Screening for Hepatocellular Carcinoma in Adults at Increased Risk

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Appendix

SEARCH STRATEGIES

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

STUDIES EXCLUDED DURING FULL-TEXT SCREENING

1. Chen VL, Yeh M-L, Yang JD, et al. Effects of Cirrhosis and Diagnosis Scenario in Metabolic-Associated Fatty Liver Disease-Related Hepatocellular Carcinoma. *Hepatology communications*. 2021;5(1):122-132. *Ineligible Comparator*
2. Curran C, Priest M, Datta S, Forrest EH, Stanley AJ, Barclay ST. Hepatocellular Carcinoma Risk Scores Predict Patients Under Surveillance at Low Risk of Benefit and High Risk of Harm. *Digestive Diseases and Sciences*. 2022; *Ineligible Comparator*
3. De Toni EN, Schlesinger-Raab A, Fuchs M, et al. Age independent survival benefit for patients with hepatocellular carcinoma (HCC) without metastases at diagnosis: A population-based study. *Gut*. 2020;69(1):168-176. *Ineligible Comparator*
4. Kurniawan J, Gani RA, Hasan I, et al. The Improvement in 1-Year Survival Rate of Patients with Hepatocellular Carcinoma BCLC Stage A and B after the Implementation of Comprehensive Management. *Journal of Gastrointestinal Cancer*. 2020;51(3):829-835. *Ineligible Comparator*
5. Lahmidani N, Hamdoun FZ, Lahlali M, et al. Prognostic Impact of Alpha Fetoprotein at Diagnosis on Overall Survival of Single Small Hepatocellular Carcinomas. *The Gulf journal of oncology*. 2020;1(33):64-67. *Ineligible Comparator*
6. Lee J, Park SB, Byun S, Kim HI. Impact of ultrasonographic blind spots for early-stage hepatocellular carcinoma during surveillance. *PLoS ONE*. 2022;17(9 September):e0274747. *Ineligible Comparator*
7. Rattanasupar A, Chartleeraha S, Akarapatima K, Chang A. Factors that Affect the Surveillance and Late-Stage Detection of a Newly Diagnosed Hepatocellular Carcinoma. *Asian Pacific journal of cancer prevention : APJCP*. 2021;22(10):3293-3298. *Ineligible Comparator*
8. Sigurdsson B, Sigurdardottir R, Arnardottir MB, Lund SH, Jonasson JG, Bjornsson ES. A nationwide study on hepatocellular carcinoma. *Cancer Epidemiology*. 2020;69:101835. *Ineligible Comparator*
9. Ali AH, Tabibian JH, Nasser-Ghodsi N, et al. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. *Hepatology*. Jun 2018;67(6):2338-2351. *Ineligible Population*
10. Wu Y, Shen L, Qi H, et al. Surveillance Strategy for Patients With BCLC Stage B Hepatocellular Carcinoma After Achieving Complete Remission: Data From the Real World. *Frontiers in Oncology*. 2020;10:574804. *Ineligible Population*
11. Attree C, Wallace M, Jeffrey G, et al. Hepatocellular cancer surveillance in cirrhotic patients with fatty liver disease. *Journal of Gastroenterology and Hepatology*. 2022;37(Supplement 1):75-76. Gastroenterological Society of Australia, GESA and Australian Gastroenterology Week, AGW 2022. Sydney, NSW Australia. *Ineligible Publication Type*
12. Bui HT, Wong K, Tran DK, Balasubramanian S. Impact of an HCC surveillance program on surveillance rates, early detection of HCC and outcomes in a community-based hepatology practice-real world experience. *Hepatology*. 2020;72(1 SUPPL):394A. 71st Annual Meeting of the American Association for the Study of Liver Diseases, AASLD. Boston, MA United States. *Ineligible Publication Type*
13. Carrieri V, Bray A, Argentieri G, Mazelli G, Lena LD, Paterno V. Liver cirrhosis in the elderly: Clinical and ecographic correlations. *European Geriatric Medicine*. 2020;11(SUPPL 1):S250. 16th International E-Congress of the European Geriatric Medicine Society. Athens Greece. *Ineligible Publication Type*

14. Chalasani NP, Porter K, Book AJ, et al. THE MULTI-TARGET HEPATOCELLULAR CARCINOMA BLOOD TEST PROVIDES HIGH SENSITIVITY FOR DETECTING EARLY-STAGE HEPATOCELLULAR CARCINOMA ACROSS IMPORTANT PATIENT SUBGROUPS. *Gastroenterology*. 2022;162(7 Supplement):S-1130. DDW 2022. San Diego United States. *Ineligible Publication Type*
15. Chen E, Holmes J, Howell J, et al. A growing problem: Non-alcoholic fatty liver disease-related hepatocellular carcinoma is increasing and associated with low rates of surveillance participation and poor overall survival. *Journal of Gastroenterology and Hepatology (Australia)*. 2020;35(SUPPL 1):75-76. Gastroenterological Society of Australia, GESA and Australian Gastroenterology Week, AGW 2020. Virtual. *Ineligible Publication Type*
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18. Consul N. Hepatocellular Carcinoma Surveillance with Abbreviated MRI Strategies. *Radiology Imaging cancer*. 2021;3(1):e219002. *Ineligible Publication Type*
19. El Sabagh A, Mohamed I, Zain Aloor F, et al. OUTCOMES OF DIFFERENT RADIOLOGICAL MODALITIES FOR HCC SURVEILLANCE OF HIGH RISK CIRRHOTIC PATIENTS. *Hepatology*. 2022;76(Supplement 1):S1414-S1415. Annual Meeting of the American Association for the Study of Liver Diseases, AASLD 2022. Virtual. *Ineligible Publication Type*
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21. Flores JE, Morgan J, Pietris K, Tse E. Fatty liver disease not associated with decreased proportion of early hepatocellular carcinoma detected on ultrasound. *Journal of Gastroenterology and Hepatology (Australia)*. 2020;35(SUPPL 1):42. Gastroenterological Society of Australia, GESA and Australian Gastroenterology Week, AGW 2020. Virtual. *Ineligible Publication Type*
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25. Gonzalez-Sanchez H, Castano-Garcia A, Celada-Sendino M, et al. CHARACTERISTICS AND SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA IN NATURAL HISTORY IN A WESTERN COUNTRY. *United European Gastroenterology Journal*.

2022;10(Supplement 8):939. 30th United European Gastroenterology Week, UEG Week 2022. Virtual. *Ineligible Publication Type*

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32. Kang S, Kim JW. Utility of CT/MR surveillance in LI-RADS Visualization Scoreassessed Liver cirrhosis patients. *Hepatology International*. 2022;16(Supplement 1):S99-S100. 31st Conference of the Asian Pacific Association for the Study of the Liver, APASL 2022. Seoul South Korea. *Ineligible Publication Type*
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35. Khan AA, Hadi Y, Kupec J. ASSESSING THE RISK: INCIDENCE OF ACUTE KIDNEY INJURY AFTER CT AND MRI FOR EVALUATION OF LESIONS IDENTIFIED ON HCC SURVEILLANCE. *Gastroenterology*. 2020;158(6 Supplement 1):S-1454. Digestive Disease Week (DDW) 2020. Chicago United States. *Ineligible Publication Type*
36. Khan V, Jiang D, Panneerselvam K, et al. Missed opportunities for hepatocellular carcinoma (HCC) screening and surveillance amongst veterans subsequently diagnosed with HCC.

Hepatology. 2020;72(1 SUPPL):646A. 71st Annual Meeting of the American Association for the Study of Liver Diseases, AASLD. Boston, MA United States. *Ineligible Publication Type*
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38. Kim SY, Lim YS. Towards a New Horizon for Individualized Surveillance Tools in Hepatocellular Carcinoma. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2021; *Ineligible Publication Type*
39. Krishna AS, Narayanasamy KNS. Clinical impact of screening for HCC in CLD patients: A south Indian teritiary centre persepective. *Hepatology International*. 2022;16(Supplement 1):S429. 31st Conference of the Asian Pacific Association for the Study of the Liver, APASL 2022. Seoul South Korea. *Ineligible Publication Type*
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42. Mezzacappa C, Kaplan DE, Mahmud N, Serper M, Taddei TH. SCREENING FOR HEPATOCELLULAR CARCINOMA AND OVERALL SURVIVAL IN A COHORT OF VETERANS WITH CIRRHOSIS: A SNAPSHOT OF THE POST-DAA ERA. *Hepatology*. 2022;76(Supplement 1):S1379-S1380. Annual Meeting of the American Association for the Study of Liver Diseases, AASLD 2022. Virtual. *Ineligible Publication Type*
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44. Navadurong H, Laohasurayotin K, Yorwittaya K, et al. PERFORMANCE OF ABBREVIATED MAGNETIC RESONANCE IMAGING VERSUS ULTRASONOGRAPHY AS AN IMAGING TOOL FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE. *Gut*. 2022;71(Supplement 2):A85. International Digestive Disease Forum, IDDF. Hong Kong Hong Kong. *Ineligible Publication Type*
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Meeting of the American Association for the Study of Liver Diseases, AASLD. Boston, MA United States. *Ineligible Publication Type*

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50. Sedki M, Horton B, Avins A, Corley DA, Chai KP, Ready JB. Chronic hepatitis b management through a dedicated surveillance program in an integrated-care setting. *Hepatology*. 2021;74(SUPPL 1):44A-45A. 72nd Annual Meeting of the American Association for the Study of Liver Diseases, AASLD 2021. Virtual. *Ineligible Publication Type*
51. Spiers J, Li W, Alazawi W. FACTORS ASSOCIATED WITH HCC STAGE AT PRESENTATION AND SURVIVAL IN AN ETHNICALLY DIVERSE UK POPULATION. *Gut*. 2022;71(Supplement 1):A85. Annual Meeting of the British Society of Gastroenterology, BSG 2022. Birmingham United Kingdom. *Ineligible Publication Type*
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55. Zambrano ES, Acosta-Lopez S, Bethencourt DD, Garrido MS, Darias RS, Perez Hernandez FA. Adherence to hepatocellular carcinoma screening in patients with hepatitis C cirrhosis treated with direct-acting antivirals against hepatitis C. *Journal of Hepatology*. 2022;77(Supplement 1):S931. The International Liver Congress. London United Kingdom. *Ineligible Publication Type*
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UNDERWAY STUDIES

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

.

RISK OF BIAS ASSESSMENTS

RANDOMIZED CONTROLLED TRIALS (ROB-2)

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

NONRANDOMIZED COMPARISON STUDIES (ROBINS-I)

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

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

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

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

PEER REVIEW COMMENTS AND RESPONSES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

RANDOMIZED CONTROLLED TRIALS

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

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

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

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

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

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

Notes. *Conducted in VHA.

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

CASE-CONTROL STUDIES

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

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

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

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

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

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

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

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

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

COHORT STUDIES

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

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

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

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

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

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

Appendix Table 8. Detailed Results for for Cohort Studies

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

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

HCC COHORT STUDIES

Appendix Table 9. Detailed Study Characteristics for HCC Cohort Studies

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

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

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

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

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

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

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

Notes. *Calculated by ESP team.

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

Appendix Table 10. Outcomes Reported for Included HCC Cohort Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abbreviations. US=ultrasound.