



Effects of dexmedetomidine on inflammation and pulmonary function after thoracoscopic surgery for lung cancer: a systematic review and meta-analysis

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Background: Surgical resection is the most effective treatment for lung cancer, but it can also lead to adverse stress reactions in the body. The minimization of lung function damage caused by one-lung ventilation and inflammatory reactions caused by surgery are new challenges faced by the field of anesthesiology. Dexmedetomidine (Dex) has been found to be effective in improving perioperative lung function. In this study, we aimed to conduct a systematic review and meta-analysis to examine the effect of Dex on inflammation and pulmonary function after thoracoscopic surgery for lung cancer.

Methods: A computer-based search was performed to retrieve controlled trials (CTs) about the effects of Dex on inflammation and lung function after thoracoscopic surgery for lung cancer from the databases of PubMed, Embase, Cochrane Library, and Web of Science. The time period for retrieval was set from inception to 1 August 2022. The articles were strictly screened according to the inclusion and exclusion criteria, and data analysis was conducted using the software Stata 15.0.

Results: A total of 11 CTs were included, involving 1,026 patients overall, with 512 assigned to the Dex group and 514 to the control group. The meta-analysis showed that after Dex treatment, the inflammatory factors of patients with lung cancer who underwent radical resection were all decreased: interleukin-6 (IL-6) [standardized mean difference (SMD) = -2.09; 95% confidence interval (CI): -3.03, -1.14; P=0.003], interleukin-8 (IL-8) (SMD = -1.12; 95% CI: -1.54, -0.71; P=0.001), and tumor necrosis factor- α (TNF- α) (SMD = -2.04; 95% CI: -3.24, 0.84; P=0.001). The pulmonary function of the patients was also improved: forced expiratory volume in the first second (FEV1) (SMD = 0.50; 95% CI: 0.24, 0.76; P=0.003), and partial pressure of oxygen (PaO₂) (SMD = 1.00; 95% CI: 0.40, 1.59; P=0.001). However, there was no significant difference between the two groups regarding adverse reactions [relative risk (RR) = 0.68; 95% CI: 0.41, 1.14; P=0.27].

Conclusions: In summary, the use of Dex in lung cancer patients after radical surgery can reduce serum inflammatory factors, and this may play an important role in postoperative inflammatory reaction and improving lung function.

Keywords: Dexmedetomidine (Dex); lung cancer; inflammatory reaction; lung function; meta-analysis

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Introduction

Lung cancer is a common malignant tumor which poses an immense threat to the health and life of those affected. Though decreasing in the United States (US), over the last few years, the incidence rate and mortality of lung cancer worldwide have been on the rise (1,2). The latest statistics show that lung cancer has become the tumor with the highest incidence rate and mortality in China (3). Patients with lung cancer may have clinical symptoms, such as cough, chest pain, chest tightness and shortness of breath, or hemoptysis (4,5). Coupled with smoking related lung injury pulmonary reserve may be compromised. Malnutrition, frailty and metabolic disorders can further increase surgical risk (6). These factors together diminish patient tolerance to surgery and anesthesia (7). Currently, surgical resection remains the most effective method for treating early-stage lung cancer. Baseline lung function as well as the impact of surgery, positive pressure ventilation and single lung isolation affect perioperative lung function and outcomes (8-10). Hypoxemia occurs more frequently during one-lung ventilation, and the degree of ischemia and hypoxia increases as the duration of single lung ventilation exceeds 3 hours. Lung injuries caused by the single lung ventilation can bring secondary harm to patients who have mild-to-moderate abnormal lung function before surgery, and severe cases can eventually develop into acute lung injury (11,12). Moreover, surgical treatment may lead to adverse stress reactions such as activation of inflammatory

reactions, limitation of immune functions, and an increase in the risks of tumor recurrence and metastasis. Minimizing damage caused by one-lung ventilation and inflammatory cascade of the surgical insult are ongoing challenges faced by the perioperative team (13,14).

Dexmedetomidine (Dex), a sedative frequently used in intensive care unit (ICU), can interact and combine with the presynaptic membrane of α_2 adrenergic receptors, and inhibit the release of neurotransmitters in the presynaptic membrane, to produce exact analgesic and sedative effects (15). Dex can also inhibit cell apoptosis, oxidative stress reactions and inflammatory reactions, potentially protecting the heart, the brain, the lungs, and other important organs, improving perioperative pulmonary function. Other study has also reported that Dex can diminish the production of reactive oxygen species (ROS) and the release of cytochrome C in lung tissues, therefore it can reduce the apoptosis of alveolar epithelial cells (16). The influence of Dex on lung injury and inflammatory factors in elderly lung cancer patients who undergo thoracoscopic lobectomy remains unknown. With this meta-analysis we hope to examine the existing data on Dex in lung resection, and consider more aggressive use of Dex for anesthetic management in patients with lung cancer. We present this article in accordance with the PRISMA reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-651/rc>).

Methods

This study has been registered in the PROSPERO platform (No. CRD42022359855).

Literature retrieval

We performed a computer search of the databases of PubMed, Embase, Cochrane Library, Web of Science for controlled trials (CTs) about the effect of Dex on inflammation and lung function after thoracoscopic surgery for lung cancer. The time period for retrieval was set from the inception of the database to 1 August 2022. The search was conducted through medical subject headings (MeSH) plus free text terms. The terms (keywords) used were: dexmedetomidine, precedex, thoracoscopy, and thoracoscopic surgery. The specific retrieval strategies are provided in [Table S1](#). There was no restriction regarding region and/or publication status, and non-English studies were not included in this study.

Highlight box

Key findings

- The use of Dex in lung cancer patients after radical surgery can reduce serum inflammatory factors, which may play a key role in diminishing postoperative inflammatory reaction and improving lung function.

What is known and what is new?

- To minimize lung function damage caused by one-lung ventilation and inflammatory reactions caused by surgery are new challenges in the field of anesthesiology.
- Dex can ameliorate the postoperative lung function of lung cancer patients after radical resection.

What is the implication, and what should change now?

- Dex can reduce the inflammatory response after radical resection for lung cancer. The conclusions we obtained need to be further validated by larger sample, high-quality, multi-center clinical studies.

Inclusion and exclusion criteria

We included the studies that met the following criteria: adults diagnosed with lung cancer; the experimental group was treated with Dex; the primary outcome measures were: interleukin-8 (IL-8), interleukin-6 (IL-6), interleukin-10 (IL-10), and forced expiratory volume in the first second (FEV1); the secondary outcome measures were: partial pressure of oxygen (PaO₂) and adverse events.

The following studies were excluded: conference summaries, systematic reviews, duplicate publications, meta-analyses, animal experiments, case reports; unobtainable full-text.

Data extraction

The literature was screened independently by two researchers based on the inclusion and exclusion criteria. The titles and abstracts of the literature were checked to delete irrelevant studies. Dissents on whether a study should be included, if any, were resolved by a third researcher. Then, the full texts of the remaining articles were downloaded and reviewed to select eligible studies. Relevant data were extracted from the included studies by two independent researchers, who then cross checked their results. The extracted data encompassed the name of first author, experimental design, year of publication, age, country, intervention measures, sample size, and outcome indicators.

Quality evaluation

The quality of the studies included was independently assessed by two researchers utilizing the risk-of-bias assessment tool provided by Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (<https://training.cochrane.org/handbook>), which involves 7 domains: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of the operators and participants (performance bias), blinding of the outcome evaluators (detection bias), integrity of data results (attrition bias), selective reporting of results (reporting bias), and other sources of bias. Each study was evaluated using the above criteria. If the original study fully met the criteria listed above, the overall risk of bias was low, indicating high quality. If the original study only partially met the above criteria, the risk of bias was unclear, indicating moderate quality. If the original study did not meet the above criteria

at all, the risk of bias was high, and the study was of low quality.

Statistical analysis

Meta-analysis was carried out using Stata 15.0 software (StataCorp. L lung cancer, College Station, TX, USA). Continuous variables were presented as weighted mean difference (WMD) and 95% confidence interval (CI), and dichotomous variables were expressed by relative risk (RR) and 95% CI. The heterogeneity test was conducted. $P \geq 0.1$ and $I^2 < 50\%$ suggested low heterogeneity, and the fixed-effects model was utilized. $P < 0.1$ and $I^2 > 50\%$ indicated the presence of heterogeneity, and subgroup analysis and sensitivity analysis were carried out to probe into the sources of heterogeneity. If it was impossible to identify the causes of heterogeneity, a random-effects model was employed for data analysis. The presence of publication bias in the meta-analysis results was determined by whether the funnel chart was symmetrical. A statistically significant difference was considered when $P < 0.05$.

Results

Literature retrieval process results

The retrieval of the databases yielded 268 articles, of which 218 remained after removing duplicates. After reviewing the titles and abstracts, 20 were then retained. According to a full-text reading, 11 (14,17-26) RCTs were finally included. The literature screening process is illustrated in *Figure 1*.

Baseline and quality evaluation of the included literature

In total, 11 CTs were included, involving 1,026 patients. Of them, 512 were in the Dex group and 514 were in the control group. Most of the articles were from China. The amount of Dex used was from 0.2 to 0.5 $\mu\text{g}/(\text{kg}\cdot\text{h})$. *Table 1* displays the specific characteristics of the articles. The risk of bias assessment for the included studies is shown in *Figures 2,3*.

Meta-analysis results

IL-6

A total of 6 (17,19,20,22,24,25) studies mentioned the index of IL-6, involving a total of 646 patients. Heterogeneity testing indicated ($I^2=95.9\%$, $P=0.000$), so the random-

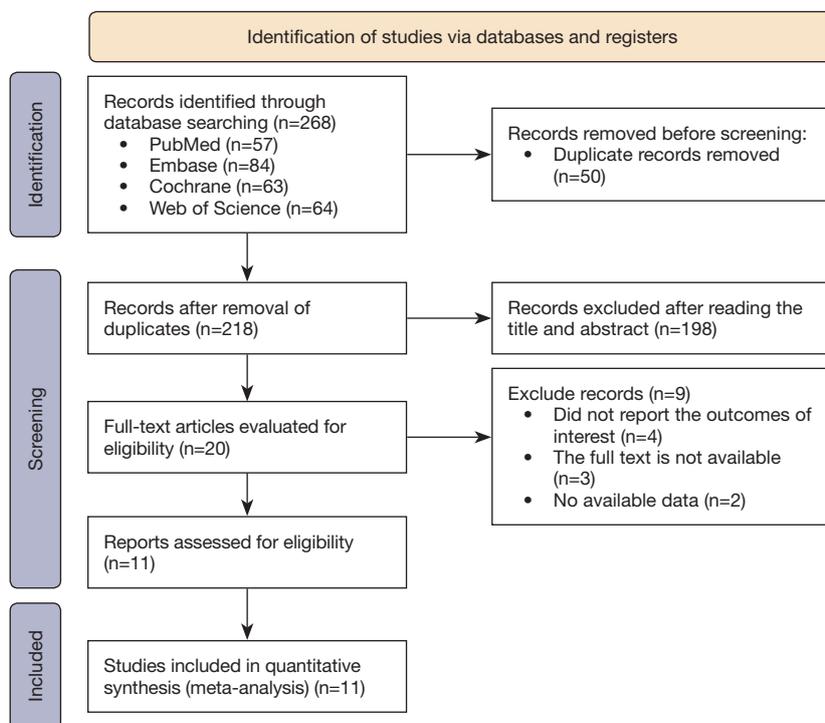


Figure 1 Flow chart of literature retrieval process.

Table 1 Basic characteristics of the included literature

Study	Country	Sample size		Gender (M/F)	Mean age (years)		Intervention		Outcome
		EG	CG		EG	CG	EG	CG	
Ding J, 2022	China	60	60	71/49	68.26	68.52	Dex 0.3 µg/(kg·h)	Saline	IL-6, IL-10, TNF-α, IL-1β, PaO ₂ , PaCO ₂
Shi HX, 2020	China	40	40	80/0	66.4	67.6	Dex 0.2 µg/(kg·h)	Saline	FVC, FEV1, adverse event
Xie Y, 2020	China	58	58	76/40	67.4	68.1	Dex 0.3 µg/(kg·h)	Saline	IL-6, TNF-α, adverse event, IL-8
Kong L, 2018	China	60	60	73/47	40.8	41	Dex 0.5 µg/(kg·h)	Saline	IL-6, TNF-α, IL-8
Meng J, 2020	China	20	20	24/16	52	58	Dex 0.5 µg/(kg·h)	Saline	Adverse event, IL-8
Jannu V, 2020	India	40	40	73/7	54	56	Dex 0.5 µg/(kg·h)	Saline	PaO ₂ , PaCO ₂ , FEV1, adverse event
Chen J, 2021	China	38	38	41/35	55.93	55.64	Dex 0.6 µg/(kg·h)	Saline	FEV1, adverse event
Liu GC, 2020	China	60	60	73/47	65	66	Dex 0.5 µg/(kg·h)	Saline	IL-6, IL-10, TNF-α, IL-8
Lee SH, 2016	Korea	50	50	49/51	62	62	Dex 1.0 µg/(kg·h)	Saline	PaO ₂ , PaCO ₂ , FEV1, adverse event
Kim JA, 2019	Korea	60	60	58/62	63	59	Dex 0.5 µg/(kg·h)	Saline	IL-6, IL-10, TNF-α, PaO ₂ , PaCO ₂ , adverse event, IL-8
Wen QP, 2020	China	26	28	33/21	54	58	Dex 0.4 µg/(kg·h)	Saline	IL-6, adverse event

EG, experimental group; CG, control group; M, male; F, female; Dex, dexmedetomidine; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; PaO₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; IL-8, interleukin-8.

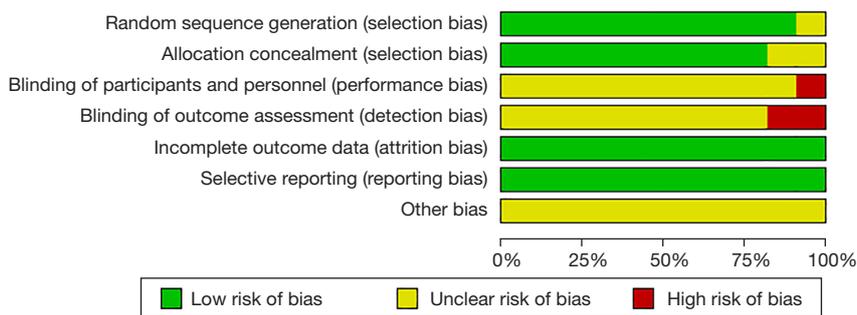


Figure 2 Risk of bias graph.

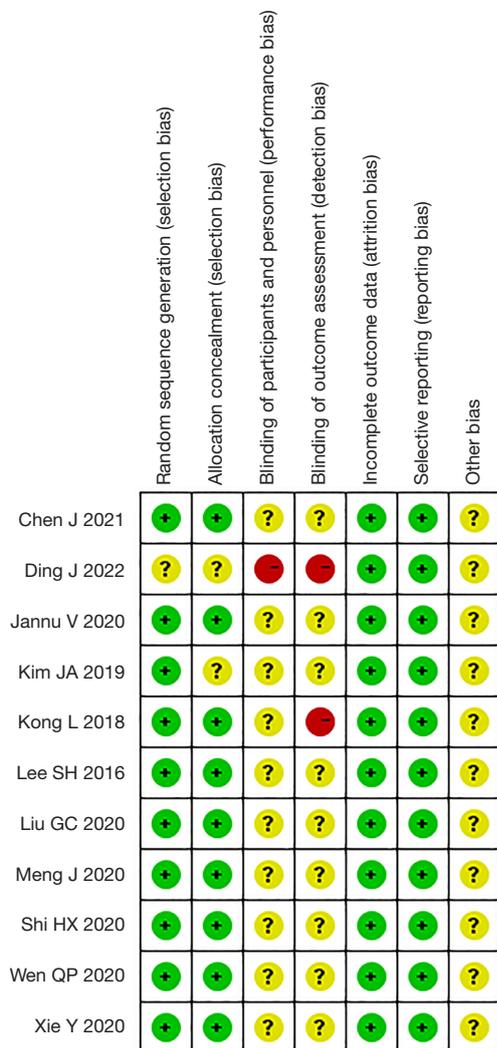


Figure 3 Risk of bias summary.

effects model was employed to conduct data analysis. The results indicated that Dex can significantly reduce IL-6 after lung cancer surgery [standardized mean difference (SMD) = -2.09; 95% CI: -3.03, -1.14], with a statistically significant difference (P=0.003), as shown in Figure 4. Since the heterogeneity of the indicator was more than 50%, sensitivity analysis was carried out by excluding the included studies one by one. The analysis results showed that Ding *et al.* (17) may be the source of heterogeneity, as shown in Figure 5.

IL-8

A total of 5 (19,21,22,24,25) studies mentioned the index of IL-8, involving 512 patients overall. Heterogeneity testing indicated ($I^2=78.5\%$, $P=0.001$), so the random-effects model was utilized for data analysis. The results suggested that Dex was able to significantly reduce IL-8 after lung cancer surgery (SMD = -1.12; 95% CI: -1.54, -0.71), with a statistically significant difference (P=0.001), as shown in Figure 6. Since the heterogeneity of the indicator was more than 50%, sensitivity analysis was carried out by excluding the included studies one by one. The analysis results showed that Kong *et al.* (25) may be the source of heterogeneity, as shown in Figure 7.

Tumor necrosis factor- α (TNF- α)

A total of 5 (17,19,22,24,25) studies mentioned TNF- α as an index, involving 592 cases in total. Heterogeneity testing indicated ($I^2=97.3\%$, $P=0.000$), so data were consolidated and analyzed using the random effects model. The results showed that Dex reduced TNF- α after lung cancer surgery

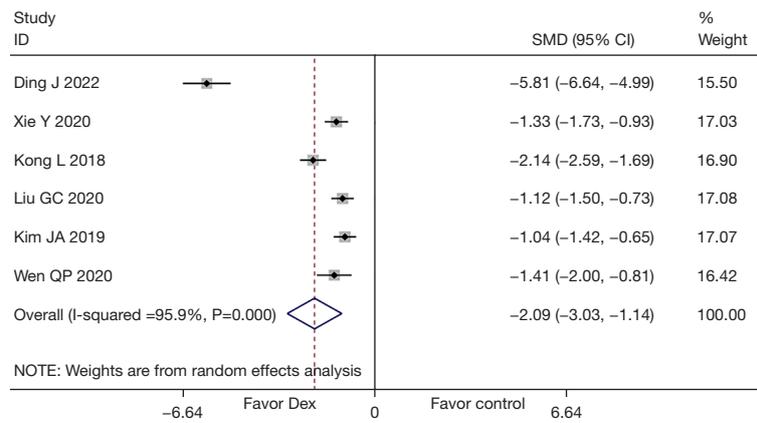


Figure 4 IL-6 meta-analysis forest plot. SMD, standardized mean difference; CI, confidence interval; Dex, dexmedetomidine; IL-6, interleukin-6.

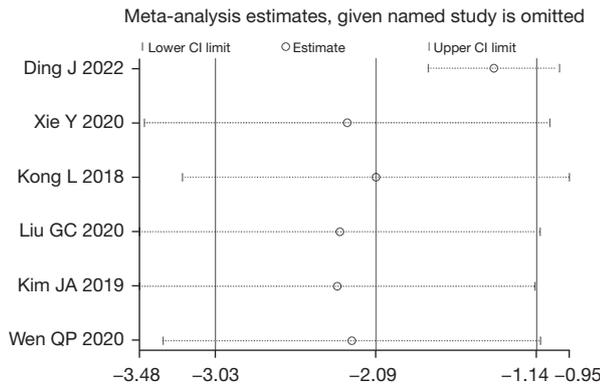


Figure 5 IL-6 sensitivity analysis. CI, confidence interval; IL-6, interleukin-6.

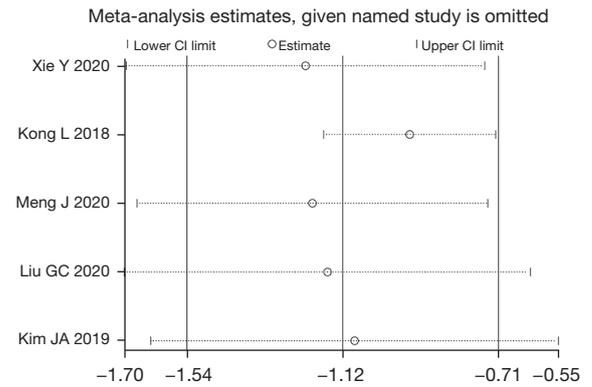


Figure 7 IL-8 sensitivity analysis. CI, confidence interval; IL-8, interleukin-8.

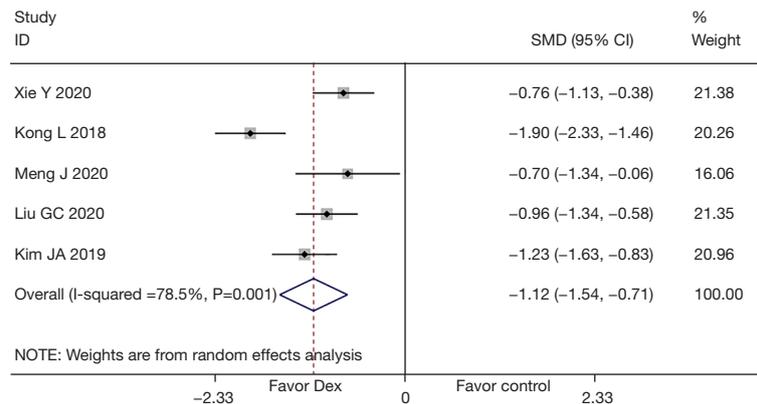


Figure 6 IL-8 meta-analysis forest plot. SMD, standardized mean difference; CI, confidence interval; Dex, dexmedetomidine; IL-8, interleukin-8.

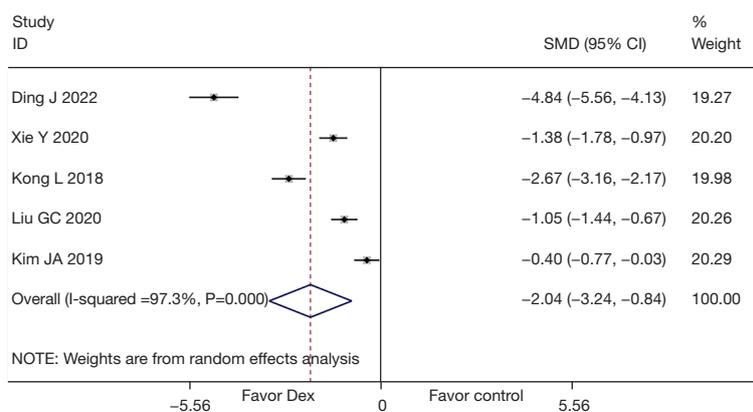


Figure 8 TNF- α analysis forest plot. SMD, standardized mean difference; CI, confidence interval; Dex, dexmedetomidine; TNF- α , tumor necrosis factor- α .

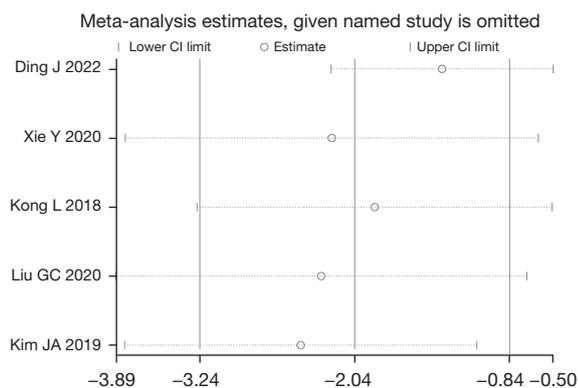


Figure 9 TNF- α sensitivity analysis. CI, confidence interval; TNF- α , tumor necrosis factor- α .

(SMD = -2.04; 95% CI: -3.24, -0.84), and the difference was statistically significant ($P=0.001$), as shown in *Figure 8*. Since the heterogeneity of the indicator was more than 50%, sensitivity analysis was carried out by excluding the included studies one by one. The analysis results showed that the sensitivity of this indicator was small and that the analysis results were stable, as shown in *Figure 9*.

FEV1

A total of 4 (14,18,23,26) studies mentioned FEV1 as an index, involving 336 patients in total. Heterogeneity testing indicated ($I^2=30.1%$, $P=0.231$), so the random-effects model was adopted to conduct data analysis. The results showed that Dex increased FEV1 after lung cancer surgery (SMD = 0.50, 95% CI: 0.24, 0.76), with a statistically significant difference ($P=0.003$), as illustrated in *Figure 10*.

PaO₂

A total of 4 (17,23,24,26) studies mentioned the FEV1 index, involving 420 patients in total. Heterogeneity testing indicated ($I^2=88.0%$, $P=0.000$), so the random-effects model was employed for data analysis. The results demonstrated that Dex increased PaO₂ after lung cancer surgery (SMD = 1.00, 95% CI: 0.40, 1.59), and the difference was statistically significant ($P=0.001$), as illustrated in *Figure 11*. Since the heterogeneity of the indicator was more than 50%, sensitivity analysis was carried out by excluding the included studies one by one. The analysis results showed that the sensitivity of this indicator was small and that the analysis results were stable, as shown in *Figure 12*.

Adverse reactions

A total of 8 (14,18-21,23,24,26) studies mentioned the indicator of adverse reactions, involving 666 patients in all. Heterogeneity testing indicated ($I^2=57.1%$, $P=0.022$), so the random-effects model was adopted for data analysis. The results revealed that regarding adverse reactions after lung cancer surgery, no significant difference was found between Dex treatment and the control group (RR = 0.68; 95% CI: 0.41, 1.14; $P=0.27$), as illustrated in *Figure 13*. Since the heterogeneity of the indicator was more than 50%, sensitivity analysis was carried out by excluding the included studies one by one. The analysis results showed that the sensitivity of this indicator was small and that the analysis results were stable, as shown in *Figure 14*.

Publication bias

Funnel charts were drawn for IL-6 and adverse reactions,

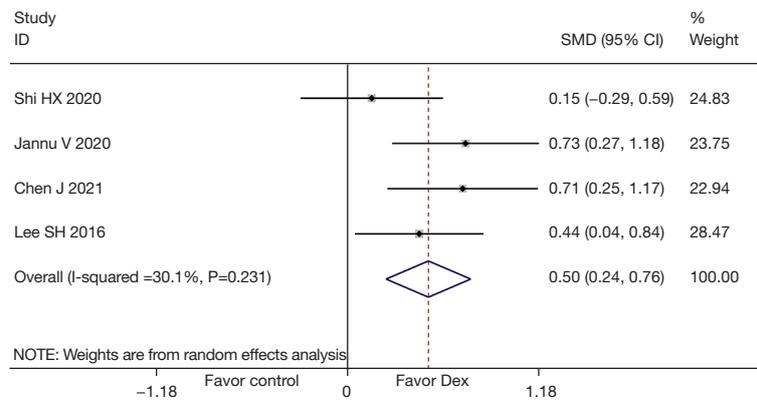


Figure 10 FEV1 meta-analysis forest plot. SMD, standardized mean difference; CI, confidence interval; Dex, dexmedetomidine; FEV1, forced expiratory volume in the first second.

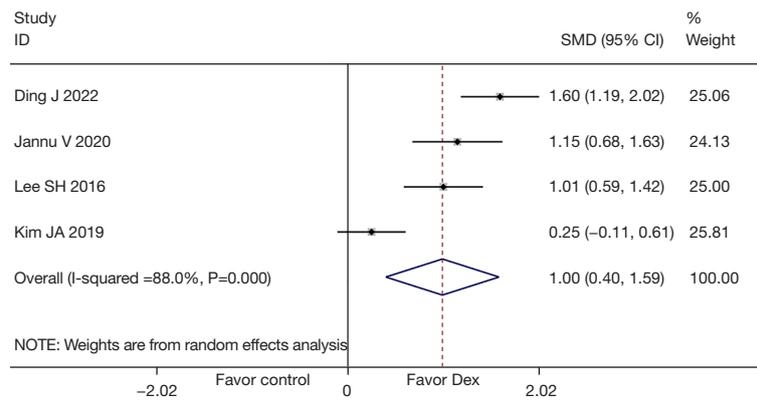


Figure 11 PaO₂ meta-analysis forest plot. SMD, standardized mean difference; CI, confidence interval; Dex, dexmedetomidine; PaO₂, partial pressure of oxygen.

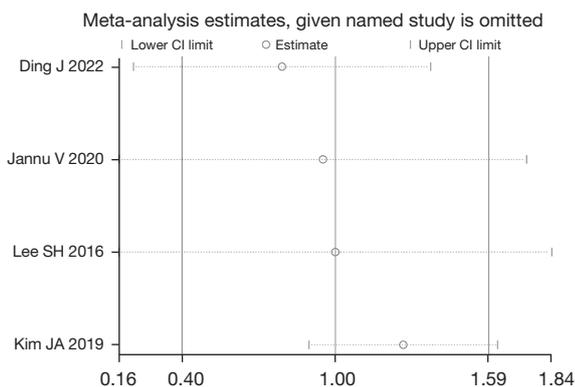


Figure 12 PaO₂ sensitivity analysis. CI, confidence interval; PaO₂, partial pressure of oxygen.

to conduct publication bias evaluation. The analysis results showed that the two sides of the funnel charts for IL-6 and adverse reactions were not completely symmetrical, suggesting that there was great possibility of publication bias for these two indicators (Figures S1,S2).

Discussion

In total, 11 RCTs were included in this study. The results showed that after Dex treatment, inflammatory factors IL-6 (SMD =-2.09; 95% CI: -3.03, -1.14; P=0.003), IL-8 (SMD =-1.12; 95% CI: -1.54, -0.71; P=0.001), and TNF-α (SMD =-2.04; 95% CI: -3.24, -0.84) were all decreased in

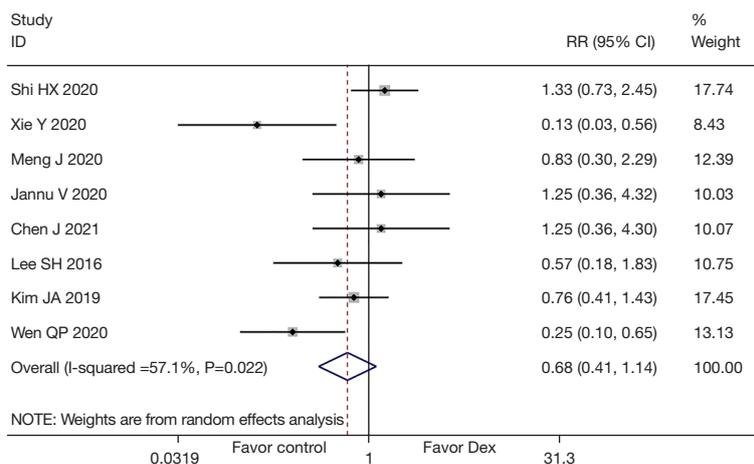


Figure 13 Forest plot of adverse reactions meta-analysis. RR, relative risk; CI, confidence interval; Dex, dexmedetomidine.

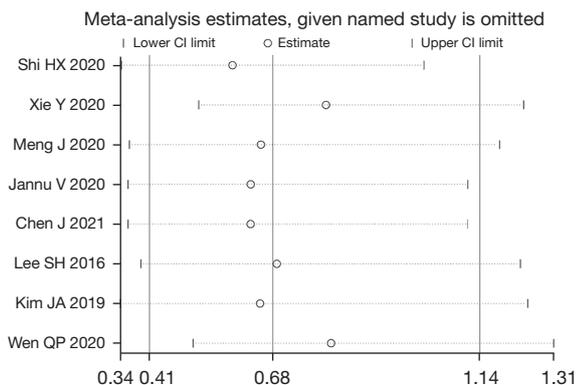


Figure 14 Sensitivity analysis of adverse reactions. CI, confidence interval.

lung cancer patients who received curative intent surgical resection. When lung cancer surgery is performed with one-lung ventilation, distribution of perfusion is altered, causing local hypoxia and increasing the number of alveolar macrophages and pulmonary neutrophils. This results in increased synthesis and release of proinflammatory factors and intercellular adhesion molecules (15,27). Taniguchi *et al.* (28) found in a rat model of endotoxin-induced shock that Dex can significantly reduce the level of serum inflammatory factors TNF- α and IL-6, in a dose- and time-dependent manner, and improve the survival rate of animals. Further studies confirmed that pretreatment with Dex significantly reduced the level of serum inflammatory factors TNF- α , IL-6, and IL-8 in endotoxemia rats. This suggests that Dex may, through increasing vagal efferent impulse, cause nerve endings to release acetylcholine

(ACh) and bind to $\alpha 7$ ACh receptor ($\alpha 7$ AChR) located in immune cells. In turn, this inhibits the release of the above inflammatory cytokines, thus playing an anti-inflammatory and protective role (29,30). In 2011, Zhang *et al.* (31) found that when the choice for the loading dose of Dex was 1.0 $\mu\text{g}/\text{kg}$ before anesthesia induction, and 0.5 $\mu\text{g}/\text{kg}$ for the maintenance of anesthesia, the concentration of serum IL-6 and IL-8 decreased during anesthesia. The above research also further confirmed our conclusion, that Dex can reduce the inflammatory response after resection for lung cancer.

Resection with curative intent for lung cancer entails the removal of all the tumor and systematic lymph node dissection. The standard of care and the most common surgical treatment is lobectomy, though sub-lobar resection has become increasingly utilized in very small tumors. Surgical manipulation coupled with one-lung ventilation can induce significant tissue inflammatory reaction. A multitude of inflammatory factors then enter the alveoli, which destroy the alveolar-capillary barrier, change the permeability, and cause interstitial edema, which then leads to reduced lung ventilation and diffusion function (32). In addition, during one-lung ventilation, the reduction of the collapsed lung's ventilation will cause hypoxemia in the body, resulting in imbalance of lung ventilation (33). Our present study revealed that Dex can increase FEV1 (SMD =0.50; 95% CI: 0.24, 0.76; P=0.003) and PaO₂ (SMD =1.00; 95% CI: 0.40, 1.59; P=0.001) in patients diagnosed with lung cancer who have undergone resection, indicating that Dex may ameliorate the postoperative lung function of lung cancer patients after radical resection, the likely mechanism is reduction of pulmonary inflammation. Our study found

that there was no statistically significant difference in adverse reactions regarding the use of Dex in postoperative lung cancer patients (RR =0.68; 95% CI: 0.41, 1.14; P=0.27). A possible reason may be that the elimination half-life of Dex is relatively short, yet the time period for which we have documented adverse reactions was longer than the half-life. This study also has the following limitations. First, there was important heterogeneity among the included studies. However, in view of the limited data provided by the original studies, it was impossible to identify the source of heterogeneity through the method of different subgroup analyses. In addition, the type of surgery in each study was different, and the size of trauma caused by different surgeries was also different, which also leads to different degrees of inflammatory reaction. Second, the number of individuals included in the studies was small, and the dose of Dex varied, which can lead to potential heterogeneity. Third, most of the included literature presented multiple potential biases, such as unclear randomization, unclear blinding, and/or unclear allocation concealment.

Conclusions

In summary, the use of Dex in lung cancer patients with surgery for curative intent can reduce serum inflammatory factors, which may play a key role in diminishing postoperative inflammatory reaction and improving lung function. Limited by the quantity and quality of the studies that were included, the conclusions we have obtained need to be further validated by larger sample, high-quality, multi-center clinical studies.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-651/rc>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-651/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-651/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 The specific retrieval strategies

Search number	Query	Results
1	“Thoracoscopy”[MeSH]	16,095
2	((((((((((Thoracoscopy[Title/Abstract]) OR (Thoracoscopies[Title/Abstract])) OR (Pleural Endoscopy[Title/Abstract])) OR (Pleuroscopy[Title/Abstract])) OR (Pleuroscopies[Title/Abstract])) OR (Endoscopy, Pleural[Title/Abstract])) OR (Endoscopies, Pleural[Title/Abstract])) OR (Pleural Endoscopies[Title/Abstract])) OR (Surgical Procedure, Thoracoscopic[Title/Abstract])) OR (Thoracoscopic Surgical Procedure[Title/Abstract])) OR (Thoracoscopic Surgery[Title/Abstract])) OR (Surgery, Thoracoscopic[Title/Abstract])) OR (Surgeries, Thoracoscopic[Title/Abstract])) OR (Thoracoscopic Surgeries[Title/Abstract]))	20,578
3	#1 OR #2	25,279
4	“Dexmedetomidine”[MeSH]	4,936
5	(((((Dexmedetomidine[Title/Abstract]) OR (MPV-1440[Title/Abstract])) OR (MPV 1440[Title/Abstract])) OR (MPV1440[Title/Abstract])) OR (Precedex[Title/Abstract])) OR (Dexmedetomidine Hydrochloride[Title/Abstract])) OR (Hydrochloride, Dexmedetomidine[Title/Abstract]))	7,760
6	#4 OR #5	7,993
7	#3 AND #6	57

MeSH, medical subject headings.

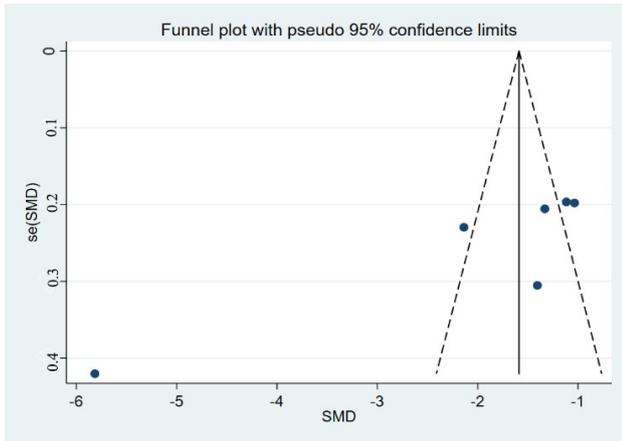


Figure S1 Funnel chart of IL-6. SMD, standardized mean difference; IL-6, interleukin-6.

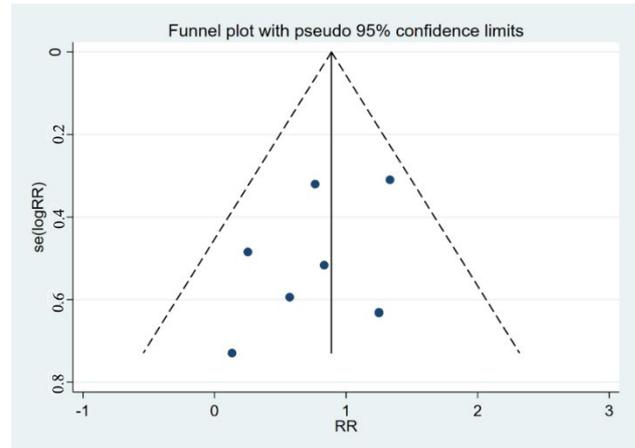


Figure S2 Funnel chart of adverse reactions. RR, relative risk.