Author’s response to reviews

Title: Comparison between clinical features and prognosis of malignancy- and non-malignancy–associated pediatric hemophagocytic lymphohistiocytosis

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Author’s response to reviews:

Dear Editor and Reviewer:

Thank you for your letter and for the reviewer’s comments concerning our manuscript entitled “Comparison between clinical features and prognosis of malignancy- and non-malignancy–associated pediatric hemophagocytic lymphohistiocytosis” (ID: BPED-D-18-00244). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main correction in the paper and the responds to the reviewer’s comments are as following:

Responds to the reviewer’s comments:

Technical Comments:

1. “The abstract of the manuscript should be identical within the main manuscript file as well as in the submission system.”

Response: The abstract of the manuscript has been identical within the main manuscript file as well as in the submission system.
2. “Please edit your manuscript file so that your correctly-structured abstract is present within the main document.”

Response: In accordance with the journal formatting guidelines, I have revised the Abstract so that it does not exceed 350 words. Currently, it contains 298 words, including headings.

3. Please upload a clean version of the manuscript and submit a copy of the manuscript with track changes as supplementary file.

Response: We have uploaded a clean version of manuscript and submitted a copy of the manuscript with track changed as supplementary.

Reviewer reports of Zühre Kaya (Reviewer 2):

4. I recommend additional statistical review.

Response: We have done additional statistical review.

5. There are lots of grammatical errors throughout the text. It should be extensively edited by professional editing center and the authors should be declared to edit it after revision.

Response: We have edited using American English and formatted according to the guidelines of BMC Pediatrics.

Reviewer 2 (Reviewer 3): REVISION ASSESSMENT FROM THE ACADEMIC PEER REVIEWER:

6. I would suggest re-phrasing and checking for using correct grammatical structure.

Response: This paper is proofread by a native English professional.

Research Square (Reviewer 4): "STATISTICAL REVIEWER ASSESSMENT:

7. Use full form of 'CSA'.
Response: We have changed “CSA” into “Cyclosporin A”.

8. Recheck Abbreviation section and remove those terms which you have not mentioned in your manuscript.

Response: We have rechecked Abbreviation section and removed those terms which we have not mentioned in our manuscript.

9. Use full form of 'HLH' in title.

Response: We have used full form of 'HLH' in title.

10. Abstract is too lengthy with the unnecessary details. So, focus on specific points in each sub-section.

Response: In accordance with the journal formatting guidelines, We have revised the Abstract so that it does not exceed 350 words. Currently, it contains 298 words, including headings.

11. Rewrite the sentence "The objective of this study was therefore to …those not-malignancy associated" clearly.

Response: We have rewrittten the sentence "The objective of this study was therefore to …those not-malignancy associated" clearly.

12. Specify the medical institution in the sentence "We retrospectively analyzed 91 pediatric HLH patients in the pediatric department of a single medical institution between January 2005 and October 2016."

Response: We have specified the medical institution.

13. Specify the age groups of the pediatric patients considered for inclusion in the study.

Response: We have specified the age groups of the pediatric patients considered for inclusion in the study.
14. These statements "22 children were diagnosed with … 2 (2.9%) demonstrated fungal infections, and 7 (10.1%) complained of other diseases" are parts of Results. So, keep them in concise form in Results.

Response: The patients were divided into the malignancy-associated group (n = 22) and non-malignancy–associated group (n = 69, also considered the control group). The clinical features were compared using the Mann–Whitney U and χ² tests.

15. Specify the conditions of the inferential statistics mentioned in the sentence "The Mann-Whitney U and Chi square tests were used to compare the clinical features of the malignancy-associated and non-malignancy-associated HLH groups. Overall survival time of the two groups was compared by both log rank and Mann-Whitney U tests."

Response: We specified the conditions of the inferential statistics mentioned in the sentence "The Mann-Whitney U and Chi square tests were used to compare the clinical features of the malignancy-associated and non-malignancy-associated HLH groups. Overall survival time of the two groups was compared by both log rank and Mann-Whitney U tests." in the part of statistical analysis.

16. Median age is not necessary as it was not exclusively ordinal dataset. Rather, mean age with standard deviation is required for numerical variable like age. This applies throughout the present manuscript.

Response: Because that age distribution is not normal distribution in our study, so we consider that it is more appropriate to use median age.

17. The statistical test 'multivariate Cox analysis' mentioned in the sentence "The results of multivariate Cox analysis showed that … were correlated with worse prognosis" has not been mentioned in Methods.

Response to comment: We have added the 'multivariate Cox analysis' in Methods. “Prognostic factors associated with malignancy-associated HLH were evaluated by univariate and multivariate Cox proportional hazard models.”
18. Conclusions: The sentence "This syndrome progresses rapidly and has a high mortality rate" has not been mentioned previously.

Response to comment: We have deleted the sentence.

19. The authors have mentioned "This study is the first to distinguish … malignancy-associated and non-malignancy-associated HLH." How can you confirm this statement?

Response to comment: We aimed to distinguish between malignancy-associated and non-malignancy–associated HLH, compare their clinical features and prognostic significance, and analyze the difference between the two conditions.

20. Specify study design, inclusion and exclusion criteria, sample size calculation.

Response: We have specified study design, inclusion and exclusion criteria, but because that the incidence of HLH is very low, sample size calculation was not done, but we will be considered in the future.

21. Specify the 'Ethics Committee' mentioned in the sentence "Clinical data on 91 patients who were diagnosed with HLH from January 2005 to October 2016 at the Children Medical Center of Affiliated Hospital of Qingdao University were retrospectively reviewed after Ethics Committee approval."

Response: Clinical data on 91 patients who were diagnosed with HLH from January 2005 to October 2016 at the Children Medical Center of Affiliated Hospital of Qingdao University were retrospectively reviewed after University of Qingdao Ethics Committee approval.

22. The authors have mentioned "Although the difference was not statistically significant (p=0.055), our results suggested a trend toward a better overall survival time in patients with non-malignancy-associated HLH (Fig. 1)" but figure has not been kept.

Response: The difference of overall survival time for patients in two groups was not statistically significant(p=0.055).
23. Role of allogeneic HSCT in malignancy-associated HLH: The authors have mentioned "Previous reports have shown the efficacy of allogeneic HSCT in malignancy-associated HLH therapy [7-9]." This statement with citation is not necessary in Results section.

Response: We have deleted "Previous reports have shown the efficacy of allogeneic HSCT in malignancy-associated HLH therapy [7-9]."

24. The sentence "Knowledge gaps have resulted in under-diagnosis or delayed diagnosis using the HLH-2004 criteria" is not supported by the results of the present study.

Response: We have deleted the sentence "Knowledge gaps have resulted in under-diagnosis or delayed diagnosis using the HLH-2004 criteria"

25. * Citation is required to support the statement "Sensitivity analysis suggested that … have a high likelihood of SHLH."

Response: We have deleted “Delavigne K, et al. [10] proposed extended 18-point diagnostic criteria that are more easily and rapidly available in smaller institutions and primary care settings than the HLH-2004 variables. Sensitivity analysis suggested that patients meeting 5 of 18 above mentioned criteria would be considered to have a high likelihood of SHLH.”

26. Conclusions: The authors have mentioned "This syndrome progresses rapidly and has a high mortality rate." Was this observed in your study?

Response: We have deleted “This syndrome progresses rapidly and has a high mortality rate.”

27. References 1 and 6 are redundant.

Response: We deleted the References 1

28. Rewrite authors' names properly in references 3 and 17.

Response: We haved rewritted authors' names properly in references 3 and 17.

29. Rewrite reference 27 properly.
Response: We have rewritten reference 27 properly.

30. Write name of journal properly in reference 29
Response: We have rewritten name of journal properly in reference 29

Table 1:
31. * Specify 'Q value'. This also applies in Table 2.
Response: We have specified Q value in table 1 and table 2

32. Keep mean±SD.
Response: Because that age distribution is not normal distribution in our study, so we consider that it is more appropriate to use median age.

33. Odds ratio is better for comparison of 2 X 2 variables to compute the odds of risks.
Response: Odds ratio was used by 2 X 2 variables to compute the odds of risks.

Table 2:
34. Keep full form of 'HR' in table footnote. This also applies in Table 3.
Response: We have added the full form of 'HR' in table 2 and Table 3.

Thank you and best regards.

Sincerely Yours,

Hua Pan