

## Review Article

# Prognostic and clinicopathological significance of MACC1 expression in hepatocellular carcinoma patients: a meta-analysis

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**Abstract:** Objective: Metastasis-associated in colon cancer-1 (MACC1) has been reported to be overexpressed in diverse human malignancies. However, the prognostic and clinicopathological value of MACC1 in hepatocellular carcinoma (HCC) remains inconclusive. Therefore, we conducted this meta-analysis to investigate the association between MACC1 expression and the outcomes of HCC. Methods: Relevant articles were searched in PubMed, Embase, Sciencedirect, CNKI, and Wanfang databases updated to October 2014. The pooled hazard ratios (HRs) and odds ratios (ORs) with their 95% confidence intervals (CIs) were assessed using STATA 10.0, and then the correlations of MACC1 expression with overall survival (OS), disease-free survival (DFS), and clinicopathological features were analyzed. Results: 9 studies with a total of 1293 HCC patients were included in this meta-analysis. Our results showed that MACC1 over-expression was significantly associated with poor OS (HR = 2.30, 95% CI 1.47-3.59, univariate analysis; HR = 2.39, 95% CI 1.49-3.82, multivariate analysis), poor DFS (HR = 1.73, 95% CI 1.40-2.13, univariate analysis). Moreover, MACC1 over-expression was significantly associated with AFP level (OR = 1.31, 95% CI 1.03-1.68), tumor number (OR = 1.37, 95% CI 1.07-1.75), differentiation (OR = 2.37, 95% CI 1.46-3.83), TNM stage (OR = 2.89, 95% CI 2.18-3.82), vascular invasion (OR = 1.89, 95% CI 1.43-2.50), capsule invasion (OR = 2.89, 95% CI 1.40-5.94), and metastasis (OR = 2.66, 95% CI 1.16-6.10). Conclusion: MACC1 over-expression indicated poor survival rate, high recurrence rate, and aggressive biological behaviors. MACC1 can serve as an indicator of prognosis and a potential novel target for treatment in HCC patients.

**Keywords:** MACC1, HCC, prognosis, meta-analysis

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of cancer-related death [1]. Every year there are 500 000 new cases in the Asia-Pacific region, often due to chronic hepatitis B virus (HBV) infection. More than 60% of the total number of HCC cases occur in China alone, and an estimated 360 000 patients residing in Far East countries, including China, Japan, Korea, and Taiwan, die from this disease each year [2]. In contrast, chronic hepatitis C virus (HCV) related HCC represents 70% of all cases in Japan [3], and increased incidence of HCV has led to an increased incidence of HCC in USA [4]. As to clinical manifes-

tations, HCC exhibits no specific symptoms in early stage. As a result, HCC is frequently diagnosed in late stage, which needs costly surgical resection, liver transplantation, and/or ablative therapies. Currently, molecular-targeted agents such as sorafenib have emerged as a promising therapy for advanced HCC. However, the prognosis after clinical treatments remains unsatisfactory due to the high recurrence rate [5]. Therefore, it is essential to identify biological markers for diagnosing HCC in its early stage and predicting the prognosis, such as recurrence after treatments.

Metastasis-associated in colon cancer-1 (MACC1) is located on chromosome 7 at position 7p21.1, which was initially discovered by

genome-wide expression analysis in primary and metastatic colon cancer [6]. This new gene can promote tumor cell growth as well as the development of distant metastasis. It has been reported that MACC1 could mediate the activation of hepatocyte growth factor (HGF)-MET signaling pathway, leading to tumor progression, invasion, and metastasis [7, 8]. In addition, MACC1 also plays an important role during the process of carcinogenesis in some malignancies, such as nasopharyngeal carcinoma and colorectal cancer through regulating Akt/ $\beta$ -catenin or  $\beta$ -catenin signaling pathway [9, 10]. Recently, MACC1 has been reported to be a new remarkable biomarker for disease prognosis and prediction of therapy response for colorectal cancer and also for a variety of additional forms of solid cancers including HCC [11].

However, the prognostic and clinicopathological significance of MACC1 expression in HCC patients remains inconclusive. Consequently, basing on available studies, we conducted this meta-analysis to systematically and comprehensively investigate whether and how the increased MACC1 expression impacted the prognosis of HCC.

### Materials and methods

#### *Literature search*

A comprehensive literature search of electronic databases PubMed, Embase, Sciencedirect, CNKI, and Wanfang was performed up to October, 2014. Studies were searched by using the following keywords: "HCC" or "hepatocellular carcinoma" or "liver cancer", "MACC1" or "metastasis-associated in colon cancer-1". The reference lists of relative articles were manually searched for additional studies.

#### *Selection criteria*

The inclusion criteria included the followings: (1) clinical study about the correlation of MACC1 expression with the outcomes of HCC; (2) HCC was confirmed by pathological methods; (3) MACC1 expression was detected by any method in primary HCC tissue rather than serum or other kinds of specimen; (4) clinicopathological features and/or prognostic results were provided in the article. Articles were excluded from the analysis if they met any item of the following criteria: (1) studies using cells lines or animals;

(2) review or duplicated articles; (3) articles without key information such as Kaplan-Meier curves, hazard ratios (HRs) with their 95% confidence intervals (CIs), or clinicopathological features. There was no limitation on language as well as the minimum of patients in every single study. When there were multiple articles by the same group based on similar patients and using the same detection methods, only the largest or the most recent article was included.

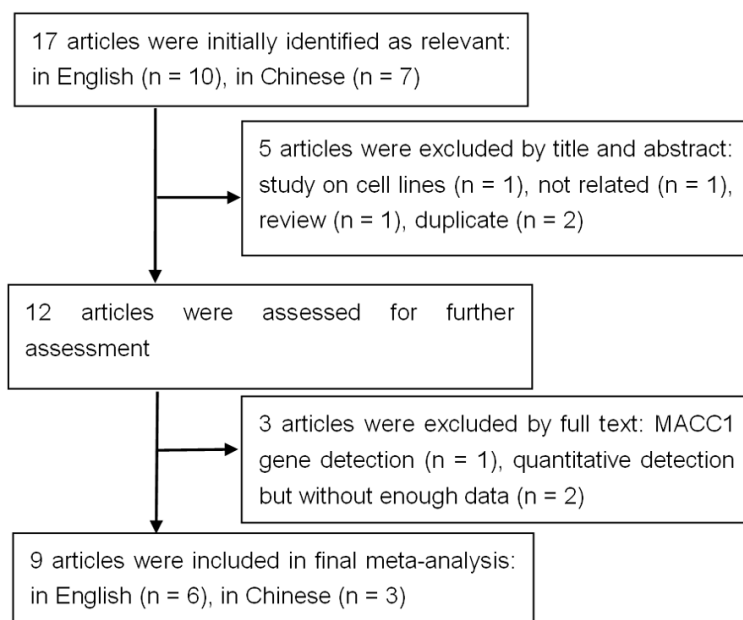
#### *Data extraction*

Included studies were assessed independently by two investigators (Sun DW and Zhang YY). All relevant data from texts, tables and figures of each included studies were extracted, including first author, publication year, country, patient number, detection method, percentage of increased MACC1 expression, range of TNM stage, therapeutic methods, and clinicopathological features such as HBV (positive vs. negative), liver cirrhosis (present vs. absent), alpha fetoprotein (AFP) level ( $> 400$  ng/L vs.  $< 400$  ng/L), tumor size ( $> 5$  cm vs.  $< 5$  cm), tumor number (multiple vs. single), grade of differentiation (poor vs. well/moderate), TNM stage (III/IV vs. I/II), vascular invasion (positive vs. negative), capsule invasion (positive vs. negative), and intrahepatic/extrahepatic metastasis (positive vs. negative). Besides, the MACC1 expression-related survival results such as OS and DFS were also extracted. When the hazard ratios (HRs) and their 95% confidence intervals (CIs) were given explicitly in the articles, we used the crude ones. If the prognosis was only plotted as Kaplan-Meier curve in some articles, the software Engauge Digitizer version 4.1 (<http://digizeer.sourceforge.net/>) was applied to digitize and extract the data. In case, controversial problems were resolved in a meeting called by Lv GY.

#### *Methodological quality of the studies*

Newcastle-Ottawa Scale (NOS) criteria was used to assess the methodological quality of included studies [12]. The NOS criteria is scored based on three aspects: (1) subject selection, (2) comparability of subject, (3) clinical outcome. NOS scores range from 0 to 9, and a score  $\geq 6$  indicates a high quality. Two investigators (Qi Y and Liu GQ) independently assessed the quality of the 9 included studies, and the discrepancies were solved by consensus.

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**Figure 1.** Flowchart of searching relevant studies used in this meta-analysis.

### Statistical analysis

To assess the correlation between MACC1 expression and the clinical outcomes in HCC patients, both HRs and ORs with their 95% CIs were used to combine as the effective value. In more details, combined HRs with their 95% CIs were used to assess the impact of MACC1 overexpression on prognostic outcomes such as OS, DFS. Then combined ORs with their 95% CIs were used to assess the impact of MACC1 overexpression on clinicopathological factors. A combined HR/OR > 1 indicated a poor outcome for increased MACC1 expression, while HR/OR < 1 indicated a favorable outcome for increased MACC1 expression. Heterogeneity among the studies was determined by chi-square test and Q test. If heterogeneity was significant ( $P < 0.1$  or  $I^2 > 50\%$ ), random-effect model was used. Otherwise, fixed-effect model was used. Both Egger's and Begg's tests were used to examine publication bias [13, 14]. All  $P$  values were two-sided, and  $P < 0.05$  was considered as statistically significant. Statistical calculations were all performed using STATA 10.0 and SPSS 13.0.

### Results

#### Literatures information

A total of 17 articles were identified initially using the search strategy above. Through read-

ing title and abstract, 5 articles above were excluded due to nonhuman experiment ( $n = 1$ ), unrelated ( $n = 1$ ), review ( $n = 1$ ), and duplicate ( $n = 2$ ). Further reading the full text remained, 3 articles were excluded due to single nucleotide polymorphisms analysis ( $n = 1$ ), and quantitative detection but without enough data ( $n = 2$ ). Finally, there were 9 studies (6 in English and 3 in Chinese) included in the present meta-analysis [15-23] (**Figure 1**).

#### Study characteristics

The main characteristics of the 9 included studies were summarized in **Table 1**. All the included studies were conducted in China, and they were published between 2010 and 2014. The total number of patients was 1293 with sample sizes ranging from 42 to 354. To screen the MACC1 expression status, immunohistochemistry (IHC) was used in 4 studies [15, 19, 21, 22] and reverse transcription-polymerase chain reaction (RT-PCR) was used in 5 studies [16-18, 20, 23]. The median rate of increased MACC1 expression was 50.0% (39.8%-80.4%). In regarding to therapeutic methods, 7 studies were based on surgical resection [15, 16, 18, 19, 21-23], one study was based on liver transplantation [20], and the other one was based on cryoablation [17]. Meanwhile, the follow up time ranged from 18 months to 100 months. What's more, 8 studies assessed the correlations of MACC1 expression with both clinicopathology and prognosis [15-22], while the remaining one only assessed the correlation between MACC1 expression and clinicopathological features [23]. According to the NOS criteria, all of the included studies got 6 scores or more, which indicated high methodological quality.

#### MACC1 and OS in HCC

For studies evaluating OS, there were two kinds of analytical methods used in the included studies. In details, univariate analysis was used in 6 studies with 777 HCC patients, while multivariate analysis was used in 5 studies with 882

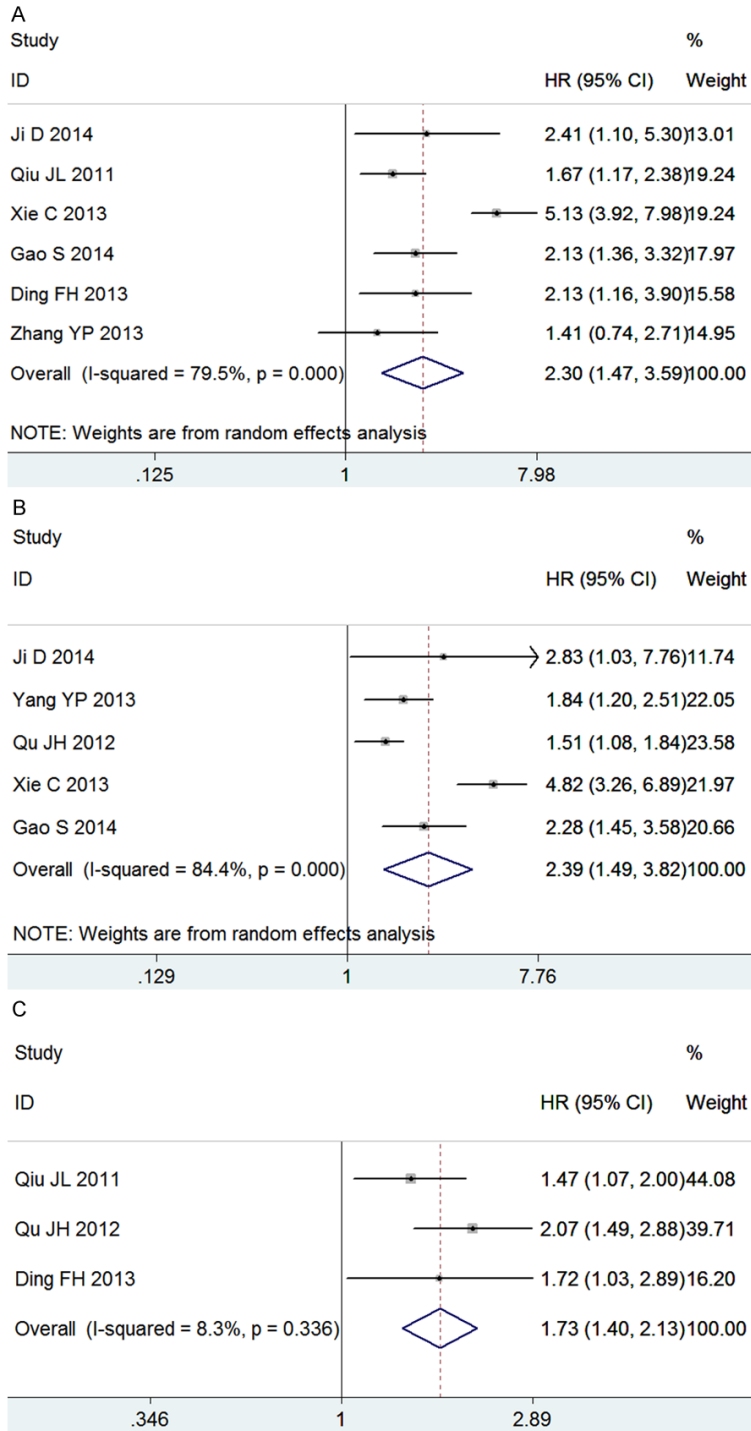
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**Table 1.** Characteristics of included studies in this meta-analysis

First author [Ref.]	Year	Country	No. of patients	Method	Increased MACC1 (%)	Stage range	Clinicopathological features	Treatments	Follow-up time	Survival analysis	HR (95% CI)	Data extract	Score
Ji D [15]	2014	China	60	IHC	41 (68.3)	I-IV	①, ②, ③, ④, ⑥, ⑦, ⑧, ⑨, ⑩	Resection	36 months	OS (U, M)	OS (U), 2.41 (1.10-5.30) OS (M), 2.83 (1.03-7.76)	Direct Direct	8
Qiu J [16]	2011	China	128	RT-PCR	51 (39.8)	I-III	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨	Resection	85 months	OS (U), DFS (U)	OS (U), 1.67 (1.17-2.38) DFS (U), 1.47 (1.07-2.00)	Curve Curve	9
Yang YP [17]	2013	China	120	RT-PCR	60 (50.0)	Advanced	①, ⑤, ⑥, ⑧	Cryoablation	18 months	OS (M)	OS (M), 1.84 (1.20-2.51)	Direct	7
Qu JH [18]	2012	China	354	RT-PCR	177 (50.0)	I-IV	①, ③, ⑤, ⑥, ⑦, ⑧	Resection	48 months	OS (M), DFS (U)	OS (M), 1.51 (1.08-1.84) DFS (U), 2.07 (1.49-2.88)	Direct Curve	8
Xie C [19]	2013	China	308	IHC	126 (40.9)	I-IV	①, ③, ⑤, ⑦	Resection	75 months	OS (U, M)	OS (U), 5.13 (3.92-7.98) OS (M), 4.82 (3.26-6.89)	Direct Direct	8
Gao S [20]	2014	China	160	RT-PCR	72 (45.0)	NA	③, ④, ⑤, ⑥, ⑧	Transplantation	100 months	OS (U, M)	OS (U), 2.13 (1.36-3.32) OS (M), 2.28 (1.45-3.58)	Direct Direct	8
Ding FH [21]	2013	China	70	IHC	33 (47.1)	I-IV	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑩	Resection	47 months	OS (U), DFS (U)	OS (U), 2.13 (1.16-3.90) DFS (U), 1.72 (1.03-2.89)	Curve Curve	9
Zhang YP [22]	2013	China	51	IHC	41 (80.4)	I-IV	①, ④, ⑤, ⑥, ⑦, ⑧, ⑨	Resection	36 months	OS (U)	OS (U), 1.41 (0.74-2.71)	Curve	7
Liu QQ [23]	2010	China	42	RT-PCR	30 (71.4)	I-IV	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧, ⑨, ⑩	Resection	NA	NA	NA	NA	6

Abbreviations: No., number; IHC, immunohistochemistry; RT-PCR, reverse transcription-polymerase chain reaction; NA, not available; ①, HBV; ②, liver cirrhosis; ③, AFP; ④, tumor size; ⑤, tumor number; ⑥, grade of differentiation; ⑦, TNM stage; ⑧, vascular invasion; ⑨, capsule invasion; ⑩, metastasis; OS, overall survival; DFS, disease-free survival; U, univariate analysis; M, multivariate analysis; HR, hazard ratio.

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**Figure 2.** Meta-analysis for the effect of MACC1 on OS from univariate analysis results (A), OS from multivariate analysis results (B), and DFS from univariate analysis results (C).

HCC patients. Obviously, there was cross lap between these two analytical methods. There was significant heterogeneity ( $I^2 = 79.5\%$ ,  $P = 0.000$ ;  $I^2 = 84.4\%$ ,  $P = 0.000$ ) within studies

performed by both univariate analysis and multivariate analysis relatively, so random-effect models were applied to calculate the pooled HRs and their 95% CIs. We found that increased MACC1 expression was significantly correlated with poor OS (HR = 2.30, 95% CI 1.47-3.59,  $P = 0.000$ , univariate analysis; HR = 2.39, 95% CI 1.49-3.82,  $P = 0.000$ , multivariate analysis), indicating that MACC1 was an indicator of poor survival rate in HCC patients (Figure 2A, 2B).

### MACC1 and DFS in HCC

Totally, there were 3 studies with a total number of 432 patients providing survival results in the form of DFS. There was no significant heterogeneity ( $I^2 = 8.3\%$ ,  $P = 0.336$ ), so a fixed-effect model was used to calculate the pooled HR and its 95% CI. Our result showed that increased MACC1 expression was also significantly associated with poor DFS (HR = 1.73, 95% CI 1.40-2.13,  $P = 0.000$ , univariate analysis), indicating that increased MACC1 expression was an indicator of high recurrence rate in HCC patients (Figure 2C).

### MACC1 and clinicopathological features in HCC

To investigate the association between MACC1 expression and clinicopathological features, we conducted meta-analysis according to each available clinicopathological parameter. Our results showed that increased MACC1 expression was significantly correlat-

ed with AFP level (OR = 1.31, 95% CI 1.03-1.68, fixed-effect model), tumor number (OR = 1.37, 95% CI 1.07-1.75, fixed-effect model), grade of differentiation (OR = 2.37, 95% CI 1.46-3.83,

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**Table 2.** Meta-analysis for the association of increased MACC1 expression and clinicopathological features in HCC

Clinicopathological features	No. of studies	No. of patients	Model	OR (95% CI)	P-Value	Heterogeneity		
						$\chi^2$	$I^2$ (%)	P-Value
HBV (positive vs. negative)	8	1114	Fixed	0.90 (0.68-1.19)	0.467	6.04	0.0	0.535
Cirrhosis (present vs. absent)	4	296	Fixed	1.45 (0.80-2.62)	0.225	2.99	0.0	0.394
AFP (> 400 ng/L vs. < 400 ng/L)	7	1108	Fixed	1.31 (1.03-1.68)	0.028	2.19	1.8	0.411
Size (> 5 cm vs. < 5 cm)	6	507	Fixed	1.28 (0.88-1.86)	0.196	1.29	21.1	0.274
Number (multiple vs. single)	8	1227	Fixed	1.37 (1.07-1.75)	0.012	5.30	0.0	0.624
Differentiation (poor vs. well/moderate)	8	981	Random	2.37 (1.46-3.83)	0.000	14.67	52.3	0.041
Stage (III/IV vs. I/II)	7	1005	Fixed	2.89 (2.18-3.82)	0.000	7.79	23.0	0.254
Vascular (positive vs. negative)	8	981	Fixed	1.89 (1.43-2.50)	0.000	9.22	24.1	0.237
Capsule (positive vs. negative)	5	347	Random	2.89 (1.40-5.94)	0.004	8.03	50.2	0.091
Metastasis (positive vs. negative)	3	168	Fixed	2.66 (1.16-6.10)	0.021	1.55	0.0	0.460

Abbreviations: HBV, hepatitis B virus; AFP, alpha-fetoprotein; No., number; OR, odds ratio; CI, confidence interval.

random-effect model), TNM stage (OR = 2.89, 95% CI 2.18-3.82, fixed-effect model), vascular invasion (OR = 1.89, 95% CI 1.43-2.50, fixed-effect model), capsule invasion (OR = 2.89, 95% CI 1.40-5.94, random-effect model), and metastasis (OR = 2.66, 95% CI 1.16-6.10, fixed-effect model). On the contrary, increased MACC1 expression was not found to be correlated with HBV status (OR = 0.90, 95% CI 0.68-1.19, fixed-effect model), liver cirrhosis (OR = 1.45, 95% CI 0.80-2.62, fixed-effect model), or tumor size (OR = 1.28, 95% CI 0.88-1.86, fixed-effect model). These results above suggested that HCC with increased MACC1 expression exhibits aggressive biological behaviors (Table 2).

### Publication bias

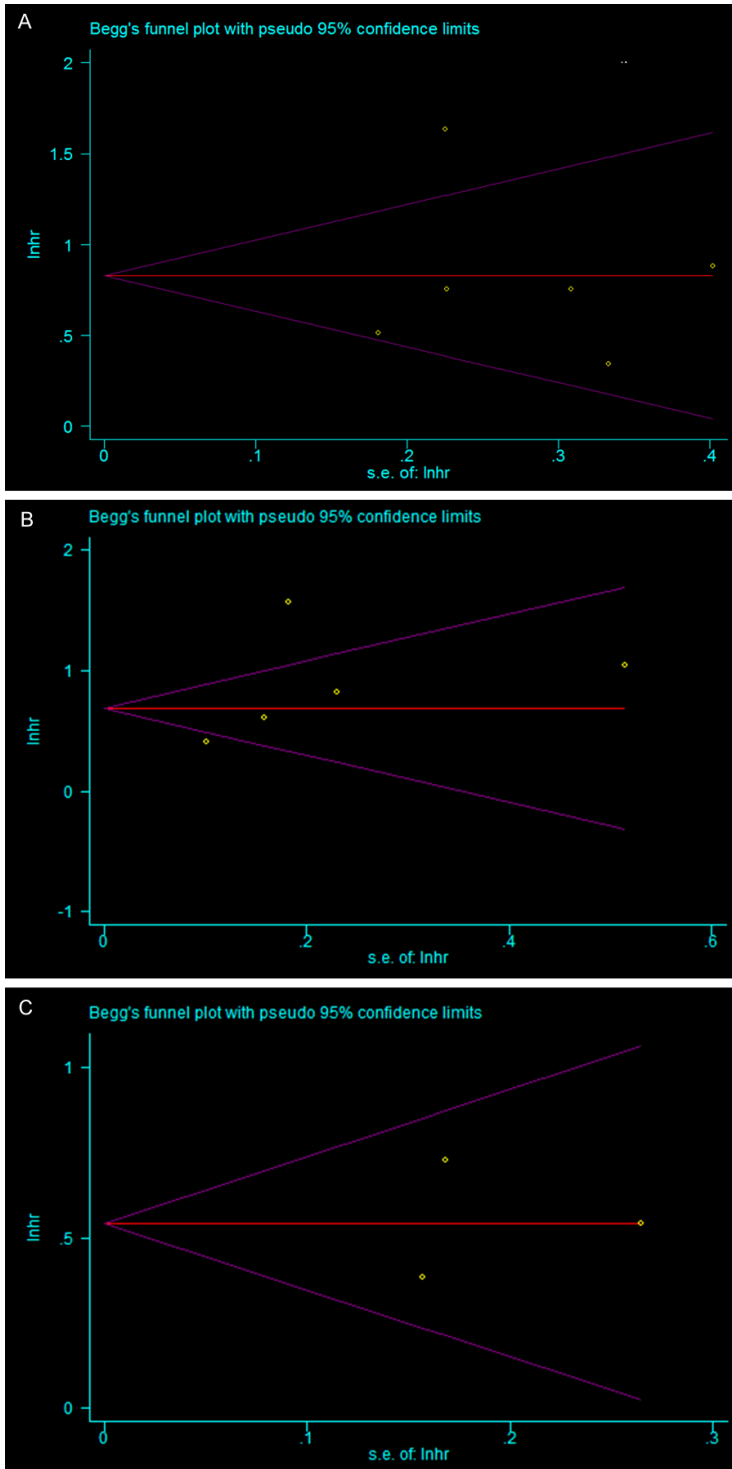
In this present meta-analysis, both Begg's and Egger's *P* value tests were used to examine the publication bias. No publication bias was observed among studies with OS (*P* = 0.702, 0.973, univariate analysis; *P* = 0.221, 0.354, multivariate analysis), DFS (*P* = 1.000, 0.915), AFP (*P* = 1.000, 0.563), liver cirrhosis (*P* = 0.734, 0.571), TNM stage (*P* = 0.133, 0.089), vascular invasion (*P* = 0.386, 0.299), capsule invasion (*P* = 0.462, 0.236), or metastasis (*P* = 0.296, 0.130). On the contrary, publication bias was observed among studies with HBV (*P* = 0.108, 0.013), tumor size (*P* = 0.024, 0.003), tumor number (*P* = 0.711, 0.030), and grade of differentiation (*P* = 0.063, 0.011). Besides, we also presented Begg's plots for the effect of MACC1 on prognosis including OS and DFS (Figure 3A-C).

### Discussion

HCC is one of the most devastating neoplasms worldwide with very poor prognosis despite therapeutic advancement. The recurrence rate after surgical resection is approximately 50% at 2 years and 75% at 5 years [24]. Therefore, it is essential to find novel prognostic and therapeutic approaches aiming at improving the outcome of patients with HCC. Since recurrence is the major cause of death for postoperative HCC patients, early identification of subjects at high-risk of recurrence is necessary to improve OS rates. MACC1 is a newly found oncogene located on chromosome 7 at position 7p21.1, which was discovered by genome-wide expression. Initially, this gene was identified as being involved in metastasis of colon cancers [6]. Further studies have revealed that MACC1 contributes to tumor progression and metastasis by regulating HGF-MET signaling pathway [7, 8], and it also plays an important role in carcinogenesis through regulating Akt/ $\beta$ -catenin or  $\beta$ -catenin signaling pathway [9, 10]. As a result, increased MACC1 expression is associated with the progression of diverse malignancies and the prognosis of the patients with these malignancies including HCC [11]. Here, the prognostic and clinicopathological value of MACC1 expression in HCC has been systematically analyzed based on available studies.

In this meta-analysis, we included 9 studies with 1293 patients to examine whether and how increased MACC1 expression impacted the prognosis of HCC patients. Notably, our results showed that increased MACC1 expression was significantly associated with OS and

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**Figure 3.** Funnel plots in the meta-analysis for the effect of MACC1 on OS from univariate analysis (A), OS from multivariate analysis (B), and DFS from univariate analysis (C). Neither Begg's test nor Egger's test showed evidence of publication bias for OS ( $P = 0.702, 0.973$ , univariate analysis;  $P = 0.221, 0.354$ , multivariate analysis), DFS ( $P = 1.000, 0.915$ , univariate analysis).

high recurrence rate. Meanwhile, MACC1 expression was also significantly associated with tumor number, grade of differentiation, TNM stage, vascular invasion, capsule invasion, and metastasis, suggesting that HCC with increased MACC1 expression exhibits aggressive biological behaviors. What's more, it has been reported that knockdown of MACC1 expression could suppress HCC cell migration and invasion, which was associated with the down-regulation of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and hepatocyte growth factor receptor (C-Met) protein [25]. Therefore, MACC1 could serve as an indicator of prognosis and a potential novel target for treatment in HCC patients.

However, there are some limitations in this meta-analysis, which should be addressed. The most important concern is whether these data can be extrapolated to other races. All the patients included in this study were Chinese, so the results of our study should be compared with other races. The second problem with this meta-analysis is heterogeneity. The cut-off values and detecting methods for MACC1 expression, and therapeutic methods for HCC patients were so variable that these factors might account for the heterogeneity. Finally, only the articles in English and Chinese were included in this study though we did not set limitation on language. Based on these reasons, the pooled HRs and ORs calculated in this meta-analysis may be just estimation, and our results should be substantiated by additional prospective studies especially in other races.

DFS of HCC patients, indicating MACC1 could serve as an indicator of poor survival rate and

In conclusion, we showed that increased MACC1 expression indicated poor survival rate,

high recurrence rate, and aggressive biological behaviors in HCC. Therefore, MACC1 can serve as an indicator of prognosis and a potential novel target for treatment in HCC patients. As our study has some limitations, more adequately and well-designed prospective studies are required to clarify the prognostic significance of MACC1 expression in HCC patients.

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### Disclosure of conflict of interest

None.

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