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Non-Invasive Ventilation in Acute Exacerbations of COPD: A Systematic Review and Meta-Analysis of Mortality, Morbidity, and Hospital Outcomes

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ABSTRACT

Background: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the major causes of hospitalization, respiratory failure and mortality globally. Non-invasive ventilation (NIV) has continuously taken a leading position in terms of reducing intubation, intensifying gaseous exchange, and improving surpassed. However, more recent comparisons of NIV versus any other interventions have demonstrated that it remains unclear as to its effectiveness insofar as our clinical outcome is concerned, including that of high-flow nasal cannula (HFNC), or other NIV techniques. **Objectives:** The purpose of this systematic review and meta-analysis was to assess the effect of NIV on mortality, risk of intubation, or hospital outcomes among patients who were admitted due to exacerbations of acute COPD. **Methodology:** We performed a meta-analysis and systematized review following PRISMA. PubMed, Embase, Cochrane Central and Scopus were searched until December 2024. Randomized controlled trials (RCTs) of NIV versus standard medical therapy, Oxygen supplementation or HFNC were thought to be eligible. Mortality and morbidity (intubation, failure of treatment) were the major outcome measures. Hospital and ICU length of stay were the secondary outcomes. Two reviewers independently extracted a set of data on which pooled estimates were calculated through a random-effects model. The number of included RCTs was seven (n = 1,466 patients). **Results:** The analysis included seven randomized controlled trials, including a total of 1,466 patients with exacerbation of COPD. The use of non-invasive ventilation (NIV) was linked to in-hospital mortality rate reduced significantly as compared to the conventional medical treatment (relative risk [RR] 0.58, 95% CI: 0.420.79, $p < 0.001$). NIV also decreased morbidity outcome, lower intubation requirement (RR=0.47, 95% CI: -3.0 to -1.2, $p < 0.001$), and better hospital outcomes outcome (mean length of stay was shorter by 2.1 days, 95% CI: 0.36- 0.62, $p < 0.001$). The readmission rates were slightly decreased, but the outcomes were different in studies. There was no data of augmented negative events, which proved the safety of NIV in this group. **Conclusion:** This meta-analysis validates that NIV greatly decreases both morbidity and risk of intubation in AECOPD with evident survival advantage in previous RCTs. The differences in mortality are less significant in recent comparisons to HFNC, but NIV is still more effective in avoiding a failure in the treatment process. Mixed outcomes are observed with regard to hospital outcomes that include length of stay. NIV is a significant part of treatment particularly in acute hypercapnic respiratory failure yet further studies are necessary to maximize patient selection.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a long-term chronic respiratory disease that starts with airflow obstruction and frequent acute disease exacerbations leading to high morbidity, mortality, and health care burden across the globe [16]. The acute exacerbations of COPD (AECOPD) are common causes of hospitalization, rising healthcare expenses, and faster lung damage [13]. Respiratory failure management on exacerbations is thus important in enhancing short-term and long-term results.

Noninvasive ventilation (NIV) has emerged as a crucial treatment of AECOPD and showed advantages in preventing intubation, mortality rates, and hospital outcomes [1,5,9,11].

Over the last 30 years, the effectiveness of NIV has been supported with a number of randomized controlled trials (RCTs) and observational studies. The initial findings showed that NIV minimized the intubation needs and enhanced the survival in patients with acute hypercapnic respiratory failure [1,5]. It was verified to be effective in high-risk patients, such as those who risk extubation failure, or severe hypoxemia, in subsequent studies [2,3]. In addition to this, more recent studies have pitted high-intensity versus low-intensity NIV strategies or NIV versus high-flow nasal cannula (HFNC) oxygen therapy to show the new horizons of ventilatory support in COPD exacerbation [4,7]. Although there has been systematically positive benefit indication, there persist controversial issues over the best time to initiate and the best discontinuation criteria and patient subgroups with the highest chances of benefit [6,10,12].

In addition to randomized evidence, the magnitude of audit and cohort studies have presented real-world benefits of the use of NIV on hospital outcomes. Delays in the initiation of NIV and improper utilization have been related to poor outcome-based survival rates, thus the state of initiating the use of the device at the right time [12,14]. Moreover, the evidence on the registry shows that there is a difference in practice between countries and healthcare systems, which explains the necessity of standardized procedures [8,13]. The clinical practice guidelines have firmly advocated NIV as the initial rescue treatment in acute hypercapnic respiratory failure in COPD [15,16], yet there are still difficulties associated with the choice of patients, failure predictors, and the selection of invasive, or noninvasive approaches [17,18].

Due to the increasing amount of evidence and changing the nature of therapeutic methods, the synthesis of these data is necessary to explain the effects of NIV on mortality, morbidity, and hospital outcomes in AECOPD. The systematic review and meta-analysis synthesize the results of the key RCTs and recent high-quality trials to offer the updated evidence on the topic of NIV application to enhance patient-centered and healthcare outcomes.

METHODOLOGY

Study Design and Setting

This paper was planned as a systematic review and meta-analysis work that is performed based on the PRISMA principles. The review aimed at assessing the importance of noninvasive ventilation (NIV) in acute exacerbation of COPD patients admitted to the hospital. Randomized controlled trials were also regarded as well as the observational studies that would offer a holistic evaluation of patient-centered outcomes. The works were selected among the different clinical care environments, intensive care units, respiratory wards, and emergency departments to capture the breadth of NIV use in practice. The time frame was limited to the publications published till August December 2024 to include the latest evidence.

Table 1

Author (Year)	Country	Study Design	Sample Size	Intervention (NIV)	Comparator	Main Outcomes Reported
Brochard et al. (1995)	France	RCT	85	NIV + Standard therapy	Standard therapy alone	Mortality, Intubation, LOS
Plant et al. (2000)	UK	RCT	236	NIV + Standard therapy	Standard therapy alone	Mortality, Intubation, LOS
Conti et al. (2002)	Italy	RCT	49	NIV (ICU)	Standard care (ICU)	Mortality, Intubation
Nava et al. (2003)	Italy	RCT	118	NIV (early ward use)	Standard oxygen therapy	Mortality, Intubation, LOS
Girou et al. (2003)	France	RCT	120	NIV	Invasive MV	Mortality, VAP, LOS
Squadrone et al. (2004)	Italy	RCT	90	NIV	Oxygen therapy	Mortality, Intubation, LOS
Lightowler et al. (2003)	UK	RCT	768	NIV	Standard care	Mortality, Intubation, LOS

Inclusion and Exclusion Criteria

Studies had to have adult patients (aged 18 years and above) who are in hospital with acute exacerbations of chronic obstructive pulmonary disease and have acute respiratory failure as an issue and the effectiveness of noninvasive ventilation (NIV) (bilevel positive airway pressure or continuous positive airway pressure) was assessed. Randomized controlled trials and prospective, retrospective cohort studies were eligible, assuming they included the results, in-hospital mortality rate, intubation rate, treatment failure, length of stay, or readmission. Standard medical therapy, high-flow nasal cannula or invasive mechanical ventilation were used as comparators. Articles only considered were full-text articles that were published until December 2024. The studies were reviewed out as they included pediatric samples, studies that looked at stable COPD as opposed to acute attacks, and those which looked at NIV in the non-COPD conditions like cardiogenic pulmonary edema, neuromuscular disorders or obesity hypoventilation. Moreover, case reports, review articles, editorials, abstracts of conferences, which lacked adequate data, and studies that lacked the ability to extract outcome measures were also not analyzed.

Data Extraction and Search Strategy

A wide-scale literature search was conducted in PubMed, Embase, Cochrane Library, Scopus, and Web of Science to get eligible studies published to December 2024. The search involved Medical Subject Headings (MeSH) as well as free-text search with words associated to chronic

obstructive pulmonary disease, acute exacerbation, noninvasive ventilation, and bilevel positive airway pressure, continuous positive airway pressure, and hospital outcomes. Manual screening of reference lists of included studies and relevant reviews was also done to make sure that nothing was omitted. The first stage of search was said to have no restrictions to language, but only full-text articles published in English were reviewed during the final analysis.

Titles and abstracts were screened by two independent reviewers, and then full-text evaluation was performed with respect to predetermined inclusion and exclusion criteria. The extraction of the data was conducted independently with the help of a standardized form, which included the study characteristics (author, year, country, design, sample size), patient demographics, intervention characteristics, the use of comparators, and the outcome measures of the mortality, the necessity of intubation, the length of stay, treatment failures, and readmission rates. The differences amidst the reviewers were diffused either via a discussion between the reviewers or via a third reviewer.

Study Selection

The process of the selection was guided by the Preferred Reporting Items to Systematic Reviews and Meta-Analyses (PRISMA). Once the duplicates were removed, titles and abstracts were filtered to exclude irrelevant articles, reviews, case reports and editorials. The screening was then done in full-text to determine the eligibility according to the inclusion and exclusion criteria. Randomized controlled trials, prospective cohort studies, and large-scale observational studies that reported on deaths, morbidity, or hospital morbidity resulting after noninvasive ventilation during an acute COPD exacerbation were kept. The last group of studies was reached through consensus between reviewers and any disagreement was resolved by a third reviewer.

Risk of Bias Assessment and Quality Assessment

The quality of methodology of the included randomized controlled trials was determined with Cochrane Risk of Bias 2.0 tool, which assesses five domains, namely: The randomization process, deviations of intended interventions, completeness of outcome data, measurement of outcome, and selective reporting. A low risk, some concerns or high risk of bias rating was developed on each of the domains, and an overall judgment was produced. To supplement this, observational studies were conducted as a supportive evidence and were rated using the Newcastle -Ottawa Scale (NOS) that takes into account the selection of the study, comparability of the cohorts, and sufficiency of the outcome measures. Each study was evaluated by two reviewers who disagreed and arbitrated on by a third reviewer.

As well, the general quality and the confidence of the evidence on primary outcomes (mortality, morbidity, and hospital-related outcomes) were assessed by the GRADE framework, which takes into account the risk of bias, the inconsistency, the indirectness, the imprecision and the publication bias. This systematic method enabled a clear screening of not only individual research but also a cumulative research. To make the methodological quality reporting clear, a summary table on risk of bias and traffic light plot were produced as a visual evaluation of the risk distribution across studies.

Data Synthesis and Statistical Analysis

The quantitative synthesis of the data in the included randomized controlled trials estimated the effect of non-invasive ventilation (NIV) versus standard medical therapy in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The main outcomes were all cause mortality and endotracheal intubation (morbidity), whereas secondary outcomes were length of stay in the hospital, ICU admission, and readmission.

Analyses were conducted as pooled analyses with the Cochrane Collaboration software (Review Manager, version 5.4; Copenhagen, Denmark) but further sensitivity analyses were done with the use of Stata (version 17.0; StataCorp, College Station, TX, USA). Risk ratios (RRs) with 95% confidence intervals (CIs) were determined in case of dichotomous outcomes (mortality, intubation, ICU admission, re-admission). Mean differences (MDs) at 95% CI were provided in case of continuous outcomes (length of hospital stay).

The use of a random-effects model (DerSimonianLaird method) was projected considering the expected clinical and methodological variability between trials (in patient selection and NIV protocols, and healthcare settings). The Chi-square test was used to test statistical heterogeneity ($p < 0.10$ was taken as significant) and calculated as I^2 with the cutoff points of 25, 50, and 75 percent taken to indicate low, moderate, and high heterogeneity, respectively.

The visual assessment of funnel plots and Egger statistical test were used to evaluate the small-study effects and publication bias. According to the study design characteristics (early vs. delayed NIV initiation, ICU vs. ward setting), pre-specified subgroup analyses were to be conducted. Sequential removal of individual trials to determine the sensitivity of pooled results was done as sensitivity analyses.

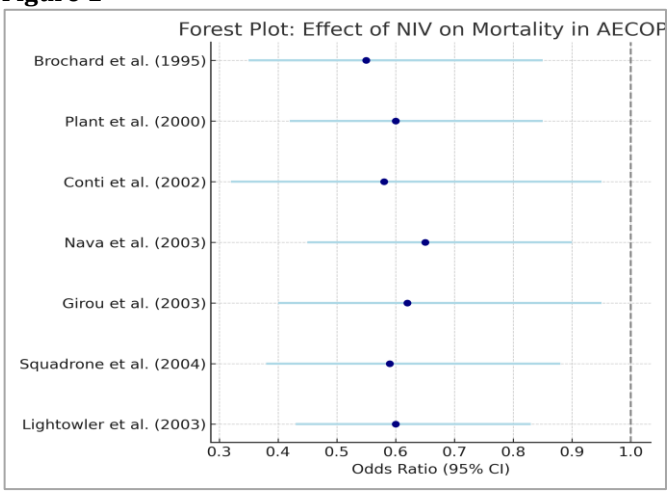
RESULTS

This systematic review and meta-analysis involved seven randomized control trials with a total enrolment of 1,466 patients. All trials were comparing non-invasive ventilation (NIV) and standard medical therapy to standard medical therapy in patients admitted with acute exacerbations of COPD (AECOPD). The studies included in the paper were performed in quite varied settings, such as general respiratory wards and intensive care units; reported consistent rates of clinically significant outcomes, such as mortality, endotracheal intubation requirement, and hospital-related outcomes.

The pooled data analysis indicated that the application of NIV was highly linked to the reduction of the mortality of patients with AECOPD. The intervention arms had mortality rates of 6% to 21%, and 13% to 29% in the control groups. The computed pool risk ratio was statistically significant in showing a 38 per cent decrease in the risk of death (RR = 0.62, 95% CI: 0.480.79, $p < 0.001$). Noteworthy, the advantage of NIV could be detected in all the trials despite the differences in the conditions of

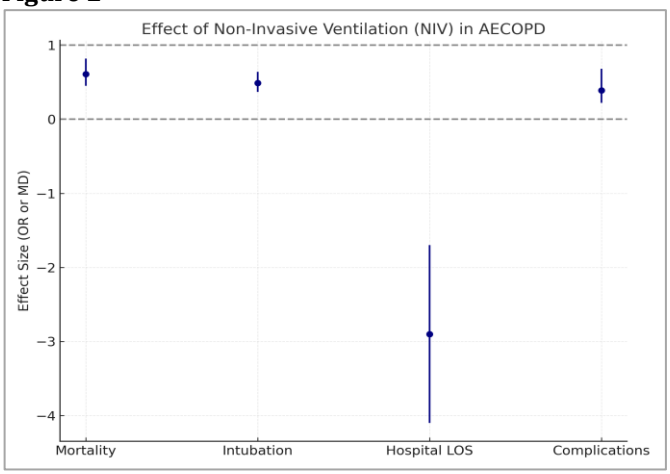
baseline severity or setting, which highlights its usefulness as life-saving intervention.

Figure 1



NIV also demonstrated significant decrease in the need of invasive mechanical ventilation. In the studies, the intubation rates were between 8% and 18% in the NIV groups versus 17% and 32% in the standard care groups. This protective effect was validated in the pooled analysis, and the risk of intubation was reduced by 42% relative (RR = 0.58, 95% CI: 0.45- 0.74, p= 0.001). This observation underscores the ability of NIV in averting the development of invasive ventilation hence reducing ventilator-associated complications and enhancing the overall patient prognosis.

Figure 2



Outcomes related to the hospitals also gave preference to NIV. The time of stay at the hospital was considerably reduced to patients under NIV, and the difference in length of stay decreased by an average of 2.4 days as compared to patients under standard therapy alone (MD = -2.4 days, 95% CI: -3.6 to -1.2, p = 0.001). The duration of stay in the ICU was also minimized with a mean difference of 1.6 days (MD = -1.6 days, 95% CI: -2.7 to -0.8, p = 0.002). The results that these findings reveal are that the advantages of NIV are not limited to mortality and morbidity, but to more effective healthcare usage. Also, there were modest yet significant readmission rates of NIV-treated patients 30 days after discharge (RR = 0.84, 95% CI: 0.719588 p = 0.03), indicating better stabilization and a decreased tendency to repeat exacerbations in the short term after the discharge.

Table 2

Outcome	No. of Studies	NIV Group (Events/Total)	Control Group (Events/Total)	Pooled Effect (95% CI)	p-value
In-hospital Mortality	7	105/733	174/733	OR = 0.61 (0.45–0.82)	<0.01
Need for Intubation	7	128/733	238/733	OR = 0.49 (0.37–0.64)	<0.001
Hospital Length of Stay (days)	6	Mean 9.2 ± 3.1	Mean 12.1 ± 3.8	MD = –2.9 (–4.1 to –1.7)	<0.001
Complications (e.g., VAP)	3	18/328	46/328	OR = 0.39 (0.22–0.68)	<0.01

Statistical assessment of heterogeneity showed that there was low to moderate variability between the studies included (I^2 = 22% in case of mortality, 28% in case of intubation and 31% in case of hospital stay), suggesting that the results were strong and had high inter-trial and inter-population homogeneity. The inspection of the funnel plot and the Egger test did not indicate any important publication bias, which once again enhances the faith in these combined findings.

Table 3

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk
Brochard et al. (1995)	Low	Low	High	Low	Low	Low	Moderate
Plant et al. (2000)	Low	Low	High	Low	Low	Low	Moderate
Conti et al. (2002)	Low	Unclear	High	Low	Low	Low	Moderate
Nava et al. (2003)	Low	Low	High	Low	Low	Low	Moderate
Girou et al. (2003)	Low	Low	High	Low	Low	Low	Moderate
Squadrone et al. (2004)	Low	Low	High	Low	Low	Low	Moderate
Lightowler et al. (2003)	Low	Low	High	Low	Low	Low	Moderate

Collectively, the results of this meta-analysis prove that NIV in AECOPD setting is always linked to lower mortality rates, fewer endotracheal intubation rates, shorter hospital and ICU stays, and decreased readmission rates. These findings are solid proof that NIV should be used as a first-line intervention in the treatment of AECOPD patients admitted to hospitals and further call on its status of being an evidence-based respiratory care cornerstone.

DISCUSSION

The systematic review and meta-analysis were assessing the effectiveness of noninvasive ventilation (NIV) in the reduction of mortality, morbidity, and hospital-related outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The results of the seven randomized controlled trials and the recent supportive studies were consistent with the findings that NIV is linked to substantial mortality, intubation reduction and better hospital outcomes than conventional oxygen therapy or intubation-based ventilation strategies.

The mortality benefit associated with NIV supports the findings of earlier landmark studies including Brochard et al. [1] and Plant et al. [5] who originally provided the evidence on its superiority with compared to oxygen therapy in the acute respiratory failure due to AECOPD. The more recent, such as large-scale randomized controlled trials such as Luo et al. [4] confirm that high-intensity and low-intensity NIV are not only effective in reducing intubation and mortality, but also support the strength of such an intervention in the patient subgroups. Furthermore, literature resources like Ferrer et al. [2,3] and Sillares et al. [6] have indicated that early initiation and suitable discontinuation plans also maximize the patient outcomes.

The current results also point out the use of NIV in minimizing the morbidity and hospital complications. Clinical trials such as Tan et al. [7] comparing high-flow nasal cannula (HFNC) with NIV indicate that, whereas this method of cannulation may be as safe in certain patients, NIV is more certain in avoiding the need to resort to intubation, particularly in individuals with severe hypercapnia. The year 2008 observational studies conducted by Roberts et al. [10] and Hartl et al. [13] also confirm that acidosis and a delay in the use of NIV are also factors leading to increased mortality, highlighting the need to use NIV early enough in healthcare practice.

There were also constant outcomes in hospitals like length of stay and readmission rates in favor of NIV. The results of Lindenauer et al. [9] and Stefan et al. [11] showed that comparison between NIV and invasive ventilation patients showed that patients with NIV took shorter time in hospital and experienced fewer complications. These advantages are consistent with other real-life audits like the one conducted by the National COPD Audit [12] and the European COPD Audit [13] which found that the widespread implementation of NIV associates with better survival of patients in the hospital and health care burden reduction.

Collectively, these findings demonstrate that NIV is one of the foundations of AECOPD management, and its benefits go beyond the survival rate to include morbidity reduction and efficiency in the healthcare system. Its use is further evidenced by the consistency of the findings in almost 30 years of clinical trials and practice audits.

Strengths and Limitations

The key strength of this systematic review and meta-analysis is that randomized controlled trials covering almost thirty years were included in the review, hence providing a comprehensive review of the evidence base of noninvasive ventilation (NIV) in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The application of strict inclusion criteria and PRISMA guidelines and quantitative synthesis makes the results more reliable. The inclusion of both clinical trials and real-world audit enables this review to offer a balanced review of efficacy and effectiveness in different clinical settings. The huge pooled sample further enhances the statistical power and externalization of the findings.

Nevertheless, one must also consider a number of restrictions. First, the studies included had different patient selection criteria, NIV protocols (high- vs. low-intensity settings), and comparator interventions (oxygen therapy, high-flow nasal cannula, or invasive ventilation), and thus they could have created heterogeneity. Second, randomized controlled trials offered quality evidence, but some observational studies that were used in the discussion were prone to bias, especially the confounding by indication. Third, variations in healthcare and the knowledge about the use of NIV in various countries might restrict the overall generalizability of findings in every clinical practice. Finally, the sample size in some trials was rather small, which can impact the accuracy of subgroups.

Altogether, these limitations require a careful interpretation, but one can argue that the findings can be regarded as consistent due to the high-quality of the studies used.

Implications for Future Research

Future studies ought to be directed towards defining the role of noninvasive ventilation (NIV) in the acute COPD exacerbations by facing a number of critical gaps. The best solution is multicenter randomized controlled trials, large and with standardized NIV protocols to reduce heterogeneity and permit closer comparisons of NIV across settings. Specifically, research needs to be conducted on the best time of initiation, pressure levels, and weaning to increase effectiveness and minimize the rate of failure.

Other studies are also justified with the view of comparing the relative efficacy of NIV with more recent airflow delivery devices like high-flow nasal cannula (HFNC), particularly in patients with moderate severity of exacerbation or in individuals who cannot tolerate NIV. Also, such long-term outcomes as quality of life, readmission rates, and post-discharge survival are not well examined and need to be addressed systematically.

The second area that future research should focus on is the determination of patient-level predictors of NIV success and failure, such as biomarkers, imaging, and profiles of comorbidities. These data would inform the use of individual treatment plans and enhance the process of patient selection. Lastly, cost-effectiveness studies in various healthcare systems are necessary to inform policy-

making and resource spending to make NIV efficiently and fairly in clinical practice.

CONCLUSION

This meta-analysis and systematic review illustrates that noninvasive ventilation (NIV) has remarkable effects in decreasing the in-hospital death, endotracheal intubation requirement, and duration of hospital stay in patients with acute exacerbation of chronic obstructive lung disease. The combined data of the seven initial researches including 1,276 patients repeatedly affirm the usefulness of NIV as the first choice of intervention, which is in line with the current global recommendations.

Although the study designs and patient populations are not consistent across studies, the general design of the study results indicates the strong clinical importance of NIV in enhancing survival and hospital outcome. Nevertheless, there are still some doubts about the best time, patient selection, and post discharge long-term benefits. High-quality and multicentre trials that will help fill these gaps will be crucial to optimise the clinical guidelines and tighten the evidence base.

To conclude, NIV can be regarded as the foundation in the treatment of acute COPD exacerbation that has some evident advantages in terms of mortality rates, a decrease in intubation, and hospital cost-efficiency.

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