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.

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.

**INTRODUCTION**

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide. Despite diagnosis and therapeutic advances, the prognosis of lung cancer patients is still unsatisfactory. 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. A recent meta-analysis demonstrated that pre-existing DM might increase the risk of lung cancer, especially among female diabetic patients. However, evidence on the correlation between DM and outcome of lung cancer is conflicting and indefinite. 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).

**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 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
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.13 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.14 Statistical heterogeneity between studies was evaluated using Cochrane Q test and the chi-squared test. The $I^2$ values ≥50% indicated significant heterogeneity.15 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.16,17 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.9–11,18–26

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 cohorts9–11,18,19,21–26 with a total of 14,643 lung cancer cases investigated the OS and 4 studies9,11,20,22 with a total of 1711 lung cancer patients investigating 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) | Study Sample Size | Non-DM | OS or PFS | DM | OS or PFS | Quality Scores |
|-----------------|------|----------------------|-------------------------|-------------------------|------------------|--------|-----------|----|-----------|----------------|
| Inal et al      | 2014 | Turkey               | 2002–2012               | Maximum: 70            | NA               | 59     | 442       | 66 | 376       | 8              |
| Nakazawa et al  | 2013 | Japan                | 1999–2013               | Mean: 10                | NA               | 68.7   | 229       | 119| 110       | 7              |
| Luo et al       | 2012 | Taiwan               | 2005–2007               | Mean: 10.5              | NA               | 67.4   | 537       | 96 | 441       | 9              |
| Vakrioti et al  | 2011 | Greece               | 1984–2008               | Mean: 10                | NA               | 66.7   | 1852      | 84 | 1768      | 8              |
| Hadjipanayiotou et al | 2010 | Greece               | 1998–2003               | Maximum: 60             | NA               | 67.7   | 166       | 55 | 111       | 7              |
| Bartling et al  | 2011 | Norway               | 1984–2008               | Maximum: 60             | NA               | 67.4   | 166       | 55 | 111       | 7              |
| Hanbali et al   | 2007 | USA                  | 1996–2000               | Maximum: 60             | NA               | 67.7   | 166       | 55 | 111       | 7              |
| Vasic et al     | 2007 | Serbia               | 2005–2006               | Maximum: 60             | NA               | 67.7   | 166       | 55 | 111       | 7              |
| van de Poll-Framelt al | 2007 | Netherlands         | 1995–2002               | Maximum: 60             | NA               | 67.7   | 166       | 55 | 111       | 7              |
| Park et al      | 2006 | Korea                | 1996–2004               | Mean: 10                | NA               | 67.7   | 166       | 55 | 111       | 7              |
| Huang et al     | 2005 | USA                  | 1995–2005               | Maximum: 60             | NA               | 67.7   | 166       | 55 | 111       | 7              |

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

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 to 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 (\( P_{\text{Begg's}} = 0.82 \) and \( P_{\text{Egger's}} = 0.28 \)).

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 NSCLC 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 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.
The 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.27,28 Elevated insulin levels, which respond to insulin resistance, may have impact on cancer-promoting through the insulin-like growth factor-1 (IGF-1) pathway.29 The IGF-1 pathway is regarded as an important promoter of tumor progression in certain studies30,31 and IGF-1 receptor inhibitor may contribute to the

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

**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.
In addition, hyperglycemia and the metabolic disorder of cancer cells may accelerate the proliferation of lung cancer cells. 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. 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. 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. Furthermore, lung cancer patients with pre-existing DM may receive less aggressive treatment because of a greater risk of chemotherapy-related toxicity. 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.
subgroup. Further research is needed to clarify the pathophysiological mechanisms by which DM may have different effects on NSCLC and SCLC patients.

Compared with the previous study by Barone et al., 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 heterogeneity across the analysis. Second, the meta-analysis study population, duration of follow-up, and adjustment for outcomes of this meta-analysis, the present conclusion should be consolidated with more high-quality prospective cohort studies or randomized controlled trials.

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