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HCC Surveillance Improves Early Detection, Curative Treatment Receipt, and Survival in Patients with Cirrhosis: A Systematic Review and Meta-Analysis

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Data Sharing: All available data used for the meta-analysis have been included in Table 1 and Supplemental Tables 1–3.

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Abstract

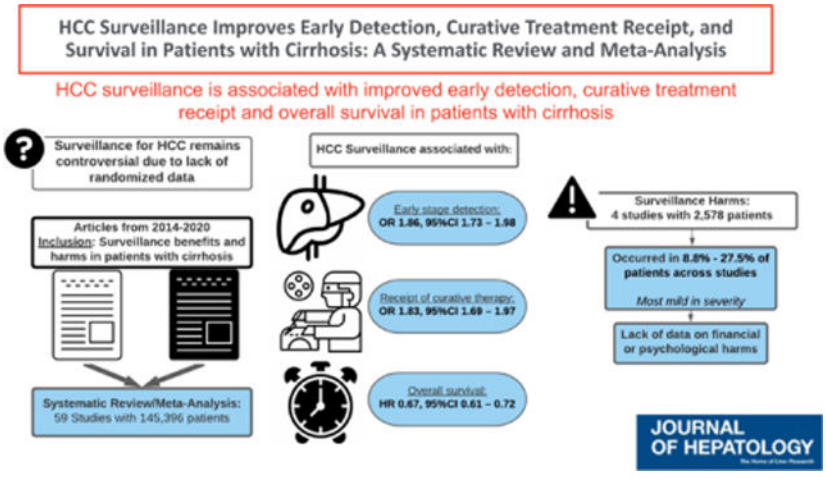
Background: There is controversy regarding the overall value of hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis given a lack of randomized controlled data. To address this issue, we conducted a systematic review and meta-analysis of cohort studies evaluating benefits and harms of HCC surveillance in patients with cirrhosis.

Methods: We performed a search of the Medline and EMBASE databases and national meeting abstracts from January 2014 through July 2020 for studies reporting early-stage HCC detection, curative treatment receipt, or overall survival, stratified by HCC surveillance status, among patients with cirrhosis. Pooled risk ratios and hazard ratios, according to HCC surveillance status, were calculated for each outcome using the DerSimonian and Laird method for random effects models.

Results: We identified 59 studies with 145,396 patients with HCC, of whom 41,052 (28.2%) were detected by surveillance. HCC surveillance was associated with improved early-stage detection (RR 1.86, 95%CI 1.73 – 1.98; I^2=82%), curative treatment receipt (RR 1.83, 95%CI 1.69 – 1.97; I^2=75%), and overall survival (HR 0.67, 95%CI 0.61 – 0.72; I^2=78%) after adjusting for lead-time bias; however, there was notable heterogeneity in all pooled estimates. Four studies examined surveillance-related physical harms due to false positive or indeterminate surveillance results, but no studies examined potential financial or psychological harms. The proportion of patients experiencing surveillance-related physical harms ranged from 8.8% to 27.5% across studies, although most harms were mild in severity.

Conclusion: HCC surveillance is associated with improved early detection, curative treatment receipt, and survival in patients with cirrhosis, although there was heterogeneity in pooled estimates. Available data suggest HCC surveillance is of high value in patients with cirrhosis, although continued rigorous studies evaluating benefits and harms are still needed.

Graphical Abstract



Lay Summary

There has been ongoing debate about the overall value of hepatocellular carcinoma (HCC) screening in patients with cirrhosis given a lack of randomized controlled data. In a systematic review of contemporary cohort studies, we found HCC screening is associated with improved early detection, curative treatment receipt, and survival in patients with cirrhosis, although there were fewer data quantifying potential screening-related harms. Available data suggest HCC screening is of high value in patients with cirrhosis, although continued studies evaluating benefits and harms are still needed.

Keywords

Screening; cirrhosis; liver cancer; early detection; ultrasound

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of death in patients with compensated cirrhosis and one of the few cancers with a rising mortality rate.[1] Despite improvements in therapeutic options for HCC, overall prognosis has remained dismal with a 5-year survival below 20%.[1] The strongest driver of HCC prognosis is tumor stage, with curative options affording 5-year survival exceeding 60% for patients with early-stage HCC compared to a median survival of 1–2 years for those with more advanced tumor stages.[2–4]

Considering this association, society guidelines recommend semi-annual HCC surveillance in patients with cirrhosis using abdominal ultrasound, with or without alpha fetoprotein (AFP).[3,4] This recommendation is supported by results from a randomized controlled trial in patients with hepatitis B virus (HBV) infection[5], but similar level I evidence for surveillance does not exist in those with cirrhosis. Additionally, competing risk of liver-related mortality and impaired visualization due to liver nodularity can impact ultrasound efficacy in patients with cirrhosis, precluding direct extrapolation of data from HBV-infected patients.[6,7] Cohort studies have suggested an association between HCC surveillance and improved survival; however, there are notable study limitations including residual confounding and lead- and length time biases.[8,9] HCC surveillance benefits also require continued evaluation considering a shifting epidemiology from predominantly active viral hepatitis to an increasing proportion of patients with sustained virological response or nonalcoholic steatohepatitis (NASH), in whom ultrasound-based surveillance may be more prone to failure.[10] The need for further data evaluating benefits of HCC surveillance was underscored when a case-control study from the Veterans Affairs health system failed to find an association between surveillance receipt and HCC-related mortality.[11]

In parallel, there is increasing recognition that the value of cancer screening programs must not only consider benefits but also physical, financial, and psychological harms.[12] Data enumerating potential harms of breast and prostate cancer screening have created controversy about guideline recommendations[13,14], highlighting a need for early evaluation of HCC surveillance-related harms. To address this need, we conducted a systematic review and meta-analysis of contemporary cohort studies evaluating the benefits and harms of HCC surveillance in patients with cirrhosis.

METHODS

Search Strategy

We conducted a computer-assisted search of the Medline and EMBASE databases to identify relevant articles published between January 1, 2014 through July 1, 2020 using the following keyword combinations: (liver ca$ OR hepatocellular ca$ OR hepatoma) AND (screen$ OR surveillance). We chose to include studies after January 2014 to update prior meta-analyses[8,9] and reflect the current status of surveillance effectiveness. We performed manual searches of reference lists to identify citations that may have been missed by the computer-assisted search. Additional searches of AASLD, EASL, DDW, and ACG conference abstracts from 2014–2019 were performed. Finally, consultation with expert hepatologists was performed to identify additional references or unpublished data. This study was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Study Selection

One investigator (EZ) reviewed citations from the search strategy to generate a list of potentially relevant articles. If the applicability of a study could not be determined by title or abstract alone, the full text was reviewed. Full texts were independently checked for possible inclusion by a second investigator (AGS) and disagreements were resolved through discussion.

Studies were included if they (i) utilized abdominal imaging, with or without AFP, for surveillance; (ii) performed surveillance in a cohort of patients with cirrhosis from any etiology; and (iii) reported the number of HCC detected at an early stage (regardless of staging system), number of HCC patients who received curative therapies, and/or overall survival, stratified by surveillance receipt. If a study included patients with and without cirrhosis, only data regarding patients with cirrhosis were extracted when possible. We excluded studies that only reported outcome measures for patients undergoing surveillance but not for those without surveillance. Additional exclusion criteria included non-human data, lack of original data, non-English studies, and incomplete reports. If duplicate publications used the same cohort of patients, the study with more complete data was included.

Data Extraction and Quality Assessment

Two investigators (EZ and AGS) independently extracted required information from eligible studies using standardized forms. Discrepancies were resolved via discussion, with a third investigator (NR) as needed. The data extraction form included the following: characteristics and size of the cohort, inclusion and exclusion criteria, surveillance tests, surveillance interval, and definition of early-stage HCC. We recorded the following data, stratified by surveillance receipt: number of patients with HCC, proportion of HCC detected at an early stage, proportion of patients who received curative treatments, and overall survival. In most studies, early-stage HCC was defined using the Barcelona Clinic Liver Cancer (BCLC) staging system, and curative treatments included liver transplantation, surgical resection, or local ablative therapy (LAT). Two investigators (EZ and AGS) assessed study quality

by a modified checklist based upon the National Institute of Health (NIH) study quality assessment tool for observational cohort studies, with discrepancies resolved by discussion with a third investigator (NR).

Statistical Analysis

For each study, we calculated a risk ratio (RR) with the exposure being surveillance receipt and clinical outcomes being proportion of patients detected at an early stage, proportion who underwent curative treatment, overall survival, and surveillance-related harms. For overall survival, we abstracted an adjusted hazards ratio (HR) for mortality when available; if not reported, we recorded median survival for both groups. For surveillance-related harms, we recorded the proportion of patients with physical, financial, or psychological harms related to surveillance from each study – as defined by an established nomenclature.[15] Physical harm is typically defined as any diagnostic testing related to false positive or indeterminate surveillance results, which can be classified as mild (one diagnostic CT or MRI), moderate (repeated diagnostic CT or MRI), or severe (any invasive evaluation such as biopsy). Financial harms include direct costs of screening and diagnostic evaluation plus indirect costs such as missed work. Psychological harms can occur at any step of the screening process and include anticipation or fear of abnormal results, cancer-specific worry, or reactions of depression after positive results.

We calculated a pooled risk ratio estimate with corresponding 95% confidence intervals for early-stage HCC detection and curative treatment receipt and pooled hazard ratio estimate for overall survival, adjusted for lead time bias, using the DerSimonian and Laird method for random effects models. Heterogeneity was evaluated graphically by examination of forest plots and statistically by the chisquared test of heterogeneity and the inconsistency index (I^2).[16] Values of <25%, 25–75% and >75% were considered as low, moderate, and high heterogeneity, respectively. We performed sensitivity analyses, in which outliers were removed, to determine if this impacted pooled effect estimates. Pre-planned subgroup analyses were performed for: (i) type of publication (full length publication versus conference abstract), (ii) location of study (Asia versus Europe versus United States), (iii) study period (cohort initiation prior to 2000 versus between 2000 – 2005 versus after 2005), (iv) study size (<200 patients versus 200–500 patients versus >500 patients), (v) inclusion of any patients without cirrhosis, (vi) surveillance modality (ultrasound alone versus ultrasound + AFP versus any abdominal imaging), and (vii) length of surveillance interval (semi-annual versus longer intervals versus surveillance-detected).

Thresholds for study period dates (i.e., 2000 and 2005) were selected based on publication dates of prior guidelines.[17,18] We also performed a post-hoc subgroup analysis by overall study quality, dichotomized at the median quality score. Publication bias was evaluated graphically using funnel plot analysis and then statistically using Egger's test. We evaluated the potential effect of publication bias on pooled estimates using the trim-and-fill method.[19] All data analysis was conducted using Stata version 11 (StataCorp, College Station TX).

RESULTS

Study Characteristics

The computer-assisted literature search yielded 8872 potentially relevant titles published between January 2014 and July 2020, of which 38 met inclusion criteria after full-text review. A recursive literature search and consultation with experts identified two additional articles and searches of annual meeting abstracts yielded 22 relevant abstracts, resulting in a total of 62 studies for inclusion – 58 studies for HCC surveillance benefits alone, three for HCC harms alone, and one for both (Supplemental Table 1, Supplemental Figure 1).

Characteristics of studies evaluating HCC surveillance benefits are described in Supplemental Table 1. Fifty-nine studies, with 145,396 patients with HCC, assessed the impact of surveillance on at least one outcome of interest. Fifteen studies were conducted in North America, 21 in Europe, 14 in Asia, and 9 elsewhere (four Australia, two New Zealand, two South America, and one Morocco). All but six were retrospective, and most cohorts were diverse in terms of liver disease etiology. Overall, 41,052 (28.2%) patients had HCC detected by surveillance and 104,596 (71.8%) presented symptomatically or incidentally. HCC was detected by surveillance in 14.0% (2692 of 19181) of patients among studies in North America, 40.8% (3033 of 7431) in Europe, 29.2% (33,916 of 116,109) in Asia, and 52.7% (1411 of 2675) of those from other countries.

Early Detection and Curative Treatment Receipt

Forty-nine studies, with a total of 35,104 HCC patients, included data on tumor stage stratified by receipt of HCC surveillance. Most studies (n=27) defined early-stage HCC using BCLC stage 0/A, whereas nine used the Milan criteria and 11 used other staging systems (e.g., tumor node metastases [TNM]); two studies provided data on early-stage detection but did not detail what staging system was used (Supplemental Table 1). Patients who underwent surveillance were more likely to have HCC diagnosed at an early stage (RR 1.86, 95%CI 1.73 – 1.98) (Figure 1); however, there was significant heterogeneity (I^2=82%, p<0.001). Although we identified outlier studies on inspection of the forest plots (e.g., Al Hasani, Branch, Eskesen, Sonovane, Wong), we did not find clinical heterogeneity justifying their exclusion. The trim-and-fill method imputed 12 studies to account for publication bias and the pooled estimate of association between surveillance and early detection was unchanged. There was also little change in effect size and heterogeneity when only including studies that defined early-stage as BCLC stage 0/A or within Milan criteria, (RR 1.92, 95%CI 1.74 – 2.09, I^2=85%) or those that defined early-stage using BCLC stage 0/A alone (RR 1.99, 95%CI 1.73 – 2.25, I^2=87%). The pooled proportion of early-stage detection among patients undergoing surveillance was 66.9% (95% CI 66.0 – 67.8%), compared to only 33.1% (95%CI 32.5 – 33.7%) among those who presented symptomatically or incidentally (Table 1). When restricted to studies that defined early-stage HCC as BCLC 0/A, pooled proportions of early-stage detection were 58.8% (95%CI 57.3 – 60.2%) for surveillance-detected and 27.0% (95%CI 26.0 – 28.1%) for non-surveillance detected. Results were consistent in all pre-planned subgroup analyses according to location of study, study period, type of surveillance tests, surveillance interval, and study size, although high heterogeneity continued to be observed. Improved early tumor detection by surveillance

receipt was consistent among studies across study locations: RR 1.85 [95%CI 1.57–2.18] in North America, 1.91 [95%CI 1.67–2.16] in Europe, 2.07 [95%CI 1.83–2.33] in Asia, and 1.63 [95%CI 1.26 −2.09] elsewhere, with I^2>70% for all subgroups. Surveillance was associated with early-stage detection among the 17 studies using ultrasound alone (RR 1.87, 95%CI 1.62 – 2.12, I^2=88%) and 15 studies using ultrasound with or without AFP (RR 2.21, 95%CI 1.90 – 2.57, I^2=81%). Finally, surveillance was associated with early-stage detection among studies classified as low risk of bias (RR 1.92, 95%CI 1.77 – 2.10, I^2=87%) and those at higher risk of bias (RR 1.78, 95%CI 1.51 – 2.04, I^2=75%).

Thirty-nine studies, comprised of 86,466 HCC patients, assessed the association between HCC surveillance and receipt of curative therapy. Of included patients, 18,762 (21.7%) were detected by surveillance and 67,704 (78.3%) presented symptomatically or incidentally. Patients diagnosed by surveillance were more likely to undergo curative therapy, with a pooled risk ratio of 1.83 (95%CI 1.69 – 1.97), although there was high heterogeneity (I^2=75%, p<0.001) (Figure 2). Similar to early detection analyses, we did not identify clinical heterogeneity justifying exclusion of outlier studies seen on forest plots (e.g., Aby, Asad, Eskesen). The trim-and-fill method imputed 25 studies but the pooled estimate for association between surveillance and curative treatment was unchanged. The pooled rate of curative treatment receipt among patients undergoing surveillance was 58.2% (95%CI 57.1 – 59.3%), compared to 34.0% (95%CI 33.1% – 34.9%) among those who presented outside of surveillance (Table 1). Patients detected by surveillance were significantly more likely to undergo curative treatment across all pre-planned subgroup analyses. The pooled RRs of curative treatment receipt were 1.85 (95%CI 1.37 – 2.33) for studies in North America, 1.69 (95%CI 1.53 – 1.85) in Europe, 1.82 (95%CI 1.51 – 2.12) in Asia and 2.12 (95%CI 1.84 – 2.41) for elsewhere, with I^2>70% for all subgroups except elsewhere (I^2=0%). Surveillance was associated with curative treatment receipt among the 11 studies using ultrasound alone (RR 1.65, 95%CI 1.49 – 1.81, I^2=44%) and the 12 studies using ultrasound with or without AFP (RR 1.99, 95%CI 1.67 – 2.30, I^2=84%). Finally, surveillance was associated with curative treatment among studies classified as low risk of bias (RR 1.87, 95%CI 1.71 – 2.04, I^2=79%) and those at higher risk of bias (RR 1.75, 95%CI 1.45 – 2.04, I^2=63%).

Overall Survival

Forty-two studies, consisting of 141,522 HCC patients (27.7% [n=39,139] detected via surveillance), included data on survival stratified by receipt of HCC surveillance. There was variability in reporting of survival data, with 22 studies reporting hazard ratios with 95% confidence intervals, 14 reporting median or mean survival, five reporting 1- or 3-year survival, and one reporting hazard ratios without confidence intervals (Supplemental Table 1). All but one study that reported median, 1-, and 3-year survival demonstrated improved survival among surveillance versus non-surveillance patients (Table 1). Of 22 studies with hazard ratios and 95% confidence intervals, seven were from North America, four from Europe, five from Asia, and six from Australia or South America. Among these studies (n=134,345 patients of whom 36,231 were surveillance-detected), HCC surveillance was significantly associated with improved survival, with a pooled hazard ratio of 0.64 (95%CI 0.59 – 0.69); however, we observed high heterogeneity (I^2=72%).

Among 12 studies that adjusted for lead time bias when assessing the association between HCC surveillance and survival (Table 1), surveillance remained associated with improved survival (HR 0.67, 95%CI 0.61 – 0.72 I^2=78%) (Figure 3). The trim-and-fill method imputed 3 studies but the pooled estimate for the association between surveillance and overall survival was unchanged (HR 0.70, 95%CI 0.63 – 0.77). There was also a consistent association between surveillance and improved survival across all subgroup analyses. Surveillance was associated with improved survival among studies from North America (HR 0.77, 95%CI 0.72 – 0.82, I^2=53%), Europe (HR 0.50, 95%CI 0.37 – 0.63, I^2=0%), Asia (HR 0.66, 95%CI 0.65 – 0.68, I^2=84%), and elsewhere (HR 0.57, 95%CI 0.46 – 0.67, I^2=0%). Surveillance was associated with improved survival among the studies using ultrasound alone (HR 0.67, 95%CI 0.65 – 0.68, I^2=68%) versus ultrasound with or without AFP (HR 0.74, 95%CI 0.69 – 0.80, I^2=66%) as well as studies using shorter (HR 0.66, 95%CI 0.64 – 0.68, I^2=61%) versus longer (HR 0.74, 95%CI 0.71 – 0.78, I^2=77%) intervals.

Emerging Surveillance Populations

Only seven studies differentiated post-SVR and actively viremic patients when describing patients with hepatitis C infection. One study specifically examined the association between surveillance and clinical outcomes in post-SVR patients with cirrhosis,[20] while another included >90% post-SVR patients.[21] Branch and colleagues reported a significant association with early-stage detection but no difference in 3-year survival between surveillance-detected patients and those who presented symptomatically.[20] In contrast, Costentin reported surveillance was significantly associated with improved early-stage detection, curative treatment receipt and overall survival, even after adjusting for lead-time bias.[21] Post-SVR patients accounted for less than 10% of cohorts for the other five studies in which data were available.

While several studies reported the proportion of NAFLD etiology in study demographics, only two studies examined the association between surveillance and clinical outcomes among those with NAFLD. Lo and colleagues reported a significant association with early-stage detection (69.6% vs. 30%, p=0.001)[22] whereas Aby et al. failed to find an association with curative treatment receipt (45.5% vs. 51.5%, p=0.72).[23] In subgroup analyses by the proportion of NAFLD patients in each study (<10%, 10–20, and >20%), we found similar point estimates for the association between surveillance and early-stage detection (RR 1.86, 2.23, and 2.04, respectively) and curative treatment receipt (RR 1.79, 2.06, and 2.02, respectively). HCC surveillance was also associated with improved survival in studies with <10% NAFLD (HR 0.75, 95%CI 0.61 – 0.89, I^2=72%) and 10–20% NAFLD (HR 0.53, 95%CI 0.45 – 0.61, I^2=0%). Studies with >20% NAFLD patients did not report survival data using hazard ratios and 95% confidence intervals; however, each study reported improved survival. For example, Clegg and colleagues reported 3-year survival of 20% vs. 8.2% for surveillance-detected vs. others,[24] and Sigurdsson reported median survivals of 17.1 and 4.5 months, respectively.[25]

Differences in Benefits by Surveillance Exposure

Fifteen studies, including 27705 HCC patients, assessed surveillance outcomes, stratified by surveillance exposure, with six studies assessing intervals shorter versus longer than

6–9 months, four assessing intervals shorter versus longer than 12 months, and five comparing semi-annual versus annual surveillance (Supplemental Table 2). There was a consistent association between shorter surveillance intervals and early detection across the nine studies with applicable data (pooled RR 1.38, 95%CI 1.32 – 1.44, I^2=84%). However, data were conflicting for curative treatment receipt, with six studies suggesting no significant association and four demonstrating higher curative treatments with shorter intervals (pooled RR 1.11, 95%CI 0.98 – 1.27, I^2=75%). Eleven studies assessed overall survival by surveillance exposure, with most demonstrating greater survival benefit with shorter surveillance intervals.

Surveillance-related Harms

We identified four studies, including 2578 patients with cirrhosis, that characterized surveillance-related harms. All studies only reported physical harms, with no studies evaluating potential financial or psychological harms. Atiq et al. evaluated surveillance and benefits and harms in 680 patients with cirrhosis undergoing surveillance over a 3-year period.[26] Although surveillance-related physical harms were observed in 187 (27.5%) patients, most cases were mild in severity. Sixty-six (9.7% of the cohort) patients experienced moderate harm, and three (0.4% of the cohort) patients experienced severe harm, such as diagnostic biopsy. The proportion experiencing physical harm increased from 11.9% among those with one surveillance exam to 29.6% among those with two or more exams. Konerman and colleagues evaluated 999 patients in a surveillance program over a median of 2.2 years.[27] Of 256 patients with abnormal surveillance ultrasound, 69 were diagnosed with HCC. Of the 187 false positive results, 87 underwent one CT or MRI (mild harm), 77 repeat CT/MRI imaging evaluation (moderate harm), and five underwent biopsy (severe harm). Eighteen patients were followed with ultrasound-based surveillance without evidence of HCC and classified as no surveillance-related harm. Therefore, moderate-severe harm was observed in 8.2% of the cohort. In a cohort of 285 patients undergoing surveillance ultrasound over a 2-year period, Frey and colleagues found 44 patients had a suspicious lesion on ultrasound, of whom nine were diagnosed with HCC.[28] The other 35 (12.3%) patients underwent a total of 17 CT exams, 11 contrast-enhanced ultrasounds, nine MRI exams, and two biopsies. An additional 23 (8.1%) patients with indeterminate ultrasounds (i.e., poor visualization) also resulted in 24 CT exams, six MRI exams, and one biopsy. There were insufficient data to determine patient-level severity of harm. Finally, Singal et al. examined outcomes in 614 patients with cirrhosis with at least one surveillance exam over an 18-month period, and surveillance-related physical harms were only observed in 54 (8.8%) patients – most of mild severity and none experiencing severe harm.[29]

Quality Assessment

Funnel plot analysis revealed potential publication bias (Egger’s test p=0.04), with fewer “negative” small studies reporting a lack of association between surveillance and improved outcomes. Using a modified NIH study quality assessment tool (Supplemental Table 3), we found most studies clearly defined the study objective and eligibility criteria, and all but one selected patients from the same population. Most studies had low risk of bias for exposure measurement; however, 17 studies stratified results as surveillance-detected vs. undetected HCC, which omits possible surveillance failure, or failed to define surveillance regimens so

were classified as medium risk of bias. There were also four studies classified as high risk of bias – three which included AFP alone as surveillance exposure and one that relied on patient report for surveillance receipt. Although most studies assessed surveillance receipt as a dichotomous outcome, 15 assessed surveillance benefits across different levels of exposure – either comparing regular vs. irregular surveillance or assessing continuous measures such as proportion time covered by surveillance. Most studies measured objective and guideline-concordant outcomes and classified as low risk of bias; however, 13 studies assessed tumor stage using measures other than the BCLC or Milan Criteria. Several studies (n=28) also failed to report measures of variance, such as 95% confidence intervals, when describing differences in clinical outcomes between groups. The most common limitation was failure to report length of follow (n=30) and/or number lost to follow-up (n=31) for studies assessing treatment receipt or survival after HCC diagnosis. Most studies reporting differences in early detection or curative treatment receipt failed to adjust for potential confounders. Of the 42 studies that reported survival estimates, only half adjusted for demographics and clinical characteristics. Of the other 21 studies which reported unadjusted differences in survival, four statistically accounted for lead-time bias.

DISCUSSION

The goal of HCC surveillance is to reduce HCC-related mortality by promoting very-early tumor detection and facilitating curative treatments. Our meta-analysis highlights a consistent association between receipt of surveillance and improved clinical outcomes, including overall survival, across cohort studies, although high heterogeneity precluded precise point estimates. Additionally, we found semi-annual surveillance intervals were associated with improved early detection and overall survival compared to longer surveillance intervals. It is therefore noteworthy that less than one-third of HCC cases were detected by surveillance. To inform discussions regarding the overall value of surveillance, we also summarized data for surveillance-related harms; however, few studies characterized surveillance-related harms, with available data focusing only on physical harms and no studies reporting psychological or financial harms. Although there was variation in the magnitude of physical harms experienced by patients, most harms appeared mild and consistent with guideline-concordant follow-up of abnormal surveillance results.

We found HCC surveillance was associated with significant improvements in early HCC detection, with two-thirds of surveillance-detected HCC identified at an early stage. This proportion parallels the sensitivity of current surveillance tools, ultrasound with or without AFP.[7] With an aim of increasing sensitivity for early HCC detection, there has been increased interest in alternative imaging (e.g., MRI) and blood-based biomarkers (e.g., GALAD).[30,31] We did not find any difference in clinical benefits of various surveillance strategies in subgroup analyses, although these were conducted at the study-instead of patient-level. Therefore, continued evaluation of screening benefits and harms of novel surveillance strategies in prospective cohort studies is still needed.

Improving early detection only addresses one step in the cancer care continuum, as survival is also dependent on the receipt of curative treatment.[32] Although HCC surveillance was associated with increased curative treatment receipt, only 58% of surveillance-detected

patients received curative therapies. These data are consistent with studies demonstrating underuse of curative treatments, including in patients with early-stage HCC. Despite this issue, surveillance was associated with a reduction in mortality, which was consistent across examined subgroups, including in those that statistically adjusted for lead time bias. It is likely the potential association between HCC surveillance and reduced mortality is underestimated across studies given downstream process failures among those detected at an early stage.

Notably, we observed heterogeneity across pooled analyses, which we were unable to eliminate across study-level subgroup analyses. Unfortunately, we were unable to explore other reasons for heterogeneity given a lack of patient-level data. For example, heterogeneity in early HCC detection may be related to several factors including variations in operator experience and technique, patient body habitus, and liver nodularity, which we were unable to explore. Similarly, we were unable to perform subgroup analyses by patient characteristics such as liver disease etiology and degree of liver dysfunction. Heterogeneity in the pooled estimate for the association with survival may be exacerbated by differences in confounders included in multivariable models. This high heterogeneity precludes precise estimates for the magnitudes of association, although the consistency of association with improved clinical outcomes across studies provides can provide some reassurance that the associations are likely true.

Although the efficacy and value of HCC surveillance would be best evaluated by a randomized clinical trial, a prior attempt suggested this may not be feasible.[33] As such, we are dependent on data from available cohort studies. Modeling and cost-effectiveness studies incorporating these data may also aid in informing important nuances of HCC surveillance, such as subgroups who have worse risk-benefit ratio, stopping rules, and optimal surveillance intervals.[34] In the interim, our data highlight the clear need for strategies to increase surveillance uptake.[35]

Notably, some data have suggested HCC surveillance may not be associated with improved clinical outcomes. For example, a case-control study with 238 patients who died of HCC and 238 matched controls from the Veterans Affairs health system failed to find an association between surveillance and reduced HCC-related mortality.[11] As above, this lack of mortality benefit may not have been related to surveillance failure but instead downstream process failures, such as underuse of HCC treatment or application of surveillance in patients who are not candidates for any HCC treatment. These conflicting data highlight the need for continued evaluation of HCC surveillance, particularly considering inherent limitations of cohort studies such as residual confounding and length time bias. For instance, few studies adjusted for hepatology subspecialty care and lower medical comorbidity, which are often associated with receipt of HCC surveillance.[35] Similarly, HCC has historically been considered a uniformly aggressive cancer although data suggest one-third of HCC may have indolent growth patterns.[36,37] Continued evaluation of HCC surveillance is also critical considering the changing at-risk population, with a shift from a viral-mediated disease to one related to alcohol and NAFLD. Studies have suggested lower recognition of cirrhosis in patients with NAFLD, resulting in lower surveillance utilization.[38,39] Further, non-viral liver disease predisposes ultrasound to poorer visualization and AFP to impaired test

performance.[40] Finally, a higher prevalence of comorbid conditions including cardiovascular disease or worse performance status may preclude surgical therapies and mitigate a survival benefit among those detected at an early stage.[41,42] Although we did not see a difference in surveillance benefits across subgroups, including study period, most study populations still largely consisted of active viral liver disease. Few studies specifically examined post-SVR or NAFLD patient populations, highlighting this as an area of future research.

It is critical that future studies evaluate overall surveillance value, by assessing not just benefits but also potential harms. While we identified 59 studies evaluating surveillance benefits, only four quantified potential harms due to false positive or indeterminate results. Furthermore, all four only examined physical harms, with no studies quantifying financial or psychological harms. These data are important to evaluate, particularly considering screening-related harms observed in other cancer types.[14] Notably, measures of specificity may not equate to screening-related harms when surveillance tests are applied in clinical practice. For example, Atiq and colleagues reported higher screening-related harms with ultrasound than AFP, despite higher specificity, due to differences in how providers interpreted and managed abnormal results for both.[26] This same principle may apply to emerging surveillance modalities, given how providers interpret longitudinal changes in biomarker values and mitigate potential harms. In contrast, ultrasound-related harms were increased by providers often performing diagnostic evaluation for subcentimeter lesions, despite most guidelines recommending short-interval ultrasound surveillance.[3,4] Studies reported a wide variation in the proportion of patients experiencing physical harms from ultrasound and AFP-based surveillance. Two studies reported less than 10% of patients experienced harm, whereas two others reported over 25% experienced harm. It is unclear if these differences relate to differences in patient populations, variation in provider practice patterns, or differences in study design including study duration. While AFP is prone to false positive results in patients with viral hepatitis, ultrasound has lower specificity in those with non-viral liver disease.[40] With a shift in cirrhosis epidemiology from viral to non-viral etiologies, biomarkers such as AFP may start to have higher specificity and lower risk of harms than ultrasound. Rigorous evaluation of benefits and harms in a single population, ideally multi-center and diverse in terms of liver disease etiology, will provide a better understanding of surveillance value.

We acknowledge limitations of our study, which should be considered when interpreting results. We observed heterogeneity across pooled analyses and, which we were unable to eliminate across study-level subgroup analyses. Unfortunately, we were unable to explore other reasons for heterogeneity given a lack of patient-level data. For example, heterogeneity in early HCC detection may be related to several factors including variations in operator experience and technique, patient body habitus, and liver nodularity, which we were unable to explore. Similarly, we were unable to perform subgroup analyses by patient characteristics such as liver disease etiology and degree of liver dysfunction. Second, non-surveillance groups were comprised of patients with incidental and symptomatic presentations, who have distinct prognosis; however, most studies did not report data separately for these two subgroups. Third, we were able to summarize physical harms of surveillance but did not find data characterizing psychological or financial harms. Finally, interpretation of results from our meta-analysis is limited by the quality of

included studies. We were pleased to observe improvement in study quality compared to a prior meta-analysis[8], including most assessing outcomes by surveillance exposure instead of surveillance detection, using BCLC or Milan Criteria to define early-stage HCC, reporting continuous measures of survival benefit (i.e., hazard ratios), and adjusting for liver dysfunction and lead time bias. There has also been increased recognition of surveillance harms contributing to the overall value of HCC surveillance. Future studies should address remaining limitations such as adjusting for potential confounders and reporting measures of variance for all outcomes, median length of follow-up, and number of patients lost to follow-up.

In summary, we observed a consistent association between HCC surveillance and improved clinical outcomes, including overall survival, across contemporary cohort studies, although high heterogeneity precluded precise point estimates. There are fewer data evaluating surveillance-related harms, although available studies found that most harms were mild in severity. Therefore, current data suggest HCC surveillance is of high value and should be promoted in patients with cirrhosis, particularly given the low proportion of surveillance-detected patients across studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest:

Amit Singal has served as a consultant or on advisory boards for Bayer, Wako Diagnostics, Exact Sciences, Roche, Glycotest, and GRAIL.

Jorge Marrero has served as a consultant for Glycotest.

Neehar Parikh has served as a consultant or on advisory boards for Bayer, Wako Diagnostics, Exact Sciences, Glycotest, and Freenome.

Maria Reig has served as consulant or advisory boards for Bayer-Shering Pharma, BMS, Roche, Ipsen, AstraZeneca, Lilly, BTG/Paid conferences: Bayer-Shering Pharma, BMS, Gilead, Lilly and is a principal investigator of research Grants of Bayer-Shering Pharma, Ipsen.

Giuseppe Cabibbo has served as a consultant or on advisory boards for Bayer, Eisai, and Ipsen.

Ju Dong Yang has served as a consultant or on advisory boards for Exact Sciences and Gilead Sciences and Eisai.

None of the other authors have any relevant conflicts of interest.

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Highlights

- HCC surveillance was associated with significantly improved early-stage detection, curative treatment receipt, and prolonged survival across contemporary cohort studies.
- Semi-annual surveillance intervals were associated with improved early HCC detection and overall survival compared to longer surveillance intervals.
- Few studies evaluated surveillance outcomes in post-SVR or NAFLD patient populations, highlighting this as an area of future research.
- Few studies characterized surveillance-related harms, although available data suggests surveillance harms are mild in severity.

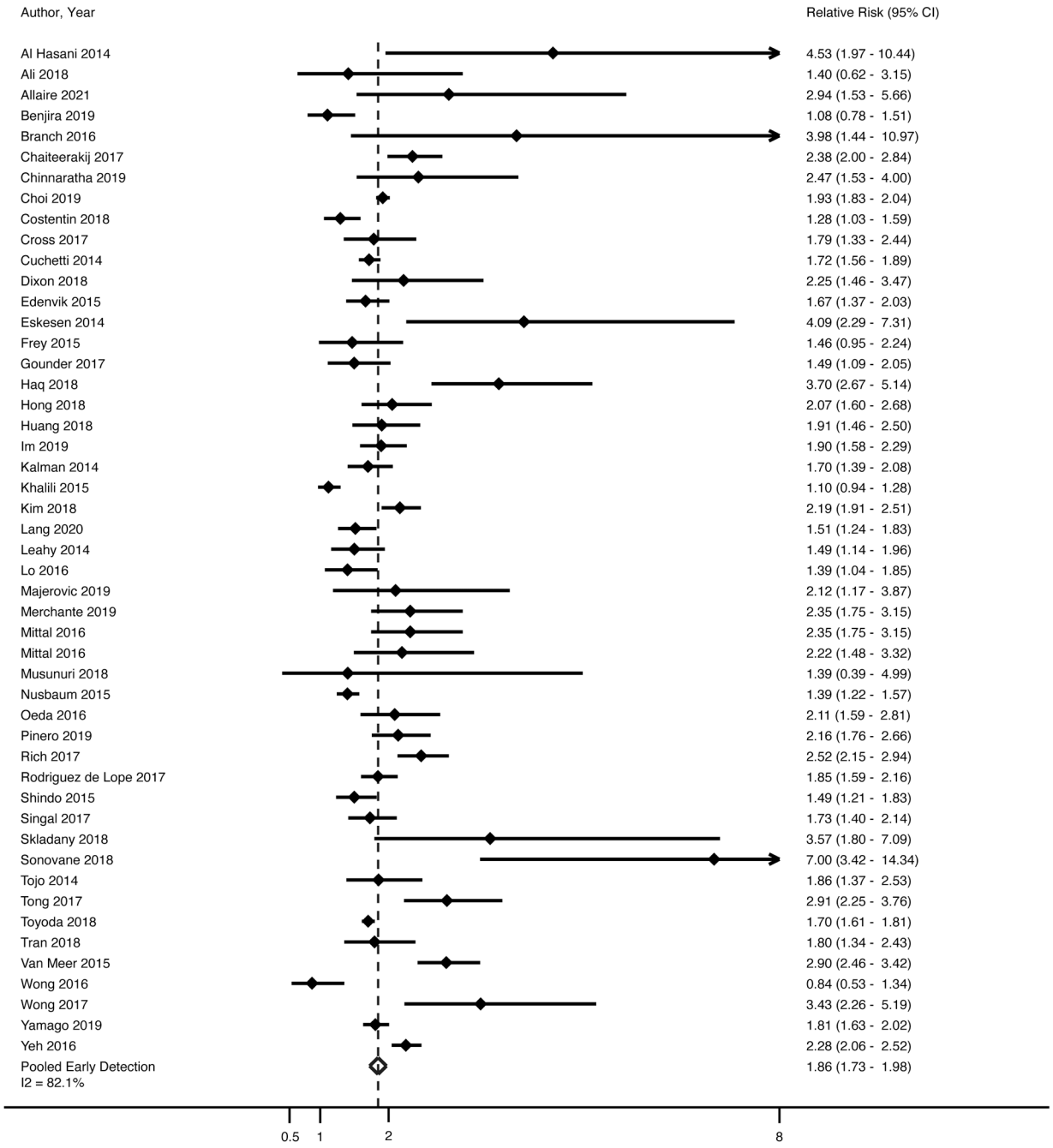

Figure 1. Association Between HCC Surveillance and Early Tumor Detection

Patients who underwent surveillance were significantly more likely to have HCC diagnosed at an early stage (OR 1.94, 95% CI 1.80 – 2.08); however, there was significant heterogeneity (I^2=84%, p<0.001). DerSimonian and Laird method was used for a random effects model.

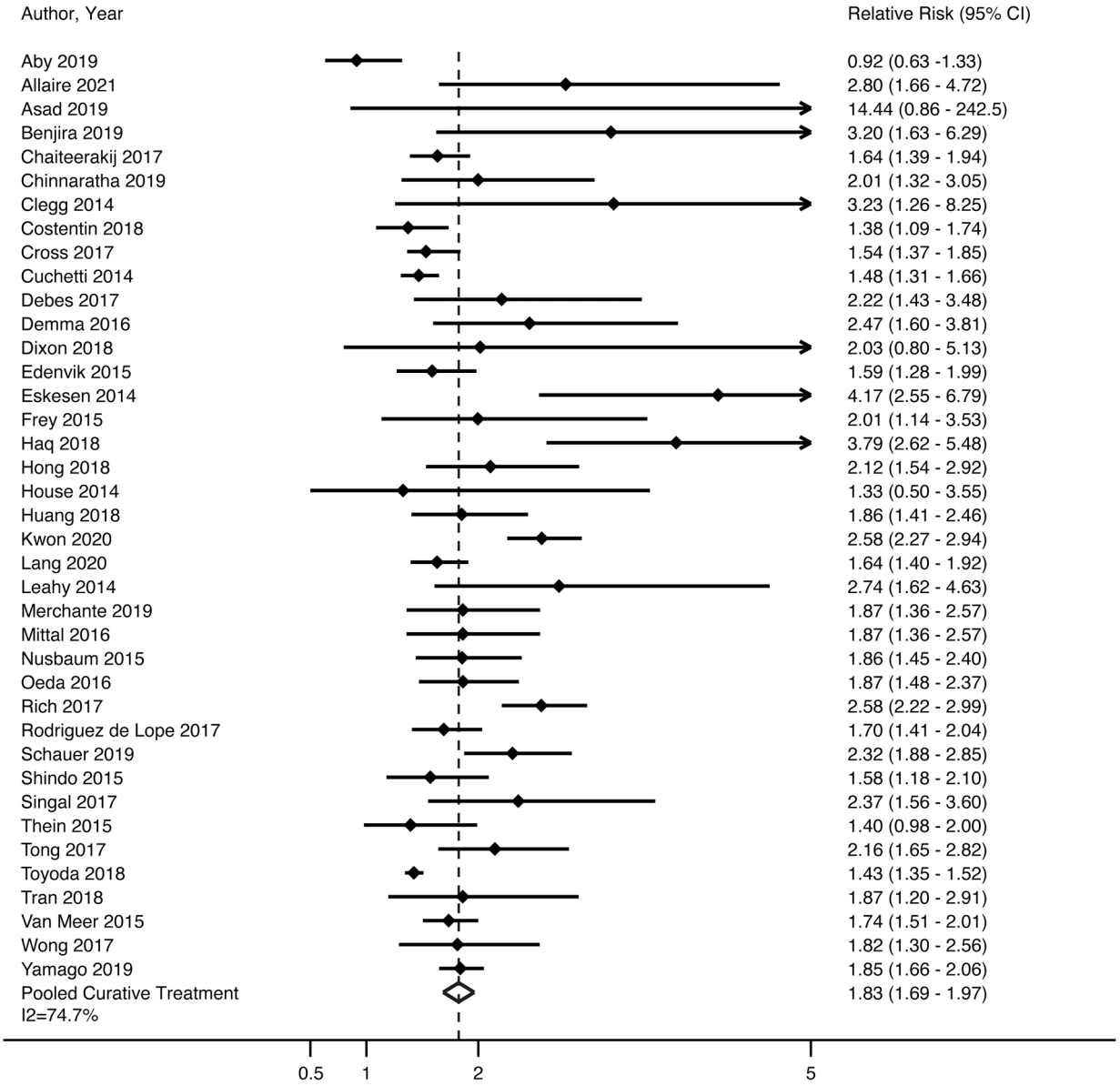

Figure 2. Association Between HCC Surveillance and Curative Treatment Receipt

Patients diagnosed by surveillance were significantly more likely to undergo curative therapy, with a pooled odds ratio of 1.83 (95%CI 1.69 – 1.97), although there was high heterogeneity among studies (I^2=75%, p<0.001). DerSimonian and Laird method was used for a random effects model.

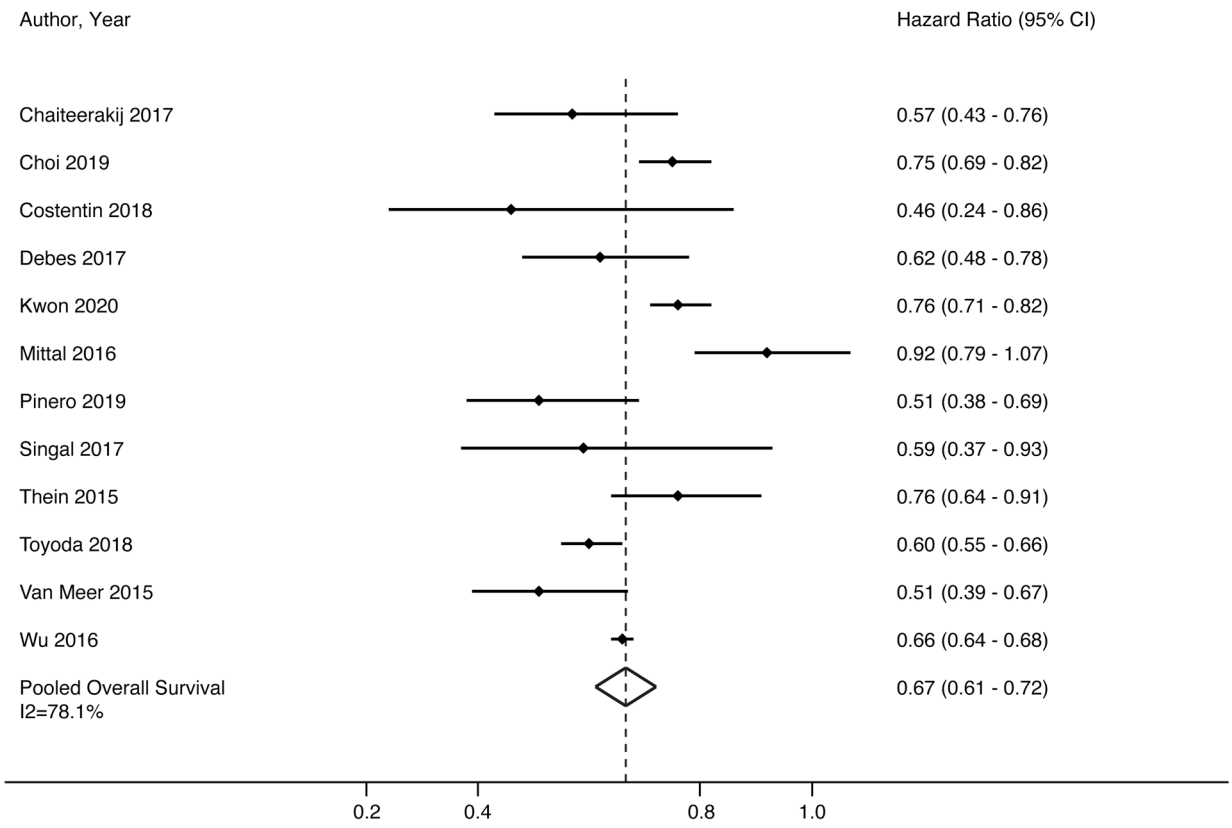

Figure 3. Association Between HCC Surveillance and Overall Survival

HCC surveillance was significantly associated with improved survival, with a pooled hazard ratio of 0.66 (95%CI 0.61 – 0.71); however, there was high heterogeneity (I^2=75%, p<0.001). DerSimonian and Laird method was used for a random effects model.

Table 1:

Clinical outcomes, stratified by surveillance receipt

Author Year	Proportion of Patients with Early HCC	Proportion of Patients with Curative Treatment	Factors adjusted for in survival analysis	Overall Survival
Aby 2019	NR	15/29 vs. 131/232	Not applicable	NR
Al Hasani 2014	32/48 vs. 5 /34	NR	Not applicable	NR
Ali 2018	14/15 vs. 2/3	NR	Not applicable	NR
Allaire 2021	39/68 vs. 8/41	51/68 vs. 11/41	None	Median survival 60 vs. 14 months * (p=0.01)
Asad 2019	NR	5/15 vs. 0/20	None	1-year survival 73% vs. 50% (p<0.05)
Benjira 2019	26/43 vs. 33/59	21/43 vs. 9/59	Not applicable	NR
Branch 2016	23/27 vs. 3/14	NR	None	3-year survival 60% vs. 62% (p=0.30)
Chaiteerakij 2017	83/103 vs. 116/343	76/103 vs. 154/343	Lead time, demographics, liver disease etiology, BCLC, Child Pugh, MELD, AFP level	HR 0.57 (95%CI 0.43 – 0.76)
Chinnaratha 2019	14/24 vs. 25/106	15/24 vs. 33/106	BCLC, MELD, AFP level	HR 0.63 (95%CI 0.28 – 1.42)
Choi 2019	596/937 vs. 4215/12777	NR	Lead time, demographics, etiology	HR 0.75 (95%CI 0.69 – 0.82)
Clegg 2014	NR	6/25 vs. 9/121	None	3-year survival 20% vs. 8.2% (p<0.05)
Costentin 2018	92/129 vs. 48/86	91/129 vs. 44/86	Lead time, demographics, liver disease etiology, hepatic decompensation, bilirubin, PT, AFP level	HR 0.46 (95%CI 0.24 – 0.86)
Cross 2017	OR 1.79 (1.33 – 2.44)	OR 1.54 (1.37 – 1.85)	Not applicable	NR
Cuchetti 2014	689/850 vs. 250/530	511/850 vs. 216/530	Lead time	Median survival 41.6 vs. 28.5 months
Debes 2018		OR 2.22 (1.43 – 3.48)	Lead time, liver disease etiology, cirrhosis, AFP level, curative treatment	HR 0.62 (95%CI 0.48 – 0.78)
Demma 2016	NR	55/108 vs. 20/97	NR	HR 0.45 (95%CI 0.30 – 0.66)
Dixon 2018	17/25 vs. 23/76	6/25 vs. 9/76	None	3-year survival 22.2% vs. 8.2%
Edenvik 2015	92/134 vs. 87/211	80/134 vs. 79/211	None	Median survival 34 vs. 21 months * (p<0.05)
Eskesen 2014	9/19 vs. 30/259	11/19 vs. 36/259	None	Mean survival 31 vs. 11 months (p<0.001)
Frey 2015	12/16 vs. 18/35	11/16 vs. 12/35	Not applicable	NR
Gounder 2017	18/22 vs. 28/51	NR	Not applicable	NR
Haq 2018	62/160 vs. 50/478	52/160 vs. 41/478	None	Mean survival 32 vs. 15 months (p<0.001)
Hassan 2016	NR	NR	None	Median survival 12.8 vs. 9.3 months (p=0.001)

Author Year	Proportion of Patients with Early HCC	Proportion of Patients with Curative Treatment	Factors adjusted for in survival analysis	Overall Survival
Hong 2018	75/110 vs. 52/158	59/110 vs. 40/158	Demographics, liver disease etiology, Child Pugh, BCLC, AFP level, curative treatment	HR 0.60 (95%CI 0.38 – 0.93)
House 2014	NR	20/45 vs. 3/9	Not applicable	NR
Huang 2018	81/128 vs. 47/142	80/128 vs. 43/128	Demographics, cirrhosis, liver disease etiology	HR 0.52 (95%CI 0.35 – 0.76)
Im 2019	102/127 vs. 81/192	Used data per Kwon 2020	Used data per Kwon 2020	Used data per Kwon 2020
Kalman 2014	48/56 vs. 65/129	NR	Not applicable	NR
Khalili 2015	87/109 vs. 67/92	NR	Not applicable	NR
Kim 2018	537/834 vs. 167/568	Used data per Kwon 2020	Used data per Kwon 2020	Used data per Kwon 2020
Kwon 2020	NR	OR 2.58 (2.27 – 2.94)	Lead time, age, sex, cirrhosis, CCI, income	HR 0.76 (95%CI 0.71 – 0.82)
Lang 2020	71/111 vs. 123/290	86/111 vs. 137/290	Cirrhosis, liver dysfunction, age	HR 0.90 (95%CI 0.69 – 1.19)
Leahy 2014	61/96 vs 43/101	39/96 vs. 15/101	None	3-year survival 65% vs. 55%; HR 0.59, p=0.08
Lo 2016	16/23 vs. 21/70	NR	Not applicable	NR
Majerovic 2019	12/23 vs. 14/57	NR	Not applicable	NR
Merchante 2019	79/186 vs. 49/160	NR	None	Median survival 13 vs. 4 months (p<0.001)
Mittal 2016	112/412 vs. 55/475	86/412 vs. 53/475	Lead time, age, comorbidity, liver disease etiology, BCLC, MELD, treatment, AFP level	HR 0.92 (95%CI 0.79 – 1.07)
Mittal 2016	71/94 vs. 17/50	NR	Lead time	Median survival 72.2 vs. 45 months (p=0.14)
Musunuri 2018	7/52 vs. 3/31	NR	None	Median survival 9 vs. 6 months (p=0.001)
Nusbaum 2015	116/126 vs. 101/162	80/131 vs. 57/174	Age, sex, race, insurance, etiology, stage, treatment	HR 0.66 (95%CI 0.43 – 0.99)
Oeda 2016	156/226 vs. 35/107	174/226 vs. 44/107	Lead time	Median survival 56.5 vs. 31.4 months (p=0.011)
Pinero 2019	244/345 vs. 68/208	NR	Lead time, age, BCLC, AFP	HR 0.51 (95%CI 0.38 – 0.69)
Rich 2017	238/359 vs. 151/573	255/359 vs. 158/573	Demographics, Child Pugh, ECOG	HR 0.52 (95%CI 0.43 – 0.62)
Rodriguez de Lope 2017	221/311 vs. 133/347	169/316 vs. 112/356	Not applicable	NR
Schauer 2019	NR	147/224 vs. 81/286	Demographics, treatment	HR 0.70 (95%CI 0.54 – 0.91)
Shindo 2015	80/93 vs 45/78	64/93 vs 34/78	Liver disease etiology, tumor stage, AFP-L3 and DCP levels, curative treatment	HR 0.22 (95%CI 0.06 – 8.26)
Sigurdsson 2019	NR	NR	None	Median survival 17.1 vs. 4.5 months (HR 0.47, p=0.008)
Singal 2017	99/157 vs. 79/217	48/157 vs. 28/217	Lead time, demographics, Child Pugh, Milan, ECOG, GI care	HR 0.59 (95%CI 0.37 – 0.93)
Skladany 2018	15/49 vs. 12/140	NR	Not applicable	NR

Author Year	Proportion of Patients with Early HCC	Proportion of Patients with Curative Treatment	Factors adjusted for in survival analysis	Overall Survival
Sonovane 2018	16/24 vs. 8/84		None	HR 0.29, p=0.002
Thein 2015	NR	11/17 vs. 677/1466	Lead time, demographics, residence, comorbidity, Child Pugh, ECOG, treatment	HR 0.76 (95%CI 0.64 – 0.91)
Tojo 2014	20/24 vs. 34/76	NR	Not applicable	NR
Tong 2017	145/175 vs. 45/158	110/175 vs. 46/158	Lead time	Median survival 40.5 vs. 14.5 months (p<0.001)
Toyoda 2018	1570/2108 vs. 783/1791	1408/2108 vs. 836/1791	Lead time, age, Child Pugh, etiology	HR 0.60 (95%CI 0.55 – 0.66)
Tran 2018	106/151 vs. 30/77	66/151 vs. 18/77	Demographics, Child Pugh, Milan, curative treatment	HR 0.34 (95%CI 0.16 – 0.72)
Van Meer 2015	179/295 vs. 163/779	167/295 vs. 253/779	Lead time, age, liver disease etiology, cirrhosis, MELD, ECOG, symptoms	HR 0.51 (95%CI 0.39 – 0.67)
Wong 2016	6/8 vs. 8/9	NR	Not applicable	NR
Wong 2017	54/91 vs. 22/127	47/91 vs. 36/127	None	Median survival 29.2 vs. 14.6 months (p<0.001)
Wu 2016	NR	2.13 (2.00 – 2.22)	Lead time, demographics, etiology, cirrhosis, comorbidity, GI care	HR 0.66 (95%CI 0.64 – 0.68)
Yamago 2019	326/398 vs. 214/474	332/398 vs. 214/474	None	Median survival 68.2 vs. 34.1 months (p<0.001)
Yeh 2016	162/194 vs. 402/1098	NR	Not applicable	NR

* Median survival estimated from Kaplan Meier curves

AFP – alpha fetoprotein; BCLC – Barcelona Clinic Liver Cancer; CCI – Charlson Comorbidity Index; ECOG – Eastern Cooperative Oncology Group; GI – Gastroenterology; MELD – Model for End-Stage Liver Disease; NR = not reported