Int J Clin Exp Med 2016;9(6):9725-9733
www.ijcem.com /ISSN:1940-5901/IJCEM0025993

Review Article

Prognostic value of POSTN in human cancer: a meta-analysis

Peng Yang[1*], Jie Wang[2*], Zipeng Xu[1], Tao Chen[1], Zhenyu He[2]

[1]*The Second Clinical Medical College of Nanjing Medical University, Nanjing, Jiangsu Province, China;*
[2]*Department of General Surgery, Second Affiliated Hospital of Nanjing Medical University, 121 Jiangjiayuan Road, Nanjing 210011, Jiangsu Province, China.* [*]*Equal contributors.*

Received February 15, 2016; Accepted May 8, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: The prognostic value of periostin (POSTN) in various cancers has been widely investigated with ambiguous results. A meta-analysis was performed to evaluate the prognostic significance of POSTN in human cancer. Hazard ratios (HRs) with 95% confidence intervals (CIs) of overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) were extracted and analyzed to clarify the relationship between POSTN expression and prognosis of different cancers. A total of 18 eligible studies with 1919 patients were included in this meta-analysis. The result suggested that POSTN overexpression was associated with poor OS (HR = 1.84, 95% CI: 1.53-2.22), PFS (HR = 2.28, 95% CI: 1.84-2.82) and DFS (HR = 2.54, 95% CI: 1.66-3.89) in cancer patients. Subgroup analyses by ethnicity, cancer type, measurement method and survival analysis indicated that POSTN had a reliable prognostic value when detecting the expression of POSTN with immunohistochemistry (IHC) method. Our meta-analysis showed that elevated POSTN expression might be significantly related to worse survival outcome in human cancer.

Keywords: POSTN, cancer, prognosis, survival outcome, overall survival, meta-analysis

Introduction

Periostin (POSTN) or osteoblast-specific factor 2 (OSF-2), which was initially identified in 1993 from mouse osteoblastic cell line by Takeshita [1]. As a major extracellular matrix (ECM) protein, POSTN is involved in kinds of physiological processes including cell proliferation, motility and survival by interacting with integrins or other signals mainly via the PI3-K/AKT pathway [2, 3]. Moreover, POSTN was shown to be an inducer of epithelial mesenchymal transition (EMT) change and reported to promote a stem cell-like phenotype [4, 5]. EMT and cancer stem-like cells were both involved in development and metastatic of cancer. Recently, POSTN has been proposed as a marker associated with survival outcome in various cancers, such as malignant pleural mesothelioma, esophageal squamous cell carcinoma, epithelial ovarian cancer, hepatocellular carcinoma, colorectal cancer, non-small cell lung cancer and cholangiocarcinoma [6-12].

However, limited by small sample sizes and controversial results, the potential prognostic value of POSTN expression in patients is still inconclusive. Be interested in acquiring a reliable conclusion of the prognostic effect of POSTN, we performed a meta-analysis to assess the relationship between POSTN expression and survival outcome in human cancer.

Materials

Search strategy and selection criteria

We searched the PubMed and EMBASE databases for the prognostic significance of POSTN in cancer up to January 2016. In the research, the key words and terms we used were “cancer” or “tumor” or “neoplasm” and “periostin” or “POSTN” “osteoblast-specific factor 2” or “OSF-2” to identify relevant studies. In addition, other eligible studies were hand-searched. The final studies were included in the meta-analysis as the following criteria: (1) POSTN expression evaluated in the human serum or human tumor tissues, (2) evaluated the correlation between POSTN and survival outcome including overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS), (3) measured

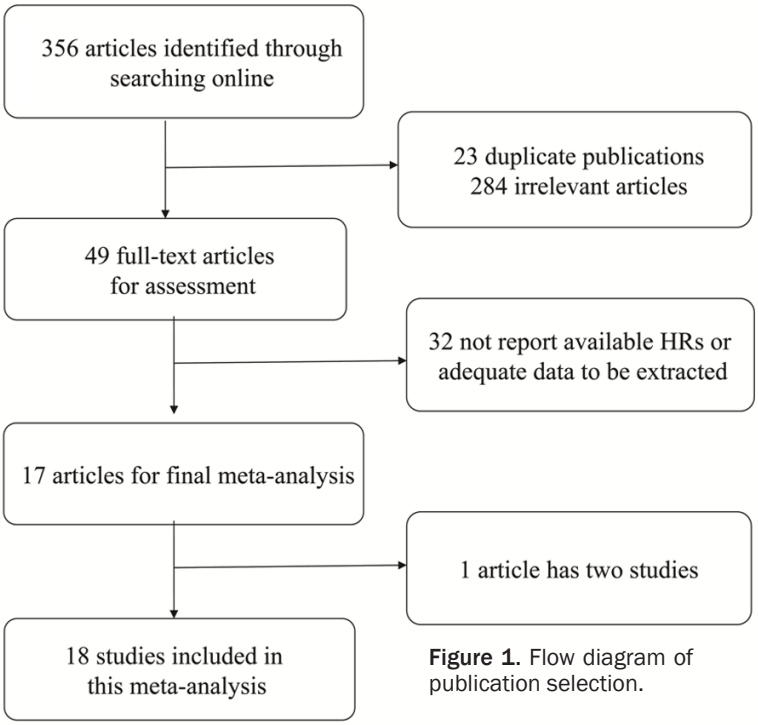

Figure 1. Flow diagram of publication selection.

POSTN expression by immunohistochemistry (IHC) or enzyme-linked immunosorbent assay (ELISA) methods, (4) description of the cut-off value of POSTN, (5) reported a hazard ratio (HR) and confidence interval (CI) or provided sufficient data to calculate, (6) published with a full-text in English.

Data extraction

Peng Yang and Zipeng Xu extracted data independently from the eligible studies, complying with a predetermined form. The following items were extracted: first author's name, year of publication, country, number, specimen, tumor type, tumor stage, measurement method, cut-off values, survival analysis method, and the sources of HRs (95% CI). In some studies, HRs could be directly extracted from the study by multivariate analysis or univariate analysis. In other cases, we extracted the relevant numerical value to extrapolate HRs with their 95% CIs from the Kaplan-Meier survival curves using Engauge Digitizer version 4.1 [13].

Statistical analysis

The impact of POSTN on survival outcome was evaluated by the HRs (CIs). For POSTN overexpression patients, an observed HR > 1 indicated a poorer prognosis. It would be considered statistically significant, if the 95% CI did not overlap with 1. The I^2 statistic was used to assess statistical heterogeneity among studies [14]. If there was significant heterogeneity between studies (I^2 > 50% or P < 0.05), the random-effects model was used. Otherwise, fixed-effects model was chosen [15]. Subgroup analysis was conducted with stratification by ethnicity, cancer type, measurement method and survival analysis. To evaluate the stability of the results, sensitivity analysis was also performed with sequential omission of each study. Additionally, Begg's test and Egger's text was carried out to evaluate the potential publication bias (P < 0.05 represents significant) [16]. All the statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, Texas, USA).

Results

Characteristics of eligible studies

A total of 356 articles were obtained by searching from PubMed and EMBASE databases. Out of these, 307 articles were excluded due to duplicate publications and irrelevant articles. After full-text reading remaining 49 articles, another 32 articles without available HRs (95% CI) or adequate data were excluded. Therefore, 17 articles were finally included in the meta-analysis [6-12, 17-26]. Because Riener reported POSTN expression was associated with two different cancer types (Hepatocellular carcinoma and Bile duct carcinomas) in one article, we treated them separately for this meta-analysis [18]. **Figure 1** showed the flow diagram of the literature research process.

The characteristics of the 18 studies in this mate-analysis were presented in **Table 1**. These studies were published between 2008 and 2015 with sample sizes ranging from 51 to 312 and a total of 1919 patients included. Among the 18 studies, a total of 12 different

Table 1. Characteristics of POSTN studies included in the meta-analysis

First author	Year	Country	Cancer type	Number	Method	Outcome	Cut-off	Survival analysis	HR estimate
Schramm [6]	2010	Switzerland	Malignant pleural mesothelioma	128	IHC	OS	Median	Multivariate, univariate	Reported
Thies [26]	2015	Switzerland	Malignant pleural mesothelioma	97	IHC	OS	Median	Multivariate, univariate	Reported
Wang [22]	2013	China	Glioma	47	IHC	OS, PFS	2	Multivariate, univariate	Reported
Tian [23]	2014	China	Glioma	312	IHC	PFS	1	Multivariate	Reported
Wang [7]	2014	China	Esophageal squamous cell carcinoma	68	IHC	OS, DFS	30%	Multivariate, univariate	Reported
Choi [8]	2011	Korea	Epithelial ovarian cancer	66	IHC	OS	10%	Univariate	Survival curve
Ryner [25]	2015	USA	Epithelial ovarian cancer	138	IHC	PFS	Median	Multivariate, univariate	Reported
Riener[1] [18]	2010	Switzerland	Hepatocellular carcinoma	91	IHC	OS	2	Univariate	Survival curve
Lv [21]	2013	China	Hepatocellular carcinoma	71	IHC	OS, DFS	10%	Multivariate, univariate	Reported
Lv [9]	2013	China	Hepatocellular carcinoma	56	ELISA	OS, DFS	Normal range	Multivariate, univariate	Reported
Ben [17]	2009	China	Colorectal Cancer	67	ELISA	OS	Normal range	Univariate	Survival curve
Li [10]	2015	China	Colorectal Cancer	115	IHC	OS	2	Multivariate, univariate	Reported
Takanami [11]	2008	Japan	Non-small cell lung cancer	88	IHC	OS	5%	Multivariate, univariate	Reported
Utispan [12]	2010	Thailand	Cholangiocarcinoma	51	IHC	OS	4	Multivariate, univariate	Reported
Riener[2] [18]	2010	Switzerland	Bile duct carcinomas	116	IHC	OS	2	Multivariate, univariate	Reported
Li [20]	2012	China	Nasopharyngeal carcinoma	132	IHC	OS	5%	Multivariate, univariate	Reported
Ben [19]	2011	China	Pancreatic cancer	94	IHC	OS	2	Univariate	Survival curve
Nuzzo [24]	2015	Italy	Breast cancer	182	ELISA	OS	Median	Univariate	Reported

Riener[1] and Riener[2] from one article. POSTN: Periostin; IHC: Immunohistochemistry; ELISA: Enzyme-linked immunosorbent assay; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; DFS: Disease-free survival.

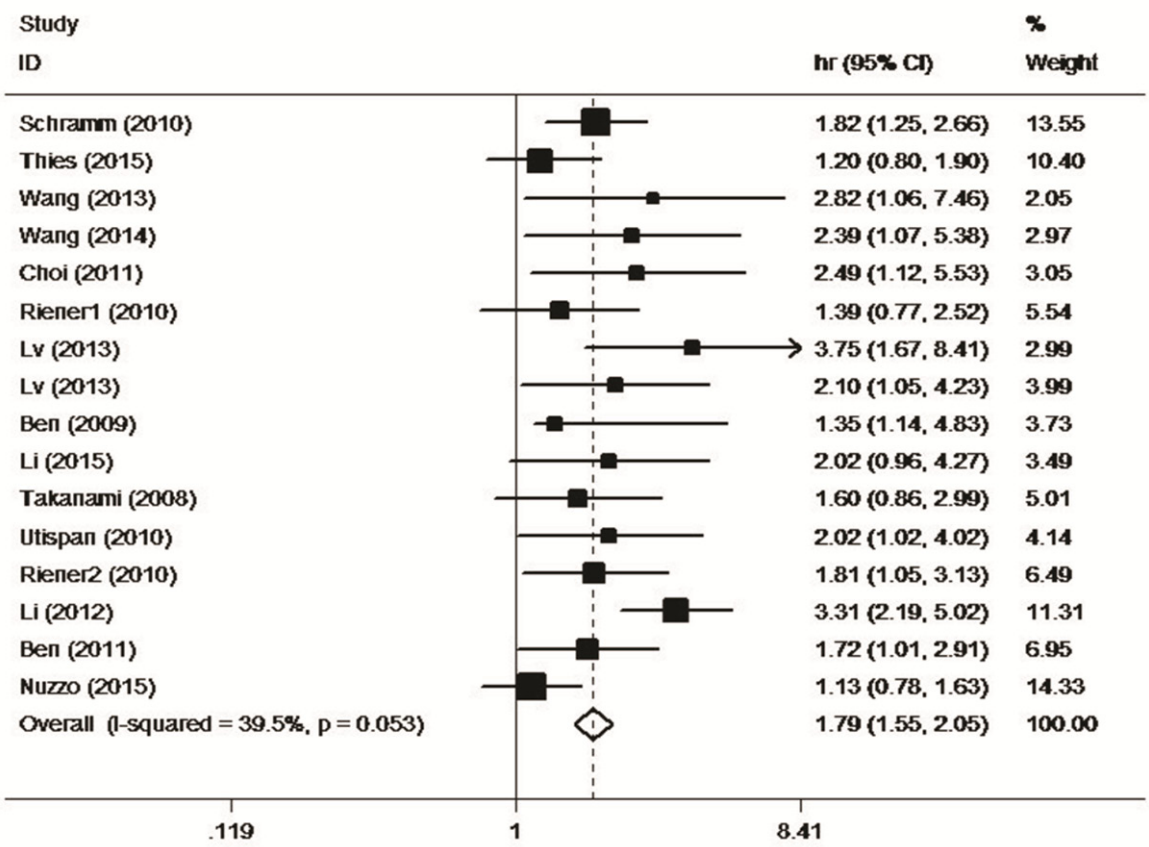

Figure 2. Forest plots for relationship between POSTN expression and OS.

Table 2. Relationship between POSTN expression and survival outcome

Survival outcome	Studies (N)	Patients (N)	HR (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	*P*-value
OS	16	1469	1.787 (1.554-2.054)	0.000	39.5	0.053
Ethnicity						
Caucasian	5	614	1.415 (1.163-1.723)	0.001	11.1	0.342
Asian	11	855	1.787 (1.554-2.787)	0.000	0.0	0.492
Cancer type						
Digestive system	9	729	1.881 (1.510-2.343)	0.000	0.0	0.729
Nondigestive system	7	740	1.816 (1.287-2.561)	0.001	68.7	0.004
Method						
IHC	13	1164	1.954 (1.668 -2.288)	0.000	28.7	0.156
ELISA	3	305	1.303 (0.968-1.754)	0.081	16.3	0.303
Survival analysis						
Multivariate	11	969	2.023 (1.705-2.401)	0.000	32.8	0.137
Univariate	5	500	1.398 (1.099-1.778)	0.006	0.0	0.421
PFS	3	497	2.28 (1.84-2.82)	0.000	0.0	0.577
DFS	3	195	2.54 (1.66-3.89)	0.000	0.0	0.538

types of cancers were evaluated by this meta-analysis, including digestive system carcinoma (three hepatocellular cancers, two colorectal cancers, one pancreatic cancer, one esophageal squamous cell carcinoma, one cholangiocarcinoma, one bile duct carcinomas), and

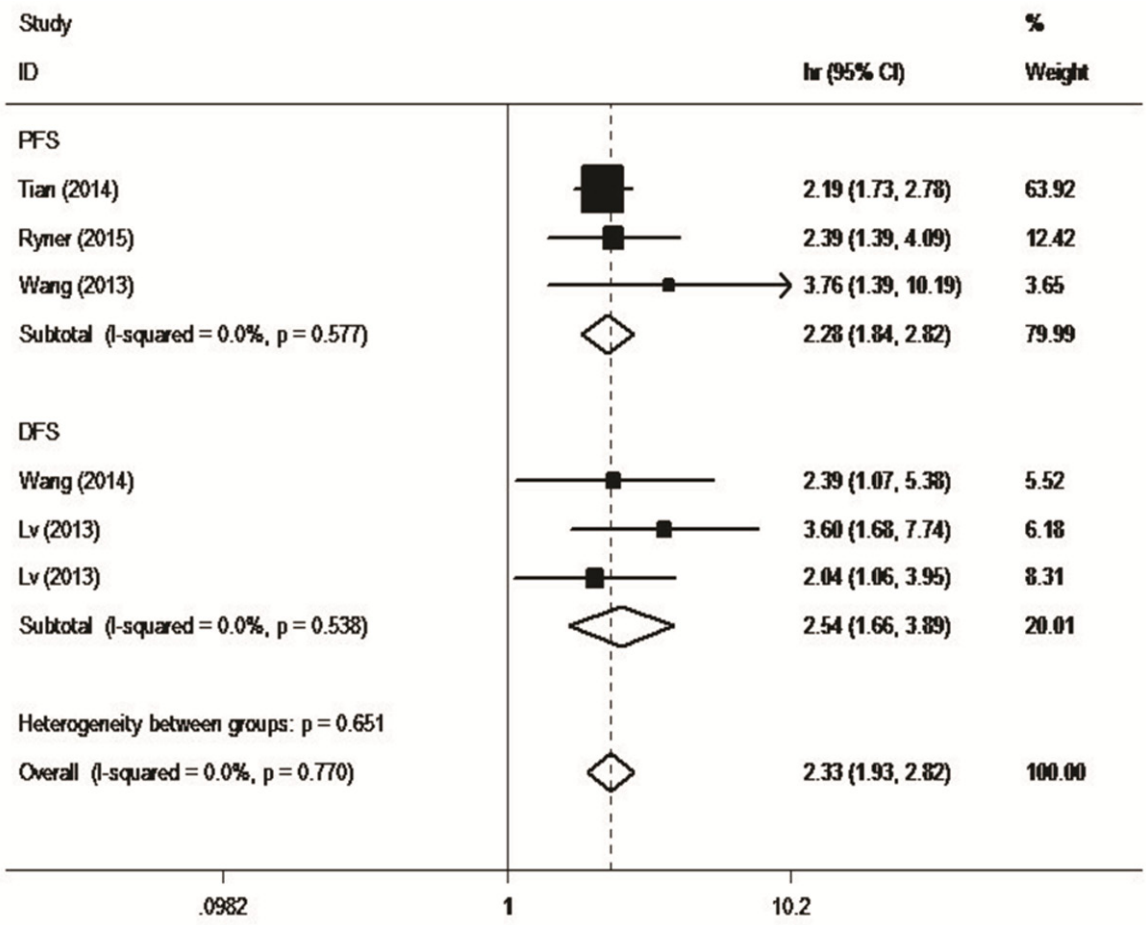

Figure 3. Forest plots for relationship between POSTN expression and PFS, DFS.

other system carcinoma (two glioma, two malignant pleural mesothelioma, two epithelial ovarian cancer, one non-small cell lung cancer, one nasopharyngeal carcinoma and one breast cancer). 3 studies used ELISA methods to detect the expression of POSTN and 15 studies used immunohistochemistry (IHC) method. HRs (95% CIs) were directly extracted from 14 studies, while 4 studies were calculated from survival curves.

Relationship between POSTN expression and survival outcome in human cancer.

To investigate the relationship between POSTN expression and survival outcome of patients with cancer, HRs for OS, DFS and PFS were extracted in this meta-analysis. Sixteen studies with a total of 1469 participants were included in the overall analysis indicated that elevated POSTN expression was predictive of poor OS (HR = 1.787, 95% CI: 1.554-2.054, **Figure 2**; **Table 2**) and no significant heterogeneity was observed among these studies (I^2 = 39.5%, P = 0.053). As shown in the forest plots (**Figure 3**; **Table 2**), POSTN over-expression was also associated with decreased PFS (HR = 2.28, 95% CI: 1.84-2.82) and DFS (HR = 2.54, 95% CI: 1.66-3.89) in human cancer without significant heterogeneity.

Next, we performed subgroup analysis based on ethnicity, cancer type, method and survival analysis to estimate the association between POSTN expression and OS (**Table 2**). A significant association was confirmed between POSTN over-expression and poor OS in Caucasian (HR = 1.415, 95% CI: 1.163-1.723) and Asian (HR = 1.787, 95% CI: 1.554-2.787). Subsequently, we examined the effect of measurement methods among the studies and found that ELISA method had no relevance to OS in patients (HR = 1.303, 95% CI: 0.968-1.754). Next, significant correlation was ob-

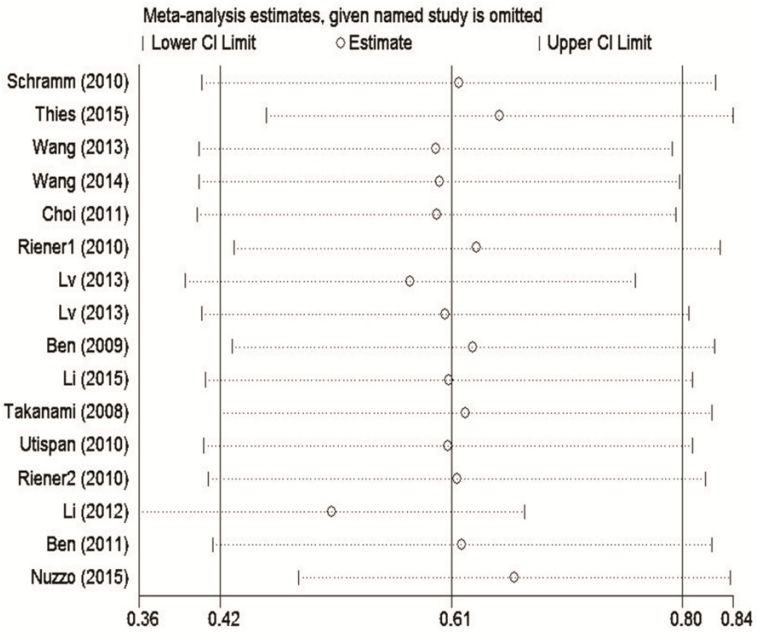

Figure 4. Sensitivity analysis of the pooled HRs of POSTN expression and OS for the included studies.

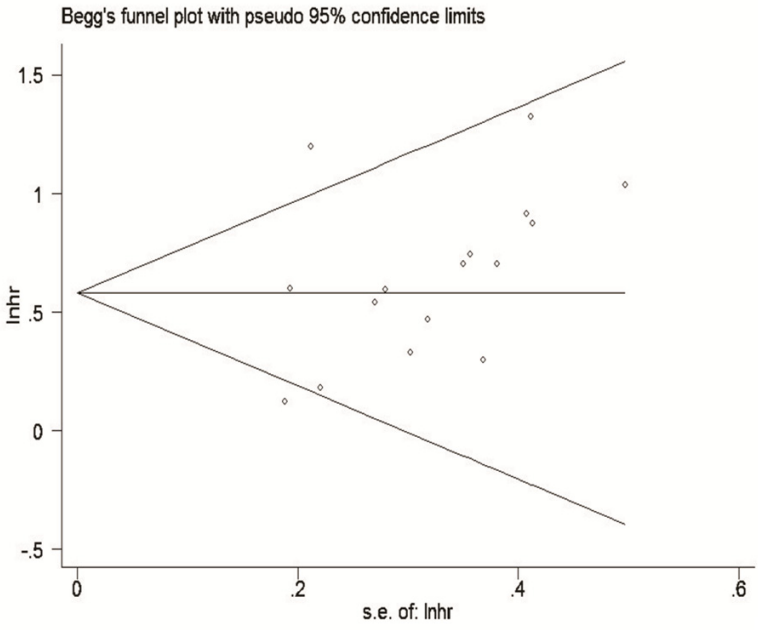

Figure 5. Begg's funnel plot to explore publication bias of the included studies between POSTN and OS.

served both in subgroup of multivariate analysis (HR = 2.023, 95% CI: 1.705-2.401) and subgroup of univariate analysis (HR = 1.398, 95% CI: 1.099-1.778). Finally, subgroup analysis by cancer type indicated that POSTN over-expression was related to the worse OS in digestive system (HR = 1.881, 95% CI: 1.510-2.343) and nondigestive system (HR = 1.881, 95% CI: 1.510-2.343). The random-effect model was used because of the significant heterogeneity (I^2 = 68.7%, P = 0.004) among the subgroup of nondigestive system.

Sensitivity analysis and publication bias

Sensitivity analysis indicated that the association between POSTN expression and OS was not significantly influenced by omitting any individual article (**Figure 4**). The shape of the Begg's funnel plot did not show any evidence of obvious asymmetry (**Figure 5**). The *P*-value of Egger's test was 0.16, indicating that the publication bias was not significant in the meta-analysis.

Discussion

Recently, many studies have reported that the aberrant expression of POSTN was associated with poor survival outcome in various cancers. While limited by the information from small sample size, studies of the prognostic role of POSTN have led to highly controversial results. To our knowledge, our meta-analysis with a total of 1919 patients was the first study to systematically assess the relationship between POSTN expression and the survival outcome in human cancers. Our result showed that overexpression of POSTN was a statistically significant prognostic factor for survival outcome (OS, PFS and DFS) on cancer patients.

To identify the specific relationship between POSTN expression and OS, subgroup analysis was conducted according to ethnicity (Asian

and Caucasian), cancer type (digestive system and nondigestive system), method (IHC and ELISA) and survival analysis (multivariate analysis and univariate analysis). The results of subgroup analysis showed that ethnicity and survival analysis did not influence the predictive value of POSTN on overall survival among the investigated cancers. As to the measurement method, high POSTN expression was significantly associated with poor OS using IHC, while no prognostic effect of POSTN were observed with ELISA. In cancer type group, we found POSTN overexpression was related to worse OS both in digestive system and nondigestive system. However, the significant heterogeneity could not be ignored in the group of nondigestive system (I^2 = 68.7%, P = 0.004). The existing heterogeneity might influence the result of this meta-analysis, which need to be illustrated. First of all, POSTN, an important ECM protein, the potential molecular mechanism of POSTN in tumorigenesis is complicated and not completely understood [2]. Studies have reported that POSTN overexpression played an oncogenic role in various cancers to promote the recruitment of EGFR and the activation of Akt/PKB and FAK-mediated signaling pathways such as colon, esophagus, pancreas, breast and so on [27-29]. Conversely, Kim reported that POSTN was frequently downregulated and functioned as a tumor suppressor in bladder cancer [30]. Moreover, due to the strict criterion, only seven studies were involved in the group of nondigestive system, which included 6 different types of cancer. The small sample sizes and diversified cancer types might partly explain the source of heterogeneity in nondigestive system. What's more, the inconsistent cut-off values dividing the POSTN expression status among studies might also a potential source of heterogeneity. In conclusion, we were more inclined to summarize that POSTN had a reliable predictive role in digestive system; nonetheless, this did not mean that POSTN did not have prognostic value in other cancers. Hence, more basic researches should be conducted to provide better understanding of biological roles of POSTN in tumorigenesis.

In this study, no publication bias was detected by Begg's test and Egger's test. However, several limitations should be acknowledged in the meta-analysis. Firstly, the HRs (CI) of four studies were estimated based on survival curve but not given directly, which might lead to inaccurate results. Secondly, the bias information were provided, because that most authors preferred publishing significant results to nonsignificant results. Thirdly, we had restricted our meta-analysis to published studies in English only, so some meaningful data might have been ignored. Fourth, some included studies with low quality and small sample sizes restricted us gaining more comprehensive results.

In summary, we have demonstrated that elevated POSTN expression is significantly associated with the poor survival outcome including OS, PFS and DFS in many cancer types. Further evaluations with larger sample sizes were still required to provide more persuasive data on this putative relationship.

Acknowledgements

This work was supported by The Research Innovation Program for College Graduates of Jiangsu Province (SJLX15_0427) and the Science and Technology projects of Jiangsu Province, Bureau of Traditional Chinese Medicine (YB2015171).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhenyu He, Department of General Surgery, Second Affiliated Hospital of Nanjing Medical University, 121 Jiangjiayuan Road, Nanjing 210011, Jiangsu Province, China. Tel: +86-25-58509900; Fax: +86-25-585-09900; E-mail: hezhenyu1968@126.com

References

[1] Takeshita S, Kikuno R, Tezuka K and Amann E. Osteoblast-specific factor 2: cloning of a putative bone adhesion protein with homology with the insect protein fasciclin I. Biochem J 1993; 294: 271-278.

[2] Ruan K, Bao S and Ouyang G. The multifaceted role of periostin in tumorigenesis. Cell Mol Life Sci 2009; 66: 2219-2230.

[3] Gillan L, Matei D, Fishman DA, Gerbin CS, Karlan BY and Chang DD. Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. Cancer Res 2002; 62: 5358-5364.

[4] Morra L and Moch H. Periostin expression and epithelial-mesenchymal transition in cancer: a

review and an update. Virchows Arch 2011; 459: 465-475.
[5] Wang X, Liu J, Wang Z, Huang Y, Liu W, Zhu X, Cai Y, Fang X, Lin S, Yuan L and Ouyang G. Periostin contributes to the acquisition of multipotent stem cell-like properties in human mammary epithelial cells and breast cancer cells. PLoS One 2013; 8: e72962.
[6] Schramm A, Opitz I, Thies S, Seifert B, Moch H, Weder W and Soltermann A. Prognostic significance of epithelial-mesenchymal transition in malignant pleural mesothelioma. Eur J Cardiothorac Surg 2010; 37: 566-572.
[7] Wang W, Sun QK, He YF, Ma DC, Xie MR, Ji CS and Hu B. Overexpression of periostin is significantly correlated to the tumor angiogenesis and poor prognosis in patients with esophageal squamous cell carcinoma. Int J Clin Exp Pathol 2014; 7: 593-601.
[8] Choi KU, Yun JS, Lee IH, Heo SC, Shin SH, Jeon ES, Choi YJ, Suh DS, Yoon MS and Kim JH. Lysophosphatidic acid-induced expression of periostin in stromal cells: Prognoistic relevance of periostin expression in epithelial ovarian cancer. Int J Cancer 2011; 128: 332-342.
[9] Lv Y, Wang W, Jia WD, Sun QK, Huang M, Zhou HC, Xia HH, Liu WB, Chen H, Sun SN and Xu GL. High preoparative levels of serum periostin are associated with poor prognosis in patients with hepatocellular carcinoma after hepatectomy. Eur J Surg Oncol 2013; 39: 1129-1135.
[10] Li Z, Zhang X, Yang Y, Yang S, Dong Z, Du L, Wang L and Wang C. Periostin expression and its prognostic value for colorectal cancer. Int J Mol Sci 2015; 16: 12108-12118.
[11] Takanami I, Abiko T and Koizumi S. Expression of periostin in patients with non-small cell lung cancer: correlation with angiogenesis and lymphangiogenesis. Int J Biol Markers 2008; 23: 182-186.
[12] Utispan K, Thuwajit P, Abiko Y, Charngkaew K, Paupairoj A, Chau-in S and Thuwajit C. Gene expression profiling of cholangiocarcinoma-derived fibroblast reveals alterations related to tumor progression and indicates periostin as a poor prognostic marker. Mol Cancer 2010; 9: 13.
[13] Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.
[14] Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
[15] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[16] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[17] Ben QW, Zhao Z, Ge SF, Zhou J, Yuan F and Yuan YZ. Circulating levels of periostin may help identify patients with more aggressive colorectal cancer. Int J Oncol 2009; 34: 821-828.
[18] Riener MO, Fritzsche FR, Soll C, Pestalozzi BC, Probst-Hensch N, Clavien PA, Jochum W, Soltermann A, Moch H and Kristiansen G. Expression of the extracellular matrix protein periostin in liver tumours and bile duct carcinomas. Histopathology 2010; 56: 600-606.
[19] Ben QW, Jin XL, Liu J, Cai X, Yuan F and Yuan YZ. Periostin, a matrix specific protein, is associated with proliferation and invasion of pancreatic cancer. Oncol Rep 2011; 25: 709-716.
[20] Li M, Li C, Li D, Xie Y, Shi J, Li G, Guan Y, Li M, Zhang P, Peng F, Xiao Z and Chen Z. Periostin, a stroma-associated protein, correlates with tumor invasiveness and progression in nasopharyngeal carcinoma. Clin Exp Metastasis 2012; 29: 865-877.
[21] Lv Y, Wang W, Jia WD, Sun QK, Li JS, Ma JL, Liu WB, Zhou HC, Ge YS, Yu JH, Xia HH and Xu GL. High-level expression of periostin is closely related to metastatic potential and poor prognosis of hepatocellular carcinoma. Med Oncol 2013; 30: 385.
[22] Wang H, Wang Y and Jiang C. Stromal protein periostin identified as a progression associated and prognostic biomarker in glioma via inducing an invasive and proliferative phenotype. Int J Oncol 2013; 42: 1716-1724.
[23] Tian B, Zhang Y and Zhang J. Periostin is a new potential prognostic biomarker for glioma. Tumour Biol 2014; 35: 5877-5883.
[24] Nuzzo PV, Rubagotti A, Argellati F, Di Meglio A, Zanardi E, Zinoli L, Comite P, Mussap M and Boccardo F. Prognostic Value of Preoperative Serum Levels of Periostin (PN) in Early Breast Cancer (BCa). Int J Mol Sci 2015; 16: 17181-17192.
[25] Ryner L, Guan Y, Firestein R, Xiao Y, Choi Y, Rabe C, Lu S, Fuentes E, Huw LY, Lackner MR, Fu L, Amler LC, Bais C and Wang Y. Upregulation of Periostin and Reactive Stroma Is Associated with Primary Chemoresistance and Predicts Clinical Outcomes in Epithelial Ovarian Cancer. Clin Cancer Res 2015; 21: 2941-2951.
[26] Thies S, Friess M, Frischknecht L, Korol D, Felley-Bosco E, Stahel R, Vrugt B, Weder W, Opitz I and Soltermann A. Expression of the Stem Cell Factor Nestin in Malignant Pleural Mesothelioma Is Associated with Poor Prognosis. PLoS One 2015; 10: e0139312.
[27] Bao S, Ouyang G, Bai X, Huang Z, Ma C, Liu M, Shao R, Anderson RM, Rich JN and Wang XF. Periostin potently promotes metastatic growth

of colon cancer by augmenting cell survival via the Akt/PKB pathway. Cancer Cell 2004; 5: 329-339.

[28] Michaylira CZ, Wong GS, Miller CG, Gutierrez CM, Nakagawa H, Hammond R, Klein-Szanto AJ, Lee JS, Kim SB, Herlyn M, Diehl JA, Gimotty P and Rustgi AK. Periostin, a cell adhesion molecule, facilitates invasion in the tumor microenvironment and annotates a novel tumor-invasive signature in esophageal cancer. Cancer Res 2010; 70: 5281-5292.

[29] Baril P, Gangeswaran R, Mahon PC, Caulee K, Kocher HM, Harada T, Zhu M, Kalthoff H, Crnogorac-Jurcevic T and Lemoine NR. Periostin promotes invasiveness and resistance of pancreatic cancer cells to hypoxia-induced cell death: role of the beta4 integrin and the PI3k pathway. Oncogene 2007; 26: 2082-2094.

[30] Kim CJ, Yoshioka N, Tambe Y, Kushima R, Okada Y and Inoue H. Periostin is down-regulated in high grade human bladder cancers and suppresses in vitro cell invasiveness and in vivo metastasis of cancer cells. Int J Cancer 2005; 117: 51-58.