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Review Article

Prognosis of Lung Transplantation in Patients with Acute Exacerbations of Interstitial Lung Disease: A Meta-Analysis Based on Cohort Studies

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Purpose: This meta-analysis aimed to examine the prognosis of patients with acute exacerbation of interstitial lung disease (AE-ILD) treated with lung transplantation compared to those with stable interstitial lung disease (ILD).
Methods: We conducted a detailed search in PubMed, Embase, Web of Science, and the Cochrane Library, with the primary outcomes being overall survival (OS), acute cellular rejection (ACR), primary graft dysfunction (PGD), and length of stay (LOS).
Results: Five cohort studies were included in this meta-analysis, with 183 patients enrolled in the AE-ILD group and 337 patients in the stable-ILD group. The results showed that in regard to perioperative outcomes, the AE-ILD group did not differ from the stable-ILD group in the incidence of ACR (relative risks [RR] = 0.34, p = 0.44) and the incidence of PGD III (RR = 0.53, p = 0.43), but had a longer LOS (mean difference = 9.15, p = 0.02). Regarding prognosis, the two also did not differ in 90-day OS (RR = 0.97, p = 0.59), 1-year OS (RR = 1.05, p = 0.66), and 3-year OS (RR = 0.91, p = 0.76).
Conclusion: Our study concluded that the efficacy of lung transplantation in patients with AE-ILD is not inferior to that of patients with stable ILD. Lung transplantation is one of the potential treatments for patients with AE-ILD.

Keywords: lung transplantation, interstitial lung diseases, prognosis, meta-analysis

Abbreviations

AE-ILD	=	acute exacerbation of interstitial lung disease
AE-IPF	=	acute exacerbation of idiopathic pulmonary fibrosis
ILD	=	interstitial lung disease
IPF	=	idiopathic pulmonary fibrosis
MV	=	mechanical ventilation
OS	=	overall survival
ACR	=	acute cellular rejection
PGD	=	primary graft dysfunction
LOS	=	length of stay
NOS	=	Newcastle–Ottawa Scale
BMI	=	body mass index
RR	=	relative risks
CI	=	confidence intervals
MD	=	mean difference
ECMO	=	extracorporeal membrane oxygenation

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Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders associated with parenchymal and diffuse interstitial inflammation that can lead to physiological limitation of the lung and includes approximately 200 diseases affecting the lung parenchyma.[1,2] Of these, idiopathic pulmonary fibrosis (IPF) is the most common type of ILD. Acute exacerbations in ILD (AE-ILD) refer to acute, clinically significant deterioration of respiratory function accompanied by new diffuse alveolar abnormalities on imaging that are not explained by heart failure or fluid volume overload. It can occur throughout the clinical course of ILD.

AE-ILD includes acute exacerbation of IPF (AE-IPF) and acute exacerbation of non-IPF ILD. The annual incidence of acute exacerbation in patients with IPF ranges from 4% to 20%, with an expected median survival of fewer than 3 months, and an inpatient mortality rate of up to 50%, and up to 90% if combined with respiratory failure and requiring mechanical ventilation (MV).[3–6] Mortality in other types of ILD ranges from 34% to 83%.[7]

Well-designed prospective clinical studies for the treatment of patients with AE-ILD are still lacking. High-dose steroid therapy is commonly used in such cases, but international guidelines have weak recommendations for corticosteroid use.[8] Lung transplantation is a potentially life-saving alternative treatment given the currently limited therapeutic options and the high mortality rate in patients with AE-ILD. Patients at some institutions may be urgently evaluated and placed on the lung transplant waiting list in the event of an acute exacerbation. However, a study published in 2018 by Dotan et al. suggested that AE-ILD may be associated with poorer post-transplant outcomes.[9] Consequently, this article examines the prognosis of patients with AE-ILD treated with lung transplantation compared to patients with stable ILD, based on published cohort studies.

Materials and Methods

This research was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement: updated guidelines for reporting systematic reviews and was registered with the Prospective Registry of International Systematic Reviews (PROSPERO) in 2024 (CRD42024518766). The purpose of this research is to investigate the prognosis of patients with AE-ILD treated with lung transplantation compared to patients with stable ILD.

Strategies for retrieving articles

Systematic and meticulous searches of PubMed, Web of Science, Embase, and Cochrane Library databases were accomplished by two researchers from the establishment of the database to February 2024, with the following search formulas used: (interstitial lung disease OR pulmonary interstitial lesions OR interstitial pneumonia OR diffuse parenchymal lung disease OR DPLD OR AE-ILD OR acute exacerbation of interstitial lung disease OR acute exacerbation of idiopathic pulmonary fibrosis OR AE-IPF) AND (lung transplantation OR lung transplant OR pulmonary transplantation). In particular, in an attempt to omit any potentially relevant articles, the references of the relevant articles were retrieved manually.

Inclusion and exclusion criteria

According to the PECOS principles, the inclusion criteria of the articles were as follows: (1) Patients: who were treated with lung transplantation with ILD; (2) exposure: patients with acute exacerbation of ILD who were treated with lung transplantation; and (3) comparison: patients with the stable stage of ILD who were treated with lung transplantation; (4) outcome: endpoints of interest typically include overall survival (OS), acute cellular rejection (ACR), primary graft dysfunction (PGD), and length of stay (LOS); and (5) study: included studies were cohort studies.

The exclusion criteria for articles were as follows: (1) the full text of the article was not available; (2) the study data were not available; (3) the language of the article was not English; and (4) updated articles for the same research cohort were elected to be considered for inclusion in the research comprising the newest or largest populations.

The definition of acute exacerbation includes (1) diagnosis of ILD (including IPF); (2) acute worsening or development of dyspnea <1 month in duration; (3) high-resolution CT chest imaging demonstrating new bilateral ground-glass opacities and/or consolidation superimposed on a background pattern consistent with fibrotic lung disease; and (4) deterioration not explained by a reversible cause (e.g., fluid overload, thromboembolic disease).[7]

Data extraction

As per the pre-designed form, two researchers independently extracted the data. For qualifying research, the following relevant information was extracted: (1)

research characteristics: authors, year of publication, recruitment time, country, sample size, and follow-up time; (2) participant characteristics: including age, gender, body mass index (BMI), preoperative lung function, the use of antifibrotic medication, and preoperative ventilation support; and (3) the outcomes that were supposed to be used for comparison within the respective periods.

Quality evaluation

The quality of the included articles was assessed with the Newcastle–Ottawa Scale (NOS). Cohort studies were assessed in three areas of object selection, intergroup comparability, and outcome measurement, and articles were categorized as low quality if the score was less than 6. Quality assessment was performed between two researchers independently, with the third researcher to be brought in to resolve conflicts if necessary.

Statistical analysis

Statistical analysis of the data was conducted by Review Manager 5.3. Relative risks (RR) and 95% confidence intervals (CI) were applied to dichotomous data, and mean difference (MD) and 95% CI were applied to continuous data. Due to the potential heterogeneity of the enrolled study population, a random-effects model was used consistently to enhance the credibility of the results. In this research, I^2 was used to calculate heterogeneity; I^2 ≥50% was deemed to be high heterogeneity, ≥25% and <50% were deemed to have moderate heterogeneity, and <25% was deemed to be low heterogeneity. Egger's test was performed to investigate publication bias when the number of included research was more than 10, and sensitivity analyses were conducted to assess the stability of the results. The $p < 0.05$ in a two-sided test was regarded as statistically significant.

Results

Study selection

Through the designed search formula, a sum of 8855 records was retrieved from the four databases, and no other articles were retrieved from other sources. The remaining records after excluding duplicates were 6287. An additional 6277 articles were excluded by reading the article titles and abstracts. Of the 10 remaining articles after careful perusal of the complete text, one article was excluded as the data were from the same cohort, three articles were excluded as the data were unavailable, and one article was excluded as it did not contain the endpoints of interest. Finally, five cohort studies were included in this meta-analysis.[9–13] In **Fig. 1**, the flowchart illustrates the detailed screening process.

Description and quality assessment of studies

Between 2018 and 2024, an aggregate of five cohort research compared the prognosis of patients with AE-ILD and stable-ILD treated with lung transplantation. Altogether 520 patients were enrolled in the research, of which 183 patients were enrolled in the exposure group (AE-ILD group), and the remaining 337 patients were enrolled in the control group (stable-ILD group). Four studies provided types of lung transplants, where patients in the exposed group would be more inclined to undergo a double-lung transplant. By contrast, patients in the control group would be more inclined to undergo a single-lung transplant. With the three studies having a mean follow-up period higher than 2 years, all five studies provided OS, three provided LOS, and two provided the incidence of PGD and ACR. The characteristics of the studies included in this meta-analysis are demonstrated in **Table 1**, **Supplementary Table 1-1**, and **Supplementary Table 1-2**.

Supplementary Table 2 demonstrates how the quality of the included studies was rated using the NOS checklist, of which three articles were assessed as 7, one article was assessed as 8, and one article was assessed as 6.

Perioperative outcomes

The incidence of ACR was reported in two studies, and the pooled results demonstrated no difference in the incidence of ACR between the AE-ILD group and the stable-ILD group treated with lung transplantation (RR = 0.34, 95% CI = 0.02–5.30, p = 0.44) (**Fig. 2**). Regarding the incidence of postoperative PGD III, the pooled results of the two studies demonstrated no difference between the two groups (RR = 0.53, 95% CI = 0.11–2.58, p = 0.43) (**Fig. 3**). Furthermore, for LOS, the pooled results of three studies demonstrated a shorter LOS in the stable-ILD group than in the AE-ILD group (MD = 9.15, 95% CI = 1.31–17.00, p = 0.02) (**Fig. 4**), which was a statistically significant result.

Prognostic analysis

Three studies provided 90-day OS, and the pooled results showed no difference in 90-day OS between the AE-ILD group and the stable-ILD group treated with

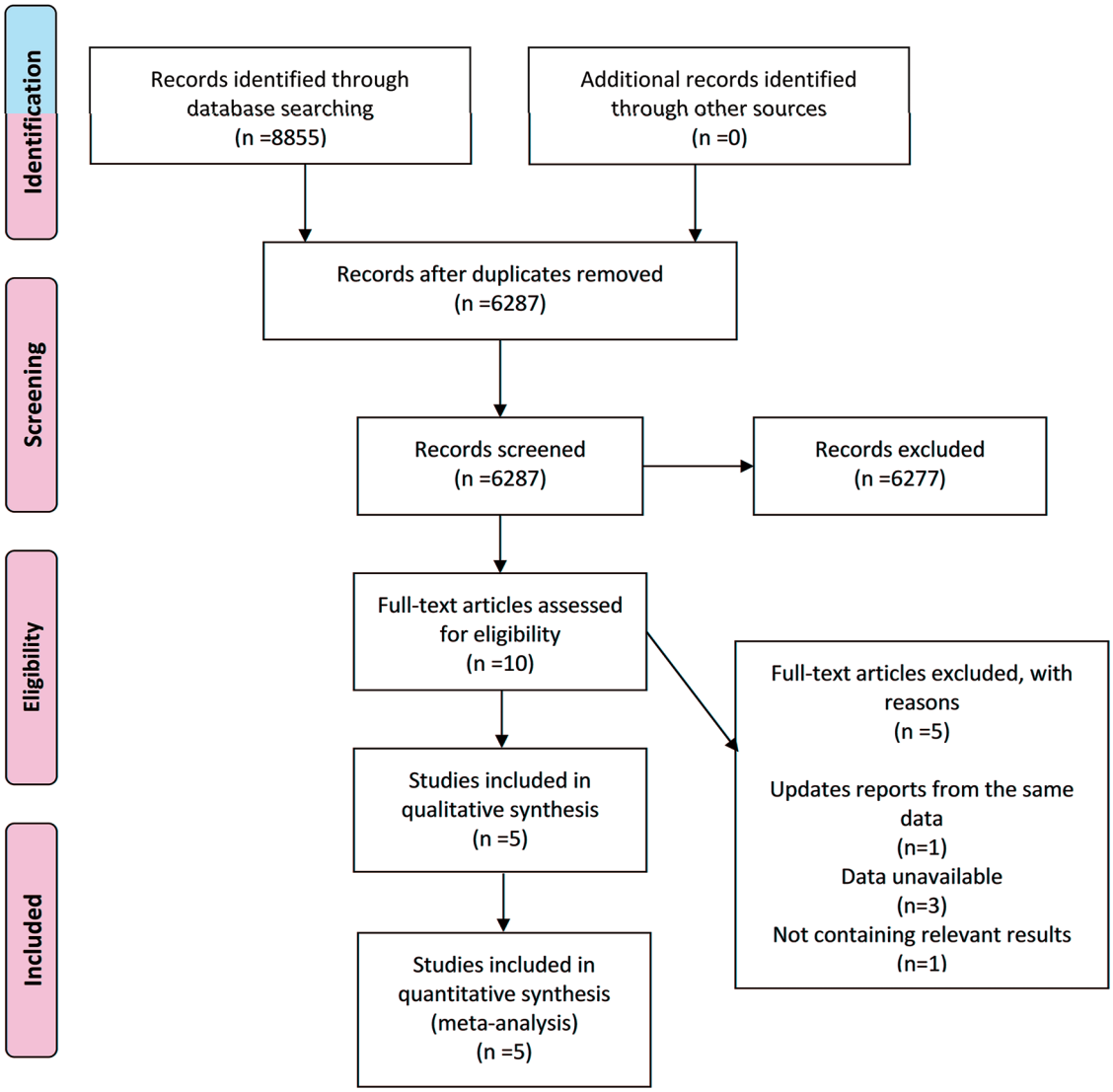

Fig. 1 Flow diagram of selection.

Table 1 Characteristics of all the studies included in the meta-analysis

Author	Year	Recruitment time	Country	Experiment	Control	Number of patients		Type of transplant (E/C, %)		Follow-up time (year)	Outcomes
						Experiment	Control	Single	Bilateral		
Dotan	2018	2012.1-2016.9	America	AE-IPF	Stable-IPF	37	52	39/67	61/33	2.4	OS, LOS
Chizinga	2022	2015.1-2018.12	America	AE-ILD	Stable-ILD	25	67	0/13	100/87	2.3	OS, LOS, PGD, ACR
Kim	2022	2008.10-2022.1	Korea	AE-ILD	Stable-ILD	52	56	/	/	3.2	OS
Guidot	2023	2005.5-2019.4	America	AE-ILD	Stable-ILD	41	31	20/32	80/68	>1	OS
Warrior	2024	2005.7-2020.7	America	AE-IPF	Stable-IPF	28	131	39/63	61/37	/	OS, LOS, PGD, ACR

AE: acute exacerbation; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; OS: overall survival; LOS: length of stay; PGD: primary graft dysfunction; ACR: acute cellular rejection; E: experiment; C: control

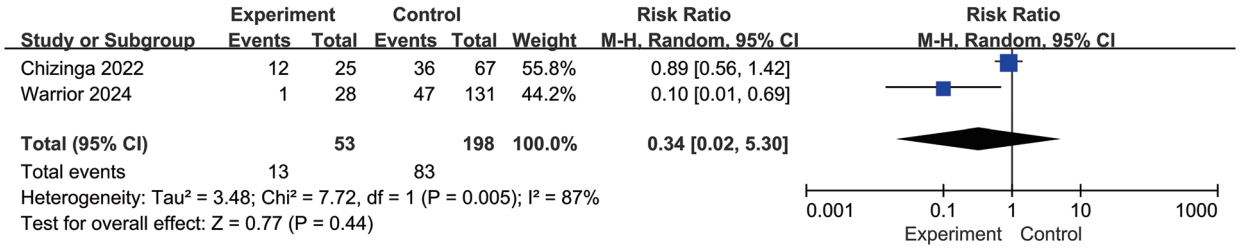

Fig. 2 Forest plot of the incidence of ACR after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. ACR: acute cellular rejection; AE-ILD: acute exacerbation of interstitial lung disease

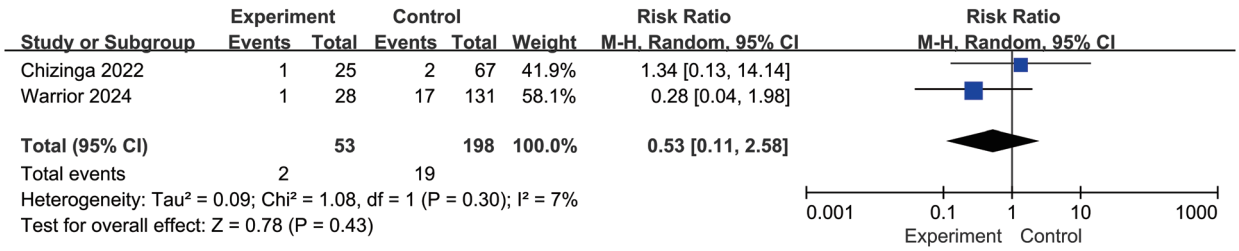

Fig. 3 Forest plot of the incidence of PGD after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. AE-ILD: acute exacerbation of interstitial lung disease; PGD: primary graft dysfunction

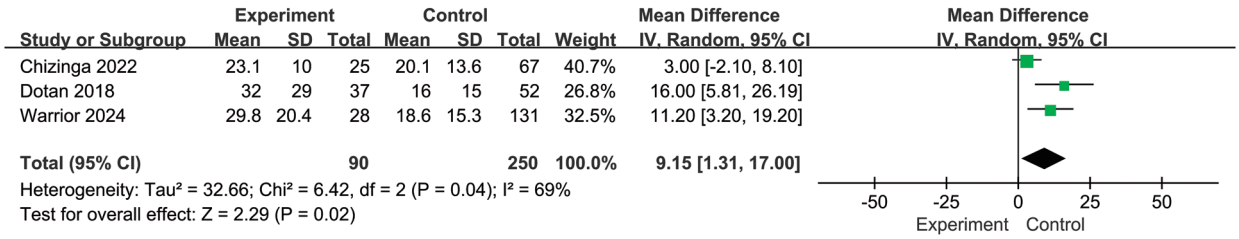

Fig. 4 Forest plot of the LOS after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. AE-ILD: acute exacerbation of interstitial lung disease; LOS: length of stay

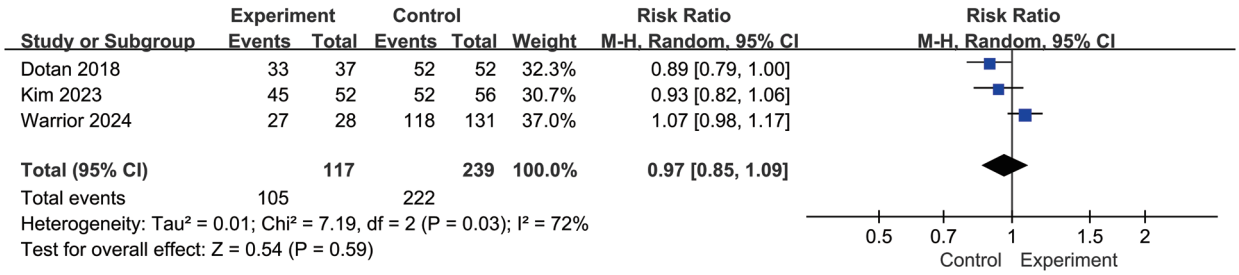

Fig. 5 Forest plot of the 90-day OS after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. AE-ILD: acute exacerbation of interstitial lung disease; OS: overall survival

lung transplantation (RR = 0.97, 95% CI = 0.85–1.09, p = 0.59) (**Fig. 5**). The pooled results of five studies demonstrated no difference between the two groups in 1-year OS (RR = 1.05, 95% CI = 0.86–1.28, p = 0.66) (**Fig. 6**). Moreover, three studies provided 3-year OS and the pooled results demonstrated no difference between the two groups (RR = 0.91, 95% CI = 0.49–1.67, p = 0.76) (**Fig. 7**).

Discussion

Lung transplantation is an important treatment for end-stage lung disease and offers hope to patients with ILD. Recent studies have shown a 51% increase in the incidence of ILD worldwide over the last decade.[14] From 1992 to 2017, the median survival after lung transplantation reached 5.2 years in patients with IPF

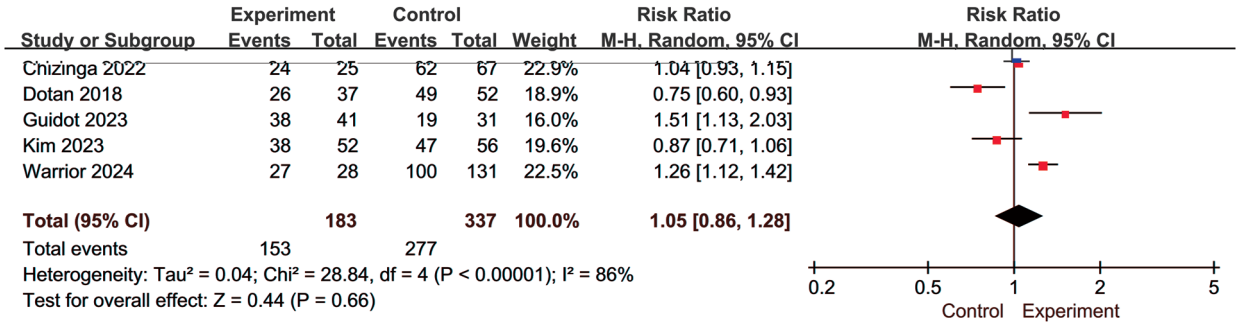

Fig. 6 Forest plot of the 1-year OS after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. AE-ILD: acute exacerbation of interstitial lung disease; OS: overall survival

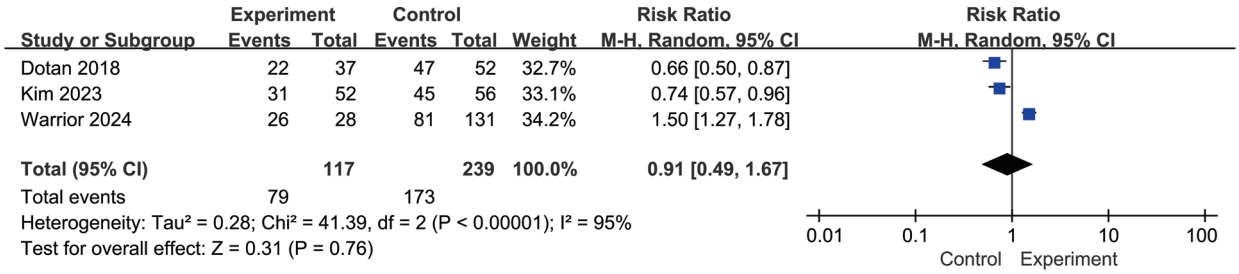

Fig. 7 Forest plot of the 3-year OS after lung transplantation therapy in patients with AE-ILD versus patients with stable-ILD. AE-ILD: acute exacerbation of interstitial lung disease; OS: overall survival

compared to 6.7 years in other ILD patients.[15] However, the published survival data on AE-ILD patients undergoing lung transplantation are still relatively scarce. Three retrospective studies were published in abstract form only between 2011 and 2016, in which Mudambi et al. and Nair et al. showed that short- or long-term post-transplant survival in patients with stable IPF versus those with AE-IPF was not significantly different.[16,17] By contrast, the study by Dotan et al. showed that patients in the AE-IPF group had a lower survival rate than patients with stable IPF.

Given the high mortality rate of AE-ILD and the scarcity of lung sources worldwide, it is crucial to assess the survival benefit of lung transplantation in patients with AE-ILD. On the one hand, as mentioned previously, the mortality rate without lung transplantation in patients with severe cases of AE-ILD is close to 90%. On the other hand, lung transplantation in patients with AE-ILD may lead to a decrease in the potential survival benefit of patients with stable ILD who are located on waiting lists due to the passage of time. This meta-analysis is based on published cohort studies comparing the prognosis of patients with AE-ILD and patients with stable ILD treated with lung transplantation. Our study suggests that patients with AE-ILD who undergo lung transplantation have non-inferior perioperative outcomes and prognosis to patients with a stable ILD, but will have a longer LOS.

In terms of perioperative outcomes, our results showed that patients with AE-ILD did not differ in the incidence of ACR and PGD compared with patients with stable ILD. ACR, after lung transplantation is mediated by T lymphocytes, which elicit a cellular immune response by recognizing foreign major histocompatibility complex, and its occurrence, is associated with donor and recipient factors and various aspects of the transplantation process. PGD represents an acute lung injury manifesting in the initial stages following lung transplantation. Its characteristic pathological pattern involves widespread alveolar damage, typically triggered by inflammation, aberrant immune responses, and other mechanisms. Considering that patients with AE-ILD are characterized by abnormal immune responses and increased lung inflammation.[18–20] and that immune dysregulation may also persist after lung transplantation, this could theoretically increase the risk of postoperative complications in patients with AE-ILD. However, our findings do not support this theoretical expectation, and the use of preoperative antifibrotic medications as well as additional interventional therapies may have contributed to this outcome. In most of the studies we included, antifibrotic drugs were used

preoperatively in both groups. Antifibrotic drugs, in addition to their anti-fibrotic effect, also have an immunosuppressive effect, which can inhibit the secretion of inflammation-related mediators and the release of cytokines, and reduce neutrophil chemotaxis, which tends to reduce the incidence of ACR.[21–23] The study by Ito et al. also suggested that in patients with AE-ILD, antifibrotic drugs attenuate inflammation and increase alveolar permeability in vivo,[24] which may be one of the reasons why the incidence of PGD is not higher in patients with AE-ILD than in patients with stable ILD. In addition, clinicians usually give additional interventional therapy to acute exacerbation patients, such as using immunosuppressive drugs (e.g., azathioprine, methotrexate, and mycophenolate) or giving empirical broad-spectrum antibiotic therapy.[25] It has been shown that a reduction in the incidence of PGD occurs in patients treated with antifibrotic drugs in combination with immunosuppressive drugs.[21] Although patients with AE-ILD have worse physiologic conditions and are more likely to develop serious complications, the incidence of ACR and PGD can be no higher than that of patients with stable ILD with a combination of preoperative and postoperative lung transplantation.

In terms of LOS, our findings demonstrated that patients with AE-ILD had a higher LOS than patients with stable ILD, and the results were statistically significant. On the one hand, patients with AE-ILD have a higher likelihood of corticosteroid use given the high mortality of AE-ILD. Previous studies have indicated that the administration of high doses of prednisolone to patients before transplantation may lead to significantly impaired wound healing and anastomotic dehiscence[26,27]; on the other hand, the high rate of MV and the use of extracorporeal membrane oxygenation (ECMO) in patients with AE-ILD compared to patients with stable ILD usually predicts a poor physical status accompanied by a more complex clinical course and a higher level of severity, which may lead to a longer recovery time for such patients.

Regarding prognosis, our results revealed no difference in 90-day OS, 1-year OS, and 3-year OS between patients with AE-ILD and patients with stable ILD. Hollebeke et al. suggested that hypoxia, inactivity, and the use of high-dose corticosteroids during acute exacerbation induced or exacerbated the likelihood of patient frailty.[28] Frail patients have a higher post-transplantation risk due to more comorbidities, functional limitations, and reduced physiologic reserve, which can increase post-transplantation mortality.[29] In turn, the results of our study indicate that the survival after lung transplantation in patients with AE-ILD is not inferior to that of patients with stable ILD, which is better than our expected results. The results of the current study can be interpreted in two ways. First, in aspect of the type of surgery, the vast majority of AE-ILD patients in the included studies opted for bilateral lung transplantation, and the potential advantage of bilateral lung transplantation for ILD is more pronounced in patients with more severe disease conditions[30]; in other words, bilateral lung transplantation may have compensated for the survival disadvantage of patients with AE-ILD so that lung transplantation of patients with AE-ILD in worse physiologic conditions also not relatively increase their mortality. Second, it can be observed from **Supplementary Table 1-1** that in the aspect of recipient characteristics, patients with AE-ILD were similar to patients with stable ILD in terms of age and BMI. It is noteworthy that AE-ILD patients did not have a significant preoperative decline in lung function, which may imply that critically ill patients did not deteriorate further, thus also favoring an improved outcome of lung transplantation. In addition, in **Supplementary Table 1-2**, we collected the time from the time a patient was placed on the waiting list to lung transplantation and given that some patients were placed on the waiting list during the stable phase and then developed an acute exacerbation and were prioritized for assignment after reassessment, we collected the LOS before lung transplantation, which to some extent reflects the time from the time a patient developed an acute exacerbation to the time they received a lung transplant. We found that the time between the onset of an acute exacerbation and the receipt of a lung transplant was not long for most patients and was shorter than for stable patients. This may indicate that timely assessment of the physiology of patients with acute exacerbations and treatment with lung transplantation is also one of the important factors for their prognosis to be no less than that of patients in the stable stage. Many limitations of our study remain. First, the small number of relevant studies included in the analysis made conducting more subgroup analyses difficult. Second, due to the lack of relevant original studies, we were unable to compare the survival of AE-ILD patients who received lung transplantation with that of other patients who were not treated with lung transplantation. Finally, we found a high degree of heterogeneity in the results of most of the trials, which may be attributed

to the fact that we analyzed the subtypes of ILD as a whole, and there are prognostic differences between the different subtypes of ILD. In addition, the relatively small size of the study sample and the variability of lung transplantation surgical techniques across regions may also have impacted the heterogeneity of the experimental results. We noted variations in the MV status of preoperative patients, which, on the one hand, may be partly due to different allocation systems in different regions, for example, the study by Kim et al. tended to have patients dependent on MV and ECMO undergo lung transplantation,[12] which would result in a higher proportion of mechanically ventilated patients; on the other hand, some physicians would have patients undergo MV, alone or in combination with ECMO, as a lung transplantation bridge. Individual differences and differences in decision-making can lead to differences in ventilation rates. Unfortunately, these limitations are difficult to avoid.

This article is the first meta-analysis assessing the impact of acute exacerbation on the prognosis of patients with ILD undergoing lung transplantation, based on five published cohort studies. Our results revealed that patients with AE-ILD and those with stable ILD had similar perioperative outcomes and prognosis after lung transplantation, and there was no difference in the incidence of PGD and ACR, but patients with AE-ILD would have a longer LOS.

Conclusion

Lung transplantation may be a potentially life-saving and life-prolonging treatment for patients with AE-ILD who have been reasonably evaluated and are eligible for transplantation option.

Declarations

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None.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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The authors have no financial support to declare.

Competing interests

The authors declare that they have no conflict of interest.

Data availability

The datasets supporting the conclusions of this article are included within the article. If detailed data about this article are required, the corresponding author can be contacted.

Author contributions

All authors contributed to the study's conception and design. Lei Yang and Zhiyi Xiang designed the research process, searched the database for corresponding articles, and drafted the meta-analysis. Min Dai extracted useful information from the articles above. Qiufeng Zhang used statistical software for analysis. Ying Zhou polished this article. All the authors had read and approved the manuscript and ensured that this was the case.

Supplementary Materials

Supplementary Table 1-1
Characteristics of all studies included in the meta-analysis
Supplementary Table 1-2
Characteristics of all studies included in the meta-analysis
Supplementary Table 2
Quality assessment of included observational studies

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