Author’s response to reviews

Title: Low birth weight contributed to increased serum IL-6 levels in infantile respiratory syncytial virus infection

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Author’s response to reviews:

Dear editor:
We carefully studied reviewer’s comments, and have made the necessary changes according to the suggestions. Our responses to reviewer’s comments are listed below:

Editorial Feedback

1) Please ensure that the study type is entered in the title
Reply: The study type “Research article” has been added in the title page.

2) Please revise the introduction as per the feedback provided by the editorial board (below) and outline clearly the aims of the study
Reply: Introduction section has been revised according to the feedback. “About 35 million episodes of RSV-associated LRTI occurred worldwide in children younger than 5 years, with incidence in developing countries more than twice that of industrialized countries.” has been deleted.

3) Please pay particular attention to the first few paragraphs of the Introduction section as it has been found to contain some text overlap. Please ensure that the paper is written in your own words and ensure that appropriate citations have been included.
Reply: The first few paragraphs of the Introduction has been revised.

4) Please ensure that your paper is formatted according to the journal guidelines. For instance, please add a Declaration section with all subheadings. Where the subheading is not relevant for
your study/paper, please include the subheading and specify 'Not Applicable'. Further information are included at the end of this email.
Reply: Our manuscript has been formatted according to the journal guidelines, and a “Declaration section” has also been added.

5) Please ensure that you include the correct headings in your paper. For instance, Introduction should be Background. Please see the following link for further guidance:
https://bmcpregnancychildbirth.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article
Reply: The format of manuscript has been revised. Introduction should be Background.

6) Please ensure that your paper is copyedited to improve clarity and understanding
Reply: Our paper has been reviewed and revised by Dr. Elizabeth L. Kramer from Cincinnati Children’s Hospital Medical Center (CCHMC), Ohio, USA.

7) When submitting your paper, please ensure that it is accompanied with a detailed cover letter which specified what revisions have been done and where. Please include a point-by-point response to the feedback provided.
Reply: A detailed cover letter has been submitted.

Editorial Board Report

1. Introduction can be summarized further. Max 1 page double spaced.
Reply: Introduction has been revised, and double line spacing is used.

2. Statistical analysis section: To include what software was used for analysis. Why did the authors choose to report SEM instead of SD? I think SD is more appropriate.
Reply: All data were analyzed with PASW Statistics 18 software (SPSS Inc. Chicago, US). In our previous study about “serum cytokine profile contributes to discriminating M. pneumoniae pneumonia in children”, statistical parameters mean and standard error of mean (SEM) were used in the paper (Xu XF et al. Cytokine 2016, 86:73-78). In order to maintain consistency, we still continued to use mean and SEM in the present manuscript. If necessary, we can also make the appropriate changes according to reviewer’s recommendation.

3. For the group of non-RSV - it is not clear whether the parainfluenzae group is counted twice: once in the non-RSV group and again in the Parainfluenzae group. Seems like Parainfluenzae group is a subgroup analysis of the non-RSV group. It will be interesting to see comparison between RSV and non-RSV group (2 groups) instead of 3.
Reply: The non-RSV group did not include parainfluenzae-infected patients. According to reviewer’s recommendation, we deleted the data of parainfluenzae group, and only analyzed the data between RSV and non-RSV groups in the present study.

4. I am not clear or sold why the authors choose to study mode of delivery. It was not established in introduction or discussion section.
Reply: “A previous study by Rusconi et al. showed that the adjusted risk ratio for development of asthma was 1.33 for elective cesarean delivery compared with spontaneous vaginal delivery.
However, Werner et al. found no support for the hypothesis that children delivered by caesarean section have an increased risk of asthma during the first 15–18 years of life. Furthermore, delivery by caesarean section was not clearly associated with hospitalizations for asthma and other wheezing disorders up to 12 years of age compared to vaginal delivery. In view of the potential role of delivery mode in the development of asthma or other wheezing diseases, we also evaluated the possible role of delivery mode in cytokine changes during infantile RSV infections. No obvious changes in serum cytokines were observed between the caesarean section and vaginal delivery groups. Therefore, the present study cannot confirm the correlation between delivery mode and cytokine changes in infantile RSV infections.” We added the relevant content in Discussion section.

5. I agree that this manuscript will need major revisions and resubmission for consideration.
Reply: We have made major revisions. The final manuscript was critically reviewed and revised by Dr. Elizabeth L. Kramer from Cincinnati Children’s Hospital Medical Center (CCHMC).

Reviewer reports:

Major points:

1. The quality of English used to express the study design and results could be improved.
Reply: We made corresponding revisions according to reviewer’s advice. The final manuscript was critically reviewed and revised by Dr. Elizabeth L. Kramer from CCHMC.

2. The viral testing results do not match most studies. Only 30% of children had RSV, which is quite low. And 63% had no pathogen detected. The authors may consider using a different testing platform to identify the viruses. Furthermore, rhinovirus is the second most common (~20-25%) cause of bronchiolitis requiring hospitalization. Would the authors consider testing for rhinovirus since the RSV-rhinovirus coinfection is the most common coinfection? And saying RSV-only really would require testing for rhinovirus.
Reply: This is a good question. Rhinovirus is the second most common cause of bronchiolitis requiring hospitalization. It is likely that the RSV-rhinovirus coinfection is the most common coinfection. However, because commercial respiratory immunofluorescence kit via NPA during our study only detected respiratory syncytial virus (RSV), influenza virus A and B, parainfluenza virus, and adenovirus, not including rhinovirus, we did not perform rhinovirus testing in the present study.

3. The main problem is statistical. The authors should consider correcting for multiple testing. While the sample was stratified by weight, there is no further multivariable testing to control for other relevant variables.
Reply: We deleted the data of parainfluenzae group and made appropriate adjustment on statistics. Clinical characteristics of patients from different birth weight groups were also provided in Table 1. “There are also no significant differences in birth weight, days of hospitalization, WBC counts, percentage of neutrophils and eosinophils between LBW and NBW groups. The age of RSV group children was lower than that of non-RSV group, there was
obviously statistical significance between them (Table 1). In RSV patients, the age of the LBW group was also significantly lower than that of the NBW group” was added in Result section.

4. Cytokines may vary over the course of a LRTI. Would the authors please comment about the timing of the blood draw and the role of disease course on cytokine levels?
Reply: Due to the short incubation period of the RSV infection, the RSV patients admitted to our hospital were often in the platform of the disease’s development. Furthermore, peripheral blood samples were collected at the day of admission. At that time, cytokine changes reach a peak, and maintain a stable state. Although cytokines may vary over the course of a LRTI, the cytokine changes in the present study among different individuals might be relatively stable, which had a better consistency.

5. The authors have (if after multivariable modeling and multiple test correction) demonstrated an association between RSV and IL-6. However, the discussion and conclusion quickly suggest causality. The pathway from RSV to asthma is multifactorial in LBW and normal weighted infants. IL-6 may be one factor, but the authors need to hedge a little more in their conclusions.
Reply: An association between RSV and IL-6 in Discussion and Conclusion sections had been revised. “Serum IL-6 level was significantly increased in RSV infected infants with LBW. It is likely that the specific serum cytokine pattern will contribute to our understanding of the pathogenesis of RSV infections, especially in RSV-infected infants with LBW.” was revised in Conclusions section of the Abstract. The sentences “IL-6 high patients had significantly worse lung function and more frequent asthma exacerbations than IL-6 low patients. Circulating IL-6 is elevated in asthmatic patients and in bronchoalveolar lavage fluid of patients in whom asthma is clinically active. IL-6 levels probably reflect an activated state of the lung, and may have a role as a biomarker for asthma. In the present study, increased serum IL-6 levels in infants with LBW might also play an important role in RSV induced wheezing or asthma.” were added in Discussion section.

Minor point:

There are some typos throughout the manuscript (e.g., in the abstract - no capitalization after Background).
Reply: We made corresponding revisions on manuscript. Moreover, the final manuscript was critically reviewed and revised by Dr. Elizabeth L. Kramer from CCHMC.
Declarations: Ethics approval and consent to participate, Consent to publish, Availability of data and materials, Competing interests, Funding, Authors’ Contributions, Acknowledgements.
Reply: Declarations section has been added according to above requirement.
We have addressed all the suggestions of reviewer. Undoubtedly, this revision will improve the quality and clarity of this manuscript. We thank again you for your consideration of this manuscript.
Sincerely yours,
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