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Prognostic value of osteopontin in patients with hepatocellular carcinoma
A systematic review and meta-analysis

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Abstract

Purpose: The prognostic value of tissue and serum osteopontin (OPN) in hepatocellular carcinoma (HCC) remain controversial. The aim of present meta-analysis was to evaluate the prognostic value of OPN in patients with HCC.

Methods: Eligible studies were systematically searched by PubMed, EMBASE, and Google scholar. A meta-analysis of 12 studies included 2117 cases was performed to estimate the association between OPN level and overall survival (OS), disease-free survival (DFS) in HCC patients. Subgroup analyses were also performed in the meta-analysis.

Results: The pooled data of studies showed that high OPN level was significantly associated with poor OS (hazard ratios [HR] 1.84; 95% confidence intervals [CI] 1.54–2.20; $P=.000$) and DFS (HR 1.67; 95% CI 1.40–1.98; $P=.000$) in HCC. Furthermore, in subgroup analysis, high tissue based OPN by immunohistochemistry detection and serum-based OPN by enzyme-linked immunosorbent assay (ELISA) detection were both significantly associated with OS (tissue: HR 1.88; 95% CI 1.53–2.31; $P<.0001$; serum: HR 2.38; 95% CI 1.58–3.59; $P<.0001$). Simultaneously, we also found that OPN expression was positively associated with stage (odds ratios [OR] 5.68; 95% CI 3.443–7.758), tumor size (Size≤5 cm vs >5 cm; OR 2.001; 95% CI1.036–3.867).

Conclusion: The current evidence indicates that OPN could serve as a prognostic biomarker and a potential therapeutic target for HCC.

Abbreviations: CI = confidence intervals, DFS = disease-free survival, ELISA = enzyme-linked immunosorbent assay, HCC = hepatocellular carcinoma, HR = hazard ratios, IHC = immunohistochemistry, NOS = Newcastle–Ottawa Scale, NR = not reported, OPN = osteopontin, OR = odds ratios, OS = overall survival.

Keywords: hepatocellular carcinoma, meta-analysis, osteopontin, prognosis

1. Introduction

Hepatocellular carcinoma (HCC) is 1 of the most aggressive malignant neoplasms worldwide and the third causes of cancer-related mortality.[1] Though advances in diagnostic techniques and treatments could improve the prognosis of HCC patients, the patients prognosis remains very poor owing to high rate of recurrence.[2,3] So it is urgent to identify novel biological markers that could predict the prognosis and metastatic recurrence of patients with HCC.

Osteopontin (OPN) is a multifunctional phosphoprotein, which could be expressed in different cell types, Including T lymphocytes, macrophages and osteoclasts.[4–6] Recent studies have demonstrated that OPN plays a crucial role in tumorigenesis and metastasis.[7,8] Earlier studies have shown that increased OPN levels are linked to poor prognosis of HCC,[9,10] and promote HCC metastasis.[11–13] Moreover, OPN overexpression has been detected in different solid tumors, including lung cancer,[14] breast cancer,[15,16] gastric cancer,[17] HCC,[18] colorectal cancer[19] and so on. It is suggested that OPN overexpression can predict the prognosis of carcinomas. However, the relationship between OPN expression and prognostic outcomes in HCC patients were controversial and inconclusive. Therefore, we conducted this meta-analysis to systematically and comprehensively evaluate the prognostic value of OPN in HCC.

In this study, we systematically reviewed studies to explore the prognostic significance of OPN for overall survival (OS) and disease-free survival (DFS) in HCC patients. And the correlation between OPN expression and clinicopathological features was also discussed.

2. Material and methods

2.1. Identification and selection of studies

Studies were identified by searching PubMed, EMBASE and Google Scholar databases covering all papers published update to October 31, 2017. The search strategy was used the following terms: (OPN or SPP1 [MESH] or OPN or sialoprotein 1 [TEXT WORD]) AND (carcinoma, hepatocellular [MESH] or HCC [TEXT WORD]). Studies in English were eligible for inclusion.

Additionally, the appropriate references of the identified studies were also checked to identify additional suitable articles. Once studies were found with overlapping data published by the same research center, only the paper with most complete data was included. This project was approved by the Institutional Review Board of Shengli Oilfield Central Hospital.

2.2. Inclusion and exclusion criteria

Eligible studies in this meta-analysis should meet the following criteria:

(1) evaluated the relationship between OPN expression and survival outcomes of HCC;

(2) reported explicit methods for the measurement of OPN expression in the primary HCC;

(3) Examined the association of OPN expression in HCC patients with survival, recurrences, and a series of clinicopathological parameters;

(4) Provided the hazard ratios (HR) or odds ratios (OR) with the 95% confidence intervals (CI) or sufficient data to calculate them;

(5) have a maximum follow-up time exceeding 3 years;

(6) editorial letters, comments or conference abstracts, reviews, and case reports were excluded.

2.3. Qualitative assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies.[20] The score was based on subject selection, comparability of subject, clinical outcome in the NOS. NOS score of 0 to 9 was used to indicate the quality of studies, and a score ≥ 6 denoted a high quality.

2.4. Data extraction

The studies information of this meta-analysis were retrieved by the reporting checklists of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[21] Data extracted from the studies included the following items:

(1) publication information: first author's last name, year of publication;

(2) patients' characteristic information: study population and regions, patients' number, follow-up time;

(3) OPN information: method, cut-off level, and relationship between OPN and OS, DFS or clinicopathological features; and

(4) HR, 95% CI for survival analysis. If the relevant data were not reported (NR), items were treated as "NR (not reported)". If without the HR and 95% CI in articles, Kaplan–Meier curve was available, data were extracted from graphical survival plot and HR was estimated.[22]

2.5. Statistical analysis

Included studies were divided into 3 groups for analysis: those with data regarding OS, DFS, and clinicopathological parameters. OR and 95% CI were used to measure the association of OPN expression with clinical parameters, while the HR and 95% CI were used for the meta-analysis of survival rates. An OR > 1 indicated higher probability for later stage, lager tumor size or the presence of vascular invasion in the group with elevated OPN expression. While a combined HR > 1 implies a poor outcome for OPN overexpression in HCC patients. Heterogeneity of pooled

results was conducted using I-squared statistic. If the $P < .10$ or $I^2 > 50\%$, we considered heterogeneity as significant heterogeneity, and then a random effect model was used. Otherwise, a fixed-effects model was used. subgroup analysis was evaluated the differences between HRs in included studies with different detection methods, treatments. Sensitivity analysis was performed to assess the reliability and validity of the meta-analysis. Both Begg funnel plot and Egger test were used to examine the publication bias. And we conducted a trim and fill analysis,[23] which yields an effect adjusted for funnel plot asymmetry. Meta-analysis was conducted with STATA version 12.0 (STATA Corporation, College Station, TX). All P values were 2 sides and $P < .05$ was considered statistically significant.

3. Results

3.1. Studies selection and characteristics of studies

A total of 462 articles were initially identified via the search criteria delineated above. After screening of the title and abstract,29 articles were selected for detailed evaluation. Subsequently, 7 studies were excluded after full assessment due to lacking relevant survival data. Another 22 studies were careful identified.[9,10,13,24–42] Of the 22 studies, 11 articles[9,10,13,27,29,31,36–40] were reported by the same research group, and the patients were partly overlapping in this studies. To avoid duplicate counting, only 3 studies[10,27,31] with complete data were included. Another 3 studies[24,41,42] were also from the same study center, however, only the most complete 1 was selected.[24] Finally, 12 studies[10,24–28,30–35] were included in our meta-analysis (Fig. 1).

The basic characteristics of the 12 studies are summarized in Table 1. A total of 2117 patients from China, Taiwan, Korea, Austria, Thailand and Japan were enrolled with sample number ranging from 46 to 454. Regarding OPN detection in HCC, immunohistochemistry (IHC) was used in 8 studies,[25–27,30–34] another 3 studies[10,28,35] used enzyme-linked immunosorbent assay (ELISA) to measure serum-based OPN expression. For HCC treatment, surgical resection as initial treatment was reported in 10 studies,[10,24–27,31–35] and liver transplantation (LT) and transhepatic arterial chem otherapy (TACE) reported in 1 study respectively.[30,28] OS was presented in all studies, however, DFS was only reported in 5 studies.[10,25,27,30–31] Meanwhile, All studies had the follow-up times exceeding 3 years, with 7 studies more than 5 years. The NOS scores ranged from 5 to 8 with a mean of 6.1.

3.2. OPN expression and clinicopathological parameters

To investigate the association between OPN expression and clinicopathological features, we conducted the meta-analysis. Five studies reported the association of tumor size >5 cm with OPN expression in HCC. Pooled data from all 4 studies showed high OPN expression was significantly associated with tumor size >5 cm (OR 2.001; 95% CI 1.036–3.867; $P = .039$). Two studies reported the association of the TNM stage with OPN expression. The combined data showed that increased OPN expression was significantly correlated to TNM stage (OR 5.680; 95% CI 3.443–7.758; $P = .000$). On the contrary, OPN overexpression was not found to be associated with age (OR 1.120; 95% CI 0.867–1.446; $P = .386$), Gender (OR 0.928, 95% CI 0.700–1.230; $P = .604$), HBsAg (OR 1.106; 95% CI 0.434–2.820; $P = .833$), Child-Pugh grade (OR 2.793; 95% CI 0.869–8.978; $P = .085$), AFP (OR 1.766; 95% CI 0.987–3.160; $P = .055$), Liver Cirrhosis
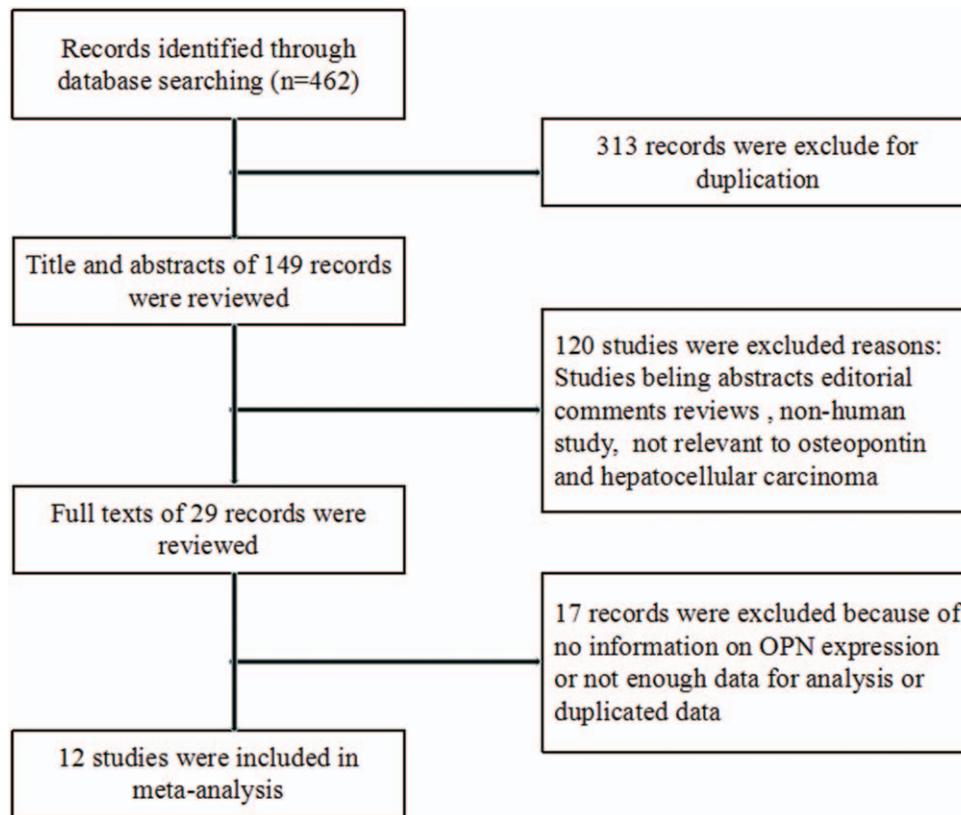
Figure 1. Flow chart of the selection of the studies in the meta-analysis.

(OR 0.941; 95% CI 0.9410.653–1.355; $P = .742$), Vascular invasion (OR 2.56; 95% CI 0.92–7.12; $P = .073$), or tumor grade (OR 1.196; 95% CI 0.611–2.336; $P = .601$). These results suggested that HCC with overexpressed OPN exhibited aggressive biological behaviors (Table 2).

3.3. OPN expression and OS in HCC

Overall, all 12 studies, including 2117 patients, had a relationship between OPN expression and OS in HCC; and 10 presented reported data on OS and OPN expression in HCC initially treated by surgical resection. Heterogeneity among studies was statistically significant ($P = .061$, $I^2 = 43.3\%$), so a random-effects model was used. Pooled data suggested that high OPN expression was significantly correlated with reduce OS (HR 1.84; 95% CI 1.52–2.22; $P = .000$) (Table 3, Fig. 2A). Sensitivity analysis was performed and the overall trend was not changed by removing the studies 1 by 1 in Figure 2B. We also performed subgroup analysis for method and treatment. subgroup analysis suggested that the detection method, either ELISA or IHC, of OPN expression had significantly influence for OS (ELISA: HR 2.38; 95% CI 1.58–3.59; $P = .000$; IHC: HR 1.88; 95% CI 1.53–2.31; $P = .000$), without significant heterogeneity in the data. For

Table 1

Characteristics of studies for association between OPN and HCC.

References	Year	Patient source	No. of patient	Stage	Treatment	median age (year)	method	Cut off level	No. of "high"OPN	Follow-up (months)	Outcome	Scores
Pan et al	2003	Taiwan	240	I–IV	S	55.86	RT-PCR	ratio> 0.6	133	120	OS	7
Zhang et al	2006	China	101	I–IV	S	50.5	ELISA	>200 ng/ml	37	24	OS/DFS	6
Xie et al	2007	China	72	NR	S	50.57	IHC	≥25%	39	60	OS/DFS	6
Korita et al	2008	Japan	125	NR	S	63	IHC	focal or diffuse staining	51	25–195	OS	5
Yang et al	2008	China	302	I–III	S	52	IHC	>5%	73	4–121	OS/DFS	7
kim et al	2009	Korea	46	I–IV	TACE	59	ELISA	>1.85 $\log_{10}$ ng/ml	13	2–42	OS	5
Sieghart et al	2011	Austria	125	I–IV	LT	54.54	IHC	>10%	40	3–195	OS/DFS	5
Tsai et al	2012	Taiwan	100	I–IV	S	61	IHC	≥25%	NR	60	OS	7
Deng et al	2013	China	454	NR	S	NR	IHC	≥5%	227	NR	OS/DFS	6
Jin et al	2014	China	305	I–IV	S	55	IHC	≥10%	212	36	OS	7
Ying et al	2014	China	90	NR	S	54.51	IHC	score>2	59	36	OS	7
Chimparlee et al	2015	Thailand	157	NR	S	NR	ELISA	>133 ng/ml	79	NR	OS	5

DFS = disease-free survival, ELISA = enzyme-linked immunosorbent assay, IHC = immunohistochemistry, LT = liver transplantation, NR = not reported, OPN = osteopontin, OS = overall survive, RT-PCR = reverse transcription-polymerase chain reaction, S = surgical resection, TACE = Transhepatic Arterial Chemotherapy And Embolization.

Table 2

Meta-analysis for the association of increased OPN expression and clinicopathological features of HCC.

Clinicopathological feature	No. of studies	No. of patient	Model	OR (95% CI)	P value	Heterogeneity X^2	I^2 (%)	P-value
Age (younger vs. older)	4	989	Fixed	1.120 (0.867–1.446)	.386	1.08	0	.783
Size (≤5 cm vs. >5 cm)	5	1373	Random	2.001 (1.036–3.867)	.039	28.1	85.8	.000
Gender (male vs. female)	6	1530	Fixed	0.928 (0.700–1.230)	.604	7.67	34.8	.176
HBsAg (Negative vs. Positive)	4	1351	Random	1.106 (0.434–2.820)	.833	23.93	87.5	.000
Child grade (A vs. B)	3	698	Random	2.793 (0.869–8.978)	.085	4.65	57.0	.098
AFP (≤400 vs. >400)	3	617	Random	1.766 (0.987–3.160)	.055	5.22	61.7	.074
Liver Cirrhosis (Yes vs. No)	3	999	Fixed	0.941 (0.653–1.355)	.742	3.00	33.3	.223
Vascular invasion (Yes vs. No)	5	1258	Random	2.56 (0.92–7.12)	.073	41.86	90.4	.000
Tumor grade (I-II vs. III-IV)	6	1498	Random	1.196 (0.611–2.336)	.601	33.14	84.9	.000
Tumor stage (I-II vs. III-IV)	2	545	Fixed	5.680 (3.443–7.758)	.000	1.02	1.4	.313

CI = confidence intervals, HCC = hepatocellular carcinoma, OPN = osteopontin, OR = odds ratios.

treatment, our results indicated that the overall HR estimate of surgical resection group for OS was 1.90 (95% CI 1.54–2.33; P = .000) (Table 3).

3.4. OPN expression and DFS in HCC

Five studies comprising a total 1054 patients reported results on OPN expression and DFS in HCC. There was no significant heterogeneity (P = .304, I^2 = 17.4%) among them, so a fixed-effect model was used. Pooled data from these studies suggested that increased OPN expression was significantly correlated with poor DFS (HR 1.67; 95% CI 1.40–1.98; P = .000), indicating that high OPN expression was an indicator of disease recurrence in HCC patients (Table 3 and Fig. 3). Meanwhile, subgroup analysis by method and treatment indicated a significant association in IHC (HR 1.61; 95% CI 1.33–1.96; P = .000), surgical resection (HR 1.61; 95% CI 1.34–1.94; P = .000) with DFS, without significant heterogeneity in the data (Table 3).

3.5. Publication bias

Publication bias was assessed by using Begg funnel plot and Egger test (Fig. 4). The results suggested evidence for

publication bias in OS studies (Egger, P = .012). There was some evidence for publication bias. Meanwhie, we drew a funnel plot and conducted a trim and fill analysis (Fig. 4A). There was some evidence of asymmetry (5 studies trimmed) but the overall effect was strongly influenced by 5 studies, and the overall HR estimate showed that there was no effect of replacing missing studies (adjusted value HR 1.554; 95% CI 1.227–1.892). There was no significantly different (P = .090). While it did not reveal significant publication bias in DFS studies (Eegger, P = .630).

4. Discussion

The patients with HCC usually have poor prognosis due to late diagnosis and high rate of recurrence. Therefore, it is of great significance to identify the clinical useful markers for predicting prognosis of HCC. In recent years, some studies have shown the potential clinical value of OPN to serve as a biomarker for prognosis and a potential therapeutic target in patients with HCC.[43,44] And the OPN overexpression could predict late-stage, high-grade, and early-recurrence of HCC.[24] So, a meta-analysis is needed to systematically evaluate the prognostic value of OPN in hepatocellular carcinoma.

Table 3

Main meta-analysis results.

Analysis	No. of studies	No. of patients	Model	HR (95% CI)	P value	Heterogeneity I^2%	P value
OS	12	2117	Random	1.84 (1.54–2.20)	.000	38.9	.081
Method							
RT-PCR	1	240	–	1.32 (1.01–1.72)	.041	–	–
ELISA	3	304	Fixed	2.38 (1.58–3.59)	.000	0.0	.801
IHC	8	1573	Fixed	1.88 (1.53–2.31)	.000	36.5	.138
Treatment							
S	10	1946	Random	1.90 (1.54–2.33)	.000	49.9	.036
LT	1	125	–	1.48 (0.34–6.39)	.599	–	–
TACE	1	46	–	1.70 (1.11–2.61)	.016	–	–
DFS	5	1054	Fixed	1.67 (1.40–1.98)	.000	17.4	.304
Method							
IHC	4	953	Fixed	1.61 (1.33–1.96)	.000	28.8	.240
ELISA	1	101	–	1.92 (1.30–2.83)	.001	–	–
Treatment							
S	4	929	Fixed	1.61 (1.34–1.94)	.000	13.1	.327
LT	1	125	–	2.30 (1.31–4.03)	.004	–	–

DFS = disease-free survival, ELISA = enzyme-linked immunosorbent assay, IHC = immunohistochemistry, LT = liver transplantation, OS = overall survival, S = surgical resection, TACE = transhepatic arterial chem otherapy.

The first meta-analysis investigating the relationship between OPN and hepatocellular carcinoma prognosis was reported by Zhang et al[45] Their results included 7 studies suggested that high OPN expression significantly predicted poor OS and DFS for HCC. Later, Cheng et al performed a meta-analysis on merely 4 studies and the evidence indicates that plasma OPN can act as an independent prognostic indicator for HCC patients.[46] In recent years, a number of studies have been carried out to analyze the protein expression profiles and prognostic significance of OPN in HCC, but the prognosis utilities of OPN are still controversial. Therefore, we performed a meta-analysis added 5 eligible studies than Zhang et al[45] in order to provide a quantitative reassessment. And we first performed the subgroup analysis to assess whether the pooled estimate of OS and DFS was different according to the different therapy methods and treatments. So, this meta-analysis may provide reliable and powerful statistics and draw a more conclusive result.

A total of 12 studies with 2117 HCC patients were subjected to quantitative analysis. First of all, we observed that several clinical features were significantly associated with OPN expression. The results of pooled data suggested that high OPN expression significantly correlated with tumor size and TNM stage. In addition, we also analyzed the association of OPN expression with the Child-Pugh stage, AFP, and vascular invasion. An evident trend toward higher OPN expression with the higher Child-Pugh stage and AFP was identified. Taken together, the pooled data of this meta-analysis supported the suggestion that

high OPN expression enhanced invasion and metastasis potential of HCC. Meanwhile, the association of OPN with survival of HCC patients was evaluated. The pooled data showed that high OPN expression predicted shorter OS and DFS. These results suggested that OPN is a novel prognostic marker and an indicator of invasiveness in HCC patients. Finally, the subgroup analysis was stratified by 3 different detection methods. And the subgroup analysis by surgical resection showed that OPN overexpression significantly predicted poorer OS and DFS ($P=.000$, both). Therefore, the pooled results in our study demonstrate that OPN might promote HCC invasion and metastasis, and can serve as a useful biomarker for HCC prognosis.

Some limitations of this meta-analysis should be discussed. First of all, in our meta-analysis, we found significantly heterogeneity among studies for OS ($P=.081$, $I^2=38.9\%$), so we used a random-effects model. We then performed a subgroup analysis on methods by RT-PCR, ELISA, IHC, which may influence the heterogeneity. Furthermore, the cutoff value and methods for levels of OPN expression varied in different studies. Different cutoff of OPN expression may impact on the accurate estimation of outcome for HCC, even may cause diametrically opposite results. These reasons may cause the heterogeneity of results. However, the statistical results by subgroup analysis and Sensitivity analysis seemed to be robust and convincing. Therefore, researchers should carry out large multicenter study to develop a definitive cut-off value and establish a method to
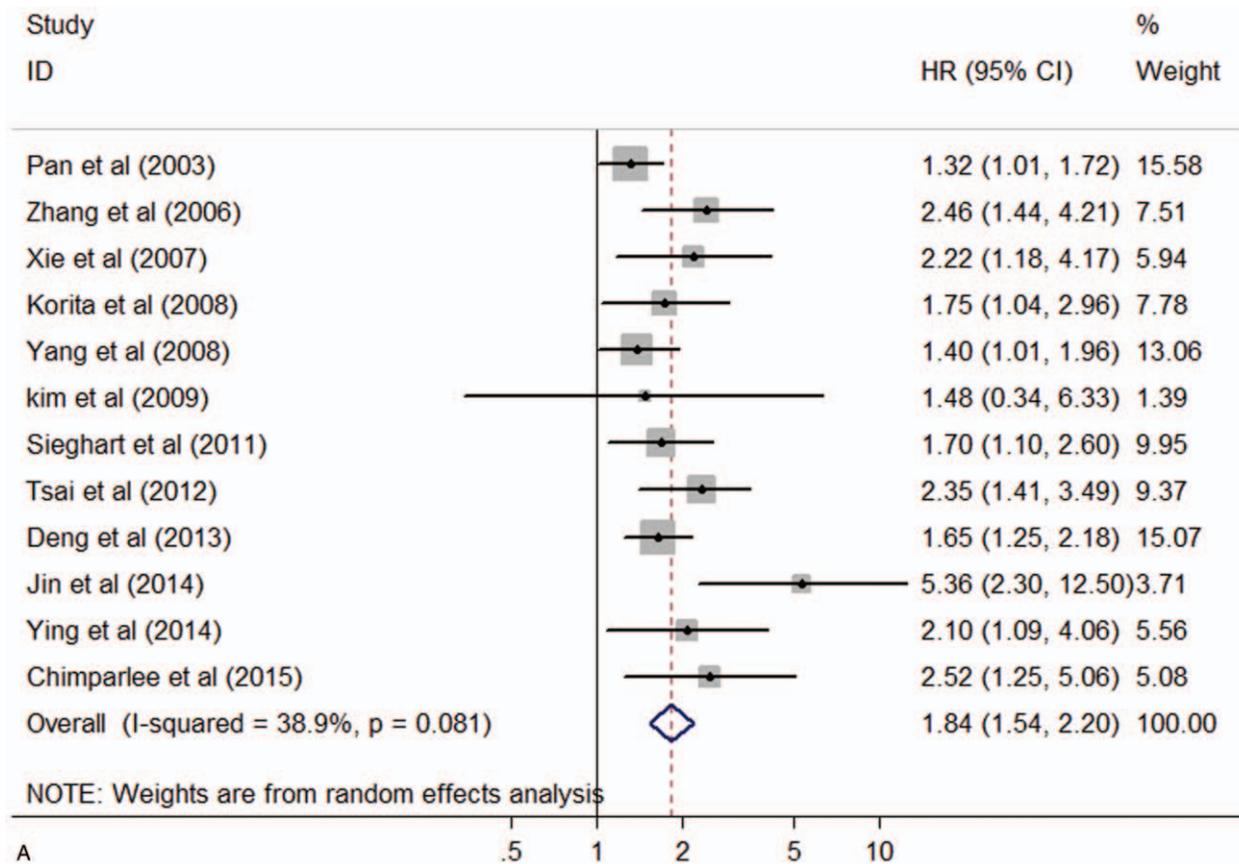

Figure 2. (A) Forest plot for the relationships between OPN expression and OS. (B) Sensitivity analysis for meta-analysis of OPN. OPN = osteopontin, OS = overall survival.
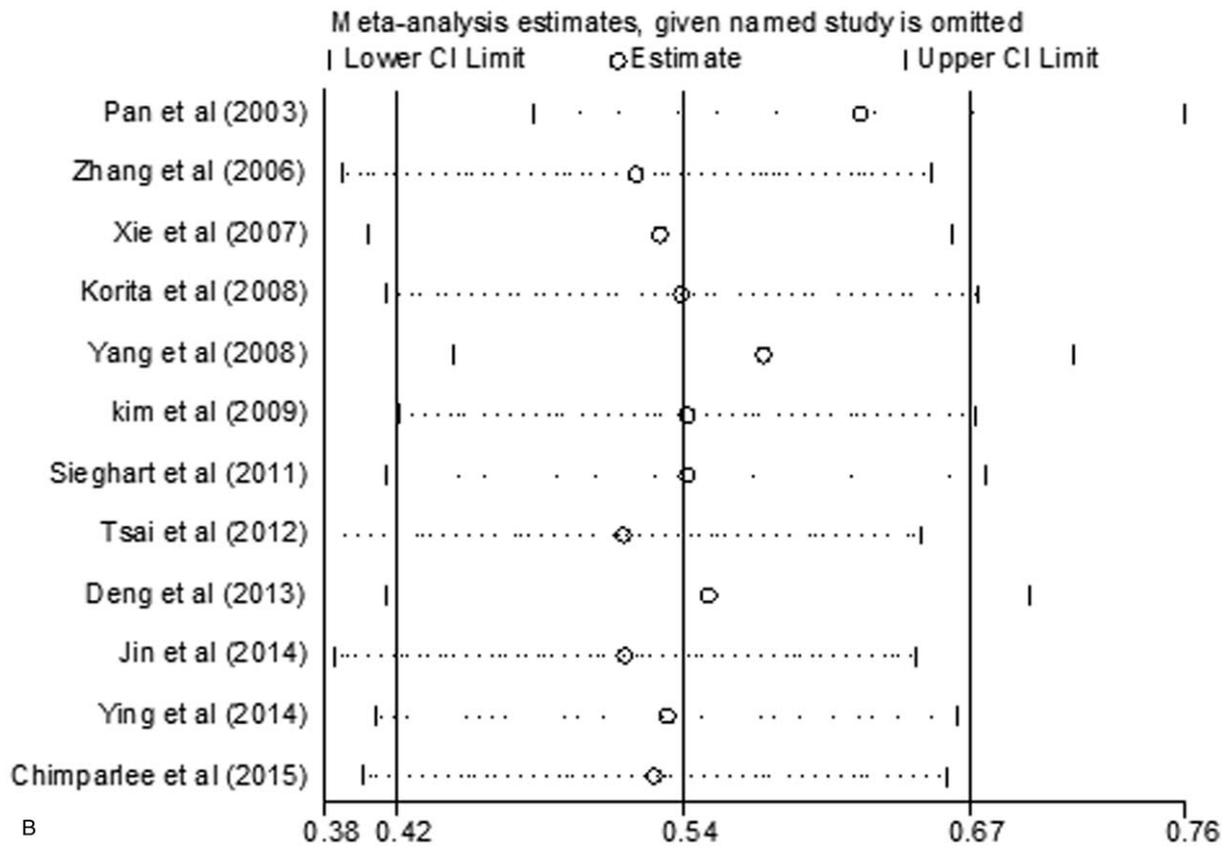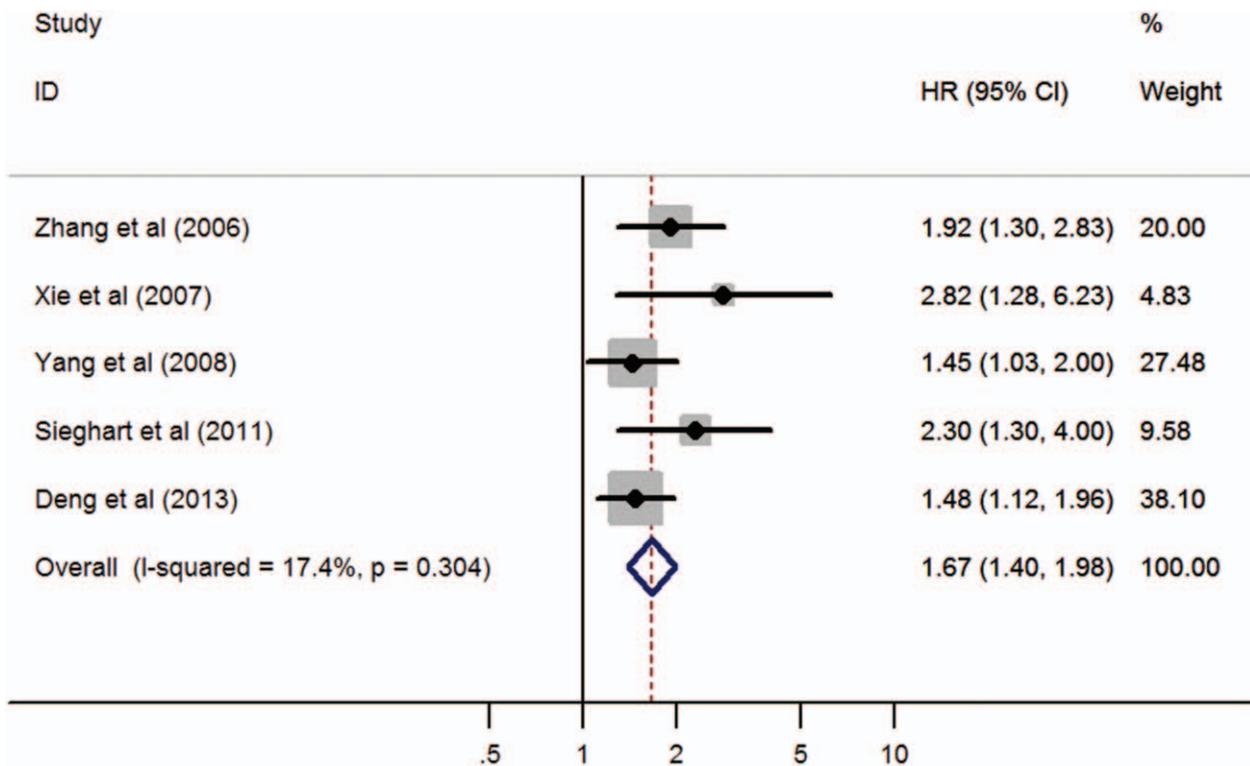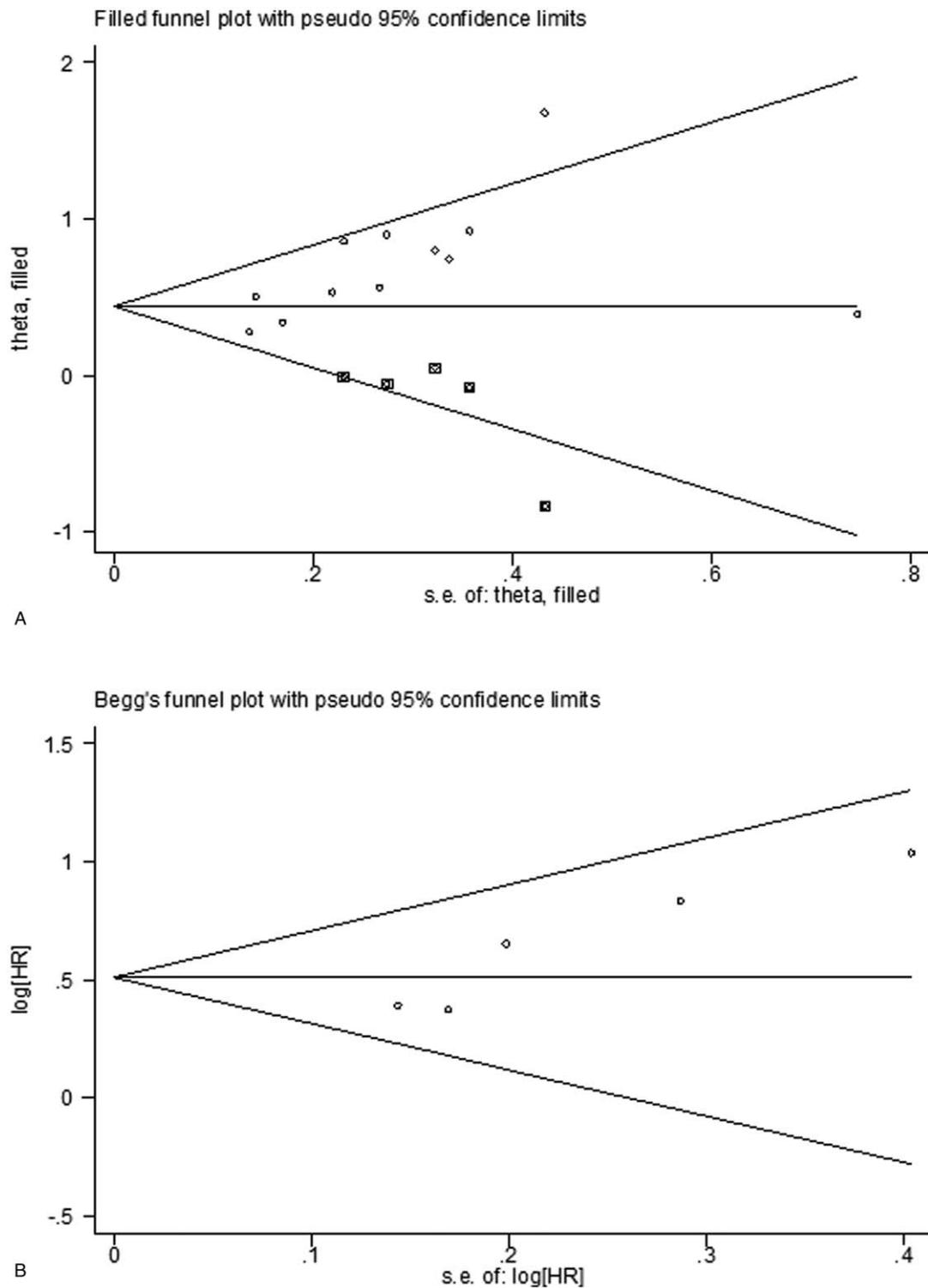
Figure 2. Continued

Figure 3. Forest plot of hazard ratio for the association of OPN overexpression and DFS. DFS=disease-free survival, OPN=osteopontin.

Figure 4. Funnel plots of publication bias in this meta-analysis. (A) OS by trim and fill analysis; (B) DFS by Begg funnel plot. DFS = disease-free survival, OS = overall survival.

classify OPN expression. Second, potential risk bias and language were a concern. Because studies with positive results were more likely to be published than negative ones. And we searched literatures written in English. However, the lack of these analyses may affect the reliability of results to some extent, and then reflected our publication bias evaluation. Moreover, the total

sample size and the total number of included reports were relatively small. These also might partly influence the validity of our analysis. Third, when we evaluated the correlation between OPN expression and vascular invasion, tumor grade, tumor size, the heterogeneity was significant. However, we could not analysis the source of heterogeneity owing to the limited of studies.

Finally, geographical bias was a concern; all patients of the included studies were from Asia, which the dominant risk factor of hepatocellular carcinom is hepatitis B virus infections. whereas hepatitis C virus-related or alcohol-related hepatocellular carcinom is the predominant tumor type in Western countries. The OPN expression and its function is still unclear in Western hepatocellular carcinom patients, because there is no data available till now.

In summary, current available evidence demonstrated the prognostic value of OPN in HCC patients. Our results indicated that OPN can serve as a novel prognostic marker in HCC patients. Due to the limitations of this study, larger and more well-designed studies are still required to clarify the prognostic value of OPN expression in HCC patients.

Author contributions

Conceptualization: Diwen Sun.
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Methodology: Peng Li, Qingao Bu.
Project administration: Peng Li.
Software: Guoqiang Li.
Writing – original draft: Tingting Sun.
Writing – review & editing: Peng Li.

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