The Prognostic Value of Periostin Expression in Non-Small Cell Lung Cancer: A Meta-Analysis

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Background: Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related death in the world and its poor prognosis is a major concern. Periostin was found to be associated with the prognosis of NSCLC. However, the research results were inconsistent. This meta-analysis evaluated the correlation between periostin expression and the prognosis of NSCLC.

Material/Methods: A meta-analysis was performed on data acquired from PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database from inception to 18 June 2022. Published and unpublished studies investigating the correlation between periostin expression and the prognosis of NSCLC were included in this meta-analysis. Eligible studies reported at least 1 of the following clinical outcome measures: overall survival, progression-free survival, cancer-specific survival, relapse-free survival, disease-free survival, or other clinical parameters of prognosis. Pooled hazard ratios (HR) with 95% confidence interval (CI) were calculated using the random-effects model. Sensitivity and subgroup analyses and assessment of publication bias were also conducted.

Results: This meta-analysis enrolled 2504 NSCLC cases from 12 eligible studies. The hazard ratio for the overall survival was 1.761 (95% CI: 1.022-3.033, P=0.041). Heterogeneity was significant among the studies, but publication bias was lacking. Subgroup analyses were performed based on different issues, such as districts, antibodies and methods for periostin detection.

Conclusions: Overexpression of periostin is a negative prognostic factor and is associated with worse overall survival (OS) in NSCLC patients. Periostin may serve as a prognostic biomarker for NSCLC patients.

Keywords: Periostin • Prognosis • Non-Small Cell Lung Cancer • Meta-Analysis

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Background

Lung cancer is the leading cause of cancer-associated mortality globally in both men and women [1]. In 2018, over 230 000 new cases of lung cancer (13% of all cancer diagnoses) and over 150 000 deaths (25% of cancer deaths) were reported in the United States [2]. NSCLC is the most common type of lung cancer, and accounts for 80-90% of all the lung cancer cases [3]. Routine treatments for NSCLC include surgery, chemotherapy, and radiotherapy, but the benefits of these treatments are limited for patients in advanced stages [4,5]. Despite the promising development of molecular-targeted therapies, the outcomes of patients with stage III/IV NSCLC remains unsatisfactory, with a 5-year survival rate around 16% [6-8]. Several serum-based tumor biomarkers have been applied to monitor cancer treatment, such as neuron-specific enolase (NSE), cytokeratin 19 fragment (CYFRA21-1), and carcinoembryonic antigen (CEA) [9]. However, due to their low sensitivity and specificity, these biomarkers have limited ability to predict the prognosis of NSCLC [10]. Therefore, new biomarkers for prognosis of NSCLC are needed.

Periostin (POSTN), also referred to as osteoblast-specific factor 2, is a 93.3-kDa extracellular matrix (ECM) protein that was identified in murine osteoblast-like cells in 1993 [11]. Periostin has been detected in a wide variety of normal tissues, and especially in tissues under stress conditions such as heart under pressure or volume overload and skeletal muscle after injury [12,13]. Previous studies have shown that a high level of periostin is strongly associated with malignant behavior in many kinds of malignancies such as esophageal cancer, breast carcinoma, and NSCLC [14-16]. Periostin has been studied and found to be associated with cancer-related death and employed as a useful prognostic indicator in many kinds of solid tumors [17]. A meta-analysis involving 993 patients with cancer demonstrated that periostin overexpression was markedly associated with poor overall survival (OS) (HR=2.35, 95% CI=1.88-2.93) and worse disease-free survival (DFS) (HR=2.70, 95% CI=2.00-3.65) [17]. These data showed that periostin could be a potential cancer prognostic biomarker.

The prognostic role of periostin in NSCLC has been reported in various studies [16,18-25]. Many studies indicated that periostin was associated with a decrease in survival and as a negative prognostic factor, while others did not reach to any conclusive and relevant result indicating that periostin was associated with the prognosis of NSCLC [26-28]. In view of the inconsistent results across these studies, we aimed to perform a systematic review and meta-analysis of published research to assess the prognostic value of periostin in NSCLC patients.

Material and Methods

This meta-analysis was performed following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2020 statement [29].

Data Sources and Searches

We searched PubMed, the Cochrane Library, EMBASE, Wanfang Database, and China National Knowledge Infrastructure (CNKI) to find relevant articles up to 18 June 2022 in all languages using the following text word or Medical Subject Heading terms: (“non-small-cell lung cancer”) OR “non-small cell lung cancer” OR “non small-cell lung cancer” OR “non-small cell lung carcinoma” OR “non-small cell lung carcinoma” OR “non small-cell lung carcinoma” OR “non small cell lung carcinoma” OR “non small cell lung carcinoma” OR “nsclc”) AND (“osteoblast-specific factor 2” OR “periostin” OR “osteoblast specific factor” OR “OSF-2 protein” OR “periostin protein”) AND (“prognosis” OR “prognostic” OR “survival” OR “recurrence”). We also manually searched the reference lists of relevant reviews and original articles to identify other eligible studies.

Study Selection

Two reviewers independently screened the titles and abstracts of the retrieved articles, then the relevant studies were reviewed as full-text articles.

Studies that met the following inclusion criteria were considered eligible and taken into consideration: (1) All articles were written and published in English with the availability of the full text of the article; (2) Patients were pathologically diagnosed with NSCLC; (3) Periostin was detected by conventional methods, and its association with survival or other clinical parameters of prognosis was demonstrated; (4) The necessary data can be acquired, including overall survival (OS), progression-free survival (PFS), cancer-specific survival (CSS), relapse-free survival (RFS), disease-free survival (DFS) or other clinical parameters of prognosis; (5) The presence of statistical analysis including hazard ratios (HRs) and the 95% confidence interval (CI), or data that could be utilized to estimate the HRs and 95% CIs such as Kaplan-Meier survival curves.

Studies not meeting the inclusion criteria were excluded. Other exclusion criteria were: (1) Articles which were a review or systematic review, conference paper, commentary, case report, letter, or expert opinion; (2) Laboratory studies, such as studies on animals or in vitro; (3) Articles without full text; (4) Studies with insufficient data, or data were not extractable.
Data Extraction and Risk of Bias Assessment

Basic information was extracted using a collection form: publication year, country, name of first author, number of patients involved, median age, sex, clinical stage, method used to detect periostin, antibodies used for detection, cut-off value to define high periostin expression, and number of patients with high and low periostin expression.

The prognostic endpoints were PFS, OS, RFS, CSS, or DFS. We extracted HRs and 95% CIs from either univariate/multivariate analysis or Kaplan-Meier survival curves by use of Engauge Digitizer 4.1 [30].

We assessed risk of bias of individual studies using the Newcastle-Ottawa Scale (NOS) criteria [31]. The NOS was used to assess 3 aspects: subject selection, comparability of the subject, and clinical outcome. The scores of NOS ranged from 0 to 9 stars. Studies with NOS score values $\geq 6$ stars were considered to be high quality.

All investigators independently conducted study selection and data extraction. Two investigators (ML and GM) independently assessed risk of bias of individual studies. Any discrepancies were resolved by consensus and arbitration by a panel of adjudicators (ML, GM, XL, and QZ).

Data Synthesis and Statistical Analysis

The STATA (version 13.1; Stata Corporation, College Station, TX, USA) was used for the process of data calculation and analysis. We extracted LogHRs and variances for survival evaluation. If provided indirectly, the HR was extracted from the Cox regression model or Kaplan-Meier curve. If both univariate and multivariate survival analyses existed, we chose multivariate analysis first. If adjusted and unadjusted HRs were both provided, we used the adjusted HR. $I^2$ statistic test and chi-square-based Q test were used to test the heterogeneity among the included studies [32]. If the heterogeneity among the studies was insignificant ($P>0.10$ or $I^2<50\%$), the pooled HR was estimated with the fixed-effect model (Mantel-Haenszel method) [33]. Otherwise, the random-effect model was used to reduce the impact of heterogeneity. Publication bias was evaluated by Begg’s method [34]. $P<0.05$ was considered to be statistically significant.

Results

Study Selection

The initial search retrieved 244 important articles, and the detailed reasons for exclusion are displayed in the flow chart (Figure 1). In total, we identified 12 cohort studies in this analysis.

Study Characteristics

The basic information of the 12 eligible studies is listed in Table 1. All the studies that met the inclusion criteria were published between 2001 and 2021, and were conducted in Japan [16,18,19,23,25,27], China [20-22], Poland [24], Germany [26], and Switzerland [28]. A total of 2504 cases were included in this meta-analysis. All the cases were diagnosed with NSCLC based on histology reports, and their clinical stages varied from I to IV. Various methods were used to detect periostin. The most common methods were immunohistochemistry (IHC) [18,19,24-28] staining of tumor tissue specimens, enzyme-linked immunosorbent assay (ELISA) [20,21], and western blot [22] analysis for serum samples. The HRs were acquired directly from
most studies [16,18-22,24-28] except for Sasaki’s [23] study, in which they were extracted from the survival curve. All the NOS scores of the included studies were no less than 7.

Meta-Analysis Results

OS and PFS evaluated the prognostic value of overexpression of periostin in NSCLC. OS was extracted from most of the included studies, and the pooled HR was 1.761 (95% CI: 1.022-3.033, P=0.041; Figure 2), indicating that high periostin was a negative prognostic factor in NSCLC patients. The heterogeneity was statistically significant (I²=76.0%, P=0.000); therefore, a random-effects model was applied. Only 4 of the included studies provided PFS, and the pooled HR was 1.296 (95% CI: 0.965-1.740, P=0.085; Figure 3). In this procedure, random-effects models were also used because of the statistically significant heterogeneity (I²=80.3%, P=0.002).

Subgroup Analysis

Subgroup analysis was performed based on the extracted information from all the eligible studies. Subgroups were stratified by region (Asian/Chinese/Japanese), detection methods of periostin (IHC/ELISA), and antibodies for periostin detection (rabbit polyclonal/mouse monoclonal), as shown in Table 2.

Region (Asian/Chinese/Japanese)

In total, there were 9 eligible studies from Asia. Among these studies, 6 were from Japan and the others were from China. Considering the Asian studies, the combined HR of OS was 2.052 (95% CI: 1.113-3.781, P=0.021), and the random-effects model was used due to its significant heterogeneity (I²=72.1%, P=0.001). For the 6 Japanese studies, the pooled HR for OS was 1.903 (95% CI: 0.826-4.384, P=0.131), and the random-effects model was used because of the significant heterogeneity in

Table 1. Characteristics of the included articles.

| Author         | Country   | Median age | N (F/M) | Clinical stage | Method      | Antibody          | HR estimation | Cut-off | Periostin (H/L) | Quality score |
|----------------|-----------|------------|---------|----------------|-------------|-------------------|----------------|---------|-----------------|---------------|
| Iwamoto 2021   | Japan     | 65         | 73 (34/39) | I-IIIA         | IHC         | MM                | HR+Cl          | Score ≥4 | 34/39           | 7             |
| Ratajczak-     | Poland    | NA         | NA      | I-IV           | IHC         | RP                | HR+Cl          | Score >7 | 360/340         | 8             |
| Wielgomas 2020 | Poland    | NA         | NA      | I-IV           | IHC         | RP                | HR+Cl          | Score >7 | 360/340         | 8             |
| Okazaki 2018   | Japan     | NA         | 189 (83/106) | I-III        | IHC         | RP                | HR+Cl          | Score ≥2 | 83/106          | 8             |
| Murakami 2018  | Japan     | 68         | 184 (83/101) | I-III        | IHC         | MM                | HR+Cl          | Score >3265.5 | 92/92         | 8             |
| Zhang 2017     | China     | NA         | 122 (34/88) | III-IV        | ELISA       | MM                | HR+Cl          | 435.04 ng/mL | NA             | 7             |
| Xu 2017        | China     | 56.6       | 296 (116/180) | I-IV        | ELISA       | kit*               | HR+Cl          | 30.87 ng/mL | NA             | 7             |
| Nitsche 2016   | Germany   | NA         | 93 (37/56)  | I-IV          | IHC         | RP                | HR+Cl          | Median value | 47/46         | 7             |
| Hong 2013      | China     | 57.132     | 49 (11/38) | I-IV          | Western Blot | RP                | HR+Cl          | NA         | 22/27           | 7             |
| Takanami 2008  | Japan     | 65.5       | 88 (25/63)  | I-IIIA        | IHC         | MM                | HR+Cl          | Score ≥2+ | 37/51           | 8             |
| Soltermann 2008| Switzerland| NA         | 516 (149/367) | I-IV        | IHC         | RP                | HR+Cl          | Score >3 | 160/356         | 7             |
| Sasaki 2001    | Japan     | 64.5       | 102 (24/78) | I-IV          | RT-PCR      | NA                | Survival curves | Ratio ≥2.0* | 50/52         | 7             |
| Sasaki 2001    | Japan     | 63         | 92 (19/73)  | I-IIIB        | Chemiluminescence | 5H8, E17**      | Survival curves | 962 ng/mL | 46/46         | 7             |

CI – confidence interval; F – female; H – high; HR – hazard ratio; IHC – immunohistochemistry; L – low; M – male; MM – mouse monoclonal anti-periostin antibody; MVD – microvessel density; N – number of patients; NA – not available; RP – rabbit polyclonal anti-periostin antibody; * kit – commercial periostin ELISA Ready-SET-Go kit; ** 5H8=monoclonal antibody and E17=polyclonal antibody; # ratio – tumor/normal ratio.
Table 2. Meta-analyses of high periostin and survival of NSCLC patients.

| Study (year) | N of study | Model | HR (95% CI) | Log-rank p | Heterogeneity (P value, I² (%) | Conclusion |
|--------------|------------|-------|-------------|------------|--------------------------------|------------|
| Iwamoto (2021) | 4          | Random | 1.296 (0.965-1.740) | 0.085 | 0.002, 80.3% | Negative |
| Total PFS | 4          | Random | 1.761 (1.022-3.033) | 0.041 | 0.000, 76.0% | Positive |
| Chinese PFS | 2          | Random | 1.350 (0.687-2.651) | 0.384 | 0.011, 84.6% | Negative |
| Asian OS | 8          | Random | 2.052 (1.113-3.781) | 0.021 | 0.001, 72.1% | Positive |
| Japanese OS | 6          | Random | 1.903 (0.826-4.384) | 0.131 | 0.000, 77.8% | Negative |
| Chinese OS | 2          | Random | 2.274 (1.320-3.918) | 0.003 | 0.227, 31.6% | Positive |
| ELISA PFS | 2          | Random | 1.350 (0.687-2.651) | 0.384 | 0.011, 84.6% | Negative |
| IHC OS | 6          | Random | 1.426 (0.653-3.116) | 0.373 | 0.000, 82.0% | Negative |
| RP OS | 3          | Random | 1.873 (0.475-7.380) | 0.370 | 0.000, 90.1% | Negative |
| MM OS | 3          | Random | 1.055 (0.385-2.890) | 0.917 | 0.044, 67.9% | Negative |

CI – confidence interval; ELISA – enzyme-linked immunosorbent assay; HR – hazard ratio; IHC – immunohistochemistry; MM – mouse monoclonal; N – number; OS – overall survival; PFS – progression-free survival; RP – rabbit polyclonal.

Note: Weights are from random-effects model.

Table 2. Meta-analyses of high periostin and survival of NSCLC patients.

Figure 2. Forest plots of overall outcomes for overall survival (OS). Hazard ratios (HRs) for each trial are represented by squares, and horizontal lines crossing the square show the 95% confidence intervals (CIs). The diamonds represent the estimated pooled effect of the overall outcome for OS in NSCLC. All P values are two-sided. STATA (version 13.1; Stata Corporation, College Station, TX, USA) was used.

Figure 3. Forest plots of overall outcomes for progression-free survival (PFS). Hazard ratios (HRs) for each trial are represented by squares, and the horizontal lines crossing the square show the 95% confidence intervals (CIs). The diamonds represent the estimated pooled effect of the overall outcome for PFS in NSCLC. All P values are two-sided. STATA (version 13.1; Stata Corporation, College Station, TX, USA) was used.
these studies. With regard to Chinese patients, the HRs of OS and PFS were 2.274 (95% CI: 1.320-3.918, P=0.003) and 1.350 (95% CI: 0.687-2.651, P=0.384), respectively. Heterogeneity of OS was not found (I²=31.6%, P=0.227). However, the heterogeneity (I²=84.6%, P=0.011) was statistically significant for PFS.

**Detection Methods for Periostin (IHC/ELISA)**

Detection methods for periostin varied among studies, and the most common were IHC and ELISA. IHC was used in 6 studies, and the pooled HR of OS was 1.426 (95% CI: 0.653-3.116, P=0.373). The random-effects model was used since statistically significant heterogeneity was found (I²=82.0%, P=0.000). For the PFS analysis of 2 studies that used ELISA, the pooled HR was 1.350 (95% CI: 0.687-2.651, P=0.384). The heterogeneity was also statistically significant (I²=84.6%, P=0.011); therefore, the random-effects model was preferred.

**Antibodies for Periostin Detection (Rabbit Polyclonal/Mouse Monoclonal)**

Three of 12 eligible studies used rabbit polyclonal. For these studies, the pooled HR for OS was 1.873 (95% CI: 0.475-7.380, P=0.370), and significant heterogeneity was found (I²=90.1%, P=0.000). For another 3 studies that used mouse monoclonal antibody, the pooled HR for OS was 1.055 (95% CI: 0.385-2.890, P=0.917), and significant heterogeneity was found (I²=67.9%, P=0.044).

All summarized results are listed in **Table 2**.

**Publication Bias**

To assess publication bias, Begg’s test was performed, but no evidence of publication bias was found (P=0.283) (**Figure 4**).

**Discussion**

The aim of this meta-analysis was to integrate the results of the previous studies to arrive at a summary conclusion on the prognostic value of the expression of periostin in NSCLC. The results demonstrated that overexpression of periostin was correlated with poorer OS in NSCLC patients. However, there was an insignificant correlation between PFS and high periostin expression in NSCLC patients. Due to the emergence of various new cancer treatments, including new targeting therapy and immunotherapy, OS and PFS of NSCLC patients have been continuously extended in recent years. Because of the different treatment plans in enrolled studies, the difference in prognosis is large. This may be the main restriction of the results of this meta-analysis.

In the subgroup analysis, high periostin expression in the Asian patients was related to shorter OS. In Japanese patients, the relationship between high periostin with OS was insignificant. Compared with the Chinese patients, high periostin was significantly linked with OS rather than PFS. Concerning the different methods for periostin detection, no relation was found between high periostin and prognosis. For now, no research has demonstrated which is the most reliable method for periostin detection. Similarly, for different antibodies for periostin detection (rabbit polyclonal or mouse monoclonal), no relation was found between high periostin and prognosis.

Since Takeshita and Kikuno [35] cloned periostin from a murine osteoblast-like cell line in 1993, advancements have been accomplished by in vitro and in vivo studies about periostin. Periostin is not only expressed in tumor tissues, but also in benign lung diseases such as asthma [36], idiopathic pulmonary fibrosis [37], and tuberculosis [38]. However, Zhang et al [20] demonstrated that the basal serum periostin levels were significantly elevated in NSCLC patients with advanced tumor stage compared with benign lung diseases. As an ECM protein, periostin plays important roles in the formation of a tumor-supportive microenvironment [39]. Recent studies revealed that periostin not only exerts its tumor-promoting effect by binding to integrins to activate cell-signaling pathways, but is also an inducer of epithelial–mesenchymal transition (EMT) [15,39,40]. Overexpressed periostin was found to be correlated with high lymphatic microvesSEL density (LMVD) and blood microvesSEL density (MVD), and activated Erk/VEGF pathway, leading to tumor angiogenesis [27,40]. The epithelial–mesenchymal transition (EMT) is an important promoter of tumor invasion and
metastasis. Recent studies have found that periostin was involved in the EMT by initiating cross-talks between the integrins and RTK at the plasma membrane, followed by activation of Akt/PKB and FAK pathways [41-45]. Moreover, preclinical studies show that periostin inhibits hypoxia-induced apoptosis via Akt/PKB and TGF-β pathways in A549 NSCLC cells and human periodontal ligament cells, respectively, which can promote tumor cell survival [46,47].

Drug resistance of tumor cells is a major cause of treatment failure, is a negative prognostic factor, and is responsible for unfavorable OS. Studies showed that periostin can induce chemoresistance by activating cell-signaling pathways, such as PI3K/Akt/survivin pathway [48-50]. Park et al [51] also found that periostin regulated tumor resistance to antiangiogenic therapy through activation of signal transducer and activator of transcription 3 (STAT3) in glioma. Thus, inhibition of periostin may sensitize tumor cells to anticancer drugs.

Despite the progress achieved, several issues remain unresolved. For example, it was reported that periostin produced by epithelial cells could inhibit proliferation and invasion in gastric cancer through stabilizing p53 and E-cadherin proteins via the Rb/E2F1/p14ARF/Mdm2 pathway [52], while in another study, periostin derived from stromal myofibroblasts markedly promoted gastric cancer cell growth [53]. These controversial results suggest that periostin derived from distinct types of cells may play different biological functions in tumorigenesis and metastasis [51]. Moreover, Kanno et al [54] demonstrated that periostin has a biphasic function of inducing and repressing pancreatic cancer. The best method to detect periostin and define the elevated periostin level remains uncertain. Thus, more comprehensive and high-quality studies on periostin are still warranted in the future.

To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the connection between overexpressed periostin and prognosis in NSCLC patients. Due to practical constraints, this study still has limitations. Firstly, all the included studies were observational studies, while no prospective RCT study was found in the literature searching process. Secondly, selection bias was inevitable in all the included studies. Thirdly, all of the included studies were published in English. Hence, it is possible that some eligible studies were omitted due to linguistic limitations. Similarly, eligible studies published in books or journals may have been missed due to the use of online databases. Fourthly, significant heterogeneities were observed in this study. Although subgroup analyses provided some potential sources of heterogeneity, we were not able to identify the source of heterogeneity entirely. There were significant differences in baseline characteristics among studies, such as cut-off value to define periostin overexpression. Because of the lack of available data, we could not evaluate their impacts on heterogeneity. However, in spite of these limitations, our study was performed with detailed protocols and careful statistical analysis with the aim to minimize bias. Therefore, the results of our study are reliable and may be used as a standard reference.

Conclusions

In conclusion, this meta-analysis suggests that overexpressed periostin was a negative prognostic factor in NSCLC patients, especially for OS. However, there was an insignificant correlation between PFS and high periostin. Variations of antibodies used and methods for periostin detection may be major sources of the heterogeneity. Further prospective clinical studies based on large samples are still needed to explore the prognostic value of periostin in NSCLC.

Declaration of Figures’ Authenticity

All figures submitted were created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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