Perioperative outcomes of combined heart surgery and lung tumor resection: A systematic review and meta-analysis

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Abstract

Objective: The coexistence of concomitant lesions of the heart and lungs needed surgical intervention is increasing. Simultaneous cardiac surgery with pulmonary resection can solve the lesions at the same time, thus avoiding the second operation. However, concern exists regarding the potentially increased mortality and complication rate of simultaneous surgery and the adequacy of lung exposure during heart surgery. Therefore, we performed a meta-analysis to evaluate the perioperative mortality and complication rate of combined heart surgery and lung tumor resection.

Methods: A comprehensive literature search was performed in July 2020. PubMed, Embase and Web of Science databases were searched to collect studies reporting the perioperative outcomes of combined heart surgery and lung tumor resection. Two reviewers independently screened literatures, extracted data and assessed the risk of bias of included studies. Pooled proportion and its 95% confidence intervals (95% CI) was performed by R version 3.6.1 using the meta package.

Results: A total of 536 patients from 29 studies were included in this analysis. Overall, the results of this meta-analysis showed that the pooled proportion of operative mortality was 0.01 (95% CI: 0.00, 0.03) and the pooled proportion of postoperative complications was 0.40 (95% CI: 0.24, 0.57) for patients underwent combined cardiothoracic surgery. Subgroup analysis by lung pathology revealed that, for lung cancer patients, the pooled proportion of anatomical lung resection was 0.99 (95% CI: 0.95, 1.00), and the pooled proportion of systematic lymph node dissection or sampling was 1.00 (95% CI: 1.00, 1.00). Subgroup analysis by heart surgery procedures found that the pooled proportion of postoperative complications of coronary artery bypass grafting (CABG) patients using off-pump method was 0.17 (95% CI: 0.01, 0.43), while the pooled proportion of on-pump method was 0.61 (95% CI: 0.38, 0.82).

Conclusion: This study presented that combined heart surgery and lung tumor resection had a low mortality rate and an acceptable complication rate. Subgroup analysis revealed most lung cancer patients underwent uncompromised anatomical resection and mediastinal lymph node sampling or dissection during combined cardiothoracic surgery, and showed off-pump CABG could potentially reduce the complication rate compared with on-pump CABG. While further researches are still needed.

Introduction

Although relatively few, the coexistence of concomitant lesions of the heart and lungs needed surgical intervention is increasing (1–3). Some patients, who required cardiac surgery, found asymptomatic indeterminate lung nodules during preoperative examination. Other patients, who were scheduled to receive lung tumor resection, had heart diseases needed surgical intervention. Handling patients who require both heart surgery and lung resection is a challenge. Treatment options include either simultaneous or staged surgical procedures (4–8). Without postponing the treatment of either heart or lung diseases, simultaneous surgery can solve heart and lung lesions at the same time, thus avoiding the second operation (3, 9–12). But, concern exists regarding the potentially increased mortality and complication rate of simultaneous surgery and the adequacy of lung exposure during heart surgery (8, 12–20).

As a result, we conducted this meta-analysis to systematically evaluate the perioperative mortality and complication rate of combined heart surgery and lung tumor resection. In the subgroup analysis, we also investigated the proportion of lung cancer patients underwent anatomic lung resection and mediastinal lymph node sampling or dissection, and the impact of cardiopulmonary bypass on perioperative complications.

Methods

Search strategy

A comprehensive literature search was conducted using PubMed, Embase and Web of Science database in 7 July 2020 to identify citations reporting perioperative outcomes of combined heart surgery and lung tumor resection with the following search algorithm: (exp Cardiac Surgical Procedures/ or ((heart$ or cardio$ or cardiac or coronary or myocardial or valve$) adj1 (surger$ or operation$ or graft$ or bypass$ or revascularization$ or plasty or replacement$)).tw.) and (exp Pneumonectomy/ or ((lung$ or pulmon$ or sublob$ or wedge$) adj1 (surger$ or operation$ or resect$)).tw.). In addition, the reference lists of the retrieved articles and related reviews were checked to identify potentially relevant additional studies. No language or publication date restrictions were adopted. The flow diagram was presented in Fig. 1. The present meta-analysis was designed, performed, and reported in accordance with the standards of quality for reporting meta-analysis.

Selection Criteria

Articles included in this study had to meet all the following criteria: the exposure of interest was combined heart surgery and lung tumor resection whether benign or malignant; the outcome of interest was incidence rates of operative mortality and postoperative complications; the study design was case-control, retrospective or prospective study; and the proportion estimates with their corresponding 95% CIs were reported or sufficient data were provided to calculate them. Operative mortality was defined as death within 30 days of operation or during hospitalization. Postoperative complications were defined as the occurrence of complications within 30 days of operation or during the postoperative stay.
Selected publications focused on lung tumor resection. Publications were excluded if lung transplantation surgery, trauma surgery, lung infectious disease surgery, esophageal surgery, mediastinal surgery were included. If they were reviews, editorial commentaries, or no extractable data were available.

Quality Assessment

Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of included researches by two independent reviewers (Yiyao Jiang, Xin Li). NOS is a 9-star system, which includes 3 dimensions: selection (4 items), comparability (1 item), and exposure/outcome (3 items). Each item represents 1 point, except for comparability (2 points). A study with ≥ 7 points was considered as a high-quality study.

Data Extraction

Data were extracted independently by the two reviewers (Shizhao Cheng, Yiyao Jiang) and any discrepancies were resolved by discussion. The following data from each included study were recorded: publication details, sample size, lung tumor histological type, operative mortality and postoperative complication proportion estimates with their corresponding 95% confidence intervals (95% CIs).

Statistical Analysis

All quantitative analysis was performed in R version 3.6.1 using the meta package. For the meta-analysis of the operative mortality and postoperative complications proportions, both fixed and random effects approaches were adopted using the Freeman-Tukey double arcsine transformation method (21). Subgroup analyses were performed based on different lung pathology or heart surgery procedures. Heterogeneity across included studies was assessed with the Cochran Q test (the level of significance was set at 0.1) (22). The $I^2$ score was used to determine the degree of heterogeneity ($I^2 < 50\%$, no obvious heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). In sensitivity analysis, meta-analysis was conducted after omitting each study in turn. Potential publication bias was evaluated Begg's test and Egger's test (23).

Results

Study searches and characteristics

The detailed process of literature retrieval procedures is shown in Fig. 1. A total of 29 eligible studies were finally included in the present meta-analysis (3, 5–20, 24–35). These studies were carried out in the following geographical regions: five in USA (8, 19, 20, 32, 35), four in China (3, 11, 25, 26), four in Netherlands (7, 13, 30, 33), three in Italy (14, 18, 29), two in Czech Republic (12, 24), two in Japan (10, 16), two in Turkey (9, 15), one in Australia (34), one in Belgium (6), one in Canada (31), one in Germany (5), one in Greece (27), one in Poland (28), and one in UK (17). All of them were retrospective observational studies, which were published between 1990 and 2019. Of these studies, the sample sizes ranged from 2 to 79 patients. Therefore, 29 studies containing 536 patients who received combined heart surgery and lung tumor resection were subjected to final analysis. In each study, the proportion estimates with their corresponding 95% CIs of the operative mortality and postoperative complications were calculated from available information from original article. Quality scores evaluated by the Newcastle–Ottawa Scale (NOS) ranged from 5 to 7. The main characteristics of all included studies have been summarized in Table 1.

Table 1: Characteristics of studies included in the meta-analysis.
The pooled proportion of operative mortality was 0.01 (95% CI: 0.00, 0.03) using both fixed-effect and random-effect models. No significant heterogeneity between studies was shown ($I^2 = 91.60\%, P = 0.79$) (Fig. 2).

Pooled Proportion Of Postoperative Complications

The pooled proportion of postoperative complications was 0.40 (95% CI: 0.24, 0.57) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 91.60\%, P < 0.01$) (Fig. 3). Furthermore, we divided the postoperative complications into three categories: reopening for bleeding; respiratory complications and cardiac complications. The pooled proportion of reopening for bleeding was 0.01 (95% CI: 0.00, 0.02) using both fixed-effect and random-effect models. No significant heterogeneity between studies was shown ($I^2 = 2.10\%, P = 0.43$) (Fig. 4). The pooled proportion of respiratory complications was 0.11 (95% CI: 0.04, 0.19) using the random-effect model. Significant
heterogeneity between studies was noted ($I^2 = 76.00\%, P<0.01$). The pooled proportion of cardiac complications was 0.15 (95% CI: 0.08, 0.23) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 72.00\%, P<0.01$).

**Subgroup Analysis**

For further assessing the incidence rates of operative mortality and postoperative complications of patients who received combined heart surgery and lung tumor resection, we classified all cases into several subgroups according to lung pathology and heart surgery procedures.

In the subgroups classified by lung pathology, 16 studies (3, 7–9, 11, 13–16, 19, 26, 28, 30, 32–34) contained 327 patients who received combined heart surgery and lung cancer resection, while the other 13 studies (5, 6, 10, 12, 17, 18, 20, 24, 25, 27, 29, 31, 35) enrolled both malignant and benign diseases. Because malignant and benign diseases were analyzed together in the 13 studies (5, 6, 10, 12, 17, 18, 20, 24, 25, 27, 29, 31, 35), further assessment of benign diseases was not done. So, we quantitatively pooled the data of 327 lung cancer cases from the 16 studies (3, 7–9, 11, 13–16, 19, 26, 28, 30, 32–34). The pooled proportion of operative mortality of patients who received combined heart surgery and lung cancer resection was 0.01 (95% CI: 0.00, 0.04) using both fixed-effect and random-effect models. No significant heterogeneity between studies was shown ($I^2 = 2.20\%, P = 0.43$). The pooled proportion of postoperative complications of patients who received combined heart surgery and lung cancer resection was 0.45 (95% CI: 0.27, 0.64) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 87.80\%, P<0.01$).

To further estimate the quality control of lung cancer surgery, we concerned about whether patients with lung cancer had underwent anatomical resection and systematic lymph node dissection or sampling. The pooled proportion of lung cancer patients underwent anatomical resection was 0.99 (95% CI: 0.95, 1.00) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 54.70\%, P<0.01$) (Fig. 5). Among the 16 studies (3, 7–9, 11, 13–16, 19, 26, 28, 30, 32–34), 1 study did not provide enough information about lymph node dissection or sampling (7). Therefore, 15 studies (3, 8, 9, 11, 13–16, 19, 26, 28, 30, 32–34) containing 303 patients who received combined heart surgery and lung cancer resection were used to analyze the proportion of systematic lymph node dissection or sampling. The pooled proportion of lung cancer patients underwent systematic lymph node dissection or sampling was 1.00 (95% CI: 1.00, 1.00) using both fixed-effect and random-effect models. No significant heterogeneity between studies was shown ($I^2 = 4.20\%, P = 0.41$) (Fig. 6).

In the subgroups classified by heart surgery procedures, 10 studies (3, 9, 11, 14, 15, 18, 26, 28, 30, 34) contained 123 patients who received combined coronary artery bypass grafting (CABG) surgery and lung tumor resection, while the other 19 studies (5–8, 10, 12, 13, 16, 17, 19, 20, 24, 25, 27, 29, 31–33, 35) enrolled both CABG surgery and other types of heart surgery procedures. Because CABG surgery and other types of heart surgery procedures were analyzed together in the 19 studies (5–8, 10, 12, 13, 16, 17, 19, 20, 24, 25, 27, 29, 31–33, 35), further assessment of heart surgery procedures other than CABG was not done. So, we quantitatively pooled the data of 123 CABG cases from the 10 studies (3, 9, 11, 14, 15, 18, 26, 28, 30, 34). The pooled proportion of operative mortality of patients who received combined CABG surgery and lung tumor resection was 0.00 (95% CI: 0.00, 0.01) using both fixed-effect and random-effect models. No significant heterogeneity between studies was shown ($I^2 = 0.00\%, P = 0.76$). The pooled proportion of postoperative complications of patients who received combined CABG surgery and lung tumor resection was 0.26 (95% CI: 0.07, 0.50) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 79.80\%, P<0.01$).

To further evaluate the impact of cardiopulmonary bypass on postoperative complications, we compared off-pump with on-pump on postoperative complications of CABG patients. The pooled proportion of postoperative complications of CABG patients using off-pump method was 0.17 (95% CI: 0.01, 0.43) using the random-effect model. Significant heterogeneity between studies was noted ($I^2 = 79.40\%, P<0.01$). The pooled proportion of postoperative complications of CABG patients using on-pump method was 0.61 (95% CI: 0.38, 0.82) using fixed-effect model. No significant heterogeneity between studies was shown ($I^2 = 67.40\%, P = 0.08$) (Fig. 7).

**Sensitivity Analysis And Publication Bias**

Sensitivity analysis showed that no individual study influenced the overall results (Fig. 8). Funnel plot for publication bias of the pooled proportion of postoperative complications for all studies was shown in Fig. 9. Begg's test ($P = 0.42$) and Egger's test ($P = 0.07$) demonstrated non-significant publication bias.

**Discussion**

This systematic review and meta-analysis involved a total of 536 patients who received combined heart surgery and lung tumor resection from 29 observational studies. Our study included comprehensive articles as far as we know. From the comprehensive data we analyzed, we demonstrated that combined heart surgery and lung tumor resection had a low mortality rate and an acceptable complication rate. The incidence rate of reopening for bleeding was quite low. The incidence rates of postoperative respiratory complications were similar to that of cardiac complications. Overall, we believe that combined heart surgery and lung tumor resection is safe with low mortality and complication rate.
Before our research, a systematic review by Tourmousoglou and associates included 15 retrospective studies from 1994–2012 (36). They compared operative mortality rate, reoperation rate, and survival rate between combined and staged surgery for patients with both coronary artery disease and lung cancer. Without quantitative comparison, the authors found that the operative mortality rate of combined procedures was 0–20.8% and of staged procedures was 0–10%. The reoperation rate for bleeding of combined procedures was 0–11% and of staged procedures was 0%. Similar to our results, a more recent systematic review and meta-analysis by Bablekos and co-workers included 22 retrospective studies from 1985–2011 (37). They summarized the operative mortality rate, complication rate, and survival rate of lung cancer patients complicated with heart disease. Without a subgroup analysis of simultaneous or staged surgery, they found the pooled operative mortality rate was 5.26% (95% CI: 3.47, 7.62) and the pooled complication rate was 45.59% (95% CI: 35.62, 55.74).

Patients who undergo combined heart surgery and lung tumor resection face a potential risk of postoperative bleeding. This concern arises from cardiopulmonary bypass (CPB) use during heart surgery and, while performing heart and lung surgery simultaneously, the more complicated surgical procedure. Potential bleeding might relate to excessive heparin use, inadequate heparin neutralization, or platelet dysfunction during CPB (38, 39). Bleeding might arise from the area of the lung resection, extensive mediastinal lymph node dissection and, not less frequently, intrapulmonary hemorrhage (20, 40). Excessive bleeding increases the reexploration rate and eventually increases the mortality and complication rate. Off-pump CABG is one solution to reduce the potential risk of postoperative bleeding. During off-pump CABG, intraoperative heparin dose was reduced and the platelet functions were less affected, leading to decreased bleeding (41). Alternatively, when CPB was necessary, the lung resection and lymph node dissection was best performed before heparinization or after reversal of heparin by protamine sulfate (19, 35). Furthermore, compared with wedge excisions, anatomical resections of the lung were preferred to reduce the risk of intrapulmonary hemorrhage (20, 40).

In the subgroups classified by lung pathology, we focused on patients who underwent combined heart surgery and lung cancer resection. As median sternotomy was often employed as a single incision to perform the cardiac and pulmonary surgery simultaneously, concern existed regarding the safety and adequacy of oncological pulmonary and lymph node resection (6, 8, 14, 17). Through a median sternotomy, left lower lobectomy was technically believed to be the most difficult pulmonary lobectomy (9, 12, 16, 33, 42). The intraoperative view of left lower lobectomy was obscured by the heart. Retraction of the heart was often needed, but possibly leaded to arrhythmias and hemodynamic instability. To facilitate exposure of the left lower lobe, CPB could be used to reduce the heart volume. Also, adding a lateral thoracotomy to the median sternotomy or extending the median sternotomy into the intercostal space could be adopted. Compared with a lateral thoracotomy, mediastinal lymph node dissection was more difficult and technic and time consuming through a median sternotomy. Although systematic mediastinal lymph node dissection could be performed through a median sternotomy, subcarinal and posterior mediastinal lymph nodes were particularity difficult to sample (8, 31). One solution was to open the posterior pericardium and mobilize the right pulmonary artery, allowing a complete dissection of the subcarinal space. Also, adding a lateral thoracotomy to the median sternotomy could be adopted.

In the subgroups classified by heart surgery procedures, we focused on patients who underwent combined CABG surgery and lung tumor resection. We compared off-pump with on-pump on postoperative complications of CABG patients. We found that off-pump CABG could reduce the complication rate. Many disadvantages of CPB have been described. With higher doses of heparin, CPB could increase the risk of bleeding (39). Manufactured from synthetic materials, CPB circuits could impair platelet function and enhance systemic inflammatory response syndrome (43). CPB could cause edema of the peribronchial and lung tissue, as well as lung injury (44–46). CPB could also impair the immune system and promote tumor cell metastasis (47). After eliminating the shortcomings of CPB, off-pump CABG might reduce the complication rate.

Several limitations should be acknowledged in the meta-analysis. First, heterogeneity between included studies was significant, which was likely due to clinical and methodological differences between studies. Second, all included studies were retrospective observational studies. Third, survival data were not included in our study. Our study focused on perioperative measures like incidence rates of operative mortality and postoperative complications.

**Conclusion**

Our systematic meta-analysis demonstrated that combined heart surgery and lung tumor resection had a low mortality rate and an acceptable complication rate. According to the subgroup analysis, although technic and time consuming, most lung cancer patients underwent anatomical resection and mediastinal lymph node sampling or dissection successfully. As for patients receiving combined CABG surgery and lung tumor resection, off-pump CABG could potentially reduce the complication rate compared with on-pump CABG. Considering the limitations of this study, our findings need to be further confirmed in large-scale prospective research.

**Abbreviations**

**CABG**: Coronary artery bypass grafting

**CPB**: Cardiopulmonary bypass
NOS: Newcastle–Ottawa Scale

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
Shizhao Cheng and Yiyao Jiang collected the data and drafted the manuscript.

Shizhao Cheng, Xin Li, Xike Lu, Xun Zhang and Daqiang Sun edited the manuscript, participated in the study design and coordination, and helped to draft the manuscript.

The authors read and approved the final manuscript.

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