Screening for Hepatocellular Carcinoma in Adults at Increased Risk

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the USA. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

ACKNOWLEDGMENTS

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

This report was prepared by the Evidence Synthesis Program Center located at the **Minneapolis VA Health Care System,** directed by Timothy J. Wilt, MD, MPH and Wei Duan-Porter, MD, PhD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

Executive Summary

KEY FINDINGS

- The evidence is very uncertain regarding the effectiveness and harms of hepatocellular carcinoma (HCC) screening in adults at increased risk.
- Evidence is generally very uncertain regarding comparative effects of different screening strategies including imaging modalities, intervals, and biomarkers.
- Most studies analyzed only individuals with an HCC diagnosis (HCC-cohorts), thus missing the target increased risk population. Major methodological issues that limit certainty include a combination of lead- and length-time bias and little controlling for confounders known to affect receipt of screening and survival.
- We found very little data from studies that could provide more reliable information (cohort, case-control, randomized controlled trials [RCTs]) regarding screening among individuals at risk for HCC. Among these studies, methodological concerns or inconsistent findings also severely limited conclusions.
- Evidence gaps could be closed with completion of RCTs, especially RCTs comparing screening with no screening, and higher methodological quality observational studies.
- Until methodologically higher quality studies are completed, the current uncertainty challenges HCC screening implementation and patient-clinician decision-making.

An estimated 41,210 Americans will be diagnosed with liver cancer in 2023 (approximately 9.5 per 100,000), with 29,380 expected to die from the disease. HCC is the sixth most common cancer and the most common form of liver bile duct cancer (accounting for approximately 75% of cases). HCC is the second leading cause of cancer-related deaths worldwide, though incidence and mortality vary by age, race or ethnicity, and sex. HCC occurs most frequently and is most deadly among males, Asians and Pacific Islanders, and older adults. Results of the Surveillance, Epidemiology, and End Results Program (SEER) show that age-adjusted rates of liver and intrahepatic bile duct cancer in the USA more than doubled between 1992 and 2012 (4.6 to 9.3 per 100,000) before leveling off over the last decade. Mortality from the disease has followed a similar trajectory (from 3.9 per 100,000 in 1992 to 6.7 per 100,000 in 2016). Shifting patterns of liver disease and cirrhosis etiology may partially account for HCC incidence and mortality trends. However, screening programs may have harms and be ineffective (*ie*, identifying individuals with HCC but not improving receipt of effective therapies).

Veterans have an unadjusted 5-fold higher HCC incidence compared with the general population. HCC incidence among Veterans receiving care in VA peaked in 2015 (31 per 100,000), then declined to 22 per 100,000 patients in 2018. This decline appears to be driven primarily by a reduction in hepatitis C-related HCC, but importantly, during the same period the incidence of non-hepatitis C-related HCC increased. Effective early HCC identification and treatment options are important. The 3-year payer costs in the VA related to cirrhosis are estimated to be $154,688 with $69,010 for HCC treatment. Early identification of liver cancers may reduce disease-specific and all-cause mortality by providing an opportunity for potentially curative therapies (surgical resection, ablative therapy, or liver transplantation). A recent systematic review highlighted that HCC treatment costs, harms, and limited mortality benefits may lead some patients to forgo treatment, underlining the importance of more effective detection and treatment options.

Screening for HCC among adults at increased risk (especially those with cirrhosis) has been recommended by several specialty societies (*eg,* American Association for the Study of Liver Diseases [AASLD], European Association for the Study of the Liver [EASL]) (typically through abdominal ultrasound imaging with AFP every 6 months) and is considered a quality metric for practice performance by AASLD. However, the National Cancer Institute's Physician Data Query concluded that based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from HCC and would result in rare but serious side effects. The United States Preventive Services Task Force and other USA medical societies have not issued HCC screening guidelines. Questions surrounding screening include whether to conduct screening, the appropriate imaging technique if conducting screening (ultrasound, magnetic resonance imaging [MRI], computed tomography [CT]), use of AFP, screening intervals (*eg,* 3, 6, or 12 months), populations defined as increased or "at risk" and thus potential screening candidates, and when to discontinue screening.

CURRENT REVIEW

The Veterans Health Administration (VA) Evidence Synthesis Program (ESP) is responding to a request from the National Gastroenterology and Hepatology Program (NGHP) for an evidence review evaluating the data regarding screening for hepatocellular carcinoma (HCC) and, specifically, to identify the benefits and harms of HCC screening among adults at increased risk. We are updating a prior review the ESP conducted in 2014 synthesizing the evidence of screening for HCC in chronic liver disease. The current review updates the evidence with the intention that findings improve health and health care by informing clinical guidelines, VA directives, and implementation strategies related to HCC screening across the VA. We conducted the systematic review to identify and critically appraise the available evidence on the effects, comparative effects, and harms of HCC screening versus no screening and different screening strategies in populations at increased risk. We also assessed whether benefits and harms varied by patient or co-existing medical characteristics, presence of cirrhosis, liver disease etiology, screening intervals, or screening modality with or without alpha-fetoprotein (AFP).

Key Question

The following key question was the focus of this review: *What are the benefits and harms of HCC screening among adults at increased risk?* We were also interested in whether benefits and harms of HCC screening varied by the following factors:

- Patient or co-existing medical characteristics (*eg*, age, sex, race/ethnicity; comorbidities)
- Presence of cirrhosis
- Liver disease etiology (hepatitis, B, C, alcohol, metabolic liver disease), severity, or HCC risk
- Screening intervals (*eg*, semiannual, annual, biennial) or abdominal imaging technique
- Screening modality with or without AFP (ultrasound, MRI, CT)

METHODS

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023406164). Two previous reviews assessing the effectiveness of screening for HCC in chronic liver disease, Kansagara et al and Singal et al, were conducted in 2014

and 2022. We utilized and updated the published search strategy by Singal et al, searching in Embase and MEDLINE from July 1, 2020, through January 24, 2023.

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias [RoB]) of each included study was rated using the Cochrane Risk of Bias Tool 2.0 (RoB-2) for RCTs and the Risk of Bias in non-Randomized Studies - of Interventions (ROBINS-I) tool for observational studies. All data abstraction and internal validity ratings were completed by 1 reviewer and then checked by another; disagreements were resolved by consensus or discussion with a third reviewer.

We anticipated with the inclusion of mostly large observational studies and with adjustment for confounders that clinical variability and statistical heterogeneity would remain high. Prior to analysis, we examined the clinical and methodological characteristics of the included studies to determine if appropriate for pooling (*ie,* screening modality and comparator, patient and disease factors including etiology and HCC risk in both the screening and control cohorts within and across studies, outcomes reported in each group, study design, country of origin). Due to the large variation in study methodology, results are summarized narratively first by study design, as it was found that the study methodology heavily impacted the risk of bias. Within each study design section, the outcomes are presented by screening method comparisons. Authors categorized the screening approach into uniquely defined groups; as such we have grouped reported outcomes by screening strategies that appeared to have the greatest similarity in protocol. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or very low.

RESULTS

Our search identified 171 potentially relevant articles after deduplication and title and abstract screening. Of these, 74 primary studies met eligibility criteria: 5 RCTs and 69 observational studies (5 cohort, 2 case-control, 62 HCC-cohort). We have differentiated cohort studies (which include the population at risk of HCC) from HCC cohort studies (which included only those diagnosed with HCC) because of the difference in target populations and potential biases. Of the 5 RCTs, 2 were rated some concerns RoB, while the other 3 were rated high RoB. Of the 5 cohort studies, 1 was rated serious RoB, and the other 4 rated critical RoB. Of the 62 HCC-cohort studies, 11 were rated serious RoB, and the remaining 51 were rated critical RoB. The large number of HCC cohort studies with critical RoB reflect possible lead time and length time bias that are intrinsic to this study design. Overall, we found very low strength evidence examining the effects of screening for HCC on all-cause and HCC mortality among patients at increased risk for HCC and thus are uncertain of the effects. A summary of the evidence for HCC and all-cause mortality outcomes by study design and screening modalities is provided below. Summary of the other identified outcomes (sensitivity, specificity, percent receiving treatment, percent receiving transplant, harms, *etc*) are provided in the main report. These outcomes were infrequently reported and were not assessed using GRADE.

CONCLUSIONS

Evidence is very uncertain whether screening for HCC in individuals at increased risk reduces all-cause or HCC mortality. Evidence is also very uncertain as to the comparative effectiveness of varying screening strategies including screening intervals, imaging modalities, additive value of AFP to imaging tests, and in what populations screening may be effective. Harms data were limited regarding psychological distress, liver biopsy complications, renal insufficiency, overdiagnosis, and financial

burden. However, all screening strategies have diagnostic- and treatment-induced harms, patient and clinician burden, and costs. Randomized trials evaluating screening versus no screening as well as different screening strategies are needed. More rigorous observational studies and use of target trial emulation as a framework for design could aid in designing observational studies to provide greater certainty. Until methodologically higher quality studies are available, the current state of the evidence provides serious challenges to HCC screening implementation and patient-clinician decision-making.

CERTAINTY OF EVIDENCE RATINGS

Study Design	Screening Methodology	Follow-Up	Total N (# Studies)	Certainty	Summary Statement
All-Cause Mortality					
RCT	US at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in all-cause mortality when screening every 3 months compared to every 6 months.
Cohort	US every 6 months vs US alternating with CT every 6 months	10 years	992 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening every 6 months on all-cause mortality compared to US with alternating CT every 6 months.
HCC Cohort	Any imaging (+/- AFP) vs no screening	5-8 years	121,822 (6)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening on all-cause mortality.
	US at 3 months vs US at 6 months	50 months	1107 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening at 3 months compared to 6 months on all-cause mortality.
	Biannual AFP + US HCC detected by positive US with negative AFP vs positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding all-cause mortality in adults with HCC detected by positive US with negative AFP vs HCC detected by positive results on both US and AFP.
	Biannual AFP + US: HCC detected by positive AFP with negative US vs positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding all-cause mortality in adults with HCC detected by positive results on Biannual AFP with negative US vs HCC detected by positive results on both US + AFP.
HCC-Specific Mortality					
RCT	US at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in HCC-specific mortality when screening every 3 months compared to every 6 months.
	US at 6 months vs CT at 12 months	31-35 months	163 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening every 6 months compared with CT screening every 12 months.
Case-Control	US +/- AFP vs no screening	4 years	814 (2)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening with ultrasound with or without AFP compared to no screening on HCC-specific mortality in adults at increased risk for HCC.
HCC Cohort	Biannual AFP + US: HCC detected based on US and AFP test results: 1) Both US & AFP positive;2) US positive but AFP negative; 3) US negative but AFP positive	5 years	1776	⊕◯◯◯ Very low	The evidence is very uncertain regarding HCC-specific mortality based on whether HCC is detected by 1) both US & AFP positive results; 2) US positive but AFP negative results or 3) US negative but AFP positive results.
Overall Survival					
RCT	US screening at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in overall survival when screening every 3 months compared to every 6 months.

Study Design	Screening Methodology	Follow-Up	Total N (# Studies)	Certainty	Summary Statement
Cohort	US at 6 months vs US alternating with CT at 6 months	10 years	992 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening at 6 months on overall survival compared to alternating US and CT screening at 6 months.
HCC Cohort	Any imaging (+/- AFP) vs no screening	5 years	3965 (5)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening on overall survival.
	US at 3 months vs US at 6 months	5 years	1107 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening at 3 months compared to 6 months on overall survival.
	Biannual AFP + US: HCC detected by positive US with negative AFP vs HCC detected by positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding overall survival in adults with HCC detect by positive US with negative AFP vs positive results on both US and AFP.
	Biannual AFP + US HCC detected by positive AFP with negative US vs HCC detected by positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding overall survival in adults with HCC detected by positive AFP with negative US versus HCC detected by positive results on both US and AFP.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; RCT=randomized controlled trial; US=ultrasound.

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
ALD	Alcohol-associated liver disease
ALT	Alanine transaminase
AST	Aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
CCRCT	Cochrane Central Register of Controlled Trials
CI	Confidence interval
COE	Certainty of evidence
CT	Computed tomography
EASL	European Association for the Study of the Liver
EMR	Electronic medical records
ESP	Evidence Synthesis Program
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HCC	Hepatocellular carcinoma
HR	Hazard ratio
MASLD	Metabolic dysfunction-associated steatotic liver disease
aMRI	Abbreviated MRI
MRI	Magnetic resonance imaging
NGHP	National Gastroenterology and Hepatology Program
OR	Odds ratio
RCT	Randomized controlled trial
RoB	Risk of bias
ROBINS-I	Risk of Bias in non-Randomized Studies
RR	Risk ratio
US	Ultrasound
VHA	Veterans Health Administration

BACKGROUND

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related death worldwide.[1] An estimated 41,210 Americans will be diagnosed with liver cancer in 2023 (approximately 9.5 per 100,000), with 29,380 expected to die from the disease.[2] Results of the Surveillance, Epidemiology, and End Results Program (SEER) show that age-adjusted rates of liver and intrahepatic bile duct cancer in the USA more than doubled between 1992 and 2012 (4.6 to 9.3 per 100,000) before leveling off over the last decade (see Figure 1).[3] Mortality from the disease has followed a similar trajectory (from 3.9 per 100,000 in 1992 to 6.7 per 100,000 in 2016). Liver cancer accounts for approximately 2% of all new cancer cases in the USA.[3]

HCC is the most common form of primary liver cancer and makes up approximately 75% of all liver and bile duct cancers.[4] HCC incidence and mortality vary by age, race or ethnicity, and sex. HCC occurs most frequently and is most deadly among males, Asian and Pacific Islanders, and older adults.[5] Mortality has increased within these high risk groups with the exception of Asian and Pacific Islanders.[6] Shifting patterns of liver disease and cirrhosis etiology over this time may also account for HCC incidence and mortality findings.

The goal of any screening program is to reduce all-cause and disease-specific morbidity and mortality with acceptable harms, burden, and costs. Screening is recommended by several specialty societies (*eg,* American Association for the Study of Liver Diseases [AASLD], European Association for the Study of the Liver [EASL]), typically through abdominal ultrasound imaging with alpha-fetoprotein (AFP) every 6 months. However, the National Cancer Institute's Physician Data Query concluded that based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from HCC and would result in rare but serious side effects.[7] Neither the United States Preventive Services Task Force nor primary care medical societies have issued HCC screening guidelines in "increased-risk individuals."

Figure 1. Liver and Intrahepatic Bile Duct Cancers

Excerpted from: https://seer.cancer.gov/statfacts/html/livibd.html

The percentage of all liver cancers detected as localized disease has increased; moving from 49.4% in 2000 to 62.1% diagnosed at a localized stage in 2016.[5] This stage shift, while potentially promising, may simply reflect increased early-stage incidence and detection without a corresponding decline in late-stage incidence or mortality reduction. Thus, stage shift is not sufficient to demonstrate evidence of screening effectiveness. Even with increased detection of localized disease, the proportion of patients receiving potentially curative treatment remained at less than one-third (27%).[5] A recent systematic review summarized the epidemiology, costs, and burden of HCC.[8] Incidence was higher in Medicare and Veterans Health Administration (VA) patients, (22.3 and 45 per 100,000 person-years, respectively), compared to the general USA population (9.5 per 100,000), though these data are not age or comorbidity adjusted.[9] Authors found that HCC incidence, costs, and health burden to patients, caregivers, and the health care system were high. Furthermore, due to costs and limited survival benefits, some patients may elect to forgo treatment, thus underlining the importance of more effective detection and treatment options.

HCC incidence among Veterans receiving care in the VA peaked in 2015 with 31 per 100,000 and then declined slightly to 22 per 100,000 patients in 2018.[10] While the incidence of hepatitis C-related HCC among VA patients has declined from 2015 to 2018, the incidence of non-hepatitis C-related HCC has increased. Effective, safe, and affordable early HCC identification and treatment options are important. The 3-year payer costs in the VA related to cirrhosis are estimated to be $154,688 with $69,010 for HCC treatment.[9] Early identification of liver cancers may reduce cancer-related and all-cause mortality by providing an opportunity for potentially curative therapies like surgical resection, ablative therapy, or liver transplantation.

Individuals with cirrhosis, hepatitis B virus, and hepatitis C virus are at increased risk of HCC. Hepatitis C treatment and vaccination for hepatitis B have reduced the contribution these diseases have to the total number of HCC cases.[11] In contrast, metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as nonalcoholic fatty liver disease) and alcohol-associated liver disease (ALD) have increased and are becoming the most common risk factors for HCC in the USA.[11,12] Other risk factors for HCC include age, male sex, and Hispanic ethnicity.[12] Of concern for the USA population, both diabetes and body mass index (BMI) are associated with HCC in individuals with cirrhosis.[12]

In addition to the question of whether HCC screening should be conducted, there are several questions about how to best implement HCC screening if screening is effective. They include: 1) the optimal imaging technique (ultrasound, magnetic resonance imaging [MRI], or computed tomography [CT]), 2) whether AFP should be included, 3) how often to screen (*eg,* 3, 6, or 12 months), and 4) whether the benefits and harms of screening vary by patient or liver disease characteristics.

In 2014, the ESP conducted a systematic review on HCC screening in chronic liver disease.[13] Authors concluded that screening tests can identify early-stage HCC but found that evidence was uncertain about survival benefits of systematic screening compared with clinical diagnosis. The current review was requested by the VA National Gastroenterology and Hepatology Program (NGHP) and aimed to identify and critically appraise currently available evidence on the effects, comparative effects, and harms of HCC screening versus no screening and different screening strategies in populations at increased risk. We also assessed whether benefits and harms varied by patient or co-existing medical characteristics, presence of cirrhosis, liver disease etiology, screening intervals, or screening modality with or without AFP. Findings will be used to inform clinical guidelines, VA directives, and implementation strategies related to HCC screening across the VA.

METHODS

REGISTRATION AND REVIEW

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023406164). A draft version of this report was reviewed by external peer reviewers; their comments and author responses are located in the Appendix.

ANALYTIC FRAMEWORK

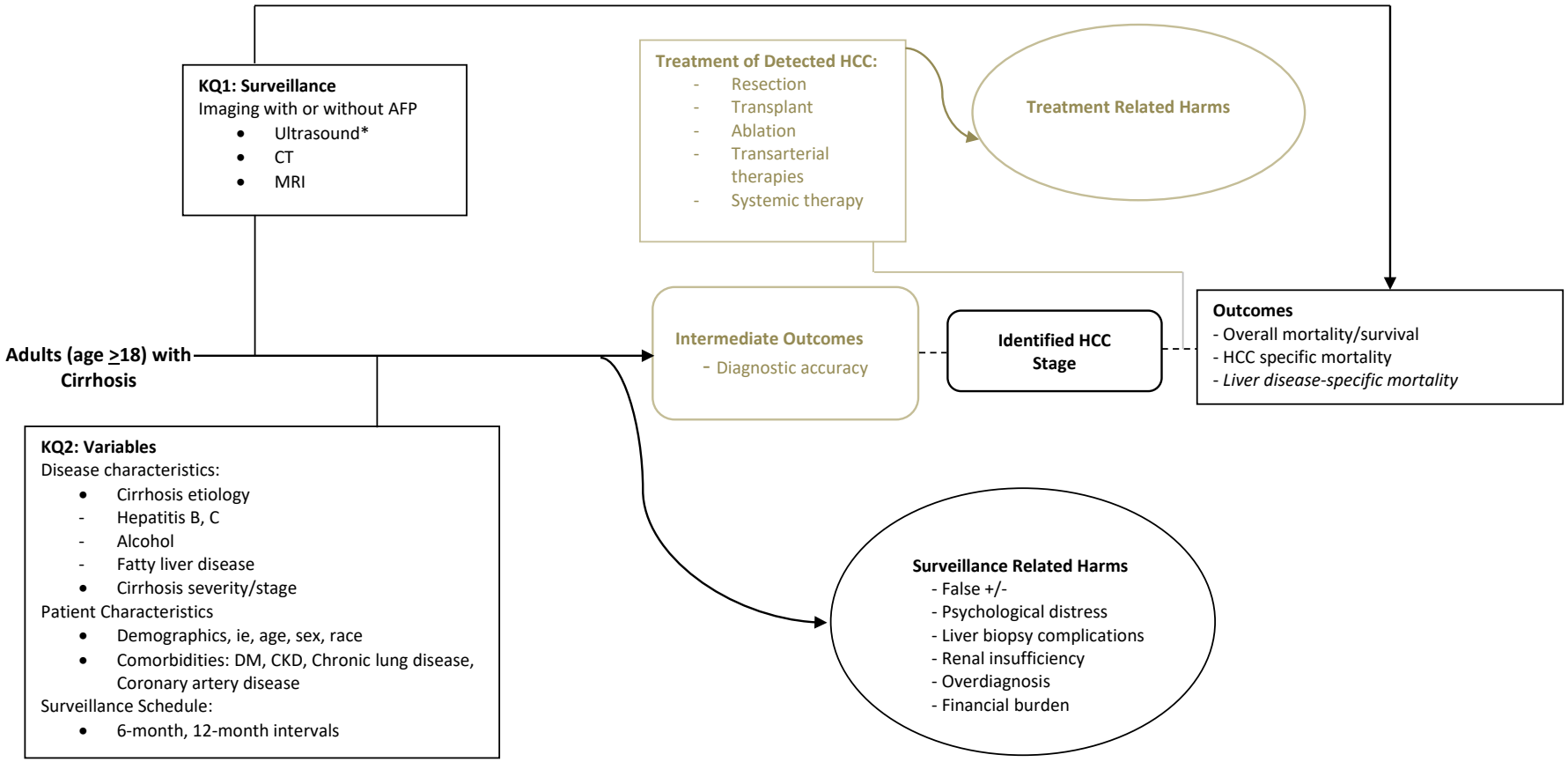
The analytic framework shown in Figure 2 provides a conceptual overview of the key questions, populations, interventions, and outcomes. The population of interest is individuals at increased risk of HCC based on a current or past history of liver disease (including cirrhosis), viral infection, or alcoholic and metabolic liver disease. We were broad in our inclusion of a definition of "increased risk," typically using author-defined populations of those undergoing screening and any included control group. Eligible outcomes judged as critical for decision-making included all-cause mortality, overall survival, HCC-specific mortality, and screening related harms (false +/-, psychological distress, liver biopsy complications, renal insufficiency, overdiagnosis, and financial burden). We also assessed stage of disease at detection and the percentage of individuals receiving potentially curative treatment, including surgical resection, ablative therapy, or liver transplantation. We did not consider intermediate outcomes associated with the intervention (*eg*, diagnostic accuracy or treatment-related harms), as they were outside the scope of the review question. We also evaluated whether screening benefits and/or risks varied by patient or disease characteristics (*eg*, patient demographics, comorbidities, disease etiology and severity) or screening protocol (*eg*, imaging modality or schedule).

KEY QUESTIONS AND ELIGIBILITY CRITERIA

The following key question was the focus of this review: *What are the benefits and harms of HCC screening among adults at increased risk?* We were also interested in whether benefits and harms of HCC screening varied by the following factors:

- Patient or co-existing medical characteristics (*eg*, age, sex, race/ethnicity; comorbidities)
- Presence of cirrhosis
- Liver disease etiology (hepatitis, B, C, alcohol, metabolic liver disease), severity, or HCC risk
- Screening intervals (*eg*, semiannual, annual, biennial) or abdominal imaging technique
- Screening modality with or without AFP (ultrasound, MRI, CT)

Figure 2. Analytic Framework



Notes. *Pending ultrasound, MRI or CT may be undertaken as an additional triage/diagnostic test.

Abbreviations. AFP=alpha-fetoprotein; CKD=chronic kidney disease; CT=computed tomography; DM=diabetes melitus; HCC=hepatocellular carcinoma; MRI=magnetic resonance imaging.

Study eligibility criteria are shown in the table below.

Population	Adults (≥18 years of age) at increased risk of HCC (broadly those with cirrhosis or current or past liver disease that may put them at increased HCC risk and as included by authors)
Intervention	Abdominal imaging (ultrasound, CT, or MRI (full or abbreviated)) with or without alpha-fetoprotein blood test for HCC screening (*ie*, not a diagnostic or monitoring test for a patient with known or suspected HCC)
Comparator	No HCC screening or compared to another abdominal imaging technique, *eg*, ultrasound vs CT or MRI (full or abbreviated) with or without alpha-fetoprotein blood test HCC screening in patient and liver disease subgroups, at different intervals
Outcomes	All-cause mortality, overall survival, HCC-specific mortality, HCC-specific survival, receipt of curative intent treatment for HCC, HCC stage at diagnosis, screening-related harms (*eg*, liver biopsies, false positive and negative tests, financial burden associated with screening adherence, opportunity costs, psychological distress at incorrect diagnosis, overdiagnosis)
Study Design	RCT, comparative experimental or observational studies
Setting	Non-hospice

SEARCHING AND SCREENING

Two previous reviews assessing the effectiveness of screening for HCC in chronic liver disease, Kansagara et al[13] and Singal et al,[14] were conducted in 2014 and 2022. We utilized and updated the published search strategy by Singal et al, searching in Embase and MEDLINE from July 1, 2020, through January 24, 2023. The publications included in those two reviews were added to the list of citations identified through the search (see the Appendix for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts and our technical expert panel. English-language titles, abstracts, and full-text articles were independently reviewed by 2 investigators, and disagreements were resolved by consensus.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias [RoB]) of each included study was rated using the Cochrane Risk of Bias Tool 2.0 (RoB-2)[15] for RCTs and the Risk of Bias in non-Randomized Studies-of Interventions (ROBINS-I)[16] tool for observational studies. As required by the ROBINS-I tool, a list of confounders that must have been addressed by study authors was developed a priori to conducting assessments. We required observational studies to have included the following variables in their models: age, comorbidities, lead time, liver disease severity, and liver disease etiology. Studies that did not address these confounding variables were judged as having critical risk of bias and were not assessed further or included in detailed data abstraction or synthesis. All data abstraction and internal validity ratings were completed by 1 reviewer and verified by another; disagreements were resolved by consensus or discussion with a third reviewer (see the Appendix for risk of bias ratings).

SYNTHESIS

Prior to analysis, we examined the clinical and methodological characteristics of the included studies to determine if appropriate for pooling. These included: screening modality (including screening intervals), HCC etiology and risk in both screening and control cohorts (within and across studies), comparison condition (*eg,* no screening or an alternate screening protocol), outcomes assessed in each

group, patient demographics and comorbidities, and study design and country of origin. Although we planned to pool study results when feasible (see registered protocol for full details), we found that methodological and clinical variation among included studies precluded meta-analysis. Instead, we narratively synthesized available evidence by studies, populations, and interventions for each outcome.

We anticipated including mostly large observational studies and that even after adjustment for confounders, clinical variability and statistical heterogeneity would remain high. Indeed, after identifying eligible studies, we found that study methodology corresponded closely to risk of bias ratings and to the comparability of populations, interventions, and methodologies. Therefore, we organized results first by study design; within each study design section, outcomes are presented by screening method comparisons. Study authors categorized screening approaches in a variety of ways, so we grouped reported outcomes by screening strategies we judged to be most similar.

Our search included observational studies; thus, in addition to separating RCTs from observational studies we also stratified observational studies by design. Case-control and cohort studies yield different effect measures. We further separated cohort studies (which include the population at risk of HCC) from HCC cohort studies (which included only those diagnosed with HCC) because of the difference in target populations and potential biases. The difference in target population means that outcome measures (*eg,* all-cause mortality) in cohort studies and HCC cohort studies are not comparable. HCC studies are also further subject to lead-time bias (screening will artificially increase duration of follow-up and survival due to earlier diagnosis) and length-time bias (screening may select those with better prognosis). The table below summarizes the final grouping by study design.

RCT	Randomized controlled trial: interventions (screening or control) were randomly assigned at individual or group level.
Case-Control	A population of cases (those with outcome of interest, *eg,* HCC mortality) and matched controls (those who did not have the outcome) were assessed for exposure to intervention.
Cohort	A population of individuals at risk for HCC were followed longitudinally over time and both exposure to intervention (screening vs control) and subsequent outcomes were assessed from this longitudinal data (often retrospective from EHR data).
HCC Cohort	Similar to a cohort study, but study selection limited to those with intermediate outcome, in this case a diagnosis of HCC. It is not possible to extrapolate outcomes in this subgroup to population at risk.

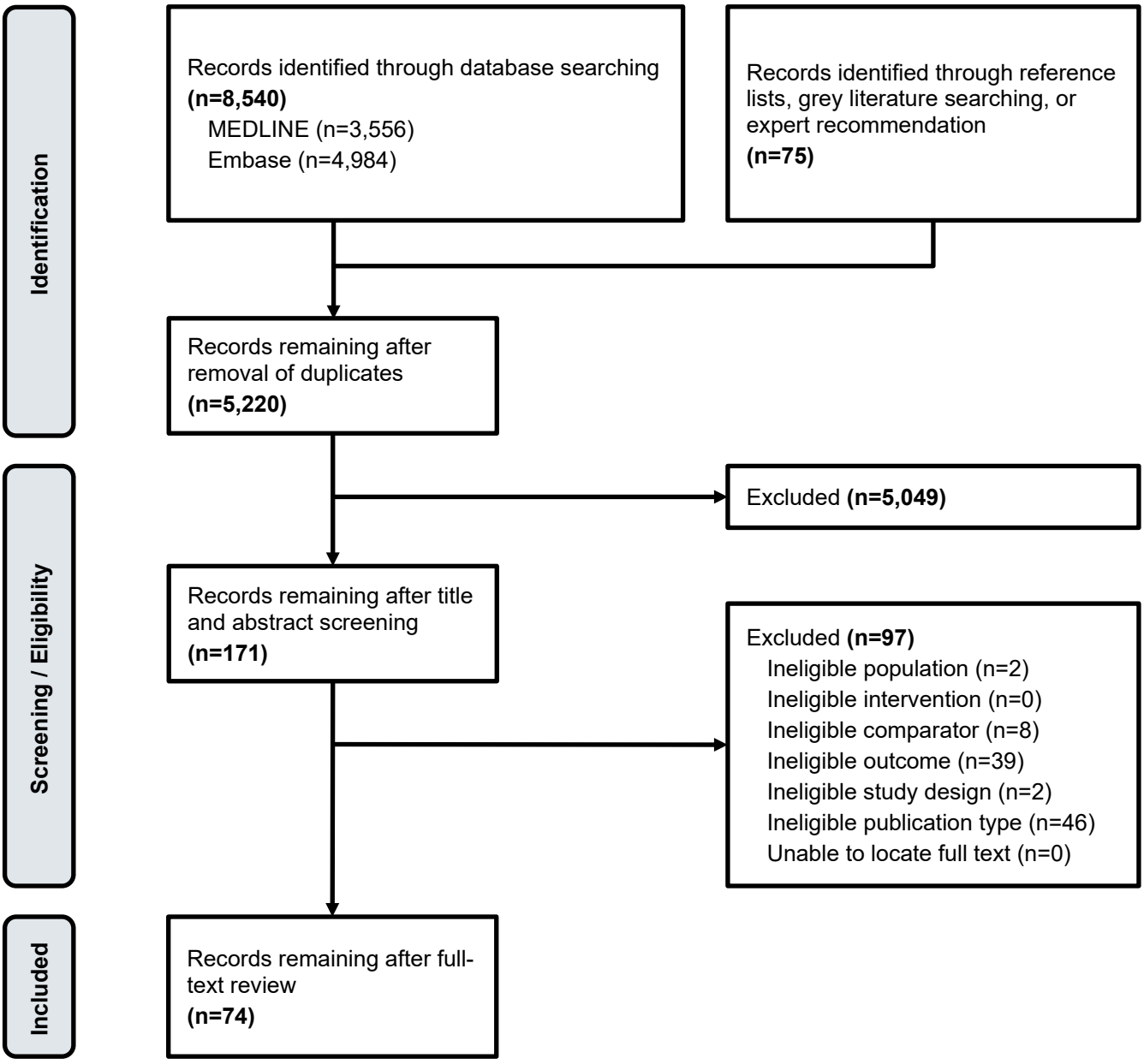
Strength of Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or very low.[17] We engaged organizational partners and a panel of clinical experts to determine outcomes critical for decision making. We also sought their input to guide decisions about comparability of populations, screening modalities, and comparisons to permit study result grouping. We did not attempt to derive minimally important thresholds, and thus our judgments on certainty of evidence rely on statistical rather than potential clinical significance.

RESULTS

LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in the Appendix.



OVERVIEW OF INCLUDED STUDIES

We identified 171 potentially relevant articles after deduplication and title and abstract screening. Of these, 74 primary studies met eligibility criteria: 5 RCTs and 69 observational studies (5 cohort, 2 case-control, 62 HCC cohort). Of the 5 RCTs, 2 were rated some concerns RoB, while the other 3 were rated high RoB. Of the 5 cohort studies, 1 was rated serious RoB, and the other 4 were rated critical RoB. Of the 62 HCC cohort studies, 11 were rated serious RoB, and the remaining 51 were rated critical RoB. Of note, we designated studies that only included in their analyses individuals who already had HCC as "HCC Cohort" to describe these separately from traditional cohorts or case-control studies or randomized controlled trials evaluating "high-risk individuals." Characteristics of all eligible studies are shown in Table 1.

Individuals with cirrhosis made up 80% or more of the study sample in 7 studies rated as at low risk of bias, having some concerns, or at serious risk of bias. Only 3 of these studies were conducted in the USA and all enrolled Veterans at VA medical centers (1 RCT, 1 case-control study, and 1 HCC cohort study). Additionally, while 5 studies reported all-cause mortality, only 1 was conducted in the USA (in a non-VA setting). None of the 5 studies reporting overall survival and only 2 of the 5 studies reporting HCC-specific mortality were conducted in North America (both in USA Veterans; 1 RCT and 1 case-control study). Among the 3 studies conducted in North America not rated as high or critical RoB, 1 RCT evaluated ultrasound +/- AFP every 6 months versus CT every 12 months plus AFP every 6 months, 1 case-control study compared ultrasound plus AFP within 4 years of a HCC diagnosis versus no screening, and 1 HCC cohort study evaluated screening with any imaging modality (ultrasound, MRI, or CT) +/- AFP versus no screening.

Table 1. Characteristics of Included Studies

Characteristics	# Studies by Risk of Bias*			Total
	Low	Some Concerns† or Serious	High† or Critical‡	
Study Design				
Randomized Controlled Trial	-	2†	3†	5
Case-Control	2	-	-	2
Cohort	-	1	4	5
HCC Cohort	-	11	51	62
Etiology Characteristics				
Cirrhosis Requirement	1	4	13	18
Large Proportion (≥80%) Cirrhosis	-	2	-	2
Population Characteristics				
Veteran Only	2	1	3	6
Country				
North America	2	4	14	20
Asia	-	6	20	26
Europe	-	3	16	19
South America	-	1	2	3
Australia/New Zealand	-	-	6	6

Outcomes Reported					
All-Cause Mortality		-	10	13	23
Overall Survival		-	9	52	61
HCC-Specific Mortality		2	4	6	12
HCC Stage at diagnosis		-	5	32	86
Sensitivity/Specificity		-	1	1	2
Percent Curative		-	7	39	46
Financial Burden		-	2	-	2
Adherence		-	-	-	0
Overdiagnosis		-	-	-	0
Diagnosis with Biopsy		2	3	-	5
Psychological Distress		-	-	-	0
Liver Transplant		2	6	19	27
Data Sources					
EMR		2	4	-	6
Chart Review		1	3	-	4
Non-USA Administrative		-	3	-	3
Non-USA Registry		-	4	-	4
Comparison					
Screening vs None	Any Imaging +/- AFP vs None	-	1	-	1
	US (6 mo) vs None	-	1	-	1
	US + AFP (6-12 mo) vs None	-	2	-	2
	US + AFP (4 years before diagnosis) vs None	1	-	-	1
	US + AFP (6-12 mo) vs incidentally detected (none) vs symptomatically detected (none)	-	1	-	1
	US +/- AFP vs None	1		-	1
Multiple Screening Intervals vs None	US (6 mo) vs US (other intervals) vs None	-	2	-	2
	US + AFP vs US (other intervals) vs None	-	1	-	1
	US +/- AFP (routine) vs US +/- AFP (irregular) vs None	-	1	-	1
Screening Intervals	US (3 mo) vs US (6 mo)	-	2	-	2
US vs Other Modalities	US vs US + CT	-	1	-	1
	US positive & AFP negative vs both US & AFP positive vs US negative & AFP positive	-	1	-	1
	US + AFP vs CT + AFP	-	1	-	1

Notes. * Risk of bias was assessed using ROBINS-I for observational studies, and RoB2 for RCTs.

† "Some concerns" and "high" used for RCTs only.

‡ Data on data sources, study start year, and comparison was not collected for studies judged to be high or critical risk of bias.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; EMR=electronic medical records; HCC=hepatocellular carcinoma; mo=month; US=ultrasound.

RANDOMIZED CONTROLLED TRIALS

We identified 5 RCTs, 3 of which were assessed as high RoB.[18-20] None were adequately designed or executed to address the effectiveness or comparative effectiveness and harms of screening especially among individuals with cirrhosis. All 3 trials (including the only 2 RCTs evaluating screening versus no screening) were assessed as high risk of bias in the domain "bias due to deviations from intended interventions," with particular concern around adherence to the intervention and the impact this would have on the outcome. The high risk of bias trials enrolled patients mainly with hepatitis B and without cirrhosis. Results may not be applicable to a USA setting or those with cirrhosis. Other domains of concern varied across studies, and included the process of randomization, missing data, and selection of the reported results. The analytic approaches used in these trials were also concerning, including not accounting for clustering[19-21] and in some instances not applying an intention-to-treat methodology or blinding of outcome assessment.[19,21] The remaining 2 trials were assessed to be some concerns (Appendix), and are discussed below and included in certainty of evidence tables.[22,23] Summary characteristics for all RCTs are shown in Table 2, and detailed trial characteristics and results for RCTs rated some concerns RoB can be found in the Appendix.

Table 2. Characteristics of All Eligible RCTs

Study Country	Sample Size *Follow-Up*	Population	Intervention Characteristics	Comparator	Outcomes Assessed
Some Concerns Risk of Bias					
Pocha, 2013[22] USA*	*N* = 163 *31-35 months*	100% cirrhosis	Ultrasound +/- AFP every 6 months	CT +/- AFP every 12 months (AFP every 6 months)	HCC-specific mortality, stage at HCC diagnosis, % receiving transplant, % diagnosed with biopsy, false +/-, financial burden
Trinchet, 2011[23] France/ Belgium	*N* = 1278 *5-years*	100% cirrhosis	Ultrasound every 3 months	Ultrasound every 6 months	All-cause mortality, overall survival, HCC-specific mortality, % receiving transplant
High Risk of Bias					
Chen, 2003[21] China	*N* = 5581	Hepatitis B	AFP (+ultrasound if AFP >200 µg/l or >100 µg/l more than twice)	No screening	All-cause mortality, overall survival, stage at HCC diagnosis, sensitivity/specificity
Wang, 2013[19] Taiwan	*N* = 744	Hepatitis B and C	Ultrasound every 4 months	Ultrasound every 12 months	Overall survival, stage at HCC diagnosis, % receiving curative treatment, % receiving transplant
Zhang, 2004[20] China	*N* = 18816	Hepatitis B or history of chronic hepatitis	Ultrasound +/- AFP every 6 months	No screening	Overall survival, HCC-specific mortality, stage at HCC diagnosis, % receiving curative treatment

Notes. * Conducted in VHA.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; US=ultrasound.

Ultrasound at 3 Months versus Ultrasound at 6 Months

Trinchet et al investigated screening for HCC via ultrasound every 3 months compared to screening via ultrasound every 6 months.[23] The trial was conducted in France and Belgium among individuals with cirrhosis (N = 1278) and reported outcomes at 5-year follow-up. Compared with screening every 6 months, ultrasound screening at 3 months did not result in any significant differences in all-cause mortality, HCC-specific mortality, or overall survival. Results suggest there may be no benefits of more frequent screening with ultrasound (every 3 months) compared with less frequent screening with ultrasound (every 6 months) (low COE, Table 3).

There was also no significant difference in the number of patients receiving liver transplants between the 2 groups (17/640; 2.4% vs 13/638; 2.0%; p = NR).

Ultrasound at 6 Months versus CT at 12 Months

A trial by Pocha et al investigated screening for HCC via ultrasound plus AFP every 6 months compared to screening via CT every 12 months (with AFP every 6 months).[22] The trial was small (N = 163) and conducted in the USA in a Veteran population with cirrhosis. Mean follow-up ranged from 31-35 months (CT arm and ultrasound arm, respectively). Compared with screening via CT at 12 months, ultrasound screening at 6 months did not result in any significant differences in HCC-specific mortality. The evidence is very uncertain on the effect of ultrasound screening every 6 months compared with CT screening every 12 months on HCC-specific mortality (very low COE, Table 3).

Compared with screening via CT at 12 months, ultrasound screening at 6 months did not result in any significant differences in number of patients receiving liver transplant (4/83; 4.8% vs 2/80; 2.5%; p-value not reported), the number of patients receiving biopsy for diagnosis, BCLC stage at HCC diagnosis, or false positive or negative imaging.

Study authors reported the sensitivity and specificity of ultrasound for detection of HCC was 71.4% and 97.5%, respectively, with a positive predictive value of 83.3% and a negative predictive value of 95.1%. For CT, sensitivity and specificity were 66.7% and 94.4%, respectively, with a positive predictive value of 50.0% and negative predictive value or 97.1%.

Study authors used VHA and Medicare 2013 cost estimates to calculate the total cost to detect 1 HCC with ultrasound. Costs ranged from $12,069 in the VA to $17,041 in non-VA settings. The estimated cost with CT ranged from $18,768 (VA) to $57,383 (non-VA). No overall cost effectiveness assessing incremental cost effectiveness ratios for quality-adjusted life years was conducted.

Table 3. Certainty of Evidence Ratings for Randomized Controlled Trials Rated Some Concerns Risk of Bias

Outcome Follow-Up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	Comments
Ultrasound Screening Every 3 Months Compared to Every 6 Months in Adults at Increased Risk for HCC						
		Screening Every 6 Months	Screening Every 3 Months	Difference		
All-Cause Mortality Follow-Up: mean 5 years *N* = 1278 (1 RCT)[23]	**RR 0.88**[†] (0.7, 1.2)	12.1%	**11.3%** (8.4, 15.2)	**1.5% fewer** (4.5 fewer to 2.3 more)	⊕⊕◯◯ Low[a,b]	There may be little to no difference in all-cause mortality when US screening every 3 months compared with US screening every 6 months.
HCC-Specific Mortality Follow-Up: mean 5 years *N* = 1278 (1 RCT)[23]	**RR 1.41**[†] (0.7, 2.9)	2.0%	**2.9%** (1.4, 6.0)	**0.8% more** (0.7 fewer to 3.9 more)	⊕⊕◯◯ Low[a,b]	There may be little to no difference in HCC-specific mortality when US screening every 3 months compared with US screening every 6 months.
Overall Survival at 5 years *N* = 1278 (1 RCT)[23]	84.9% survival at 5 years in the 3-month screening group, compared to 85.8% survival in the 6-month screening group (p = 0.38).				⊕⊕◯◯ Low[a,b]	There may be little to no difference in overall survival when US screening every 3 months compared with US screening every 6 months.
Ultrasound Screening Every 6 Months Compared to CT Screening Every 12 Months in Adults at Increased Risk for HCC						
		CT Screening Every 12 Months	US Screening Every 6 Months	Difference		
HCC-Specific Mortality Follow-Up: 31-35 months *N* = 163 (1 RCT)[22]	**RR 0.71**[†] (0.2, 2.1)	8.8%	**6.2%** (2, 18.7)	**2.5% fewer** (6.7 fewer to 10 more)	⊕◯◯◯ Very low[a,c]	The evidence is very uncertain on the effect of US screening every 6 months compared with CT screening every 12 months on HCC-specific mortality.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[†] Calculated by review team.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 1 level for risk of bias (rated some concerns overall)

b. Downgraded 1 level for imprecision (wide confidence interval)

c. Downgraded 2 levels for imprecision (wide confidence intervals and optimal information size criterion not met)

Abbreviations. CI=confidence interval; CT=computed tomography; HCC=hepatocellular carcinoma; no.=number; RCT=randomized controlled trial; RR=risk ratio.

CASE-CONTROL STUDIES

We identified 2 case-control studies, both assessed as low risk of bias (Appendix) and conducted in the VHA.[24,25] Summary characteristics for both studies are shown in Table 4 below, and detailed study characteristics and results can be found in the Appendix.

Ultrasound With or Without AFP versus No Ultrasound

Both case-control studies investigated HCC screening defined as at least 1 ultrasound in the 4 year period prior to index date.[24,25] Both studies were of a matched case-control design and were conducted in a VA population. In the first study, Moon et al,[24] defined cases as individuals with cirrhosis who died of HCC, whereas Su et al[25] defined cases as individuals with hepatitis B who died of HCC. Controls were defined as patients with cirrhosis (Moon et al) or hepatitis B (Su et al) who did not die of HCC. As the population of interest for each study was different, there were slight differences in matching criteria, as follows: in the Moon et al study cases and controls were matched on: 1) year of diagnosis, 2) race and ethnicity, 3) age, 4) sex, 5) primary etiology of cirrhosis, 6) MELD score at time of cirrhosis diagnosis, and 7) VA facility in which the diagnosis of cirrhosis was made. Individuals in Su et al were matched on 1) hepatitis B diagnosis date, 2) age, 3) sex, 4) race/ethnicity, 5) cirrhosis, 6) antiviral therapy exposure, 7) hepatitis B antigen status, and 8) viral load.

For HCC-specific mortality, Moon reported an odds ratio (OR) of 0.87 (95% CI [0.44, 1.72]) for ultrasound plus AFP compared with no screening among individuals with cirrhosis.[24] In contrast, for HCC-specific mortality, Su et al reported an OR of 0.21 (95% CI [0.09, 0.50]) in favor of ultrasound screening with or without AFP versus no screening among a population of individuals with hepatitis B.[25] We downgraded for imprecision, study limitations, and inconsistency in effects across these 2 studies and their included cases/controls (cirrhosis/hepatitis B). We concluded that the overall evidence is very uncertain on the effect of ultrasound screening plus AFP compared with no screening on HCC-specific mortality among adults at increased risk for HCC (very low COE, Table 5).[24,25]

Both Moon and Su provided a count of the number of cases that were diagnosed via histology, 69 (29%) and 79 (46.7%), respectively, and those that received a transplant, 0 and 2 (1.2%), respectively.

Table 4. Characteristics of All Eligible Case-Control Studies

Study Country Risk of Bias	Sample Size *Follow-Up*	Population	Intervention Characteristics	Comparator	Outcomes Assessed
Moon, 2018[24] USA (VHA) Low	*N* = 476 *4 years*	100% Cirrhosis	Ultrasound + AFP at least once in past 4 years	No screening	HCC-specific mortality, diagnosis with biopsy, % receiving transplant
Su, 2021[25] USA Low	*N*= 338 *4 years*	100% Hepatitis B	Ultrasound +/- AFP at least once in past 4 years	No screening	HCC-specific mortality, diagnosis with biopsy, % receiving transplant

Abbreviations. AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma.

Table 5. Certainty of Evidence Ratings for Case-Control Studies

Outcomes	No. of Participants (Studies)	No. Cases With Event	No. Controls With Event	Relative Effect (95% CI)	Certainty	Comments
Screening with Ultrasound With or Without AFP Compared With No Screening in Adults at Increased Risk for HCC						
HCC-Specific Mortality Timing of Exposure: 0-4 years before index date	407 cases 407 controls (2 observational studies)[24,25]	168	214	Not pooled	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain on the effect of screening with ultrasound with or without AFP compared with no screening on HCC-specific mortality in adults at increased risk for HCC.

Notes. GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded 1 level for study limitations (concerns about population chosen by study authors for control group)

b. Downgraded 1 level for inconsistency (one study in individuals with increased risk (cirrhosis) found no benefit while another study of individuals with increased risk (hepatitis B) showed benefit)

c. Downgraded 1 level for imprecision (optimal information size criterion not met)

d. Downgraded 2 levels for imprecision (wide confidence intervals and optimal information size criterion not met)

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; HCC=hepatocellular carcinoma; no.=number; OR=odds ratio.

COHORT STUDIES

We identified 1 cohort study among individuals at increased risk. The study was assessed as serious risk of bias (Appendix).[26] Summary characteristics for the study are shown in Table 6 below, and study characteristics and results can be found in the Appendix.

Ultrasound versus Ultrasound Alternated With CT

This study investigated ultrasound every 6 months after a diagnosis of cirrhosis versus ultrasound alternating with dynamic computed tomography (CT) every 6 months, with the expectation that CT exams should be performed at least 2 times every 2 years on a regular basis, after diagnosis of cirrhosis to screen for very-early-stage HCC.[26] The study retrospectively captured 1,235 patients over a median follow up time of 4.5 years with hepatitis B-related cirrhosis from 4 hospitals in South Korea. Authors reported 10-year overall mortality was significantly lower in those with alternating ultrasound and CT versus those with ultrasound alone (hazard ratio [HR] = 0.42, 95% CI [0.24, 0.73]) after adjusting for age, gender, diabetic status, hepatitis B status, HBV serum DNA levels, serum aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, creatinine, prothrombin time, platelet count, Child-Pugh score, model for end-stage liver disease score, fibrosis index, platelets, and gender-hepatitis B scores. The evidence is very uncertain on the effect of ultrasound screening at 6 months on overall mortality compared to alternating ultrasound and CT screening every 6 months (very low COE). The authors reported an overall survival of patients undergoing ultrasound alternating with CT at 96.5% versus 93.3% ($p = 0.03$) for those receiving ultrasound alone. The evidence is very uncertain on the effect of ultrasound screening at 6 months on overall survival compared to alternating ultrasound and CT screening at 6 months (very low COE).

Table 6. Characteristics of Cohort Studies (Rated Serious RoB)

Study Country Risk of Bias	Sample Size *Follow-Up*	Population	Intervention Characteristics	Comparator	Outcomes Assessed
Kim, 2020[26] Korea Serious	N=992 *4.5 years (median)*	100% cirrhosis	Ultrasound every 6 months	Ultrasound alternating with CT every 6 months	All-cause mortality Overall survival

Abbreviations. CT=computed tomography.

Table 7. Certainty of Evidence Ratings for Cohort Studies

Outcomes	Follow-Up (Studies)	Reported Results	Certainty	Comments
Ultrasound Screening at 6 Months Compared With Ultrasound Alternating With CT Screening At 6 Months in a Population Diagnosed With HCC				
All-Cause Mortality	10 years (1 observational study)[26]	US alternating with CT had significant association with all-cause mortality compared to US exam alone (HR = 0.42, 95% CI [0.24, 0.73], p = 0.002)	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect of US screening at 6 months on all-cause mortality compared with alternating US and CT screening at 6 months.
Overall Survival	10 years (1 observational study)[26]	10-year overall survival among those undergoing US alternating with CT at 96.5% which was significantly higher than 93.3% among those with US exam alone.	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect of US screening at 6 months on overall survival compared with alternating US and CT screening at 6 months.

Notes. GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations:
a. Downgraded 2 levels for study limitations (various concerns related to confounding, selection bias, and misclassification of interventions)
b. Downgraded for imprecision (optimal information size criterion not met)
Abbreviations. CI=confidence interval; CT=computed tomography; HCC=hepatocellular carcinoma; HR=hazard ratio; US=ultrasound.

HCC COHORT STUDIES

We identified 62 HCC cohort studies, 51 of which were assessed as critical RoB. The remaining 11 studies were deemed as serious RoB (Appendix). We present summary characteristics in Table 8 below and detailed study characteristics in the Appendix. However, as noted, all HCC cohort studies were rated as either critical or serious RoB. Additionally, all HCC cohorts were solely comprised of individuals with HCC and cannot validly assess HCC screening effectiveness and harms.

Table 8. Characteristics of HCC Cohort Studies (Serious RoB)

Study Country Risk of Bias	Sample Size *Follow-Up*	Population	Intervention Characteristics	Comparator	Outcomes Assessed
An, 2020[27] Korea Serious	*N* = 1776 *5 years*	100% cirrhosis 81.9% HBV	Ultrasound + AFP biannually	HCC detected by 1 of 3 test results: US positive but AFP negative; both US & AFP positive; US negative but AFP positive	All-cause mortality Overall survival HCC-specific mortality HCC stage at diagnosis Diagnosis with biopsy %Curative treatment %Transplant
Bae, 2021[28] Korea Serious	*N* = 64674 *5 years*	63.4% cirrhosis 53.8% HBV	Ultrasound + AFP at least every 6 months	US + AFP intervals every 7-12m, every 13-24m, every 25-36m, No screening	All-cause mortality %Curative
Kim, 2018[29] Korea Serious	*N* = 1402 *5 years*	78.3% cirrhosis 82.7% HBV	Ultrasound +/- AFP at least every 8 months for at least 2 years prior to diagnosis	No screening, Irregular screening	All-cause mortality Overall survival HCC stage at diagnosis %Curative treatment
Mittal, 2016[30] USA* Serious	*N* = 887 *NR*	100% cirrhosis	US/MRI/CT +/- AFP ≥1 test in 2 years prior to diagnosis	No screening	All-cause mortality HCC stage at diagnosis %Transplant
Pelizzaro, 2022[31] Italy Serious	*N* = 1107 *3.1 years (median)*	100% cirrhosis	Ultrasound every 3±1 months	Ultrasound every 6±1 months	All-cause mortality Overall survival HCC-specific mortality %Curative %Transplant Financial burden
Piñero, 2019[32] Argentina Serious	*N* = 553 *5 years*	Cirrhosis NR	Ultrasound every 6 months for at least 1 year	No screening	All-cause mortality HCC stage at diagnosis
Tanaka, 2006[33] Japan Serious	*N* = 384 *5 years*	80% cirrhosis	Ultrasound + AFP every 6 months	No screening	Overall survival

Study Country Risk of Bias	Sample Size *Follow-Up*	Population	Intervention Characteristics	Comparator	Outcomes Assessed
Thein, 2015[34] Canada Serious	*N* = 1483 *5 years*	Viral hepatitis with or without cirrhosis	Ultrasound ≥1 tests annually	No screening, Inconsistent screening	All-cause mortality Overall survival %Curative
Tong, 2017[35] USA Serious	*N* = 333 *5 years*	77% cirrhosis 51.5% HBV	Ultrasound + AFP every 6-12 months	No screening	Overall survival %Transplant %Curative
Trevisani, 2004[36] Italy Serious	*N* = 363 *17 months*	Cirrhosis NR 9.5% HBV	Ultrasound + AFP every 6-12 months	No screening	Overall survival
Wu, 2016[37] Taiwan Serious	*N* = 52823 *5 years*	52.4% cirrhosis 28.32% HBV	Ultrasound every 1-6 months	Ultrasound every 7-12m, every 13-24m, every 25-36m, No screening	All-cause mortality Diagnosis with biopsy %Curative treatment

Notes. *Conducted in VHA.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; m=months; MRI=magnetic resonance imaging; US=ultrasound.

Any Imaging versus No Screening

Nine HCC cohort studies investigated outcomes of screening using imaging (+/- AFP) compared to no imaging undertaken before HCC diagnosis. The screening modality utilized in each study is captured in Table 8. Two studies compared routine screening to no screening and irregular screening.[29,34] A third study compared routine screening to 2 non-screening arms: HCC detected symptomatically and HCC detected incidentally.[36] Two studies compared the effects of routine screening (1-6 months) to other screening intervals (7-12 months/13-24 months/25-36 months) in addition to comparisons with no screening.[28,37]

The HCC cohort studies varied geographically: 4 studies were conducted in Asia (Taiwan,[37] Japan,[33] South Korea,[28,29]), 3 in North America (Canada,[34] USA[30,35]), 1 in South America (Argentina[32]), and 1 in Europe (Italy[36]). Studies relied upon patient data retrieved from various sources. Studies used a variety of data sources to draw the population. Three studies used administrative claims databases;[28,34,37] 2 used EMR data,[30,35] and 2 used data from chart review.[33,36] Two studies used data from national (non-USA) registries, 1 with EMR[32] while the other supplemented with chart review.[29]

Studies varied widely in sample size (ranging from 333 to 64,674), liver disease etiologies (cirrhosis, hepatitis B, hepatitis C, alcohol-related disease), and follow-up (17 months to 8 years) (Table 8).

Six studies reported all-cause mortality rates when comparing screening with no screening.[28-30,32,34,37] Authors reported hazard ratios that ranged from 0.51 to 0.79. Four of the studies reporting an all-cause mortality outcome also included arms which compared the effects of routine versus irregular screening schedules.[28,29,34,37] These results and information relating to lead-time adjustment are shown in the Appendix. We downgraded the evidence due to study limitations and indirectness and assessed the evidence as very uncertain on the effect of screening on all-cause mortality (very low COE).

Five studies evaluated the effects of imaging versus no screening on overall survival.[29,33-36] Results for this outcome were not consistently reported, although authors reported significantly longer survival for those under screening using imaging when compared to those not under screening. We assessed, downgrading for study limitations and indirectness, that the evidence is very uncertain regarding the effect of screening on all-cause survival (very low COE). Two of these studies also compared routine screening to irregular screening schedules.[29,34] These results are shown in the Appendix.

Three studies reported BCLC HCC stage at diagnosis as an outcome.[29,30,32] Kim et al reported a higher proportion of patients receiving early stage diagnosis (BCLC 0-A-B) in the routine screening group (ultrasound +/- AFP, ≤8 months) compared with no screening (69.3% vs 40.3%).[29] Piñero et al only reported the proportion diagnosed in early stage, 93.3% among patients undergoing ultrasound imaging at 6 month intervals.[32] In a study investigating patients who had at least 1 imaging test (ultrasound/MRI/CT +/- AFP) performed in the 2 years prior to diagnosis, Mittal et al reported that early stage HCC was seen in 50% in patients compared to 33.7% in a non-screening group.[30]

Four studies reported the proportion of patients who received curative treatment in screening versus non-screening arms. Studies showed that routine screening was associated with increased receipt of curative treatment upon HCC diagnosis compared to non-screening arms. Tong et al investigated the effect of screening using ultrasound plus AFP and reported 60.1% of patients receiving curative treatment versus 26.6% of patients in the non-screening arm.[35] Kim et al reported that 51.9% versus 19.7%, patients received curative treatment compared to non-screening and Bae et al reported 52.2% versus 23.3%. With respect to patients receiving ultrasound alone, Wu et al[37] reported 29.4% received curative treatment compared to 19.7% in a mixed hepatitis B/C population, and Thein et al[34] reported 59.3% in the routine imaging group received curative treatment compared to 43.1% in the non-screening group.

Two studies reported the number of patients receiving liver transplant as an outcome. Mittal et al reported that a similar proportion of patients undergoing regular screening (imaging +/- AFP) received liver transplant (3.6%) compared to a non-screening group (3.8%).[30] Tong et al reported that in a population that included a substantial proportion of HBV patients (>50%), individuals undergoing routine imaging (ultrasound plus AFP) were more likely to receive liver transplant (21.7%) than those in a non-screening group (5.7%).[35]

Ultrasound Every 3 Months versus Ultrasound Every 6 Months

A single study, Pelizzaro et al, investigated the effects of ultrasound imaging at 3±1month intervals (*N* = 109) compared to 6±1 month intervals (*N* = 998).[31] This study took place in Italy and acquired patient data from a national registry. The population was comprised primarily of patients with hepatitis C (79%) liver disease etiology; all had cirrhosis.

Authors reported 5-year all-cause mortality of 69/109 (63.3%) in the 3-month group and 373/668 (55.8%) in the 6-month group (risk ratio [RR] = 1.02, 95% CI [0.88, 1.32]). With respect to HCC-specific mortality, the authors reported mortality in the 3-month group of 66.7% and 57.4% in the 6-month group. The authors reported a 5-year overall survival of 40.7% in the 3-month group and 47.2% in the 6-month group (HR = 0.87, 95% CI [0.67, 1.13]). Due to study limitations, imprecision, and indirectness of the study population, we assessed the evidence as very uncertain on the effect of screening at 3 months compared with 6 months on overall and HCC-specific mortality and overall survival (very low COE). These results and information relating to lead-time adjustment are shown in the Appendix.

Pelizzaro et al reported the proportion of patients receiving curative treatment: 69.7% and 68.2% in the 3- and 6-month arms, respectively (OR = 0.93, 95% CI [0.60, 1.45]). The authors also reported the proportion of patients receiving liver transplant, with 10.1% versus 0.5% in the 3- and 6-month arms, respectively.[31] The authors reported financial burden of screening, with an average total cost per patient of €2905 in the 3-month arm compared to €1823 in the 6-month arm.[31]

Ultrasound Plus AFP Every 6 Months With Outcomes Stratified by Ultrasound/AFP Test Results

*Ultrasound and AFP Positive versus Ultrasound **Positive** but AFP **Negative***

One HCC cohort, An et al, investigated the effects of biannual ultrasound with AFP every 6 months.[27] This study was conducted in South Korea with a population total of 1,776 patients. Data for the study population were accessed from the South Korean national registry and included a large majority of patients with cirrhosis (87.7%) and liver disease due to HBV (81.9%).[27] Median follow-up (IQR) was 3.1 years (1.6-5.1).

The authors evaluated HCC cases and categorized them according to the results of ultrasound and AFP screening prior to HCC confirmation: 1) both Ultrasound and AFP positive: suspected malignant lesion on ultrasound and a high serum AFP test [≥20 ng/mL]); 2) ultrasound positive but AFP negative: suspected malignant lesion on ultrasound with a normal AFP result; 3) ultrasound negative but AFP positive. The reported HR for 5-year all-cause mortality for individuals with HCC detected by ultrasound and having a normal AFP versus those detected with both an ultrasound and AFP abnormality was 0.57 (95% CI [0.47, 0.69]). For overall survival, authors reported a survival of 69.9% in the ultrasound-positive alone group compared to 55.5% in the ultrasound- and AFP-positive group. For HCC-specific mortality, the HR for ultrasound positive versus ultrasound and AFP positive was 0.50 (95% CI [0.40, 0.63]).[27] Due to serious study limitations and indirectness of the study population, we assessed that the evidence is very uncertain regarding the effect of screening based on both a positive ultrasound and AFP result versus ultrasound positive but AFP normal on overall and HCC-specific mortality (very low COE). Detailed results and information relating to lead-time adjustment are shown in the Appendix.

An et al reported HCC stage at diagnosis (BCLC), proportion of patients receiving curative treatment, and proportion receiving liver transplant. In the ultrasound-positive but AFP-normal group, 93.1% of patients were diagnosed with early stage HCC (BCLC 0-A-B) compared to 86% in the both ultrasound- and AFP-positive group.[27] In the ultrasound-positive but AFP-normal group, 63.1% of patients were able to receive curative treatment compared with 56.4% of those in the both ultrasound- and AFP-positive group; 2.3% of patients in the ultrasound-positive and AFP-normal group versus 2.0% in the both ultrasound- and AFP-positive group received a liver transplant.[27]

*Ultrasound and AFP Positive versus Ultrasound **Negative** but AFP **Positive***

An et al also evaluated the differences between the groups detected by AFP but ultrasound negative or HCC detected based on abnormal findings from both ultrasound and AFP. Over a maximum follow-up of 5.1 years, the mortality for AFP positive but ultrasound negative was 88/298 (29.5%) compared to both ultrasound and AFP positive (98/500 [39.6%]). The authors reported an HR of 0.74 (95% CI [0.57, 0.95]). HCC-specific mortality was 20.1% in the AFP-positive and ultrasound-negative group compared to 29.6% in the ultrasound- and AFP-positive group (HR = 0.67, 95% CI [0.50, 0.90]). Authors reported a survival of 55.5% in the ultrasound- and AFP-positive group compared to 64.8%

survival in the AFP-positive but ultrasound-negative group.[27] Due to severe study limitations and indirectness of the study population, we assessed that the evidence is very uncertain on the effect of screening based on both ultrasound- and AFP-positive results versus AFP positive but ultrasound negative on overall survival and overall and HCC-specific mortality (very low COE).

An et al reported differences with respect to HCC stage at diagnosis, proportion of patients receiving curative treatment, and proportion receiving liver transplant in the ultrasound- plus AFP-positive group compared to the AFP-positive but ultrasound-negative group. The authors reported that 86% of patients in the ultrasound- plus AFP-positive group and 89.6% in the AFP-positive but ultrasound-negative group were diagnosed with early-stage HCC (BCLC 0-A-B). Among those in the ultrasound-plus AFP-positive group, 56.4% received curative treatment compared with 60.1% in the AFP-positive but ultrasound-negative group, with 2% of patients in the ultrasound- plus AFP-positive group and 5% in the AFP-positive group receiving liver transplant.[27]

Table 9. Certainty of Evidence Ratings for HCC Cohort Studies

Outcomes	Follow-Up (Studies)	Reported Results	Certainty	Comments
Any Imaging (+/- AFP, Prior to HCC Diagnosis) Compared to No Screening (Prior to HCC Diagnosis) in a Population Diagnosed With HCC				
All-Cause Mortality	5-8 years (6 observational studies)[28-30,32,34,37]	HRs that ranged from 0.51 to 0.79.	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect of screening with any imaging modality on all-cause mortality.
Overall Survival	5-years (5 observational studies)[29,33-36]	Multiple point estimates that generally suggest overall survival is significantly longer in those under screening when compared with those not under screening.	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect of screening with any imaging modality on overall survival.
Ultrasound Screening at 3 Months Compared to Ultrasound Screening at 6 Months in a Population Diagnosed With HCC				
All-Cause Mortality	Median 50 months (1 observational study)[31]	69/109 (63.3%) in 3-mo group and 373/668 (55.8%) in 6-mo group (HR 0.93 [0.65 to 1.32]).	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain on the effect of US screening every 3 months compared with US screening every 6 months on all-cause mortality.
Overall Survival	5-year (1 observational study)[31]	40.7% in 3-mo group and 47.2% in 6-mo group (HR = 0.87, 95% CI [0.67, 1.13], p = 0.43).	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain on the effect of US screening every 3 months compared with US screening every 6 months on overall survival.
HCC-Specific Mortality	5-year (1 observational study)[31]	66.7% in 3-mo group and 57.4% in 6-mo group attributed to HCC progression.	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain on the effect of US screening every 3 months compared with US screening every 6 months on HCC-specific mortality.
Screening Biannually With US & AFP: Outcomes Stratified by US And AFP Results: (Prior to HCC) in a HCC Population: US Positive				
All-Cause Mortality	5-year (1 observational study)[27]	HR = 0.53 (95% CI [0.43, 0.64]).	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain regarding all-cause mortality for HCC detected based on biannual ultrasound positive compared with HCC detected with both ultrasound and AFP positive.
Overall Survival	5-year (1 observational study)[27]	69.9% in ultrasound group and 55.5% in ultrasound + AFP group.	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on overall survival for HCC detected based on ultrasound positive but AFP negative compared with HCC detected by both ultrasound and AFP positive.

Outcomes	Follow-Up (Studies)	Reported Results	Certainty	Comments
HCC-Specific Mortality	5-year (1 observational study)[27]	HR = 0.46 (95% CI [0.37, 0.58]).	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on HCC-specific mortality for HCC detected based on ultrasound positive but AFP negative compared with HCC detected based on both ultrasound and AFP positive.
Screening Biannually With US & AFP: Outcomes Stratified by US and AFP Results: (Prior to HCC) in a HCC Population: AFP Positive				
All-Cause Mortality	5-year (1 observational study)[27]	HR = 0.74 (95% CI [0.57, 0.95]).	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect on all-cause mortality for HCC detected based on both ultrasound and AFP positive compared to AFP positive but US negative.
Overall Survival	5-year (1 observational study)[27]	55.5% in ultrasound + AFP group and 64.8% in AFP group.	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect on overall survival for HCC detected based on ultrasound and AFP positive compared with AFP positive but US negative.
HCC-Specific Mortality	5-year (1 observational study)[27]	HR = 0.67 (95% CI [0.50, 0.90]).	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain on the effect on HCC-specific mortality for HCC detected based on both ultrasound and AFP positive compared to AFP positive but US negative.

Notes. Calculated by review authors.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (various concerns related to confounding, selection bias and misclassification of interventions).

b. Downgraded 1 level for indirectness (HCC population only, missing portion of at-risk population).

c. Downgraded for imprecision (wide confidence intervals).

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; HCC=hepatocellular carcinoma; HR=hazard ratio; mo=month; RR=risk ratio.

DISCUSSION

Our systematic review found that the evidence was very uncertain regarding the effectiveness and harms of screening for hepatocellular carcinoma in adults at increased risk. Uncertainty is mostly due to methodological limitations in the published literature. While we identified 74 eligible studies (including 5 RCTs), all but 15 were assessed as being high or critical risk of bias. We found very limited data from studies with a standard design typically used to determine screening effectiveness (cohort, case-control, RCT). Instead, the vast majority of studies analyzed individuals who already had an HCC diagnosis (HCC cohort), thus preventing reliable assessment of HCC screening benefits and harms in the target "at-risk" population.

When limited to studies judged not at high or critical risk of bias, only 7 studies enrolled exclusively or predominately individuals with cirrhosis, the relevant target screening population in the USA (90% of all HCC cases occur among those with cirrhosis). Only 3 of these studies were conducted in the USA, 1 reporting all-cause mortality and 2 reporting HCC mortality. For the 2 studies reporting HCC mortality, 1 low RoB case-control study in Veterans found no association of ultrasound plus AFP screening with HCC mortality compared with no screening. A small RCT in Veterans (with some risk of bias concerns) found no statistically significant reductions in HCC mortality among individuals screened with ultrasound plus AFP every 6 months versus CT every 12 months plus AFP every 6 months.

Screening test accuracy and epidemiologic data do not provide supportive evidence of HCC screening benefits and RCT findings are inconclusive. Based on a meta-analysis, screening with ultrasound and AFP has poor diagnostic accuracy for early-stage disease with sensitivity and specificity of the combination of modalities of 63% and 84%, respectively.[38] When limited to studies conducted in the USA, diagnostic accuracy is much lower (31.7% and 35.9%, respectively).[39,40] Epidemiologic results also suggest that screening has resulted in increased detection without mortality declines; a pattern consistent with overdiagnosis and detection and treatment programs with, at best, limited effectiveness. For example, from 2006-2016, age-adjusted cirrhosis incidence remained fairly stable (12.1 per 100,000 to 14.3 per 100,000 in males and 5.8 to 7.5 per 100,000 in women).[41] However, age-standardized HCC incidence increased more than 3-fold from 2.6 HCC cases per 100,000 person-years in 1975 to 8.7 per 100,000 person-years in 2017.[42] Trends in HCC incidence have been accompanied by a stage shift, *ie,* an increased percentage of HCC cases with local disease. There has been no concurrent increase of curative-aim treatments nor a decrease in HCC mortality. Instead, more than a 2-fold increase in HCC-attributable death has occurred (2.8 HCC deaths per 100,000 person-years in 1975 to 6.6 per 100,000 person-years in 2017). Shifting patterns of liver disease and cirrhosis etiology over this time may partially account for HCC incidence and mortality findings.

Simply asked, are epidemiologic findings that fail to find a reversal in HCC mortality due to poor screening test performance, wrong screening tests or intervals, wrong choice of screening population, changes in risk population, and/or shifts in underlying etiology? Or is it possible that some screening strategies work in some individuals and have overall net benefit? The evidence does not provide sufficient answers. However, conclusive evidence for cancer screening has rarely been derived from epidemiologic or observational studies. A notable exception is Pap testing to reduce cervical cancer incidence and mortality.[43] In this situation, cervical cancer incidence and mortality dropped dramatically following widespread implementation of Pap testing. These findings led to recommendations for screening.[43] However, in almost all other instances, development of high-quality cancer screening recommendations required evidence of effectiveness from RCTs due to limitations in

establishing causal effects from observational data. For instance, early enthusiasm for ovarian cancer screening with transvaginal ultrasound and CA-125 testing was based on nonrandomized trials purportedly demonstrating screening effectiveness based on stage shift, greater use of curative therapies, and improved survival for screen-detected disease (similar to HCC screening).[44] However, later RCTs demonstrated harms of screening without benefits. Guidelines now recommend against ovarian cancer screening.[44]

There are several challenges for the assessment of screening effectiveness and harms using cohort studies limited only to those with an HCC diagnosis. Many have been noted previously (including in the 2014 ESP report[13]), yet misinterpretation of published evidence and conduct of studies with previously noted limitations persists. A major issue is the combination of *lead-time bias* (when a diagnostic approach merely identifies the disease earlier thus increasing perceived survival time without significant modification of the disease course) and *length-time bias* (when screening detects slower progressing cancer which has a better prognosis, including longer survival). Despite attempts in some studies to control for these biases, solutions are limited and based on assumptions about tumor growth and spectrum of disease. While sensitivity analyses can test the robustness of results under different assumptions, they do not resolve all uncertainty. Another major bias concerns patient and coexisting disease cofounders known to affect both receipt of screening and survival such as comorbidities, liver disease severity, or etiology (*selection bias*). Finally, decision making surrounding classification of intervention groups and outcomes was commonly omitted. A priori decision making and investigation of data missingness, selection biases, and misclassification would provide greater clarity regarding data source limitations.

We found only 5 cohort studies in the target population, and all had serious or critical risk of bias. Case-control studies are a useful alternative approach when used with methodology to control potential bias.[45-47] The 2 case-control studies had limitations, including small sample size. However, the design is still preferable to the more common HCC cohort studies since they include control subjects from the target population. Both case-control studies were conducted at VHA medical centers but provided contrasting results, albeit in different at-risk groups. The first study, in individuals with HBV, found that a history of being screened with ultrasound +/- AFP was associated with a reduction in HCC mortality versus no prior screening. The second study, among individuals with cirrhosis, found no association of HCC mortality with prior receipt of screening with ultrasound plus AFP.[24]

Our findings update 2 prior systematic reviews. In 2014, Kansagara et al[13] concluded that evidence was uncertain regarding the effects of screening for HCC in adults with increased risk. The noted issues related to HCC cohort studies were common to both our report and the previous report. For example, Kansagara et al found that only 5 of the studies included in their review adjusted for lead time. Furthermore, they noted that sensitivity analysis for some studies showed no benefit under certain assumptions of doubling time. Our review differs from Kansagara et al in that their list of required adjustment for confounders only included age, sex, and liver disease severity. The cohort study and the case-control studies in the current report are not included in the earlier report.

A systematic review by Singal et al[14] of published literature and meeting abstracts from January 2014–July 2020 informed a guidance statement by the AASLD. Authors concluded that HCC screening (semiannual screening) was associated with improved early detection, curative treatment receipt, and survival in patients with cirrhosis, although there was heterogeneity in pooled estimates. As in the review by Kansagara, Singal noted that HCC screening was associated with improved early-stage detection and curative treatment receipt but that few studies assessed screening-related harms.

Methodologic limitations exist in this review. For example, the review did not clearly differentiate increased-risk cohort studies from HCC cohort studies. Combining results for these studies is problematic because it assumes that the impact of screening on all-cause mortality in populations with increased risk can be determined from an HCC cohort. Authors included studies that do not fully adjust for lead, length, and indication biases. Unadjusted analyses are not useful for determining causal effects of screening. Only 12 studies reported hazard ratios adjusted for lead time and these 12 studies were pooled. As noted earlier, results often varied by lead time values used both within and between studies, while none of these choices has been validated. Singal did not provide consideration of length bias and other confounding does not appear to have been assessed. Overall risk of bias domains were not provided. Harms of subsequent treatment were not considered. Reports provided no measure of overdiagnosis or overtreatment particularly relevant in screen-detected tumors among individuals with high competing mortality risk. Finally, there was no overall assessment of certainty of evidence.

The AASLD recently issued guidance regarding screening for HCC.[48] AASLD guidance statements are intended to help clinicians understand and implement the most recent evidence based on comprehensive review and analysis of the literature.[49] AASLD recommends the following: HCC screening with semiannual ultrasound plus AFP in at-risk individuals, including those with cirrhosis from any etiology, individuals with non-cirrhotic chronic HBV infection from endemic countries or with a family history of HCC (Level 2: Strong recommendations); interventions such as best practice alerts or outreach programs to increase HCC screening adherence given the underuse of screening in clinical practice (Level 2: Strong recommendation); diagnosis based on noninvasive imaging criteria and/or pathology (Level 1: Strong recommendation). AASLD does not recommend routine use of CT or MRI based imaging and tumor biomarkers outside of AFP (Level 5: Weak recommendation).

Strengths of the AASLD guidance statements include clear actionable information and accompanying strength of recommendations, stated use of methods to rate level of evidence, acknowledgement of evidence limitations including poor diagnostic accuracy of screening methods, recommendations against screening groups at very low risk (*ie,* < 0.2% per year; those with Hepatitis C or NASH without cirrhosis), focusing screening to "at risk" individuals who would be HCC treatment candidates, and noting that in some individuals HCC diagnosis may be made noninvasively, thus reducing harms of liver biopsies.

However, based on a validated quality metric checklist for assessing clinical guidelines and guidance statements (AGREE), we identified several factors in the AASLD guidance development that do not adhere to established standards for high-quality clinical guidelines.[50-52] AASLD guidance authors stated that they used a literature review that was comprehensive and unbiased but did not mandate systematic reviews to facilitate more rapid publication. However, there is no accompanying guidance document protocol, description of search strategies, or study eligibility criteria. Thus, there is no information to determine if the review was comprehensive or unbiased. The guidance committee chair authored the accompanying screening evidence report; several limitations of that systematic review are noted above. Guidance statements are based on expert consensus yet still derive evidence levels and recommendations. They are also used to develop quality measures in HCC by the Practice Metrics Committee of the AASLD.[53] The recently published measures reference AASLD guidance statements and closely align with their conclusions. Thus, AASLD guidance statements and guidelines seem to have similar implications for practice metrics. Most guidance panel members, including the chair, had stated conflicts of interest, including serving as advisors or consultants to pharmaceutical or biotechnology industry or owning stock, which appears inconsistent with AASLD policies.[54] Additionally, no primary care clinicians or public representatives were included.

The stated highest quality data for AASLD recommending HCC screening is a single cluster randomized trial of screening with ultrasound plus AFP every 6 months in adults with hepatitis B conducted in Shanghai, China, where the prevalence of HCC is higher than in the USA.[20] The study reported that death from HCC occurred less frequently in the screening group; rate ratio 0.63, 95% CI [0.41 to 0.98]. Absolute HCC mortality reduction was small (48 per 100,000 person years). We rated this study as high risk of bias. Limitations included: results varied in different publications, patients in the control group were not made aware of the study or actively followed. There was no information about randomization technique and very little information on baseline characteristics; potential differences in baseline characteristics are particularly relevant in cluster-randomized studies when control groups are not aware of study participation and when all-cause mortality is not reported. Intention-to-treat analyses were not used, outcome assessment was not blinded, and generalizability to populations without hepatitis B or those with lower HCC risk is uncertain. Statistical analyses did not adjust for clustering. "Ignoring the clustering results in confidence intervals which are too narrow and P values which are too small; hence it is likely to produce spuriously significant differences."[55]

The recommendation for screening individuals with cirrhosis, the population comprising nearly 90% of individuals who develop HCC, was made despite the lack of RCT evidence, and acknowledgement that a case-control study among USA adults (judged as the only low RoB study in adults with cirrhosis) found no association of ultrasound plus AFP screening with HCC mortality. AASLD recommends semiannual screening for individuals with an estimated annual incidence of ≥0.2 per year, thus subjecting a large proportion of individuals to long-term intensive screening. AASLD notes some "potential limitations" in the "cohort" studies (more appropriately described as HCC cohorts rather than cohorts of "at-risk" adults) but does not acknowledge all individuals in HCC cohorts had HCC. Such study designs target the wrong population, cannot answer the questions regarding screening in "at-risk" adults, and thus do not provide information on the benefits and harms of screening. Some harms of screening were considered (though harms information was sparse) but harms and burden of treatment were not. Given that AASLD states that up to 30% of screen-detected tumors are indolent, substantial overdiagnosis and overtreatment is present with notable treatment-related harms without improved outcomes. Even if screening and treatment are demonstrated to reduce HCC mortality, the harms and costs of treatments, which include surgical resection, ablation, or liver transplantation, require careful assessments to determine overall net clinical benefit, including effect on overall mortality.[56] In the case of liver transplantation, scarce resources are used due to limited donor availability. Listed cost-effectiveness estimates base conclusions on highly uncertain effect estimates and do not include all harms. Finally, evidence does not support screening semiannually or including AFP with ultrasound. Such a strategy is more intensive than other recommended cancer screening programs and increases costs as well as patient, clinician, and health system burden.

In contrast to AASLD conclusions, the National Cancer Institute states that "based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from hepatocellular cancer" and "based on fair evidence, screening would result in rare but serious harms".[57] The United States Preventive Services Task Force, the American Cancer Society, as well as primary care medical societies including the American College of Physicians and American Academy of Family Physicians make no recommendations on HCC screening. Given limitations in evidence regarding benefits, harms, and costs, it is challenging to conclude that unproven screening benefits outweigh known drawbacks.

Limitations

While the primary limitations to our findings are those inherent to the existing evidence, our review was limited to English language publications. There may be relevant studies published in non-English language. However, discussion with our nominating partners and Technical Expert Panel members did not lead to identification of important studies not included in our report. Furthermore, the primary focus of this report is screening individuals at increased risk in the USA. Potential differences in patients, disease etiology, screening performance, and treatment approaches from non-English language countries probably have lower applicability to USA settings. Thus, limiting our inclusion to English language is unlikely to change findings.

Other limitations are primarily due to the existing evidence. The use of the HCC diagnosed population does not permit reliable assessment of evidence related to the questions precluding assessment of individuals undergoing screening not diagnosed with HCC. We were unable to capture harms or cost data associated with screening, as individuals with increased risk are not included in these studies.

FUTURE RESEARCH

Nearly 10 years ago, Kansagara and colleagues identified evidence gaps and provided research suggestions.[58] These gaps are long standing, have been noted by others, and remain today. For example, Lederle and Pocha as well as Atkins et al, noted uncertainty as to whether HCC screening among individuals at increased risk reduces all-cause or HCC mortality as well as the comparative effectiveness of screening strategies including intervals, imaging modalities, additive value of AFP to imaging tests, and in which at-risk populations screening may be effective.[59] Lee and Brennan[60] point out that rather than implementation of wide-spread HCC screening in at-risk adults, "a good case can be made that professional ethics prohibits providing unproven diagnostic screening tests, even if there is substantial demand from patients." They noted uncertainty about the natural history of HCC, especially smaller lesions suspicious for HCC detected by imaging as well as harms of overdiagnosis and overtreatment. Understanding the cost, burden, and financial toxicity of screening and downstream evaluation and treatment as well as the cost effectiveness of screening programs is required. Our review demonstrated that some of the highlighted research gaps persist. In particular, randomized trials of screening versus no screening are needed in the target populations. Rigorous studies are needed to address choice and implementation of screening strategies. Screening requires adequate performance, feasibility, and limited harms. These issues can be addressed with study designs appropriate to the question, with emphasis on inclusion of the at-risk population and, where feasible, randomization.

The VA-CSP #2023: PREventing liver cancer Mortality through Imaging with Ultrasound versus MRI (PREMIUM Study) is an important large, randomized trial evaluating the comparative effectiveness of HCC screening by ultrasound + AFP every 6 months versus abbreviated MRI (aMRI) + AFP every 6 months among patients with cirrhosis who have a high risk of HCC based on an estimated annual HCC risk >2.5%. The primary outcome is HCC-related mortality, with overall survival as a secondary outcome. Study sample size and follow-up are intended to detect reductions in HCC mortality judged as clinically meaningful when including screening and treatment harms as well as health system and patient burdens and costs (*ie,* 30% relative reduction).[61]

Study principal investigators focus enrollment on individuals with cirrhosis at highest HCC risk yet with limited co-morbidities and note weaknesses in existing evidence and the need for screening RCTs with better strategies than currently used. While screening with ultrasound +/- AFP is recommended by

some organizations, they note that it has unacceptably low sensitivity and specificity for early-stage HCC and no demonstrable effectiveness in reducing HCC-related mortality.

This trial cannot assess the fundamental unanswered question of whether any screening is effective compared with no screening. PREMIUM will also not assess whether less intensive ultrasound screening (*eg,* ultrasound every 12 months +/- AFP) results in similar mortality with lower screening burden and costs than more intensive strategies. A 3-arm study that included no screening was not proposed due to feasibility. If aMRI is found not more effective than ultrasound + AFP, attempts to estimate whether ultrasound + AFP reduces mortality versus no screening will be challenging.

The PREMIUM design has been considered analogous to the NCI's National Lung Screening Trial in which plain chest radiography was compared to low-dose computed tomography without a no screening arm. However, prior to NLST findings of computed tomography effectiveness versus chest x-ray, there was not a widely recommended or implemented lung cancer screening program, unlike the current situation with HCC. Thus, a null NLST finding would not have resulted in implementation of widespread CXR screening. Furthermore, because the annual HCC incidence for the large majority of individuals in whom screening is recommended by AASLD is more than 10-fold lower than those eligible for enrollment in PREMIUM (0.2% versus 2.5%), any HCC mortality reduction in this lower risk population will be much smaller than could be detected in PREMIUM. Thus, incorporating harms, costs, and burden is especially relevant in developing screening recommendations in this large population of lower risk individuals and emphasizes the importance of conducting RCTs of screening versus no screening in individuals with HCC incidence <2.5%.

Observational research may also be able to address evidence gaps. A useful research framework is target trial emulation. The focus is on a hypothetical trial designed to answer the question. The trial PICOT is used to define the observation study and analysis. If the target population is those at high risk of HCC, then this population must be included. Target trial emulation of colon cancer screening is described in Garcia-Albeniz et al.[62] This framework provides a tool for analysis of observational data that addresses biases specific to cancer screening. The comparison group to the exposed group must be similar, and thus would include those eligible to be screened who were not screened when first eligible. This strategy avoids the time-dependent confounding due to screening history.

The current review highlights continued uncertainty. Future work should focus on filling evidence gaps reinforcing clinical equipoise around our key questions and suggest research to address these, including whether screening is effective; the harms, burden and costs of screening and associated evaluations and treatments; choice of screening method, intervals, and populations considered at increased HCC risk; and, if of net benefit, efficient and effective implementation strategies.

CONCLUSIONS

Evidence is very uncertain whether screening for HCC in individuals at increased risk reduces all-cause or HCC mortality. Evidence is also very uncertain as to the comparative effectiveness of varying screening strategies including screening intervals, imaging modalities, additive value of AFP to imaging tests, and in what populations screening may be effective. Harms data were limited regarding psychological distress, liver biopsy complications, renal insufficiency, overdiagnosis, and financial burden. However, all screening strategies have diagnostic- and treatment-induced harms, patient and clinician burden, and costs. Randomized trials evaluating screening versus no screening as well as different screening strategies are needed. More rigorous observational studies and use of target trial

emulation as a framework for design could aid in designing observational studies to provide greater certainty. Until methodologically higher quality studies are available, the current state of the evidence seriously challenges HCC screening implementation and patient-clinician decision-making.

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Appendix

SEARCH STRATEGIES

Search Date: January 24, 2022		Search Statement
MEDLINE	1	(liver ca* or hepatocellular ca* or hepatoma).tw.
	2	(screen* or surveillance).tw.
July 1, 2020 – January 24, 2022	3	1 and 2
	4	limit 4 to yr="2020 - 2022"
Embase	1	(liver ca* or hepatocellular ca* or hepatoma).tw.
	2	(screen* or surveillance).tw.
July 1, 2020 – January 24, 2022	3	1 and 2
	4	limit 4 to yr="2020 - 2022"

STUDIES EXCLUDED DURING FULL-TEXT SCREENING

1. Chen VL, Yeh M-L, Yang JD, et al. Effects of Cirrhosis and Diagnosis Scenario in Metabolic-Associated Fatty Liver Disease-Related Hepatocellular Carcinoma. *Hepatology communications*. 2021;5(1):122-132. *Ineligible Comparator*
2. Curran C, Priest M, Datta S, Forrest EH, Stanley AJ, Barclay ST. Hepatocellular Carcinoma Risk Scores Predict Patients Under Surveillance at Low Risk of Benefit and High Risk of Harm. *Digestive Diseases and Sciences*. 2022; *Ineligible Comparator*
3. De Toni EN, Schlesinger-Raab A, Fuchs M, et al. Age independent survival benefit for patients with hepatocellular carcinoma (HCC) without metastases at diagnosis: A population-based study. *Gut*. 2020;69(1):168-176. *Ineligible Comparator*
4. Kurniawan J, Gani RA, Hasan I, et al. The Improvement in 1-Year Survival Rate of Patients with Hepatocellular Carcinoma BCLC Stage A and B after the Implementation of Comprehensive Management. *Journal of Gastrointestinal Cancer*. 2020;51(3):829-835. *Ineligible Comparator*
5. Lahmidani N, Hamdoun FZ, Lahlali M, et al. Prognostic Impact of Alpha Fetoprotein at Diagnosis on Overall Survival of Single Small Hepatocellular Carcinomas. *The Gulf journal of oncology*. 2020;1(33):64-67. *Ineligible Comparator*
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UNDERWAY STUDIES

NCT05486572 Preventing Liver Cancer Mortality Through Imaging With Ultrasound vs. MRI (PREMIUM)
NCT05095714 FAST-MRI for HCC surveillance in patients With High risk of Liver Cancer. (FASTRAK)
NCT00912847 Validity and Cost-Effectiveness of a New Screening Test for Hepatocellular Carcinoma
NCT02551250 Annual MRI Versus Biannual Ultrasound for Surveillance of Hepatocellular Carcinoma in Liver Cirrhosis (MAGNUS-HCC)
NCT00190385 Screening of Hepatocellular Carcinoma in Patients With Compensated Cirrhosis

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RISK OF BIAS ASSESSMENTS

RANDOMIZED CONTROLLED TRIALS (ROB-2)

Trial Name or Author Year	Bias from randomization process	Bias from deviation from intended interventions (Assignment)	Bias from deviation from intended interventions (Adherence)	Bias from missing outcome data	Bias in measurement of outcome	Bias in selection of reported result	Overall risk of bias (Low, Some concerns, High)
Chen, 2003[21]	Some concerns	Low	High	Some concerns	Low	Some concerns	High
Pocha, 2013[22]	Some concerns	Low	Some concerns	Some concerns	Low	Low	Some concerns
Trinchet, 2011[23]	Low	Low	Some concerns	Low	Low	Low	Some concerns
Wang, 2013[19]	High	Low	High	Low	Low	Low	High
Zhang, 2004[20]	Some concerns	Low	High	Low	Low	Some concerns	High

NONRANDOMIZED COMPARISON STUDIES (ROBINS-I)

Study Name or Author Year	Bias due to confounding*†	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions (Assignment)	Bias due to departures from intended interventions (Adherence)	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias† (Low, Moderate, Serious, Critical, No Information)
Aby, 2019[63]	Critical	-	-	-	-	-	-	-	Critical
Alencar, 2022[64]	Critical	-	-	-	-	-	-	-	Critical
An, 2020[27]	Low	Serious	Moderate	Low	Moderate	Serious	Low	Low	Serious
Bae, 2021[28]	Serious	Serious	Low	Serious	Moderate	Serious	Low	Low	Serious
Bolondi, 2001[65]	Critical	-	-	-	-	-	-	-	Critical
Chaiteerakij, 2017[66]	Critical	-	-	-	-	-	-	-	Critical
Chen, 2002[18]	Critical	-	-	-	-	-	-	-	Critical
Chen, 2020[67]	Critical	-	-	-	-	-	-	-	Critical
Chinnaratha, 2019[68]	Critical	-	-	-	-	-	-	-	Critical
Choi, 2019[69]	Low	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Costentin, 2018[70]	Critical	-	-	-	-	-	-	-	Critical
Cucchetti, 2014[71]	Critical	-	-	-	-	-	-	-	Critical
Davila, 2007[72]	Critical	-	-	-	-	-	-	-	Critical

Study Name or Author Year	Bias due to confounding*†	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions (Assignment)	Bias due to departures from intended interventions (Adherence)	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias† (Low, Moderate, Serious, Critical, No Information)
Debes, 2018[73]	Critical	-	-	-	-	-	-	-	Critical
Edenvik, 2015[74]	Critical	-	-	-	-	-	-	-	Critical
El-Serag, 2011[75]	Critical	-	-	-	-	-	-	-	Critical
Eskesen, 2014[76]	Critical	-	-	-	-	-	-	-	Critical
Giannini, 2022[77]	Critical	-	-	-	-	-	-	-	Critical
Giannini, 2000[78]	Critical	-	-	-	-	-	-	-	Critical
Haq, 2021[79]	Critical	-	-	-	-	-	-	-	Critical
Hong, 2018[80]	Critical	-	-	-	-	-	-	-	Critical
Huang, 2018[81]	Critical	-	-	-	-	-	-	-	Critical
Hwang, 2022[82]	Critical	-	-	-	-	-	-	-	Critical
Im, 2019[83]	Critical	-	-	-	-	-	-	-	Critical
Jasirwan, 2020[84]	Critical	-	-	-	-	-	-	-	Critical
Karim, 2022[85]	Critical	-	-	-	-	-	-	-	Critical
Kemp, 2005[86]	Critical	-	-	-	-	-	-	-	Critical
Kim, 2018[29]	Low	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Kim, 2020[26]	Low	Serious	Low	Low	Low	Low	Low	Low	Serious
Kuo, 2021[87]	Critical	-	-	-	-	-	-	-	Critical
Kuo, 2010[88]	Critical	-	-	-	-	-	-	-	Critical
Kwon, 2020[89]	Critical	-	-	-	-	-	-	-	Critical
Lang, 2020[90]	Critical	-	-	-	-	-	-	-	Critical
Leykum, 2007[91]	Critical	-	-	-	-	-	-	-	Critical
Merchante, 2019[92]	Critical	-	-	-	-	-	-	-	Critical
Mittal, 2016[30]	Low	Serious	Moderate	Low	Low	Moderate	Low	Low	Serious
Moon, 2018[24]	Low	Low	Low	Low	Low	Low	Low	Low	Low
Nusbaum, 2015[93]	Critical	-	-	-	-	-	-	-	Critical
Oeda, 2016[94]	Critical	-	-	-	-	-	-	-	Critical
Papageorge, 2022[95]	Critical	-	-	-	-	-	-	-	Critical
Pascual, 2008[96]	Critical	-	-	-	-	-	-	-	Critical
Pelizzaro, 2021[97]	Critical	-	-	-	-	-	-	-	Critical
Pelizzaro, 2022[31]	Low	Serious	Moderate	Low	Moderate	Moderate	Low	Low	Serious

Study Name or Author Year	Bias due to confounding*†	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions (Assignment)	Bias due to departures from intended interventions (Adherence)	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias† (Low, Moderate, Serious, Critical, No Information)
Piñero, 2019[32]	Serious	Serious	Low	Low	Low	Low	Low	Low	Serious
Rodriguez, 2017[98]	Critical	-	-	-	-	-	-	-	Critical
Schauer, 2020[99]	Critical	-	-	-	-	-	-	-	Critical
Schauer, 2019[100]	Critical	-	-	-	-	-	-	-	Critical
Shindo, 2015[101]	Critical	-	-	-	-	-	-	-	Critical
Singal, 2020[102]	Critical	-	-	-	-	-	-	-	Critical
Singal, 2017[103]	Critical	-	-	-	-	-	-	-	Critical
Sohn, 2022[104]	Critical	-	-	-	-	-	-	-	Critical
Su, 2021[25]	Low	Low	Low	Low	Low	Low	Low	Low	Low
Tanaka, 2006[33]	Low	Serious	Low	Low	Low	Low	Low	Low	Serious
Taura, 2005[105]	Critical	-	-	-	-	-	-	-	Critical
Thein, 2015[34]	Moderate	Serious	Moderate	Low	Moderate	Moderate	Low	Low	Serious
Tong, 2010[106]	Critical	-	-	-	-	-	-	-	Critical
Tong, 2017[35]	Low	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious
Toyoda, 2018[107]	Critical	-	-	-	-	-	-	-	Critical
Tran, 2018[108]	Critical	-	-	-	-	-	-	-	Critical
Trevisani, 2004[36]	Serious	Serious	Moderate	Low	Moderate	Serious	Low	Low	Serious
Trevisani, 2002[109]	Critical	-	-	-	-	-	-	-	Critical
van Meer, 2015[110]	Critical	-	-	-	-	-	-	-	Critical
Vaz, 2023[111]	Critical	-	-	-	-	-	-	-	Critical
Wong, 2008[112]	Critical	-	-	-	-	-	-	-	Critical
Wu, 2016[37]	Low	Low	Moderate	Low	Moderate	Low	Low	Low	Serious
Yamago, 2019[113]	Critical	-	-	-	-	-	-	-	Critical
Yeh, 2016[114]	Critical	-	-	-	-	-	-	-	Critical
Yu, 2004[115]	Critical	-	-	-	-	-	-	-	Critical

Notes. *Publications rated critical in Domain 1 did not undergo full ROBINS-I assessment.†Low=low, except for concerns about uncontrolled confounding.

PEER REVIEW COMMENTS AND RESPONSES

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	Thank you.
2	3	Yes	Thank you.
3	4	Yes	Thank you.
4	5	Yes	Thank you.
5	6	Yes	Thank you.
6	7	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
7	2	No	Thank you.
8	3	No	Thank you.
9	4	No	Thank you.
10	5	No	Thank you.
11	6	No	Thank you.
12	7	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
13	2	No	Thank you.
14	3	No	Thank you.
15	4	No	Thank you.
16	5	No	Thank you.
17	6	No	Thank you.
18	7	No	Thank you.
Additional suggestions or comments can be provided below.			
19	2	Well written review that updates the continued lack of sufficient data to make recommendations for HCC screening. Continues to make the argument for more large scale studies like the PREMIUM study to identify best imaging and likely effect for HCC screening.	Thank you.

Comment #	Reviewer #	Comment	Author Response
20	3	This evidence synthesis review examines the efficacy of screening for HCC in adults at increased risk for HCC. This review is comprehensive, detailed with robust methodology. Congratulations to the authors and contributors on this important and impressive work.	Thank you.
21	3	1) In the discussion, when discussing incidence and mortality rates, would suggest including the Annual report on cancer (which comes out each fall and should be published soon) and SEER website that have updated epidemiological data. The incidence of HCC has plateaued since 2016 and the mortality rates are plateauing as well.	Included in both introduction and discussion
22	3	2) The point of view of the discussion is perhaps not as neutral as one would expect from an evidence synthesis review, and would encourage more neutral language. For example: --> "very" page 42, line 6 and again page 42, line 10 --> "surprisingly" p.43, line 31 --> page 42, line 3- This sentence is purely editorial and does not enhance what should be an objective assessment of the evidence, would suggest removing. "While shifting patterns of liver disease and cirrhosis etiology over this time period may partially account for HCC incidence and mortality findings an equally plausible explanation is that current screening programs may not be effective but are identifying and labeling individuals with HCC without improving receipt of effective therapies."	Thank you for your thoughtful review, we have updated the discussion with a more neutral voice. We modified this sentence to read: *Shifting patterns of liver disease and cirrhosis etiology over this time may partially account for HCC incidence and mortality findings. However, current screening programs may be ineffective while identifying and labelling individuals with HCC without improving receipt of effective therapies.*
23	3	3) page 44 line 23- The AASLD document is a guidance, and is not a guideline. There are differing criteria for development of these documents two types of documents. Would rewrite this paragraph in this context. The primary source document should be reviewed by this group Singal et al. Hepatology 2023 which clearly describes the differences between the two in the introduction. It is clear that the AASLD guidance is not equivalent to an evidence synthesis review and should not be viewed in the same vein.	We changed this to note that it is a guidance statement and reviewed the source document, as we had previously. Of note, guidance statement authors state that this “document was based on consensus of a multidisciplinary expert panel and provides guidance statements based on formal review and analysis of the literature… the literature review for this document is comprehensive and unbiased, the lack of mandatory systematic reviews facilitated more rapid publication”. The guidance statement provides “levels of evidence” and “strength of recommendations”. Furthermore, the AASLD website places both AASLD guidelines and

Comment #	Reviewer #	Comment	Author Response
			guidance statement under a single link for practice guidelines. AASLD states: “AASLD develops evidence-based guidelines, practice guidances, and patients guidances to share recommended approaches to diagnostic, therapeutic, and preventive aspects of care.” notes that “Guidance statements help clinicians understand and implement the most recent evidence based on comprehensive review and analysis of the literature”. AASLD has developed quality measures in HCC care based on practice guidelines including AASLD. Final set of quality measures in HCC care include surveillance for HCC with HS every 6 months in all patents with cirrhosis and in Asian individuals with hepatitis B regardless of cirrhosis status. (Asrani, Sumeet K.*; et al Quality measures in HCC care by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology 75(5):p 1289-1299, May 2022. | DOI: 10.1002/hep.32240) Thus guidance statements have strong practice, policy, and performance implications that appear similar to recommendations made in AASLD guidelines. Finally, AASLD conflict of interest policy documents indicate that writing group panel members and chairs are not permitted to have engaged in consulting or own stock in pharmaceutical or biotechnology firms relevant to the topic. The chair and most panel writing members acknowledged such conflicts.
24	3	Other minor comments- 1) "Notably" used twice in the same paragraph page 42, line 30 and line36 2) "Of particular note is temporal confounding (changes in screening availability concurrent with changes in cancer treatment and survival or changes in underlying liver disease etiology)" - p. 43, line 22 awkward sentence structure, consider refining/editing 3) page 43, line 31, suggest k=5 be placed after "cohort studies"	Thank you, these sentences have been edited to be clearer.

Comment #	Reviewer #	Comment	Author Response
25	4	I appreciate all the work that went in to this review. Now the authors need to devote a similar effort to its communication. The central finding is that there is no rigorous evidence to support screening high risk patients for HCC. While I don't doubt this finding, I don't think the authors have made a strong, clear case to specialist clinicians and VA policymakers. More attention should be given to explaining why the existing evidence is weak and to taking the opportunity to educate the reader. Note, this does not mean that the document needs to be lengthen. Instead, you can avoid the detailed description of the findings that you think are flawed. Relegate those to an appendix. Here are some suggestions for improvement.	Thank you.
26	4	**1. Give more weight (i.e., details) to the RCTs, less to the observational data** I suspect the authors would agree that observational data on screening are subject to huge biases and can be extraordinarily misleading. Thus, screening is one place where randomized trails are particularly important. There are only 5 RCTs and you dispense with 3 of them. Why? I get you assess the risk of bias as extraordinarily high, but why? The table says something about adherence, but problems with screening adherence only biases the effect towards the null. I suspect you have identified more fundamental problems. If so, you should describe them. I suggest you do that in the final comment column of Table 3 (which is now used for boilerplate language). For example, the Zhang study (Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130(7):417-422.) randomized 18,000 high risk patients and report a 37% decrease in HCC mortality. Of course, that's all I can see in the abstract. But were I a proponent, I'd sure want to know why you threw that one out.	We provided greater detail regarding the risk of bias domains that raised our concerns with the identified RCTs in the text. We have provided additional information specifically relevant to the Zhang study in the discussion. To remain consistent throughout the document we chose not to include these details in the characteristics table.
27		There are only two case-control studies, but both are from VA. Table 5 is very confusing: each trial is judged as "low	We have revised this to provide a single GRADEd statement related to the case-control studies. The

Comment #	Reviewer #	Comment	Author Response
		certainty", but when you combine the two together they become "very low certainty". What's with that? Why combine the two at all? You are not pooling them. And you don't do that for the RCTs. What is the risk of bias here? You gotta say more than "concerns about population chosen by study authors for control group".	decision was based after reviewing this comment and the overarching main question of whether screening is effective in "at risk adults". Individuals with cirrhosis and Hepatitis B are both subsets of that overall population. We describe the individual studies without a separate GRADE statement thus providing the reader with results information by population group of interest. We elected to provide fairly substantial discussion of these two studies and populations because they are of higher methodological quality and conducted in VA.
28		At the other extreme are the HCC cohort studies. You imply these have little value, but are not clear about why. I imagine these are retrospective cohorts of HCC patients, looking backwards in time to determine the exposure: screen-detected vs clinically detected. Of course, that is an awful design. Because the decision of who to screen reflects a choice (made by either the patient or the provider) there is a strong tendency for sicker patients to be in the not screened group. Additionally, there are all the biases related to survival from the time of diagnosis (lead, length and overdx). A strong section explaining why HCC cohort studies contribute no useful information would obviate the rest of this section: the tables and text could go in the appendix.	Thank you for your careful review, we updated our methods section to provide greater detail regarding the study design and limitations. We have chosen to retain the section describing the HCC cohort evidence. While we have strong reservations and concerns regarding the evidence we believe it is more informative to readers including clinicians, policy makers and researchers to list the studies, highlight reservations with the evidence and remain grounded in systematic review methods while presenting the information. We have incorporated some of these suggestions in our discussion.
29	4	**2. Take the opportunity to educate the clinician reader** Why not start each section for the 4 categories of studies (RCT, Case-control, Cohort, HCC Cohort) with a simple diagram of their design? (These could serve as a template for other evidence reviews as well.) It would be particularly useful to delineate/distinguish the 3 observational study designs (e.g., a case has experienced the outcome: HCC death. Who are the controls? A patient with cirrhosis? Who is in the non-HCC cohorts? What is the HCC cohort?). Then devote a few words to the generic weakness of each.	We added a 4x2 table to the methods section to briefly orient the reader to the difference between the observational study designs. Additional information is a bit beyond our review scope and perhaps adds too much technical description.
30	4	**3. Better distinguish systematic error (bias) and random error (precision).** I know you want to combine the two for the "level of certainty" assessment, but they are very different issues and deserve separate consideration. I think you want to emphasize bias,	To remain transparent and unbiased ourselves we chose to report all non-high risk of bias trials/studies in the results document.

Comment #	Reviewer #	Comment	Author Response
		"While we identified 74 eligible studies (including 5 RCTs) all but 15 were assessed as being high or critical risk of bias." Who cares about a precise study that is precisely wrong?	GRADE Certainty of Evidence assessment incorporates both of these different domains and are considered separately.
31	4	**4. Avoid reinforcing biased measures of early detection: Stage distribution & Survival** The word "survival" appears more than 100 times in the document – with the implication that it is a valid metric in the context of screening. It is not. But I fear your frequent use of the tern will lead readers to infer that any data showing prolonged survival associated with screening is evidence of benefit. I understand you are primarily using the word in the context of "Overall Survival" (but not always). Find a different name: 10 year risk of death? Nevertheless, the starting point is ambiguous (e.g. measured from the time of diagnosis or the time of the cohort entry?) Better yet ask yourself, What does this metric adds to all-cause mortality? I understand one is a risk and the other a rate but they are essentially the same information. I tend to lose the duplicative metric; simpler is better. I suggest you avoid the word "survival" entirely, unless you want to explain why it is biased in the setting of early detection. Make sure readers understand the ultimate goal of screening is to reduce mortality, not increase survival. You don't refer to the stage distribution per se, but you do lapse into the measure, "a higher proportion of patients receiving early stage diagnosis" and "Detection of localized disease has increased with increased screening; moving from 49.4% in 2000 to 62.1% diagnosed at a localized stage in 2016." Without further explanation, readers may infer this as evidence of benefit. As I'm sure the authors recognize, this change may simply reflect increased early-stage incidence, without necessitating any decline in late-stage incidence. You should be clear that the intermediate goal of screening is to reduce the clinical presentation of late-stage	We reviewed and limited the use of the word "survival" to studies specifically reported on "overall survival". We agree that use of disease specific survival is not a valid metric of the effectiveness of screening.

Comment #	Reviewer #	Comment	Author Response
		cancer (i.e. late-stage incidence), not simply finding more early stage cancers.	
32	4	**5. Use more precise language/Reduce unneeded text & abbreviations** "Screening" and "surveillance" appear to be used as synonyms throughout the text. "Screening" implies the search for disease in individuals without symptoms of the disease. I believe "surveillance" should be reserved for treated cancer patients who have no symptoms of recurrence, but undergo testing for cancer recurrence. I understand the term is also applied to screening high risk groups. But you don't need to muddy the water. Your working title is clear: Screening for hepatocellular carcinoma in increased risk adults: A systematic review. Stick with screening throughout.	The text has been updated to use the term "screening" throughout.
		Now that I write this, I found myself wondering whether this is about screening for hepatocellular carcinoma or screening for liver cancer. You do highlight that the former is a subset of the latter, "HCC is the most common form of liver cancer and accounts for approximately 75% of cases". (I assume this refers to liver primaries, not metastatic disease.)	Regarding liver cancer and HCC. We use these as synonymous. In most cancer statistics bile duct cancers are included in the category of "liver cancers". We have clarified this to state that we are referring to this as screening for HCC/liver cancer and that these make up approximately 75% of all liver and bile duct cancers. While beyond the scope of this review we believe it is likely that cancers of the bile duct would likely be detected and treated incidentally in HCC screening programs. The net benefit of that is is not known and beyond our review scope.
33		It feels like some text has been recycled from other reviews. For example, there is an entire methods paragraph on pooling. Yet there are no pooled results. Go through the text and ruthless remove irrelevant boilerplate language.	Thanks for pointing this out. We have updated our methods section to remove what we anticipated we were going to do (and listed in our protocol) with what was actually done (narrative synthesis).
34		Finally, a pet peeve. Do you really need so many abbreviations? They make the document harder to read. I first got tripped up in the executive summary "incidence of HCV-related HCC". Fine to use a select few (like HCC), but why not "incidence of hepatitis C-related HCC". Of course, a gastroenterologist won't get tripped up by HCV. But they sure will with COE and RoB… Your goal should be to make it easier.	Thanks for this suggestion, we have updated the report to remove abbreviations that are only used seldomly, in favor of spelling out the term(s).

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35	4	**6. Reconsider the executive summary** First, you are right to start with the descriptive epidemiology. But why not draw a graph of the US incidence/mortality trends? A picture is worth 1000 words… (Again, you'll have to decide if this is for HCC or all liver cancers). It is also important to emphasize that the risk of HCC/liver cancer is higher among veterans. But this sentence missed the mark: "Incidence was higher in Medicare and Veterans Health Administration (VA) patients, (22.3 and 45 per 100,000 person-years respectively), compared to the USA population (9.5 per 100,000)" Of course, the incidence is elevated in the population over age 65 (Medicare) relative to the general population – as it would be for virtually all cancers. See if you can compare the VA and non-VA population adjusted to the same age standard. (Failing this, you could argue the VA incidence is twice that of Medicare, despite the VA population being younger. But you need to explain it.)	We included the recent SEER data as a graph. We note that these data are not age or comorbidity adjusted.
36	4	Second, address the question: Who is at increased risk? (It's in your title) You don't really deal with this question until the Background and then overwhelm the reader with lists and no sense of magnitude of the risk. (Does Hispanic ethnicity and cirrhosis confer the same increase in risk?) I suggest a simple table here: major risk factors and the associated RR (go for big ones RR>2). I have the sense that you believe that cirrhosis for any reason (Hep C, Hep B, alcohol) is the central element for identifying the high risk population. If that's right, say it.	We have streamlined the information provided. We agree that there are multiple risk factors for HCC. We also state that "increased risk" is broadly and variably defined by different authors. We noted that we took an expansive definition of increased risk, described the populations in the respective studies and stratified results where possible by "risk category" (*eg*, cirrhosis, Hep B (with or without cirrhosis). We also highlight how existing guidance statements provide similar stratified patient level recommendations by similar categories
37		Third, how about a small table of the various screening tests proposed. Maybe subcategorized by imaging, biochemical. You could define some abbreviations here (e.g. MRI, CT, US, AFP).	We believe these are described in text and the included tables of identified studies: *ie*, imaging modalities, including at various intervals (MRI, CT, US alone or in combination and with or without AFP). No additional tables are provided.
38	4	Finally, I am confused by your summary table. I can find no reference to it in the text. It follows a results paragraph that	Thank you for catching the missing RCT from our summary table, it has been added in. We used

Comment #	Reviewer #	Comment	Author Response
		includes “Of the 5 RCTs, 2 were rated some concerns RoB, while the other 3 were rated high RoB.” – yet the table includes only one RCT. More space is devoted to observation studies (particularly those I believe you think contribute least information: HCC cohort). Similarly, a lot of space is devoted to repeating one of two phrases: “The evidence is very uncertain” or “There may be little to no difference”. Invent a way to do this more efficiently. And, again, ask yourselves whether Overall Survival (or 10-year risk of death) adds anything to All-Cause Mortality.	standard language recommended by GRADE to describe the summary results. The phrases: “The evidence is very uncertain” or “There may be little to no difference” are standard in the GRADE framework.
39	4	**7. Call for a RCT in VA CSP** Why not end by calling for a VA trial of screening vs. no screening? You report that the risk of HCC death among VA patients with cirrhosis is about 8% @ 3years (Table 3 Pocha). That is really high. If that’s right, the sample size required to detect a 25% reduction in HCC mortality is only ≈ 5000 patients. Smaller, of course, with a 5 year trial. That’s feasible, right?	We have included this. We did previously but have highlighted some more. We note that the Premium trial claimed such a RCT would not be feasible. We include an article by Lederle et al that proposed such a trial, which was submitted to VA-CSP but not approved for planning.
40	4	In general, there are too many numbers in the text. Some numbers are just not relevant to the central question at hand: Does screening reduce HCC mortality? (I understand there is no information on harms)	Thank you we have reviewed and streamlined when possible.
41	4	I suggest you get rid of costs…distracting, more words…focus on the question of effectiveness. I also suggest you get rid of diagnostic performance measures (sensitivity, specificity, etc.). They are not only distracting, but also potentially misleading.	Thank you for the suggestion, however these were outcomes that were listed in our protocol to identify, extract data, and report on.
42	4	Avoid repeating findings in tables and text – tables are where numbers are best digested, just focus on the most important (e.g. main effect, primary finding) in text.	Thank you we have reviewed and reduced repetitious use of findings when possible.
43	5	Conclusions • Page X (lines 14-16): The report concludes that, “Until evidence gaps are closed regarding HCC screening in adults at increased risk should be incorporated into patient, clinician and health system communication, decision-making and implementation strategies.” I believe that the extremely weak evidence of any benefits, the potential for harms, and the burden of time for patient/clinician communication of the issue, warrant a stronger statement. For example, I think that the report could state that until stronger studies are available,	We updated the conclusions to be more informative while avoiding statements that are more in scope for our topic nominators, particularly around recommendations for implementation or not.

Comment #	Reviewer #	Comment	Author Response
		the state of evidence does not justify a role for HCC screening/surveillance in routine management or discussions with patients unless the patient spontaneously inquires. Instead, the VA may wish to incorporate that conclusion into a guideline rather than the evidence report. But at the least, you can make a clear statement of fact: the current state of the evidence presents a serious challenge to patient-clinician communication and informed decision-making.	
44	5	Methods (Analytic Framework • Page 6 (line 27): You did not include treatment-related harms triggered by screening/surveillance, a reasonable decision given the lack of evidence. However, you refer to treatment-related harms as an "intermediate outcome." Treatment-related harms are true health outcomes if increased by screening/surveillance. For example, you list overdiagnosis as a true, direct harm. A salient harm of overdiagnosis is unnecessary harm from treatment. So, if the data were available (e.g., from randomized clinical trials), excess harms associated with screening would count as a true health outcome along with overdiagnosis. This is analogous to excess all-cause mortality noted in some RCTs of cancer screening.	Thank you. We agree. Our analytic framework has treatment related harms in a separate oval consistent with Analytic Framework infographic methods. Our review was not intended to address treatment related harms as that would have markedly expanded review scope. We agree that treatment related harms for identified HCC (whether found on screening or otherwise) are important considerations.
45	5	Discussion • Page 29 (line 57-58): The increased incidence of HCC is identified as accompanied by a stage shift to local stage. However, simple increase in incidence of early-stage disease is not equivalent to an true stage shift. True stage shift implies an accompanying reduction in late-stage disease, not simply an increase in early-stage disease.	Thank you. Agree. Modified in the discussion. In our introduction we noted that the percentage of liver cancers detected as localized disease has increased with increased screening; moving from 49.4% in 2000 to 62.1% diagnosed at a localized stage in 2016
46	5	Conclusions • Page 34: Same comment as for Page X regarding a factual statement that the current state of the evidence presents a serious challenge to patient-clinician communication and informed decision-making. Preferably, you could make the statement that the state of evidence does not justify a role for HCC screening/surveillance in routine management or discussions with patients unless the patient spontaneously inquires.	We modified to emphasize the former while avoiding policy statements that are beyond the scope of our review.

Comment #	Reviewer #	Comment	Author Response
47	6	US vs. CT; cohort studies: (page 32 [19]) why were the studies considered to be low quality (what was the reason)	Individual risk of bias assessments for each study are available in the Appendix.
48	6	Page 43, line53: remove extra “that”	This has been addressed.
49	7	I appreciate the opportunity to review this ESG which is thoughtfully written. The authors are honest in their examination of the flaws in existing studies and helpful in proposing methodological approaches to close the evidence gaps. The writing is unclear at times and lacks uniformity. It is a highly methodological assessment of the analytical flaws and weakness of the evidence in a field fraught with heterogeneity. On the brighter side, future directions are offered with constructive suggestions and promising new studies are highlighted.	Thank you.
50	7	The terms "screening" and "surveillance" are used interchangeably in this manuscript. However, HCC occurs in an at-risk population and we are performing surveillance (rather than screening which would be for an average risk/healthy population). It would be helpful if the language was uniform throughout the manuscript.	We used screening throughout for consistency. Screening is conducted in asymptomatic individuals and the term can be applied to those at “increased risk”. We recognize some variation in the field with these two terms. We prefer screening as surveillance may also include those with abnormalities on imaging tests that might undergo additional and more intensive “surveillance” and were out of scope for this review.
51	7	In the conclusion, it is important to note that reference 45 is a guidance paper, not a guideline paper. The AASLD issued a guideline on HCC in 2018 with accompanying systematic reviews. The guidance published in 2023 is meant to be an update to the guideline. GRADE methodology was NOT used. In fact, we clearly state in the introduction: "AASLD guidelines are supported by systematic reviews of the literature, formal ratings of evidence quality and strength of recommendations, and, if appropriate, meta-analysis of results using the Grading of Recommendations Assessment Development and Evaluation system. In contrast, this document was developed by consensus of a multidisciplinary expert panel and provides guidance statements based on formal review and analysis of the literature on the topics and questions related to the prevention, diagnosis, and treatment of HCC. Although the literature review for this document is comprehensive and unbiased, the lack of mandatory	We have noted that change and more fully described the AASLD guidance document, processes and AASLD stated use of guidance documents and their incorporation into AASLD practice metrics.

Comment #	Reviewer #	Comment	Author Response
		systematic reviews facilitated more rapid publication. The expert panel rated the level of evidence for each recommendation based on the Oxford Center for Evidence-Based Medicine.1 Additionally, the panel categorized the strength of recommendations based on the level of evidence, risk–benefit ratio, and patient preferences."	
52	7	Please change all "guideline(s)" terms to "guidance" in this paragraph (page 31, lines 24, 37, 38, 39, and 42). The sentence beginning, "Most guideline panel members had industry financial conflicts of interest..." is frankly untrue. The AASLD has strict policies regarding conflict of interest (COI) for authors on guidance/guideline writing groups. Both the AASLD and IOM require the majority of Writing Group members to be free of all commercial COI. In addition, the AASLD sets a financial limit on compensation that can be received for those members with COI (please see https://doi.org/10.1002/hep.29810). Furthermore, the writing group included medical, surgical, and radiation oncologists, radiologists, interventional radiologists, and transplant surgeons in addition to hepatologists - with broad geographical and institutional diversity. I don't see primary care physicians or public representatives on ASCO or other specialty society guidelines, so why is the AASLD held to a higher standard?	Done. We included the AASLD “strict policies” regarding COI. Of note, the guidance chair and most of the writing group members have listed disclosues that appear to be in conflict with AASLD policies (*ie*, consultation with and ownership of stocks in pharmaceutical and biotechnology companies. AASLD and other guideline committees are held to standards set by the Institute of Medicine and Guidelines International for High Quality Guidelines. The intent of clinical guidelines is to provide rigorous, readable, relevant information that is free of real or perceived bias and incorporates a broad perspective. We reference and used an established metric for assessment (AGREE) for assessing quality of guideline. Primary care clinicians are often responsible for implementing screening strategies, referring patients and engaging in discussions. A detailed discussion of the AASLD guidance statement, their stated methods, processes and policy implications is now provided in the Discussion.
53	7	The use of the abbreviation USA is important to distinguish this from ultrasound, abbreviated as US. Please check for uniformity of this abbreviation (e.g., page 12, lines 36 and 39; page 24, line 48) and introduce the abbreviation properly on page 4, line 8 as "United States of America".	We have updated the text to spell out the word “ultrasound” and reserved the abbreviation (US) for the tables only. We have also reviewed the report to make sure all instances of “USA” are accurate.
54	7	On page 4, line 20, "A recently published, 2022, systematic review..." in erroneous as this paper was published in 2020.	This sentence was revised and the review has been cited appropriately.
55	7	On page 4, line 34 (and throughout the manuscript), consider adopting the new nomenclature of Steatotic Liver Disease to replace NAFLD.	This has been updated to MASLD throughout the text.
56	7	Page 4, line 39-41 should be restated as "Of concern for the USA population, both diabetes and body mass index (BMI)	Thank you for the suggested wording, we have updated for clarity.

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		have been associated with HCC in individuals with ALD cirrhosis. The association between diabetes and HCC is also observed in individuals with NAFLD cirrhosis." (The term cirrhotic is pejorative and the sentence is awkward.)	
57	7	Page 4, line 47, "populations have a 5-fold HCC incidence" - should be "5-fold higher HCC incidence"	Thank you, this has been corrected.
58	7	Page 4, line 49, "costs in the VA related to cirrhosis is..." - "is" should be changed to "are"	Thank you, this has been corrected.
59	7	Page 4, line 51, "indentification of liver cancers may reduce disease specific and..." is nebulous (remember that people who get liver cancer usually have liver disease, so I would clarify this as "identification of liver cancers may reduce cancer-related and...")	Thank you, this has been corrected.
60	7	Page 6, line 17, should read "...HCC based on a current or past history of liver disease (including cirrhosis) or infection." This sentence and the analytic framework are a bit nebulous. The population at risk are those with cirrhosis (all etiologies) and chronic hepatitis B, correct?	Thank you, this has been corrected.
61	7	Page 7, the analytic framework - in the Treatement of Detected HCC box, change "radiofrequency ablation" to "ablation" as there are many techniques (RFA, microwave, cryo, etc.). Consider transarterial therapies, rather than transarterial chemoembolization, as some centers use bland embolization and some centers use Y90. Chemotherapy should be changed to "systemic therapy" as conventional chemotherapy is not used for HCC. In the box labeled KQ2: Variables, take out the double hash marks for the etiologies and have a uniform approach to either capitalize (or not) the patient characteristics.	We agree and updated the analytic framework as suggested.
62	7	Page 8, line 12, why is "severity" in quotes? Liver disease severity is a key factor in HCC treatment assignment, as often times, treating HCC in a patient with severe liver disease will cause great harm.	The quotes have been removed.
63	7	Page 8, line 32, All-cause mortality (rather than All-Cause Mortality)	Thank you, this has been corrected.
64	7	Page 8, line 34, a liver biopsy is not a screening related harm - it may be a screening related necessity (e.g., for a LI-RADS M lesion). a liver biopsy complication may be a screening related harm.	A liver biopsy is an invasive and costly procedure. At a minimum there is patient inconvenience and time. Biopsies result in patient anxiety, worry and pain and out of pocket costs even in the absence of a

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			"complication" such as bleeding or infection. A biopsy is a harm as a downstream consequence. Harris and colleagues have written about a taxonomy of screen related harms. These include psychological and financial and physical. Liver biopsies are associated with all of these even if there are not more severe harms such as a "complication".
65	7	Page 12, the language changes, for example, the phrase "reporting on" becomes frequent. The phrase "reporting on" should be changed to "reporting" on page 12, lines 39 and 40; page 23, line 38; page 24, line 8.	Thank you, this has been corrected.
66	7	Page 14, lines 4 and 5, the terms "fewer" and "more" are odd choices when referring to overall mortality - lower or higher make more sense.	This entire paragraph has been reworked for clarity, the terms “fewer” and “more” refer to the absolute effect estimates of all-cause mortality (e.g., fewer deaths).
67	7	Page 17, line 16, "The first study" should read "In the first study..."	Thank you, this has been corrected.
68	7	Page 23, lines 41-44, consider changing the last sentence of the paragraph to "Tong, et al reported that in a population including a substantial portion of HBV patients (>50%), individuals undergoing routine imaging ultrasound (ultrasound plus AFP) were more likely to receive liver transplant (21.7%) than those in a non-screening group (5.7%).	Thank you for the suggestion, we have updated this sentence.
69	7	Page 29, line 50 should read "increased detection without decline in mortality"	Thank you, this has been corrected.
70	7	Page 29, line 60 should read "...increase in HCC attributable death has occurred..."	Thank you, this has been corrected.
71	7	Page 30, line 16 should read "...slower progressing cancer which has a better prognosis..."	Thank you, this has been corrected.
72	7	Page 30, line 31 "(k=5)" is that n=5?	“k” is typically used to indicate number of studies identified in a review (while “n” is used to indicate sample size of a study); however, this sentence has been revised for clarity.
73	7	Page 30, line 32 should read "...The remaining study by Kim, et al in 2020..."	Thank you, this has been corrected.
74	7	Page 30, line 35 makes no sense to me: "While unique to individual studies these issue highlight data limitations and	This sentence has been deleted.

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		evidence uncertainty." Are you talking about unique biases? Unique methodological flaws?	
75	7	Page 30, line 53, the word "that" is repeated twice: "Kansagara et al in that that their..." (also, the convention in this paper is Author, et al - so a comma needs to follow Kansagara)	Thank you, this has been corrected.
76	7	Page 32, line 3, this sentence is odd. All treatments, curative or palliative may have attendant harms. The statement "Treatments have considerable harms due to surgical resection, ablation or liver transplantation." makes absolutely no sense and connotes that treatment is equivalent to harm which is the antithesis of what we hope to achieve.7	All treatments have harms. They may also have benefits. Surgery, ablation and liver transplantation have important physical, financial, psychologic, resource, time, societal harms. These exist beyond the typically viewed harms of “serious complications” of a procedure such as sepsis, perioperative bleeding, or death. It is surprising to us that the reviewer views our factual statement as odd. We now include a reference supporting our statement and slightly modified the statement Harris RP, Sheridan SL, Lewis CL, Barclay C, Vu MB, Kistler CE, Golin CE, DeFrank JT, Brewer NT. The harms of screening: a proposed taxonomy and application to lung cancer screening. JAMA Intern Med. 2014 Feb 1;174(2):281-5. doi: 10.1001/jamainternmed.2013.12745. Erratum in: JAMA Intern Med. 2014 Mar;174(3):484. PMID: 24322781.
77	7	Page 32, line 44, choose a term - outlined or identified	Thank you, this has been corrected.

RANDOMIZED CONTROLLED TRIALS

Appendix Table 1. Outcomes Reported for Randomized Controlled Trials Rated Some Concerns Risk of Bias

Author, Year, Comparison	Overall Mortality k=1	Overall Survival k=1	HCC-Specific Mortality k=2	HCC Stage at Diagnosis k=1	% Receiving Curative Treatment k=0	% Receiving Liver Transplant k=2	% Diagnosed with Biopsy k=1	Sensitivity/ Specificity k=1	Financial Burden k=1
Pocha, 2013,[22] US (6m) vs US (12m)			X	X		X	X	X	X
Trinchet, 2011,[23] US (3m) vs US (6m)	X	X	X			X			

HCC=hepatocellular carcinoma; m=months; US=ultrasound

Appendix Table 2. Detailed Characteristics and Outcomes Reported for RCTs Rated Some Concerns Risk of Bias

Author, Year Country	Inclusion Criteria Mean Follow-up	Baseline Characteristics		Outcomes Reported	
		Intervention	Comparison	Intervention	Comparison
Pocha*, 2013[22] USA	Adults aged 18-70 with Child's A cirrhosis and were potential candidates for treatment of HCC. CT arm: 31 months (range 0–84) Ultrasonography arm: 35 months (range 0–90)	US + AFP every 6 months N=83 Age: 59.2 (SD 5.3) % Female: 0 % Black: 4.8 % Hispanic: 2.4 % White: 88 % HBV: 2.4 % HCV: 86.7 % Alcohol-related: 7.2 % Cirrhosis: 100	CT+AFP every 12 months (AFP every 6 months) N=80 Age: 59.5 (SD 5.3) % Female: 1.2 % Black: 12.5 % Hispanic: 2.4 % White: 78.8 % HBV: 1.3 % HCV: 87.5 % Alcohol-related: 7.5 % Cirrhosis: 100	HCC-specific mortality 5/83 (6%) BCLC Stage 0/A/B at diagnosis 66.6% BCLC Stage C/D at diagnosis 33.3% Liver transplant 4/83 (4.8%) HCC diagnosis with biopsy 6/9 (66.7%) False negative 2/83 (2.4%)	HCC-specific mortality 7/80 (8.8%) BCLC Stage 0/A/B at diagnosis 75% BCLC Stage C/D at diagnosis 25% Liver transplant 2/80 (2.5%) HCC diagnosis with biopsy 6/8 (37.5%) False negative 1/80 (1.2%)

Author, Year Country	Inclusion Criteria Mean Follow-up	Baseline Characteristics		Outcomes Reported	
		Intervention	Comparison	Intervention	Comparison
				False positive 3/83 (3.6%) Total cost per HCC detected: 12069 (VA); $17041 (nonVA)	False positive 9/80 (5.6%) Total cost per HCC detected: 18768 (VA); $57383 (nonVA)
Trinchet, 2011[23] France/ Belgium	Adults >18 with histologically proven cirrhosis without previous complications of cirrhosis or focal liver lesion 3m arm: 47 months (range 29–65) 6m arm: 46 months (range 30–66)	US every 3 months N=640 Age: 54 (IQR 47-61) % Female: 30.5 % HBV: 12.8 % HCV: 44.7 % Alcohol-related: 39.4 % Cirrhosis: 100	US every 6 months N=638 Age: 55 (48-64) % Female: 31.3 % HBV: 12.2 % HCV: 43.6 % Alcohol-related: 39.0 % Cirrhosis: 100	All-Cause Mortality 72/640 (11.3%) Overall survival (estimated at 5 years) 84.9% P=0.38 HCC-specific mortality 17/640 (23.6%) Liver transplant 17/640 (2.7%)	All-Cause Mortality 82/638 (12.1%) Overall survival (estimated at 5 years) 85.8% HCC-specific mortality 12/638 (14.6%) Liver transplant 13/638 (2.0%)

Notes. *Conducted in VHA.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; IQR=interquartile range; m=months; SD=standard deviation; US=ultrasound; USA=United States of America; VA=Veteran's Health Administration.

CASE-CONTROL STUDIES

Appendix Table 3. Detailed Study Characteristics for Case-Control Studies

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity	Outcomes Reported
Moon, 2018[24] Low	USA VA CDW (2013-2015)	US + AFP: within 4 years before HCC diagnosis None: "probably not" and "definitely not"	N=476 Arm A N=241 Mean Age: NR Race: White 74% Black 15% Asian NR Arm B N=235 Mean Age: NR Race: White 74% Black 15% Asian NR Overall Mean Age: 62 Veterans: Yes	Arm A Cirrhosis 100% Hepatitis B: NR Hepatitis C: 80% Hepatitis B+C: NR Alcohol: 13% Metabolic disease: 2.9% Arm B Cirrhosis: 100% Hepatitis B: NR Hepatitis C: 80% Hepatitis B+C: NR Alcohol: 13% Metabolic disease: 2.9%	NR	HCC-specific mortality Diagnosis by biopsy %Transplant
Su, 2021[25] Low	USA VA CDW (2004-2017)	US +/- AFP: Unclear, up to 4 years before index date None	N=338 Arm A N=169 Mean Age: 59.9 Race: White 46.2% Black 39.1% Asian NR Arm B N=169 Mean Age: 60.3 Race: White 44.4% Black 34.9% Asian NR Veterans: Yes	Arm A Cirrhosis 36.7% Hepatitis B: 100% Hepatitis C: NR Hepatitis B+C: NR Alcohol: 36.7% Metabolic disease: NR Arm B Cirrhosis: 36.7% Hepatitis B: 100% Hepatitis C: NR Hepatitis B+C: NR Alcohol: 42% Metabolic disease: NR	NR	HCC-specific mortality Diagnosis by biopsy %Transplant

Abbreviations. AFP=alpha-fetoprotein; CDW=corporate data warehouse; HCC=hepatocellular carcinoma; NR=not reported; US=ultrasound; USA=United States of America; VA=Veteran's Health Administration.

Appendix Table 4. Outcomes Reported for Included Case-Control Studies

Author, Year, Comparison	Overall Mortality k=0	Overall Survival k=0	HCC-Specific Mortality k=2	HCC Stage at Diagnosis k=0	% Receiving Curative Treatment k=0	% Receiving Liver Transplant k=2	% Diagnosed with Biopsy k=2	Sensitivity/ Specificity k=0	Financial Burden k=0
Moon, 2018,[24] US + AFP vs none			X			X	X		
Su, 2021,[25] US +/- AFP vs none			X			X	X		

Abbreviations. AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma; US=ultrasound.

Appendix Table 5. Detailed Results for for Case-Control Studies

Author, Year Risk of Bias Follow-Up	Intervention/ Comparison Definition	HCC-Specific Mortality			Receiving Liver Transplant		HCC Diagnosis Using Biopsy	
		Intervention Events (n) Total (N) (%)	Comparison Events (n) Total (N) (%)	Results	Intervention Events (n) Total (N) (%)	Comparison Events (n) Total (N) (%)	Intervention Events (n) Total (N) (%)	Comparison Events (n) Total (N) (%)
Moon, 2018[24] Low 0-4 years before index date, adjusted	US + AFP: within 4 years before HCC diagnosis None: "probably not" and "definitely not"	n: 111/238 N: 238 46.6%	n: 115 N: 238 48.3%	US + AFP vs no screening HR 0.87 (95% CI 0.44, 1.72)	n: 0 N: NR 0%	n: NR N: NR % NR	n: 69 N: 238 29.0%	n: NR N: NR % NR
Su, 2021[25] Low 0-4 years before index date, adjusted	US +/- AFP: Unclear, up to 4 years before the index date None	n: 57 N: 169 33.7%	None: NA n: 99 N: 169 58.6%	US +/- AFP vs no screening aOR 0.21 (95% CI 0.09-0.50)	n: 2 N: 239 1.2%	n: NR N: NR % NR	n: 79 N: 239 46.7%	n: NR N: NR % NR

Abbreviations. AFP=alpha-fetoprotein; aOR=adjusted odds ratio; CI=confidence interval; HCC=hepatocellular carcinoma; HR=hazard ratio; NR=not reported; US=ultrasound.

COHORT STUDIES

Appendix Table 6. Detailed Study Characteristics for Cohort Studies Rated Serious Risk of Bias

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
Kim, 2020[26] Serious	Korea Four tertiary hospitals in Korea (2007-2016)	US: q6m US+CT: q6m	N=992 Arm A N=496 Mean Age: NR Race: NR Arm B N=496 Mean Age: NR Race: NR	Arm A Cirrhosis 100% Hepatitis B: 100% Hepatitis C: 0% Hepatitis B+C: 0% Alcohol: NR Metabolic disease: NR Arm B Cirrhosis: 100% Hepatitis B: 100% Hepatitis C: 0% Hepatitis B+C: 0% Alcohol: NR Metabolic disease: NR	%A/%B/%C Arm A: 87.1/12.9/0 B: 88.4/11.6/0	Overall mortality Overall survival

Abbreviations. CT=computed tomography; m=months; NR=not reported; q=every; US=ultrasound.

Appendix Table 7. Outcomes Reported for Cohort Studies Rated Serious Risk of Bias

Author, year, Comparison	Overall Mortality k=1	Overall Survival k=1	HCC-Specific Mortality k=0	HCC Stage at Diagnosis k=0	% Receiving Curative Treatment k=0	% Receiving Liver Transplant k=0	% Diagnosed with Biopsy k=0	Sensitivity/ Specificity k=0	Financial Burden k=0
Kim, 2020,[26] US vs US+CT	X	X							

Abbreviations. CT= computed tomography; HCC=hepatocellular carcinoma; US=ultrasound.

Appendix Table 8. Detailed Results for for Cohort Studies

Author, Year Risk of Bias Follow-Up	Intervention/ Comparison Definition	Overall Mortality		Overall Survival		
		Intervention Events (n) Total (N) (%)	Comparison Events (n) Total (N) (%)	Results	Intervention Events (n) Total (N) (%)	Comparison Events (n) Total (N) (%)
Kim, 2020[26] Serious 10 years	US: 6 months US+CT: 6 months	NR	NR	US vs US+CT HR = 0.42, 95% CI [0.24, 0.73], p=0.002	n: NR N: 659 93.3%	n: NR N: 576 96.5%

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; HR=hazard ratio; NR=not reported; US=ultrasound.

HCC COHORT STUDIES

Appendix Table 9. Detailed Study Characteristics for HCC Cohort Studies

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
An, 2020[27] Serious	Korea Prospective hospital-based registry - Asan Medical Center (2007-2015)	AFP: biannually US: biannually US + AFP: biannually	N=1776 Arm A N=298 Mean Age: NR Race: White 0% Black 0% Asian 100% Arm B N=978 Mean Age: NR Race: White 0% Black 0% Asian 100% Arm C N=500 Mean Age: NR Race: White 0% Black 0% Asian 100%	Arm A Cirrhosis 92.3% Hepatitis B: 80.2% Hepatitis C: 12.1% Hepatitis B+C: NR Alcohol: NR Metabolic disease: NR Arm B Cirrhosis: 85.2% Hepatitis B: 81.8% Hepatitis C: 7.9% Hepatitis B+C: NR Alcohol: NR Metabolic disease: NR Arm C Cirrhosis: 85.6% Hepatitis B: 83.8% Hepatitis C: 9.8% Hepatitis B+C: NR Alcohol: NR Metabolic disease: NR	%A/%B/%C Arm A: 85.9/14.1/0 B: 91.8/8.2/0 C: 92/8/0	Overall mortality Overall survival HCC-specific mortality HCC stage at diagnosis Diagnosis with biopsy %Curative treatment %Transplant

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
Bae, 2021[28] Serious	Korea National Health Insurance Service Database of Korea (2008-2017)	US + AFP: q≤6m US + AFP: q7-12m US + AFP: q13-24m US + AFP: q25-36m No screening	N=64674 Arm A N=15587 Arm B N=6569 Arm C N=7383 Arm D n=3853 Arm E N=31282 Mean Age: NR Race: NR	Overall Cirrhosis 63.4% Hepatitis B: 53.8% Hepatitis C: 11.1% Hepatitis B+C: 3.6% Alcohol: 12.4% Metabolic disease: NR	%A/%B/%C NR	Overall mortality %Curative
Kim, 2018[29] Serious	Korea Seoul National University Hospital (2005-2012)	US +/- AFP: mean of ≤ 8 months for ≥ 2 years US +/- AFP: Irregular None	N=1402 Arm A N=834 Mean Age: 58.4 (9.2) Race: White 0% Black 0% Asian 100% Arm B N=104 Mean Age: 57.6 (9.3) Race: White 0% Black 0% Asian 100% Arm C N=464 Mean Age: 57 (10.5) Race: White 0% Black 0% Asian 100%	Arm A Cirrhosis 86% Hepatitis B: 83.5% Hepatitis C: 11% Hepatitis B+C: 0.4% Alcohol: NR Metabolic disease: NR Arm B Cirrhosis: 86.5% Hepatitis B: 92.3% Hepatitis C: 4.8% Hepatitis B+C: 1% Alcohol: 0% Metabolic disease: NR Arm C Cirrhosis: 62.3% Hepatitis B: 72.2% Hepatitis C: 7.3% Hepatitis B+C: 0.2% Alcohol: 0% Metabolic disease: NR	%A/%B/%C Arm A: 67.6/15.3/3 B: 69.2/11.5/5.8 C: 38.8/19/4.5	Overall mortality Overall survival HCC stage at diagnosis %Curative treatment
Mittal, 2016[30] Serious	USA VA administrative data files	US/MRI/CT +/- AFP: HCC surveillance defined	N=887 Arm A N=412	Arm A Cirrhosis 100% Hepatitis B: 4.6%	%A/%B/%C Arm A: 40.8/35.6/17.5	Overall mortality HCC stage at diagnosis %Transplant

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
	(2004-2011)	as receipt of ≥1 liver imaging test with or without AFP for surveillance purposes within 2 years prior to HCC diagnosis date. AFP surveillance defined as receipt of 2 or more AFP tests at least 6 months apart None	Race: White 63.6% Black 19.4% Asian NR Arm B N=475 Race: White 57.7% Black 26.3% Asian NR Overall mean age: 62.5 (8.9) US Veterans	Hepatitis C: 86.9% Hepatitis B+C: NR Alcohol: 86.7% Metabolic disease: 1.5% Arm B Cirrhosis: 100% Hepatitis B: 4.6% Hepatitis C: 70.1% Hepatitis B+C: NR Alcohol: 90.3% Metabolic disease: 4.4%	B: 42.2/44.2/11.7	
Pelizzaro, 2022[31] Serious	Italy Italian Liver Cancer (ITA.LI.CA) database (1987-2017)	US: q3±1 months US: q6±1 months	N=1107 Arm A N=109 Arm B N=998 Mean Age: NR Race: NR	Arm A Cirrhosis 100% Hepatitis B: 22% Hepatitis C: 73.4% Hepatitis B+C: 4.6% Alcohol: NR Metabolic disease: NR Arm B Cirrhosis: 100% Hepatitis B: 12.6% Hepatitis C: 85% Hepatitis B+C: 2.4% Alcohol: 0% Metabolic disease: NR	%A/%B/%C Arm A: 69.8/28.4/1.8 B: 71.3/25.9/2.8	Overall mortality Overall survival HCC-specific mortality %Curative %Transplant Financial burden
Pinero, 2019[32] Serious	Argentina 14 hospitals in Argentina (2009-2014)	US: Every 6 months during last year of follow-up until HCC diagnosis None	N=553 Arm A N=345 Race: NR Arm B N=208 Race: NR	Arm A Cirrhosis NR Hepatitis B: 4.3*% Hepatitis C: 44.9*% Hepatitis B+C: NR Alcohol: 18.8*% Metabolic disease: 11.6*%	%A/%B/%C Overall Population 53.3/41.9/4.7	Overall mortality HCC stage at diagnosis

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
			Overall Mean Age: 62 (9)	Arm B Cirrhosis: NR Hepatitis B: NR Hepatitis C: 44.2*% Hepatitis B+C: NR Alcohol: 0% Metabolic disease: 13.0*%		
Tanaka, 2006[33] Serious	Japan Okayama University Hospital (1991-2003)	US + AFP: q6m None	N=384 Arm A N=182 Mean age: 65 Arm B N=202 Mean age: 65 Race: NR	Arm A Cirrhosis 84% Hepatitis B: 0% Hepatitis C: 100% Hepatitis B+C: 0% Alcohol: 14% Metabolic disease: NR Arm B Cirrhosis: 76% Hepatitis B: 0% Hepatitis C: 100% Hepatitis B+C: 0% Alcohol: 18% Metabolic disease: NR	%A/%B/%C Arm A: 64/32/3 B: 58/39/3	Overall survival
Thein, 2015[34] Serious	Canada Ontario Cancer Registry (OCR) linked health administrative data (2000-2010)	US: Routine surveillance US: Inconsistent screening None	N=1483 Arm A N=302 Arm B N=641 Arm C N=540 Race NR Mean age: NR	Arm A Cirrhosis NR Hepatitis B: NR Hepatitis C: NR Hepatitis B+C: NR Alcohol: 3.6% Metabolic disease: NR Arm B Cirrhosis: NR Hepatitis B: NR Hepatitis C: NR Hepatitis B+C: NR Alcohol: 11.2%	%A/%B/%C NR	Overall mortality Overall survival %Curative

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
				Metabolic disease: NR Arm C Cirrhosis: NR Hepatitis B: NR Hepatitis C: NR Hepatitis B+C: NR Alcohol: 18.1% Metabolic disease: NR		
Tong, 2017[35] Serious	USA Liver Center, Pasadena, CA (1984-2014)	US + AFP: 6-12 months None: NA	N=333 Arm A N=175 Mean age: 63.5 (11.1) Arm B N=158 Mean age: 59.8 (13.2) Overall race White 18% Black 2% Asian 70%	Arm A Cirrhosis 80% Hepatitis B: 46% Hepatitis C: 54% Hepatitis B+C: <1% Alcohol: NR Metabolic disease: NR Arm B Cirrhosis: 74% Hepatitis B: 57% Hepatitis C: 41% Hepatitis B+C: 2% Alcohol: NR Metabolic disease: NR	%A/%B/%C Arm A: 83/13/5 B: 63/32/4	Overall survival %Transplant %Curative
Trevisani, 2004[36] Serious	Italy Clinic records from 7 Italian medical institutions (1988-2001)	US + AFP: q6-12m None: Incidentally detected None: Detected by symptoms	N=363 Arm A N=158 Mean Age: 73.9 (3.6) Arm B N=138 Mean age: 74.9 (3.7) Arm C N=67 Mean age: 74.6 (4.5) Race: NR	Arm A Cirrhosis NR Hepatitis B: 9.5% Hepatitis C: 67.1% Hepatitis B+C: 2.5% Alcohol: 5.7% Metabolic disease: NR Arm B Cirrhosis: NR Hepatitis B: 6.5% Hepatitis C: 58% Hepatitis B+C: 3.6%	%A/%B/%C Arm A: 76.8/18..5/4.6 B: 68.7/29.8/1.5 C: 42.4/43.9/13.6	Overall survival HCC stage at diagnosis

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
				Alcohol: 12.3% Metabolic disease: NR Arm C Cirrhosis: NR Hepatitis B: 11.9% Hepatitis C: 53.7% Hepatitis B+C: 7.5% Alcohol: 10.4% Metabolic disease: NR		
Wu, 2016[37] Serious	Taiwan Taiwan's National Health Insurance Research Database (NHIRD) (2002-2007)	US: q1-6m US: q7-12m US: q13-24m US: q25-36m months No screening: never/not in last 3 years	N=52823 Arm A N=19115 Mean Age: 63 (11.9) Arm B N=4837 Mean Age: 63.9 (12.5) Arm C N=4795 Mean Age: 64.5 (13) Arm D N=2957 Mean Age: 64.3 (13.0) Arm E N=21119 Mean Age: 60.8 (14.7) Race: NR	Arm A Cirrhosis 69.4% Hepatitis B: 32.2% Hepatitis C: 33.7% Hepatitis B+C: % Alcohol: 12.8% Metabolic disease: % Arm B Cirrhosis: 56.7% Hepatitis B: 29% Hepatitis C: 30.7% Hepatitis B+C: % Alcohol: 9.4% Metabolic disease: % Arm C Cirrhosis: 50.6% Hepatitis B: 28.3% Hepatitis C: 24.7% Hepatitis B+C: % Alcohol: 8.1% Metabolic disease: % Arm D Cirrhosis: 46.8% Hepatitis B: 25.1%	%A/%B/%C NR	Overall mortality Diagnosis with biopsy %Curative treatment

Author, Year Risk of Bias	Country Data Source (Year)	Screening Comparison	Population Characteristics	Disease Characteristics	Liver Disease Severity Child-Pugh Score	Outcomes Reported
				Hepatitis C: 22.5% Hepatitis B+C: % Alcohol: 7.9% Metabolic disease: NR Arm E Cirrhosis: 38.6% Hepatitis B: 27% Hepatitis C: 12% Hepatitis B+C: % Alcohol: 5% Metabolic disease: %		

Notes. *Calculated by ESP team.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; m=months; MRI=magnetic resonance imaging; NR=not reported; q=every; US=ultrasound; USA=United States of America; VA=Veteran's Health Administration.

Appendix Table 10. Outcomes Reported for Included HCC Cohort Studies

Author, Year, Comparison	Overall Mortality k=8	Overall Survival k=7	HCC-Specific Mortality k=2	HCC Stage at Diagnosis k=4	% Receiving Curative Treatment k=7	% Receiving Liver Transplant k=4	% Diagnosed with Biopsy k=2	Sensitivity/ Specificity k=0	Financial Burden k=1
An, 2020,[27] US vs AFP vs US + AFP (biannually)	X	X	X	X	X	X	X		
Bae, 2021,[28] US + AFP (1-6m) vs different intervals	X				X				
Kim, 2018,[29] US +/- AFP (routine) vs irregular vs none	X	X		X	X				
Mittal, 2016,[30] Any imaging +/- AFP vs none	X			X		X			
Pelizzaro, 2022,[31] US (3m) vs US (6m)	X	X	X		X	X			X
Piñero, 2019,[32] US (6m) vs none	X			X					
Tanaka, 2006,[33] US + AFP (6m) vs none		X							

Author, Year, Comparison	Overall Mortality k=8	Overall Survival k=7	HCC-Specific Mortality k=2	HCC Stage at Diagnosis k=4	% Receiving Curative Treatment k=7	% Receiving Liver Transplant k=4	% Diagnosed with Biopsy k=2	Sensitivity/ Specificity k=0	Financial Burden k=1
Thein, 2015,[34] US (routine) vs different intervals vs none	X	X			X				
Tong, 2017,[35] US + AFP (6-12m) vs none		X			X	X			
Trevisani, 2004,[36] US + AFP vs none		X							
Wu, 2016,[37] US (1-6m) vs different intervals	X				X		X		

Abbreviations. AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma; m=months; US=ultrasound.

Appendix Table 11. Results for All-Cause Mortality for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Mortality Events (n) Total (N) (%)	Arm B Intervention Mortality Events (n) Total (N) (%)	Arm C, D, E Intervention Mortality Events (n) Total (N) (%)	Results
An, 2020[27] Serious 5 years	AFP: biannually n: 88 N: 298 29.5%	US: biannually n: 253 N: 978 25.9%	US + AFP: biannually n: 198 N: 500 39.6%	US biannually vs US + AFP: biannually HR (95% CI) 0.53 (0.43, 0.64)* no lead time adjustment AFP biannually vs US + AFP: biannually HR (95% CI) 0.74 (0.57, 0.95) with lead time=120 days
Bae, 2021[28] Serious 8 years	US + AFP: 6 months or fewer n: 5608 N: 15587 36.0%	US + AFP: 7-12 months n: 2185 N: 6569 33.3%	US + AFP: 13-24 months n: 2751 N: 7383 37.3 US + AFP: 25-36 months n: 1666 N: 3853 43.2% No screening: NA	7-12 months vs ≤6 months HR (95% CI) 0.91 (0.87, 0.96)[a]; HR (95% CI) 0.91 (0.86, 0.95)[b] 13-24 months vs ≤6 months HR (95% CI) 1.01 (0.97, 1.06)[a]; HR (95% CI) 1.01 (0.96, 1.06)[b] 25-36 months vs ≤6 months HR (95% CI) 1.08 (1.02, 1.14)[a]; HR (95% CI) 1.07 (1.01, 1.13)[b]

Author, Year Risk of Bias Follow-Up	Arm A Intervention Mortality Events (n) Total (N) (%)	Arm B Intervention Mortality Events (n) Total (N) (%)	Arm C, D, E Intervention Mortality Events (n) Total (N) (%)	Results
			n: 16069 N: 31282 51.4%	No screening vs ≤6 months HR (95% CI) 1.28 (1.24, 1.32)[a]; HR (95% CI) 1.27 (1.23, 1.31)[b] [a] lead time=157 days [b] lead time=174 days
Kim, 2018[29] Serious 5 years	US +/- AFP: mean of < or = to 8 months for at least 2 years n: NR N: NR % NR	US +/- AFP: Irregular n: NR N: NR % NR	None: NA n: NR N: NR % NR	Irregular vs none HR (95% CI) 0.94 (0.69, 1.28) Mean ≤8 months for at least 2 years vs none HR (95% CI) 0.69 (0.57, 0.83) Lead time=140 days
Mittal, 2016[30] Serious Follow-up NR	US/MRI/CT +/- AFP: ≥1 imaging test in 2 years prior to HCC diagnosis n: NR N: NR % NR	None: NA n: NR N: NR % NR	-	Surveillance vs none HR (95% CI) 0.77 (0.67, 0.90), adjusting for HCC stage and treatment Lead time=100 days
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months n: 69 N: 109 63.3%	US: 6±1 months n: 373 N: 668 55.8%	-	3±1 months vs 6±1 months HR (95% CI) 0.93 (0.65, 1.32) Lead time=85 days
Piñero, 2019[32] Serious 5 years	US: Every 6 months during last year of follow-up until HCC diagnosis n: NR N: 345 27%	None: NA n: NR N: 208 36.4%	-	Every 6 months during last year of follow-up until HCC diagnosis vs none HR (95% CI) 0.51 (0.38, 0.69) Lead time=3.5 months

Author, Year Risk of Bias Follow-Up	Arm A Intervention Mortality Events (n) Total (N) (%)	Arm B Intervention Mortality Events (n) Total (N) (%)	Arm C, D, E Intervention Mortality Events (n) Total (N) (%)	Results
Thein, 2015[34] Serious 5 years	US: Routine surveillance (≥1 imaging annually) n: NR N: NR % NR	US: Inconsistent screening n: NR N: NR % NR	None: NA n: NR N: NR % NR	Routine surveillance vs none HR (95% CI) 0.76 (0.64, 0.91) Inconsistent screening vs none HR (95% CI) 0.86 (0.75, 0.98) Lead time=70 days
Wu, 2016[37] Serious 5 years	US: 1-6 months n: 14626 N: 19115 76.5%	US: 7-12 months n: 3740 N: 4837 77.3%	US: 13-24 months n: 3799 N: 4795 79.2% US: 25-36 months n: 2418 N: 2957 81.8% No screening: never/not in last 3 years n: 17883 N: 21119 84.7%	7-12 months vs 1-6 months HR (95% CI): 1.11 (1.07, 1.15) 12-25 months vs 1-6 months HR (95% CI): 1.23 (1.19, 1.28) 25-35 months vs 1-6 months HR (95% CI): 1.31 (1.26, 1.37) No screening vs 1-6 months HR (95% CI): 1.47 (1.43, 1.51) Lead time=140 days

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; CT=computed tomography; HCC=hepatocellular carcinoma; HR=hazard ratio; MRI=magnetic resonance imaging; NA=not applicable; NR=not reported; US=ultrasound.

Appendix Table 12. Results for Overall Survival for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)	Results
An, 2020[27] Serious 5 years	AFP: biannually n: NR N: NR 64.8%	US: biannually n: NR N: NR 69.9%	US + AFP: biannually n: NR N: NR 55.5%	-
Kim, 2018[29] Serious 5 years	US +/- AFP: Regular screening (mean interval ≤8 months) n: NR N: NR 64.4%	US +/- AFP: Irregular screenig n: NR N: NR 52.7%	None: NA n: NR N: NR 25.3%	Regular screening vs irregular screening HR (95% CI) 0.77 (0.64, 0.93) With lead time=140 days
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months n: NR N: 109 40.7%	US: 6±1 months n: NR N: 668 47.2%	-	US: 3±1 months vs US: 6±1 months HR (95% CI) 0.87 (0.67, 1.13) with lead time=63 days
Tanaka, 2006[33] Serious 5 years	US + AFP: 6 months n: 46 N: 182 25.2%	None: NA n: 32 N: 202 15.8%	-	US + AFP vs none RR: 0.63 (95% CI 0.48-0.82) Lead time adjusted results NR
Thein, 2015[34] Serious 5 years	US: Routine surveillance (≥1 imaging annually) n: NR N: NR 31.9% (95% CI: 25.8, 38.2)	US: Inconsistent screening n: NR N: NR 22.4% (95% CI: 18.7, 26.3)	None: NA n: NR N: NR 20.7% (95% CI: 16.9, 24.7)	-
Tong, 2017[35] Serious 5 years	US + AFP: 6-12 months n: NR N: NR 37.5%	None: NA n: NR N: NR 14.2% (p<0.001)	-	-
Trevisani, 2004[36] Serious Median 17 months	US + AFP: 6-12 months NR	None (Incidentally detected HCC) NR	None (Symptom-detected HCC) NR	Unable to extract; authors provided figure but no in-text numbers

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; CT=computed tomography; HCC=hepatocellular carcinoma; HR=hazard ratio; NA=not applicable; NR=not reported; US=ultrasound.

Appendix Table 13. Results for HCC-Specific Mortality for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C, D, E Intervention Events (n) Total (N) (%)	Results
An, 2020[27] Serious 5 years	AFP: biannually n: 63 N: 298 20.1%	US: biannually n: 162 N: 978 16.6%	US + AFP: biannually n: 148 N: 500 29.6%	AFP vs US + AFP HR (95% CI) 0.67 (0.50, 0.90) with lead time=120 days Ultrasound vs US + AFP HR (95% CI) 0.46 (0.37, 0.58) p<0.001*not adjusted for lead time
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months n: NR N: NR 66.7%	US: 6±1 months n: NR N: NR 57.4%	-	NR

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; HCC=hepatocellular carcinoma; HR=hazard ratio; US=ultrasound.

Appendix Table 14. Results for HCC Stage at Diagnosis for HCC Cohort Studies

Author, Year **Risk of Bias** **Follow-Up**	**Arm A Intervention** **Events (n)** **Total (N)** **(%)**	**Arm B Intervention** **Events (n)** **Total (N)** **(%)**	**Arm C Intervention** **Events (n)** **Total (N)** **(%)**
Kim, 2018[29] Serious 5 years	US +/- AFP: Regular screening (mean interval ≤8 months) BCLC Stage 0-A-B n: 578 N: 834 % 69.3% BCLC Stage C-D n: 256 N: 834 30.7%	US +/- AFP: Irregular BCLC Stage 0-A-B n: 53 N: 104 % 51.0% BCLC Stage C-D n: 51 N: 104 49.0%	None: NA BCLC Stage 0-A-B n: 187 N: 464 % 40.3% BCLC Stage C-D n: 277 N: 464 59.7%

Author, Year **Risk of Bias** **Follow-Up**	**Arm A Intervention** **Events (n)** **Total (N)** **(%)**	**Arm B Intervention** **Events (n)** **Total (N)** **(%)**	**Arm C Intervention** **Events (n)** **Total (N)** **(%)**
Piñero, 2019[32] Serious 5 years	US: Every 6 months during last year of follow-up until HCC diagnosis BCLC Stage 0-A-B n: 322 N: 345 93.3% BCLC Stage C-D n: 23 N: 345 6.7%	None: NA BCLC Stage 0-A-B n: NR N: NR % NR BCLC Stage C-D n: NR N: NR % NR	-
Mittal, 2016[30] Serious Follow-up NR	US/MRI/CT +/- AFP: ≥1 imaging test in 2 years before HCC diagnosis BCLC Stage 0-A-B n: 206 N: 412 50.0% BCLC Stage C-D n: 171 N: 412 41.5%	None: NA BCLC Stage 0-A-B n: 160 N: 475 33.7% BCLC Stage C-D n: 283 N: 475 59.8%	-

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)
An, 2020[27] Serious 5 years	AFP: biannually BCLC Stage 0-A-B n: 267 N: 298 89.6% BCLC Stage C-D n: 31 N: 298 10.4%	US: biannually BCLC Stage 0-A-B n: 911 N: 978 93.1% BCLC Stage C-D n: 67 N: 978 6.9%	US + AFP: biannually BCLC Stage 0-A-B n: 430 N: 500 86.0% BCLC Stage C-D n: 70 N: 500 14.0%

Abbreviations. AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; CT=computed tomography; HCC=hepatocellular carcinoma; HR=hazard ratio; MRI=magnetic resonance imaging; US=ultrasound.

Appendix Table 15. Results for Diagnosis Using Biopsy for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)	Arm D Intervention Events (n) Total (N) (%)	Arm E Intervention Events (n) Total (N) (%)
An, 2020[27] Serious 5 years	AFP: biannually n: 140 N: 298 46.9%	US: biannually n: 450 N: 978 46.0%	US + AFP: biannually n: 232 N: 500 46.4%	-	-
Wu, 2016[37] Serious 5 years	US: 1-6 months n: 9256 N: 19115 48.4%	US: 7-12 months n: 2503 N: 4837 51.8%	US: 13-24 months n: 2333 N: 4795 48.6%	US: 25-36 months n: 1434 N: 2957 48.5%	No screening: never/not in last 3 years n: 9710 N: 21119 46.0%

Abbreviations. AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma; RoB=risk of bias; US=ultrasound.

Appendix Table 16. Results for Receiving Curative Treatment for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)	Arm D Intervention Events (n) Total (N) (%)	Arm E Intervention Events (n) Total (N) (%)
An, 2020[27] Serious 5 years	AFP: biannually n: NR N: NR 60.1%	US: biannually n: NR N: NR 63.1%	US + AFP: biannually n: NR N: NR 56.4%	-	-
Bae, 2021[28] Serious 8 years	US + AFP: 6 months or fewer n: 8095 N: 15587 51.9%	US + AFP: 7-12 months n: 3176 N: 6559 48.3%	US + AFP: 13-24 months n: 3236 N: 7383 43.8%	US + AFP: 25-36 months n: 1591 N: 3853 41.3%	No screening: NA n: 10787 N: 31282 34.5%
Kim, 2018[29] Serious 5 years	US +/- AFP: Regular screening (mean interval ≤8 months) n: 437 N: 834 52.4%	US +/- AFP: Irregular n: 41 N: 104 39.4%	None: NA n: 108 N: 464 23.3%	-	-
Mittal, 2016[30] Serious Follow-up NR	US/MRI/CT +/-AFP: ≥1 imaging test in 2 years prior to HCC diagnosis n: 86 N: 412 20.8%	None: NA n: 53 N: 475 11.2%	-	-	-
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months n: 76 N: 109 69.7%	US: 6±1 months n: 456 N: 668 68.2% Compared to 3 months, OR (95% CI) 0.93 (0.60, 1.45) p=0.76	-	-	-
Thein, 2015[34] Serious 5 years	US: Routine surveillance (≥1 imaging annually) n: NR N: NR 59.3%	US: Inconsistent screening n: NR N: NR 45.6% p<0.001 vs routine surveillance	None: NA n: NR N: NR 43.1% p<0.001 vs routine surveillance	-	-

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)	Arm D Intervention Events (n) Total (N) (%)	Arm E Intervention Events (n) Total (N) (%)
Tong, 2017[35] Serious 5 years	US + AFP: 6-12 months n: 106 N: 175 60.1%	None: NA n: 42 N: 158 26.6%	-	-	-
Wu, 2016[37] Serious 5 years	US: 1-6 months n: 5613 N: 19115 29.4%	US: 7-12 months n: 1472 N: 4837 30.4%	US: 13-24 months n: 1211 N: 4795 25.3%	US: 25-36 months n: 694 N: 2957 23.5%	No screening: never/not in last 3 years n: 4195 N: 21119 19.7%

Abbreviations. AFP=alpha-fetoprotein; CI=confidence interval; CT=computed tomography; HCC=hepatocellular carcinoma; MRI=magnetic resonance imaging; NA=not applicable; OR=odds ratio; RoB=risk of bias; US=ultrasound.

Appendix Table 17. Results for Receiving Liver Transplant for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)	Arm C Intervention Events (n) Total (N) (%)
An, 2020[27] Serious 5 years	AFP: biannually n: 15 N: 298 5.0%	US: biannually n: 22 N: 978 2.3%	US + AFP: biannually n: 10 N: 500 2.0%
Mittal, 2016[30] Serious Follow-up NR	US/MRI/CT +/- AFP: ≥1 imaging test in 2 years before HCC diagnosis n: 15 N: 412 3.6%	None: NA n: 18 N: 475 3.8%	-
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months n: 11 N: 109 10.1%	US: 6±1 months n: 32 N: 668 0.5%	-
Tong, 2017[35] Serious 5 years	US + AFP: 6-12 months n: 38 N: 175 21.7%	None: NA n: 9 N: 158 5.7%	-

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; MRI=magnetic resonance imaging; NA=not applicable; US=ultrasound.

Appendix Table 18. Results for Financial Burden for HCC Cohort Studies

Author, Year Risk of Bias Follow-Up	Arm A Intervention Events (n) Total (N) (%)	Arm B Intervention Events (n) Total (N) (%)
Pelizzaro, 2022[31] Serious 5 years	US: 3±1 months Arm overall cost: €316,645; cost for a patient tested quarterly: €2,905	US: 6±1 months Arm overall cost €1,217,764; cost for a patient tested twice a year €1,823

Abbreviations. US=ultrasound.