EDITORIAL

Alternatives to Invasive Ventilation in the COVID-19 Pandemic

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Since its invention in the 1940s, the positive pressure ventilator has always been known to have both risks and benefits. Although mechanical ventilation is unquestionably lifesaving, there are numerous associated drawbacks. Beyond the obvious and immediate limitations that patients require translaryngeal intubation and are physically attached to a ventilator, delivery of gas by positive pressure also creates mechanical stress and causes strain on lung tissue. This stress can lead to ventilator-induced lung injury, compounding the underlying lung condition that precipitated the initial respiratory failure.[1] Despite advances in knowledge about protective ventilation strategies to limit ventilator-induced lung injury (most notably use of low tidal volumes), concern remains for this iatrogenic injury in all patients undergoing intubation and mechanical ventilation.

Related article

While noninvasive ventilation (NIV) techniques (ie, techniques that avoid translaryngeal intubation) have substantially reduced the need for invasive mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema, defining the role of these techniques in acute hypoxemic respiratory failure (AHRF) from lung injury has remained elusive. Initial reports of improved outcomes with NIV delivered by face mask in immunocompromised patients[2,3] were later questioned in a larger clinical trial.[4] Although high-flow nasal cannula (HFNC), another method of noninvasively delivering oxygen, seemed poised to fill an important gap for this vulnerable population, a clinical trial involving more than 700 patients found that HFNC did not significantly improve survival.[5] As the pursuit to spare patients exposure to invasive ventilation in AHRF continues, there is a countermovement questioning the wisdom of such an approach, given concerns that spontaneous breathing at large tidal volumes during use of NIV or HFNC may exacerbate lung injury.[6]

Coronavirus disease 2019 (COVID-19), which causes one type of AHRF, has accelerated the need to add clarity to this ongoing debate of whether to intubate early and, if not, which type of noninvasive support (NIV, HFNC, or standard oxygen therapy) is the most efficacious. Early series suggested high mortality for patients with COVID-19–associated respiratory failure who received invasive mechanical ventilatory support,[7] raising the concern that these patients may be particularly vulnerable to ventilator-induced lung injury. In addition, the surge of patients in some locales has already strained and exceeded the capacity of some health care facilities, including availability of ventilators. Strategies that could at least safely spare patients invasive ventilation or shorten the duration of invasive ventilation could be of enormous importance. Thus, a useful assessment of the existing literature informing such decisions would be welcome.

In this issue of *JAMA*, Ferreyro et al[8] report findings from a network meta-analysis that evaluated the association of noninvasive oxygenation strategies (with comparisons among face mask NIV, helmet NIV, HFNC, and standard oxygen therapy) with outcomes in adults with AHRF. The use of a network approach leverages direct evidence from published clinical trials that share common comparators to generate indirect evidence to rank order them. For example, given that no clinical trial has compared helmet NIV with HFNC, separate clinical trials that directly compared helmet NIV[9] and HFNC[10] with a common comparator, face mask NIV, could be used to generate indirect evidence for the relative benefit associated with helmet NIV vs HFNC.

The authors included 25 studies with 3804 patients with AHRF in this analysis and found that compared with standard oxygen therapy, helmet NIV (based on 3 trials with 330 patients; network risk ratio [RR], 0.26; 95% credible interval [CrI], 0.14-0.46), face mask NIV (14 trials with 1725 patients; RR, 0.76; 95% CrI, 0.62-0.90), and HFNC (5 trials with 1479 patients; RR, 0.76; 95% CrI, 0.55-0.99) were associated with a lower risk of endotracheal intubation. Both forms of NIV, helmet (RR, 0.40; 95% CrI, 0.24-0.63) and face mask (RR, 0.83; 95% CrI, 0.68-0.99), were also associated with a lower risk of death.

Even though these overall findings suggest the potential benefits of noninvasive oxygenation support, there are nuances to these data, which are revealed in the various sensitivity analyses. The association of face mask NIV with lower mortality was no longer statistically significant among patients with severe hypoxemia (PaO_2:FIO_2 ratio ≤200) after excluding trials that included patients known to have established benefit from NIV, specifically those with chronic obstructive pulmonary disease, heart failure, and postoperative state. Furthermore, the association of face mask NIV with rates of endotracheal intubation was also not statistically significant when noninformative priors were considered to account for the views of clinicians who may have greater confidence in HFNC than in face mask NIV. These analyses illuminate the controversial role of face mask NIV in the management of severe AHRF, as prior studies[10,11] have suggested increased harm, possibly due to excessive tidal volumes, high transpulmonary pressures, and resulting patient self-inflicted lung injury.[6] However, these sensitivity analyses did not alter the association of helmet NIV with reduced rate of intubation and reduced mortality, suggesting that any evaluation of the potential role in AHRF should incorporate the interface by which NIV is applied.

The physiologic effects of helmet and face mask NIV may differ in AHRF. With face mask NIV, pressure support is often needed to reduce effort,[12] potentially setting the stage for excessive and thus injurious tidal volumes. In contrast, helmet NIV is able to deliver higher levels of positive end-expiratory pressure (PEEP) to improve oxygenation, reduce inspiratory effort,[13] and possibly render spontaneous breathing noninjurious.[14] However, the certainty of the evidence supporting helmet NIV compared with all other modes of noninvasive oxygen support is low due to the limited number of available published clinical trials and small number of participants.

Questions remain for clinicians regarding when and for which patients these various noninvasive oxygen support strategies fit into the algorithm of AHRF management and specifically for patients with COVID-19. Although some have argued that the risk of spontaneous breathing should preclude any noninvasive oxygen support, the data from the analysis by Ferreyro et al indicate that it is a reasonable approach to spare a subset of patients with AHRF invasive mechanical ventilation and its inherent complications. Although this network metanalysis may suggest a rank order of potential efficacy associated with these techniques, it is clear that a one-size-fits-all approach to AHRF is misguided. Choosing the right noninvasive oxygen support likely requires a precision-based approach that matches a given strategy to the observed phenotype of AHRF coupled with incorporating clinician experience and comfort with each technology. For instance, perhaps lung injury that is nonresponsive to PEEP is best served with a trial of HFNC. Alternatively, NIV may be considered if the lung injury seems PEEP responsive, with milder hypoxemia (Pa_{O_2}:F_{IO_2} ratio >200) reserved for the face mask interface and severe hypoxemia with a prolonged need of NIV application reserved for helmet.

Although further studies are needed, the meta-analysis by Ferreyro et al has provided a useful summary of the available data to help inform clinicians as they determine locally the best way to choose wisely among several options for care of patients with AHRF, especially in the wave of patients with COVID-19 currently being encountered. Future clinical trials comparing these strategies should not focus on declaring a "winner" per se but rather on identifying the patient phenotypes that stand to benefit from each noninvasive oxygenation support method. In the management of heterogeneous syndromes like AHRF, it is better to have multiple options than to focus on limiting clinical practice to a single choice.

ARTICLE INFORMATION

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Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure
A Systematic Review and Meta-analysis

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IMPORTANCE Treatment with noninvasive oxygenation strategies such as noninvasive ventilation and high-flow nasal oxygen may be more effective than standard oxygen therapy alone in patients with acute hypoxemic respiratory failure.

OBJECTIVE To compare the association of noninvasive oxygenation strategies with mortality and endotracheal intubation in adults with acute hypoxemic respiratory failure.

DATA SOURCES The following bibliographic databases were searched from inception until April 2020: MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and LILACS. No limits were applied to language, publication year, sex, or race.

STUDY SELECTION Randomized clinical trials enrolling adult participants with acute hypoxemic respiratory failure comparing high-flow nasal oxygen, face mask noninvasive ventilation, helmet noninvasive ventilation, or standard oxygen therapy.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted individual study data and evaluated studies for risk of bias using the Cochrane Risk of Bias tool. Network meta-analyses using a bayesian framework to derive risk ratios (RRs) and risk differences along with 95% credible intervals (CrIs) were conducted. GRADE methodology was used to rate the certainty in findings.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality up to 90 days. A secondary outcome was endotracheal intubation up to 30 days.

RESULTS Twenty-five randomized clinical trials (3804 participants) were included. Compared with standard oxygen, treatment with helmet noninvasive ventilation (RR, 0.40 [95% CrI, 0.24-0.63]; absolute risk difference, −0.19 [95% CrI, −0.37 to −0.09]; low certainty) and face mask noninvasive ventilation (RR, 0.83 [95% CrI, 0.68-0.99]; absolute risk difference, −0.06 [95% CrI, −0.15 to −0.01]; moderate certainty) were associated with a lower risk of mortality (21 studies [3370 patients]). Helmet noninvasive ventilation (RR, 0.26 [95% CrI, 0.14-0.46]; absolute risk difference, −0.32 [95% CrI, −0.60 to −0.16]; low certainty), face mask noninvasive ventilation (RR, 0.76 [95% CrI, 0.62-0.90]; absolute risk difference, −0.12 [95% CrI, −0.25 to −0.05]; moderate certainty) and high-flow nasal oxygen (RR, 0.76 [95% CrI, 0.55-0.99]; absolute risk difference, −0.11 [95% CrI, −0.27 to −0.01]; moderate certainty) were associated with lower risk of endotracheal intubation (25 studies [3804 patients]). The risk of bias due to lack of blinding for intubation was deemed high.

CONCLUSIONS AND RELEVANCE In this network meta-analysis of trials of adult patients with acute hypoxemic respiratory failure, treatment with noninvasive oxygenation strategies compared with standard oxygen therapy was associated with lower risk of death. Further research is needed to better understand the relative benefits of each strategy.

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Editorial

Supplemental content

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Acute hypoxemic respiratory failure is among the leading causes of intensive care unit admission in adult patients, often leading to endotracheal intubation and invasive mechanical ventilation.[1] The current coronavirus disease 2019 (COVID-19) pandemic has further highlighted the importance of understanding the best approach to providing respiratory support for patients with respiratory failure. Invasive mechanical ventilation is associated with severe adverse events,[2] and avoiding unnecessary endotracheal intubation remains a major goal in the management of patients with acute hypoxemic respiratory failure.[3] Multiple noninvasive oxygenation strategies have been developed to support oxygenation and ventilation that may lead to a reduced risk of endotracheal intubation and mortality. However, it remains unclear which of these is most effective.[4]

Standard oxygen therapy, typically at flow rates of less than 15 L/min, has been the conventional approach to delivering supplemental oxygen to patients with acute hypoxemic respiratory failure. Alternatively, noninvasive ventilation using either a face mask or helmet interface has been promoted to reduce the risk of endotracheal intubation. Oxygen delivery at high flow via nasal cannula has been gaining acceptance because of the ability to more closely match a patient's inspiratory demand in the setting of hypoxemia.[5] Randomized clinical trials (RCTs) comparing the effectiveness of noninvasive ventilation or high-flow nasal oxygen with standard oxygen therapy have produced conflicting results.[6-12] Patients in the control groups in most of these trials received standard oxygen therapy, and there have been few head-to-head comparisons of the other different noninvasive oxygenation modalities.[7,11] Moreover, most meta-analyses have been limited to traditional pairwise comparisons and therefore have not combined direct and indirect evidence for all potential comparisons.[13-16]

To provide additional clinical information, a network meta-analysis was conducted to compare the association of different noninvasive oxygenation strategies with mortality and receipt of endotracheal intubation in adult patients with acute hypoxemic respiratory failure.

Key Points

Question What are the associations between noninvasive oxygenation strategies and outcomes among adults with acute hypoxemic respiratory failure?

Findings In this systematic review and network meta-analysis that included 25 studies and 3804 patients with acute hypoxemic respiratory failure, compared with standard oxygen therapy there was a statistically significant lower risk of death with helmet noninvasive ventilation (risk ratio, 0.40) and face mask noninvasive ventilation (risk ratio, 0.83).

Meaning Noninvasive oxygenation strategies compared with standard oxygen therapy were significantly associated with lower risk of death.

Methods

This review has been conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols statement extension for network meta-analysis.[17,18] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019121755) and has been published.[19] No institutional review board approval was required because all study data had been published previously and this study did not include individual patient data.

Eligibility Criteria, Literature Search, and Study Selection

A systematic literature search was conducted through April 2020 to identify RCTs enrolling adult patients (>18 years of age) with acute hypoxemic respiratory failure comparing high-flow nasal oxygen, face mask noninvasive ventilation, helmet noninvasive ventilation, or standard oxygen therapy and evaluating 1 or both of the 2 key outcomes of mortality or endotracheal intubation. Studies that were primarily focused on the treatment of acute exacerbations of chronic obstructive pulmonary disease (ie, >50% of the study population) or congestive heart failure (ie, >50% of the study population) and those evaluating noninvasive oxygen strategies in the immediate postextubation period and after major cardiovascular surgery were excluded. The rationale for excluding studies primarily enrolling these patients was based on the established efficacy of noninvasive ventilation for these conditions.[20,21] However, we anticipated that some included randomized studies would also include patients with congestive heart failure and chronic obstructive pulmonary disease, given that the etiology of acute respiratory failure is often unclear at presentation or may have an acute on chronic component.

The following electronic bibliographic databases were searched from inception until April 2020 using a comprehensive search strategy developed by an information specialist: Ovid MEDLINE, Ovid Embase, PubMed (non-MEDLINE records only), Ovid Evidence-Based Medicine Reviews-Cochrane Central Register of Controlled Trials, EBSCO CINAHL Complete, Web of Science, and LILACS. The search also included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the International Standard Randomized Controlled Trial Number Registry (ISRCTN) for all registered clinical trials and RCTs. The search strategy was structured according to the Peer Review of Electronic Search Strategies (PRESS) 2015 guidelines.[22] A validated search filter for RCTs from the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, Section 6.4.11, was used to screen Ovid MEDLINE, Embase, and PubMed. A pretested search filter for RCTs from the Scottish Intercollegiate Guidelines Network was used to screen CINAHL Complete and Web of Science. No limits were applied to language, sex, or race.

The full texts of all articles identified as relevant during the title and abstract screening stage were obtained and reviewed. The comprehensive search strategy and detailed inclusion and exclusion criteria are described in eAppendix 1 in the Supplement.

Outcomes

The primary outcome was all-cause mortality, measured at the longest time point reported in the first 90 days after randomization. The secondary outcome was endotracheal intubation, measured at the longest time point reported up to 30 days. Additional secondary outcomes included patient comfort, dyspnea scores, intensive care unit and hospital lengths of stay, and 6-month mortality.

Data Extraction, Risk of Bias, and GRADE Certainty Assessment

Two reviewers (B.L.F. and F.A.) independently extracted individual study data and evaluated studies for risk of bias using a previously piloted standardized form and the Cochrane Risk of Bias tool for RCTs.[23] The following domains of each of the primary studies were assessed: random sequence generation, allocation concealment, blinding of study participants, incomplete outcome data, selective reporting, and other biases. Based on these domains, the overall risk of bias for each included study was assessed. The certainty of each direct, indirect, and network meta-analysis estimate was estimated based on the 4-step approach suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (ie, high, moderate, low, and very low certainty).[24] In the presence of incoherence (ie, differences between direct and indirect evidence), the lower certainty of the 2 assessments was assigned to the corresponding network estimate.[24]

Statistical Analysis

A series of pairwise conventional meta-analyses were performed with random-effects models to assess for direct associations between interventions and study outcomes. Network meta-analyses using bayesian random-effects models (log-link, binomial likelihood) were conducted to derive head-to-head treatment estimates comparing all interventions. Analyses were based on Markov chain Monte Carlo methods using minimally informative treatment effect estimates and informative prior distributions for heterogeneity estimates, following the approach suggested by Turner et al.[25]

Although these prior distributions were derived in the log odds scale, it was expected that these would be wide enough to cover possible values in the log relative risk scale. Correction of the treatment associations for multigroup trials was applied.[26] Further details on the model specification are in eAppendix 2 in the Supplement. Pairwise and network risk ratios (RRs) were derived, estimating summary estimates from the medians and corresponding 95% credible intervals (CrIs) from the 2.5 and 97.5 percentiles of the posterior distribution. In addition to relative associations, bayesian analyses were used to produce risk differences and 95% CrIs between treatment groups. Prior distributions for event rates of intubation and all-cause mortality in the standard oxygen therapy group were derived from the data and from previous literature.[27] The probability for each treatment to obtain each possible rank (probability of being best, second best, etc) was also estimated.[28] Specifically, in the bayesian framework and in each Markov chain Monte Carlo cycle, each treatment was ranked according to the estimated effect size. The proportion of cycles in which a treatment ranks first out of the total turns into the probability of being first, second, and so forth.[29]

Heterogeneity in treatment effects between studies was quantified using the posterior distribution τ^2. Incoherence between direct and indirect comparisons was estimated using the node-splitting approach contrasting estimates from both direct and indirect evidence.[30,31] Model convergence was assessed using the Brooks-Gelman-Rubin diagnostic, trace plots, and autocorrelation plots. Goodness of fit was assessed by comparing the mean residual deviance with the number of contributing data points. Statistical significance was defined as 95% CrIs that did not include the value 1.0. All analyses were performed in R version 3.6 (R Foundation; packages meta, gemtc, coda, pcnetmeta, and rjags) using Just Another Gibbs Sampler (JAGS) version 4.3.0 and OpenBUGS.

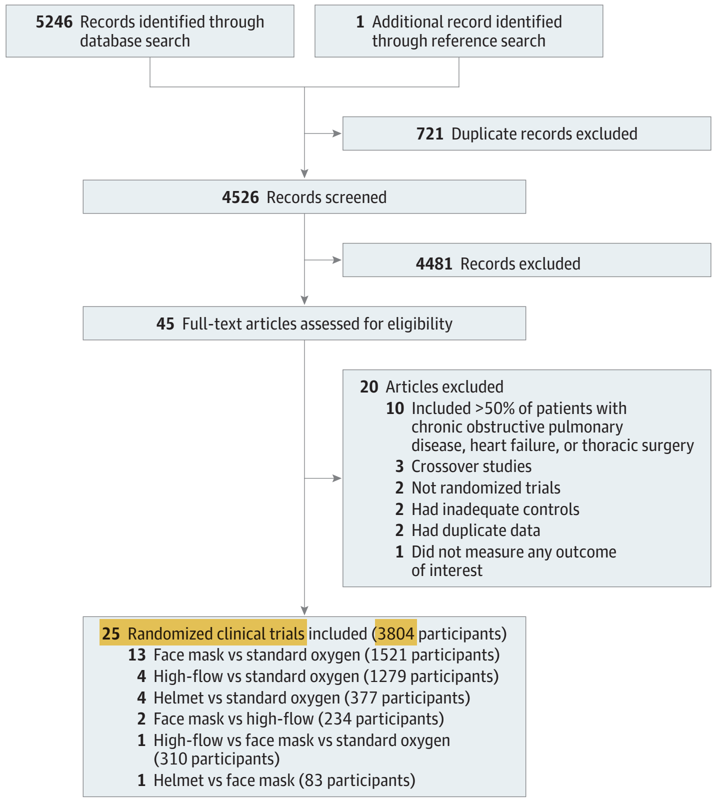
Sensitivity Analyses

Several sensitivity analyses were performed to assess the robustness of the pooled RRs for the main outcomes. These analyses excluded studies that enrolled any patient with acute exacerbation of chronic obstructive pulmonary disease or congestive heart failure, studies that enrolled postoperative patients, and studies that included patients with less severe respiratory failure (mean partial pressure of arterial oxygen [Pa_{O_2}] to fraction of inspired oxygen [F_{IO_2}] ratio >200). Because there was variability in the timing of reporting of mortality, the analysis of the primary outcome was limited to studies that reported mortality at hospital discharge. An analysis restricted to studies that included at least 50% of immunocompromised patients (ie, >50% of patients with hematologic malignancies, solid tumors with active chemotherapy, treatment with immunosuppressant drugs, or solid organ transplants) was also conducted. Furthermore, to assess the effect of study quality, an analysis restricted to studies with the lowest risk of bias was performed. In addition, to assess the robustness of the findings, the main analyses were refitted using noninformative priors for heterogeneity and also using moderately enthusiastic priors for treatment effects for high-flow nasal oxygen and skeptical priors for face mask noninvasive ventilation, based on measures of association and distributions obtained from recent evidence.[7,27,32] These latter sensitivity analyses were intended to account for a subgroup of clinicians who may have greater confidence in high-flow nasal oxygen compared with face mask noninvasive ventilation. Details are in eAppendix 2 in the Supplement. In addition, we performed post hoc sensitivity analyses to explore sources of incoherence when this was present.

Results

The search strategy identified 5246 records, including 25 RCTs (3804 participants; range, 30-776 participants) that were eligible for inclusion (**Figure 1**). Included trials evaluated 4 different interventions, and these included 5 of 6 potential head-to-head comparisons. Specifically, 13 trials compared face mask noninvasive ventilation with standard

Figure 1. Summary of Study Retrieval and Identification for Network Meta-analysis



oxygen therapy, 4 trials compared high-flow nasal oxygen with standard oxygen therapy, 2 trials compared face mask noninvasive ventilation with high-flow nasal oxygen, 1 trial compared face mask with helmet noninvasive ventilation, and 4 trials compared helmet noninvasive ventilation with standard oxygen therapy (**Table** and **Figure 2**). In addition, a 3-group study directly compared face mask noninvasive ventilation with high-flow nasal oxygen and also with standard oxygen therapy (therefore, there were a total of 27 comparisons for 25 RCTs).[7] No studies compared high-flow nasal oxygen with helmet noninvasive ventilation.

The Table describes the main study and cohort characteristics of the included trials. Mean age at randomization ranged from 30 to 75 years, mean PaO_2:FIO_2 ratio was predominantly below 200 (14 trials [56%]), and more than half of the trials (14 trials [56%]) allowed inclusion of immunocompromised patients. Community-acquired pneumonia was the most common cause of acute hypoxemic respiratory failure in 16 trials (64%). Pairwise comparisons are shown in eFigure 1 in the Supplement.

Noninvasive Oxygenation Strategies and Risk of Mortality

Twenty-one trials (3370 patients) were included in the mortality analysis, of which 1 (47 patients) did not report any deaths in any of the treatment groups.[37] Despite the absence of blinding, the risk of bias was determined to be low for the outcome of mortality in most (16 trials [76%]) of these trials (eTable 1 in the Supplement).

Using standard oxygen as the reference, helmet noninvasive ventilation (RR, 0.40 [95% CrI, 0.24-0.63]; absolute risk difference, −0.19 [95% CrI, −0.37 to −0.09]; low certainty) and face mask noninvasive ventilation (RR, 0.83 [95% CrI, 0.68-0.99]; absolute risk difference, −0.06 [95% CrI, −0.15 to −0.01]; moderate certainty) were significantly associated with a lower risk of mortality. High-flow nasal oxygen (RR, 0.87 [95% CrI, 0.62-1.15]; absolute risk difference, −0.04 [95% CrI, −0.15 to 0.04]; moderate certainty) was not associated with a statistically significant lower risk of mortality compared with standard oxygen therapy. **Figure 3**A and eFigure 2 in the Supplement show the results for all potential comparisons in the network meta-analysis for all-cause mortality. Helmet noninvasive ventilation was also associated with a significant decrease in mortality compared with high-flow nasal oxygen (RR, 0.46 [95% CrI, 0.26-0.80]; absolute risk difference, −0.15 [95% CrI, −0.34 to −0.05]; low certainty) and face mask noninvasive ventilation (RR, 0.48 [95% CrI, 0.29-0.76]; absolute risk difference, −0.13 [95% CrI, −0.27 to −0.05]; low certainty). There was no significant difference in the association with mortality when comparing face mask noninvasive ventilation with high-flow nasal oxygen (RR, 0.95 [95% CrI, 0.69-1.37]; absolute risk difference, −0.02 [95% CrI, −0.14 to −0.07]; low certainty). Incoherence between direct and indirect RRs was observed for the comparison of face mask noninvasive ventilation vs high-flow nasal oxygen (eFigure 3 in the Supplement). The probability of being best in reducing all-cause mortality among all possible interventions was higher for helmet noninvasive

Table. Main Characteristics of Included Studies

Source	Funding	Total No. of patients	Main reason for hypoxemic respiratory failure (main baseline risk factor)	Age, mean, y	Pao_2:Fio_2 ratio	Respiratory rate, /min	Main exposure	Comparator	Outcomes of interest assessed	Timing of measurement for study outcomes
Antonelli et al,[6] 2000	Undisclosed	40	Mixed ARF (immunocompromised [100%])	45	129	38	Face mask noninvasive ventilation (n = 20)	Standard oxygen (n = 20)	Death, intubation	ICU discharge, hospital discharge
Azevedo et al,[33] 2015	Undisclosed	30	CAP (CHF [43%])	67	NA	NA	High-flow nasal oxygen (n = 14)	Face mask noninvasive ventilation (n = 16)	Intubation	ICU discharge
Azoulay et al,[34] 2018	French Ministry of Health	776	CAP (immunocompromised [100%])	64[a]	132	33	High-flow nasal oxygen (n = 388)	Standard oxygen (n = 388)	Death, intubation	ICU discharge, hospital discharge, 28 days
Bell et al,[35] 2015	Fisher & Paykel	100	Mixed ARF	73	NA	33	High-flow nasal oxygen (n = 48)	Standard oxygen (n = 52)	Intubation	Emergency department, ICU discharge
Brambilla et al,[9] 2014	IRCCS Fondazione Ca'Granda, Ospedale Maggiore Policlinico, Milan	81	CAP (immunocompromised [32%])	67	141	34	Helmet noninvasive ventilation (n = 40)	Standard oxygen (n = 41)	Death, intubation	Hospital discharge
Confalonieri et al,[36] 1999	Undisclosed	56	CAP	64	175	37	Face mask noninvasive ventilation (n = 28)	Standard oxygen (n = 28)	Death, intubation	ICU discharge, 60 days
Cosentini et al,[37] 2010[b]	Undisclosed	47	CAP	69	248	27	Helmet noninvasive ventilation (n = 20)	Standard oxygen (n = 27)	Death, intubation	Emergency department
Delclaux et al,[38] 2000	Vital Signs Inc	123	CAP	58[a]	144	33	Face mask noninvasive ventilation (n = 62)	Standard oxygen (n = 61)	Death, intubation	ICU discharge, hospital discharge
Doshi et al,[10] 2018	Vapotherm	204	Mixed ARF (acute exacerbation COPD [26%])	63	NA	30	High-flow nasal oxygen (n = 104)	Face mask noninvasive ventilation (n = 100)	Intubation	72 hours
Ferrer et al,[39] 2003	Red GIRA, Red Respira, and Carburos Metalicos SA	105	CAP (immunocompromised [20%]; CHF [28%])	62	103	37	Face mask noninvasive ventilation (n = 51)	Standard oxygen (n = 54)	Death, intubation	ICU discharge
Frat et al,[7] 2015	French Ministry of Health	310	CAP (immunocompromised [26.5%])	60	155	33	High-flow nasal oxygen (n = 106)	Face mask noninvasive ventilation (n = 110); standard oxygen (n = 94)	Death, intubation	ICU discharge, 90 days
Hernandez et al,[40] 2010	Consejería de Sanidad de Castilla	50	Chest trauma	43	109	NA	Face mask noninvasive ventilation (n = 25)	Standard oxygen (n = 25)	Death, intubation	ICU discharge, hospital discharge
He et al,[41] 2019	National Natural Science Foundation of China	200	CAP	55	231	25	Face mask noninvasive ventilation (n = 102)	Standard oxygen (n = 98)	Death, intubation	ICU discharge, hospital discharge
Hilbert et al,[42] 2001	Undisclosed	52	CAP (immunocompromised [100%])	49	139	36	Face mask noninvasive ventilation (n = 26)	Standard oxygen (n = 26)	Death, intubation	ICU discharge, hospital discharge
Jaber et al,[43] 2016	Montpellier University Hospital and APARD Foundation	293	Mixed ARF (abdominal surgery [100%]; active cancer [50%])	64	195	29	Face mask noninvasive ventilation (n = 148)	Standard oxygen (n = 145)	Death, intubation	ICU discharge, 30 days, 90 days
Jones et al,[44] 2016	Greenlane Research and Education Fund	303	Mixed ARF (COPD [23.9%]; CHF [12.3%])	73	NA	33	High-flow nasal oxygen (n = 165)	Standard oxygen (n = 138)	Death, intubation	ICU discharge, hospital discharge, 90 days
Lemiale et al,[8] 2015	Legs Poix (Chancellerie des Universités de Paris) and OUTCOMEREA Study Group	374	Pneumonia (immunocompromised [100%])	63[a]	142	26	Face mask noninvasive ventilation (n = 191)	Standard oxygen (n = 183)	Death, intubation	ICU discharge, 30 days, 180 days
Lemiale et al,[45] 2015	Fisher & Paykel	100	Mixed ARF (immunocompromised [100%])	62[a]	114	27	High-flow nasal oxygen (n = 52)	Standard oxygen (n = 48)	Intubation	2 hours
Martin et al,[46] 2000	Undisclosed	61	Mixed ARF (COPD [38%])	61	199	28	Face mask noninvasive ventilation (n = 32)	Standard oxygen (n = 29)	Death, intubation	ICU discharge
Patel et al,[11] 2016	National Institutes of Health/National Heart, Lung, and Blood Institute	83	CAP (immunocompromised [100%])	60[a]	131	28	Helmet noninvasive ventilation (n = 44)	Face mask noninvasive ventilation (n = 39)	Death, intubation	ICU discharge, hospital discharge

(continued)

Table. Main Characteristics of Included Studies (continued)

Source	Funding	Total No. of patients	Main reason for hypoxemic respiratory failure (main baseline risk factor)	Age, mean, y	Pa_{O_2}:F_{IO_2} ratio	Respiratory rate, /min	Main exposure	Comparator	Outcomes of interest assessed	Timing of measurement for study outcomes
Squadrone et al,[47] 2005	Università di Torino	209	Mixed ARF (abdominal surgery [100%]; solid organ transplant [14%]; cancer [62%])	66	251	NA	Helmet noninvasive ventilation (n = 105)	Standard oxygen (n = 104)	Death, intubation	7 days, ICU discharge, hospital discharge
Squadrone et al,[48] 2010	Regione Piemonte (CEP AN RAN 07) and Ministero dell'Università (PRIN RANI 07)	40	Mixed ARF (hematologic malignancies [100%])	49	269	30	Helmet noninvasive ventilation (n = 20)	Standard oxygen (n = 20)	Death, intubation	ICU discharge, hospital discharge, 90 days
Wermke et al,[49] 2012	Undisclosed	86	CAP (immunocompromised [100%])	52[a]	270	NA	Face mask noninvasive ventilation (n = 42)	Standard oxygen (n = 44)	Death, intubation	ICU discharge, 100 days
Wysocki et al,[50] 1995	Undisclosed	41	CAP (CHF [30%])	63	207	35	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 20)	Death, intubation	ICU discharge
Zhan et al,[51] 2012	Beijing Municipal Science and Technology Commission Program	40	ALI (immunocompromised [30%])	46	230	20	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 19)	Death, intubation	ICU discharge, hospital discharge

Abbreviations: ALI, acute lung injury; ARF, acute respiratory failure; CAP, community-acquired pneumonia; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; F_{IO_2}, fraction of inspired oxygen; ICU, intensive care unit; NA, not available; Pa_{O_2}, partial pressure of arterial oxygen.

[a] Age was reported as median.

[b] No patients died or were intubated (ie, no events were available for analysis).

ventilation, followed by face mask noninvasive ventilation, high-flow nasal oxygen, and standard oxygen therapy (eFigure 4 in the Supplement). eTable 2 in the Supplement summarizes the evidence grading for all comparisons (direct, indirect, and network estimates) and for both study outcomes.

Noninvasive Oxygenation Strategies and Risk of Endotracheal Intubation

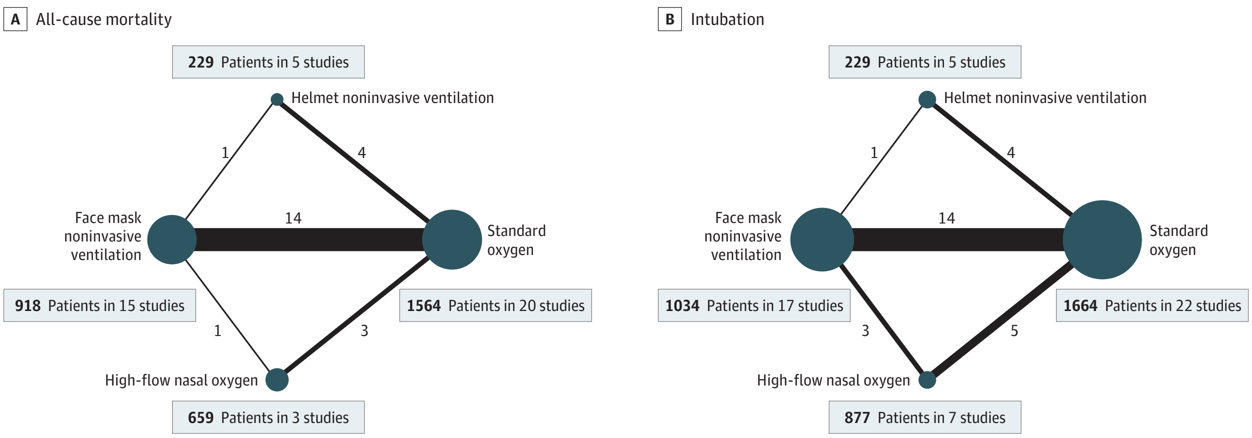
Twenty-five RCTs (3804 patients) were included in the analysis of endotracheal intubation, of which 1 RCT (47 patients) did not report any intubation events in any of the treatment groups.[37] All studies were unblinded for this outcome, and the risk of bias for this outcome was assessed as high due to potential cointerventions and variable criteria for endotracheal intubation between groups. The overall risk of bias assessed across all domains was deemed to be high for 7 (28%) and unclear for 18 (72%) of the 25 trials included (eTable 3 in the Supplement).

Helmet noninvasive ventilation (RR, 0.26 [95% CrI, 0.14-0.46]; absolute risk difference, −0.32 [95% CrI, −0.60 to −0.16]; low certainty), face mask noninvasive ventilation (RR, 0.76 [95% CrI, 0.62-0.90]; absolute risk difference, −0.12 [95% CrI, −0.25 to −0.05]; moderate certainty), and high-flow nasal oxygen (RR, 0.76 [95% CrI, 0.55-0.99]; absolute risk difference, −0.11 [95% CrI, −0.27 to −0.01]; moderate certainty) were associated with a lower risk of endotracheal intubation compared with standard oxygen therapy (Figure 3B and eFigure 5 in the Supplement). Helmet noninvasive ventilation was associated with decreased risk of endotracheal intubation compared with high-flow nasal (RR, 0.35 [95% CrI, 0.18-0.66]; absolute risk difference, −0.20 [95% CrI, −0.43 to −0.08]; low certainty) and face mask noninvasive ventilation (RR, 0.35 [95% CrI, 0.19-0.61]; absolute risk difference, −0.20 [95% CrI, −0.40 to −0.09]; low certainty). No significant difference was observed for the association with endotracheal intubation when comparing face mask noninvasive ventilation and high-flow nasal oxygen (RR, 1.01 [95% CrI, 0.74-1.38]; absolute risk difference, −0.00 [95% CrI, −0.13 to 0.10]; low certainty). There was incoherence between the direct and indirect RRs for the comparison of face mask noninvasive ventilation vs high-flow nasal oxygen (eFigure 6 in the Supplement). A post hoc sensitivity analysis demonstrated that the incoherence was eliminated when studies that included patients with chronic obstructive pulmonary disease and congestive heart failure and the study by Frat et al[7] were excluded (eFigure 7 in the Supplement). The probability of being best in reducing risk of endotracheal intubation was highest for helmet noninvasive ventilation, followed by face mask noninvasive ventilation, high-flow nasal oxygen, and standard oxygen therapy (eFigure 8 in the Supplement). Model fit and convergence characteristics are shown in eFigures 9 and 10 and eTable 4 in the Supplement.

Additional Secondary Outcomes

Median intensive care unit and hospital lengths of stay for different noninvasive strategies are presented in eTable 5 in the Supplement; no significant differences were evident between groups. Meaningful results for prespecified secondary outcomes of patient comfort (reported in only 28% of

Figure 2. Network Plots for the Association of Noninvasive Oxygenation Strategies With All-Cause Mortality and Intubation



Network geometry shows nodes as interventions and each head-to-head direct comparison as lines connecting these nodes. There is no direct comparison between high-flow nasal oxygen and helmet noninvasive ventilation for any of the study outcomes. The size of the nodes is proportional to the number of participants in each node. The thickness of the connecting line is proportional to the number of randomized clinical trials in each comparison. Both network plots include 1 study (n = 47) that did not report any event of death or intubation and 1 three-group study (face mask noninvasive ventilation, high-flow nasal oxygen, and standard oxygen therapy). Therefore, the total number of comparisons is higher than the number of randomized clinical trials for each outcome. Patients may be included in multiple comparisons, and this is accounted within the bayesian model and does not mean participants are duplicated.

studies) and dyspnea score (reported in only 16% of studies) could not be generated because insufficient information for all network comparisons was available. In addition, 6-month mortality was available in only 1 study.[8]

Sensitivity Analyses

For the primary outcome, the observed association between face mask noninvasive ventilation and reduced risk of mortality was no longer significant when considering studies that included only patients with more severe respiratory failure (mean PaO_2:FIO_2 ratio <200), when using noninformative priors for heterogeneity, and after excluding studies that enrolled any patients with chronic obstructive pulmonary disease, with congestive heart failure, or who were in the postoperative period (eTable 6 in the Supplement). However, the association of helmet ventilation with a lower risk of mortality remained significant across all sensitivity analyses. For the secondary outcome, all noninvasive ventilation strategies remained significantly associated with reduced risk of intubation across multiple sensitivity analyses when compared with standard oxygen therapy. Finally, the analyses restricted to studies with low risk of bias yielded results similar to the main analysis for all comparisons (eTables 6 and 7 in the Supplement).

The overall results were robust when the analyses considered moderately optimistic priors that high-flow nasal oxygen would be associated with benefit and skeptical priors that face mask ventilation would be associated with harm. In these analyses, helmet noninvasive ventilation remained associated with a lower risk of endotracheal intubation and all-cause mortality compared with standard oxygen therapy. However, face mask noninvasive ventilation was no longer associated with a lower risk of intubation compared with standard oxygen therapy (eTables 8 and 9 in the Supplement).

Discussion

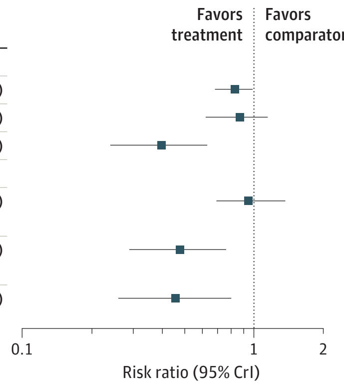
In this network meta-analysis of trials of adults with acute hypoxemic respiratory failure, treatment with noninvasive oxygenation strategies compared with standard oxygenation therapy was associated with a lower risk of death, the primary outcome, and endotracheal intubation, a secondary outcome.

The results of this study exhibit the potential benefit of delivering noninvasive ventilation using a helmet interface to patients with acute hypoxemic respiratory failure, although the low certainty should be considered when interpreting these results. These findings are consistent with a recent systematic review and traditional pairwise meta-analysis that showed that use of helmet noninvasive ventilation was associated with decreased risk of intubation and mortality compared with other modalities.[13] However, in addition to not including indirect evidence, this previous study included both randomized and observational studies and included studies primary targeting patients with acute exacerbation of chronic obstructive pulmonary disease. The results of this network meta-analysis also raise the question of whether helmet noninvasive ventilation and face mask noninvasive ventilation should be considered distinct therapeutic interventions with potentially different physiological and clinical effects. Physiological studies have shown that the helmet interface decreases air leaks compared with the face mask interface; decreased air leaks may allow for more effective delivery of higher levels of positive end-expiratory pressure, potentially increasing alveolar recruitment and decreasing respiratory effort.[3,52-54] Patients with acute hypoxemic respiratory failure may also have better tolerance for a helmet interface compared with other strategies, minimizing interruptions in therapy.[11]

Figure 3. Forest Plots for the Association of Noninvasive Oxygenation Strategies With Study Outcomes

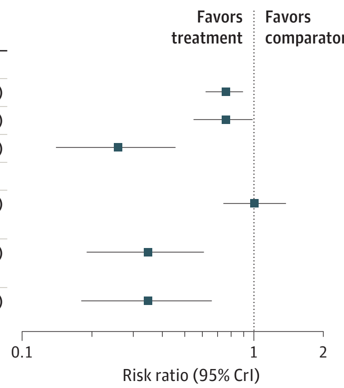
A All-cause mortality

	No. of patients	No. of trials	Quality	Absolute risk difference (95% CrI)	Network risk ratio (95% CrI)
Compared with standard oxygen					
Face mask noninvasive ventilation	1725	14	Moderate	-0.06 (-0.15 to -0.01)	0.83 (0.68-0.99)
High-flow nasal oxygen	1279	3	Moderate	-0.04 (-0.15 to 0.04)	0.87 (0.62-1.15)
Helmet noninvasive ventilation	330	3	Low	-0.19 (-0.37 to -0.09)	0.40 (0.24-0.63)
Additional comparisons					
Face mask noninvasive ventilation vs high-flow nasal oxygen	216	1	Low	-0.02 (-0.14 to 0.07)	0.95 (0.69-1.37)
Helmet noninvasive ventilation vs face mask noninvasive ventilation	83	1	Low	-0.13 (-0.27 to -0.05)	0.48 (0.29-0.76)
Helmet noninvasive ventilation vs high-flow nasal oxygen	0	0	Low	-0.15 (-0.34 to -0.05)	0.46 (0.26-0.80)



B Intubation

	No. of patients	No. of trials	Quality	Absolute risk difference (95% CrI)	Network risk ratio (95% CrI)
Compared with standard oxygen					
Face mask noninvasive ventilation	1725	14	Moderate	-0.12 (-0.25 to -0.05)	0.76 (0.62-0.90)
High-flow nasal oxygen	1479	5	Moderate	-0.11 (-0.27 to -0.01)	0.76 (0.55-0.99)
Helmet noninvasive ventilation	330	3	Low	-0.32 (-0.60 to -0.16)	0.26 (0.14-0.46)
Additional comparisons					
Face mask noninvasive ventilation vs high-flow nasal oxygen	450	3	Low	0.00 (-0.13 to 0.10)	1.01 (0.74-1.38)
Helmet noninvasive ventilation vs face mask noninvasive ventilation	83	1	Low	-0.20 (-0.40 to -0.09)	0.35 (0.19-0.61)
Helmet noninvasive ventilation vs high-flow nasal oxygen	0	0	Low	-0.20 (-0.43 to -0.08)	0.35 (0.18-0.66)



A, For the primary outcome, all-cause mortality, the longest follow-up was up to 90 days. B, For the secondary outcome, intubation, the longest follow-up was up to 30 days. All outcomes are reported as network risk ratios and absolute risk differences with 95% credible intervals (CrIs). The certainty for each network meta-analysis estimate was estimated based on the 4-step approach suggested by the GRADE Working Group. Initially, each direct and indirect comparison was rated independently using the GRADE approach (risk of bias, inconsistency, indirectness, imprecision), and these were used to rate the network estimate. In case of disagreement between the direct and indirect rating, the network estimate was assigned the higher rating. In the presence of incoherence, the network estimate was assigned the lower rating of the direct/indirect assessment. For estimating risk ratios for the comparison of helmet noninvasive ventilation vs high-flow nasal cannula, only indirect evidence was used because no direct pairwise comparisons were available. The estimated absolute risk of mortality and endotracheal intubation was 30% and 40%, respectively, in the standard oxygen group. Between-study heterogeneity was assessed by using the posterior distribution for τ, τ^2, and the I^2 statistic. For all-cause mortality, τ = 0.17 (95% CrI, 0.056-0.23), τ^2 = 0.0284 (95% CrI, 0.00317-0.0508), and I^2 = 12%. For endotracheal intubation, τ = 0.21 (95% CrI, 0.07-0.27), τ^2 = 0.0437 (95% CrI, 0.00554-0.0743), and I^2 = 15%.

The finding that face mask noninvasive ventilation was associated with a lower rate of overall mortality and endotracheal intubation when compared with standard oxygen therapy needs to be assessed in the context of the uncertainty existing in the literature and relatively small sample size of included studies. It is possible that this association is driven by inclusion of patients with acute hypoxemic respiratory failure who also have chronic obstructive pulmonary disease and/or congestive heart failure; face mask noninvasive ventilation has been demonstrated to be helpful in these situations.[21,55-59] In the sensitivity analyses excluding trials that included such patients, the association with decreased mortality was no longer observed.

Concerns regarding the safety of face mask noninvasive ventilation for patients with acute hypoxemic respiratory failure have been raised based on associations with increased mortality in large observational studies in patients with acute respiratory distress syndrome.[27,60] Clinicians who believe that face mask noninvasive ventilation may be harmful for acute hypoxemic respiratory failure might consider the sensitivity analysis using skeptical priors, in which face mask ventilation was no longer associated with a lower risk of intubation and mortality when compared with standard oxygen therapy and might even be associated with increased harm when compared with high-flow nasal oxygen therapy. Potential mechanisms for such harm include higher-than-targeted tidal volumes while patients breathe spontaneously, leading to high transpulmonary pressures and patient self-inflicted lung injury.[60,61] Although these potential harms might be especially important for face mask noninvasive ventilation, they may be common to all noninvasive oxygenation strategies, particularly by further delaying intubation and perpetuating lung injury in patients with high respiratory effort.[61-63] This might be especially relevant for more severely ill patients.

The association between noninvasive oxygenation strategies and lower mortality was less apparent in the sensitivity analysis restricted to patients with more severe hypoxemia. Additional considerations influencing decisions to use these therapies include familiarity with the specific noninvasive oxygenation strategy, perceived patient comfort, ease of deployment, and level of patient monitoring required.

The results of this study also showed a significant association with a lower risk of intubation but not mortality with the use of high-flow nasal oxygen when compared with standard oxygen therapy. These findings are consistent with other recent systematic reviews.[14,15] However, the sensitivity analysis using optimistic priors suggested there may still be a potential benefit of high-flow nasal oxygen in reducing mortality. Overall, these discordant conclusions reinforce the need for additional RCTs of high-flow nasal oxygen therapy to treat acute hypoxemic respiratory failure.

Limitations

This study has several limitations. First, an assumption of the network meta-analysis is that the individual trials enrolled similar populations and that the intervention protocols were also similar across different studies. The analyses demonstrated only minimal incoherence, specifically in the comparison of high-flow nasal oxygen vs face mask noninvasive ventilation, which could be partially explained by the influence of 1 large trial and the partial inclusion of patients with chronic obstructive pulmonary disease and congestive heart failure.[7] Trials that predominantly targeted patients with exacerbations of chronic obstructive pulmonary disease or congestive heart failure were excluded, but several trials in this network meta-analysis included some of these patients, potentially leading to an overestimation of the beneficial effect of noninvasive ventilation strategies for patients with acute hypoxemic respiratory failure.[6,39,44] However, the overall findings, in particular for endotracheal intubation, were consistent in sensitivity analyses that excluded these trials.

Second, aggregated study-level covariates to conduct this network meta-analysis were not included, and assessment of which patient-level characteristics were associated with an increased likelihood of response to any of these individual therapies could not be conducted.

Third, this study included patients with a range of severity of respiratory failure (based on baseline PaO_2:FIO_2 ratio), representing a source of potential intransitivity. However, the relative effects of interventions can remain consistent even in the case of different baseline risk of the outcomes.[64]

Fourth, although helmet noninvasive ventilation had a higher probability to be ranked first, these findings should be assessed with caution. The use of rank probabilities might seem intuitive for clinicians but does not consider the certainty of the evidence, which was deemed to be low for comparisons with helmet noninvasive ventilation. Indeed, the studies evaluating the effectiveness of this intervention were scarce and included a small number of participants when compared with other strategies.[29] Therefore, uncertainty remains about the effectiveness of this treatment.

Fifth, the primary studies included in this review have the important limitation of lack of blinding of treatment groups. Although this is unlikely to bias assessment of the primary outcome of all-cause mortality, it is possible that clinicians had different thresholds to provide endotracheal intubation to patients allocated to different treatment groups (eg, helmet noninvasive ventilation).

Sixth, another potential source of heterogeneity is that included studies reported different follow-up times for all-cause mortality. However, the sensitivity analyses that focused on mortality assessed at hospital or intensive care unit discharge yielded results similar to the main analysis.

Conclusions

In this network meta-analysis of trials of adults with acute hypoxemic respiratory failure, treatment with noninvasive oxygenation strategies compared with standard oxygen therapy was associated with lower risk of death. Further research is needed to better understand the relative benefits of each strategy.

ARTICLE INFORMATION

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