

Clinicopathological and prognostic significance of Nanog expression in non-small cell lung cancer: a meta-analysis

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Background: Nanog has been found to be overexpressed in various cancers. However, the association between Nanog expression and prognosis or clinicopathological features is still controversial. Therefore, this meta-analysis was conducted to identify whether Nanog expression was associated with prognosis or clinicopathological characteristics in non-small cell lung cancer (NSCLC).

Methods: We searched Embase, PubMed, Web of Science, the Cochrane Library, the Chinese National Knowledge Infrastructure database (CNKI), and the Wanfang database for articles. Pooled hazard ratios (HR), odds ratios (OR), and corresponding 95% confidence intervals (CI) were utilized to evaluate the relationship between Nanog expression and prognosis or clinicopathological characteristics in NSCLC.

Results: The results showed that high expression of Nanog was significantly associated with poor overall survival (OS) (HR=1.95, 95% CI: 1.38–2.75, $P=0.000$). Additionally, high Nanog expression was significantly correlated with tumor differentiation (OR=3.18, 95% CI: 1.69–5.98, $P=0.000$) and TNM stage (OR=1.78, 95% CI: 1.28–2.47, $P=0.001$). However, no significant relationship was observed between Nanog expression and other clinicopathological features, including gender (OR=0.95, 95% CI: 0.69–1.33, $P=0.783$), age (OR=0.78, 95% CI: 0.57–1.07, $P=0.119$), tumor size (OR=0.87, 95% CI: 0.26–2.95, $P=0.824$), and lymph node metastasis (OR=1.29, 95% CI: 0.94–1.77, $P=0.121$).

Conclusion: High Nanog expression was associated with poor prognosis in patients with NSCLC, and Nanog may serve as a prognostic predictor in NSCLC.

Keywords: Nanog, NSCLC, meta-analysis

Background

Lung cancer is the leading cause of cancer incidence and mortality worldwide.

According to the guidelines of GLOBOCAN 2018, there will be an estimated 2.1 million new lung cancer cases and 1.8 million cancer deaths in 2018.¹ Lung cancer can be divided into two major pathological subgroups: small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for 80~85% of all lung cancer cases, and contains three major histologic subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.² Although great advances have been made in the diagnosis of and treatment for NSCLC, the clinical outcomes still remain poor. Therefore, it is urgent that a specific therapeutic target and prognostic biomarker for NSCLC is discovered.

Nanog is a homeobox domain transcription factor, and is a key regulator in embryonic development and cellular reprogramming.³ Nanog belongs to the NK-2 gene of the ANTP superfamily, in which the NK-2 gene is primarily expressed in the inner cell mass of blastocysts.⁴ Many studies have shown that Nanog is overexpressed in various cancers, including gastric cancer,⁵ breast cancer,⁶ ovarian cancer,⁷ liver cancer,⁸ and lung cancer.⁹ Li et al¹⁰ found that increased Nanog expression was related to poor overall survival (OS) and differentiation of NSCLC. However, Gialmanidis et al¹¹ reported that high Nanog expression had no association with differentiation, lymph node metastasis, and tumor clinical stage in NSCLC. Park et al¹² found that Nanog expression was not related to prognosis in lung squamous cell carcinoma. Therefore, the association between Nanog expression and prognosis and clinicopathological features remains controversial. We conducted this meta-analysis to evaluate whether the expression of Nanog is related to prognosis and clinicopathological features in NSCLC patients.

Material and methods

Literature search strategy

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹³ Embase, PubMed, Web of Science, the Cochrane Library database, the Chinese National Knowledge Infrastructure database (CNKI), and the Wanfang database were utilized for this meta-analysis. The keywords searched in the database were “Nanog or NANOG” and “lung cancer or lung neoplasm or lung carcinoma or lung tumor or pulmonary cancer.” The search period ended on January 3, 2019. Titles and abstracts were assessed to identify the relevant literature, and then full texts were read.

Inclusion and exclusion criteria

Inclusion criteria for articles were as follows: (1) studies included were case-control studies (divided into either Nanog-positive and -negative groups or high and low Nanog expression groups) that evaluated the relationship between Nanog expression and prognosis or clinicopathological features in NSCLC; (2) sufficient data was provided for calculating HR, OR, and its corresponding 95% CI; (3) the number of NSCLC patients was greater than or equal to 30; (4) the expression of Nanog in NSCLC

patients was detected by immunohistochemistry (IHC); (5) the full text was published in English or Chinese.

Exclusion criteria for the articles were as follows: (1) letters, reviews, conference abstracts, case reports, and expert opinions; (2) duplicate publications; (3) studies without available data.

Data extraction and quality assessment

All publications were screened independently by two reviewers (Guichuan Huang and Jing Zhang). The following information was extracted from eligible studies: the name of the primary author, year of publication, country, language, the number of patients, detection method, patient clinicopathological features, HR, and 95% CI. The HR and corresponding 95% CI were directly or indirectly extracted from eligible studies according to the research of Tierney et al¹⁴. If both a multivariate analysis and univariate analysis were provided in the study, the data with multivariate analysis was adopted. If only Kaplan-Meier curves were provided, survival data was extracted using Engauge Digitizer software (Version 4.1). The quality of each study was evaluated with the use of the Newcastle-Ottawa Scale (NOS). Studies with a NOS score ≥ 6 was considered to be of high quality. Any disagreements were resolved via discussion.

Statistical analysis

This meta-analysis was performed using Stata SE 12.0 software. For the data on overall survival, HR and its corresponding 95% CI were applied to evaluate the strength of the relationship between Nanog expression and clinical prognosis in NSCLC patients. Pooled OR and corresponding 95% CI were used for clinicopathological parameters. The chi-squared test and I^2 were used to evaluate the heterogeneity among the studies. A fixed-effect model was utilized if there was no obvious heterogeneity ($I^2 \leq 50\%$ or $P \geq 0.05$). On the contrary, if $I^2 \geq 50\%$ or $P \leq 0.05$, a random-effect model was applied.

The publication bias was assessed with the use of Begg's test and Egger's test. A sensitivity analysis was also conducted to evaluate the stability of results. $P \leq 0.05$ was considered statistically significant.

Results

Literature search and selection

The literature selection process is demonstrated in Figure 1. We identified 776 articles from Embase, PubMed, Web of Science, the Cochrane Library, CNKI, and the Wanfang

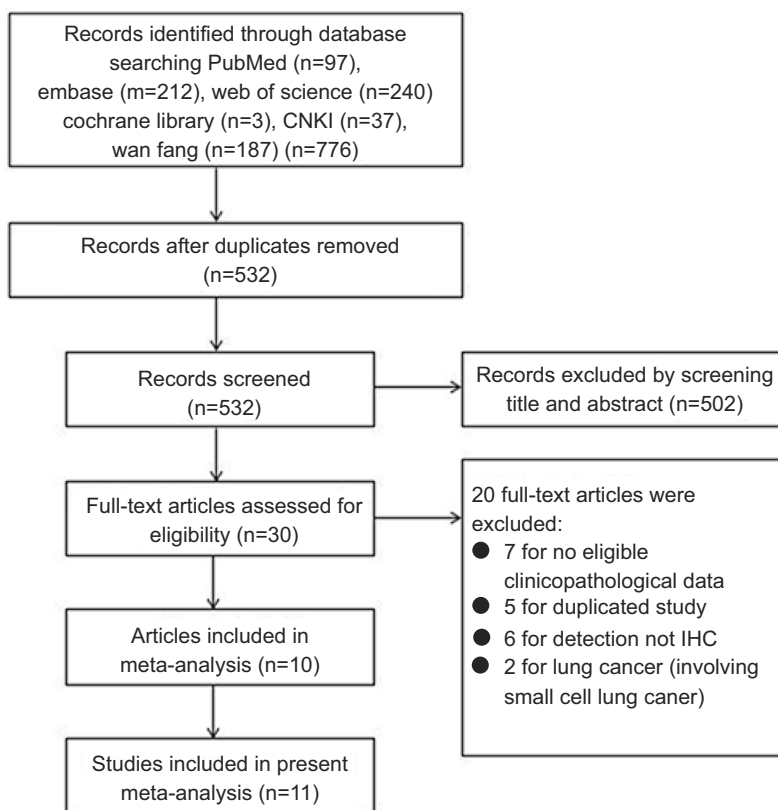


Figure 1 Flow chart of literature search and selection.

Abbreviations: CNKI, China National Knowledge Infrastructure; IHC, immunohistochemistry.

database. After the removal of duplicates, 532 potentially related articles remained. After 502 articles were excluded by screening their titles and abstracts, 30 articles remained for further full-text analysis. Finally, a total of 10 eligible studies that included 11 data sets with 1492 patients were included to conduct this meta-analysis.^{10–12,15–21}

Characteristics of included studies

The characteristics of the included studies are listed in Table 1. These studies were published between 2010 and 2017. Of the 10 studies, 6 studies were conducted in China, 1 in Greece, 1 in Japan, and 2 in Korea. A total of 6 studies were published in English, and 4 studies were published in Chinese. The expression of Nanog was detected by IHC in all studies. The NOS scores of all included studies were greater than or equal to 6, which implied that the studies were all of high quality.

Association between nanog expression and OS

A total of 5 articles that included 6 data sets with 963 patients reported the information on OS. As shown in

Figure 2, a random-effect model was used for the pooled HR and 95% CI due to heterogeneity ($P=0.034$, $I^2=58.5\%$). The analysis indicated that high Nanog expression was related to poor OS in NSCLC patients (HR=1.95, 95% CI: 1.38–2.75, $P<0.01$). Furthermore, subgroup analyses were conducted according to publication year, sample size, and ethnicity to examine the sources of heterogeneity. As shown in Table 2, Nanog expression was associated with poor OS in the subgroup based on publication year, but heterogeneity was also found in these two subgroups. In the analysis stratified by sample size, Nanog expression was found to be significantly related to poor OS, and no heterogeneity was found in the subgroup with sample size ≤ 140 ($P=0.000$, HR=2.64, 95% CI: 1.94–3.60, $I^2=0\%$). Interestingly, no association between Nanog expression and OS was found in the subgroup with sample size >140 ($P=0.125$, HR=1.46, 95% CI: 0.90–2.37, $I^2=55.3\%$). Likewise, there was no association between Nanog expression and OS in the subgroup of Korean ethnicity ($P=0.237$, HR=1.61, 95% CI: 0.73–3.55, $I^2=78.9\%$). We then conducted a sensitivity analysis to ascertain the probable source of heterogeneity. We found that the heterogeneity significantly dropped ($I^2=37.7\%$,

Table 1 Characteristics of included studies in the meta-analysis

Author	Year	Country	Language	No. of patients	Detection method	Gender: male (+/-) female (+/-)	Age: ≥50(+/-) <50(+/-)	Tumor size: >3cm(+/-) ≤3cm(+/-)	Differentiation: low (+/-) high and moderate (+/-)	Lymph node metastasis: yes (+/-) no (+/-)	TNM stage: I/II (+/-) III/IV (+/-)	Survival information	NOS scores
Chiou et al ¹⁵	2010	China	English	118	IHC	NA	NA	NA	NA	NA	NA	OS(S)	8
Sun et al ¹⁶	2012	China	Chinese	186	IHC	110/27 42/7	60/15 92/19	NA	76/1 76/33	96/21 56/13	82/30 70/4	NA	8
Li et al ¹⁰	2013	China	English	309	IHC	44/90 50/125	44/116 50/99	NA	41/30 53/185	NA	53/136 41/79	OS(M)	8
Gialmanidis et al ¹¹	2013	Greece	English	80	IHC	NA	NA	NA	39/4	32/2	53/5	NA	8
Kiritani et al ¹⁷	2013	Japan	English	107	IHC	NA	NA	NA	35/2	32/3	11/0	NA	7
Luo et al ¹⁸	2013	China	Chinese	106	IHC	18/63 8/17	13/48 13/32	NA	13/20 13/60	16/31 10/49	NA	NA	7
Park et al ¹²	2016	Korea	English	226	IHC	NA	NA	51/46	30/17	55/51	58/89	OS(M)	8
Park et al ¹²	2016	Korea	English	142	IHC	NA	NA	45/84	66/113	41/79	38/41	OS(S)	8
Yao et al ¹⁹	2016	China	Chinese	56	IHC	7/8 22/19	18/22 11/5	NA	NA	75/6	37/1	OS(M)	6
Zhong et al ²⁰	2016	China	Chinese	50	IHC	3/17 8/4	11/2 28/9	21/9	18/1	20/10	NA	NA	6
Chang et al ²¹	2017	Korea	English	112	IHC	29/49 15/19	28/43 16/25	NA	13/16 31/52	40/61 4/7	NA	OS(M)	8

Abbreviations: IHC, immunohistochemistry; NA, not available; OS, overall survival; M, multivariate analysis; S, survival curves; NOS, Newcastle-Ottawa Scale.

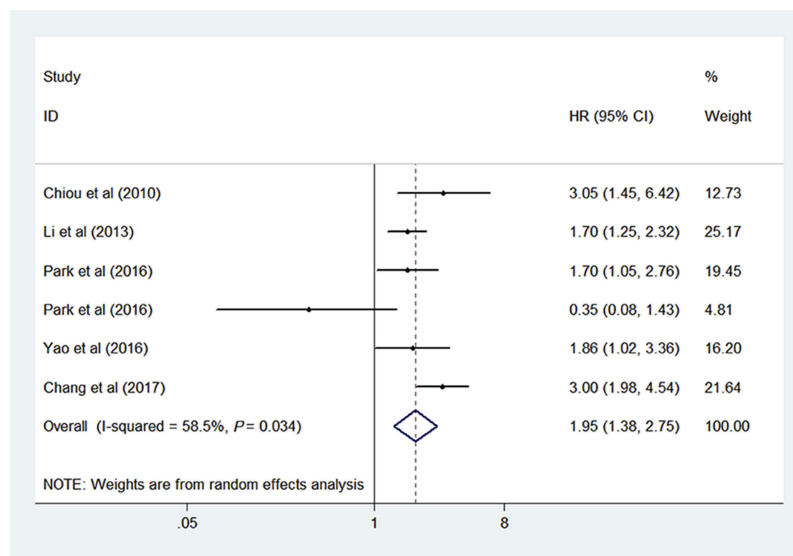


Figure 2 Forest plot for the association between Nanog expression and OS.
Abbreviation: OS, overall survival.

Table 2 Results of subgroup analysis of overall survival by publication year, sample size and ethnicity

Subgroup analysis	No. of studies	No. of patients	P-value	HR (95% CI)	Heterogeneity	
					I ² (%)	P-value
Total	6	963	0.000	1.95 (1.38–2.75)	58.5	0.034
Publication year						
≤2013	2	427	0.008	2.05 (1.20–3.52)	50.5	0.155
>2013	4	536	0.040	1.77 (1.03–3.06)	69.0	0.022
Sample size						
≤140	3	286	0.000	2.64 (1.94–3.60)	0.0	0.399
>140	3	677	0.125	1.46 (0.90–2.37)	55.3	0.107
Ethnicity						
Chinese	3	483	0.000	1.86 (1.43–2.41)	1.1	0.364
Korean	3	480	0.237	1.61 (0.73–3.55)	78.9	0.009

$P=0.170$) without a change in pooled outcome (HR=2.09, 95% CI: 1.60–2.74) after excluding the Park study¹² conducted on lung squamous cell carcinoma.

Association between nanog expression and clinicopathological features

The meta-analysis was performed to evaluate the association between Nanog expression and clinicopathological characteristics of NSCLC. As shown in both Figure 3 and Table 3, high Nanog expression was related to differentiation ($P=0.000$, OR=3.18, 95% CI: 1.69–5.98, $I^2=62.5%$) and TNM stage ($P=0.001$, OR=1.78, 95% CI: 1.28–2.47, $I^2=49.0%$). However, no significant relationship was observed between

Nanog expression and other clinicopathological features, including gender ($P=0.783$, OR=0.95, 95% CI: 0.69–1.33, $I^2=0.0%$), age ($P=0.119$, OR=0.78, 95% CI: 0.57–1.07, $I^2=0.0%$), tumor size ($P=0.824$, OR=0.87, 95% CI: 0.26–2.95, $I^2=71.9%$), and lymph node metastasis ($P=0.121$, OR=1.29, 95% CI: 0.94–1.77, $I^2=49.4%$). Due to significant heterogeneity in tumor differentiation, the subgroup analysis of tumor differentiation was subsequently conducted via publication year, sample size, and ethnicity. As shown in Table 4, there was a significant relationship in the subgroup analysis of sample size between high Nanog expression and tumor differentiation in the large group ($n>140$) (OR=5.08, 95% CI: 2.21–11.69, $P=0.000$), but not in the small group ($n\leq 140$) (OR=1.93, 95% CI: 0.84–4.45, $P=0.122$). In the

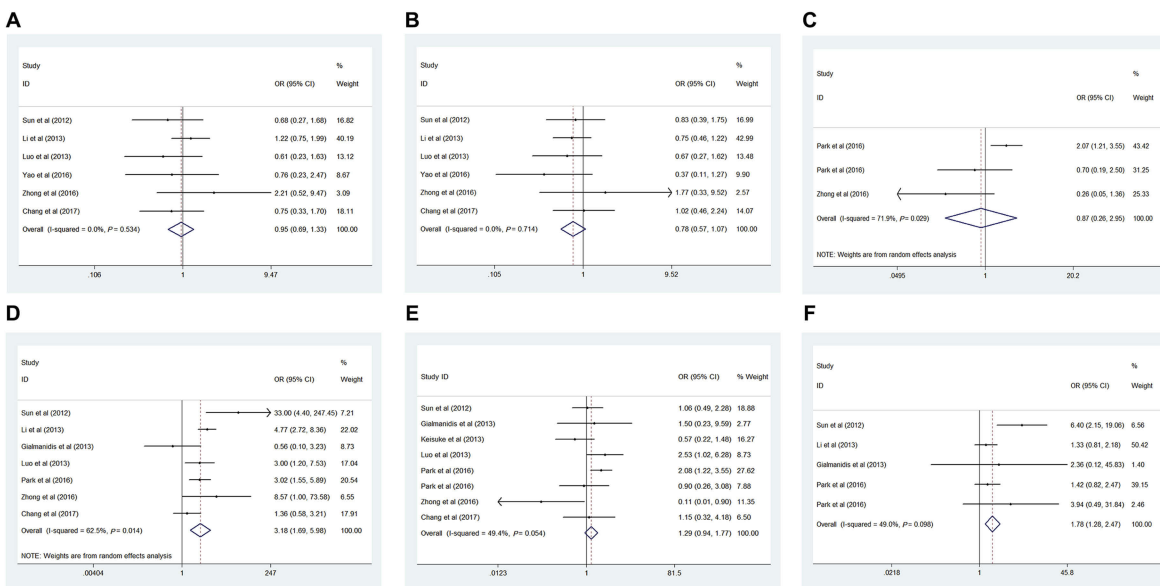


Figure 3 Forest plot for the association between Nanog expression and clinicopathological characteristics, including (A) gender, (B) age, (C) tumor size, (D) tumor differentiation, (E) lymph node metastasis, and (F) TNM stage.

Table 3 The association between Nanog expression and clinicopathological features

Clinicopathological features	No. of studies	No. of patients	P-value	OR (95% CI)	Heterogeneity		Model
					I ² (%)	P-value	
Gender	6	819	0.783	0.95 (0.69–1.33)	0.0	0.534	Fixed
Age	6	819	0.119	0.78 (0.57–1.07)	0.0	0.714	Fixed
Tumor size	3	418	0.824	0.87 (0.26–2.95)	71.9	0.029	Random
Differentiation	7	1069	0.000	3.18 (1.69–5.98)	62.5	0.014	Random
LNM	8	1009	0.121	1.29 (0.94–1.77)	49.4	0.054	Fixed
TNM stage	5	943	0.001	1.78 (1.28–2.47)	49.0	0.098	Fixed

Abbreviation: LNM, lymph node metastasis.

Table 4 Results of subgroup analysis of tumor differentiation by publication year, sample size and ethnicity

Subgroup analysis	No. of studies	No. of patients	P-value	OR (95% CI)	Heterogeneity	
					I ² (%)	P-value
Total	7	1069	0.000	3.18 (1.69–5.98)	62.5	0.014
Publication year						
≤2013	4	681	0.013	3.79 (1.32–10.83)	70.7	0.017
>2013	3	388	0.021	2.47 (1.15–5.32)	42.9	0.173
Sample size						
≤140	4	348	0.122	1.93 (0.84–4.45)	43.4	0.151
>140	3	721	0.000	5.08 (2.21–11.69)	64.5	0.060
Ethnicity						
Chinese	4	651	0.000	5.50 (2.53–11.92)	44.9	0.142
Korean + Greek	3	418	0.214	1.69 (0.74–3.86)	53.1	0.118

subgroup analysis of ethnicity, high Nanog expression was associated with tumor differentiation for Chinese patients (OR=5.50, 95% CI: 2.53–11.92, P=0.000), but not for

Korean or Greek patients. Although subgroup analyses of tumor differentiation were conducted by publication year, sample size, and ethnicity, there still existed heterogeneity in

every subgroup. The heterogeneity of Nanog expression and tumor differentiation, therefore, was not likely caused by publication year, sample size, or ethnicity. Because only three studies reported tumor size information, neither the subgroup analysis nor sensitivity analysis of tumor size were performed.

Publication bias and sensitivity analysis

We evaluated the publication bias in this meta-analysis via Begg's test and Egger's test. As shown in Table 5, there was no potential publication bias for OS, gender, age, tumor size, tumor differentiation, lymph node metastasis, or tumor TNM stage.

Sensitivity analysis was conducted to test whether a single study affected the pooled HR or OR. As shown in Figure 4, the pooled results were not influenced by removing individual studies.

Discussion

Many studies from the past several years have indicated that cancer stem-like cells (CSCs) play a crucial role in tumor development, progression, and metastasis. CSCs have been identified in many human cancer types, including hepatocellular carcinoma,²² bladder cancer,²³ prostate cancer,²⁴ breast cancer,²⁵ and lung cancer.²⁶ The identification and isolation of CSCs mainly depend on the use of surface markers which include CD44, CD90, CD13, SOX2, and OCT4.²⁷ In recent years, Nanog was also identified as a surface marker of CSCs.²⁸

Recently, many studies have indicated that Nanog expression is associated with various tumors. Liang et al²⁹ found that Nanog expression was related to poor OS, tumor differentiation, and TNM stage in hepatocellular carcinoma. Likewise, Nanog expression was associated with the poor prognosis of gastrointestinal luminal cancer.³⁰ Zhao et al³¹

Table 5 Publication bias evaluation by Begg's test and Egger's test

Groups of outcomes	No. of studies	Estimates	Begg's test (P-value)	Egger's test (P-value)	Publication bias
OS	6	HR+95%CI	1.000	0.564	Not significant
Gender	6	OR+95%CI	1.000	0.570	Not significant
Age	6	OR+95%CI	1.000	0.873	Not significant
Tumor size	3	OR+95%CI	0.296	0.079	Not significant
Differentiation	7	OR+95%CI	0.764	0.939	Not significant
LNM	8	OR+95%CI	0.462	0.232	Not significant
TNM stage	5	OR+95%CI	0.462	0.240	Not significant

Abbreviations: OS, overall survival; LNM, lymph node metastasis.

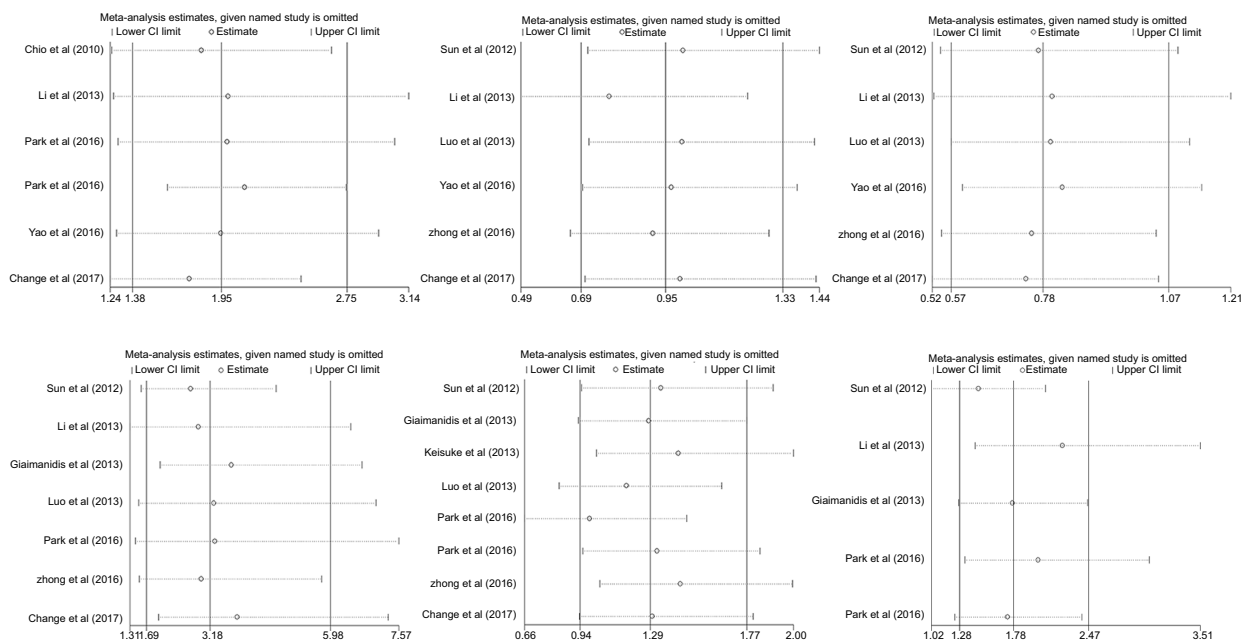


Figure 4 Sensitivity analysis for meta-analysis of (A) OS, (B) gender, (C) age, (D) tumor differentiation, (E) lymph node metastasis, and (F) TNM stage.

found that high Nanog expression predicted a poor prognosis in solid tumors. However, the role of Nanog in NSCLC is still controversial, hence the performance of this meta-analysis. We believe that this meta-analysis is the first to identify the clinical significance of Nanog expression in NSCLC. A total of 10 studies containing 11 data sets with 1492 patients were included. The results indicated that high Nanog expression was related to poor OS, tumor differentiation, and tumor TNM stage in NSCLC, but not correlated with gender, age, tumor size, or lymph node metastasis. Cheng et al³² also found that the overexpression of Nanog was correlated with decreased OS and was related to tumor differentiation in lung cancer. Both of these findings were consistent with our results. However, Cheng et al³² also found that high Nanog expression was associated with tumor size and lymph node metastasis, which differed from our results. The following reasons may have led to this discrepancy. In Chen's meta-analysis, only 4 of the included studies for lymph node metastasis and 2 of the included studies for tumor size were combined in meta-analysis, which was less than the number of our included studies. Furthermore, the included studies in Chen's meta-analysis involved small cell lung cancer, which may also contribute to the difference in results.

In this meta-analysis, five of the six studies analyzed found that high Nanog expression was correlated with poor OS. Our pooled results also found that high Nanog expression was associated with poor OS. Additionally, sensitivity analysis was conducted to identify the source of heterogeneity for OS. We found that the heterogeneity significantly dropped ($I^2=37.7%$, $P=0.170$) without a change in pooled analysis (HR=2.09, 95% CI: 1.60–2.74) after excluding the Park study¹² on lung squamous cell carcinoma. As is evident from these results, Nanog might be a potential prognostic biomarker in NSCLC. Of the seven studies, four studies indicated that Nanog expression was not associated with tumor differentiation. However, the pooled results indicated that Nanog expression was related to tumor differentiation. The reason for this result may be that Nanog is a surface marker in cancer stem-like cells that can self-renew and regulate differentiation. Similarly, four of the five studies demonstrated that high Nanog expression was not correlated with TNM stage. However, the pooled analysis indicated that high Nanog expression was related to advanced TNM stage. Park et al¹² reported that Nanog expression was related to tumor size in lung adenocarcinoma but not in lung squamous cell carcinoma. Zhong et al²⁰ declared that Nanog expression was not associated

with tumor size in NSCLC. In the present meta-analysis, the combined results indicated that there was no statistical relationship between Nanog expression and tumor size. The reason for this may be that the sample size is small, and the histologic subtypes of NSCLC is not the same.

Limitations

There do exist some limitations of this study. First, HRs and their 95% CIs were obtained from Kaplan-Meier survival curves instead of from the primary studies. Second, the cut-off value of positive or negative (high or low) Nanog expression is different in each study, which may cause heterogeneity. Third, moderate heterogeneity was found in the analysis of tumor size, tumor differentiation, and OS, which may influence the reliability of outcomes. Fourth, although no significant publication bias was found, the selection bias may exist in this retrospective meta-analysis. Finally, the number of included studies was relatively small. Therefore, additional high-quality and better-designed studies must be conducted to confirm our conclusion.

Conclusion

High Nanog expression was associated with poor prognosis in NSCLC patients, and Nanog may serve as a potential prognostic biomarker in NSCLC.

Disclosure

The authors report no conflicts of interest in this work.

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