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META-ANALYSIS

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Risk factors for acute exacerbation of interstitial lung disease following lung cancer resection: a systematic review and meta-analysis

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Key question

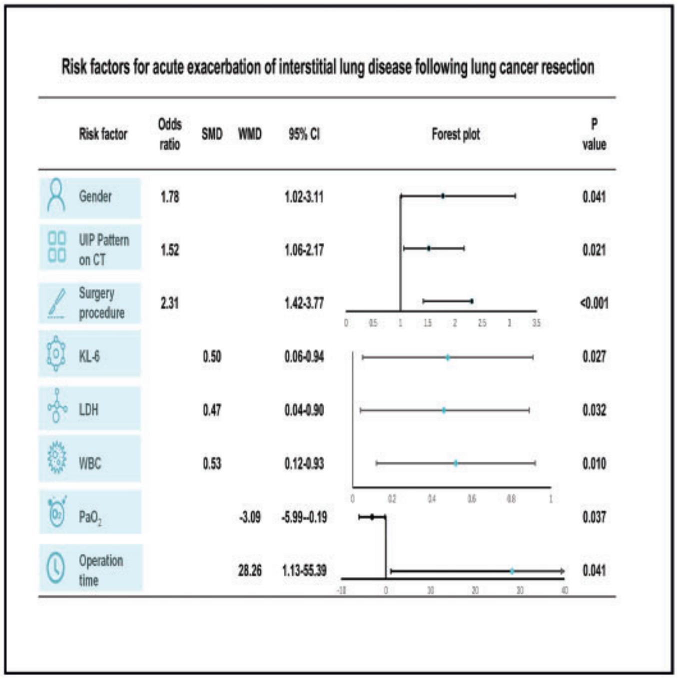
What are the risk factors for acute exacerbation of interstitial lung disease following lung cancer resection?

Key finding(s)

Risk factors are being male, pattern on CT, KL-6, WBC, LDH, partial pressure of oxygen, surgical procedure and operating time.

Take-home message

Patients with these risk factors should be more prudently selected for surgical treatment and should be monitored more carefully after surgery.



Abstract

OBJECTIVES: The aim of this study was to investigate the risk factors for acute exacerbation (AE) of interstitial lung disease (ILD) following lung cancer resection.

METHODS: We performed a literature screening on the databases including PubMed, Embase, Ovid MEDLINE® and the Web of Science for related studies published up to January 2021. Eligible studies were included and data on risk factors related to postoperative AE were extracted. All analyses were performed with random-effect model.

RESULTS: A total of 12 studies of 2655 lung cancer patients with ILD were included in this article. The meta-analysis indicated that male [odds ratios (ORs) = 1.78, 95% confidence interval (CI): 1.02–3.11, $P = 0.041$], usually interstitial pneumonia pattern on CT (OR = 1.52, 95%

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CI: 1.06–2.17, $P = 0.021$), Krebs von den Lungen-6 [standardized mean difference (SMD) = 0.50, 95% CI: 0.06–0.94, $P = 0.027$], white blood cell (SMD = 0.53, 95% CI: 0.12–0.93, $P = 0.010$), lactate dehydrogenase (SMD = 0.47, 95% CI: 0.04–0.90, $P = 0.032$), partial pressure of oxygen (weighted mean difference = -3.09, 95% CI: -5.99 to -0.19, $P = 0.037$), surgery procedure (OR = 2.31, 95% CI: 1.42–3.77, $P < 0.001$) and operation time (weighted mean difference = 28.26, 95% CI: 1.13–55.39, $P = 0.041$) were risk factors for AE of ILD following lung cancer resection.

CONCLUSIONS: We found that males, usually interstitial pneumonia pattern on CT, higher levels of Krebs von den Lungen-6, lactate dehydrogenase, white blood cell, lower partial pressure of oxygen, greater scope of operation and longer operation time were risk factors for AE of ILD following lung cancer resection. Patients with these risk factors should be more prudently selected for surgical treatment and be monitored more carefully after surgery.

Keywords: Interstitial lung disease • Lung cancer surgery • Acute exacerbation • Postoperative complications • Risk factors

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ABBREVIATIONS

AE	Acute exacerbation
CI	Confidence interval
ILD	Interstitial lung disease
KL-6	Krebs von den Lungen-6
LDH	Lactate dehydrogenase
ORs	Odds ratios
SMD	Standardized mean difference
UIP	Usually interstitial pneumonia
WBC	White blood cell
WMD	Weighted mean difference

INTRODUCTION

Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease, is characterized by progressive dyspnoea and irreversible deterioration of lung function [1, 2]. It is already known that ILD shares similar risk factors and pathophysiological processes with lung cancer [3, 4], and there have been studies confirming that the relative risk of lung cancer in patients with ILD is 3.5–7.8 times that of the general population [5–9].

Surgery is recommended by the guidelines as one of the treatment strategies for lung cancer patients with ILD [10]. However, it may cause acute exacerbation (AE) of ILD after surgery, which often requires more intensive care and may cause serious consequences. A multicentre retrospective study [11] found that the incidence of postoperative AE of ILD in lung cancer patients with ILD was 9.3% [95% confidence interval (CI): 8.0–10.8]. In other single-institution studies, the incidence may be as high as 32.1% [12]. Although the postoperative 30-day mortality rate of lung cancer patients has gradually decreased in recent years [13], it was 43.9% among the population with AE of ILD [11], which was the leading course of death after lung cancer surgery [14]. Therefore, exploring the risk factors for AE of ILD following lung cancer resection is of great significance for surgeons to weigh the pros and cons of surgery and prevent postoperative AE.

Although existing studies have found some risk factors for AE of ILD following lung cancer resection, such as surgical methods, lung function, gender and tumour location, the conclusions were inconsistent and the number of included patients was limited [11, 15–17]. The purpose of this systematic review and meta-analysis is to explore the risk factors for AE of ILD following lung cancer resection.

METHODS

Search strategy

This study was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

According to the guidelines for performing meta-analyses, we performed a comprehensive literature screening on the acknowledged databases including PubMed, Embase, Ovid MEDLINE® and the Web of Science for related studies published up to January 2021. Search strategy was comprised of 'lung cancer', 'surgery', 'interstitial lung disease', 'interstitial pneumonia', 'interstitial lung disease'. The following search items were used in PubMed: ((((interstitial lung disease [Title/Abstract]) OR (interstitial pneumonia [Title/Abstract])) OR (interstitial lung disease [Title/Abstract])) AND (lung cancer [Title/Abstract])) AND (surgery).

Inclusion and exclusion criteria

We included studies that fulfilled the following criteria: (i) all included adult patients were diagnosed with lung cancer by pathology and ILD by computed tomography or pathology; (ii) all included adult patients were treated with surgery; (iii) studies including risk factors of AE of ILD following lung cancer resection; and (iv) full-text publication in English.

Studies were excluded if they met one or more of the following criteria: (i) case report, letter, experimental studies, review, conference abstract and introduction; (ii) comparable data could not be extracted; and (iii) basic essential data were incomplete.

Data abstraction and outcome measures

Two experienced researchers (Jianqi Hao and Cong Chen) independently analysed finally defined articles for primary parameters, which indicated the risk factor of ILD and secondary parameters concerning the basic information of the article. The basic information data abstracted from eligible studies included the year of publication and first author's name, country, number of patients, type of studies and so on. The related risk factor parameters, including gender, age, cancer stage, tumour location, surgery procedure, lung functions and laboratory examination, were abstracted into a standard data table.

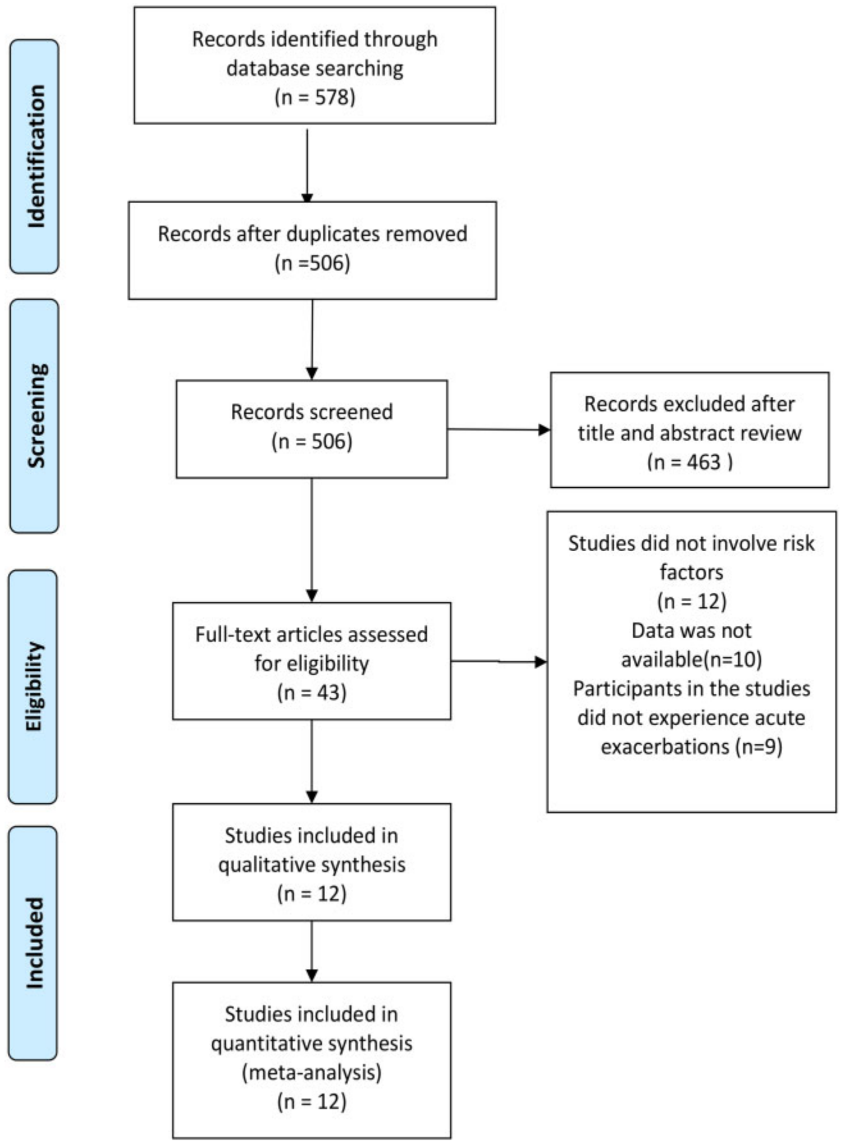

Figure 1: Flow chart of the identification of relevant studies.

QUALITY ASSESSMENT AND PUBLISH BIAS

The Newcastle–Ottawa Scale was used to assess the quality of original non-randomized studies by 2 researchers (Jianqi Hao and Cong Chen). The scale includes 3 aspects of evaluation: selection, comparability and exposure. The high-quality studies were defined as with at least 8 stars. Studies with at least 6 stars were included in our meta-analysis. If there were any discrepancies, they would be solved by discussion or consultation with a 3rd reviewer (Xiaohu Hao). To assess publication bias, funnel plots were generated for each result.

Statistical analysis

RevMan 5.3 software (freeware available from The Cochrane Collaboration, http://www.ccims.net/revman/download) and STATA version 16.0 (Stata Corp, College Station, TX, USA) were used to perform all the statistical data analysis. Weighted mean difference (WMD) or standardized mean difference (SMD) and 95% CI were used for continuous variables. Comparative odds ratios (ORs) were reported with their associated 95% CI for the dichotomous variable. The I^2-statistic was used to assess the extent of heterogeneity of the included studies. All analyses were performed with random-effect model. A funnel plot was generated for each result. A value of $P < 0.050$ was considered statistically significant.

RESULTS

Included studies and characteristics

After a comprehensive literature screening, database searches retrieved 578 results, with 43 full-text articles assessed for eligibility. Twelve were in conformity with the inclusion criteria and included in our analysis (Fig. 1).

The basic information is shown in Table 1. The included studies were published from 2004 to 2020. A total of 2655 lung cancer patients with ILD were included in our analysis. ILD was

Table 1: Characteristics of the included studies

Author	Year	Country	Sample size	No. acute exacerbation, n (%)	Recruitment period	Diagnosis of interstitial lung disease	Quality assessment
Fukui et al. [15]	2020	Japan	337	14 (4.2)	2009–2018	CT	8
Iyoda et al. [18]	2011	Japan	22	5 (22.7)	NA	Prior patient history, CT, Pathology	7
Kanzaki et al. [19]	2011	Japan	40	12 (30)	2001–2009	CT, Pathology	8
Kobayashi et al. [16]	2016	Japan	137	17 (12.4)	2006–2015	CT, Pathology	8
Koizumi et al. [20]	2004	Japan	47	7 (14.9)	1982–2003	CT	8
Maniwa et al. [21]	2013	Japan	89	8 (9.0)	2002–2011	CT	8
Oishi et al. [22]	2020	Japan	31	5 (16.1)	2012–2017	CT	8
Sato et al. [11]	2013	Japan	1763	164 (9.3)	2000–2009	Prior patient history, CT, Pathology	8
Shintani et al. [23]	2010	Japan	40	6 (15.0)	1990–2005	Pathology	8
Suzuki et al. [12]	2011	Japan	28	9 (32.1)	2000–2006	CT, Pathology	8
Taniguchi et al. [24]	2017	Japan	59	5 (8.5)	1994–2013	Prior patient history, CT	8
Yano et al. [17]	2012	Japan	62	6 (9.7)	2004–2009	HRCT	8

NA: not available; HRCT: high-resolution computed tomography.

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mainly diagnosed by CT and pathology. Finally, we focused on the risk factors that may be associated with AE of ILD after lung cancer surgery.

Positive risk factors for acute exacerbation of interstitial lung disease

Gender. Twelve studies with 2655 patients reported the association between gender and AE of ILD after lung cancer surgery [11, 12, 15–24]. The result showed that male lung cancer patients with ILD may be more prone to suffer from AE of ILD than females (OR = 1.78, 95% CI: 1.02–3.11, $P = 0.041$) (Fig. 2A).

Usually interstitial pneumonia pattern on CT. Four articles involving 2299 patients reported the high risk of AE of ILD among lung cancer patients with usually interstitial pneumonia (UIP), which corresponded with our combined analysis (OR = 1.52, 95% CI: 1.06–2.17, $P = 0.021$) (Fig. 2B) [11, 15–17].

Laboratory examination. We also studied the role of laboratory examination in the postoperative AE of lung cancer patients with ILD. After a combined analysis of 568, 587 and 208 patients, respectively, we found that serum Krebs von den Lungen-6 (KL-6), white blood cell (WBC) and lactate dehydrogenase (LDH) might be potential risk factors for AE of ILD following lung cancer surgery (SMD = 0.50, 95% CI: 0.06–0.94, $P = 0.027$; SMD = 0.53, 95% CI: 0.12–0.93, $P = 0.010$; SMD = 0.47, 95% CI: 0.04–0.90, $P = 0.032$, respectively) (Figs 2C and D and 3A). A high level of those markers generally predicts a high risk of AE after surgery. C-reactive protein may not be a risk factor (WMD = 0.61, 95% CI: -0.32 to 1.55, $P = 0.200$) (Supplementary Material, Fig. S1A).

Blood gas analysis. Many researchers thought that blood gas analysis might be an effective predictor for AE of ILD after lung cancer surgery. However, according to our combined analysis of 5 studies with 511 patients [12, 15, 20, 23, 24], only partial pressure of oxygen was a risk factor for AE, while partial pressure of carbon dioxide was not (WMD = -3.09, 95% CI: -5.99 to -0.19, $P = 0.037$; WMD = 0.13, 95% CI: -1.25 to 1.51, $P = 0.854$, respectively) (Fig. 3B and Supplementary Material, Fig. S1B).

Surgery procedure. Nine articles with 2527 patients studied the association between surgery procedure and AE of ILD after lung cancer surgery [11, 15–21, 23]. Our result suggested that patients undergoing sublobar resection were less likely to have AE of ILD. The greater the scope of surgery, the higher the incidence of acute postoperative exacerbations (OR = 2.31, 95% CI: 1.42–3.77, $P < 0.001$) (Fig. 3C).

Time of operation. Operation time is an essential factor affecting postoperative complications. Six studies with 576 patients reported the relationship between the operation time and AE of ILD following lung cancer resection [15, 17, 19, 20, 22, 24]. We found that operation time was a risk factor for AE (WMD = 28.26, 95% CI: 1.13–55.39, $P = 0.041$) (Fig. 3D).

Negative risk factors for acute exacerbation of interstitial lung disease

Pulmonary function. We also studied the relationship between pulmonary function and AE after surgery. The result showed that percentage of vital capacity (MD = -7.70, 95% CI: -16.60 to 1.21, $P = 0.090$), forced expiratory volume in 1 s (SMD = -0.01, 95% CI: -0.33 to 0.31, $P = 0.955$), % of forced expiratory volume in 1 s (WMD = 0.33 95% CI: -3.74 to 4.41, $P = 0.873$) and % of diffusion capacity for carbon monoxide (WMD = -3.16, 95% CI: -12.5 to 6.17, $P = 0.506$) might not be risk factors for AE of ILD.(Supplementary Material, Figs S1C and D and S2A and B).

Tumour location. We initially suspected that different tumour locations might affect the prognosis of patients, so we extracted the data of tumour location from 4 related studies with 248 patients [18, 20, 21, 24]. The result showed no significant difference in the incidence of AE of ILD following lung cancer resection whether the tumour was in the left or right lobe (OR = 1.29, 95% CI: 0.51–3.24, $P = 0.594$) (Supplementary Material, Fig. S2C).

The stage for lung cancer. Six articles with 507 patients studied the relationship between pathological cancer staging and AE [15, 17, 19–21, 23]. We found that the pathological stage was not the risk factor for postoperative AE (OR = 0.71, 95% CI: 0.38–1.35, $P = 0.296$) (Supplementary Material, Fig. S2D).

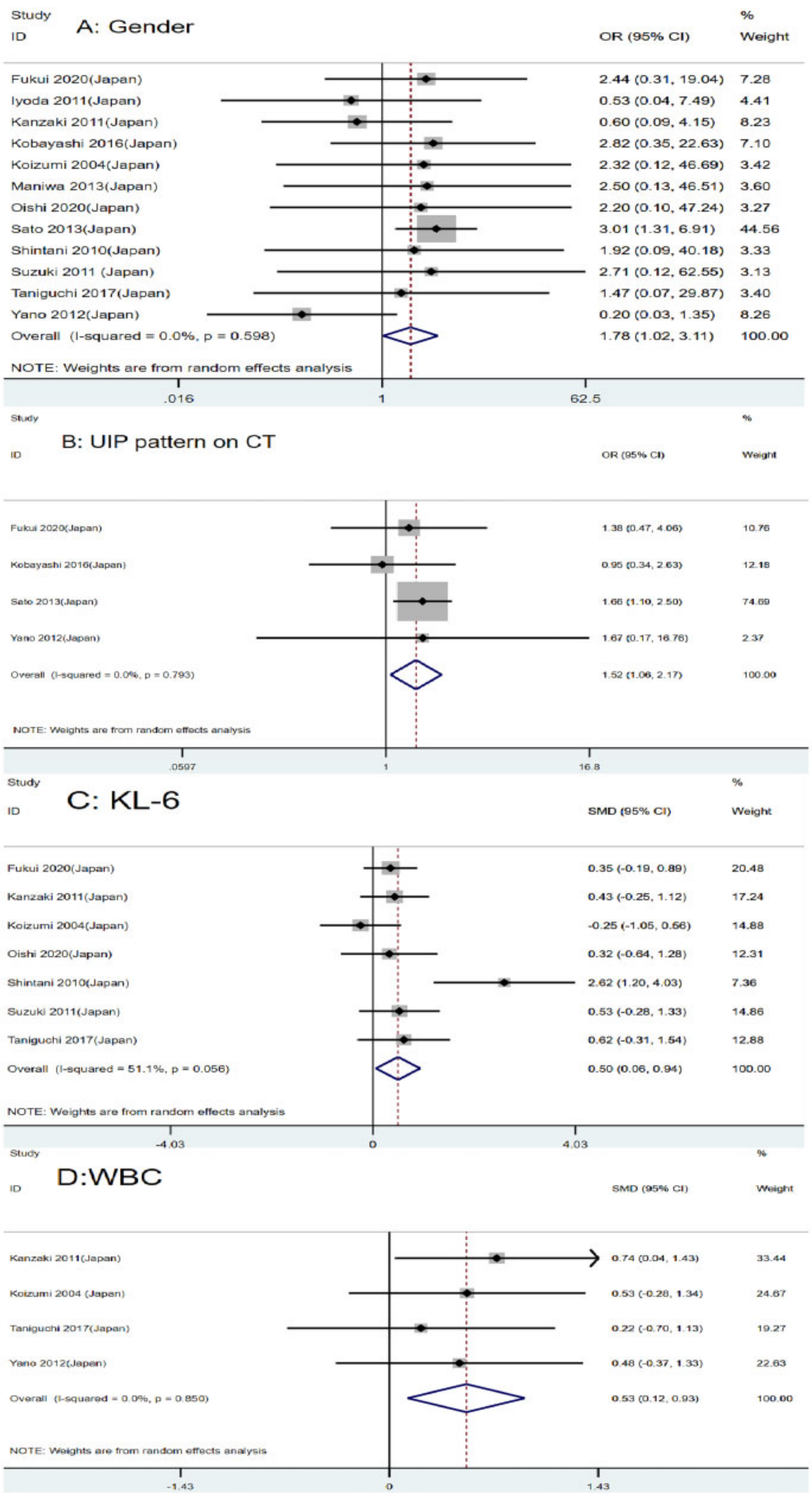

Figure 2: Forest plot of the potential risk factors of acute exacerbation of interstitial lung disease following lung cancer resection: (**A**) gender; (**B**) usually interstitial pneumonia pattern on CT; (**C**) Krebs von den Lungen-6; and (**D**) white blood cell.

Quality assessment and publication bias. Standard quality evaluation of the 12 included studies was performed based on the Newcastle–Ottawa Scale. According to the evaluating system, the 12 included studies were reliable (Table 2). The funnel plot indicated that there was no publication bias in these studies (Supplementary Material, Fig. S3).

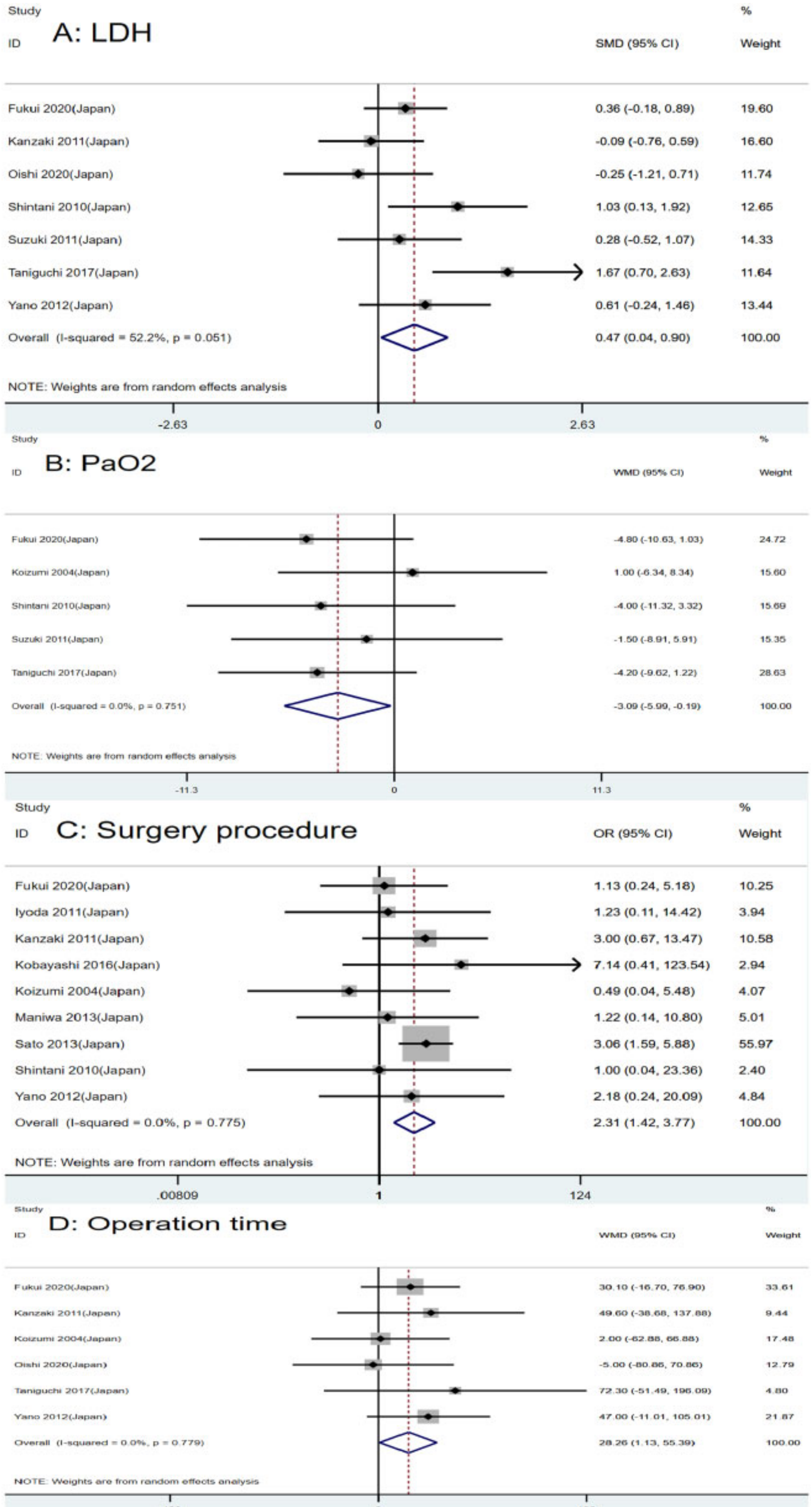

Figure 3: Forest plot of the potential risk factors of acute exacerbation of interstitial lung disease following lung cancer resection: (**A**) lactate dehydrogenase; (**B**) partial pressure of oxygen; (**C**) surgery procedure; and (**D**) operation time.

DISCUSSION

Postoperative AE of ILD was defined as those that occur within 30 days after surgery and cannot be explained by lung infections or other diseases, progressive dyspnoea, increasing interstitial shadows on chest CT or X-ray, and decreased blood oxygen partial pressure by >10 mmHg [10, 25]. The pulmonary function of patients with ILD and lung cancer is often significantly impaired,

Table 2: Result of the quality assessment by the Newcastle–Ottawa Scale

Study	Selection				Comparability	Outcome			Total
	Case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Fukui *et al.* [15]	*	*	*	*	*	*	*	*	8
Iyoda *et al.* [18]	*	*	*	*	–	*	*	*	7
Kanzaki *et al.* [19]	*	*	*	*	*	*	*	*	8
Kobayashi *et al.* [16]	*	*	*	*	*	*	*	*	8
Koizumi [20]	*	*	*	*	*	*	*	*	8
Maniwa *et al.* [21]	*	*	*	*	*	*	*	*	8
Oishi *et al.* [22]	*	*	*	*	*	*	*	*	8
Sato *et al.* [11]	*	*	*	*	*	*	*	*	8
Shintani *et al.* [23]	*	*	*	*	*	*	*	*	8
Suzuki *et al.* [12]	*	*	*	*	*	*	*	*	8
Taniguchi *et al.* [24]	*	*	*	*	*	*	*	*	8
Yano *et al.* [17]	*	*	*	*	*	*	*	*	8

*This criterion is met.

and surgery is likely to be a fatal blow to induce the AE of ILD. However, there is no recognized predictor, which is an urgent problem for surgeons to identify patients prone to AE of ILD following lung cancer surgery. As far as we know, this is the first meta-analysis to explore risk factors of AE of ILD following lung cancer surgery. In this study, 8 factors were found to be the potential risk factors for AE of ILD following lung cancer surgery: gender, UIP pattern on CT, KL-6, LDH, WBC, partial pressure of oxygen, surgery procedure and operation time.

Laboratory examination, chest radiography and spirometry are the most important objective preoperative assessment of lung cancer patients. KL-6, a circulating glycoprotein secreted by alveolar epithelium and bronchial epithelium, is a crucial serum biomarker to assess the activity of interstitial pneumonia [26]. KL-6 can predict the survival outcomes of ILD patients without lung cancer and the early clinical effectiveness of therapy [27–29]. This study confirmed that KL-6 was a significant risk factor for postoperative AE. LDH is also a biomarker of interstitial pneumonia activity and can be used to predict postoperative AE [23, 30, 31]. However, the elevation of LDH is gradual and often occurs in the late stage of the disease, so it may not be suitable as an early predictive marker [32]. Other serum biomarkers such as surfactant proteins A and D may also have predictive effects [33], but they were not included in our analysis due to the small number of studies. We found that patients diagnosed with UIP based on preoperative chest CT were more likely to experience postoperative AE, possibly because the UIP group had more typical honeycomb lesions, which were associated with prognosis and fibrosis [2]. Suzuki *et al.* found that the scores for fibrosis, consolidation and ground-glass opacity were significantly higher in AE patients [12]. Therefore, the type and severity of lesions in patients should be carefully evaluated by chest computed tomography (CT) before surgery. Positron emission tomography (PET–CT) plays a significant role in the diagnosis and staging of lung cancer. Some studies have also found that maximum standardized uptake value and the ratio of the ILD area's peak standard uptake value (SUV) to of the mediastinum's mean SUV can predict postoperative AE [22, 34, 35]; more large-scale studies are necessary to confirm. It was a pity that pulmonary function examination could not predict postoperative AE in this study, which was consistent with previous studies [19, 36], though pulmonary function examination is an effective method to evaluate the severity of pulmonary lesions in patients. However, some studies have found that diffusing capacity of the lung for carbon monoxide and vital capacity percentage may have a predictive effect, but the conclusions were not consistent [11, 23, 37]. We think it may be due to the heterogeneity of lung function tests in different institutions and individual differences in patients.

Choosing an appropriate surgical procedure for lung cancer patients with ILD is a dilemma for surgeons to make serious decisions. This study found that the larger the scope of resection, the higher risk of AE, which may be caused by lymphatic drainage disorder and increased endothelium pressure after surgery. Wedge resection was less likely to trigger postoperative AE than segmentectomy and lobectomy [11]. However, limited excision may lead to poor oncology outcomes. Sato *et al.* [38] reported that patients with stage IA lung cancer who underwent wedge resection had poorer long-term survival than lobectomy and segmentectomy (OR 2.98 (95% CI, 1.56–5.68, $P = 0.001$) and 2.56 (95% CI, 1.15–5.67, $P = 0.021$), respectively). Tsutani *et al.* reached a different conclusion. There was no statistical difference in overall survival between patients who underwent lobectomy and sublobar resection with stage IA lung cancer and ILD ($P = 0.87$) [39]. The jury is still out on this, and more studies are needed to address this question. Surgeons need to comprehensively consider short-term and long-term prognoses and choose the most appropriate surgical procedure. Operative time is also a predictor of postoperative AE, but it may be related to the surgical procedure. Koizumi *et al.* [20] compared the effects of video-assisted thoracoscopic surgery (VATS) and thoracotomy on postoperative AE. Although VATS did not prevent AE, the incidence of postoperative complications in VATS seemed to be lower, and VATS may be one of the beneficial options for patients with lung cancer and ILD.

In addition, some studies have found that age, smoking history, pathological type, stage, single-lung ventilation, postoperative pyothorax and chest-tube drainage have predictive effects [11, 15, 16, 18, 20, 21]. However, these results were not included or confirmed in this study, thus remaining to be clarified by further studies. Staging is of great value in treatment decisions and prognosis prediction of cancer patients, but it does not seem to be a prognostic factor for AE. Only Iyoda *et al.*'s [18] study found that patients with advanced-stage were more likely to develop AE, but this study only included 5 patients with AE ($P = 0.0344$). We think it is due to the fact that patients with advanced lung cancer and ILD rarely undergoes surgical treatment. Some studies have speculated that the high concentration of oxygen used in single-lung ventilation during lung cancer surgery may lead to AE by producing reactive oxygen species [40–42]. There are too few studies to be included in the meta-analysis. More clinical trials are needed to determine whether AE can be avoided by reducing oxygen concentration.

The current guidelines do not recommend the use of drugs to prevent postoperative AE. Preoperative prophylactic corticosteroid and sivelestat seem to be ineffective [10, 43]. However, a small prospective trial found that pirfenidone may have a preventive effect [44]. The guidelines weakly recommend the use of corticosteroid therapy, including pulse therapy and immunosuppressive therapy [10, 25, 45, 46]. However, the level of evidence is low; there is still much to be done to improve treatment strategies.

Limitations

This study has some limitations. First, all the included studies were retrospective, so there may be some bias that cannot reflect the actual situation of all patients. Second, almost all the study population were from Japan, and the results may lack generality. It is hoped that large-scale and multicentre studies can be done to confirm the results of this article in the future.

CONCLUSION

We found that gender, UIP pattern on CT, KL-6, LDH, WBC, partial pressure of oxygen, surgery procedure and operation time were risk factors for AE of ILD following lung cancer resection. Patients with these risk factors should be more prudently selected for surgical treatment and be monitored more carefully after surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its supporting Information files.

Author contributions

Xiaohu Hao: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing—original draft. **Jianqi Hao:** Conceptualization; Data curation; Formal analysis; Methodology; Writing—original draft. **Cong Chen:** Conceptualization; Data curation; Formal analysis; Writing—review & editing. **Haoning Peng:** Data curation; Writing—original draft. **Jian Zhang:** Formal analysis; Writing—review & editing. **Qi Cao:** Formal analysis; Writing—review & editing. **Lunxu Liu:** Conceptualization; Funding acquisition.

Reviewer information

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