Review Article
Prognostic significance of osteopontin in patients with lung cancer: a meta-analysis

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Received September 26, 2014; Accepted November 25, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Both plasma/serum/pleural effusion osteopontin concentration (PSPO) and tumor tissue osteopontin expression (TTO) have recently been reported to be involved in the prognosis of lung cancer. In this study, we performed a meta-analysis to demonstrate the association between PSPO/TTO and survival in patients with lung cancer. We searched in PubMed, EMBASE, Cochrane library, Web of Science and Chinese Biomedical database (CBM) for relevant literatures. Stata 12.0 was applied to pool the eligible studies and synthesize hazard ratios (HRs) and its corresponding 95% confidence interval (CI). For PSPO, a total of 8 studies with 1000 patients were included in final analysis. Combined HR suggested high PSPO predicted an unfavorable overall survival (OS) (HR=1.52, 95% CI: 1.13-2.05) and progress-free survival (PFS) (HR=1.73, 95% CI: 1.35-2.21). For TTO, 5 studies with a total of 747 patients were employed in final analysis. Pooled HR indicated that elevated TTO was associated with poor OS (HR=2.16, 95% CI: 1.65-2.83) and disease/relapse-free survival (D/RFS) (HR=2.36, 95% CI: 1.79-3.12). Subgroup analysis was performed to explore the causes of heterogeneity. Publication bias by begg’s test was not statistically significant. Sensitivity analysis showed that the pooled results were robust. This study revealed that both high TTO and PSPO are associated with poor prognosis in patients with lung cancer.

Keywords: Osteopontin, lung cancer, prognosis, meta-analysis

Introduction
Lung cancer is the most prevalent and lethal cancer with a total of more than 1.3 million deaths each year world-wide [1]. The prognosis of lung cancer patients is not optimistic, with a five-year survival rate of only 15% [2]. Despite rapid progress made in diagnostic area and individual therapy, the prognosis of these patients remains dismal. Consequently, it is urgent to find practical prognostic markers to guide clinical practice.

Osteopontin (OPN) is a multifunctional phosphorylated acidic glycoprotein secreted from malignant epithelial cells [3]. OPN interacts with integrin family members and variants of CD44, thus activating a variety of downstream processes correlated with tumor progression and cell transformation [4-7]. Previous studies have demonstrated that tumor tissue osteopontin expression (TTO) were markedly associated with unfavorable prognosis in several cancers as well as lung cancer [8-17]. In addition, elevated plasma/serum OPN (PSO) has also been investigated in numbers of cancers, such as breast, ovarian, hepatocellular and lung cancer [18-24]. Systemic reviews and meta-analysis focusing on the relationship between PSO and TTO and prognosis have been reported in liver cancer [25, 26]. Several studies have demonstrated that elevated PSO, pleural effusion osteopontin level (PEO) and TTO were associated with poor prognosis in lung cancer [9, 27-33]. Moreover, a latest meta-analysis indicated that tumor tissue osteopontin expression played a key role in the development of lung cancer [34]. Nevertheless, there were no systemic reviews and meta-analysis that demonstrated the correlation between PSO, PEO and TTO and prognosis. Therefore, this meta-analysis was conducted to verify the exact prognostic value of PSO/PEO and TTO in lung cancer.

Method
Search strategy
We searched in PubMed, EMBASE, Cochrane library, Web of Science and Chinese Biomedical
Osteopontin in lung cancer

Records identified through database searching
PubMed: n=65
Embase: n=65
Cochrane library: n=0
Web of science: n=241

Records after duplicated (n=233)

Records excluded by title/abstract: (n=210)

Full text articles selected for further assessment (n=23)

Records (n=13) excluded due to:
- No sufficient data (n=9)
- Duplicate publication (n=1)
- Reviews (n=3)

Eligible articles from Chinese biomedical databases (CBM): n=2

Studies included in the meta-analysis (n=12)

Figure 1. Flow chart representing the process of literature search and study selection.

database (CBM) for relevant literatures until June 2014, without lower date restriction. Articles were identified using the following medical terms: ((lung OR pulmonary) AND (neoplasm* OR cancer* OR carcinoma* OR tumor*)) AND (osteopontin OR Secreted Phosphoprotein 1 or OPN or SPP1) AND (Prognosis or prognostic or survival). The above words/phrases were restricted to title and abstract. Language was limited to English and Chinese. References of the identified articles were also searched manually.

Selection criteria

Articles included in our meta-analysis should meet the criteria as follows: 1) plasma/serum/pleural effusion OPN concentration (PSPO) or TTO was measured in pathologically diagnosed non-small cell lung cancer patients; 2) relationship demonstrated between PSPO or TTO and overall survival (OS), progress-free survival (PFS), relapse-free survival (RFS) or disease-free survival (DFS); 3) sufficient information provided to calculate hazard ratio (HR) and its 95% confidence interval (CI); 4) for studies with the same or partially overlapping patients, only the most complete study was included. The following studies were excluded: (1) letters, reviews, meta-analysis, case(s) related studies, conference abstracts and editorials; 2) non-English/Chinese language articles.

Quality assessment and data extraction

All potential articles were scanned and checked by two independent reviewers (Peng and Wang) according to the established criteria. Quality assessment for included literatures was based on the scale designed by De Graeff and his colleagues [35]. Any disagreement in quality assessment and data extraction was settled by discussion. The basic information extracted from eligible studies included: first author, publication year, source country, sample size, gender, age, specimens, detection methods, tumor stage, tumor histology, treatments, cutoff value, endpoints (such as OS, PFS, RFS and DFS) and HR estimation methods.

Statistical analysis

In this meta-analysis, HR and its 95% CI were applied to evaluate the association between OPN and OS, PFS, DFS and RFS. When the results of a study were presented as Kaplan-Meier curves, we extracted and calculated HR and its 95% CI according to the methods described by Parmar and Tierney [36, 37]. When both multivariate analysis and univariate analysis were used to calculate HR and its 95% CI in the study, we chose the former for data combination. Specially, for a study with multiple cutoff values, we chose the HR of “top versus bottom group” for synthesis [38]. Heterogeneity was tested by using the Cochran’s test and by quantifying the inconsistency (I^2). A fixed-effect model was used when heterogeneity was not detected (P: 0.10); otherwise, we employed random-effect model. Subgroup analyses were carried out to explore the potential causes of heterogeneity. Robustness of this meta-analy-
Table 1. Clinical and methodological characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>Country</th>
<th>No. of patients</th>
<th>Mean age (y)</th>
<th>Specimens</th>
<th>Detection method</th>
<th>stages (III-IV/I-II)</th>
<th>Histology (SCC/ADC/others)</th>
<th>treatment methods</th>
<th>Cut-off</th>
<th>survival analysis</th>
<th>HR estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostheimer</td>
<td>2014</td>
<td>Germany</td>
<td>55</td>
<td>63.0</td>
<td>plasma</td>
<td>ELISA</td>
<td>52/3</td>
<td>28/24/3</td>
<td>RT</td>
<td>median</td>
<td>OS</td>
<td>UV</td>
</tr>
<tr>
<td>Zhang</td>
<td>2014</td>
<td>China</td>
<td>85</td>
<td>64.0</td>
<td>PE</td>
<td>ELISA</td>
<td>85/0</td>
<td>13/67/5</td>
<td>chemo</td>
<td>1247.90 ng/ml</td>
<td>OS/PFS</td>
<td>MV/UV</td>
</tr>
<tr>
<td>Takenaka</td>
<td>2013</td>
<td>Japan</td>
<td>244</td>
<td>69.8</td>
<td>Serum</td>
<td>ELISA</td>
<td>55/189</td>
<td>49/172/23</td>
<td>surgery</td>
<td>81.3 ng/ml</td>
<td>OS</td>
<td>MV</td>
</tr>
<tr>
<td>Rud [1]</td>
<td>2013</td>
<td>Norway</td>
<td>210</td>
<td>65.0</td>
<td>Serum</td>
<td>ELISA</td>
<td>32/178</td>
<td>58/128/24</td>
<td>surgery</td>
<td>32.9 ng/ml</td>
<td>OS/RFS</td>
<td>UV/UV</td>
</tr>
<tr>
<td>Han</td>
<td>2013</td>
<td>Korea</td>
<td>53</td>
<td>70.6</td>
<td>plasma</td>
<td>ELISA</td>
<td>46/7</td>
<td>31/18/4</td>
<td>mixed</td>
<td>93.07 ng/ml</td>
<td>OS</td>
<td>UV</td>
</tr>
<tr>
<td>Sun</td>
<td>2013</td>
<td>China</td>
<td>159</td>
<td>61.0</td>
<td>TT</td>
<td>IHC</td>
<td>64/95</td>
<td>102/55/2</td>
<td>surgery</td>
<td>3 score</td>
<td>OS/DFS</td>
<td>UV/UV</td>
</tr>
<tr>
<td>Cui</td>
<td>2012</td>
<td>China</td>
<td>114</td>
<td>61.2</td>
<td>Serum</td>
<td>ELISA</td>
<td>84/30</td>
<td>52/62/0</td>
<td>mixed</td>
<td>58.5 ng/ml</td>
<td>OS</td>
<td>UV</td>
</tr>
<tr>
<td>Wu</td>
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<td>China</td>
<td>89</td>
<td>39-78</td>
<td>TT</td>
<td>IHC</td>
<td>43/46</td>
<td>48/41/0</td>
<td>surgery</td>
<td>1 score</td>
<td>OS</td>
<td>UV</td>
</tr>
<tr>
<td>Isa</td>
<td>2009</td>
<td>Japan</td>
<td>67</td>
<td>64.5</td>
<td>Serum</td>
<td>ELISA</td>
<td>67/0</td>
<td>15/49/3</td>
<td>chemo</td>
<td>69.0 ng/ml</td>
<td>OS/PFS</td>
<td>NA</td>
</tr>
<tr>
<td>Mack</td>
<td>2008</td>
<td>USA</td>
<td>172</td>
<td>NA</td>
<td>plasma</td>
<td>ELISA</td>
<td>172/0</td>
<td>144/28/0</td>
<td>chemo</td>
<td>592 ng/ml</td>
<td>OS/PFS</td>
<td>MV/MV</td>
</tr>
<tr>
<td>Donati</td>
<td>2005</td>
<td>Italy</td>
<td>207</td>
<td>65.0</td>
<td>TT</td>
<td>IHC</td>
<td>46/161</td>
<td>122/85</td>
<td>surgery</td>
<td>0.2</td>
<td>OS/DFS</td>
<td>MV/MV</td>
</tr>
</tbody>
</table>

NA, not available; SCC, squamous cell carcinoma; ADC, adenocarcinoma; others, other types of lung cancer; MV, multivariate analysis; UV, univariate analysis; PE, pleural effusion; TT, tumor tissue, Chemotherapy; RT, radiotherapy, Mixed patients with different treatments.
sis was tested by sensitivity analysis. In this case, every single study was deleted and the remaining studies were pooled. Begg’s funnel plots were performed to test publication bias. All statistical calculations as well as graphical presentations were performed by Stata 12.0 (STATA Corporation, College Station, TX, USA).

Results

Study selection and characteristics

The search strategy was showed in Figure 1. A total of 233 articles were reviewed from PubMed, Embase and Web of Science, of which 10 studies were eligible [9-11, 27-29, 31-33, 39]. Additionally, another two eligible studies were screening out from Chinese Biomedical database [12, 30]. Finally, a total of 12 studies were included in this analysis. The basic information was summarized in Table 1. Of the 12 studies, 4 studies investigated the relationship between TTO and survival [10-12, 39]; 1 study focused on association between PEO and prognosis [27]; 6 studies paid attention to the correlation between PSO and survival [28-33]; and 1 study highlighted the association between both the PSO and TTO and prognosis [9].
Considering the similarity of PSO and PEO as body fluid sample, we combined them together as PSPO in this study. However, we combined HRs separately for TTO and PSPO in our meta-analysis. Likewise, we combined DFS and RFS together as D/RFS. Finally, 5 studies with a total of 747 patients were included which investigated the relationship between TTO and survival [9-12, 39]; 8 studies with a total of 1000 patients focusing on the association between PSPO and prognosis were employed [9, 27-33]. As for quality assessment, the total score of each study ranged from 5 to 8.

### Meta-analysis

**TTO and survival:** Five studies with a total of 747 patients were included in this analysis. The pooled results indicated that elevated TTO was found to be significantly associated with poor OS (HR=2.16, 95% CI: 1.65-2.83; I^2=0.0%, P=0.087) (Figure 2A) and D/RFS (HR=2.36, 95% CI: 1.79-3.12; I^2=0.0%, P=0.479) (Figure 2B) without any heterogeneity.

Subgroup analysis revealed that elevated TTO was correlated inversely with OS in both Asian and western population (HR=2.15, 95% CI: 1.51-3.07; HR=2.17, 95% CI: 1.43-3.29, respectively) without any significant heterogeneity (I^2=0.0%, P=0.454; I^2=0.0%, P=0.748, respectively). Elevated TTO was also markedly associated with OS for patients based on immunohistochemistry (IHC) detection (HR=2.15, 95% CI: 1.61-2.86, I^2=0.0%, P=0.769).

When studies were stratified by HR estimation method, pooled results showed that elevated TTO was significantly related with OS for both multivariate and univariate analysis without any heterogeneity (HR=2.14, 95% CI: 1.32-3.49, I^2=0.0%, P=0.450; HR=2.17, 95% CI: 1.57-3.00, I^2=0.0%, P=0.750; respectively). Moreover, stratified analysis based on study design suggested that elevated TTO had an unfavorable impact on OS for both prospective and retrospective studies (HR=2.80, 95% CI: 1.20-6.52; HR=2.10, 95% CI: 1.58-2.79, I^2=0.0%, P=0.863; respectively). For a clear display, we presented the results of subgroup analysis in Table 2.

**PSPO and survival:** A total of 8 studies with 1000 patients were included in this analysis. For the overall population, pooled HR suggested that high PSPO was significantly associated with unfavorable OS (HR=1.52, 95% CI: 1.13-2.05; I^2=30.6%, P=0.237) (Figure 3A) and PFS (HR=1.73, 95% CI: 1.35-2.21; I^2=30.6%, P=0.237) (Figure 3B).

Subgroup analysis was conducted to explore the potential causes of heterogeneity for OS. As showed in Table 3, elevated PSPO in Asians correlated significantly with poor OS (HR=1.60, 95% CI: 1.23-2.09) with a significant reduced heterogeneity (I^2=7.3%, P=0.365), compared with westerners (HR=1.42, 95% CI: 0.88-2.29; I^2=85.0%, P=0.001). When stratified by statistical method, high PSPO predicted an unfavorable OS (HR=1.82, 95% CI: 1.40-2.35) without any significant heterogeneity (I^2=0.0%, P=0.450).

### Table 2. Subgroup analysis of summarized hazard ratios reflecting the association between tumor tissue osteopontin expression and OS in lung cancer

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N. of studies</th>
<th>Cases</th>
<th>Pooled-data-(random)</th>
<th>Test-for-heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>248</td>
<td>2.15</td>
<td>1.51-3.07</td>
</tr>
<tr>
<td>Western</td>
<td>3</td>
<td>499</td>
<td>2.17</td>
<td>1.43-3.29</td>
</tr>
<tr>
<td>Survival analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>2</td>
<td>417</td>
<td>2.14</td>
<td>1.32-3.49</td>
</tr>
<tr>
<td>UV</td>
<td>3</td>
<td>330</td>
<td>2.17</td>
<td>1.57-3.00</td>
</tr>
<tr>
<td>Detection</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IHC</td>
<td>4</td>
<td>665</td>
<td>2.15</td>
<td>1.61-2.86</td>
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<tr>
<td>PCR</td>
<td>1</td>
<td>82</td>
<td>2.25</td>
<td>1.00-5.06</td>
</tr>
<tr>
<td>Study design</td>
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<tr>
<td>Prospective</td>
<td>1</td>
<td>210</td>
<td>2.80</td>
<td>1.20-6.52</td>
</tr>
<tr>
<td>Retrospective</td>
<td>4</td>
<td>537</td>
<td>2.10</td>
<td>1.58-2.79</td>
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</table>

* MV, Multivariate analysis; UV, Univariate analysis.*
out heterogeneity ($I^2=0.0\%$, $P=0.655$) based on multivariate analysis, compared with univariate analysis ($HR=1.29$, 95% CI: 0.95-1.76; $I^2=58.2\%$, $P=0.048$). Furthermore, we stratified the studies according to the percentage of patients of Stage III-IV. For studies with a percentage of patients of Stage III-IV more than 50%, pooled results indicated higher PSPO was more likely associated with worse OS ($HR=1.59$, 95% CI: 1.29-1.96) without any heterogeneity ($I^2=0.0\%$, $P=0.611$). However, for those of Stage III-IV less than 50%, pooled HR was 1.43 (95%CI: 0.65-3.17, $P=0.375$). When studies were stratified by specimens, in plasma/serum subgroup, high PSPO had an inverse effect on OS ($HR=1.49$, 95% CI: 1.09-2.04) without eliminating the heterogeneity ($I^2=77.6\%$, $P=0.000$), compared with pleural effusion subgroup ($HR=1.83$, 95% CI: 1.00-3.35, $P=0.049$). As for stratification analysis based on study design, in prospective subgroup, high PSPO had an unfavorable impact on OS ($HR=1.49$, 95% CI: 1.09-
Osteopontin in lung cancer

Table 3. Subgroup analysis of summarized hazard ratios reflecting the association between PSPO and OS in lung cancer

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N. of studies</th>
<th>Cases</th>
<th>Pooled-data-(random)</th>
<th>Test-for-heterogeneity</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<td>Area</td>
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<tr>
<td>Asia</td>
<td>5</td>
<td>563</td>
<td>1.60</td>
<td>1.23-2.09</td>
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<tr>
<td>Western</td>
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<td>Survival analysis</td>
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<tr>
<td>MV</td>
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<td>501</td>
<td>1.82</td>
<td>1.40-2.35</td>
</tr>
<tr>
<td>UV</td>
<td>5</td>
<td>499</td>
<td>1.29</td>
<td>0.95-1.76</td>
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<td>Stage</td>
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<tr>
<td>(III-IV) &gt;50%</td>
<td>6</td>
<td>546</td>
<td>1.59</td>
<td>1.29-1.96</td>
</tr>
<tr>
<td>(III-IV) &lt;50%</td>
<td>2</td>
<td>454</td>
<td>1.43</td>
<td>0.65-3.17</td>
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<tr>
<td>Study design</td>
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<tr>
<td>Prospective</td>
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<td>915</td>
<td>1.49</td>
<td>1.09-2.04</td>
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<td>Retrospective</td>
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<td>85</td>
<td>1.83</td>
<td>1.00-3.35</td>
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<td>Specimens</td>
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<td>Plasma/serum</td>
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<td>915</td>
<td>1.49</td>
<td>1.09-2.04</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>85</td>
<td>1.83</td>
<td>1.00-3.35</td>
</tr>
</tbody>
</table>

MV, Multivariate analysis; UV, Univariate analysis; PE, pleural effusion; PSPO, plasma/serum/pleural effusion osteopontin concentration.

2.04, I^2=77.6%, P=0.000), compared with retrospective subgroup (HR=1.83, 95% CI: 1.00-3.35, P=0.049).

Publication bias and sensitivity analysis

Begg's test for publication bias suggested there was no statistical significance for OS based on TTO (P=0.806) (Figure 4A) and OS based on PSPO (P=0.902) (Figure 4B).

Furthermore, sensitivity analysis was conducted to test the robustness of the results by deleting one study each time. However, there was no evidence indicated that any single study had a significant effect on the pooled HRs for both OS of TTO and OS of PSPO (Not showed).

Discussion

Lung cancer is the most lethal cancer which accounts for at least 1.3 million deaths around the world every year [34]. Therefore, it is critical to identify candidate biomarkers for early detection, individual treatment and prediction of prognosis. Osteopontin (OPN) is a secreted arginine-glycine-aspartic acid (RGD)-containing phosphorylated glycoprotein [26, 27]. It is originally described as a transformation-associated protein in the epithelial cells in 1979 [26]. It has been found that the expression of OPN is high in numerous malignancies including lung cancer [32]. Several studies have demonstrated abnormal expression of OPN is closely associated with occurrence and development of colon cancer, breast cancer and liver cancer. Some reports suggested that elevated OPN concentration correlated with neovascularization, chemotactic transfer and adhesion of cytokines [34]. Thus, this meta-analysis is conducted to assess the prognostic and diagnostic value of OPN in lung cancer patients.

In this meta-analysis, we investigated the relationship between TTO and PSPO and prognosis in patients with lung cancer. Our results supported the hypothesis that both elevated TTO and PSPO were associated with poor survival. It was worth mentioning that a latest meta-analysis revealed that high OPN expression was correlated with advanced tumor stage, lymph node metastasis and large tumor size [34]. As we all know, TNM stage has been confirmed to be the most important prognostic factors, which provided support for our conclusions.

It is necessary to explore the heterogeneity in this meta-analysis. For TTO, the pooled results did not show any heterogeneity for both OS and D/RFS. Subgroup analysis according to ethnicity, statistical method, detection method, and study design showed no heterogeneity as well.
For PSPO, however, the heterogeneity was significant for pooled HR of OS ($I^2=77.2\%$, $P=0.000$) but not for that of PFS ($I^2=30.6\%$, $P=0.237$). Next, we made a subgroup analysis.
to uncover the causes of heterogeneity. When stratified by ethnicity, pooled results suggested that the heterogeneity was significantly reduced in Asians with a positive prognosis, while for Westerners, the heterogeneity was still significant with a negative prognosis. When stratified by statistical method, the heterogeneity was 0.0% (P=0.655) by multivariate analysis and 58.2% (P=0.048) by univariate analysis. Furthermore, subgroup analysis based on tumor stage showed that the heterogeneity in studies with more (III-IV >50%) advanced stage patients was completely eliminated (I^2=0.0%, P=0.611) with a positive prognosis, which was not for studies with less (III-IV <50%) advanced stage patients, suggesting that, as a predictive marker, PSPO was more suitable for patients with advanced disease. Lastly, we tested the publication bias and the robustness of OS of TTO and PSPO, and found that there was no statistical significance by begg’s funnel plot and sensitivity analysis.

There were some limitations in this meta-analysis. First, the detection methods of TTO were either IHC or PCR. Although PSPO was based on ELISA for all studies, the sample was from plasma to serum to pleural effusion. Second, the cutoff value was different for both TTO and PSPO, which was a big barrier to clinical practice. Third, some differences in demographic characteristics such as, sex, age, sample size and race could not be neglected. Besides, the differences in statistical method to estimate HR, publication bias due to a restriction to English/Chinese literatures, treatment regimens and tumor characteristics probably contributed to bias.

This study has some clinical implications. Firstly, both elevated expression of OPN and high plasma/serum/pleural effusion were associated with poor survival, suggesting that they could be used as potential markers for clinical guidance. Secondly, anti-OPN treatment may become a potential means for patients with overexpression of OPN, high serum/plasma and pleural effusion OPN level.

In conclusion, our study indicates that: 1) elevated TTO predicts poor prognosis despite of ethnicity, detection methods, statistical methods and study design; 2) high PSPO was significantly correlated with unfavorable survival, especially in patients with Asian ethnicity and UICC Stage III-IV. However, to consolidate the conclusions, high-quality prospective studies with unified cutoff value are proposed.

Disclosure of conflict of interest

None.

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