OPEN

Noninvasive Ventilation in Acute Hypoxemic Nonhypercapnic Respiratory Failure: A Systematic Review and Meta-Analysis

Xiu-Ping Xu, MD[1]; Xin-Chang Zhang, MD[2]; Shu-Ling Hu, MD[1]; Jing-Yuan Xu, MD[1]; Jian-Feng Xie, MD[1]; Song-Qiao Liu, MD, PhD[1]; Ling Liu, MD, PhD[1]; Ying-Zi Huang, MD, PhD[1]; Feng-Mei Guo, MD, PhD[1]; Yi Yang, MD, PhD[1]; Hai-Bo Qiu, MD, PhD[1]

Objective: To evaluate the effectiveness of noninvasive ventilation in patients with acute hypoxemic nonhypercapnic respiratory failure unrelated to exacerbation of chronic obstructive pulmonary disease and cardiogenic pulmonary edema.

Data Sources: PubMed, EMBASE, Cochrane library, Web of Science, and bibliographies of articles were retrieved inception until June 2016.

Study Selection: Randomized controlled trials comparing application of noninvasive ventilation with standard oxygen therapy in adults with acute hypoxemic nonhypercapnic respiratory failure were included. Chronic obstructive pulmonary disease exacerbation and cardiogenic pulmonary edema patients were excluded. The primary outcome was intubation rate; ICU mortality and hospital mortality were secondary outcomes.

Data Extraction: Demographic variables, noninvasive ventilation application, and outcomes were retrieved. Internal validity was assessed using the risk of bias tool. The strength of evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation methodology.

Data Synthesis: Eleven studies (1,480 patients) met the inclusion criteria and were analyzed by using a random effects model. Compared with standard oxygen therapy, the pooled effect showed that noninvasive ventilation significantly reduced intubation rate with a summary risk ratio of 0.59 (95% CI, 0.44–0.79; $p = 0.0004$). Furthermore, hospital mortality was also significantly reduced (risk ratio, 0.46; 95% CI, 0.24–0.87; $p = 0.02$). Subgroup meta-analysis showed that the application of bilevel positive support ventilation (bilevel positive airway pressure) was associated with a reduction in ICU mortality ($p = 0.007$). Helmet noninvasive ventilation could reduce hospital mortality ($p = 0.0004$), whereas face/nasal mask noninvasive ventilation could not.

Conclusions: Noninvasive ventilation decreased endotracheal intubation rates and hospital mortality in acute hypoxemia nonhypercapnic respiratory failure excluding chronic obstructive pulmonary disease exacerbation and cardiogenic pulmonary edema patients. There is no sufficient scientific evidence to recommend bilevel positive airway pressure or helmet due to the limited number of trials available. Large rigorous randomized trials are needed to answer these questions definitely. (*Crit Care Med*; 45:e727–e733)

Key Words: acute hypoxemic respiratory failure; hospital mortality; intensive care unit mortality; intubation rate; noninvasive ventilation

[1]Department of Critical Care Medicine, Nanjing Zhong-da Hospital, School of Medicine, Southeast University, Nanjing, P. R. China.

[2]Department of Pain Management, Subei People's Hospital of Jiangsu Province and Clinical Medical School, Yang Zhou University, Yangzhou, P. R. China.

Drs. X-P. Xu and Qiu had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. Drs. X-P. Xu, Zhang, and Qiu performed the systematic review, study selection, statistical analysis, and elaboration of the article for publication. Drs. S-Q. Liu and L. Liu contributed to the data extraction and quality assessment. All the authors participated in the article writing and figure elaboration.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by grants from the National Natural Science Foundation of China (grant numbers: 81372093, 81501705, 81571874), the Ministry of Health of China (health research special funds for public welfare projects, grant number: 201202011), the projects of Jiangsu province's medical key discipline (project 889-KJXW 11.3), and the Fundamental Research Funds for the Central Universities and the Graduate Innovation Project in Jiangsu Province of China (KYLX15_0181). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Dr. S. Liu disclosed work for hire. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: haiboq2000@163.com

DOI: 10.1097/CCM.0000000000002361

Noninvasive ventilation (NIV) application has become increasingly important in the management of acute respiratory failure (ARF) in recent years (1). Especially, the 2011 Canadian guidelines for the use of NIV in critical care settings suggest the use of NIV in exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (CPE) patients with a grade 1A recommendation (2), mainly because NIV is effective in reducing endotracheal intubation and mortality (3–5). Nevertheless, so far the benefits of NIV remain on debate in patients with acute hypoxemic nonhypercapnic respiratory failure particularly unrelated to CPE or underlying chronic pulmonary disease.

In 2004, Keenan et al (6) made a systematic review to assess the effect of NIV in acute hypoxemic respiratory failure (AHRF) patients not due to CPE or an exacerbation of COPD according to studies published in the beginning of the 2000s, which suggested that the application of NIV could reduce the rate of endotracheal intubation. However, it included a part of patients with hypercapnia which could lead to an overestimation of the benefits of NIV when compared with standard oxygen therapy. What is more important, several most recent prospective, randomized trials (7–10) reported conflicting results about the effect of NIV on AHRF patients unrelated to CPE or COPD exacerbation.

These considerations led us to conduct a systematic review and meta-analysis to compare the effect of NIV and standard oxygen therapy focusing on acute hypoxemic nonhypercapnic respiratory failure patients not due to COPD and CPE. Furthermore, the overall failure of NIV occurred in 16–30% of patients (11, 12), which depended on not only the severity of AHRF but also the multiple technical causes including NIV interface (13) and ventilation mode or settings (14, 15). Hence, we tried to make subgroup analysis according to different NIV interfaces, NIV modes, and hypoxic severity with the intention to give specific recommendations for clinicians.

METHODS

Ethical approval and patient consent are not required since this is a meta-analysis based on previous published studies.

Data Sources and Searches

Randomized controlled trials (RCTs) of NIV in patients with AHRF were independently searched for in PubMed, the Cochrane Library, EMBASE, and Web of Science using the following key word terms ("acute respiratory failure" or "acute hypoxemic respiratory failure" or "acute hypoxemic respiratory distress" or "ARF" or "AHRF") and ("nippv" or "bipap" or "cpap" or "niv" or "nipsv" or "noninvasive positive pressure ventilation" or "non invasive positive pressure ventilation" or "noninvasive ventilation" or "non invasive ventilation" or "bilevel positive airway pressure" or "continuous positive airway pressure" or "noninvasive pressure support ventilation" or "non invasive pressure support ventilation" or "mask ventilation" or "nasal ventilation") (6, 16). Our research was limited to studies using adult participants.

Study Selection

Figure 1 summarizes the study selection process. Two investigators (X-P.X., X-C.Z.) assessed the retrieved studies independently, including titles, abstracts, and citations. Any differences were resolved by consensus. In the absence of sufficient detail to inform decision making, full texts were sourced and the process repeated. The investigators selected the retrieved studies that fulfilled the following inclusion and exclusion criteria.

Inclusion Criteria

Inclusion criteria were as follows: 1) A trial was conducted comparing NIV with standard oxygen therapy in patients with acute hypoxemic nonhypercapnic respiratory failure; 2) acute hypoxemic nonhypercapnic respiratory failure, defined as a respiratory rate of more than 25 breaths/min, Pa_{O_2} less than 60 mm Hg on room air, or a ratio of the Pa_{O_2}/F_{IO_2} (P/F) of 300 mm Hg or less while the patients were breathing oxygen at 10 L/min ≤ flow rate ≤ 15 L/min for at least 15 minutes; Pa_{CO_2} less than or equal to 50 mm Hg; labored breathing or respiratory distress or dyspnea at rest; 3) a clinical RCT was employed; 4) intubation rate, ICU mortality, or hospital mortality were available; and 5) the number of patients in the NIV and oxygen therapy groups was provided.

Exclusion Criteria

Exclusion criteria were as follows: 1) participants were children or adolescents (< 14 yr old); 2) patients with CPE or an exacerbation of COPD; 3) patients with hypercapnia (Pa_{CO_2} > 50 mm Hg); 4) application of NIV with invasive weaning (mechanical ventilation for > 48–72 hr) in intubated patients; 5) the trial did not use oxygen therapy as a control (e.g., invasive ventilation or high-flow oxygen therapy); 6) the study was a review, letter, case report, or other type of publication not based on original research (e.g., cell culture and isolated organs) or employing animal models; 7) the study did not include extractable outcomes or mortality data; and 8) the full text was unavailable.

Data Extraction

For each eligible study, two authors (X-P.X., X-C.Z.) independently abstracted data. Our primary outcome was intubation rate. The secondary outcome was ICU mortality and hospital mortality. Disagreements between the two investigators were resolved by discussion and consensus.

Subgroup Analysis

For the primary and secondary outcomes, we performed the following a priori subgroup analyses: patients with face/nasal mask versus helmet (NIV interface); bilevel positive support ventilation (BiPAP) versus continuous positive airway pressure (CPAP) (NIV mode); and 100 mm Hg ≤ P/F ≤ 200 mm Hg versus 200 mm Hg < P/F ≤ 300 mm Hg (according to the average P/F provided by all RCTs, hypoxic severity). Due to inadequate comparative reporting of pulmonary or extrapulmonary originated AHRF, we were unable to perform subgroup analysis

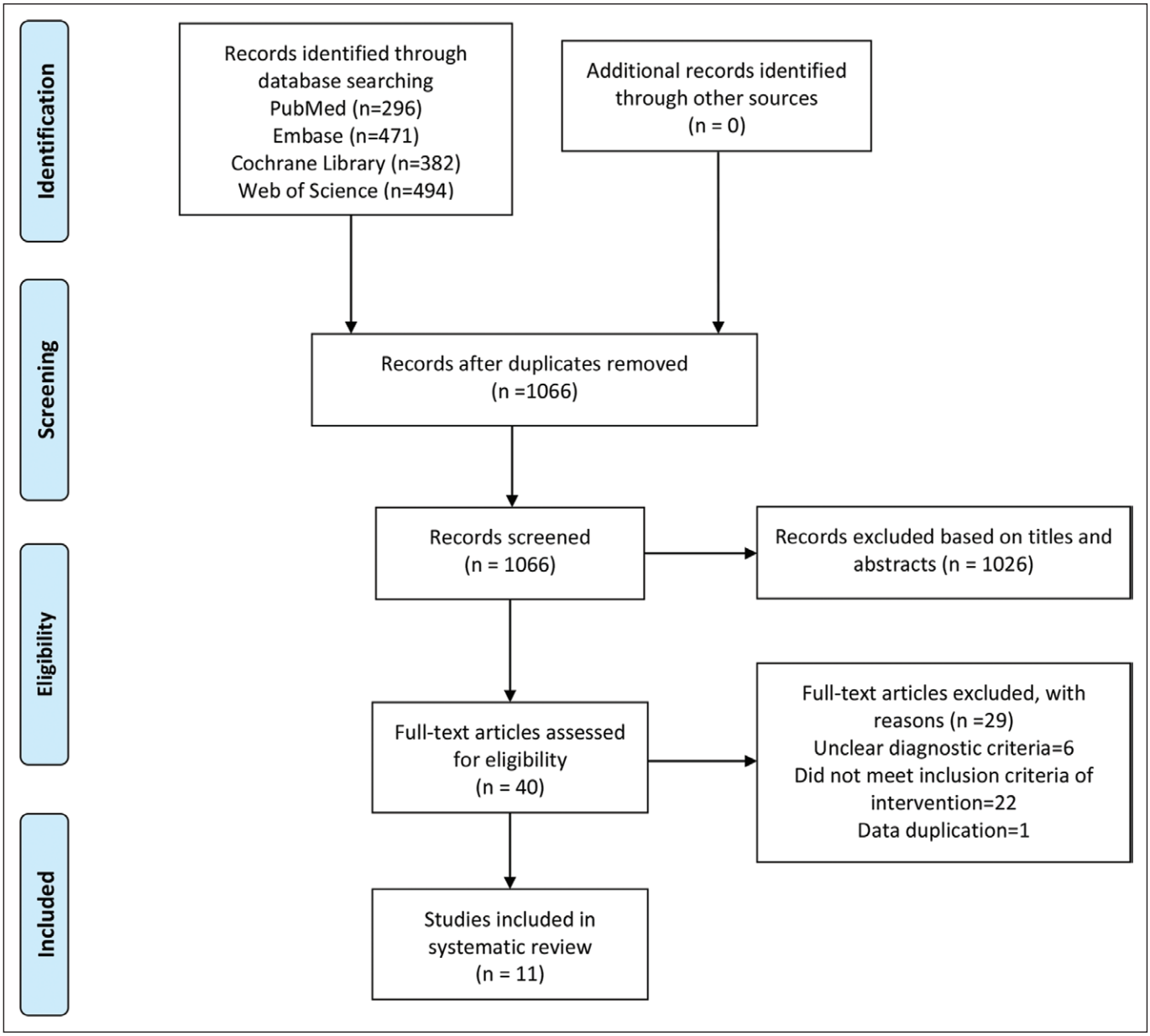

Figure 1. Flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of trial selection.

according to etiology. Analyses according to unilateral versus bilateral involvement were similarly not possible.

Assessment of Risk of Bias

Internal validity of the included studies was assessed according to the Cochrane Collaboration methodology (17), which consists of six domains as shown in **Figure 2**.

Grading the Evidence

We graded the strength of evidence by applying the Grading of Recommendations Assessment, Development, and Evaluation (GRADE, GRADEPro GDT2016 https://gradepro.org/) (18). This grading includes levels of high, moderate, low, and very low based on the quality of design, limitations, inconsistencies, indirectness, imprecision, and possible publication bias. Two investigators (S-Q.L., L.L.) independently evaluated the studies, abstracted data on methods and outcomes, and assessed the risk of bias.

Data Synthesis and Analysis

The meta-analysis of the included studies was performed using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen Denmark), which provided the risk ratio (RR) with 95% CI for primary and secondary outcomes. Heterogeneity among trials was quantified using visual inspection of the forest plots following a chi-square test, which is expressed as I^2. Statistical heterogeneity was considered relevant if I^2 greater than 30%. In cases of significant heterogeneity ($I^2 > 30\%$), a random effects model was used; otherwise, a fixed effects model was applied. Publication bias was evaluated by visual inspection of funnel plots. We considered a p value of less than 0.05 statistically significant.

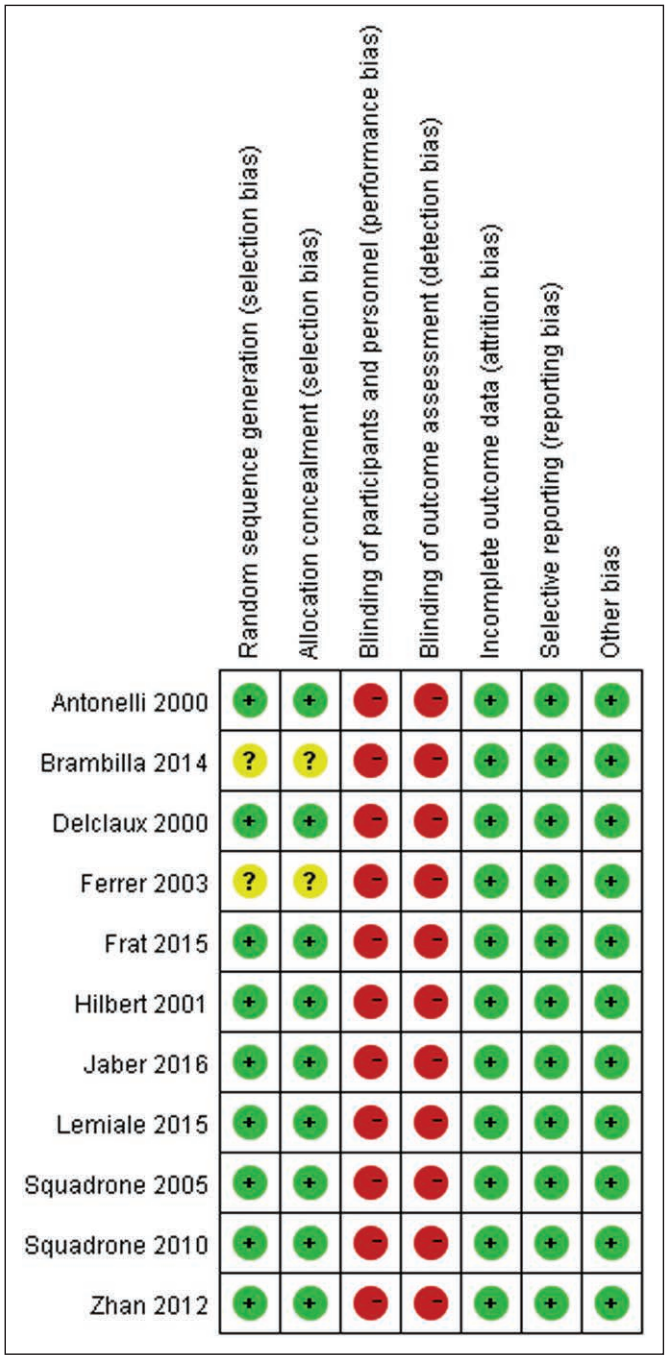

Figure 2. Risk of bias summary for each included study. *Red* (–) indicates high risk of bias; *yellow* (?) indicates unclear risk; and *green* (+) indicates low risk of bias.

RESULTS

Search Results and Trial Characteristics

We identified 1,066 citations; 40 studies were retrieved for detailed evaluation; and 11 RCTs (7–10, 19–25) met inclusion criteria (Fig. 1). These 11 RCTs included a total of 1,480 adult patients (NIV, 753 [50.9%]; control, 727 [49.1%]).

The main characteristics of the included studies are summarized in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C519) and **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/C520). The years of publication ranged from 2000 to 2016. The mean age of patients ranged from 46.5 to 65.5. Of the 11 included trials, two were single-center trials (22, 25), and all were conducted in Europe except one, which was conducted in Asia (19).

Assessment of the risk of bias is summarized in Figure 2. Among the 11 RCTs, none of the trials were double blinded. However, blinding of patients and caregivers was impossible in these trials, and the authors proposed that the outcomes were likely not influenced by a lack of blinding. Two trials were classified as having an unclear risk of bias (7, 23).

NIV Decreased Endotracheal Intubation Rate in Patients With Acute Hypoxemia Nonhypercapnic Respiratory Failure

Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C519) shows that endotracheal intubation rates were reported in 11 trials. Of the 753 patients treated with NIV, 230 (30.5%) were intubated compared with 319 of the 727 (43.9%) receiving standard oxygen therapies. Significant differences in intubation rates were found between the NIV and oxygen therapy groups (RR, 0.59; 95% CI, 0.44–0.79; $p = 0.0004$) (**Fig. 3**). The funnel plot indicates no obvious publication bias in the meta-analysis of endotracheal intubation rate (**Fig. S1**, Supplemental Digital Content 3, http://links.lww.com/CCM/C521; **legend**, Supplemental Digital Content 12, http://links.lww.com/CCM/C530). We graded the overall strength of the evidence as moderate (**Supplemental Table 3**, Supplemental Digital Content 4, http://links.lww.com/CCM/C522).

A subgroup meta-analysis was performed to determine the effect of NIV on specific group of patients. No significant differences in intubation rates were found between two groups of patients with different interfaces (**Fig. S2**, Supplemental Digital Content 5, http://links.lww.com/CCM/C523; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530), NIV modes (**Fig. S3**, Supplemental Digital Content 6, http://links.lww.com/CCM/C524; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530), or severity (**Fig. S4**, Supplemental Digital Content 7, http://links.lww.com/CCM/C525; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530), suggesting that all mild to moderate target patients could benefit from NIV in reducing the intubation rate, no matter what kind of interface or NIV ventilator mode is used.

NIV Did Not Decrease ICU Mortality in Acute Hypoxemia Nonhypercapnic Respiratory Failure Patients

Seven studies (503 patients) reported ICU mortality, which we stratified according to NIV interfaces, modes, and hypoxic severity. There were 62 of 253 deaths (24.5%) in the NIV group, compared with 90 of 250 (36.0%) in the control group. No obvious publication bias was found (**Fig. S5**, Supplemental Digital Content 8, http://links.lww.com/CCM/C526; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530). The RR estimate for ICU mortality in patients treated with NIV compared with standard oxygen therapy was 0.73 (95%

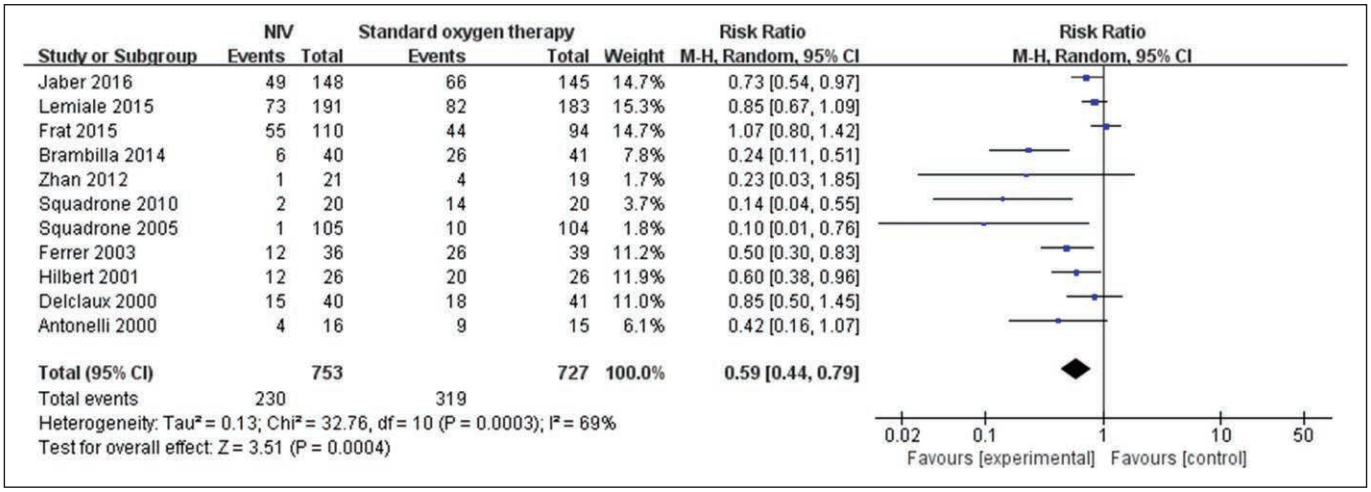

Figure 3. Intubation rate in acute hypoxemic nonhypercapnic respiratory failure patients randomized to noninvasive ventilation (NIV) versus standard oxygen therapy. M-H = Mantel-Haenszel.

CI, 0.51–1.03; $p = 0.08$) (**Fig. 4**). However, we graded the overall strength of the evidence as low (Supplemental Table 3, Supplemental Digital Content 4, http://links.lww.com/CCM/C522), which means the further research will likely change the estimate.

Notably, subgroup analysis showed that NIV significantly decreased the ICU mortality of patients with BiPAP mode but not with CPAP (**Fig. S6*A***, Supplemental Digital Content 9, http://links.lww.com/CCM/C527; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530), indicating that NIV with BiPAP modes might be effective to improve outcome of acute hypoxemia nonhypercapnic respiratory failure patients. In contrast, no significant differences in ICU mortality were found between two groups of patients with different hypoxic severity (**Fig. S6*B***, Supplemental Digital Content 9, http://links.lww.com/CCM/C527; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530). Among seven RCTs reporting ICU mortality, there is only one research (20) using helmet NIV. Thus we did not show the results of subgroup analysis according to interfaces.

NIV Decreased Hospital Mortality in Hypoxemia Nonhypercapnic Respiratory Failure Patients

Investigators reported hospital mortality in six trials, with no obvious publication bias (**Fig. S7**, Supplemental Digital Content 10, http://links.lww.com/CCM/C528; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530). Of the 252 patients treated with NIV, 31 (12.3%) died when in the hospital, compared with 62 of the 251 (24.7%) receiving standard oxygen therapies. Evidently, there is significant decrease of hospital mortality in the NIV group (RR, 0.46; 95% CI, 0.24–0.87; $p = 0.02$) (**Fig. 5**). We graded the overall strength of the evidence as moderate (Supplemental Table 3, Supplemental Digital Content 4, http://links.lww.com/CCM/C522).

The subgroup analysis showed that NIV decreased the hospital mortality of patients especially with helmet or 200 mm Hg < P/F ≤ 300 mm Hg but not with face/nasal mask or 100 mm Hg ≤ P/F ≤ 200 mm Hg (**Fig. S8**, Supplemental Digital Content 11, http://links.lww.com/CCM/C529; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/C530). The results suggest that mild AHRF patients could benefit from NIV with helmet in reducing the hospital mortality. Similarly, among six RCTs reporting hospital mortality, there is only one research (19) applying BiPAP mode. Therefore, we did not show the results of subgroup analysis according to NIV modes.

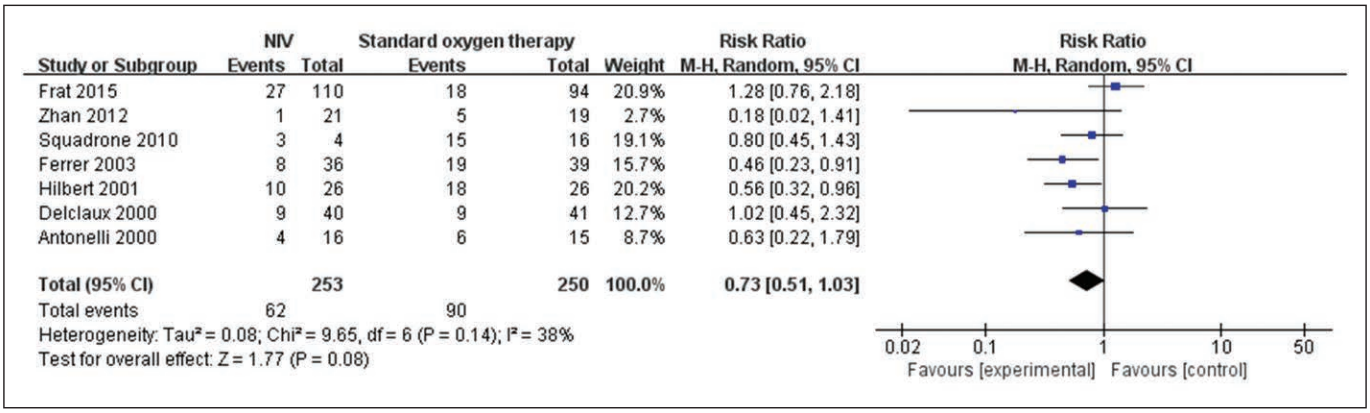

Figure 4. ICU mortality in acute hypoxemic nonhypercapnic respiratory failure patients randomized to noninvasive ventilation (NIV) versus standard oxygen therapy. M-H = Mantel-Haenszel.

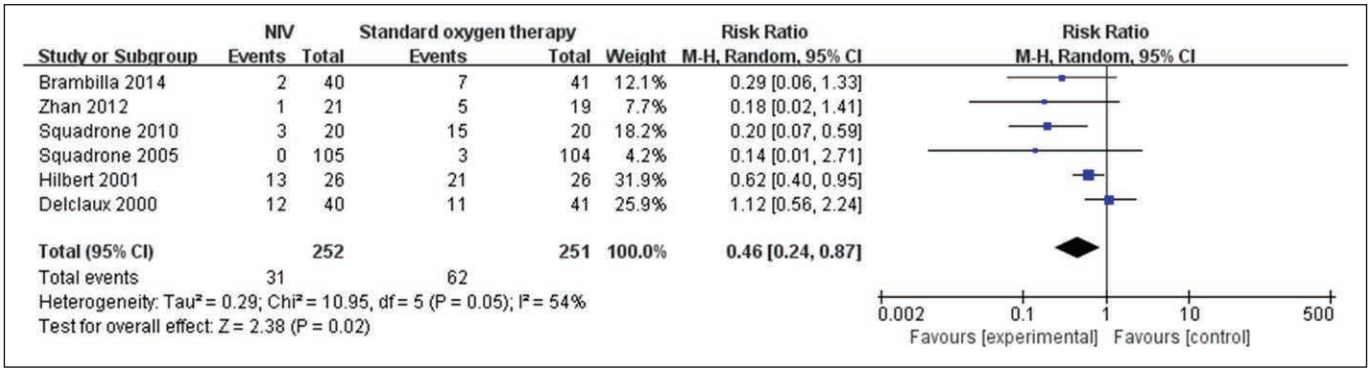

Figure 5. Hospital mortality in acute hypoxemic nonhypercapnic respiratory failure patients randomized to noninvasive ventilation (NIV) versus standard oxygen therapy. M-H = Mantel-Haenszel.

DISCUSSION

The present systematic review and meta-analysis suggest that the application of NIV was associated with significant lower endotracheal intubation rate (13.4% relative reduction) and hospital mortality (12.4% relative reduction) compared with standard oxygen therapy in patients with acute hypoxemic nonhypercapnic respiratory failure unrelated to COPD exacerbation or CPE. Furthermore, subanalyses suggested that the application of BiPAP was associated with a reduction in ICU mortality. Helmet NIV could reduce hospital mortality, whereas face/nasal mask NIV could not.

Recently, Cabrini et al (26) made a comprehensive systematic review and meta-analysis of 78 RCTs, which reported that NIV improves survival in all acute care settings and it is also widely used (27, 28). However, much of the current evidence for the use of NIV was overestimated by including a heterogeneous population of patients with ARF who had COPD exacerbation or CPE (26). To our knowledge, this is the first systematic review and meta-analysis to evaluate the effect of NIV in patients with acute hypoxemic nonhypercapnic respiratory failure in absence of a CPE or COPD exacerbation. Eleven high-quality RCTs were included, and the robust results recommended application of NIV in patients with acute hypoxemic nonhypercapnic respiratory failure without COPD exacerbation or CPE.

The subgroup analysis of NIV interfaces suggested that helmet NIV could reduce intubation rate and hospital mortality, whereas face/nasal mask NIV could not, which is consistent with much of the current evidence (29–31). This effect might be attributed to good amenity, better tolerance, and universal application of helmet ventilation (31). However, it should be noted that only three studies with small sample sizes (165 vs 588 using mask) had investigated this variable in this meta-analysis. Therefore, larger RCTs are still needed to confirm the results.

Studies have shown that CPAP can improve gas exchange, decrease respiratory and heart rate, reduce the need for invasive ventilation, and reduce hospital mortality (7, 20). BiPAP delivers positive airway pressure at two different levels during inspiration and expiration, and can decrease inspiratory work of breathing more than CPAP can alone (8, 19). As shown in the subgroup analysis by ventilation mode, different ventilator modes have no difference in reducing the intubation rate. However, BiPAP could reduce the ICU mortality, whereas CPAP could not. Similarly, RCTs with BiPAP involved fewer patients (221 vs 532 receiving CPAP). Therefore, conclusions regarding the relative effectiveness of BiPAP mode are limited. More studies are needed to answer this question definitively.

P/F ratio is considered a simple and useful variable. For example, according to the new Berlin definition of acute respiratory distress syndrome (ARDS), patients are now categorized into three different categories (mild, moderate, or severe), based on the P/F under positive airway pressure (32). Despite its limitations, P/F ratio is actually used for predicting outcome and response to therapy in patients with ARDS (33). Accordingly, we set the mild to moderate margin at 200 mm Hg on the basis of the average P/F ratio provided by all RCTs and made a subgroup analysis (34). The results showed that NIV could decrease the intubation rate associated with lower hospital mortality in the 200 mm Hg < P/F ≤ 300 mm Hg (mild) group. Another exciting finding was that NIV could also decrease the intubation rate in the 100 mm Hg ≤ P/F ≤ 200 mm Hg (moderate) group. However, it was not associated with lower hospital mortality, which might be affected by the limited number of RCTs. It should be noted that since our observations regarding hypoxic severity are according to the provided average P/F, conclusions regarding the relative effectiveness of NIV in subgroups of patients would be misleading. Nonetheless, we are able to generate hypotheses that may be tested by future trials.

Strengths of this systemic review and meta-analysis include the comprehensive research methodology, which render it unlikely that important scientific studies of NIV for target patients were omitted. Article selection, data abstraction, and assessment of trial methods were performed independently and in duplicate. We used the Cochrane Risk of Bias approach to evaluate methodologic quality enhancing the generalizability of our findings. Potential weakness lies in possible bias that blinding with NIV in all RCTs was not feasible. Furthermore, studies have suggested that a failure of NIV might result in excess mortality, possibly because of delayed intubation (35, 36); however, we did not analyze the risk factors for NIV failure. Finally, the difference of NIV duration and application strategies (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/C520) between studies is another potential source of bias.

CONCLUSIONS

NIV associated with decreased endotracheal intubation rates and hospital mortality in acute hypoxemia nonhypercapnic respiratory failure excluding COPD exacerbation and CPE patients. It should be noted that there is no sufficient scientific evidence to recommend BiPAP or helmet due to the limited number of trials available. Large rigorous randomized trials are needed to answer these questions definitely.

ACKNOWLEDGMENTS

We sincerely thank Dr. Hao Chen (Nanjing University of Chinese Medicine) for his guidance with the statistical methods. We also greatly appreciate our colleagues for their helpful advice during the course of this study.

REFERENCES

1. Schnell D, Timsit JF, Darmon M, et al: Noninvasive mechanical ventilation in acute respiratory failure: Trends in use and outcomes. *Intensive Care Med* 2014; 40:582–591
2. Keenan SP, Sinuff T, Burns KE, et al; Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group: Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011; 183:E195–E214
3. Brochard L, Mancebo J, Wysocki M, et al: Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333:817–822
4. Pisani L, Mega C, Vaschetto R, et al: Oronasal mask versus helmet in acute hypercapnic respiratory failure. *Eur Respir J* 2015; 45:691–699
5. Masip J, Roque M, Sánchez B, et al: Noninvasive ventilation in acute cardiogenic pulmonary edema: Systematic review and meta-analysis. *JAMA* 2005; 294:3124–3130
6. Keenan SP, Sinuff T, Cook DJ, et al: Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. *Crit Care Med* 2004; 32:2516–2523
7. Brambilla AM, Aliberti S, Prina E, et al: Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Med* 2014; 40:942–949
8. Jaber S, Lescot T, Futier E, et al; NIVAS Study Group: Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: A randomized clinical trial. *JAMA* 2016; 315:1345–1353
9. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network: High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372:2185–2196
10. Lemiale V, Mokart D, Resche-Rigon M, et al; Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH): Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2015; 314:1711–1719
11. Esteban A, Ferguson ND, Meade MO, et al; VENTILA Group: Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008; 177:170–177
12. Lee JS, O'Dochartaigh D, MacKenzie M, et al: Factors associated with failure of non-invasive positive pressure ventilation in a critical care helicopter emergency medical service. *Prehosp Disaster Med* 2015; 30:239–243
13. Carron M, Freo U, BaHammam AS, et al: Complications of non-invasive ventilation techniques: A comprehensive qualitative review of randomized trials. *Br J Anaesth* 2013; 110:896–914
14. Li H, Hu C, Xia J, et al: A comparison of bilevel and continuous positive airway pressure noninvasive ventilation in acute cardiogenic pulmonary edema. *Am J Emerg Med* 2013; 31:1322–1327
15. Carteaux G, Millán-Guilarte T, De Prost N, et al: Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: Role of tidal volume. *Crit Care Med* 2016; 44:282–290
16. Hu SL, He HL, Pan C, et al: The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *Crit Care* 2014; 18:R109
17. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928
18. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
19. Zhan Q, Sun B, Liang L, et al: Early use of noninvasive positive pressure ventilation for acute lung injury: A multicenter randomized controlled trial. *Crit Care Med* 2012; 40:455–460
20. Squadrone V, Massaia M, Bruno B, et al: Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med* 2010; 36:1666–1674
21. Squadrone V, Coha M, Cerutti E, et al; Piedmont Intensive Care Units Network (PICUN): Continuous positive airway pressure for treatment of postoperative hypoxemia: A randomized controlled trial. *JAMA* 2005; 293:589–595
22. Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001; 344:481–487
23. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168:1438–1444
24. Delclaux C, L'Her E, Alberti C, et al: Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA* 2000; 284:2352–2360
25. Antonelli M, Conti G, Bufi M, et al: Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: A randomized trial. *JAMA* 2000; 283:235–241
26. Cabrini L, Landoni G, Oriani A, et al: Noninvasive ventilation and survival in acute care settings: A comprehensive systematic review and metaanalysis of randomized controlled trials. *Crit Care Med* 2015; 43:880–888
27. Hess DR: Noninvasive ventilation for acute respiratory failure. *Respir Care* 2013; 58:950–972
28. Nava S, Hill N: Non-invasive ventilation in acute respiratory failure. *Lancet* 2009; 374:250–259
29. Thille AW, Contou D, Fragnoli C, et al: Non-invasive ventilation for acute hypoxemic respiratory failure: Intubation rate and risk factors. *Crit Care* 2013; 17:R269
30. Patel BK, Wolfe KS, Pohlman AS, et al: Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2016; 315:2435–2441
31. Liu Q, Gao Y, Chen R, et al: Noninvasive ventilation with helmet versus control strategy in patients with acute respiratory failure: A systematic review and meta-analysis of controlled studies. *Crit Care* 2016; 20:265
32. Ferguson ND, Fan E, Camporota L, et al: The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38:1573–1582
33. Villar J, Fernández RL, Ambrós A, et al; Acute Lung Injury Epidemiology and Natural history Network: A clinical classification of the acute respiratory distress syndrome for predicting outcome and guiding medical therapy. *Crit Care Med* 2015; 43:346–353
34. Stéphan F, Barrucand B, Petit P, et al; BiPOP Study Group: High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: A randomized clinical trial. *JAMA* 2015; 313:2331–2339
35. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al: Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med* 2012; 38:458–466
36. Esteban A, Frutos-Vivar F, Ferguson ND, et al: Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; 350:2452–2460