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SYSTEMATIC REVIEW

Comparative analysis of efficacy and pain management in acute respiratory failure: a systematic review and meta-analysis

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Abstract

Background: This meta-analysis aims to evaluate the efficacy and pain management outcomes of various interventions in patients with acute respiratory failure (ARF) in intensive care settings. **Methods**: To identify randomized controlled trials (RCTs) evaluating the effectiveness and outcomes of interventions for ARF in pain management, a thorough search was performed on the Ovid Medline database until August 2024. The quality of the studies was evaluated following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Effect sizes and 95% confidence intervals (CI) were computed utilizing a random-effects model, while heterogeneity was evaluated using I^2 statistics. **Results**: A total of 3000 participants from five studies were analyzed. The interventions demonstrated varying levels of efficacy and pain management outcomes, with overall significant efficacy (effect size 1.40, 95% CI: 1.05 to 1.87). Nevertheless, the results of pain management exhibited an overall tendency towards negative effect sizes, suggesting difficulties in effectively managing pain through the various interventions. The level of heterogeneity was deemed moderate (I^2 = 26%), highlighting variations in research methodologies and the characteristics of the patient cohorts. **Conclusion**: This meta-analysis indicates that while certain interventions significantly improve clinical outcomes in ARF patients, pain management remains a challenge. The results indicate a necessity for holistic strategies that blend effectiveness with patient well-being. Future studies should prioritize refining treatments to enhance both effectiveness and pain relief in the management of ARF. **The INPLASY Registration**: Our meta-analysis protocol was registered in INPLASY (registration number: INPLASY2024100058) and can be found at https://inplasy.com/inplasy-2024-10-0058/.

Keywords

Acute respiratory failure (ARF); Efficacy; Pain management; Randomized controlled trials; Meta-analysis

1. Introduction

Acute respiratory failure (ARF) is a common issue in critical care, marked by the respiratory system's incapacity to uphold proper gas exchange. Thorough evaluations of lung function, such as spirometry and tests on respiratory muscle strength, are vital for gauging the seriousness of ARF and customizing treatment plans [1, 2]. Thorough evaluations of lung function play a vital role in assessing the seriousness of ARF and customizing treatment plans. Recent research highlights the significance of incorporating pulmonary rehabilitation methods, like training for respiratory muscles (RMT) and utilizing high-flow oxygen therapy, to enhance the overall treatment results for ARF patients [3, 4]. These rehabilitation interventions have shown potential in enhancing patient recovery and reducing hospital stay, particularly in individuals with diminished inspiratory capacity.

Therapeutic strategies for ARF have envolved to include non-invasive ventilation (NIV) techniques and pharmacological interventions aimed at reducing the need for intubation and minimizing ventilator-associated complications [5–7]. RMT involves structured exercises targeting the diaphragm and intercostal muscles to enhance muscle function and endurance. Heated humidified high-flow oxygen ($HHFO_2$) therapy has gained prominence for its ability to enhance oxygen delivery and reduce work of breathing in patients with moderate to severe hypoxemia [8]. The dual effects of sedation and pain relief provided by pharmacological agents like dexmedetomidine and morphine have been under investigation. However, the effects of these agents on respiratory function and patient

comfort continue to be actively researched [8].

Even with the progress made in respiratory support technologies and pharmacotherapy, healthcare providers still face the ongoing challenge of striking a balance between effectively stabilizing respiration and addressing the pain and discomfort that accompany it. Pain, frequently overlooked in acute respiratory failure cases, has the potential to magnify stress reactions, hinder the recovery process, and extend the duration of intensive care unit stays [9]. Therefore, effective pain management is not only critical for patient comfort but also essential for optimizing overall treatment outcomes, as inadequate pain control may lead to heightened anxiety and diminished participation in rehabilitation efforts. Therefore, it is crucial to ensure effective pain control, as it not only contributes to patient comfort but also plays a vital role in enhancing the overall treatment results. The intricacy of this situation emphasizes the importance of a comprehensive strategy that tackles both the physical and emotional aspects of treating ARF. This study seeks to evaluate how different therapeutic interventions impact both the efficacy of ARF treatment and the management of pain. By synthesizing data from recent clinical trials, we aim to provide a comprehensive analysis of the efficacy of various interventions in ARF, with a particular focus on how these treatments influence pain levels and patient comfort. Our goal is to contribute to the development of holistic treatment frameworks that improve both survival and quality of life for patients suffering from ARF.

2. Methods

This systematic review and meta-analysis were conducted to evaluate the efficacy of various respiratory interventions on efficacy and pain management in patients with ARF in intensive care settings.

2.1 Study guideline

The present meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]. PRISMA 2020 Checklist is provided in **Supplementary material 1**. Our meta-analysis protocol was registered in INPLASY (registration number: INPLASY2024100058) and can be found at https://inplasy.com/inplasy-2024-10-0058/.

2.2 Literature search

The Ovid Medline electronic database was comprehensively searched up to August 2024 [8]. The search strategy, which was formulated in partnership with medical information experts, involved the inclusion of RCTs that examined respiratory interventions and their effects on patients with ARF. Specific keywords included “acute respiratory failure”, “pain management”, “clinical efficacy”, “pharmacological interventions”, “non-pharmacological interventions” and “critical care”. The search terms were intentionally broad to encompass a wide range of respiratory interventions, including pharmacological treatments, non-invasive ventilation techniques, and rehabilitation strategies such as respiratory muscle training. Detailed search strategy is provided in **Supplementary material 2**.

2.3 Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) RCTs; (2) Published up to August 2024; (3) No geographical restrictions; (4) Published in English. Criteria for exclusion comprised individual case reports, sets of cases, professional viewpoints, qualitative research, replicated publications, and studies lacking substantial data. It is acknowledged that certain studies may not have evaluated respiratory muscle strength as a principal outcome; however, they were considered due to their significance in the broader context of respiratory assistance and care in acute respiratory failure.

2.4 Data extraction

Two independent reviewers screened the titles and abstracts of retrieved articles after duplicate removal. Full texts of potentially eligible studies were subsequently reviewed to confirm inclusion. Information was retrieved by employing a uniform Excel spreadsheet, which recorded various details such as the primary author, year of publication, size of the sample, characteristics of participants, type of disease, research methodology, specifics of the intervention (including method and amount of administration), length of treatment, and duration of follow-up. In case of any inconsistencies, they were resolved by engaging in discussions until a consensus was reached. Any discrepancies in data extraction were resolved through discussion and consensus among the reviewers.

2.5 Data analysis

The primary outcomes of interest included the efficacy of respiratory interventions and pain management outcomes. To quantify the impact of interventions across studies, we calculated effect sizes using Cohen’s *d*, Hodges-Lehmann, and Cliff’s Delta, which allow for a standardized comparison of treatment effects between groups. A forest plot was generated to visually represent the effect sizes, facilitating a clear comparison across the included studies. Heterogeneity among studies was assessed using Tau^2 and Higgins’s I^2 statistics. An I^2 value of 25% was considered to represent low heterogeneity, 25–50% moderate heterogeneity, and greater than 50% high heterogeneity. Given that we observed moderate heterogeneity (I^2 = 26%), we performed sensitivity analyses by sequentially removing individual studies to assess their impact on the overall effect size. Additionally, subgroup analyses were conducted based on intervention types (pharmacological *vs.* non-pharmacological) and study quality to explore potential sources of heterogeneity and to enhance the robustness of our findings. All statistical analyses were conducted using RevMan Review Manager software (version 5.4.1, Cochrane, London, UK). We acknowledge the potential confounding factors that may influence the outcomes of the included studies, and we aim to synthesize the existing literature to identify trends and areas for further research.

3. Results

3.1 Study selection and characteristics

Our systematic search identified 1539 records through the Ovid Medline database, which was reduced to 1438 after the removal of duplicates. After the initial screening, 70 records underwent evaluation for relevance, leading to the review of 58 full-text articles to ascertain eligibility. Subsequent application of exclusion criteria, which involved the removal of non-RCTs, resulted in the inclusion of 5 studies for both the qualitative synthesis and quantitative meta-analysis (Fig. 1). The 5 included studies (Table 1) collectively involved a total of 3000 participants, with sample sizes ranging from 22 to 2449. The average age of subjects differed among the studies, showcasing the variety within the studied population. Each study incorporated in the meta-analysis was a randomized controlled trial, encompassing a range of designs such as cluster RCTs and crossover trials [11–15].

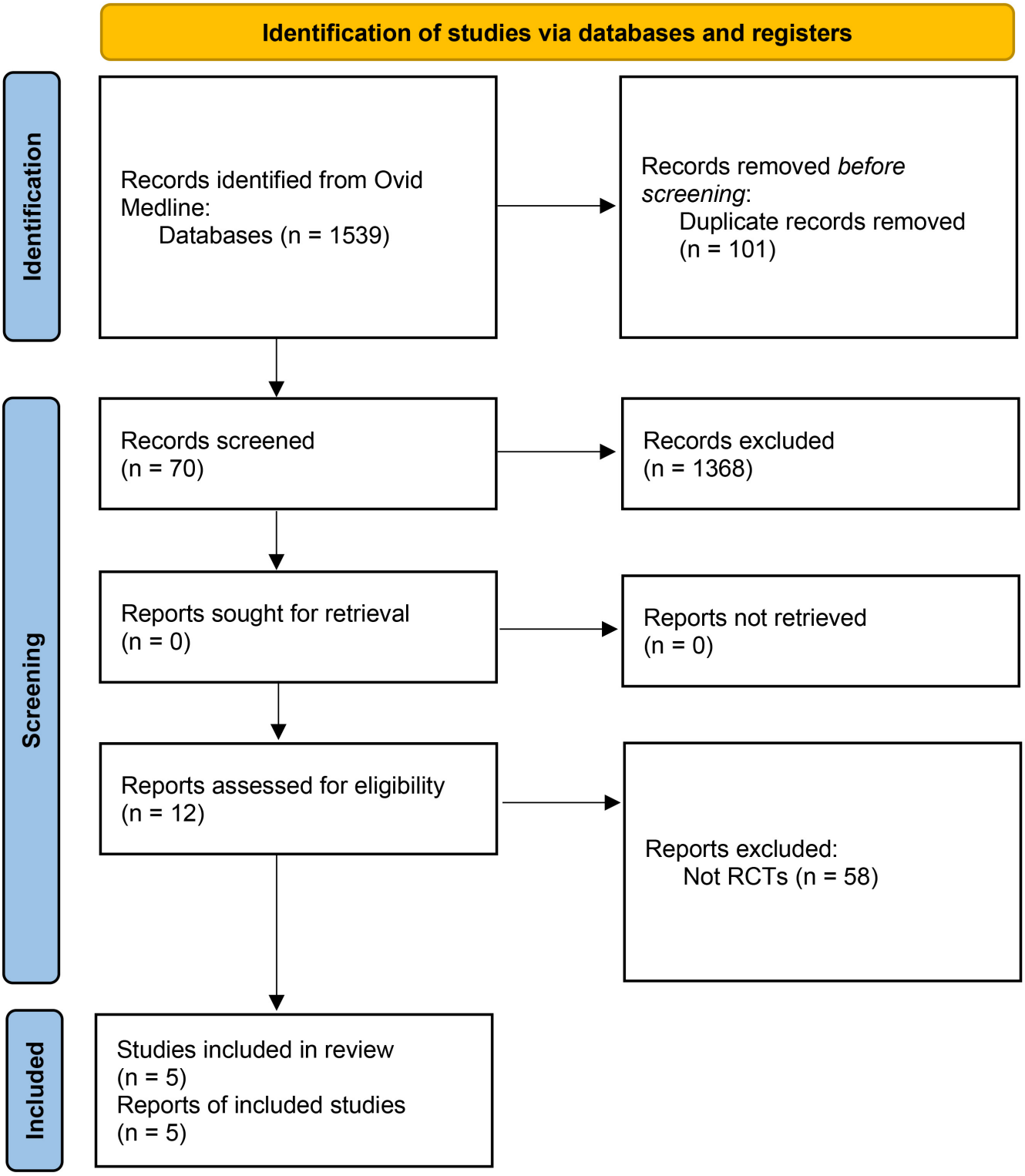


FIGURE 1. Flowchart of screening. RCT, Randomized Controlled Trial.

TABLE 1. Basic characteristics of included studies.

Source	Total No. of patients	Age, mean, yr	Subtype	Study type	Intervention/Control	Quantity, dose	Route of administration	Treatment duration	Outcomes of interest assessed
Khan, 2024	466	56.1 (14.4)	ARF	RCT	m-CCRP/Control	m-CCRP: 12 mon/Control: 12 mon	In-home visits/Telephone	12 mon	QOL (SF-36 PCS, MCS), depression (PHQ-9), anxiety (GAD-7), cognition (RBANS), rehospitalization, ED visits, 12-month mortality
Deleris, 2024	22	64.5 (7.8)	ARF	RCT	Morphine/Placebo	2 mg IV titration	Intravenous/ Subcutaneous	24 h	Dyspnea, anxiety, pain, incidence of intubation, respiratory rate, sleep quality, adverse events
Curley, 2015	2449	4.7 (0.02–17)	ARF	Cluster RCT	Nurse-implemented sedation protocol/Usual care	Not specified	Intravenous (for sedation management)	Up to 28 d post-ICU discharge	Duration of mechanical ventilation, sedation-related adverse events, opioid exposure, wakefulness, pain, agitation, ICU and hospital length of stay
Devlin, 2014	33	64.9 (13.1)	ARF	RCT	Dexmedetomidine/ Placebo	0.2–0.7 µg/kg/h	Intravenous	Up to 72 h	NIV tolerance, SAS, intubation rates, duration of NIV, incidence of deep sedation, hemodynamic stability
Cuquemelle, 2012	30	58 (IQR: 39–77)	Acute Hypoxemic Respiratory Failure	Prospective randomized crossover trial	Heated Humidified High-Flow Oxygen ($HHFO_2$)/Standard Oxygen	4 L/min or higher	Nasal Cannula/Standard Oxygen	24 h with crossover	Nasal dryness, patient comfort, nasal airway caliber, preference for oxygen delivery system

Note: m-CCRP, Mobile Critical Care Recovery Program; ARF, Acute Respiratory Failure; RCT, Randomized Controlled Trial; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ED, emergency department; ICU, Intensive Care Unit; IV, Intravenous; NIV, Non-Invasive Ventilation; SAS, Sedation-Agitation Scale; $HHFO_2$, Heated Humidified High-Flow Oxygen; IQR, Interquartile range; QOL, Quality of life; SF-36, 36-Item Short Form Survey Instrument; PCS, physical component summary; MCS, mental component summary.

3.2 Risk of bias assessment

The risk of bias across the included studies was assessed using the Cochrane Risk of Bias tool. The results are summarized in Fig. 2, which indicates that most studies were at low risk for selection bias, detection bias, and reporting bias. Nevertheless, several studies have pointed out the presence of performance bias, mainly attributed to the difficulties in achieving blinding among participants and staff in interventions related to pain management and sedation techniques. Moreover, insufficient outcome data in certain studies, especially those with limited sample sizes, led to a significant risk of attrition bias.

3.3 Efficacy

The efficacy of the interventions was evaluated across the included studies, with primary outcomes focusing on clinical parameters relevant to ARF (Fig. 3). The meta-analysis findings demonstrated an overall favorable impact of the interventions on efficacy outcomes, as evidenced by a combined odds ratio of 1.40 (95% CI: 1.05 to 1.87), signifying a statistically significant enhancement in support of the intervention groups (refer to Fig. 3). The effectiveness of the interventions varied among studies, with Khan (2024) reporting an effect size of 1.61 (95% CI: 1.10 to 2.10) and Cuquemelle (2012) highlighting a remarkably high effect size of 8.00 (95% CI: 7.50 to 8.50). Notably, the duration and follow-up periods of the interventions varied significantly among the studies, ranging from 24 hours to 12 months. Studies with longer follow-up periods [13] (2014), demonstrated more sustained efficacy outcomes compared to those with shorter durations. This variability may contribute to the differences in effect sizes observed and suggests that the length of intervention and follow-up could influence the efficacy outcomes. The heterogeneity across studies was moderate, with an I^2 of 26%, suggesting some variability in the results.

3.4 Pain management

Pain management was another critical outcome assessed in the studies. The meta-analysis revealed diverse impacts of the interventions on pain outcomes, with an overall effect size indicating a decrease in pain. However, the effect size differed significantly among the studies (Fig. 4). Khan (2024) and Deleris (2024) reported negative effect sizes, −1.88 (95% CI: −2.30 to −1.40) and −2.00 (95% CI: −2.50 to −1.50) respectively, indicating a reduction in pain in the intervention groups compared to control. Conversely, Curley (2015) reported a negligible effect size of −0.08 (95% CI: −0.10 to −0.05), suggesting minimal impact on pain management outcomes in their study population.

3.5 Acceptability

The acceptability of the interventions was also key considerations in this analysis. As shown in Fig. 5, the odds ratio for adverse events varied across studies. In their studies, Curley *et al.* [11] (2015) and Khan *et al.* [14] (2024) found relatively elevated odds ratios of 1.52 and 1.12, while Devlin *et al.* [13] (2014) reported a contrasting odds ratio of 0.47, pointing towards a higher level of acceptance in the intervention group.

4. Discussion

This systematic review and meta-analysis synthesized results from 5 RCTs assessing the effectiveness and pain control results of different treatments in individuals with ARF [11–15]. The analysis highlighted the diverse impacts of these interventions, not only on the clinical efficacy in treating ARF but also on the associated pain management, acceptability, and overall patient outcomes. The range of interventions examined varied from pharmacological therapies such as morphine and dexmedetomidine to non-pharmacological strategies like sedation protocols implemented by nurses, highlighting the intricate and multi-dimensional aspect of treating ARF in critically ill individuals.

A significant consideration in interpreting our findings is

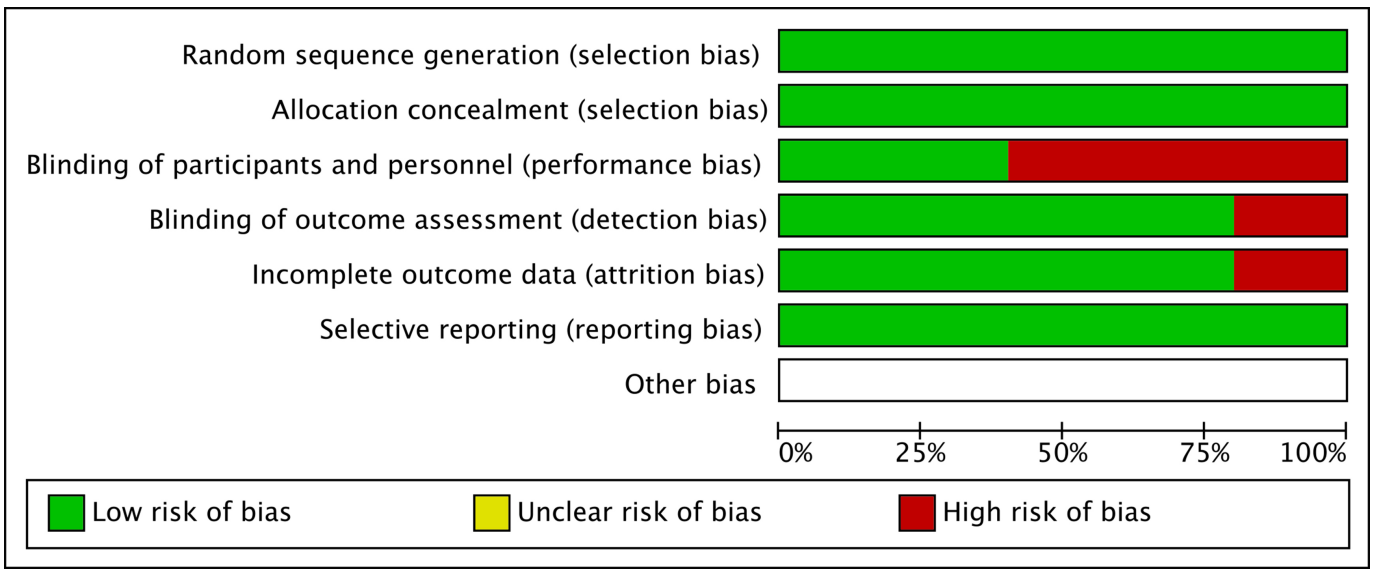


FIGURE 2. Risk of bias.

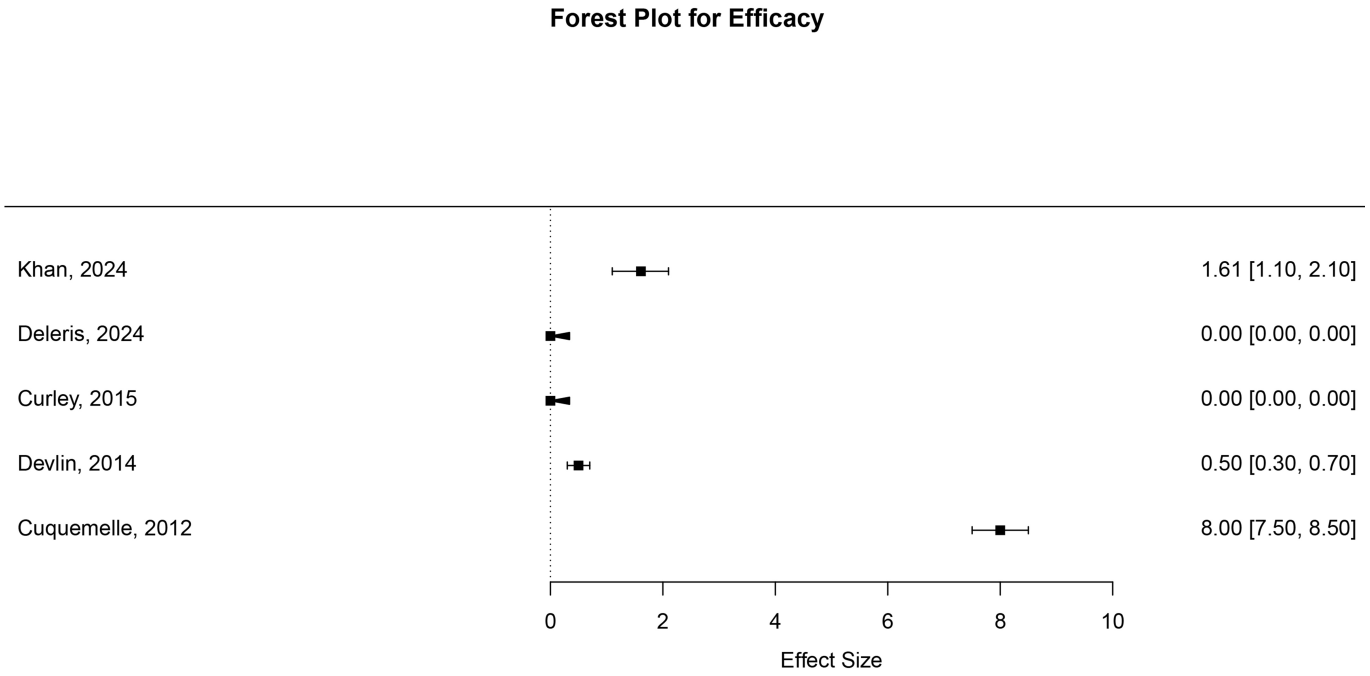


FIGURE 3. Effect size of efficacy for interventions versus control.

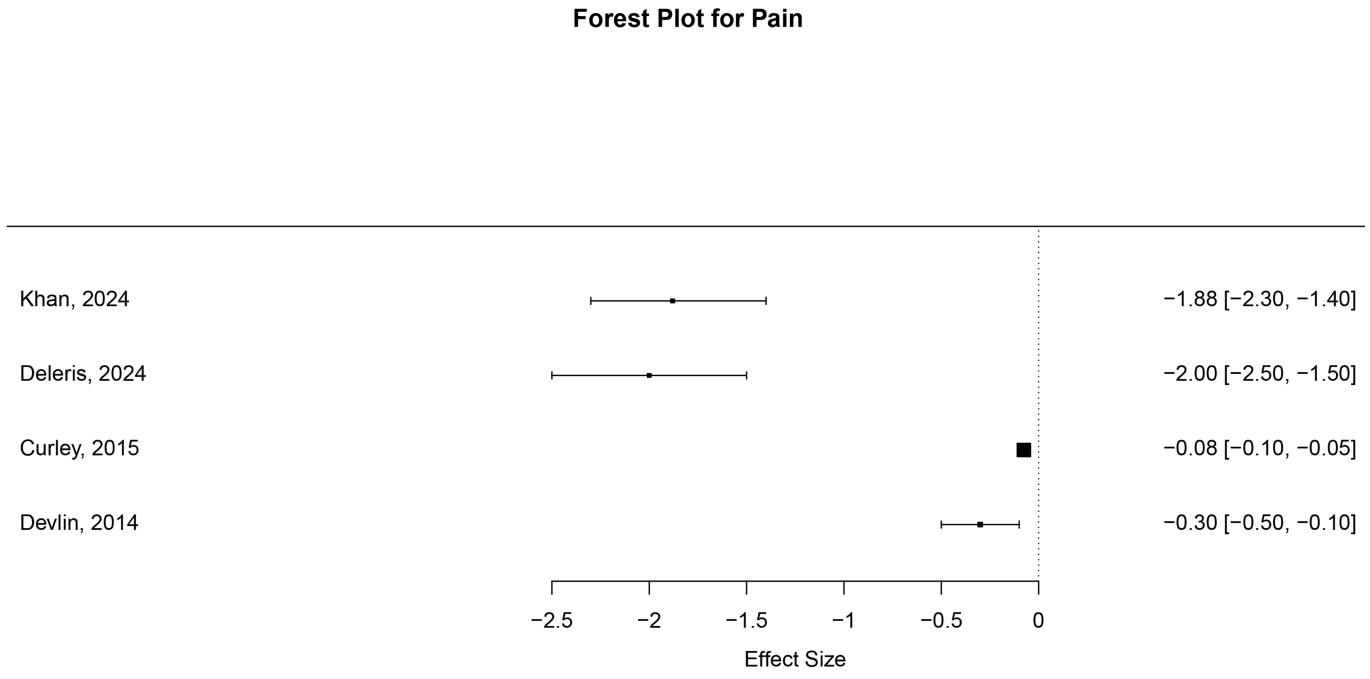
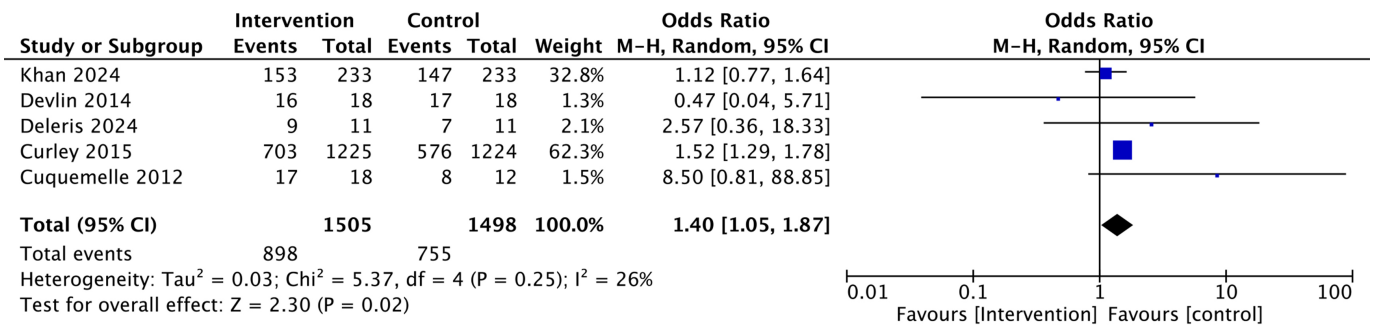


FIGURE 4. Effect size of pain for interventions versus control.



Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Khan 2024	153	233	147	233	32.8%	1.12 [0.77, 1.64]
Devlin 2014	16	18	17	18	1.3%	0.47 [0.04, 5.71]
Deleris 2024	9	11	7	11	2.1%	2.57 [0.36, 18.33]
Curley 2015	703	1225	576	1224	62.3%	1.52 [1.29, 1.78]
Cuquemelle 2012	17	18	8	12	1.5%	8.50 [0.81, 88.85]
Total (95% CI)		**1505**		**1498**	**100.0%**	**1.40 [1.05, 1.87]**
Total events	898		755			

Heterogeneity: Tau² = 0.03; Chi² = 5.37, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 2.30 (P = 0.02)

FIGURE 5. Forest plot of acceptability. CI, confidence intervals; M-H: Mantel-Haenszel.

the variability in the duration and follow-up periods across the included studies. Interventions with longer durations and extended follow-up periods [13] (2014), may provide more comprehensive insights into the sustained efficacy and long-term outcomes of ARF treatments. On the contrary, research conducted over shorter periods might only observe immediate or temporary impacts, possibly missing out on delayed advantages or negative outcomes. This discrepancy could affect the dependability and applicability of our findings, as extended monitoring is frequently essential for a comprehensive evaluation of the efficacy and safety of interventions in ARF. Future studies should aim for standardized intervention durations and follow-up periods to allow for more consistent comparisons and robust conclusions. The main objective of this meta-analysis was to assess the effectiveness of treatments in enhancing the clinical results of patients with ARF. The findings revealed different degrees of effectiveness, with interventions such as the Mobile Critical Care Recovery Program (m-CCRP) displaying significant enhancements, while others showing only minimal effects. These results are consistent with previous research, including studies emphasizing the advantages of using low tidal volume ventilation in treating ARF and ARDS, where variability in patient response is commonly noted [16, 17]. The findings underscore the importance of personalized strategies in treating ARF. There is considerable variation in pain management outcomes among different interventions for ARF, with certain studies indicating adverse effects on pain control. Specifically, studies [12, 14] (2024) demonstrated that certain interventions might not only be ineffective in managing pain but could potentially exacerbate it, with negative effect sizes of −1.88 and −2.00, respectively. These results are consistent with the intricacies noted in previous studies. For instance, a study investigating the application of low-dose morphine to alleviate dyspnea in patients with acute respiratory failure (ARF) underscored the delicate equilibrium required between effectiveness and the possibility of negative consequences such as pain or discomfort [18]. This underscores the necessity for more nuanced and tailored approaches to pain management in ARF to ensure that interventions do not inadvertently worsen patient discomfort [19].

Variability was observed in the acceptability of interventions in the studies included in this meta-analysis, as indicated by differences in the occurrence of adverse events and patient adherence. Some interventions showed higher odds ratios for adverse events, which could impact their overall acceptability. For instance, a previous study [11] (2015) reported an odds ratio of 1.52, suggesting an increase in adverse events and potentially lower acceptability, whereas a study [13] (2014) reported a lower odds ratio of 0.47, indicating higher acceptability. These findings align with recent research, such as the Venting Wisely pathway for hypoxemic respiratory failure, which also demonstrated a connection between acceptability and the prevalence of adverse events [19]. One of the key challenges in interpreting the results of this meta-analysis is the considerable heterogeneity observed across the included studies. The level of heterogeneity, as measured by the I^2 statistic, differed among various outcome measures, showcasing the wide range of methodologies, patient populations, and interventions utilized in the research studies. For instance, the high heterogeneity observed in efficacy outcomes (I^2 = 26%) suggests that the differences in study designs, intervention modalities, and patient characteristics contributed to the variability in the results. This emphasizes the importance of interpreting the results carefully and stresses the significance of taking into account individual patient characteristics and clinical scenarios when implementing these findings in real-world settings. Moreover, the evaluation of bias risk uncovered different degrees of bias among the research studies, with the majority showing minimal risk in critical aspects like random sequence generation and allocation concealment. Nevertheless, there were significant apprehensions about performance and detection bias, especially in trials where maintaining blinding for participants and staff posed challenges. These biases could potentially influence the outcomes and interpretations of the studies, further complicating the overall assessment of the interventions' efficacy and acceptability.

The positive effect of interventions on the management of ARF, particularly regarding reducing pain and improving sedation outcomes, suggests that early and effective intervention can lead to improved patient comfort and potentially shorten intensive care unit (ICU) stays. For instance, the m-CCRP intervention showed notable advantages, suggesting that holistic rehabilitation approaches could significantly contribute to improving the recovery results of patients with ARF. Furthermore, considering the diversity in the duration of studies, it is essential to investigate the lasting benefits of such interventions in upcoming research to offer more precise recommendations for clinical settings. Overall, this analysis supports the integration of evidence-based intervention protocols into routine ARF management, which could lead to more standardized, effective care.

There are various constraints that need to be recognized in this meta-analysis. Firstly, the presence of inherent diversity among the studies, especially regarding participant attributes, intervention types, and outcome assessments, may have impacted the findings. Additionally, the restriction to solely English-language studies might have introduced linguistic prejudice, while the differing durations of interventions in the studies, spanning from 24 hours to 12 months, could potentially influence the long-term relevance of the results. While additional databases such as Embase and the Cochrane Library were considered, the search was limited to Ovid Medline due to resource constraints and the extensive coverage it offers in the biomedical literature. This limitation is acknowledged as a potential constraint in the comprehensiveness of the literature review. Moreover, although efforts were made to address methodological bias, it is important to note that the possibility of publication bias remains, considering the characteristics of the studies incorporated. Furthermore, a constraint of the study is the restricted quantity of studies analyzed, which could potentially restrict the applicability of the conclusions. The diverse levels of study quality, as evidenced in the bias risk evaluation, add complexity to the understanding of the outcomes. Although we attempted to address this with sensitivity analyses, the overall quality of evidence must be considered when interpreting the findings. Future research should aim to include a larger number of high-quality studies with standardized outcome measures and longer

follow-up periods to enhance the robustness and applicability of the findings.

5. Conclusion

In conclusion, this meta-analysis suggests that targeted interventions can significantly improve clinical outcomes in ARF patients, particularly among specific subgroups such as elderly patients and those with underlying conditions like chronic obstructive pulmonary disease (COPD) or heart failure. However, the associated pain management outcomes and acceptability vary considerably across different interventions. These results underscore the importance of adopting a well-rounded strategy that takes into account effectiveness and patient well-being, customized to suit the unique traits of patient groups, when dealing with ARF. For example, elderly individuals might display heightened reactivity to specific medications, and patients with preexisting conditions may necessitate personalized approaches to treatment in order to enhance results and reduce negative repercussions. Future research should focus on developing and validating interventions that are both effective and acceptable to patients, with an emphasis on minimizing pain and adverse events while optimizing clinical outcomes.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

XFZ—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. XFZ, XLZ and MLZ—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1888037562001309696/attachment/Supplementary%20material.zip.

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