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Use of Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis: A Systematic Review and Meta-Analysis

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BACKGROUND AND AIMS: Hepatocellular carcinoma (HCC) surveillance is associated with early tumor detection and improved survival; however, it is often underused in clinical practice. We aimed to characterize surveillance use among patients with cirrhosis and the efficacy of interventions to increase surveillance.

APPROACH AND RESULTS: We performed a systematic literature review using the MEDLINE database from January 2010 through August 2018 to identify cohort studies evaluating HCC surveillance receipt or interventions to increase surveillance in patients with cirrhosis. A pooled estimate for surveillance receipt with 95% confidence intervals was calculated. Correlates of surveillance use were defined from each study and prespecified subgroup analyses. Twenty-nine studies, with a total of 118,799 patients, met inclusion criteria, with a pooled estimate for surveillance use of 24.0% (95% confidence interval, 18.4-30.1). In subgroup analyses, the highest surveillance receipt was reported in studies with patients enrolled from subspecialty gastroenterology/hepatology clinics and lowest in studies characterizing surveillance in population-based cohorts (73.7% versus 8.8%, $P < 0.001$). Commonly reported correlates of surveillance included higher receipt among patients followed by subspecialists and lower receipt among those with alcohol-associated or nonalcoholic steatohepatitis (NASH)–related cirrhosis. All eight studies (n = 5,229) evaluating interventions including patient/provider education, inreach (e.g., reminder and recall systems), and population health outreach strategies reported significant increases (range 9.4%-63.6%) in surveillance receipt.

CONCLUSIONS: HCC surveillance remains underused in clinical practice, particularly among patients with alcohol-associated or NASH-related cirrhosis and those not followed in subspecialty gastroenterology clinics. Interventions such as provider education, inreach including reminder systems, and population health outreach efforts can significantly increase HCC surveillance. (Hepatology 2021;73:713-725).

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide and one of the fastest increasing causes of cancer-related mortality in the United States.[1-3] Patients with cirrhosis are the primary at-risk cohort for HCC in the Western world, with an annual incidence of 2%-4%; and HCC is a leading cause of death in patients with compensated cirrhosis.[3,4] The primary driver of prognosis in patients with HCC is tumor stage at diagnosis, with curative options affording 5-year survival exceeding 70% if patients are detected at an early stage. Despite improvements over time, most patients with HCC continue to be

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; EASL, European Association for the Study of the Liver; EMR, electronic medical record; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis.

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detected beyond an early stage and are therefore only eligible for palliative therapies.[3]

Professional societies including the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend HCC surveillance in patients with cirrhosis to promote early HCC detection and curative treatment receipt.[5,6] Several cohort studies have demonstrated an association between receipt of HCC surveillance and improved survival, even after adjusting for lead time and length time biases.[7] However, the effectiveness of HCC surveillance at reducing mortality in clinical practice relies on test effectiveness and surveillance use. Current surveillance tools, ultrasound and alpha-fetoprotein (AFP), have a sensitivity of only ~63% for early HCC detection, with additional imaging and blood-based tests potentially years away from implementation in clinical practice. These data highlight the need for optimizing HCC surveillance use.

Implementation of HCC surveillance in clinical practice can be affected by suboptimal patient and provider adherence with surveillance recommendations. Prior studies have suggested that many primary care providers have suboptimal knowledge about the benefits of HCC surveillance, which can lead to providers not ordering surveillance in at-risk patients.[8,9] Patients also report barriers to surveillance completion, such as difficulty with the scheduling process, costs of surveillance testing, and concerns about transportation.[10] Accordingly, prior studies have demonstrated that only a minority of patients with cirrhosis undergo HCC surveillance, with even lower rates when considering consistent surveillance every 6 months. Studies have also suggested racial/ethnic and socioeconomic disparities, with lower surveillance rates among racial/ethnic minorities and patients of low socioeconomic status.[11]

Given increasing data highlighting the underuse of surveillance in clinical practice, there is a clear need for interventions to increase HCC surveillance. Interventions have included those at the system level (e.g., mailed outreach), provider level (e.g., a best practice advisory), and patient level (e.g., patient navigation); however, no study has summarized this literature to inform which interventions may be most effective.[12-19]

The aims of our study were to (1) quantify use of HCC surveillance among patients with cirrhosis, (2) examine sociodemographic correlates of HCC surveillance, and (3) summarize the efficacy of intervention efforts to increase HCC surveillance receipt.

Materials and Methods

LITERATURE SEARCH

We conducted a computer-assisted search with the Ovid interface to Medline to identify relevant published articles. We searched the Medline database from January 1, 2010, through August 7, 2018, with the following keyword combinations: [screen$ or surveillance or detect$ or diagnosis] AND [liver ca$ or hepatocellular ca$ or hcc or hepatoma]. Given our focus on current use of surveillance within the United States, our search updated a prior systematic review and was limited to human studies published in English after 2010.[20] Abstracts from the Digestive Disease Week, AASLD, and EASL conferences from 2017 and 2018 were manually searched for relevant studies. We performed manual searches of references from relevant articles to identify studies that were

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missed by our computer-assisted search. Finally, we consulted expert hepatologists to identify additional references or unpublished data.

One investigator (E.W.) reviewed all publication titles of citations identified by the search strategy. Potentially relevant studies were retrieved, and selection criteria were applied. The articles were independently checked for inclusion, and any uncertainties were resolved through discussion with another author (A.S.). Inclusion criteria included (1) cohort studies that described receipt of HCC surveillance in patients with cirrhosis and (2) studies published after 2010 so as to be representative of current delivery of care. We excluded studies which characterized receipt of one-time screening and survey studies describing self-reported surveillance use, given a bias to overestimating surveillance receipt. Additional exclusion criteria included non-English language, nonhuman data, and lack of original data. If publications used the same patient cohort, data from the most recent article were included. The study was conducted in accordance with PRISMA guidelines.

DATA EXTRACTION

We independently extracted the required information from eligible studies using standardized forms. We collected data regarding the study period, population of interest (patients with cirrhosis versus patients with HCC), surveillance definition and interval, and duration of follow-up. Data were collected on potential correlates of surveillance receipt including patient age, gender, race/ethnicity, socioeconomic status, and receipt of hepatology care. For the subset of studies assessing interventions to increase surveillance receipt, we recorded a description of the intervention and surveillance receipt in the intervention and control groups. Finally, data were collected on study design, geographic location and date of the study, and number of patients in each study. We assessed the risk of bias for each study using a modified Newcastle-Ottawa scale, which assesses selection of the patient cohort, comparability of study groups, and adequacy of assessing the outcome of interest. Specifically, we assessed (1) selection of patients (population-based versus recruited from academic centers), (2) exclusion of patients for whom surveillance is not recommended (e.g., Child C cirrhosis), (3) methods for ascertainment of surveillance receipt, (4) inclusion of cross-sectional imaging toward satisfying need for surveillance imaging, (5) length of follow-up, and (6) reporting of loss to follow-up or death.

STATISTICAL ANALYSIS

Our primary study outcome was HCC surveillance rates among patients with cirrhosis. Surveillance receipt was defined as the proportion of patients who underwent evaluation with repeated imaging and/or AFP prior to HCC diagnosis. The proportion of patients who received surveillance was derived for each study, and 95% confidence intervals were calculated using the adjusted Wald method. A weighed pooled estimate of surveillance rates was computed by multiplying the surveillance rate point estimate for each study by the proportion of individuals with cirrhosis in that study relative to the number of individuals in all included studies. Subset analyses were planned for the following predefined subsets of studies: (1) study location, (2) at-risk population, (3) definition of surveillance, (4) duration of follow-up, and (5) clinical setting including access to subspecialty care. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

Results

STUDY SELECTION

The computer-assisted search yielded 12,728 potentially relevant articles. After initial review, 855 titles were potentially appropriate, and these abstracts were reviewed. Among 69 publications that underwent full-text review, the most common reasons for exclusion were evaluation of one-time screening, duplicate patient cohorts, and nonoriginal data. The remaining 24 studies met all inclusion criteria (Supporting Fig. S1). Recursive literature searches identified one additional article and four conference abstracts that met inclusion criteria, producing a total of 29 studies (n = 118,799 patients) for inclusion in this meta-analysis (Table 1).[11,21-48] We also identified eight studies (n = 5229) evaluating interventions to increase HCC surveillance (Table 2).[12-19]

TABLE 1. Characteristics of Studies

Reference	Study Period	Study Setting	Population (% Cirrhosis)	Surveillance Definition	Follow-Up	No. of Patients
21	2002-2008	MarketScan Database, USA	HCV-related HCC (100)	q6-12 US ± AFP	NR	751
			NASH-related HCC (100)	q6-12 US ± AFP	NR	1,186
22	1994-2002	SEER-Medicare Database, USA	HCC (100)	q12 US ± AFP 2 of 3 years for screening intent	3 years prior	1,873
23	2002-2004	Chang Gung Memorial Hospital, Taiwan	HCC (100)	2 US ± AFP within 1 year	1 year prior	1,436
24	1998-2005	Veterans Affairs system, USA	HCV cirrhosis (100)	US or AFP 2 consecutive years for screening intent	4 years	9,369
25	1996-2010	Partners Healthcare, USA	Cirrhosis	q12 abdominal imaging	Mean 3.6 (0.3-12.5)	156
26	2008-2009	23 hospitals, Italy	HCC (94.7)	q6 US ± AFP	1 year prior	401
27	2007-2009	Mayo Clinic, USA	HCC (100)	Q6 abdominal imaging	1 year prior	368
28	2005-2011	Parkland Health & Hospital System, USA	HCC (100)	q12 US	2 years prior	149
29	2000-2010	Santa Croce Hospital, Italy	HCC (91.4)	q6 US	1 year prior	256
31	2000-2009	HALT-C Cohort, USA	HCV cirrhosis (100)	q12 US and AFP	6.1 years	408
30	2006-2007	North Carolina Medicaid, USA	Cirrhosis	≥2 abdominal imaging	1.25 years	5,061
32	2010-2011	University of Bern, Switzerland	HCC (100)	q6 US	1 year prior	71
33	2005-2012	Karolinska University, Sweden	HCC (82)	≥67% max interval q8 US	NR	616
11	2008-2011	Parkland Health & Hospital System, USA	Cirrhosis	q6 US	3 years	786
34	2000-2010	Ontario Cancer Registry, Canada	Virus-related HCC (51.4)	Q12 US	2 years prior	1,483
35	2005-2012	5 academic centers, the Netherlands	HCC (100)	2 tests (imaging ± AFP) in 3 years, with last < 18 months prior	3 years prior	756
36	2004-2011	Veterans Affairs system, USA	HCC (100)	q6-12 imaging	2 years prior	556
37	2012-2014	2 health systems, Brazil	Cirrhosis	q6 US	4.1 years	253
38	1996-2013	4 California community/academic centers, USA	HBV cirrhosis (100)	q6 imaging	5.9 (1-15.7)	164
39	2009-2016	University of California Los Angeles, USA	NASH-related HCC (100)	q6 imaging and AFP	2 years prior	101
40	2000-2004	ITA.LI.CA cohort, Italy	HCC (94.3)	q7 US	≥1 year prior	1,147
	2010-2014		HCC (90.4)	q7 US	≥1 year prior	2,421
41	2008-2010	Veterans Affairs System, USA	Cirrhosis	> 75% PTC imaging	4.7 (IQR 3.1-6) years	26,577
42	1992-2013	University of Oviedo, Spain	Cirrhosis	q6 imaging ± AFP	3.5 (IQR 5) years	770
43	2007-2012	Seoul National University, Korea	HBV-related HCC (90)	> 80% q6, US, or CT	2 years prior	401
44	2014-2017	Alameda Health System, USA	Cirrhosis	q6-12 US	≥2 years	235
45	2010-2012	Group Health Cooperative, USA	Cirrhosis	q6 US	2	1,053
46	2001-2015	Stanford University, USA	HCV cirrhosis (100)	q6 imaging	2.97 (1.83- 5.17)	2,366
47	2007-2014	MarketScan Database, USA	Cirrhosis	q6 imaging	114,070 person-years	43,915
48	2003-2013	SEER-Medicare Database	HCC	q12 US	3 years prior	13,714

Abbreviations: CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NR, not reported; PTC, proportion time covered; US, ultrasound.

TABLE 2. Implemented Interventions and Subsequent Outcomes

Reference	Study Setting	Study Period	Intervention	Outcome	Preintervention, n (%)	Postintervention, n (%)	Absolute Difference (%)	Relative Difference (%)
12*	University of Michigan, USA	2008-2011	Nurse-based protocol	One-time abdominal imaging	119/160[†] (74.4)	331/355 (93.2)	18.8	25.3
13	Flinders Medical Center, Australia	2007-2009	PCP and patient education, system redesign[†]	Semiannual US and AFP for 2 years	0/22 (0)	14/22 (63.6)	63.6	—
14	Northwest Veterans Affairs, USA	2011-2012	EMR reminder	≥2 abdominal imagings within 18 months	103/564 (18.2)	218/790 (27.6)	9.4	51.6
15	120 PCPs, Italy	1994-2013	PCP education	HCC diagnosed by surveillance	85/244 (34.8)	105/190 (55.3)	20.5	58.9
16	Royal Perth Hospital, Australia	2010-2015	Nurse-led clinic	Semi-annual surveillance	—	40/76 (52.6)	—	—
18	Royal Liverpool Hospital, UK	2009-2013	Radiology-led recall	Semiannual US	—	368/804 (45.8)	—	—
17	KP Northern California, USA	NR	EMR identification and physician extender	3 abdominal imagings in 2 years	51/224 (22.8)	183/224 (81.7)	58.9	258.3
19	Parkland, Dallas, TX	2014-2017	Mailed outreach	Semiannual US over 18 months	44/600 (7.3)	247/1,200 (20.6)	13.3	182.2

* Singal[49] provides the comparison cohort for the intervention.
[†]System redesign, creation of hepatitis nurse for coordinating surveillance and a patient database with automated recall function.
Abbreviations: NR, not reported; PCP, primary care provider; US, ultrasound.

STUDY CHARACTERISTICS

Characteristics of included studies are detailed in Tables 1 and 2. Most studies were conducted in the United States (n = 18), with fewer conducted in Europe (n = 7), Asia (n = 2), Canada (n = 1), and South America (n = 1). The majority were cohort studies examining HCC surveillance receipt prior to HCC diagnosis, with 13 characterizing surveillance use in patients with cirrhosis. Nearly half of studies evaluated surveillance receipt in academic centers, whereas others were conducted in community practices, the Veterans Affairs system, or using large administrative data sets. Although many early studies used operational definitions for surveillance receipt (e.g., annual ultrasound completed in 2 of 3 years), most studies published after 2013 assessed semiannual surveillance consistent with AASLD and EASL guideline recommendations.

SURVEILLANCE USE

Overall, the pooled proportion of patients who underwent surveillance was 24.0% (95% confidence interval 18.4%-30.1%), although there was a wide range across studies (1.1%-81.5%) (Fig. 1). In subgroup analyses, there was no difference in surveillance receipt between studies conducted among patients with cirrhosis and those with HCC (21.8% versus 25.8%, $P = 0.57$), studies with one-year duration and those with longer follow-up (29.4% versus 22.0%, $P = 0.38$), or studies conducted prior to and after 2014 (27.4% versus 24.0%, $P = 0.29$). However, we found notable geographic variation in surveillance receipt, with the lowest surveillance receipt among studies from the United States compared to those from Europe and Asia (17.8% versus 43.2% versus 34.6%, $P < 0.001$) (Supporting Fig. S2B). Similarly, surveillance receipt differed by availability of subspecialty care, with highest surveillance receipt among studies in which patients were enrolled from subspecialty gastroenterology and hepatology clinics, intermediate among studies from academic centers including both subspecialty and primary care patients, and lowest among studies reporting population-based cohorts (73.7% versus 29.5% versus 8.8%, $P < 0.001$) (Fig. 2).

CORRELATES OF SURVEILLANCE USE

Table 3 describes correlates associated with HCC surveillance use. Most studies did not find any significant

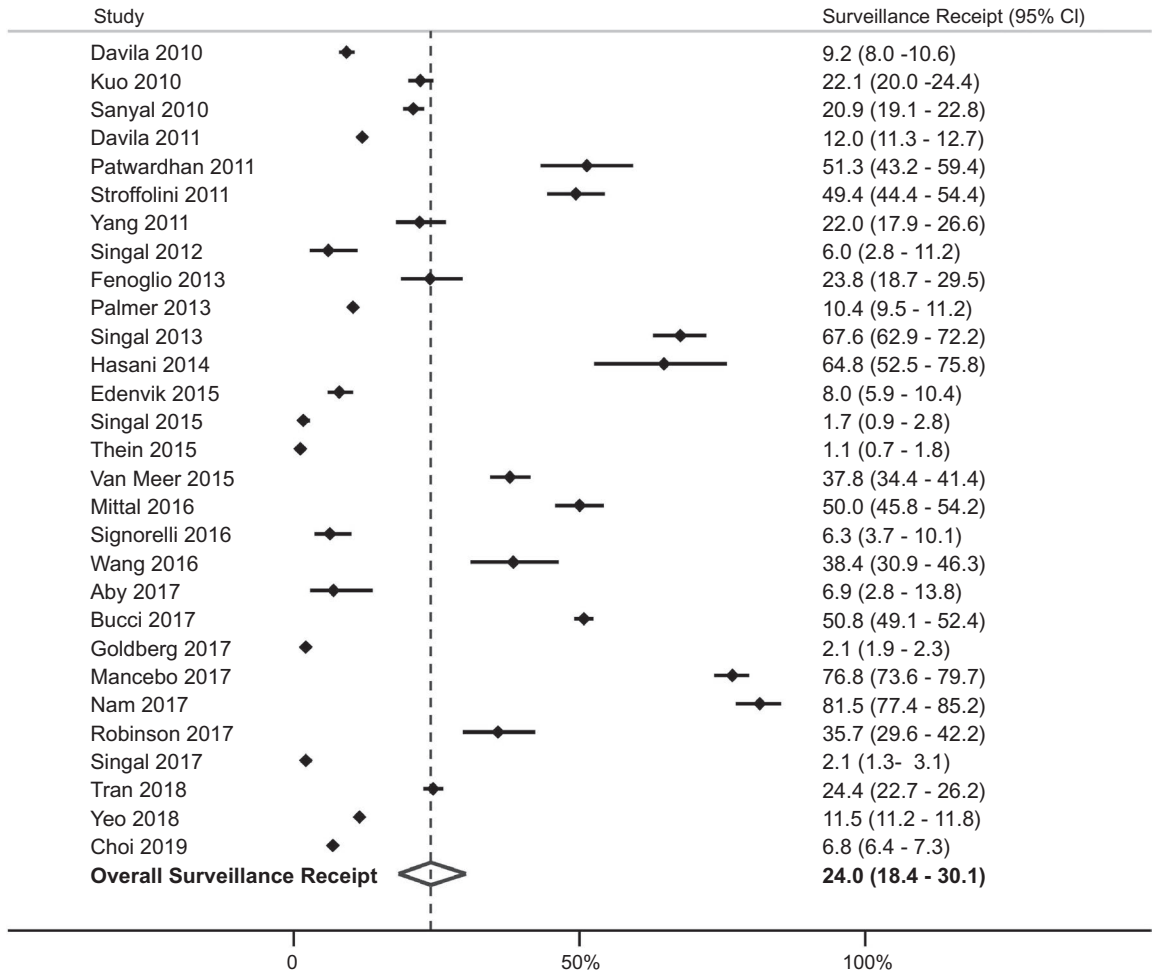

FIG. 1. Pooled surveillance use. Abbreviation: CI, confidence interval.

difference in surveillance receipt by age or sex; however, two studies reported an association between older age with higher surveillance receipt. Similarly, most studies did not report racial/ethnic disparities in HCC surveillance receipt, although two large studies found lower surveillance receipt in blacks compared to whites.[24,41] Several studies noted differences by liver disease etiology, with lower surveillance in patients with nonalcoholic steatohepatitis (NASH) or alcohol-associated cirrhosis than other etiologies. Surveillance was less likely in patients with significant medical comorbidities[24,32] and those with ongoing alcohol abuse,[24,28,29,33,34,41,42] likely given perceived lower benefit of HCC surveillance in these subgroups; however, many studies found that surveillance is more likely in patients with decompensated cirrhosis.[28,42,46,50] The strongest and most consistent correlates of surveillance receipt across studies were number of clinic visits and receipt of hepatology subspecialty care.

QUALITY ASSESSMENT

The quality assessment of individual studies is demonstrated in Table 4. Many of the studies (n = 16) assessed surveillance receipt among patients followed at academic centers, with only 13 using population-based registries or cohorts from large integrated health systems. Nearly all studies included patients in whom HCC surveillance was not recommended, such as those with Child-Pugh C cirrhosis or significant medical comorbidity, which may have resulted in a lower pooled point estimate for surveillance receipt. Similarly, 14 studies used medical records to determine surveillance use, and 17 studies did not account

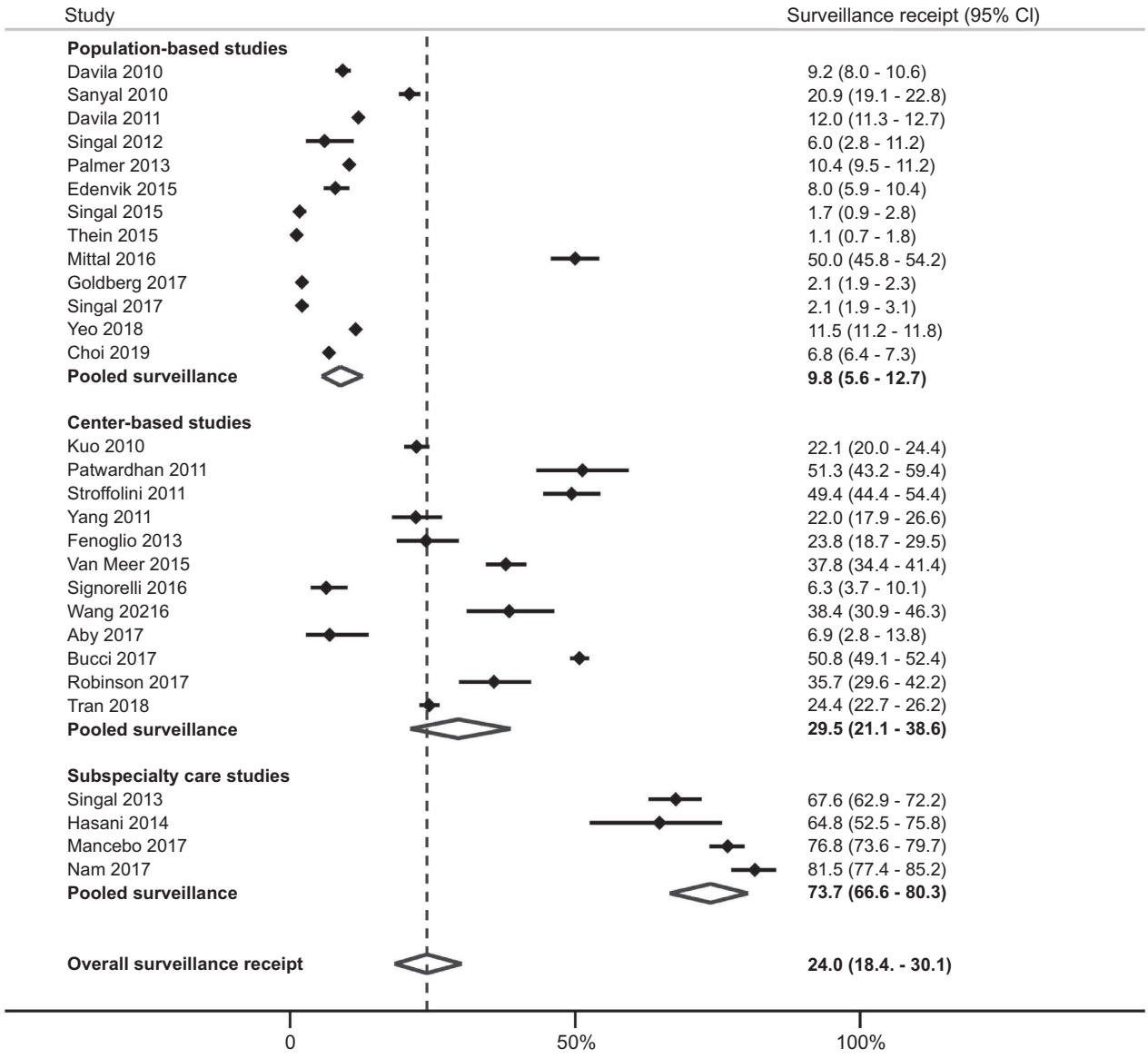

FIG. 2. Surveillance use, stratified by receipt of subspecialty care. Abbreviation: CI, confidence interval.

for nonultrasound imaging, both of which may have resulted in ascertainment bias and an underestimation of surveillance receipt. Finally, some studies had high risk of bias related to short duration of follow-up, < 1 year (n = 7), or did not account for patients lost to follow-up (n = 4).

INTERVENTIONS TO INCREASE SURVEILLANCE USE

We identified eight studies that evaluated the efficacy of interventions to increase HCC surveillance (Table 2). In a study evaluating the efficacy of primary care provider education alone, Del Poggio and colleagues found a significant increase in the proportion of HCC detected by surveillance after the education program in the intervention group (55.3% versus 34.8%), whereas the proportion of HCC detected by surveillance did not significantly differ in others (39.2% versus 25.9%).[15] Five studies found significant increases in surveillance use using inreach efforts such as electronic medical record (EMR) reminders or nurse-based protocols. Aberra and colleagues found that a nurse-based surveillance protocol

TABLE 3. Correlates of Surveillance Use for HCC

Reference	Age	Gender	Race	Socioeconomic Status	Alcohol Abuse	NAFLD/Metabolic Syndrome*	Comorbidities	Liver Decompensation	Hepatology Care	Number of Clinic Visits
22							NS		+	
24	– (<50)	NS	– (Black)		–	–	+	–		
25	NS	NS	NS	NS	NS	NS			+	
28	NS	NS	NS	NS	–	NS		+	+	NS[†]
29					–	–				
30	NS	+ (F)	NS							+[‡]
31	NS	NS	NS	NS	NS					NS[‡]
32	NS	NS		+ (private insurance)	NS	NS	+		NS	
33	NS	NS			–	–				
11	NS	+ (M)	NS	NS	NS	–		NS		+[‡]
34	NS	NS		NS	–	NS	NS	NS		+[§]
38	NS	NS		NS			NS			+[‡]
41	+ (older)		– (Black)		–	–				+[‡]
42	NS	NS			–			+		
44		NS	NS			+		+		
45	NS	NS	NS		–	–	NS	NS	+	NS[†]
46	+ (>54)	NS	+ (Asian)		NS			+		+[§]

Factors with (–) indicate a negative correlation and those with (+), a positive correlation.
*Considered metabolic syndrome if any component is reported.
[†]Primary care visits.
[‡]Hepatology visits.
[§]Unclear specialty visit.
Abbreviations: NAFLD, nonalcoholic fatty liver disease; NS, not significant.

TABLE 4. Quality Assessment of Studies

Reference	Population-Based Cohort	Exclusion Child C or Comorbidities	Ascertainment of Surveillance Receipt	Accounting for Non-US Imaging	Length of Follow-up	Accounting for Loss to Follow-up
22	High	Low	High	Low	High	High
23	Low	Low	Low	Low	Low	High
21	High	Low	High	Low	Low	High
24	High	Low	High	Low	High	High
25	Low	Low	Low	High	High	High
26	Low	Low	High	Low	Low	High
27	Low	Low	Low	High	Low	High
28,29	High	Low	High	Low	High	High
31	Low	Low	Low	Low	Low	High
30	Low	High	High	Low	High	High
32	High	Low	High	High	High	Low
33	Low	Low	Low	Low	Low	High
11	High	Low	High	Low	Low	High
34	High	Low	High	Low	High	Low
35	High	Low	High	Low	High	High
36	Low	Low	Low	High	High	High
37	Low	Low	Low	High	High	High
38	Low	Low	Low	High	High	High
39	Low	Low	Low	Low	High	High
40	High	Low	High	High	High	High
41	Low	High	Low	High	High	High
42	Low	Low	Low	High	High	High
43	Low	Low	Low	Low	High	High
44,45	High	Low	High	Low	High	High
46	Low	Low	Low	High	High	High
47	High	Low	High	High	High	Low
48	High	Low	High	Low	High	High

increased one-time abdominal imaging, despite high baseline surveillance use given that all patients were followed by hepatology subspecialists at an academic center (74.4% to 93.2%).[12] Bui and colleagues similarly reported that a dedicated pharmacist-led team increased adequate HCC surveillance (three imaging studies within 24 months) among patients with cirrhosis followed in a large community practice (22.8% versus 81.7%), with the largest relative difference in surveillance use among all studies.[17] Nazareth et al. found that a nurse-led clinic yielded semiannual ultrasound surveillance in 368 (52.6%) of 804 patients.[16] Farrell et al. also evaluated a radiology-led recall protocol for patients enrolled in HCC surveillance and found that 368 (45.8%) of 804 patients completed semiannual surveillance imaging.[18] Kennedy and colleagues found that an automated reminder system, paired with provider and patient education, increased consistent semiannual HCC surveillance over 2 years from 0% to 63.6% in a small cohort of 22 patients with cirrhosis.[13] In the largest study evaluating inreach to date, Beste and colleagues found that an EMR reminder alert in the Veterans Affairs system increased adequate HCC surveillance (≥2 imaging studies within 18 months) from 18.2% to 27.6% among patients with cirrhosis, whereas control sites without the intervention had no appreciable change in surveillance use (16.1% versus 17.5%).[14] In this study, many patients were followed by primary care providers, and surveillance use remained low postintervention. Finally, Singal and colleagues[19,51] conducted a large randomized controlled trial evaluating a population health outreach strategy in a safety-net health system among 1,800 patients identified as having cirrhosis using *International Classification of Diseases*, Ninth Revision, codes. In this study, one-time screening

within 6 months significantly increased from 24.3% in the usual care visit-based screening arm to 44.5% in the mailed outreach arm; the addition of patient navigation did not significantly increase one-time screening completion (47.2%) compared to outreach alone. In a follow-up study, the team found continued benefits of outreach and navigation over longer periods of time; semiannual surveillance over an 18-month period was performed in 23.3% of outreach/navigation patients, 17.8% of outreach-alone patients and 7.3% of usual care patients ($P < 0.001$ for both versus usual care and $P = 0.02$ for outreach ± navigation).

Discussion

Despite the clinical practice guidelines developed by multiple professional societies, our meta-analysis reveals that HCC surveillance use continues to be suboptimal in the clinical setting. Surveillance varied widely depending on study setting, with use in gastroenterology and hepatology clinics approaching 75% compared to as low as <10% in large population-based cohorts. Consistently observed correlates of surveillance across studies included higher receipt with subspecialty gastroenterology care and lower receipt in patients with alcohol-associated or NASH-related cirrhosis—increasingly common etiologies of HCC. There have been few studies evaluating interventions to increase surveillance use; however, tested interventions appear promising, with relative increases of 60%-80%.

We found low receipt of HCC surveillance in this meta-analysis, with a pooled estimate of only 24%. These data highlight minimal improvement over time compared to the 18% pooled estimate reported in a prior systematic review characterizing surveillance receipt in studies through 2010.[20] These data highlight that HCC surveillance use is substantially lower than that of other cancer screening programs including colorectal, breast, and cervical cancer, with screening rates of approximately 60%, 80%, and 90%, respectively in 2015.[52] Lower use of HCC surveillance has been attributed to multiple factors including poor provider knowledge of surveillance guidelines, underrecognition of cirrhosis or liver disease, and patient-reported barriers.[10,28,53,54] Survey studies among primary care providers in both safety-net and academic settings found multiple provider-reported barriers including lack of knowledge about surveillance benefits and limited time in clinic with competing clinical concerns.[10,53] Prior chart review studies also suggest that providers may have difficulty recognizing the at-risk population, with approximately one third of patients with HCC having unrecognized cirrhosis at the time of HCC presentation.[28,54] In contrast, unlike the poor patient adherence seen in colorectal cancer screening ranging from 40%-50%,[55,56] adherence to HCC surveillance has not historically been believed to be a major issue.[11,28] However, recent data have highlighted that patient-level barriers such as cost of ultrasound and uncertainty over where to get testing completed may result in lower surveillance receipt.[10]

One of the most consistent correlates of HCC surveillance receipt across studies was receipt of subspecialty care. This association was reinforced by subgroup analyses, with the highest surveillance receipt among studies in which patients were enrolled from subspecialty gastroenterology and hepatology clinics and lowest among studies reporting a population-based cohort, in which many patients were likely followed by primary care providers. Although we also noted variation by geographic location, this was likely driven by type of study in each area, with most population-based cohort studies from the United States and most studies from Europe being conducted in academic centers. This association may be related to higher provider awareness of HCC surveillance and its potential benefits. Whereas most gastroenterologists strongly believe that HCC surveillance is associated with reduced mortality, many primary care providers believe that HCC surveillance is associated with early detection but express a desire for more data showing reduced mortality and quantifying possible screening-related harms.[53] Studies also noted lower HCC surveillance in patients with alcohol-associated or NASH-related cirrhosis, which is concerning given that these etiologies account for an increasing proportion of HCC cases. Studies have suggested increased difficulty recognizing chronic liver disease or cirrhosis in these patients prior to HCC presentation compared to chronic hepatitis C cirrhosis; however, further studies should explore other potential barriers such as differential medical comorbidity or patient adherence.

Despite extensive literature highlighting underuse of HCC surveillance, we identified only eight studies

evaluating interventions to increase HCC surveillance. Most evaluated inreach strategies with or without provider education, such as EMR reminders or nurse-led surveillance protocols. Each study reported significant increases in HCC surveillance, although this was only effective for patients who had a clinic visit during the study period. One study evaluating population health outreach reported significant differences in surveillance receipt—for both patients who were actively seen in clinic as well as those without clinic visits. Although each study including patients followed by primary care providers reported improved surveillance receipt, postintervention surveillance use remained at ~50% or less, highlighting the need for more intensive interventions, including potential for multilevel interventions combining inreach and outreach. It is possible that other advances in HCC surveillance, including biomarker-based testing, may also reduce barriers to completion and increase surveillance use.

We noted that the current literature evaluating HCC surveillance use has several limitations. First, studies used varying definitions for HCC surveillance, with some using a guideline-concordant definition of semiannual surveillance but others using operational definitions, e.g., receipt of two imaging studies over a period of 18-24 months. Clear and standardized surveillance definitions across studies should be used to provide an accurate interpretation and analysis of surveillance rates. Defining surveillance using a time interval of every 6 months would only count patients with perfect adherence toward surveillance rates. One potential measure that incorporates frequency and number of tests during a period of interest is the proportion of time up to date with screening, which gives a more continuous measure of screening adherence. Second, there was wide variation of enrollment periods and follow-up intervals between studies, and studies have shown that adherence decreases dramatically over time.[44] Although we attempted to reduce the effect of short follow-up times by excluding studies that included one-time screening events, some studies encompassed a follow-up time of > 10 years, while others limited the follow-up period to 1 year. Third, few studies described reasons for surveillance underuse, which is an important step to inform effective intervention strategies. It is possible that surveillance "underuse" may have been appropriate in some cases if patients had comorbid conditions or liver dysfunction and surveillance was not recommended. Finally, most studies evaluating interventions have been conducted in single-center settings with unclear generalizability, have short durations of follow-up with unclear long-term sustainability of intervention effect, and have no comparative effectiveness data, so optimal intervention strategies have not been defined.

In summary, this systematic review and meta-analysis highlights that HCC surveillance continues to be underused, with only 1 in 4 patients with cirrhosis receiving surveillance. HCC surveillance underuse appears particularly problematic among patients with nonviral liver disease and those followed by primary care providers or outside academic centers. It is clear that interventions are needed to increase HCC surveillance. The current literature evaluating such intervention strategies is limited, although each strategy significantly improved surveillance use and provides a blueprint to improve early tumor detection and reduce HCC-related mortality.

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