


## ORIGINAL ARTICLE

# Diabetes mellitus and survival of non-small cell lung cancer patients after surgery: A comprehensive systematic review and meta-analysis

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## Keywords

Diabetes mellitus; lung cancer; meta-analysis; prognosis; surgery.

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## Abstract

**Background:** Diabetes mellitus (DM) is one of the most common comorbidities in surgically treated non-small cell lung cancer (NSCLC) patients and has a negative impact on short-term outcomes. However, the impact of DM on long-term survival of such patients remains controversial; therefore, we conducted a comprehensive updated meta-analysis.

**Methods:** We systematically searched relevant studies in PubMed, Embase, Cochrane Library, and Web of Science up to 6 September 2018. Hazard ratios (HRs) for the impact of DM on overall survival (OS) and recurrence-free survival (RFS) of patients with surgically treated NSCLC were extracted and analyzed using the STATA 12.0 package.

**Results:** We included 13 cohort studies consisting of 4343 patients (730 patients with DM and 3613 patients without) with surgically treated NSCLC. Meta-analysis showed that patients with DM had significantly poorer OS (random effects: HR 1.30, 95% confidence interval 1.05–1.60;  $P = 0.016$ ) than those without. However, with a limited sample size, there was no significant difference in RFS (random effects: HR 1.06, 95% confidence interval 0.71–1.58;  $P = 0.786$ ) between patients with and without DM after surgical resection of NSCLC.

**Conclusion:** DM is an independent unfavorable prognostic factor for patients with surgically treated NSCLC. High-quality studies with appropriate adjustment for confounding factors are needed to confirm our conclusions.

## Introduction

Lung cancer is the leading cause of cancer-related death worldwide and non-small cell lung cancer (NSCLC) accounts for approximately 85%.<sup>1,2</sup> Lung cancer has a very poor prognosis, with a five-year relative survival rate of 16%.<sup>3</sup> Currently, surgery remains the preferred option for treating resectable NSCLC. In patients with surgically resected NSCLC, in addition to tumor characteristics, such as tumor size and lymph node metastasis, comorbidities are also reported to have an impact on prognosis.<sup>4</sup> Diabetes mellitus (DM), one of the most common comorbidities in NSCLC patients,<sup>5</sup> is an independent risk factor for developing NSCLC.<sup>6</sup> The unfavorable impact of DM on short-term

outcomes of patients with surgically treated NSCLC has been well established.<sup>5,7</sup> However, no definitive conclusion has been made as to the impact of DM on long-term survival in such patients. Some studies have reported that patients with DM have significantly poorer overall survival (OS) and recurrence-free survival (RFS) than those without,<sup>8–10</sup> while others found that DM had no significant impact on the prognosis of surgically treated NSCLC patients.<sup>11–13</sup> A previous meta-analysis of three studies published up to 2013 explored the impact of DM on surgically treated NSCLC patients;<sup>8,12,13</sup> however, because of the limited sample size no statistically significant impact was observed.<sup>14</sup> Since 2013, more and more studies investigating the impact of DM on the survival of patients with

surgically treated NSCLC have been published.<sup>9,15–17</sup> The previous meta-analysis did not examine the impact of DM on RFS of patients with surgically treated NSCLC, which we deem important in order to draw a relatively objective conclusion about the impact of DM on long-term prognosis of patients with surgically treated NSCLC. Therefore, we pooled the updated data and conducted a meta-analysis to explore the actual impact of DM on survival and recurrence in surgically treated NSCLC patients. To our knowledge, this is the most comprehensive meta-analysis to focus on this topic.

## Methods

### Search strategies

We conducted a systematic search of PubMed, Embase, Cochrane Library, and Web of Science to identify the relevant studies published to 6 September 2018, using the following search terms: (diabetes OR diabetes mellitus OR hyperglycemia OR high blood glucose OR DM) AND (non-small cell lung cancer OR nonsmall cell lung cancer OR NSCLC) AND (surgery OR surgical OR resection) AND (survival OR prognosis OR prognostic OR recurrence). We also scanned all reference lists from the studies selected by electronic searching to identify further relevant studies.

### Study selections

The study inclusion criteria were as follows: (i) either observational studies or randomized controlled trials (RCTs) comparing survival between patients with and without DM after surgical resection of NSCLC; (ii) sufficient data could be obtained for retrieving hazard ratios (HRs) for OS or RFS; and (iii) if the studies were conducted on the same overlapping patients, the completed or most recent study was included. The exclusion criteria were: (i) studies including patients with small cell lung cancer or patients who were not surgically treated; (ii) studies published in non-English language; (iii) studies without any relevant data extracted for analysis; and (iv) reviews, case reports, conference abstracts, and experiments.

### Data extraction and quality assessment

Two authors extracted data from the included studies and compared the results independently. Discrepancy was resolved by the third author's adjudication to avoid bias. Data were carefully retrieved from full articles by using a standardized data collection form, which consisted of first author, country and year of publication, number of patients, disease stage, age, follow-up time, and study type.

The outcomes for analysis in our meta-analysis consisted of HRs of OS and RFS. The Jadad scale was used for quality assessment of RCTs,<sup>18</sup> while quality assessment and risk-of-bias analysis of observational studies was evaluated using the Newcastle–Ottawa Scale (NOS), as previously described,<sup>19</sup> which consisted of three factors: patient selection, comparability of the study groups, and assessment of outcome. We assigned a score of 0–9 (allocated as stars) to each study after careful evaluation, with a high quality study defined as a study with a quality score of no less than seven. The name of the first author and year of publication were used for identification in our analysis.

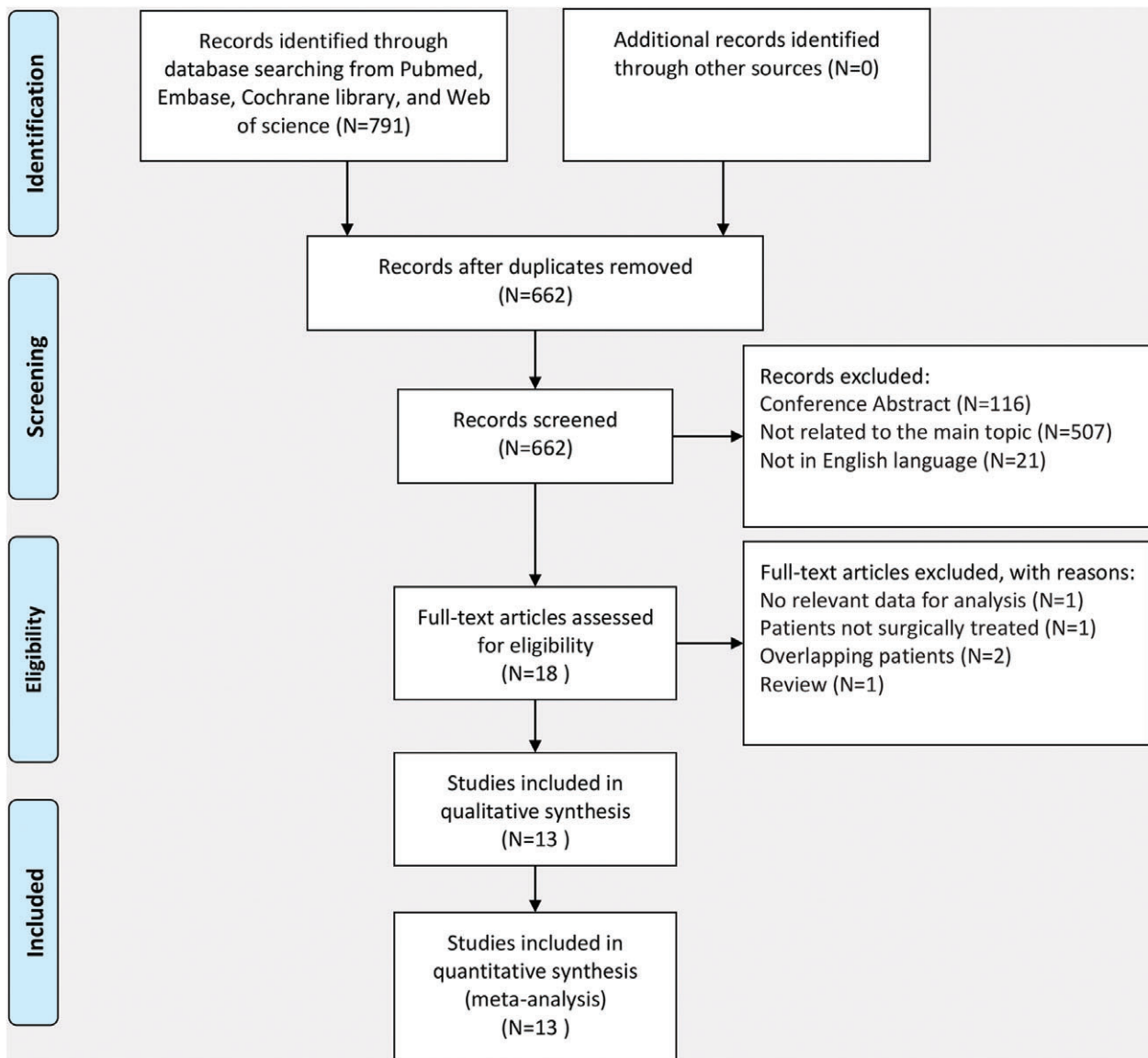
### Statistical analysis

We performed all analyses using the STATA 12.0 package (StataCorp, College Station, TX, USA) in accordance to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.<sup>20</sup> HRs of OS and RFS of patients with DM compared to those without with a 95% confidence interval (CI) were extracted from the original studies to evaluate the impact of DM on survival of patients with surgically treated NSCLC. When the HR was not directly reported in the original study, it was estimated as demonstrated by Parmar *et al.* by using five-year OS or RFS rates extracted directly from the text or Kaplan–Meier curve.<sup>21</sup> The between-study heterogeneity of each study was assessed using  $\chi^2$ -based Q statistics and  $I^2$  tests. If high heterogeneity ( $P < 0.10$  or  $I^2 > 50\%$ ) was observed, random effects models were applied; otherwise, fixed effects models were used. We conducted sensitivity analysis by sequential removal of each study. We also used a funnel plot to estimate potential publication bias, the asymmetry of which was tested by Begg's and Egger's tests.<sup>22</sup> We set the statistical significance at  $P < 0.05$ .

## Results

### Description of studies

A flow chart showing the process of study evaluation is shown in Figure 1. A total of 791 papers were identified in the initial search. After evaluation, 18 papers qualified for detailed evaluation. A previous meta-analysis and a cohort study were excluded because they did not focus on surgically treated patients.<sup>14,23</sup> Another study was excluded because no relevant data could be extracted to analyze the impact of DM.<sup>5</sup> There were three studies by the same research group based on overlapping patients; therefore, only the study with the most complete data was included.<sup>4,10,24</sup> Finally, 13 retrospective cohort studies but no RCTs were included, with a total of 4343 patients (730 patients with DM and 3613 patients without).<sup>8–13,15–17,25–28</sup> The main data extracted from



**Figure 1** Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram showing the progress of studies through the review.

these included studies is listed in Table 1. Almost all of the patients had localized resectable disease and all had undergone relatively long follow-up. The survival data analyzed in these included studies consisted of OS and RFS. The HRs of OS could be obtained directly from five studies and estimated with five-year OS rates from another five studies, while the HRs of RFS could be obtained directly from four studies and estimated with five-year RFS rates from two studies (Table 2).

### Quality assessment and risk of bias

Because all of the included studies were cohort studies, quality assessment and risk-of-bias analysis were evaluated

using NOS. Quality assessment of the included cohort studies is listed in Table 1. Eight studies were ranked as high quality, while five studies were ranked as low quality, which suggested a potential risk of bias.

### Meta-analysis of the impact of diabetes mellitus on the survival of surgically treated non-small cell lung cancer patients

Ten studies, including a total of 3426 patients, reported the impact of DM on OS of patients with surgically treated NSCLC. Meta-analysis showed that patients with DM had significantly shorter OS than those without after surgical resection of NSCLC (random effects: HR 1.30, 95%

**Table 1** Characteristics of the included studies

Author	Country	Patients	Age (range, years)	Follow-up	Sample size (n)	DM (n)	Non-DM (n)	Study design	Quality assessment
Dominguez-Ventura et al. <sup>11</sup>	United States	Pathologic stage I–IV (majority stage I–II)	Median: 82 (80–94)	Median: 2.2 years (range: 1 month–13.6 years)	288	16	272	Cohort study	NOS: 7 stars
Win et al. <sup>8</sup>	United Kingdom	Pathologic stage I–IIIA	Mean: 69 (42–85)	All patients had at least 3 years and up to 5 years follow-up	110	12	98	Cohort study	NOS: 7 stars
Bartling et al. <sup>12</sup>	Germany	Majority T1–4N0–1; only 4 had distant metastasis	Median: 68 for DM and 66 for non-DM group (51–80)	60 months	166	55	111	Cohort study	NOS: 7 stars
Varlotta et al. <sup>10</sup>	United States	Stage I–IIIB (majority stage I)	Median: 68 (38–96)	Median: 33 months (range: 3–98)	537	96	441	Cohort study	NOS: 7 stars
Fan et al. <sup>25</sup>	China	Pathologic T1–3N1M0	NA	Median: 53.8 months (range: 1.4–81.8)	199	15	184	Cohort study	NOS: 7 stars
Nakazawa et al. <sup>13</sup>	Japan	NA	NA	NA	388	69	319	Cohort study	NOS: 6 stars
Washington et al. <sup>26</sup>	United States	Pathological stage I–IIIA	Median: 67 (21–92)	Median: 30 months (range: 1–149)	957	122	835	Cohort study	NOS: 9 stars
Dhillon et al. <sup>15</sup>	United States	Pathologic stage I	Mean: 68.5 (21–93)	Median: 44 months	409	71	338	Cohort study	NOS: 7 stars
Jeon et al. <sup>27</sup>	Korea	Pathologic stage I	NA	Median: approximately 40 months	211	29	182	Cohort study	NOS: 6 stars
Kuo et al. <sup>28</sup>	Taiwan, China	Pathologic stage I	Mean: 63.9	More than 3 months for each patient	181	48	133	Cohort study	NOS: 6 stars
Jeon et al. <sup>9</sup>	Korea	Pathologic stage I and II	Median: 64 (32–81)	Median: 40 months	271	42	229	Cohort study	NOS: 6 stars
Medeiros et al. <sup>16</sup>	United States	Pathologic stage I and II	Mean: 69.0	Median: 19.5 months	158	81	77	Cohort study	NOS: 6 stars
Motoishi et al. <sup>17</sup>	Japan	Pathologic stage I–IIIB	Mean: 70.1 (44–88)	Median: 1136 days (range: 11–3598)	468	74	394	Cohort study	NOS: 7 stars

DM, diabetes mellitus; NA, not available; NOS, Newcastle-Ottawa Scale.

CI 1.05–1.60;  $P = 0.016$ ;  $I^2 = 47.1\%$ ) (Fig 2a). Six studies, including a total of 2500 patients, reported the impact of DM on RFS of patients with surgically treated NSCLC. Meta-analysis showed that there was no significant difference in RFS between patients with and without DM (random effects: HR 1.06, 95% CI 0.71–1.58;  $P = 0.786$ ;  $I^2 = 68.5\%$ ) (Fig 2b). However, potential heterogeneities were observed during analysis.

**Sensitivity analysis and publication bias**

We conducted sensitivity analysis by sequentially removing each study to evaluate the stability of our results based on OS and RFS. Sequential removal of each study did not change the outcomes of primary analysis (Fig 3). Publication bias was tested with a funnel plot to analyze OS, which had a symmetrical appearance (Begg’s test:  $P = 0.421$ ; Egger’s test:  $P = 0.490$ ), suggesting no significant publication bias (Fig 4).

**Discussion**

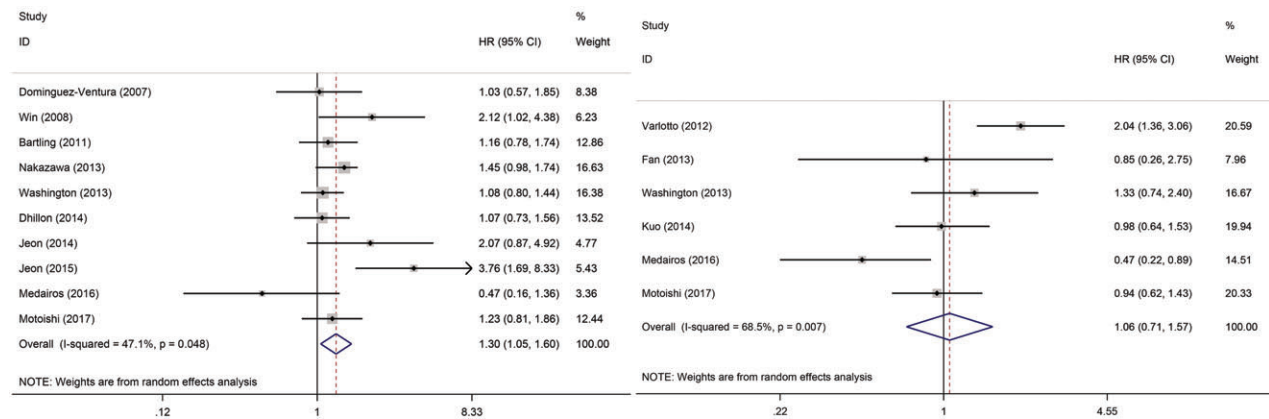
DM has become a major global health problem causing significant morbidity and mortality, which was estimated at a prevalence of 6.4% in 2010 and is expected to increase to 7.7% in 2030.<sup>29</sup> In China, the prevalence of DM is as high as 9.1%, which causes significant disease burdens.<sup>30</sup> DM is an independent risk factor in the development of lung cancer<sup>6</sup> and is also reported to have a negative impact on the short-term outcomes of patients with surgically treated NSCLC.<sup>5,7,26</sup> However, opinions over the impact of DM on long-term prognosis of patients with surgically treated NSCLC are mixed. A previous meta-analysis found that DM had no significant impact on the survival of these patients (HR 1.71, 95% CI 0.94–3.08;  $P = 0.08$ ); however a limited sample was included.<sup>14</sup> Therefore, in order to draw a relatively reliable conclusion about the impact of DM on the prognosis of patients with surgically treated NSCLC, we conducted an updated meta-analysis by pooling all available evidence.

We included 13 studies with a total of 4400 patients with surgically treated NSCLC. Ten studies were included to analyze OS and our results showed that patients with DM had significantly poorer OS than those without (HR 1.30, 95% CI 1.05–1.60;  $P = 0.016$ ). However, only six studies were included in RFS analysis, and no significant difference in RFS between patients with and without DM after surgical resection of NSCLC was observed (HR 1.06, 95% CI 0.71–1.58;  $P = 0.786$ ). Regarding the impact of DM on the prognosis of surgically treated NSCLC patients, previous studies have drawn controversial conclusions. Some studies found that DM was significantly correlated with worse OS and RFS in patients with

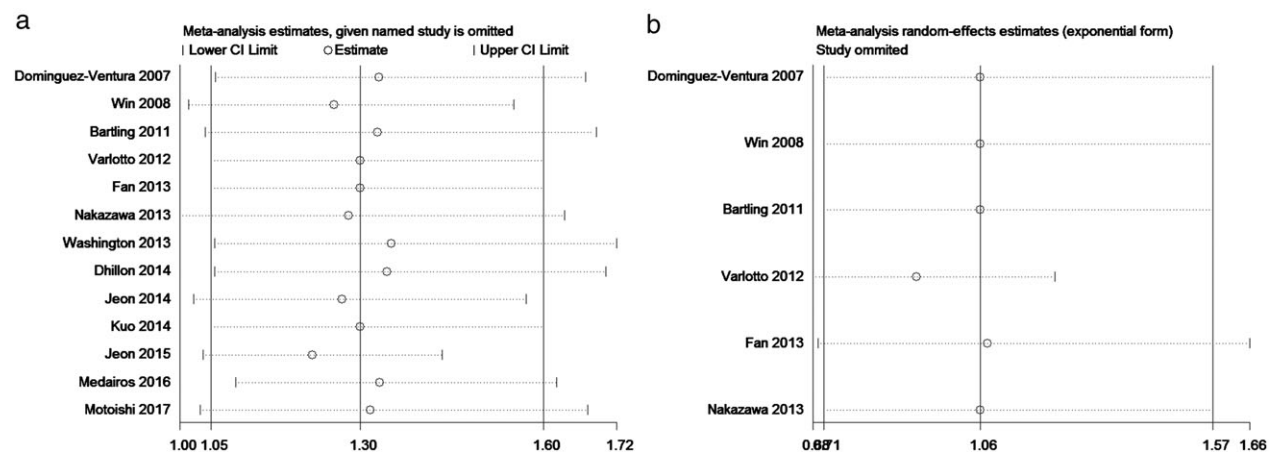
**Table 2** Main outcomes extracted from included studies

Author	Comparison	Overall survival		Recurrence-free survival	
		HR	95% CI	HR	95% CI
Dominguez-Ventura <i>et al.</i> <sup>11</sup>	DM vs. non-DM	1.03‡	0.57–1.85	NA	NA
Win <i>et al.</i> <sup>8</sup>	DM vs. non-DM	2.12	1.02–4.38	NA	NA
Bartling <i>et al.</i> <sup>12</sup>	DM vs. non-DM	1.16‡	0.78–1.74	NA	NA
Varlotto <i>et al.</i> <sup>10</sup>	DM vs. non-DM	NA	NA	2.04	1.36–3.06
Fan <i>et al.</i> <sup>25</sup>	DM vs. non-DM	NA	NA	0.85‡	0.26–2.75
Nakazawa <i>et al.</i> <sup>13</sup>	DM vs. non-DM	1.45‡	0.98–2.15	NA	NA
Washington <i>et al.</i> <sup>26</sup>	DM vs. non-DM	1.08	0.80–1.44	1.33	0.74–2.40
Dhillon <i>et al.</i> <sup>15</sup>	DM vs. non-DM	1.07‡	0.73–1.56	NA	NA
Jeon <i>et al.</i> <sup>27</sup>	DM vs. non-DM	2.07	0.87–4.92	NA	NA
Kuo <i>et al.</i> <sup>28</sup>	DM vs. non-DM	NA	NA	0.98	0.64–1.53
Jeon <i>et al.</i> <sup>9</sup>	DM vs. non-DM	3.76	1.69–8.33	NA	NA
Medeiros <i>et al.</i> <sup>16</sup>	DM vs. non-DM	0.47	0.16–1.36	0.47	0.22–0.89
Motoishi <i>et al.</i> <sup>17</sup>	DM vs. non-DM	1.23‡	0.81–1.86	0.94‡	0.62–1.43

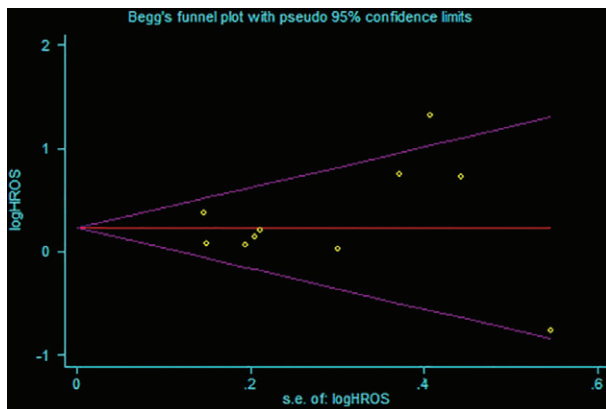
‡Hazard ratios (HRs) for overall and Recurrence-free survival were estimated using the five-year rates, as demonstrated by Parmar *et al.*<sup>21</sup> CI, confidence interval; DM, diabetes mellitus; NA, not available.



**Figure 2** Forest plots of (a) overall and (b) recurrence-free survival. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.



**Figure 3** Sensitivity analysis for (a) overall and (b) recurrence-free survival. CI, confidence interval.



**Figure 4** Funnel plot of the included studies for analysis of overall survival. Begg's test:  $P = 0.421$ ; Egger's test:  $P = 0.490$ . HR, hazard ratio of overall survival; SE, standard error.

surgically treated NSCLC,<sup>8–10</sup> while others found no significant difference.<sup>11–13</sup> However, it should be noted that almost all previous studies included a very limited sample of patients with DM,<sup>8–13,15–17,25–28</sup> with only one study including a sample of over 100 DM patients.<sup>26</sup> A previous meta-analysis with a sample of 146 DM patients found that patients with DM tended to have a poor prognosis compared to those without, with marginal statistical significance.<sup>14</sup> A larger sample of DM patients may reveal a significant difference in survival between the groups. As a result, we included a total of 730 patients with DM and our study proved that patients with DM had significantly poorer OS than those without after surgical resection of NSCLC. However, similarly, because of a limited sample to analyze RFS, no sufficient evidence of a significant difference in RFS between patients with and without DM was observed. DM is also independently correlated with poor prognosis in patients with various cancers, such as pancreatic cancer,<sup>31</sup> renal cell carcinoma,<sup>32</sup> and breast cancer.<sup>33</sup> These results suggest that DM is an independent unfavorable prognostic factor for NSCLC after surgical resection. As a result, surgically treated NSCLC patients with DM might benefit from better glucose control and closer postoperative follow-up.<sup>10</sup>

The potential association between DM and prognosis of patients with surgically treated NSCLC remains complex. Some studies have reported that type 2 DM is characterized by insulin resistance and is associated with chronic hyperinsulinemia, which could enhance growth hormone receptor expression and increase IGF-1 receptor production and availability, thus leading to IGF-1 receptor signal pathway activation.<sup>34,35</sup> The activated IGF-1 receptor signal pathway plays a central role in cell growth, differentiation, transformation, metastasis, and survival.<sup>13</sup> Evidence has shown that increased serum hemoglobin A1c, C-peptide, and IGF-1 levels are

significantly correlated with the development and progression of lung cancer.<sup>36</sup> Moreover, high expression of IGF-1 receptor is also significantly associated with poor prognosis in NSCLC.<sup>37</sup> These results may, to some degree, explain why lung cancer patients with DM have a significantly poorer prognosis than those without. However, in contrast, one study reported that DM could delay NSCLC progression by increasing the level of long-lived proteins modified with advanced glycation end product, which could lead to beneficial effects.<sup>12</sup> Moreover, the impact of DM on the prognosis of patients with NSCLC could be complicated with the administration of an anti-diabetic therapeutic agent, such as metformin, which exerts its anti-diabetic effect predominantly via liver kinase B1 (LKB1)-dependent activation of adenosine monophosphate-activated protein kinase (AMPK).<sup>38</sup> Because it regulates the LKB1/AMPK signal pathway, metformin has also been proven to significantly inhibit cell proliferation, induce apoptosis, and block cell cycle progression in NSCLC cells,<sup>39</sup> thus exerting an antitumor effect in NSCLC patients with DM. Therefore, further studies are needed to elucidate the actual interaction of DM with lung cancer.

Our meta-analysis had several limitations. First, because of the lack of RCTs, only retrospective cohort studies were included for analysis, which might reduce the statistical power of our results. Second, potential heterogeneities and the low quality of several studies could also affect the validity of our results. Third, RFS data was only available from six studies, and as a result, the impact of DM on RFS should be further verified. Moreover, the impact of DM on the prognosis of patients with NSCLC could be biased by the effect of administration of an anti-diabetic therapeutic agent, such as metformin. Finally, we could not extract the HRs of OS or RFS directly from some studies and therefore, we could only estimate HRs for these studies based on five-year OS or RFS rates as previously described.<sup>19</sup> Therefore, further well-conducted RCTs are needed to confirm and update our conclusions.

In this updated meta-analysis, we attempted to draw an objective conclusion about the impact of DM on long-term survival of patients with surgically treated NSCLC by including all relevant up-to-date studies. We found that patients with DM had significantly poorer OS than those without. Therefore, DM is an independent unfavorable prognostic factor for patients with surgically treated NSCLC. Further studies, however, are needed to confirm and update our conclusions.

## Disclosure

No authors report any conflict of interest.

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