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SYSTEMATIC REVIEW

Early non-invasive ventilation for the management of patients with acute respiratory failure: a systematic review and meta-analysis

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Abstract

Background: Non-invasive ventilation (NIV) is a well-established treatment for the management of acute respiratory failure (ARF), particularly in patients with acute exacerbations of chronic obstructive pulmonary disease. Its early application in prehospital and non-intensive care unit (ICU) settings may prevent deterioration and improve several clinical outcomes in patients with ARF due to various causes, but evidence remains inconclusive. **Methods**: We conducted a systematic review and meta-analysis of randomized and quasi-randomized trials comparing early NIV, defined as its application before or soon after hospital admission (prehospital, emergency department, or general ward initiation), versus standard oxygen therapy in adult patients with ARF. The primary outcome was the need for endotracheal intubation. Secondary outcomes included mortality, ICU admission rate, and hospital length of stay. **Results**: Thirteen trials including 2172 patients met the inclusion criteria and were included in this analysis. Early NIV significantly reduced intubation rate compared to standard care (56/1085 [5.2%] *vs.* 113/1047 [10.8%]; relative risk (RR) = 0.49; 95% confidence interval (CI), 0.36–0.66; $p < 0.001$; $I^2 = 0\%$), corresponding to a number needed to treat (NNT) of 18. ICU admissions were also significantly reduced (129/831 [15.5%] *vs.* 153/798 [19.2%]; RR = 0.78; 95% CI, 0.62–0.97; $p = 0.02$; $I^2 = 9\%$; NNT = 27). No significant differences were observed in mortality (15.0% *vs.* 17.1%) and hospital length of stay (mean difference = −0.59 days). **Conclusions**: Early initiation of NIV in patients with ARF in prehospital or non-ICU settings reduces the rate of intubation and ICU admission. These findings support the use of NIV in prehospital and non-ICU settings for the management of ARF. **The PROSPERO Registration**: CRD420251153734.

Keywords

Acute respiratory failure; Bilevel positive airway pressure; Continuous positive airway pressure; Emergency medical services; Non-invasive ventilation

1. Introduction

Respiratory failure is a syndrome with a wide range of underlying conditions, affecting over 1200 per 100,000 adults in the United States per year [1]. Among its presentations, acute respiratory failure (ARF) represents one of the most time-critical forms, often leading to admission to the intensive care unit (ICU) [2]. In the hospital setting, ARF is the primary cause of clinical deterioration [3] and is associated with poor outcomes, with mortality rates reaching up to 40% [4].

Non-invasive ventilation (NIV) is widely recognized as an effective treatment for the management of respiratory distress [5], with robust evidence demonstrating improvements in gas exchange, reduction in work of breathing and decreased rates of intubation and mortality [6] in specific conditions such as chronic obstructive pulmonary disease (COPD) exacerbations [7, 8]. Traditionally, the use of NIV was limited to ICU [9], but its application has recently expanded to emergency departments, medical wards, and prehospital settings (including emergency medical services (EMS)). Early NIV initiation may allow timely stabilization before hospital arrival and prevent further deterioration, potentially reducing the need for endotracheal intubation and improving short-term outcomes [5, 10].

However, outside of COPD exacerbation, the evidence supporting the early use of NIV in patients with respiratory distress remains limited. Small prehospital studies suggested

reductions in dyspnea and improvement in symptoms [11, 12]. Recently, Monti *et al.* [13] reported a lower rate of progression to severe ARF in patients treated with early NIV outside the ICU, compared to those receiving usual care. Nevertheless, important knowledge gaps remain regarding the role of early NIV in respiratory distress, particularly concerning its true impact on meaningful outcomes, such as the need for endotracheal intubation and prevention of ICU admission. Most available studies are small, heterogeneous, or limited to specific subgroups, leaving clinicians with limited guidance for broader implementation in current practice.

To address this research gap, we conducted an updated systematic review and meta-analysis of randomized studies evaluating the early application of NIV in respiratory distress, including both out-of-hospital patients and hospitalized patients not yet admitted to the ICU. By synthesizing the most recent evidence, this study aims to clarify the effectiveness and safety of NIV on patient-centered outcomes, inform clinical decision-making, and guide future implementation strategies.

2. Methods

2.1 Study design and review question

We performed a systematic review and meta-analysis and reported the findings in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (**Supplementary Table 1**) [14]. The Population, Intervention, Control, Outcome (PICO) framework was used to develop the review question: among patients with ARF (P), does early application of NIV (I), compared to standard treatment (C), reduce the intubation rate (O)?

The review protocol was registered in the prospective international register of systematic reviews (PROSPERO) (CRD420251153734).

2.2 Search strategy, study selection, and data extraction

Two trained investigators independently searched for pertinent peer-reviewed journal articles through web databases (PubMed, EMBASE via OVID, and the Cochrane Controlled Trials Register), from inception up to 04 September 2025. We included randomized and quasi-randomized studies (*e.g.*, randomized by ambulance) published in peer-reviewed journals that compared the early application of NIV, defined as its application before or soon after hospital admission (including out-of-hospital, prehospital, and out of ICU scenarios), versus standard of care, used in adult patients with ARF. We considered NIV modalities including both Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure (BIPAP) when delivered noninvasively; high-flow nasal cannula (HFNC) was not considered a NIV technique. Studies were eligible for inclusion only if they reported data on the primary outcome. Corresponding authors of selected publications were contacted by email up to three times to retrieve missing information. Since NIV is a well-established treatment for COPD exacerbations, we excluded studies only related to COPD exacerbation as the main cause of ARF. Studies with HFNC as comparator were also excluded.

After duplicates removal, the initial screening was conducted at the title and abstract level. The final selection of pertinent articles was conducted considering the full-text evaluation. In each phase, disagreements were solved by a third senior investigator.

2.3 Primary and secondary outcomes

The primary outcome of our systematic review and meta-analysis was the number of patients requiring endotracheal intubation during the index hospitalization. Secondary outcomes were:

- Mortality rate evaluated at multiple timepoints: short-term ($\leq$30 days); medium-term (6–12 months); and at the longest follow-up available, as reported by each manuscript (Table 1, Ref. [13, 15–26]);

- Number of patients admitted to the ICU during the index hospitalization;

- Hospital length of stay.

We performed sensitivity analyses excluding quasi-randomized studies, excluding studies assessed as high risk of bias, and excluding studies that did not report the use of face mask interfaces. Finally, we performed planned subgroup analyses based on different NIV modalities (*e.g.*, CPAP, BIPAP), type of provider (lay responders, physicians, nurses, paramedics), and etiology of ARF.

2.4 Risk of bias and certainty of evidence assessment

For each included trial, two authors independently assessed the risk of bias using the revised Cochrane risk of bias tool for randomized trials (RoB2), accessible online at https://www.riskofbias.info [27]. Disagreements were resolved through discussion with a third senior author to reach consensus. Risk levels were classified as “high risk of bias”, “some concerns”, or “low risk of bias”. Only if all domains were assessed as low risk of bias, we considered a trial as low risk of bias. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall quality of evidence for our primary and secondary outcomes [28]. Overall certainty of evidence was assessed as “high”, “moderate”, “low”, or “very low”. This information was summarized in the summary of findings table, which was created using the GRADEpro online tool (available at https://www.gradepro.org/).

2.5 Statistical analysis

Quantitative analyses were performed using the Cochrane Review Manager online version (https://revman.cochrane.org/). For dichotomous outcomes, relative risk (RR) and 95% confidence intervals (CIs) were calculated, whereas mean differences (MDs) with 95% CIs were used for continuous outcomes. We used an inverse-variance method with a random effect model, and results were summarized using forest plots. Heterogeneity analysis was performed with Cochran Q statistic and quantified with I^2 statistic. We interpreted the heterogeneity as outlined: 0% to 25% (might not be important); 25%

TABLE 1. Characteristics of included studies ordered by first author surname (alphabetic order) and including the longest follow-up.

Study [Ref.]	Journal*	Year	Country	Study design	Intervention	Control	Etiology	Longest follow-up
Austin *et al.* [15]	F1000Res	2018	Australia	RCT	CPAP	Usual care	ACPE	In-hospital†
Craven *et al.* [16]	Acad Emerg Med	2000	USA	Quasi-RCT	BIPAP	Usual care	ACPE	In-hospital†
Ducros *et al.* [17]	Intensive Care Med	2011	France	RCT	CPAP	Usual care	ACPE	In-hospital†
Finn *et al.* [18]	Emerg Med J	2022	Australia	RCT	CPAP	Usual care	Any cause	30 days
Frontin *et al.* [19]	Am J Emerg Med	2011	France	RCT	CPAP	Usual care	ACPE	30 days
Fuller *et al.* [20]	BMJ Open	2020	UK	RCT	CPAP	Usual care	Any cause	30 days
Mas *et al.* [21]	Intensive Care Med**	2002	Spain	RCT	BIPAP	Usual care	Acute dyspnea (RR >28 and SpO_2 <92%)	n/a
Monti *et al.* [13]	Br J Anaesth	2025	Italy	RCT	Early CPAP/BIPAP	Usual care	Any cause	90 days
Plaisance *et al.* [22]	Eur Heart J	2007	France	RCT	Early CPAP	Late CPAP	ACPE	In-hospital†
Roessler *et al.* [23]	Emerg Med J	2012	Germany	RCT	BIPAP	Usual care	Any cause	90 days
Squadrone *et al.* [24]	Intensive Care Med	2010	Italy	RCT	CPAP	Usual care	Acute dyspnea (RR >25 and SpO_2 <90%)	90 days
Thompson *et al.* [25]	Ann Emerg Med	2008	Canada	RCT	CPAP	Usual care	Any cause	In-hospital†
Wermke *et al.* [26]	Bone Marrow Transplant	2012	Germany	RCT	CPAP/BIPAP	Usual care	Acute dyspnea (RR >25; OI <300 or SpO_2 <92%)	100 days

**Journal names are abbreviated according to PubMed abbreviations.*
***Abstract.*
†Death occurring during the indexed hospital stay.
ACPE: acute cardiogenic pulmonary edema; BIPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; n/a: not available; RCT: randomized clinical trial; RR: respiratory rate; OI: oxygenation index; SpO_2: peripheral oxygen saturation.

to 50% (may represent moderate heterogeneity); 50% to 75% (may represent substantial heterogeneity); and 75% to 100% (would attest considerable heterogeneity). An unadjusted *p*-value of 0.05 was considered statistically significant. We calculated the number needed to treat (NNT) for primary and secondary outcomes with statistically significant differences between the two groups (intervention *vs.* usual care). Publication bias was evaluated using funnel plots for both primary and secondary outcomes.

Finally, we performed a trial sequential analysis (TSA) to assess the robustness of our findings, using TSA Viewer (Version 0.9.5.10 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) and a two-sided alpha of 0.05, a power of 80%, an anticipated relative risk reduction of 40%, and a control event rate of 15%.

3. Results

3.1 Study characteristics

Our search strategy (**Supplementary material 1**) identified a total of 782 records. After removing duplicates and conducting the initial title and abstract screening, 27 documents were selected and underwent the full-text assessment. Finally, 13 trials [13, 15–26] including a total of 2172 patients (1109 in the NIV group *vs.* 1063 in the usual care group) met

the inclusion and exclusion criteria and were included in this analysis (Fig. 1).

All included studies were published between 2000 and 2025; nine were conducted in Europe [13, 17, 19–24, 26], two in North America [16, 25], and two in Australia [15, 18]. Twelve studies were randomized [13, 15, 17–26], and one was quasi-randomized (randomized by ambulance unit) [16].

Five studies investigated prehospital NIV in patients with acute cardiogenic pulmonary edema [15–17, 19, 22], while the remaining studies included patients with ARF due to any cause, including high-risk populations such as those with hematologic malignancies or following hematopoietic stem cell transplantation [24, 26]. Eight studies used CPAP as the only mode of NIV [15, 17–20, 22, 24, 25]. All studies compared NIV (initiated prehospital or early outside the ICU) with standard oxygen therapy. Six studies were assessed at high risk of bias [15, 16, 20–23], two as having some concerns [17, 18], and five as low risk of bias [13, 19, 24–26] (**Supplementary Fig. 1**). The characteristics of included studies are summarized in Table 1 and **Supplementary Table 2**, while **Supplementary Table 3** reports general characteristics of the major excluded studies.

3.2 Primary and secondary outcomes

We found a significant reduction in rate of endotracheal intubation among patients receiving early NIV (prehospital or early ward-based) compared with standard oxygen therapy (56/1085 [5.2%] *vs.* 113/1047 [10.8%]; RR = 0.49; 95% CI, 0.36–0.66; $p < 0.001$; $I^2 = 0\%$; 13 studies included) (Fig. 2). The NNT was 18.

These findings were confirmed in all the subgroup and sensitivity analyses performed (**Supplementary Figs. 2,3,4,5,6,7**), with no significant difference between CPAP and BIPAP (interaction $p = 0.73$) (**Supplementary Fig. 2**) (Table 2). The funnel plot did not suggest the presence of small studies publication bias for the primary outcome (**Supplementary Fig. 8**). The TSA confirmed a conclusive benefit, as the total number of patients included in this meta-analysis (2132 for the primary outcome) exceeded the required information size (1152 patients) (RR = 0.49; alpha-spending adjusted 95% CI, 0.34–0.70) (**Supplementary Fig. 9**). The overall certainty of evidence for the rate of endotracheal intubation was assessed as moderate, specifically downgraded due to risk of bias (**Supplementary Table 4**).

Furthermore, our findings showed that early NIV reduced the ICU admission rate compared to the controls (129/831

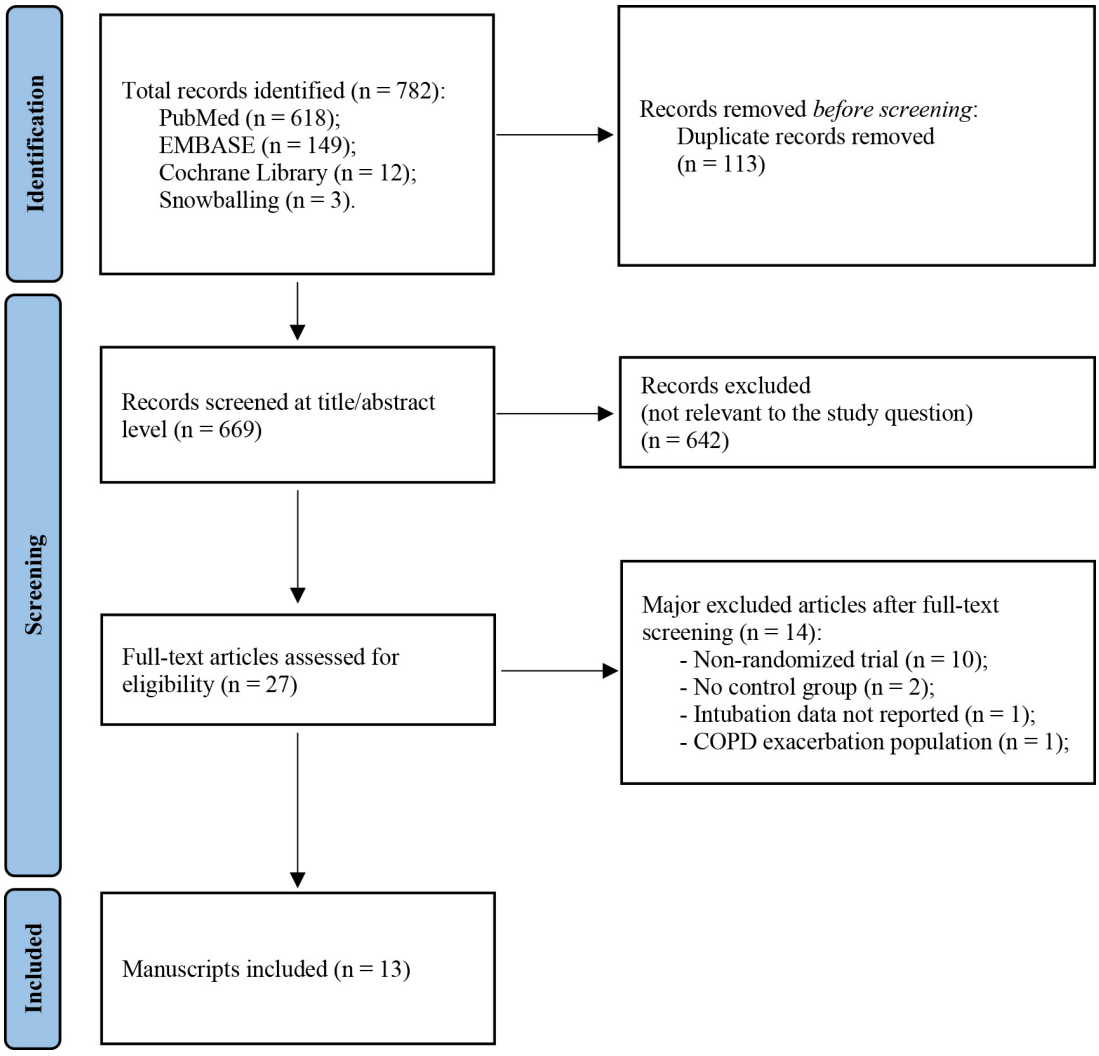

FIGURE 1. PRISMA flowchart of the literature search process. COPD: chronic obstructive pulmonary disease.

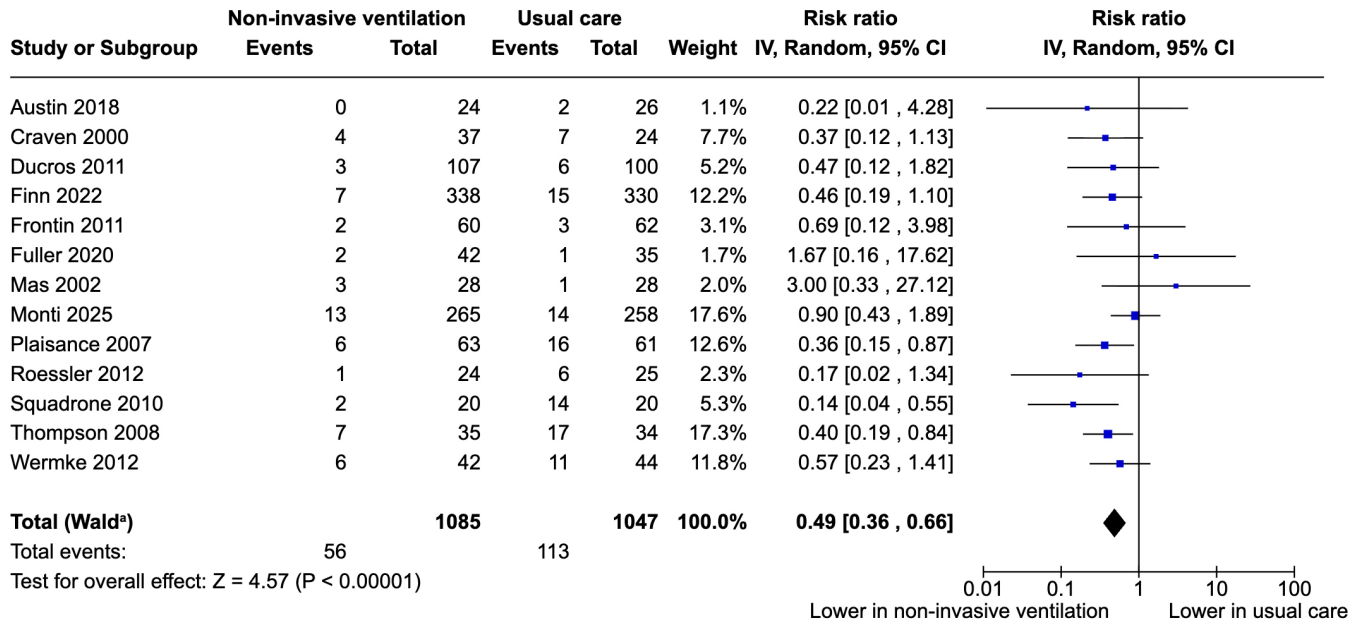

FIGURE 2. Effect of non-invasive ventilation on the rate of endotracheal intubation. CI: confidence interval; IV: inverse variance.

[15.5%] *vs.* 153/798 [19.2%]; RR = 0.78; 95% CI, 0.62–0.97; $p = 0.02$; $I^2 = 9\%$; with nine studies included) (Fig. 3) (**Supplementary Fig. 10**) (Table 2), with a NNT of 27.

Early treatment with NIV did not significantly reduce mortality at the longest follow-up available compared with standard oxygen therapy (166/1109 [15.0%] *vs.* 182/1063 [17.1%]; RR = 0.80; 95% CI, 0.57–1.12; $p = 0.19$; $I^2 = 51\%$; with 13 studies included) (**Supplementary Figs. 11,12**). The longest follow-up available for each study is reported in Table 1 (Table 1). Short- and medium-term mortality were also similar between the two groups (**Supplementary Figs. 13,14**) (Table 2).

There was no significant difference in hospital length of stay between groups (MD = −0.59 days; 95% CI, −2.18 to 1.00; $p = 0.46$; $I^2 = 74\%$; with eight studies included) (**Supplementary Fig. 15**) (Table 2).

4. Discussion

4.1 Key findings

Our systematic review and meta-analysis documented a substantial reduction in intubation rate in patients with ARF who were randomized to receive NIV either prehospital or out of the ICU, when compared to standard care. These results came from over 2000 patients randomized into 13 trials, with low heterogeneity observed. The TSA showed that we reached the required information size, confirming a conclusive benefit of NIV on endotracheal intubation and strengthening the robustness of our findings. Furthermore, early NIV was associated with a significant reduction in ICU admissions by more than 20%.

4.2 Relation to previous studies

Previous meta-analyses provided complementary insights that support our findings. In evaluating early NIV versus conventional oxygen therapy in immunocompromised patients with respiratory failure, authors found that early NIV significantly reduced intubation and ICU mortality rates, as well as ICU length of stay, although no clear benefit on all-cause mortality at the longest follow-up was observed [29, 30]. Another meta-analysis compared HFNC with NIV in patients with COPD exacerbation and hypercapnic ARF [31], demonstrating that HFNC was associated with a higher rate of treatment failure and treatment switch rates.

Our findings expand upon those by Scquizzato *et al.* [10]. First, we broadened the inclusion criteria, involving hospital general ward settings (out of the ICU). Our meta-analysis includes three additional randomized trials [13, 26, 28], and excludes one study focused on COPD exacerbation as the main cause of ARF [32], since the role of NIV in this population is well-established. Overall, the updated evidence comprises more than 500 additional patients. We also performed a TSA for the rate of endotracheal intubation, which confirmed the robustness of our results and a conclusive benefit. Finally, among secondary outcomes, we found a significant reduction in the rate of ICU admission, a finding not previously identified.

A recent position paper strongly recommended the application of early NIV by prehospital providers as an effective intervention to reduce intubation and mortality rates [9]. How-

TABLE 2. Summary of main outcomes.

Outcomes	No. of studies	Non-invasive ventilation No. of patients/Total no. (%)	Usual care No. of patients/Total no. (%)	Relative Risk or Mean Difference (95% CI)	*p*-value	I^2 (%)
Primary outcome						
Rate of endotracheal intubation	13	56/1085 (5.2%)	113/1047 (10.8%)	0.49 (0.36 to 0.66)	<0.001	0
- CPAP as non-invasive ventilation modality	8	29/689 (4.2%)	74/668 (11.1%)	0.39 (0.26 to 0.59)	<0.001	0
- BIPAP as non-invasive ventilation modality	3	8/89 (9.0%)	14/77 (18.2%)	0.50 (0.13 to 1.94)	0.320	45
- Paramedics as non-invasive ventilation providers	5	20/476 (4.2%)	42/449 (9.4%)	0.43 (0.26 to 0.70)	<0.001	0
- Physicians as non-invasive ventilation providers	8	36/609 (5.9%)	71/598 (11.9%)	0.51 (0.31 to 0.83)	0.006	25
- ACPE as a cause of acute respiratory failure	5	15/291 (5.2%)	34/273 (12.5%)	0.40 (0.23 to 0.71)	0.002	0
- Other causes of respiratory failure	8	41/794 (5.2%)	79/774 (10.2%)	0.52 (0.33 to 0.81)	0.003	21
- Sensitivity excluding the quasi-randomized study	12	52/1048 (5.0%)	106/1023 (10.4%)	0.49 (0.35 to 0.69)	<0.001	4
- Sensitivity excluding studies assessed at high risk of bias	7	40/867 (4.6%)	80/848 (9.4%)	0.50 (0.34 to 0.74)	<0.001	10
- Sensitivity restricted to studies using a face mask interface	10	40/776 (5.2%)	79/744 (10.6%)	0.47 (0.33 to 0.67)	<0.001	0
Secondary outcomes						
Rate of intensive care unit admission	9	129/831 (15.5%)	153/798 (19.2%)	0.78 (0.62 to 0.97)	0.020	9
Mortality						
- Short-term	7	126/815 (15.5%)	123/790 (15.6%)	1.01 (0.81 to 1.27)	0.920	0
- Medium-term	4	61/351 (17.4%)	72/347 (20.7%)	0.65 (0.27 to 1.54)	0.320	79
- At the longest follow-up available	13	166/1109 (15.0%)	182/1063 (17.1%)	0.80 (0.57 to 1.12)	0.190	51
Hospital length of stay	8	846	801	−0.59 (−2.18 to 1.00)	0.460	74

CI: confidence interval; CPAP: continuous positive airway pressure; BIPAP: bilevel positive airway pressure; ACPE: acute cardiogenic pulmonary edema.

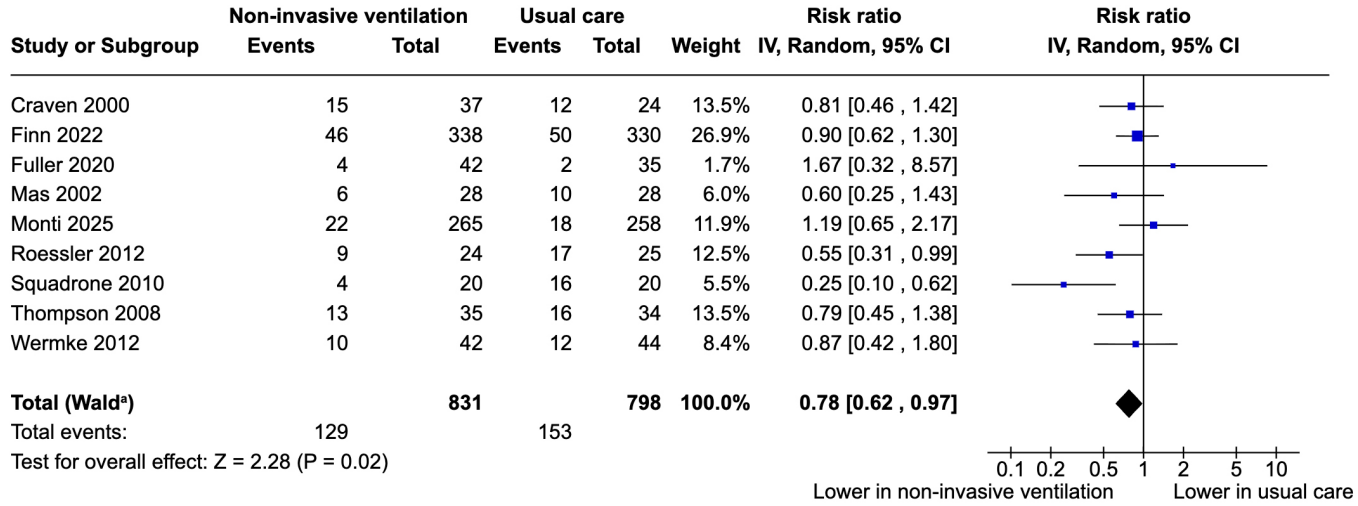

FIGURE 3. Effect of non-invasive ventilation on the rate of intensive care unit admission. CI: confidence interval; IV: inverse variance.

ever, despite this evidence and formal endorsement, the actual implementation of NIV in the prehospital setting remains limited worldwide [9], likely due to the variability in training, protocols, and logistical barriers [33].

The exact timing of early NIV remains a critical and unresolved issue. Most trials did not precisely capture the interval between ARF onset and NIV initiation, representing a key limitation. Nevertheless, in patients with acute cardiogenic pulmonary edema, even a brief 15-minute delay in CPAP initiation worsened short-term mortality, emphasizing the potential importance of very early application [24]. Considering that the median time from EMS call to ambulance arrival is approximately 10–15 minutes, and transport to the hospital can take up to one hour (shorter in urban areas), the prehospital phase represents a valuable window of opportunity to initiate NIV and potentially influence outcomes [34].

Complementing these findings, the NAVIGATE trial [13] evaluated early NIV in patients with mild ARF admitted to non-ICU wards. This is the largest multicenter trial to date, demonstrating that early NIV reduced progression from mild to severe ARF, primarily by preventing severe respiratory distress and hypoxemia. The safety of early NIV was confirmed, as it did not increase complications such as pneumothorax, vomiting, or excessive airway secretions. Importantly, these benefits were consistent across prespecified subgroups, and early NIV did not result in excess adverse events.

Prehospital NIV was feasible across multiple randomized and pilot studies. CPAP was well tolerated in patients with acute cardiogenic pulmonary edema and ARF, with successful application in the majority of cases [25, 35]. Finally, a new CPAP device optimized for prehospital use was recently reported and may support broader implementation of early NIV strategies [36].

4.3 Significance of the study findings and contribution to existing knowledge

ARF remains one of the most frequent causes of critical illness and is associated with substantial morbidity and mortality, with in-hospital mortality rates up to 30% [4]. It frequently presents as a clinical emergency, requiring rapid intervention by EMS and subsequent advanced hospital care. Previous evidence from small randomized trials suggested that early initiation of NIV in the prehospital setting was effective in reducing dyspnea, improving oxygenation, and safe in terms of hemodynamic stability.

Our systematic review and meta-analysis confirms that the application of early NIV is generally safe and effective. Early NIV was associated with a substantial reduction in the risk of endotracheal intubation, with a 51% relative risk reduction and a NNT of 18. Avoiding invasive ventilation is a key goal in ARF management, as intubation is strongly associated with complications, especially in the prehospital setting, as well as prolonged hospitalization and adverse outcomes [2].

In our meta-analysis, NIV was safe with no significant differences in mortality (15.0% in the NIV group *vs.* 17.1% in controls). The frequent crossover to NIV in patients in control groups likely dilutes differences between treatment arms, potentially underestimating the true effect of early NIV.

4.4 Strengths and limitations

This systematic review and meta-analysis represents the most up-to-date synthesis of evidence on the use of early NIV outside of the ICU. The research question was well defined, following the established PICO framework. We reported our findings in accordance with the PRISMA guidelines, ensuring methodological transparency and reproducibility. The meta-analysis was conducted using a random-effects model, pro-

viding conservative estimates. We included more than 2000 patients and performed a TSA, which showed conclusive beneficial results for the primary outcome. Overall, the observed effects are physiologically plausible and in line with previous findings in ICU and other settings, reinforcing their external validity.

However, some limitations should be acknowledged. One of the included studies was quasi-randomized, potentially introducing selection bias, although it was excluded in a sensitivity analysis without affecting the main findings. Furthermore, several studies were assessed as having a high risk of bias, which is common in trials conducted in prehospital settings. Furthermore, although none of the patients included in these trials were in the ICU, there was heterogeneity between in-hospital and out-of-hospital settings, which may affect generalizability.

4.5 Future perspective

The heterogeneity of trial designs, EMS systems, NIV modalities, and patient populations contributes to ongoing uncertainty and underscores the need for further high-quality research. A RAND/UCLA consensus across experts could help define which patients, clinical indications, and NIV modalities would provide the greatest benefit, while large multicenter trials remain essential to establish definitive evidence.

However, our meta-analysis suggests that all out-of-hospital emergency services should be equipped and have the expertise to deliver NIV, thus implementing its routine use in the early management of patients with ARF with the goal of reducing the need for endotracheal intubation.

5. Conclusions

Prehospital and out of ICU NIV reduced the rate of endotracheal intubation by approximately 50% in patients with ARF. While these findings suggest its immediate adoption in ambulances, emergency departments, and non-ICU wards, feasibility depends on equipment availability and triage protocols.

AVAILABILITY OF DATA AND MATERIALS

Data and materials supporting this study are available from the corresponding author upon reasonable and well-justified request.

AUTHOR CONTRIBUTIONS

RL, PP, TS, AZ and GL—designed the research study. PP, FC, FD and KD—conducted the research. RL, TS, FMO, LC and GM—analyzed the data. RL, PP and GL—drafted the initial version of the manuscript. FC, TS, FD, FMO, LC, GM, AZ and KD—critically reviewed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giacomo Monti serves as one of the Editorial Board members of this journal. Giovanni Landoni serves as the Editor-in-Chief. We declare that Giacomo Monti and Giovanni Landoni had no involvement in the peer review of this article and had no access to information regarding its review. Full responsibility for the editorial process of this article was delegated to YK.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at https://oss.signavitae.com/mre-signavitae/article/2059157322322591744/attachment/Supplementary%20material.docx.

APPENDIX

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