

# The association between osteopontin and survival in non-small-cell lung cancer patients: a meta-analysis of 13 cohorts

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**Abstract:** In the last decade, osteopontin (OPN) was identified as one of the important proteins that promote the metastasis of tumor. However, the association between OPN overexpression and clinical outcome of non-small-cell lung cancer (NSCLC) was unclear. The purpose of this study is to investigate the role of OPN in NSCLC patients. A total of 13 studies are included to explore the relationship between the OPN elevation and the overall survival (OS) and disease-free survival (DFS) in NSCLC patients. We searched for related articles in PubMed, Web of Science, Google Scholar, and Cochrane Library databases, which were published before January 31, 2015. Hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI) in the high OPN expression group compared with the low OPN expression group were calculated and analyzed. Primary results were summarized by using a fixed-effects model or a random-effects model. The stratified analyses in subgroups were also performed. Thirteen cohort studies, which involved 1,630 patients, were included. Subgroup analyses were performed by area and test method of OPN. We found that OPN was significantly associated with poor OS (HR =2.20, 95% CI 1.71–2.83,  $P<0.001$ ) and DFS (HR =2.11, 95% CI 1.62–2.74,  $P<0.001$ ) in NSCLC patients. OPN overexpression tended to be associated with the presence of advanced tumor TNM stage (III and IV) (OR =2.57, 95% CI 1.61–4.11,  $P<0.001$ ). The Egger's test suggested that there was no publication bias in OS studies ( $P=0.062$ ) and DFS studies ( $P=0.740$ ). These data indicate that OPN seems to have a significant predictive potential in estimating survival in NSCLC.

**Keywords:** metastasis, overall survival, disease-free survival, tumor stage

## Introduction

Lung cancer is one of the most frequently diagnosed solid tumors in the world as well as the most common causes of cancer mortality worldwide, with an overall 5-year survival rate of 15%.<sup>1</sup> Non-small-cell lung cancer (NSCLC) accounts for ~80%–85% of all lung cancers.<sup>2</sup> In spite of early detection and obvious improvements in surgical techniques, the postoperative recurrence rate is higher in lung cancer compared to other types of cancer.<sup>3</sup> As the current TNM staging system for NSCLC does not provide satisfactory prognostication, it is essential to identify the novel biomarkers that will contribute to recognize a high risk of metastasis and recurrence of patients. Moreover, novel therapies are certainly warranted in NSCLC, and as targeted treatment is becoming important gradually, identifying molecular markers as potential therapeutic targets is urgent.

Osteopontin (OPN) is a 32-kDa multifunctional protein with features of both a matrix protein and a cytokine, which is involved in tissue remodeling, malignant transformation, and immune-mediated response. Furthermore, OPN was found to be frequently overexpressed in many solid tumors, such as breast, hepatocellular,

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gastric, colorectal, and lung carcinomas.<sup>4-7</sup> Although the correlation between OPN and tumor has been discussed for several years, the existing data have not been analyzed thoroughly till now. It has been demonstrated that OPN is associated with cancer development, progression, and metastasis in different malignancies, including NSCLC.<sup>5-10</sup> An overexpression of OPN has been found to occur not only in pathologic conditions, such as ischemia or inflammation, but also in many types of malignancies. Recent clinical and experimental studies suggested that overexpression of OPN in NSCLC patients may correlate with disease stage<sup>9-11</sup> and survival.<sup>12,13</sup> However, the clinical implications of OPN in NSCLC patients have not been fully investigated.

Therefore, it is necessary to conduct a meta-analysis to systematically understand the relationship between OPN and survival in NSCLC. The aim of this study is to evaluate the significance of serum- and elevated tissue-based OPN levels for overall survival (OS) and disease-free survival (DFS) in patients with NSCLC.

## Materials and methods

### Publication search

Relevant literatures were identified by searching the PubMed, Web of Science, Google Scholar, and Cochrane Library databases before January 31, 2015. The search strategy was based on the following keywords: osteopontin or OPN, lung cancer or pulmonary carcinoma, and survival. Articles written in English were all eligible for inclusion. In addition, in order to omit any other relevant studies, the references to all identified publications were also searched, and investigators were contacted to supply additional data when key information relevant to the meta-analysis was missing.

### Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) measured OPN expression in the NSCLC patients with enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), or immunohistochemistry (IHC); 2) provided information on survival; and 3) provided the hazard ratio (HR) and 95% confidence interval (CI) or raw data. The excluded criteria were as follows: review articles, laboratory studies, animal studies, and case reports.

### Quality assessment

Quality assessment was carried out in the available studies using the Newcastle–Ottawa quality assessment scale for cohort studies by two researchers independently (Table 1).<sup>14</sup> The scores range from 0 to 9. When publications had  $\geq 6$  scores, they were graded as the high-quality ones.

**Table 1** Newcastle–Ottawa quality assessment scale for cohort studies

#### Selection

- 1) Representativeness of the exposed cohort
  - a) Truly representative of the average NSCLC patients (describe) in the community (\*)
  - b) Somewhat representative of the average NSCLC patients in the community (\*)
  - c) Selected group of users, eg, nurses, volunteers
  - d) No description of the derivation of the cohort
- 2) Selection of the nonexposed cohort
  - a) Drawn from the same community as the exposed cohort (\*)
  - b) Drawn from a different source
  - c) No description of the derivation of the nonexposed cohort
- 3) Ascertainment of exposure (proof of NSCLC and osteopontin measurement)
  - a) Secure record (eg, surgical records) (\*)
  - b) Structured interview (\*)
  - c) Written self-report
  - d) No description
- 4) Demonstration that outcome of interest was not present at start of study
  - a) Yes (\*)
  - b) No

#### Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
  - a) Study controls for recurrence or metastasis (select the most important factor) (\*)
  - b) Study controls for any additional factor (age, stage, grade, cirrhosis, etc) (\*)

#### Outcome

- 1) Assessment of outcome
  - a) Independent blind assessment (\*)
  - b) Record linkage (\*)
  - c) Self-report
  - d) No description
- 2) Was follow-up long enough for outcomes to occur
  - a) Yes (2 years) (\*)
  - b) No
- 3) Adequacy of follow-up of cohorts
  - a) Complete follow-up – all subjects accounted for (\*)
  - b) Subjects lost to follow-up unlikely to introduce bias – small number lost  $>25\%$  (select an adequate%) follow-up, or description provided of those lost) (\*)
  - c) Follow-up rate  $<75\%$  (select an adequate%) and no description of those lost
  - d) No statement

**Notes:** A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

**Abbreviation:** NSCLC, non-small-cell lung cancer.

### Definitions and data extraction

OS was defined as the time interval between the medical treatment (including lung resection, chemotherapy, radiotherapy, etc) and death or the last observation. DFS was measured from the date of treatment to the recurrence or the last assessment. Data were carefully extracted from all eligible publications independently by two authors

(YW and JY) based on the inclusion and exclusion criteria. Disputes were settled through friendly consultations. But if necessary, the third author (HL) could be consulted to help settle disputes. The following variables in each study were extracted: 1) primary author's name and year of publication; 2) characteristics of the study population (sex and number); 3) the measurement method of OPN; and 4) tumor stage, follow-up time, and the outcome of patients.

## Statistical analysis

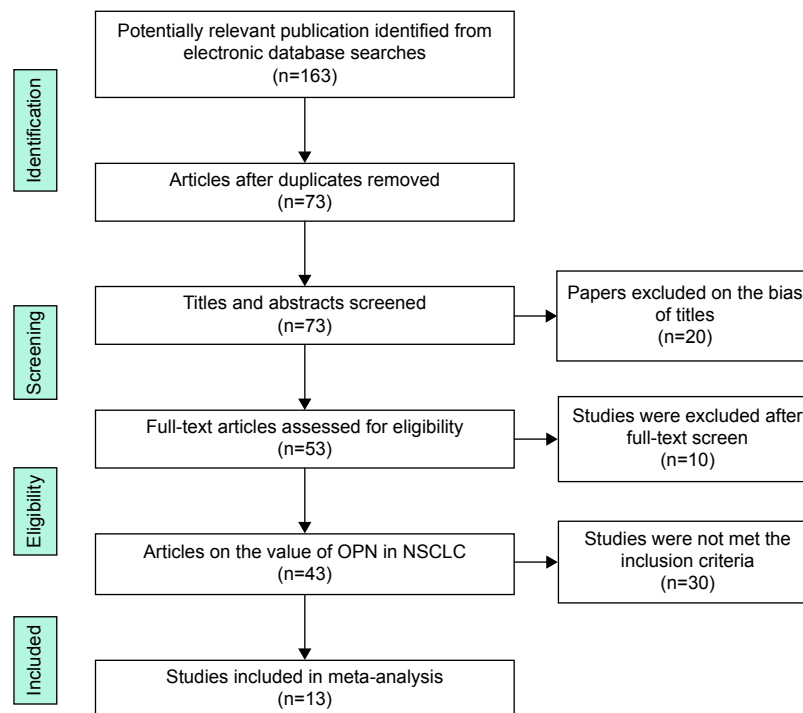
All statistical analyses were carried out with Stata/SE, Version 10 (StataCorp LP, College Station, TX, USA). For the assessment of the association between OPN overexpression and survival in patients with NSCLC, the HR and 95% CI were extracted from studies or calculated with the raw data if provided. For the assessment of the association between OPN overexpression and tumor stage in patients with NSCLC, the odds ratio (OR) and 95% CI were extracted from studies. In the subgroup analyses, we explored the effects of different testing methods and crowd from different areas on the strength of the association between OPN and survival results. Statistical heterogeneity was measured using the chi-square test and  $I^2$  test. If the  $I^2$  value is  $<50\%$  or the  $P$ -value is  $>0.10$ , significant heterogeneity will not be considered.<sup>15</sup> A random-effects model was used for pooled analyses when between-study heterogeneity was substantial;

otherwise, a fixed-effects model was used. We conducted the Egger's test to evaluate the publication bias of eligible studies, and publication bias was considered when a  $P$ -value was  $<0.05$ .<sup>16</sup>

## Results

### Selection and characteristics of studies

By the initial literature search, 163 relevant articles were identified regarding the association of OPN and NSCLC. After the careful screening process, 120 studies were excluded as they were review articles, experimental research, and studies irrelevant to the current analysis. Forty-three relevant studies were selected for detailed evaluation. Of the remaining 43 studies, 30 publications did not meet the inclusion criteria and were excluded. Finally, a total of 13 studies<sup>7,10,12,13,17–25</sup> with 1,630 patients were included in our meta-analysis (Figure 1). Four studies were performed in People's Republic of China,<sup>17,20,22,25</sup> two in Japan,<sup>12,13</sup> two in America,<sup>10,21</sup> one in Norway,<sup>19</sup> one in England,<sup>18</sup> one in Italy,<sup>7</sup> one in Germany,<sup>24</sup> and one in Korea.<sup>23</sup> The sample size of each study varied from 25 to 244. Seven studies used IHC, five used ELISA, and one used PCR. The quality of study was assessed by Newcastle–Ottawa quality assessment scale, whose scores ranged from 5 to 7 (median =6). The characteristic of each article included in this meta-analysis is revealed in Table 2.



**Figure 1** Flow diagram of the study selection process.

**Abbreviations:** OPN, osteopontin; NSCLC, non-small-cell lung cancer.

Table 2 Characteristics of studies included in the meta-analysis

Study	Year	Study design	Sample size, n (M/F)	Country	Tumor stage <sup>a</sup> (I–II/III–IV, n)	Follow-up (months)	Sample	Osteopontin detection method	Survival analysis	Hazard ratio estimated	Adjusted factors	NOS scores <sup>b</sup>
Chambers et al <sup>18</sup>	1996	Prospective	25 (17/8)	England	20/5	34	Tumor tissue	IHC	OS	UV		6/9
Schneider et al <sup>10</sup>	2004	Prospective	82 (63/19)	America	58/24	86	Tumor tissue	PCR	OS	UV		5/9
Donati et al <sup>7</sup>	2005	Retrospective	163	Italy	NR	49	Tumor tissue	IHC	OS and DFS	MV	NR	6/9
Mack et al <sup>21</sup>	2008	Prospective	156	America	NR	NR	Plasma	ELISA	OS and DFS	UV		5/9
Isa et al <sup>12</sup>	2009	Prospective	67 (46/21)	Japan	0/67	NR	Serum	ELISA	OS and DFS	UV		6/9
Zhang et al <sup>20</sup>	2010	Retrospective	180 (136/44)	People's Republic of China	110/70	25	Tumor tissue	IHC	DFS	MV	Sex, histopathological type, T staging, N staging, and BSP expression	5/9
Rud et al <sup>19</sup>	2013	Prospective	191	Norway	NR	37	Tumor tissue	IHC	OS and DFS	MV	Age, sex, pT category, pN category, and tumor differentiation and histology	6/9
Sun et al <sup>17</sup>	2013	Retrospective	159 (109/50)	People's Republic of China	95/64	46	Tumor tissue	IHC	OS and DFS	UV		5/9
Takenaka et al <sup>13</sup>	2013	Prospective	244 (166/78)	Japan	189/55	48	Serum	ELISA	OS	MV	Sex, smoking, histology, T factor, and N factor	7/9
Ostheimer et al <sup>24</sup>	2014	Prospective	55 (47/8)	Germany	3/52	37	Plasma	ELISA	OS	UV		7/9
Han et al <sup>23</sup>	2013	Prospective	53 (47/6)	Korea	7/46	30	Plasma	ELISA	OS	UV		7/9
Yan et al <sup>25</sup>	2015	Prospective	163 (104/59)	People's Republic of China	86/77	50	Tumor tissue	IHC	OS and DFS	MV	Lymph node staging and TNM stage	7/9
Zhang et al <sup>22</sup>	2014	Retrospective	92 (53/39)	People's Republic of China	0/92	NR	Tumor tissue	IHC	OS and DFS	MV	Sex, age, pathological type, metastasis and chemotherapy regimens, and grade of differentiation	6/9

**Notes:** <sup>a</sup>Tumor stage was classified according to International Union Against Cancer (UICC, sixth edition). <sup>b</sup>Study quality is listed using the results of the Newcastle–Ottawa questionnaire.

**Abbreviations:** M, male; F, female; NOS, Newcastle–Ottawa Scale; IHC, immunohistochemistry; OS, overall survival; PCR, polymerase chain reaction; DFS, disease-free survival; NR, not reported; ELISA, enzyme-linked immunosorbent assay; MV, multivariate analysis; UV, univariate analysis.

## OPN expression and OS in NSCLC

A total of 12 studies, which included 1,450 patients, reported data on OPN expression and OS in NSCLC. The sample size of each study varied from 25 to 244. OPN levels were detected by IHC in six articles – five by ELISA and one by PCR. OPN overexpression seemed to be correlated with poor OS in all studies (Figure 2). Combined data from all the 12 studies showed that increased OPN levels were associated with OS with a pooled HR estimate of 2.20 (95% CI 1.71–2.83,  $P<0.001$ ), with significant heterogeneity in the data ( $I^2=69.6\%$ ,  $P<0.001$ ).

Subgroup analyses were performed by area and test method of OPN. For area, the analysis was stratified into two subgroups: non-Asia and Asia. A significantly increased risk was found in Asia (HR =2.68, 95% CI 1.63–4.43,  $P<0.001$ ) and also in non-Asia (HR =1.66, 95% CI 1.43–1.93,  $P<0.001$ ). For the test method of OPN, the analysis was stratified into two subgroups: ELISA and IHC. A significantly increased risk was found by ELISA (HR =1.80, 95% CI 1.43–2.27,  $P<0.001$ ) and also by IHC (HR =2.63, 95% CI 1.65–4.22,  $P<0.001$ ) (Table 3). The result of analysis whose subgroup stratified into tumor tissue was HR =2.50, 95% CI 1.68–3.73,  $P<0.001$ ; into plasma was HR =1.71, 95% CI 1.28–2.28,  $P<0.001$ ; and into serum was HR =1.98, 95% CI 1.35–2.92,  $P=0.001$ .

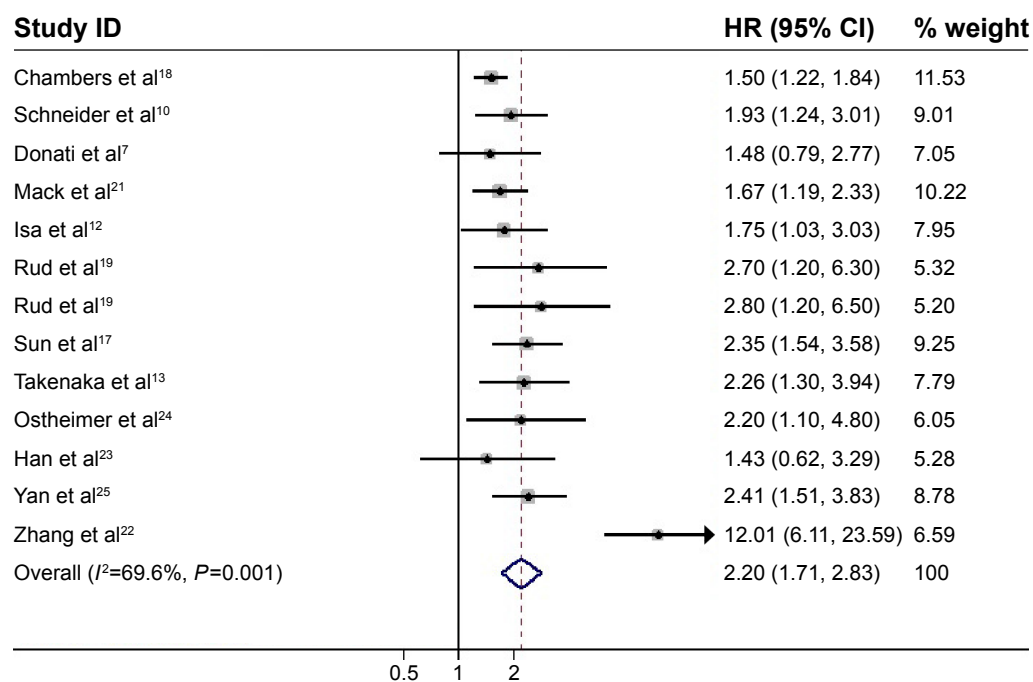
## OPN expression and DFS in NSCLC

Eight studies reported data on OPN expression and DFS in NSCLC. A high OPN expression was significantly correlated with poor DFS in all studies (Figure 3). Pooled data from all the eight studies showed that increased OPN levels were associated with DFS with a pooled HR estimate of 2.11 (95% CI 1.62–2.74,  $P<0.001$ ), with significant heterogeneity in the data ( $I^2=50.3\%$ ,  $P=0.050$ ).

The result of analysis whose subgroup stratified into Asia was HR =2.40, 95% CI 1.86–3.09,  $P<0.001$  and into non-Asia was HR =1.74, 95% CI 1.10–2.76,  $P=0.017$ . For test method of OPN (Table 3), likewise, a significantly increased risk was found by ELISA (HR =1.79, 95% CI 1.11–2.86,  $P=0.016$ ) and also by IHC (HR =2.36, 95% CI 1.89–2.96,  $P<0.001$ ). For sample type, a significantly increased risk was found in tumor tissue (HR =2.36, 95% CI 1.89–2.96,  $P<0.001$ ).

## OPN expression and tumor stage in NSCLC

Three studies reported data on OPN expression and tumor TNM stage in NSCLC.<sup>17,24,25</sup> High OPN expression seemed to be associated with high tumor stage (III and IV) in two studies and low tumor stage in one study. Combined data from all the three studies showed a trend for a correlation between



**Figure 2** Meta-analysis of the association between OPN overexpression and OS of NSCLC.

**Notes:** The summary HR and 95% CIs were also shown (according to the random-effect estimations). Weights are from random-effects analysis.

**Abbreviations:** OPN, osteopontin; OS, overall survival; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

**Table 3** Subgroup analysis of the OPN levels in NSCLC patients

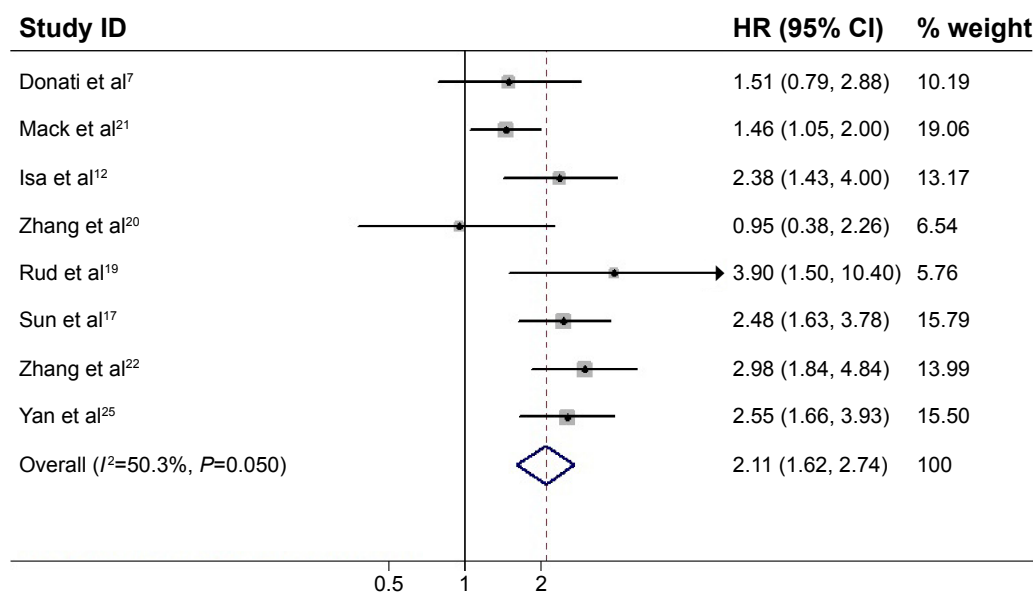
Outcome	Variable	N	Model	HR (95% CI)	P-value	I <sup>2</sup> (%)	P <sub>heterogeneity</sub>
OS	All	12	Random	2.20 (1.71, 2.83)	<0.001	69.6	<0.001
	Area						
	Non-Asia	6	Fixed	1.66 (1.43, 1.93)	<0.001	0.0	0.562
	Asia	6	Random	2.68 (1.63, 4.43)	<0.001	79.4	<0.001
	Method						
	ELISA	5	Fixed	1.80 (1.43, 2.27)	<0.001	0.0	0.840
	IHC	6	Random	2.63 (1.65, 4.22)	<0.001	84.1	<0.001
	PCR	1		1.93 (1.24, 3.01)			
	Sample type						
	Tumor tissue	7	Random	2.50 (1.68, 3.73)	<0.001	81.4	<0.001
DFS	All	8	Random	2.11 (1.62, 2.74)	<0.001	50.3	0.050
	Area						
	Non-Asia	3	Fixed	1.74 (1.10, 2.76)	0.017	44.4	0.166
	Asia	5	Fixed	2.40 (1.86, 3.09)	<0.001	20.3	0.285
	Method						
	ELISA	2	Random	1.79 (1.11, 2.86)	0.016	59.8	0.115
	IHC	6	Fixed	2.36 (1.89, 2.96)	<0.001	37.2	0.158
	Sample type						
	Tumor tissue	6	Fixed	2.36 (1.89, 2.96)	<0.001	37.2	0.158
	Plasma	1		1.46 (1.05, 2.00)			
	Serum	1		2.38 (1.43, 4.00)			

**Abbreviations:** OPN, osteopontin; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; OS, overall survival; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; PCR, polymerase chain reaction; DFS, disease-free survival.

high OPN expression and high tumor TNM stage (III and IV) (OR =2.57, 95% CI 1.61–4.11,  $P<0.001$ ) (Figure 4) without any heterogeneity ( $I^2=0\%$ ,  $P=0.417$ ). Regrettably, only two studies provided relevant data on the correlation of OPN with tumor grade.<sup>22,24</sup> The pooled analysis could not be performed.

## Publication bias

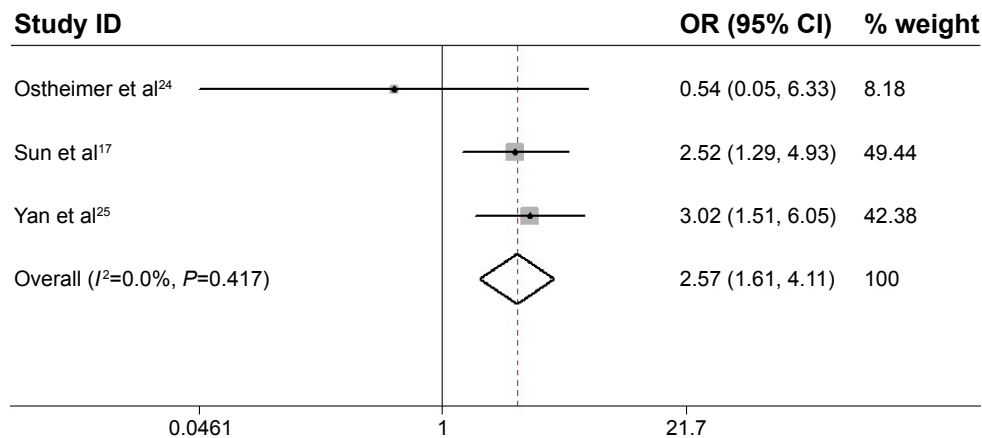
Publication bias was mainly used to evaluate the reliability of meta-analysis results, especially those that showed statistical significance.<sup>7</sup> The Egger's test (statistical significance was set at  $P<0.05$ ) indicated that publication bias was absent

**Figure 3** Meta-analysis of the association between OPN overexpression and DFS of NSCLC.

**Notes:** The summary HR and 95% CIs were also shown (according to the random-effect estimations). Weights are from random-effects analysis.

**Abbreviations:** OPN, osteopontin; NSCLC, non-small-cell lung cancer; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.





**Figure 4** Meta-analysis of the association between OPN overexpression and tumor TNM stage of NSCLC.

**Note:** The summary OR and 95% CIs were also shown (according to the fixed-effect estimations).

**Abbreviations:** OPN, osteopontin; NSCLC, non-small-cell lung cancer; OR, odds ratio; CI, confidence interval.

in studies on OPN associated with OS ( $P=0.062$ ) and DFS ( $P=0.740$ ).

## Sensitivity analysis

To assess the stability to the results of this meta-analysis, we performed a sensitivity analysis by excluding each study sequentially. Statistically similar results were obtained after excluding each study sequentially, which indicates the stability to this meta-analysis.

## Discussion

Despite significant advances in supervising and clinical treatment strategies, the overall prognosis of NSCLC remains dismal.<sup>26–30</sup> It is important to classify the patients with a high possibility of tumor recurrence and metastasis in order to initiate intervention in time. The existing TNM stage cannot predict the outcome of all NSCLC patients accurately. Therefore, identifying effective biomarkers involved in tumor spreading and survival is an essential step to improve the prognosis of this disease.<sup>9,31–33</sup>

In this article, we first evaluated the association between high OPN expression and survival in NSCLC patients. The pooled results demonstrated that high OPN expression significantly predicted poor OS and DFS for NSCLC ( $P<0.001$  and  $P<0.001$ , respectively). After subgroup analyses using the detection methods, OPN elevation was significantly associated with OS and DFS in patients who were tested by ELISA ( $P<0.001$  and  $P<0.001$ , respectively) and by IHC ( $P<0.001$  and  $P<0.001$ , respectively). When the subgroup was stratified separately according to area, OPN overexpression was significantly associated with OS of patients in non-Asia ( $P<0.001$ ) and also in Asia ( $P<0.001$  and  $P<0.001$ , respectively).

The reasons for the diversities of OS and DFS among NSCLC patients with high and low OPN expressions were still unclear. Approximately two-thirds of recurrences for early stage cancer after surgery occurred on distant sites. Therefore, the elimination of micrometastases should be given a high priority as soon as possible. OPN played an essential role in tumorigenesis, progression, and metastasis in NSCLC, and patients in TNM stage II or III younger than 70 years received adjuvant chemotherapy after surgery, in which OPN-negative patients showed a good outcome as their 3-year relapse-free survival was similar to stage I patients younger than 70 years.<sup>19</sup> Whereas the OPN-positive patients showed an obviously poor outcome, tumor OPN expression was an unfavorable prognostic factor not only for cases of advanced NSCLC but also for patients with stage I of the disease.<sup>13</sup> They also pathologically evaluated the association between OPN levels and tumor invasiveness. They found that a higher OPN level was particularly associated with higher incidences of vascular invasions, suggesting that patients with NSCLC with high OPN levels had a more aggressive tumor phenotype. Ostheimer et al<sup>34</sup> reported in a trial of 69 patients with inoperable NSCLC that OPN level changes over time, particularly after treatment, and may yield additional prognostic information in curative-intent radiotherapy of NSCLC. Collectively, these results have built OPN levels as an indicator for NSCLC patients.

The association between OPN overexpression and clinical outcome of NSCLC is unclear. Thus, a meta-analysis was performed to examine the effect estimate of OPN on clinical outcome. Broad search terms and multiple bibliographic databases were used in the searches to capture as many relevant articles as possible, and a robust systematic

approach was used to select the final articles. Although we have assessed the value of OPN in NSCLC comprehensively, some limitations of our meta-analysis should not be ignored, such as patient selection, different outcome measures, and statistical techniques.<sup>35</sup> First, potential language and risk bias were concerned, as positive research results were published more than negative ones frequently. We have tried to identify all correlative information, but several missing data are still unavoidable. Second, data on clinical outcomes were quite limited, so more articles designed to evaluate the clinical outcomes were specifically needed, and for the association of OPN with some clinical readouts, there exist differences that require further research for clarification.

## Conclusion

Our meta-analysis suggested that OPN overexpression was correlated with poor survival in NSCLC, and it might provide important information for the prediction of NSCLC invasion, metastasis, and prognosis.

## Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (grant number 8140010845) and Anhui Provincial Natural Science Foundation (grant number 1208085QH165).

## Disclosure

The authors report no conflicts of interest in this work.

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