

Noninvasive Ventilation and Oxygen Therapy after Extubation in Patients with Acute Respiratory Failure: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: Role of noninvasive ventilation (NIV) following extubation in patients with acute respiratory failure is debatable. NIV may provide benefit in post surgical patients, but its role in nonsurgical patients is controversial.

Materials and methods: PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched (from 1946 to 20th November 2017) to identify prospective randomized controlled trials, where postextubation NIV has been compared with standard oxygen therapy in adult patients with acute respiratory failure.

Results: Data of 1525 patients from 11 randomized trials have been included in this meta-analysis. Two trials used NIV to manage post-extubation respiratory failure. Pooled analysis found that mortality rate at longest available follow-up [OR (95% CI) 0.84 (0.50, 1.42); $p = 0.52$] and reintubation rate [OR (95% CI) 0.75 (0.51, 1.09); $p = 0.13$] were similar between NIV and standard oxygen therapy. NIV did not decrease intubation rate when used as preventive modality [OR (95% CI) 0.65 (0.40, 1.06); $p = 0.08$]. Duration of ICU stay was also similar in the two groups [MD (95% CI) 0.46 (-0.43, 1.36) days; $p = 0.3$]

Conclusion: Post extubation NIV in non-surgical patients with acute respiratory failure does not provide any benefit over conventional oxygen therapy.

Keywords: BiPAP, CPAP, Length of stay, Mortality, Noninvasive ventilation, Postextubation respiratory failure, Reintubation

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Postextubation respiratory failure is an established factor responsible for mortality in critically ill patients.¹ Noninvasive positive pressure ventilation (NIV) has been used both as a therapeutic and preventive strategy for postextubation respiratory failure. An observational study has reported that use of NIV in various clinical settings including postextubation respiratory failure patients is increasing over the last 15 years.² A large observational study in 2014 found survival benefit from NIV, in comparison to invasive mechanical ventilation when used as a first-line strategy in immunocompromised and acute-on-chronic respiratory failure patients.³ A recent Cochrane database systematic review⁴ also reported benefit from NIV as first-line intervention in patients with acute hypercapnic respiratory failure secondary to an acute exacerbation of chronic obstructive pulmonary disease (COPD). As endotracheal intubation is associated with several complications such as ventilator-associated pneumonia, barotrauma and tracheo-oesophageal fistula; intubation and mechanical ventilation associated with complications may be reduced with the use of NIV. However, benefits of NIV in the postextubation respiratory failure is less clear. A meta-analysis of 1382 patients published in 2014 found that neither early application of NIV following extubation preemptively nor after established respiratory failure following extubation associated with a benefit in terms of mortality or reintubation.⁵ A recent randomized controlled trial reported that post extubation NIV use in COPD patients is associated with a less incidence of respiratory failure but an increased duration of intensive care unit (ICU) stay.⁶ However, no benefit was reported in terms of reintubation rate or mortality. We designed this meta-analysis and systematic review to know the clinical utility of NIV in prevention and management of postextubation respiratory failure.

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MATERIALS AND METHODS

We have followed the recommendations of *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement for conducting and reporting results of this meta-analysis.⁷

Eligibility Criteria

Prospective randomized controlled trials comparing any modality of NIV such as bi level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) or non-invasive pressure support ventilation (NIV-PSV) with a standard oxygen therapy protocol in the prevention or management of post-extubation respiratory failure in adult patients has been included in this meta-analysis.

Studies where NIV has been compared with invasive ventilation as a weaning modality or where it has been compared with high flow oxygen therapy has not been included in this meta-analysis. We included RCTs where mortality data at least in one time point or reintubation rate were reported.

Information Sources

PubMed and CENTRAL (Cochrane Central Register of Controlled Trials) were searched for potentially eligible trials from inception to 20th November 2017. We did not impose any language restriction or date restriction in search strategy. References of the previously published meta-analyses were also searched manually to identify eligible trials.

Search Strategy

Following keywords were used to search database: “acute hypoxemic respiratory failure, acute respiratory failure, noninvasive ventilation, BiPAP, CPAP, NIV, post extubation respiratory failure”. Details of PubMed search strategy have been provided in online supplementary material.

Study Selection

Two authors (SM and SB) independently searched title and abstract of the potentially eligible articles. Finally, full text of the possible articles was retrieved and assessed for eligibility. Any disputes between the two authors were solved by discussion.

Data Collection Process

Two authors (SM & SB) independently extracted required data from the eligible RCTs and all data were initially tabulated in a Microsoft Excel™ (Microsoft Corp., Redmond, WA) data sheet.

Data Items

Following data were retrieved from the full text for all studies: First author, year of publication, country where work was done, sample size, characteristics of included patients, respiratory goals (oxyhemoglobin saturation, arterial oxygen and $\text{PaO}_2/\text{FiO}_2$), details of noninvasive ventilation (type of NIV, timing of NIV and duration, details of rescue therapy), details of oxygen therapy, clinical outcome (reported complications, organ dysfunction, length of hospital and ICU stay, and mortality at different time points).

Risk of Bias in Individual Studies

Two authors (SM and AS) independently assessed the methodological quality of the included studies. Following methodological questions were searched from the studies as per the Cochrane methodology: method of randomization, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, incomplete data reporting, selective reporting and any other bias. For each area of bias, we will designate the trials as low risk of bias, unclear risk of bias or high risk of bias. Risk of bias at individual study level will be graphically presented in the review.

Summary Measures and Synthesis of Results

Primary outcome of this meta-analysis is ‘mortality at longest available follow-up’ in the included patients. Secondary outcomes are reintubation rate and length of hospital and ICU stay.

For continuous variables such as length of ICU stay and hospital stay, mean and standard deviation (SD) values were extracted for

both group of patients, a mean difference was computed at the study level, and a weighted mean difference was computed in order to pool the results across all studies. If the values were reported as median and an interquartile range or total range of values, the mean value was estimated using the median and the low and high end of the range for samples smaller than 25; for samples greater than 25, the median itself was used. The standard deviation (SD) was estimated from the median and the low and high end of the range for samples smaller than 15, as $\text{range}/4$ for samples from 15 to 70, and as $\text{range}/6$ for samples more than 70. If only an interquartile range was available, SD was estimated as $\text{interquartile range}/1.35$.⁸

For binary outcomes, we calculated the odds ratio (OR) for each trial and the pooled OR using the inverse variance method. All statistical variables were calculated with 95% confidence interval (95% CI). The Q test was used to analyze heterogeneity of trials. Considering possible clinical heterogeneity due to study design and patients’ population, we used a random effect model for all pooled analysis. RevMan software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for statistical analysis. Publication bias was assessed by visual inspection of funnel plot. A meta-regression analysis was planned to assess the effects of sample size, baseline risk of events in control group patients and year of publication on postoperative outcome. *Metareg* command in STATA version 13.0 (STATA SE 13.0, Stata Corp, College Station, TX, USA) was used for meta-regression analysis. We used *GRADEpro* software (GRADEpro Guideline Development Tool, McMaster University, 2015) to assess the quality of evidence and strength of recommendations as per GRADE methodology.

RESULTS

Database searching and searching of references of previous meta-analyses revealed 9060 articles and total 160 articles were screened from abstract and title to identify potentially eligible trials. A flow diagram as per PRISMA methodology showing stages of database searching and study selection has been provided in Figure 1. Finally, data of 1525 patients from 11 randomized controlled trials have been included in this meta-analysis.^{6,9-18} Two trials ($n = 302$) used NIV to manage postextubation respiratory failure^{10,11} and in rest of the trials NIV was used immediately after extubation. Three trials^{6,14,15} recruited patients with COPD or chronic respiratory disorders only and another two trials^{12,13} recruited patients who are at risk of postextubation respiratory failure. Possible risk of biases as per Cochrane methodology in the individual studies has been provided in Figure 2. A summary of the study characteristics has been provided in Table 1. Quality of evidences in this review was low to moderate (Tables 2 and 3).

Mortality

Postextubation NIV does not decrease mortality at the longest available follow-up [OR (95% CI) 0.84 (0.50, 1.42); $p = 0.52$, $I^2 = 56\%$; $n = 1393$]. Sub group analysis found that neither prophylactic nor therapeutic use of NIV is associated with a mortality benefit [OR (95% CI) 0.68 (0.36, 1.23); $p = 0.21$, $I^2 = 48\%$; $n = 1091$ and OR (95% CI) 1.52 (0.78, 2.97); $p = 0.22$, $I^2 = 27\%$; $n = 302$ respectively; Fig. 3].

Postextubation NIV in patients with COPD or chronic respiratory diseases significantly decreases mortality [OR (95% CI) 0.42 (0.20, 0.88); $p = 0.02$, $I^2 = 8\%$; $n = 249$; respectively (Fig. 4). Begg’s test did

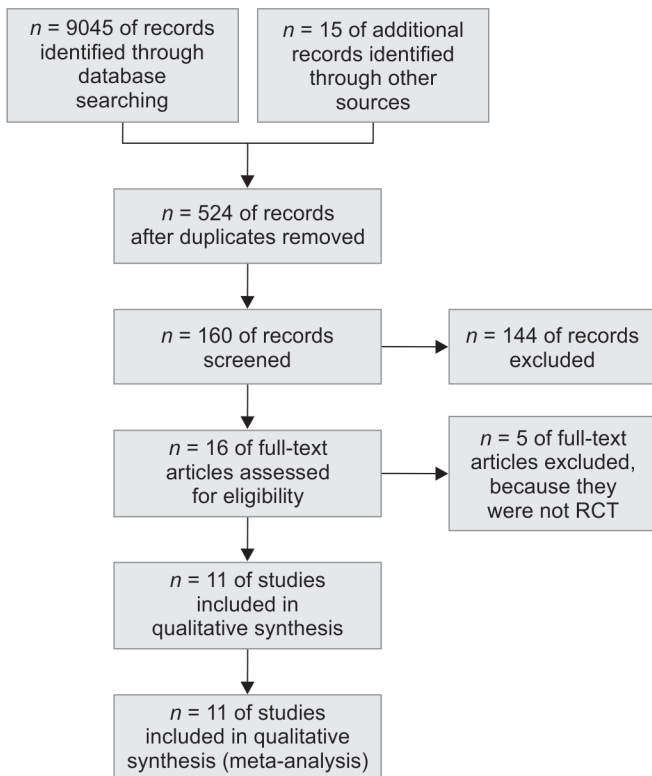


Fig. 1: Stages of database searching and study selection

not reveal any publication bias and a funnel plot for assessment of publication bias has been provided in (Fig. 5).

Reintubation

Rate of reintubation is also not decreased with the use of NIV [OR (95% CI) 0.75 (0.51, 1.09); $p = 0.13$, $I^2 = 44%$, $n = 1525$]. Subgroup analysis found that neither prophylactic nor therapeutic use of NIV is associated with a benefit in terms of reintubation [OR (95% CI) 0.65 (0.40, 1.06); $p = 0.08$, $I^2 = 51%$; $n = 1223$ and OR (95% CI) 1.05 (0.66, 1.67); $p = 0.84$, $I^2 = 0%$; $n = 302$ respectively; Fig. 6]. However, post-extubation NIV in patients with COPD or chronic respiratory diseases, significantly decreases rate of reintubation [OR (95% CI) 0.48 (0.24, 0.94); $p = 0.03$, $I^2 = 0%$; $n = 289$]. No evidence of publication bias was found in Begg’s test.

A meta-regression analysis found that sample size of the studies ($I^2 = 11.7%$, adjusted $R^2 = 100%$, $p = 0.28$), year of publication ($I^2 = 5.8%$, adjusted $R^2 = -174.7%$, $p = 0.18$) and baseline risk of intubation in the standard therapy group patients ($I^2 = 19.8%$, adjusted $R^2 = 10.6%$, $p = 0.22$; considering only studies where ‘prophylactic’ NIV was used) did not affect the rate of reintubation.

Length of Stay

Use of NIV after extubation does not decrease length of ICU stay [MD (95% CI) 0.46 (-0.43, 1.36) days; $p = 0.31$, $I^2 = 0%$; $n = 890$]. Subgroup analysis found that neither prophylactic nor therapeutic use of NIV is associated with a benefit in terms of length of ICU stay [MD (95% CI) 0.56 (-0.38, 1.49) days; $p = 0.25$, $I^2 = 0%$; $n = 588$ and MD (95% CI) -0.60 (-3.69, 2.50) days; $p = 0.70$, $I^2 = 0%$; $n = 302$, respectively; Fig. 7]. Only four studies reported length of hospital stay and it was

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Esteban 2004							
Ferrer 2006	?	+	-	-	+	+	-
Ferrer 2009	+	+	-	-	+	+	-
Girault 2011	+	+	-	-	+	+	-
Jiang 1199	?	?	?	?	+	?	-
Keenan 2002	+	+	-	-	+	+	+
Khilnani 2011	?	+	-	-	+	+	+
Nava 2005	+	?	-	-	+	+	+
Ornico 2013	?	+	-	-	+	+	+
Su 2012	+	?	-	?	+	+	+
Vargas 2017	+	?	-	?	+	+	+

Fig. 2: Risk of biases as per Cochrane methodology in the individual studies

similar in two groups [SMD (95% CI) 0.07 (-0.13, 0.27); $p = 0.99$, $I^2 = 0%$; $n = 389$]. In patients with COPD, neither length of ICU stays nor hospital stay is decreased with the use of NIV.

DISCUSSION

Principal finding of this meta-analysis is that postextubation NIV does not provide any benefit in terms of reintubation rate, mortality and length of stay when used either as either a prophylactic or therapeutic strategy. However, in patients with chronic respiratory diseases, rate of reintubation and mortality are decreased with the use of NIV.

Extubation failure and reintubation after planned weaning in the ICU is a common problem. A prospective observational study¹⁹ found that extubation failure rate was 29% and reintubation



Table 1: Characteristics of the included studies

Author	Patients	Intervention	NIV duration	Standard therapy
Jiang 1999	After extubation of the patients who required MV	BiPAP (initial IPAP 12 cm H ₂ O and EPAP 5 cm H ₂ O)	72 hours with temporary interruption up to 2 hours	Oxygen therapy by face mask or nasal cannula at 2–15 l/m
Keenan 2002	Postextubation respiratory distress	BiPAP (initial IPAP 9 cm H ₂ O and EPAP 4 cm H ₂ O)	Continuously for 12 hours followed by unassisted breathing for increasing duration	Supplemental oxygen
Esteban 2004	Postextubation respiratory failure	NIV-PSV to achieve a Vt >5 mL/ kg of body weight and a RR <25 breaths/minute	4 hours continuously and discontinuation by attending physician	Supplemental oxygen
Nava 2005	Patients who are at risk of extubation failure	NIV pressure support with PEEP	NIV was withdrawn after 48 hours in patients were clinically stable	Supplemental oxygen to maintain SaO ₂ >92%
Ferrer 2006	Patients who are at risk of extubation failure	BiPAP (mean IPAP 14 cm H ₂ O and EPAP 5 cm H ₂ O)	Continuously for 24 hours followed by oxygen therapy	Oxygen by Venturi mask
Ferrer 2009	Patients with chronic respiratory disorder with hypercapnia during SBT	BiPAP (IPAP 12–20 cm H ₂ O and EPAP 5–6 cm H ₂ O)	Continuously for 24 hours followed by oxygen therapy	Oxygen by Venturi mask
Girault 2011	After extubation of the patients with acute respiratory failure	NIV-PSV or BiPAP	NIV was discontinued when, required <6 hours/day or respiratory stability with standard oxygen therapy for at least 12 hours	Standard oxygen therapy to maintain SaO ₂ ≥90%
Khilnani 2011	After extubation of the patients with acute exacerbation of COPD	BiPAP (initial IPAP 8 cm H ₂ O and EPAP 4 cm H ₂ O)	7 hours per day	Oxygen by nasal prongs or mask
Su 2012	After extubation of the patients who required mechanical ventilation for >48 hours	BiPAP (initial IPAP 10–12 cm H ₂ O and EPAP 5 cm H ₂ O)	Patients were allowed to have unassisted breathing intermittently at increasing intervals after 12 h of NIV	Supplemental oxygen by mask to maintain SpO ₂ ≥92%
Ornico 2013	After extubation of the patients with acute respiratory failure	BiPAP (initial IPAP 8 cm H ₂ O and EPAP 4 cm H ₂ O)	Continuously for 24 hours	Supplemental oxygen by face mask at 5 l/min
Vargas 2017	After extubation of the patients with chronic respiratory diseases	NIV pressure support (initial PEEP 4 cm H ₂ O)	NIV was used for 1 hour every 3 hours and at least 6 hours/day	Standard oxygen therapy targeting SaO ₂ ≥90%

NIV, Noninvasive ventilation; MV, mechanical ventilation; BiPAP, Bi-level positive airway pressure; NIV-PSV, Noninvasive pressure support ventilation; Vt, tidal volume; RR, Respiratory rate; COPD, chronic obstructive pulmonary disease; SBT, spontaneous breathing trial

within 48-hour of extubation was 16% and it was independently associated with mortality with an odds of more than 5. Despite of being increasingly used in postextubation period both as preventive or therapeutic strategy, evidence in support of NIV in these setting is limited. Most of the randomized controlled trials conducted in this setting are of small sample size, limiting their generalizability. Benefits of 'prophylactic' use of NIV in the post-extubation period to prevent respiratory failure may be limited only to the patients who are at high risk of reintubation¹⁸ or in the postoperative patients.²⁰ Glossop et al in a meta-analysis found that NIV decreases reintubation rate and pneumonia in postsurgical patients, and a reduction in ICU stay when NIV was used as weaning

strategy.²¹ Authors of this meta-analysis concluded that a reduction in reintubation reduced the incidence of ventilator-associated pneumonia.

Routine use of NIV in postextubation period has been criticized because NIV may delay the intubation and delay in intubation is a risk factor for poor outcome. Esteban et al.¹¹ reported that the interval between the onset of respiratory failure and reintubation was significantly longer in patients who received NIV and they also found that ICU mortality appeared to be higher in NIV group which may have contributed to delaying of intubation. NIV failure has also been identified as an independent risk factor ICU mortality in patients with acute respiratory failure.²²

Table 2A: Quality of evidences as judged by GRADE methodology: Summary of findings

Noninvasive ventilation compared to standard oxygen therapy for after extubation

Patient or population: after extubation

Setting:

Intervention: Noninvasive ventilation

Comparison: standard oxygen therapy

Outcome No. of participants (studies)	Relative effect (95% CI)*	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Mortality at longest follow-up No. of participants: 1393 (9 RCTs)	OR 0.84 (0.50–42)	14.8%	12.7% (8.0 to 19.8)	2.1% fewer (6.8 fewer to 5 more)	⊕⊕○○ LOW ^{a, b, c}	
Rate of reintubation No. of participants: 1525 (11 RCTs)	OR 0.75 (0.51–1.09)	25.4%	20.4% (14.8 to 27.1)	5.1% fewer (10.6 fewer to 1.7 more)	⊕⊕○○ LOW ^{a, b, c}	
Length of hospital stay No. of participants: 389 (4 RCTs)				SMD 0.07 SD higher (0.13 lower to 0.27 higher)	⊕⊕○○ LOW ^{a, b, c}	
Length of ICU stay No. of participants: 890 (7 RCTs)		The mean length of ICU stay was 0		MD 0.46 higher (0.43 lower to 1.36 higher)	⊕⊕○○ LOW ^{a, b, c}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI, confidence interval; OR, odds ratio; SMD, standardised mean difference; MD, mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

^aNonblinded

^bUse of NIV in standard therapy

^cTherapeutic versus prophylactic use

On the contrary, NIV has been found to provide a benefit in terms of mortality and intubation rate in acute respiratory failure patients when compared to invasive mechanical ventilation or standard oxygen therapy.²¹ In our meta-analysis we have found benefit of NIV in terms of reintubation and mortality only in patients with COPD or chronic respiratory diseases, but not in other settings and it is well established that COPD patients are at high risk of extubation failure. A recent Cochrane database systematic review⁴ reported that use of NIV in the management of acute hypercapnic respiratory failure in COPD patients decreased mortality by 46% and need for intubation by 65%. The quality of the evidence reported by the authors was 'moderate'. The official European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines also recommends use of NIV in these settings.²³ However, in our univariate meta-regression analysis, we did not find any significant contribution of risk of reintubation in standard therapy group patients towards the ultimate effect of NIV on reintubation.

It is worth mentioning that most of the trials included in this meta-analysis used NIV as a rescue therapy in patients who received standard oxygen therapy also; hence magnitude of actual benefit

from NIV may be higher than what is reported in the individual trials. In the RCT by Vargas et al.,¹⁸ it was reported that incidence of respiratory failure was lower in patients who received NIV after extubation, but not the rate of reintubation or 90-day mortality. As the patients in standard oxygen therapy group also received NIV as rescue therapy, NIV might have some role in preventing re-intubation. Practice guidelines of American College of Chest Physicians (ACCP)/American Thoracic Society (ATS) recommends that NIV should be used after extubation in patients who are risk of extubation failure.²⁴ We believe that this may be the single most important reason behind the lack of benefit from NIV in our meta-analysis.

A previous meta-analysis of 13 RCTs published in 2017 also evaluated role of NIV in post-extubation respiratory failure. The authors of this meta-analysis reported a significant reduction in rate of reintubation and mortality benefit in patients who received prophylactic NIV.²⁵ However, our meta-analysis different from this one, as we have included patients who received post-operative mechanical ventilation and no subgroup analysis including patients with chronic respiratory disorders was reported.



Table 3: Quality of evidences as judged by GRADE methodology when NIV is used as preventive strategy: Summary of findings

Noninvasive ventilation compared to standard oxygen therapy for after extubation						
Patient or population: after extubation						
Setting:						
Intervention: Noninvasive ventilation						
Comparison: standard oxygen therapy						
Outcome No. of participants (studies)	Relative effect (95% CI)*	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Mortality at longest follow-up NIV as preventive strategy No. of participants: 1091 (7 RCTs)	OR 0.68 (0.38–1.23)	13.7%	9.7% (5.7–16.3)	4.0% fewer (8 fewer to 2.6 more)	⊕⊕⊕○ Moderate ^{a,b}	
Rate of reintubation NIV as preventive strategy No. of participant: 1223 (9 RCTs)	OR 0.65 (0.40–1.06)	18.6%	12.9% (8.4–19.5)	5.7% Fewer (10.2 fewer to 0.9 more)	⊕⊕⊕○ Moderate ^{a,b}	
Length of ICU stay- NIV as preventive strategy No. of participants: 588 (5 RCTs)			The mean length of ICU stay - NIV as preventive strategy was 0	MD 0.56 Higher (0.38 lower to 1.49 higher)	⊕⊕⊕○ Moderate ^b	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; OR, odds ratio; SMD, standardised mean difference; MD, mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations: ^aNon-blinded; ^bUse of NIV in standard therapy; ^cTherapeutic versus prophylactic use

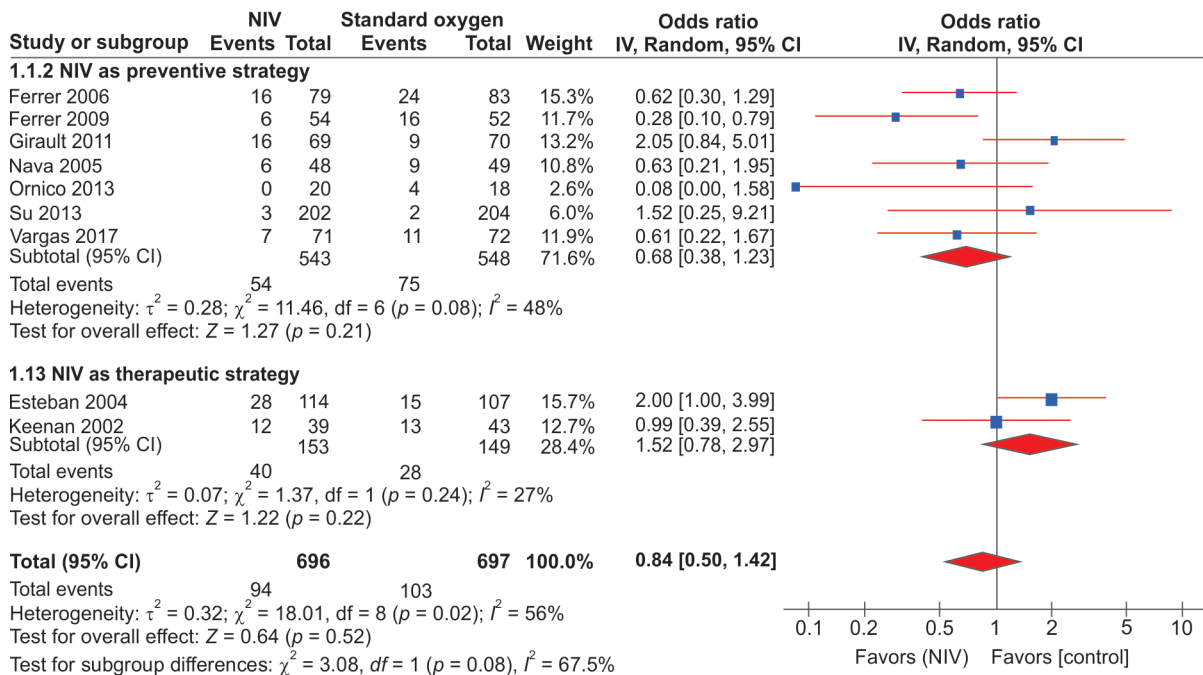


Fig. 3: Forest plot showing mortality at the longest available follow-up at individual study level and at pooled analysis level with the use of noninvasive ventilation and standard therapy.

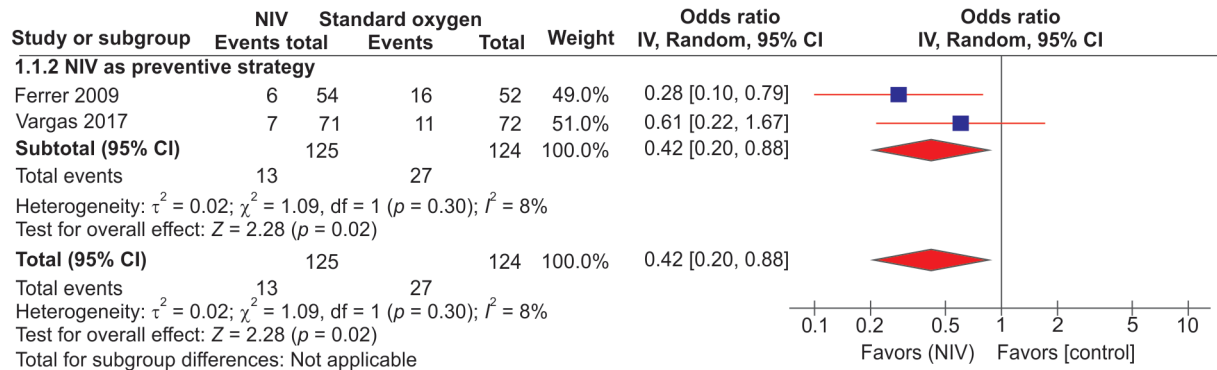


Fig. 4: Forest plot of odds ratio of mortality at longest available follow-up in patients with COPD or chronic lung diseases at individual study level and pooled analysis level

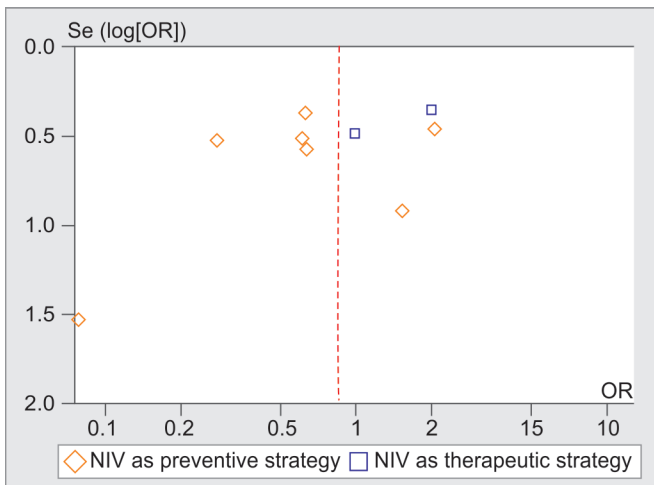


Fig. 5: Funnel plot for detection of publication bias in 'mortality at longest follow-up'

LIMITATIONS

Our meta-analysis has several limitations. We have found a significant amount of statistical heterogeneity in most of our analysis. Statistical heterogeneity is probably due to heterogeneous patients' population and also a varied NIV protocol across the studies also. Though some benefit of NIV has been found in COPD patients, number of patients in this sub-group analysis is small.

CONCLUSION

Postextubation NIV does not provide any benefit in terms of reintubation rate, mortality and length of stay when used either as a prophylactic or therapeutic strategy in patients with acute respiratory failure. Quality of evidences generated from this review was low to moderate. In patients with COPD or chronic lung diseases, rate of reintubation and mortality are decreased with the use of NIV.

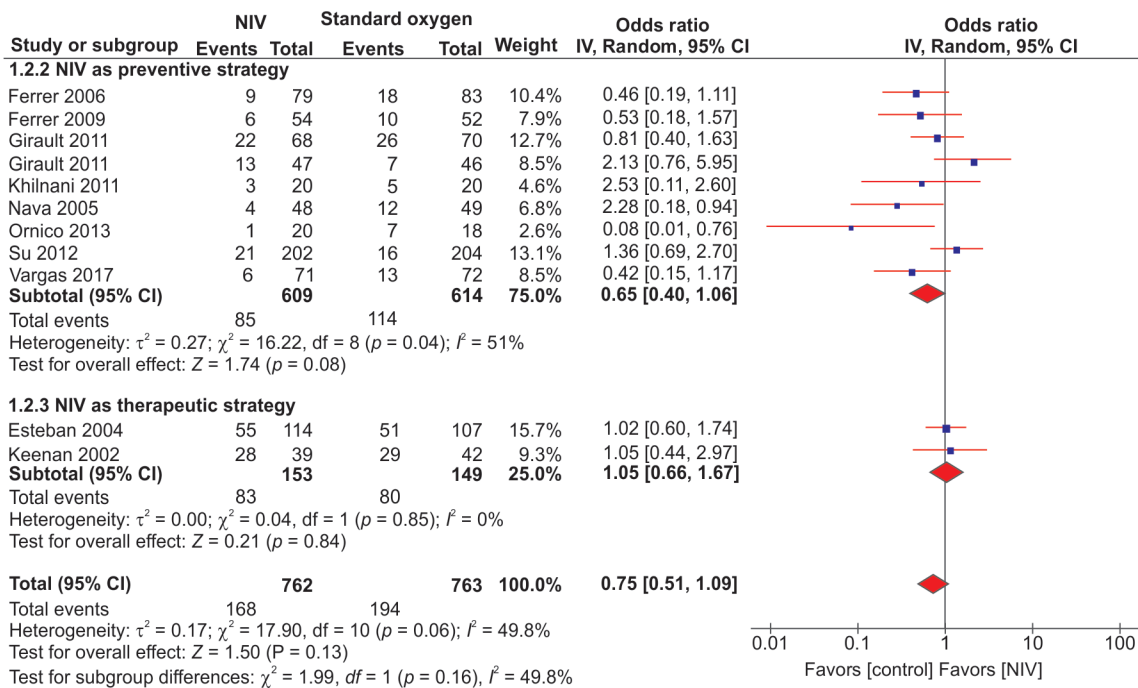


Fig. 6: Forest plot showing rate of reintubation at individual study level and at pooled analysis level with the use of noninvasive ventilation and standard therapy.



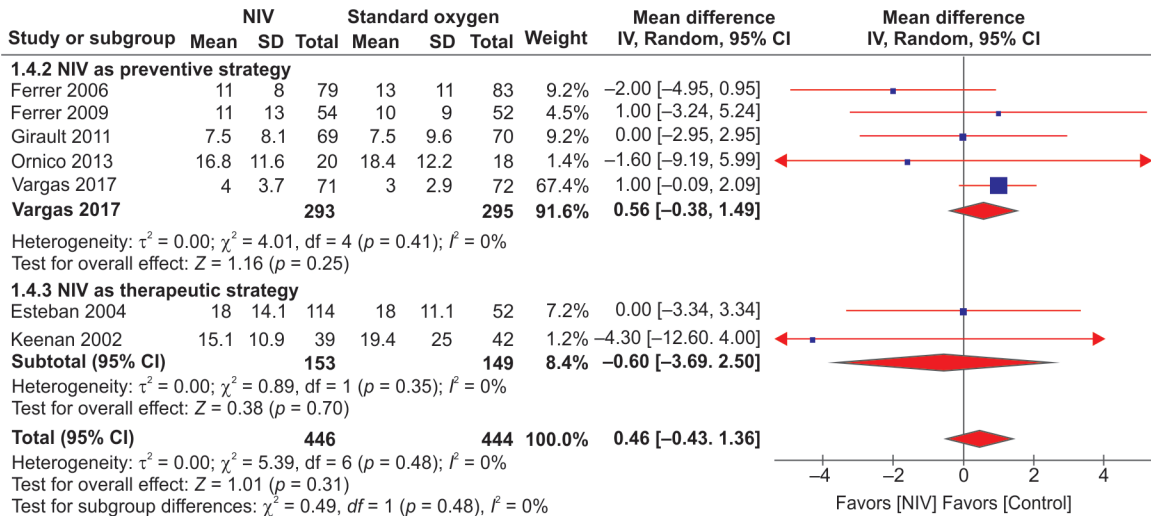


Fig. 7: Forest plot showing length of ICU stay at individual study level and at pooled analysis level with the use of noninvasive ventilation and standard therapy.

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