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Benefits and harms of screening for hepatocellular carcinoma in high-risk populations: systematic review and meta-analysis

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ABSTRACT

Objective: The incidence and mortality of hepatocellular carcinoma (HCC) have been increasing around the world. Current guidelines recommend HCC screening in high-risk population. However, the strength of evidence of benefits and harms of HCC screening to support the recommendation was unclear. The objective is to systematically synthesize current evidence on the benefits and harms of HCC screening.

Methods: We searched PubMed and nine other databases until August 20, 2021. We included cohort studies and RCTs that compared the benefits and harms of screening and non-screening in high-risk population of HCC. Case series studies that reported harms of HCC screening were also included. Pooled risk ratio (RR), according to HCC screening status, was calculated for each benefit outcome (e.g., HCC mortality, survival rate, proportion of early HCC), using head-to-head meta-analysis. The harmful outcomes (e.g., proportion of physiological harms provided by non-comparative studies were pooled by prevalence of meta-analysis. Analysis on publication bias and quality of life, subgroup analysis, and sensitivity analysis were also conducted.

Results: We included 70 studies, including four random clinical trials (RCTs), 63 cohort studies,three case series studies. The meta-analysis of RCTs showed HCC screening was significantly associated with reduced HCC mortality (RR [risk ratio], 0.73 [95% CI, 0.56–0.96]; I^2 = 75.1%), prolonged overall survival rates (1-year, RR, 1.72 [95% CI, 1.13–2.61]; I^2 = 72.5%; 3-year, RR, 2.86 [95% CI, 1.78–4.58]; I^2 = 10.1%; and 5-year, RR, 2.76 [95% CI, 1.37–5.54]; I^2 = 28.3%), increased proportion of early HCC detection (RR, 2.68 [95% CI, 1.77–4.06]; I^2 = 50.4%). Similarly, meta-analysis of cohort studies indicated HCC screening was more effective than non-screening. However, pooled proportion of physiological harms was 16.30% (95% CI: 8.92%–23.67%) and most harms were of a mild to moderate severity.

Conclusion: The existing evidence suggests HCC screening is more effective than non-screening in high-risk population. However, harms of screening should not be ignored.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death in the world, with an estimated global incidence of HCC per 100,000 person-years of 9.3 and a corresponding mortality of 8.5 in 2018.[1] The incidences of HCC in high-rate areas such as Asia and Africa remain high, while the incidences in low-rate areas such as Europe and the United States have been increasing.[2] China has the greatest number of cases (incidence of 17.5 per 100,000) and the world's largest population (1.4 billion).[3] The total global disability adjusted life years (DALYs) of HCC increased from 13.31 million person-years in 1990 to 21.14 million person-years in 2016.[4]

The most common risk factors for HCC are infection with the Hepatitis B virus (HBV) or the Hepatitis C virus (HCV), excessive alcohol intake, obesity, type 2 diabetes, and aflatoxin.[2] Screening can help detect HCC at an early stage when it is amenable to curative therapy to reduce mortality.[5] Most current guidelines[6–8] recommend screening with ultrasound (US) with or without alpha-fetoprotein (AFP) every 6 months in high-risk population, i.e., those with HBV, HCV, and/or cirrhosis, as

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well as other chronic liver diseases. However, current guidelines only cite the Zhang 2004 trial[9] as the major source of evidence supporting the recommendations. The current guidelines do not rest on a systematic review of the current evidence or an evaluation of its strength.

The World Health Organization and American College of Physicians emphasize that "screening is not a single test but a comprehensive intervention with a cascade of subsequent events of either benefit or harm".[10,11] Benefits are only found for truly positive patients who can be treated at the early stages of the disease. In other cases, screening can lead to harm to patients and a waste of resources. To determine whether a screening program is worth implementing, it is necessary to identify the benefits of screening against their harms and costs. The prognosis of HCC depends on the tumor stage. Patients detected in early stages can have higher survival rates resulting from transplantation or resection. Regorafenib and trans-arterial radioembolization represent valuable and relatively safe therapeutic options in intermediate/advanced HCC, whereas more advanced cases have a median survival of less than 1 year and a 3-year survival rate of only 27%.[12,13] US and AFP are the most common screening modalities for HCC, and these have no direct physiological harm to patients and are of a relatively low cost.[6,8] It is suggested that screening for HCC may be beneficial, but the harms of HCC screening (e.g., unnecessary biopsies, radiation exposure, and physiological anxiety) should not be ignored.[5,10]

The U.S. Preventive Services Task Force (USPSTF) evaluated the benefits and harms of more than 10 kinds of evidence-based cancer screening by performing systematic reviews, such as lung, colorectal, and breast cancer screening,[14–16] but they did not examine HCC screening. On the other hand, there only have been three qualitative reviews and two meta-analyses of the benefits of HCC screening.[17–21] Two qualitative reviews published in 2003 and 2012 only summarized the random clinical trials (RCTs) of AFP and/or US for HCC screening in patients with HBV.[17,20] Another qualitative review published in 2014 only reviewed studies that evaluated the benefits of HCC screening in patients with chronic liver disease.[18] Only two meta-analyses have evaluated the benefits of HCC surveillance in patients with cirrhosis.[19,21] Therefore, we performed a systematic review and meta-analysis to comprehensively assess the benefits and harms of HCC screening in all high-risk populations.

2. Materials and methods

We conducted and report this systematic review following the recommendations of the PRISMA 2020 statement.

2.1. Protocol and registration

This review was prospectively registered on the PROSPERO website as No. CRD42020148258 (https://www.crd.york.ac.uk/prospero/).

2.2. Search strategy

PubMed, Embase, the Cochrane library, Clinicaltrials.gov, Web of Science, Google scholar, and Chinese databases (CNKI, WanFang, VIP, and SinoMed) were searched from their inception to October 31, 2019, and an updated search was conducted through August 20, 2021. We used the keywords "screening" and "hepatocellular carcinoma" to search for relevant studies. The details of the search strategy are shown in Supplementary Table 1. In addition, we manually searched the reference lists of relevant reviews.

2.3. Study selection

Two reviewers (JCY and SQY) independently screened the titles and abstracts of studies based on the predefined inclusion and exclusion criteria. The reviewers resolved any discrepancies through discussion or, if necessary, by seeking a decision from a third reviewer (FS or ZRY).

Studies were included if they met all of the following criteria: (i) study population including high-risk population of HCC (e.g., those with HBV, HCV, cirrhosis, and/or another chronic liver disease); (ii) interventions including screening modalities (e.g., AFP, US, CT, and MRI); (iii) comparators: non-screening; (iv) outcomes: benefits and/or harm outcomes (the outcomes of interest are listed below in Section 2.4); and (v) a study design in which the benefit outcomes were included in comparative studies (RCTs and cohort studies), and the harm outcomes were included in the comparative and non-comparative studies.

We excluded duplicate studies and studies in which outcome data were lacked or unavailable. Studies that compared different screening intervals or modalities were also excluded. If the same study was reported in more than one publication, we only included the most informative article or the longest follow-up study to avoid duplication of information.

2.4. Definition of outcomes

2.4.1. Outcomes of benefits

HCC mortality: This was the main benefit outcome, given that the goal of cancer screening is to reduce mortality. This is measured by the total number of deaths from HCC over a defined time interval (e.g., 1 year), divided by the number of people at risk for HCC in the population (screening population) during the same interval.[22]

Survival rate: the number of people diagnosed with HCC who are still alive, for example, 1, 3, and 5 years after diagnosis, divided by the total number of HCC at those time points.[22]

Proportion of early HCC: the total number of early HCC divided by the total number of HCC; this was the intermediate benefit outcome.

2.4.2. Outcomes of harms

Proportion of physiological harm: the number of people who suffer physiological harm from screening divided by the total screening population. Physiological harm is defined as any harm requiring subsequent follow-up testing related to false-positive or indeterminate screening results, which can be classified as mild (one diagnostic CT or MRI), moderate (multiple CT and/or MRI exams), or severe (any invasive evaluation, such as a biopsy or angiogram).[23]

Proportion of psychological harm: the number of people who suffer psychological harm divided by the total screening population. Psychological harm includes any psychological problems (e.g., anxiety, psychological distress, and psychological anxiety) developed in response to positive screening results.[16]

2.5. Data extraction

The following information was extracted from each eligible study: basic information (first author, year of publication), population characteristics, screening modalities, screening intervals, benefits outcomes, harms outcomes, and study design. Two groups of reviewers (JCY with SQY and XYZ with LG) independently extracted data from the selected studies. The reviewers resolved any discrepancy through discussion or, if necessary, by seeking a decision from a third reviewer (FS or ZRY).

2.6. Assessment of risk of bias

Cochrane's tool for assessing risk of bias in randomized trials (CROB) was used to assess the risk of bias of RCTs based on seven domains.[24] If studies were rated as low risk of bias in at least four domains, it would be of moderate to high quality. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies.[25] Each study was assigned from 0 to 9 stars across three domains: selection (0–4), comparability (0–2), and outcome (0–3). Studies with at least 6 stars were considered to be of moderate to high quality. We assessed case series studies with the National Institute for Clinical Excellence criteria (NICE).[26] Each item was assigned a score of 1 (yes) or 0 (no), and the scores were summed

across items to generate an overall study quality score. Studies with a quality score of at least 4 points were considered moderate to high quality. The reviewers resolved any discrepancy through discussion or, if necessary, by seeking a decision from a third reviewer (FS or ZRY).

2.7. Data synthesis and statistical analysis

2.7.1. Data synthesis

STATA software version 15.0 (StataCorp LP, College Station, TX) was used for all statistical analyses and to generate forest plots. We pooled results separately for RCTs and observational studies, as those studies are designed differently. Pooled risk ratios (RRs) according to HCC screening status were calculated for each benefit outcome (e.g., HCC mortality, survival rate, proportion of early HCC), using a random effects model of head-to-head meta-analysis. Harms outcomes (e.g., proportions of physiological and psychological harm) were provided by non-comparative studies and were pooled by prevalence of meta-analysis. The threshold for statistical significance was defined as $P < 0.05$. Heterogeneity was assessed with the chi-square test using Cochrane's Q statistic and was quantified using I^2 values.

2.7.2. Assessment of publication bias

For the symmetry of funnel plots, Egger's test was used to evaluate the presence of publication bias when 10 or more studies were available, and $P < 0.05$ was considered indicative of statistically significant publication bias.

2.7.3. Subgroup analyses

We performed pre-planned subgroup analyses according to screening modalities, screening population, screening intervals, whether the included studies adjusted lead-time bias, location of study, study period, proportion of Child Pugh C, and mean age of population to explore potential sources of heterogeneity.[27]

2.7.4. Sensitivity analysis

We performed a sensitivity analysis by excluding studies with high risk of bias.

2.8. Rating the quality of evidence

Two reviewers (JCY and SQY) independently rated the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The reviewers resolved any discrepancies through discussion, if necessary, or by seeking a decision from a third reviewer (FS or ZRY). Based on the GRADE guideline, we downgraded the quality of evidence based on five dimensions (limitation, inconsistency, indirections, imprecision, and reporting bias) for RCTs and observational studies, and we only upgraded the quality of evidence on three dimensions (large effect, plausible confounding, and dose response) for observational studies.[28]

3. Results

3.1. Literature search

The inclusion process is presented in the PRISMA diagram shown in Fig. 1. The database and manual searches yielded 7846 potentially relevant records. After abstracts and full texts were screened, 70 studies[9,23,29–96] were ultimately included in the meta-analysis.

3.2. Characteristics of included studies

The characteristics of the included studies are summarized in Supplementary Table 2. All of the studies were published between 1990 and 2021. Four RCTs compared benefits outcomes in the HCC screening and non-screening groups. In all, 63 cohort studies compared benefits outcomes in the HCC screening and non-screening group; however, only 5 cohort studies[34,68,83,91,96] provided the size of the screening population. Therefore, the total size of the screening population of cohort studies could not be obtained. In addition, three case series studies and one cohort study reported harms outcomes of HCC screening.

In addition, all RCTs had high risk of bias. However, only 11 cohort studies had high risk of bias. The three case series studies had low risk of bias. Details of the risk of bias assessment are presented in Supplementary Table 3–5.

3.3. Benefits of HCC screening

3.3.1. HCC mortality

As shown in Fig. 2, three RCTs[9,35,88] and three cohort studies[34,68,91] compared HCC mortality with and without screening. The meta-analysis of these RCTs (with 31,051 members of the screened population vs. 61,856 members of the population that were not screened) indicated that HCC mortality was significantly lower in the screened group (RR, 0.73 [95% CI, 0.56–0.96]; I^2 = 75.1%). For the cohort studies (with 16,723 screened vs. 5365 not screened), meta-analysis of these cohort studies showed HCC mortality was significantly lower in the screened group (RR, 0.53 [95% CI, 0.36–0.78]; I^2 = 8.1%). Because only three RCTs and cohort studies reported HCC mortality, subgroup, sensitivity, publication bias analyses were not conducted.

3.3.2. Survival rates

As shown in Supplementary Table 2, four RCTs and 47 cohort studies were included to assess overall survival in patients with screen-detected HCC versus those with HCC presenting symptomatically or who were diagnosed incidentally instead of being detected through screening. Most included studies have reported 1-, 3-, and 5-year survival rates, so these survival rates were used for the analysis.

As shown in Fig. 3, head-to-head meta-analyses of three RCTs (451 vs. 228 HCC patients) and 22 cohort studies (2714 vs. 3753 HCC patients) provided pooled 1-year survival rates in screen-detected HCC that were higher than those in the non-screening group, with the pooled RR being 1.72 (95% CI, 1.13–2.61; I^2 = 72.5%) and 1.47 (95% CI, 1.35–1.59; I^2 = 58.9%), respectively. In addition, subgroup analysis showed that the pooled 1-year survival rates differed according to screening intervals, adjusted for lead-time bias and study period. No significant differences were observed in the other subgroups, and the details are shown in Supplementary Table 6.

As shown in Fig. 4, head-to-head meta-analyses of three RCTs (435 vs. 218 HCC patients) and 26 cohort studies (5499 vs. 6064 HCC patients) suggested that the pooled 3-year survival rates for screen-detected HCC were higher than those in the non-screening group, with the pooled RR being 2.86 (95% CI, 1.78–4.58; I^2 = 10.1%) and 1.58 (95% CI, 1.42–1.76; I^2 = 68.9%), respectively. In addition, subgroup analysis showed that pooled 3-year survival rates differed after adjusting for lead-time bias and mean age No significant differences were observed in the other subgroups, and the details are shown in Supplementary Table 7.

As shown in Fig. 5, head-to-head meta-analyses of three RCTs (435 vs. 218 HCC patients) and 12 cohort studies (2886 vs. 3050 HCC patients) suggested that the pooled 5-year survival rates for screen-detected HCC were higher than those in the non-screening group, with the pooled RR being 2.76 (95% CI, 1.37–5.54; I^2 = 28.3%) and 1.62 (95% CI, 1.47–1.79; I^2 = 14.0%), respectively. No significant differences were observed in the subgroups, and the details are shown in Supplementary Table 8.

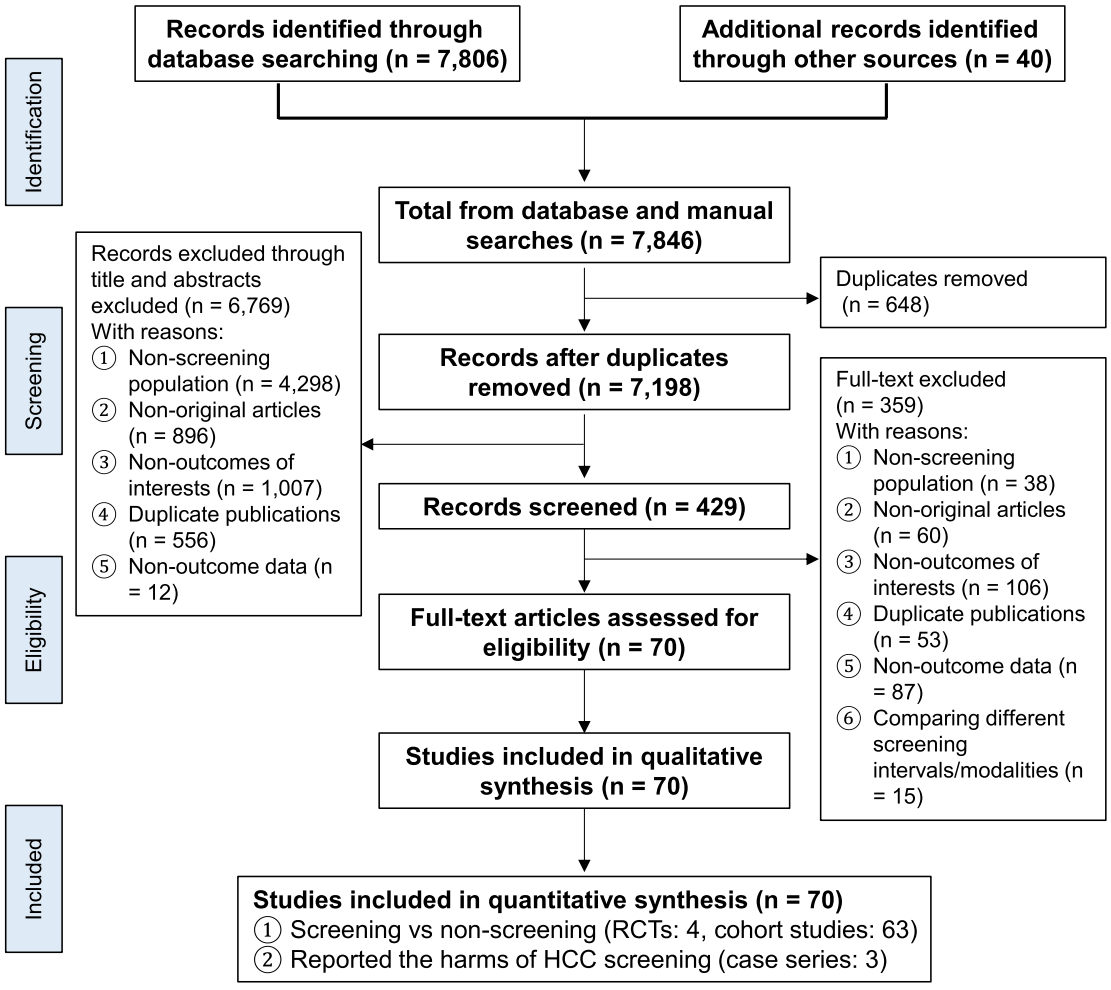

Fig. 1. PRISMA flowchart of included studies. RCT, randomized controlled trial.

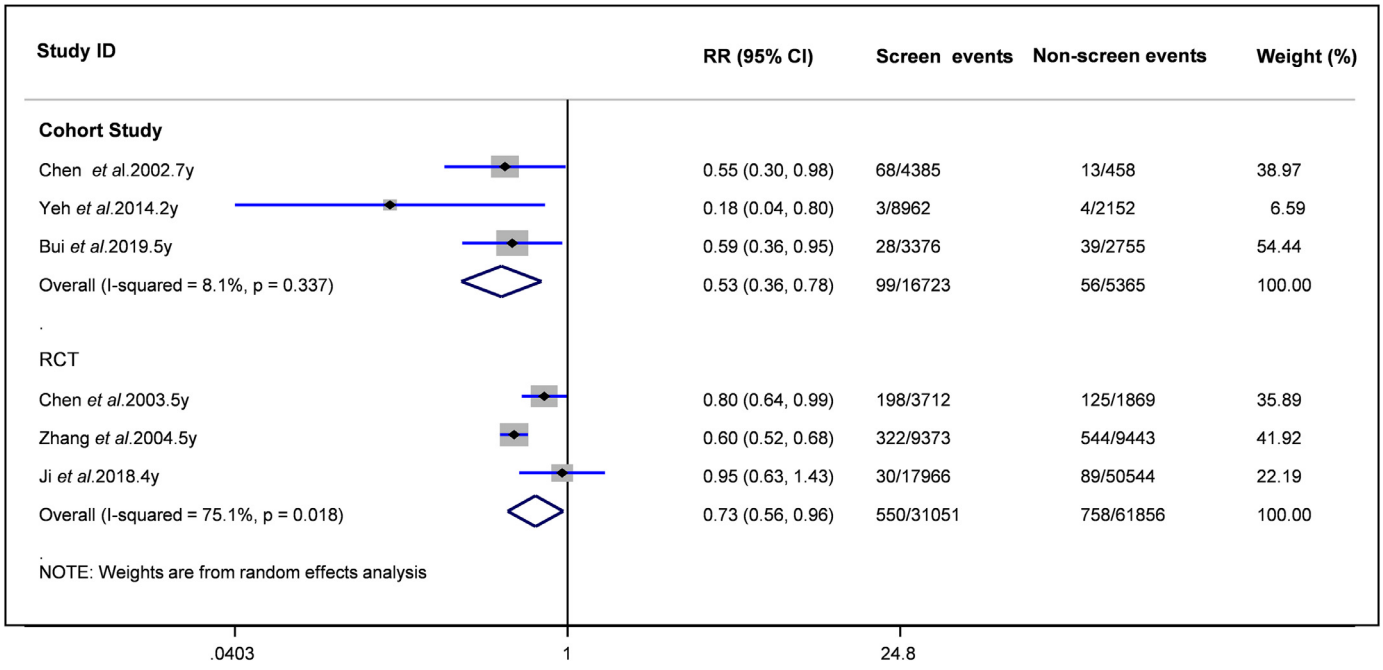

Fig. 2. Comparison of hepatocellular carcinoma mortality between the screening group and the non-screening. CI, confidence interval; RCT, random clinical trail; RR, risk ratio; Y, years.

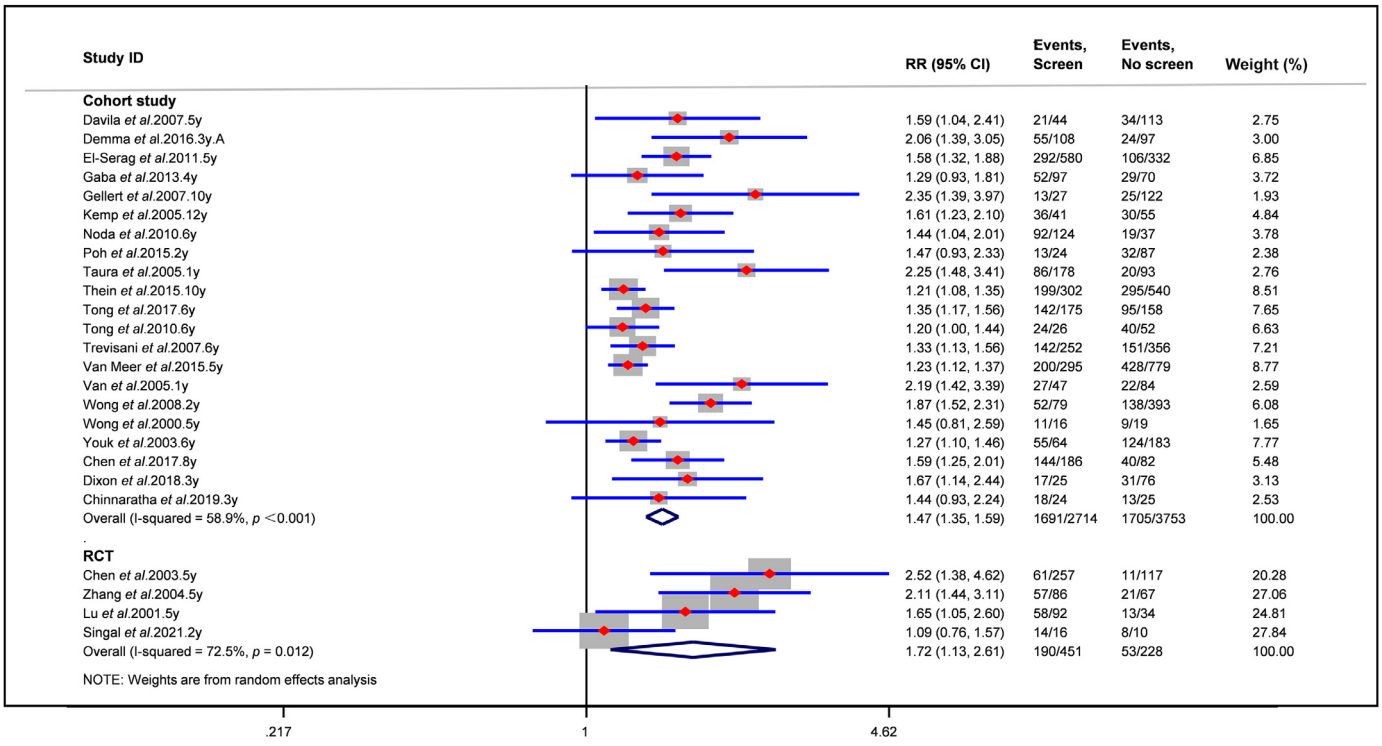

Fig. 3. Comparison of 1-year survival rates between the screening group and the non-screening. CI, confidence interval; RCT, random clinical trail; RR, risk ratio; Y, years.

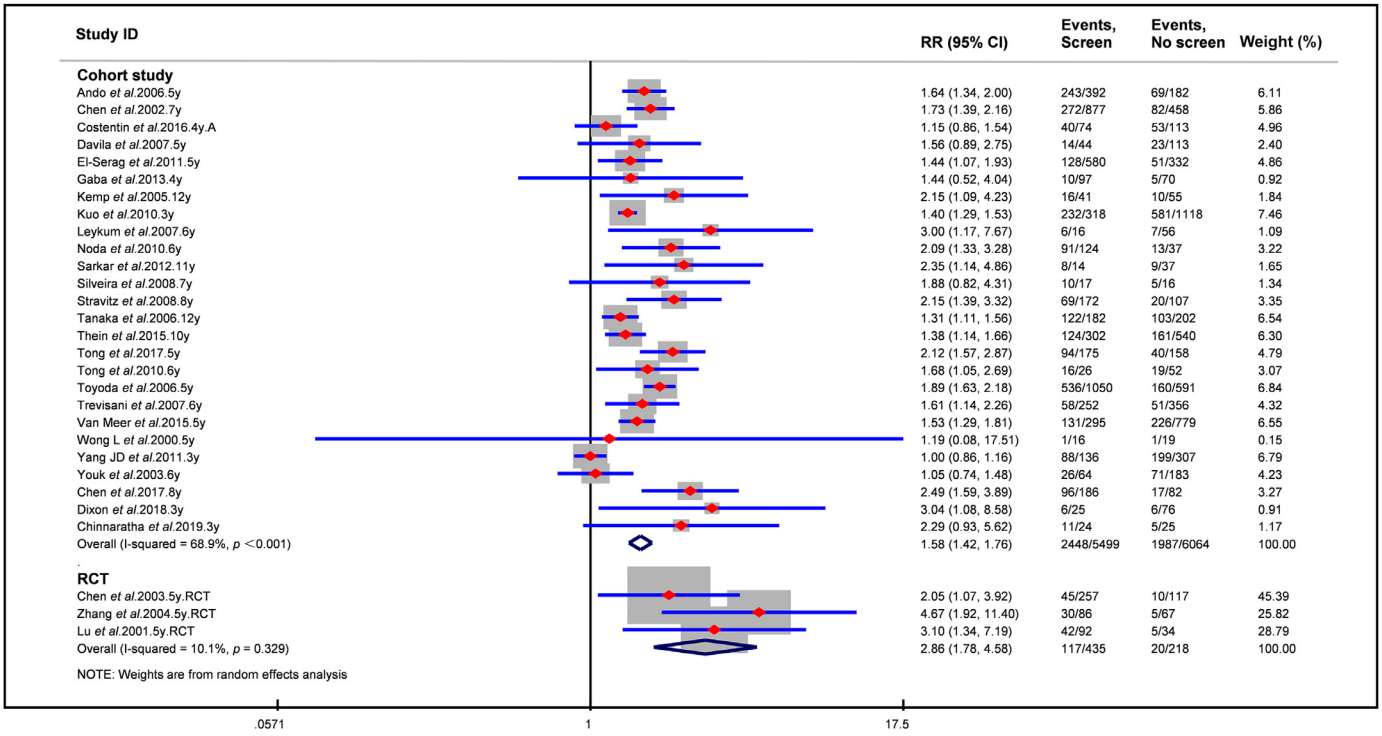

Fig. 4. Comparison of 3-year survival rates between the screening group and the non-screening. CI, confidence interval; RCT, random clinical trail; RR, risk ratio; Y, years.

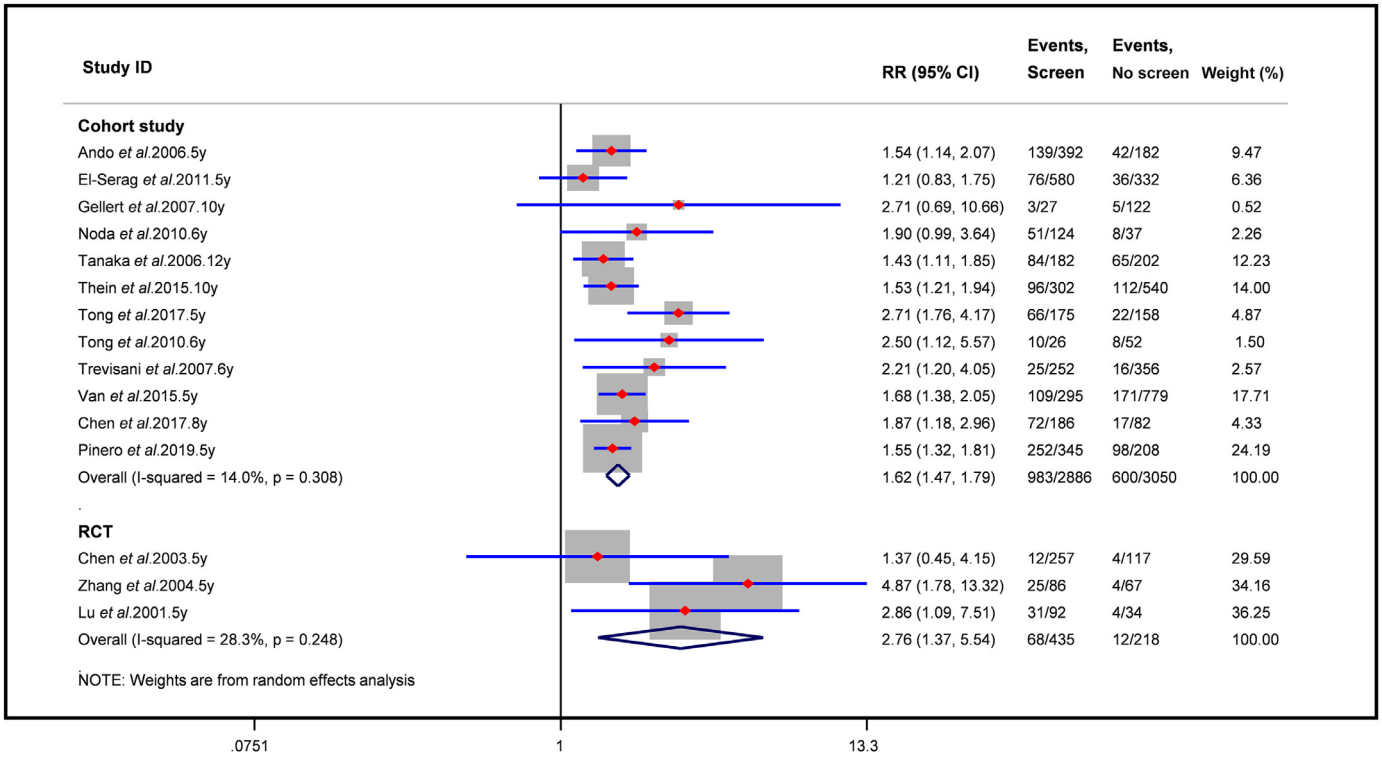

Fig. 5. Comparison of 5-year survival rates between the screening group and the non-screening. CI, confidence interval; RCT, random clinical trail; RR, risk ratio; Y, years.

3.4. Benefits of HCC screening: proportion of early HCC

As presented in Fig. 6, four RCTs (492 vs. 322 HCC patients) and 50 cohort studies (9908 vs. 12,433 HCC patients) investigated the proportion of early HCC in the screening versus the no-screening group. A meta-analysis of the RCTs ((RR, 2.68 [95% CI, 1.77–4.06]; $I^2 = 50.4\%$) and cohort studies ((RR, 2.16 [95% CI, 2.00–2.34]; $I^2 = 81.9\%$) indicated that patients who underwent screening were significantly more likely to have their HCC found in an early stage. The results of subgroup analysis suggest that mean age of HCC may affect the association. No significant differences were observed in the other subgroups, and the details are shown in Supplementary Table 9.

3.5. Harms of HCC screening: proportion of physiological harm

No previous studies have reported or quantified the proportion of psychological harm caused by HCC screening. Three case series studies[23,70,94] and one cohort study[96] reported the proportion of physiological harm. The cohort study compared the benefits outcomes of the screening versus the non-screening group and reported the proportion of physiological harm in the screening group. Therefore, four studies evaluated the physiological harm caused by HCC screening in 2578 cirrhosis studies where participants underwent at least one AFP or US screening. After 2 or 3 years of follow-up, the proportion of physiological harm in the screening population was calculated.

The results of meta-analysis are shown in Fig. 7. The pooled proportion of physiological harm was 16.30% (95% CI, 8.92%–23.67%). However, there was significant heterogeneity among the included studies ($I^2 = 95.7\%$, $P < 0.01$). Because only study location and years of follow-up differed among the included studies, we conducted subgroup analyses based on study location and years of follow-up as grouping factors. The heterogeneity was slightly reduced by the subgroup analysis using years of follow-up while using location of study did not change. This suggests that years of follow-up may influence the proportion of physiological harm.

In addition, three of four included studies classified the severity of physiological harm, so we also pooled the proportion of mild (10.88% [95% CI, 5.80%–15.95%]), moderate (6.32% [95% CI, 0.82%–11.83%]), and severe physiological harm (0.31% [95% CI, 0.08%–0.54%]) based on those three studies (Fig. 8).

3.6. Sensitivity analyses

As shown in Supplementary Table 10, no significant change was seen in the results before and after the exclusion of studies with high risk of bias.

3.7. Publication bias

As shown in Supplementary Fig. 1–4, the funnel plot analysis of publication bias suggests that there was potential publication bias in 1-year survival rates and proportion of early HCC. No significant publication bias was observed in 3- and 5-year survival rates.

3.8. Quality of evidence

As shown in Supplementary Table 11, the quality of evidence was very low for each benefit outcome according to GRADE guidelines. GRADE is only used to rate the quality of pooled evidence from comparative studies such as RCTs and cohort studies, while the proportion of physiological harm was provided by non-comparative studies. Therefore, the proportion was not evaluated using GRADE. However, there is

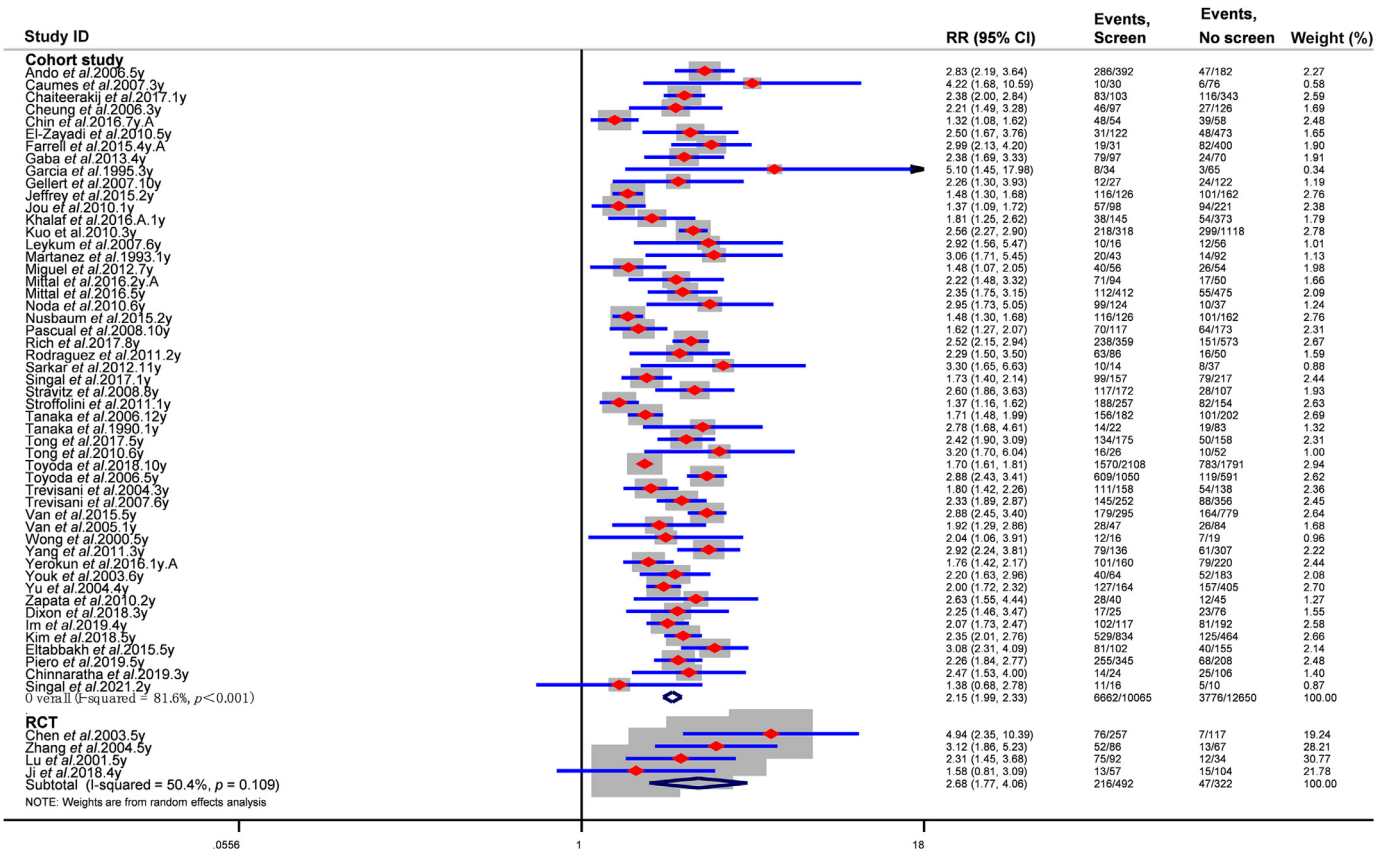

Fig. 6. Comparison of proportion of early hepatocellular carcinoma between the screening group and the non-screening. CI, confidence interval; RCT, random clinical trail; RR, risk ratio; Y, years.

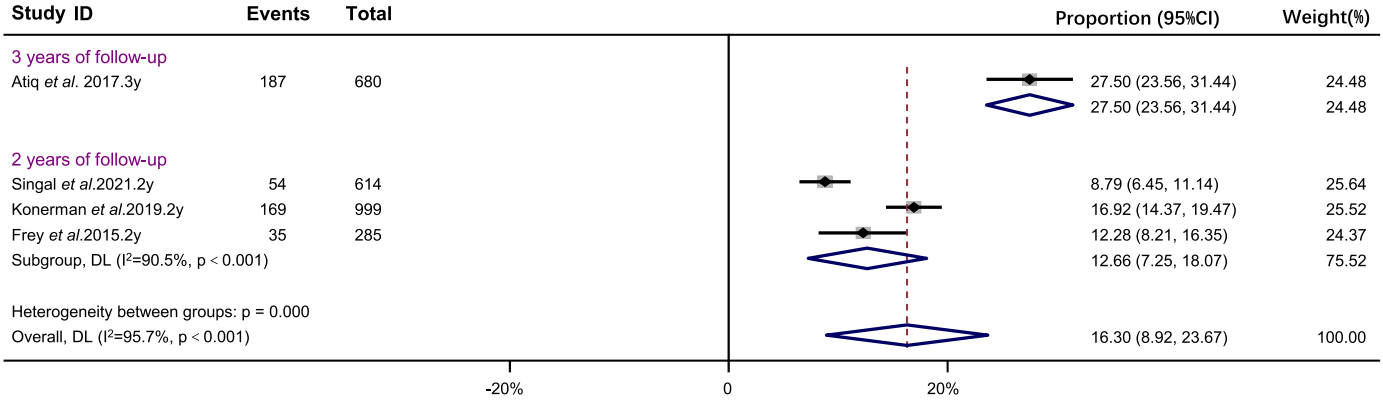

Fig. 7. Pooled proportion of physiological harm. CI, confidence interval; DL, discrete logarithm; RCT, random clinical trail; USA, the United States of America; Y, years.

a great heterogeneity in pooled proportion of physiological harm. Therefore it is necessary to be cautious in quoting it.

4. Discussion

4.1. Benefits of HCC screening versus non-screening

In this meta-analysis, evidence from RCTs indicated that HCC screening reduced HCC mortality by 47%, prolonged overall survival regardless of length of follow-up, and increased the proportion of early HCC. Similarly, meta-analyses of cohort studies have indicated that HCC screening is more effective than non-screening. The strength of evidence of all outcomes was very low. Subgroup analysis indicated that the benefits of screening may differ according to screening intervals, adjusting for lead time bias, location of study, and mean age.

One meta-analysis, published by Singal et al. in 2014, conducted a systematic review to quantitatively evaluate the benefits of HCC screening.[19] It included 47 observational studies that compared the proportion of early HCC (odds ratio [OR], 2.08 [95% CI, 1.80–2.52]) and 3-year

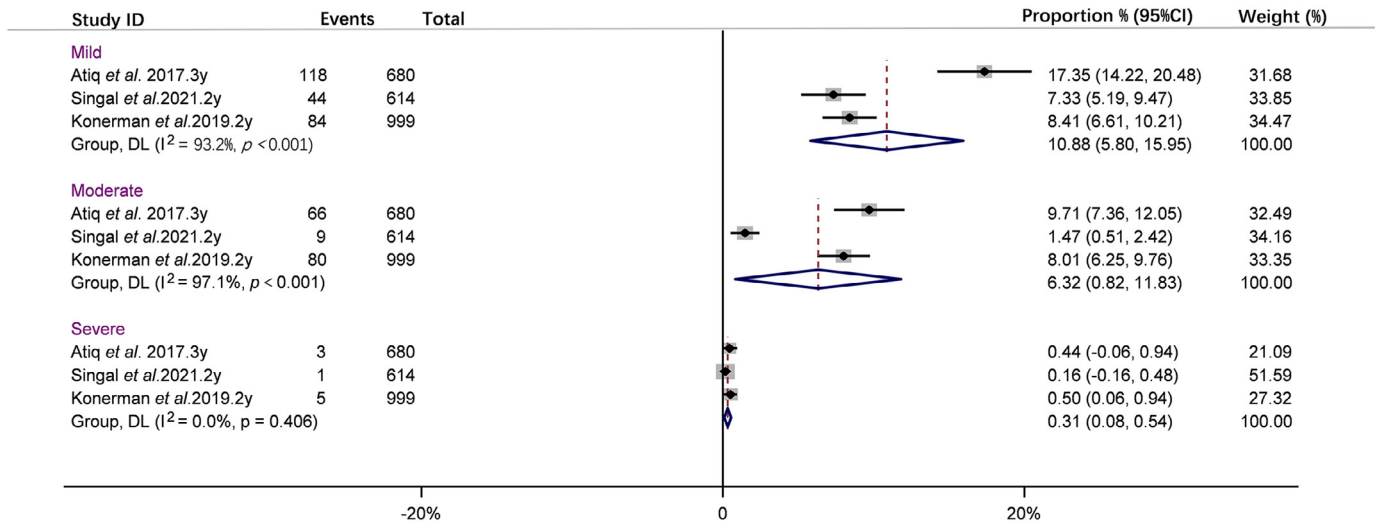

Fig. 8. Pooled proportion of different levels of physiological harm. CI, confidence interval; DL, discrete logarithm.

survival rate ((OR, 1.90 [95% CI, 1.67–2.77]) between HCC screening and no screening groups in cirrhosis patients. In addition, another meta-analysis published by Singal et al. in 2022[21] was an update of the meta-analysis published in 2014, which evaluated the benefits and harms of HCC screening in patients with cirrhosis from cohort studies. In terms of benefit outcomes, it reported similar results as the meta-analysis in 2014. The results of our meta-analysis are similar to the main results of those two previous meta-analyses. However, the previous studies only evaluated the benefits of HCC screening in patients with cirrhosis. Our meta-analysis included 67 studies, including four RCTs and 63 cohort studies. Our study also evaluated the screening benefits for all high-risk populations (those with HBV, HCV, cirrhosis, and/or another chronic liver disease). In addition, we pooled HCC mortality.

The personal and public health consequences of HCC are enormous, and even a small benefit from screening could save many lives. The general goal of cancer screening is to decrease cancer mortality or increase survival in cancer patients by focusing on detecting cancer patients as early as possible.[5] Prognosis for HCC patients depends on tumor stage, with curative therapies only available for patients detected at an early stage. Patients detected at an early stage can achieve higher 5-year survival rates with transplant or resection, whereas those with advanced HCC are only eligible for palliative treatments and have a median survival of less than 1 year.[12,13] Our findings suggest that HCC screening can reduce HCC mortality and prolong overall survival, which increases the proportion of early HCC.

In practice, the 6-month screening interval is recommended by guidelines.[6,8] Our subgroup analysis supports this recommendation, suggesting that this recommendation should be followed to realize the benefits of screening. Our subgroup analyses also suggest that lead-time bias may exaggerate the benefits of screening. Therefore, tumor volume doubling time (TVDT) can be used to adjust the lead-time bias to the real benefits of HCC screening.[90] We also found substantial differences according to study location. This may be related to the differences in characteristics of screening population, medical level and cancer screening rate in different countries. Age of patients also affects the benefits of HCC screening. Incidences of HCC and age are directly correlated until approximately 75 years of age in most populations.[2] The incidence of disease is closely related to the benefits of screening.

4.2. Harms of HCC screening

Three case series studies and one cohort study reported the proportion of physiological harm. The meta-analysis indicated that the pooled proportion of physiological harm was 16.3%, and most harms were of a mild to moderate severity, with few patients experiencing severe harm. The results of subgroup analysis showed different proportions of physiological harm in the 2- and 3-year follow-up subgroups. The results suggest that the proportion of physiological harm increased with an extension of follow-up years. Although an increase in the number of follow-up years can increase the proportion of early HCC, the resulting proportion of physiological harm should not be ignored.

At present, only one meta-analysis, published by Singal et al. in 2022,[21] has summarized the evidence on HCC screening-related harms. However, it only describes proportions of screening-related physiological harm reported by current articles. In addition, high-quality systematic reviews performed by the USPSTF on breast cancer, cervical cancer, colorectal cancer, lung cancer, and others have shown that cancer screening causes psychological harms such as psychological anxiety.[14–16] However, there were no studies have reported or quantified the psychological harms caused by HCC screening. Only three studies have reported the proportion of physiological harm. Screen-relevant physiological harm can include direct complications of screening tests and subsequent diagnostic testing, whether invasive or noninvasive.[97] Although most common screening modalities (e.g., US and AFP) cause minimal direct physiological harm, they can lead to high rates of diagnostic imaging for false-positive or indeterminate lesions. Imaging modalities such as CT and MRI are associated with contrast injury, radiation exposure, and high cost. Liver biopsy may be required for liver lesions not detected by CT or MRI and can be associated with bleeding, tumor seeding, and/or injury to nearby organs.[98,99] A review indicated that screening in patients with liver function child Pugh C who are not transplant candidates may cause over diagnosis.[97] The evidence of harms from HCC screening is insufficient.

4.3. Strengths and limitations

A major strength of our study is that we comprehensively evaluated the benefits and harms of HCC screening in all high-risk populations by including both RCTs and observational studies. We also used the GRADE approach to assess the quality of evidence.

Some limitations to our systematic review should be acknowledged. First, most evidence came from retrospective studies in which all patients with diagnosed HCC were first identified and then the screening status was determined. These studies tended to suffer selection bias, lead-time bias, and length bias. Second, the evidence on harms in HCC screening is insufficient, with only four studies available. Finally, other

factors including US operator experience and technique, patient body habitus, and liver nodularity may have led to heterogeneity between studies, which we were unable to explore given the lack of data.

In conclusion, the currently available, very low-quality evidence shows that the benefits of HCC screening are better than non-screening. Current evidence of the harms of HCC screening is insufficient. High-quality trials that examine the balance of benefits and harms of HCC screening in populations with chronic liver disease and other high-risk population should be considered in the future.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

F.S. and J.Y. conceived the study. Z.Y. and J.Y. drafted the protocol. F.S. and J.Y. conducted the literature search. J.Y., S.Y. selected the studies. J.Y., S.Y., X.Z. and L.G. extracted the data. J.Y. and S.Y. assessed the quality of evidence using the GRADE framework. Z.Y. and F.S. verified the data. J.Y. analyzed the data and wrote the manuscript. Y.J. gave opinions on data analysis. All authors have approved final draft of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.02.001.

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