

Diabetes Mellitus and Risk of Bronchopleural Fistula After Pulmonary Resections: A Meta-Analysis

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We conducted this meta-analysis to evaluate the association between diabetes mellitus and the risk of bronchopleural fistula in patients undergoing pulmonary resection. The PubMed and EMBASE databases were searched, and 15 retrospective observational studies were included. The pooled analysis showed that diabetes mellitus was significantly associated with the formation of bronchopleural fistula after pulmonary resection (odds ratio = 1.97; 95% confidence interval = 1.39 to 2.80;

$p < 0.001$). This association remained statistically prominent in the subgroups classified by statistical analysis, diagnoses and operative modes and in Asian patients. Therefore, diabetes mellitus can be an independent risk factor for bronchopleural fistula after pulmonary resection.

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Diabetes mellitus (DM) has become a major worldwide challenge to human health in the past 30 years [1, 2]. According to official estimates, approximately 347 million people have DM, and 1.3 million deaths per year are caused by cardiovascular and renal diseases, which are directly related to DM progression [2, 3]. On the basis of many relevant investigations, the serious pathologic damages to the vascular system of DM patients induced by abnormal glucose metabolism and other metabolic derangements have been commonly recognized in clinical practice [4].

For patients requiring surgical intervention, surgeons usually consider DM an important contributor to some fatal adverse events [5–7]. A recent systematic review has demonstrated the effects of DM on the risk of anastomotic leakage in gastrointestinal tracts and has indicated that DM is significantly associated with postoperative gastrointestinal leakage [7]. In thoracic operations, bronchopleural fistula (BPF) is similarly a devastating leakage from airways into the pleural space, and it can lead to high mortality after pulmonary resection [8, 9]. Surgical procedures remain the leading cause of BPF [9]. Besides, the potential impact of DM on BPF formation after pulmonary resection has also been of concern in many research studies.

However, some controversy still exists, and a consensus on an association between DM and risk of BPF has not been reached until now. Additionally, the investigations focusing on the impact of DM on postoperative BPF have not yet been systematically reviewed and summarized.

Thus, we conducted this meta-analysis to systematically evaluate the relationship between DM and BPF risk after pulmonary resection.

Methods and Materials

A systematic review and meta-analysis does not require patients' consent or ethical approval. We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. The additional PRISMA 2009 checklist is given in the [Appendix, data 1](#).

Search Strategy

Literature retrieval for this meta-analysis was conducted between July 24, 2015, and August 7, 2015. Two universal electronic databases, PubMed and EMBASE (through the Ovid interface), were selected for identification of full-text literature reports published between January 1, 1980, and July 24, 2015. We established five search strings, which were combined with seven key words and two Boolean operators ("and" and "or"), to search the selected databases. These key words were listed as follows: (1) "bronchopleural fistula" and "bronchial fistula," (2) "risk factor," "incidence," and "etiology," (3) and "diabetes mellitus" and "diabetes." The complete details of each search string are listed in the [Appendix, "PubMed search strategy"](#) and "EMBASE search

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The [Appendix](#) can be viewed in the online version of this article [<http://dx.doi.org/10.1016/j.athoracsur.2016.01.013>] on <http://www.annalsthoracicsurgery.org>.

strategy." Moreover, we also manually screened the reference lists of identified studies for possible eligible studies with no duplication.

Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were applied to determine the appropriateness of studies for our meta-analysis.

Inclusion criteria: (1) The target diseases included primary lung cancers, infectious diseases, benign tumors, and metastatic or recurrent carcinomas. Pulmonary trauma and pleural diseases were not considered. (2) BPF developed after surgical procedures rather than as progression of primary diseases. (3) The risk factors analyzed in original literature reports contained the status of DM. (4) Demographic or statistical data assessing the relationship between DM and postoperative BPF were reported in the full text of literature publications. (5) Only reports published in the English language were eligible.

Exclusion criteria: (1) The following literature reports were directly excluded: reviews, case reports, letters, preclinical experiments, and conference abstracts. (2) The development of BPF was uncertain. (3) Lung transplantations were not considered. (4) Literature reports not in English were excluded.

Quality Assessment

We systematically evaluated five key points of study quality proposed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) collaboration [11]. These key points are as follows: (1) clear identification of the studied population, (2) clear definition of outcome and outcome assessment, (3) independent assessment of outcome parameters, (4) selective loss during follow-up, and (5) elimination of major confounders. We rated the value of each point as "Yes" or "No." If its definition was unclear, we regarded it as "No."

Data Collection

We designed a Microsoft Excel sheet to collect the following records: (1) publication details including authors, publication years, and nations; (2) experimental details including study design, study period, diagnoses, operative modes, and the onset of BPF; (3) demographic details including age, enrolled samples, and the number of patients with DM and postoperative BPF; (4) statistical details including statistical results reported in original literature studies, such as odds ratio (OR), relative risk (RR), and hazard ratio (HR) with corresponding 95% confidence interval (95% CI). Additionally, the β value and standard error (SE) conducted from multivariate or univariate analysis were also collected to calculate the OR outcomes.

Statistical Analysis

The incidence of postoperative BPF was generally far lower than 20% [9]. Therefore, there was no evidence to show any significant difference between OR and RR, and the risk of overestimating the impact of DM on BPF formation could be largely avoided [12]. In this

meta-analysis, OR with 95% CI served as the appropriate summarized statistic for quantitative synthesis. Generally, it could be directly extracted from the statistical details published in the original literature reports. If no statistical result was reported, we extrapolated the OR outcomes from the demographic data reported in the included studies by SPSS 19.0 (SPSS Inc., Chicago, IL). Besides, we could also calculate the OR with 95% CI using the reported β value and SE, according to a previously reported protocol [13]. Remarkably, the significant relationship between DM and increased BPF risk could be shown by the summarized OR with 95% CI more than 1.

We used the Q test and the I^2 statistic to evaluate the level of heterogeneity within this meta-analysis. Fine heterogeneity was defined as $I^2 < 50\%$ and $p > 0.1$, and a standard fixed-effect model (Mantel-Haenszel method) was applied for integration of ORs. Otherwise, a random-effect model (DerSimonian and Laird method) was accepted if significant heterogeneity was shown by $I^2 \geq 50\%$ or $p \leq 0.1$ [14]. We performed a sensitivity analysis to further identify the possible origins of heterogeneity. Then, the study that might contribute to high heterogeneity would be excluded, and a repeated meta-analysis of the remaining studies would be performed for adjustments. The strong robustness of our meta-analysis would be confirmed if no substantial variations were observed between the adjusted outcomes and the primary outcomes [15].

Publication bias in this meta-analysis was detected by Begg's test and Egger's test. Its presence could be suggested by the symmetry of funnel plot conducted by Begg's test, in which log ORs were plotted against their corresponding SEs [16]. The significant bias was confirmed if the p value was < 0.05 .

Finally, all of the above statistical analyses were accomplished by Stata 12.0 (Stata Corporation, College Station, TX).

Results

Selection of Included Studies

The complete procedure of literature retrieval is summarized in Figure 1. A total of 1,584 citations were identified after primary retrieval, including 922 citations in PubMed and 662 citations in EMBASE. Then, 912 of these citations were initially filtered after exclusion of the duplicates. After careful screening of the titles and abstracts, 454 unqualified literature studies were directly excluded, including 119 reviews, 90 case reports, two animal experiments, 166 non-English studies, and 77 conference abstracts. Further filtration was based on reading through the full text of the remaining 458 reports. Then, 18 of them were considered for possible eligibility for quantitative synthesis [17–34]. Finally, a total of 15 studies met the eligibility criteria and were included in our meta-analysis [17–31]. The other three studies were finally excluded because details of DM and BPF formation were incomplete [32–34].

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