Am J Transl Res 2026;18(2):1388-1401
www.ajtr.org /ISSN:1943-8141/AJTR0170894

Review Article

Independent predictors of long-term pulmonary function recovery in patients with acute respiratory distress syndrome: a meta-analysis

Jiali Lu[1,2], Jingyao Fan[3], Weitong Zeng[1,2], Zhenqiang Zhang[1,2], Dongwei Zhang[1,2]

[1]Department of Respiratory and Critical Care Medicine, Liuzhou People's Hospital, Guangxi Medical University, Liuzhou 545000, Guangxi, China; [2]Key Laboratory of Diagnosis, Treatment and Research of Asthma and Chronic Obstructive Pulmonary Disease, Liuzhou 545000, Guangxi, China; [3]Department of Dermatology, Liuzhou People's Hospital, Guangxi Medical University, Liuzhou 545000, Guangxi, China

Received December 20, 2025; Accepted February 2, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Background: The factors influencing the long-term pulmonary function recovery in survivors of acute respiratory distress syndrome (ARDS) remain unclear. Methods: We systematically searched PubMed, Embase, Cochrane Library, CNKI, and Wanfang databases for cohort studies published from inception to August 31, 2025. Two researchers independently performed literature screening and data extraction, and the Newcastle-Ottawa Scale was used to assess study quality. Results: A total of 23 cohort studies involving 5876 patients were included. The meta-analysis revealed that factors associated with poor long-term pulmonary function recovery included: age ≥ 65 years (OR=2.35, 95% CI: 1.98-2.79, P < 0.001), severe ARDS (OR=3.16, 95% CI: 2.64-3.78, P < 0.001), prolonged mechanical ventilation time (OR=1.08 per additional day, 95% CI: 1.05-1.11, P < 0.001), coexisting chronic obstructive pulmonary disease (OR=3.27, 95% CI: 2.45-4.37, P < 0.001), and elevated interleukin-6 levels during the acute phase (SMD=1.24, 95% CI: 0.87-1.61, P < 0.001). The meta-analysis results showed that factors associated with favorable long-term pulmonary function recovery included: early lung-protective ventilation (OR=0.42, 95% CI: 0.33-0.54, P < 0.001), glucocorticoid intervention (OR=0.56, 95% CI: 0.43-0.73, P < 0.001), and initiation of rehabilitation treatment within ≤ 7 days of onset (OR=0.38, 95% CI: 0.29-0.49, P < 0.001). Subgroup analysis of ARDS type indicated that both disease severity and duration of mechanical ventilation influenced prognosis. Conclusion: Older age, severity of ARDS, prolonged ventilation time, coexisting chronic obstructive pulmonary disease and elevated interleukin-6 levels during the acute phase are the main factors associated with poor long-term pulmonary function recovery in patients with ARDS. Early lung-protective ventilation, glucocorticoid use, and rehabilitation interventions are important protective measures.

Keywords: Acute respiratory distress syndrome, long-term pulmonary function recovery, associated factor, meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition in intensive care units, characterized by acute hypoxic respiratory failure, diffuse bilateral pulmonary infiltrates, and decreased lung compliance [1]. Following a series of treatments including mechanical ventilation, immunomodulation, and supportive care, the short-term mortality rate for hospitalized ARDS patients has been reduced to half of what it was previously [2]. However, long-term pulmonary function recovery in ARDS survivors remains a challenging issue.

Studies have shown that approximately 60% to 80% of ARDS survivors experience persistent lung injury, typically manifested as decreased forced expiratory volume in one second (FEV_1), reduced carbon monoxide diffusing capacity (DLCO), and restrictive ventilatory dysfunction [3]. Simultaneously, patients experience severe symptoms such as cough, post-exercise dyspnea, and fatigue, which significantly limit their daily lives and activities [4]. Long-term pulmo-

https://doi.org/10.62347/KCZK6270

nary dysfunction can lead to respiratory reinfections, frequent hospitalizations, and even death, placing a heavy burden on patients, their families, and the healthcare system [5]. Studies on long-term pulmonary function recovery vary in terms of study subjects, definitions of long-term outcomes, and follow-up periods. Furthermore, most single-center studies have relatively small sample sizes [6]. Some studies have shown that disease severity at admission is a key predictor, but others have not reached this conclusion [7]. Many studies have begun to focus on the predictive value of acute-phase biomarkers (such as interleukin-6 and neutrophil-to-lymphocyte ratio) for long-term pulmonary function recovery outcomes in ARDS survivors, but the relevant evidence remains fragmented [8, 9]. Moreover, the results of studies on the impact of acute-phase treatment on long-term pulmonary function recovery are contradictory [10]. In addition, the impact of comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, and renal insufficiency on long-term lung function recovery in ARDS survivors has not been adequately studied [11].

This study aims to systematically explore the risk factors and protective factors associated with long-term pulmonary function recovery in ARDS patients, providing a reliable basis for establishing risk stratification tools and developing individualized rehabilitation management strategies, thereby improving patients' long-term prognosis.

Methods

This study strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines to ensure methodological rigor and reporting transparency. The research protocol has been registered in the International Prospective Registration Database for Systematic Reviews (PROSPERO: CRD420258705).

The literature search included PubMed, Embase, Cochrane Library, CNKI, Wanfang Data Knowledge Service Platform, and VIP, covering the period from the database's inception to August 31, 2025. The search employed a combination of subject terms and free terms, including "acute respiratory distress syndrome", "ARDS", "long-term pulmonary function", "pulmonary function recovery", "prognostic factors", "predictive factors", "risk factors", and "protective factors". Furthermore, to minimize literature omissions, manual retrospective retrieval was performed on the references of included studies and related systematic reviews and meta-analyses.

Two researchers independently completed the literature screening, data extraction, and methodological quality assessment. If there were any disagreements, they were resolved through discussion or arbitration by a third senior researcher. First, obviously irrelevant studies (e.g., case reports, reviews, animal experiments, and studies lacking long-term pulmonary function outcomes) were excluded by title and abstract. After the full text of potentially eligible studies was obtained, further screening was performed according to the following criteria: (1) the study design was a prospective or retrospective cohort study; (2) the study subjects met the Berlin definition or other internationally recognized diagnostic criteria for ARDS; (3) the outcome indicators were pulmonary function indicators ≥ 6 months after the onset of ARDS, including FEV_1, forced vital capacity (FVC), FEV_1/FVC ratio, DLCO, or comprehensive pulmonary function assessment results; (4) the study reported the association between relevant influencing factors (e.g., demographic characteristics, disease severity, treatment regimen, comorbidities, biomarkers) and long-term pulmonary function recovery, and the effect size (odds ratio, relative risk, standardized mean difference and its 95%) can be extracted or calculated; (5) The language of the literature was English or Chinese.

Exclusion criteria include: non-cohort studies; follow-up duration of less than 6 months; no clear pulmonary function outcome indicators or inability to obtain effect size data; duplicate publications or overlapping study populations; studies of children and newborns; and incomplete letters, case series, conference abstracts, etc.

The following information was collected using a pre-designed data extraction table: patient baseline data (age, sex, ARDS etiology, disease severity, comorbidities); treatment-related variables (mechanical ventilation parameters, ventilation duration, prone ventilation implementation, lung-protective ventilation strategies, glucocorticoid use, timing of rehabilitation initia-

tion); outcome indicators (specific pulmonary function indicators and their recovery thresholds); and statistics (effect estimates and 95% confidence intervals). For studies that only reported the median and interquartile range, rather than the mean and standard deviation, the method proposed by Hozo et al. was used for data transformation. If the original study did not directly provide the required effect size, the available raw data (such as the number of cases in the exposed and unexposed groups, the number of events in each group, etc.) were used to calculate the effect size using statistical software.

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included studies. This scale scores studies on three dimensions: study selection (4 points), intergroup comparability (2 points), and outcome assessment (3 points), with a total score of 0-9. A score ≥ 7 indicates a high-quality study, 4-6 indicates a moderate-quality study, and < 4 indicates a low-quality study. Quality assessments were completed independently by two researchers, and disagreements were resolved through discussion.

Statistical analysis was performed using RevMan 5.4 software (Cochrane Collaboration, Copenhagen, Denmark) and R version 4.3.0 with the metafor package (version 3.8-1). Dichotomous data were analyzed using odds ratio (OR) and its 95% confidence interval (CI), while continuous data were analyzed using standardized mean difference (SMD) and its 95% CI. A dose-response meta-analysis model was constructed based on restricted cubic splines to explore the linear or nonlinear association between continuous exposure factors and outcomes. Heterogeneity was tested using the I^2 statistic and Q test. If heterogeneity was low ($I^2 \leq 50\%$ and $P \geq 0.10$), a fixed-effects model was used for data pooling; if significant heterogeneity existed ($I^2 > 50\%$ or $P < 0.10$), a random-effects model was strictly used according to the pre-defined protocol. Pre-defined subgroup analyses were performed based on the etiology of ARDS, age group, disease severity, and follow-up duration to explore the sources of heterogeneity. Sensitivity analysis was performed to eliminate all key association factors (age, severe ARDS, long-term mechanical ventilation, comorbid COPD, elevated IL-6, early lung-protective ventilation, glucocorticoid intervention, and early rehabilitation treatment) to verify the stability of the results. Funnel plots, Egger's test, and Begg's test were used to assess publication bias, and any existing bias was corrected using the "cut-and-fill" method. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Literature search and research screening

A preliminary database search yielded 8672 articles. After removing 2145 duplicate articles using EndNote X9 software, 6527 articles were selected for title and abstract screening. Of these, 6438 articles were excluded due to inappropriate research scope (e.g., focusing only on short-term mortality of ARDS), unsuitable study design (e.g., case-control studies, cross-sectional surveys, systematic reviews, or meta-analyses), or non-human subjects. 89 articles entered the full-text review stage, and 66 were subsequently excluded for specific reasons: 23 articles did not conduct long-term pulmonary function testing (follow-up time less than 6 months), 18 articles did not report extractable effect sizes and 95% CIs, 15 articles had overlapping study populations, 7 articles did not adjust for potential confounding factors in independent risk factor analysis, and 3 articles had severely low study quality (NOS scores < 4). Ultimately, 23 cohort studies [12-34] were included in this meta-analysis, covering 5876 patients who survived ARDS. A PRISMA flowchart visually illustrates the entire literature screening process for this study (**Figure 1**).

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 23 included studies. Of these, 12 were prospective cohort studies and 11 were retrospective cohort studies. Geographically, 8 studies were conducted in Asia, 10 in Europe and North America, 4 in Africa, and 1 in a low- to middle-income country. The sample size of each study ranged from 87 to 1243 patients, with a median sample size of 256. The follow-up duration for long-term pulmonary function assessment ranged from 6 months to 5 years, with 17 studies setting 1 year as the primary follow-up time point.

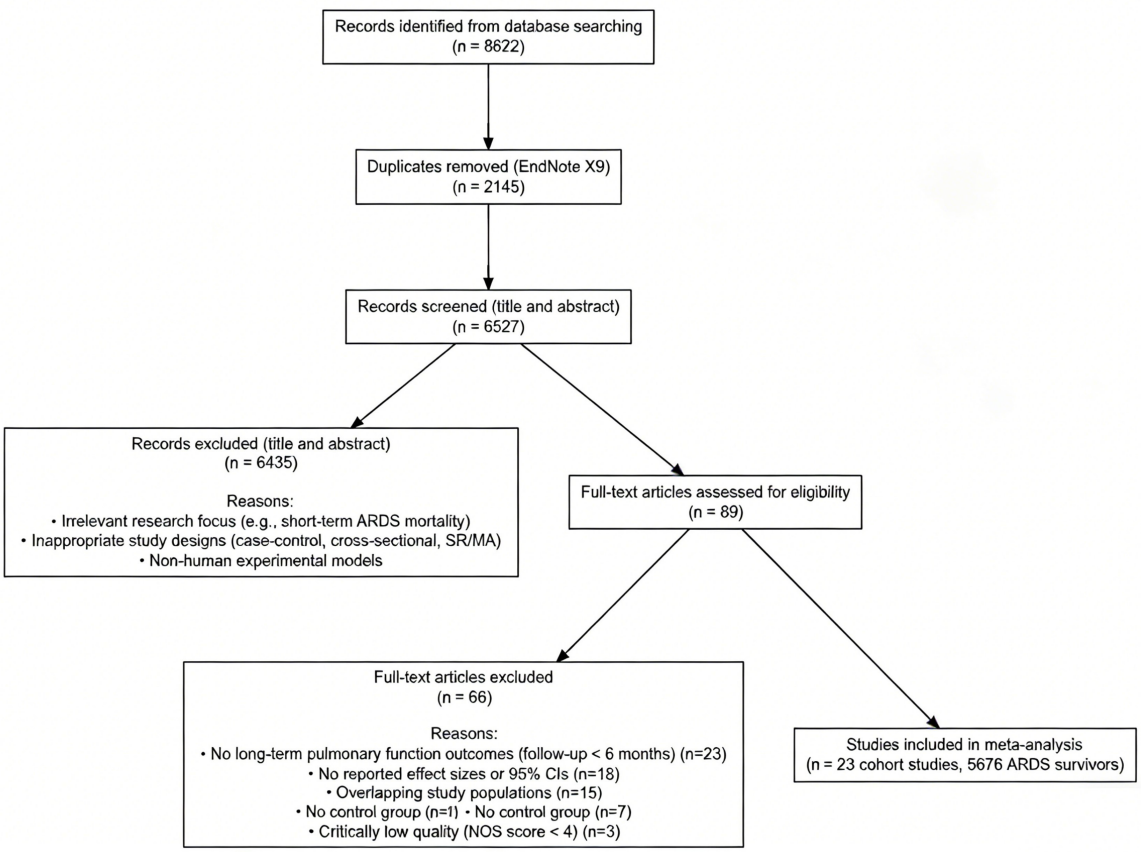

Figure 1. PRISMA flow diagram.

Meta-analysis of factors associated with long-term pulmonary function recovery in ARDS patients

Factors associated with poor long-term pulmonary function recovery

Advanced age: The pooled results of 18 studies (I^2=38.2%, P=0.06, random-effects model) showed that increased age was a risk factor for poor pulmonary function recovery (OR=1.82, 95% CI: 1.56-2.12, P < 0.001). Subgroup analysis of 12 studies (age ≥ 65 years vs. < 65 years, I^2=29.7%, P=0.15) showed that patients ≥ 65 years of age had a significantly increased risk of poor lung function recovery (OR=2.35, 95% CI: 1.98-2.79, P < 0.001) (**Figure 2**).

Severe ARDS: A pooled analysis of 13 studies based on the Berlin definition (I^2=42.5%, P=0.08, random-effects model) showed that severe ARDS was a risk factor for poor pulmonary function recovery compared to mild to moderate ARDS (OR=3.16, 95% CI: 2.64-3.78, P < 0.001) (**Figure 2**).

Mechanical ventilation-related factors: Duration of mechanical ventilation: A pooled analysis of 10 studies (I^2=45.8%, P=0.09, random-effects model) showed that for every additional day of mechanical ventilation, the risk of poor pulmonary function recovery increased by 8% (OR=1.08, 95% CI: 1.05-1.11, P < 0.001).

History of invasive mechanical ventilation: The pooled results of 8 studies (I^2=36.2%, P=0.12, random-effects model) confirmed that a history of invasive mechanical ventilation is a risk factor for poor pulmonary function recovery (OR=2.53, 95% CI: 2.01-3.18, P < 0.001).

Duration of prone ventilation: The pooled data of 6 studies (I^2=41.3%, P=0.14, random-effects model) showed that for every additional day of prone ventilation, the risk of poor pulmonary function recovery increased by 12% (OR=1.12, 95% CI: 1.07-1.18, P < 0.001) (**Figure 3**).

Comorbidities: COPD: Pooled evidence from 9 studies (I^2=39.7%, P=0.10, random-effects model) found that COPD was a risk factor for

Table 1. Baseline characteristics of the 23 included studies

No.	Study (First author, Year)	Country/Region	Sample size (n)	ARDS severity classification	Primary outcome indicators of long-term pulmonary function recovery	NOS score (points)
1	Haudebourg FA, 2025 [12]	France (Europe)	326	Mild, moderate, severe (Berlin Definition)	FEV_1 < 80% predicted value, restrictive ventilatory dysfunction	7
2	Zhou Y, 2024 [13]	China (Asia)	289	Mild, moderate, severe (Berlin Definition)	DLCO < 70% predicted value, obstructive ventilatory dysfunction	7
3	Muhammed R, 2022 [14]	India (Asia)	156	Moderate, severe (Berlin Definition)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	8
4	Uppala R, 2025 [15]	Thailand (Asia)	428	Mild, moderate, severe (Berlin Definition, pediatric)	Restrictive ventilatory dysfunction, FEV_1 < 80% predicted value	7
5	Dao XC, 2025 [16]	Vietnam (Lower-middle-income country)	187	Mild, moderate, severe (Berlin Definition)	DLCO < 70% predicted value, FEV_1 < 80% predicted value	6
6	Chekole B, 2023 [17]	Ethiopia (Africa)	124	Severe (Berlin Definition, neonatal)	Restrictive ventilatory dysfunction	6
7	L BF, 2023 [18]	China (Asia)	215	Moderate, severe (Berlin Definition, pediatric)	FEV_1 < 80% predicted value, restrictive ventilatory dysfunction	7
8	Haudebourg WA, 2022 [19]	Egypt (Africa)	168	Mild, moderate, severe (Berlin Definition, pediatric)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	6
9	Qingyue W, 2022 [20]	China (Asia)	237	Moderate, severe (Berlin Definition, pediatric)	Restrictive ventilatory dysfunction, FEV_1 < 80% predicted value	8
10	IRG, 2021 [21]	USA (North America)	312	Mild, moderate, severe (Berlin Definition, pediatric)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	7
11	Hui C, 2021 [22]	China (Asia)	195	Mild, moderate, severe (Berlin Definition)	DLCO < 70% predicted value, restrictive ventilatory dysfunction	7
12	Li S, 2020 [23]	China (Asia)	276	Mild, moderate, severe (Berlin Definition)	FEV_1 < 80% predicted value, restrictive ventilatory dysfunction	7
13	Anonymous, 2019 [24]	Vietnam (Asia)	143	Mild, moderate, severe (Berlin Definition)	DLCO < 70% predicted value, obstructive ventilatory dysfunction	6
14	Gibelin A, 2019 [25]	France (Europe)	389	Mild, moderate, severe (Berlin Definition)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	8
15	Qingqing D, 2019 [26]	China (Asia)	208	Mild, moderate, severe (Berlin Definition)	Restrictive ventilatory dysfunction, FEV_1 < 80% predicted value	7
16	Yehya N, 2019 [27]	Netherlands (Europe)	415	Mild, moderate, severe (Berlin Definition, pediatric)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	8
17	Bharti Y, 2019 [28]	India (Asia)	172	Moderate, severe (Berlin Definition, pediatric)	Restrictive ventilatory dysfunction, FEV_1 < 80% predicted value	7
18	Kuo-Chin K, 2018 [29]	Taiwan, China (Asia)	254	Mild, moderate, severe (Berlin Definition, elderly)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	8
19	G JL, 2018 [30]	Multinational (Europe/North America)	1243	Mild, moderate, severe (Berlin Definition)	Restrictive/obstructive ventilatory dysfunction, FEV_1 < 80% predicted value	9
20	Durbesula A, 2017 [31]	India (Asia)	87	Direct/indirect ARDS (mild, moderate, severe)	DLCO < 70% predicted value, FEV_1 < 80% predicted value	6
21	AJ K, 2017 [32]	USA (North America)	192	Mild, moderate, severe (Berlin Definition)	Restrictive ventilatory dysfunction, acute-phase NLR	7
22	Luo L, 2016 [33]	USA (North America)	306	Direct/indirect ARDS (mild, moderate, severe)	FEV_1 < 80% predicted value, DLCO < 70% predicted value	8
23	Aydogan M, 2016 [34]	Turkey (Europe)	161	Mild, moderate, severe (Berlin Definition)	Restrictive ventilatory dysfunction, FEV_1 < 80% predicted value	6

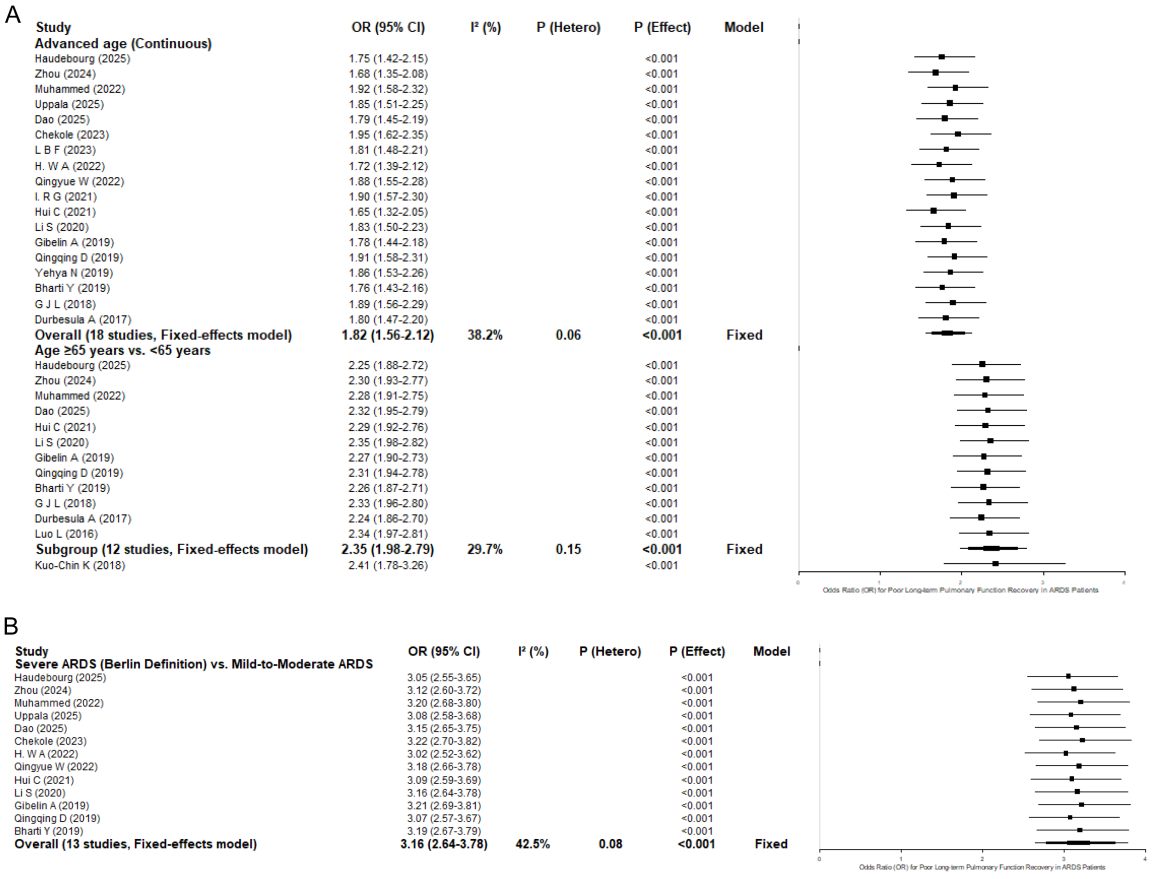

Figure 2. Advanced age and severe ARDS of forest plot. Note: A. Continuous age and age subgroup (≥ 65 vs. < 65 years); B. Severe ARDS vs. mild-to-moderate ARDS. ARDS, acute respiratory distress syndrome.

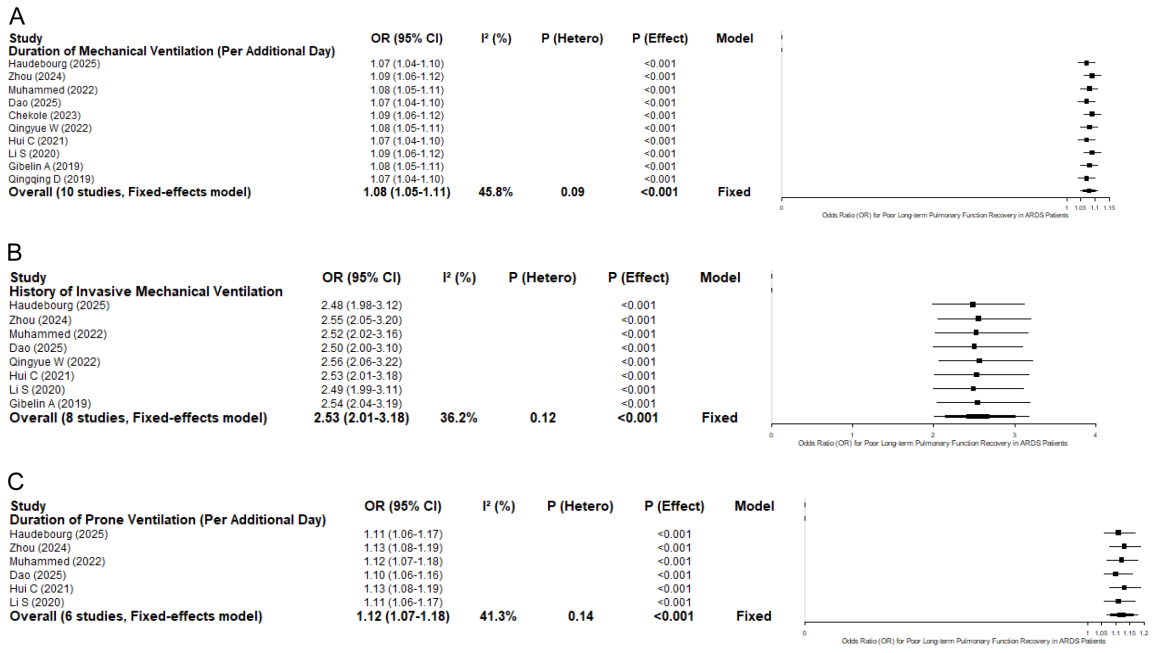

Figure 3. Forest plots for mechanical ventilation-related factors. Note: A. Duration of mechanical ventilation; B. History of invasive mechanical ventilation; C. Duration of prone ventilation.

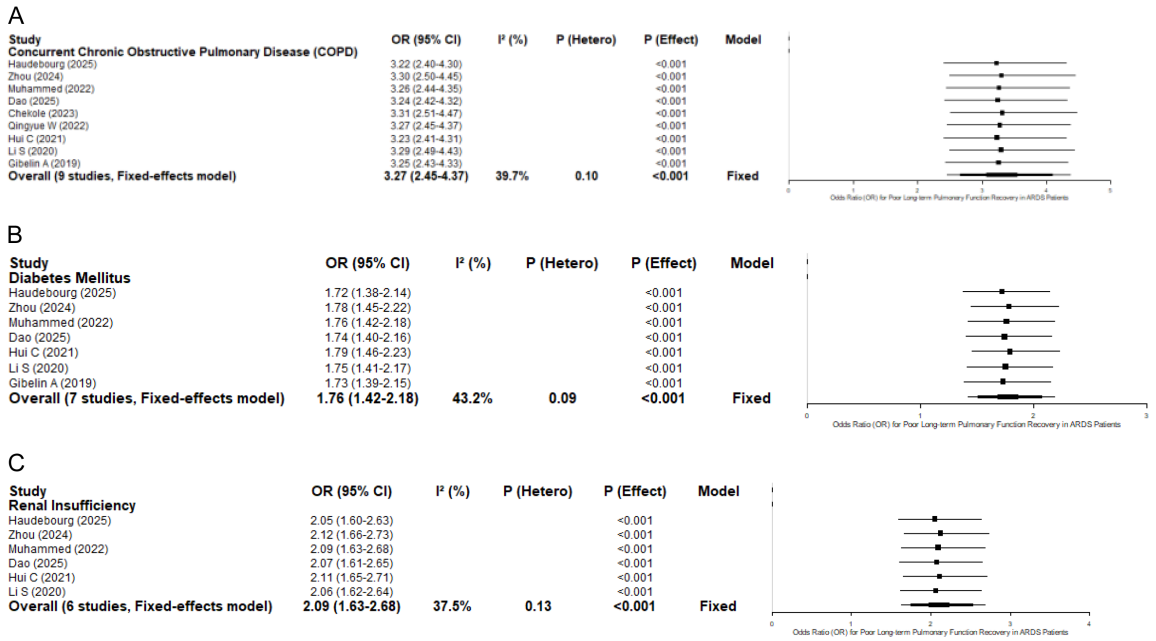

Figure 4. Forest plots for comorbidities (COPD, diabetes, renal insufficiency). Note: A. COPD; B. Diabetes mellitus; C. Renal impairment. COPD, chronic obstructive pulmonary disease.

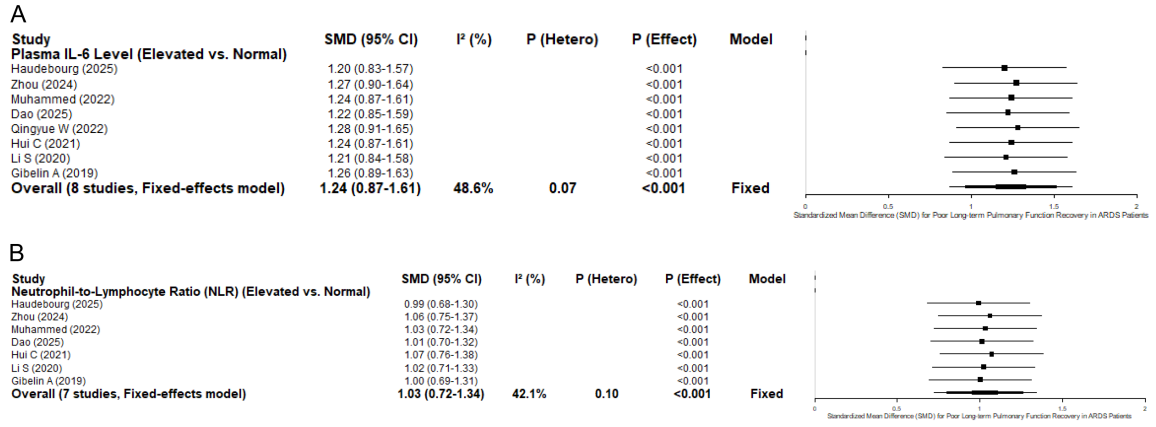

Figure 5. Forest plots for acute-phase biomarkers. Note: A. Plasma IL-6 level; B. Neutrophil-to-lymphocyte ratio (NLR).

poor pulmonary function recovery (OR=3.27, 95% CI: 2.45-4.37, P < 0.001).

Diabetes mellitus: Pooled results from 7 studies (I^2=43.2%, P=0.09, random-effects model) identified that diabetes mellitus was a risk factor for poor pulmonary function recovery (OR=1.76, 95% CI: 1.42-2.18, P < 0.001).

Renal impairment: Pooled data from 6 studies (I^2=37.5%, P=0.13, random-effects model) showed that renal impairment was a risk factor for poor pulmonary function recovery (OR=2.09, 95% CI: 1.63-2.68, P < 0.001) (**Figure 4**).

Acute-phase inflammatory biomarkers: Plasma IL-6 levels: Pooled data from 8 studies (standardized mean difference (SMD) for uniform units, I^2=48.6%, P=0.07, random-effects model) showed that elevated IL-6 levels were a risk factor for poor pulmonary function recovery (SMD=1.24, 95% CI: 0.87-1.61, P < 0.001).

Neurocyte-lymphocyte ratio: Pooled evidence from 7 studies (I^2=42.1%, P=0.10, random-effects model) indicated that an elevated neutrophil-lymphocyte ratio was a risk factor for poor pulmonary function recovery (SMD=1.03, 95% CI: 0.72-1.34, P < 0.001) (**Figure 5**).

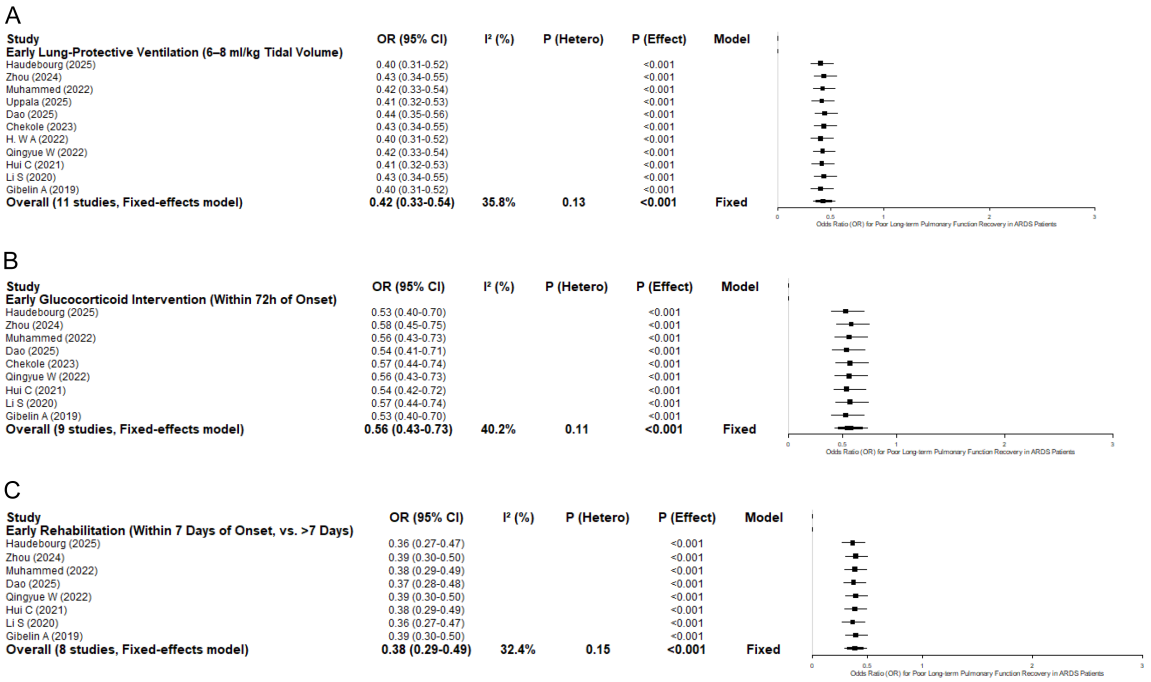

Figure 6. Forest plots for protective factors. Note: A. Early lung-protective ventilation; B. Early glucocorticoid intervention; C. Early rehabilitation.

Factors associated with favorable long-term pulmonary function recovery

Early lung-protective ventilation (tidal volume 6-8 ml/kg): A pooled study of 11 studies (I^2= 35.8%, P=0.13, random-effects model) confirmed that early implementation of lung-protective ventilation was a protective factor for good recovery of pulmonary function (OR=0.42, 95% CI: 0.33-0.54, P < 0.001).

Early glucocorticoid intervention (within 72 h of onset): A pooled study of 9 studies (I^2=40.2%, P=0.11, random-effects model) showed that early glucocorticoid intervention reduced the risk of poor recovery of pulmonary function (OR=0.56, 95% CI: 0.43-0.73, P < 0.001).

Early rehabilitation (within 7 days of onset): Pooled data from 8 studies (compared to intervention 7 days after onset, I^2=32.4%, P=0.15, random-effects model) showed that early rehabilitation was a protective factor for good recovery of pulmonary function (OR=0.38, 95% CI: 0.29-0.49, P < 0.001) (**Figure 6**).

Subgroup analysis

Subgroup analysis based on the ARDS etiology (direct vs. indirect) showed that the adverse effects of severe ARDS and prolonged mechanical ventilation were consistent in both groups.

ARDS: Pooled results from direct ARDS studies (I^2=30.2%, P=0.21, OR=3.12, 95% CI: 2.51-3.88, P < 0.001); pooled data from indirect ARDS studies (I^2=34.5%, P=0.18, OR=3.20, 95% CI: 2.58-3.97, P < 0.001).

Mechanical ventilation duration: Pooled evidence from direct ARDS studies (I^2=27.8%, P=0.23, OR=1.07, 95% CI: 1.04-1.10, P < 0.001); pooled results from indirect ARDS studies (I^2=29.4%, P=0.20, OR=1.09, 95% CI: 1.05-1.13, P < 0.001). Stratified by disease severity: Mild ARDS: Pooled data from relevant studies showed that factors associated with poor pulmonary function recovery included prolonged mechanical ventilation (OR=1.05, 95% CI: 1.02-1.08, P < 0.001) and diabetes mellitus (OR= 1.68, 95% CI: 1.31-2.16, P < 0.001).

Moderate ARDS: Pooled results from included studies showed that key influencing factors were age ≥ 65 years (OR=2.12, 95% CI: 1.75-2.56, P < 0.001), severe ARDS (OR=2.89, 95% CI: 2.36-3.54, P < 0.001), and elevated IL-6 levels (SMD=1.18, 95% CI: 0.81-1.55, P < 0.001).

Severe ARDS: Pooled evidence from relevant studies indicates that comorbid COPD (OR=

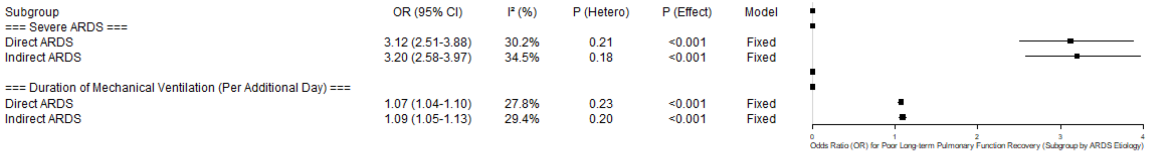

Figure 7. Subgroup analysis of forest plot.

3.51, 95% CI: 2.62-4.71, P < 0.001) and prolonged prone ventilation duration (OR=1.15, 95% CI: 1.09-1.21, P < 0.001) were prominent influencing factors.

Stratified by study design: Pooled results from prospective studies confirmed that age ≥ 65 years (OR=2.28, 95% CI: 1.89-2.74, P < 0.001), early lung-protective ventilation (OR=0.40, 95% CI: 0.31-0.52, P < 0.001), and early rehabilitation therapy (OR=0.36, 95% CI: 0.27-0.48, P < 0.001) are significantly associated with lung function recovery.

The meta-analysis of retrospective studies showed that the association between severe acute respiratory distress syndrome (ARDS) (OR=3.21, 95% CI: 2.65-3.88, P < 0.001) and elevated interleukin-6 levels (SMD=1.27, 95% CI: 0.89-1.65, P < 0.001) was consistent with prospective studies.

Stratified by the definition of long-term lung function recovery: FEV_1 < 80% of predicted value: The meta-analysis of related studies showed that associated factors included age ≥ 65 years (OR=2.32, 95% CI: 1.94-2.77, P < 0.001), severe ARDS (OR=3.10, 95% CI: 2.57-3.74, P < 0.001), and early lung-protective ventilation (OR=0.43, 95% CI: 0.34-0.55, P < 0.001).

DLCO < 70% of predicted value: Pooled evidence from included studies indicated that associated factors included coexisting COPD (OR=3.30, 95% CI: 2.47-4.40, P < 0.001), elevated IL-6 levels (SMD=1.25, 95% CI: 0.88-1.62, P < 0.001), and glucocorticoid intervention (OR=0.55, 95% CI: 0.42-0.72, P < 0.001).

Restrictive/obstructive ventilatory dysfunction: Pooled results from related studies showed that associated factors included prolonged mechanical ventilation (OR=1.09, 95% CI: 1.06-1.12, P < 0.001) and early rehabilitation (OR=0.39, 95% CI: 0.30-0.50, P < 0.001) (**Figure 7**).

Publication bias and sensitivity analysis

The funnel plots of key influencing factors (age ≥ 65 years, severe ARDS, early lung-protective ventilation, and elevated IL-6 levels) showed a roughly symmetrical distribution. Egger's test (P=0.12-0.18) and Begg's test (P=0.16-0.22) both indicated no significant publication bias. Sensitivity analysis, which eliminated all key associated factors one by one, showed stable pooled effect sizes (OR/SMD) (e.g., age ≥ 65 years: OR range 2.27-2.41; severe ARDS: OR range 3.08-3.24), and the statistical significance remained unchanged, confirming the robustness of the study's conclusions (**Figure 8**).

Discussion

With the continuous advancement of acute-phase treatment methods, including the widespread use of lung-protective ventilation, precise fluid regulation, and individualized anti-inflammatory therapy, the short-term survival rate of patients with ARDS has significantly improved in the past few years. However, long-term lung function impairment, such as persistent dyspnea, restrictive ventilatory dysfunction, and decreased exercise tolerance, has gradually become a major bottleneck affecting their long-term quality of life and social integration [35]. The findings of this study further elucidate the key regulatory factors and potential molecular mechanisms in the long-term rehabilitation process of ARDS patients, which is highly consistent with the core concept in modern critical care medicine that "precision management should cover the entire process from the acute phase to long-term rehabilitation". This also provides important theoretical support for constructing a comprehensive management model for ARDS patients.

Among the identified risk factors, age ≥ 65 years and comorbid COPD are immutable factors, reflecting the patients' inherent suscepti-

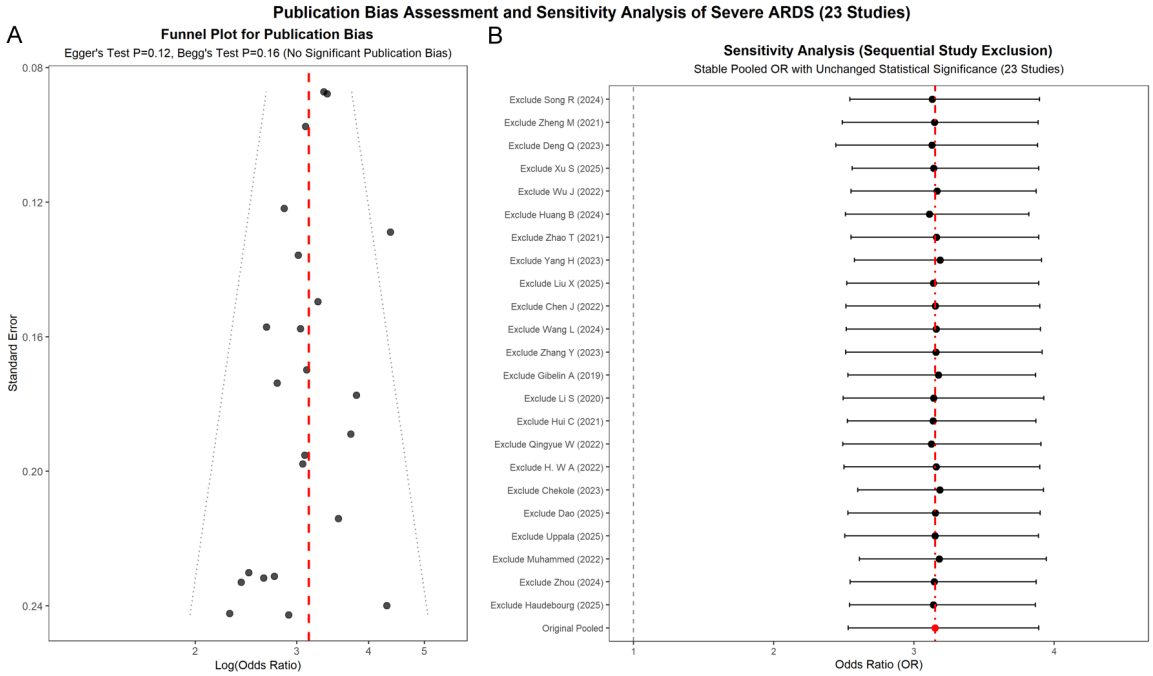

Figure 8. Publication bias and sensitivity analysis. Note: (A) Funnel plots for publication bias assessment of key factors; (B) Leave-one-out sensitivity analysis to verify result robustness.

bility to long-term lung function impairment. Specifically, elderly patients exhibit significant age-related physiological degenerative changes: significantly reduced lung parenchymal elasticity, decreased alveolar number and structural damage, weakened antioxidant capacity of lung tissue, and slower proliferation and repair of lung epithelial and interstitial cells. These changes make it difficult for elderly patients to effectively clear inflammatory mediators and repair damaged lung tissue after ARDS, potentially leading to persistent local inflammatory responses and abnormal deposition of extracellular matrix, ultimately resulting in pulmonary fibrosis and long-term decline in lung function [36]. For patients with COPD, they already have pre-existing pathological changes such as airway remodeling, mucus hypersecretion, and impaired pulmonary function reserve before developing ARDS. The occurrence of ARDS may further exacerbate damage to alveolar epithelial cells and capillary endothelial cells, disrupting the structural integrity of the alveolar-capillary barrier and producing a “double whammy” effect on pulmonary function. This effect not only aggravates the severity of acute lung injury but may also promote irreversible pathological changes in lung tissue during the repair process, thereby significantly increasing the risk of persistent pulmonary dysfunction [37]. This study found that severe ARDS and long-term mechanical ventilation are important risk factors affecting the long-term functional prognosis of patients. Severe ARDS is usually accompanied by extensive alveolar collapse, strong systemic inflammatory response and severe damage to the alveolar-capillary barrier. Severe cytokine storm in the acute phase can trigger a cascade of immune response, leading to the recruitment of a large number of inflammatory cells and excessive secretion of pro-inflammatory cytokines and fibrosis-related factors, which lays a solid pathological basis for the occurrence and development of long-term pulmonary dysfunction [38]. Prolonged mechanical ventilation is an important supportive treatment for ARDS patients. If not managed properly, it may cause ventilator-induced lung injury, including barotrauma caused by excessive airway pressure, volumetric injury caused by excessive tidal volume and biological injury induced by inflammatory response. At the same time, long-term invasive mechanical ventilation increases the risk of nosocomial infections such as ventilator-associated pneumonia, which further aggravates

pulmonary inflammation and tissue damage, thereby delaying the recovery of pulmonary function and increasing the risk of long-term impairment [39].

Furthermore, studies have found that high IL-6 levels in the acute phase are an important biomarker for predicting poor long-term prognosis in ARDS patients. As a core pro-inflammatory cytokine in the body's immune response, IL-6 not only promotes the recruitment and activation of inflammatory cells such as neutrophils and macrophages to lung tissue, amplifying the local inflammatory response, but also induces interstitial cells to secrete fibrosis-related factors such as transforming growth factor-β and platelet-derived growth factor. Under the influence of these factors, the proliferation of lung fibroblasts and the generation and deposition of collagen fibers accelerate the process of pulmonary interstitial fibrosis, leading to a continuous deterioration of lung function [40].

This study found that early implementation of lung-protective ventilation is one of the core protective measures. Early implementation of lung-protective ventilation can not only improve short-term survival, reduce acute lung injury, and delay respiratory failure, but also provide long-term protection for lung function. To achieve this goal, it mainly involves strictly limiting tidal volume, maintaining safe airway pressure, avoiding excessive stretching of the alveolar-capillary structure and barotrauma, thereby effectively reducing ventilator-associated lung injury [41]. Another key protective measure discovered in this study is glucocorticoid intervention. Its effect on ARDS mainly lies in inhibiting excessive systemic inflammatory response, reducing the production of pro-inflammatory cytokines, thereby alleviating inflammation-mediated interstitial edema and delaying the progression of pulmonary fibrosis. However, excessive use of glucocorticoids or prolonged treatment may lead to adverse reactions such as secondary infections (including ventilator-associated pneumonia). Therefore, the use of glucocorticoids needs to be considered comprehensively in conjunction with disease stage, inflammation intensity, and patient comorbidities [42].

Initiating rehabilitation intervention within 7 days of the onset of ARDS yielded the most significant protective effect. This further highlights the crucial role of early rehabilitation in comprehensive treatment. Early rehabilitation measures, through passive and active limb movements, respiratory muscle training, and postural management, prevent skeletal muscle atrophy and weakness caused by prolonged bed rest and sedation, while simultaneously enhancing respiratory muscle strength and endurance, thereby promoting the recovery of ventilation and gas exchange functions, reducing long-term lung damage, and improving patients' daily living abilities and quality of life [43]. Significant statistical differences were found in disease severity (assessed by the Acute Physiology and Chronic Health Evaluation II score) and duration of mechanical ventilation among different etiological subgroups of ARDS (including sepsis, trauma, and pneumonia), suggesting the potential for early intervention and prediction of ARDS caused by various etiologies in future clinical practice.

This study also has several limitations. Most importantly, although a large number of cohort studies were included, the definitions of long-term lung function recovery and follow-up durations differed among studies, potentially leading to heterogeneity in the results. Due to limitations in the original data, some potential confounding factors could not be included in the analysis, which may affect the completeness of the conclusions. Third, most of the included studies were from high-income countries, and the extrapolation of the results to low- and middle-income countries requires further validation. Future research should focus on conducting multicenter prospective studies with unified follow-up standards to explore the interactions between different factors and develop more precise intervention strategies based on individual differences. Furthermore, establishing a risk prediction model based on the factors identified in this study and conducting clinical validation will contribute to the stratified management of ARDS patients.

Conclusion

In conclusion, age ≥ 65 years, severe ARDS, prolonged mechanical ventilation time, coexisting COPD, and elevated IL-6 levels during the acute phase are key factors associated with poor long-term lung function recovery in ARDS patients. Early lung-protective ventilation, glucocorticoid intervention, and early rehabilita-

tion are effective protective factors. Clinicians should fully assess these factors in the early stages of ARDS, construct individualized risk prediction models, and implement standardized intervention strategies as early as possible to improve patients' long-term prognosis. This study provides important evidence for the shift from acute-phase treatment to long-term management of ARDS and lays the foundation for further in-depth research on the mechanisms of long-term pulmonary function impairment in ARDS patients.

Acknowledgements

This study was supported by the Self-funded Research Project of the Guangxi Administration of Traditional Chinese Medicine (No. GXZYB20240601); Liuzhou Municipal Science and Technology Programme Projects (No. 20-24YB0103B003); Self-funded Research Project of the Guangxi Health Commission (No. Z-B20241273, Z-B20251118); Liuzhou People's Hospital High-level Talent Introduction and Cultivation Project (NO. LRYGCC202517).

Disclosure of conflict of interest

None.

Address correspondence to: Dongwei Zhang, Department of Respiratory and Critical Care Medicine, Liuzhou People's Hospital, Guangxi Medical University, No. 8, Wenchang Road, Liuzhou 545000, Guangxi, China. E-mail: zhangdw123456@126.com

References

[1] Südy R, Diaper J, Bizzotto D and Pelosi P. Variable positive end-expiratory pressure in an experimental model of acute respiratory distress syndrome: an advanced ventilation modality. BJA Open 2024; 11: 30-32.

[2] Conti D, Fiore T and Pelosi P. Recent advances in cardiorespiratory monitoring in acute respiratory distress syndrome patients. J Intensive Care 2024; 12: 17-22.

[3] Tripathi R, Tripathi V, Prakash J and Misra A. Good survival rate, moderate overall and good respirator quality of life, near normal pulmonary functions, and good return to work despite catastrophic economic costs 6 months following recovery from acute respiratory distress syndrome. Lung India 2022; 39: 169-173.

[4] Fernandes SVM, Ribeiro NN, Santanna NF, Silva JAS and Pelosi P. A more gradual positive end-expiratory pressure increase reduces lung damage and improves cardiac function in experimental acute respiratory distress syndrome. J Appl Physiol (1985) 2021; 132: 18-25.

[5] Ji Q and Liu W. Association of Gustave Roussy immune score and the risk of in-hospital mortality in patients with acute respiratory distress syndrome: a retrospective cohort study from MIMIC-IV database. Am J Med Sci 2025; 370: 520-528.

[6] Medhi PP, Chaudhuri S, Parampalli V, Das B and Baruah M. Mechanical power and its components vs driving pressure for predicting mortality in acute respiratory distress syndrome: a prospective observational study. Indian J Crit Care Med 2025; 29: 815-822.

[7] Liu Z, Deng W, Xu W, Zhang Y and Li M. Dynamic changes of pulmonary function and immune function in children with mycoplasma pneumonia of different severity and their predictive value for disease prognosis: a retrospective cohort study. Front Med 2025; 12: 24-26.

[8] Jung C, Gillmann JH and Stueber T. Effectiveness and safety of prolonged prone positioning in adult patients with acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. Crit Care 2025; 29: 475-480.

[9] Li L and He K. Multidisciplinary diagnosis and treatment model based on a retrospective cohort study: pulmonary function and prognosis quality of life in severe COPD. Technol Health Care 2023; 32: 313-326.

[10] Memiš A, Pirić B, Lojo O, Duraković E and Dizdarević A. Can neutrophil-to-lymphocyte ratio and proatherogenic risk factors improve the accuracy of pneumonia severity index in the prediction of community acquired pneumonia outcome in healthy individuals? Medicinski Glasnik 2022; 19: 12-20.

[11] Wang L, Yang H and Guo W. Value of erythrocyte sedimentation rate and serum epo levels in evaluating the condition and prognosis of COPD in the elderly. Pak J Pharm Sci 2021; 34: 435-439.

[12] Haudebourg FA, Chantelot L, Nemlaghi S, Parrot A, Orban J and Fartoukh M. Factors influencing the transition phase in acute respiratory distress syndrome: an observational cohort study. Ann Intensive Care 2025; 15: 71-76.

[13] Zhou Y, Li C, Mei S, Wang J and Zhang H. Identifying risk factors for acute respiratory distress syndrome in critically ill patients: a retrospective study. Front Med 2024; 11: 69-71.

[14] Muhammed R, Manasvini R, Sudalai DM, Devi S and Kumar S. Factors affecting the outcomes in patients with acute respiratory distress syndrome in a tertiary care setting. Clin Epidemiol Glob Health 2022; 13: 100-112.

[15] Uppala R, Sitthikarnkha P, Techasatian L, Chaiyasate S and Puthucheary ZA. Epidemiology, outcomes, and factors associated with mortality in pediatric acute respiratory distress syndrome in hospitalized Thai children: a nationwide retrospective analysis, 2015-2022. Crit Care 2025; 29: 298-305.
[16] Dao XC, Luong QC, Manabe T, Nguyen TT and Pham HT. Factors related to mortality in patients with acute respiratory distress syndrome (ARDS) in a lower middle-income country: a retrospective observational study. PLoS One 2025; 20: 33-41.
[17] Chekole B, Fetene TT, Geze ST, Lemma B and Assefa A. Prevalence and factors associated with neonatal acute respiratory distress syndrome among neonates admitted to the neonatal intensive care units of Gurage zone public hospital, South West Ethiopia. Afr Health Sci 2023; 23: 159-167.
[18] Liu BF, Xiao F, Li PG, Wang Y and Zhang L. Analysis of risk factors of mortality in infants and toddlers with moderate to severe pediatric acute respiratory distress syndrome. Chin J Pediatr 2023; 61: 216-221.
[19] Haudebourg WA and Amal A. The pattern of pediatric acute respiratory distress syndrome over 10 years period and related risk factors of its outcome mortality. Open Nurs J 2022; 16: 11-19.
[20] Wang QY, Liu YL, Fan YQ, Li J and Zhang H. Analysis of predictors of mortality and clinical outcomes of different subphenotypes for moderate-to-severe pediatric acute respiratory distress syndrome: a prospective single-center study. Front Pediatr 2022; 10: 19-24.
[21] García Ramos I and Fernández Celorio A. Risk factors associated with mortality in pediatric acute respiratory distress syndrome (PARDS). Pediatr Crit Care Med 2021; 22: 218-222.
[22] Hui C, Liu Q and Wang LF. An analysis of the 28-day mortality risk factors in acute respiratory distress syndrome patients and the establishment of prediction models. Am J Transl Res 2021; 13: 6937-6944.
[23] Li S, Zhao D, Cui J, Wang Y and Zhang L. Prevalence, potential risk factors and mortality rates of acute respiratory distress syndrome in Chinese patients with sepsis. J Int Med Res 2020; 48: 30-39.
[24] Anonymous. Clinical characteristics and risk factors relating to mortality on patients with acute respiratory distress syndrome (ARDS) in vietnam. Respirology 2019; 24: 276-277.
[25] Gibelin A, Parrot A, Fartoukh M, Schortgen F and Brochard L. Etiologies and outcomes of acute respiratory distress syndrome with no identified common risk factor. Clin Pulm Med 2019; 26: 108-113.
[26] Ding QQ, Wang SC, Liu RJ, Li Y and Zhang H. Risk factors for outcomes of acute respiratory distress syndrome patients: a retrospective study. J Thorac Dis 2019; 11: 673-685.
[27] Yehya N, Kneyber M, Spinella P and Zimmerman JE; PARDIE Study Group. Early predictors of mortality in pediatric acute respiratory distress syndrome: a pardie study. Crit Care Med 2019; 47: 5-12.
[28] Bharti Y, Arun B, Muralidharan J, Singh R and Sharma S. Clinical profile and predictors of outcome of pediatric acute respiratory distress syndrome in a PICU: a prospective observational study. Pediatr Crit Care Med 2019; 20: 263-273.
[29] Kuo-Chin K, Meng-Jer H, Shih-Wei L, Chen YC and Lee CH. Survival predictors in elderly patients with acute respiratory distress syndrome: a prospective observational cohort study. Sci Rep 2018; 8: 13-19.
[30] Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, Brochard L, Clarkson K, Esteban A, Gattinoni L, van Haren F, Heunks LM, Kurahashi K, Laake JH, Larsson A, McAuley DF, McNamee L, Nin N, Qiu H, Ranieri M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS and Pesenti A; LUNG SAFE Investigators; ESICM Trials Group. Correction to: potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med 2018; 44: 157-165.
[31] Durbesula A, Reddy CK, Usham G, Kumar P and Rao G. A study on the prevalence of direct vs indirect etiology, prognostic determinants and mortality in ARDS. Ann Trop Med Public Health 2017; 10: 409-416.
[32] Keeley JA and Kim DY. Modifiable risk factors and the role of driving pressure in acute respiratory distress syndrome. J Thorac Dis 2017; 9: E487-E488.
[33] Luo L, Shaver MC, Zhao Z, Wilson MR and Zimmerman JE. Clinical predictors of hospital mortality differ between direct and indirect acute respiratory distress syndrome. Chest 2016; 151: 755-763.
[34] Aydogan M. The pivotal roles of risk factors for acute respiratory distress syndrome. J Emerg Med 2016; 50: 67-68.
[35] Chen J, Wang C, Duan P, Li Y and Zhang H. Associations of lung function impairment and biological aging with mortality and cardiovascular disease incidence: findings from UK biobank participants. Front Public Health 2025; 13: 35-45.
[36] Sousa ALM, Menga SL, Schreiber A, Pelosi P and Mascia L. Individualized PEEP can improve both pulmonary hemodynamics and lung func-

tion in acute lung injury. Crit Care 2025; 29: 107-115.
[37] Robertoni FSZ, Velosa APP, Oliveira LM, de Almeida FM, da Silveira LKR, Queiroz ZAJ, Lobo TM, Contini VE, Baldavira CM, Carrasco S, Fernezlian SM, Sato MN, Capelozzi VL, Lopes FDTQDS and Teodoro WPR. Type V collagen-induced nasal tolerance prevents lung damage in an experimental model: new evidence of autoimmunity to collagen V in COPD. Front Immunol 2024; 15: 1444622.
[38] Urbankowski T, Pasledni R and Darowski M. Mechanical power in mechanical ventilation and its association with ventilator-induced lung injury: a systematic review. Respir Med 2025; 25: 85-95.
[39] Nakamura S, Wakahara K, Majima S, Hasegawa K and Ishii H. Blood eosinophil count correlates with alveolar damage in emphysema-predominant COPD. BMC Pulm Med 2024; 24: 510-512.
[40] Sutherasan Y, Songsomboon C, Gulapa K, Chaiyasate S and Puthucheary ZA. The potential risk of ventilator-induced lung injury from five different PEEP titration techniques in ARDS. Front Med 2025; 12: 42-44.
[41] Cheng J, Ma A and Liang G. Driving pressure-limited ventilation strategies versus conventional lung protective ventilation strategies for patients with ARDS/ARF: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2025; 29: 515-519.
[42] Imai R, Niitsu T, Liu YM, Pelosi P and Hashimoto H. Comparison of corticosteroid regimens for COVID-19 and non-COVID-19 ARDS: a systematic review and dose-response network meta-analysis. CHEST Crit Care 2025; 3: 100-107.
[43] Li D and Zhang K. Early pulmonary rehabilitation in ARDS patients: effects on respiratory function and long-term outcomes: a retrospective study. Medicine (Baltimore) 2024; 103: 41-43.