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Comparative effectiveness of different hepatocellular carcinoma screening intervals or modalities: a systematic review and meta-analysis

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Abstract

Background: Current guidelines recommend hepatocellular carcinoma (HCC) screening in high-risk populations. However, the ideal HCC screening interval and screening modality have not been determined. This study aimed to compare the screening efficacy among different modalities with various intervals.

Methods: PubMed and other nine databases were searched through June 30, 2021. Binary outcomes were pooled using risk ratio (RR) with 95% confidence intervals (CIs). Survival rates were also pooled using RR with 95% CIs because most eligible studies only provided the number of survival patients instead of hazard ratio.

Results: In all, 13 studies were included. Two random controlled trials (RCTs) and six cohort studies compared screening intervals for ultrasonography (US) screening and found no significant differences between shorter (3- or 4-month) and longer (6- or 12-month) screening intervals in terms of early HCC proportion, HCC significant mortality, 1-year survival rate; screening at 6-month interval significantly increased the proportion of early HCC (RR = 1.17, 95% confidence interval [CI]: 1.08–1.26) and prolonged the 5-year survival rate (RR = 1.39, 95% CI: 1.07–1.82) relative to the 12-month interval results. Three other RCTs and two cohort studies compared different screening modalities in cirrhosis or chronic hepatitis B, which indicated no statistical differences in the proportion of early HCC (RR = 0.89, 95% CI: 0.40–1.96) and HCC mortality (RR = 0.69, 95% CI: 0.23–2.09) between the biannual US and annual computed tomography (CT screening). Biannual US screening showed a lower proportion of early HCC than biannual magnetic resonance imaging (MRI) (RR = 0.60, 95% CI: 0.37–0.97) and biannual US combined with annual CT (RR = 1.31, 95% CI: 1.13–1.51) screening. The proportion of early HCC in the contrast-enhanced US group was slightly higher than that in the B-mode US (RR = 1.08, 95% CI: 1.00–1.23) group.

Conclusions: The evidence suggests that 6 months may be the best HCC screening interval for US screening. The effectiveness of CT and MRI is better than US during same screening intervals. However, MRI and CT are more expensive than US, and CT also can increase the risk of radiation exposure. The selection of CT or MRI instead of US should be carefully considered.

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Keywords: Hepatocellular carcinoma; Screening interval; Screening modality; Effectiveness; Systematic review; Meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, with about 841,000 new cases and 782,000 deaths recorded annually.[1] The incidence and mortality of HCC are still high in Asian regions, but are increasing in lower risk areas as well, such as Europe and the United States.[2-8] Screening may detect cancers at an early stage and thereby reduce mortality. Screening involves performing the initial testing, following up patients with positive results with other tests or procedures to confirm the suspected diagnosis, and treating the diagnosed disease or precursor. The performance of screening programs includes initial tests and downstream assessment and treatment.[9] Similarly, the process of HCC screening also includes these steps (Figure 1).

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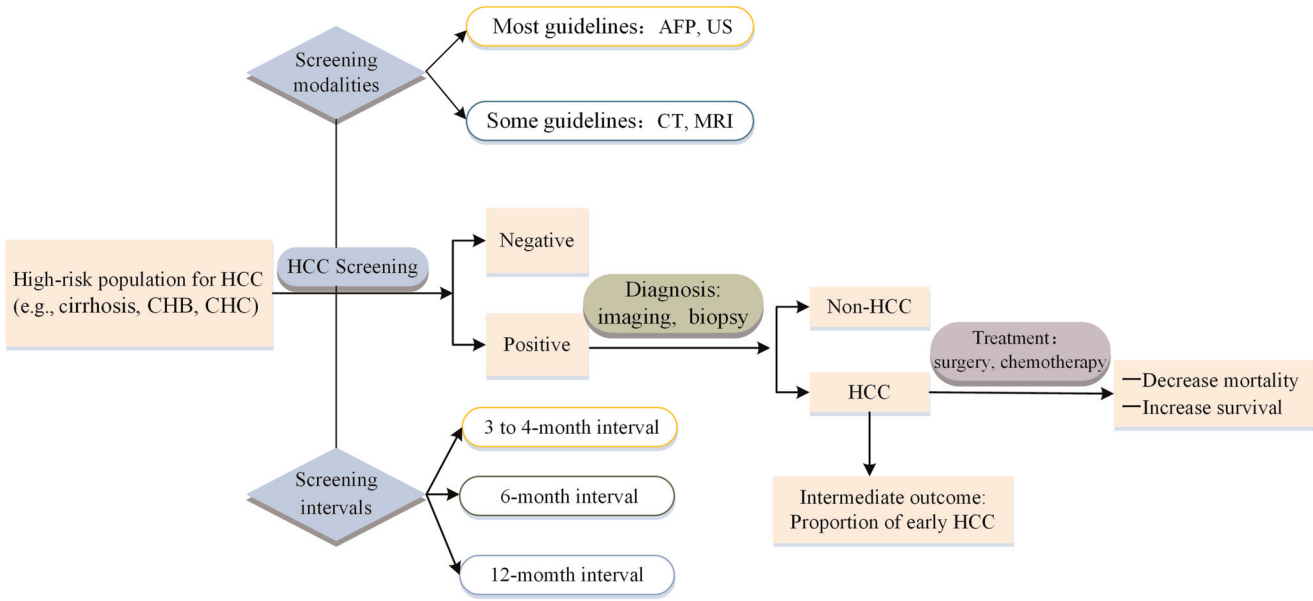

Figure 1: The process of HCC screening. AFP: Alpha-fetoprotein; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; CT: Computed tomography; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; US: Ultrasonography.

Current guidelines recommend HCC screening to reduce HCC mortality in high-risk populations, that is, those with chronic hepatitis, such as chronic hepatitis B (CHB), chronic hepatitis C (CHC), and/or cirrhosis.[10] However, different guidelines provide different specific HCC screening strategies for high-risk populations.

The ideal screening interval for HCC screening is controversial, ranging from a 3- to 12-month periodicity. A 6-month screening interval is recommended by most guidelines (e.g., the American Association for the Study of Liver Disease [AASLD],[11] the European Association for the Study of the Liver [EASL],[12] and the Asian Pacific Association for the Study of the Liver [APASL]).[13] The guideline of the Japan Society of Hepatology (JSH) recommends a 3 to 4-month screening interval for extremely high-risk patients with both viral hepatitis and cirrhosis.[14]

Which screening modality should be used for HCC screening has also been a subject of debate. Screening for HCC using ultrasonography (US) and alpha-fetoprotein (AFP) has been recommended by professional societies for more than a decade. AFP was omitted from European and American guidelines in 2010 due to its lack of sensitivity, but it remains in the recommendations given by Asian guidelines. How to optimize the performance of US for HCC screening is also not a settled question. US screening can lead to an inadequate quality of HCC screening due to rib shadowing and inadequate beam penetration.[15] In recent years, some guidelines have proposed computed tomography (CT) or magnetic resonance imaging (MRI) for extremely high-risk populations.[14] However, CT and MRI are expensive and CT may lead to screening populations' exposure to radiation.

The current guidelines recommend HCC screening strategies for high-risk populations. However, none of these guidelines are based on a systematic review of relevant studies with a critical appraisal of their internal validity. Most guidelines have only cited several other trials/observational studies[16-19] as their major source of evidence to support their recommendations. In addition, few systematic reviews have evaluated the comparative effectiveness and harm of different screening intervals or modalities. For this reason, we performed this systematic review and meta-analysis to fill this gap.

Methods

We conducted this systematic review following the recommendations laid out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] This review was prospectively registered on the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/) as No. CRD42020148258.

Database and search strategy

The following databases were searched: PubMed, Embase, the Cochrane library, Clinicaltrials.gov, Web of Science, Google scholar, and Chinese databases (China National Knowledge Infrastructure, Wanfang, VIP, and SinoMed). We searched the literature from inception to June 30, 2021, using the keywords "screening and hepatocellular carcinoma." The details of the search strategy are presented in Supplementary Table 1, http://links.lww.com/CM9/B259. We examined the reference lists of reviews of screening for HCC retrieved by our searches to identify additional studies.

Study selection

Two groups of reviewers (JCY and SQY, LG and XYZ) independently screened the titles and abstracts of studies

and resolved any disagreement by consensus. Next, the full-text paper of each potentially eligible article identified in the screening was retrieved. The two groups independently assessed articles for inclusion. Any discrepancies were resolved by discussion among the reviewers, or if necessary, by consulting a fifth reviewer (FS).

Studies were included for analysis if they (1) had a study population including a high-risk population for HCC (those with CHB, CHC, and/or cirrhosis); (2) exhibited interventions/comparators that compared HCC screening intervals or modalities; (3) described effectiveness and/or harm outcomes; and (4) were comparative studies (randomized controlled trials [RCTs] or cohort studies).

We excluded duplicate studies and studies whose data were lacking or unavailable. Studies comparing screening and non-screening were also excluded. If one 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.

Definition of outcomes

HCC-related mortality was the main outcome, given that the goal of cancer screening was to reduce mortality. It refers to 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 the disease in the given population over the same interval.[21]

Survival rate was the number of people diagnosed with HCC who were still alive (e.g., 1, 3, and 5 years after diagnosis), divided by the total number of people who had the disease originally.[21]

Median survival time was the corresponding survival time when the cumulative survival rate is 0.5 indicates that only 50% of the individuals can survive this time. It provides a general index of survival and prognosis for cancer patients.

The proportion of early HCC was the total number of early HCC cases divided by the total number of HCC cases, representing the intermediate effectiveness outcome of HCC screening. It was defined by Milan criteria or Barcelona clinic liver cancer (BCLC) stage system.

Data extraction

Two reviewers (JCY and XYZ) independently reviewed and extracted the required information from eligible studies using standardized forms. The reviewers resolved any discrepancy through discussion or, if necessary, by conferring with a third reviewer (FS or ZRY). The data extraction form included the following study design items: basic information, population characteristics, screening modalities, screening intervals, effectiveness outcomes, study design, and so on.

Risk of bias assessment in individual studies

Cochrane's tool for assessing risk of bias was used to assess quality in RCTs.[22] Studies with low risk of bias ratios in at least four domains were considered of moderate to high quality. The Newcastle-Ottawa Scale was used to assess the quality of cohort studies.[23] Each study was rated from 0 to 9 stars based on three domains: selection (0–4), comparability (0–2), and outcome (0–3). Studies with at least 6 stars were considered of high quality. The reviewers resolved any discrepancy through discussion or, if necessary, by seeking a decision from a third reviewer (FS or ZRY).

Statistical analysis

Data synthesis

STATA software version 15.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses and to generate forest plots. For proportion of early HCC and HCC mortality, the results were expressed as risk ratio (RR) with 95% confidence intervals (CIs). Because most eligible studies only provide the number of survival patients instead of the hazard ratio, survival rates were also pooled using RR with 95% CIs; the median survival time was expressed as median survival ratio (MSR) with 95% CIs.

We pooled results for RCTs and observational studies separately, using a random-effects model separately. For cases with limited data (with only one study), narrative analyses were conducted to summarize the results. Heterogeneity was assessed using the chi-square test on Cochrane's Q and quantified with I^2 values.

Assessment of publication bias

To assess symmetry in the funnel plots, Egger's test was used to evaluate the presence of publication bias when ten or more studies were available; $P < 0.05$ was considered indicative of statistically significant publication bias.[24] We did not evaluate the presence of publication bias because only one to three studies were available for each outcome.

Subgroup analyses

We did not perform subgroup analyses because only one to three studies were available for each outcome.

Sensitivity analyses

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

Results

Literature search

The inclusion process is presented in the PRISMA diagram [Figure 2]. The search yielded 7846 potentially relevant records. After abstracts and full texts were screened, 13 studies were included in the meta-analysis.

Characteristics of included studies

The characteristics of the eligible studies are summarized in Table 1. All studies were published between 2002 and

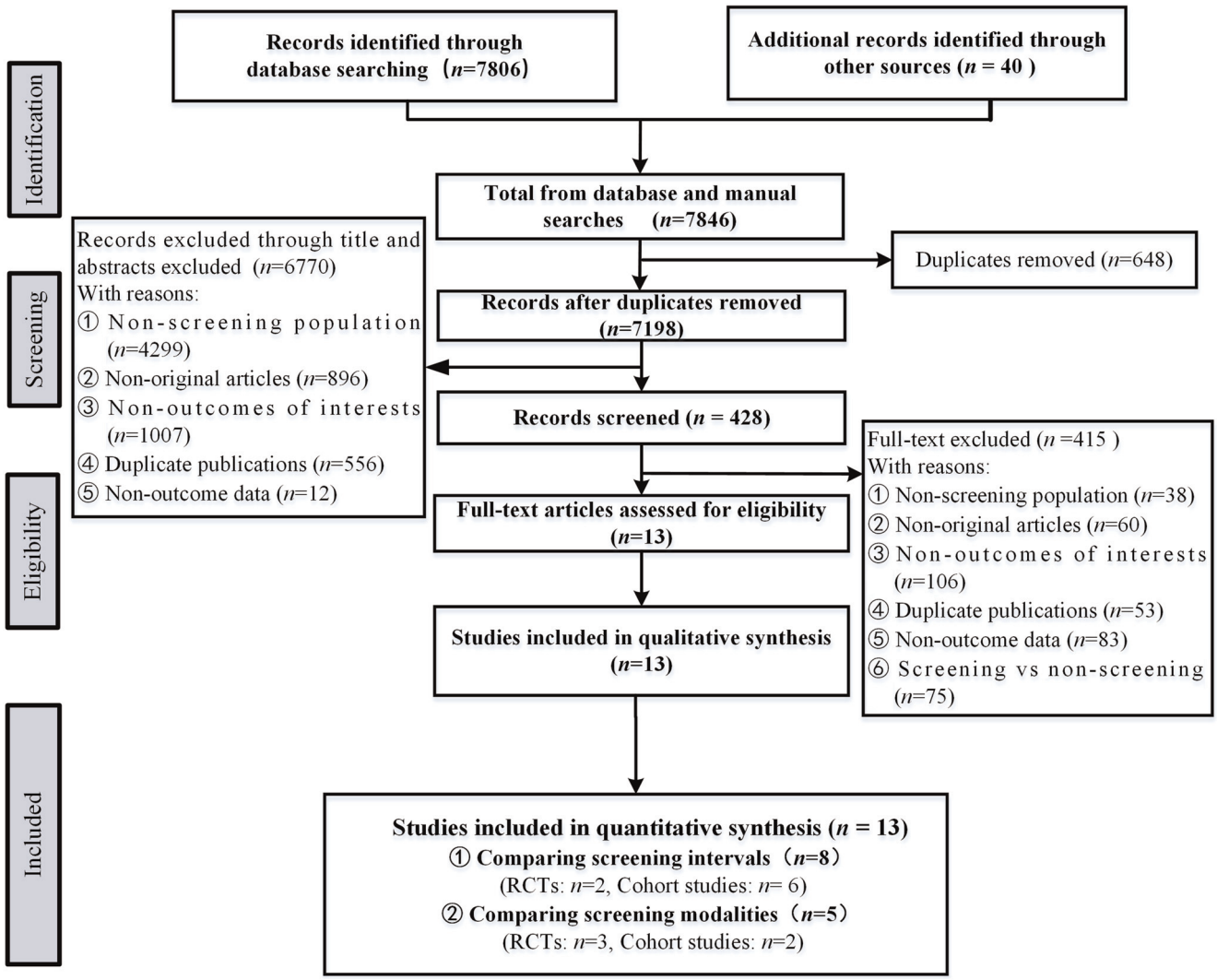

Figure 2: PRISMA flowchart of included studies on hepatocarcinoma screening. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials.

2021, and most were conducted in Europe and Asia. No study compared the potential harm of different screening intervals/modalities. Of the 13 studies reviewed, including two RCTs and six cohort studies, compared the effectiveness of different screening intervals; the other three RCTs and two cohort studies compared the effectiveness of different screening modalities. In terms of reporting outcomes, 11 studies reported proportion of early HCC, which four studies defined early HCC using Milan criteria and other four studies using BCLC stage system, whereas three studies did not report the definition of early HCC. Two studies provided HCC mortality, one study reported 1-year survival rate, three studies reported the 5-year survival rate, and four studies provided median survival time. There were no studies reported the harm outcomes.

In addition, most cohort studies and RCTs exhibited a low risk of bias. The details of the bias risk assessment are presented in Supplementary Table 2, http://links.lww.com/CM9/B259.

Comparison of different screening intervals

One RCT in France compared the effectiveness of 3-month *vs.* 6-month screening intervals. [19] Among cirrhosis patients screened with US in the study (640 for 3-month screening *vs.* 638 for 6-month screening), 53 and 70 cases were diagnosed with HCC, respectively. After 3 years of follow-up, there were no differences in the risk for early HCC (RR = 1.18, 95% confidence interval [CI]: 0.97–1.42) or HCC mortality (RR = 0.87, 95% CI: 0.65–1.18) between the two screening intervals.

Another RCT, conducted in China, compared 4- and 12-month screening intervals in patients with chronic viral hepatitis, who were screened via US.[25] After 4 years of follow-up, HCC was detected in 24 of 387 participants screened in a 4-month interval and 15 of 357 screened in a 12-month interval. There were no differences in the proportion of early HCC (RR = 1.75, 95% CI: 0.50–2.68) and 1-year survival rate (RR = 1.07, 95% CI: 0.28–4.17) between the two screening intervals.

Table 1: Characteristics of included studies comparing different screening intervals and modalities of hepatocarcinoma screening.

Included studies	Study location	Study design	Comparators-1	Comparators-2	Screening population (C-1/C-2)	HCC (C-1/C-2)	Outcome	Proportion of Child-Pugh C (%)	Definition of early HCC
Shorter screening intervals *vs.* longer screening intervals									
Trinchet *et al*[19]	France	RCT	US/3M	US/6M	Cirrhosis (640/638)	53/70	①②	NA	Milan criteria
Wang *et al*[25]	China	RCT	US/4M	US/12M	CH (387/357)	24/15	①③	NA	BCLC stage
Del Poggio *et al*[26]	Italy	Cohort study	US/6M	US/12M	CH	281/889	①	0	Milan criteria
Santi *et al*[17]	Italy	Cohort study	US/6M	US/12M	Cirrhosis	510/139	①④⑤	0	Milan criteria
Trevisani *et al*[18]	Italy	Cohort study	US/6M	US/12M	Cirrhosis	215/155	①⑤	5.4	NA
Wu *et al*[27]	China	Cohort study	US/6M	US/12M	CLD	19,115/4837	④⑤	NA	NA
Song *et al*[28]	China	Cohort study	US/6M	US/12M	Cirrhosis	89/103	④⑤	29.6	NA
Khalili *et al*[29]	Canada	Cohort study	US/<12M	US/≥12M	Cirrhosis	97/38	①	3.0	Milan criteria
Screening modality-1 *vs.* screening modality-2									
Pocha *et al*[30]	USA	RCT	US/6M	CT/12M	Cirrhosis (83/80)	9/8	①②	NA	BCLC stage
Rhee *et al*[31]	Korea	RCT	US/6M	MRI/6M	Cirrhosis (188/189)	10/12	①	NA	NA
Kudo *et al*[32]	Japan	RCT	CEUS/4M	B-mode US/4M	Cirrhosis (309/313)	28/26	①	0.2	NA
Kim *et al*[33]	Korea	Cohort study	US/6M	US/6M + CT/12M	CHB (825/822)	96/105	①	0	BCLC stage
Kim *et al*[34]	Korea	Cohort study	US/6M	US/6M + CT/12M	Cirrhosis (659/576)	90/94	①	NA	BCLC stage

AFP: Alpha-fetoprotein; BCLC: Barcelona clinic liver cancer; CEUS: Contrast-enhanced US; CH: Chronic hepatitis (chronic hepatitis included chronic hepatitis B, chronic hepatitis C, alcoholic liver disease, and so on); CHB: Chronic hepatitis B; CLD: Chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); CT: Computed tomography; HCC: Hepatocellular carcinoma; M: Screening interval is *x* months (e.g., 3M means screening interval was 3 months); MRI: Magnetic resonance imaging; NA: Not reported; Outcomes: Outcomes of effectiveness (① = proportion of early HCC, ② = HCC mortality, ③ = 1-year survival rate, ④ = 5-year survival rate, ⑤ = median survival time); RCT: Random clinical trial; US: Ultrasound; USA: The United States of America.

Five retrospective cohort studies compared the 6-month *vs.* 12-month screening intervals (20,210 *vs.* 6123 HCC patients) screened via US in cirrhosis and chronic hepatitis patients.[17,18,26-28] However, no cohort studies provided the size of the screening population, so we could not create an overall figure for this. As shown in Figures 3–5, the pooled results in meta-analysis demonstrated that the 6-month group had a higher proportion of early HCC (RR = 1.17, 95% CI: 1.08–1.26, $I^2 = 0.0\%$), higher 5-year survival rate (RR = 1.39, 95% CI: 1.07–1.82, $I^2 = 63.8\%$), and longer median survival (MSR = 1.30, 95% CI: 1.28–1.31, $I^2 = 0.0\%$) than the 12-month screening interval.

The other retrospective cohort study[29] compared the ≤12-month *vs.* >12-month screening intervals in cirrhosis patients screened via US, 97 and 38 cases were diagnosed HCC, respectively. And found that the ≤12-month group had a higher proportion of early HCC (RR = 1.53, 95% CI: 1.26–1.87) than the >12-month screening group.

Comparison of different screening modalities

Three RCTs and two cohort studies compared the effectiveness of different screening modalities (e.g., US, CT, and MRI) in cirrhosis or CHB patients. Because only one study examined each outcome, descriptive analysis was conducted, with the results shown in Table 2.

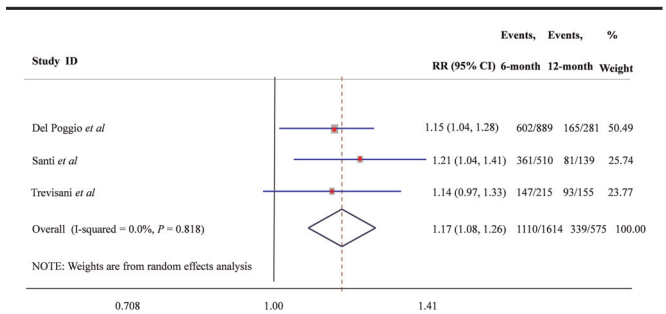

Figure 3: Comparison of proportion of early HCC between the 6- and 12-month screening intervals. CI: Confidence interval; HCC: Hepatocellular carcinoma; RR: Risk ratio.

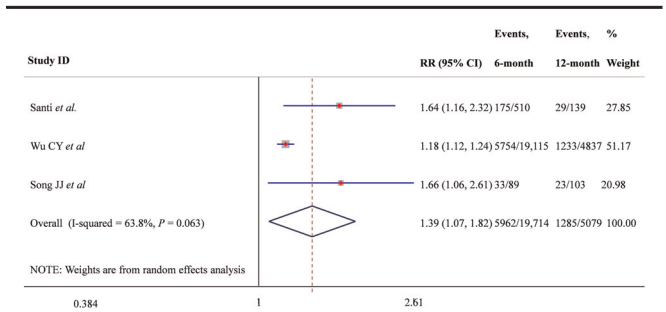

Figure 4: Comparison of 5-year survival rate between the 6- and 12-month screening intervals. CI: Confidence interval; HCC: Hepatocellular carcinoma; RR: Risk ratio.

One RCT compared the biannual US to annual CT for HCC screening in cirrhosis patients. [30] The results showed no statistically significant difference between US and CT groups in terms of the proportion of early HCC (RR = 0.89, 95% CI: 0.40–1.96) or HCC mortality (RR = 0.69, 95% CI: 0.23–2.09). Another RCT compared the biannual US to biannual MRI in patients with cirrhosis.[31] The results showed that the risk for early HCC was lower (RR = 0.60, 95% CI: 0.37–0.97) in the biannual US group than in the biannual MRI group. Another RCT compared the proportion of early HCC between the contrast-enhanced US and B-mode US in cirrhosis patients with a 4-month screening interval.[32] The results indicated that the proportion of early HCC in the contrast-enhanced US group was slightly higher than that in the B-mode US group (RR = 1.08, 95% CI: 1.00–1.23).

In addition, two cohort studies compared the screening effectiveness of the biannual US and biannual US combined with annual CT in patients with cirrhosis and CHB patients, respectively.[33,34] The proportion of early HCC in the latter group was higher than that in the biannual US group in both cirrhosis (RR = 1.31, 95% CI: 1.13–1.51) and CHB patients (RR = 2.15, 95% CI: 1.56–2.98).

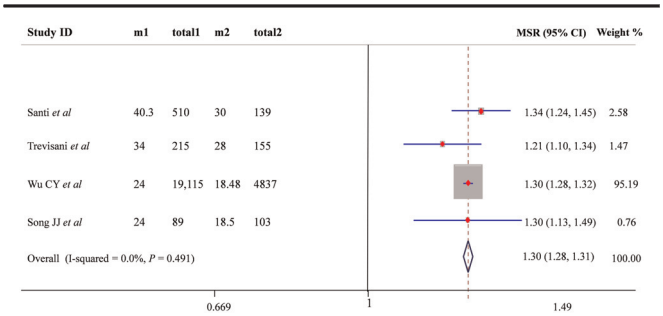

Figure 5: Comparison of median survival time between the 6- and 12-month screening intervals. m1: Median survival of 6-month group; m2: Median survival of 12-month group; MSR: Median survival ratio; total1: The number of HCC in the 6-month group; total2: The number of HCC in the 12-month group.

Results of sensitivity analyses

As shown in Supplementary Table 3, http://links.lww.com/CM9/B259, there were no significant changes to our main results after excluding studies with a high risk of bias, suggesting the robustness of the summary estimates.

Discussion

Comparison of different screening intervals

The results of comparing different screening intervals indicated that shorter screening intervals (3- or 4-month) were no better than longer ones (6- or 12-month). However, within the longer intervals, 6-month screening was better than 12-month screening when US was used. No studies have reported on the potential harm of different screening intervals. Our study was a systematic review to compare the effectiveness of different HCC screening intervals in a high-risk population.

Most guidelines suggest that tumor screening intervals should be determined based on the mean tumor volume doubling time (TVDT).[12] TVDT is used to present the natural growth rate of a tumor. Relevant studies have shown that the range of TVDT of HCC is 94 to 210 days,[35-37] and 6 months (180 days) falls within this range. Shortening the screening interval to 3 months would not improve the effectiveness of screening, but increase the cost. If the screening interval is extended to 12 months, the cost would be lower, but the effectiveness of the screening would be decreased.

Current evidence and most guidelines recommend screening only for high-risk populations, those with chronic hepatitis such as CHB, CHC, and cirrhosis. However, the guideline of JSH further classified high-risk groups into generally high-risk group and extremely high-risk group who have both viral hepatitis and cirrhosis. JSH believed extremely high-risk group are more likely to develop HCC than generally high-risk group. JSH proposed that the

Table 2: Summary of comparing different screening modalities.

Included studies	Study design	Screen modalities	*N* of screen population	*N* of HCC	Effectiveness outcome (RR, 95% CI)	
					Mortality	Proportion of early HCC
Pocha *et al*[30]	RCT	US/6M *vs.* CT/12M	Cirrhosis (83 *vs.* 80)	9 *vs.* 8	0.69 (0.23–2.09)	0.89 (0.40–1.96)
Rhee *et al*[31]	RCT	US/6M *vs.* MRI/6M	Cirrhosis (188 *vs.* 189)	10 *vs.* 12	NA	0.60 (0.37–0.97)
Kudo *et al*[32]	RCT	CEUS/4M *vs.* B-mode US/4M	Cirrhosis (309 *vs.* 313)	28 *vs.* 26	NA	1.08 (1.00–1.23)
Kim *et al*[33]	Cohort study	US/6M *vs.* US/6M + CT/12M	CHB (825 *vs.* 822)	96 *vs.* 105	NA	2.15 (1.56–2.98)
Kim *et al*[34]	Cohort study	US/6M *vs.* US/6M + CT/12M	Cirrhosis (659 *vs.* 576)	90 *vs.* 94	NA	1.31 (1.13–1.51)

CEUS: Contrast-enhanced US; CHB: Chronic hepatitis B; CI: Confidence interval; CT: Computed tomography; HCC: Hepatocellular carcinoma; M: Screening interval is *x* months (e.g., 3M means screening interval was 3 months); MRI: Magnetic resonsance imaging; NA: Not reported; RCT: Random clinical trial; RR: Risk ratio; US: Ultrasound.

detectability of small nodules (<2 cm in diameter) in the liver was superior in the 3-month interval group than in the 6-month interval group. Therefore, it recommended different screening intervals using US and/or AFP for two groups: every 6 months for the generally high-risk group, and every 3 to 4 months for the extremely high-risk group.[14]

The current evidence suggest that the 6-month screening interval is the best for HCC screening with US in patients in a high-risk population. However, it is maybe necessary to classify high-risk populations into subgroups and recommend different screening intervals according to the natural history of different subgroups.

Comparison of different screening modalities

There were three RCTs and two cohort studies that compared the effectiveness of different screening modalities in patients with cirrhosis and CHB. The results indicated that the effectiveness of biannual MRI or biannual US combined with annual CT was better than the biannual US, and there were no differences between the biannual US and annual CT. In addition, one RCT showed that screening by contrast-enhanced US increased the proportion of early HCC over B-mode US in cirrhosis patients with a 4-month screening interval. We did not find a systematic review that had compared different screening modalities in a HCC high-risk population.

Most current guidelines generally recommend US and AFP for HCC screening in a high-risk population. Considering that the accuracy of AFP is low, European and American guidelines (e.g., EASL guidelines, AASLD guidelines) only recommend US as the screening modality. This may be related to the fact that there are more cirrhosis patients in Europe and the United States and the accuracy of AFP screening for HCC in cirrhosis patients is low.[11,12] However, the guidelines for APASL still recommend AFP combined with US for HCC screening. This may be based on fact that the prevalence of CHB in Asia is high and the accuracy of AFP screening for CHB patients is also high.[13] US screening can lead to inadequate quality of HCC screening under some conditions. The most common reason for unsatisfactory quality is rib shadowing and inadequate US beam penetration. Therefore, the accuracy of US screening for obese patients or patients with fatty liver disease may be low.[38] CT and MRI were more sensitive than US for detecting HCC.[39] In addition, most current guidelines recommend CT and MRI as diagnostic tools, while only the JSH guidelines recommend them to screen in extremely high-risk populations (e.g., coexistence of viral hepatitis and cirrhosis) for increasing the detection rate of small HCC.[14] However, MRI and CT are more expensive than US. CT also increases radiation exposure.[15,30] Therefore, the choice of whether to use CT / MRI or US combined CT/MRI screening should be carefully considered.

As mentioned above, current guidelines and many studies only recommend using US to screen HCC in a high-risk population, instead of classifying US subtypes. However, the results of one RCT suggested that it may be necessary to select the appropriate US subtypes for HCC screening in different high-risk populations (i.e., chronic hepatitis including CHB, CHC, and/or cirrhosis).

In the future, we should choose different screening modalities for different populations to improve the effectiveness of HCC screening. Without a doubt, high-quality prospective studies are needed to better define the roles of different screening modalities.

Our study had several strengths. It is a systematic review to compare the effectiveness of different HCC screening intervals/modalities in a high-risk population. Moreover, we systematically identified and included both RCTs and observational studies of the effectiveness of HCC screening.

Despite these strengths, our systematic review had several limitations. First, the lack of RCTs data comparing 6- to 12-month HCC screening intervals may cause question on the cost-effectiveness of 6-month screening intervals. Second, publication bias could not be analyzed because there were <10 studies for each outcome, which rendered the use of funnel plots improper. Finally, due to the authors' limited knowledge of health economics, our study did not compare evidence-based evaluations of the effects of different screening intervals or different screening modalities on health economics.

In summary, a comparison of different screening intervals suggested that 6 months may be the best interval for US screening. The result indicated that the effectiveness of CT and MRI is better than US when screening intervals are the same, there were no differences between the biannual US and annual CT. However, MRI and CT are more expensive than US, CT also can increase the risk of radiation exposure. The fact there are few relevant studies provide evidence for the effectiveness of screening intervals and screening modalities at present. Most evidence came from retrospective cohort studies. Moreover, the incidence of HCC varies with different disease backgrounds. Future studies and guidelines need to recommend more accurate screening strategies based on the natural history of the different high-risk populations (i.e., CHB, CHC, and other chronic hepatitis, cirrhosis). High-quality prospective studies are needed to determine the actual effectiveness and harm of different screening intervals and modalities.

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Conflicts of interest

None.

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