

Clinicopathological and prognostic significance of FoxM1 in hepatocellular carcinoma patients: a meta-analysis

Chaojie Liang^{1,*}

Jingyang Zhao^{2,*}

Hua Ge¹

Guangming Li¹

Jixiang Wu¹

¹Department of General Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China; ²Department of Tumor Center, Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China

*These authors contributed equally to this work

Background and aims: Recently, the abnormal expression of FoxM1 has been found in many malignant tumors. However, the clinicopathological and prognostic value of FoxM1 expression in hepatocellular carcinoma (HCC) patients remains controversial. We conducted a meta-analysis to establish the relationship between FoxM1 expression and the clinicopathological features and prognostic value in patients with HCC.

Methods: An electronic search for relevant articles was conducted according to a set of criteria in the PubMed, Cochrane Library, Web of Science, EMBASE, Chinese CNKI and Chinese WanFang databases. The correlation data between FoxM1 expression and clinicopathological features and survival outcomes were analyzed. Pooled odds ratios (ORs) and hazard ratios (HRs) with 95% CIs were calculated using STATA14.2.

Results: A total of 14 studies comprising of 2,036 patients were enrolled in this meta-analysis. The results showed that FoxM1 expression was related to the incidence, tumor size (>5 cm), vascular invasion, differentiation and TNM stage. Moreover, overexpression of FoxM1 indicated a poor 3- and 5-year overall survival rate (OS) and recurrence-free survival rate (disease-free survival rate).

Conclusion: Our meta-analysis indicated that FoxM1 expression was associated with incidence, tumor size (>5 cm), vascular invasion, differentiation and TNM stage. Accordingly, FoxM1 may be a reliable prognostic biomarker for patients with HCC. However, additional high-quality studies are still needed to further support these findings.

Keywords: FoxM1, hepatocellular carcinoma, clinicopathological feature, prognosis, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, which ranks fifth in incidence and second in mortality rate among all cancers worldwide, with about 690,000 patients' deaths each year.¹ At present, radical resection and liver transplantation are the main treatment options for HCC. However, the clinical symptoms of liver cancer in its early stage are atypical and many patients who have undergone treatment progress to middle-late stage. Moreover, HCC is not sensitive to radiotherapy and chemotherapy, and it easily recurs and metastasizes, which all contribute to its poor prognosis.²⁻⁴ Therefore, it is very important to study the molecular mechanism of recurrence, invasion and metastasis of liver cancer and find a more suitable prognostic target for HCC.

FoxM1 is a member of the Fox transcription factor family, and the human *FoxM1* gene is located on chromosome 12p13.3 and contains 10 exons.⁵ FoxM1 plays an

Correspondence: Jixiang Wu;
Guangming Li
Department of General Surgery, Beijing
Tongren Hospital, Capital Medical
University, No 2, Chongwenmennei
Street, Dongcheng, Beijing, 100730, China
Tel +86 1380 1015 118;
+86 1350 1122 244
Email trwujixiang2016@126.com;
liguangming2016@126.com

important role in the cell cycle phases G1/S and G2/M as a proliferation-specific transcription factor.^{6,7} Recently, studies have found that FoxM1 was highly expressed in a variety of malignant tumors, such as prostate cancer,⁸ cervical cancer,⁹ pancreatic cancer,¹⁰ lung cancer.¹¹ Moreover, the expression of FoxM1 was related to clinical features and prognosis. Several studies also found that FoxM1 is abnormally expressed in HCC. However, the relationship between the expression of FoxM1 and the clinicopathological characteristics and prognostic value in patients with HCC remains controversial. Lin et al¹² found that FoxM1 expression was associated with differentiation and TNM stage, but was not related to vascular invasion, tumor size and liver cirrhosis. Egawa et al¹³ found that FoxM1 expression was associated with alpha fetoprotein (AFP) level, tumor size differentiation, TNM stage and poor prognosis. Sun et al¹⁴ found that positive FoxM1 expression was correlated with tumor size, tumor number, TNM stage, but was not associated with AFP level, liver cirrhosis, vascular invasion and differentiation. Shi et al¹⁵ found that FoxM1 expression was related to differentiation, but was not associated with tumor size, tumor number, differentiation and TNM stage. Additionally, they found no significant correlation between FoxM1 expression and overall survival rate by multivariate analysis. In contrast, Meng et al¹⁶ found that overexpression of FoxM1 was related to tumor size, tumor number, vascular invasion and TNM stage, but not to differentiation. In view of the above discrepancies, it is necessary to conduct a meta-analysis to assess the role of FoxM1 in HCC.

Methods

Search strategy

A comprehensive literature search was conducted in electronic databases including the PubMed, Cochrane Library, Web of Science, EMBASE, Chinese CNKI and Chinese WanFang databases. The search ended on October 1, 2017. The following key words were used: (“FoxM1” or “FoxM1a” or “FoxM1b” or “FoxM1c”) and (“hepatocellular carcinoma” or “hepatic tumor” or “liver tumor” or “hepatic cancer” or “liver cancer” or “HCC”). No language limitation was imposed. We also searched the references cited in the identified articles to find out other applicable studies.

Inclusion criteria and exclusion criteria

The following inclusion criteria were used for all articles identified in the literature search: 1) The patients were clearly diagnosed with HCC and the FoxM1 expression status was directly examined; 2) The expression of FoxM1 was mainly tested by immunohistochemistry (IHC) analysis or RT-PCR

analysis; 3) Results that included clinicopathological characteristics, disease-free (recurrence-free) survival and overall survival and Hazard ratios (HRs) were reported or could be calculated from the published data.

Studies were excluded if: 1) they were non-eligible trials including ecological studies, case reports, reviews, editorials, letters, conference abstracts and animal trials; 2) they were repeat studies based on the same database or patients.

Data extraction and quality assessment

Two authors (Chaojie Liang, Jingyang Zhao) inspected the search findings. The titles and abstracts were inspected for potentially eligible studies. Discrepancies were resolved by discussion, re-extraction, or third-party adjudication. Extracted data included first author, publication year, experimental methods, antibody, antibody concentration, cut-off value, control, clinicopathological features and HRs with 95% CI for overall survival, recurrence-free survival and disease-free survival. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the studies, when the NOS \geq 6, we considered the study to be high quality, otherwise it was deemed as low quality. All of the studies included in this meta-analysis were considered to be high quality.

Statistical analysis

In this meta-analysis, the STATA 14.2 software (StataCorp LLC., College Station, TX, USA) was used to calculate the pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). Engauge Digitizer 10.0 software (GitHub, Inc., San Francisco, CA, USA) was used to extract the survival data from Kaplan–Meier curves in the articles. The relationship between FoxM1 expression and clinicopathological features, including gender, hepatitis B surface antigen (HBsAg), AFP, liver cirrhosis, tumor size (5 cm), vascular invasion, tumor number, differentiation and TNM stage was evaluated by fixed- or random-effects models when I^2 was $>50\%$ or $<50\%$. The HR or OR was considered to be statistically significant if the 95% CI did not overlap 1. The potential publication bias was examined by the funnel plots and Begg's test.

Results

Characteristics of studies

The details of the selection process are shown in Figure 1. Fourteen studies,^{12–25} comprising a total of 2,036 patients, were included in this meta-analysis. The included studies were published from 2010 to 2017, the sample size ranged from 52 to 406 patients. Thirteen of these studies were from China, and one from Japan. Nine of these studies were

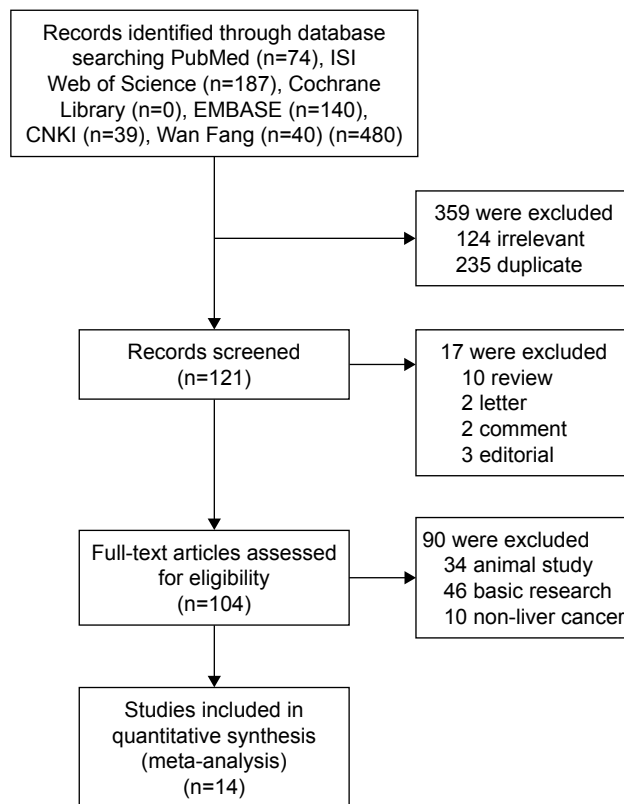


Figure 1 Flowchart of the study selection process.

published in English, and 5 in Chinese. All these studies scored ≥ 6 in the methodological assessment, which implied that they were of high quality.

The relationship between FoxM1 expression and clinicopathological features in patients with HCC

As shown in Table 1, the relationship between the FoxM1 expression and the clinicopathological features of HCC was established in this meta-analysis. Seven studies comprising

1,659 patients were used to evaluate the difference in FoxM1 expression between HCC tissue and normal tissue. The expression of FoxM1 in HCC was significantly higher than that in normal tissue (OR=6.54, 95% CI=3.84–11.14, $P<0.001$, Figure 2A). However, the expression of FoxM1 was not significantly associated with gender (OR=0.89, 95% CI=0.67–1.17, $P=0.391$, Figure 2B), HBsAg (OR=1.33, 95% CI=0.93–1.91, $P=0.871$, Figure 3A), liver cirrhosis (OR=1.05, 95% CI=0.81–1.37, $P=0.693$, Figure 3B), AFP (OR=1.26, 95% CI=1.00–1.59, $P=0.054$, Figure 4A) and tumor number (OR=0.90, 95% CI=0.42–1.93, $P=0.793$, Figure 5A). Six studies comprising 783 patients exhibited a significant relationship between FoxM1 expression and tumor size (≤ 5 cm: >5 cm) (OR=0.47, 95% CI=0.35–0.64, $P<0.001$, Figure 4B). The ORs for vascular invasion were calculated for 11 studies, including 1,491 patients. The results indicated a significant association between FoxM1 expression and vascular invasion (OR=2.61, 95% CI=1.93–3.53, $P<0.001$, Figure 5B). Additionally, FoxM1 expression was related to differentiation (OR=2.87, 95% CI=2.14–3.84, $P=0.000$, Figure 6A) and TNM stage (OR=0.34, 95% CI=0.26–0.44, $P<0.001$, Figure 6B).

The association between FoxM1 expression and overall survival in patients with HCC

The HRs for the 3-year and 5-year overall survival rate were calculated for 9 studies (Mo Ping had two data sets), which comprised 981 cases with positive FoxM1 expression and 705 cases with negative FoxM1. The results indicated that the expression of FoxM1 was related to poor 3-year overall survival (positive: negative, HR=1.48, 95% CI=1.10–1.87, $P=0.000$, Figure 7A) and 5-year overall survival (positive: negative, HR=1.73, 95% CI=1.37–2.09, $P=0.000$, Figure 7B).

Table 1 FoxM1 clinicopathological features for HCC

Heterogeneity							
Clinicopathological features	No. of studies	No. of patients	Pooled OR (95% CI)	PHet	I^2 (%)	P-value	Model used
Expression	7	1,659	6.54 (3.84–11.14)	0.000	78.4	<0.001	Random
Gender	11	1,491	0.89 (0.67–1.17)	0.536	0.0	0.391	Fixed
HBsAg	8	1,042	1.33 (0.93–1.91)	0.173	32.0	0.871	Fixed
Liver cirrhosis	8	1,300	1.05 (0.81–1.37)	0.054	49.3	0.693	Fixed
AFP	10	1,258	1.26 (1.00–1.59)	0.157	31.4	0.054	Fixed
Tumor size	6	783	0.47 (0.35–0.64)	0.164	36.4	<0.001	Fixed
Tumor number	4	502	0.90 (0.42–1.93)	0.079	55.9	0.793	Random
Vascular invasion	11	1,491	2.61 (1.93–3.53)	0.091	38.7	<0.001	Fixed
Differentiation	12	1,516	2.87 (2.14–3.84)	0.106	35.5	<0.001	Random
TNM stage	10	1,453	0.34 (0.26–0.44)	0.322	13.1	<0.001	Fixed

Abbreviations: HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; OR, odds ratio; AFP, alpha fetoprotein.

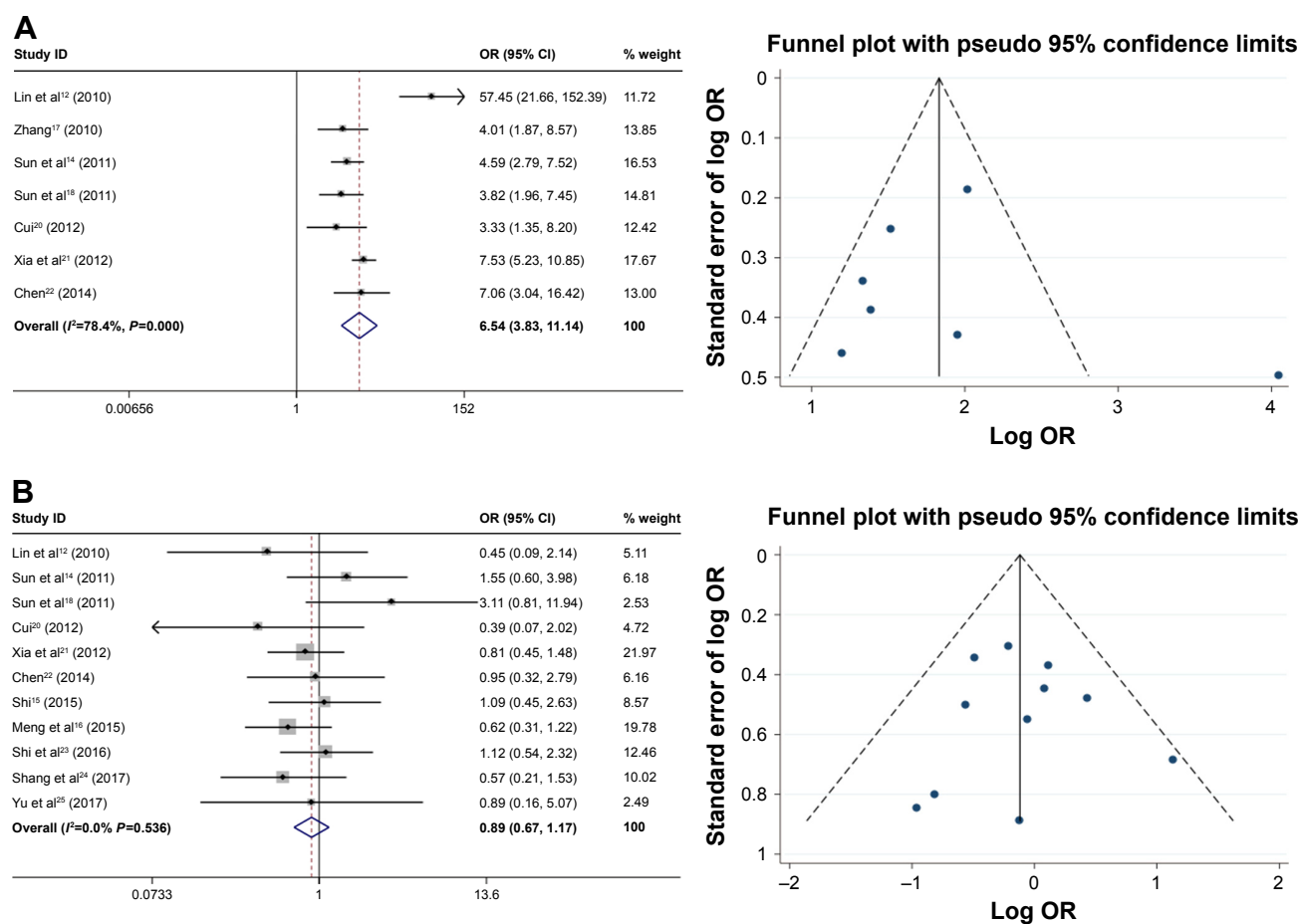


Figure 2 Forest plot and funnel plots of the studies evaluating the relationship between FoxM1 expression and clinicopathological features.

Notes: (A) expression; (B) gender. Weights are from random-effects analysis.

The association between FoxM1 expression and recurrence-free (disease-free) survival in patients with HCC

The HRs for the 3-year and 5-year recurrence-free survival rate were assessed for five studies (Mo Ping had two data sets), which included 676 cases with positive FoxM1

expression and 457 cases with negative FoxM1. The results indicated that expression of FoxM1 was related to poor 3-year recurrence-free survival (positive: negative, HR=1.85, 95% CI=1.40–2.30, $P=0.000$, Figure 8A) and 5-year recurrence-free survival (positive: negative, HR=1.94, 95% CI=1.53–2.35, $P=0.000$, Figure 8B). The HRs for

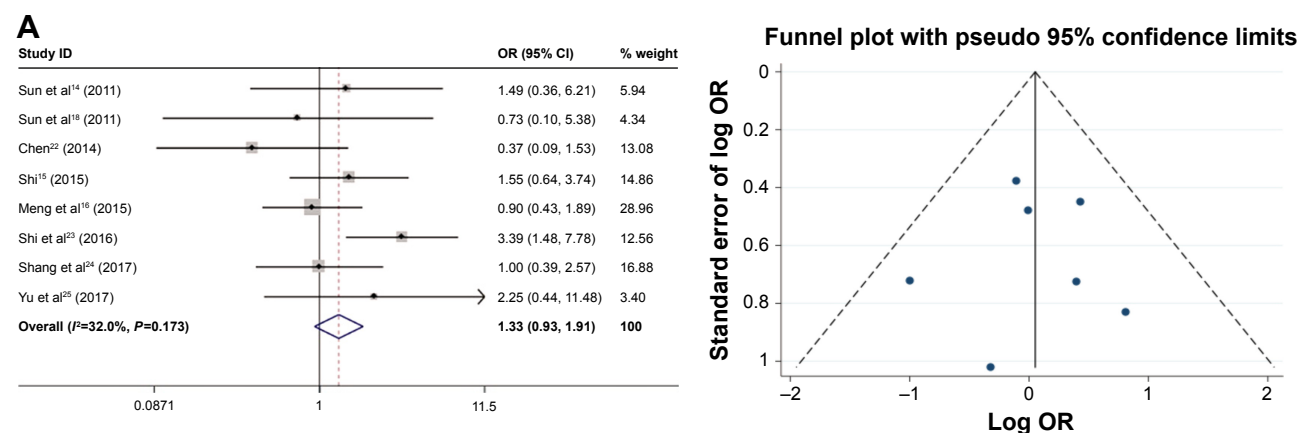
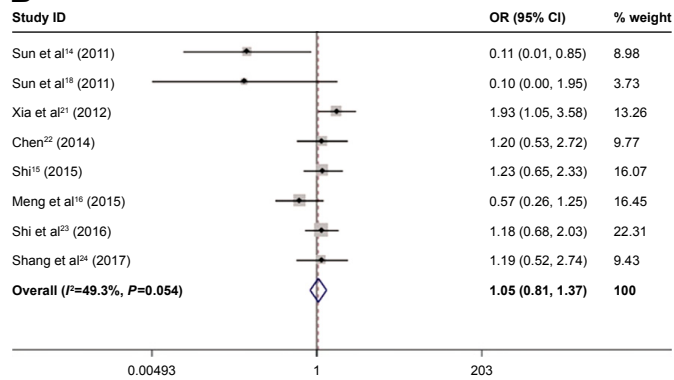
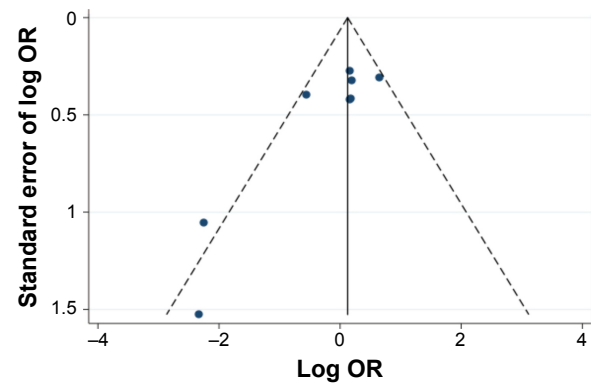


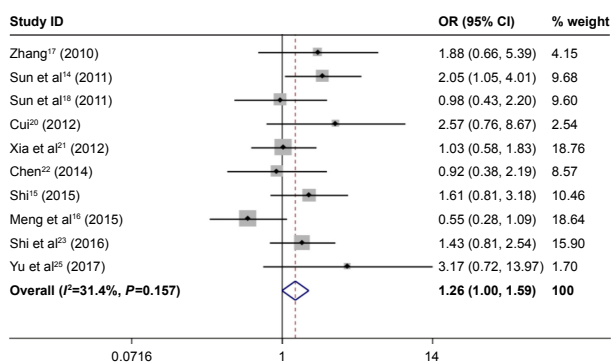
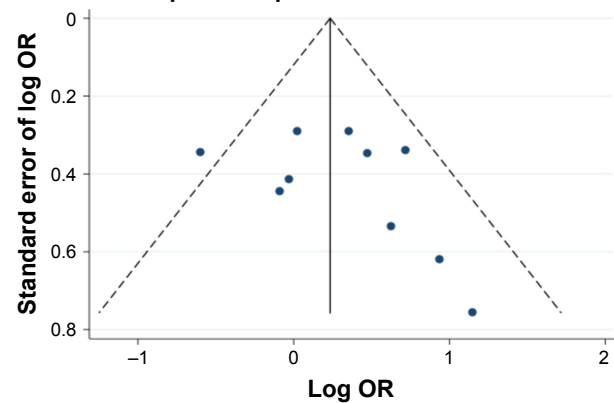
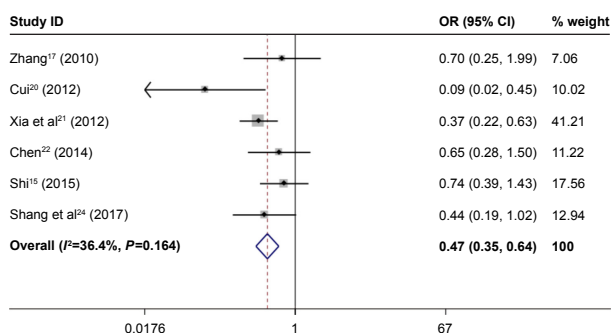
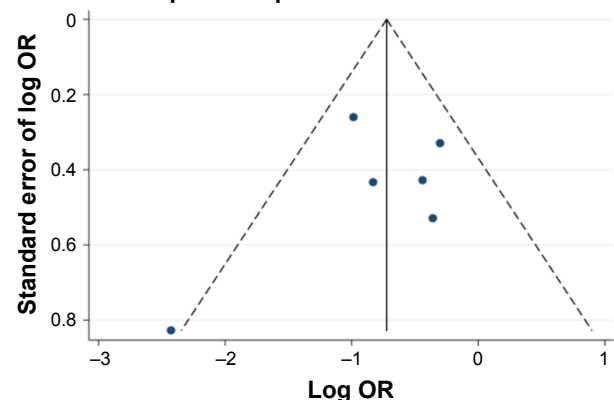
Figure 3 (Continued)

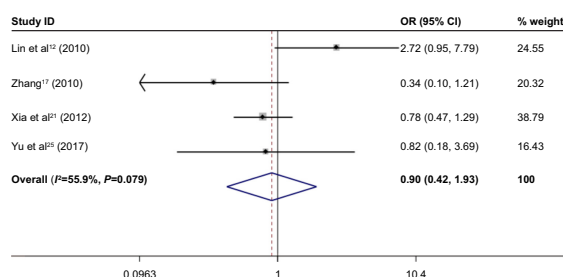
B**Funnel plot with pseudo 95% confidence limits****Figure 3** Forest plot and funnel plots of studies evaluating the relationship between FoxM1 expression and clinicopathological features.**Notes:** (A) HBsAg; (B) AFP.

disease-free survival rate were assessed for four studies, which included 305 cases with FoxM1 expression and 248 cases with FoxM1 suppression, the results showed that expression of FoxM1 was associated with poor disease-free survival (positive: negative, HR=1.72, 95% CI=1.19–2.35, $P=0.000$, Figure 8C).

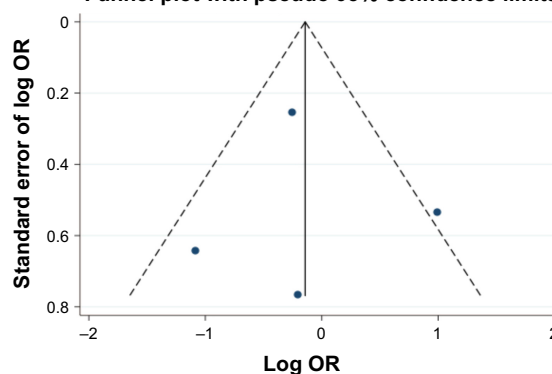
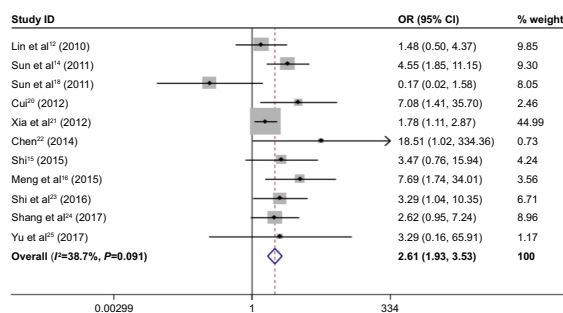
Publication bias and sensitivity analysis

According to the results of the Begg's test, there was no publication bias for FoxM1 expression ($P=0.734$), gender ($P=1$), HBsAg ($P=1$), liver cirrhosis ($P=0.063$), AFP ($P=0.296$), tumor size ($P=1$), vascular invasion ($P=0.755$), differentiation ($P=0.945$), TNM stage ($P=0.592$), 3-year

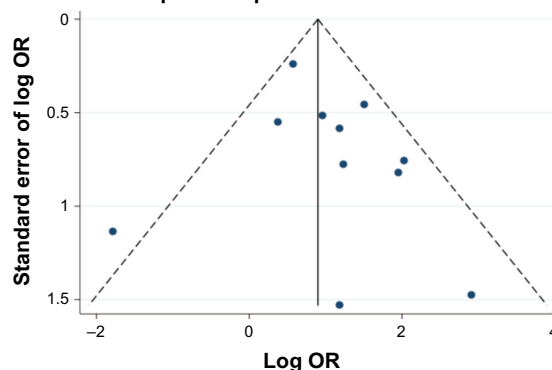
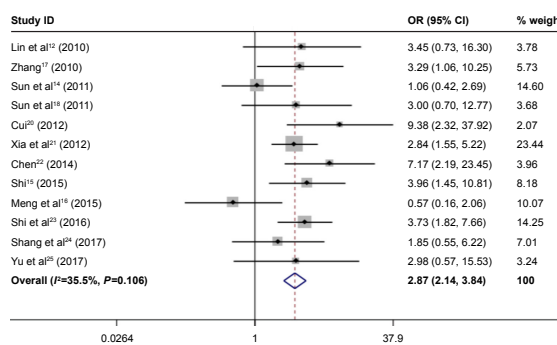
A**Funnel plot with pseudo 95% confidence limits****B****Funnel plot with pseudo 95% confidence limits****Figure 4** Forest plot and funnel plots of studies evaluating the relationship between FoxM1 expression and clinicopathological features.**Notes:** (A) Liver cirrhosis; (B) tumor size.

A

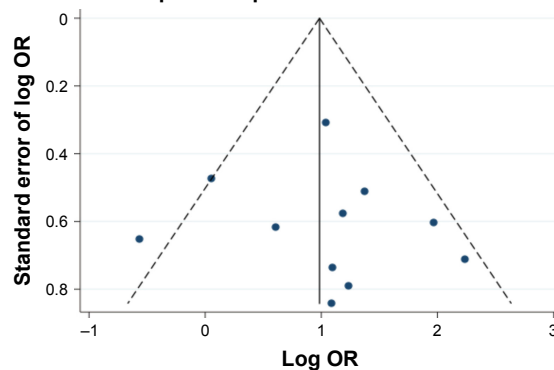
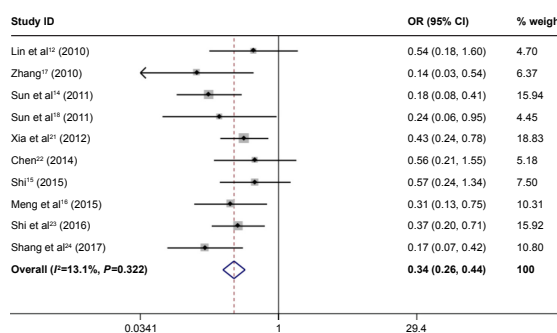
Funnel plot with pseudo 95% confidence limits

**B**

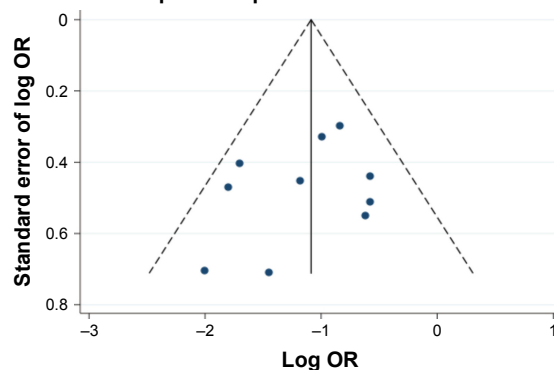
Funnel plot with pseudo 95% confidence limits

**Figure 5** Forest plot and funnel plots of studies evaluating the relationship between FoxM1 expression and clinicopathological features.**Notes:** (A) Vascular invasion; (B) tumor number. Weights are from random-effects analysis.**A**

Funnel plot with pseudo 95% confidence limits

**B**

Funnel plot with pseudo 95% confidence limits

**Figure 6** Forest plot and funnel plots of studies evaluating the relationship between FoxM1 expression and clinicopathological features.**Notes:** (A) Differentiation; (B) TNM stage.

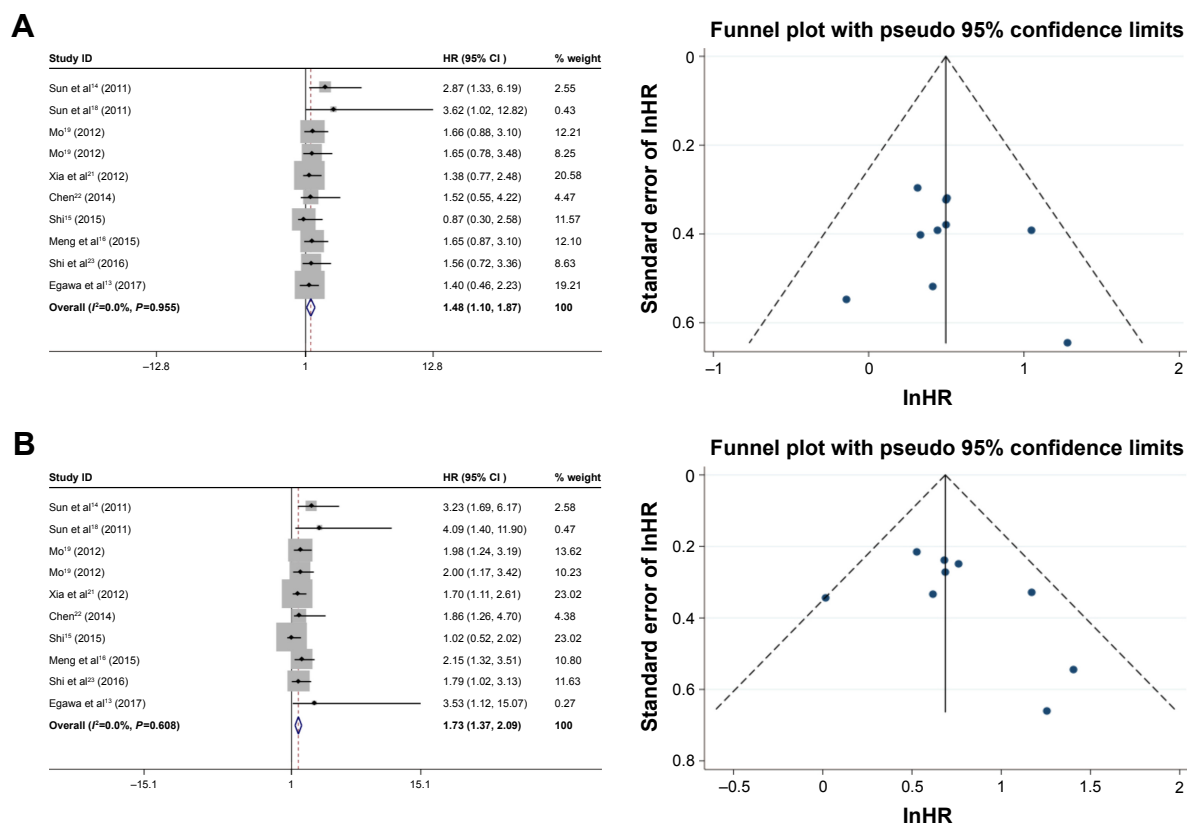


Figure 7 Forest plot and funnel plots of studies evaluating the relationship between FOXM1 expression and prognosis.

Notes: (A) 3-year overall survival; (B) 5-year overall survival.

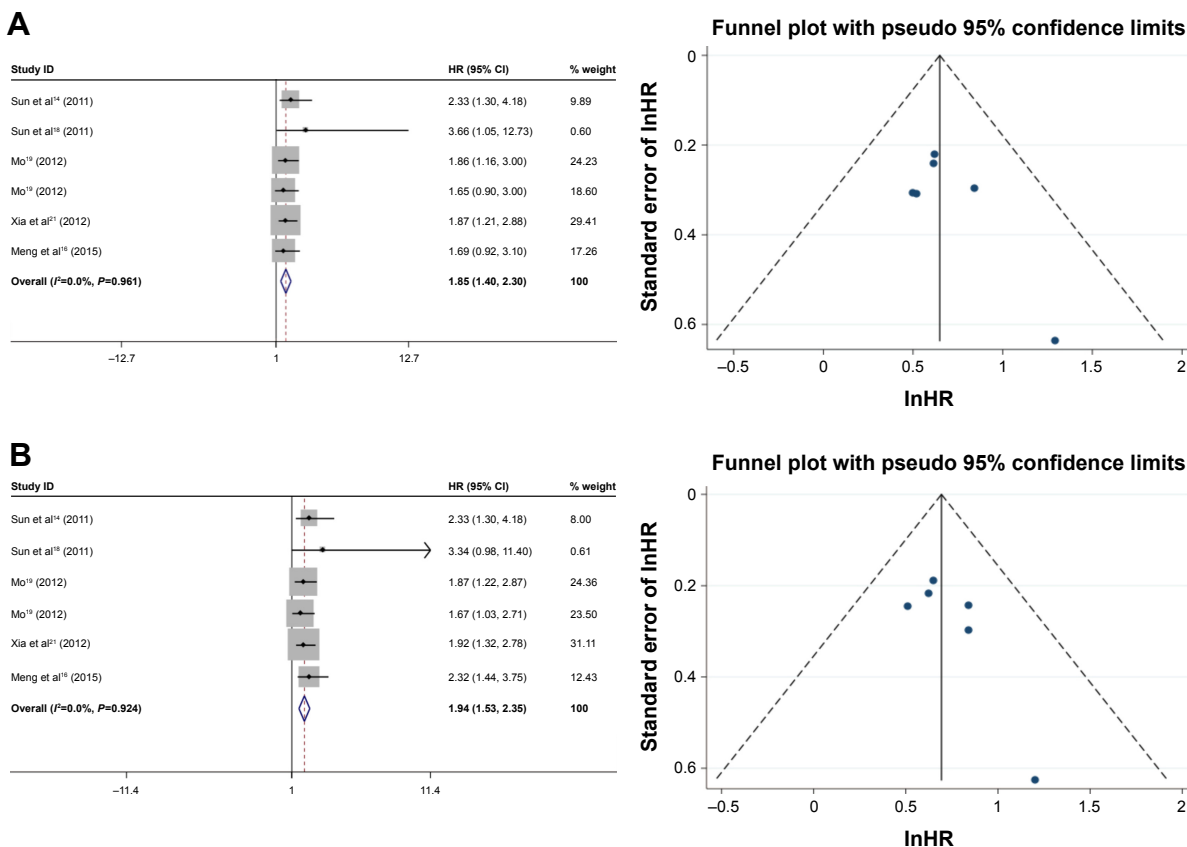


Figure 8 (Continued)

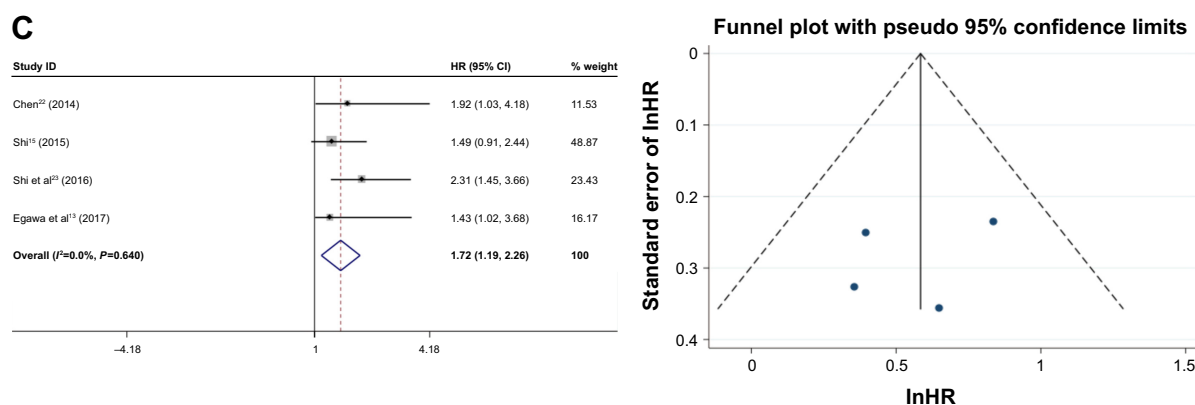


Figure 8 Forest plot and funnel plots of studies evaluating the relationship between FoxM1 expression and prognosis.

Notes: (A) 3-year recurrence-free survival; (B) 5-year recurrence-free survival; (C) disease-free survival.

overall survival rate ($P=0.592$), 5-year overall survival rate ($P=0.474$), 3-year recurrence-free survival rate ($P=1$), 5-year recurrence-free survival rate ($P=0.452$) and disease-free survival rate ($P=0.452$).

Discussion

FoxM1 is a member of the fork head transcription factor family, which is located at chromosome 12p13. The *FoxM1* gene encodes three isoforms: FoxM1A is a transcriptional

Table 2 Characteristics of studies included in the meta-analysis

Author	Year	Country	Kind	No of patients	Experimental method	Antibody	Antibody concentration	Cut-off value	Expression: cancer (+/-) control (+/-)	Gender male (+/-) female (+/-)
Lin et al ¹²	2010	China	HCC	91	IHC	Santa Cruz	1:100	>25%	73/18 6/85	57/16 16/2
Lijie et al ¹⁷	2010	China	HCC	60	IHC	Abcam	1:50	>10%	39/21 19/41	NA NA
Sun et al ¹⁴	2011	China	HCC	150	IHC	Santa Cruz	1:50	>10%	89/62 36/115	79/51 10/10
Sun et al ¹⁸	2011	China	HCC	99	IHC	Santa Cruz	1:50	>10%	42/57 16/83	39/46 3/11
Mo ¹⁹	2012	China	HCC	406	IHC	Santa Cruz	NA	>25%	NA	NA
Cui ²⁰	2012	China	HCC	52	IHC	Beijing Boasosen	NA	>10%	35/17 13/21	26/15 9/2
Xia et al ²¹	2012	China	HCC	306	IHC	Santa Cruz	NA	>25%	201/105 62/244	158/86 43/19
Chen ²²	2014	China	HCC	92	IHC	ABGENT	1:300	>25%	45/47 8/59	37/39 8/8
Shi ¹⁵	2015	China	HCC	173	IHC	ABGENT	1:300	>25%	NA	99/48 17/9
Meng et al ¹⁶	2015	China	HCC	172	IHC	Santa Cruz	NA	NA	NA	68/48 39/17
Shi et al ²³	2016	China	HCC	210	IHC	ABGENT	1:300	>25%	NA	95/80 18/17
Egawa et al ¹³	2017	Japan	HCC	79	RT-PCR	NA	NA	NA	NA	NA
Shang et al ²⁴	2017	China	HCC	100	IHC	ProteinTech Group	NA	>25%	NA	45/29 19/7
Yu et al ²⁵	2017	China	HCC	46	IHC	Santa Cruz	1:100	>25%	NA	28/9 7/2

Abbreviations: UICC, Union for International Cancer Control; NOS, The Newcastle-Ottawa Scale; IHC, immunohistochemistry; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival.

repressor, whereas FoxM1B and FoxM1C are both transcriptional activators.^{26–28} Previous studies have shown that FoxM1 plays a key role in cell cycle progression, through the regulation of the transcription of Cyclin B1, Cyclin D1, CDC25A and CDC25B to promote cell cycles from the G1 to S phase and the G2 to M phase.^{26,29} Downregulation of FoxM1 leads to cell cycle progression arrest and abnormal chromatin accumulation.^{30,31} In addition, as a typical transcription factor, FoxM1 plays an important role in embryonic development and tissue regeneration as it is involved in DNA repair and protein synthesis through the transcriptional regulation of many cell proliferation-related genes.³²

Recently, FoxM1 was found to be highly expressed in a variety of malignant tumor tissues and its expression is closely related to the occurrence and development of tumor, and indicated a poor differentiation, high degree of malignancy, distant metastasis, and poor prognosis.^{33,34} However, the relationship between FoxM1 expression and clinicopathological and prognostic value in patients with

HCC remains controversial. The 14 articles included in this study, comprising 2,036 patients, indicated that FoxM1 was highly expressed in HCC, and FoxM1 expression was related to tumor size, vascular invasion, differentiation and TNM stage. Five of 11, six of 12 and three of 10 studies suggested that FoxM1 expression was not correlated to vascular invasion, differentiation and TNM stage, but the overall results indicated the opposite. This suggested that the FoxM1 expression was associated with tumor progression.

Two previous meta-analyses^{35,36} investigated the relationship between FoxM1 expression and the prognosis of solid tumors. Their results suggested that the FoxM1 expression was associated with poor prognosis, and the same result was obtained in the subgroup of HCC. However, the number of studies and patients included in these meta-analyses were limited, and there was no report about the relationship between FoxM1 expression and recurrence-free survival. Our meta-analysis included nine studies and 1,686 patients, suggesting that overexpression of FoxM1 predicted a poor

HBsAg i yes (+/-) no (+/-)	Liver cirrhosis yes (+/-) no (+/-)	AFP positive (+/-) negative (+/-)	Tumor number single (+/-) multiple (+/-)	Tumor size ≤5 cm (+/-) >5 cm (+/-)	Vascular invasion yes (+/-) no (+/-)	Differentiation low (+/-) : high and moderate (+/-)	UICC stage I, II (+/-) III, IV (+/-)	Survival information	Quality score (NOS)
NA	NA	NA	NA	50/8 23/10	31/6 42/12	22/2 51/16	38/12 35/6	NA	7
NA	NA	18/9 17/16	18/16 16/10	23/18 15/4	NA	21/6 17/16	17/15 25/3	NA	6
85/57 4/4	77/60 12/1	54/28 31/33	NA	NA	33/7 56/54	24/8 65/53	43/51 46/10	OS RFS	8
40/55 2/2	39/57 3/0	18/26 22/31	NA	NA	38/56 4/1	6/3 36/54	34/54 8/3	OS RFS	8
NA	NA	NA	NA	NA	NA	NA	NA	OS RFS	8
NA	NA	26/9 9/8	14/15 21/2	NA	17/2 18/15	30/4 8/10	NA	NA	6
NA	174/80 27/24	158/82 43/23	102/77 99/28	124/71 76/34	115/45 86/60	68/16 133/89	136/87 65/18	OS RFS	9
38/44 7/3	25/24 20/23	16/19 23/25	27/26 24/15	NA	7/0 38/47	18/4 27/43	33/39 12/8	OS DFS	7
102/47 14/10	61/27 55/30	71/29 35/23	65/36 51/21	NA	13/2 103/55	32/5 84/52	90/49 26/8	OS DFS	9
82/51 25/14	79/54 28/11	52/38 47/19	NA	NA	21/2 86/63	5/5 98/56	77/58 30/7	OS RFS	8
104/75 9/22	60/47 53/49	47/34 56/58	NA	NA	14/4 99/93	39/12 74/85	72/80 41/17	OS DFS	9
NA	NA	NA	NA	NA	NA	NA	NA	OS DFS	8
16/9 48/27	40/21 24/15	NA	18/17 46/19	NA	22/6 42/30	12/4 52/32	11/20 53/16	NA	7
30/8 5/3	NA	19/3 16/8	NA	24/8 11/3	4/0 31/11	13/2 24/11	NA	NA	6

3-year, 5-year overall survival. Moreover, the results also indicated a poor 3-year, 5-year recurrence-free survival and disease-free survival. FoxM1 may be one of the reliable prognostic indicators of liver cancer.

With the advances in the study of FoxM1, researchers have found that FoxM1 is involved in a variety of malignant biological behaviors of tumor, which suggest that FoxM1 has potential as a target for future cancer therapies.^{33,37} FoxM1 is involved in the development of tumors mainly through its role in promoting tumor cell proliferation and cell cycle progression. Yu et al³⁸ found that upregulation of FoxM1 expression in HCC cell lines upregulated the level of cyclin B1 and cyclin D1 in order to enhance cell proliferation. Chen et al³⁹ reported that downregulation of FoxM1 can significantly inhibit the tumorigenic ability of HCC cells. Also, Yu et al²⁵ found that FoxM1 enhanced the invasion and metastatic ability of hepatoma cells by upregulating SNAI1 expression and promoting the epithelial–mesenchymal transition (EMT) process in hepatocellular carcinoma. In addition, Meng et al¹⁶ found that FoxM1 expression was negatively correlated with E-cadherin expression in HCC tissues, and the expression level of E-cadherin was decreased after overexpression of FoxM1, the invasion ability was enhanced and the EMT process was promoted by activating the SNAI1. Shang et al²⁴ found that FoxM1 regulated glycolysis in hepatoma cells by downregulating GLUT1 expression.

Limitations

This meta-analysis, however, had some limitations: 1) there are some unpublished studies with different results, which may cause publication bias; 2) most of the articles included in this meta-analysis were from China, and the results may only be applicable for Chinese or Asian populations, and more articles from other regional areas should be included to support this meta-analysis; 3) the experimental methods in most of the articles included immunohistochemistry analysis, which is a semi-quantitative assay, and the results were likely to be affected by the antibody used, concentration of antibody and cut-off value. As shown in Table 2, the antibodies and concentrations were different, while the cut-off values were not the same, and these would have an impact on the results and may be the reason for the heterogeneity; 4) the number of articles and patients included in this meta-analysis are insufficient, and more high-quality studies are still needed to support the results; 5) the HRs were obtained using the Engauge Digitizer 10.0 software from the K-M curve, which may cause some errors.

Although there are some limitations in the article, the results are still meaningful, our meta-analysis found that

FOXM1 expression was related to the incidence, tumor size, vascular invasion, differentiation, and TNM stage. Additionally, the results also indicated a poor 3-year, 5-year OS and recurrence-free survival (disease-free survival), and FOXM1 may be a reliable biomarker for the prognosis of HCC patients. However, more high-quality studies to support these findings are still needed.

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Disclosure

The authors report no conflicts of interest in this work.

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