (I) 34.2% (9,101) were up to date with surveillance 1–25% of the time; (II) 18.2% (4,844) were up to date with surveillance 26–50% of the time; (III) 7.6% (2,019) were up to date with surveillance 51–75% of the time; (IV) 2.1% (556) were up to date with surveillance 76–100% of the time	Factors associated with no surveillance: amount of time from ordering US to appointment date >90 days (OR 0.90, 95% CI, 0.85–0.94), >180 days (OR 0.77, 95% CI, 0.72–0.82); cirrhosis etiology: NASH (OR 1.12, 95% CI, 1.03–1.21), cryptogenic (OR 1.19, 95% CI, 0.92–1.53.), ETOH (OR, 1.05, 95% CI, 0.99–1.12); living >35 miles from VA hospital: OR decreased with increasing distance; number of visits to a specialist (gastro or ID) in year of cirrhosis diagnosis: >5 visits: (OR, 1.32, 95% CI, 1.25–1.41); African-American race (OR, 0.88, 95% CI, 0.83–0.92); 34% of ordered US were not completed	Mostly male patients, other demographic specifics not clear
Palmer, Kappelman, Sandler & Hayashi, 2013	Retrospective chart review; patients enrolled in North Carolina (NC) Cost & Quality Initiative database for NC Medicaid with cirrhosis with at least 15 months enrollment; 2006–2007	To identify factors associated with imaging in patients with cirrhosis in database	N=5,061 cirrhotic patients; all settings (inpatient and outpatient: mean age 54; 54% male, 35% African American, 56% Caucasian	26% underwent imaging over 15 months, 59% had 1 imaging test, 41% 2 or more; included any imaging within 15-month period	All patient's factors associated with imaging: (I) GI visit in period (OR, 2.81; 95% CI, 2.81–3.41); (II) care in academic center (at least one episode) (OR, 2.13; 95% CI, 1.82–2.50); (III) viral hepatitis (OR, 1.98; 95% CI, 1.67–2.35); (IV) alcohol (ETOH) abuse (OR, 1.21; 95% CI, 1.00–1.47); (V) medicare dual-eligible (OR, 1.69; 95% CI, 1.38–2.0); (VI) female sex (OR, 1.18; 95% CI, 1.02–1.37); advancing age associated with DEC probability of surveillance (P<0.001); factors related to surveillance in outpatient setting: (I) viral hepatitis (OR, 4.44; 95% CI, 2.81–7.01); (II) being seen in university setting highest rates of imaging (OR, 3.46; 95% CI, 2.29–5.24)	Only 30% seen in outpatient settings
McGowan, Edwards, Luong & Hayashi, 2015	Survey of 391 primary care providers, representing 14% of PCPs in North Carolina; 12 item questionnaire addressing HCC surveillance knowledge and practice	To evaluate primary care providers practice of HCC screening	Random sample of 1,000 NC primary care providers, 391 filled out survey (39%), 345 saw cirrhotics (89%); varied population focus	Of providers who saw cirrhotic patients: 45% screened for HCC	Reasons for surveillance: supported by evidence (72%), recommended by medical societies (42%), malpractice (26%); reasons for not screening: referred to GI for surveillance decisions (84%), 24% unaware of recommendations, 8% uncertain of benefits, 8% concerned over cost; surveillance defined as imaging every 12 months	Survey response 39%; for those that did not screen, 84% assumed specialists made decisions- implications of that?
Patwardhan *et al*., 2011	Retrospective chart review of comprehensive registry of partners' healthcare system claims; 1996–2010; outpatient GI and primary care practices	Examination of screening rates related to etiology of cirrhosis	N=156 cirrhotic patients; mean follow up 43 months; mean age: 56.2; male 66%; race: 81% Caucasian, 11% Hispanic, 3% Black; insurance: medicare: 40%, private: 46%, medicaid: 14%	51% of patients got recommended screening US for HCC; screening if seen by GI (58.8) *vs*. primary care or surgery (18.8%); surveillance rates by etiology of cirrhosis: NASH: 29.7%, viral hep: 58.4%, ETOH: 62.5%, other: 33.3%	Positively associated with HCC screening: (I) seen by GI/hepatology (P<0.001); (II) if seen by GI at least once a year increased rate of screening (P<0.001); least likely to screen: nonalcoholic steatohepatitis (NASH) cirrhosis: (I) followed by other non-viral non-nash cirrhosis; (II) surgically discovered cirrhosis least likely to have HCC surveillance (P<0.0001)	Part of sample from before recommendations for screening by AASLD [2005]; small sample size
A. G. Singal *et al*., 2013	Retrospective review of trial data (initial trial was prospective trial); patients enrolled in HALT study to look at hepatitis C patients with cirrhosis	Aim of study was to assess the reasons behind surveillance process failures amongst patients enrolled in HALT-C trial	N=1,005 with advanced fibrosis/cirrhosis; academic center, patients selected for compliance (within 6-week window) in formalized surveillance program (near optimal setting for surveillance); for study, PTS visited clinic every 3 months during 3.5 years of trial and every 6 months after; age: 50.2; gender: consistent surveillance (male 70.7%), inconsistent surveillance: 71.6%; race: consistent surveillance (Caucasian: 72.3%, Black: 18.4%, Hispanic: 7.1%), inconsistent surveillance (Caucasian: 70.9%, Black: 17.6%, Hispanic: 9.3%)	Of 1,005, 692 had consistent surveillance (68.9%), 313 inconsistent surveillance (31.3%)	Positive predictors of screening: (I) study site (P<0.001); (II) platelet count >150,000/mm^3 (HR, 1.28; 95% CI, 1.05–1.56); (III) complete visit adherence (HR, 1.72; 95% CI, 1.11–2.63); defined consistent surveillance as US + AFP Q 1 year	Near perfect surveillance conditions, PTS already proven adherent to study, so bias in selection of patients; unknown cause of differences in screening amongst sites
A. G. Singal *et al*., 2015; racial	Retrospective cohort study; July 2008–July 2011	To characterize HCC surveillance rates and determinants of surveillance among cirrhotic patients	N=904 patients with cirrhosis; 11 clinics, 1 hepatology outpatient clinic, tertiary hospital (same EMR); eligibility: 1 outpatient primary care visit 2008–2011, and continued follow up through last year of study period; urban safety-net hospital—Parkland outside of Dallas; median age: 54.8; male 65%; race: 22% African American, 36% Caucasian, 40% Hispanic; 43% uninsured, 53%: medicare/caid, 4% private insurance	603 (67%) had inconsistent surveillance (1 US over study period for surveillance purposes); 98 (13.4%) had annual surveillance, 13 (1.7%) had biannual surveillance; of the 301 that did not get surveillance, 193 had US for other purpose, only 22 had US ordered and did not perform test; biannual screening: 11.4% with 5 or more hepatology visits per year, 2.7% with 2–5 visits per year	Inconsistent surveillance: associated with having (I) >1 primary care visit per year (OR, 3.80; 95% CI, 2.06–7.01); (II) >1 hepatology visit per year (OR, 2.30; 95% CI, 1.20–4.39). Negatively associated with: (I) African-American race (OR, 0.40; 95% CI, 0.21–0.77); (II) NASH cirrhosis (OR, 0.34; 95% CI, 0.15–0.77); (III) child Pugh C (OR, 0.47; 95% CI, 0.24–0.90). Consistent annual surveillance: (I) male gender (OR, 1.63; 95% CI, 1.00–2.67); (II) number of hepatology visits per year (OR, 1.99; 95% CI, 1.28–3.10). Negatively associated: NASH cirrhosis (OR, 0.41; 95% CI, 0.17–0.99); consistent biannual surveillance: number of hepatology visits per year (OR, 8.38; 95% CI, 2.28–3.07)	Strength: population at safety net hospital- not likely getting care elsewhere
Amit G. Singal *et al*., 2012; failure rates	Retrospective data cohort study of cirrhotic patients diagnosed with HCC at safety net system; June 2005–June 2100	Purpose was to characterize surveillance process failures amongst cirrhotic patient's with HCC	N=178; racially diverse population, urban Parkland Memorial Safety—net hospital Dallas; age mean: 56.9; gender 77.5% male; race: Caucasian: 23%, Black: 40.5%, Hispanic: 28.1%, Asian 8.4%; insurance: medicare 29.2%, medicaid: 14.6%, private insurance: 7.3%, none: 48.9%	Only 20% of PTS with HCC received surveillance in 2 years preceding HCC diagnosis; 79.8% received no surveillance	Factors associated with consistent surveillance: hepatologist care (OR, 7.39; 95% CI, 1.48–37.0); inconsistent surveillance (1 US over 2-year period prior to HCC diagnosis): hepatologist care (OR, 6.11; 95% CI, 2.52–14.81); negative associated with surveillance: (I) ETOH abuse (OR, 0.14; 95% CI, 0.03–0.65); (II) factors associated with non-adherence: (i) lack of HCC surveillance orders (61.5%); (ii) failure of patient to complete orders (14.3%); (iii) failure to recognize liver disease (20.2%)	Going backwards, looking at only cases with HCC and seeing screening patterns; small sample size
A. G. Singal *et al*., 2011	Prospective—self-administered survey of Child Pugh A/B cirrhotic patients. Also surveillance rates and clinical data extracted from electronic medical record; October 2008–March 2009	To determine HCC surveillance rates and patient predictors of having surveillance	N=160; University Michigan, tertiary care center liver clinics; median age: 56; race: 81.7% White; male: 60.6%; education: college or higher: 63%, high school: 37%	Surveillance rates 76.4% for PTS involved in their care, *vs*. 62.5% for PTS who did not feel involved	Predictors of surveillance (at least 1 US in 1 year): patient involvement in their care/decision making process (P=0.005); surveillance defined as at least 1 US in 1 year	Sampling bias- 63% with college education or advanced degree; **much higher surveillance rates/education in this population, PTS also around 80% white, married, educated; enrolled at hepatology clinic- may over sample those involved in care; not representative of most patients
Wong *et al*., 2009	Retrospective cohort study; initiated screening 2001–2005 until December 2008, PTS followed for at least 12 months; also control group— HCC without any routine screening at first visit or within 6 months	Evaluate HCC screening rates and predictors of adherence to screening in community setting.	N=557 patients at high risk of HCC: cirrhotic patients and patients with chronic hepatitis B; N=134 cirrhotic patients; 97% Asian population, 97.4% foreign born, median 13 years in USA—mostly Vietnamese and Chinese; 2 community—GI/hepatology clinics in Northern California; mean age: 55.9; male: 59.3; ethnicity: Asian 97.0%; insurance: medicaid: 41.6%, medicare 7.6%	40.6% poor or no screening (AFP + imaging <12 months); 9% optimal screening (AFP + imaging Q6mo); 50.5% suboptimal screening (AFP + imaging Q6 –12 months)	Screening associated with (I) greater number of clinic visits per year; (II) care at university hospital (P<0.001)	Much of study occurred before AASLD guidelines; mostly Asian American immigrant patients- applicability to other populations? data for cirrhotics and non-cirrhotics

HCC, hepatocellular carcinoma; PCP, primary care physician; AFP, alpha-fetal protein; VA, Veterans Affairs; GI, gastroenterology; ID, infectious disease; RFA, radiofrequency ablation; AASLD, American Association for the Study of Liver Disease; OR, odds ratio; CI, confidence interval; NASH, non-alcoholic steatohepatitis; ETOH, alcohol.