

Manuscript No: 43003

Title: Extreme Hyperbilirubinemia: An Indicator of Morbidity and Mortality in Sickle Cell Disease

Authors: John P Haydek MD, Cesar Taborda MD, Rushikesh Shah MD, Preeti A Reshamwala MD, Morgan L. McLemore MD, Fuad El Rassi MD, Saurabh Chawla MD

Response to Reviewers:

We thank the reviewers for taking the time out to review this manuscript and their insightful comments.

We have made the changes as requested and suggested by the reviewers and hope that the reviewers find them acceptable.

Reviewer 1:

1. Introduction: I think the introduction of the manuscript can be more summarized. Authors in this part should more focus on the necessity of performing their study as we already know that hyperbilirubinemia in SCD patients is associated with a higher rate of mortality.

Response: We thank the reviewer for their time and comments. We have removed the overview paragraph about sickle cell disease and added a sentence about the sample size limitations of previous studies.

2. Materials and Methods: 1- Some sentences in the section of data analysis is not related to this part and should be brought elsewhere. Also, Authors should not mention some very simple and primary fact about data analysis in this section.

Response: We thank the reviewer for this comment. We have removed non-pertinent information from this section and removed simple information about data analysis.

3. 2- What is the definition of authors for chronic hyperbilirubinemia?

Response: We thank the reviewer for this comment. We have added a clarification: Patients were identified as having EH if total bilirubin was chronically elevated over the course of a hospitalization or for at least 6 weeks as an outpatient to levels >13.0 mg/dL with direct bilirubin >50% of total bilirubin

4. 3- Have Authors considered conditions, diseases, and medicines that impact on the serum level of bilirubin? They can be counted as confounding variables in this project

Response: We thank the reviewer for this insightful comment. We have clarified the inclusion and exclusion criteria that we followed, which included an ultrasound confirming absence of biliary obstruction, and the following as part of the exclusion criteria: Exclusion criteria also included patients with known infection with hepatitis A, B or C; diagnosis of autoimmune hepatitis; alcoholism; cirrhosis of different etiologies; follow-up less than one year and patients for whom a complete set of required data was unavailable.

5. Results: 1- In the results section we are not allowed to say why or bring reasons. So the sentence of likely due to small sample sizes can be considered as an interpretation and should be moved to the discussion section

Response: We thank the reviewer for this comment. We have removed the sentence about the small sample size.

6. 2- Authors should clearly mention the exact number of the control group.

Response: We thank the reviewer for this comment. We have added a sentence about the total number of patients in the control group.

7. Discussion This part has only 4 references. However, I believe that authors should compare the results of their project with other previous studies.

Response: We thank the reviewer for this insightful comment. There are very limited studies evaluating hyperbilirubinemia or sickle cell hepatopathy, but we have included the following sentences:

While there are very limited studies evaluating hyperbilirubinemia or sickle cell hepatopathy as a predictor of mortality, our findings are consistent with other small analyses that showed associations between direct hyperbilirubinemia and increased mortality [8, 16]. Our mortality rates are lower than that seen in Feld et. al, although our length of follow-up was much shorter than used in their study. Additionally, Feld et al. did not perform subgroup analysis on patients with very high levels of hyperbilirubinemia.

8. References: Authors should use more updated references.

Response: We thank the reviewer for this comment. There are limited additional references, but we have included 1 additional updated reference to the paper.

Reviewer 2:

The manuscript Extreme Hyperbilirubinemia: An Indicator of Morbidity and Mortality in Sickle Cell Disease. it is well described and presented. Congratulations to the authors.

Response: We thank the reviewer for their time and encouraging comments

Edits within Document:

1. A short running title of no more than 6 words should be provided. It should state the topic of the paper. e.g. Losurdo G *et al.* Two-year follow-up of duodenal lymphocytosis.

Response: We thank the editorial team for this comment. We have added a running title.

2. Please provide the postcode.

Response: We thank the editorial team for this comment. We have added a zip codes.

3. Please add the institutional review board statement.

Response: We thank the editorial team for this comment. We have added an institutional review board statement.

4. Please upload the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors' country to the system

Response: We thank the editorial team for this comment. We have added a statement regarding informed consent forms:

This study was retrospective in nature and was not associated with any clinical intervention and thus was exempt from informed consent per our institutional policies.

5. Please download and complete the 'STROBE Statement—checklist of items' to ensure that the manuscript meets the requirements of the STROBE Statement.

Response: We thank the editorial team for this comment. We have used the STROBE statement checklist while preparing our manuscript.

6. Telephone and fax numbers should consist of +, country number, district number and telephone or fax number; for example, +86-10-85381892

Response: We thank the editorial team for this comment. We have added telephone and fax numbers to the manuscript.

7. This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis.

Response: We thank the editorial team for this comment. We have added a background section.

8. Please offer the audio core tip.

Response: We thank the editorial team for this comment. An audio core tip has been uploaded with our section.

9. Similar sentences with other articles, please rephrase. (Line 173)

Response: We thank the editorial team for this comment. We have re-written the sentence as the following:

There were no demographic differences between patients with and without EH (see Table 1).

10. Similar sentences with other articles, please rephrase. (Line 185)

Response: We thank the editorial team for this comment. We have re-written the sentence as the following:

Given limited data, comparisons were not performed for prothrombin time or lactate dehydrogenase.

11. Similar sentences with other articles, please rephrase. (Line 194)

Response: We thank the editorial team for this comment. We have re-written the sentence as the following:

Two deaths occurred within the severe SCH group, and were due to acute chest syndrome and septic shock.

12. The guidelines for writing and formatting Article Highlights are as follows

Response: We thank the editorial team for this comment. We have added an Article Highlights, and followed the provided guidelines in the process.

13. Please insert abbreviations in the table.

Response: We thank the editorial team for this comment. We have added abbreviations into the tables.