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Noninvasive ventilation in acute hypoxemic respiratory failure: A systematic review and meta-analysis

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ABSTRACT

Purpose: Evaluate current recommendation for the use of noninvasive ventilation (Bi-level positive airway pressure- BiPAP modality) in hypoxemic acute respiratory failure, excluding chronic obstructive pulmonary disease.
Methods: Electronic searches in MEDLINE, Web of Science, Clinical Trials, and The Cochrane Central Register of Controlled Clinical Trials. We searched for randomized controlled trials comparing BiPAP to a control group in patients with hypoxemic acute respiratory failure. Endotracheal intubation and death were the assessed outcomes.
Results: Of the **563** studies found, nine met the inclusion criteria for this systematic review. The pooled RR (95% CI) for intubation in patients with acute pulmonary edema (APE)/community acquired pneumonia (CAP) and in immunosuppressed patients (cancer and transplants) were 0.61 (0.39–0.84) and 0.77 (0.60–0.93), respectively. For Intensive Care Units (ICU) mortality, the RR (95% CI) in patients with APE/CAP was 0.51 (0.22–0.79). The heterogeneity was low in all comparisons.
Conclusions: NIV showed a significant protective effect for intubation in immunosuppressed patients (cancer and transplants) and in patients with APE/CAP. However, the benefits of NIV for other etiologies are not clear and more trials are needed to prove these effects.

1. Introduction

Acute Respiratory Failure (ARF) is the leading cause of emergency admissions. The mortality rate is almost 20%, and its annual cost is US $54 billion [1]. In Brazil, there are no official data showing the impact of ARF, but a recent study, evaluating 45 public and private ICUs across the country for a 2-month period observed a mortality rate of 34% in patients with ARF, and the hospital mortality of 42%. The major etiologies were pneumonia (27%), neurological causes (19%), nonpulmonary sepsis (12%), chronic obstructive pulmonary disease (COPD) (6%), and acute pulmonary edema (APE) (6%). 80% of those patients used invasive mechanical ventilation and 20% used noninvasive mechanical ventilation (NIV) [2].

The BiPAP modality has been used for ARF in hospital settings for >30 years [3]. NIV is considered the standard treatment for COPD exacerbation. Many randomized controlled trials (RCTs) have shown the benefits of NIV in decreasing mortality, the use of sedatives, delirium, upper airway injuries, and length of stay in the ICU in COPD patients [4].

However, benefits of NIV have not been clarified in hypoxemic respiratory failure etiologies, such as pneumonia, asthma, acute respiratory distress syndrome (ARDS) and immunosuppression, since results from studies remain conflicting [5-9]. A Canadian Guideline for the use of NIV recommended this mode of ventilatory support only for COPD and acute pulmonary edema; and weakly recommended NIV for other hypoxemic diseases [10]. Furthermore, a Brazilian Guideline for Mechanical Ventilation failed to demonstrate benefits of NIV in hypoxemic acute respiratory failure, based on a few trials, heterogeneous population, and weak level of evidence in retrospective studies and systematic reviews [11,12]. Similarly, Keenan et al. conducted a systematic review on the use of NIV in hypoxemic patients and failed to show any supporting evidence, due to similar limitations: mixed population,

Abbreviations: NIV, Non-invasive ventilation; BiPAP, Bi-level positive airway pressure; RR, Relative risk; CI, Confidence interval; APE, Acute pulmonary edema; CAP, Community acquired pneumonia; ARDS, Acute respiratory distress syndrome; ICU, Intensive Care Unit; ARF, Acute respiratory failure; COPD, Chronic obstructive pulmonary disease; RCT, Randomized clinical trial; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation System II; IPAP, Inspiratory positive airways pressure; EPAP, Expiratory positive airways pressure; PEEP, Positive end-expiratory pressure.

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RCTs with a limited number of patients and lack of relevant information [13].

Therefore, the aim of this study was to review the latest evidence on the use of noninvasive ventilation (BiPAP) in patients with hypoxemic acute respiratory failure and to determine the efficacy of this intervention on mortality and intubation.

2. Methods

2.1. Search strategy

This review was conducted in accordance with the PRISMA protocol [14] – Supplementary File 1. PRISMA Checklist. The search was performed at electronic libraries such as MEDLINE, Web of Science, Clinical Trials, and The Cochrane Central Register of Controlled Clinical Trials, from March 1995 to June 2018. The combination of keywords (MeSH) related to the population (respiratory insufficiency), exposure (noninvasive ventilation), and outcomes (endotracheal intubation and death) was used, with no language restriction. In addition, unpublished studies were assessed in Clinical Trials. Two independent authors reviewed the abstracts of all articles identified in the reference list. Details of the search strategy are provided in the Supplementary File 2 – PubMed Search strategy.

2.2. Selection criteria

The following criteria were used to select articles: (a) RCTs; (b) patients with acute hypoxemic respiratory failure older than 18 years; (c) the intervention included noninvasive ventilation or noninvasive ventilation plus standard therapy vs. standard therapy alone. Mortality and/or need for endotracheal intubation were the outcomes. Two independent reviewers worked together to screen the title and abstracts of all studies identified using the selection criteria. After duplicates were excluded, the authors evaluated the titles and abstracts independently. Any differences were discussed to a consensus or by consulting a third author. Subsequently, full texts were retrieved for studies that satisfied all selection criteria.

2.3. Data abstraction and analysis

In this systematic review, studies were classified in subgroups according to the etiologies of hypoxemic respiratory failure. Some studies presented more than one control group. Data was abstracted from the most similar group to other studies in this review. It was selected the most prevalent etiology for analysis in studies with heterogeneous population.

Data was obtained by the authors through a predesigned data collection chart that contained date of publication, location and number of sites enrolled, characteristics of participants, inclusion and exclusion criteria, type of intervention, specification of the therapy used in the control group, and number of patients in both the intervention and group controls.

If risk estimates were not included in the RCT, relative risks (RR) and their 95% confidence intervals (CI) were calculated using the events reported by the authors in each study.

2.4. Risk of bias

Quality was validated by the Cochrane risk of bias tool [15], in which eight possible sources of bias are evaluated: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias and intention to treat. Studies were classified into low, unclear, or high risk of bias. Two independent authors assessed the risk of bias for each study.

2.5. Statistical analysis

A meta-analysis of binary data was performed. Relative risks (RR) were estimated using the events reported in each study. Variance between studies was estimated by DerSimonian-Laid method, assuming Mantel-Haenzel pooled RR for Q statistic estimation. Heterogeneity was measured by $I^2$and Cochran Q test was performed to test for homogeneity assuming and alpha level of 0.10. The pooled RR estimated under the assumption of fixed effects was performed by Mantel-Haenzel method when the estimated heterogeneity was not significant based on Cochran Q test. In the presence of significant heterogeneity, random effects model was assumed. Significance of overall effect was evaluated by a two-tailed Z test, defining significance as $P < 0.05$. Analyses were undertaken within sets of studies defined by reported outcomes. All analyses were conducted using Stata version 14.0.

3. Results

The search strategy identified 563 citations, 21 duplicates were eliminated. Of the 542 abstracts, 421 articles were excluded for the reasons shown in Fig. 1. PRISMA flow diagram of systematic searches and selection process. The remaining 121 titles were reviewed by two authors; 44 reports were fully read. Nine articles met the criteria and were included in this systematic review.

The characteristics of these nine studies are described in Table 1**.** One study analyzed patients with acute pulmonary edema [16], one study analyzed patients post-extubation [17], two studies analyzed patients that were immunosuppressed [18,19], one study analyzed patients with postoperative abdominal surgery [20] and two studies analyzed patients with community acquired pneumonia [21,22].

For the two remaining studies enrolled, there was a heterogeneous population, so the most prevalent etiologies of hypoxemic ARF that were present in both studies were considered: acute pulmonary edema and community acquired pneumonia [23,24]. All studies reported intubation as an outcome, and, in most articles, this was the primary outcome. Only one study reported mortality as a primary outcome [19].

Severity of the patients was determined by the Simplified Acute Physiology Score (SAPS II) [25] and Acute Physiology and Chronic Health Evaluation System II (APACHE II), which are widely used in the critical care setting to evaluate prognosis [26]. In many studies, patient severity was classified as moderate, with a predicted mortality of 25%. Only two studies reported patients with SAPS II or APACHE II at high levels, with a predicted mortality over 70%.

Contraindications for the use of noninvasive ventilation were also exclusion criteria [12], such as recent esophageal or upper airway surgery, facial trauma or deformities, neurological disorders (either acute or chronic diseases, and a Glasgow Coma Scale <12), terminal diseases and do-not-resuscitation orders, lack of cooperation, tracheostomy, difficulty in airway protection, upper gastrointestinal bleeding, or any severe conditions with an imminent risk of death (emergent intubation, arrhythmia or acute myocardial ischemia and cardiac arrest).

In the included studies, the baseline ratio of PaO2/FiO2 was <300 mmHg, but no studies were conducted with severe hypoxia (PaO2/FiO2 < 100 mmHg). The inclusion criteria in most of the studies was a PaO2 < 60 mmHg in room air or PaO2 < 80 mmHg with supplementary oxygen.

Still, some studies included patients who had clinical signs of respiratory insufficiency, such as high respiratory rates and signs of respiratory fatigue. In four studies, a population with hypercapnic ARF, in addition to the hypoxemia, were included, but the authors analyzed the groups with and without high pCO2 separately, [16, 17, 21, 24] and in this systematic review only the hypoxia groups were considered. In four studies that described comorbidities, the patients had some of chronic respiratory disorder, such as COPD, but distribution was equal

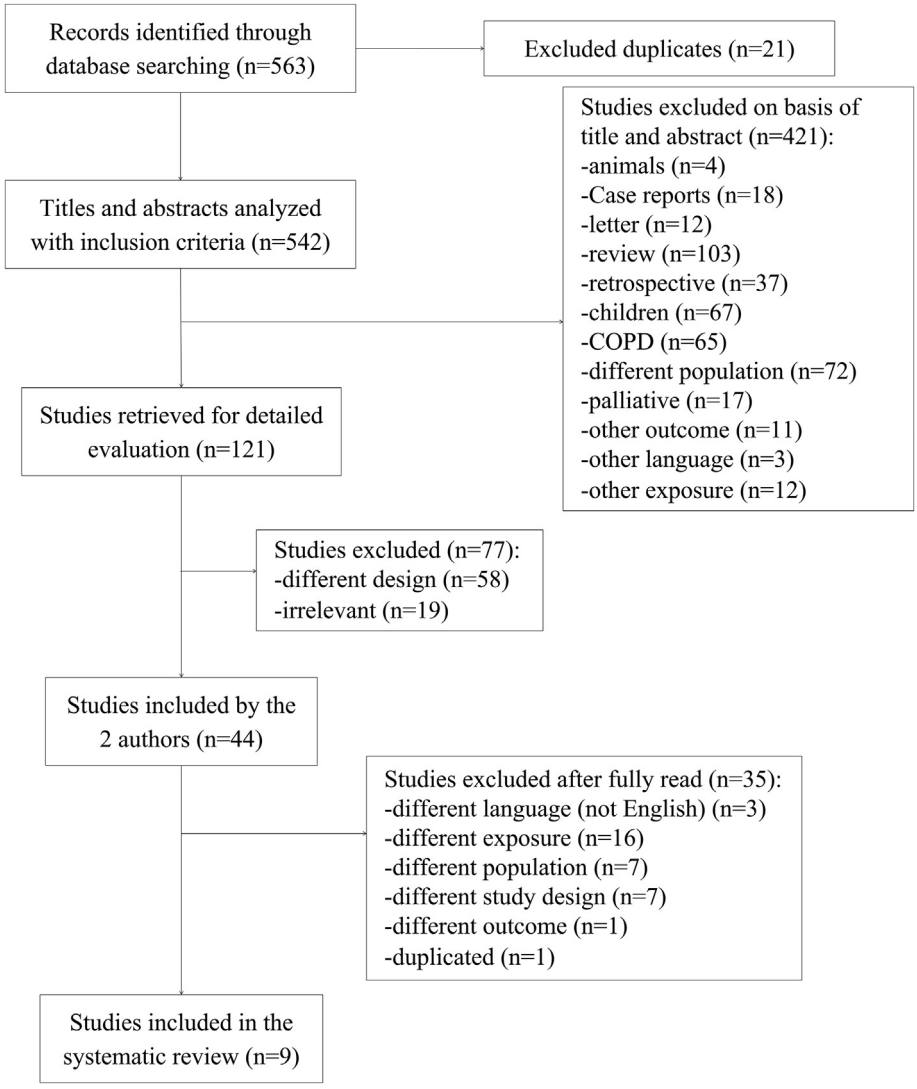

Fig. 1. PRISMA flow diagram of systematic searches and selection process.

in both the intervention and control groups and this was not the primary cause of the acute respiratory insufficiency.

A full-face mask was the chosen device for the intervention groups. Even though the protocols for inspiratory positive airways pressure (IPAP) and expiratory positive airways pressures (EPAP)/ positive end-expiratory pressure (PEEP) were different, the IPAP set was adjusted to maintain the tidal volume between 6 and 10 mL/Kg and EPAP/PEEP was adjusted in increasing sets of 1–2 cm H2O to achieve SO2 > 92% or to improve PaO2/FiO2. In studies where FiO2 was reported, it was titrated to maintain SO2 > 92%. Medications, such as antibiotics, diuretics, and bronchodilators were used in addition to BiPAP in some intervention groups, depending on etiology. The control groups mostly used oxygen devices such as nasal catheters and Venturi masks with of oxygen (10–15 L/min) to maintain adequate oxygenation.

The quality of the studies was assessed using the Cochrane tool for the risk of bias (Fig. 2. Quality of included studies). For randomization and allocation concealment, the risk of bias was not high, but in some studies, this was not clear. In addition, Participants were not blinded in all studies. In only one study, it was reported the assessors were blinded by receiving results for the outcome from a computer. All included studies had complete reports related to characteristics, design, and outcomes. Only one study had a high risk of selective reports in this analysis, and three studies did not report intention to treat.

The relative risks according to the outcomes are shown in Fig. 3. Relative Risks of all population and outcomes. Meta-analysis for APE/CAP population and ICU mortality outcome was performed with 2 studies, with a pooled RR of 0.51 (0.22–0.79), showing a protective effect of NIV in this group, with no heterogeneity ($I^2 = 0.0\%$, $p = 0.520$) (Fig. 4. Relative Risks for ICU mortality in Acute Pulmonary Edema/ Community Acquired Pneumonia).

For the intubation outcome, we pooled the RR for 3 etiologies (Fig. 5. Relative Risks for Intubation in Pneumonia, Immunosuppression and APE + CAP).

In the pneumonia subgroup, pooled RR did not show a protective effect for intubation, but in the immunosuppressed subgroup, there was a decreased risk for intubation in 23% of the cases, with low heterogeneity ($I^2 = 47.5\%$, $p = 0.168$). In the APE/CAP population, a protective effect for this outcome is noticed in 39% of the cases, with non-significant heterogeneity ($p = 0.118$).

4. Discussion

This systematic review and meta-analysis on the effect of NIV/BiPAP on need for intubation and mortality in patients with acute hypoxemic respiratory failure showed benefits in patients that were immunosuppressed and in patients with acute pulmonary edema/ community acquired pneumonia for the outcomes of interest.

Table 1
Characteristics of the studies included.

Study	Location	Number of centers	Inclusion criteria	Exclusion criteria	Intervention	Control	N participants intervention	N participants Control
ACUTE PULMONARY EDEMA								
Nava et al. 2003	Italy	5	- PO2/FiO2 < 250 - Use of O2 < 10 L/min for 15 min - Dyspnea (respiratory rate > 30/min) - physical signs of pulmonary edema	- immediate endotracheal intubation - severe sensorial impairment - shock, ventricular arrhythmias - SO2 < 80% with oxygen - acute myocardial infarction+thrombolysis - severe chronic renal failure - pneumothorax	- full face mask - PEEP initially set at 5 cm H2O with increase of 1 cm H2O until raise of SpO2 - IPAP initially set at 10 cmH2O with increase of 2 cm H2O to the maximum tolerated.	- face mask with an FiO2 to maintain an SpO2 > 90% + medical treatment	32	34
POST EXTUBATION								
Ferrer et al. 2006	Spain	2	- intubation >48 h - recovery form disease, spontaneous breathing trial - risk of ARF after extubation: >65 yr, cardiac failure as cause of intubation, APACHEII>12	facial or cranial trauma or surgery, recent gastric or esophageal surgery or active upper gastrointestinal bleeding, respiratory secretions, lack of cooperation, do-not-resuscitation orders or support limits	BiPAP immediately after extubation for 24 h continuously	- Extubation after spontaneous breathing trial -immediaty Venturi mask oxygen	79	83
IMMUNOSSUPRESSION								
Hilbert et al., 2001	France	1	pulmonary infiltrates on radiographs and fever (>38.3 °C), severe dyspnea at rest (respiratory rate > 30/min), PO2/FiO2 < 200 – Venturi mask.	emergency intubation (cardiac or respiratory arrest or GCS <8); hemodynamic instability (SBP < 80 mmHg or miocardyal ischemia or ventricular arrhythmias;), COPD respiratory failure of cardiac origin, pCO2 > 55 mmHg + pH <7,35, recent failure of more than two organs, uncorrected bleeding diathesis, tracheotomy, a facial deformity, or a recent esophageal, oral or gastric surgery.	Medications: antimicrobial agents, diuretics, bronchodilators, immunosuppressive Agents NIV: full face mask, FiO2 to maintain SO2 > 90%, IPAP adjust to tidal volume 7-10 mL/Kg; PEEP increasing by 2cmH2O up to 10cmH2O until FiO2 < 65%	Venturi mask to achieve SO2 > 90% Medications: antimicrobial agents, diuretics, bronchodilators, immunosuppressive Agents	26	26
Lemiale et al., 2015	France	28	PaO2 < 60 mmHg on room airor dyspnea or RR > 30/min at rest respiratory symptom duration <72 h; and immune deficiency defined as hematologic malignancy or solid tumor, solid organ transplant, long-term (>30 days) or high-dose (>1 mg/kg/d) steroids, immunosuppressive drug >30 days	pCO2 > 50 mmHg, immediate intubation, cardiogenic acute pulmonary edema, need for vasopressors, myocardial infarction or acute coronary syndrome, GCS < 13, do-not-intubate decision, long-term oxygen therapy, postoperative acute respiratory failure	Face mask,pressure support IPAP adjusted to tidal volume of 7-10 mL/Kg; PEEP 2-10cmH2O; FiO2 to maintain SO2 > 92%	Oxygen therapy	191	183
POSTOPERATIVE								
Jaber et al., 2016	França	20	laparoscopic or nonlaparoscopic elective or nonelective abdominal surgery under general anesthesia. pO2 < 60 mmHg in room air or pO2 < 80 mmHg with 15 L/min O2 ans SO2 < 90%, clinical signs of intense respiratory effort	withholding of life-sustaining treatment,contraindications to noninvasive ventilation, sleep apnea syndrome, immediate tracheal intubation emergent surgical procedure	IPAP 5-15cmH2o until tidal voume 6-8 mL/Kg RR < 25/min PEEP 5-10cmH2o until SO2 > 94%, titrating FiO2 Standard therapy between sessions	Supplemental oxygen up to 15 L/min until SO2 > 94%	148	145

(continued on next page)

Table 1 (*continued*)

Study	Location	Number of centers	Inclusion criteria	Exclusion criteria	Intervention	Control	N participants intervention	N participants Control
PNEUMONIA								
Frat et al., 2015	France, Belgium	23	RR > 25/min PO2/FiO2 < 300 with O2 10 L/min over 15 min pCO2 < 45mmhg no history of chronic respiratory disease	pCO2 > 45 mmHg exacerbation of asthma or chronic respiratory failure,cardiogenic pulmonary edema, severe neutropenia, hemodynamic instability, vasopressors, GCS < 12, need for intubation, do-not-intubate order	Face mask IPAP –adjust to obtain tidal volume 7-10 mL/Kg EPAP – 2-10cmH2O FiO2 and PEEP to maintain SO2 > 92%	Nonrebreather face mask with O2 10 L/min or more to maintain Sat O2 92%	110	94
Confalioneri et al., 1999	Italy	3	severe dyspnea at rest and RR > 35 with respiratory effort, PaO2 <68 mmHg With FIO2 > 0.4, or a PaO2/FIO2 < 250 while receiving an FIO2 > 50%, PaCO2>. 50 mmHg) with respiratory acidosis (pH < 7.33)	emergent intubation, respiratory arrest, severe hemodynamic instability, encephalopathy, severe neurologic disease, terminal disease(e.g., advanced cancer), long-term oxygen therapy or home mechanical ventilation, tracheostomy or facial deformities, or inability to expectorate.	IPAP – 5-10cmH2O to maintain tidal volume > 6 mL/kg, a RR < 25 breaths/min, and patient comfort. PEEP – 2-8cmH2O to improve oxygenation	Antibiotics +Oxygen to SO2 > 90%. Bronchodilators,corticosteroids if necessary	16	17
ACUTE PULMONARY EDEMA + PNEUMONIA								
Wysocki et al., 1995	France	1	2 of: RR > 25, pO2 < 60 in room air or pO2 < 80mmHgwith oxygen, pCO2 > 50 mmHg, pH < 7,38	Chronic respiratory insufficiency, asthma, neurologic disease, > 2 organ failures, a facial deformity, or a recent esophageal, oral or gastric surgery, immediate intubation	Medications+ full face mask, IPAP –adjust to obtain tidal volume 7-10 mL/Kg FiO2 to maintain SO2 > 95% PEEP: titrating to increase PO2/FiO2 and prevent atelectasis	Medications (antibiotics, diuretic, inotropics) + O2 nasal catheter to maintain SO2 > 95%	21	20
Ferrer et al., 2003		1	PaO2 < 60 mmHg for 6-8 h or SO2 < 90% while Venturi mask oxygen at a maximal concentration (50%)	PaCO2 > 45 mmHg, emergency intubation; recent esophageal, facial, or cranial trauma or surgery and other upper airway disorders; GCS < 11, severe hemodynamic instability, lack of cooperation; severe ventricular arrhythmia or myocardial ischemia; active upper gastrointestinal bleeding; respiratory secretions; >1 organ dysfunction	Face mask, FiO2 to maintain SO2 > 92% or pO2 > 65 mmHg	Oxygen high concentration to maintain SO2 > 92% or pO2 > 65 mmHg	51	54

Our study showed protection for intubation with the use of NIV in patients with hypoxemic acute respiratory failure with immunosuppression, for the causes cited above. Furthermore, our study showed protection for intubation and mortality with the use of NIV in patients with APE/CAP.

We found trials reporting all etiologies, except asthma, according to our predefined inclusion criteria. However, for post-extubation, isolated acute pulmonary edema and postoperative, only one study for each of these etiologies was present; therefore, we were not able to perform the meta-analysis in these populations. ARDS was not studied as a single condition on any trial, so we could not separate this subgroup.

For the studies reporting as "acute pulmonary edema/community acquired pneumonia," this was not the only population enrolled. Some studies [23,24] included a "miscellaneous" population, therefore we decided to analyze the most prevalent population, in which sampling represented >60% of the patients.

In both studies which reported immunosuppression, the characteristic was mostly the presence of cancer (hematologic or solid tumors) and the use of immunosuppressive drugs after organ transplantation.

In a previous review [13], the authors demonstrated that early application of NIV decreased the rate for intubation and mortality. However, they performed the analysis with all studies together in the same forest plots for all outcomes. Due to the heterogeneity of the population, with different etiologies, this comparison raised several questions about their results. A recent meta-analysis looked at available evidence on hypoxemic ARF and provided similar results to those presented in this review [27]. However, the authors did not perform analysis in single etiologies. Given we provided analysis according to clinically meaningful prespecified groups, our data is suitable for recommending treatment, especially in immunocompromised patients.

In one trial [18], the participants were immunosuppressed and did not present complications at the time of inclusion and were randomized

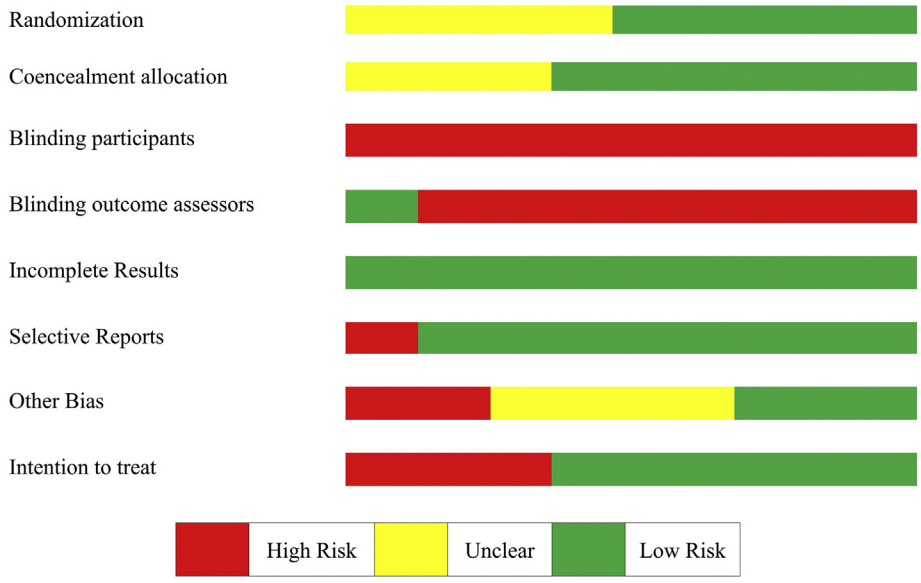

Fig. 2. Quality of included studies.

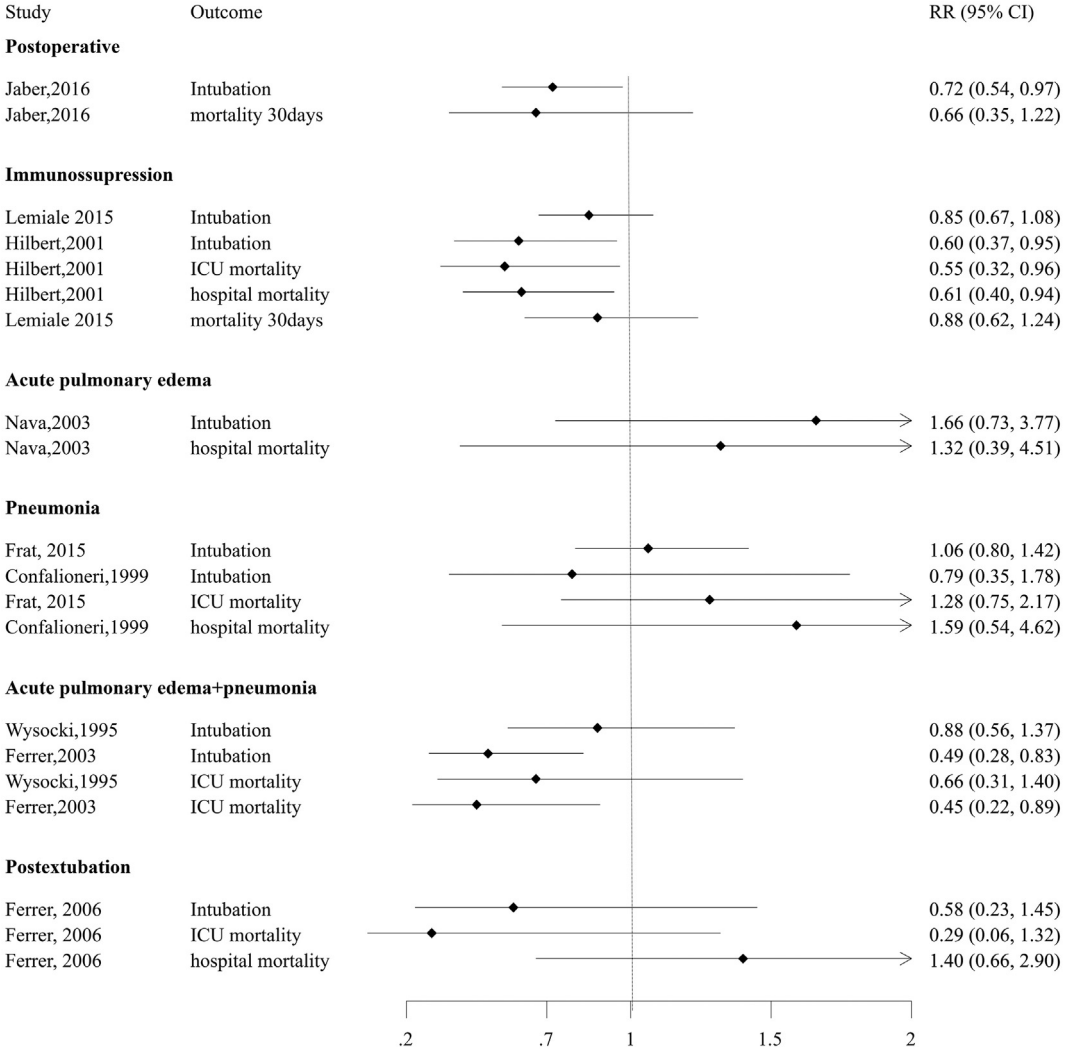

Fig. 3. Relative Risks of all population and outcomes.

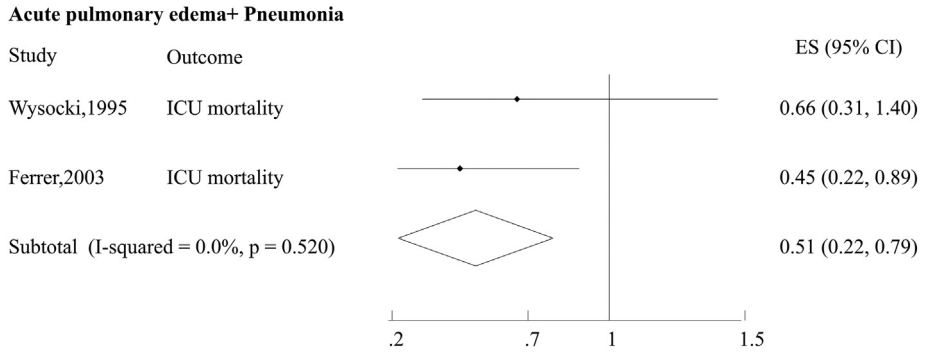

Fig. 4. RR for ICU mortality in Acute Pulmonary edema and Community Acquired Rneumonia.

if they presented pulmonary infiltrates, fever, and hypoxia. In another study [19] population had complications due to the immunosuppression and the most prevalent etiology was pneumonia. This trial showed no protection for all-cause mortality, as this was their primary outcome. Nevertheless, when we summarized both studies, we found significant protection for intubation with low heterogeneity. Our findings should be interpreted with caution, since the RCT that showed better results was conducted almost 20 years ago [18].

One possible explanation is the minimization of ventilator-acquired pneumonia, a condition that is associated with higher mortality. Another explanation for the protection in the use of BiPAP in those studies is that hypoxia was not so severe, as previous studies. Moreover, the use of PEEP, redistribution of extravascular fluids, alveolar recruitment, treating atelectasis and reducing the work of breathing in this population could contribute to the improvement in the prevention of intubation. Moreover, the studies for immunosuppressed patients had similar baseline etiologies and ratio of PaO2/FiO2 at randomization.

For the acute pulmonary edema/community acquired pneumonia group, one trial [23] showed benefits for the use of BiPAP, especially in the pneumonia group. However, these results contradicted with those in another trial [24]. Nevertheless, we observed protection for mortality and intubation, when we summarized both studies.

Compared to the Confalonieri trial [21], which failed to demonstrate protection and studied only community acquired pneumonia, Ferrer [23] included more severe hypoxemic patients. Therefore, NIV may be better than oxygen alone in more severe patients. In addition, APACHE scores differed among studies, which could explain the better results in the latter study. This comparison is important since there is a lack of evidence for the use of NIV due to the many differences in the selection criteria of patients across trials.

Even though many authors have shown great benefits with the use of noninvasive ventilation in acute pulmonary edema patients, the Three Intervention in Cardiogenic Pulmonary Oedema (3-CPO) trial [28] did not show many benefits for this population. The physiopathology of acute pulmonary edema can potentially help in interpreting some of the benefits of NIV, such as redistribution of fluids and decrease of preload and post-load. Unfortunately, the trial conducted by Nava and colleagues [16] for APE alone was the only one included in our study, so we could not perform the statistical analysis for that isolated population.

In our systematic review, we calculated the relative risks for outcomes of interest for other etiologies, as well. Among studies that were not included in meta-analysis for the intubation outcome, the postoperative trial showed protection [20] while post-extubation [16] and acute pulmonary edema studies [17] did not show good results. For ICU mortality, the post-extubation trial showed protection [17]. However, a decrease in hospital mortality was not demonstrated in either the post-extubation or APE trials.

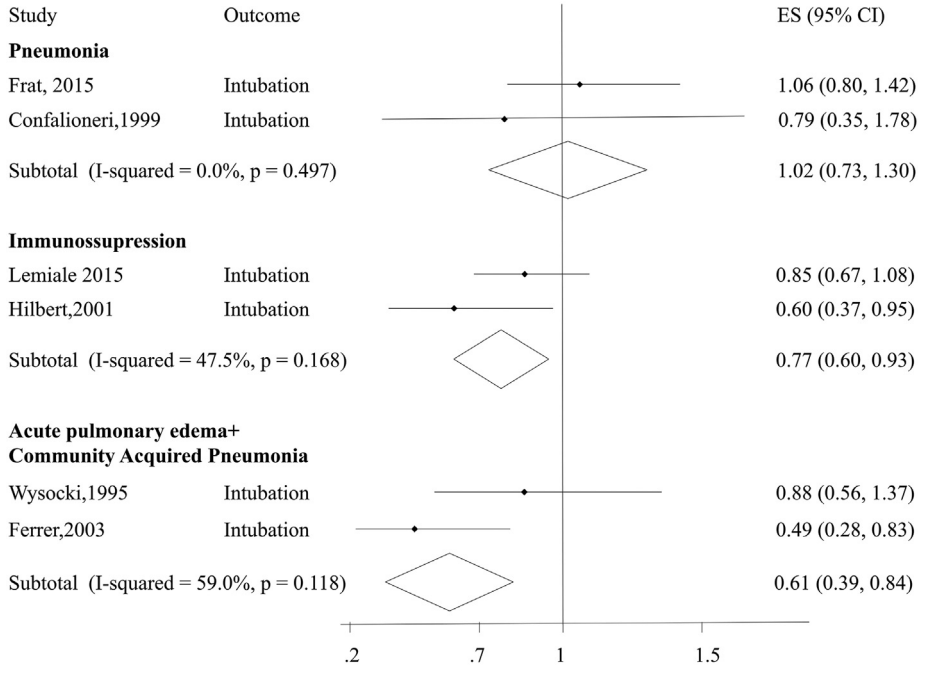

Fig. 5. RR for Intubation in Pneumonia, Immunosuppression and Acute Pulmonary Edema/Community Acquired Pneumonia.

Some limitations should be considered at this point. Some trials included in our analysis have limited number of patients, and a population with severe hypoxia was not enrolled, probably because of the high risk of cardiac arrest or immediate intubation for this population. All authors described the effects of NIV in mild (PaO2/FiO2 < 300 mmHg and > 200 mmHg) or moderate hypoxia (PaO2/FiO2 < 200 mmHg and > 100 mmHg) [29].

Nevertheless, no heterogeneity was observed for the intubation outcome, which strengthens our results. In the immunosuppressed group, 426 patients were enrolled, and the heterogeneity was low.

According to the GRADE Score, since our study showed results from well-performed RCTs for the immunosuppressed and APE/CAP populations, NIV can be considered to have a high-level of evidence and strong recommendation for theses etiologies.

The most recent European Guidelines for the use of NIV in acute respiratory failure failed to provide strong recommendations for the use of noninvasive ventilation among hypoxemic ARF patients, while it confirmed the benefits among COPD patients, as previously described in the literature [30-32]. Considering the subgroups of immunosuppressed patients and APE/CAP, the paucity of data from well-designed randomized clinical trials and the conflicting results among observational studies significantly limited the certainty of evidence for recommendations in such population [32]. In this sense, our meta-analysis could contribute to provide stronger level of evidence for the use of NIV in the population of immunosuppressed patients as well as in the population with APE/CAP.

For other subgroup of patients such as those with asthma, ARDS, postoperative, post-extubation and acute pulmonary edema, it remains unclear whether the effect of NIV benefits the rate of intubation and/or mortality, given the lack of well-designed clinical studies.

5. Conclusions

NIV decreases the need for intubation in immunosuppressed and APE/CAP population, as well as ICU mortality. There is a great need for new big trials in to better elucidate effects of BiPAP in other etiologies of hypoxemic acute respiratory failure.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.012.

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