Screening for Hepatocellular Carcinoma in Adults at Increased Risk

November 2023

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Recommended citation: Landsteiner A, Ullman K, Langsetmo L, Zerzan N, Kalinowski C, Haglund J, Wilt TJ. Screening for Hepatocellular Carcinoma in Adults at Increased Risk: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-009; 2023.

AUTHORS

Author roles, affiliations, and contributions (using the CRediT taxonomy) are listed below.

Author	Role and Affiliation	Report Contribution
Adrienne Landsteiner, PhD, MPH	Senior Scientist, Minneapolis Evidence Synthesis Program (ESP) Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision, Project administration
Kristen Ullman, MPH	Program Manager, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Project administration
Lisa Langsetmo, PhD, MS	Statistician, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing
Nick Zerzan, MPH	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing
Caleb Kalinowski, MS	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing
Jennifer Haglund, MD	Assistant Professor, Transplant Hepatology/GI, Minneapolis VA Medical Center Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Timothy J. Wilt, MD, MPH	Director, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Project administration

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

The authors are grateful to external peer reviewers, and the following individuals for their contributions to this project:

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.

Timothy Morgan, MD
Deputy Director
National GI & Hepatology Program

Jason Dominitz, MD
National Director
VHA Gastroenterology

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:

Angela L. Denietolis, MD
Executive Director
VACO Office of Primary Care

Michael Kelley, MD
Executive Director
National Oncology Program

Sophia Califano, MD
Deputy Chief Consultant for Preventive Medicine
VA National Center for Health Promotion and Disease Prevention

Devan Kansagara, MD
Physician (internal medicine)
VA Portland Healthcare System

George Ioannou, MD, MS
Physician (gastroenterology)
VA Puget Sound Health Care System

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.

Main Report

Evidence Synthesis Program

TABLE OF CONTENTS

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

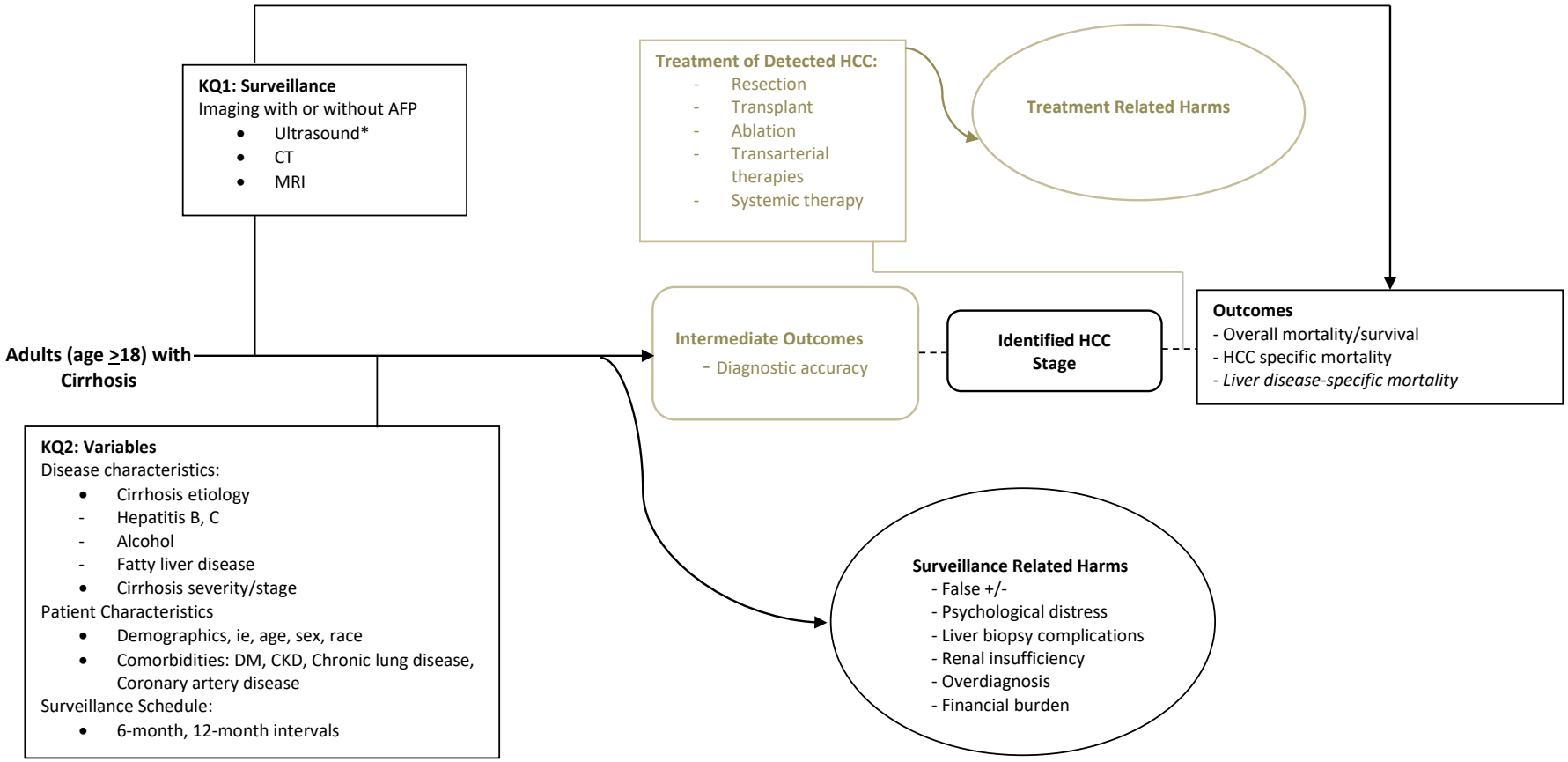
The analytic framework shown in Figure 2 provides a conceptual overview of the key questions, populations, interventions, and outcomes. The population of interest is individuals at increased risk of HCC based on a current or past history of liver disease (including cirrhosis), viral infection, or alcoholic 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.

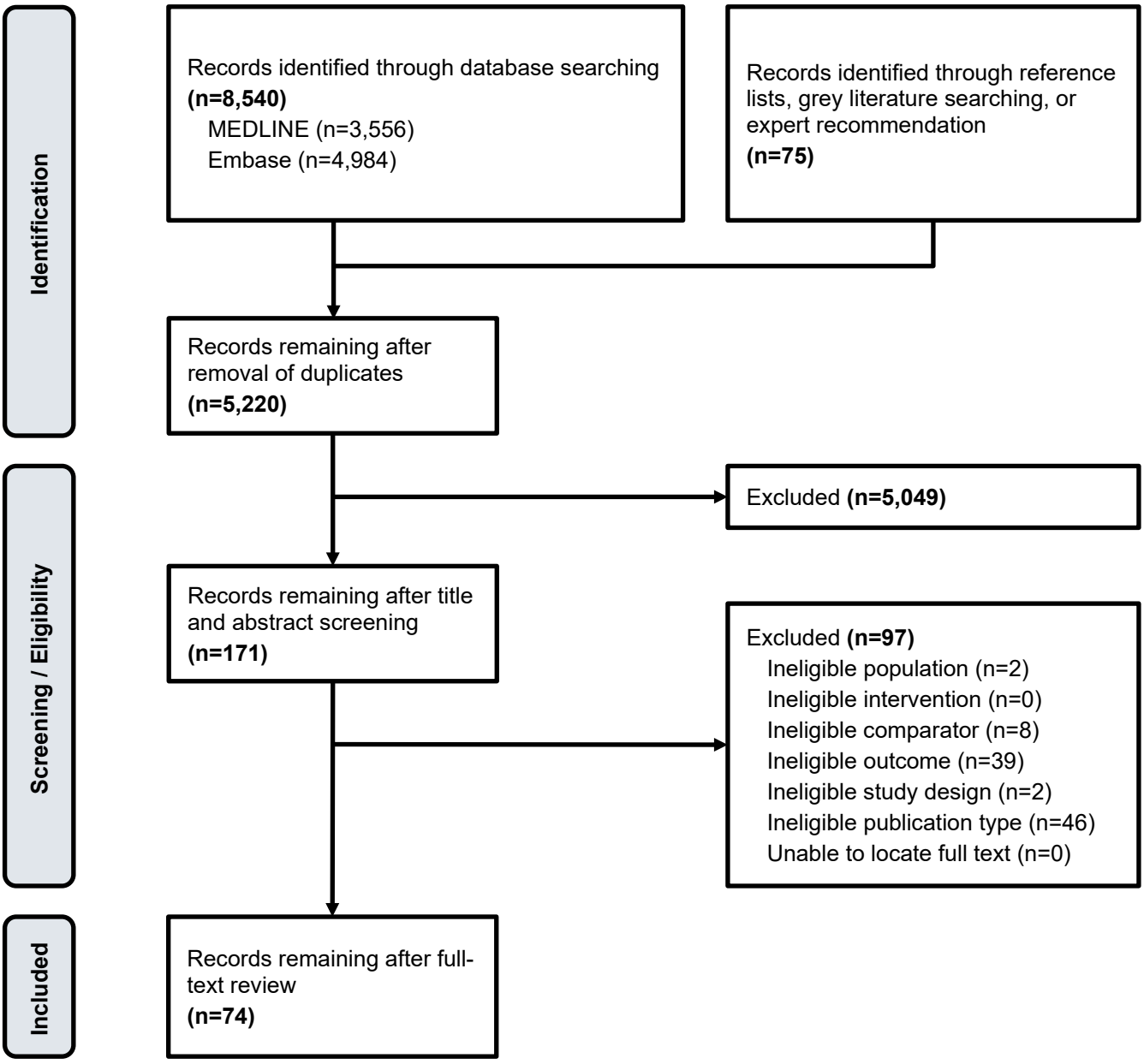
Strength of Evidence

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.

REFERENCES

1. Ju MR, Karalis JD, Chansard M, et al. Variation of Hepatocellular Carcinoma Treatment Patterns and Survival Across Geographic Regions in a Veteran Population. *Ann Surg Oncol*. Dec 2022;29(13):8413-8420. doi:10.1245/s10434-022-12390-7
2. American Cancer Society. Key statistics about liver cancer. Accessed June 27, 2023. https://www.cancer.org/cancer/types/liver-cancer/about/what-is-key-statistics.html
3. National Cancer Institute. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. Accessed June 27, 2023. https://seer.cancer.gov/statfacts/html/livibd.html
4. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a cancer journal for clinicians*. 2021;71(3):209-249. doi:https://dx.doi.org/10.3322/caac.21660
5. Lee YT, Wang JJ, Luu M, et al. The Mortality and Overall Survival Trends of Primary Liver Cancer in the United States. *J Natl Cancer Inst*. Nov 2 2021;113(11):1531-1541. doi:10.1093/jnci/djab079
6. Lee Y-T, Wang JJ, Luu M, et al. The Mortality and Overall Survival Trends of Primary Liver Cancer in the United States. *Journal of the National Cancer Institute*. 2021;113(11):1531-1541. doi:https://dx.doi.org/10.1093/jnci/djab079
7. National Cancer Institute. Liver (Hepatocellular) Cancer Screening (PDQ®)–Health Professional Version. Updated May 2, 2023. Accessed July 21, 2023. https://www.cancer.gov/types/liver/hp/liver-screening-pdq#_76
8. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. *Journal of Hepatology*. 2022;77(1):128-139. doi:https://dx.doi.org/10.1016/j.jhep.2022.01.023
9. Aly A, Ronnebaum S, Patel D, Doleh Y, Benavente F. Epidemiologic, humanistic and economic burden of hepatocellular carcinoma in the USA: a systematic literature review. *Hepat Oncol*. Jul 21 2020;7(3):HEP27. doi:10.2217/hep-2020-0024
10. Beste LA, Green P, Berry K, Belperio P, Ioannou GN. Hepatitis C-Related Hepatocellular Carcinoma Incidence in the Veterans Health Administration After Introduction of Direct-Acting Antivirals. *JAMA*. Sep 8 2020;324(10):1003-1005. doi:10.1001/jama.2020.10121
11. Philips CA, Rajesh S, Nair DC, Ahamed R, Abduljaleel JK, Augustine P. Hepatocellular Carcinoma in 2021: An Exhaustive Update. *Cureus*. 2021;13(11):e19274. doi:https://dx.doi.org/10.7759/cureus.19274
12. Ioannou GN, Green P, Lowy E, Mun EJ, Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. *PLoS One*. 2018;13(9):e0204412. doi:10.1371/journal.pone.0204412
13. Kansagara D, Papak J, Pasha AS, et al. Screening for Hepatocellular Cancer in Chronic Liver Disease: A Systematic Review. 2014. *VA Evidence-based Synthesis Program Reports*.
14. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. *J Hepatol*. Jul 2022;77(1):128-139. doi:10.1016/j.jhep.2022.01.023
15. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Aug 28 2019;366:l4898. doi:10.1136/bmj.l4898
16. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. Oct 12 2016;355:i4919. doi:10.1136/bmj.i4919
17. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. Apr 2011;64(4):401-6. doi:10.1016/j.jclinepi.2010.07.015

18. Chen THH, Chen CJ, Yen MF, et al. Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan. *International journal of cancer*. 2002;98(2):257-261.
19. Wang J-H, Chang K-C, Kee K-M, et al. Hepatocellular carcinoma surveillance at 4-vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. *Official journal of the American College of Gastroenterology| ACG*. 2013;108(3):416-424.
20. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. Jul 2004;130(7):417-22. doi:10.1007/s00432-004-0552-0
21. Chen J, Parkin D, Chen Q, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *Journal of medical screening*. 2003;10(4):204-209.
22. Pocha C, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography -- a randomised study. *Aliment Pharmacol Ther*. Aug 2013;38(3):303-12. doi:10.1111/apt.12370
23. Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3-and 6-month periodicities. *Hepatology*. 2011;54(6):1987-1997.
24. Moon AM, Weiss NS, Beste LA, et al. No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis. *Gastroenterology*. Oct 2018;155(4):1128-1139 e6. doi:10.1053/j.gastro.2018.06.079
25. Su F, Weiss NS, Beste LA, et al. Screening is associated with a lower risk of hepatocellular carcinoma-related mortality in patients with chronic hepatitis B. *Journal of Hepatology*. 2021;74(4):850-859. doi:https://dx.doi.org/10.1016/j.jhep.2020.11.023
26. Kim JH, Kang SH, Lee M, et al. Improved Detection of Hepatocellular Carcinoma by Dynamic CT in Cirrhotic Patients With Chronic Hepatitis B: A Multi-Center Study. *Journal of gastroenterology and hepatology*. 2020;doi:https://dx.doi.org/10.1111/jgh.15046
27. An J, Kim HI, Chang S, Shim JH. Continued value of the serum alpha-fetoprotein test in surveilling at-risk populations for hepatocellular carcinoma. *PLoS ONE*. 2020;15(8 August):e0238078. doi:https://dx.doi.org/10.1371/journal.pone.0238078
28. Bae H, Lee SA, Choi JW, Hwang SH, Park S, Park MS. Effectiveness of hepatocellular carcinoma surveillance and an optimal surveillance interval: Nationwide cohort of Korea. *Yonsei Medical Journal*. 2021;62(8):758-766. doi:https://dx.doi.org/10.3349/ymj.2021.62.8.758
29. Kim H, Nam J, Lee JH, et al. Intensity of surveillance for hepatocellular carcinoma determines survival in patients at risk in a hepatitis B-endemic area. *Alimentary pharmacology & therapeutics*. 2018;47(11):1490-1501.
30. Mittal S, Kanwal F, Ying J, et al. Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: a United States cohort. *Journal of hepatology*. 2016;65(6):1148-1154.
31. Pelizzaro F, Peserico G, D'Elia M, et al. Surveillance for hepatocellular carcinoma with a 3-months interval in "extremely high-risk" patients does not further improve survival. *Dig Liver Dis*. Jul 2022;54(7):927-936. doi:10.1016/j.dld.2021.08.025
32. Piñero F, Rubinstein F, Marciano S, et al. Surveillance for hepatocellular carcinoma: does the place where ultrasound is performed impact its effectiveness? *Digestive Diseases and Sciences*. 2019;64(3):718-728.
33. Tanaka H, Nouso K, Kobashi H, et al. Surveillance of hepatocellular carcinoma in patients with hepatitis C virus infection may improve patient survival. *Liver International*. 2006;26(5):543-551.
34. Thein H-H, Campitelli MA, Yeung LT, Zaheen A, Yoshida EM, Earle CC. Improved survival in patients with viral hepatitis-induced hepatocellular carcinoma undergoing recommended

abdominal ultrasound surveillance in Ontario: a population-based retrospective cohort study. *PLoS One*. 2015;10(9):e0138907.
35. Tong MJ, Rosinski AA, Huynh CT, Raman SS, Lu DS. Long-term survival after surveillance and treatment in patients with chronic viral hepatitis and hepatocellular carcinoma. *Hepatology communications*. 2017;1(7):595-608.
36. Trevisani F, Cantarini MC, Labate AM, et al. Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effects on cancer staging and patient survival. *Official journal of the American College of Gastroenterology| ACG*. 2004;99(8):1470-1476.
37. Wu CY, Hsu YC, Ho HJ, Chen YJ, Lee TY, Lin JT. Association between ultrasonography screening and mortality in patients with hepatocellular carcinoma: a nationwide cohort study. *Gut*. Apr 2016;65(4):693-701. doi:10.1136/gutjnl-2014-308786
38. Tzartzeva K, Obi J, Rich NE, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. *Gastroenterology*. May 2018;154(6):1706-1718 e1. doi:10.1053/j.gastro.2018.01.064
39. Singal AG, Conjeevaram HS, Volk ML, et al. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2012;21(5):793-9. Comment in: Expert Rev Gastroenterol Hepatol. 2012 Aug;6(4):441-4 PMID: 22928896 [https://www.ncbi.nlm.nih.gov/pubmed/22928896]. doi:https://dx.doi.org/10.1158/1055-9965.EPI-11-1005
40. Lok AS, Sterling RK, Everhart JE, et al. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology*. 2010;138(2):493-502. doi:https://dx.doi.org/10.1053/j.gastro.2009.10.031
41. National Center for Health Statistics. Chronic liver disease and cirrhosis death rates among persons aged 25 and over, by sex and age: United States, 2006–2016. Accessed August 30, 2023. https://www.cdc.gov/nchs/hus.htm
42. Yao Z, Dai C, Yang J, et al. Time-trends in liver cancer incidence and mortality rates in the U.S. from 1975 to 2017: a study based on the Surveillance, Epidemiology, and End Results database. *Journal of gastrointestinal oncology*. 2023;14(1):312-324. doi:10.21037/jgo-23-25
43. U.S. Preventive Services Task Force. Cervical Cancer: Screening. Accessed August 30, 2023. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening
44. U.S. Preventive Services Task Force. Ovarian Cancer: Screening. Accessed August 30, 2023. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/ovarian-cancer-screening
45. Weiss NS, Etzioni R. Estimating the influence of rescreening interval on the benefits associated with cancer screening: approaches and limitations. *Epidemiology (Cambridge, Mass)*. 2002;13(6):713-7.
46. Weiss NS, Dhillon PK, Etzioni R. Case-Control Studies of the Efficacy of Cancer Screening: Overcoming Bias From Nonrandom Patterns of Screening. *Epidemiology*. 2004;15(4)
47. Doria-Rose VP, Kamineni A, Barrett MJ, Ko CW, Weiss NS. Case-Control Studies of the Efficacy of Screening Tests That Seek to Prevent Cancer Incidence: Results of an Approach That Utilizes Administrative Claims Data That Do Not Provide Information Regarding Test Indication. *American Journal of Epidemiology*. 2019;188(4):703-708. doi:10.1093/aje/kwy274
48. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology (Baltimore, Md)*. 2023;Publish Ahead of Printdoi:10.1097/HEP.0000000000000466

49. American Association for the Study of Liver Diseases. Practice Guidelines Accessed October 16, 2023. https://www.aasld.org/practice-guidelines
50. Qaseem A, Forland F, Macbeth F, Ollenschlager G, Phillips S, Wees PJvd. Guidelines International Network: toward international standards for clinical practice guidelines. *Annals of internal medicine*. 2012;156(7):525-31. doi:10.7326/0003-4819-156-7-201204030-00009
51. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. *Clinical Practice Guidelines We Can Trust*. Washington DC: National Academies Press (US); 2011.
52. AGREE Enterprise. Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. Accessed August 30, 2023. https://www.agreetrust.org/
53. Asrani SK, Ghabril MS, Kuo A, et al. Quality measures in HCC care by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. *Hepatology*. 2022;75(5)
54. Zucker SD, Fried MW. Parsing the guidelines on guidelines: Balancing sensibility and conflict of interest. *Hepatology*. 2018;68(3)
55. Sally MK, Bland JM. Analysis of a trial randomised in clusters. *BMJ*. 1998;316(7124):54. doi:10.1136/bmj.316.7124.54
56. Harris RP, Sheridan SL, Lewis CL, et al. The Harms of Screening: A Proposed Taxonomy and Application to Lung Cancer Screening. *JAMA Internal Medicine*. 2014;174(2):286. doi:10.1001/jamainternmed.2013.12745
57. National Cancer Institute. Liver (Hepatocellular) Cancer Screening (PDQ®)–Health Professional Version. Accessed August 30, 2023. https://www.cancer.gov/types/liver/hp/liver-screening-pdq
58. Kansagara D, Papak J, Pasha AS, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Ann Intern Med*. Aug 19 2014;161(4):261-9. doi:10.7326/M14-0558
59. Lederle FA, Pocha C. Screening for Liver Cancer: The Rush to Judgment. *Annals of Internal Medicine*. 2012/03/06 2012;156(5):387-389. doi:10.7326/0003-4819-156-5-201203060-00012
60. Lee TH, Brennan TA. Direct-to-Consumer Marketing of High-Technology Screening Tests. *New England Journal of Medicine*. 2002/02/14 2002;346(7):529-531. doi:10.1056/NEJM200202143460715
61. VA Cooperative Studies Program. PREventing liver cancer Mortality through Imaging with Ultrasound vs. MRI (PREMIUM). Accessed August 30, 2023. https://www.vacsp.research.va.gov/CSP_2023/CSP_2023.asp
62. Garcia-Albeniz X, Hsu J, Hernan MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. *Eur J Epidemiol*. Jun 2017;32(6):495-500. doi:10.1007/s10654-017-0287-2
63. Aby E, Phan J, Truong E, Grotts J, Saab S. Inadequate Hepatocellular Carcinoma Screening in Patients With Nonalcoholic Steatohepatitis Cirrhosis. *J Clin Gastroenterol*. Feb 2019;53(2):142-146. doi:10.1097/MCG.0000000000001075
64. Alencar RSDSM, Oliveira CP, Chagas AL, et al. Hepatocellular carcinoma (HCC) in patients with Non-Alcoholic Fatty Liver Disease (NAFLD): screening, treatment and survival analysis in a Brazilian series. *Clinics*. 2022;77:100097. doi:https://dx.doi.org/10.1016/j.clinsp.2022.100097
65. Bolondi L, Sofia S, Siringo S, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut*. 2001;48(2):251-259.

66. Chaiteerakij R, Chattieng P, Choi J, Pinchareon N, Thanapirom K, Geratikornsupuk N. Surveillance for hepatocellular carcinoma reduces mortality: an inverse probability of treatment weighted analysis. *Annals of hepatology*. 2017;16(3):421-429.
67. Chen VL, Singal AG, Tapper EB, Parikh ND. Hepatocellular carcinoma surveillance, early detection, and survival in a privately-insured US cohort. *Liver international : official journal of the International Association for the Study of the Liver*. 2020;doi:https://dx.doi.org/10.1111/liv.14379
68. Chinnaratha MA, Campbell K, Mathias R, McCormick RJ, Woodman RJ, Wigg AJ. Improved Survival of Hepatocellular Carcinoma Patients Diagnosed with a Dedicated Screening Programme—a Propensity Score Adjusted Analysis. *Journal of Gastrointestinal Cancer*. 2019;50(4):888-893.
69. Choi DT, Kum H-C, Park S, et al. Hepatocellular carcinoma screening is associated with increased survival of patients with cirrhosis. *Clinical Gastroenterology and Hepatology*. 2019;17(5):976-987. e4.
70. Costentin CE, Layese R, Bourcier V, et al. Compliance With Hepatocellular Carcinoma Surveillance Guidelines Associated With Increased Lead-Time Adjusted Survival of Patients With Compensated Viral Cirrhosis: A Multi-Center Cohort Study. *Gastroenterology*. Aug 2018;155(2):431-442 e10. doi:10.1053/j.gastro.2018.04.027
71. Cucchetti A, Trevisani F, Pecorelli A, et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *Journal of Hepatology*. 2014;61(2):333-341.
72. Davila JA, Weston A, Smalley W, El-Serag HB. Utilization of screening for hepatocellular carcinoma in the United States. *Journal of clinical gastroenterology*. 2007;41(8):777-782.
73. Debes JD, Chan AJ, Balderramo D, et al. Hepatocellular carcinoma in South America: Evaluation of risk factors, demographics and therapy. *Liver International*. 2018;38(1):136-143.
74. Edenvik P, Davidsdottir L, Oksanen A, Isaksson B, Hultcrantz R, Stål P. Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice? *Liver International*. 2015;35(7):1862-1871.
75. El-Serag HB, Kramer JR, Chen GJ, Duan Z, Richardson PA, Davila JA. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. *Gut*. Jul 2011;60(7):992-7. doi:10.1136/gut.2010.230508
76. Eskesen AN, Bjøro K, Aandahl EM, Line PD, Melum E. Low use of surveillance and early diagnosis of hepatocellular carcinoma in Norway—a population-based cohort study. *Cancer epidemiology*. 2014;38(6):741-747.
77. Giannini EG, Pieri G, Labanca S, et al. Characteristics and survival of patients with primary biliary cholangitis and hepatocellular carcinoma. *Digestive and Liver Disease*. 2022;54(9):1215-1221. doi:https://dx.doi.org/10.1016/j.dld.2022.03.002
78. Giannini E, Arzani L, Borro P, et al. Does surveillance for hepatocellular carcinoma in HCV cirrhotic patients improve treatment outcome mainly due to better clinical status at diagnosis? *Hepato-gastroenterology*. 2000;47(35):1395-1398.
79. Haq MI, Drake TM, Goh TL, et al. Effect of hepatocellular carcinoma surveillance programmes on overall survival in a mixed cirrhotic uk population: A prospective, longitudinal cohort study. *Journal of Clinical Medicine*. 2021;10(13):2770. doi:https://dx.doi.org/10.3390/jcm10132770
80. Hong TP, Gow PJ, Fink M, et al. Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. *Medical Journal of Australia*. 2018;209(8):348-354.

81. Huang Y, Wallace MC, Adams LA, et al. Rate of Nonsurveillance and Advanced Hepatocellular Carcinoma at Diagnosis in Chronic Liver Disease. *J Clin Gastroenterol*. Jul 2018;52(6):551-556. doi:10.1097/MCG.0000000000000916
82. Hwang JA, Kang TW, Min JH, et al. Association between intensity of imaging surveillance and clinical outcomes in patients with hepatocellular carcinoma. *European Journal of Radiology*. 2022;151:110328. doi:https://dx.doi.org/10.1016/j.ejrad.2022.110328
83. Im S, Jang ES, Lee JH, et al. Surveillance rate and its impact on survival of hepatocellular carcinoma patients in South Korea: a cohort study. *Cancer research and treatment: official journal of Korean Cancer Association*. 2019;51(4):1357-1369.
84. Jasirwan COM, Hasan I, Sulaiman AS, et al. Risk factors of mortality in the patients with hepatocellular carcinoma: A multicenter study in Indonesia. *Current Problems in Cancer*. 2020;44(1):100480. doi:https://dx.doi.org/10.1016/j.currproblcancer.2019.05.003
85. Karim MA, Singal AG, Kum HC, et al. Clinical Characteristics and Outcomes of Nonalcoholic Fatty Liver Disease-Associated Hepatocellular Carcinoma in the United States. *Clinical Gastroenterology and Hepatology*. 2022;doi:https://dx.doi.org/10.1016/j.cgh.2022.03.010
86. Kemp W, Pianko S, Nguyen S, Bailey MJ, Roberts SK. Survival in hepatocellular carcinoma: impact of screening and etiology of liver disease. *Journal of gastroenterology and hepatology*. 2005;20(6):873-881.
87. Kuo SC, Lin CN, Lin YJ, Chen WY, Hwang JS, Wang JD. Optimal Intervals of Ultrasonography Screening for Early Diagnosis of Hepatocellular Carcinoma in Taiwan. *JAMA Network Open*. 2021;4(6):e2114680. doi:https://dx.doi.org/10.1001/jamanetworkopen.2021.14680
88. Kuo Y-H, Lu S-N, Chen C-L, et al. Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. *European Journal of Cancer*. 2010;46(4):744-751.
89. Kwon JW, Tchoe HJ, Lee J, Suh JK, Lee JH, Shin S. The impact of national surveillance for liver cancer: Results from real-world setting in Korea. *Gut and Liver*. 2020;14(1):108-116. doi:https://dx.doi.org/10.5009/GNL18522
90. Lang S, Martin A, Kasper P, et al. Hepatocellular carcinoma surveillance with liver imaging is not associated with improved survival. *Scandinavian Journal of Gastroenterology*. 2020;55(2):222-227. doi:https://dx.doi.org/10.1080/00365521.2020.1718747
91. Leykum LK, El–Serag HB, Cornell J, Papadopoulos KP. Screening for hepatocellular carcinoma among veterans with hepatitis C on disease stage, treatment received, and survival. *Clinical Gastroenterology and Hepatology*. 2007;5(4):508-512.
92. Merchante N, Figueruela B, Rodríguez-Fernández M, et al. Low performance of ultrasound surveillance for the diagnosis of hepatocellular carcinoma in HIV-infected patients. *AIDS*. 2019;33(2):269-278.
93. Nusbaum JD, Smirniotopoulos J, Wright HC, et al. The effect of hepatocellular carcinoma surveillance in an urban population with liver cirrhosis. *Journal of clinical gastroenterology*. 2015;49(10):e91-e95.
94. Oeda S, Iwane S, Takasaki M, et al. Optimal follow-up of patients with viral hepatitis improves the detection of early-stage hepatocellular carcinoma and the prognosis of survival. *Internal Medicine*. 2016;55(19):2749-2758.
95. Papageorge MV, de Geus SWL, Woods AP, et al. Surveillance Patterns for Hepatocellular Carcinoma among Screening-Eligible Patients in the Medicare Population. *Annals of Surgical Oncology*. 2022;29(13):8424-8431. doi:https://dx.doi.org/10.1245/s10434-022-12360-z

96. Pascual S, Irurzun J, Zapater P, et al. Usefulness of surveillance programmes for early diagnosis of hepatocellular carcinoma in clinical practice. *Liver International*. 2008;28(5):682-689.
97. Pelizzaro F, Vitale A, Sartori A, et al. Surveillance as determinant of long-term survival in non-transplanted hepatocellular carcinoma patients. *Cancers*. 2021;13(4):1-16. doi:https://dx.doi.org/10.3390/cancers13040897
98. de Lope CR, Reig M, Matilla A, et al. Clinical characteristics of hepatocellular carcinoma in Spain. Comparison with the 2008–2009 period and analysis of the causes of diagnosis out of screening programs. Analysis of 686 cases in 73 centers. *Medicina Clínica (English Edition)*. 2017;149(2):61-71.
99. Schauer C, Mules T, Van Rijnsoever M, Gane E. Increasing burden of advanced hepatocellular carcinoma in New Zealand - The need for better surveillance. *New Zealand Medical Journal*. 2020;133(1515):25-34.
100. Schauer C, van Rijnsoever M, Gane E. Surveillance factors change outcomes in patients with hepatocellular carcinoma due to chronic hepatitis C virus infection in New Zealand. *Journal of viral hepatitis*. 2019;26(12):1372-1376.
101. Shindo K, Maekawa S, Komatsu N, et al. Semiannual imaging surveillance is associated with better survival in patients with non-B, non-C hepatocellular carcinoma. *Mediators of Inflammation*. 2015;2015
102. Singal AG, Patibandla S, Obi J, et al. Benefits and Harms of Hepatocellular Carcinoma Surveillance in a Prospective Cohort of Patients with Cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2020;doi:https://dx.doi.org/10.1016/j.cgh.2020.09.014
103. Singal AG, Mittal S, Yerokun OA, et al. Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. *The American journal of medicine*. 2017;130(9):1099-1106. e1.
104. Sohn W, Kang D, Kang M, Guallar E, Cho J, Paik Y-H. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. *Clinical and molecular hepatology*. 2022;28(4):851-863. Comment in: Clin Mol Hepatol. 2022 Oct;28(4):810-813 PMID: 36064304 [https://www.ncbi.nlm.nih.gov/pubmed/36064304]. doi:https://dx.doi.org/10.3350/cmh.2022.0037
105. Taura N, Hamasaki K, Nakao K, et al. Clinical benefits of hepatocellular carcinoma surveillance: a single-center, hospital-based study. *Oncology reports*. 2005;14(4):999-1003.
106. Tong MJ, Sun H-E, Hsien C, Lu DS. Surveillance for hepatocellular carcinoma improves survival in Asian-American patients with hepatitis B: results from a community-based clinic. *Digestive diseases and sciences*. 2010;55(3):826-835.
107. Toyoda H, Kumada T, Tada T, et al. Impact of hepatocellular carcinoma aetiology and liver function on the benefit of surveillance: A novel approach for the adjustment of lead-time bias. *Liver International*. 2018;38(12):2260-2268.
108. Tran SA, Le A, Zhao C, et al. Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis. *BMJ open gastroenterology*. 2018;5(1):e000192.
109. Trevisani F, De Notariis S, Rapaccini G, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *The American journal of gastroenterology*. 2002;97(3):734-744.
110. van Meer S, Robert A, Coenraad MJ, et al. Surveillance for hepatocellular carcinoma is associated with increased survival: results from a large cohort in the Netherlands. *Journal of hepatology*. 2015;63(5):1156-1163.

111. Vaz J, Stromberg U, Midlov P, Eriksson B, Buchebner D, Hagstrom H. Unrecognized liver cirrhosis is common and associated with worse survival in hepatocellular carcinoma: A nationwide cohort study of 3473 patients. *Journal of Internal Medicine*. 2023;293(2):184-199. doi:https://dx.doi.org/10.1111/joim.13570
112. Wong GLH, Wong VWS, Tan GM, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver International*. 2008;28(1):79-87.
113. Yamago H, Hiraoka A, Murakami T, et al. Ultrasonography surveillance improves prognosis of patients with hepatocellular carcinoma. *Molecular and Clinical Oncology*. 2019;11(3):325-330.
114. Yeh J-H, Hung C-H, Wang J-H, Kuo Y-H, Tai W-C, Lu S-N. Hepatocellular carcinoma detected by regular surveillance: Does timely confirmation of diagnosis matter? *Digestive and Liver Disease*. 2016;48(6):661-666.
115. Yu EW-R, Chie W-C, Chen TH-H. Does screening or surveillance for primary hepatocellular carcinoma with ultrasonography improve the prognosis of patients? *The Cancer Journal*. 2004;10(5):317-325.