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Review

Noninvasive ventilation improves the outcome in patients with pneumonia-associated respiratory failure: Systematic review and meta-analysis

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ABSTRACT

Background: Noninvasive ventilation (NIV) is beneficial in exacerbations of chronic obstructive pulmonary disease (COPD), but its effectiveness in pneumonia-associated respiratory failure is still controversial. In the current meta-analysis, we aimed to investigate whether the use of NIV before intubation in pneumonia improves the mortality and intubation rates of respiratory failure as compared to no use of NIV in adults.

Methods: We searched three databases from inception to December 2019. We included studies, in which pneumonia patients were randomized initially into either NIV-treated or non-NIV-treated groups. Five full-text publications, including 121 patients, reported eligible data for statistical analysis.

Results: With NIV the overall hospital mortality rate seemed lower in patients with pneumonia-associated respiratory failure, but this was not significant [odds ratio (OR) = 0.39; 95% confidence interval (CI): 0.13–1.14; P = 0.085]. In the intensive care unit, the mortality was significantly lower when NIV was applied compared to no NIV treatment (OR = 0.22; 95% CI: 0.07–0.75; P = 0.015). NIV also decreased mortality compared to no NIV in patient groups, which did not exclude patients with COPD (OR = 0.25; 95% CI: 0.08–0.74; P = 0.013). The need for intubation was significantly reduced in NIV-treated patients (OR = 0.22; 95% CI: 0.09–0.53; P = 0.001), which effect was more prominent in pneumonia patient groups not excluding patients with pre-existing COPD (OR = 0.13; 95% CI: 0.03–0.46; P = 0.002).

Conclusion: NIV markedly decreases the death rate in the intensive care unit and reduces the need for intubation in patients with pneumonia-associated respiratory failure. The beneficial effects of NIV seem more pronounced in

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1 Deceased

populations that include patients with COPD. Our findings suggest that NIV should be considered in the therapeutic guidelines of pneumonia, given that future clinical trials confirm the results of our meta-analysis.

Availability of data and materials: All data and materials generated during the current study are available from the corresponding author on reasonable request.

Contents

Introduction

Pneumonia often requires hospital admission among both adults and children in the United States [1]. According to a retrospective cohort study that analyzed representative healthcare claims of approx. 4 million adults in 2015 in Germany, the overall incidence rate of community-acquired pneumonia was 1054 cases per 100,000 person-years of observation [2]. The number was almost two times higher in the elderly (≥60 years), while it was half as small in the age group between 18 and 59 years (incidence rates of 2032 and 551, respectively). Adult patients hospitalized with community-acquired pneumonia had high mortality rates during their stay in the hospital (18.5%), as well as at 30 days (22.9%) and at one-year (44.5%) after the onset of the disease. The death rate was more than doubled in older adults as compared to younger patients [2]. The higher occurrence rate of pneumonia in the elderly population (≥65 years) was also observed in another study conducted in the USA [3].

When patients with pneumonia are at risk for developing respiratory failure despite the antibiotic and regular supportive treatments, ventilatory support is often necessary. Different methods of ventilator support are available in clinical practice, ranging from invasive to noninvasive ventilation (NIV). According to a study in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) or hypercapnic cardiogenic pulmonary edema, the main objectives of NIV application include decreased risk for ventilator-associated pneumonia, less antibiotic use, shorter length of intensive care unit (ICU) stay, and decreased mortality [4]. Moreover, in patients with respiratory failure, the use of NIV decreased the need for sedatives and intubation, consequently, reduced the number of subsequent upper airway-related complications [5]. A further important advantage is that NIV can be also used outside of the ICU, for example, in ambulance cars, emergency rooms, and pulmonology wards, though the option for prompt intubation should be always available. Alternatively, high-flow nasal oxygen cannula therapy is also suggested as an effective choice of early treatment in pneumonia [6]. It is well established that NIV decreases the mortality and intubation rates in acute exacerbations of COPD and in cardiogenic pulmonary edema [7–9]. In a recent meta-analysis, the beneficial effects of NIV were also demonstrated in acute respiratory failure not associated with extubation, cardiogenic pulmonary edema, and exacerbation of COPD [10]. From 2001 to 2015, an increase in NIV use was observed in patients hospitalized with community-acquired pneumonia in Spain (from 0.91 to 12.84 per 100,000 inhabitant) [11], however its effectiveness compared to different methods of oxygen supplementation and to invasive interventions has remained controversial. Certain confounding factors were identified that can influence the effect of NIV, such as pre-existing organ failure, the initial response to antimicrobial treatment, PaO_2/FiO_2 ratio, and the extent of the pulmonary damage at admission [12,13]. These findings suggest that the success of NIV also depends on the characteristics of the patient population. The most recent guideline of the European Respiratory Society makes recommendations with moderate certainty of evidence about the use of NIV in several diseases, including cardiogenic pulmonary edema, immunocompromised patients, post-operative care, palliation, chest trauma, and weaning in hypercapnic patients [14], but it does not give clear indications about the use of NIV in pneumonia. Similarly, the Canadian clinical practice guideline makes no recommendations on NIV in pneumonia, because of insufficient evidence [15]. In contrast, an Indian guideline recommends the use of NIV in patients with community-acquired pneumonia and acute respiratory failure with 2A level of evidence [16]. In the present study, we aimed at clarifying whether the use of NIV in adult patients with pneumonia and respiratory failure improves the major clinical outcomes (i.e.,

mortality and intubation rates) by performing an extensive literature search and meta-analysis of randomized clinical trials (RCTs).

Methods

Search strategy

The meta-analysis was registered in the PROSPERO database (CRD42018095250). The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) were followed (Table S1) [17], and the Patients, Intervention, Comparison, Outcome (PICO) model was used: in adult patients with pneumonia and respiratory failure in any medical treatment unit, we wanted to compare patient groups randomized primarily to NIV therapy with patient groups randomized primarily to standard therapy including the option for invasive mechanical ventilation as obligatory inclusion criteria. We aimed to assess the effect of NIV on the mortality ratio as primary outcome and on intubation rate as secondary outcome. An extensive literature search was performed for RCTs in PubMed, EMBASE, and Cochrane Controlled Trials Registry databases.

The database search for RCTs was performed without language limitations from inception to December 2019 with the query: "("non-invasive ventilation" OR "non-invasive ventilation" OR NIV OR NPPV OR CPAP OR "airway pressure" OR BiPAP) AND (conventional OR "invasive ventilation" OR "mechanical ventilation" OR intubation OR "standard therapy") AND (pneumonia OR pulmonary OR respiratory OR lung) AND mortality". We used the same search key in all three databases, and then in PubMed and EMBASE, we enabled the filters „human" and „randomized controlled trial", while in the Cochrane Controlled Trials Registry database we selected the "trials" option. The use of subject headings for PubMed (MeSH) and Embase (Emtree) instead of the original search key did not identify any additional papers eligible for the quantitative analysis. The references of the identified papers were also checked and searched for relevant studies for the analysis but no additional studies were identified. Two of the authors (IR and ZRu) independently conducted the literature search, and eligibility assessment. A third author (AG) was involved to reach an agreement, if necessary.

Study selection and data extraction

After screening on titles and abstracts of the search results, full texts of relevant papers were accessed. We included RCTs in which NIV-treated patients with pneumonia-associated respiratory failure were compared with patients without the use of NIV, and the mortality ratios or intubation rates were also described. Two of the authors (IR and ZRu) independently conducted the data extraction. The extracted data included the number of patients, the type of ventilation, as well as, the intubation rate and the mortality ratio. The influence of NIV on intubation rate and mortality ratio in pneumonia-associated respiratory failure was assessed based on data collected from the two ventilation groups (i.e., NIV or no NIV at initiation of therapy) in each study.

Quality assessment

To evaluate the quality of the trials, two independent reviewers (IR and ZRu) assessed the bias of the included studies according to the Cochrane Handbook 2019 (Table S2) [18]. We aimed to assess the methodology described for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective outcome reporting during the analysis. The overall risk of each study was determined as low if the risk of bias was low for all key domains; unclear if the risk of bias was low or unclear for all key domains; and high if the risk of bias was high for at least one key domain. Since blinding was not feasible in these type of studies

because of the noticeable nature of the intervention, according to the Cochrane Handbook 2019 [18], we did not consider the trial as low quality because of the absence of blinding.

Quality of evidence

The quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for each outcome according to the GRADE Handbook [19]. The outcomes of interest were tested against the following main criteria: study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. The baseline grade was downgraded by 1 level for serious concerns or by 2 levels for very serious concerns and finally, the quality of the evidence for each outcome was graded as "high," "moderate," "low," or "very low".

Statistical analysis

Studies were grouped based on the presence or absence of NIV. Odds ratio (OR) with 95% confidence intervals (CI) for mortality and intubation in the adult patients with pneumonia-associated respiratory failure were calculated in a random-effects model of meta-analysis. OR was calculated by dividing the ratio of events to no events in the NIV group with the same ratio in the no NIV group, and then the data were analyzed with classical meta-analysis methods (i.e., forest plots). Statistical heterogeneity among the studies was assessed with the I^2 test, as in the past [20]. Results of the meta-analyses are depicted as forest plots.

Since the included studies reported comparison of NIV with oxygen therapy or NIV with intubation, moreover, different ventilator strategies were used (e.g., nasal prongs, Venturi mask, other interfaces) in the no NIV group, we performed a subgroup analysis to separately compare NIV with oxygen supplementation and NIV with invasive ventilation, as well as to compare the different types of ventilator strategies. We also performed subgroup analysis of the hospital and ICU mortality separately. Since the benefits of NIV were confirmed earlier in COPD patients [14], as part of our analysis, we divided the patients into subgroups based on the exclusion of underlying COPD. One of these subgroups consisted of studies in patients definitely without COPD (COPD excluded), while the other subgroup (COPD not excluded) involved studies in patients with reported COPD, as well as, studies in which COPD was not mentioned as exclusion criteria.

Funnel plots were used to assess publication bias. Sensitivity analysis (i.e., iteratively omitting one study from the analyses and recalculating OR to investigate the impact of the individual study on the summary estimate) was performed to test the impact of the individual studies. The Stata software (version 14SE; StataCorp LLC, College Station, TX, USA) was used for all statistical analyses.

Results

Study selection

Until December 1, 2019 the electronic literature search identified altogether 10,188 studies from the three databases. The PRISMA flow chart is presented in Fig. 1. By using filters for humans and RCTs and also removing duplicates, 1,643 articles remained. The selection based on titles and abstracts resulted in the exclusion of 1,617 articles (Fig. 1), which were not suitable for quantitative analysis because of reasons, mostly including the study type (e.g., not RCT), study design (e.g., improper arms in RCT), patient population (e.g., children), and the studied disease (e.g., not pneumonia). After checking titles and abstracts, the full text of 26 articles were obtained and reviewed. Twenty-one studies were excluded because of insufficient data or outcome measure reporting. Five full-text publications were included in the statistical analysis, which contained
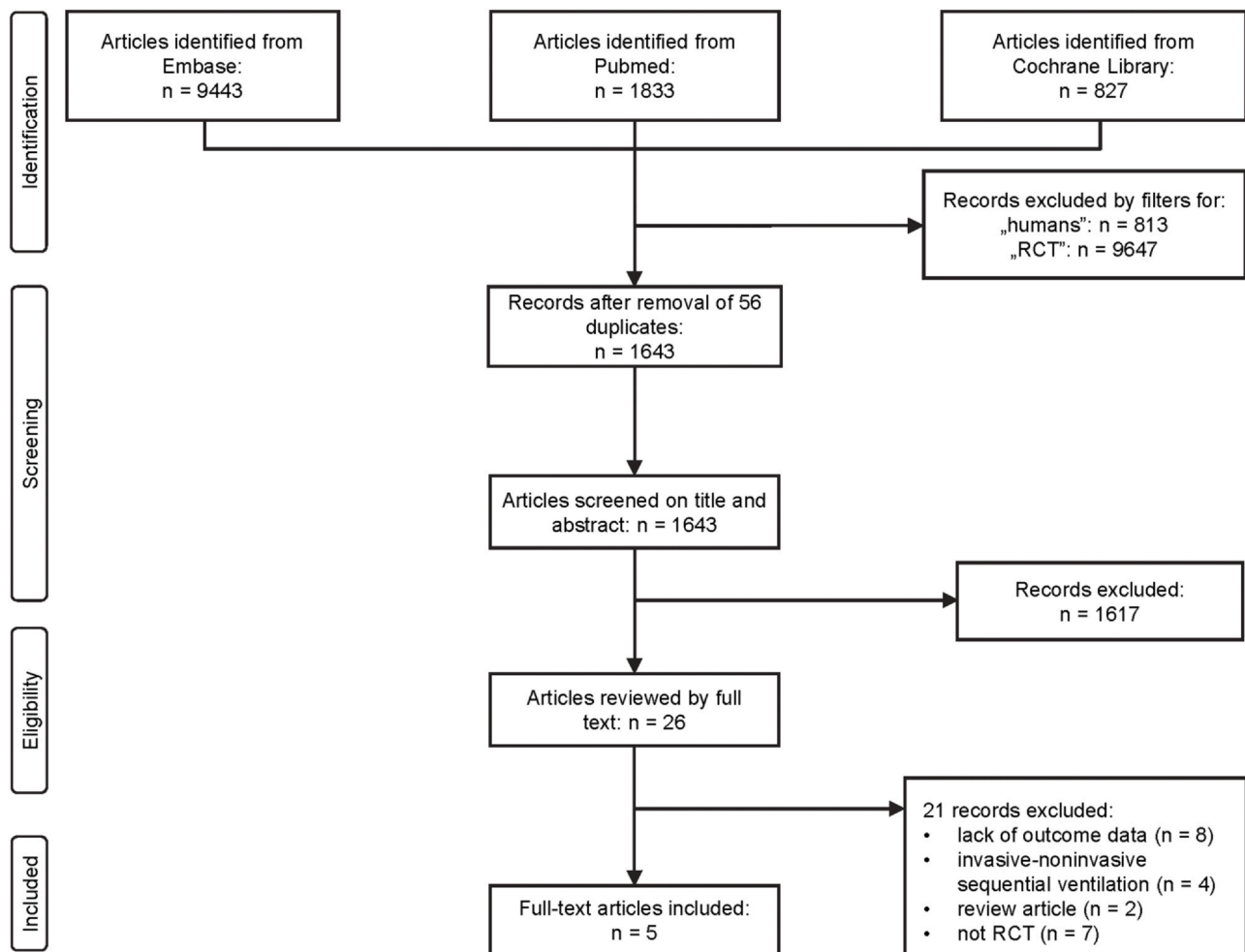
Fig. 1. Flow chart of study selection and inclusion. RCT, randomized clinical trial.

data from a total of 121 patients [21–25]. In these studies, 61 patients were randomly assigned to NIV, which was applied with face or nasal mask. Sixty patients were randomly assigned to the no NIV group, in which the patients received standard oxygen therapy in three studies [21–23], invasive ventilation in one study [24], and oxygen by face mask or bag-valve mask ventilation in one study [25]. The characteristics of these studies are summarized in Table 1.

Quality assessment, quality of evidence, sensitivity analysis, and publication bias

Risk of bias within studies was assessed according to the Cochrane Handbook (Table S2) [26]. All five trials were randomized and clearly described the treatment protocols, thus all studies had low risk of bias for "random sequence generation". However, the randomization was not concealed in one study resulting high risk of bias in "the allocation concealment" [23], while none of the studies used blinding (because of the noticeable nature of the intervention) therefore "blinding of participants and personnel" and "blinding of outcome assessment" were high risk of bias. The "incomplete outcome data" and "selective reporting" domains were low risk of bias for all studies. In one of the studies, patients with solid organ transplants were enrolled [22], which we assessed as high risk of other bias (Table S2), because opportunistic pneumonia occurs more often in patients receiving immunosuppressive therapy (e.g., because of solid organ transplantation) and its clinical course, outcome, and severity are different from community-

acquired pneumonia [27]. In addition, hydrocortisone treatment (which is often used in organ transplantation) was associated with a significant reduction in length of hospital stay and mortality of severe community-acquired pneumonia [28]. A recent systematic review also highlighted that immunosuppressed patients with acute pulmonary edema and pneumonia may benefit most from NIV [29]. These confounding factors may change the outcomes of pneumonia, and thereby the effect of NIV, resulting in high risk of bias.

According to the Cochrane Handbook 2019 [18], 3 studies were considered overall as fair quality [21, 24, 25], because 2 or 3 points were determined as "potentially unclear risk of bias", while 2 studies were considered overall as poor quality [22,23], because 2 or 3 points were determined as "potentially high risk of bias". Quality of the evidence for each outcome is shown in Table 2, with the details of rating each study by the GRADE approach presented in Tables S3 and S4.

Sensitivity analysis was performed for overall OR of mortality and intubation rates, as well as for ORs of subgroups consisting of at least 3 studies by omitting each study (one by one). The pooled (overall and subgroup) ORs did not vary substantially after excluding any individual study, indicating that the results were not driven by one of the analyzed individual studies (Tables S5-S8).

Based on visual inspection of the funnel plots (Figs. S1-S4), some asymmetry may be present, indicating the possible existence of publication bias, but statistical tests could not be performed, because for those at least 10 studies are required according to the Cochrane Handbook.

Table 1
Summary of study characteristics for publications included in the meta-analyses.

First author (year)	Country	Intervention group (severity score)	Control group (severity score)	NIV mode (interface)	Sample size (pneumonia/total)	Patients with pre-existing COPD (n; ratio)	Outcomes
Confalonieri (1999)	Italy	NIV (20 ± 5)[a]	Standard oxygen therapy (18 ± 5)[a]	BiPAP (full face mask)	56/56	Separately included[b] (n = 23; 41%)	Mortality, tracheal intubation
Antonelli[c] (2000)	Italy	NIV (13 ± 4)[d]	Standard oxygen therapy (13 ± 3)[d]	BiPAP (full face mask)	4/40	Not excluded (NR; NR)	Mortality, tracheal intubation
Ferrer (2003)	Spain	NIV (34 ± 10)[d]	Standard oxygen therapy (33 ± 8)[d]	BiPAP (full face mask or nasal mask)	34/105	Not excluded (NR; some)	Mortality, tracheal intubation
Honrubia (2005)	Spain	NIV (25 ± 7)[a]	Invasive ventilation (24 ± 10)[a]	BiPAP (face mask)	18/64	Some included (n ≥ 4; ≥22%)	Mortality
Thompson (2008)	Canada	NIV (NR)	Oxygen by facemask, bag-valve mask ventilation (NR)	CPAP (face mask)	9/71	Separately included[b] (n = 2; 22%)	Mortality, tracheal intubation

BiPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous airway pressure; NIV, noninvasive ventilation; NR, not reported
[a] Acute Physiology and Chronic Health Evaluation II score and
[b] Patients without COPD were also separately included.
[c] This study was conducted in recipients of solid organ transplantation. Severity score was reported as
[d] Simplified Acute Physiology Score.

Effects of NIV on mortality

The analysis of the association between the use of NIV and mortality revealed an OR of 0.39 (95% CI: 0.13–1.14; P = 0.085) with the use of NIV for overall hospital mortality (Fig. 2), which included death rates reported both at the ICU [22–24] and outside the ICU [21,25]. The heterogeneity was moderate (I^2 = 28.3%, P = 0.233). In four of the analyzed studies, NIV was compared with standard oxygen therapy [21–23, 25] while in one study NIV and tracheal intubation were compared [24]. Moreover, the type of ventilator strategy was different among the studies, including Venturi mask [21–23], face mask, bag-valve mask [25], and intubation [24]. Therefore, we analyzed the effect of NIV on mortality rate by comparing NIV with oxygen supplementation and NIV with invasive ventilation as two separate subgroups (Fig. S5A) and by comparing the effect of NIV in subgroups of different ventilator strategies (viz., non-Venturi face mask and Venturi mask) (Fig. S5B). We did not find a significant difference in the OR for mortality rate in any of the analyzed subgroups. Then, we narrowed our interest to the effect of NIV on death rate in the ICU. This resulted in substantial reduction of heterogeneity (I^2 = 0.0%, P = 0.699). On the contrary, the heterogeneity was high (I^2 = 58.8%, P = 0.119) for the studies reporting mortality outside the ICU. We found that the use of NIV significantly decreased the risk of death in pneumonia-associated respiratory failure during the ICU stay (OR = 0.22; 95% CI: 0.07–0.75; P = 0.015) (Fig. 3). Outside the ICU, NIV had no significant effect on mortality (OR = 0.48; 95% CI: 0.04–5.92; P = 0.565).

Effect of NIV on the risk of death in subgroups excluding and not excluding patients with COPD

We also analyzed whether the effect of NIV on mortality is influenced by the presence of pre-existing COPD, at least to some extent, in the patient population. Due to data availability, we could divide the patients groups into subgroups that strictly excluded COPD patients [21, 22, 25] and that did not exclude COPD patients [21, 23–25] (Fig. 4). We found that NIV significantly decreased the risk of death in the subgroup that did not exclude COPD patients (OR 0.25; 95% CI: 0.08–0.74; P = 0.013). Though NIV had no significant effect in patient groups without COPD, this group included only 2 studies, which is not sufficient for proper meta-analysis. Statistical heterogeneity was negligible in both of the subgroups. The sensitivity analysis of the "COPD not excluded" subgroup showed that the overall mortality rate was not driven by any of the individual studies (Table S6).

Effect of NIV on intubation rate

As secondary outcome, we examined whether NIV has an effect on the need for intubation in pneumonia-associated respiratory failure. Among the identified articles, 4 studies reported the rate of intubation [21, 23–25]. In three of these studies NIV was compared with standard oxygen therapy [21, 23, 25], while in one study NIV and tracheal intubation were compared [24]. We found that NIV was associated with a significantly decreased OR for intubation (0.22; 95% CI: 0.09–0.53; P = 0.001). There was no statistical heterogeneity (I^2 = 0.0%, P = 0.772) (Fig. 5). Sensitivity analysis showed no difference in the final pooled results, as indicated by the similar coefficients and overlapping CIs (Table S7), however these results should be interpreted with caution due to the very low number (n = 3) of included studies. We also wanted to know whether the use of NIV affects the intubation rate when compared with oxygen supplementation or with intubation in separate subgroups (Fig. S6A) and when compared to different ventilator strategies (Fig. S6B). Our meta-analysis revealed that the intubation rate was significantly decreased when NIV was used at the initiation of the therapy instead of standard oxygen therapy (0.21; 95% CI: 0.09–0.51; P = 0.001) (Fig. S6A). There was no meaningful difference in the intubation rate when NIV was compared with invasive ventilation, but

Table 2
Summary of findings using GRADE approach.

Measured outcomes	Specified outcomes	Articles investigating the specified outcomes	Quality of the evidence[a]
Mortality	Mortality overall	Thompson (2008), Ferrer (2003), Honrubia (2005), Antonelli (2000), Confalonieri (1999)	**moderate**
	Mortality Non-ICU	Thompson (2008), Confalonieri (1999)	**low**
	Mortality ICU	Ferrer (2003), Honrubia (2005), Antonelli (2000)	**moderate**
	Mortality NIV vs. oxygen	Thompson (2008), Ferrer (2003), Antonelli (2000), Confalonieri (1999)	**moderate**
	Mortality NIV vs. intubation	Honrubia (2005)	**low**
	Mortality COPD not excluded	Ferrer (2003), Honrubia (2005), Confalonieri (1999), Antonelli (2000)	**moderate**
	Mortality COPD excluded	Thompson (2008), Confalonieri (1999)	**low**
	Mortality Face mask, bag-valve-mask	Thompson (2008)	**low**
	Mortality Venturi mask	Ferrer (2003), Antonelli (2000), Confalonieri (1999)	**low**
	Mortality Intubation	Honrubia (2005)	**low**
Intubation	Intubation rate overall	Ferrer (2003), Thompson (2008), Confalonieri (1999), Honrubia (2005)	**moderate**
	Intubation rate NIV vs. oxygen	Ferrer (2003), Thompson (2008), Confalonieri (1999)	**moderate**
	Intubation rate NIV vs. intubation	Honrubia (2005)	**low**
	Intubation rate COPD not excluded	Confalonieri (1999), Ferrer (2003), Honrubia (2005)	**moderate**
	Intubation rate COPD excluded	Thompson (2008), Confalonieri (1999)	**low**
	Intubation rate Venturi mask	Ferrer (2003), Confalonieri (1999)	**moderate**
	Intubation rate Face mask, bag-valve-mask	Thompson (2008)	**low**
	Intubation rate Intubation	Honrubia (2005)	**low**

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NIV, noninvasive ventilation
[a] : based on the GRADE approach the quality of evidence was determined based on the final number of points as high (4 and above), moderate [3], low [2], or very low (1 or less), for details see also Tables S3 and S4;

this result must be considered with scrutiny, since there was only one study in the subgroup (Fig. S6A). The intubation rate-decreasing effect of NIV seemed to be the most pronounced in patients with Venturi mask (0.21; 95% CI: 0.08–0.53; P = 0.001), but this result was based on only 2 studies, while in the other subgroups of ventilation strategies (i.e., face mask and invasive ventilation) just one study could be included (Fig. S6B). It has to be stated that the number of patients in some of these groups was very small to make solid conclusion. It should be noted that Honrubia et al. [24] compared groups with NIV and invasive ventilation, but it is not likely that standard oxygen therapy was not applied prior to intubation in the invasive ventilation group. It is also

interesting that in the end all patients were intubated in the NIV group too, which resulted in 100% intubation rate in both groups. This was not only unexpected for the authors of that study [24], but also raised the possibility of inclusion bias as suggested by other authors [30].

Effect of NIV on intubation rate in subgroups excluding and not excluding patients with COPD

Last, we analyzed the effect of NIV on intubation rate in the subgroups that excluded and did not exclude patients with COPD. We found that the intubation rate decreased markedly with use of
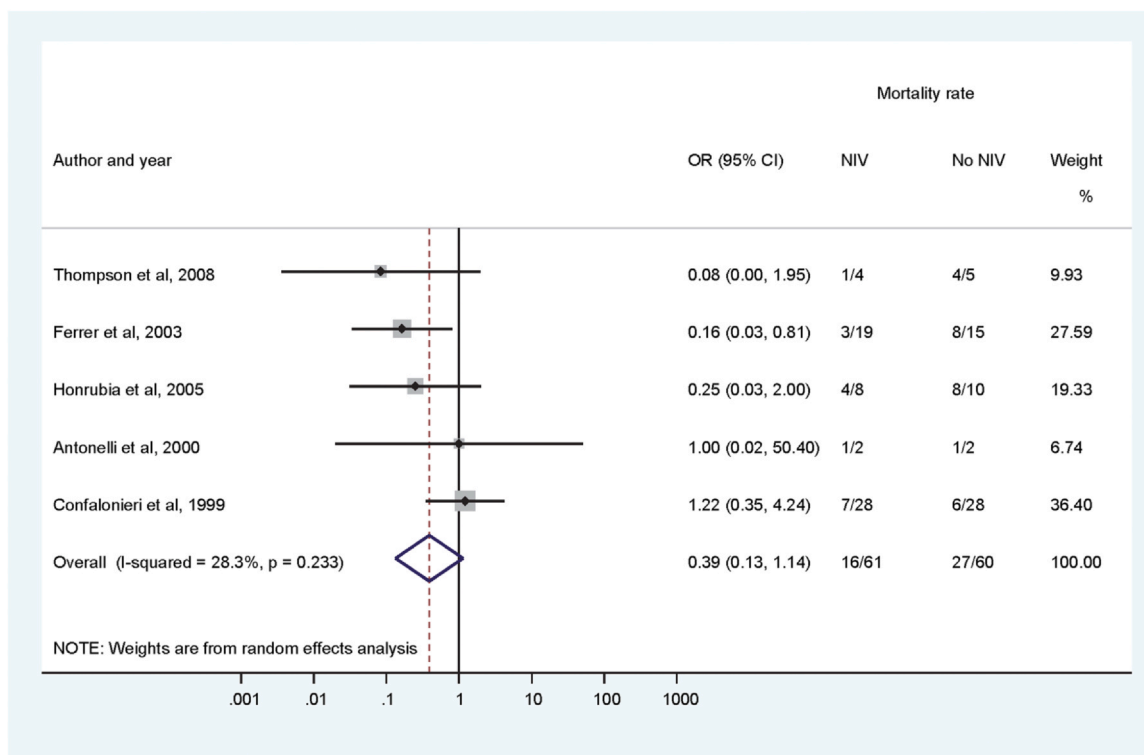
Fig. 2. Forest plot of the ORs for overall hospital mortality rate between NIV and no NIV groups of patients using random-effects model. Here, and in Figs. 3–6, an OR lower than 1 indicates that the use of NIV is beneficial, whereas an OR higher than 1 indicates a harmful effect of NIV. NIV, noninvasive ventilation; OR, odds ratio.
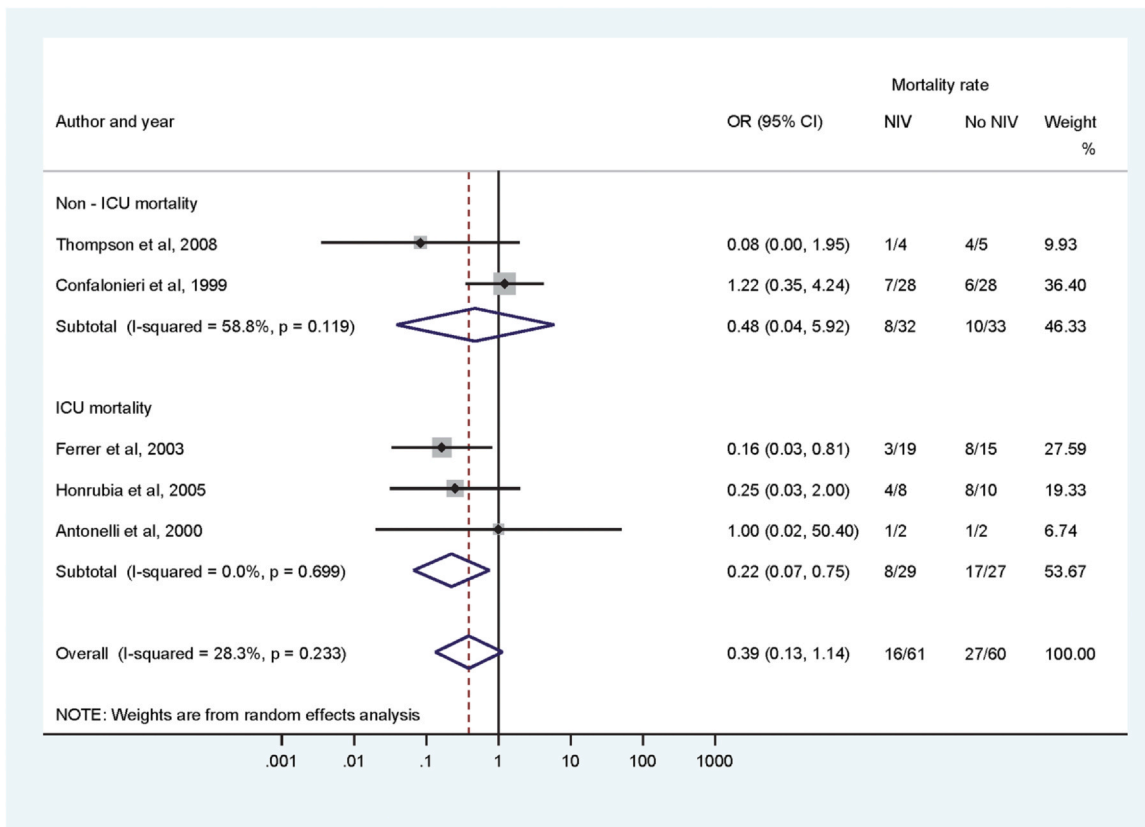
Fig. 3. Forest plot of the ORs for ICU and non-ICU mortality rate between NIV and no NIV groups of patients using random-effects model. ICU, intensive care unit; NIV, noninvasive ventilation; OR, odds ratio.
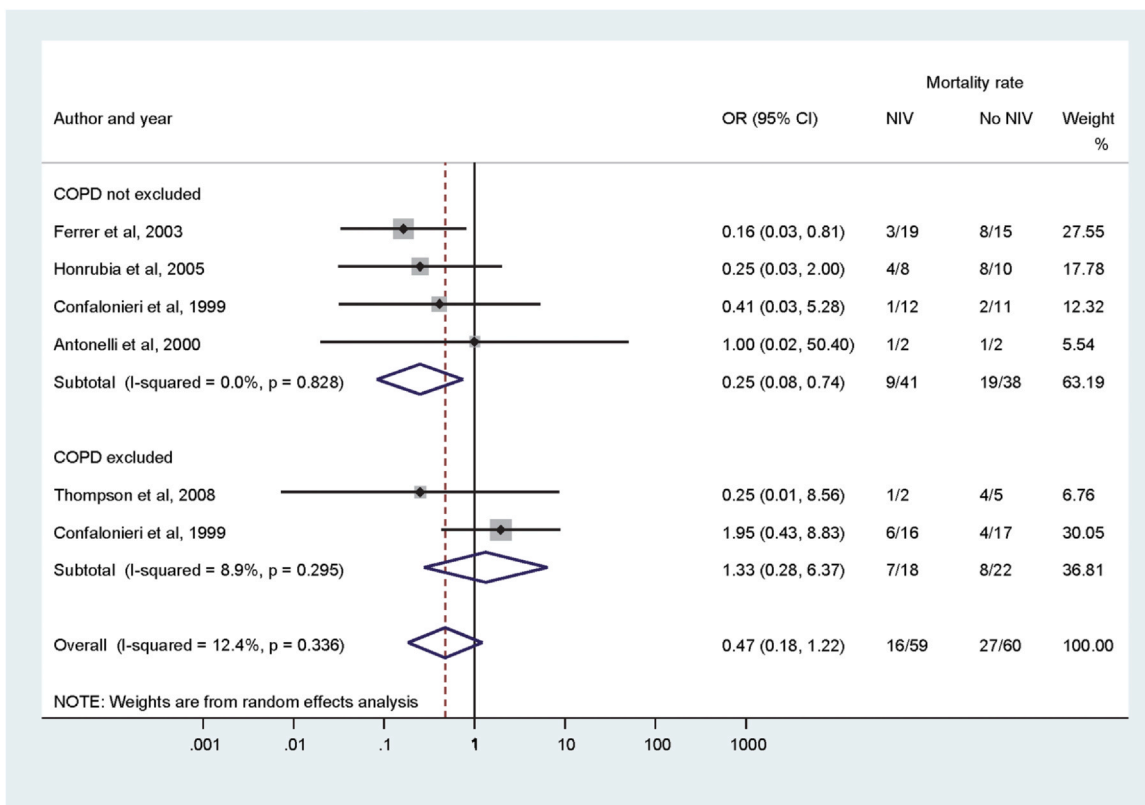
Fig. 4. Forest plot of the ORs for mortality rates between NIV and no NIV groups of patients divided into subgroups that excluded or did not exclude patients with COPD. Note that Confalonieri et al. [21] and Thompson et al. [25] appear in both subgroups as these studies reported data separately from patients with and without COPD, which distinct patient populations could be included in the corresponding subgroups. COPD, chronic obstructive pulmonary disease; NIV, noninvasive ventilation; OR, odds ratio.
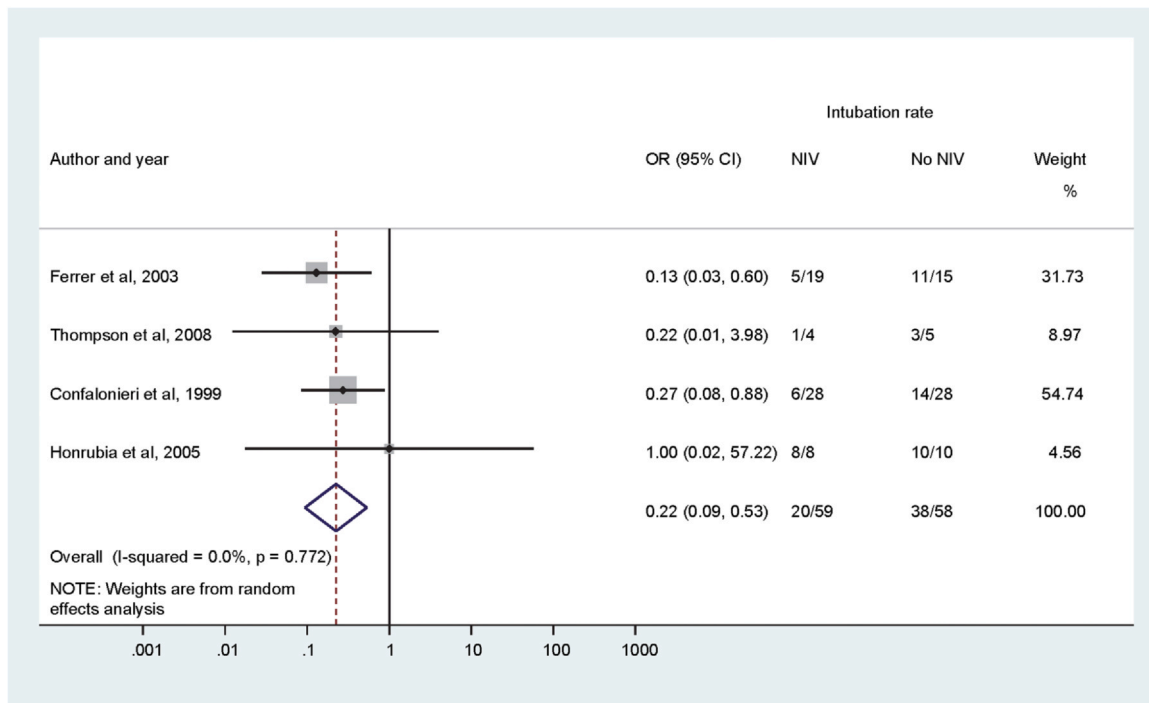
Fig. 5. Forest plot of the ORs for intubation rate NIV and no NIV groups of patients using random-effects model. NIV, noninvasive ventilation; OR, odds ratio.

NIV if patients with COPD were not excluded (0.13; 95% CI: 0.03–0.36; P = 0.002) (Fig. 6). The use of NIV was without an effect in either of 2 studies in the subgroup excluding COPD patients (Fig. 6), but caution is needed regarding their averaged OR due to the low number of studies in this subgroup. Statistical heterogeneity was negligible in all subgroups. The sensitivity analysis of the "COPD not excluded" subgroup showed that the overall intubation rate was not driven by any of the individual studies (Table S8).
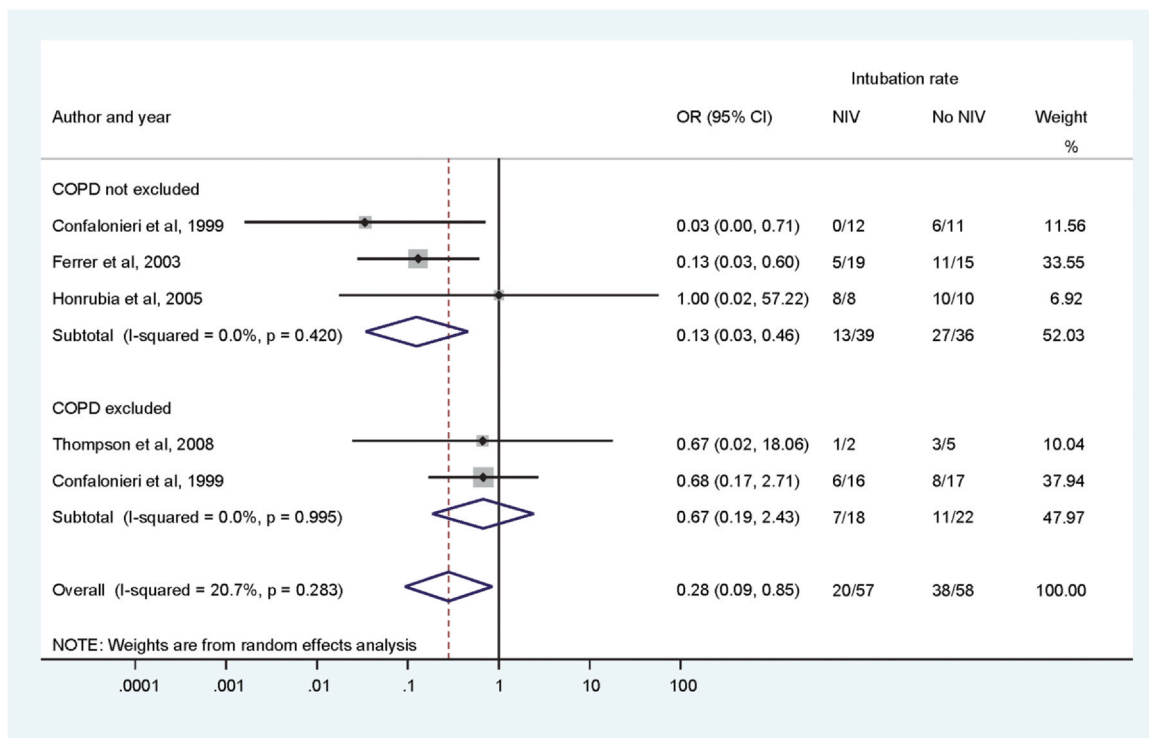

Fig. 6. Forest plot of the ORs for intubation rate of subgroups between NIV and no NIV groups of patients divided into subgroups that excluded or did not exclude patients with COPD. Note that Confalonieri et al. [21] and Thompson et al.[25] appear in both subgroups as these studies reported data separately from patients with and without COPD, which distinct patient populations could be included in the corresponding subgroups. COPD, chronic obstructive pulmonary disease; NIV, noninvasive ventilation; OR, odds ratio.

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Discussion

We showed that NIV does not have a significant effect on the overall hospital mortality, however, with subgroup analysis we demonstrate that the use of NIV strongly decreases ICU mortality and the need for intubation in patients with pneumonia-associated respiratory failure. NIV reduced the risk of death and the need of intubation in patient groups, which did not exclude subjects with pre-existing COPD, while in those groups which strictly excluded patients with COPD, NIV was without an effect on mortality and intubation rates.

In earlier studies, the benefit of NIV in pneumonia has not been clearly defined, but there is an increasing trend of using NIV in pneumonia in the United States [31]. Previous randomized and observational studies demonstrated that NIV treatment decreased the need for endotracheal intubation and the length of ICU stay in pneumonia [21, 23, 32–34], but the effectiveness of NIV on mortality has remained controversial, as NIV was shown to decrease death rate in some studies [23,34], but it had no or even adverse effect on the mortality in other studies [21, 22, 24, 32, 33]. Unfortunately, some of these studies did not have randomized design [32–34], thus could not be included in the present analysis. Here, we aimed to clarify whether NIV is beneficial for patients with pneumonia associated with respiratory failure by performing a meta-analysis of the available RCTs. By identifying 5 eligible studies [21–25], we included 121 patients with pneumonia in our analysis. In all eligible trials, the patients received either NIV or conventional/standard therapy, but there were geographical and methodological differences in the characteristics of the studies (Table 1), even though all of the articles included similar exclusion criteria (e.g., life-threatening conditions, contraindication of NIV use).

Our result, that NIV reduced the mortality, is in accordance with the findings of Ferrer et al. [23] showing lower ICU mortality in NIV-treated patients and with the data of Honrubia et al. [24] showing a tendency for reduced ICU and overall mortality by using NIV. On the contrary, some other studies found no difference between the mortality rates of NIV-treated and control (no NIV) groups [21, 32, 33]. Differences in study design, inclusion criteria, and methodology could account for these contradictions. For example, two of the latter studies are not RCTs, but retrospective studies [32,33], which have lower level of evidence [35]. The use of NIV in pneumonia with underlying COPD has not been clarified yet. A retrospective cohort study including 3,791 patients demonstrated better survival with the use of NIV in hospitalized patients with pneumonia who had pre-existing COPD or heart failure [34]. Patients who failed to respond to NIV in this cohort had high in-hospital mortality, emphasizing the importance of careful patient selection and monitoring when managing severe pneumonia with NIV [34]. In an RCT, which included 56 patients, the mortality of NIV-treated patients with pneumonia and pre-existing COPD tended to decrease, though the difference did not reach the level of significance [21]. In our meta-analysis, we could include data from three studies in the subgroup that did not exclude COPD patients [21, 23, 24], whereas in three studies patient groups solely without COPD were enrolled [21, 22, 25]. Interestingly, the risk of death was lower in the subgroup which did not exclude patients with COPD despite the fact that this group was characterized by the highest severity scores (as assessed by the Acute Physiology and Chronic Health Evaluation II and the Simplified Acute Physiology Score II scoring systems).

The present meta-analysis suggests that NIV reduces the overall need for invasive mechanical ventilation, viz., endotracheal intubation. The beneficial effect of NIV was most pronounced in populations also including patients with pre-existing COPD, whereas it was negligible in the subgroup without COPD. These results were mainly driven by Confalonieri et al. [21] and Ferrer et al. [23], both showing decreased need for intubation in the whole group, and in the subgroup not excluding COPD. It is notable that NIV is considered as the gold standard therapy in acute exacerbations of COPD [14]. A possible explanation for the advantageous effect of NIV in pneumonia-associated respiratory failure of patients with COPD is that the signs and symptoms of acute respiratory failure can be recognized earlier when pneumonia develops in patients with pre-existing COPD. In contrast, in patients without COPD the occurrence of acute respiratory failure may represent a more severe case of pneumonia or indicate the development of severe sepsis.

Multiple mechanisms might be implicated as reasons for the better outcomes of pneumonia-associated respiratory failure by using NIV. First, by reducing the workload of respiration and by improving the breathing pattern, NIV leads to better gas exchange, particularly in the patients with underlying COPD [36]. Second, NIV facilitates the opening of small airways, consequently it improves the ventilation of peripheral airways and helps to prevent atelectasis [37]. Third, by avoiding the need for intubation, NIV reduces the incidence of ventilator-associated airway inflammation and edema formation.

In harmony with our findings, a recent systematic review and meta-analysis also showed that NIV/BiPAP is advantageous in patients with acute hypoxemic respiratory failure of various etiologies [29]. Similarly to our study, the authors analyzed RCTs comparing NIV with standard oxygen therapy, but they did not focus only on pneumonia-associated acute respiratory failure and excluded studies using CPAP only and involving hypercapnic and COPD patients. As result, only 2 studies were included in the pneumonia subgroup, which were not sufficient for appropriate meta-analysis. The authors circumvented this issue by merging the pneumonia and acute pulmonary edema subgroups, but this resulted in a mixed population of patients with acute respiratory failure. Our study was designed to analyze the effect of NIV in pneumonia-associated acute respiratory failure without any predefined exclusion criteria, which resulted in the inclusion of more eligible studies, hence our results can serve as important extensions of the preliminary data reported in the pneumonia group by David-Joao et al. [29] and, for the first time to our knowledge, quantitatively confirm the benefits of NIV in this patient group. The quality of the evidence for each outcome ranged from low to moderate. Based on our grading at baseline, high quality was given for RCTs. Each outcome was downgraded by 2 level because of the small sample size, but in some cases the "large magnitude of effect" provided a reason to upgrade some outcomes resulting in moderate quality of evidence. According to these results, the need for RCTs with high-quality of evidence is warranted, which is also in accordance with the previous systematic review [29].

Some limitations of our analysis should be also mentioned. First, due to the unavailability of more eligible studies, the overall sample size (n = 121) can be considered relatively small, which further decreased when we divided the studies into subgroups (e.g., ICU vs non-ICU, COPD not excluded vs COPD excluded). Therefore, the results of our analysis should be interpreted with great care and generalization of our findings to the overall population requires future clinical trials. Based on visual inspection of the funnel plots (Figs. S1-S4), some asymmetry may be present, indicating the possible existence of publication bias, but statistical tests could not be performed, because for those at least 10 studies are required according to the Cochrane Handbook. Second, we wanted to create two subgroups: only COPD patients and patients without COPD. However, the number of studies, which included only or absolutely no COPD patients was not sufficient for subgroup analysis. Collecting all available information about COPD patients allowed us to divide the studies into two subgroups: COPD explicitly excluded and COPD not excluded. While this solution might not be ideal, only in this way could we have enough studies in at least one of the subgroups to perform a meta-analysis and obtain some quantitative results about the influence of COPD (or the lack of thereof) on the outcome.

Among the analyzed studies, nasal mask as an interface during NIV was used only in the study by Ferrer et al. [23]. In that study, a face mask was used as the first choice, while nasal mask was a

secondary option if the patients did not tolerate the face mask. Out of 51 patients with severe hypoxemic respiratory failure (not only due to pneumonia), in the NIV group 14 patients were ventilated with a nasal mask. Nineteen patients were diagnosed with pneumonia in the NIV group, but for them it was not reported whether they received nasal mask or not. Since nasal mask was used in only one study, we could not perform a formal subgroup analysis to investigate the difference between the effect of nasal versus face mask on mortality and intubation rate. We took an alternative approach to determine the impact of the use of nasal versus face mask. We performed sensitivity analysis (i.e., iteratively omitting one study from the analyses and recalculating OR to investigate the impact of the individual study on the summary estimate) for all groups in which at least 3 studies were included (Tables S5-S8). The pooled ORs of the outcomes (mortality and intubation rate) did not vary substantially after excluding the study by Ferrer et al. [23], indicating that the overall results were not driven by this study and the nasal mask as an option during NIV did not influence the results in the present analysis.

Third, there can be individual differences in the success rate of the NIV treatment, which is determined by less organ failure and good initial response to the antimicrobial treatment. A good response is strongly associated with better survival [13], but the response rate was not reported in proper details in the studies, thus we could not include it in our analysis. Fourth, the blinding of the hospital staff and the patients was not possible in the analyzed RCTs because NIV is a noticeable intervention, which can constitute a high risk of bias in all studies. Fifth, the clinical heterogeneity between the studies should be also taken into account, which includes differences in the techniques of ventilation (see Table 1), as well as, in the severity scores of the patients among the analyzed trials. For example, severity scores (Acute Physiology and Chronic Health Evaluation II and the Simplified Acute Physiology Score II scoring systems) were higher in two studies [23,24] than in the other studies [21,22]. Last, the management of community- and hospital-acquired pneumonia differ from each other, but we could not analyze patient groups solely with community-acquired pneumonia due to data unavailability.

Conclusion

In conclusion, with meta-analysis of published RCTs, we show that the use of NIV is associated with a significant reduction of intubation rate in patients with pneumonia-associated respiratory failure, and this effect seems to be prominent in patients with pre-existing COPD. Our meta-analysis also demonstrates lower ICU mortality and seemingly, but not significantly reduced (P = 0.085) overall mortality with the use of NIV. Considering the relatively small number of the included studies, firm conclusions should not be drawn from this meta-analysis. Our findings clearly indicate the need for further RCTs to determine the exact patient population and clinical preconditions that can benefit the most from the use of NIV treatment.

Ethics approval and consent to participate

Not required.

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CRediT authorship contribution statement

IR and ZRu: conception and design of the study; AC: administrative support; PH and AG: provision of study materials; IR, AG, and ZRu: acquisition of data; IR, PM, DN, AC, PH, AG, and ZRu: data analysis and interpretation; IR, AG, and ZRu: drafting the manuscript; JT, BE, GVa, MB, EP, GVe, RS, ZRa, and AV: critical revision of the study and editing of the manuscript; All authors: final review and approval of the manuscript.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.02.004.

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