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Respiratory support strategy in adults with acute hypoxemic respiratory failure: a systematic review and network meta-analysis

Hiromu Okano^{1,2}, Masaaki Sakuraya^{3*}, Tomoyuki Masuyama⁴, Shunsuke Kimata⁵ and Satoshi Hokari⁶

Abstract

Introduction: Network meta-analyses (NMAs) of respiratory management strategies for acute hypoxemic respiratory failure (AHRF) have been reported, but no previous study has compared noninvasive ventilation (NIV), high-flow nasal oxygen (HFNO), standard oxygenation therapy (SOT), and invasive mechanical ventilation (IMV) for de novo AHRF. Therefore, we conducted an NMA to assess the effectiveness of these four respiratory strategies in patients with de novo AHRF.

Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Ichushi databases were searched. Studies including adults aged ≥ 18 years with AHRF and RCTs that compared two different oxygenation techniques (SOT, NIV, HFNO, or IMV) were selected. A frequentist-based approach with multivariate random-effects meta-analysis was used. The outcomes were mortality and intubation rates.

Results: Among the 14,263 records initially identified, 25 studies (3302 patients) were included. In the analysis of mortality, compared to SOT, NIV (risk ratio [RR], 0.76; 95% confidence interval [CI], 0.61–0.95) reduced mortality; however, IMV (RR, 1.01; 95% CI, 0.57–1.78) and HFNO (RR, 0.89; 95% CI, 0.66–1.20) did not. For assessments of the intubation incidence, compared to SOT, NIV use (RR, 0.63; 95% CI, 0.51–0.79) was associated with a reduction in intubation, but HFNO (RR, 0.82; 95% CI, 0.61–1.11) was not significant.

Conclusions: Our NMA demonstrated that only NIV showed clinical benefits compared with SOT as an initial respiratory strategy for de novo AHRF. Further investigation, especially comparison with HFNO, is warranted.

Trial registration: PROSPERO (registration number: [CRD42020213948](https://www.crd.org/CRD42020213948), 11/11/2020).

Keywords: Noninvasive ventilation, High-flow nasal oxygen, Acute hypoxemic respiratory failure, Network meta-analysis

Background

Acute hypoxemic respiratory failure (AHRF) is frequently found in critically ill patients and associated with poor outcomes. Noninvasive respiratory strategies, including noninvasive ventilation (NIV) and high-flow nasal oxygen (HFNO), have been investigated as

an initial respiratory support for patients with AHRF. NIV is recommended to reduce the risk of endotracheal intubation and mortality in patients with AHRF due to cardiopulmonary edema [1]. However, the efficacy of NIV has not been consistent among patients with AHRF because it can occur due to various factors. De novo AHRF is defined as significant hypoxemia in the absence of chronic lung disease and excluding respiratory failure occurring in the immediate postoperative or post-extubation period [2]. Recent clinical practice guidelines do not recommend NIV but HFNO for

*Correspondence: masaaki.sakuraya@gmail.com

³ Department of Emergency and Intensive Care Medicine, JA Hiroshima General Hospital, 1-3-3 Jigozen, Hatsukaichi-City, Hiroshima 738-8503, Japan

Full list of author information is available at the end of the article

patients with de novo AHREF, based on the evidence compared with standard oxygen therapy (SOT) [3, 4].

Acute respiratory distress syndrome (ARDS) is a major cause of de novo AHREF. As an initial management among noninvasive and invasive respiratory strategies, NIV is recommended for patients with mild ARDS [5]. In the post hoc analysis of the LUNG SAFE study, NIV was used in ARDS patients (15%) [6]. In contrast, HFNO is preferred to manage de novo AHREF patients with novel coronavirus disease 2019 (COVID-19), compared with SOT and NIV [7]. HFNO has also gained attention as an initial respiratory management, compared with early initiation of invasive mechanical ventilation (IMV) [8]. Thus, noninvasive respiratory strategies are commonly used to manage patients with de novo AHREF, despite inconclusive evidence.

Although noninvasive respiratory strategies are expected to improve clinical outcomes by avoiding endotracheal intubation and its adverse events [9], treatment failure and delayed intubation contribute to poor outcomes [6, 10–12]. No meta-analyses have been reported to compare noninvasive respiratory strategies with IMV in patients with AHREF. It is warranted to clarify which noninvasive respiratory strategy is effective in avoiding endotracheal intubation and to evaluate the efficacy in reducing mortality for patients with de novo AHREF as an initial respiratory strategy, compared with SOT and IMV. Therefore, we conducted a network meta-analysis (NMA) to compare the four respiratory strategies (NIV, HFNO, SOT, and IMV) as an initial strategy in adult patients with de novo AHREF.

Research question

Which is the most effective respiratory strategy among NIV, HFNO, SOT, and IMV in patients with de novo AHREF?

Methods

Protocol and registration

This systematic review was conducted in accordance with the methods recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 guidelines [13]. The protocol has been registered in PROSPERO, a prospective international register of systematic reviews of the National Institute for Health Research and Center for Reviews and Dissemination at the University of York (<http://www.crd.york.ac.uk/PROSPERO/>; registration no. CRD42020213948, on 11/11/2020).

Inclusion criteria

Types of studies

We included randomized controlled trials (RCTs) that compared two of the following four methods:

SOT (low-flow nasal cannula, facemask, and venturi mask with limitless flow rate) and NIV (mask type, ventilation duration, management during the interval, and methods of weaning were not limited). Additionally, studies were selected regardless of the mode, i.e., continuous positive airway pressure or pressure support ventilation, HFNO (the flow rate and fraction of inspired oxygen were not limited), and IMV (mechanical ventilation via endotracheal intubation, not tracheostomy).

Types of outcomes

The outcome measures included a primary outcome of short-term mortality at the end of the follow-up period (≤ 100 days). The secondary outcomes included incidence of intubation during intensive care unit (ICU) stay, ventilator-free days, and adverse events reported as any critical events by the authors of each study.

Types of patients

We included patients aged >18 years who had acute respiratory failure defined by new-onset (<7 days) of clinical signs (e.g., tachypnea, increased work of breathing), radiologic signs (unilateral or bilateral chest radiograph opacities), and hypoxemia. Hypoxemia was defined as the ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) below 300, $\text{SaO}_2/\text{SpO}_2 <94\%$ at and $\text{PaO}_2 <60$ mmHg at room air or <80 mmHg with O_2 . We considered studies that included patients treated in the ICU, intermediate care unit, and emergency department.

Exclusion criteria

Types of studies

Randomized crossover trials, cluster-randomized trials, and quasi-experimental trials were excluded.

Types of patients

We excluded patients who met the following criteria: hypercapnia ($\text{PaCO}_2 >50$ mmHg), with congestive heart failure, chronic obstructive pulmonary disease (COPD), or asthma as the cause of respiratory failure, post-extubation respiratory failure, post-surgical, and post-trauma constituting $>50\%$ of the study population; had not provided informed consent and had provided do-not-resuscitate orders; and had undergone interventions limited to the emergency department or pre-hospital care.

Search strategy

Databases used for the search were PubMed (Supplemental e-Table 1 a), Cochrane Central Register of Controlled Trials (CENTRAL; Supplemental e-Table 1 b), EMBASE (Supplemental e-Table 1 c), and Ichushi, a database of Japanese papers (Supplemental e-Table 1 d). The languages in which the studies were conducted were restricted to English and Japanese. A literature search was performed from the database inception up to June 22, 2020. A literature search was also performed from the inception of the database up to May 30, 2021. This systematic review was conducted for clinical practice guidelines for the ARDS management in Japan, and we included articles in English and Japanese only.

Selection of the studies and data extraction

At the first screening, two of the three physicians (HO, SK, and SH) analyzed the title and abstract. At the second screening, the full text of the relevant studies was studied, and data were extracted independently from the included studies onto the standardized data-recording forms. Disagreements were resolved by discussing with one of the three physicians not involved in screening the studies. We also asked the original authors for additional details when necessary. For example, we contacted the authors if only abstracts were available, and the information was insufficient to determine whether the study met our review criteria. In cases involving discrepancies between the two reviewers, an agreement was reached through discussion or by including a third reviewer, if necessary.

We extracted the following study characteristics: methods (design, total duration, number and locations, setting, withdrawals, and date of the study); participants (number, mean age, age range, sex, the severity of the condition, diagnostic criteria, and inclusion and exclusion criteria), interventions (intervention and comparison methods), and outcomes (specified and collected primary and secondary outcomes, and time points reported).

Quality assessment

Risk of bias within individual studies

The risk of bias of outcomes in the included studies was assessed independently by two of the five authors (HO, TM, SH, SK, and MS) using a modified version of the Cochrane “Risk of Bias” instrument [14]. They assessed the overall risk of bias as the worst in any of the following domains: from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported results. The risk of each bias was graded as “low risk of bias,” “some concerns,” or “high risk of bias.”

Discrepancies between two reviewers were resolved through discussion among themselves or with a third reviewer, as necessary.

Planned methods of analyses

Direct comparison meta-analysis

A pair-wise meta-analysis was performed using Review Manager (RevMan) 5.3 (RevMan 2014) [15]. Forest plots were used for the meta-analysis, and the effect size was expressed as risk ratio (RRs) with 95% confidence intervals (CIs) for the categorical data. The outcome measures were pooled using a random-effects model for the measure of study-specific effects. For all the analyses, a two-sided P value <0.05 was considered to be statistically significant.

Network comparison meta-analysis

Data synthesis An NMA was performed using a frequentist approach with Confidence in Network Meta-Analysis (CINeMA) [16]. The network RR was estimated based on both direct and indirect comparisons. We constructed forest plots of the RRs with 95% CIs for each treatment strategy in the network.

Ranking Ranking plots (rankograms) were constructed based on the probability that a given treatment had the highest event rate for each outcome. The surface under the cumulative ranking curve (SUCRA), which is a simple transformation of the mean rank, was used to determine the treatment hierarchy [17]. Higher values of the SUCRA statistic, which range from 0 to 100%, increase the likelihood that a therapy is ranked amongst the best in an NMA [18]. We performed ranking analysis using the `mvmeta` command in Stata 15.1 (StataCorp LLC, College Station, TX, USA).

Assessment of inconsistency

Study heterogeneity among trials for each outcome was assessed by inspecting the forest plots visually and using the I^2 statistic to quantify any inconsistencies [19]. Publication bias was assessed visually using a funnel plot [18]. Coherence in NMA referred to consistency in the estimates of treatment effects between direct and indirect comparisons [20]. For each pair-wise comparison, we assessed the global inconsistency test with a fitting design-by-treatment model was used to identify the disagreement between the direct and indirect estimates as a measure of inconsistency [21]. The transitivity assumption was evaluated by comparing the distribution of potential effect modifiers across treatment comparisons [22]. We used a side-splitting approach as a local method

and the design-by-treatment model as a global method to detect inconsistency in the network [23]. We also estimated the prediction intervals in the results to express the impact of the common heterogeneity assumed across comparisons.

The certainty of evidence for each network comparison

The certainty of the network estimates of the primary outcomes was assessed using the framework of CINeMA. The CINeMA approach is based on the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) framework, which covers six domains of the certainty of evidence: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity, and inconsistency [24].

Sensitivity analysis

The effect of NIV varies depending on the severity of hypoxemia [5]. Sensitivity analyses, which excluded patients with mild hypoxemia (mean P/F ratio ≥ 200) and type II respiratory failure, were conducted to assess the heterogeneity of clinical study participants and interventions. We also performed a sensitivity analysis; studies that reported long-term mortality (≥ 2 -month mortality) were excluded.

Difference between protocol and review

Differences between the protocol and studies included in this review were noted. In the protocol, short-term mortality was defined as within 90 days, but among the included studies, we found a study that reported 100-day mortality. Therefore, the definition of mortality was changed from within 90 to 100 days because we thought that increasing the sample size would improve the accuracy of the study. In addition, we performed a post-hoc sensitivity analysis for short-term mortality according to the follow-up period, given that a wider follow-up period range might contribute to inconsistency.

Results

Study selection

We searched 14,263 records (Fig. 1). After the study selection process, 25 studies [12, 25–48] were included in this NMA. The network structures for short-term mortality and intubation are shown in Fig. 2a, b, respectively.

Study characteristics

The characteristics of each study included in the final dataset of the meta-analysis are summarized in Table 1. Quantitative analysis included 3302 patients. Five trials compared HFNO with SOT [25, 40, 43, 45, 46], fourteen compared NIV with SOT [27–38, 41, 44], three compared NIV with IMV [26, 42, 47], two compared NIV

with HFNO [39, 48], and one compared NIV with HFNO and SOT [12].

Risk of bias within studies

Supplementary e-Table 2 shows the data for the risk of bias; 19 studies are judged to have some biased concerns.

Network meta-analysis

We performed network meta-analyses for mortality and intubation, but not for ventilator-free days and adverse events due to few included studies. The results of pairwise comparisons are shown in Supplementary e-Figures 1 (for mortality), 2 (for intubation), and 3 (for ventilator-associated lung injury). Publication bias was not detected considering the results of the funnel plots (Supplementary e-Fig. 4).

Risk of short-term mortality

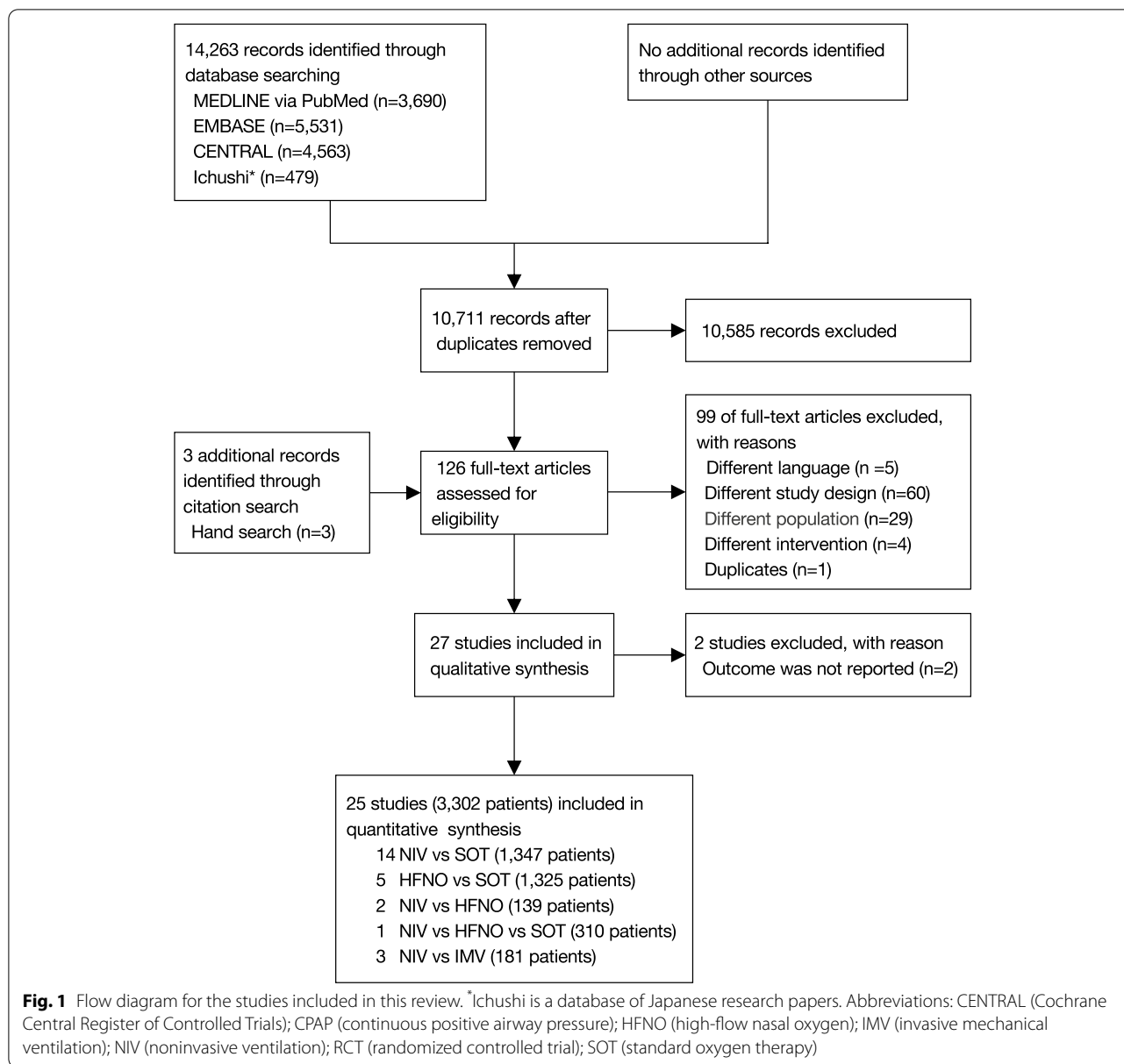
In the current analysis for mortality (including 3169 patients across 23 studies), compared to SOT, NIV (RR, 0.76; 95% CI, 0.61–0.95; low certainty) reduced mortality (Fig. 3a). However, IMV (RR, 1.01; 95% CI, 0.57–1.78; very low certainty) and HFNO (RR, 0.89; 95% CI, 0.66–1.20; low certainty) did not reduce mortality. Compared to IMV, HFNO (RR, 0.89; 95% CI, 0.47–1.65; very low certainty) and NIV (RR, 0.76; 95% CI, 0.45–1.27; very low certainty) showed no decrease in mortality risk. The confidence assessment in the RR of each comparison is shown in Table 2.

The ranking analysis revealed that the hierarchy for efficacy in reducing mortality was NIV (SUCRA 87.5), followed by HFNO (SUCRA 54.1), IMV (SUCRA 33.5), and finally, SOT (SUCRA 25.0) (Fig. 4a). As per the results of the current NMA for short-term mortality, we demonstrate the SoF table (Table 3).

Risk of endotracheal intubation

Twenty-two studies (3118 patients) were included in the analysis for intubation. In comparison with SOT, HFNO (RR, 0.89; 95% CI, 0.61–1.11; moderate certainty) was not associated with a statistically significant lower risk of endotracheal intubation. NIV (RR, 0.63; 95% CI, 0.51–0.79; low certainty) was associated with statistically significant lower risks of endotracheal intubation (Fig. 3b), while no significant difference was observed between NIV and HFNO use in terms of the risk of intubation (RR, 0.77; 95% CI, 0.56–1.06; moderate certainty). The confidence assessment in the RR of each comparison is shown in Table 2.

The ranking analysis revealed that the hierarchy for efficacy in reducing intubation was NIV (SUCRA 96.6),



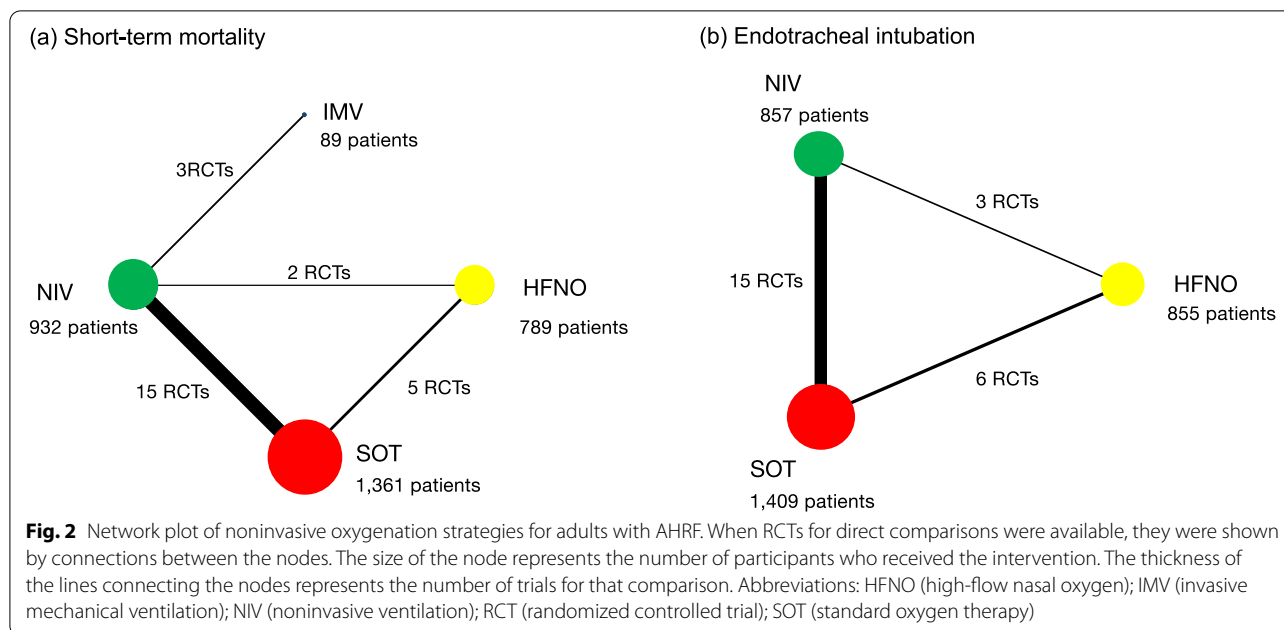
followed by HFNO (SUCRA 47.7), and ultimately SOT (SUCRA 5.6) (Fig. 4b).

Other outcomes

For ventilator-free days, an NMA was not conducted because only one trial reported this outcome [12]. Results of the pairwise meta-analysis demonstrated that the incidence of ventilator-associated lung injury was not different between NIV and SOT (RR, 1.38; 95% CI, 0.22–8.54, Supplementary e-Fig. 3). We did not perform a meta-analysis for adverse events, since we did not find any adverse events that were consistently increasing in noninvasive respiratory strategies.

Sensitivity analysis

As per the results of the sensitivity analyses compared with SOT, the tendency to reduce the risk of mortality was observed when excluded studies involved patients with mild hypoxemia, although not significant (Supplementary e-Table 3) [12, 25, 26, 29–32, 34, 36, 41, 42, 45, 47, 48]. When studies involving patients with hypercapnia were excluded [12, 26–28, 30, 31, 34–36, 38, 42, 44, 46–48], NIV decreased the risk of mortality, when compared with SOT (Supplementary e-Table 4). For intubation, NIV demonstrated the efficacy in these pre-planned analyses, in contrast, HFNO and IMV were effective in neither analysis. In a post hoc sensitivity analysis



excluding studies that reported long-term mortality outcomes (60 days [48], 2 months [29], 90 days [12, 25, 43], and 100 days [37]), NIV decreased the risk of mortality compared with SOT (Supplementary e-Table 5).

Discussion

In the current NMA of trials among adults with AHRE, in comparison with SOT, NIV was associated with a lower risk of mortality and intubation. Ranking analyses showed that NIV was the best strategy for reducing both outcomes. However, as compared to IMV, NIV and HFNO did not decrease mortality. The results of the sensitivity analyses were similar to those of the main analysis, and the efficacy of NIV was similar in almost all the sensitivity analyses. This NMA is the fourth study to evaluate the effectiveness of NIV and HFNO in patients with ARE. The novelty of our NMA is that we compared noninvasive oxygenation strategies with SOT and IMV.

Comparison with SOT

Our results were similar to those of previous systematic reviews using NMA [49] but different from those of other NMAs [2, 50]. These differences could be attributed to differences in the study inclusion criteria and, consequently, the studies included in the previous NMAs [2, 49, 50].

Ferreyro et al. [49] reported an NMA describing the effects of noninvasive oxygenation strategies. They showed that treatment with NIV was associated with a lower risk of mortality and intubation, and HFNO decreased the risk of intubation compared to SOT. Their

NMA included patients with postoperative respiratory failure or chest trauma. These patients showed various causes of respiratory failure, including atelectasis due to poor pain control, chest wall and lung injury, and pleural effusion. In contrast, we excluded some trials to assess the efficacy of noninvasive oxygenation strategies in patients with AHRE.

Yasuda et al. [50] reported an NMA evaluating the effects of noninvasive oxygenation strategies, and they concluded that NIV and HFNO were associated with a lower risk of endotracheal intubation; however, they observed no significant differences in short-term mortality. Although their study was similar to our study for assessing the efficacy of noninvasive respiratory strategies in patients with de novo AHRE, Yasuda et al. [50] included patients who not only had de novo AHRE but also cardiogenic pulmonary edema, which is an established indication for NIV. Since there was insufficient number of RCTs comparing noninvasive respiratory strategies in only patients with de novo AHRE, we excluded studies in which >50% of patients had acute respiratory failure caused by cardiogenic pulmonary edema. Although pulmonary edema is one of the major causes of AHRE, determining whether it is due to increased hydrostatic pressure or increased permeability is challenging in clinical practice; we included a certain number of patients with heart failure. Thus, our inclusion criteria may be more acceptable in clinical practice.

In the NMA conducted by Zayed et al. [2], RCTs that exclusively enrolled subjects with COPD and cardiogenic pulmonary edema were excluded. Their study seemed

Table 1 Summary of the characteristics of the studies included in the network meta-analysis

| Source | Total no. of patients | Main reason for hypoxemic respiratory failure (main baseline risk factor) | Main exposure | Comparator | P/F ratio (mean) | Outcomes of interest assessed |
|-------------------------------|-----------------------|---|----------------|--------------------------------|------------------|-------------------------------|
| Wysocki [27] 1995 | 41 | Mixed AHRF (CAP 39.0%, CPE 34.1%) | NIV (n = 21) | SOT (n = 20) | 207 | Mortality, intubation |
| Antolnelli [26] 1998 | 64 | Mixed AHRF (CPE 19%, atelectasis 25%) | NIV (n = 32) | IMV (n=32) | 120 | Mortality |
| Confalonieri [29] 1999 | 56 | CAP | NIV (n = 28) | SOT (n = 28) | 175 | Mortality, intubation |
| Antonelli [28] 2000 | 40 | Mixed AHRF (ARDS 37.5%, atelectasis 25%) | NIV (n = 20) | SOT (n = 20) | NA | Mortality, intubation |
| Delcaux [30] 2000 | 123 | Mixed AHRF (CAP 54.5%) | NIV (n = 62) | SOT (n = 61) | 144 | Mortality, intubation |
| Martin [32] 2000 | 61 | Mixed AHRF (COPD 38%) | NIV (n = 32) | SOT (n = 29) | 199 | Mortality, intubation |
| Hilbert [31] 2001 | 52 | CAP in immunocompromised patients | NIV (n = 26) | SOT (n = 26) | 139 | Mortality, intubation |
| Ferrer [34] 2003 | 105 | Mixed AHRF (CAP 32.4%, CPE 28.6%) | NIV (n = 51) | SOT (n = 54) | 103 | Mortality, intubation |
| Cosentini [33] 2010 | 47 | CAP | NIV (n = 20) | SOT (n = 27) | 248 | Mortality, intubation |
| Squadrone [35] 2010 | 40 | Mixed AHRF in immunocompromised patients | NIV (n = 20) | SOT (n = 20) | 269 | Mortality, intubation |
| Wermke [37] 2012 | 86 | CAP in immunocompromised patients | NIV (n = 42) | SOT (n = 44) | 270 | Mortality, intubation |
| Zhan [38] 2012 | 40 | ALI (immunocompromised 30%) | NIV (n = 21) | SOT (n = 19) | 230 | Mortality, intubation |
| Brambilla [36] 2014 | 81 | CAP (immunocompromised 32%) | NIV (n = 40) | SOT (n = 41) | 141 | Mortality, intubation |
| Azevedo [39] 2015 | 30 | CPE (43.3%), CAP (33.3%) | NIV (n=16) | HFNO (n=14) | NA | Intubation |
| Frat [12] 2015 | 310 | Mixed ARF (CAP 63.5%) | NIV (n = 110) | HFNO (n = 106) SOT (n = 94) | 155 | Mortality, intubation |
| Lamiale [40] 2015 | 100 | Mixed AHRF in immunocompromised patients (sepsis related 50%) | HFNO (n = 52) | SOT (n = 48) | 114 | Intubation |
| Lemiale [41] 2015 | 374 | Pneumonia in immunocompromised patients | NIV (n = 191) | SOT (n = 183) | 142 | Mortality, intubation |
| Jones [43] 2016 | 303 | Mixed AHRF (COPD 23.9%, Pneumonia 23.8%) | HFNO (n = 165) | SOT (n = 138) | NA | Mortality, intubation |
| Muncharaz [42] 2017 | 65 | Mixed AHRF (CAP 63.1%) | NIV (n = 34) | IMV (n = 31) | 97 | Mortality |
| Azoulay [25] 2018 | 776 | Mixed AHRF in immunocompromised patients (Pneumonia 53.0%) | HFNO (n = 388) | SOT (n = 388) | 132 | Mortality, intubation |
| He [44] 2019 | 200 | CAP | NIV (n = 102) | SOT (n = 98) | 231 | Mortality, intubation |
| Andino [45] 2020 | 46 | Mixed AHRF (CAP 30%) | HFNO (n = 24) | SOT(n=22) | 96 | Mortality, intubation |
| Alptekinoglu Mendil [46] 2021 | 100 | Mixed AHRF (pneumonia 74%) | HFNO (n = 51) | SOT(n=49) | 262 | Mortality, intubation |
| Awadallah [47] 2021 | 52 | ARDS | NIV (n = 26) | IMV (n = 26) | 95 | Mortality |
| Grieco [48] 2021 | 109 | AHRF in COVID-19 patients | NIV (n = 54) | HFNO (n = 55) | 102 | Mortality, intubation |

AHRF acute hypoxemic respiratory failure, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *ARF* acute respiratory failure, *CAP* community-acquired pneumonia, *COPD* chronic obstructive pulmonary disease, *CPE* cardiopulmonary edema, *HFNO* high-flow nasal oxygen, *IMV* invasive mechanical ventilation, *NA* not available, *NIV* noninvasive ventilation, *P/F* ratio ratio of arterial oxygen partial pressure to fractional inspired oxygen, *SOT* standard oxygen therapy

to have a higher percentage of de novo AHRF cases. Their NMA demonstrated that NIV was associated with a significant reduction in intubation rates but not mortality as compared with SOT. Furthermore, HFNO was not effective for both outcomes, similar to our results.

Considering the results from previous NMAs, our findings imply that the effects of noninvasive respiratory strategies were not robust because the point estimates and confidence intervals varied with differences in the inclusion criteria.

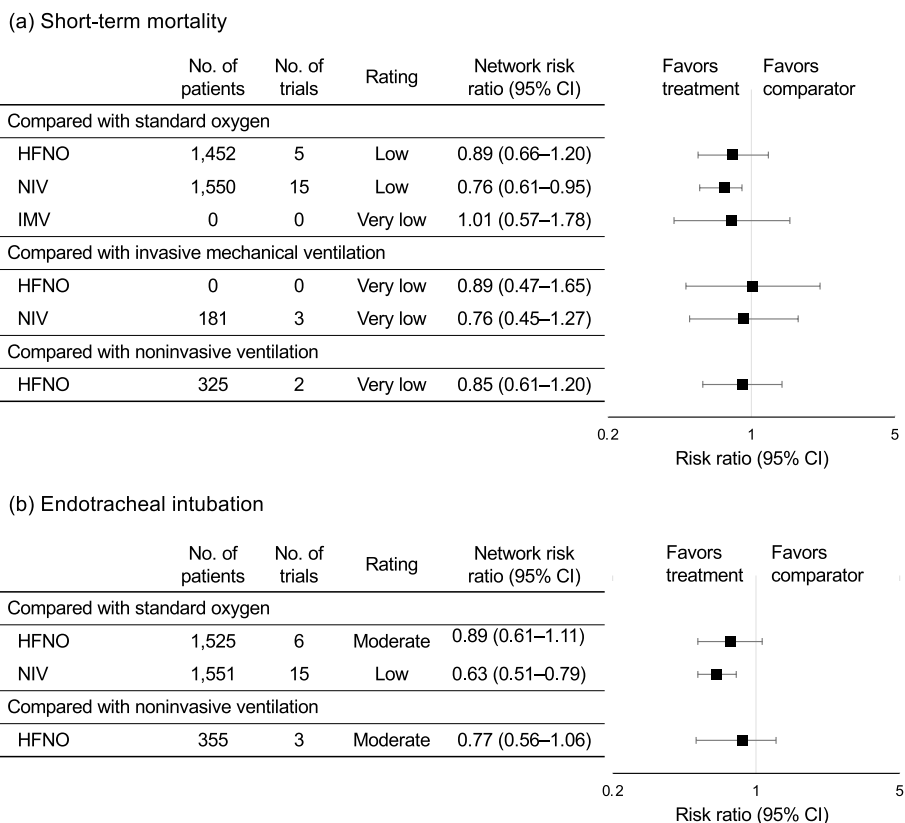


Fig. 3 Forest plots for the association of noninvasive oxygenation strategies with study outcomes. **a** For the primary outcome, short-term mortality. **b** For the secondary outcome, endotracheal intubation, all outcomes were reported as network risk ratios and absolute risk differences with 95% confidence intervals (CIs). Risk ratios were estimated for the comparisons of HFNO vs. SOT, NIV vs. SOT, IMV vs. SOT, HFNO vs. IMV, NIV vs. IMV, and HFNO vs. NIV. Abbreviations: CI (confidence interval), HFNO (high-flow nasal oxygen), IMV (invasive mechanical ventilation), NIV (noninvasive ventilation), RR (risk ratio), and SOT (standard oxygen therapy)

Comparison with IMV

Another crucial difference between our NMA and the previous NMAs is the comparison of noninvasive respiratory strategies with not only SOT but also IMV. For a healthy lung, spontaneous breathing is associated with improved oxygenation through alveolar recruitment, whereas inspiratory effort in an impaired lung is known to cause patient self-inflicted lung injury (P-SILI) [51]. Since maintaining the tidal volume and inspiratory effort within the appropriate ranges is often difficult during NIV, we should be careful to P-SILI [52]. The post hoc analysis of the LUNG SAFE Trial [6] has reported that severer hypoxemia was a risk for NIV failure among patients with ARDS. In our trial, NIV did not reduce mortality as compared with IMV which was not considered to be lung-protective ventilation. Because excessive tidal volume was reported to be associated with NIV failure in patients with AHRF [53], we should not hesitate to initiate lung protective ventilation via endotracheal intubation if patients are at risk for P-SLI.

Comparison of noninvasive respiratory support strategies

An RCT evaluating NIV, HFNO, and SOT among patients with de novo AHRF demonstrated that HFNO reduced short-term mortality, although intubation rates were not different [12]. Based on these results, HFNO is preferred for patients with de novo AHRF. However, similar to the results of previous NMAs, our NMA did not show significant differences in the comparison of noninvasive respiratory support strategies [2, 49, 50]. Assigning superiority to these noninvasive devices is also difficult, considering the physiological effects as NIV can provide high positive end-expiratory pressures but may increase dead space ventilation. In an RCT comparing noninvasive respiratory support strategies with SOT [54], NIV use reduced the incidence of intubation, but not mortality, possibly because the prolonged time to intubation weakened the positive effects of avoiding intubation. Both noninvasive respiratory support strategies may contribute to delayed intubation and worsened lung injury [55]. It is necessary to assess these strategies with standardized intubation strategies.

Table 2 Confidence assessment in the risk ratio of each comparison and outcome

| | Risk of bias across studies | Imprecision | Heterogeneity | Indirectness | Publication bias | Incoherence | Confidence in relative risk of the event |
|--------------------------------|-----------------------------|---|---|--------------|------------------|--|--|
| Short-term mortality | | | | | | | |
| HFNO vs SOT | Undetected | Major concerns ^(a) 95% CI (0.66–1.20) | No concerns 95% PI (0.47–1.70) | Low | Not suggested | Some concerns <i>P</i> =0.07* | Low |
| NIV vs SOT | Undetected | No concern 95% CI (0.61–0.95) | Major concerns ^(b) 95% PI (0.42–1.39) | Low | Not suggested | No concerns <i>P</i> =0.05* | Low |
| IMV vs SOT | Undetected | Major concerns ^(a) 95% CI (0.57–1.78) | No concerns 95% PI (0.45–2.29) | Low | Not suggested | Major concerns ^(c) <i>P</i> = 0.01** | Very low |
| HFNO vs IMV | Undetected | Major concerns ^(a) 95% CI (0.47–1.65) | No concerns 95% PI (0.37–2.10) | Low | Not suggested | Major concerns ^(c) <i>P</i> =0.01** | Very low |
| NIV vs IMV | Undetected | Major concerns ^(a) 95% CI (0.45–1.27) | No concerns 95% PI (0.34–1.65) | Low | Not suggested | Major concern ^(c) <i>P</i> = 0.01** | Very low |
| NIV vs HFNO | Undetected | Major concerns ^(a) 95% CI (0.61–1.20) | No concern 95% PI (0.44–1.67) | Low | Not suggested | Major concern ^(c) <i>P</i> =0.01* | Very low |
| Endotracheal intubation | | | | | | | |
| HFNO vs SOT | Undetected | Some concerns 95% CI (0.61–1.11) | Some concerns 95% PI (0.41–1.64) | Low | Not suggested | No concern <i>P</i> = 0.50* | Moderate |
| NIV vs SOT | Undetected | No concern 95% CI (0.51–0.79) | Major concerns ^(b) 95% PI (0.33–1.22) | Low | Not suggested | No concern <i>P</i> = 0.85* | Low |
| NIV vs HFNO | Undetected | Some concerns 95% CI (0.56–1.06) | Some concerns 95% PI (0.38–1.56) | Low | Not suggested | No concern <i>P</i> =0.24* | Moderate |

CI confidence interval, SOT standard oxygenation therapy, HFNO high-flow nasal oxygen, IMV invasive mechanical ventilation, NIV noninvasive ventilation, PI prediction interval

* We used a side-splitting approach as a local method

** We used the design-by-treatment model as a global method

^a Confidence interval extends into clinically important effects in both directions

^b Prediction interval extends into clinically important effects in both directions

^c *P* value of inconsistency was <0.05

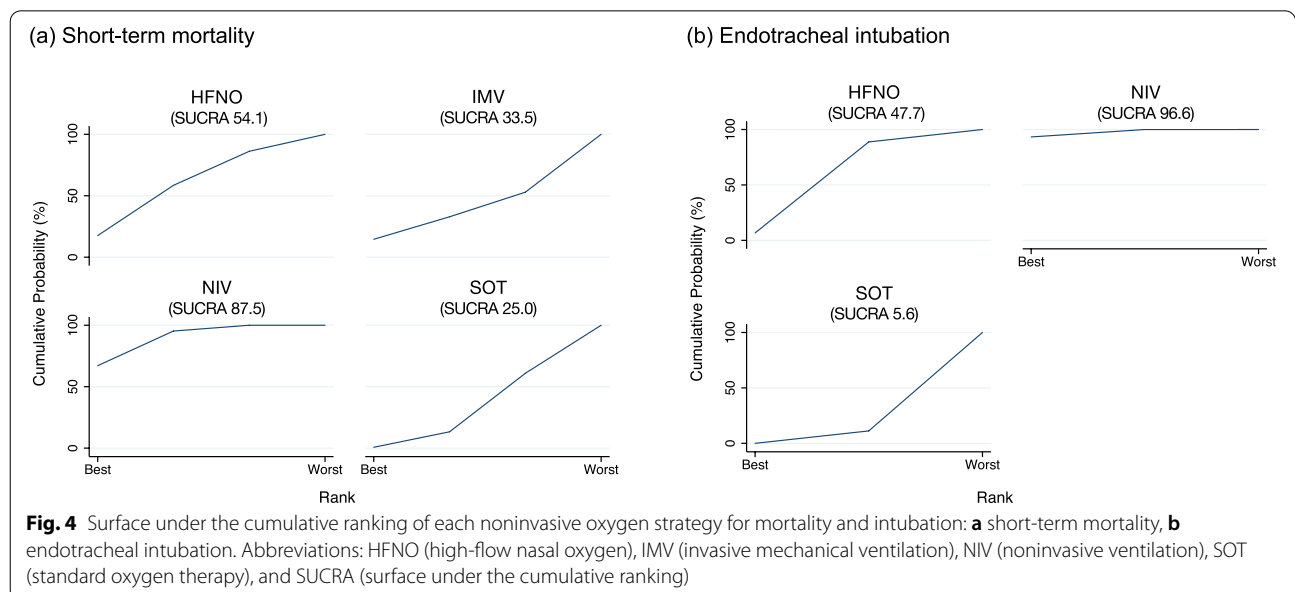


Table 3 Summary of findings of the network meta-analysis for short-term mortality

| Estimates of effects, credible intervals, and certainty of the evidence for respiratory support strategies in adults with acute hypoxemic respiratory failure | | | | | | |
|---|--------------------------|---|-------------------|--|--|--|
| <i>Frequency theory NMA-SoF table</i> | | | | | | |
| <p>Patient or population: Critically ill patients with acute hypoxemic respiratory failure.</p> <p>Interventions: One of the following respiratory support strategies: NIV, HFNO, IMV or SOT.</p> <p>Comparator (reference): One of the other strategies other than the strategy included intervention.</p> <p>Outcome: Short-term mortality</p> <p>Settings: Patients treated in the intensive care unit, intermediate care unit, and emergency department.</p> | | | | | | |
| | | | | | <p style="text-align: right;">Geometry of the Network*</p> | |
| Total studies: 23 RCT Total Participants: 3,169 | Risk ratio** (95% CI) | Anticipated absolute effect*** (95% CI) | | | Certainty of the evidence | |
| | | Without intervention | With intervention | Difference | | |
| Compared with SOT | | | | | | |
| ● HFNO (Direct evidence; 5 RCT; 1,452 participants) | 0.89 (0.66–1.20) | 345 per 1,000 [†] | 307 per 1,000 | 38 per 1,000 fewer (from 69 fewer to 117 more) | ⊕⊕○○ Low ^{a)} | |
| ● NIV (Direct evidence; 15 RCT; 1,550 participants) | 0.76 (0.61–0.95) | 345 per 1,000 [†] | 157 per 1,000 | 90 per 1,000 fewer (from 17 fewer to 135 fewer) | ⊕⊕○○ Low ^{a)} | |
| ● IMV (No direct evidence) | 1.01 (0.57–1.78) | 345 per 1,000 [†] | 348 per 1,000 | 3 per 1,000 more (from 269 fewer to 148 more) | ⊕○○○ Very low ^{a), b)} | |
| ● SOT | Comparator | No estimable | No estimable | No estimable | Comparator | |
| Compared with IMV | | | | | | |
| ● HFNO (No direct evidence) | 0.89 (0.47–1.65) | 404 per 1,000 [†] | 400 per 1,000 | 4 per 1,000 more (from 263 fewer to 214 more) | ⊕○○○ Very low ^{a), b)} | |
| ● NIV (Direct evidence; 3 RCT; 181 participants) | 0.76 (0.45–1.27) | 404 per 1,000 [†] | 307 per 1,000 | 97 per 1,000 fewer (from 109 fewer to 222 more) | ⊕○○○ Very low ^{a), b)} | |
| ● IMV | Comparator | No estimable | No estimable | No estimable | Comparator | |

CI confidence interval, SOT standard oxygenation therapy, HFNO high-flow nasal oxygen, IMV invasive mechanical ventilation, NIV noninvasive ventilation, NMA network meta-analysis, PI prediction interval, RCT randomized controlled trial, SoF summary of findings

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis [54] estimates are reported as risk ratio. CI confidence interval

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group

† Information is reported from studies included in the network metanalysis for the comparison displays

Certainty in the evidence

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

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

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

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

Explanatory Footnotes

a) Serious imprecision

b) Serious incoherence

Limitations

Our current network meta-analysis had several limitations. First, we used indirect comparisons to evaluate the effects of HFNO versus those of IMV, and none of the studies included in the current meta-analysis directly compared IMV and HFNO. This does not reflect the strength of the NMA, which is a property of narrowing the confidence intervals. Second, the mean P/F ratio in the two studies involving comparisons

with IMV was lower than that in the studies involving comparisons with SOT. These differences in treatment effects may affect intransitivity and incoherence in a network meta-analysis. Third, a potential source of heterogeneity was the different follow-up times for all-cause mortality in the included studies. In the sensitivity analyses that focused on the 30-day mortality, NIV was associated with lower mortality, similar to the main analysis.

Conclusions

The current NMA of trials involving adult patients with AHRF showed that in comparison with SOT, only NIV reduced the risk of death, while HFNO and IMV did not. Further investigation, especially a comparison of NIV with HFNO, is warranted.

Abbreviations

AHRF: Acute hypoxemic respiratory failure; ARDS: Acute respiratory distress syndrome; CENTRAL: Cochrane Central Register of Controlled Trials; CI: Confidence interval; CINeMA: Confidence in Network Meta-Analysis; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; GRADE: Grades of Recommendation, Assessment, Development and Evaluation Working Group; HFNO: High-flow nasal oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; NIV: Noninvasive ventilation; NMA: Network meta-analysis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; P-SILI: Patient self-inflicted lung injury; RCT: Randomized controlled trial; RevMan: Review manager; RR: Risk ratio; SOT: Standard oxygen therapy; SUCRA: Surface under the cumulative ranking curve.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40981-022-00525-4>.

Additional file 1: Supplementary e-Table 1. Search strategy. **Supplementary e-Table 2.** Risk of bias summary. **Supplementary e-Table 3.** Sensitivity analysis excluding studies with P/F ratio ≥ 200 . **Supplementary e-Table 4.** Sensitivity analysis excluding studies with Type II respiratory failure. **Supplementary e-Table 5.** Sensitivity analysis for mortality excluding studies that reported long-term mortality. **Supplementary e-Fig. 1.** Forest plots for the pairwise comparison of short-term mortality. **Supplementary e-Fig. 2.** Forest plots for the pairwise comparison of endotracheal intubation. **Supplementary e-Fig. 3.** Forest plots for the pairwise comparison of ventilator associated lung injury. **Supplementary e-Fig. 4.** Funnel plots for each outcome.

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Authors' contributions

MS participated in designing the study, acquiring data, performing statistical analyses, and interpreting the data. HO and TM conceived the study and participated in the interpretation of the data and acquisition of data. SK and SH conceived the data acquisition. The first draft of the manuscript was written by HO, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

None declared.

Author details

¹Department of Critical Care and Emergency Medicine, National Hospital Organization Yokohama Medical Center, 3-60-2 Harajuku, Totsuka-ku, Yokohama-shi, Kanagawa 245-8575, Japan. ²International University of Health and Welfare Graduate School of Public Health, 4-1-26 Akasaka, Minato City, Tokyo 107-8402, Japan. ³Department of Emergency and Intensive Care Medicine, JA Hiroshima General Hospital, 1-3-3 Jigozen, Hatsukaichi-City, Hiroshima 738-8503, Japan. ⁴Department of Emergency and Critical Care Medicine, Misato Kenwa Hospital, 4-494-1 Takano, Misato-shi, Saitama 341-8555, Japan. ⁵Department of Preventive Services, School of Public Health, Kyoto University, Yoshida-konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. ⁶Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Chuo-ku, Niigata 951-8510, Japan.

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References

- Berbenetz N, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev*. 2019;4:Cd005351. <https://doi.org/10.1002/14651858.CD005351.pub4>.
- Zayed Y, Barbarawi M, Kheiri B, Haykal T, Chahine A, Rashdan L, et al. Initial noninvasive oxygenation strategies in subjects with de novo acute hypoxemic respiratory failure. *Respir Care*. 2019;64:1433. <https://doi.org/10.4187/respcare.06981>.
- Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50. <https://doi.org/10.1183/13993003.02426-2016>.
- Rochweg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med*. 2020;46:2226–37. <https://doi.org/10.1007/s00134-020-06312-y>.
- Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012;38:1573–82. <https://doi.org/10.1007/s00134-012-2682-1>.
- Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Non-invasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med*. 2017;195:67–77. <https://doi.org/10.1164/rccm.201606-1306OC>.
- Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854–87. <https://doi.org/10.1007/s00134-020-06022-5>.
- Mellado-Artigas R, Ferreyro BL, Angriman F, Hernández-Sanz M, Arruti E, Torres A, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. *Crit Care*. 2021;25:58. <https://doi.org/10.1186/s13054-021-03469-w>.
- Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *Jama*. 2002;287:345–55. <https://doi.org/10.1001/jama.287.3.345>.
- Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. *Am J Respir Crit Care Med*. 2019;199:1368–76. <https://doi.org/10.1164/rccm.201803-0589OC>.
- Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. *Intensive Care Med*. 2017;43:192–9. <https://doi.org/10.1007/s00134-016-4601-3>.

12. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372:2185–96. <https://doi.org/10.1056/NEJMoa1503326>.
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777–84. <https://doi.org/10.7326/M14-2385>.
14. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj*. 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>.
15. The Cochrane Collaboration. RevMan 5 Download and installation. Secondary RevMan 5 download and installation. 2014. <https://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download/installation>. Accessed 23 Apr 2021.
16. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17:e1003082. <https://doi.org/10.1371/journal.pmed.1003082>.
17. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64:163–71. <https://doi.org/10.1016/j.jclinepi.2010.03.016>.
18. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8:e76654. <https://doi.org/10.1371/journal.pone.0076654>.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–58. <https://doi.org/10.1002/sim.1186>.
20. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002;21:2313–24. <https://doi.org/10.1002/sim.1201>.
21. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3:98–110. <https://doi.org/10.1002/jrsm.1044>.
22. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9:e99682. <https://doi.org/10.1371/journal.pone.0099682>.
23. Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Undertaking network meta-analyses. *Cochrane Handb Syst Rev Intervent*. 2019:285–320.
24. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev*. 2020;16:e1080. <https://doi.org/10.1002/cl2.1080>.
25. Azoulay E, Lemiale V, Mokart D, Nseir S, Argaud L, Pène F, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. *JAMA*. 2018;320:2099–107. <https://doi.org/10.1001/jama.2018.14282>.
26. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med*. 1998;339:429–35. <https://doi.org/10.1056/nejm199808133390703>.
27. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. A randomized comparison with conventional therapy. *Chest*. 1995;107:761–8. <https://doi.org/10.1378/chest.107.3.761>.
28. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283:235–41. <https://doi.org/10.1001/jama.283.2.235>.
29. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto MG. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med*. 1999;160:1585–91. <https://doi.org/10.1164/ajrccm.160.5.9903015.30>.
30. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, 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;284:2352–60. <https://doi.org/10.1001/jama.284.18.2352>.
31. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*. 2001;344:481–7. <https://doi.org/10.1056/nejm200102153440703>.
32. Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med*. 2000;161:807–13. <https://doi.org/10.1164/ajrccm.161.3.9808143>.
33. Cosentini R, Brambilla AM, Aliberti S, Bignamini A, Nava S, Maffei A, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. *Chest*. 2010;138:114–20. <https://doi.org/10.1378/chest.09-2290>.
34. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med*. 2003;168:1438–44. <https://doi.org/10.1164/rccm.200301-072OC>.
35. Squadrone V, Massaia M, Bruno B, Marmont F, Falda M, Bagna C, et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med*. 2010;36:1666–74. <https://doi.org/10.1007/s00134-010-1934-1>.
36. Brambilla AM, Aliberti S, Prina E, Nicoli F, Del Forno M, Nava S, et al. Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Med*. 2014;40:942–9. <https://doi.org/10.1007/s00134-014-3325-5>.
37. Wermke M, Schiemann S, Höffken G, Ehninger G, Bornhäuser M, Illmer T. Respiratory failure in patients undergoing allogeneic hematopoietic SCT—a randomized trial on early non-invasive ventilation based on standard care hematology wards. *Bone Marrow Transplant*. 2012;47:574–80. <https://doi.org/10.1038/bmt.2011.160>.
38. Zhan Q, Sun B, Liang L, Yan X, Zhang L, Yang J, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. *Crit Care Med*. 2012;40:455–60. <https://doi.org/10.1097/CCM.0b013e318232d75e>.
39. Azevedo JR, Montenegro WS, Leitao AL, Silva MM, Prazeres JS, Maranhao JP. High flow nasal cannula oxygen (hfnc) versus non-invasive positive pressure ventilation (nippv) in acute hypoxemic respiratory failure: a pilot randomized controlled trial. *Intensive Care Med Exp*. 2015;3:A166. <https://doi.org/10.1186/2197-425X-3-S1-A166>.
40. Lemiale V, Mokart D, Mayaux J, Lambert J, Rabbat A, Demoule A, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care*. 2015;19:380. <https://doi.org/10.1186/s13054-015-1097-0>.
41. Lemiale V, Mokart D, Resche-Rigon M, Pène F, Mayaux J, Faucher E, et al. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. *JAMA*. 2015;314:1711–9. <https://doi.org/10.1001/jama.2015.12402>.
42. Belenguer-Muncharaz A, Cubedo-Bort M, Blasco-Asensio D, Mateu-Campos L, Vidal-Tegedor B, Madero-Pérez J, et al. Non-invasive ventilation versus invasive mechanical ventilation in patients with hypoxemic acute respiratory failure in an Intensive Care Unit. A randomized controlled study. *Minerva. Respir Med*. 2017;56:1–10. <https://doi.org/10.23736/S0026-4954.16.01770-3>.
43. Jones PG, Kamona S, Doran O, Sawtell F, Wilsher M. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: the HOT-ER study. *Respir Care*. 2016;61:291–9. <https://doi.org/10.4187/respcare.04252>.
44. He H, Sun B, Liang L, Li Y, Wang H, Wei L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. *Crit Care*. 2019;23:300. <https://doi.org/10.1186/s13054-019-2575-6>.
45. Andino R, Vega G, Pacheco SK, Arealillo N, Leal A, Fernández L, et al. High-flow nasal oxygen reduces endotracheal intubation: a randomized clinical trial. *Ther Adv Respir Dis*. 2020;14:1753466620956459. <https://doi.org/10.1177/1753466620956459>.
46. Alptekinoglu Mendil N, Temel Ş, Yüksel RC, Gündoğan K, Eser B, Kaynar L, et al. The use of high-flow nasal oxygen vs. standard oxygen therapy in hematological malignancy patients with acute respiratory failure in hematology wards. *Turk. J Med Sci*. 2021;51:1756–63. <https://doi.org/10.3906/sag-2007-228>.

47. Awadallah M, Taha A, Sarhan T. Cardiorespiratory changes and outcome during noninvasive and invasive mechanical ventilation in ARDS: a comparative study. *Res Opin Anesth Intens Care*. 2021;8:6–12. https://doi.org/10.4103/roaic.roaic_15_19.
48. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. *JAMA*. 2021;325:1731–43. <https://doi.org/10.1001/jama.2021.4682>.
49. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochweg B, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA*. 2020;324:1–12. <https://doi.org/10.1001/jama.2020.9524>.
50. Yasuda H, Okano H, Mayumi T, Nakane M, Shime N. Association of noninvasive respiratory support with mortality and intubation rates in acute respiratory failure: a systematic review and network meta-analysis. *J Intensive Care*. 2021;9:32. <https://doi.org/10.1186/s40560-021-00539-7>.
51. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. *Crit Care Med*. 2013;41:536–45. <https://doi.org/10.1097/CCM.0b013e3182711972>.
52. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195:438–42. <https://doi.org/10.1164/rccm.201605-1081CP>.
53. Carreaux G, Millán-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med*. 2016;44:282–90. <https://doi.org/10.1097/ccm.0000000000001379>.
54. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. *JAMA*. 2022;327:546–58. <https://doi.org/10.1001/jama.2022.0028>.
55. Gorman E, Connolly B, Couper K, Perkins GD, McAuley DF. Non-invasive respiratory support strategies in COVID-19. *Lancet Respir Med*. 2021;9:553–6. [https://doi.org/10.1016/s2213-2600\(21\)00168-5](https://doi.org/10.1016/s2213-2600(21)00168-5).

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