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# The Effect of Diabetes Mellitus on Lung Cancer Prognosis

## A PRISMA-compliant Meta-analysis of Cohort Studies

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**Abstract:** Previous studies suggested that diabetes mellitus (DM) was associated with risk and mortality of cancer, but studies investigating the correlation between DM and lung cancer prognosis remain controversial. Herein, a meta-analysis was performed to derive a more precise estimate of the prognostic role of DM in lung cancer.

Medline and Embase were searched for eligible articles from inception to October 25, 2015. The pooled hazard ratio (HR) with its 95% confidence interval (95% CI) was calculated to evaluate the correlation between DM and lung cancer prognosis. Subgroup meta-analysis was performed based on the histology and the treatment methods.

A total of 20 cohort studies from 12 articles were included in the meta-analysis. Also, 16 studies investigated the overall survival (OS) and 4 studies investigated the progression-free survival (PFS). DM was significantly associated with the inferior OS of lung cancer with the pooled HR 1.28 (95% CI: 1.10–1.49,  $P = 0.001$ ). The association was prominent in the nonsmall cell lung cancer (NSCLC) subgroup (HR 1.35, 95%CI: 1.14–1.60,  $P = 0.002$ ), whereas the association was not significant in the small cell lung cancer (SCLC) subgroup (HR 1.33, 95% CI: 0.87–2.03,  $P = 0.18$ ). When NSCLC patients were further stratified by treatment methods, DM had more influence on the surgically treated subgroup than the nonsurgically treated subgroup. There was no obvious evidence for publication bias by Begg's and Egger's test.

The results of this meta-analysis exhibit an association of DM with inferior prognosis amongst lung cancer patients, especially the surgically treated NSCLC patients. Given the small number of studies included in this meta-analysis, the present conclusion should be consolidated with more high-quality prospective cohort studies or randomized controlled trials.

**Abbreviations:** 95% CI = 95% confidence interval, DM = diabetes mellitus, EGF = epidermal growth factor, HR = hazard ratio, IGF = insulin-like growth factor, NA = not available, NSCLC = nonsmall cell lung cancer, OS = overall survival, PFS = progression-free survival, SCLC = small cell lung cancer.

## INTRODUCTION

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide.<sup>1</sup> Despite diagnosis and therapeutic advances, the prognosis of lung cancer patients is still unsatisfactory.<sup>2</sup> To guide decision-making for therapeutic strategies for lung cancer patients and improve their prognosis, a better understanding of the relevant factors affecting lung cancer prognosis is urgently needed. In addition to some established indicator for survival, such as age, smoking status, histology, and stage, diabetes mellitus (DM) maybe another effective prognostic factors for lung cancer patients. Epidemiologic evidence suggests that people with DM are at a significantly higher risk of cancer incidence or mortality, such as breast, bladder, gastric, prostate, and kidney.<sup>3–7</sup> A recent meta-analysis demonstrated that pre-existing DM might increase the risk of lung cancer, especially among female diabetic patients.<sup>8</sup> However, evidence on the correlation between DM and outcome of lung cancer is conflicting and indefinite.<sup>9–11</sup> To derive a more precise estimate of the prognostic value of DM in lung cancer patients, we performed this meta-analysis of eligible published articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>12</sup>

## METHODS

### Search Strategy

We searched the electronic databases Medline and Embase from inception to October 25, 2015 by Internet Explorer (version 8.0, Microsoft Corp), for articles investigating the correlation of DM with any prognostic outcome in lung cancer patients. Our search strategy included terms for diabetes (diabetes, diabetes mellitus, and glucose) and lung cancer (lung cancer, lung neoplasm, and lung carcinoma). All references in retrieved articles were also reviewed manually for possible inclusions. Our search strategy was limited to English language and human studies. No additional unpublished study was identified.

### Study Selection

We included studies investigating the effect of DM on overall survival (OS) or progression-free survival (PFS) in lung cancer patients, and the DM diagnosis were determined by the criterions described by the American Diabetes Association or

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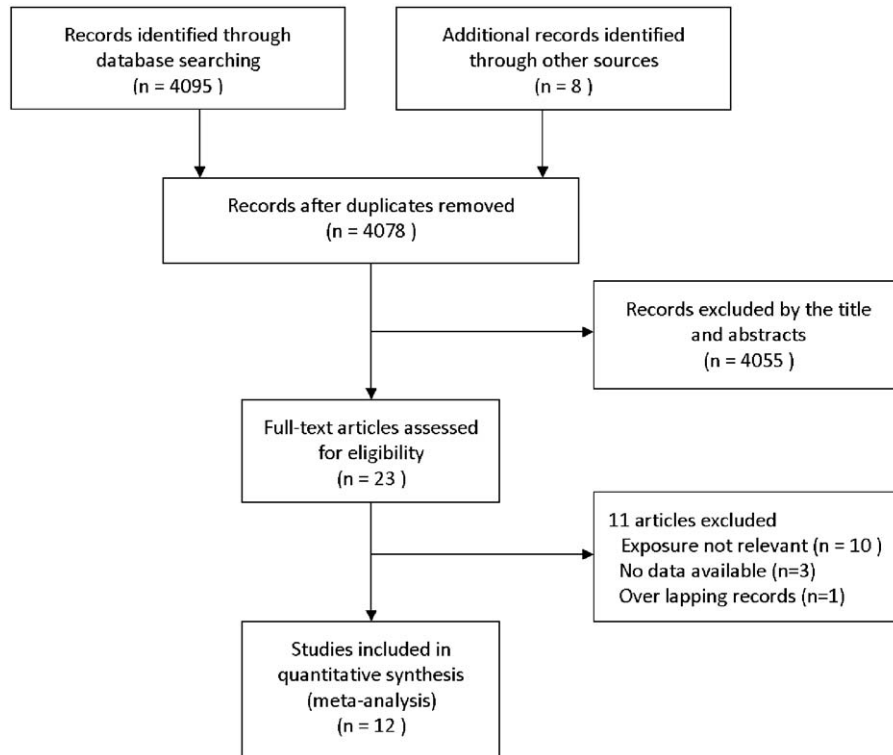


FIGURE 1. Flowchart representing the articles selection process.

the World Health Organization. We excluded studies for which no hazard ratio (HR) with its 95% confidence interval (95% CI) could be elicited from any form of outcomes. Provided that multiple articles based on the same population, only the most informative and/or the recently published article was enrolled.

### Data Extraction and Quality Assessment

Relevant data were extracted from all the eligible studies by 2 investigators independently using a purpose-designed form. The results were compared and discrepancies were resolved by mutual discussions. The following items, if available, were extracted from the articles included: first author's name, publication year, data source, study recruitment years, follow-up period, tumor histology, treatment method, age, sample size, HR with its 95% CI for the association of DM and lung cancer, and statistical adjustments for confounding factors. HR that was not directly reported was calculated according to the data presented in the graphs or tables. On condition that there were no enough data in the origin article, we contacted the corresponding author by e-mail. Quality assessment for studies included in this meta-analysis was conducted according to the Newcastle Ottawa scale (NOS) criteria.<sup>13</sup> Because all analyses were based on previous published studies, no ethical approval and patient consent were necessary.

### Statistical Analysis

We calculated the pooled HRs with their corresponding 95% CIs to assess the prognostic significance of DM status in lung cancer patients, and the HR > 1 implied an inferior prognosis for patients with DM. A random-effect model was adopted in this meta-analysis since considerable heterogeneity presented.<sup>14</sup> Statistical heterogeneity between studies was evaluated using

Cochrane  $Q$  test and the chi-squared test. The  $I^2$  values  $\geq 50\%$  indicated significant heterogeneity.<sup>15</sup> For additional analyses, subgroup meta-analysis was performed on the basis of the histology (SCLC or NSCLC) and the treatment methods (undergoing resection or nonsurgical treatment). Sensitivity analysis was performed by sequential omission of individual studies to examine the stability of the outcomes in this meta-analysis. Furthermore, Begg's and Egger's tests were applied to evaluate the potential publication bias.<sup>16,17</sup> All analyses were performed using Stata software (version 12.0, Stata Corp, College Station, TX). A 2-tailed  $P$  value < 0.05 was considered significant in statistical tests.

## RESULTS

### Literature Search

Figure 1 represented the steps of retrieving articles for inclusion in the meta-analysis. Our original search identified 4103 potentially relevant articles, of which we scanned the titles and abstracts. After further evaluating the articles identified, 12 articles with a total of 15,180 lung cancer patients stratifying by DM status were included in the meta-analysis.<sup>9–11,18–26</sup>

### Study Characteristics

The main characteristics of 12 studies included in the meta-analysis were summarized in Table 1. A total of 20 cohorts from 12 studies were included, which were published between 2003 and 2014. Of the 20 cohorts, 16 cohorts<sup>9–11,18,19,21–26</sup> with a total of 14,643 lung cancer cases investigated the OS and 4 studies<sup>9,11,20,22</sup> with a total of 1711 lung cancer patients investigated the PFS. The outcomes of all the 20 cohorts were adjusted for several potential confounders, including age,

TABLE 1. Main Characteristic of 12 Eligible Studies in this Meta-Analysis

Author	Year	Data Source	Study Recruitment Years	Follow-up Time (Months)	Histology	Treatment Methods	Age (Years) Mean	Sample Size (n)	DM (n)	Non-DM (n)	Outcomes	Quality Scores
Inal et al <sup>9</sup>	2014	Turkey	2002–2012	Maximum:70	NSCLC	Nonsurgical treatment	59	442	66	376	OS or PFS	8
Nakazawa et al <sup>18</sup>	2013	Japan	1999–2011	Maximum:180	NSCLC or SCLC	Undergoing resection or nonsurgical treatment	NA	1798	338	1460	OS	7
Luo et al <sup>19</sup>	2012	Taiwan	2005–2007	Mean:10.5	NSCLC	NA	67.8	229	119	110	OS	7
Varlotto et al <sup>20</sup>	2012	USA	2000–2006	Mean:3.3	NSCLC	Undergoing resection	67.7	537	96	441	PFS	9
Hatlen et al <sup>10</sup>	2011	Norway	1984–2008	Maximum:40	Lung cancer or NSCLC	Undergoing resection or nonsurgical treatment	67.4	1852	84	1768	OS	8
Bartling et al <sup>11</sup>	2011	Germany	1998–2003	Maximum:60	NSCLC	Undergoing resection	66.7	166	55	111	OS or PFS	7
Win et al <sup>21</sup>	2008	UK	2000–2006	Mean:72	NSCLC	Undergoing resection	69	110	12	98	OS	7
Hanbali et al <sup>22</sup>	2007	USA	1996–2000	NA	NSCLC	NA	NA	566	NA	NA	OS or PFS	5
Vasic <sup>23</sup>	2007	Serbia	2005–2006	Mean:6	NSCLC	Nonsurgical treatment	63.7	87	11	76	OS	6
van de Poll-Franse et al <sup>24</sup>	2007	Netherlands	1995–2002	Maximum:60	NSCLC or SCLC	NA	65.7	6690	581	6109	OS	6
Park et al <sup>25</sup>	2006	Korea	1996–2004	Mean:22.44	Lung cancer	NA	50.8	1548	NA	NA	OS	5
Tammemagi et al <sup>26</sup>	2003	USA	1995–2000	Mean:27.3	Lung cancer	NA	NA	1155	NA	NA	OS	5

DM = diabetes mellitus, OS = overall survival, PFS = progression-free survival, NA = not available, NSCLC = nonsmall cell lung cancer, SCLC = small cell lung cancer.

gender, smoking status, performance status, body mass index, and so on. Study quality was assessed according to the NOS, and the mean score was 6.7.

**Meta-analysis**

To evaluate the prognostic significance of DM status in lung cancer patients, a meta-analysis was conducted on HRs of OS and PFS. As shown in Figure 2, the pooled HR with its corresponding 95% CI of OS in 16 cohorts was 1.28 (95% CI: 1.10–1.49, *P* = 0.001). Sensitivity analysis through sequential omission of single study did not change the original outcomes, which supported the credibility and stability of the results. Furthermore, subgroup meta-analyses were conducted by stratifying based on histology and treatment methods. Subgroup analysis by histology suggested DM is associated with worse OS in NSCLC (HR 1.36, 95% CI: 1.12–1.67, *P* = 0.002), but not the SCLC (HR 1.33, 95% CI: 0.87–2.03, *P* = 0.18) (Figure 3). However, the association between DM and OS in SCLC is inconclusive due to limited data. After that, we conducted subgroup analysis stratified by treatment methods in NSCLC patients. DM seemed have more effect on surgically treated NSCLC (HR 1.71, 95% CI: 0.94–3.08, *P* = 0.08) than NSCLC treated by the nonsurgical method (HR 1.53, 95% CI: 0.52–4.52, *P* = 0.44) (Figure 4), though there was no significant correlation between DM and OS in the 2 subgroups. The insignificant association between DM and OS in NSCLC when stratified by treatment methods might be due to the exclusion of some data that could not be stratified. In addition, 4 studies were eligible for examining the relationship between DM and PFS in NSCLC patients. As shown in Figure 5, the pooled HR of the PFS was 1.12 (95% CI: 0.59–2.10, *P* = 0.73), which should be regarded with caution due to inadequate amount of studies included. Considering the pooled data about DM and lung cancer survival, DM status is predicted to have a significant poor prognostic effect on OS in lung cancer patients, especially in NSCLC.

**Publication Bias Analyses**

The funnel plot, Begg’s test, and Egger’s test were performed to detect publication bias in the meta-analysis. No obvious publication bias was revealed after assessing the funnel plot for the eligible studies (Figure 6). In addition, the results from Begg’s and Egger’s test for the studies evaluating OS in lung cancer did not reveal obvious publication bias (*P*<sub>Begg’s</sub> = 0.82 and *P*<sub>Egger’s</sub> = 0.28).

**DISCUSSION**

This meta-analysis summarized the previous studies to evaluate the effect of DM on the prognosis of lung cancer patients. In our meta-analysis, the included articles were limited to the English language because the non-English language articles were generally in poor quality and tended to bring about more bias. The results of this meta-analysis indicated that DM was associated significantly with a worse OS in lung cancer patients. When subgroup analysis was performed stratifying by histology, worse survival was presented in the NSCLC subgroup other than the SCLC subgroup. However, the association between DM and OS in SCLC should be regarded with caution because of only 2 eligible studies included. Furthermore, when stratifying by treatment methods among the NSCLC patients, the association of DM with surgically treated NSCLC subgroup was more prominent than the nonsurgically treated NSCLC subgroup narrowly. However, there was no significant

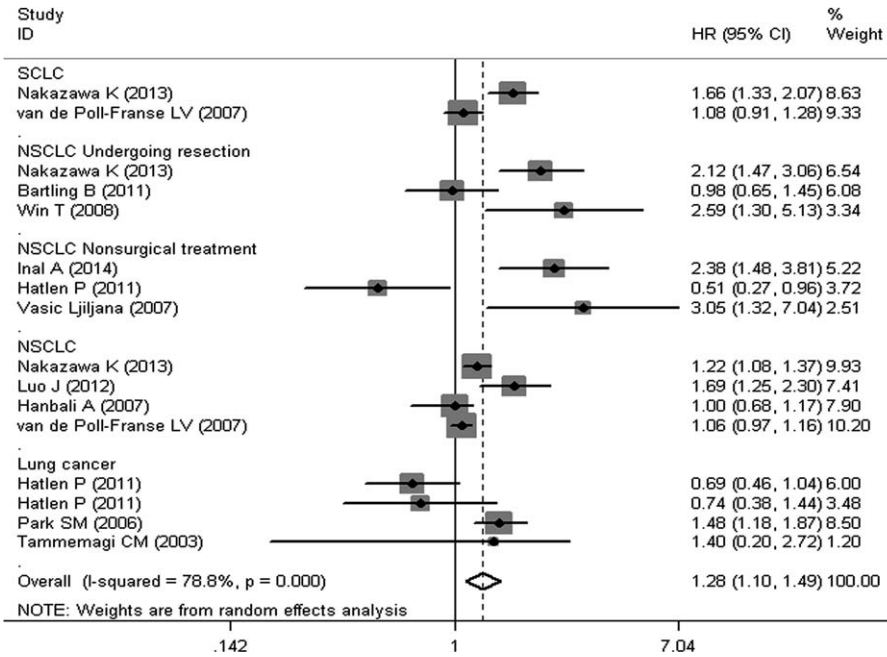


FIGURE 2. Meta-analysis of the association between diabetes mellitus and overall survival in lung cancer.

association between DM and the PFS in NSCLC patients with only 4 eligible studies included.

Although epidemiologic evidence support a role for DM in lung cancer progression, the genuine biological linkage between DM and lung cancer is still uncertain. Several mechanisms have been proposed to explain the negative effect of DM on the survival of lung cancer. Hyperinsulinemia, hyperglycaemia,

and metabolic disorder of cancer cells may be the potential factors contributing to the development of lung cancer.<sup>27,28</sup>

Elevated insulin levels, which respond to insulin resistance, may have impact on cancer-promoting through the insulin-like growth factor-1 (IGF-1) pathway.<sup>29</sup> The IGF-1 pathway is regarded as an important promoter of tumor progression in certain studies<sup>30,31</sup> and IGF-1 receptor inhibitor may contribute to the

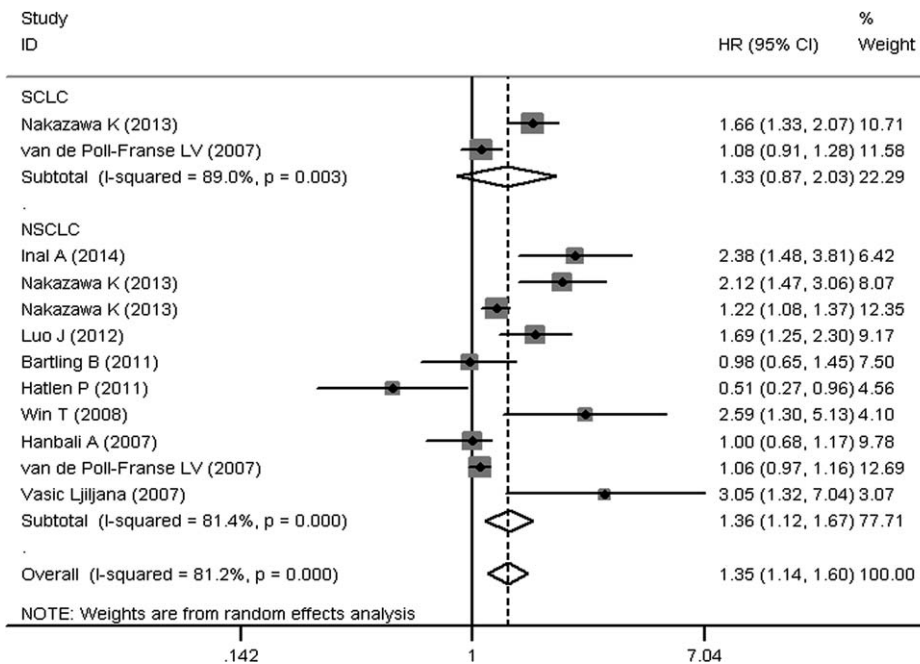


FIGURE 3. Subgroup meta-analysis of the association between diabetes mellitus and overall survival in lung cancer according to histology (SCLC or NSCLC). NSCLC = non small cell lung cancer, SCLC = small cell lung cancer.

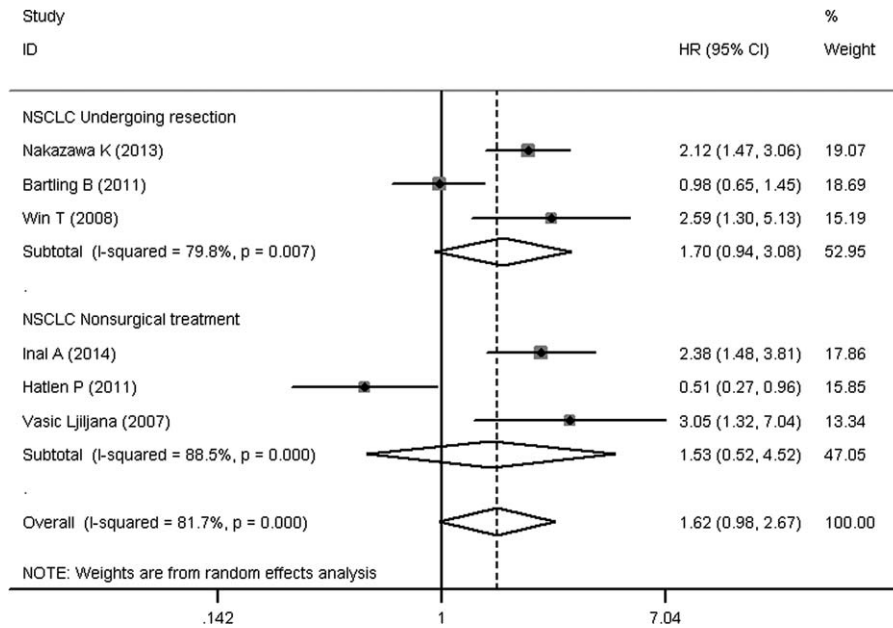


FIGURE 4. Subgroup meta-analysis of the association between diabetes mellitus and overall survival in NSCLC according to the treatment methods (undergoing resection or nonsurgical treatment). NSCLC = non small cell lung cancer.

cancer therapy.<sup>32,33</sup> In addition, hyperglycemia and the metabolic disorder of cancer cells may accelerate the proliferation of lung cancer cells.<sup>28</sup> Han et al have made an important discovery that high glucose can promote cancer proliferation via the induction of epidermal growth factor (EGF) expression and transactivation of EGF receptor.<sup>34</sup> Further research by De Rosa et al indicate that EGF pathways are associated with cancer metabolism and inhibition of EGF pathways may have the synergistic antitumor effect with the therapeutic strategies targeting glucose metabolism through reversal of Warburg effect and reactivation of oxidative phosphorylation in NSCLC.<sup>35</sup> However, except for the cancer-

promoting effects of DM, there may be some other feasible effects of DM on the poor survival in lung cancer patients. For example, patients with DM generally present with more advanced stages of lung cancer, which may contribute to the inferior OS of lung cancer patients with DM.<sup>36</sup> Furthermore, lung cancer patients with pre-existing DM may receive less aggressive treatment because of a greater risk of chemotherapy-related toxicity.<sup>36</sup> As for the histology of lung cancer, different results between NSCLC and SCLC subgroups indicate that the influence of DM might differ on the NSCLC and SCLC patients. However, the difference may also be due to only 2 studies focusing on the SCLC

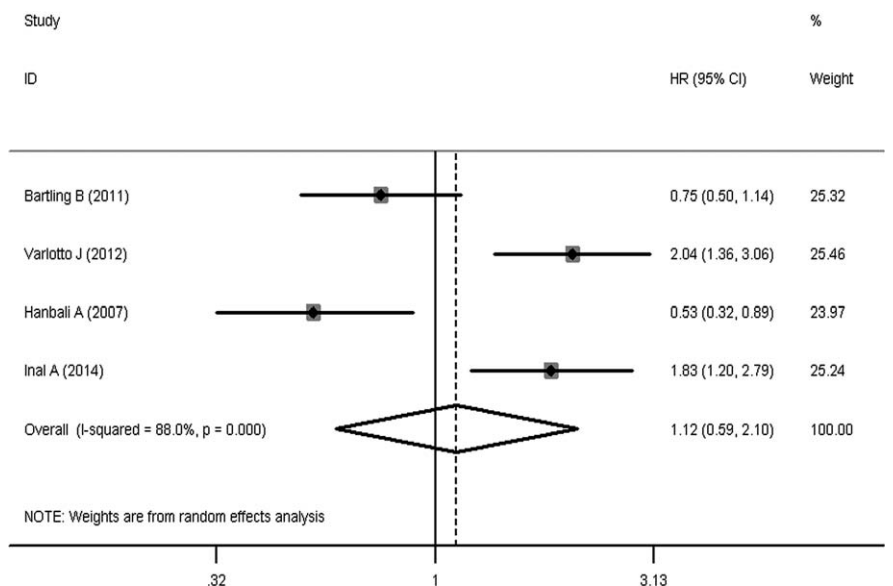
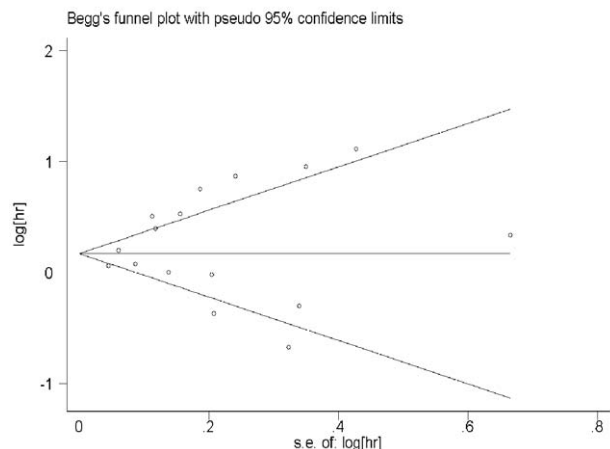


FIGURE 5. Meta-analysis of the association between diabetes mellitus and progression-free survival in NSCLC. NSCLC = non small cell lung cancer.



**FIGURE 6.** Funnel plot of hazard ratios for the overall survival in lung cancer patients.

subgroup. Further research is needed to clarify the pathophysiologic mechanisms by which DM may have different effects on NSCLC and SCLC patients.

Compared with the previous study by Barone et al,<sup>37</sup> our meta-analysis has several strengths. Compared with Barone's study, which included only 4 studies focusing on lung cancer mortality and could inevitably include more risk of bias, Our meta-analysis included 20 eligible studies with a total of 15,180 lung cancer patients stratified by DM status, which should provide a stronger statistical power and have less risk of bias. Furthermore, subgroup analyses by the histology and treatment methods were also performed in our meta-analysis, and indicated that DM might be an independent prognostic factor for NSCLC, especially for the surgically treated NSCLC subgroup. These strengths above all provide a more persuasive evidence for the prognosis role of DM in lung cancer patients.

However, several limitations should be pointed out. First, studies were much inconsistent in their confirmation of DM, study population, duration of follow-up, and adjustment for confounding variables, which might produce a high level of heterogeneity across the analysis. Second, the meta-analysis did not think over the methods of DM therapy used or their impact on lung cancer outcomes. Different therapies may have different effects on cancer progression.<sup>38,39</sup> Third, DM durations varied in different studies and we could not investigate whether DM duration have effect on lung cancer outcomes. Finally, our search was restricted to published articles in electronic databases and no additional unpublished studies or original data were taken into account, which might bring about publication bias.

In conclusion, our meta-analysis showed a significant correlation between DM state with worse survival in lung cancer patients, especially in the surgically treated NSCLC subgroup. On the basis of outcomes of this meta-analysis, more attention should be paid to lung cancer patients with pre-existing DM. Given the small number of studies included in this meta-analysis, the present conclusion should be consolidated with more high-quality prospective cohort studies or randomized controlled trials.

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