



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

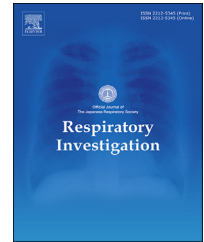
Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

## Respiratory Investigation

journal homepage: [www.elsevier.com/locate/resinv](http://www.elsevier.com/locate/resinv)

## Original article

# Complications of a lung biopsy for severe respiratory failure: A systematic review and meta-analysis

Hiroshi Sugimoto<sup>a,\*</sup>, Yosuke Fukuda<sup>b</sup>, Yoshie Yamada<sup>c</sup>, Hiroyuki Ito<sup>d</sup>, Takeshi Tanaka<sup>e</sup>, Takuo Yoshida<sup>f</sup>, Satoshi Okamori<sup>g</sup>, Koichi Ando<sup>b</sup>, Yohei Okada<sup>h,i</sup>

<sup>a</sup> Department of Respiratory Medicine, Kobe Red Cross Hospital, Hyogo, Japan

<sup>b</sup> Division of Respiratory Medicine and Allergology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

<sup>c</sup> Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto, Japan

<sup>d</sup> Department of Pulmonology, Kameda Medical Center, Chiba, Japan

<sup>e</sup> Infection Control and Education Center, Nagasaki University Hospital, Nagasaki, Japan

<sup>f</sup> Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

<sup>g</sup> Department of Medicine, Division of Pulmonary Medicine, Keio University School of Medicine, Tokyo, Japan

<sup>h</sup> Department of Primary Care and Emergency Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

<sup>i</sup> Preventive Services, School of Public Health, Kyoto University, Kyoto, Japan

## ARTICLE INFO

## Article history:

Received 22 February 2022

Received in revised form

23 August 2022

Accepted 28 August 2022

Available online xxx

## Keywords:

Acute respiratory failure

Acute respiratory distress syndrome (ARDS)

Lung biopsy

Complications

## ABSTRACT

**Background:** This systematic review and meta-analysis aimed to evaluate the complications of lung biopsy in patients with acute respiratory failure (ARF), including acute respiratory distress syndrome (ARDS).

**Methods:** We searched the MEDLINE and Cochrane Central Register of Controlled Trials. The primary outcomes were biopsy-related death, respiratory failure, cardiac complications, bleeding, and other major complications. We used the McMaster Quality Assessment Scale of Harms (McHarm) to evaluate the risk of bias. A random-effects model was used to calculate the pooled frequencies.

**Results:** Thirteen studies (consisting of 574 patients) were included in the meta-analysis. Furthermore, most of the included studies had a high or unclear risk of bias in half of the items in MCHarm. All included studies evaluated surgical lung biopsies. The median overall hospital mortality was 53% (range: 17%–90%). The pooled frequencies of biopsy-related death, respiratory failure, cardiac complication, bleeding, and other major complications were 0.00% (95% confidence interval [CI]: 0.00%–0.21%), 1.30% (95% CI: 0.00%

**Abbreviations:** AECC, American-European consensus conference; ARDS, Acute respiratory distress syndrome; ARF, Acute respiratory failure; CIs, Confidence intervals; DAD, Diffuse alveolar damage; GRADE, Grading of recommendations assessment development evaluation; OLB, Open lung biopsy; PRISMA, Preferred reporting items for systematic reviews and meta-analysis; SLB, Surgical lung biopsy; TBLB, Transbronchial lung biopsy.

\* Corresponding author. Department of Respiratory Medicine, Kobe Red Cross Hospital, 1-3-1 Wakinohama Kaigan-dori, Chuo-ku, Kobe 651-0073, Japan.

E-mail address: [dr.sugimoto@gmail.com](mailto:dr.sugimoto@gmail.com) (H. Sugimoto).

<https://doi.org/10.1016/j.resinv.2022.08.008>

2212-5345/© 2022 [The Author/The Authors] Published by Elsevier B.V. on behalf of The Japanese Respiratory Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Please cite this article as: Sugimoto H et al., Complications of a lung biopsy for severe respiratory failure: A systematic review and meta-analysis, Respiratory Investigation, <https://doi.org/10.1016/j.resinv.2022.08.008>

–5.69%), 1.03% (95% CI: 0.00%–3.73%), 1.46% (95% CI: 0.16%–3.56%), and 4.26% (95% CI: 0.00%–13.0%), respectively.

**Conclusions:** The results of this study will be valuable information in considering the indications of lung biopsy in patients with ARF, including ARDS.

**Trial registration:** The protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000040650).

© 2022 [The Author/The Authors] Published by Elsevier B.V. on behalf of The Japanese Respiratory Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS) are caused by various underlying conditions, such as pneumonia, sepsis, and trauma [1]. Therefore, in their management, diagnosing the underlying condition and prompting specific treatment is essential because the mortality rate of ARDS remains high (approximately 30%) [2].

Previous studies have suggested lung biopsy is useful for verifying the cause of ARF or ARDS. It has been reported that open lung biopsy (OLB) provides a specific diagnosis in 85% of patients and contributes to management changes in 73% of patients with ARDS [3]. As a specific diagnosis, interstitial lung disease (25%), infectious disease (24%), and neoplastic disease (12%) were more common than diffuse alveolar damage (DAD) (9%), which is commonly observed in ARDS [3]. Therefore, pathological assessment using lung biopsy may play an important role in managing ARF and ARDS.

However, the safety and feasibility of lung biopsy for severe respiratory failure remain unclear. Furthermore, some meta-analyses on lung biopsy in patients with ARDS have shown that 22%–29% of patients undergoing OLB suffer biopsy-related complications such as pneumothorax, persistent air leaks, bleeding, and infections [3,4]; these studies were not derived from a systematic review using a rigorous approach. Furthermore, while the definition of ARDS was revised from the American-European Consensus Conference (AECC) criteria to the Berlin criteria in 2012 [1], the latest meta-analysis of 14 studies assessing the complications of a lung biopsy for patients with ARDS contained only one study published after the ARDS definition change [4]. Therefore, an updated systematic review and meta-analysis focused on the safety of lung biopsy for severe respiratory failure is required.

As a result, we conducted a systematic review and meta-analysis of the frequency of complications caused by lung biopsy in patients with ARF or ARDS.

## 2. Materials and methods

This study is a systematic review and meta-analysis of the frequency of lung biopsy complications in patients with ARDS or ARF. We used the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) [5] and its extension, which addresses harm (PRISMA harms) [6], to report our findings. The review protocol was pre-registered with the

University Hospital Medical Information Network Clinical Trials Registry (UMIN 000040650) and has been previously published [7]. In addition, the need for ethical approval and consent was waived due to the nature of the systematic review.

### 2.1. Population and study eligibility

The study participants were critically ill adult patients (16 years or older) with ARDS or ARF in an ICU or emergency department who required mechanical ventilation and those who underwent lung biopsy. For lung biopsy, we defined the procedures, including surgical lung biopsy (SLB), which consists of OLB and video-assisted thoracoscopic surgery (VATS), transbronchial lung biopsy (TBLB), and cryobiopsy. In OLB, the lung tissue was surgically removed through an incision between the ribs. In VATS, a thoracoscope and forceps were inserted into the chest cavity through minimal incisions in the chest wall, and the lung tissue was collected under the view of the thoracoscope. TBLB and cryobiopsy were performed using flexible bronchoscopy, and the lung tissue was collected by forceps or cryoprobe (for freezing the lung tissue).

In addition, we considered the definitions used in primary studies. We included all studies, including randomized controlled trials and observational (cross-sectional, prospective cohort, and retrospective cohort) studies. We excluded case reports, case-control studies, review articles, and studies that did not attempt to evaluate the complications of lung biopsy.

### 2.2. Search strategy

To identify all eligible studies, we searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) using PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) on May 22, 2020. In addition, we restricted the search to literature published in English. Details of the search strategy are presented in [Table S1](#). The literature search was supported by medical librarians at the Kyoto Prefectural University of Medicine.

### 2.3. Study selection and data collection

Two authors (HS and YF) independently screened all studies identified in the search strategy by reviewing the titles and abstracts. After the first screening, two independent authors (YF and HI) assessed each study for eligibility. Disagreements

between the reviewers were resolved through discussion or by a third reviewer (HS). Furthermore, two authors (YF and HI, or HS and YY) independently extracted information from the included studies, and the mismatch was resolved through discussion. We attempted to contact the corresponding authors through email regarding the unknown data.

The following data were extracted using a pre-defined data extraction form: study characteristics (author, year of publication, country, design, sample size, clinical settings, number of studies, and funding source), patient characteristics (inclusion/exclusion criteria, number of dropouts with reason, and patient demographics such as age and sex), type of lung biopsy procedure, and frequency of lung biopsy complications (biopsy-related death, respiratory failure, cardiac complication, bleeding, pneumothorax, infection, and other complications). The primary outcomes were biopsy-related death, respiratory failure, cardiac complications, bleeding, or other major complications, and the secondary outcomes were pneumothorax, infection, or other minor complications.

#### 2.4. Assessment of study quality and risk of bias

To evaluate the risk of bias, we used the McMaster Quality Assessment Scale of Harms (McHarm), which consists of 15 items (Table S2) [8]. MCHarm is a reliable criterion developed for assessing the internal validity of harms in intervention studies by Santaguida and colleagues using a literature review of harms and the Delphi method. Two investigators (YF and HI, or HS and YY) independently evaluated the risk of bias in each included study. Any disagreements were resolved through discussion or by a third reviewer. Due to the absence of evidence for publication bias in the studies on harm and the lack of reliable methods for its assessment, no statistical evaluation of publication bias was performed. In addition, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence for each complication of lung biopsy [9].

#### 2.5. Statistical analysis and data synthesis

The frequency of complication estimates with 95% confidence intervals (CIs) was indicated in paired forest plots to inspect the between-study variance. Because the frequency of adverse events was often expected to be small or zero, we used Freeman-Tukey Double Arcsine transformation to stabilize the variances and then performed a random effects meta-analysis using the DerSimonian-Laird method [10,11]. We excluded studies lacking data for each outcome from the meta-analysis. We performed post hoc sensitivity analyses for the included studies to assess the design bias. All analyses were performed using Review Manager 5.4 (Cochrane Collaboration, London, United Kingdom) and STATA 16 (StataCorp LLC, College Station, TX, USA).

### 3. Results

A total of 2214 studies were identified and screened. Among them, 13 studies (consisting of 574 patients) met the eligibility criteria and were included in the quality assessment and

meta-analysis (Fig. 1). The characteristics of the included studies are presented in Table 1 and Table S3 [12–24]. No randomized controlled trial was identified. Two studies were prospective cohort studies, and the remaining 11 were retrospective cohort studies. The median number of patients in each study was 36 (range: 14–101). The median age of the patients and the proportion of male sex in each study ranged from 33 to 67 years and 44%–75%, respectively. The median overall hospital mortality was 53% (range: 17% [in 7 days]–90%). The conditions of the participants were ARF requiring mechanical ventilation (five studies) and acute lung injury or ARDS (eight studies). Five studies and three studies used the AEC and Berlin criteria for diagnosing ARDS, respectively. All studies assessed the complications of SLB in ICU patients, and biopsy procedures were performed in the ICU or operating room. Complications in the included studies are presented in Table 2.

#### 3.1. Risk of bias assessment

The summary of the risk of bias in the included studies is shown in Fig. 2. Furthermore, most studies were evaluated as having a high or unclear risk of bias in half of the items in MCHarm. For example, in the item regarding the timing and frequency of collection of the harms, 10 of 13 studies were considered to have a high risk of bias because these studies did not clearly specify in the methods section when or how often information on complications was collected. We present the GRADE evidence profile of each complication of lung biopsy in Table 3. For each outcome, we judged the component for the risk of bias as very serious or serious based on the number of studies evaluated as high or unclear risk of bias in the items in MCHarm.

#### 3.2. Primary outcome

We present the forest plot for the pooled frequency of primary outcomes in Fig. 3. Respiratory failure and cardiac complications had high heterogeneity in the primary outcomes (Table 3).

For biopsy-related death, no cases were observed in 11 studies ( $n = 502$ ), and the pooled frequency was 0.00% (95% CI: 0.00%–0.21%,  $I^2 = 0.0\%$ ) (Fig. 3A).

Respiratory failure was observed in 6 of 277 patients (five studies), and its pooled frequency was 1.30% (95% CI: 0.00%–5.69%,  $I^2 = 69.7\%$ ) (Fig. 3B). There were eight cases of cardiac complications in seven studies ( $n = 414$ ). All cases involved hypotension, and one case was accompanied by arrhythmia (bigeminy), thereby requiring additional treatment. The pooled frequency of cardiac complications was 1.03% (95% CI: 0.00%–3.73%,  $I^2 = 60.1\%$ ) (Fig. 3C). Bleeding was observed in 11 of 453 patients (10 studies), and the pooled frequency was 1.46% (95% CI: 0.16%–3.56%,  $I^2 = 25.1\%$ ) (Fig. 3D). For other major complications, there were two persistent air leaks requiring surgery in two studies ( $n = 46$ ), and the pooled frequency was 4.26% (95% CI: 0.00%–13.0%,  $I^2 = 0.0\%$ ) (Fig. 3E).

#### 3.3. Secondary outcome

We present a forest plot for the secondary outcomes in Fig. 4. All secondary outcomes showed high heterogeneity (Table 3).

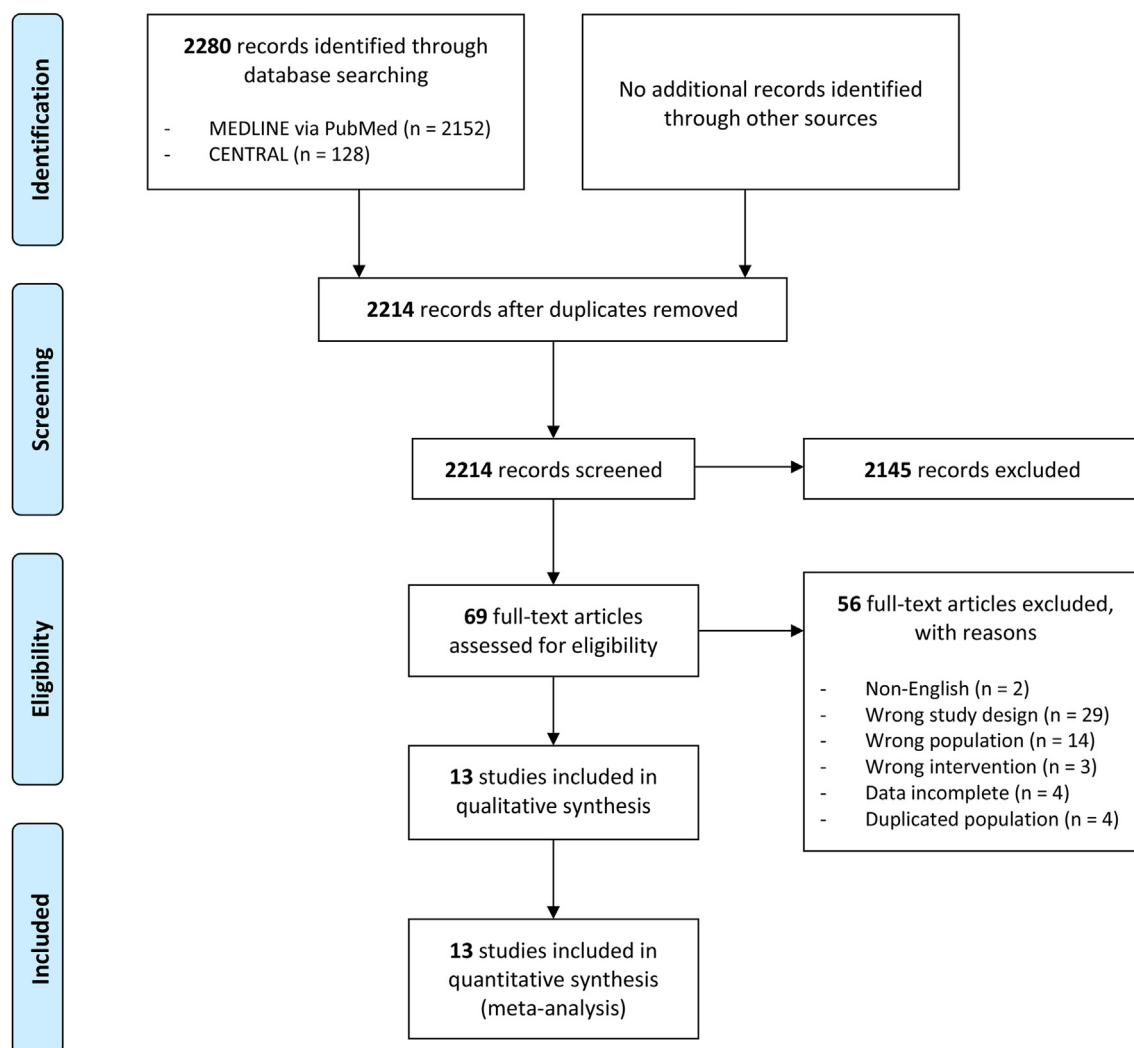


Fig. 1 – PRISMA flow diagram.

A total of 23 patients with pneumothorax were observed in eight studies (n = 337), with a pooled frequency of 6.51% (95% CI: 1.89%–13.0%,  $I^2 = 70.0\%$ ) (Fig. 4A). For infection, three cases of wound infection and one case of empyema were observed in three studies (n = 159), and the pooled frequency was 2.70% (95% CI: 0.00%–12.6%,  $I^2 = 76.8\%$ ) (Fig. 4B). In 10 studies (n = 511), most other minor complications were persistent air leak that did not require surgery (n = 75), while others included subcutaneous emphysema (n = 3) and bronchopleural fistula (n = 2). The pooled frequency of other minor complications was 16.4% (95% CI: 9.71%–24.3%,  $I^2 = 77.7\%$ ) (Fig. 4C).

### 3.4. Sensitivity analysis

In the sensitivity analysis, the pooled frequencies in prospective cohort studies tended to be lower than those in retrospective cohort studies; however, the results were similar (Table S4). The results of this study are robust.

## 4. Discussion

### 4.1. Key findings

This systematic review and meta-analysis, including 13 studies, revealed that the median overall hospital mortality was 53%, and no biopsy-related deaths were reported in lung biopsies for ARDS or ARF. Furthermore, less than 5% of other severe complications occurred. While most included studies had a high or unclear risk of bias in half of the items in McHarm, we believe these results may help consider the feasibility of performing lung biopsy for patients with ARF or ARDS.

### 4.2. Strengths

To the best of our knowledge, no previous PRISMA-compliant systematic reviews and meta-analyses have focused on the complications of a lung biopsy for severe respiratory failure.

**Table 1 – Characteristics of the included studies.**

First author Year	Study design	Country	No. of participants	Age	Sex male (%)	Condition	Overall hospital mortality	PaO <sub>2</sub> /FiO <sub>2</sub> ratio (mmHg)	Apache II score	Sofa score
Arabi 2007 [12]	Retrospective cohort	Saudi Arabia	14	51 ± 19	7 (50%)	ARF	57%	153 ± 60	23 ± 6	Unknown
Baumann 2008 [13]	Retrospective cohort	Germany	27	48 ± 14	12 (44%)	ALI or ARDS <sup>a</sup>	48%	188 ± 109	Unknown	7.9 ± 3.0
Charbonney 2009 [14]	Retrospective cohort	Switzerland	19	50 ± 15	11 (58%)	ARDS <sup>a</sup>	90%	119.3 ± 34.2	Unknown	Unknown
Cho 2006 [15]	Retrospective cohort	USA	53	52 ± 18	33 (62%)	ARDS <sup>a</sup>	17% (in 7 days)	147 ± 63	Unknown	Unknown
Donaldson 2016 [16]	Retrospective cohort	Australia	30	62 (57–69)	20 (67%)	ARF	53%	Unknown	Unknown	Unknown
Depuydt 2013 [17]	Retrospective cohort	Belgium	60	62 ± 14	36 (61%)	ARF	75%	189 (140–216)	Unknown	Unknown
Gerard 2018 [18]	Retrospective cohort	Belgium	51	67 (52–76)	28 (55%)	ARDS <sup>b</sup>	55%	128 (101–155)	17.5 (15–21.5)	7 (5–9)
Kao 2015 [19]	Retrospective cohort	Taiwan	101	57 ± 17	65 (64%)	ARDS <sup>b</sup>	60%	148.7 ± 67.9	23.2 ± 5.5	7.0 ± 3.4
Lim 2007 [20]	Retrospective cohort	South Korea	36	59 (20–77)*	25 (69%)	ARF	50% (in the ICU stay)	158.6 (52–320)*	17 (7–27)*	5 (1–12)
Ortiz 2019 [21]	Retrospective cohort	Colombia	15	33 (25–45)	7 (47%)	ARDS <sup>b</sup>	40%	109 (87.5–138.5)	22 (17–23)	Unknown
Papazian 1998 [22]	Prospective cohort	France	36	59 ± 15	Unknown	ARDS <sup>a</sup>	51%	118 (60–190)**	Unknown	Unknown
Papazian 2007 [23]	Prospective cohort	France	100	58 ± 16	67 (67%)	ARDS <sup>a</sup>	45% (in 28 days)	129 ± 41	Unknown	Unknown
Soh 2005 [24]	Retrospective cohort	Taiwan	32	51 ± 22	24 (75%)	ARF	56%	163.0 ± 90.4	19.2 ± 5.5	Unknown

PaO<sub>2</sub>, arterial partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ARF, acute respiratory failure; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Data are described as mean ± SD or median (IQR).

\*Mean (range).

\*\*Median (range).

<sup>a</sup> Defined by the American-European Consensus Conference (AECC) criteria.

<sup>b</sup> Defined by the Berlin criteria.

**Table 2 – Complications in the included studies.**

First author Year	No. of participants	Biopsy-related death	Respiratory failure	Cardiac complication	Bleeding	Other major complications	Pneumothorax	Infection	Other minor complications
Arabi 2007 [12]	14	0	Unknown	Unknown	0	Unknown	0	Unknown	Unknown
Baumann 2008 [13]	27	0	Unknown	Unknown	1	1*	9	2 <sup>a</sup>	3**
Charbonney 2009 [14]	19	Unknown	Unknown	Unknown	2	1*	2	Unknown	Unknown
Cho 2006 [15]	53	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	16**
Donaldson 2016 [16]	30	0	4	0	0	Unknown	4	Unknown	Unknown
Depuydt 2013 [17]	60	0	2	0	4	Unknown	3	Unknown	5**
Gerard 2018 [18]	51	0	0	1	0	Unknown	2	Unknown	3**
Kao 2015 [19]	101	0	Unknown	2	1	Unknown	Unknown	Unknown	11 <sup>c</sup>
Lim 2007 [20]	36	0	Unknown	5	Unknown	Unknown	Unknown	Unknown	15**
Ortiz 2019 [21]	15	0	Unknown	Unknown	1	Unknown	Unknown	Unknown	3**
Papazian 1998 [22]	36	0	0	0	1	Unknown	1	Unknown	5**
Papazian 2007 [23]	100	0	0	0	1	Unknown	2	0	8**
Soh 2005 [24]	32	0	Unknown	Unknown	Unknown	Unknown	Unknown	2 <sup>b</sup>	11 <sup>d</sup>

\*Persistent air leak that required surgery.

\*\*Persistent air leak that did not require surgery.

<sup>a</sup> Wound infection (n = 2).

<sup>b</sup> Wound infection (n = 1) and empyema (n = 1).

<sup>c</sup> Persistent air leak that did not require surgery (n = 8) and subcutaneous emphysema (n = 3).

<sup>d</sup> Persistent air leak that did not require surgery (n = 9) and bronchopleural fistula (n = 2).

	Were the harms PRE-DEFINED using standardized or precise definitions?	Were SERIOUS events precisely defined?	Were SEVERE events precisely defined?	Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Was the mode of harms collection specified as ACTIVE?	Was the mode of harms collection specified as PASSIVE?	Did the study specify WHO collected the harms?	Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	Did the study specify the TIMING and FREQUENCY of collection of the harms?	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Did the author(s) specify the type of analyses undertaken for harms data?
Arabi 2007	+	-	-	+	?	-	-	-	+	?	-	-	+	+	-
Baumann 2008	+	+	+	+	+	?	+	-	-	?	-	+	+	+	-
Charbonney 2009	-	-	-	+	?	-	-	-	-	?	-	-	-	+	-
Cho 2006	+	+	+	+	+	?	-	-	+	?	-	+	+	+	+
Depuydt 2013	-	-	-	+	?	-	-	-	-	?	-	-	+	+	-
Donaldson 2016	-	-	-	+	?	-	-	-	-	-	-	-	+	+	-
Gerard 2018	-	-	-	+	?	-	+	-	-	?	-	-	+	+	-
Kao 2015	+	-	-	+	?	-	-	-	-	?	-	-	+	+	-
Lim 2007	+	+	-	+	+	-	-	-	-	?	+	-	+	+	-
Ortiz 2019	+	+	+	+	?	-	-	-	-	?	-	-	+	+	-
Papazian 1998	+	-	-	-	?	?	-	-	+	?	-	-	-	+	-
Papazian 2007	+	-	-	+	?	?	-	-	-	?	-	-	-	+	+
Soh 2005	-	-	-	+	?	-	-	-	-	?	-	-	+	+	-

Fig. 2 – The summary of the risk of bias in the included studies.



**Table 3 – Summary of findings.**

Patients/populations		ARDS or acute respiratory failure							
Settings	ICU or OR								
Intervention	SLB (OLB or VATS)								
Study design	Cohort study								
Outcomes	No. of participants (studies)	Frequency (95% CI)	Frequency per 1000 patients (95% CI)	Factors that may decrease the quality of evidence					Quality of evidence (GRADE)
				Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
Biopsy-related death	502 (11)	0.000% (0.000–0.206%)	0 (0–2)	Very serious <sup>c</sup>	Not serious	Not serious (I <sup>2</sup> = 0.0%)	Serious <sup>e</sup>	Not applicable	Low
Respiratory failure	277 (5)	1.303% (0.000–5.692%)	13 (0–57)	Very serious <sup>c</sup>	Not serious	Very serious (I <sup>2</sup> = 69.7%)	Serious <sup>e</sup>	Not applicable	Very low
Cardiac complication	414 (7)	1.027% (0.000–3.727%)	10 (0–37)	Very serious <sup>c</sup>	Not serious	Serious (I <sup>2</sup> = 60.1%)	Serious <sup>e</sup>	Not applicable	Very low
Bleeding	453 (10)	1.460% (0.163–3.556%)	15 (2–36)	Very serious <sup>c</sup>	Not serious	Not serious (I <sup>2</sup> = 25.1%)	Serious <sup>e</sup>	Not applicable	Low
Other major complications <sup>a</sup>	46 (2)	4.255% (0.000–13.02%)	43 (0–130)	Serious <sup>d</sup>	Not serious	Not serious (I <sup>2</sup> = 0.0%)	Very serious <sup>e,f</sup>	Not applicable	Low
Pneumothorax	337 (8)	6.506% (1.886–13.03%)	65 (19–130)	Very serious <sup>c</sup>	Not serious	Very serious (I <sup>2</sup> = 70.0%)	Very serious <sup>e,f</sup>	Not applicable	Very low
Infection	159 (3)	2.704% (0.000–12.56%)	27 (0–126)	Very serious <sup>c</sup>	Not serious	Very serious (I <sup>2</sup> = 76.8%)	Very serious <sup>e,f</sup>	Not applicable	Very low
Other minor complications <sup>b</sup>	511 (10)	16.42% (9.712–24.34%)	164 (97–243)	Very serious <sup>c</sup>	Not serious	Very serious (I <sup>2</sup> = 77.7%)	Serious <sup>f</sup>	Not applicable	Very low

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; OR, operating room; SLB, surgical lung biopsy; OLB, open lung biopsy; VATS, video-assisted thoracoscopic surgery; CI, confidence interval; GRADE, grading of recommendations, assessment, development, and evaluation.

<sup>a</sup> Persistent air leak that required surgery.

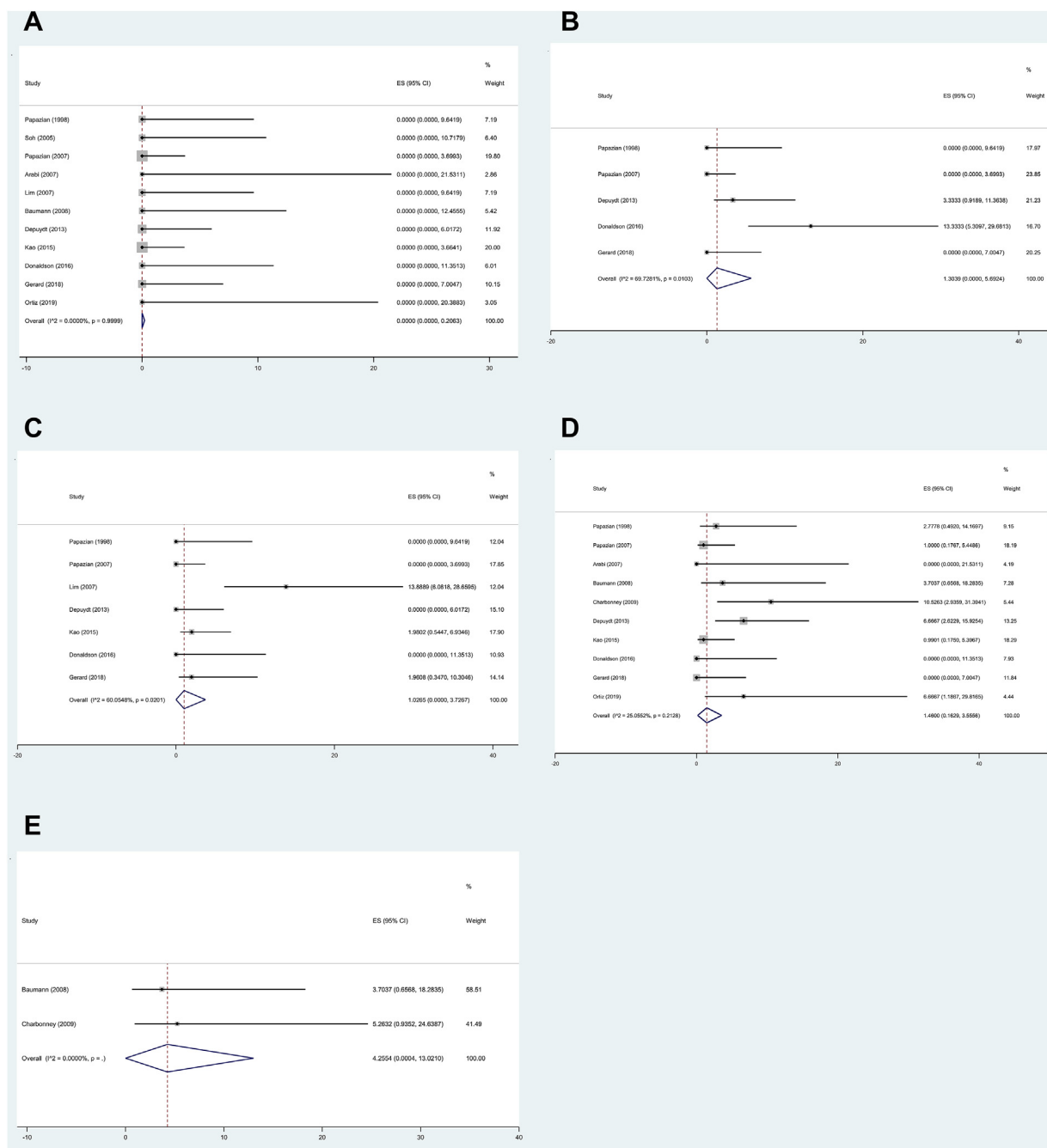
<sup>b</sup> Persistent air leak that did not require surgery, subcutaneous emphysema, and bronchopleural fistula.

<sup>c</sup> We judged this component as very serious because more than two-thirds of the studies were considered to have a high or unclear risk of bias in half of the items in the McMaster Quality Assessment Scale for Harms.

<sup>d</sup> We judged this component as serious because a certain number of studies were considered to have a high or unclear risk of bias in the items in the McMaster Quality Assessment Scale for Harms.

<sup>e</sup> Downgrade due to number of participants was less than optimal information size.

<sup>f</sup> Downgrade due to the possibility of a change in clinical action at the upper versus lower of the confidence interval.



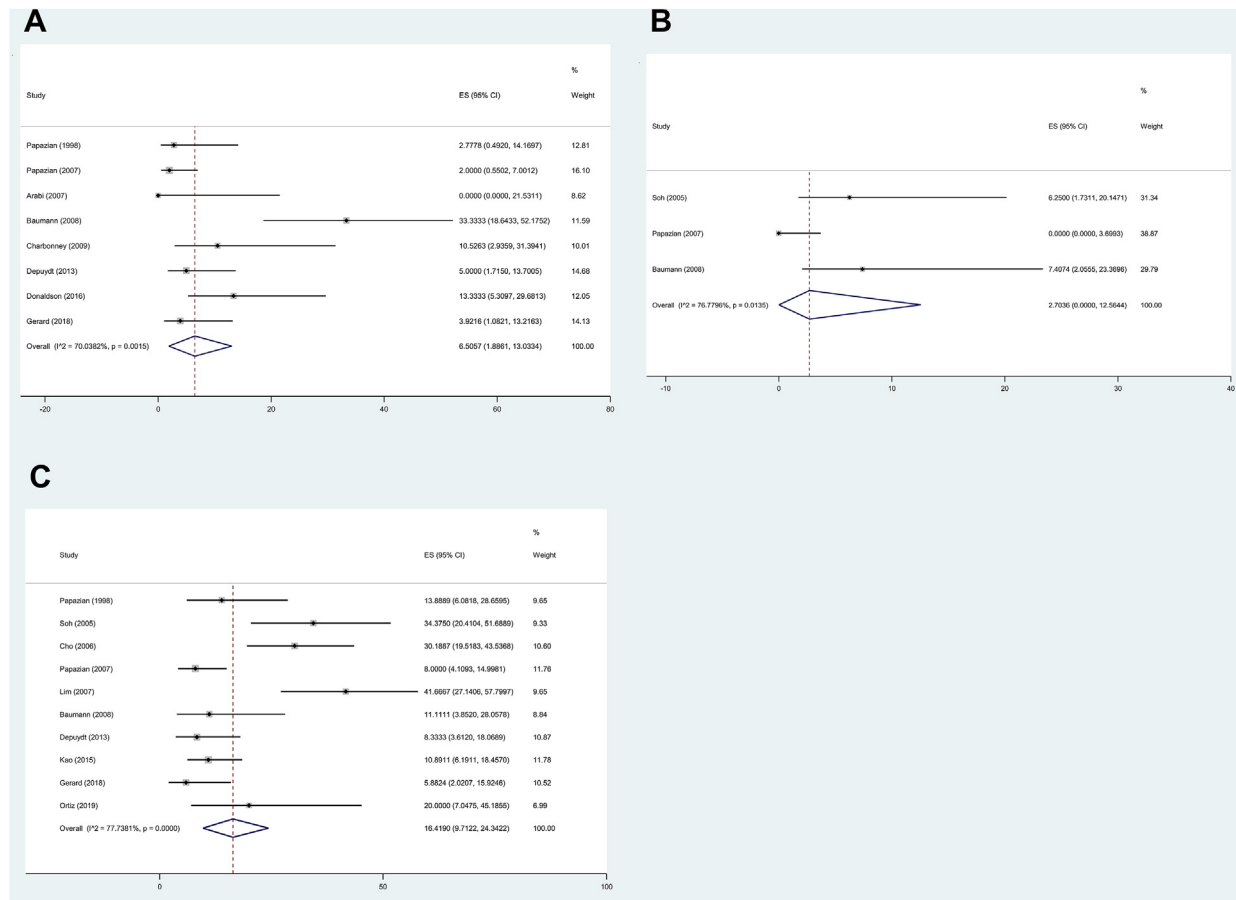
**Fig. 3 – Forest plot for the primary outcomes. (A) biopsy-related death; (B) respiratory failure; (C) cardiac complication; (D) bleeding; (E) other major complications.**

We found two previous meta-analyses; one assessed 22 studies and reported the frequency of all complications [3], and another assessed 14 studies and reported the frequency of all complications and persistent air leaks [4]. However, both studies focused on the diagnostic use of lung biopsy rather than safety and did not estimate 95% CIs in the frequency of each complication. In these studies, the frequencies of all complications, mixed from severe to mild complications, were insufficient for clinical decisions. In addition, the risk of bias assessment was not performed in the included studies, and the literature review process was not rigorous.

Furthermore, this study is the first systematic review and meta-analysis following the reporting guidelines (PRISMA-harm) and appropriate methodology. We assessed the risk of bias using McHarm and calculated the frequency of each complication with 95% CIs. Therefore, this study may be more valuable than previous studies regarding appropriate methodology.

#### 4.3. Clinical implications

Clinicians should determine whether to perform a lung biopsy for ARDS based on a balance between disadvantages and



**Fig. 4 – Forest plot for the secondary outcomes. (A) pneumothorax; (B) infection; (C) other minor complications.**

clinical benefits; therefore, the results of this study may be valuable as evidence considering safety and disadvantages.

The disadvantages of lung biopsy include complications and costs, such as medical resources. No study that assessed the cost of lung biopsy was included. In this study, serious complications of lung biopsy were less than 5%, with the most common complication being persistent air leak. These results are consistent with those of previous studies [3,4]. According to a recent meta-analysis published in 2015, the complication rate of OLB was 29% (95% CI: 25%–33%), and the most common complication was persistent air leak [4]. These results are similar to those of this study, although we excluded studies lacking data for each outcome from the meta-analysis to avoid underestimation. Therefore, the results of this study are reasonable. Persistent air leaks that required surgery were relatively rare (two of 77 persistent air leaks) and may not be a reason to avoid lung biopsy if properly managed. However, considering the potential risk of indirect lung injury associated with the biopsy procedures and complications is also necessary. For instance, air leaks may limit high positive-end expiratory pressure, and prone positioning is difficult if chest tube placement is required.

In addition to the merits of confirmation or exclusion of diagnosis, some clinical benefits of a lung biopsy for ARDS have been reported. First, lung biopsy for ARDS may be useful in predicting the response to corticosteroid therapy. While it is still controversial, corticosteroids are considered effective

against ARDS [25]. It has been reported that OLB could identify a corticosteroid-sensitive pathology associated with lower hospital mortality in patients with ARDS [18]. Furthermore, lung biopsy for ARDS may be able to estimate the prognosis of ARDS. It has been reported that ARDS patients with pathological DAD have poorer survival than those without DAD [26,27].

Consequently, the information about the complications of lung biopsy in patients with severe respiratory failure, including ARDS, may be useful, particularly in patients with unknown etiology and in settings that require justification for using corticosteroids.

#### 4.4. Limitations

This study has some limitations. First, this systematic review and meta-analysis did not include all studies that should be included. We did not search for EMBASE and excluded non-English publications because of poor accessibility in Japan. Furthermore, some studies were excluded from our meta-analysis due to a lack of data, although we had tried to contact the authors of the primary studies; therefore, a risk of selection bias may be present.

Second, the number of studies and patients included in this study may be too small to assess rare complications, such as biopsy-related death. In addition, most included studies had a high risk of bias, and the quality of the study design in

each included study was poor. No randomized controlled trial was identified in this study, and only two of the 13 included studies were prospective cohort studies. These limitations may decrease the certainty of the results of this study.

Furthermore, the inclusion criteria for each included study had heterogeneity (i.e., ARDS defined by the Berlin criteria or by the AECG criteria and ARF). Patients' conditions, such as coagulopathy, have not been evaluated appropriately. Therefore, more studies and patients may enable us to create subgroups that assess heterogeneity. In addition, studies differed in their definition of complications. It was difficult to distinguish between biopsy-related deaths and deaths due to underlying diseases, particularly in a retrospective cohort study. While no biopsy-related death was identified in our study, real-world data showed that non-elective SLB for interstitial lung disease had a 16.0% in-hospital mortality [28]. This discrepancy suggests that the results of the meta-analysis may be underestimated, and further studies are needed to clarify the definition of complications.

Finally, we could not determine the complications of TBLB or cryobiopsy for ARDS because of a lack of data. In addition, this study did not evaluate the effect of bronchoalveolar lavage, which is often performed simultaneously with a lung biopsy. Therefore, further studies on the complications of lung biopsies using bronchoscopy for ARDS are required.

---

## 5. Conclusions

We conducted a systematic review and meta-analysis that focused on the complications of a lung biopsy for ARF or ARDS. In this study, no biopsy-related deaths were identified under the median overall hospital mortality of 53%, and the pooled frequency of severe complications was <5%. These results will be valuable information in considering the indications of lung biopsy in patients with ARF, including ARDS.

---

## Ethics approval and consent to participate

Not Applicable.

---

## Consent for publication

Not applicable.

---

## Availability of data and materials

The data used in this meta-analysis were obtained from the articles corresponding to references in our reference list.

---

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

---

## Author contributions

Study design: All authors.

Literature Search: YF.

Screening: YF, HS, and HI.

Data extraction: YF, HS, HI, and YY.

Quality assessment: YF, HS, HI, and YY.

Analysis: HS, YY, and KA.

Writing the draft: HS.

All authors discussed the important intellectual content in the draft and revised the manuscript. All authors also approved the final draft and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

---

## Conflicts of Interest

The authors have no conflicts of interest.

---

## Acknowledgments

We thank all the members of the Japanese ARDS Clinical Practice Guideline Committee of the Japanese Society of Respiratory Care Medicine, the Japanese Respiratory Society, and the Japanese Society of Intensive Care Medicine. We also appreciate the librarian at Kyoto Prefectural University of Medicine Medical Library for developing the search strategy.

---

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resinv.2022.08.008>.

---

## REFERENCES

- [1] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al., ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526–33.
- [2] Zhang Z, Spieth PM, Chiumello D, Goyal H, Torres A, Laffey JG, et al. Declining mortality in patients with acute respiratory distress syndrome: an analysis of the acute respiratory distress syndrome network trials. *Crit Care Med* 2019;47:315–23.
- [3] Libby LJ, Gelbman BD, Altorki NK, Christos PJ, Libby DM. Surgical lung biopsy in adult respiratory distress syndrome: a meta-analysis. *Ann Thorac Surg* 2014;98:1254–60.
- [4] Wong AK, Walkey AJ. Open lung biopsy among critically ill, mechanically ventilated patients. A Metaanalysis. *Ann Am Thorac Soc* 2015;12:1226–30.
- [5] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–34.

- [6] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016;352:i157.
- [7] Fukuda Y, Sugimoto H, Yamada Y, Ito H, Tanaka T, Yoshida T, et al. Safety and feasibility of lung biopsy in diagnosis of acute respiratory distress syndrome: protocol for a systematic review and meta-analysis. *BMJ Open* 2021;11:e043600.
- [8] Chou R, Aronson N, Atkins D, Ismaila A, Santaguida P, Smith D, et al. Assessing harms when comparing medication interventions. *Methods guide for effectiveness and comparative effectiveness reviews*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008.
- [9] Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.
- [10] Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat* 1950;21:607–11.
- [11] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;7:177–88.
- [12] Arabi Y, Ahmed R, Ahmed Q, Rahman MU, Yamani N. Risks and benefits of open-lung biopsy in the mechanically ventilated critically ill population: a cohort study and literature review. *Med Sci Mon Int Med J Exp Clin Res* 2007;13:CR365–71.
- [13] Baumann HJ, Kluge S, Balke L, Yekebas E, Izbicki JR, Amthor M, et al. Yield and safety of bedside open lung biopsy in mechanically ventilated patients with acute lung injury or acute respiratory distress syndrome. *Surgery* 2008;143:426–33.
- [14] Charbonney E, Robert J, Pache JC, Chevrolet JC, Eggimann P. Impact of bedside open lung biopsies on the management of mechanically ventilated immunocompromised patients with acute respiratory distress syndrome of unknown etiology. *J Crit Care* 2009;24:122–8.
- [15] Cho MH, Malhotra A, Donahue DM, Wain JC, Harris RS, Karpaliotis D, et al. Mechanical ventilation and air leaks after lung biopsy for acute respiratory distress syndrome. *Ann Thorac Surg* 2006;82:261–6.
- [16] Donaldson LH, Gill AJ, Hibbert M. Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review. *Intern Med J* 2016;46:1306–10.
- [17] Depuydt OE, Daeze C, Benoit D, Praet M, Vermassen E, Decruyenaere M. Diagnostic potential of open lung biopsy in mechanically ventilated patients with diffuse pulmonary infiltrates of unclear aetiology. *Anaesth Intensive Care* 2013;41:610–7.
- [18] Gerard L, Bidoul T, Castanares-Zapatero D, Wittebole X, Lacroix V, Froidure A, et al. Open lung biopsy in nonresolving acute respiratory distress syndrome commonly identifies corticosteroid-sensitive pathologies, associated with better outcome. *Crit Care Med* 2018;46:907–14.
- [19] Kao KC, Hu HC, Chang CH, Hung CY, Chiu LC, Li SH, et al. Diffuse alveolar damage associated mortality in selected acute respiratory distress syndrome patients with open lung biopsy. *Crit Care* 2015;19:228.
- [20] Lim SY, Suh GY, Choi JC, Koh WJ, Lim SY, Han J, et al. Usefulness of open lung biopsy in mechanically ventilated patients with undiagnosed diffuse pulmonary infiltrates: influence of comorbidities and organ dysfunction. *Crit Care* 2007;11:R93.
- [21] Ortiz G, Garay M, Mendoza D, Cardinal-Fernández P. Impact and safety of open lung biopsy in patients with acute respiratory distress syndrome (ARDS). *Med Intensiva* 2019;43:139–46.
- [22] Papazian L, Thomas P, Bregeon F, Garbe L, Zandotti C, Saux P, et al. Open-lung biopsy in patients with acute respiratory distress syndrome. *Anesthesiology* 1998;88:935–44.
- [23] Papazian L, Doddoli C, Chetaille B, Gernez Y, Thirion X, Roch A, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med* 2007;35:755–62.
- [24] Soh LH, Chian CF, Su WL, Yan HC, Perng WC, Wu CP. Role of open lung biopsy in patients with diffuse lung infiltrates and acute respiratory failure. *J Formos Med Assoc* 2005;104:17–21.
- [25] Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. *Nat Rev Dis Prim* 2019;5:18.
- [26] Cardinal-Fernández P, Bajwa EK, Dominguez-Calvo A, Menéndez JM, Papazian L, Thompson BT. The presence of diffuse alveolar damage on open lung biopsy is associated with mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Chest* 2016;149:1155–64.
- [27] Cardinal-Fernandez P, Ortiz G, Chang CH, Kao KC, Bertreau E, Philipponnet C, et al. Predicting the impact of diffuse alveolar damage through open lung biopsy in acute respiratory distress syndrome—the PREDATOR study. *J Clin Med* 2019;8:829.
- [28] Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016;193:1161–7.