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 again, and have made the necessary changes according to the suggestions. Our responses to reviewer’s comments are listed below:

Editorial Feedback:

1) Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.
Reply: Cover letter with a point-by-point response to all the comments has been provided. The first revised changes to the manuscript were indicated in the text by the red, and the second revised changes were highlighted by the underline or strikethrough. Furthermore, our revised manuscript has been adapted to conform to the journal style.

Reviewer reports:

1) Despite the inclusion of a physician scientist from University of Cincinnati, the writing needs much more editing. In particular the background could be much shorter and the discussion more logical.
Reply: According to reviewer’s suggestion, the sections of Background and Discussion have been revised.
2) The authors have not conducted a multivariable analysis. The stratified analysis by weight is interesting, but this analysis does not help assess for the independent association between multiple potential confounders and the outcome of interest, IL-6. Is there any other factor beyond weight that may influence the level of IL-6? And is weight a significant factor among all enrolled patients or just those with RSV? Other variables to consider are: sex of the patient, use of respiratory support modalities, acute severity of illness, IV fluids, etc. Further, the discussion states that only low birth weight would be likely to cause an increase in IL-6. Why? Are the data about IL-6 in LRTI so clear that the authors are certain that weight is the only potential confounder? In their reply, the authors state that they made the appropriate adjustment in statistics, but they do not detail what these adjustments were. Please clarify.

The authors have not corrected for multiple testing. If the authors do not plan to make this correction they will need to justify this decision to the readers.
Reply: In the original manuscript, patients were divided into 3 groups (RSV, non-RSV, and Parainfluenza Virus III), and the IL-6 levels were analyzed using one-way ANOVA. In the present revised manuscript, patients were only divided into 2 groups, and comparison was performed using independent-sample T test. Of course, we also considered the effects of other variables on the changes of IL-6 levels. Since our data contains continuous and categorical variables, we performed a statistical analysis of general linear model (F = 2.308, P = 0.007) using SPSS. We found that body weight at admission (P = 0.425), days of hospitalization (P = 0.89), gender (P = 0.53), delivery mode (P = 0.768), eczema history (P = 0.972), and wheezing (P = 0.958) were not obviously associated with IL-6 levels. Only low birth weight (P = 0.035) was strongly correlated with changes of serum IL-6 levels. The corresponding content has been added to the “Results” section.

3) The authors have not listed the poor performance of their viral detection methods in the limitations section. If the authors are going to make this analysis about IL-6 in infants with RSV, it would help if their detection of RSV (32%) were closer to most other studies (65-80%). Please comment.
Reply: Rhinovirus is the second most common cause of bronchiolitis requiring hospitalization. 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, we did not perform rhinovirus testing in the present study. It is likely that the RSV-rhinovirus co-infection is the most common co-infection, or Non-RSV infected patients might have Rhinovirus infection. In our manuscript, RSV group represented these patients with only RSV infection, while non-RSV group patients had no detectable pathogens (including virus and bacteria). Bacterial infections can cause obvious changes of serum cytokine levels, and some co-infections could also induce responding changes of serum cytokine levels. In China, many RSV-infected children were co-infected with atypical bacteria (Mycoplasma pneumoniae, or Chlamydia pneumoniae). To reduce the effects of such factors, we only chose these patients who were only infected by RSV. The patients co-infected with other virus or bacteria were excluded. In our hospital, the overall rate of RSV detection is similar to most other studies.

4) In Table 4, the authors discuss the infants with wheezing. However, in infant LRTI what one person calls wheezing another person calls coarse breath sounds or crackles. Was the wheezing diagnosed by one clinician or multiple clinicians? Please discuss in Methods.
Reply: “Wheezing symptoms were assessed by at least two clinicians” has been added to the “Method” section.

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.
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