PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis
AUTHORS	Lu, Zhonghua; Chang, Wei; Meng, Shan-Shan; Zhang, Xiwen; Xie, Jianfeng; Xu, Jing-Yuan; Qiu, Haibo; Yang, Yi; Guo, Fengmei

VERSION 1 - REVIEW

REVIEWER	Shengyu Wang The First Affiliated Hospital of Xi'an Medical University, China Pulmonary and Critical Care
REVIEW RETURNED	17-Nov-2018

GENERAL COMMENTS	1. In Table 1, Futier's study showed age is 62/661(Page 8 Line 24). I think it is mistake. 2. In Table 2, it is better that colurful figure describes the quality of literatures.

REVIEWER	Zongan Liang Sichuan University West China Hospital, China
REVIEW RETURNED	21-Nov-2018

GENERAL COMMENTS	The language should be revised. There were too much spelling error and grammar mistake. The author included four papers written in Chinese. So, they may miss the paper written in other languages other than Chinese and English. If the author delete this four paper, the result might be different.

REVIEWER	Ho Chun Man Nguyen Tat Thanh University Vietnam
REVIEW RETURNED	16-Dec-2018

GENERAL COMMENTS	Thank you for inviting me to be the statistical reviewer for "The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis".

In general, this meta-analysis is of high quality with sound methodology. I have the following recommendations:
1. For the title, patient should be plural: patients

2. Please note that for random-effects model, the effects should be plural.

3. On Pg 7, under Data Synthesis and Analysis, please add an explanation for fixed-effect and random-effects model
Line 21, … fixed-effect model was applied. Fixed-effect models assume that the population effect sizes are the same for all studies ((Cheung et al 2012). In contrast, random-effects model attempted to generalise findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Lim et al 2018).

References:
Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415

Lim RBC et al (2018) Prevalence of All-Cause Mortality and Suicide among Bariatric Surgery Cohorts: A Meta-Analysis. Int J Environ Res Public Health. 2018 Jul 18;15(7). PMID: 30021983

4. The authors stated that publication bias was assessed by visual inspection of funnel plots. I recommend to provide an explanation why regression method was not used.

Line 23: … by visual inspection of funnel plots. Regression test was not required to examine publication bias because there wee 10 or less studies for each outcome (Ng et al 2018).

Reference
Ng A et al (2018) IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression
or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018 Aug 13;8(1):12050. PMID: 30104698

REVIEWER	Karla Solo
	London Health Sciences Centre and Canada
REVIEW RETURNED	10-Jan-2019

| GENERAL COMMENTS | Thank you for the opportunity to review the manuscript entitled "The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patient: a systematic review and meta-analysis". The objective of this study was to assess the effects of high-flow nasal cannula oxygen therapy on reintubation and respiratory support escalation in post-extubated surgical patients. This meta-analysis included ten studies and a total of 1327 sample patients. Of ten included studies, 7 were RCTs. The authors concluded that compared with conventional oxygen therapy, high-flow nasal cannula oxygen therapy was significantly associated with lower rates of intubation (low heterogeneity) and respiratory support (moderate heterogeneity) in surgical patients. The author also stated that the main limitation of this study was that the evidence was heterogeneous; timing and duration of treatment as well as baseline respiratory risks may be sources of heterogeneity in this review. While this paper is clinically relevant, I have concerns |

about the methodology used to synthesize data, the lack of accurate reporting of results, and a lack of sophistication in the interpretation of results. My comments to the authors are as follow:

Abstract

1. Data extraction and synthesis: Please add important details on methodology of the study (ex statistical model, etc).
2. Results: non-significant results do not mean weak evidence. To assess the quality evidence, a systematic approach that rates the certainty of evidence (such as GRADE approach) should be used.
3. Conclusion: Please add an explanation as to how the study findings are relevant and important for current practice.

Data Sources and Searches

1. Did the author make an attempt to search for unpublished studies through grey literature?
2. Was the search strategy drafted in consultation with a librarian? If not, why not?
3. Please define the outcomes and interventions used in this review. It would be helpful to note any variations on the intervention definitions across trials and explain how such differences may influence the treatment effect?

Data Synthesis and Analysis

1. The authors stated that "If the data heterogeneity is obvious (I2 > 50%), we used the random effects model; otherwise, a fixed effects model was applied." However, according to Borenstein et al, 2009, "it is a bad idea to use a non-significant heterogeneity test as evidence that the studies share a common effect size. The test for heterogeneity often has poor power, and therefore can be non-significant even if the true level of heterogeneity is substantial…. The selection of a model must be based solely on the question of which model fits the distribution of effect sizes and takes account of the relevant source(s) of error. When studies are gathered from the published literature, the random-effects model is generally a more plausible match." Please provide some justification for why the authors relied on I2 test when selecting a statistical model.

Results

1. The authors performed risk of bias assessment for RCTs and non-RCTs separately. However, findings were not summarized and discussed in Result section. How does risk of bias influence the conclusions?
2. The interpretation of subgroup analyses was not accurate. I'd suggest reviewing some articles published on this topic. Cochrane handbook may be a good place to start.

Other comments:

1. The writing of this manuscript could be improved dramatically. I'd suggest the manuscript be edited by a native English speaker
2. I would suggest that you include the PRISMA checklist for meta-analysis.

Reference

	Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010 Apr;1(2):97-111.

REVIEWER	Wagner Luis Nedel, MD, MSc. Intensive Care Unit Hospital Nossa Senhora da Conceição Porto Alegre, Brazil
REVIEW RETURNED	03-Mar-2019

GENERAL COMMENTS	This manuscript has great limitations that precludes its publication in the current form: 1. Included studies must be better described: population, comorbidities, main baseline characteristics of included patients (if there is any risk of selection bias in the studies), follow up. Characteristics of included studies also must be better described: uni or multicentric studies, trials randomized or not, a general description of the risk of bias. 2. Table 1: describe which means "retrospective" in study design. Retrospective cohort? 3. Table 1: describe the comparative in each study (NIV, Venturi mask, conventional oxygen therapy) and the incidence of the main outcome (reintubation? Escalation of respiratory support?) 4. "exclusion of study by Futier … resolved the heterogeneity": this approach to heterogeneity in meta-analysis was stablished a priori? The authors must justify adequately that they aren't just "fishing" an adequate result. 5. "Weak evidence of a reduction of mortality with HFNC versus COT …, P=0.10). This is a wrong sentence. That is a non-significant result, this not means that is translated to a "weak" or "strong" evidence. With the current results, the authors can't suggest that there is some kind of "trend" of the result. 6. There is a publication bias in the funnel plot, inadequately reported by authors 7. Random effects meta-analysis should be performed in all the analysis performed in this study. There is a great variability in treatment effect between the studies, that have different populations (age, type of surgery), different controls (Venturi mask, NIV, conventional oxygen therapy) and different follow up. Despite the low statistical heterogeneity, there is an important clinical heterogeneity among the included studies.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 requests (Reviewer Name: Shengyu Wang)

Question 1: In Table 1, Futier's study showed age is 62/661(Page 8 Line 24).   I think it is mistake.

Response: Thank you for noting this error. These data have been corrected in the revised manuscript.

Question 2: In Table 2, it is better that colorful figure describes the quality of literatures.

Response: Thank you for your comment. Accordingly, a new Figure 2A has been included in the revised manuscript.

Reviewer 2 requests (Reviewer Name: Zongan Liang)

Question 1: The language should be revised. There were too much spelling error and grammar mistake.

Response: Thank you for your comment. The revised manuscript has been edited and proofread by Medjaden Bioscience Ltd.

Question2: The author included four papers written in Chinese. So, they may miss the paper written in other languages other than Chinese and English. If the author delete this four paper, the result might be different.

Response: Thank you for your comment. Due to language barriers, we did not include databases other than Chinese and English. To maximize the number of included studies, we chose to include studies published in the Chinese language.

Reviewer 3 requests (Reviewer Name: Ho Chun Man)

Question 1: For the title, patient should be plural: patients

Response: Thank you for your comment. Accordingly, the title has been amended in the revised manuscript.

Question 2: Please note that for random-effects model, the effects should be plural???

Response: Thank you for your comment. Accordingly, this text has been amended in the revised manuscript.

Question 3: On Pg 7, Line 21,under Data Synthesis and Analysis, please add an explanation for fixed-effect and random-effects model

Response: Thank you for your comment. A random effects model was used to account for the substantial clinical heterogeneity (patients' age, type of surgery, types of controls [CM/NC or face mask], length of follow-up) between studies. Appropriate text has been added to the revised manuscript.

Question 4: The authors stated that publication bias was assessed by visual inspection of funnel plots. I recommend to provide an explanation why regression method was not used.

Line 23: … by visual inspection of funnel plots. Regression test was not required to examine publication bias because there were 10 or less studies for each outcome (Ng et al 2018).

Response: Thank you for your comment. Publication bias was evaluated by Begg's funnel plot with pseudo 95% confidence limits. Univariable random-effects meta-regression was performed to investigate sources of heterogeneity between studies. Appropriate text has been added to the revised manuscript.

Reviewer 4 requests (Reviewer Name: Name: Karla Solo)

Question 1: Abstract: Data extraction and synthesis: Please add important details on methodology of the study (ex statistical model, etc).

Response: Thank you for your comment. Appropriate text has been added to the revised manuscript.

Question 2: Results: non-significant results do not mean weak evidence. To assess the quality evidence, a systematic approach that rates the certainty of evidence (such as GRADE approach) should be used.

Response: Thank you for your comment. The level of evidence of included studies was qualified using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework. Appropriate text has been added to the revised manuscript.

Question 3: Conclusion: Please add an explanation as to how the study findings are relevant and important for current practice.

Response: Thank you for your comment. Text discussing the clinical relevance of our study has been added to the Conclusion of the revised manuscript.

Question 4: Did the author make an attempt to search for unpublished studies through grey literature?

Response: Thank you for your comment. The gray literature was not searched for this review.

Question 5: Was the search strategy drafted in consultation with a librarian? If not, why not?

Response: Thank you for your comment. A librarian was not consulted as the search strategy was developed by the authors, who are all clinicians with experience using HFNC in postoperative surgical patients.

Question 6: Please define the outcomes and interventions used in this review. It would be helpful to note any variations on the intervention definitions across trials and explain how such differences may influence the treatment effect?

Response: Thank you for your comment. The outcomes and interventions used in this review have been defined and discussed in the revised manuscript.

Question 7: The authors stated that "If the data heterogeneity is obvious (I2 > 50%), we used the random effects model; otherwise, a fixed effects model was applied." However, according to Borenstein et al, 2009, "it is a bad idea to use a non-significant heterogeneity test as evidence that the studies share a common effect size. The test for heterogeneity often has poor power, and therefore can be non-significant even if the true level of heterogeneity is substantial…. The selection of a model must be based solely on the question of which model fits the distribution of effect sizes and takes account of the relevant source(s) of error. When studies are gathered from the published literature, the random-effects model is generally a more plausible match." Please provide some justification for why the authors relied on I2 test when selecting a statistical model.

Response: Thank you for your comment. A random effects model was used to account for the substantial clinical heterogeneity (patients' age, type of surgery, types of controls [CM/NC or face mask], length of follow-up) between studies. Appropriate text has been added to the revised manuscript.

Question 8: The authors performed risk of bias assessment for RCTs and non-RCTs separately. However, findings were not summarized and discussed in Result section. How does risk of bias influence the conclusions?

Response: Thank you for your comment. Accordingly, the risk of bias for randomized and non-randomized studies has been summarized in the Results of the revised manuscript.

Question 9: The interpretation of subgroup analyses was not accurate. I'd suggest reviewing some articles published on this topic. Cochrane handbook may be a good place to start.

Response: Thank you for your comment. Accordingly, we have reviewed some articles that are relevant to our subgroup analyses and amended our interpretation in the Discussion of the revised manuscript.

Question10: The writing of this manuscript could be improved dramatically. I'd suggest the manuscript be edited by a native English speaker

Response: Thank you for your comment. The revised manuscript has been edited and proofread by Medjaden Bioscience Ltd.

Question 11: I would suggest that you include the PRISMA checklist for meta-analysis.

Response: Thank you for your comment. Accordingly, a PRISMA checklist has been submitted with the revised manuscript.

Reviewer 5 requests（Reviewer Name: Wagner Luis Nedel, MD, MSc）

Question1: Included studies must be better described: population, comorbidities, main baseline characteristics of included patients (if there is any risk of selection bias in the studies), follow up. Characteristics of included studies also must be better described: uni or multicentric studies, trials randomized or not, a general description of the risk of bias.

Response: Thank you for your comment. Accordingly, in the revised manuscript, Table 1 shows the characteristics of the included studies, Figure2A and Table 2 shows the quality assessment.

Question 2: Table 1: describe which means "retrospective" in study design. Retrospective cohort?

Response: Thank you for your comment. Accordingly, the study designs have been amended in Table 1 of the revised manuscript.

Question 3: Table 1: describe the comparative in each study (NIV, Venturi mask, conventional oxygen therapy) and the incidence of the main outcome (reintubation? Escalation of respiratory support?)

Response: Thank you for your comment. Accordingly, Table 1 has been amended in the revised manuscript.

Question 4: "exclusion of study by Futier … resolved the heterogeneity": this approach to heterogeneity in meta-analysis was stablished a priori? The authors must justify adequately that they aren't just "fishing" an adequate result.

Response: Thank you for your comment. Begg's funnel plot revealed no evidence of publication bias for the primary outcomes, except for one outlier in the analysis of escalation of respiratory support. Sensitivity analysis and meta-regression were performed to evaluate the influence of this study on the effect size.

Question 5: "Weak evidence of a reduction of mortality with HFNC versus COT …, P=0.10). This is a wrong sentence. That is a non-significant result, this not means that is translated to a "weak" or "strong" evidence. With the current results, the authors can't suggest that there is some kind of "trend" of the result.

Response: Thank you for noting this error. This text has been corrected in the revised manuscript.

Question 6: There is a publication bias in the funnel plot, inadequately reported by authors

Response: Thank you for your comment. Begg's funnel plot revealed no evidence of publication bias for the primary outcomes, except for one outlier in the analysis of escalation of respiratory support. Sensitivity analysis and meta-regression were performed to evaluate the influence of this study on the effect size. Appropriate text has been added to the revised manuscript.

Question 7: Random effects meta-analysis should be performed in all the analysis performed in this study. There is a great variability in treatment effect between the studies, that have different populations (age, type of surgery), different controls (Venturi mask, NIV, conventional oxygen therapy) and different follow up. Despite the low statistical heterogeneity, there is an important clinical heterogeneity among the included studies.

Response: Thank you for your comment. A random effects model was used to account for the substantial clinical heterogeneity (patients' age, type of surgery, types of controls [CM/NC or face mask], length of follow-up) between studies. Appropriate text has been added to the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Ho Chun Man National University of Singapore Singapore
REVIEW RETURNED	01-May-2019

GENERAL COMMENTS	Pg 11 Line 22, I suggest to add the following statement: Random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung et al 2012). Cheung MWL, Ho RCM, Lim Y, Mak A (2012) Conducting a meta-analysis: Basics and Good Practices. International Journal of Rheumatic Diseases. Apr;15(2):129-35. PMID:22462415

REVIEWER	Karla Solo Canada
REVIEW RETURNED	01-May-2019

GENERAL COMMENTS	Thank you for the opportunity to review a revision of the manuscript entitled "The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis". I suggest adding the wording "statistical heterogeneity" (instead of heterogeneity alone) in the Result Section for clarity.

REVIEWER	Wagner Luis Nedel, MD, MSc., Grupo Hospitalar Conceição Brazil
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	In my opinion, the manuscript can be accepted in its current format. The limitations of this study were adequately described by the authors, and important modifications were made to the article, improving its quality.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3 requests (Reviewer Name: Ho Chun Man)

Question 1: Please state any competing interests or state 'None declared': None

Response: Thank you for your comment. Accordingly, competing interests have been stated as "None to declare" in the revised manuscript.

Question 2: Pg 11 Line 22, I suggest to add the following statement:

Random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung et al 2012).

Cheung MWL, Ho RCM, Lim Y, Mak A (2012) Conducting a meta-analysis: Basics and Good Practices. International Journal of Rheumatic Diseases. Apr15(2):129-35. PMID:22462415

Response: Thank you for your comment. Accordingly, we have added the following statement in the revised manuscript: Random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung et al 2012).

Reviewer 4 requests (Reviewer Name: Name: Karla Solo)

Question 1: Please state any competing interests or state 'None declared': None declared

Response: Thank you for your comment. Accordingly, competing interests have been stated as "None to declare" in the revised manuscript.

Question 2: I suggest adding the wording "statistical heterogeneity" (instead of heterogeneity alone) in the Result Section for clarity.

Response: Thank you for your comment. Accordingly, we have added the wording "statistical heterogeneity" instead of "heterogeneity" in the revised manuscript.

Reviewer 5 requests（Reviewer Name: Wagner Luis Nedel, MD, MSc）

Question1: Please state any competing interests or state 'None declared': none declared

Response: Thank you for your comment. Accordingly, competing interests have been stated as "None to declare" in the revised manuscript.