

Point by Point reply to Reviewers' comments

Thank you very much for reviewing our manuscript No. 41060, titled, 'Intensive care unit complications and outcomes of adult patients with Hemophagocytic Lymphohistiocytosis- A retrospective study of 16 cases' for publication in the 'World Journal of Critical Care Medicine'.

Reviewer 1 (04334222)

- **The major importance of this study is that the HLH population comes from medical ICUs of general medical-surgical hospital and not specialized hematology/oncologic centers, thereby mimicking setup of most of the adult North American ICUs. The major limitations of this study are single center population, retrospective design and relatively small sample size. This retrospective study reported data over 4 years whereas previous ICU studies reported data over 10-12 years, thereby explaining our small sample size.**

No specific comments made to changes in the manuscript.

Reviewer 2 (00502903)

- **The Results section could be better organized into paragraphs by demographics, clinical presentation, diagnosis, and outcomes.**

We made suggested changes in the manuscript results section as advised by the reviewer.

- **A summary of how the diagnosis was established in each case would be helpful - i.e., what combinations or patterns of HLH-2004 criteria.**

We summarized the number of HLH-2004 criteria met in all 16 cases, with the median of 5 out of 8 criteria with IQR of 5 to 6.

- **A description of treatment and management was notably lacking.**

We included it in the results section that 15 out of 16 patients (94%) were initiated on 8 week standard chemotherapy with dexamethasone and etoposide per HLH-94 protocol.

- **Another major limitation of this study is the lack of clarity on whether the described outcomes occurred before or after chemotherapy.**

Described outcomes in the study occurred both before and after the initiation of chemotherapy. Median time to diagnose HLH was 3 days. We included it in the results section, "Of note, the ICU complications occurred both before and after starting chemotherapy"

- **The Discussion is excessively long and meandering. Rather than summarizing the literature in detail and recapping the numerical results, comments might instead focus on how the current study fits into the literature - what new knowledge was gained, how this study supports or differs from others, and what scientific conclusions (if any) can be drawn from the data.**

We made necessary changes to the discussion and made it shorter.

- **The Conclusions are overly prescriptive and would be more appropriately limited to general observations made in the Results.**

We made necessary changes in the conclusion section- highlighted in the manuscript with track changes.

Reviewer 3 (03342506)

- **I suggest to revise the conclusion part of manuscript. Recommendations needs to be moved from conclusion to discussion, and conclusion should better reflect the results of this particular study.**

We made the changes in the manuscript. Conclusion section reflects the important results of our particular study. Recommendations made in the conclusion section are moved to the discussion section.

- **Also, please clarify if the diagnosis of HLH was established before ICU admission or during the ICU stay. That is not clear from the text (“study of adult patients with the diagnosis of HLH admitted to the two academical medical ICUs” and from Table 1 (Time from hospital to ICU admission is 0.5 (0-7) days and time to diagnose HLH is 3 (1-7) days).**

We included this point in results section, in 4 patients, the diagnosis was established before ICU admission and in 12, it was diagnosed during ICU stay.

- **Minor comments: - The abbreviation “DIC” is mentioned in the abstract without explanation.**

We added ‘Disseminated Intravascular coagulation’ before “DIC” in the abstract.

- **The number of references to some statements looks excessive. For the phrase “Multiple studies have investigated morbidity, mortality and predictors of poor outcomes in patients with HLH but very few have been conducted in an ICU setting” in the Discussion part 21 references used (7-27).**

There are large number of studies that reviewed hospital course and complications in patients with HLH but only 3 have been conducted in the ICU setting. To be comprehensive and include all the relevant studies, we have lot of references to the mentioned statement.

Reviewer 4 (02730715)

- **The conclusions are a little overstated. For example, the study just show sixteen adult cases of HLH even Hemophagocytic Lymphohistiocytosis (HLH) is a rare fatal syndrome.**

We made the changes in the conclusion section and now, it reflects only the important results of our particular study.

- **The research will be better if more patients were admitted.**

HLH is a rare, rapidly fatal and under diagnosed syndrome in ICU. Only 3 prior studies on HLH had sample size of 10 or more ICU patients. That's why, our study over 4 years also had less number of patients. With better understanding of the HLH and keeping high index of suspicion, the number of diagnosed cases should increase in future.