PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Aetiology and prognostic risk factors of mortality in pneumonia patients receiving glucocorticoids alone or glucocorticoids and other immunosuppressants: a retrospective cohort study
AUTHORS	Li, Lijuan; Hsu, Steven H.; Gu, Xiaoying; Jiang, Shan; Shang, Lianhan; Sun, Guolei; Sun, Lingxiao; Zhang, Li; Wang, Chuan; Ren, Yali; Wang, Jinxiang; Pan, Jianliang; Liu, Jiangbo; Bin, Cao

VERSION 1 – REVIEW

REVIEWER	Antoni Torres University of Barcelona Spain
REVIEW RETURNED	19-Feb-2020

GENERAL COMMENTS	This is a potentially interesting ms about pneumonia in patients receiving corticosteroids. There is not much information in the literaturare about this topic However, authors mixed for most of the data presented HAP and CAP. I strongly suggest to separate the two populations clearly for all the nalyses,.Pooling everything together is probably misleading for clinicians The second point is that authors included patients with other inmunosuppressed conditions. These patients should be excluded or analyzed separately Personally I would only keep patients with only corticosteroids In summary authors recruite a large cohort of patients treated for several conditions with corticosteroids + pneumonia They mixed for most of the analyses CAP and HAP. They should present these population separately as they did for microbial etiology They should exclude patients with several immunosuppressed conditions in addition to corticosteroids

REVIEWER	Alan Kaplan Family Physician Airways Group of Canada
REVIEW RETURNED	21-Apr-2020

GENERAL COMMENTS	Interesting work, thank you A few comments 1) I think you should put your definition of high dose glucocorticoids in the abstract 2) Outcomes may be related to the underlying illness, ie., the reason they were ON OCS in addition to just being on OCS. Can the data be cross evaluated by diagnosis also to see if there were any differences. You nicely showed that HAP and CAP had

	different pathogens for instance. Your table I think shows no p values comparing different underlying disease; probably worth mentioning in the actual text. 3) You discuss high dose OCS as the outcome, but since you included anyone with a daily dose of 10 mg for three weeks, what happened to those patients? Were the results significantly different? 4) One big issue leading to morbidity and mortality is the adrenal suppression that occurs being on systemic steroids. Was this evaluated? Were the steroid replacement strategies consistent in these patients? 5) It is wonderful that you could get the diagnostic tests to assess these unusual organisms and this can drive treatment decisions beyond our ordinary CAP guidelines. Unfortunately, most communities do not have access to these tests, so it might be clinically useful to have a table of the unusual pathogens to look for in patients with background OCS use presenting with pneumonia, including current management strategies for each pathogen. I see this as a useful resource for clinicians and potentially future CAP guideline creation activities. Were there any 'pearls' that your study shows to differentiate clinically the different pathogens? Your table does not seem to show anything particular, but this is worth discussing in the text also. Lymphocytopenia as a risk factor is made even more fascinating by the Covid evidence that associates it with increased severity risk and mortality risk. Probably worth a mention in this time of Covid viral pneumonia new reality.

REVIEWER	Pradeesh Sivapalan Pradeesh Sivapalan MD PhD Resp. traineeDepartment of Internal Medicine, Zealand University Hospital, Roskilde &Post Doc Respiratory Medicine Section, Herlev-Gentofte Hospital
REVIEW RETURNED	23-Apr-2020

GENERAL COMMENTS	Review 23th of April 2020 General comments: This is a retrospective investigation of the etiology and prognostic risk factors of pneumonia in patients with long-term glucocorticoid use. The main findings of the present study are summarized as follows: (1) More than 60% of the patients developed pneumonia within 6 months of glucocorticoid therapy initiation, especially patients with PCP and CMV pneumonias. General comments: It is an interesting and relevant study further shows the effects of prednisolone. However, there are some methodological shortcomings that should be elucidated a) Also, short-term consumption of corticosteroids has been shown to increase the risk of lung infections and mortality i. Sivapalan et. Al 2019. BMJ Open Respir Res. 2019 Mar 30;6(1):e000407. doi: 10.1136/bmjresp-2019-000407. eCollection 2019. ii. Waljee et al. BMJ. 2017 Apr 12;357:j1415. doi: 10.1136/bmj.j1415. b) Can you describe your pneumonia criterion in more detail in the method section "increased levels of C-reactive or procalcitonin proteins". How high should the level of c-reative protein and procalcitonin be

	c) what was the accumulated dose of glucocorticoids in the patients receiving high vs. low doses during the study. d) How much glucocorticoids patients had received before inclusion in the study, eg if you look back 5 years e) what do you think about confounding by indication in this study? f) “Patients using high dose glucocorticoids were significantly more likely to develop opportunistic pneumonias than patients using low dose glucocorticoids.” However, patients receving high doses of glucocorticoids also received more immunosuppresants and antibiotics. So, it may be because these patients were more ill? g) Do you have any data on the blood eosinophil count? it could be interesting to see if those patients who had a low eosinophil count needed more long-term prednisolone treatment and if they did worse? h) Cox regression models were used for survival analysis. Page 9 , line 21. What did you analyse with the cox logistic analysis? Minor comments a) Page 9, Line 41 “1397patients” A space is missing b) Page 4, line 4 “susceptibility patterns,30-day and 90-day mortality” A space is missing c) “Between 1st January 2013 and 31st December 2017, 1397patients with pneumonia had connective tissue disease, nephrotic syndrome, chronic nephritis, idiopathic pulmonary fibrosis, or other diseases with immunocompromised.” will you rephrase this sentence?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Antoni Torres

Institution and Country: University of Barcelona, Spain

Please state any competing interests or state ‘None declared’: I have not competing interests

We do not have any competing interests to declare, and thus state: None declared by all authors.

However, authors mixed for most of the data presented HAP and CAP.

I strongly suggest to separate the two populations clearly for all the analyses, Pooling everything together is probably misleading for clinicians

I have separated CAP and HAP and performed a comparative analysis of etiology. Additionally, prognostic factors were analyzed in only CAP patients, because the number of HAP cases was too small for analysis.

The second point is that authors included patients with other immunosuppressed conditions. These patients should be excluded or analyzed separately. Personally, I would only keep patients with only

corticosteroids. In summary authors recruited a large cohort of patients treated for several conditions with corticosteroids + pneumonia. They mixed for most of the analyses CAP and HAP. They should present these population separately as they did for microbial etiology

They should exclude patients with several immunosuppressed conditions in addition to corticosteroids

In clinical practice, glucocorticoids and immunosuppressant therapy are administered simultaneously for many diseases. This situation is more likely than administration of glucocorticoids alone. Because there were only 297 cases in which glucocorticoids were administered alone in this study, this paper discussed and analyzed the two situations separately.

Reviewer: 2

Reviewer Name: Alan Kaplan

Institution and Country: Family Physician Airways Group of Canada

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

Interesting work, thank you

A few comments

1) I think you should put your definition of high dose glucocorticoids in the abstract
   Thank you for your suggestion. I have included the definition in the abstract.
   Outcomes may be related to the underlying illness, ie., the reason they were ON OCS in addition to just being on OCS. Can the data be cross evaluated by diagnosis also to see if there were any differences? You nicely showed that HAP and CAP had different pathogens for instance. Your table I think shows no p values comparing different underlying disease; probably worth mentioning in the actual text.
   This conclusion was supported by the data presented in the Supplemental Table 2.
2) You discuss high dose OCS as the outcome, but since you included anyone with a daily dose of 10 mg for three weeks, what happened to those patients? Were the results significantly different?
   This is a retrospective study. Patients receiving only low-dose glucocorticoids (a daily dose of 10 mg for three weeks) were not included.
3) One big issue leading to morbidity and mortality is the adrenal suppression that occurs being on systemic steroids. Was this evaluated? Were the steroid replacement strategies consistent in these patients?
   Patients on chronic corticosteroids were not routinely assessed for adrenal function on admission. We do not have the data on whether ACTH stimulation was performed. If adrenal insufficiency was encountered, the patient would receive a higher than baseline dose during the hospital stay. The steroids were continued at their usual dosage or the dosage was adjusted based on the clinician's judgement.

5) It is wonderful that you could get the diagnostic tests to assess these unusual organisms and this can drive treatment decisions beyond our ordinary CAP guidelines. Unfortunately, most communities do not have access to these tests, so it might be clinically useful to have a table of the unusual pathogens to look for in patients with background OCS use presenting with pneumonia, including current management strategies for each pathogen. I see this as a useful resource for clinicians and potentially future CAP guideline creation activities.

Were there any 'pearls' that your study shows to differentiate clinically the different pathogens? Your table does not seem to show anything, but this is worth discussing in the text also.

Lymphocytopenia as a risk factor is made even more fascinating by the Covid evidence that associates it with increased severity risk and mortality risk. Probably worth a mention in this time of Covid viral pneumonia new reality.

> This study did not include abnormal etiological tests; however, we investigated the relationship between common etiology and high-dose glucocorticoids, time of steroids use, and lymphocytopenia

Reviewer: 3

Reviewer Name: Pradeesh Sivapalan

Institution and Country: Pradeesh Sivapalan MD PhD Resp. traineeDepartment of Internal Medicine, Zealand University Hospital, Roskilde &Post Doc Respiratory Medicine Section, Herlev-Gentofte Hospital

Please state any competing interests or state ‘None declared’: None declared

a) Also, short-term consumption of corticosteroids has been shown to increase the risk of lung infections and mortality

i. Sivapalan et. Al 2019. BMJ Open Respir Res. 2019 Mar 30;6(1):e000407. doi: 10.1136/bmjresp-2019-000407. eCollection 2019.

ii. Waljee et al. BMJ. 2017 Apr 12;357:j1415. doi: 10.1136/bmj.j1415.

In this study, more than 100 patients were infected within one month after glucocorticoid administration. Most of the infections were caused by bacteria and Aspergillus, followed by viruses and PCP. PCP caused the least number of infections, most of which occurred in 2-6 months（Figure 4）

b) Can you describe your pneumonia criterion in more detail in the method section

"increased levels of C-reactive or procalcitonin proteins". How high should the level of c-reative protein and procalcitonin be.

Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph or infiltrate or interstitial changes on CT scan combined with one or more of the following clinical manifestations: (1) recent cough, sputum or aggravation of respiratory symptoms, the emergence of purulent sputum, with or without chest pain; (2) fever (defined as axillary temperature ≥37.3°C) 11 or hypothermia (axillary temperature <36°C); (3) signs of pulmonary consolidation and (or) moist crackles; or (4) white blood cell count $>10\times10^9$/L or $<4\times10^9$/L, with or without neutrophil predominance (page 4)

c) what was the accumulated dose of glucocorticoids in the patients receiving high vs. low doses during the study.

I have added the accumulated dose of glucocorticoids in Table 1 and Supplemental Table 2.

d) How much glucocorticoids patients had received before inclusion in the study, eg if you look back 5 years

Our hospital has an excellent Rheumatology and Immunology Department, and therefore we receive many such patients. Approximately 100 such patients are admitted in one month.

e) what do you think about confounding by indication in this study?

Cox regression was used to control the confounding factors in this study.

f) "Patients using high dose glucocorticoids were significantly more likely to develop opportunistic pneumonias than patients using low dose glucocorticoids." However, patients receving high doses of glucocorticoids also received more immunosuppresants and antibiotics. So, it may be because these patients were more ill?

We analyzed the patients who received glucocorticoids only and found that their characteristics of infection were similar to those of patients who received glucocorticoids and immunosuppressants. Opportunistic infections related to the decline of cellular immune function occurred in both groups of patients.

g) Do you have any data on the blood eosinophil count? it could be interesting to see if those patients who had a low eosinophil count needed more long-term prednisolone treatment and if they did worse?

Because most of the patients who used glucocorticoids in this study were patients with connective tissue disease, nephrotic syndrome, and organ transplantation and only a few had bronchial asthma or eosinophilic pneumonia, we excluded eosinophils from the analysis. If necessary, we can include the analysis for eosinophils as well.

h) Cox regression models were used for survival analysis. Page 9 , line 21. What did you analyse with the cox logistic analysis?

Logistic regression was not used in this study.

VERSION 2 – REVIEW

REVIEWER	Antoni Torres Department of Pulmonology Hospital Clinic Barcelona Spain
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	Dear authors You have done a good job I have one major comment 1-The title does not reflect the content of the ms Now that you have separated patients receiving corticosteroids alone vs corticosteroids + other inmunosuppressants you should change the title and to focuss all the ms according to this What is useful for clinicians if microorganisms and prognosis of CAP are different when comparing patients receiving corticosteroids or corticosteroids vs inmmunosupresants

REVIEWER	Alan Kaplan Family Physician Airways Group of Canada
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	thanks for the revisions

REVIEWER	Pradeesh Sivapalan Herlev and Gentofte Hospital
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	I think the manuscript has been substantially improved. I only have one comment: I think the authors should mention in the limitation that it is a observational study and the possibility of bias by indication cannot be ruled out.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Antoni Torres
Institution and Country: Department of Pulmonology, Hospital Clinic, Barcelona Spain
Please state any competing interests or state 'None declared': I have not competing interests
I've revised it as required

Dear authors
You have done a good job
I have one major comment
1-The title does not reflect the content of the ms
Now that you have separated patients receiving corticosteroids alone vs corticosteroids + other inmunosuppressants you should change the title and to focuss all the ms according to this
Aetiology and prognostic risk factors of mortality in pneumonia patients receiving glucocorticoids alone or glucocorticoids and other immunosuppressants: a retrospective cohort study

Reviewer: 2
Reviewer Name: Alan Kaplan
Institution and Country: Family Physician Airways Group of Canada
Please state any competing interests or state 'None declared': none
I've revised it as required

thanks for the revisions

Reviewer: 3
Reviewer Name: Pradeesh Sivapalan
Institution: Herlev and Gentofte Hospital
Please state any competing interests or state 'None declared': None declared

I think the manuscript has been substantially improved. I only have one comment:

I think the authors should mention in the limitation that it is an observational study and the possibility of bias by indication cannot be ruled out.

I've revised it as required

What is useful for clinicians if microorganisms and prognosis of CAP are different when comparing patients receiving corticosteroids or corticosteroids vs inmmunosupresants

There was no significant difference between the two groups, but this study showed the similar characteristics of the two groups.