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REVIEW ARTICLE

Effect of microvascular invasion on the postoperative long-term prognosis of solitary small HCC: a systematic review and meta-analysis

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Abstract

Background: The effect of microvascular invasion (MVI) on the postoperative long-term prognosis of solitary small hepatocellular carcinoma remains controversial. We compared the long-term outcomes of MVI-positive and MVI-negative groups of patients with solitary small hepatocellular carcinoma.

Methods: The PubMed, EMBASE, Cochrane Library, VIP, Wan Fang, and Sino Med databases were systematically searched to compare the long-term outcomes of MVI-positive and MVI-negative groups of patients with solitary small hepatocellular carcinoma from inception to November 1, 2018. The study outcomes, including overall survival (OS) and disease-free survival (DFS), were extracted independently by two authors.

Results: Fourteen studies involving 3033 patients were evaluated. A meta-analysis of all 14 studies suggested that the OS of the MVI-positive group was significantly worse than that of the MVI-negative group (HR = 2.39, 95% CI = 2.02–2.84, I^2 = 22.8%; P < 0.001). Twelve studies were included in the meta-analysis of DFS, and MVI showed a worse prognosis (HR = 1.79, 95% CI = 1.59–2.02, I^2 = 25.3%; P < 0.001). Subgroup analysis demonstrated that MVI still showed a negative effect on the long-term OS and DFS of patients with solitary small HCC measuring up to 2 cm, 3 cm, or 5 cm.

Conclusion: Microvascular invasion was a risk factor for poorer prognosis for solitary small hepatocellular carcinoma.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and third leading cause of cancer deaths worldwide with dismal outcomes.[1] Currently, hepatic resection remains the potential curative treatment modality for small HCC.[2] However, the postoperative 5-year recurrence rate is as high as 70%–80%, leading to unsatisfactory long-term overall survival outcomes.[3,4] Small HCC has commonly been defined as a special type of hepatocellular carcinoma with a maximum tumor diameter ≤3 cm,[5,6] yet some studies also adopted a size cutoff of 2 cm or 5 cm to define small HCC.[7–10] Among all the various risk factors related to the recurrence of HCC, microvascular invasion (MVI) is the most important risk factor that is significantly associated with the early postoperative recurrence of HCC and is further confirmed as an independent predictor of both overall and disease-free survival after liver resection.[11–13] MVI is defined as the presence of tumor cells in portal veins, in large capsule vessels, or in a vascular space lined by endothelial cells.[5] MVI is only visible under microscopy, and it is difficult to be detected before hepatic resection.[14] The prevalence of MVI ranges from 15% to 57% in HCC specimens.[15] To date, several staging systems have been established to predict the prognosis of HCC, including the tumor-node-metastasis (TNM) staging system, the Barcelona Clinic Liver Cancer (BCLC) classification, and the Chinese University Prognostic Index (CUPI).[16–18] Among the variable staging systems, the TNM stage is the only staging system that considers microvascular invasion (MVI) as a staging criterion.

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To our knowledge, MVI is more common in advanced HCC patients with large tumors (size > 5 cm) and multiple lesions, and it was reported to perform well in prognosing the long-term outcomes of these patients.[19] For small HCC patients with tumors up to 5 cm, there are several studies demonstrating that MVI is associated with a poor prognosis after hepatectomy.[9,10,20,21] Additionally, regarding HCC patients with tumors up to 2 cm, Wang *et al.* recently concluded that MVI had a negative impact on the prognosis of solitary HCC up to 2 cm after curative hepatectomy.[7] Nevertheless, there still exist some high-quality studies concluding that MVI does not predict long-term survival for patients with HCC up to 2 cm.[8,22] Therefore, it still remains controversial whether MVI can predict long-term survival in solitary small HCC patients. Unfortunately, there is no reported systematic review or meta-analysis resolving the disagreement.

Here, we present the first systematic review and meta-analysis exploring the effect of microvascular invasion on the post-operative long-term prognosis of solitary small hepatocellular carcinoma.

Methods

Study protocol

This meta-analysis was performed according to the Cochrane Collaboration recommendations.[23] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] A systematic search of the PubMed, Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure (CNKI), VIP, Wan Fang, and Sino Med databases was performed. Meanwhile, we comprehensively searched ClinicalTrials.gov to obtain the available outcomes of ongoing studies exploring the effect of microvascular invasion on the postoperative long-term prognosis of solitary small hepatocellular carcinoma. There were no limitations on language, and the search was updated on November 1, 2018. The following search terms were used: "small" or "solitary small" or "up to 5 cm" or "up to 3 cm" or "up to 2 cm" or "< 5 cm" or "< 3 cm" or "< 2 cm" AND "(liver or hepatic or hepatocellular or hepatocellular) and (carcinom* OR cancer OR neoplasm* OR malign* OR tumor* OR tumour*)" or "HCC" or "hepatoma*" AND "microvascular invasion" or "mVI" or "MVI". All abstracts were independently screened by Chen ZH, Zhang XP and Wang Hang, and full-text reports of the included papers were obtained for another screen.

Selection criteria

This meta-analysis focused on exploring the effect of microvascular invasion on the long-term prognosis of patients with solitary small hepatocellular carcinoma after liver resection. Therefore, only comparative analyses concerning the clinical value of the MVI-positive group versus the MVI-negative group of solitary small HCC patients were included in the study.

The inclusion criteria were as follows: (i) clinical trials exploring the effect of microvascular invasion on the post-operative long-term prognosis of solitary small hepatocellular carcinoma; (ii) relevant degree papers, conference summaries, and cohort studies with no publication language limitation applied; (iii) and studies with sufficient data available, such as the baseline characteristics, the overall survival (OS) and disease-free survival (DFS) analysis outcomes.

The exclusion criteria were as follows: (i) macrovascular invasion, such as macroscopic portal vein tumor thrombus (m-PVTT), macroscopic hepatic vein tumor thrombus (m-HVTT), or bile duct tumor thrombus (BDTT); (ii) HCC patients with tumor diameter large than 5 cm; (iii) case reports, narrative reviews, letters, comments, or studies unrelated to the topic of interest; and (iv) studies based on overlapping cohorts derived from the same center.

Data extraction

All the data were extracted and assessed by 2 independent authors (Chen ZH and Zhang XP). In cases where there was disagreement, a third author (Wang Hang) was invited to participate in resolving the disagreements through discussion and consensus.

Data extraction was performed using a standardized form:

1. Basic data included the authors' names, year of publication, study design, sex, number of patients and baseline characteristics
2. Basic data from the patients with solitary small HCC after hepatic resection, including long-term survival outcomes of HCC with MVI group and without MVI group.

Quality assessment

We used the modified Newcastle-Ottawa Scale (NOS) to assess the methodological quality of nonrandomized controlled trials (NRCTs).[25] This scale assesses studies according to the selection of patients in the exposed and the nonexposed groups, the comparability of the two groups and the outcome of the single studies.

Statistical analysis

Pooled HRs for DFS and OS with 95% confidence intervals (CIs) were calculated using the methods reported by Tierney *et al.*[26] If the hazard ratio was reported with a CI or p value, estimates of standard error could be obtained as described in the Cochrane Handbook.[23] A generic inverse variance model was used to calculate pooled HRs, 95% confidence intervals (CIs) and values. According to the suggestions of the Cochrane collaboration, we quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies that is due to heterogeneity, with significant heterogeneity indicated at $P < 0.1$ and an I^2-index >50%.[27] The estimates were pooled with a fixed-effects model if no significant heterogeneity

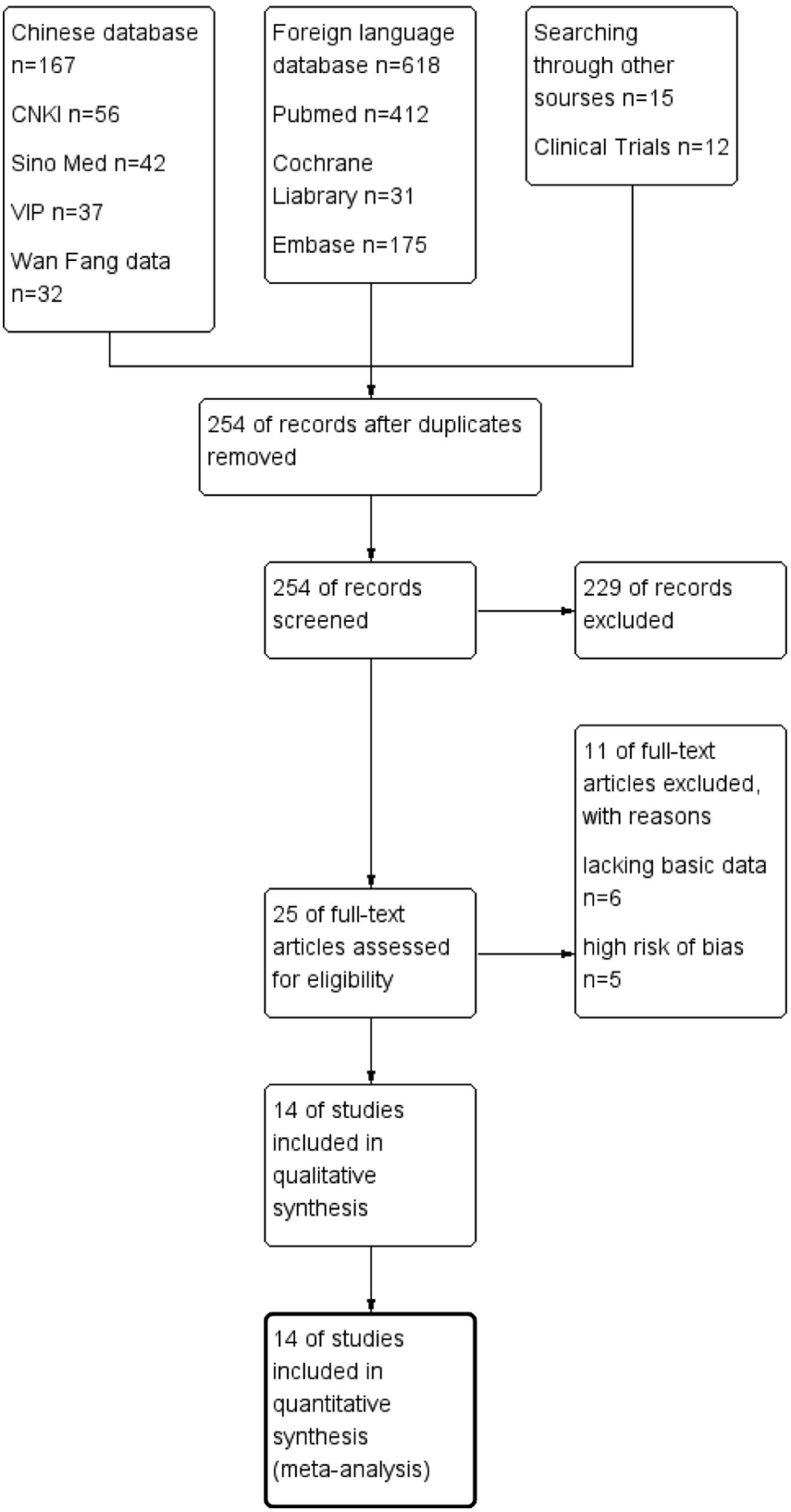

Figure 1 PRISMA flow diagram of the process for the identification of eligible studies. CNKI: Chinese National Knowledge Infrastructure; Sino Med: Chinese Biological Medical Literature Database; VIP: Chongqing VIP database for Chinese Technical Periodicals; Wan Fang: Wan Fang Database

Table 1 Basic characteristics of patients. R (1996–1998): Retrospective study and the time of patients included in case-control cohort, NA: Not applicable, MVI: microvascular invasion

Study (year)	Country	Study type	Treatment received	Incidence of MVI	Subgroups (number)	AGE	Sex (M/F)
Wang, 2018	China	R (PSM) (2010–2012)	Resection	33.1%	MVI negative (332)	51.42 ± 9.86	278/54
					MVI Positive (164)	49.01 ± 9.24	139/25
Katsunoi, 2018	Japan	R (2000–2015)	Resection	18.1%	MVI negative (122)	70/52 (<70/≥70)	89/33
					MVI Positive (27)	21/6 (<7/≥70)	18/9
Yamashita, 2011	Japan	R (1994–2010)	Resection	28.9%	MVI negative (106)	67 ± 9	69/38
					MVI Positive (43)	66 ± 9	31/12
Du, 2014	China	R (2006–2008)	Resection	18.1%	MVI negative (375)	218/157 (≥50/<50)	315/60
					MVI Positive (83)	44/39 (≥50/<50)	69/14
Huang, 2017	China	R (2007–2008)	Resection	12.4%	MVI negative (170)	53.3 ± 11.7	139/31
					MVI Positive (24)	52.1 ± 11.6	18/6
You, 2014	China	R (2008–2011)	Resection	19.1%	MVI negative (174)	49.79 ± 10.82	146/28
					MVI Positive (41)	52.54 ± 11.50	36/5
Zhao, 2017	China	R (2004–2013)	Resection	39.0%	MVI negative (125)	5 (22–81)	110/15
					MVI Positive (51)	53 (29–80)	45/6
Shindoh, 2013	USA	R (1981–2011)	Resection	26.5%	MVI negative (114)	62.5 (28–82)	86/28
					MVI Positive (41)	63 (11–78)	27/14
Hui Zhao, 2017	China	R (2004–2013)	Resection	37.3%	MVI negative (146)	51/95 (>60/≤60)	118/28
					MVI Positive (87)	25/62 (>60/≤60)	67/20
Yu, 2017	China	R (2010–2014)	Resection	26.1%	MVI negative (116)	38/78 (<50/≥50)	83/33
					MVI Positive (41)	11/30 (<50/≥50)	31/10
Li, 2017	China	R (2010–2013)	Resection	43.8%	MVI negative (54)	47.6 ± 4.3	32/22
					MVI Positive (42)	46.8 ± 5.1	25/17
Liu, 2017	China	R (2000–2012)	Resection	46.5%	MVI negative (77)	NA	NA
					MVI Positive (67)	NA	NA
Zhang, 2015	China	R (2001–2008)	Resection	25.8%	MVI negative (46)	58.01 ± 11.90	26/20
					MVI Positive (16)	58.09 ± 9.56	10/6
Bai, 2017	China	R (2008)	Resection	22.6%	MVI negative (247)	64/183 (>60/≤60)	206/41
					MVI Positive (72)	15/57 (>60/≤60)	62/10

was identified; otherwise, a random-effects model was used for estimates with heterogeneity. Subgroup analyses of outcomes were performed to reveal the potential factors that might affect the prognosis of MVI in solitary small HCC. Sensitivity analyses were performed to determine the stability of the overall prognosis effects. Cumulative meta-analyses were performed to assess the stability of the effect sizes. Statistical significance was taken as 2-sided ($P < 0.05$). Publication bias was assessed using funnel plots, Begg's test and Egger's test,[28] with the effect of bias assessed using the fail-safe number method. For all analyses, statistical analyses were performed with the software programs Review Manager (Version 5.3, Cochrane Collaboration, Copenhagen, Denmark) and Stata (Version 12.0, Stata Corp LP, College Station, TX).

Results

Study selection and quality assessment

A total of 254 studies were identified in our initial broad search. A large number of studies were excluded because they were abstracts, animal studies, laboratory projects, or case studies. After carefully reading titles and abstracts, 25 articles were selected for possible inclusion in the review. Following reading the full text, 11 were excluded owing to insufficient basic data or the high risk of bias. Ultimately, 14 studies met our inclusion criteria,[5–10,20–22,29–33] and all were observational studies (Fig. 1). Then, the study designs were collected, and their quality was assessed. All observational studies were evaluated by the modified Newcastle-Ottawa Scale. We removed all the low-

Tumor size (cm)	Child-Pugh (A/B/C)	Virology HBV/Other	Total bilirubin level (μmol/L)	Serum albumin level (g/L)	AFP (mg/L) (<400/≥400)
1.62 ± 0.32	331/1/0	304/28	14.59 ± 5.81	42.65 ± 4.03	310/22 (≤20/>20 ng/ml)
1.66 ± 0.27	162/2/0	156/8	14.81 ± 5.84	42.95 ± 4.06	147/17 (≤20/>20 ng/ml)
51/71 (<2/2–5)	NA	31/91	97/25 (≤1/>1 mg/ml)	10/112 (≤3.5/>3.5) (g/dl)	88/34 (<15/≥15 ng/ml)
4/23 (<2/2–5)	NA	10/17	23/4 (≤1/>1 mg/ml)	1/26 (≤3.5/>3.5) (g/dl)	12/15 (<15/≥15 ng/ml)
1.6 ± 0.4	97/9 (A/B + C)	10/96	0.8 ± 0.4 (mg/day)	3.8 ± 0.4 (g/dl)	100 ± 263 (ng/ml)
1.8 ± 0.3	42/1 (A/B + C)	7/36	0.7 ± 0.4 (mg/day)	3.9 ± 0.4 (g/dl)	139 ± 327 (ng/ml)
NA	NA	NA	NA	NA	122/244 (≥200/<200 ug/ml)
NA	NA	NA	NA	NA	25/55 (≥200/<200 ug/ml)
1.5 ± 0.3	145/20/5	NA	NA	41.6 ± 4.6	80/90 (>200/≤200 ng/dL)
1.9 ± 0.5	18/5/1	NA	NA	40.9 ± 4.9	13/11 (>200/≤200 ng/dL)
3.20 ± 1.04	NA	87/87	16.01 ± 6.63	40.93 ± 6.33	50/124 (>400/≤400 ng/mL)
3.98 ± 0.79	NA	27/14	15.50 ± 6.47	1.03 ± 0.12	24/17 (>400/≤400 ng/mL)
3.40 ± 1.20	112/10/2	102/23	15.5 (5.6–47.7)	41.9 (29.3–50.8)	25.3 (0.7–350000 ng/ml)
3.67 ± 0.99	44/4/3	40/11	17.3 (5.8–86.2)	41.6 (30.2–52.8)	130 (1.3–311000 ng/ml)
1.7 (0.5–2.0)	102/12	40/74	NA	NA	14 (1–6417 ng/ml)
1.8 (0.9–2.0)	38/3	17/24	NA	NA	82 (1.6–135094 ng/ml)
68/78 (>3.5/≤3.5)	142/4/0	111/35	50/96 (>17.1/≤17.1 umol/L)	138/8 (>35/≤35 g/L)	44/102 (>200/≤200 ng/mL)
65/22 (>3.5/≤3.5)	84/3/0	72/15	41/46 (>17.1/≤17.1 umol/L)	83/4 (>35/≤35 g/L)	46/41 (>200/≤200 ng/mL)
42/74 (<3/3–5)	98/18	NA	NA	NA	96/20 (<200/≥200 ug/L)
7/34 (<3/3–5)	32/9	NA	NA	NA	14/27 (<200/≥200 ug/L)
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
26/51 (≤3/3–5)	63/10/4	NA	68/9 (≤20/>20 g/dl)	NA	18/59 (≤400/>400 ng/mL)
12/55 (≤3/3–5)	53/9/5	NA	56/11 (≤20/>20 g/dl)	NA	13/54 (≤400/>400 ng/mL)
1.70 ± 4.2	37/9	41/5	NA	NA	21/25 (≤20/>20 ng/ml)
1.47 ± 0.46	14/2	12/4	NA	NA	8/8 (≤20/>20 ng/ml)
NA	NA	210/37	172/75 (<17/≥17 umol/L)	14/233 (≤35/>35 g/L)	124/123 (≤20/>20 ug/L)
NA	NA	37/5	51/21 (<17/≥17 umol/L)	7/65 (≤35/>35 g/L)	19/53 (≤20/>20 ug/L)

quality observational studies and eventually included 14 high-quality studies. Finally, due to the low risk scores of the evaluation indicators, such as source of funding, comparability of cohorts, and selection of cohorts (Table S1), the risk of quality assessment bias for all the articles included in the study was low (Fig. S4).

Patient characteristics

The baseline characteristics of the patients in the included studies are presented in Table 1. All the included studies were retrospective study, and one study conducted the Propensity Score Matching method. All the patients in our study underwent liver resection. The prevalence of MVI in HCC ranged from 12.4% to 46.5% among the 14 different studies. The percentage of studies that described the mean age of their patients was 92.9% (13 of 14), the sex of patients was 92.9% (13 of 14), the tumor size was 78.6% (11 of 14), the tumor number was 28.6% (4 of 14), the Child-Pugh score was 78.6% (11 of 14), and the virology status, such as HBV, was 71.4% (10 of 14). In total, 3003 solitary small HCC patients were included, among whom 799 had microvascular invasion and 2204 did not. The 14 studies were published from 2011 to 2018. Additional details of the patients' characteristics are listed in Table 1.

Overall survival

The median OS was reported in all 14 studies for the meta-analysis of OS (Table S2). For all 3033 solitary small HCC patients, the median OS ranged from 24 to 120 months in the MVI-positive group and from 41 to 126 months in the MVI-negative group. Based on the preliminary data described in Table S2, the MVI-negative group showed better 1-, 2-, 3-, and 5-year OS rates than the MVI-positive group.

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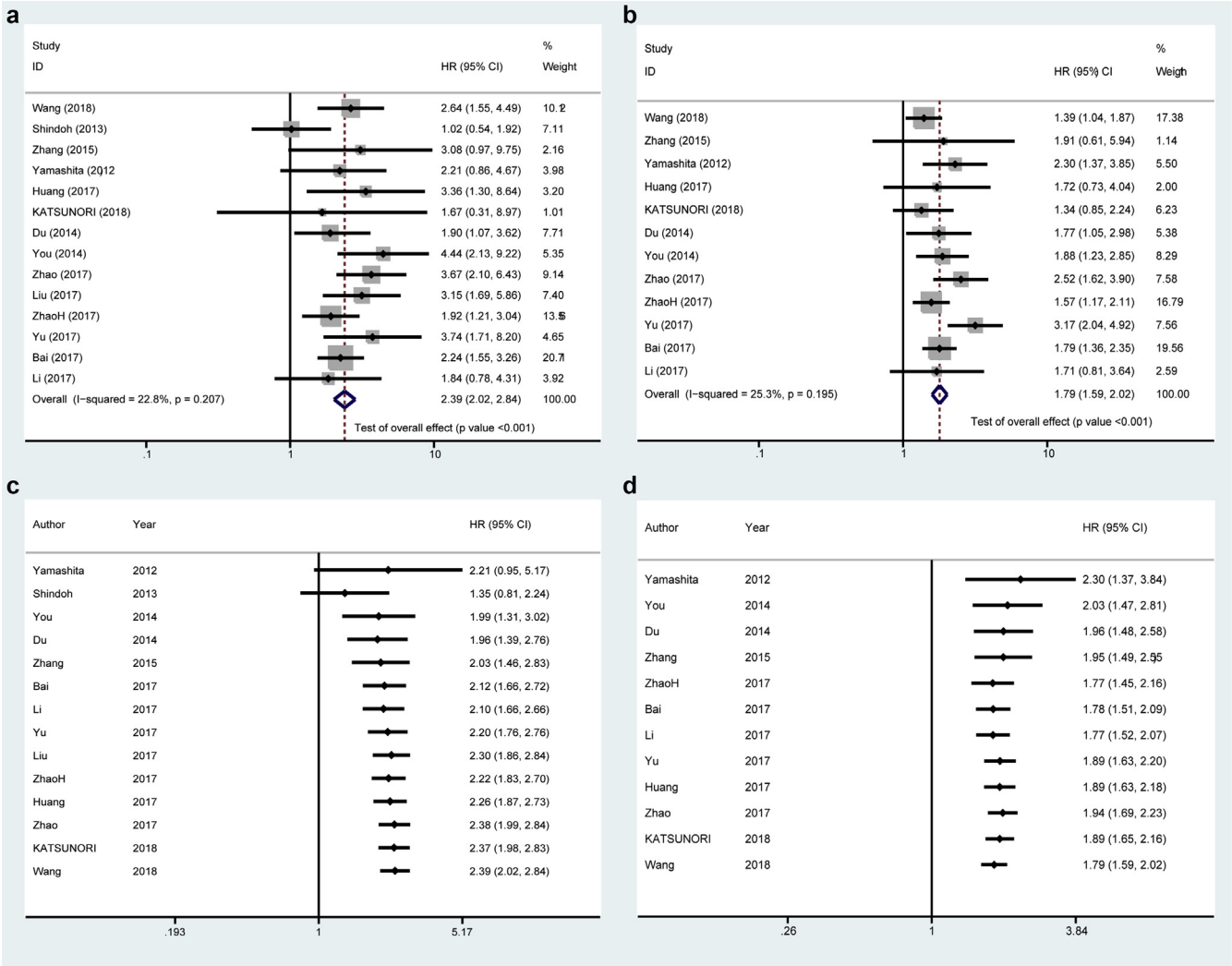

Figure 2 Pooled hazard ratio and cumulative meta-analysis for overall survival and disease-free survival. Outcomes: a. Pooled hazard ratio of overall survival; b. Pooled hazard ratio of disease-free survival; c. Cumulative meta-analysis of overall survival; d. Cumulative meta-analysis of disease-free survival

In total, 14 studies reporting the overall survival data of 3033 patients with solitary small HCC tumors measuring up to 5 cm were evaluated. Our meta-analysis showed that the MVI-positive group had a statistically significant worse OS than the MVI-negative group (HR = 2.39, 95% CI = 2.02–2.84, I^2 = 22.8%; $P < 0.001$; Fig. 2a) in all the included studies, with 799 patients in the MVI-positive group and 2204 patients in the MVI-negative group. A cumulative meta-analysis showed that the significant difference in favor of the MVI-negative group was first observed in the first study in 2014, and then the 95% CI narrowed, and the combined effect size became stable (Fig. 2c).

Disease free survival

The median DFS was reported in 12 of the included studies for the meta-analysis of DFS (Table S3). For all 2704 solitary small HCC patients, the median DFS ranged from 5 to 100 months in the MVI-positive group and from 4 to 111 months in the MVI-negative group. Based on the preliminary data described in Table S3, the MVI-negative group showed better 1-, 2-, 3-, and 5-year DFS rates than the MVI-positive group.

In total, 12 studies reporting the disease-free survival data of 2704 patients with solitary small tumors measuring up to 5 cm were evaluated. Our meta-analysis showed that the MVI-positive group had a statistically significant worse DFS than the MVI-negative group (HR = 1.79, 95% CI = 1.59–2.02, I^2 = 25.3%; $P < 0.001$; Fig. 2b) in all the included studies, with 691 patients in the MVI-positive group and 2013 patients in the MVI-negative group. A cumulative meta-analysis showed that the significant difference in favor of the MVI-negative group was first observed in 2012, and this trend did not change as subsequent studies were included (Fig. 2d).

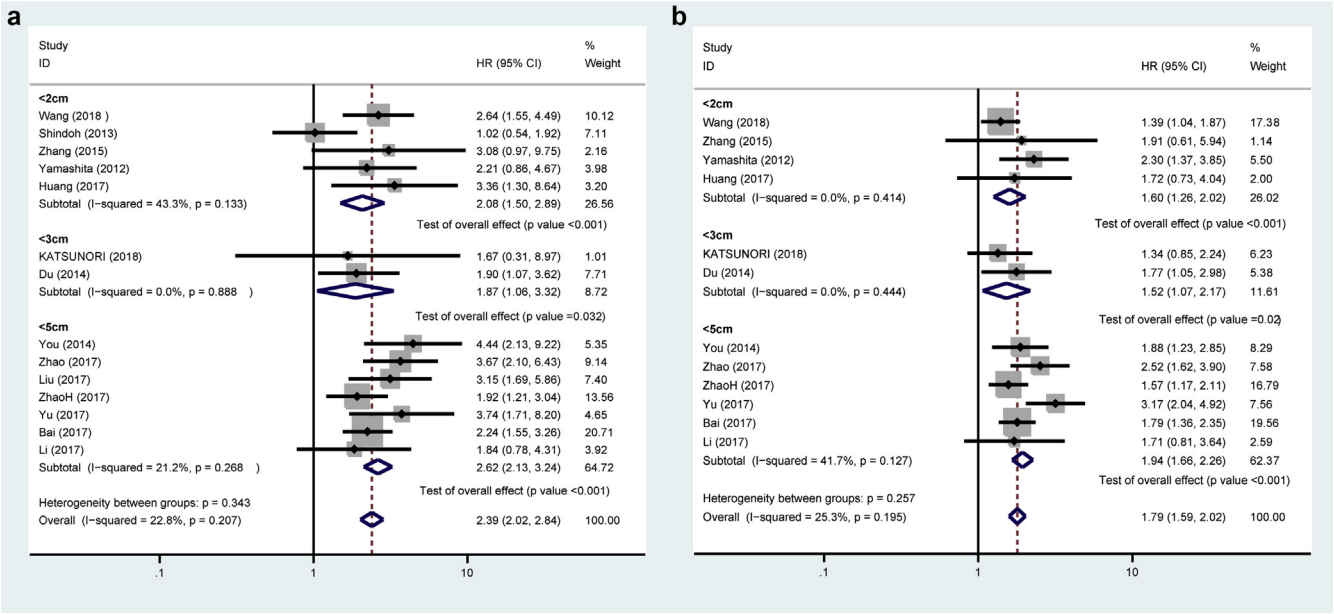

Figure 3 Pooled hazard ratio for overall survival and disease-free survival in subgroup analysis. Outcomes: a. Pooled hazard ratio for overall survival; b. Pooled hazard ratio for disease-free survival

Subgroup analysis

We performed a subgroup analysis based on the tumor diameter. In the subgroup analysis (Fig. 3), the results showed that for patients with solitary small HCC tumors measuring up to 5 cm, the MVI-positive group had a statistically significant worse overall survival (HR = 2.62, 95% CI = 2.13 to 3.24, I^2 = 21.2%, P < 0.001) and disease-free survival (HR = 1.94, 95% CI = 1.66 to 2.26, I^2 = 41.7%, P < 0.001). For patients with small HCC tumors measuring up to 3 cm, the MVI-positive group still had a relatively worse overall survival (HR = 1.87, 95% CI = 1.06–3.32, I^2 = 0%, P = 0.032) and disease-free survival (HR = 1.52, 95% CI = 1.07–2.17, I^2 = 0%, P = 0.02) compared with the MVI-negative group. Most notably, even for patients with small HCC tumors with a diameter up to 2 cm, the MVI-positive group also had poor overall survival (HR = 2.08, 95% CI = 1.50–2.89, I^2 = 43.3%, P < 0.001) and disease-free survival (HR = 1.60, 95% CI = 1.26–2.02, I^2 = 0%, P < 0.001), and the difference between the two groups was statistically significant. Therefore, we concluded that for solitary small HCC patients after hepatic resection of tumors with diameters up to 2 cm, 3 cm, or 5 cm, the microvascular invasion significantly showed a negative effect on the long-term overall survival and disease-free survival.

Publication bias and sensitivity analysis

The funnel plots of OS and DFS are shown in Fig. S2, and visual inspection of the funnel plots suggested a symmetric distribution of the main studies. Begg and Egger tests confirmed that there was no significant publication bias (Fig. S1). A sensitivity analysis was performed by excluding each study to determine the stability of the overall treatment effects. This did not influence the results (Fig. S3).

Discussion

To date, our study is the first systematic review and meta-analysis to explore the effect of MVI on the postoperative long-term prognosis of patients with solitary small hepatocellular carcinoma. Additionally, this study is the first comprehensive research to focus on exploring the effect of MVI on the postoperative OS and DFS only in patients with solitary small HCC up to 5 cm. Furthermore, we first reviewed 14 high-quality studies that included 3003 solitary small patients, which is the largest sample size to explore the effect of MVI on the postoperative long-term prognosis of solitary small HCC.

Microvascular invasion is a histological feature of hepatocellular carcinoma related to aggressive biological behavior, and HCC is also characterized by a tendency for vascular invasion. During the past decades, many studies have addressed the prognostic significance of MVI in HCC, either as a primary or secondary object. Rodriguez- Peralvarez *et al.*[11] conducted a meta-analysis (n = 1501) concluding that the presence of MVI shortened disease-free survival at 3 and 5 years (RR = 1.82, 95% CI = 1.61–2.07; RR = 1.51, 95% CI = 1.29–1.77). Nevertheless, the meta-analysis did not explore the prognostic significance of MVI especially for solitary small HCC, and the effect of MVI on the postoperative long-term prognosis remained controversial for solitary small HCC. This meta-analysis provides evidence that MVI is a predictor of poorer OS and DFS prognosis in patients with solitary small HCC measuring up to 5 cm (OS:

HR = 2.39, 95% CI = 2.02–2.84, I^2 = 22.8%, P < 0.001; DFS: HR = 1.79, 95% CI = 1.59–2.02, I^2 = 25.3%; P < 0.001). The prognosis of HCC patients remains unsatisfactory despite the improvement in surgical techniques and perioperative management. Hepatic resection is considered the most effective treatment for small HCC patients. However, recurrence is the leading cause of death during the initial 5-year period after intensive radical resection. High incidence rate of intrahepatic recurrence remains one major obstacle for further improving the long-term prognosis of solitary small HCC patients after curative resection. As MVI was a predictor of poorer prognosis in solitary small HCC, the detection and prevention for MVI will be a target for this subset of patients.

Our study further indicates that MVI is still a predictor of poorer OS and DFS prognosis in patients with smaller HCC measuring up to 2 cm or 3 cm. The tumor size cut-off value of 2 cm in solitary HCC was the criterion for very early stage HCC both in the Barcelona Clinic Liver Cancer staging system and the TNM staging system.[16,17] The TNM stage is the only staging system that considers microvascular invasion (MVI) as a staging criterion. However, the 8th Edition of the AJCC Cancer Staging Manual no longer discusses the prognostic impact of MVI on this type of HCC based on a multicenter clinical retrospective study.[8] Currently, Wang *et al.* demonstrated that MVI predicts a poor prognosis of solitary hepatocellular carcinoma measuring up to 2 cm based on propensity score matching analysis with a large number of patients (n = 496). In our subgroup meta-analysis, five studies regarding OS and 4 studies regarding DFS were included in the analysis of solitary small HCC measuring up to 2 cm. Our meta-analysis provides conclusive evidence that MVI is still a poorer prognosis prediction factor for patients with small HCC measuring up to 2 cm, which may play an important role in reclassifying the 8th Edition of the AJCC Cancer Staging Manual for TNM staging system to reconsider MVI as a significant staging criterion for solitary HCC up to 2 cm. Furthermore, the common staging system for HCC such as the Barcelona Clinic Liver Cancer (BCLC) classification and the Chinese University Prognostic Index (CUPI) staging system may attach enough importance to the MVI on the prognosis for solitary small HCC patients as to provide more targeted, stratified, and selective therapy for these patients.

Based on the findings of the study, even for solitary small HCC patients with MVI, adjuvant postoperative transarterial chemoembolization (TACE) may serve as a reasonable therapy to better the long-term survival of these patients. Currently, our group[34] has demonstrated the effectiveness of adjuvant TACE in a research of 322 HCC patients with MVI. In addition, some studies[35–37] have suggested that adjuvant TACE might benefit HCC patients with MVI as a promising postoperative therapy modality. In addition, based on some easy and precise methods to predict MVI before surgery,[38] anatomical resection or wider resection margins can be adopted to provide prognosis benefit for solitary small HCC patients with MVI.[10,39]

Several limitations persist in this analysis that should be considered. First, this meta-analysis contained NRCT studies; therefore, selection bias was possible. Second, the lack of consensus on the definition of MVI in HCC may influence the outcomes of each study included in the meta-analysis. We have systematically searched databases based on our search strategy, and all relevant studies were included in our analysis. The above limitations could have affected the results of this meta-analysis.

Conclusion

In conclusion, this systematic review and meta-analysis suggests that microvascular invasion was a risk factor of poorer prognosis for solitary small hepatocellular carcinoma. Importantly, these results need to be validated in further high-quality clinical trials.

Authors contributions

Conception and design: Shu-Qun Cheng, Zhen-Hua Chen, Xiu-Ping Zhang, Hang Wang.

Financial support: Shu-Qun Cheng.

Provision of study materials or patients: Zong-Tao Chai, Ju-Xian Sun, Wei-Xing Guo, Jie Shi.

Collection and assembly of data: Zhen-Hua Chen, Xiu-Ping Zhang, Hang Wang.

Data analysis and interpretation: Zhen-Hua Chen, Xiu-Ping Zhang, Hang Wang.

Manuscript writing: Zhen-Hua Chen, Xiu-Ping Zhang.

Final approval of manuscript: All authors.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.02.003.