Efficacy of Non-Invasive and Invasive Respiratory Managements in Adult Patients with Acute Hypoxaemic Respiratory Failure: A Systematic Review and Network Meta-Analysis

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Research

Keywords: acute hypoxaemic respiratory failure, continuous positive airway pressure, high-flow nasal oxygen, network meta-analysis, non-invasive ventilation

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Abstract

**Background:** Although non-invasive respiratory managements are performed to avoid intubation, patients with *de novo* acute hypoxaemic respiratory failure (AHRF) are high risk for treatment failure. Choosing the most effective primary respiratory management for adults with *de novo* AHRF is a complex problem. In the previous meta-analyses, the effect of non-invasive ventilation was not sufficiently evaluated according to ventilation modes in patients with AHRF. Furthermore, no meta-analyses comparing non-invasive respiratory managements with invasive mechanical ventilation (IMV) have been reported. We performed a network meta-analysis to compare the efficacy of non-invasive ventilation according to ventilation modes with high-flow nasal oxygen (HFNO), standard oxygen therapy (SOT), and IMV in adult patients with AHRF.

**Methods:** The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Ichushi databases were searched. Studies including adults with AHRF and randomised controlled trials comparing two different respiratory managements (continuous positive airway pressure [CPAP], pressure support ventilation [PSV], HFNO, SOT, or IMV) were reviewed. A network meta-analysis was performed via a frequentist approach with a multivariate random-effects meta-analysis. The certainty of evidence was assessed based on the Grades of Recommendation, Assessment, Development and Evaluation Working Group approach. The primary outcome was short-term mortality.

**Results:** Using SOT as the reference, CPAP (risk ratio [RR], 0.55; 95% confidence interval [CI], 0.31–0.95; very low certainty) was significantly associated with a lower risk of mortality. Compared with SOT, PSV (RR, 0.81; 95% CI, 0.62–1.06; low certainty) and HFNO (RR, 0.90; 95% CI, 0.65–1.25; very low certainty) were not associated with a significantly lower risk of mortality. Compared with IMV, no non-invasive respiratory management was associated with a significantly lower risk of mortality, although all certainties of evidence were very low. The probability of being best in reducing short-term mortality among all possible interventions was higher for CPAP, followed by PSV and HFNO; IMV and SOT were tied for the worst.

**Conclusions:** Our findings imply that CPAP may be the most effective strategy as the primary non-invasive respiratory management for AHRF to avoid unnecessary pressure support.

**Trial registration:** protocols.io (Protocol integer ID 49375, April 23, 2021), dx.doi.org/10.17504/protocols.io.buf7nrt.

Background

Acute hypoxaemic respiratory failure (AHRF) is the most common cause of intensive care unit (ICU) admission among adult patients, with a hospital mortality rate of approximately 30% [1]. Non-invasive respiratory management has been widely investigated among patients with AHRF. Non-invasive ventilation is recommended to reduce the risk of endotracheal intubation and mortality in patients with AHRF due to cardiopulmonary oedema [2] but not in patients with *de novo* AHRF [3]. Acute respiratory distress syndrome (ARDS) is a major cause of *de novo* AHRF. Non-invasive ventilation is used in 15% of patients with ARDS, but it may be associated with higher ICU mortality, especially in patients with severe ARDS [4]. Although high-flow nasal oxygen (HFNO) is recommended for patients with AHRF [5], its efficacy is not consistent among patients with *de novo* ARDF [6, 7].

A systematic review and network meta-analysis (NMA) was recently performed to compare the efficacy of non-invasive respiratory managements in adult patients with AHRF [8]. This NMA showed that non-invasive respiratory managements, including non-invasive ventilation and HFNO, were superior than standard oxygen therapy (SOT), and that helmet non-invasive ventilation was the most effective in reducing the risk of all-cause mortality and endotracheal intubation. However, continuous positive airway pressure (CPAP) was used as a non-invasive ventilation mode along with helmet non-invasive ventilation in most randomised controlled trials (RCTs) included in this NMA. Excessive tidal volume was reportedly associated with treatment failure in patients with AHRF [9], and non-invasive ventilation failure increased hospital mortality [4]. CPAP might contribute to the superiority of helmet non-invasive ventilation, possibly avoiding pressure support and larger tidal volume in patients with AHRF. A pair-wise meta-analysis that included RCTs and observational studies also reported the benefit of helmet non-invasive ventilation [10]. CPAP mode was selected in patients without hypercapnia in half of the included studies. In the previous meta-analyses, the effect of non-invasive ventilation was not sufficiently evaluated according to ventilation modes in patients with AHRF. It is unknown whether CPAP is an effective strategy for AHRF. Furthermore, in the previous NMA, non-invasive respiratory managements were not compared with invasive mechanical ventilation (IMV). Although non-invasive respiratory managements have been used to avoid complications of IMV and improve outcomes, few meta-analyses comparing non-invasive respiratory managements with IMV have been reported.

In this study, we hypothesised that CPAP is the most effective strategy among non-invasive respiratory managements for patients with AHRF. We performed an NMA to compare the efficacy of non-invasive ventilation according to the ventilation modes with HFNO, SOT, and IMV in adult patients with *de novo* AHRF.

Methods

**Protocol and registration**

This systematic review was designed according to the Preferred Reporting Items for Systematic review and Meta-Analyses extension statement for reviews incorporating network meta-analyses (details shown in Supplementary Table S1) [11], and the protocol was registered at protocols.io (Protocol integer ID 49375) [12].

**Eligibility criteria**

**Type of studies**
We included all RCTs reported in English and Japanese regardless of the publication status (published, unpublished, and academic abstracts). Randomised crossover, cluster-randomised, or quasi-experimental trials were excluded.

**Type of participants**

This review included adults (age ≥ 18 years) with AHFR, defined by any of the following criteria: new onset (< 7 days) of clinical signs (e.g. tachypnoea, increased work of breathing); radiologic signs (unilateral or bilateral chest X-ray opacities); and hypoxaemia. Hypoxaemia was defined as a ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) below 300 cmH₂O, arterial or percutaneous oxygen saturation < 94% in room air, partial pressure of arterial oxygen < 60 mmHg in room air or < 80 mmHg with oxygen. The current meta-analysis excluded studies in which more than half of the patients had cardiopulmonary oedema, acute exacerbation of chronic obstructive pulmonary disease (COPD) or acute exacerbation of asthma, hypercapnia (e.g. >50 mmHg), post-extubation respiratory failure, post-surgical status, trauma, do-not-resuscitate orders, or limited intervention in the emergency department or pre-hospital care.

**Types of interventions and comparators**

We included RCTs comparing two of the following five methods:

1. 1. SOT: Low-flow nasal cannula, face mask, and venturi mask (with no limit on the flow rate).
2. 2. CPAP: CPAP was used for an initial non-invasive ventilation mode. The type of mask, duration of ventilation, management during the non-invasive ventilation interval, and methods of weaning were not limited.
3. 3. PSV: Pressure support ventilation (PSV), pressure control ventilation, bi-level positive airway pressure, or spontaneous/timed was used for an initial non-invasive ventilation mode. The type of mask, duration of ventilation, management during the non-invasive ventilation interval, and methods of weaning were not limited.
4. 4. HFNO: The flow rate and fraction of inspired oxygen were not limited.
5. 5. IMV: Mechanical ventilation via endotracheal intubation not tracheostomy with or without a lung-protective strategy.

**Type of outcomes**

The outcome measures included a primary outcome of short-term mortality at the end of the follow-up period (< 100 days), ICU discharge, and hospital discharge. The secondary outcome was the incidence of intubation during ICU stay.

**Information sources**

We searched the following databases for eligible trials: The Cochrane Central Register of Controlled Trials; MEDLINE via PubMed; EMBASE; and Ichushi, a database of Japanese research papers. We also performed a manual search.

**Search**

We used the terms ‘ARDS’, ‘adult respiratory distress syndrome’, ‘respiratory failure’, or ‘acute lung injury’ AND ‘non-invasive ventilation’, ‘NIV’, ‘oxygen therapy’, ‘HFNO’, or ‘high-flow therapy’ in searches performed in June 2020 (details in Supplementary Table S2). Search terms included ‘pediatric’ or ‘neonate’ because the systematic review was originally performed for clinical questions in the Japanese ARDS Clinical Practice guideline for adults and paediatrics. During the screening process, we excluded studies with paediatric patients.

**Study selection**

Two of the five physicians (HO, TM, SH, SK, and MS) screened the title and abstract or the full text for relevant studies during the first and second screenings, respectively, and independently extracted data from the included studies into standardised data forms. Disagreements, if any, were resolved by discussion with one of five physicians who did not screen that particular study; original authors were contacted for clarification as required. For abstract-only studies that could not be evaluated for eligibility based on our review criteria, we attempted to contact the authors. Discrepancies between two reviewers were resolved by mutual discussion or discussion with a third reviewer as needed.

**Data collection process**

After identifying studies in the second screening, data were extracted from each study by the reviewers (HO, TM, SH, SK, and MS) using two tools: the Cochrane Data Collection Form (RCTs only) [13] and Review Manager software (RevMan version 5.4.1, The Cochrane Collaboration, 2020) [14]. For cases with unknown data, the authors were contacted.

**Data items**

We extracted the following study characteristics:

1. 1. Methods: study design, total study duration, number and locations of study centres, study setting, withdrawals, date of study initiation, and funding sources.
2. 2. Participants: number, mean age, age range, sex, severity of condition, diagnostic criteria, and inclusion/exclusion criteria.
3. 3. Interventions: treatment approaches and comparison methods.
4. 4. Outcomes: primary and secondary outcomes that were specified and collected and the timepoints reported.

**Geometry of the network**
Network plots were constructed to determine the number of studies and patients included in this meta-analysis. We showed network geometry that presented nodes as interventions and each head-to-head direct comparison as lines connecting these nodes. The size of the nodes was proportional to the number of participants in each node. The thickness of the connecting line was proportional to the number of randomised clinical trials in each comparison.

**Risk of bias within individual studies**

The risk of bias of outcomes in the included studies was independently assessed by two of the five authors (HO, TM, SH, SK, and MS) using a modified version of the Cochrane ‘Risk of Bias’ instrument [15]. They judged the overall risk of bias as the worst in any of the following domains: from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. 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 RevMan 5.3 (RevMan 2014) [14]. Forest plots were used for meta-analysis, and the effect size was expressed as a risk ratio (RR) with 95% confidence interval (CI) for categorical data. Outcome measures were pooled using a random-effects model for study-specific effects in measures. For all analyses, a two-sided p value < 0.05 was considered statistically significant.

**Network comparison meta-analysis**

*Data synthesis.* An NMA was performed via a frequentist approach with multivariate random-effects meta-analysis using the mvmeta command in Stata 15.1 (StataCorp LLC, College Station, TX, USA).

The Network Meta command allowed us to fit consistency models and estimate network RRs for each treatment strategy based on both direct and indirect comparisons [16]. We constructed forest plots of the RR with 95% CI 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 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].

**Assessment of inconsistency**

Study heterogeneity among trials for each outcome was assessed by visually inspecting forest plots and with an I^2 statistic to quantify inconsistency [19]. Publication bias was visually assessed using a funnel plot [18].

Coherence in NMA refers to consistency in the estimates of treatment effect between direct and indirect comparisons [20]. For each pair-wise comparison, we assessed coherence using the node-splitting method [21]. We also examined coherence globally across the network using the Wald chi-square test, obtained by fitting the inconsistency model [16].

Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) assessments of the certainty of evidence for each network comparison

To assess the certainty of evidence for direct comparisons, we used standard GRADE methodology [22–24]. We rated down for risk of bias, indirectness, inconsistency, and publication bias but did not rate down for imprecision because this occurred at a later step [25, 26]. For indirect comparisons, we started with the lowest certainty of evidence for the contributing direct comparisons and then rated down if there was substantial intransitivity. The transitivity assumption underlying the NMA was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons. We judged the certainty in each network comparison considering the highest certainty of evidence between direct and indirect evidence [27]; the network estimate was subsequently rated considering imprecision and incoherence [28].

**Additional analysis**

A pre-planned sensitivity analysis, which excluded studies using a helmet interface, was performed to assess the robustness of the findings.

**Results**

**Study selection**

The search strategy identified 14,263 records, including 25 RCTs (3,302 participants; range, 30–776 participants) that were eligible for inclusion (Fig. 1).

**Presentation of network structure and summary of network geometry**

The included trials evaluated five different interventions, and these included 5 of 10 potential head-to-head comparisons for short-term mortality and four different interventions and 4 of 6 potential head-to-head comparisons for intubation. Specifically, nine trials compared PSV with SOT [29–37], five trials compared CPAP with SOT [38–42], five trials compared HFNO with SOT [7, 43–46], three trials compared PSV with IMV [47–49], and two trials compared PSV with HFNO [50, 51] (Table 1 and Fig. 2). In addition, a three-group study directly compared PSV with HFNO and SOT [6]. No studies compared CPAP or HFNO with IMV. There were 27 comparisons in 25 RCTs.
<table>
<thead>
<tr>
<th>Source</th>
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<th>Main exposure</th>
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<th>Outcome of intervention</th>
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<tbody>
<tr>
<td>Wysock</td>
<td>Undisclosed</td>
<td>41</td>
<td>Mixed ARF (CAP 39.0%, CPE 34.1%)</td>
<td>63</td>
<td>207</td>
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<td>43</td>
<td>noninvasive ventilation (N = 21)</td>
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**Table 1**

Summary of Characteristics of the studies included in the Network Meta-analysis

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*Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CAP, community-acquired pneumonia; CPAP, continuous positive airway pressure; CPO, cardiopulmonary oedema; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NA, not available; NIV, noninvasive ventilation; P/F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaCO$_2$, partial pressure of arterial carbon dioxide; Ppl, plateau pressure; PBW, predicted body weight; RR, respiratory rate.*

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*a. Age was reported as median.*
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<th>Interface, NIV mode</th>
<th>Comparator</th>
<th>Outcomes of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brambilla 38</td>
<td>RCCS Fondazione Ca’Granda, Ospedale Maggiore Policlínico, Milan</td>
<td>81</td>
<td>CAP (immunocompromised 32%)</td>
<td>67</td>
<td>141</td>
<td>34</td>
<td>33</td>
<td>noninvasive ventilation (N = 40)</td>
<td>helmet, CPAP</td>
<td>standard oxygen (N = 41)</td>
<td>Hospit morta</td>
</tr>
<tr>
<td>Azevedo 39</td>
<td>Undisclosed</td>
<td>30</td>
<td>CPO (43.3%), CAP (33.3%)</td>
<td>67</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>noninvasive ventilation (N = 16)</td>
<td>face, mask, pressure support</td>
<td>high-flow nasal oxygen (N = 14)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Frat 6</td>
<td>French Ministry of Health</td>
<td>310</td>
<td>Mixed ARF (CAP 63.5%)</td>
<td>60</td>
<td>155</td>
<td>33</td>
<td>35</td>
<td>noninvasive ventilation (N = 110)</td>
<td>face, mask, pressure support</td>
<td>high-flow nasal oxygen (N = 106); standard oxygen (N = 94)</td>
<td>90-day morta intuba</td>
</tr>
<tr>
<td>Lamiale 40</td>
<td>Fisher &amp; Paykel</td>
<td>100</td>
<td>Mixed ARF in immunocompromised patients (sepsis related 50%)</td>
<td>62</td>
<td>114</td>
<td>27</td>
<td>NA</td>
<td>high-flow nasal oxygen (N = 52)</td>
<td>-</td>
<td>standard oxygen (N = 48)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Lemiale 41</td>
<td>Legs Poix (Chancellerie des Universités de Paris) and OUTCOMEREA Study Group</td>
<td>374</td>
<td>Pneumonia in immunocompromised patients</td>
<td>63 a</td>
<td>142</td>
<td>26</td>
<td>NA</td>
<td>noninvasive ventilation (N = 191)</td>
<td>face, mask, pressure support</td>
<td>standard oxygen (N = 183)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Jones 42</td>
<td>Greenlane Research and Education Fund</td>
<td>303</td>
<td>Mixed ARF (COPD 23.9%, Pneumonia 23.8%)</td>
<td>73</td>
<td>NA</td>
<td>33</td>
<td>NA</td>
<td>high-flow nasal oxygen (N = 165)</td>
<td>-</td>
<td>standard oxygen (N = 138)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Muncharaz 43</td>
<td>Undisclosed</td>
<td>65</td>
<td>Mixed ARF (CAP 63.1%)</td>
<td>62 a</td>
<td>97</td>
<td>36</td>
<td>44</td>
<td>noninvasive ventilation (N = 34)</td>
<td>face, mask, pressure support</td>
<td>invasive ventilation, tidal volume 8–10 ml/kg (PBW), Ppl &lt; 35 (N = 31)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Azoulay 7</td>
<td>French Ministry of Health</td>
<td>776</td>
<td>Mixed ARF in immunocompromised patients (Pneumonia 59.0%)</td>
<td>64</td>
<td>132</td>
<td>33</td>
<td>NA</td>
<td>high-flow nasal oxygen (N = 386)</td>
<td>-</td>
<td>standard oxygen (N = 388)</td>
<td>Intuba</td>
</tr>
<tr>
<td>He 44</td>
<td>National Natural Science Foundation of China</td>
<td>200</td>
<td>CAP</td>
<td>55</td>
<td>231</td>
<td>25</td>
<td>34</td>
<td>noninvasive ventilation (N = 102)</td>
<td>face, mask, pressure support</td>
<td>standard oxygen (N = 98)</td>
<td>Intuba</td>
</tr>
<tr>
<td>Andino 45</td>
<td>Spanish Ministry of Health, Social Services, and Equality</td>
<td>46</td>
<td>Mixed ARF (CAP 30%, HAP 25%)</td>
<td>60</td>
<td>96</td>
<td>32</td>
<td>34.3</td>
<td>high-flow nasal oxygen (N = 24)</td>
<td>standard oxygen (N = 22)</td>
<td>Intuba</td>
<td>90-day morta intuba</td>
</tr>
<tr>
<td>Awadallah 46</td>
<td>None</td>
<td>52</td>
<td>ARDS (pulmonary ARDS 50%)</td>
<td>52</td>
<td>94.5</td>
<td>NA</td>
<td>33</td>
<td>noninvasive ventilation (N = 26)</td>
<td>face, mask, pressure support</td>
<td>invasive ventilation, tidal volume 6-7 ml/kg (PBW), Ppl &lt; 30 (N = 26)</td>
<td>Intuba</td>
</tr>
</tbody>
</table>

---

*a. Age was reported as median.

Abbreviations: ALL, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CAP, community-acquired pneumonia; CPAP, continuous positive airway pressure; COP, cardiopulmonary oedema; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NA, not available; NIV, noninvasive ventilation; P/F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaCO₂, partial pressure of arterial carbon dioxide; Ppl, plateau pressure; PBW, predicted body weight; RR, respiratory rate.
b) Intubation

Short-term mortality

Table 2

Results of network rank test in the Network Meta-analysis

a) Short-term mortality


<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of patients</th>
<th>Main reason for hypoxic respiratory failure</th>
<th>Age, year</th>
<th>P/F</th>
<th>RR, /min</th>
<th>PaCO₂, mmHg</th>
<th>Main exposure</th>
<th>Interface, NIV mode</th>
<th>Comparator</th>
<th>Outco of intub</th>
<th>Outco of intr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grieco 47, 2021</td>
<td>107</td>
<td>ARF in COVID-19 patients</td>
<td>65 a</td>
<td>102</td>
<td>28 a</td>
<td>34 a</td>
<td>noninvasive ventilation (N = 54)</td>
<td>helmet, pressure support</td>
<td>high-flow nasal oxygen (N = 55)</td>
<td>60-day morta intub</td>
<td></td>
</tr>
<tr>
<td>Alptekin &amp; Mendii 48, 2021</td>
<td>100</td>
<td>Mixed ARF in immunocompromised patients (pneumonia 74%)</td>
<td>59 a</td>
<td>262 a</td>
<td>NA</td>
<td>30 a</td>
<td>high-flow nasal oxygen (N = 51)</td>
<td>standard oxygen (N = 49)</td>
<td>28-day morta intub</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CAP, community-acquired pneumonia; CPAP, continuous positive airway pressure; CPO, cardiopulmonary oedema; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NA, not available; NIV, noninvasive ventilation; P/F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaCO₂, partial pressure of arterial carbon dioxide; Ppl, plateau pressure; PBW, predicted body weight; RR, respiratory rate.

Study characteristics and risk of bias assessment

Table 1 shows the participants, interventions, comparisons, outcomes, and cohort characteristics of the included trials. The mean age at randomisation ranged from 46 to 73 years, mean P/F ratio was predominantly < 200 (16 trials [64.0%]); 6, 7, 30, 32, 33, 36, 38, 39, 42, 43, 45, 47–51], and mean partial pressure of arterial carbon dioxide (PaCO₂) was > 50 mmHg in one trial (4.0%) [39], and nine trials (36.0%) included immunocompromised patients [7, 32, 34–36, 41–43, 46]. Community-acquired pneumonia was the most common cause of AHRF in 14 trials (56.0%) [6, 7, 29, 30, 32–34, 36–38, 40, 42, 45, 48]. Helmet interfaces were used in three of five trials comparing CPAP with SOT [40–42] and in a trial comparing PSV with HFNO [51]. In two of three trials comparing PSV with IMV [47, 48], target tidal volume was set at 8 ml/kg (of predicted body weight) or more for mechanically ventilated patients.

Non-invasive respiratory managements and risk of short-term mortality

Twenty-three trials (3,169 patients) were included in the short-term mortality analysis. Pair-wise comparisons are shown in Supplementary Figure S1. The risk of bias was determined to be high for the outcome of mortality in six (26.1%) trials (Supplementary Table S3). We did not rate down due to publication bias (funnel plot shown in Supplementary Figure S2); however, we judged that the risk of bias was substantial between CPAP and SOT and rated down. We also rated down considering inconsistency in the direct comparison of CPAP vs SOT, PSV vs IMV, and PSV vs HFNO (Supplementary Table S4). Incoherence between direct and indirect RRs was observed for the comparison of HFNO vs SOT, PSV vs SOT, and PSV vs HFNO. We also identified a significant incoherence globally across the network.

Using SOT as the reference, CPAP (RR, 0.55 [95% CI, 0.31–0.95]; risk difference [RD], − 0.14 [95% CI, − 0.21 to − 0.02]; very low certainty) was significantly associated with a lower risk of mortality (Fig. 3). Compared with SOT, PSV (RR, 0.81 [95% CI, 0.62–1.06]; RD, − 0.06 [95% CI, − 0.11 to 0.02]; low certainty) and HFNO (RR, 0.90 [95% CI, 0.65–1.25]; RD, − 0.03 [95% CI, − 0.11 to 0.08]; very low certainty) were not associated with a statistically significant lower risk of mortality.

Table 2 Results of network rank test in the Network Meta-analysis

a) Short-term mortality


| Source          | Total No. of patients | Main reason for hypoxic respiratory failure | Age, year | P/F | RR, /min | PaCO₂, mmHg | Main exposure | Interface, NIV mode | Comparator | Outco of intub | Outco of intr | SUCRA |
|------------------|-----------------------|--------------------------------------------|-----------|-----|---------|-------------|---------------|------------------|------------|----------------|--------------|
| Grieco 47, 2021  | 107                   | ARF in COVID-19 patients                   | 65 a      | 102 | 28 a    | 34 a        | noninvasive ventilation (N = 54) | helmet, pressure support | high-flow nasal oxygen (N = 55) | 60-day morta intub |        |
| Alptekin & Mendii 48, 2021 | 100 | Mixed ARF in immunocompromised patients (pneumonia 74%) | 59 a | 262 a | NA | 30 a | high-flow nasal oxygen (N = 51) | standard oxygen (N = 49) | 28-day morta intub |        |
Non-invasive respiratory managements and risk of endotracheal intubation

Twenty-two trials (3,118 patients) were included in the intubation analysis. Pair-wise comparisons are shown in Supplementary Figure S1. The risk of bias was determined to be high for the outcome of intubation in six (27.3%) trials (Supplementary Table S3). We judged that the risk of bias was serious between CPAP and SOT and rated down. We did not rate down due to publication bias (funnel plot shown in Supplementary Figure S2) and incoherence. We rated down because serious inconsistency was observed in the comparison of PSV vs SOT and CPAP vs SOT (Supplementary Table S4).

Using SOT as the reference, CPAP (RR, 0.48 [95% CI, 0.22–1.15]; RD, −0.15 [95% CI, −0.23 to 0.05]; very low certainty), PSV (RR, 0.75 [95% CI, 0.43–1.30]; RD, −0.08 [95% CI, −0.17 to 0.09]; very low certainty), and HFNO (RR, 0.83 [95% CI, 0.43–1.62]; RD, −0.05 [95% CI, −0.17 to 0.19]; very low certainty) were not associated with a statistically significant lower risk of mortality, and all certainties of evidence were very low. There were no significant differences among non-invasive respiratory managements, although CPAP tended to be associated with a lower risk of mortality. The probability of being best in reducing short-term mortality among all possible interventions was higher for CPAP, followed by PSV and HFNO; IMV and SOT were tied for the worst (Table 2 and Supplementary Figure S3).

Results of additional analyses

Results of a pre-planned sensitivity analysis excluding four studies using helmet interfaces revealed that CPAP was not associated with a lower mortality and incidence of intubation (Supplementary Table S5 and S6). However, for the studies comparing CPAP with SOT, which were included this analysis, there was concern with respect to the risk of bias [38, 39].

Discussion

Summary of evidence

In the current network meta-analyses of trials of adults with AHRF, compared with SOT, CPAP decreased the risk of death and both CPAP and PSV were associated with a lower risk of endotracheal intubation. Meanwhile, the treatment effect was not different between non-invasive respiratory managements and IMV for these outcomes. Ranking analyses showed that CPAP was the best strategy for reducing mortality and intubation.

Association with previous studies

Non-invasive ventilation is associated with a lower mortality in patients with acute respiratory failure due to cardiopulmonary oedema and COPD [2, 52]. However, the efficacy of non-invasive respiratory managements in patients with de novo AHRF has been unclear [3, 6, 7]. Liu et al. [10] performed a pair-wise meta-analysis to compare helmet non-invasive ventilation with control strategies, including face mask non-invasive ventilation and SOT, and demonstrated that helmet non-invasive ventilation was associated with reduced hospital mortality and intubation requirement. Although both CPAP and PSV showed significant benefit in subgroup analyses, six of eight studies using PSV were conducted among patients with acute exacerbation of COPD. The efficacy of non-invasive ventilation according to ventilation modes could not be evaluated in patients with AHRF. In 2020, Ferreyro et al. [8] reported an NMA in which the efficacy of non-invasive respiratory managements was compared with that of SOT among adult patients with AHRF, and helmet non-invasive ventilation was associated with a lower risk of mortality and intubation compared with SOT, HFNO, and face mask non-invasive ventilation. However, the NMA included patients with postoperative respiratory failure or chest trauma. Those patients had various causes of respiratory failure, including atelectasis due to poor pain control, chest wall injury, and pleural effusion, not only because of lung injury. We included trials in which more than half of the patients were experiencing de novo AHRF. Although the cause of AHRF was still inconsistent, our analysis could include a higher proportion of patients with de novo AHRF compared with the previous NMA.
There were insufficient data examining HFNO compared to non-invasive ventilation among patients with de novo AHRF. As per the results from an RCT comparing helmet PSV with HFNO in patients with AHRF due to coronavirus disease 2019, helmet PSV was associated with higher P/F ratio and PaCO$_2$ [51]. Although the rate of intubation was lower in patients with helmet PSV, mortality was not different. A helmet interface can decrease air leaks and provide higher levels of positive end-expiratory pressure, potentially increasing alveolar recruitment and improving oxygenation [53], but increasing dead space may worsen ventilation and contribute to lager tidal volume. Although the positive end-expiratory pressure effect of HFNO may not be sufficient to avoid intubation, it is unclear which is a better strategy, HFNO or non-invasive ventilation, considering dead space. In our NMA, HFNO did not show a reduction in the rate of mortality and incidence of intubation compared with other respiratory managements. Further evaluation is needed to provide conclusive recommendations, although HFNO was recommended for patients with AHRF compared with SOT [5].

In all trials comparing helmet non-invasive ventilation with SOT, which were included in the previous NMA, CPAP was used as a ventilation mode [8]. The use of CPAP might contribute to the superiority of helmet non-invasive ventilation. According to an RCT comparing helmet interface to face mask in patients who underwent non-invasive ventilation, patients with a helmet interface were set at a lower level of pressure support and had a lower mortality [54]. Since excessive tidal volume may worsen outcome [9], it may be important to set lower levels of pressure support for patients with AHRF. CPAP also has advantages over non-invasive ventilation in terms of simpler technology, better synchrony, and potentially less expensive equipment [3]. Our findings imply that CPAP is the most effective among non-invasive respiratory managements, in concordance with these physiological effects.

Significance and implications

Although non-invasive ventilation is performed to avoid intubation, treatment failure was reported to occur in 37.5% of patients with AHRF [4]. De novo AHRF, including ARDS, was one of the risk factors for non-invasive ventilation failure [55]. A high respiratory drive and large tidal volume may contribute to patient self-inflicted lung injury and poor outcomes in such patients [56–58]. Positive end-expiratory pressure, recruiting the lungs and maintaining them open, may reduce respiratory drive and contribute to lung protection. In contrast, pressure support without sufficient positive end-expiratory pressure may worsen lung injury during non-invasive ventilation. In our NMA, PSV and HFNO were not associated with lower mortality, but CPAP decreased mortality and the incidence of endotracheal intubation compared with SOT. Furthermore, ranking analyses showed that CPAP was the best strategy for reducing mortality and intubation. We did not find a significant difference between non-invasive respiratory managements and IMV, which was not considered lung-protective ventilation in most included trials, to decrease mortality. It remains unclear whether it is better to ensure lung protection or avoid complications of endotracheal intubation. We should perform CPAP as a first non-invasive respiratory management for de novo AHRF to avoid unnecessary pressure support and then should not hesitate to intubate considering the risk of self-inflicted lung injury.

Strengths and limitations

To the best of our knowledge, no systematic reviews and meta-analyses have been performed to evaluate non-invasive ventilation according to ventilation modes and compare it with IMV in adults with AHRF. However, the current NMA also had several limitations. First, we included studies with patients with cardiopulmonary oedema and COPD who were at a low risk of non-invasive ventilation failure. This may contribute to overestimating the treatment effect. The NMA assumption is that individual trials enrol similar populations, and the intervention protocol is similar across different studies. We excluded studies in which more than half of the patients had cardiopulmonary oedema or COPD. The proportion of those patients was lower in the current NMA than in the previous NMA. Second, the effect of non-invasive ventilation might not be consistent with respect to patient severity [4]. The mean P/F ratio in studies comparing with IMV was lower than that in studies that compared with SOT. The difference in treatment effect may affect intransitivity and incoherence in an NMA. We did not perform a sensitivity analysis with respect to patient severity, because of non-reporting of the P/F ratio in some trials. Third, there was a concern about the primary studies included in our review regarding the lack of blinding of the treatment groups. Although this was unlikely to bias the assessment of hard outcomes, it may have contributed to performance bias. Fourth, we did not report a significant benefit of CPAP in the sensitivity analysis that excluded studies using helmet interfaces. However, this result may be uncertain possibly because two studies comparing CPAP with SOT were included this analysis and had a small sample size and a concern in risk of bias [38, 39]. Further studies evaluating face mask CPAP with more participants are needed for robust evidence. Fifth, network RR was only estimated by indirect evidence in some comparisons. Specifically, few studies compared non-invasive respiratory managements with IMV. Further studies are needed for higher certainty of evidence. Finally, ranking results should be evaluated with caution because these do not consider certainty of the evidence. Although CPAP seemed to be the best management considering ranking probabilities, this result did not imply a significant clinical difference between CPAP and other non-invasive respiratory managements.

Conclusions

Our findings imply that CPAP may be the best strategy as the primary non-invasive respiratory management for AHRF to avoid unnecessary pressure support, although most certainties of evidence were very low. Further studies are needed for a higher certainty of evidence, particularly compared with IMV.

List of abbreviations

AHRF, acute hypoxemic respiratory failure; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; GRADE, Grades of Recommendation, Assessment, Development and Evaluation Working Group; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; NMA, network meta-analysis; PSV, pressure support ventilation; P/F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaCO$_2$, partial pressure of arterial carbon dioxide; PaO$_2$, partial pressure of arterial oxygen; PBW, predicted body weight; RCT, Randomized controlled trial; RevMan, Review manager; RR, risk ratio; RD, risk difference; SOT, standard oxygen therapy; SUCRA, Surface under the cumulative ranking curve.
Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current network meta-analysis are available from the corresponding author upon reasonable request.

Competing interests

All the authors declare that they have no conflicts of interest.

Funding

Not applicable.

Authors' contributions

MS designed the study, acquired data, performed statistical analyses, and interpreted the data. HO and TM conceived the study and acquired and interpreted the data. SK and SH conceived the acquisition of data. The first draft of the manuscript was written by MS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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References


Figures

Flow diagram of studies included in this review. Ichushi is a database of Japanese research papers CENTRAL, Cochrane Central Register of Controlled Trials; CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; PSV, pressure support ventilation; RCT, randomised controlled trial; RR, risk ratio; SOT, standard oxygen therapy.
a) Short-term mortality

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of patients</th>
<th>No. of trials</th>
<th>Rating</th>
<th>Absolute risk difference (95% CI)</th>
<th>Network risk ratio (95% CI)</th>
<th>Forest treatment</th>
<th>Forest comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFNO vs PSV</td>
<td>1,212</td>
<td>6</td>
<td>Medium</td>
<td>-0.10 (-0.16 to -0.04)</td>
<td>0.89 (0.81-0.97)</td>
<td></td>
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</tr>
<tr>
<td>HFNO vs CPAP</td>
<td>1,199</td>
<td>10</td>
<td>Medium</td>
<td>-0.11 (-0.20 to -0.02)</td>
<td>0.87 (0.79-0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP vs PSV</td>
<td>353</td>
<td>5</td>
<td>Low</td>
<td>-0.21 (-0.28 to -0.15)</td>
<td>0.49 (0.30-0.79)</td>
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</tr>
<tr>
<td>Additional comparison</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV vs HFNO</td>
<td>325</td>
<td>2</td>
<td>Very low</td>
<td>-0.03 (-0.11 to 0.04)</td>
<td>0.96 (0.90-1.02)</td>
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<td></td>
</tr>
<tr>
<td>CPAP vs HFNO</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>-0.12 (-0.20 to -0.05)</td>
<td>0.83 (0.65-1.04)</td>
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<td></td>
</tr>
<tr>
<td>CPAP vs PSV</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>-0.10 (-0.15 to -0.05)</td>
<td>0.84 (0.67-1.04)</td>
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<td></td>
</tr>
</tbody>
</table>

b) Intubation

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of patients</th>
<th>No. of trials</th>
<th>Rating</th>
<th>Absolute risk difference (95% CI)</th>
<th>Network risk ratio (95% CI)</th>
<th>Forest treatment</th>
<th>Forest comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFNO vs PSV</td>
<td>355</td>
<td>3</td>
<td>Low</td>
<td>-0.03 (-0.13 to 0.06)</td>
<td>0.88 (0.55-1.40)</td>
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</tr>
<tr>
<td>HFNO vs CPAP</td>
<td>353</td>
<td>5</td>
<td>Low</td>
<td>-0.21 (-0.28 to -0.15)</td>
<td>0.49 (0.30-0.79)</td>
<td></td>
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</tr>
<tr>
<td>Additional comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PSV vs CPAP</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>-0.17 (-0.27 to -0.07)</td>
<td>0.87 (0.62-1.20)</td>
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</tr>
<tr>
<td>PSV vs PSV</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>-0.10 (-0.15 to -0.05)</td>
<td>0.84 (0.63-1.24)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2

Network plot for non-invasive respiratory managements for adults with AHFR When RCTs for direct comparisons exist, this is shown by connections between nodes. The size of the node represents the number of participants who received the intervention. The thickness of lines connecting nodes represents the number of trials for the comparison CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; PSV, pressure support ventilation; RCT, randomised controlled trial; SOT, standard oxygen therapy.

Figure 3

Forest plots for association of non-invasive respiratory managements with study outcomes a) For the primary outcome, short-term mortality, the longest follow-up was up to 100 days. b) Secondary outcome, endotracheal intubation All outcomes are reported as network risk ratios and absolute risk differences with 95% CIs. For estimating risk ratios for the comparison of HFNO vs IMV, CPAP vs IMV, CPAP vs HFNO, and CPAP vs PSV only indirect evidence was used, because no direct pair-wise comparisons were available. The estimated absolute risks of mortality and endotracheal intubation were 30% and 40%.
respectively, in the control group CI, confidence interval; CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; PSV, pressure support ventilation; RR, risk ratio; SOT, standard oxygen therapy

**Supplementary Files**

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