**Reviewer’s report**

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

**Version:** 1  **Date:** 08 Feb 2019

**Reviewer:** Research Square

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**Reviewer's report:**

"STATISTICAL REVIEWER ASSESSMENT:

Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?

No - there are minor issues

Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?

No - there are minor issues

Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?

No - there are minor issues

Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?

No - there are minor issues

Could an appropriately REVISED version of this work represent a statistically sound contribution?"
STATISTICAL REVIEWER COMMENTS:

The findings of the study may help the clinical practitioners distinguish between malignancy-associated Hemophagocytic lymphohistiocytosis (HLH) and non-malignancy-associated HLH group during diagnosis. This will suggest them to conduct early diagnosis and prompt treatment of malignancy-associated HLH.

The authors have applied various relevant inferential statistical tests such as Mann-Whitney U, Chi square tests, Correlation analysis, univariate and multivariate Cox analyses. These have made the conclusion reliable.

The authors have mentioned in the Methods section that they applied Mann-Whitney U, Chi square tests, Correlation analysis, univariate and multivariate Cox analyses but they have not mentioned the conditions for their respective application. This has created ambiguity in the statement of applications of the aforementioned statistical tests. Other comments have been given with this peer review.

REQUESTED REVISIONS:

General comments:

* Use full form of 'CSA'.

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

Specific comments:

Title: Use full form of 'HLH' in title.

Abstract:

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

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

* Methods:
o 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."

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

o 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.

o 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."

* Results:

o 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.

o 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.

* Conclusions: The sentence "This syndrome progresses rapidly and has a high mortality rate" has not been mentioned previously.

Main text:

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

Methods:

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

* Participants: 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.

* Outcome: 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.

* 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. Focus on your own results or findings.

Discussion:
* 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.

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

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

References:
* References 1 and 6 are redundant.
* Rewrite authors' names properly in references 3 and 17.
* Rewrite reference 27 properly.
* Write name of journal properly in reference 29.

Table 1:
* Specify 'Q value'. This also applies in Table 2.
* Keep mean±SD.
Odds ratio is better for comparison of 2 X 2 variables to compute the odds of risks.

Table 2: Keep full form of 'HR' in table footnote. This also applies in Table 3.

ADDITIONAL REQUESTS/SUGGESTIONS:

See comments above"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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Please complete a declaration of competing interests, considering the following questions:

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