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Complete List of Authors:	Li, Zongru; Peking Union Medical College Hospital, Department of pulmonary medicine Wang, Tao; Peking Union Medical College Hospital, Emergency Department Yang, Yi; Peking Union Medical College Hospital, Emergency Department Zhang, Lixi; Department of Cardiology Wang, Meng; Beijing Tiantan Hospital, Capital Medical University, Department of Science and Technology Liu, Gang; Peking Union Medical College Hospital, Department of orthopaedics He, Kun; Peking Union Medical College Hospital, Department of Gastroenterology Shi, Juhong; Peking Union Medical College Hospital, Department of Pulmonary medicine Ma, Chao; Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Department of Anatomy, Histology and Embryology He, Jianqiang; Peking Union Medical College Hospital, Emergency Department Ma, Yong; Peking Union Medical College Hospital, Emergency Department Li, Yi; Chinese Academy of Medical Sciences and Peking Union Medical College, Emergency department Zhu, Huadong; Peking Union Medical College Hospital, Emergency Department Yu, Xuezhong; Peking Union Medical College Hospital, Emergency Department
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Efficacy of non-invasive ventilation and oxygen therapy on immunocompromised patients with acute respiratory failure: protocol for a systematic review and meta-analysis of randomized controlled trials

Zongru Li[1†], Tao Wang[2†], Yi Yang[2†], Lixi Zhang[3], Meng Wang[4], Gang Liu[5], Kun He[6], Juhong Shi[1], Chao Ma[7], Jianqiang He[2], Yong Ma[2], Yi Li[2*], Huadong Zhu[2*] and Xuezhong Yu[2*]

ABSTRACT

Background The number of immunocompromised patients has increased in recent years. Acute respiratory failure is a common complication leading to ICU admission and high mortality among such patients. The use of non-invasive ventilation(NIV) or oxygen therapy among these patients remains controversial, according to the inconsistent results of several randomized clinical trials(RCTs). This meta-analysis aims to evaluate whether NIV or oxygen therapy is the more appropriate initial oxygenation strategy for the immunocompromised patients with acute respiratory failure.

Method We will search all the RCTs that compared the efficacy of NIV and oxygen therapy on immunocompromised adult patients with acute respiratory failure on the major databases (Cochrane Library, MEDLINE, EMBASE, Web of science etc.), conference proceedings and grey literature. Eligible RCTs will be included according to the pre-specified eligibility criteria. The risk of bias will be assessed using the Cochrane Collaboration criteria and the quality of evidence will be assessed with the GRADE system. Data will be extracted with a standardized form and analyzed using RevMan 5.3 analyses software. Heterogeneity will be assessed using I2 statistic and the source of which will be investigated. Publication bias will be identified with the funnel plot.

Discussion: The finding of this meta-analysis will provide evidence for the use of NIV or oxygen therapy as the initial oxygenation strategy among adult immunocompromised patients with ARF.

Strengths and limitations of this study

□There are no existing meta-analysis on the use of non-invasive ventilation among immunocompromised patients with acute respiratory failure.

□This meta-analysis includes only randomized clinical trials and will thus provide the highest quality of evidence for clinical practice.

□Subgroup analysis based on different levels of severity might support the use of NIV in more severe patients.

□The number of included studies is likely to be small.

KEY WORDS: Immunocompromised patients, acute respiratory failure, non-invasive ventilation, oxygen therapy, mortality, intubation rate

† Zongru Li, Tao Wang and Yi Yang contributed equally to this article.
* Correspondence: billliyi@126.com (Y. Li), zhuhuadong1970@126.com (H. Zhu) and yxz@medmail.com.cn (X.Yu).
[2] Emergency Department, Peking Union Medical College Hospital, Beijing, 100730, China.
Full list of author information is available at the end of the article.

BACKGROUND

Description of the problem

Owing to the epidemic of AIDS,[1] improved survival rates of active malignancies,[2 3] innovative advances in organ transplantation,[4] better outcomes of allogeneic hematopoietic cell transplantations[5] and the more common application of immunosuppressive therapy, there is an increasing number of immunocompromised patients. These patients are more vulnerable to infection due to their inadequate immune response to foreign antigens. Some life-threatening complications can lead to requirement of ICU admission for these patients, among which acute respiratory failure(ARF) is the most frequent with particularly high mortality.[6] ARF is a relatively sudden onset of dysfunction of the respiratory system, and the most common causes among immunocompromised patients are immunosuppression-related infection,[7 8] disease-specifc infiltration,[9] chemotherapy-associated organ toxicity[10] and idiopathic pneumonia syndrome associated with GVHD.[11] For severe ARF patients, invasive ventilation is required in order to support alveolar ventilation; however, such intervention also contributes to the high mortality due to the risk of ventilator-associated pneumonia.[12] Therefore, the strategy of delivering oxygen is of great importance for improvement of oxygenation, which may lead to reduction of intubation rate and mortality.

Description of the intervention

The percentage of usage of non-invasive ventilation(NIV) has increased from 29% in the year of 1997 to 42% in 2011 among patients with ARF[13]. The benefits NIV may bring are associated not only with the degree of inspiratory workload spared by the positive airway pressure provided, but also with the invasive-ventilation-associated complications that are prevented by NIV.[14 15] However, the failure of NIV was identified as an independent risk factor for ICU mortality, which occured in half the critically ill hematologic patients.[16] Oxygen therapy, operated via either nasal cannula, venturi mask or reservoir mask, is the basic technique used in patients with acute lung injury. Patients might benefit from oxygen therapy for less discomfort or intolerance compared with NIV.[17]

Why is it important to do this review?

The use of NIV was recommended for patients with acute respiratory in the setting of immunosuppression weak(Grade 2B) , [18] which is based on Antonelli's and Hilbert's randomized clinical trials published in 2000 and 2001, [19 20] respectively. Findings of these two studies showed that NIV was associated with reduced intubation rate and mortality in immunocompromised patients with ARF. However, outcomes supporting opposing viewpoint were published by M Wermke et al. in 2012,[21] which showed that NIV was not associated with lowered intubation rate or mortality compared with oxygen therapy in patients with early respiratory failure undergoing allogeneic hematopoietic stem cell transplantation. No solid conclusion could be drawn based on the data currently available according to the reviews published in recent years, except that NIV should be applied with great caution in this group of patients.[22 23] Since the application of NIV in immunocompromised patients with ARF remains controversial, a systematic review and meta-analysis that summarizes all the available RCTs and provide guidance for the management of this group of patients is necessary. To our knowledge, no meta-analysis about this topic has yet been published.

The aim of this study is to determine the efficacy of NIV in comparison with oxygen therapy as the initial oxygenation strategy on the immunocompromised patients with ARF, with respect to mortality, intubation rate and hospital length of stay, and also to explore the patient selection strategy for the initial oxygenation strategy. Furthermore, the proposed systematic review will provide evidences for the use of NIV in subgroups of patients, with a certain disease severity, cause of immunosuppression

and cause of ARF etc.

METHOD

This protocol of systematic review was reported following Preferred reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guidelines.[24]

Eligibility criteria: participants, interventions, comparisons and outcomes

Type of studies

Only randomized clinical trials will be included. Other types of studies such as observational studies, cohort studies, case–control studies and laboratory studies will be excluded.

Type of participants

This review will include RCTs involving immunocompromised adult patients with acute respiratory failure. The immunocompromised patients include patients with hematological malignancy, solid cancer, AIDS or who receives corticosteroid or cytotoxic therapy, or have gone through solid organ or stem cell transplantation. ARF was defined as respiratory rate >30 breaths/min and respiratory distress symptoms, PaO2 <60 mm Hg on room air or need for invasive or noninvasive MV.[16] RCTs with a subgroup of participants who meet the criteria above will also be included, on the condition that the data of outcome for this subgroup is available. It should be noted that RCTs will be included as long as more than 85% of the involved participants meet the eligibility criteria, even if the outcomes of these eligible participants are unavailable.

Type of intervention

The intervention group refers to patients treated with NIV, which includes two main modes: continuous positive airways pressure (CPAP) and bi-level positive airway pressure (BiPAP).

The control group refers to patients treated with oxygen therapy. High-flow nasal oxygen(HFNO) therapy is a relatively new method of oxygen therapy, that provides positive pressure which makes it different from standard oxygen therapy.[25] Therefore, this review will not include the trials where HFNO was applied.

We will include RCTs which directly compare NIV with oxygen therapy as the first oxygenation strategy for acute respiratory failure, regardless of whether the other oxygenation method was applied later.

Type of outcome measures

- Primary outcome

(1)Mortality: hospital mortality, ICU mortality and mortality at the last time available, in case that mortalities of all included studies were not measured at the same time period.

(2) Incidence of tracheal intubation.

- Secondary outcome

(1) Length of ICU stay.

(2) Length of hospital stay.

(3) Complications related to NIV

(4) Rate of pulmonary complications not present on admission.

The eligible RCT should include at least one of the primary outcomes listed above.

Search strategy for identification of studies

Electronic searches

Two reviewers (Dr. Y.Y. and Dr. L.Z.) will search the following databases: The Cochrane Library, MEDLINE, EMBASE, Web of science, CINAHL, LILACS and PEDro by using database-specific

search strategies. These electronic databases will be searched from January 1980 to date. No limitation of language or publication status will be applied. The filter for clinical trials will be used for each database. The following keywords were used in the database searching: immunosuppression, hematological malignancy, cancer, transplantation, corticosteroid, cytotoxic, AIDS, non-invasive ventilation, acute respiratory failure. The detailed search strategy can be seen in Supplement 1 and 2.

Searching other resources

The references of relevant studies and review articles will be sought for potential information missing in database search. Conference proceedings and grey literature will be checked. The experts in the field will be contacted to identify published and unpublished trials. We will also access www.controlledtrials.com and clinicaltrials.gov. for ongoing and unpublished studies, and the conductors or authors will be contacted for further information.

Screening of studies

All the relevant results identified by the search strategy will be screened by two reviewers (Dr. Z.L. and Dr. T.W.) independently. The first step of screening will be performed on titles and abstracts in sequence respectively, during which the irrelevant studies will be excluded according to the eligibility criteria. Then full texts of the studies that haven't been excluded will be downloaded and screened. Reasons of exclusion will be documented and classified. Any disagreements between the reviewers will be solved through discussion and consensus. The third author (Dr. Y.L.) will be consulted if a consensus cannot be reached.

Data extraction and management

Two reviewers (Dr. Z.L. and Dr. T.W.) will independently extract all the data in the included studies. We will use a standard form to extract the following data:

1. Characteristics of the study: design, setting, method of randomization, allocation concealment, blinding, and dropouts.

2. Participants: number enrolled in each group, gender, age, respiratory rate, oxygen saturation, oxygenation index(PaO_2/FiO_2), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation(APACHE II), new Simplified Acute Physiology Scale (SAPS II), cause of ARF, cause of immunosuppression.

3. Interventions: mode of NIV(CPAP or BiPAP), frequency and duration of ventilation; oxygen therapy and co-interventions.

4. Outcome: primary outcomes and secondary outcomes listed above.

We will contact the authors for the missing data or data of subgroup that are unavailable from the text. The consistency of data will be ensured by these two reviewers.

Assessment of risk of bias

For the included articles, the risk of bias will be assessed by two reviewers(Dr. Y.Y. and Dr. L.Z.) independently, using the Cochrane Collaboration criteria[26] which includes random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting. Each criterion will be explicitly judged and classified as 'low risk', 'high risk', or 'unclear risk'. The author will be contacted for supplemental information if details for assessment reported in the text are considered inadequate. The risk will be rated as 'unclear' if no further information is obtained. The result of assessment of each study will be summarized in a chart. Overall risk of bias for each study will be defined as 'low' if risk of all bias components are ranked as 'low', or 'moderate' if at least one component is ranked 'unclear' with no component ranked as 'high', or 'high' if one or more component is ranked as having a 'high' risk of bias.

Data analyses and assessment of heterogeneity

Measures of treatment effect

The statistical analyses will be performed using RevMan 5.3 analyses software of the Cochrane Collaboration. Continuous data such as length of ICU stay and length of hospital stay will be presented as mean differences(MD) with 95% confidence intervals (95% CIs). Dichotomous data such as the number of intubation and death will be presented as risk ratios (RR) with 95% CIs. When the rate rather than the numbers are reported, we will calculate the numbers based on the data provided.

Dealing with missing data

Missing data will be dealt with following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Corresponding authors will be contacted for further information. If the missing data cannot be obtained, we will specify the assumptions of the methods used to cope with missing data according to the reason of loss (i.e. random dropout or poor outcome). We will perform sensitivity analyses to evaluate how sensitive results are to the changes in the assumptions that are made. In the Discussion section of the review, we will analyze the potential impact the missing data may have on the findings of the review.

Assessment of heterogeneity

Before any outcome is pooled, we will assess the impact of heterogeneity using $\chi 2$ test and I^2 statistic [classified as low (< 40%), moderate (40-60%) or high (> 60%)]. I^2 values greater than 60% will be considered as having substantial heterogeneity. If substantial heterogeneity is present, we will investigate the potential source of heterogeneity by conducting exploratory analyses.

Assessment of reporting biases

Protocols of included trials will be searched using the databases mentioned above. We will contact the authors to obtain a full data set claimed in the protocol and reasons for the non-reporting of certain outcomes. Publication bias will be assessed by visual analysis of the funnel plot if the number of included studies is equal to or greater than 10.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore potential sources of heterogeneity. Possible sources of heterogeneity are:

1. severity of acute respiratory failure before randomization indicated by oxygenation index, SOFA, SAPS II and APACHE II as the baseline characteristics of included patients,
2. different causes of immunosuppression.
3. different causes of acute respiratory failure.
4. types of NIV(CPAP or BiPAP).

Sensitivity analysis will be carried out to assess the effect of excluding the studies with high overall risk of bias or the studies in which immunocompromised patients with ARF are a subgroup other than the overall participants.

Assessment of pooled effect estimates

For the pooled assessment of treatment effect, the Mantel-Haenszel method will be used for fixed effects estimation and the DerSimonian and Laird method for random effects estimation. The random effects model was preferred if heterogeneity of treatment effects was present; otherwise a fixed effect model would be used. P values < 0.05 will be considered statistically significant. Where data aggregation is not possible due to substantial heterogeneity, the results will be presented in tables and discussed afterwards.

The quality of evidence contributing to pooled effect estimates will be evaluated following the principle of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[27] According to GRADE system, the starting point of quality of each evidence from RCT is considered to be high, and will be downgraded with the presence of study limitations, imprecision, inconsistency, indirectness or publication bias.

Finally, all the findings will be summarized in a table using the GRADE principles.

DISCUSSION

The benefit of NIV among immunocompromised patients with ARF is unclear. The recommendation of the use of NIV in those patients has been challenged by the different results of the RCTs conducted in recent years. This systematic review and meta-analysis will synthesize evidences from all the available RCTs on the efficacy of NIV and oxygen therapy as the first oxygenation strategy on adult immunocompromised patients with ARF. The evidence would be useful for clinicians regarding the use of NIV or oxygen therapy in those patients. We have noticed that severity of patients in the M Wermke's study is lower than those in Antonelli's and Hilbert's studies, which indicates that NIV might be more appropriate among severe patients, especially patients in ICU. The expected result is likely to be obtained by performing subgroup analysis. In the worst case where no conclusion could be reached, the finding of this meta-analysis could still provide guidance for the RCTs in the future to find out the characteristics of patients who will benefit from NIV.

Author affiliations

[1]Department of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing, China.
[2]Emergency Department, Peking Union Medical College Hospital, Beijing, China.
[3]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China.
[4]Department of Science and Technology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.
[5]Department of Orthopaedics, Peking Union Medical College Hospital, Beijing, China.
[6]Department of Gastroenterology, Peking Union Medical College Hospital, Beijing, China.
[7]Department of Anatomy, Histology and Embryology; Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China.

Contributors

YL, TW and ZL developed the initial idea for this protocol. LZ, GL and KH contributed to the search strategy. Data abstraction forms were designed by MW. JS and CM were consulted about intensive care and pulmonary medicine. JH, YM, YL, HZ and XY were consulted about emergency medicine. YY and ZL contributed to the original draft. YL, TW and LZ were responsible for the revision of the draft. ZL, TW and YY were considered equal contributors to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared

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Supplement 1. MEDLINE Search Strategy.

((((((((((((((((Randomized Controlled Trial) OR RCT) OR Controlled Clinical Trial) OR Clinical Trial) OR random allocation) OR CCT)) OR (((Randomized Controlled Trial [Publication Type]) OR Controlled Clinical Trial [Publication Type]) OR Clinical Trial [Publication Type])))) OR (((Clinical Trials as Topic[MeSH Terms]) OR Controlled Clinical Trials as Topic[MeSH Terms]) OR Randomized Controlled Trials as Topic[MeSH Terms])))))) AND ((((hematological) OR(hematological malignancy) OR(hematologic malignancy) OR(Hematologic) OR(Hematology)OR(cancer)OR(Stem Cell Transplantation)OR(SCT)) OR (Neutropenia[MeSH Terms]) OR(Hematologic Neoplasms[MeSH Terms]) OR(Lymphoma[MeSH Terms]) OR(Leukemia[MeSH Terms]) OR(Multiple Myeloma[MeSH Terms]) OR(Myelodysplastic Syndromes[MeSH Terms]) OR(Bone Marrow Transplantation[MeSH Terms])OR(Neoplasms[MeSH Terms])OR(Stem Cell Transplantation[MeSH Terms])))) AND ((((((((((Respiration, Artificial[MeSH Terms]) OR Noninvasive Ventilation [MeSH Terms]) OR High-Frequency Ventilation[MeSH Terms]) OR Continuous Positive Airway Pressure[MeSH Terms]) OR Positive-Pressure Respiration[MeSH Terms]) OR Intermittent Positive-Pressure Ventilation[MeSH Terms])) OR ((((((((((((((((((((((((((((Mechanical ventilation) OR niv) OR nppv) OR nippv) OR non invasive positive pressure ventilation) OR non invasive ventilation) OR positive end expiratory pressure) OR peep) OR assisted ventilation) OR artificial ventilation) OR assist control) OR pressure support ventilation) OR bipap) OR bilevel positive airway pressure) OR bi-level positive airway pressure) OR cpap) OR Continuous positive airway pressure ventilation) OR continuous positive airway pressure) OR proportional assist ventilation) OR PAV)) OR controlled mechanical ventilation) OR intermittent mandatory ventilation) OR volume controlled ventilation) OR pressure controlled ventilation) OR assisted CMV)) OR IMV) OR VCV) OR PCV) OR SIMV))) OR ventilation)))) AND ("1980/01/01"[PDat] : "2016/12/20"[PDat]) AND Humans[Mesh]) Filters: Publication date from 1980/01/01 to 2016/12/20; Humans

Supplement 2. EMBASE Search Strategy.

('immune deficiency'/exp OR 'immunocompromized patient'/exp OR 'immunosuppressive treatment'/exp OR 'immunosuppressive agent'/exp OR 'antineoplastic agent'/exp OR 'leukopenia'/exp OR 'organ transplantation'/exp OR 'bone marrow transplantation'/exp OR 'glucocorticoid'/exp OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus infection'/exp OR 'hematologic malignancy'/exp OR 'chemotherapy'/exp OR 'corticosteroid'/exp OR 'solid tumor'/exp OR 'leukopenia'/exp OR 'lymphoma'/exp OR 'multiple myeloma'/exp OR 'Myelodysplastic Syndromes'/exp OR 'immune deficiency' OR 'immunocompromized patient' OR 'immunosuppressive treatment' OR 'immunosuppressive agent' OR 'antineoplastic agent' OR 'leukopenia' OR 'organ transplantation' OR 'bone marrow transplantation' OR 'glucocorticoid' OR 'human immunodeficiency virus' OR 'human immunodeficiency virus infection' OR 'hematologic malignancy' OR 'chemotherapy' OR 'corticosteroid' OR 'solid tumor' OR 'leukopenia' OR 'lymphoma' OR 'multiple myeloma' OR 'Myelodysplastic Syndromes' OR 'aids' OR 'mds' OR 'mm' OR 'hiv') AND ('respiratory distress syndrome'/exp OR 'acute respiratory failure'/exp OR 'adult respiratory distress syndrome'/exp OR 'chronic obstructive lung disease'/exp OR 'asthma'/exp OR 'obesity hypoventilation syndrome'/exp OR 'lung edema'/exp OR 'pneumonia'/exp OR 'interstitial lung disease'/exp OR 'respiratory distress syndrome' OR 'acute respiratory failure' OR 'adult respiratory distress syndrome' OR 'chronic obstructive lung disease' OR 'asthma' OR 'obesity hypoventilation syndrome' OR 'lung edema' OR 'pneumonia' OR 'interstitial lung disease' OR 'cardiogenic pulmonary edema' OR 'acute lung injury' OR 'dpld' OR 'cpe' OR 'ohs' OR

'copd' OR 'ards' OR 'ali') AND ('ventilator' OR 'ventilator'/exp OR 'artificial ventilation' OR 'artificial ventilation'/exp OR 'mechanical ventilation' OR 'niv' OR 'nppv' OR 'nippv' OR 'non invasive positive pressure ventilation' OR 'non invasive ventilation' OR 'positive end expiratory pressure' OR 'peep' OR 'assisted ventilation' OR 'artificial ventilation' OR 'assist control' OR 'pressure support ventilation' OR 'bipap' OR 'bilevel positive airway pressure' OR 'bi-level positive airway pressure' OR 'cpap' OR 'continuous positive airway pressure ventilation' OR 'continuous positive airway pressure' OR 'proportional assist ventilation' OR 'pav' OR 'controlled mechanical ventilation' OR 'intermittent mandatory ventilation' OR 'volume controlled ventilation' OR 'pressure controlled ventilation' OR 'assisted cmv') AND('Randomized Controlled Trial'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'Randomized Controlled Trial' OR 'controlled clinical trial' OR 'clinical trial' OR 'RCT' OR 'CCT')

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Checklist result
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 2, Line 3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	None
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 2, Line 7, 55
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 7, Line 38
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 7, Line 47
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 7, Line 47
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3 Line 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, Line 14
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4, Line 9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 4, Line 53
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4, Line 53

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6, Line 4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5, Line 17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5, Line 27
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5, Line 27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 4, Line 41
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5, Line 44
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6, Line 6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6, Line 29, 49
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6, Line 35
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, Line 55
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6, Line 30
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6, Line 58

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Efficacy of non-invasive ventilation and oxygen therapy on immunocompromised patients with acute respiratory failure: protocol for a systematic review and meta-analysis of randomized controlled trials

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Complete List of Authors:	Li, Zongru; Peking Union Medical College Hospital, Emergency Department Wang, Tao; Peking Union Medical College Hospital, Emergency Department Yang, Yi; Peking Union Medical College Hospital, Emergency Department Zhang, Lixi; Department of Cardiology Wang, Meng; Beijing Tiantan Hospital, Capital Medical University, Department of Science and Technology Liu, Gang; Peking Union Medical College Hospital, Department of orthopaedics He, Kun; Peking Union Medical College Hospital, Department of Gastroenterology Shi, Juhong; Peking Union Medical College Hospital, Department of Pulmonary medicine He, Jianqiang; Peking Union Medical College Hospital, Emergency Department Ma, Yong; Peking Union Medical College Hospital, Emergency Department Li, Yi; Chinese Academy of Medical Sciences and Peking Union Medical College, Emergency department Zhu, Huadong; Peking Union Medical College Hospital, Emergency Department Yu, Xuezhong; Peking Union Medical College Hospital, Emergency Department
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Efficacy of non-invasive ventilation and oxygen therapy on immunocompromised patients with acute respiratory failure: protocol for a systematic review and meta-analysis of randomized controlled trials

Zongru Li[1†], Tao Wang[1†], Yi Yang[1†], Lixi Zhang[2], Meng Wang[3], Gang Liu[4], Kun He[5], Juhong Shi[6], , Jianqiang He[1], Yong Ma[1], Yi Li[1*], Huadong Zhu[1] and Xuezhong Yu[1*]

ABSTRACT

Background The number of immunocompromised patients has increased in recent years. Acute respiratory failure is a common complication leading to ICU admission and high mortality among such patients. The use of non-invasive ventilation(NIV) or oxygen therapy among these patients remains controversial, according to the inconsistent results of several randomized clinical trials(RCTs). This meta-analysis aims to evaluate whether NIV or oxygen therapy is the more appropriate initial oxygenation strategy for the immunocompromised patients with acute respiratory failure.

Method We will search all the RCTs that compared the efficacy of NIV and oxygen therapy on immunocompromised adult patients with acute respiratory failure on the major databases (Cochrane Library, MEDLINE, EMBASE, Web of science etc.), conference proceedings and grey literature. Eligible RCTs will be included in accordance with the pre-specified eligibility criteria. The risk of bias will be assessed using the Cochrane Collaboration criteria and the quality of evidence will be assessed with the GRADE system. Data will be extracted with a standardized form and analyzed using RevMan 5.3 analyses software. Heterogeneity will be assessed using I2 statistic and the source of which will be investigated. Publication bias will be identified with the funnel plot.

Discussion: The finding of this meta-analysis will provide evidence for the use of NIV or oxygen therapy as the initial oxygenation strategy among adult immunocompromised patients with ARF.

Strengths and limitations of this study

□There is no existing meta-analysis on the use of non-invasive ventilation among immunocompromised patients with acute respiratory failure.

□This meta-analysis includes only randomized clinical trials and will thus provide the highest quality of evidence for clinical practice.

□Subgroup analysis based on different levels of severity might support the use of NIV in more severe patients.

□The number of included studies is likely to be small.

KEY WORDS: Immunocompromised patients, acute respiratory failure, non-invasive ventilation, oxygen therapy, mortality, intubation rate

† Zongru Li, Tao Wang and Yi Yang contributed equally to this article.
* Correspondence: billliyi@126.com (Y. Li), and yxz@medmail.com.cn (X.Yu).
[1] Emergency Department, Peking Union Medical College Hospital, Beijing, 100730, China.
Full list of author information is available at the end of the article.

BACKGROUND

Description of the problem

Numerous factors such as the epidemic of AIDS,[1] improved survival rates of active malignancies,[2 3] innovative advances in organ transplantation,[4] better outcomes of allogeneic hematopoietic cell transplantations[5] and the more common application of immunosuppressive therapy have contributed to an increasing number of immunocompromised patients. These patients are more vulnerable to infection due to their inadequate immune response to foreign antigens.[6] Some life-threatening complications can lead to requirement of ICU admission for these patients, among which acute respiratory failure(ARF) is the most common with particularly high mortality.[7] ARF is a relatively sudden onset of dysfunction of the respiratory system, and the most common causes among immunocompromised patients are immunosuppression-related infection,[8-10] disease-specific infiltration,[11] chemotherapy-associated organ toxicity[12] and idiopathic pneumonia syndrome associated with GVHD.[13] For severe ARF patients, invasive ventilation is required in order to support alveolar ventilation; however, such intervention also contributes to high mortality due to the risk of ventilator-associated pneumonia.[14] Therefore, the strategy of delivering oxygen is of great importance for improvement of oxygenation, which may lead to reduction of intubation rate and mortality.

Description of the intervention

The percentage of usage of non-invasive ventilation(NIV) has increased from 29% in the year of 1997 to 42% in 2011 among patients with ARF[15]. The benefits NIV may bring are associated not only with the degree of inspiratory workload spared by the positive airway pressure provided, but also with the invasive-ventilation-associated complications that are prevented by NIV.[16-18] However, the failure of NIV was identified as an independent risk factor for ICU mortality, which occurred in half of the critically ill hematologic patients.[19] Oxygen therapy, conducted via either nasal cannula, venturi mask or reservoir mask, is the basic technique used in patients with acute lung injury. Patients might benefit from oxygen therapy for less discomfort or intolerance compared with NIV.[20]

Why is it important to do this review?

The use of NIV was recommended for patients with acute respiratory failure in the setting of immunosuppression weak(Grade 2B) , [21] based on Antonelli's and Hilbert's randomized clinical trials(RCTs) published in 2000 and 2001, [22 23] respectively. Findings of these two studies showed that NIV was associated with reduced intubation rate and mortality in immunocompromised patients with ARF. However, findings to the contrary can be found in the publications of Wermke et al. [24] and Lemiale et al.[25] Both of their studies showed that NIV was not associated with lowered intubation rate or mortality compared with oxygen therapy. No solid conclusion could be drawn based on the data currently available according to the reviews published in recent years, except that NIV should be applied with great caution in this group of patients.[26] [27] Since the application of NIV in immunocompromised patients with ARF remains controversial, a systematic review and meta-analysis that summarizes all the available RCTs is called for to provide guidance for the management of this group of patients. To our knowledge, no meta-analysis about this topic has yet been published.

The aim of this study is to determine the efficacy of NIV in comparison with oxygen therapy as the initial oxygenation strategy on the immunocompromised patients with ARF, with respect to mortality, intubation rate and hospital length of stay and also to explore the patient selection strategy for the initial oxygenation strategy. Furthermore, the proposed systematic review will provide evidence for the use of NIV in subgroups of patients with different levels of disease severity, cause of immunosuppression and cause of ARF etc.

METHOD

This protocol of systematic review was reported following Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guidelines.[28]

Eligibility criteria: participants, interventions, comparisons and outcomes

Type of studies

Only RCTs will be included. Other types of studies such as observational studies, cohort studies, case–control studies and laboratory studies will be excluded. All included studies have to comply with international ethic rules.

Type of participants

This review will include RCTs involving immunocompromised adult patients with acute respiratory failure. The immunocompromised patients include patients with hematological malignancy, solid cancer, AIDS or those receiving corticosteroid or cytotoxic therapy, or those having gone through solid organ or stem cell transplantation. ARF is defined as respiratory rate >30 breaths/min, PaO2 <60 mm Hg on room air or labored breathing.[19] RCTs with a subgroup of participants who meet the criteria above will also be included, on the condition that the data of outcome for this subgroup is available. It should be noted that RCTs will be included if more than 85% of the involved participants meet the eligibility criteria, even if the outcomes of these eligible participants are unavailable.

Type of intervention

The intervention group refers to patients treated with NIV, which includes two main modes: continuous positive airways pressure (CPAP) and bi-level positive airway pressure (BiPAP).

The control group refers to patients treated with oxygen therapy. High-flow nasal oxygen(HFNO) therapy is a relatively new method of oxygen therapy that differentiates itself from oxygen therapy by providing positive pressure;[29] Patients who have been treated with HFNO are therefore excluded from this study. As for the reports where mixed usage of HFNO and oxygen were adopted, the trial will be included if the data of sole oxygen therapy can be retrieved.We will include RCTs which directly compare NIV with oxygen therapy as the initial oxygenation strategy for acute respiratory failure, regardless of whether the other oxygenation method was applied later.

Type of outcome measures

- Primary outcome

(1)Mortality: hospital mortality, ICU mortality and mortality at the last time available, in case that mortalities of all included studies were not measured at the same time period.

- Secondary outcome

(1) Incidence of tracheal intubation.

(2) Length of ICU stay.

(3) Length of hospital stay.

(4) Complications related to NIV.

(5) Rate of pulmonary complications not present on admission.

Eligible RCTs should include at least one of the primary outcomes listed above.

Search strategy for identification of studies

Electronic searches

Two reviewers (Dr. Y.Y. and Dr. L.Z.) will search the following databases: The Cochrane Library, MEDLINE, EMBASE, Web of science, CINAHL, LILACS and PEDro by using database-specific search strategies. These electronic databases will be searched from January 1980 to date. No limitation

of language or publication status will be applied. The filter for clinical trials will be used for each database. The following keywords will be used during the database searching: immunosuppression, hematological malignancy, cancer, transplantation, corticosteroid, cytotoxic, non-invasive ventilation, acute respiratory failure. The detailed search strategy can be found in Supplement 1 and 2.

Searching other resources

The references of relevant studies and review articles will be sought for potential information missing in database search. Conference proceedings and grey literature will be checked. The experts in the field will be contacted to identify published and unpublished trials. We will also access www.controlledtrials.com and clinicaltrials.gov. for ongoing and unpublished studies, and the conductors or authors will be contacted for further information if necessary.

Screening of studies

All results identified by the search strategy will be screened by two reviewers (Dr. Z.L. and Dr. T.W.) independently. Initial screening will be performed on titles and abstracts respectively, where irrelevant studies will be excluded according to the eligibility criteria; full texts of the remaining studies will subsequently be downloaded and screened. Reasons of exclusion will be documented and classified. Any disagreements between the reviewers will be solved through discussion, and the third author (Dr. Y.L.) will be consulted if consensus cannot be reached.

Data extraction and management

Two reviewers (Dr. Z.L. and Dr. T.W.) will independently extract all the data in the included studies. A standard form will be used in extracting the following data:

1. Characteristics of the study: design, setting, method of randomization, allocation concealment, blinding, and dropouts.

2. Participants: number enrolled in each group, gender, age, respiratory rate, oxygen saturation, oxygenation index(PaO_2/FiO_2), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), new Simplified Acute Physiology Scale (SAPS II), cause of ARF, cause of immunosuppression.

3. Interventions: mode of NIV (CPAP or BiPAP), frequency and duration of ventilation; oxygen therapy and co-interventions.

4. Outcome: primary outcomes and secondary outcomes listed above.

Authors will be contacted for the missing data or subgroup data that are unavailable from the text. The consistency of data will be ensured by these two reviewers.

Assessment of risk of bias

For the included articles, the risk of bias will be assessed by two reviewers (Dr. Y.Y. and Dr. L.Z.) independently, using the Cochrane Collaboration criteria[30] which includes random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting. Each criterion will be explicitly judged and classified as ‘low risk’, ‘high risk’, or ‘unclear risk’. Authors will be contacted for supplemental information if details for assessment reported in the text are considered inadequate. The risk will be rated as ‘unclear’ if no further information is obtained. The result of assessment of each study will be summarized in a chart. Overall risk of bias for each study will be defined as ‘low’ if risk of all bias components is ranked as ‘low’, or ‘moderate’ if at least one component is ranked ‘unclear’ with no component ranked as ‘high’, or ‘high’ if one or more component is ranked as having a ‘high’ risk of bias.

Data analyses and assessment of heterogeneity

Measures of treatment effect

The statistical analyses will be performed using RevMan 5.3 analyses software of the Cochrane Collaboration. Continuous data such as length of ICU stay and length of hospital stay will be presented as mean differences (MD) with 95% confidence intervals (95% CIs). Dichotomous data such as the number of intubation and death will be presented as risk ratios (RR) with 95% CIs. When the rates rather than the numbers are reported, we will calculate the numbers based on the data provided.

Dealing with missing data

Missing data will be dealt with following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Corresponding authors will be contacted for further information. If the missing data cannot be obtained, we will specify the assumptions of the methods used to cope with missing data according to the cause of data loss (i.e. random dropout or poor outcome). We will perform sensitivity analyses to evaluate how sensitive results are to the changes in the assumptions that are made. In the Discussion section of the review, we will analyze the potential impact the missing data may have on the findings of the review.

Assessment of heterogeneity

Before any outcome is pooled, we will assess the impact of heterogeneity using $\chi 2$ test and I^2 statistic [classified as low (< 40%), moderate (40-60%) or high (> 60%)]. I^2 values greater than 60% will be considered as having substantial heterogeneity. If substantial heterogeneity is present, we will investigate the potential source of heterogeneity by conducting exploratory analyses.

Assessment of reporting biases

Protocols of included trials will be searched using the databases mentioned above. We will contact the authors to obtain complete data of the protocols' envisioned outcomes as well as reasons for the non-reporting of certain outcomes. Publication bias will be assessed by visual analysis of the funnel plot if the number of included studies is equal to or greater than 10.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore potential sources of heterogeneity. Possible sources of heterogeneity are:

1. severity of acute respiratory failure before randomization indicated by oxygenation index, SOFA, SAPS II and APACHE II as the baseline characteristics of included patients,
2. different causes of immunosuppression, i.e HIV or non-HIV
3. different causes of acute respiratory failure.
4. types of NIV (CPAP or BiPAP).

Sensitivity analysis will be carried out to assess the effect of exclusion of the studies with high overall risk of bias or the studies in which immunocompromised patients with ARF are a subgroup of the overall participants.

Assessment of pooled effect estimates

As to the pooled assessment of treatment effect, the Mantel-Haenszel method will be used for fixed effects estimation and the DerSimonian and Laird method for random effects estimation. The random effects model was preferred if heterogeneity of treatment effects was present; otherwise a fixed effect model would be used. P values < 0.05 will be considered statistically significant. Results will be presented in tables and discussed afterwards where data aggregation is not possible due to substantial heterogeneity.

The quality of evidence contributing to pooled effect estimates will be evaluated following the principle of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

system.[31] According to GRADE system, quality of each evidence from RCT is considered to be high, and will be downgraded with the presence of study limitations, imprecision, inconsistency, indirectness or publication bias.

Finally, all the findings will be summarized in a table following the GRADE principles.

DISCUSSION

The benefit of NIV among immunocompromised patients with ARF is unclear. The recommendation of the use of NIV in those patients has been challenged by the different results of the RCTs conducted in recent years. This systematic review and meta-analysis will synthesize evidences from all the available RCTs, which would be useful for clinicians regarding the use of NIV or oxygen therapy in those patients. Besides, subgroup analysis will be performed to find out more specific indications for clinical decision making.

Patients who have been treated with HFNO will not be included in our studies, since HFNO is distinctively different from oxygen therapy in terms of equipment, cost and tolerance. HFNO requires more advanced equipment, thus it's not as popularized as standard oxygen therapy especially in developing countries such as China. Besides, the effect of HFNO is different from traditional oxygen therapy. Maggiore SM's study showed that HFNO results in fewer oxygen desaturations, lower reintubation rate and less discomfort compared to oxygen therapy after exubation.[32] And in Frat's RCT conducted among patients with ARF, HFNO resulted in reduced mortality compared with standard oxygen therapy or NIV.[33] Therefore, exclusion should be made so that HFNO would not become a confounding factor when we compare NIV with oxygen therapy.

HIV patients is a specific group, thus will be analyzed in subgroup analysis. A systematic review conducted by our team showed that non-invasive ventilation had great advantage over invasive ventilation for HIV patients, and this advantage is less obvious among non-HIV patients.[34] Furthermore, recent studies showed a higher mortality rate of Pneumocystis pneumonia infection in non-HIV patients in comparison with HIV patients.[35 36] Therefore, we propose a hypothesis that the effect of NIV is different between HIV and non-HIV patients, which will be examined by subgroup analysis in this meta-analysis.

The overall purpose of this study is to determine whether NIV is better than oxygen therapy as the initial oxygenation strategy in adult immunocompromised patients with ARF. We will also explore the patient selection strategy for the initial oxygenation strategy, with respect to severity, cause of immunosuppression and cause of ARF. The finding of this meta-analysis could also provide guidance for the RCTs in the future to find out the characteristics of patients who might benefit from NIV.

Author affiliations

[1]Emergency Department, Peking Union Medical College Hospital, Beijing, China.

[2]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China.

[3]Department of Science and Technology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

[4]Department of Orthopaedics, Peking Union Medical College Hospital, Beijing, China.

[5]Department of Gastroenterology, Peking Union Medical College Hospital, Beijing, China.

[6]Department of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing, China.

Contributors

YL, TW and ZL developed the initial idea for this protocol. LZ, GL and KH contributed to the search strategy. Data abstraction forms were designed by MW. JS was consulted about intensive care and pulmonary medicine. JH, YM, YL, HZ and XY were consulted about emergency medicine. YY and ZL

contributed to the original draft. YL, TW and LZ were responsible for the revision of the draft. ZL, TW and YY were considered equal contributors to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared

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Supplement 1. MEDLINE Search Strategy.

((((((((((((((((((((Immunosuppression[MeSH Terms]) OR Immunocompromised Host[MeSH Terms]) OR Immunologic Deficiency Syndromes[MeSH Terms]) OR Neutropenia[MeSH Terms]) OR Acquired Immunodeficiency Syndrome[MeSH Terms]) OR HIV[MeSH Terms]) OR Carcinoma[MeSH Terms]) OR Hematologic Neoplasms[MeSH Terms]) OR Lymphoma[MeSH Terms]) OR Leukemia[MeSH Terms]) OR Multiple Myeloma[MeSH Terms]) OR Myelodysplastic Syndromes[MeSH Terms]) OR Organ Transplantation[MeSH Terms]) OR Bone Marrow Transplantation[MeSH Terms]) OR Glucocorticoids [Pharmacological Action]) OR Antineoplastic Agents [Pharmacological Action]) OR Immunosuppressive Agents [Pharmacological Action])) OR ((((((((((((((immunocompromise) OR immunocompromised) OR immunodeficiency) OR immunosuppressive) OR immunosuppressed) OR immune defect) OR hematological patients) OR hematological malignancies) OR hematologic malignancies) OR cancer) OR AIDS) OR acquired immunodeficiency syndrome) OR cytotoxic therapy) OR glucocorticoid) OR corticosteroid) OR chemotherapy))) AND ((((((((((acute lung injury[MeSH Terms]) OR Respiratory Distress Syndrome, Adult[MeSH Terms]) OR Pulmonary Disease, Chronic Obstructive[MeSH Terms]) OR asthma[MeSH Terms]) OR obesity hypoventilation syndrome[MeSH Terms]) OR pulmonary edema[MeSH Terms]) OR pneumonia[MeSH Terms]) OR Lung Diseases, Interstitial[MeSH Terms])) OR ((((((((((((DPLD) OR Diffuse Parenchymal Lung Disease) OR interstitial lung disease) OR CPE) OR cardiogenic pulmonary edema) OR OHS) OR COPD) OR chronic obstructive pulmonary disease) OR ARDS) OR acute respiratory distress syndrome) OR ALI) OR ARF) OR acute respiratory failure))) AND ((((((((Respiration, Artificial[MeSH Terms]) OR Noninvasive Ventilation [MeSH Terms]) OR High-Frequency Ventilation[MeSH Terms]) OR Continuous Positive Airway Pressure[MeSH Terms]) OR Positive-Pressure Respiration[MeSH Terms]) OR Intermittent Positive-Pressure Ventilation[MeSH Terms])) OR ((((((((((((((((((((((((((((Mechanical ventilation) OR niv) OR nppv) OR nippv) OR non invasive positive pressure ventilation) OR non invasive ventilation) OR positive end expiratory pressure) OR peep) OR assisted ventilation) OR artificial ventilation) OR assist control) OR pressure support ventilation) OR bipap) OR bilevel positive airway pressure) OR bi-level positive airway pressure) OR cpap) OR Continuous positive airway pressure ventilation) OR continuous positive airway pressure) OR proportional assist ventilation) OR PAV)) OR controlled mechanical ventilation) OR intermittent mandatory ventilation) OR volume controlled ventilation) OR pressure controlled ventilation) OR assisted CMV)) OR IMV) OR VCV) OR PCV) OR SIMV))) AND ((((((((((Randomized Controlled Trial) OR RCT) OR Controlled Clinical Trial) OR Clinical Trial) OR random allocation) OR CCT)) OR (((Randomized Controlled Trial [Publication Type]) OR Controlled Clinical Trial [Publication Type]) OR Clinical Trial [Publication Type]))) OR (((Clinical Trials as Topic[MeSH Terms]) OR Controlled Clinical Trials as Topic[MeSH Terms]) OR Randomized Controlled Trials as Topic[MeSH Terms]))) AND ("1980/01/01"[PDat] : "2017/03/05"[PDat]) AND Humans[Mesh]) Filters: Publication date from 1980/01/01 to 2017/03/05; Humans

Supplement 2. EMBASE Search Strategy.

('immune deficiency'/exp OR 'immunocompromized patient'/exp OR 'immunosuppressive treatment'/exp OR 'immunosuppressive agent'/exp OR 'antineoplastic agent'/exp OR 'leukopenia'/exp OR 'organ transplantation'/exp OR 'bone marrow transplantation'/exp OR 'glucocorticoid'/exp OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus infection'/exp OR 'hematologic malignancy'/exp OR 'chemotherapy'/exp OR 'corticosteroid'/exp OR 'solid tumor'/exp OR 'leukopenia'/exp OR 'lymphoma'/exp OR 'multiple myeloma'/exp OR 'Myelodysplastic Syndromes'/exp

OR 'immune deficiency' OR 'immunocompromized patient' OR 'immunosuppressive treatment' OR 'immunosuppressive agent' OR 'antineoplastic agent' OR 'leukopenia' OR 'organ transplantation' OR 'bone marrow transplantation' OR 'glucocorticoid' OR 'human immunodeficiency virus' OR 'human immunodeficiency virus infection' OR 'hematologic malignancy' OR 'chemotherapy' OR 'corticosteroid' OR 'solid tumor' OR 'leukopenia' OR 'lymphoma' OR 'multiple myeloma' OR 'Myelodysplastic Syndromes' OR 'aids' OR 'mds' OR 'mm' OR 'hiv') AND ('respiratory distress syndrome'/exp OR 'acute respiratory failure'/exp OR 'adult respiratory distress syndrome'/exp OR 'chronic obstructive lung disease'/exp OR 'asthma'/exp OR 'obesity hypoventilation syndrome'/exp OR 'lung edema'/exp OR 'pneumonia'/exp OR 'interstitial lung disease'/exp OR 'respiratory distress syndrome' OR 'acute respiratory failure' OR 'adult respiratory distress syndrome' OR 'chronic obstructive lung disease' OR 'asthma' OR 'obesity hypoventilation syndrome' OR 'lung edema' OR 'pneumonia' OR 'interstitial lung disease' OR 'cardiogenic pulmonary edema' OR 'acute lung injury' OR 'dpld' OR 'cpe' OR 'ohs' OR 'copd' OR 'ards' OR 'ali') AND ('ventilator' OR 'ventilator'/exp OR 'artificial ventilation' OR 'artificial ventilation'/exp OR 'mechanical ventilation' OR 'niv' OR 'nppv' OR 'nippv' OR 'non invasive positive pressure ventilation' OR 'non invasive ventilation' OR 'positive end expiratory pressure' OR 'peep' OR 'assisted ventilation' OR 'artificial ventilation' OR 'assist control' OR 'pressure support ventilation' OR 'bipap' OR 'bilevel positive airway pressure' OR 'bi-level positive airway pressure' OR 'cpap' OR 'continuous positive airway pressure ventilation' OR 'continuous positive airway pressure' OR 'proportional assist ventilation' OR 'pav' OR 'controlled mechanical ventilation' OR 'intermittent mandatory ventilation' OR 'volume controlled ventilation' OR 'pressure controlled ventilation' OR 'assisted cmv') AND('Randomized Controlled Trial'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'Randomized Controlled Trial' OR 'controlled clinical trial' OR 'clinical trial' OR 'RCT' OR 'CCT')

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Checklist result
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 2, Line 3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	None
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 2, Line 7, 55
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 7, Line 38
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 7, Line 47
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 7, Line 47
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3 Line 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, Line 14
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4, Line 9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 4, Line 53
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4, Line 53

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6, Line 4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5, Line 17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5, Line 27
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5, Line 27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 4, Line 41
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5, Line 44
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6, Line 6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6, Line 29, 49
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6, Line 35
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, Line 55
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6, Line 30
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6, Line 58

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Efficacy of non-invasive ventilation and oxygen therapy on immunocompromised patients with acute hypoxemic respiratory failure: protocol for a systematic review and meta-analysis of randomized controlled trials

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Complete List of Authors:	Li, Zongru; Peking Union Medical College Hospital, Emergency Department Wang, Tao; Peking Union Medical College Hospital, Emergency Department Yang, Yi; Peking Union Medical College Hospital, Emergency Department Zhang, Lixi; Department of Cardiology Wang, Meng; Beijing Tiantan Hospital, Capital Medical University, Department of Science and Technology Liu, Gang; Peking Union Medical College Hospital, Department of orthopaedics He, Kun; Peking Union Medical College Hospital, Department of Gastroenterology Shi, Juhong; Peking Union Medical College Hospital, Department of Pulmonary medicine He, Jianqiang; Peking Union Medical College Hospital, Emergency Department Ma, Yong; Peking Union Medical College Hospital, Emergency Department Li, Yi; Chinese Academy of Medical Sciences and Peking Union Medical College, Emergency department Zhu, Huadong; Peking Union Medical College Hospital, Emergency Department Yu, Xuezhong; Peking Union Medical College Hospital, Emergency Department
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Respiratory medicine, Emergency medicine
Keywords:	Immunocompromised patients, acute hypoxemic respiratory failure, non-invasive ventilation, oxygen therapy, mortality, intubation rate

Efficacy of non-invasive ventilation and oxygen therapy on immunocompromised patients with acute hypoxemic respiratory failure: protocol for a systematic review and meta-analysis of randomized controlled trials

Zongru Li[1†], Tao Wang[1†], Yi Yang[1†], Lixi Zhang[2], Meng Wang[3], Gang Liu[4], Kun He[5], Juhong Shi[6], , Jianqiang He[1], Yong Ma[1], Yi Li[1*], Huadong Zhu[1] and Xuezhong Yu[1*]

ABSTRACT

Background The number of immunocompromised patients has increased in recent years. Acute respiratory failure(ARF) is a common complication leading to ICU admission and high mortality among such patients. The use of non-invasive ventilation(NIV) or oxygen therapy among these patients remains controversial, according to the inconsistent results of several randomized clinical trials(RCTs). This meta-analysis aims to evaluate whether NIV or oxygen therapy is the more appropriate initial oxygenation strategy for the immunocompromised patients with acute respiratory failure.

Method We will search all the RCTs that compared the efficacy of NIV and oxygen therapy on immunocompromised adult patients with acute hypoxemic respiratory failure on the major databases (Cochrane Library, MEDLINE, EMBASE, Web of science etc.), conference proceedings and grey literature. Eligible RCTs will be included in accordance with the pre-specified eligibility criteria. The risk of bias will be assessed using the Cochrane Collaboration criteria and the quality of evidence will be assessed with the GRADE system. Data will be extracted with a standardized form and analyzed using RevMan 5.3 analyses software. Heterogeneity will be assessed using I2 statistic and the source of which will be investigated. Publication bias will be identified with the funnel plot.

Ethics and dissemination Ethical approval is not required since it is not carried out in humans. The systematic review will be published in peer-reviewed journals and disseminated extensively through conferences.

Strengths and limitations of this study

□There is no existing meta-analysis on the use of non-invasive ventilation among immunocompromised patients with acute hypoxemic respiratory failure.

□This meta-analysis includes only randomized clinical trials and will thus provide the highest quality of evidence for clinical practice.

□Subgroup analysis based on different levels of severity might support the use of NIV in more severe patients.

□The number of included studies is likely to be small.

KEY WORDS: Immunocompromised patients, acute hypoxemic respiratory failure, non-invasive ventilation, oxygen therapy, mortality, intubation rate

† Zongru Li, Tao Wang and Yi Yang contributed equally to this article.
* Correspondence: billliyi@126.com (Y. Li), and yxz@medmail.com.cn (X.Yu).
[1] Emergency Department, Peking Union Medical College Hospital, Beijing, 100730, China.
Full list of author information is available at the end of the article.

BACKGROUND

Description of the problem

Numerous factors such as the epidemic of AIDS,[1] improved survival rates of active malignancies,[2 3] innovative advances in organ transplantation,[4] better outcomes of allogeneic hematopoietic cell transplantations[5] and the more common application of immunosuppressive therapy have contributed to an increasing number of immunocompromised patients. These patients are more vulnerable to infection due to their inadequate immune response to foreign antigens.[6] Some life-threatening complications can lead to requirement of ICU admission for these patients, among which acute respiratory failure(ARF) is the most common with particularly high mortality.[7] ARF is a relatively sudden onset of dysfunction of the respiratory system, and the most common causes among immunocompromised patients are immunosuppression-related infection,[8-10] disease-specific infiltration,[11] chemotherapy-associated organ toxicity[12] and idiopathic pneumonia syndrome associated with GVHD.[13] For severe ARF patients, invasive ventilation is required in order to support alveolar ventilation; however, such intervention also contributes to high mortality due to the risk of ventilator-associated pneumonia.[14] Therefore, the strategy of delivering oxygen is of great importance for improvement of oxygenation, which may lead to reduction of intubation rate and mortality.

Description of the intervention

The percentage of usage of non-invasive ventilation(NIV) has increased from 29% in the year of 1997 to 42% in 2011 among patients with ARF[15]. The benefits NIV may bring are associated not only with the degree of inspiratory workload spared by the positive airway pressure provided, but also with the invasive-ventilation-associated complications that are prevented by NIV.[16-18] However, the failure of NIV was identified as an independent risk factor for ICU mortality, which occurred in half of the critically ill hematologic patients.[19] Oxygen therapy, conducted via either nasal cannula, venturi mask or reservoir mask, is the basic technique used in patients with acute lung injury. Patients might benefit from oxygen therapy for less discomfort or intolerance compared with NIV.[20]

Why is it important to do this review?

The use of NIV was recommended for patients with acute hypoxemic respiratory failure in the setting of immunosuppression weak(Grade 2B) , [21] based on Antonelli's and Hilbert's randomized clinical trials(RCTs) published in 2000 and 2001, [22 23] respectively. Findings of these two studies showed that NIV was associated with reduced intubation rate and mortality in immunocompromised patients with acute hypoxemic respiratory failure. However, findings to the contrary can be found in the publications of Wermke et al. [24] and Lemiale et al.[25] Both of their studies showed that NIV was not associated with lowered intubation rate or mortality compared with oxygen therapy. No solid conclusion could be drawn based on the data currently available according to the reviews published in recent years, except that NIV should be applied with great caution in this group of patients.[26 27] Since the application of NIV in immunocompromised patients with acute hypoxemic respiratory failure remains controversial, a systematic review and meta-analysis that summarizes all the available RCTs is called for to provide guidance for the management of this group of patients. To our knowledge, no meta-analysis about this topic has yet been published.

The aim of this study is to determine the efficacy of NIV in comparison with oxygen therapy as the initial oxygenation strategy on the immunocompromised patients with acute hypoxemic respiratory failure, with respect to mortality, intubation rate and hospital length of stay and also to explore the patient selection strategy for the initial oxygenation strategy. Furthermore, the proposed systematic review will provide evidence for the use of NIV in subgroups of patients with different levels of

disease severity, cause of immunosuppression and cause of ARF etc.

METHOD

This protocol of systematic review was reported following Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guidelines.[28]

Eligibility criteria: participants, interventions, comparisons and outcomes

Type of studies

Only RCTs will be included. Other types of studies such as observational studies, cohort studies, case–control studies and laboratory studies will be excluded. All included studies have to comply with international ethic rules.

Type of participants

This review will include RCTs involving immunocompromised adult patients with acute respiratory failure. The immunocompromised patients include patients with hematological malignancy, solid cancer, AIDS or those receiving corticosteroid or cytotoxic therapy, or those having gone through solid organ or stem cell transplantation. Acute hypoxemic respiratory failure is defined as respiratory rate >30 breaths/min, PaO2 <60 mm Hg on room air or labored breathing, and a partial pressure of arterial carbon dioxide ($PaCO_2$) not higher than 45 mmHg.[19] RCTs with a subgroup of participants who meet the criteria above will also be included, on the condition that the data of outcome for this subgroup is available. It should be noted that RCTs will be included if more than 85% of the involved participants meet the eligibility criteria, even if the outcomes of these eligible participants are unavailable.

Type of intervention

The intervention group refers to patients treated with NIV, which includes two main modes: continuous positive airways pressure (CPAP) and bi-level positive airway pressure (BiPAP).

The control group refers to patients treated with oxygen therapy. High-flow nasal oxygen(HFNO) therapy is a relatively new method of oxygen therapy that differentiates itself from oxygen therapy by providing positive pressure.[29] Patients who have been treated with HFNO are therefore excluded from this study. As for the reports where mixed usage of HFNO and oxygen were adopted, the trial will be included if the data of sole oxygen therapy can be retrieved. We will include RCTs which directly compare NIV with oxygen therapy as the initial oxygenation strategy for acute respiratory failure, regardless of whether the other oxygenation method was applied later.

Type of outcome measures

- Primary outcome

(1)Mortality: hospital mortality, ICU mortality and mortality at the last time available, in case that mortalities of all included studies were not measured at the same time period.

- Secondary outcome

(1) Incidence of tracheal intubation.

(2) Length of ICU stay.

(3) Length of hospital stay.

(4) Complications related to NIV.

(5) Rate of pulmonary complications not present on admission.

Eligible RCTs should include at least one of the primary outcomes listed above.

Search strategy for identification of studies

Electronic searches

Two reviewers (Dr. Y.Y. and Dr. L.Z.) will search the following databases: The Cochrane Library, MEDLINE, EMBASE, Web of science, CINAHL, LILACS and PEDro by using database-specific search strategies. These electronic databases will be searched from January 1980 to date. No limitation of language or publication status will be applied. The filter for clinical trials will be used for each database. The following keywords will be used during the database searching: immunosuppression, hematological malignancy, cancer, transplantation, corticosteroid, cytotoxic, non-invasive ventilation, acute respiratory failure. The detailed search strategy can be found in Supplement 1 and 2.

Searching other resources

The references of relevant studies and review articles will be sought for potential information missing in database search. Conference proceedings and grey literature will be checked. The experts in the field will be contacted to identify published and unpublished trials. We will also access www.controlledtrials.com and clinicaltrials.gov. for ongoing and unpublished studies, and the conductors or authors will be contacted for further information if necessary.

Screening of studies

All results identified by the search strategy will be screened by two reviewers (Dr. Z.L. and Dr. T.W.) independently. Initial screening will be performed on titles and abstracts respectively, where irrelevant studies will be excluded according to the eligibility criteria; full texts of the remaining studies will subsequently be downloaded and screened. Reasons of exclusion will be documented and classified. Any disagreements between the reviewers will be solved through discussion, and the third author (Dr. Y.L.) will be consulted if consensus cannot be reached.

Data extraction and management

Two reviewers (Dr. Z.L. and Dr. T.W.) will independently extract all the data in the included studies. A standard form will be used in extracting the following data:

1. Characteristics of the study: design, setting, method of randomization, allocation concealment, blinding, and dropouts.

2. Participants: number enrolled in each group, gender, age, respiratory rate, oxygen saturation, oxygenation index(PaO_2/FiO_2), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), new Simplified Acute Physiology Scale (SAPS II), cause of ARF, cause of immunosuppression.

3. Interventions: mode of NIV (CPAP or BiPAP), frequency and duration of ventilation; oxygen therapy and co-interventions.

4. Outcome: primary outcomes and secondary outcomes listed above.

Authors will be contacted for the missing data or subgroup data that are unavailable from the text. The consistency of data will be ensured by these two reviewers.

Assessment of risk of bias

For the included articles, the risk of bias will be assessed by two reviewers (Dr. Y.Y. and Dr. L.Z.) independently, using the Cochrane Collaboration criteria[30] which includes random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting. Each criterion will be explicitly judged and classified as ‘low risk’, ‘high risk’, or ‘unclear risk’. Authors will be contacted for supplemental information if details for assessment reported in the text are considered inadequate. The risk will be rated as ‘unclear’ if no further information is obtained. The result of assessment of each study will be summarized in a chart. Overall risk of bias for each study will be defined as ‘low’ if risk of all bias components is ranked as ‘low’, or ‘moderate’ if at least one component is ranked ‘unclear’ with no component ranked as ‘high’,

or 'high' if one or more component is ranked as having a 'high' risk of bias.

Data analyses and assessment of heterogeneity

Measures of treatment effect

The statistical analyses will be performed using RevMan 5.3 analyses software of the Cochrane Collaboration. Continuous data such as length of ICU stay and length of hospital stay will be presented as mean differences (MD) with 95% confidence intervals (95% CIs). Dichotomous data such as the number of intubation and death will be presented as risk ratios (RR) with 95% CIs. When the rates rather than the numbers are reported, we will calculate the numbers based on the data provided.

Dealing with missing data

Missing data will be dealt with following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Corresponding authors will be contacted for further information. If the missing data cannot be obtained, we will specify the assumptions of the methods used to cope with missing data according to the cause of data loss (i.e. random dropout or poor outcome). We will perform sensitivity analyses to evaluate how sensitive results are to the changes in the assumptions that are made. In the Discussion section of the review, we will analyze the potential impact the missing data may have on the findings of the review.

Assessment of heterogeneity

Before any outcome is pooled, we will assess the impact of heterogeneity using $\chi 2$ test and I^2 statistic [classified as low (< 40%), moderate (40-60%) or high (> 60%)]. I^2 values greater than 60% will be considered as having substantial heterogeneity. If substantial heterogeneity is present, we will investigate the potential source of heterogeneity by conducting exploratory analyses.

Assessment of reporting biases

Protocols of included trials will be searched using the databases mentioned above. We will contact the authors to obtain complete data of the protocols' envisioned outcomes as well as reasons for the non-reporting of certain outcomes. Publication bias will be assessed by visual analysis of the funnel plot if the number of included studies is equal to or greater than 10.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore potential sources of heterogeneity. Possible sources of heterogeneity are:

1. severity of acute respiratory failure before randomization indicated by oxygenation index, SOFA, SAPS II and APACHE II as the baseline characteristics of included patients,
2. different causes of immunosuppression, i.e HIV or non-HIV
3. different causes of acute respiratory failure.
4. types of NIV (CPAP or BiPAP).

Sensitivity analysis will be carried out to assess the effect of exclusion of the studies with high overall risk of bias or the studies in which immunocompromised patients with ARF are a subgroup of the overall participants.

Assessment of pooled effect estimates

As to the pooled assessment of treatment effect, the Mantel-Haenszel method will be used for fixed effects estimation and the DerSimonian and Laird method for random effects estimation. The random effects model was preferred if heterogeneity of treatment effects was present; otherwise a fixed effect model would be used. P values < 0.05 will be considered statistically significant. Results will be presented in tables and discussed afterwards where data aggregation is not possible due to substantial

heterogeneity.

The quality of evidence contributing to pooled effect estimates will be evaluated following the principle of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[31] According to GRADE system, quality of each evidence from RCT is considered to be high, and will be downgraded with the presence of study limitations, imprecision, inconsistency, indirectness or publication bias.

Finally, all the findings will be summarized in a table following the GRADE principles.

DISCUSSION

The benefit of NIV among immunocompromised patients with acute hypoxemic respiratory failure is unclear. The recommendation of the use of NIV in those patients has been challenged by the different results of the RCTs conducted in recent years. This systematic review and meta-analysis will synthesize evidences from all the available RCTs, which would be useful for clinicians regarding the use of NIV or oxygen therapy in those patients. Besides, subgroup analysis will be performed to find out more specific indications for clinical decision making.

Patients who have been treated with HFNO will not be included in our studies, since HFNO is distinctively different from oxygen therapy in terms of equipment, cost and tolerance. HFNO requires more advanced equipment, thus it's not as popularized as standard oxygen therapy especially in developing countries such as China. Besides, the effect of HFNO is different from traditional oxygen therapy. Maggiore SM's study showed that HFNO results in fewer oxygen desaturations, lower reintubation rate and less discomfort compared to oxygen therapy after exubation.[32] And in Frat's RCT conducted among patients with acute hypoxemic respiratory failure, HFNO resulted in reduced mortality compared with standard oxygen therapy or NIV.[33] Therefore, exclusion should be made so that HFNO would not become a confounding factor when we compare NIV with oxygen therapy.

HIV patients is a specific group, thus will be analyzed in subgroup analysis. A systematic review conducted by our team showed that non-invasive ventilation had great advantage over invasive ventilation for HIV patients, and this advantage is less obvious among non-HIV patients.[34] Furthermore, recent studies showed a higher mortality rate of Pneumocystis pneumonia infection in non-HIV patients in comparison with HIV patients.[35 36] Therefore, we propose a hypothesis that the effect of NIV is different between HIV and non-HIV patients, which will be examined by subgroup analysis in this meta-analysis.

The overall purpose of this study is to determine whether NIV is better than oxygen therapy as the initial oxygenation strategy in adult immunocompromised patients with acute hypoxemic respiratory failure. We will also explore the patient selection strategy for the initial oxygenation strategy, with respect to severity, cause of immunosuppression and cause of ARF. The finding of this meta-analysis could also provide guidance for the RCTs in the future to find out the characteristics of patients who might benefit from NIV.

Author affiliations

[1]Emergency Department, Peking Union Medical College Hospital, Beijing, China.

[2]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China.

[3]Department of Science and Technology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

[4]Department of Orthopaedics, Peking Union Medical College Hospital, Beijing, China.

[5]Department of Gastroenterology, Peking Union Medical College Hospital, Beijing, China.

[6]Department of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing, China.

Contributors

YL, TW and ZL developed the initial idea for this protocol. LZ, GL and KH contributed to the search strategy. Data abstraction forms were designed by MW. JS was consulted about intensive care and pulmonary medicine. JH, YM, YL, HZ and XY were consulted about emergency medicine. YY and ZL contributed to the original draft. YL, TW and LZ were responsible for the revision of the draft. ZL, TW and YY were considered equal contributors to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared.

Ethics and dissemination Ethics approval is not a requirement since no primary data will be collected from humans. This study is expected to provide evidence for the initial ventilation in immunocompromised patients with acute hypoxemic respiratory failure. The finding of this study will be submitted to a peer-reviewed journal for publication and will be disseminated in conferences.

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Supplement 1. MEDLINE Search Strategy.

((((((((((((((((((((Immunosuppression[MeSH Terms]) OR Immunocompromised Host[MeSH Terms]) OR Immunologic Deficiency Syndromes[MeSH Terms]) OR Neutropenia[MeSH Terms]) OR Acquired Immunodeficiency Syndrome[MeSH Terms]) OR HIV[MeSH Terms]) OR Carcinoma[MeSH Terms]) OR Hematologic Neoplasms[MeSH Terms]) OR Lymphoma[MeSH Terms]) OR Leukemia[MeSH Terms]) OR Multiple Myeloma[MeSH Terms]) OR Myelodysplastic Syndromes[MeSH Terms]) OR Organ Transplantation[MeSH Terms]) OR Bone Marrow Transplantation[MeSH Terms]) OR Glucocorticoids [Pharmacological Action]) OR Antineoplastic Agents [Pharmacological Action]) OR Immunosuppressive Agents [Pharmacological Action])) OR ((((((((((((((immunocompromise) OR immunocompromised) OR immunodeficiency) OR immunosuppressive) OR immunosuppressed) OR immune defect) OR hematological patients) OR hematological malignancies) OR hematologic malignancies) OR cancer) OR AIDS) OR acquired immunodeficiency syndrome) OR cytotoxic therapy) OR glucocorticoid) OR corticosteroid) OR chemotherapy))) AND ((((((((((acute lung injury[MeSH Terms]) OR Respiratory Distress Syndrome, Adult[MeSH Terms]) OR Pulmonary Disease, Chronic Obstructive[MeSH Terms]) OR asthma[MeSH Terms]) OR obesity hypoventilation syndrome[MeSH Terms]) OR pulmonary edema[MeSH Terms]) OR pneumonia[MeSH Terms]) OR Lung Diseases, Interstitial[MeSH Terms])) OR ((((((((((((DPLD) OR Diffuse Parenchymal Lung Disease) OR interstitial lung disease) OR CPE) OR cardiogenic pulmonary edema) OR OHS) OR COPD) OR chronic obstructive pulmonary disease) OR ARDS) OR acute respiratory distress syndrome) OR ALI) OR ARF) OR acute respiratory failure))) AND ((((((((Respiration, Artificial[MeSH Terms]) OR Noninvasive Ventilation [MeSH Terms]) OR High-Frequency Ventilation[MeSH Terms]) OR Continuous Positive Airway Pressure[MeSH Terms]) OR Positive-Pressure Respiration[MeSH Terms]) OR Intermittent Positive-Pressure Ventilation[MeSH Terms])) OR ((((((((((((((((((((((((((((Mechanical ventilation) OR niv) OR nppv) OR nippv) OR non invasive positive pressure ventilation) OR non invasive ventilation) OR positive end expiratory pressure) OR peep) OR assisted ventilation) OR artificial ventilation) OR assist control) OR pressure support ventilation) OR bipap) OR bilevel positive airway pressure) OR bi-level positive airway pressure) OR cpap) OR Continuous positive airway pressure ventilation) OR continuous positive airway pressure) OR proportional assist ventilation) OR PAV)) OR controlled mechanical ventilation) OR intermittent mandatory ventilation) OR volume controlled ventilation) OR pressure controlled ventilation) OR assisted CMV)) OR IMV) OR VCV) OR PCV) OR SIMV))) AND ((((((((((Randomized Controlled Trial) OR RCT) OR Controlled Clinical Trial) OR Clinical Trial) OR random allocation) OR CCT)) OR (((Randomized Controlled Trial [Publication Type]) OR Controlled Clinical Trial [Publication Type]) OR Clinical Trial [Publication Type]))) OR (((Clinical Trials as Topic[MeSH Terms]) OR Controlled Clinical Trials as Topic[MeSH Terms]) OR Randomized Controlled Trials as Topic[MeSH Terms]))) AND ("1980/01/01"[PDat] : "2017/03/05"[PDat]) AND Humans[Mesh]) Filters: Publication date from 1980/01/01 to 2017/03/05; Humans

Supplement 2. EMBASE Search Strategy.

('immune deficiency'/exp OR 'immunocompromized patient'/exp OR 'immunosuppressive treatment'/exp OR 'immunosuppressive agent'/exp OR 'antineoplastic agent'/exp OR 'leukopenia'/exp OR 'organ transplantation'/exp OR 'bone marrow transplantation'/exp OR 'glucocorticoid'/exp OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus infection'/exp OR 'hematologic malignancy'/exp OR 'chemotherapy'/exp OR 'corticosteroid'/exp OR 'solid tumor'/exp OR 'leukopenia'/exp OR 'lymphoma'/exp OR 'multiple myeloma'/exp OR 'Myelodysplastic Syndromes'/exp

OR 'immune deficiency' OR 'immunocompromized patient' OR 'immunosuppressive treatment' OR 'immunosuppressive agent' OR 'antineoplastic agent' OR 'leukopenia' OR 'organ transplantation' OR 'bone marrow transplantation' OR 'glucocorticoid' OR 'human immunodeficiency virus' OR 'human immunodeficiency virus infection' OR 'hematologic malignancy' OR 'chemotherapy' OR 'corticosteroid' OR 'solid tumor' OR 'leukopenia' OR 'lymphoma' OR 'multiple myeloma' OR 'Myelodysplastic Syndromes' OR 'aids' OR 'mds' OR 'mm' OR 'hiv') AND ('respiratory distress syndrome'/exp OR 'acute respiratory failure'/exp OR 'adult respiratory distress syndrome'/exp OR 'chronic obstructive lung disease'/exp OR 'asthma'/exp OR 'obesity hypoventilation syndrome'/exp OR 'lung edema'/exp OR 'pneumonia'/exp OR 'interstitial lung disease'/exp OR 'respiratory distress syndrome' OR 'acute respiratory failure' OR 'adult respiratory distress syndrome' OR 'chronic obstructive lung disease' OR 'asthma' OR 'obesity hypoventilation syndrome' OR 'lung edema' OR 'pneumonia' OR 'interstitial lung disease' OR 'cardiogenic pulmonary edema' OR 'acute lung injury' OR 'dpld' OR 'cpe' OR 'ohs' OR 'copd' OR 'ards' OR 'ali') AND ('ventilator' OR 'ventilator'/exp OR 'artificial ventilation' OR 'artificial ventilation'/exp OR 'mechanical ventilation' OR 'niv' OR 'nppv' OR 'nippv' OR 'non invasive positive pressure ventilation' OR 'non invasive ventilation' OR 'positive end expiratory pressure' OR 'peep' OR 'assisted ventilation' OR 'artificial ventilation' OR 'assist control' OR 'pressure support ventilation' OR 'bipap' OR 'bilevel positive airway pressure' OR 'bi-level positive airway pressure' OR 'cpap' OR 'continuous positive airway pressure ventilation' OR 'continuous positive airway pressure' OR 'proportional assist ventilation' OR 'pav' OR 'controlled mechanical ventilation' OR 'intermittent mandatory ventilation' OR 'volume controlled ventilation' OR 'pressure controlled ventilation' OR 'assisted cmv') AND('Randomized Controlled Trial'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'Randomized Controlled Trial' OR 'controlled clinical trial' OR 'clinical trial' OR 'RCT' OR 'CCT')

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Checklist result
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 2, Line 3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	None
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 2, Line 7, 55
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 7, Line 38
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 7, Line 47
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 7, Line 47
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3 Line 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, Line 14
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4, Line 9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 4, Line 53
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4, Line 53

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6, Line 4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5, Line 17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5, Line 27
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5, Line 27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 4, Line 41
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5, Line 44
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6, Line 6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6, Line 29, 49
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6, Line 35
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6, Line 55
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6, Line 30
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6, Line 58

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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