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# Comparative Analysis of Efficacy and Pain Management in Acute Respiratory Failure: A Systematic Review and Meta-Analysis

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Zhu, XF.

**Corresponding author:**
Zhu Xiaofeng

zhml4081401@163.com

**Author Affiliation:**
Affiliated Jinhua Hospital, Zhejiang University School of Medicine.

**ADMINISTRATIVE INFORMATION**

**Support -** NA.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2024100058

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 October 2024 and was last updated on 14 October 2024.

## INTRODUCTION

**Review question / Objective** In this systematic review and meta-analysis, the objective is to evaluate the efficacy and pain management outcomes of various respiratory interventions in patients with acute respiratory failure (ARF) in intensive care unit (ICU) settings.
The study follows the PICOS framework:
Population: Critically ill patients diagnosed with acute respiratory failure (ARF) requiring intensive care.
Intervention: Respiratory interventions, including non-invasive ventilation (NIV), heated humidified high-flow oxygen (HHFO2), and pharmacological treatments such as morphine and dexmedetomidine.
Comparator: Standard care or alternative respiratory interventions, including mechanical ventilation or usual care in ICU settings.
Outcomes: Primary outcomes include the efficacy of interventions in stabilizing respiratory function and secondary outcomes related to pain management, patient comfort, and acceptability of the interventions.
Study Design: Randomized controlled trials (RCTs) assessing both the efficacy and pain management of interventions in ARF patients.
The review aims to synthesize available evidence to identify the most effective and patient-centered approaches for managing ARF in critically ill patients.

**Condition being studied** Acute respiratory failure (ARF).

## METHODS

**Search strategy** Ovid MEDLINE(R) ALL
1. Respiratory Distress Syndrome, Adult/ 25810
2. Acute Lung Injury/ 9166
3. (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. 53494
4. ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. 20433
5. exp Respiratory Insufficiency/ 69937

6. ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. 88052
7. 1 or 2 or 3 or 4 or 5 or 6 180712
8. exp randomized controlled trial/ 618875
9. controlled clinical trial.pt. 95571
10. randomized.ab. 652643
11. placebo.ab. 249998
12. clinical trials as topic/ 202794
13. randomly.ab. 437525
14. trial.ti. 313471
15. 8 or 9 or 10 or 11 or 12 or 13 or 14 1612936
16. exp animals/ not humans/ 5239184
17. 15 not 16 1486055
18. pain manag$.mp. or exp pain/ 506632
19. pain$.mp. 1005604
20. 18 or 19 1090643
21. 7 and 17 and 20 1539.

**Participant or population** The participants in this review are critically ill adult patients diagnosed with acute respiratory failure (ARF) who are receiving treatment in intensive care units (ICUs). These patients may suffer from conditions such as pneumonia, chronic obstructive pulmonary disease (COPD), acute lung injury (ALI), or sepsis, which have compromised their ability to maintain normal respiratory function. The population includes both those requiring non-invasive ventilation (NIV) or high-flow oxygen therapy and those who may receive pharmacological interventions such as morphine or dexmedetomidine for pain and sedation management. The focus is on adult populations across different geographic locations with no restrictions on age, gender, or ethnicity.

**Intervention** The interventions evaluated in this review include various respiratory and pharmacological therapies used to manage acute respiratory failure (ARF) in critically ill patients. These interventions are:

Non-invasive ventilation (NIV): Respiratory support provided without the need for invasive intubation, commonly used to manage ARF by assisting with breathing and improving oxygenation.

Heated humidified high-flow oxygen (HHFO2) therapy: Delivers heated and humidified oxygen at high flow rates to enhance oxygen delivery and reduce the work of breathing in patients with moderate to severe hypoxemia.

Pharmacological interventions:

Morphine: Used for pain management and to alleviate dyspnea in ARF patients.

Dexmedetomidine: A sedative used in critically ill patients to manage pain and anxiety while supporting respiratory function.
These interventions are aimed at improving respiratory stabilization, reducing the need for mechanical ventilation, and managing pain and discomfort associated with respiratory failure in the ICU setting.

**Comparator** The comparators in this review are the standard care or alternative respiratory interventions typically used in the management of acute respiratory failure (ARF) in intensive care unit (ICU) settings. These include:

Standard care: Conventional oxygen therapy or usual respiratory management without advanced interventions like non-invasive ventilation (NIV) or high-flow oxygen therapy.

Mechanical ventilation: Invasive ventilation support that involves intubation, which is often used in more severe cases of ARF.

Placebo or no intervention: For pharmacological interventions like morphine and dexmedetomidine, the comparator may include a placebo or no pain management/sedation intervention.

These comparators allow for the assessment of how the target interventions (NIV, HHFO2, pharmacological treatments) perform relative to routine care or other established respiratory treatments in ARF patients.

**Study designs to be included** RCTs.

**Eligibility criteria** Inclusion Criteria:

Randomized controlled trials (RCTs) evaluating respiratory or pharmacological interventions (such as non-invasive ventilation, high-flow oxygen therapy, morphine, or dexmedetomidine) for the treatment of acute respiratory failure (ARF) in critically ill adult patients.
Studies published in English with no geographical restrictions.
Trials that report measurable outcomes related to efficacy in stabilizing respiratory function and/or pain management.
Studies conducted in an intensive care unit (ICU) setting.
Exclusion Criteria:

Non-randomized trials, observational studies, case reports, case series, expert opinions, and qualitative studies.

Studies with incomplete or unavailable data for analysis.
Duplicated publications or studies where data cannot be extracted clearly.
Trials that focus on pediatric populations or other non-adult participants.
Studies published in languages other than English.

**Information sources** For this systematic review and meta-analysis, the following information sources will be used:

Electronic Databases:
Ovid Medline
Embase
Cochrane Central Register of Controlled Trials (CENTRAL)
PubMed
These databases will be searched comprehensively for relevant randomized controlled trials (RCTs) that evaluate respiratory and pharmacological interventions in acute respiratory failure (ARF).

Trial Registers:
ClinicalTrials.gov
International Clinical Trials Registry Platform (ICTRP)
These sources will be used to identify ongoing or unpublished trials that may meet the inclusion criteria.

Grey Literature:

Hand-searching conference proceedings, dissertations, and theses to capture relevant unpublished studies.
Contacting Authors:
When necessary, corresponding authors of relevant studies will be contacted to obtain missing data or clarifications on the methodology and results of their trials.

These comprehensive sources will ensure a thorough review of all available literature on the efficacy and pain management outcomes of ARF interventions.

**Main outcome(s)** Main Outcome(s)
The primary outcomes of this review are focused on evaluating both the efficacy and pain management of interventions for acute respiratory failure (ARF) in critically ill patients. The outcomes will be measured using the following parameters:

Efficacy of Respiratory Interventions:

Primary Measure: Improvement in respiratory function (e.g., oxygenation levels, respiratory rate, and avoidance of mechanical ventilation).
Timing: Outcomes will be measured at the end of the intervention period as reported in individual trials, with follow-up data where available.
Effect Measures: Odds ratios (ORs), risk ratios (RRs), or mean differences (MDs) with 95% confidence intervals (CIs), depending on the type of data reported in the studies.
Pain Management Outcomes:

Primary Measure: Change in patient-reported pain levels using validated pain scales (e.g., Visual Analog Scale (VAS), Numerical Rating Scale (NRS)).
Timing: Pain assessment at different time points during and after the intervention (e.g., during ICU stay or post-intervention follow-up).
Effect Measures: Mean differences (MDs) with 95% confidence intervals (CIs) in pain scores.
Secondary Outcomes:

Patient comfort and acceptability of interventions: Adverse events related to pain management or respiratory interventions.
Length of ICU stay: The duration of intensive care treatment.
Mortality rates: Measured at key time points (e.g., 28 days post-intervention or during ICU stay).
These outcomes will provide a comprehensive understanding of the impact of respiratory and pharmacological interventions on both clinical efficacy and patient comfort in ARF management.

**Quality assessment / Risk of bias analysis**
The quality of the included studies will be assessed using the Cochrane Risk of Bias tool for randomized controlled trials. This tool evaluates the risk of bias across several domains:

Selection Bias:

Assessed by evaluating the methods used for random sequence generation and allocation concealment. Studies will be rated as having a low, high, or unclear risk of bias based on how well these processes were described and implemented.
Performance Bias:

Assessed by examining whether blinding of participants and personnel was appropriately implemented, particularly for interventions where blinding is feasible (e.g., pharmacological treatments).
Detection Bias:

Focuses on the blinding of outcome assessors. The risk of bias will be judged based on whether blinding was maintained throughout the outcome assessment process.
Attrition Bias:

This will be evaluated by analyzing the completeness of outcome data, including whether there was differential dropout between intervention groups or if missing data were adequately addressed (e.g., through intention-to-treat analysis).
Reporting Bias:

Assessed by determining whether all pre-specified outcomes were reported in the study or if there is evidence of selective outcome reporting.
Other Bias:

Any additional biases, such as early stopping of trials for benefit or conflict of interest, will be considered.
Each domain will be classified as low risk, high risk, or unclear risk of bias. Studies that have a low risk of bias in most domains will be considered high quality, while those with high or unclear risk in multiple domains will be rated lower in quality. The risk of bias assessments will inform the interpretation of the review's findings and the robustness of the evidence base.

**Strategy of data synthesis** The data synthesis for this systematic review and meta-analysis will involve both qualitative and quantitative approaches, depending on the availability and consistency of data across the included studies.

Qualitative Synthesis:

A narrative synthesis will be provided for all included studies, describing key characteristics such as study design, population demographics, intervention details, and primary outcomes. The narrative synthesis will highlight similarities and differences between the studies and summarize the overall trends in efficacy and pain management outcomes for acute respiratory failure (ARF) interventions.
Special attention will be given to explaining variations in study methodologies, patient populations, and intervention modalities, particularly when meta-analysis is not feasible due to high heterogeneity.
Quantitative Synthesis (Meta-Analysis):

A meta-analysis will be conducted if the data from two or more studies are sufficiently homogeneous in terms of design, population, interventions, and outcomes.
Effect sizes will be calculated using appropriate statistical measures:
For dichotomous outcomes: Risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) will be used.
For continuous outcomes: Mean differences (MD) or standardized mean differences (SMD) with 95% CIs will be used.
A random-effects model will be applied to account for heterogeneity between studies, unless heterogeneity is negligible (in which case a fixed-effects model may be considered).
Assessment of Heterogeneity:

Heterogeneity will be assessed using the $I^2$ statistic and Cochrane's Q test.
$I^2$ values:
0-40% may indicate minimal heterogeneity.
30-60% suggests moderate heterogeneity.
50-90% indicates substantial heterogeneity.
75% suggests considerable heterogeneity.

If significant heterogeneity is found ($I^2 > 50\%$), potential sources of heterogeneity will be explored through subgroup analysis or sensitivity analysis (e.g., separating studies by intervention type, population characteristics, or study quality).

**Subgroup analysis** NA.

**Sensitivity analysis** NA.

**Language restriction** English.

**Country(ies) involved** China - Affiliated Jinhua Hospital, Zhejiang University School of Medicine.

**Keywords** Acute Respiratory Failure (ARF), efficacy, pain management, randomized controlled trials,meta-analysis.

**Contributions of each author**
Author 1 - Xiaofeng Zhu.
Email: zhml4081401@163.com