Screening for hepatocellular carcinoma in chronic liver disease: A systematic review and meta-analysis of randomized controlled trials comparing screening methodologies

James O'Connell (jamesoconnell@rcsi.com)
Royal College of Surgeons in Ireland https://orcid.org/0000-0003-1553-4489

Systematic Review

Keywords: screening, hepatocellular carcinoma, chronic liver disease, cancer, cirrhosis

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1123641/v1

Version of Record: A version of this preprint was published at Journal of Global Health Reports on June 17th, 2020. See the published version at https://doi.org/10.29392/001c.12924.

Screening for hepatocellular carcinoma in chronic liver disease: A systematic review and meta-analysis of randomized controlled trials comparing screening methodologies

James O Connell[1], Siobhan Rooney[2]

[1]Department of International Health and Tropical Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

[2]University College Hospital Galway, Saolta Healthcare Group, Health Service Executive, Galway, Ireland

Background Hepatocellular carcinoma (HCC) is the 5th most prevalent cancer and the second most common cause of cancer-related mortality worldwide. HCC is often asymptomatic until an advanced stage. Current guidelines recommend ultrasound surveillance with or without measurement of serum alpha-fetoprotein. Our objective was to determine if screening for HCC is beneficial or harmful in patients with chronic liver disease. Primary outcomes were all-cause mortality and quality of life. Secondary outcomes were mortality due to HCC, the number of cases of HCC detected and adverse events.

Methods This is a systematic review and meta-analysis of data from randomized controlled trials. To be included trials had to randomize patients to either an HCC screening group or non-screening group, randomize patients to different screening frequencies or randomize patients to different screening methods. All published reports of randomized trials on screening for HCC were eligible for inclusion, irrespective of the language of publication. Studies had to include patients with chronic liver disease. Data extraction and analysis were performed independently by two reviewers.

Results When screening with six-monthly alpha-fetoprotein and ultrasound abdomen was compared to no screening there was no evidence of difference in HCC related mortality when adjusted for clustering across a range of intracluster correlation coefficients (Intracluster coefficient (ICC) 0.02, odds ratio (OR) 0.60, 95% confidence interval (CI) 0.31-1.15). Screening with six-monthly alpha-fetoprotein when compared to a single alpha-fetoprotein check did not result in a statistically significant difference in all-cause mortality (OR 1.02, 95% confidence interval (CI) 0.65-1.60), mortality due to HCC (OR 1.01, 95% CI 0.57-1.78) or the number of HCC detected (OR 1.11 95% CI 0.64-1.92). There was no evidence of difference in all-cause mortality (OR 0.81, 95% CI 0.26-2.53), mortality due to hepatocellular carcinoma (OR 0.81, 95% CI 0.26-2.53) or the number of patients with HCC detected (OR 1.09 95% CI 0.40-2.99) when twice-a-year ultrasound was compared with annual CT. There was no statistically significant difference when screening more frequently was compared to less frequently in terms of all-cause mortality (OR 0.86, 95% CI 0.56-1.32), mortality due to hepatocellular carcinoma (OR 1.42, 95% CI 0.55-3.64) and the number of cases of hepatocellular carcinoma detected (OR 0.90 95% CI 0.47-1.71).

Conclusions There is currently insufficient evidence from randomized controlled trials to support the routine screening for HCC in patients with chronic liver disease.

Hepatocellular carcinoma (HCC) is the 5th most prevalent cancer and the second most common cause of cancer-related mortality worldwide (1). In 2012 there are estimated to have been 782,000 new cases of hepatocellular carcinoma worldwide. 83% of these cases occurred in less developed regions with 50% occurring in China alone (1). It is 2-4 times more common in men than women (2). Chronic liver diseases such as hepatitis B, hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease are major risk factors for HCC (3, 4). It usually occurs in patients where liver disease has progressed to liver cirrhosis (5,6). The incidence of hepatocellular carcinoma is increasing in certain regions such as the United States (incidence men: 8.11/100,000, women: 2.47/100,000). This may be related to an increase in the prevalence of hepatitis C in the United States of America and increased immigration from high prevalence regions (7). The incidence in China decreased over the time period 2000-2014 (incidence men: 38.3/100,000, women: 14.3/100,000) (8,9). The median age at diagnosis varies between populations. According to data from the Surveillance Epidemiology and End Results (SEER) program the median age of HCC diagnosis by region of birth in those living in the United States was 70-74 years for people from Europe, 65-69 years for people from Asia and 40-45 years for people from West Africa (9). Hepatocellular carcinoma is often asymptomatic until an advanced stage. Early-stage tumors are more likely to be amenable to treatment and have better overall survival (10). There is no curative treatment for intermediate or late-stage tumors. Patients with symptomatic hepatocellular carcinoma have a 3-year survival of 8% (11). Patients with well-compensated liver disease may be considered for surgical resection. The survival rates are 58% at 3 years and 42% at 5 years in non-cirrhotic patients with surgical resection (12). Liver transplantation is the main course of therapy in patients with cirrhosis of the liver. 5-year survival rates after liver transplantation are 69%, with a tumor recurrence rate of 7% (13). Patients with intermediate-stage hepatoma treated with transcatheter arterial chemo-embolization (TACE) have a median overall survival of 19-20 months (10).

Screening is the periodic application of a test in people at risk of developing a given disease to identify an early or latent stage. Screening for hepatocellular carcinoma fits many of the

requirements of a screening program because it follows a known clinical course, has an early treatable stage and is an important health problem. The rationale for screening is that patients at high risk of HCC, such as those with chronic liver diseases, can be identified and invited to participate. However, HCC often occurs in those with undiagnosed liver cirrhosis (14). Patients with undiagnosed liver cirrhosis or chronic liver disease will not be captured by screening programs founded on this rationale. Screening may result in harm. Invasive procedures may be performed based on a positive screening test. Liver biopsy has a 0.5% incidence of hematoma, a 0.1% risk of infection and a 0.05% risk of death associated with liver biopsy (15). Negative psychosocial consequences occur in 3-20% of patients undergoing screening (16). In the absence of an effective means of identifying patients with an early-stage HCC however, most patients will die. Observational studies have shown that patients undergoing screening had earlier stage disease compared to patients who did not undergo screening (17,18). Non-randomized studies are subject to lead and length time bias. Lead-time is the time by which diagnosis is anticipated by screening with respect to the symptomatic detection of disease. Length time bias is an overestimation of survival duration due to the relative excess of cases detected that are slowly progressing. Even when non-randomized studies account for lead time bias the effects of screening on survival vary with the assumed tumor doubling time (19). Survival time in one study was significantly longer in a screened group compared to a non-screened group when the tumor doubling time was assumed to be less than 90 days, but this was not evident if the tumor doubling time was assumed to be greater than 90 days (20). Most clinical guidelines recommend screening for hepatocellular carcinoma (**Table 1**). A well designed randomized controlled trial could eliminate lead-time bias. The purpose of this review is to determine if there is evidence from randomized controlled trials evaluating the efficacy of screening for HCC in patients with chronic liver disease.

OBJECTIVES

The objective was to determine if screening for HCC is effective in reducing mortality while being safe and acceptable to the screening population.

METHODS

Included studies were randomized controlled trials. Other types of studies were excluded. This was to minimize confounding due to the potential for selection bias, performance bias and detection bias in non-randomized studies. Studies that evaluated the diagnostic accuracy of a test in the confirmation of suspected hepatocellular carcinoma were excluded. There were no restrictions based on language, publication status or year of study. Only studies of Individuals with chronic liver disease were included for review. Studies including individuals with a history of hepatocellular carcinoma were excluded. To be included studies had to compare screening with no screening, compare different screening methodologies or compare different screening intervals. Screening methodologies included for review were alpha-fetoprotein, ultrasound, computed tomography (CT) and Magnetic Resonance Imaging (MRI). A protocol for this systematic review and meta-analysis is available in the Online Supplementary Document.

Primary outcomes chosen were:

1. All-cause mortality

2. Quality of Life (any reported measure of quality of life was accepted)

Secondary outcomes were:

1. Mortality due to hepatocellular carcinoma

2. Number of cases of hepatocellular carcinoma detected

3. Adverse Events (According to the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH 1997) adverse event was defined as any untoward medical occurrence in the

participant in the clinical trial which does not necessarily have a causal relationship with this treatment (28). A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect) (28).

Search methods for identification of studies

Electronic searches were performed on the 20th of May 2018 using MEDLINE (1946- May 2018), EMBASE (1974- May 2018), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (1974- May 2018) and the Web of Science Citation Index Expanded (1900- May 2018) were all searched according to the search strategy (Online Supplementary Document). The databases used in the search strategy were chosen based on guidance contained within the Cochrane Handbook. It states that at least two databases should be used. They suggest CENTRAL, MEDLINE or EMBASE. The handbook states that CENTRAL is the most comprehensive source of controlled trials (29). Clinical trial registries were also searched (clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) search portal). The references of identified relevant randomized controlled trials were searched.

Data collection and analysis

The first systematic reviewer screened titles and abstracts for inclusion. The full articles of studies deemed eligible were then assessed by both first and second systematic reviewers for inclusion. All studies which were excluded were recorded with the relevant explanation. Any disagreements between the first and second systematic reviewers were resolved by discussion. It was planned that for any discrepancies that arose during data extraction where agreement could not be reached between the first and second reviewers, a third reviewer would be invited to resolve the discrepancy. Data extraction was performed independently by two reviewers. A standardized data extraction spreadsheet was used. Any disagreement between systematic reviewers about data extracted was resolved by discussion. The assessment of the risk of bias in included studies was

performed using the Cochrane Collaboration's recommended domain-based evaluation (30). The odds ratio was used as the measure of treatment effect for all-cause mortality, mortality secondary to hepatocellular carcinoma and the number of cases of hepatocellular carcinoma. Using a random effect model the Manthel-Haensel method was used to calculate an odds ratio as the measure of treatment effect. Studies that were cluster randomized controlled trials that had not accounted for this in their statistical analyses were adjusted for clustering using guidance from the Cochrane Consumers and Communication Group (31). An intracluster correlation coefficient (ICC) of 0.02 was used for adjustment. There were no intracluster correlation coefficients referenced in the included studies. An intracluster coefficient of 0.02 was chosen based on empirical estimates for randomized controlled trials with continuous and binary outcome measures which were generally less than 0.064 with a median value of 0.02 (32). It is thought an intracluster coefficient of less than 0.05 is reasonable for outcome variables.

Missing data was deemed to be acceptable if the explanation provided by the study authors was deemed likely not to impact on the study outcomes (e.g. when a participant with a history of hepatocellular carcinoma was randomized but subsequently excluded in studies which randomized participants in clusters which had pre-specified the exclusion of anyone with a history of hepatocellular carcinoma) or if the number missing was negligible. We accepted intention-to-treat analyses and modified intention-to-treat analyses but not per-protocol analyses.

Heterogeneity was assessed using forest plots of the measures of treatment effect. We looked for overlap of the confidence intervals of the measure of treatment effect and whether the point estimates of treatment effect were on the same side of the line of no effect. If all point estimates were on the same side of the line of no effect, we looked for the magnitude of those treatment effects. The chi-square test was used to assess for heterogeneity. A P-value of less than 0.10 was used as a cut-off for the detection of heterogeneity. The I2 test for heterogeneity was also used. An I2 of 30-60% was considered to represent moderate heterogeneity, 50-90% was considered to

represent substantial heterogeneity and 75-90% was thought to be considerable heterogeneity. Interpretation of the I2 also required concomitant interpretation of the chi-square test as well as the direction and magnitude of treatment effects point estimates and their confidence intervals.

If sufficient studies (10 or more) met the review inclusion criteria it was planned to generate a funnel plot and obtain the Egger test and Begg test to check for asymmetry as an indicator of reporting bias. Data was synthesized and analyzed using RevMan (Review Manager) 5.2 (33).

Any heterogeneity detected between studies was investigated by considering both clinical and methodological factors. Clinical factors to considered were the baseline risk of hepatocellular carcinoma of study participants, whether the study was performed in primary care, secondary care or both and the etiology of cirrhosis of trial participants. The investigation of heterogeneity due to any potential methodological factors was performed by assessing the risk of bias in each study. For any heterogeneity detected we planned on changing the measure of treatment effect from odds ratio to risk difference to determine if it altered heterogeneity. It was planned to perform a subgroup analysis for all outcomes of participants who had hepatitis B or hepatitis C where studies reported the necessary data to explore any heterogeneity and determine the primary and secondary outcomes in these subgroups. It was planned to perform a sensitivity analysis to examine the effect of non-hepatitis B or C participants on the review outcomes where studies reported the necessary data. The quality of evidence was assessed using guidance from the GRADE handbook for grading quality of evidence and strength of recommendations and GRADEpro software (34,35).

RESULTS

Results of the search

We identified a total of 7753 references through the electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (n = 709), MEDLINE (n= 4255), EMBASE (n = 720), and Web of Science Citation Index Expanded (n =2069) (see flow diagram **Figure**

1). We excluded 152 duplicates and 7585 irrelevant references through reading abstracts. 16 references were retrieved for further assessment. No references were identified through searching reference lists of the identified studies. Of the 16 references, we excluded 7. In total, 9 publications describing 6 studies fulfilled the inclusion criteria.

Included studies

Included studies are shown in **Table 2** (summarised from Table S2 in the **Online Supplementary Document**).

Excluded studies

7 studies were excluded compromising of 1 multi-centre prospective cohort study evaluating the effectiveness of ultrasound plus MRI in the detection of hepatocellular carcinoma (42), 1 randomized controlled trial evaluating the efficacy of contrast-enhanced ultrasonography for the detection of hepatocellular carcinoma (43), 2 review articles (44.45), 1 randomized controlled trial comparing symptomatic treatment versus interferon alfa for the treatment of hepatocellular carcinoma (46), 1 retrospective cohort study which evaluated the usefulness of regular screening by ultrasonography and contrast-enhanced imaging for detection of hepatocellular carcinoma (47) and 1 study evaluating contrast-enhanced ultrasound with perfluorobutane (Sonazoid) for the detection of hepatocellular carcinoma (48).

Risk of bias in included studies

The risk of bias assessment was performed using the Cochrane Risk of Bias tool for Randomized Controlled Trials (**Table 3**) (30).

Allocation (selection bias)

Information regarding allocation concealment was not available in the studies by Zhang et al (36) Chen et al (37), Pocha et al (38), Sherman et al (39), Wang et al (41). The risk of selection bias in these studies is therefore unclear. Allocation concealment in the study by Trinchet et al (40) was achieved

using a centralized phone procedure to the data-management center. The risk of selection bias in this study is low.

Blinding (performance bias and detection bias)

In the study by Wang et al (41) the public health nurses followed up patients with newly detected nodules with regard to survival. It is unclear if the nurses were blinded as to which group the patients belonged to. The risk of performance bias is unclear. Information regarding blinding was not available in the studies by Zhang et al (36) Chen et al (37), Pocha et al (38), Sherman et al (39), Trinchet et al (40). The risk of performance bias and detection bias, as a result, is unclear.

Incomplete outcome data (attrition bias)

In the study by Chen et al (37), there was considerable attrition bias. 400/3712 (10.8%) subjects in the intervention group did not attend for any further follow up after their enrolment screening alpha-fetoprotein. It is unclear what follow up if any, these subjects had. Compliance was poor in the intervention group. 1070/3712 (28.8%) of participants were considered to not have complete compliance, meaning they missed 1 or more of their scheduled screening examinations. As a result, the risk of bias in this study is high. Information regarding incomplete outcome data was not available in the studies by Zhang et al (36) Pocha et al (38), Sherman et al (39), Trinchet et al (40) Wang et al (41). The risk of bias due to incomplete outcome data is unclear in these studies.

Selective reporting (reporting bias)

In the studies by Chen et al (37) and Pocha et al (38) detection rates, the characteristics of the screening test and the outcomes with respect to incidence, stage, survival, and mortality in the screened and control group were reported. The risk of selective reporting bias in these studies is low. In the study by Sherman et al (39) the authors have not reported on all-cause mortality and disease-specific mortality in the screening group compared to the control group however they state that this study was not designed to evaluate these outcomes and that this trial was a preliminary

study preparatory to a larger study. The risk of selective reporting bias in this study is low. Trinchet et (40) reported on most important outcomes and the risk of reporting bias is low. Wang et al (41) reported on overall survival in patients with hepatocellular carcinoma but did not report on all-cause mortality. The risk of reporting bias in this study is therefore high. Similarly, Zhang et al (36)did not report all-cause mortality and the risk of reporting bias is also high.

Other potential sources of bias

Four of the studies, Zhang et al (36) Chen et al (37), Trinchet et al (38), and Wang et al (41), were cluster randomized controlled trials with no adjustment for clustering or use an intracluster correlation coefficient reported in their statistical analysis. There may be a correlation of observations within the clusters and the resulting standard errors of the effect of the interventions will be too small, along with the confidence intervals and *P*-values.

Effects of interventions (Forest Plots in Figures S1-22, and in the Quality of Evidence and Summary of Findings in Tables S3-S5 in the Online Supplementary Document)

There was one study that compared screening with six-monthly alpha-fetoprotein to no screening (36). There was no difference in the number of cases of hepatocellular carcinoma detected across a range of intracluster coefficients (ICC 0.02,OR 1.30, 95% 0.81-2.08) (ICC 0.05, OR 1.30, 95% CI 0.68-2.48) (ICC 0.1, OR 1.30,95% CI 0.10-3.07). In the same study there was no evidence of difference in hepatocellular carcinoma related mortality using a range of intracluster coefficients (ICC) (ICC 0.02, OR 0.60, 95% CI 0.31-1.15), (ICC 0.05, OR 0.60, 95% CI 0.25-1.45) (ICC 0.1 OR 0.60 95% CI 0.19-1.94) (**Figure 2**). When the number of clusters was assumed to be 350 there was no statistically significant difference in either the mortality due to hepatocellular carcinoma (ICC=0.02, OR 0.59 95% CI 0.32-1.11) or the number of cases of hepatocellular carcinoma detected (ICC=0.02, OR 1.30, 95% CI 0.83-2.04). When the number of clusters was assumed to be 399 there was no statistically significant difference in either the mortality due to hepatocellular carcinoma (ICC=0.02, OR 0.59,95% CI 0.32-

1.09) or the number of cases of hepatocellular carcinoma detected (ICC 0.02, OR 1.30 95% CI 0.83-2.04).

Figure 2. Forest plot of comparison.

In the study by Chen et al (37), there was no statistically significant difference in all-cause mortality when screening with six-monthly alpha-fetoprotein was compared to a single alpha-fetoprotein check (OR 1.02, 95% CI 0.65-1.60). There was no evidence of difference in mortality due to hepatocellular carcinoma in the same study (OR 1.01, 95% CI 0.57-1.78). There was no evidence to support any difference in the number of cases of hepatocellular carcinoma detected also in the same study (OR 1.11 95% CI 0.64-1.93). There were 5581 participants in this study.

There was no evidence of difference in all-cause mortality when ultrasound was compared to CT (OR 0.81, 95% CI 0.26-2.53) in the Pocha et al which made this comparison with 163 participants (38). In the same study, there was no statistically significant difference between the two groups in terms of hepatocellular carcinoma related mortality (OR 0.67 95% CI 0.20-2.20) or the number of cases of hepatocellular carcinoma detected (OR 1.09 95% CI 0.40-2.99). A subgroup analysis of the number of cases of hepatocellular carcinoma detected in participants with hepatitis C did not show any evidence of difference between the two groups (OR 1.11, 95% CI 0.40-3.05) (Appendix 6 Figure 17 Online Supplementary Document Document). There were no cases of hepatocellular carcinoma in participants with hepatitis B in this study, so it was not possible to do a subgroup analysis of hepatitis B participants.

Wang et al and Trinchet et al compared more versus less frequent screening using ultrasound (40,41). When adjusted for clustering there was no evidence of difference in all-cause mortality when screening with ultrasound every 3 months was compared to screening with ultrasound every 6 months (OR 0.86, 95% CI 0.56-1.32). There was also no evidence of difference in hepatocellular carcinoma related mortality (OR 1.42, 95% CI 0.55-3.64) in the same study. There was no significant

heterogeneity between the two studies as demonstrated by a significant overlap of the 95% confidence intervals ((I^2= 0%, χ^2=0.67, df=1 (*P*=-0.41)(Appendix 6 Figure 20 Online

Supplementary Document Document). Meta-analyses of these studies did not find any statistically significant difference in the number of cases of hepatocellular carcinoma detected by more frequent screening compared to less frequent screening (OR 0.90 95% CI 0.47-1.71).

A subgroup analysis of patients with hepatitis B of the participants in the study by Wang et al (41) did not show any evidence of difference in the number of cases of hepatocellular carcinoma detected (ICC 0.02, OR 1.45, 95% CI 0.31-6.68). Similarly, for patients with hepatitis C in the same study, subgroup analysis did not show any evidence of difference in the number of cases of hepatocellular carcinoma detected (ICC 0.02 OR 1.42, 95% CI 0.23 -8.61).

It was not possible to perform a sensitivity analysis on the effect of non-hepatitis B or C patients on the outcomes with the data reported in the included studies. No studies reported on quality of life or adverse effects.

No studies reported on quality of life or adverse events. It was not possible to perform a subgroup analysis for all outcomes of participants who had hepatitis B or hepatitis C because studies had not reported the necessary data to explore any heterogeneity and determine the primary and secondary outcomes in these subgroups. It was not possible to perform a sensitivity analysis to examine the effect of non-hepatitis B or C participants on the review outcomes. There were insufficient studies to meet the review inclusion criteria as planned to generate a funnel plot and obtain the Egger test and the Begg test to check for asymmetry as an indicator of reporting bias.

Quality of the evidence

The number of hepatocellular carcinoma related deaths and the number of cases of hepatocellular carcinoma detected in the study by Zhang et al (36) was small. The confidence intervals were wide suggesting imprecision. There was no inconsistency or indirectness. The quality of evidence in this

study is therefore moderate. In the studies by Chen et al (37), Pocha et al (38), Wang et al (41), and Trinchet et al (40) there was a high risk of attrition bias because of poor compliance with follow up screening tests. The confidence intervals were wide and would likely include a minimal clinically important difference for a trial comparing screening frequencies for hepatocellular carcinoma or comparing screening methodologies. There was no inconsistency or indirectness in these four studies. For these reasons the quality of evidence from these studies is low. There were insufficient studies to formally assess for publication bias with a funnel plot.

DISCUSSION

There was no evidence from this review to support screening for hepatocellular carcinoma in patients with chronic liver disease to reduce mortality. A significant finding was the effect of adjusting for clustering on study outcomes. Understandably, clustering is used in randomized controlled trials for logistical and feasibility reasons. Correlation of observations occurs within clusters and this must be accounted for in the statistical analysis. This is because participants within clusters are more likely to be similar to each other than participants in other clusters. In the study by Zhang et al, they reported a 37% reduction in the HCC related mortality (36). When adjusted for clustering there was no evidence of difference in the HCC related mortality ratio. This finding remained true across a range of intracluster correlation coefficients and across a range of assumed number of clusters (the number of clusters in the study was reported as “more than 300”, we performed our analysis assuming there were 301,350 and 399 clusters respectively). A potential bias in the review process was the use of an intracluster coefficient of 0.02 to adjust for clustering. We could not find previous similar studies to give guidance on the estimation of a suitable intracluster coefficient. The choice of too small an intracluster coefficient can have a substantial impact on confidence interval width. We demonstrated that the use of a range of intracluster coefficients (0.02, 0.05, 0.1) did not change the outcome dramatically. Of note, there was a lack of studies that included quality of life and adverse events as outcomes. These are important outcomes when

considering a screening test. A screening test with significant adverse events or reductions in quality of life may not be acceptable to the target population.

It is important to consider the treatments patients received when discussing the benefits of screening and its impact on mortality. In the study by Zhang et al (36), no reduction in HCC related mortality was seen despite the screening group detecting more early-stage tumors and receiving more liver transplantation compared to the control group (46.5% vs. 7.5%). Similarly, in the study by Trinchet et al (41) more patients with HCCs <10mm were detected. More patients received liver transplantation when screened every 3 months with ultrasound compared to 6-monthly screening in this trial (18.9% vs. 4.3%). This did not translate to a reduction in all-cause mortality or HCC related mortality. Wang et al (40) found that when comparing screening every 4 months versus every 12 months they detected more early-stage tumors and it resulted in more curative therapy being given but did not confer a benefit in survival in the 4-year follow-up. From these trials it appears despite early diagnosis and treatment, mortality was unchanged, suggesting treatments were not an effective means of cure in HCC detected by screening.

Nil evidence of effect is not evidence of no effect. Reasons why the studies included in this review may not have detected an effect if it was truly there may be related to the patients enrolled. Within some studies, for example, Chen et al (37), patients with non-cirrhotic chronic liver disease and cirrhotic liver disease were included in each arm. The patients with non-cirrhotic liver disease would be at low risk of HCC and may have diminished any potential significant findings in cirrhotic liver disease patients. The studies by Chen et al (37) and Zhang et al (36) were performed in what the authors note to be high prevalence settings. This may limit the applicability of evidence from these studies to lower prevalence settings. However, given there was a lack of evidence of effect in a high prevalence setting it is unlikely to materialize in a low prevalence setting.

A limitation of this study may have been the choice of all-cause mortality as the primary outcome. All-cause mortality would be a standard primary outcome for studies evaluating screening tests.

However, patients with chronic liver disease die for many reasons other than HCC and often before its development if it was going to be an occurrence. As such, a screening test for HCC may not result in any significant reduction in all-cause mortality. A second limitation was the small number of studies that met the inclusion criteria (N=6). The strengths of this review include rigorous methodology and adherence to PRISMA guidelines for reporting on systematic reviews (Online Supplementary Document Table 1).

Current NICE guidelines state "offer ultrasound (with or without measurement of serum alpha-fetoprotein) every 6 months as surveillance for hepatocellular carcinoma (HCC) for people with cirrhosis who do not have hepatitis B virus infection" and "Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis" (20). This recommendation is based on evidence from a systematic review and meta-analysis performed by the NICE guidelines development group. There is very low-quality evidence from 2 retrospective cohort studies (n=351) which indicated a clinical benefit of surveillance for survival when analyzed using time-to-event data (50,51). They also evaluated annual versus 6-monthly surveillance and found only very low-quality evidence from 1 observational study (n=649) which indicated a clinical benefit of 6-monthly surveillance for survival (52). Low-quality evidence from the same study indicated a clinical benefit of 6-monthly surveillance for the detection of HCC beyond a very early stage. Moderate quality evidence from 1 randomized controlled trial (n=1278) indicated a clinical benefit of 3-monthly surveillance for survival and HCC occurrence when compared to 6-monthly surveillance (40). Evidence ranging from very low to moderate quality from the same randomized controlled trial indicated no clinical difference in HCC diameter >30 mm at detection, the number of HCC nodules detected or the HCC stage at detection. A Cochrane review performed in 2012 examined whether alpha-fetoprotein and/or ultrasound was effective for screening for hepatocellular carcinoma (53). They concluded there was insufficient evidence. The purpose of our systematic review was to determine if there was any high-quality evidence to support or refute

screening for hepatocellular carcinoma, screening frequencies, and screening methodologies. The systematic review and meta-analysis we have conducted included studies that included patients with all stages of chronic liver disease and was not limited to alpha-fetoprotein and ultrasound as the only interventions. Conducted in 2018 it is more up to date and has broader inclusion criteria. Of note, all studies identified in this review were published after 1995 and all in English.

An increase in worldwide use of the hepatitis B vaccine and a reduction in global hepatitis C burden due to recent treatment advances may result in reductions in the global incidence of HCC. According to the WHO at the end of 2017, 187 countries had the hepatitis B vaccine nationwide. Global coverage with the uptake of all 3 vaccines is estimated at 87% (54). Should the incidence of HCC decline, in the absence of a high-quality evidence base to support screening, then resource-limited healthcare programs may opt to allocate resources to higher impact evidence-based interventions for other conditions of importance to their population. Screening has the potential to have the greatest benefit in high-risk populations such as those with hepatitis B. There is a need for new effective evidence-based hepatocellular carcinoma screening methods and treatments to reduce disease burden in these high-risk populations.

Screening according to current guidelines also requires resource allocation for laboratory measurement and reporting of alpha-fetoprotein and radiology staffing and infrastructure to perform ultrasonography. Consideration should be given to the possibility that screening for HCC is potentially harmful to patients and consumes significant healthcare resources. Screening may even detract from other aspects of chronic liver disease care. In the absence of high-quality evidence evaluating adverse events and the psychosocial impact of screening for HCC, it may not be correct to advocate for screening on a population level. Current guidelines that recommend screening may even act as a deterrent to such a high quality randomized controlled trial being undertaken. A feasibility study in Australia found that 99.5% of people would not participate in a randomized controlled trial comparing screening for hepatocellular carcinoma to no screening. Of this 88 %

elected for a nonrandomized screening program (55). Notably in this study important information was omitted from the decision aid presented to patients. There was no mention of the potential for invasive investigations such as liver biopsy being performed based on the results of screening tests. There was no mention of the risks associated with invasive investigations such as liver biopsy. Only non-invasive further investigations such as CT or MRI were discussed. There was no discussion of the potential consequences of radiation exposure with CT or the consequences of finding radiological lesions elsewhere such as "incidentalomas". We feel the researchers also did not point out to patients the best available evidence on screening for hepatocellular carcinomas comes from the randomized controlled trial by Zhang et al (36) which, despite its limitations, did not find evidence that screening reduced all-cause mortality or HCC related mortality (when adjusted for clustering). We also feel the potential for negative psychosocial consequences with screening could have been discussed in greater detail. The provision of this information which is relevant when discussing the disadvantages of screening may have changed the outcome of the feasibility study.

Hepatocellular carcinoma is an important health problem globally with no curative treatment for those diagnosed with intermediate or late-stage tumors. If a curative treatment for HCC emerges then the question of whether screening should be performed deserves a large well-conducted randomized controlled trial to evaluate its effect on all-cause mortality, HCC related mortality, adverse events, quality of life and cost-effectiveness.

CONCLUSION

There is no evidence of effect from randomized controlled trials that screening for hepatocellular carcinoma reduces all-cause mortality, HCC related mortality or results in more HCCs being detected. There is a need for a high quality randomized controlled trial which should include adverse events and quality of life as outcomes.

Acknowledgments: None.

Funding: None.

Competing interests: The authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author), and declare no conflicts of interest.

Ethical approval: Not required because this was an analysis of secondary data.

Authorship contributions: JOC performed the systematic review design, search, data extraction, analysis and manuscript writing. SR performed data extraction, analysis, and manuscript writing.

REFERENCES

1 World Health Organisation International Agency for Research on Cancer GLOBOCAN 2012 Summary Statistic. Available: http://gco.iarc.fr/today/home. Accessed: 20 June 2019.

2 Bosch XF, Ribes J, Diaz M, Cleries R. Primary liver cancer: Worldwide incidence and trends. Gastroenterology. 2004;127(Suppl): S5-S16.

3 Ascha Mustafa S, Hanouneh Ibrahim A, Lopez Rocio, Tamimi Tarek Abu-Rajab, Feldstein Ariel F, Zein Nizar N. The incidence and risk factors of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. Hepatology. 2010;516:1972-8.

4 Gomaa I, Khan A, Toledano B, Waked I, Taylor-Robinson D. Hepatocellular carcinoma: Epidemiology, risk factors and pathogenesis. World Journal of Gastroenterology. 2008;14:4300-8.

5 El-Serag Hashem B. Epidemiology of viral hepatitis and hepatocellular Carcinoma. Gastroenterology 2012;142:1264-1273.e1.

6 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. Gastroenterology 2004;127(5, Supplement 1):S35-50.

7 Centre for Disease Control, Surveillance for Viral Hepatitis, United States in 2016. Available: https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm. Accessed: 20 June 2019.

8 Zheng R, Qu C, Zhang S, Zeng H, Sun K, Gu X et al. Liver cancer incidence and mortality in China: Temporal trends and projections to 2030. Chin J Cancer Res. 2018;30:571-79.

9 Yang JD, Altekruse S, Nguyen MH, Gores GJ, Roberts LR.. Impact of country of birth on the age of diagnosis of hepatocellular carcinoma in the United States. Cancer. 2017;123:81-89.

10 European Association for The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. Hepatol. 2012;56:908-43.

11 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907-17.

12 Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. J Gastrointest Surg. 2005;9:1207-15.

13 Doyle MB, Vachharajani N, Maynard E, Shenoy S, Anderson C, Wellen JR, Lowell JA, Chapman WC. Liver transplantation for hepatocellular carcinoma: long-term results suggest excellent outcomes. J Am Coll Surg. 2012;215:19-28.

14 Zaman SN, Johnson PJ, Williams R. Silent cirrhosis in patients with hepatocellular carcinoma. Implications for screening in high-incidence and low-incidence areas. Cancer. 1990;65:1607-10.

15 Boyum JH, Atwell TD, Schmit GD, Poterucha JJ, Schleck CD, Harmsen WS, Kamath PS. Incidence and risk factors for adverse events related to image-guided liver biopsy. Mayo Clin Proc. 2016;91:329-35.

16 Heleno B, Thomsen MF, Rodrigues DS, Jørgensen KJ, Brodersen J. Quantification of harms in cancer screening trials: literature review. BMJ. 2013 Sep 16;347:f5334.

17 Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut. 2001;48:251-9.

18 Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnù L, Zoli M et al Italian Liver Cancer Group. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol. 2002;97:734-44.

19 Wong GL, Wong VW, Tan GM, Ip KI, Lai WK, Li YW et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. Liver Int. 2008;28:79-87.

20 Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50, recommendation 1.2.4. Available: https://www.nice.org.uk/guidance/ng50. Accessed: 21 June 2019.

21 Hepatitis B (chronic): diagnosis and management (2013) NICE guideline CG165, recommendation 1.7.1. Available: https://www.nice.org.uk/guidance/cg165. Accessed: 21 June 2019.

22 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS et al Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723-50.

23 Expert Panel on Gastrointestinal Imaging: Horowitz JM, Kamel IR, Arif-Tiwari H, Asrani SK, Hindman NM, Kaur H, McNamara MM, Noto RB, Qayyum A, Lalani T. ACR Appropriateness Criteria(®) Chronic Liver Disease. J Am Coll Radiol. 2017Nov;14(11S):S391-S405.

24 APASL Guidelines for HCC. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11: 317-70.

25 European Association for the Study of the Liver. Electronic address:easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines:

Management of hepatocellular carcinoma. J Hepatol. 2018;69:182-236. Erratumin: J Hepatol. 2019;70:817.

26 Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y et al Liver Cancer Study Group of Japan. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014;3:458-68.

27 Méndez-Sánchez N, Ridruejo E, Alves de Mattos A, Chávez-Tapia NC, Zapata R, Paraná R et al. Latin American Association for the Study of the Liver (LAASL) clinical practice guidelines: management of hepatocellular carcinoma. Ann Hepatol. 2014;13 Suppl 1:S4-40.

28 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. Int Dig Health Legis. 1997;48:231-4.

29 Cochrane Handbook for Systematic Reviews of Interventions, Part 2: General Methods for Cochrane Reviews, 6.2.1.1 Bibliographic databases- general introduction. Available: https://handbook-5-1.cochrane.org/chapter_6/6_2_1_1_bibliographic_databases_-_general_introduction.htm. Accessed: 22 June 2019.

30 Higgins Julian P T, Altman Douglas G, Gøtzsche Peter C, Jüni P, Moher D, Oxman Andrew D, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials BMJ 2011;343:d5928.

31 McKenzie J, Ryan R, Di Tanna GL Cochrane Consumers and Communication Review Group: Cluster randomized controlled trials. December 2016. https://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/clusterrcts_revising_december_1st.pdf Accessed July 20th 2018

32 Campbell M, Grimshaw J, Steen N. Sample Size Calculations for Cluster Randomised Trials. Journal of Health Services Research & Policy. 2000;5:12-6.

33 The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

34 Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading the quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available: guidelinedevelopment.org/handbook. Accessed: July 20th 2018

35 GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available: gradepro.org. Accessed: July 20th 2018

36 Zhang B, Yang B, Tang Z. Randomized controlled trial of screening for hepatocellular carcinoma. Journal of Cancer Research & Clinical Oncology. 2004;130:417-22.

37 Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, et al. Screening for liver cancer: results of a randomized controlled trial in Qidong, China. Journal of Medical Screening. 2003;10:204-9.35.

38 Pocha C, Dieperink E, McMaken Ka, Knott A, Thuras P, Ho Sb. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography -- a randomized study. Alimentary Pharmacology and Therapeutics. 2013;38:303-12.

39 Sherman M, Peltekian Km, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology. 1995;22:432-8.

40 Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3- and 6-month periodicities. Hepatobillary Malignancies. 2011;54:1987-1997.

41 Wang JH, Chang KC, KeeKM, et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in the community. The American Journal of Gastroenterology. 2013;108:416-424.

42 Kim H, Kim K, Choi J., et al. Comparison of biannual ultrasonography and annual non-contrast liver magnetic resonance imaging as surveillance tools for hepatocellular carcinoma

in patients with liver cirrhosis (MAGNUS-HCC): a study protocol. BMC Cancer 2017. Ovid;17:1471-2407.

43 Kudo, M, Ueshima, K, Osaki, Y, et al. B-mode ultrasonography versus contrast-enhanced ultrasonography for surveillance of hepatocellular carcinoma: a prospective multicenter randomized controlled trial [2013]. Hepatology1(64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013. Washington, DC United States. Conference Publication):289A.

44 Miller Z A, Lee KS. Screening for hepatocellular carcinoma in high-risk populations. Clinical Imaging. 2016. 40:311-14.

45 Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet. 2001 357:196-97.

46 Noda I, Kitamoto M, Nakahara H, Hayashi R, Okimoto T, Monzen Y et al. Regular surveillance by imaging for early detection and better prognosis of hepatocellular carcinoma in patients infected with hepatitis C virus. Journal of Gastroenterology 2010 Ovid;45:105-12.

47 Saab, S. Liver cancer screening in a high-risk population in China fails to reduce mortality. Evidence-Based Healthcare. 2004;8:221-23.

48 Park MS, Park J, Lee S, et al. Contrast (Sonzoid)-enhanced US as a screening tool for hepatocellular carcinoma in cirrhosis: An exploratory clinical trial (Scan trial). Journal of Hepatology. 2015;62:5851.

49 Stahl-Timmins W. Graphical Overview for Evidence Reviews (GOfER). School of Medicine, University of Exeter; 2011.

50 Trevisani F, Cantarini MC, Labate AM, De Notariis S, Rapaccini G, Farinati F et al. Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effects on cancer staging and patient survival. American Journal of Gastroenterology. 2004;99:1470-76.

51 Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnu L et al. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? American Journal of Gastroenterology. 2007;102:2448-57.

52 Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. Journal of Hepatology. 2010;53:291-97.

53 Aghoram R, Cai P, Dickinson JA. Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B. Cochrane Database of Systematic Reviews. 2012;9:CD002799.

54 World Health Organisation, Global Vaccine Action Plan Secretariat Annual Report 2017, Page 64. Available: https://www.who.int/immunization/global_vaccine_action_plan/web_regional_gvap_reports_2017.pdf?ua=1. Accessed: 22 June 2019.

55 Poustchi H, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J. Feasibility of conducting a randomized control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed? Hepatology. 2011;54:1998-2004.

Table 1. Summary of current HCC screening guidelines

Guideline	Year of Publication	Recommendation
NICE (20,21)	2016	Ultrasound screening every 6 months for adults with cirrhosis Ultrasound screening every 6 months with alpha-fetoprotein measurement for adults with chronic hepatitis B

AASLD (22)	2018	Ultrasound with or without AFP every 6 months
ACR (23)	2017	Ultrasound recommended except in subgroups with technical limitations where CT or MRI is recommended (eg, obesity, fatty liver, nodular cirrhotic liver)
APASL (24)	2017	Ultrasound and AFP every 6 months AFP alone not recommended
EASL (25)	2018	Ultrasound every 6 months No recommendation for AFP
JSH (26)	2014	Extremely high-risk patients: ultrasound every 3-4 months, AFP every 3-4 months, Computed tomography/magnetic resonance imaging (optional) every 6-12 months High risk: ultrasound and AFP every 6 months
LAASL (27)	2014	In cirrhotic patients ultrasound should be performed every 6 months If quality ultrasound is not available, AFP level may be considered as a biomarker

NICE - National Institute of Clinical Excellence, AASLD - American Association for the Study of Liver Diseases, ACR - American College of Radiology, Asian Pacific Association for the Study of the Liver, European Association for the Study of

the Liver, JSH - Japan Society of Hepatology, LAASL - Latin American Association for the Study of the Liver. AFP - Alpha-fetoprotein

Table 2. Included studies

Study	Year of Publication	Study design	Country	Patients	Comparison	Outcomes
Zhang et al[36]	2004	Cluster randomized controlled trial	China	Aged 35-59 years with hepatitis B virus infection or a history of chronic hepatitis	Alpha-fetoprotein and ultrasound every 6 months versus no screening	Number of HCC detected, HCC related mortality, 5-year survival
Chen et al[37]	2003	Cluster randomized controlled trial	China	Men aged 30-69 who were chronic carriers of the hepatitis-B virus during the period 1989-1995	Alpha-fetoprotein every 6 months versus no screening	Number of HCC detected, HCC related mortality and all-cause mortality
Pocha et al[38]	2013	Randomised controlled trial	United States of America	Patients aged 18-70. Child's A cirrhosis, documented	Ultrasound and alpha-fetoprotein every 6	Number of HCC detected, HCC

				cirrhosis, potential candidates for HCC treatment if diagnosed	months versus annual CT plus alpha-fetoprotein every 6 months	related mortality and all-cause mortality
Sherman et al[39]	1995	Randomised controlled trial	Canada	Aged over 18 years old and hepatitis B surface antigen-positive for more than 6 months	Serial alpha-fetoprotein alone every 6 months versus alpha-fetoprotein in combination with ultrasound every 6 months	Incidence of HCC is reported but not reported separately for each arm of the study
Trinchet et al[40]	2011	Cluster randomized controlled trial	France	Adults aged 18 years or older, histologically proven cirrhosis related to hepatitis B, hepatitis C,	Ultrasound every 3-months versus ultrasound every 6-	Number of HCC detected, all-cause mortality, HCC

				alcohol or hereditary hemochromatosis, Child-Pugh A or B	months	related mortality, 5-year survival
Wang et al[41]	2013	Cluster randomized controlled trial	Taiwan	Adults aged 40 years or older, platelets less than or equal to 150x 10^9/L, positive hepatitis B surface antigen or positive hepatitis C antibody	Ultrasound every 4-months versus ultrasound every 12-months	Number of HCC detected, tumor size, 4-year survival

HCC – Hepatocellular carcinoma CT- Computed tomography

Table 3. Risk of bias assessment

Bias	**Zhang et al[36]**	**Chen et al[37]**	**Pocha et al[38]**	**Sherman et al[39]**	**Trinchet et al[40]**	**Wang et al[41]**
Random sequence generation (selection bias)	Unclear risk	Low risk	Low risk. A computer-generated random number list was used to allocate and randomize subjects	Unclear risk	Low risk. Randomization was computer-generated, a permuted block design was used	Unclear risk
Allocation concealment (selection bias)	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*	Low risk. Allocation was concealed using a centralized phone procedure to	Unclear risk*

					the data-management center.	
Blinding of participants and personnel (performance bias)	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*
Bias	**Zhang et al[36]**	**Chen et al[37]**	**Pocha et al[38]**	**Sherman et al[39]**	**Trinchet et al[40]**	**Wang et al[41]**
Blinding of outcome assessment (detection bias)	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*	Unclear risk*	High risk Outcome assessors not blinded
Incomplete outcome data (attrition bias)	Unclear risk*	High risk. In the screening group, 400 subjects (10.8%) were tested at enrolment only and did not attend for further screening. It is unclear how these were followed up.	High risk. There were post-randomization drop-outs. Non-liver related death (6), Non-adherence to the protocol (12), withdrew from participation (8), followed by transplant center (10), others (8)	High risk. 72 subjects did not return for the first follow up screening visit. During the study period, an additional 182 subjects withdrew from the screening program having completed at least one follow up visit.	High risk. Compliance was estimated as inadequate in 143 (11.9%) of patients.	Unclear risk*
Selective reporting (reporting bias)	High risk- different reports of this study exist. All-cause mortality	Low risk. Detection rates, the characteristics of the screening test and the	Low risk. Most important outcomes were reported	Low risk. No reporting of all-cause mortality and disease-specific mortality in	Low risk. Most important outcomes were reported	High risk. Did not report on all-cause mortality or disease-

	not reported.	outcome with respect to incidence, stage, survival and mortality in the screened and control group were reported.		individual arms however the authors state the study was not designed or powered to detect these outcomes, it was designed as a feasibility study.		specific mortality
Bias	**Zhang et al[36]**	**Chen et al[37]**	**Pocha et al[38]**	**Sherman et al[39]**	**Trinchet et al[40]**	**Wang et al[41]**
Other bias	High risk. Follow up in the control and screening group was not the same.	High risk. Alpha-fetoprotein testing performed using RPHA method which has a low sensitivity for detecting HCC.		High risk. Supported by a grant from Schering Canada Inc. Contained patients enrolled from hospitals and the community of unclear proportions.		

HCC – Hepatoceullar carcinoma RPHA= Reversed passive hemagglutination assay

*Unclear risk stated when information to judge the risk of bias was not available in the report.

Correspondence to:

Dr. James O'Connell, MB BCh BAO, MSc

Department of International Health and Tropical Medicine

Beaux Lane House

Lower Mercer Street

Dublin 2

Dublin

Ireland

jamesoconnell@rcsi.com

Figures

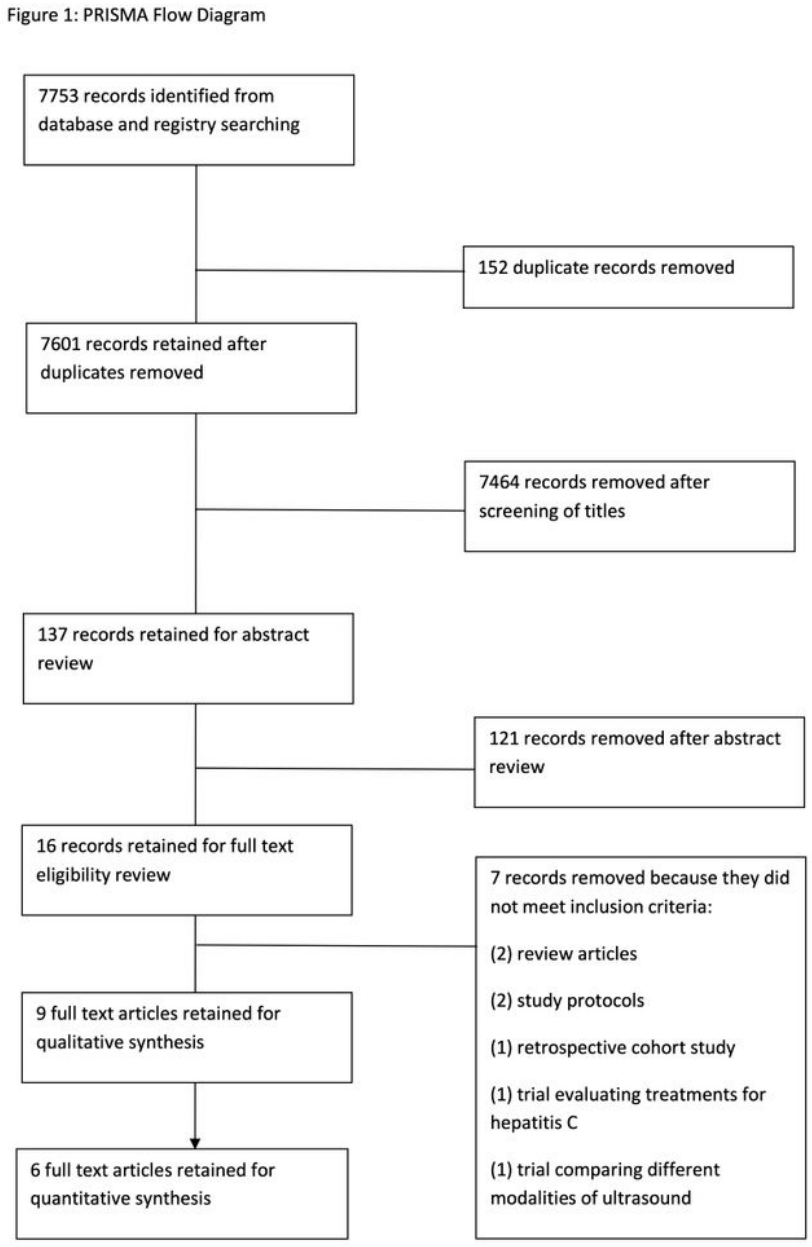
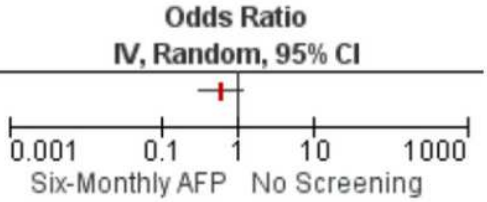


Figure 1

PRISMA Flow DIagram

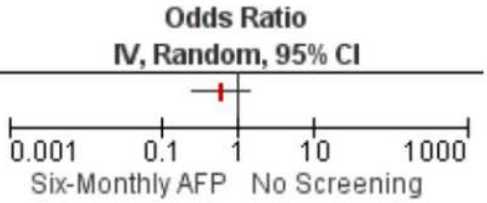
a) Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.1 Mortality due to Hepatocellular Carcinoma (ICC=0.02).

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Zhang 2004	-0.511	0.33		0.60 [0.31, 1.15]



b) Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.2 Mortality due to Hepatocellular Carcinoma (ICC=0.05).

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Zhang 2004	-0.511	0.45		0.60 [0.25, 1.45]



c) Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.3 Mortality due to Hepatocellular Carcinoma (ICC=O.1).

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Zhang 2004	-0.511	0.6		0.60 [0.19, 1.94]

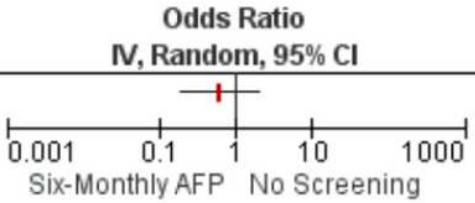


Figure 2

Forest Plots

Supplementary Files

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