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Prof. Lian-Sheng Ma
Company Editor-in-Chief, Editorial
Office
World Journal of Gastroenterology

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Dear Prof. Lian-Sheng Ma

I sincerely thank the opportunity to revise our manuscript “Diagnosis and treatment of iron-deficiency anemia in gastrointestinal bleeding: A systematic review”. Moreover, considering my position as Senior Scholar of the WJG, I’m particularly satisfied to expand the quality of this paper taking into account the pertinent comments that were done.

We thank the Science Editor and the Reviewer for their insightful and constructive comments, as well as for their effort and time put into the review of the manuscript, which have helped us to significantly improve the manuscript. We have carefully addressed all comments and suggestions point-by-point and revised our manuscript accordingly. All the changes are highlighted in the manuscript using the Track Changes mode in MS Word.

Please find below a point-by-point response to the Reviewer’s and the Science Editor’s comments and a summary of the changes.

We look forward to hearing from you regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

José Cotter, MD, PhD
Corresponding Author

Response to the science editor's and reviewer's comments on manuscript "Diagnosis and treatment of iron-deficiency anemia in gastrointestinal bleeding: A systematic review"

Reviewer #1 comments

General comment:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Authors of the systematic review entitled Diagnosis and treatment of iron-deficiency anemia in gastrointestinal bleeding: A systematic review have developed recommendations regarding one of the most common health issues observed in the field of gastroenterology. This is an important work which should be helpful for clinicians (gastroenterologists and other fields of internal medicine) in their everyday work with patients. Still, there are certain issues which I would like to be addressed by authors.

Response: We thank very much for the positive and encouraging comments.

Comment 1: Authors should explain more clearly why is there a need for a standalone guideline for diagnosis and treatment of IDA in GI bleeding as there are for example for anemia in chronic kidney disease. Also, is there a need for this guideline when one takes into account the already existing general guidelines for diagnosis and treatment of IDA, and how do they differ from recommendations proposed by the authors of this manuscript.

Response: We thank the Reviewer for this comment. We have re-written the last paragraph of the Introduction, to further explain the relevance of our manuscript. Given the scarcity of clinical practice recommendations and guidelines on the management of IDA in gastrointestinal bleeding patients, and given the lack of standardization on the management of these patients, a systematic review of the current literature is needed to develop evidence-based recommendations for clinicians to better diagnose and treat iron-deficiency anemia in gastrointestinal bleeding patients.

Comment 2. The coexistence of IDA and anemia caused by inflammation is a challenge for clinicians during differential diagnosis. Authors suggest the use of CRP levels to distinguish between 2 forms of anemia, but CRP is not an ideal indicators for this use, especially since

anemia caused by inflammation can occur due to acute and chronic conditions. WHO publications (The interpretation of indicators of iron status during an acute phase response and Serum transferrin receptor levels for the assessment of iron status and iron deficiency in populations) suggest that sTFR or $\log(\text{sTFR}/\text{ferritin})$ ratio may help in this direction, although there are shortcomings in the use of sTFR as well. Still, role of sTFR should be discussed in the context of IDA vs anemia of inflammation and when both are present in a patient. Additional references regarding this issue can be read from Shin et al. "Utility of access soluble transferrin receptor (sTFR) and sTFR/ \log ferritin index in diagnosing iron deficiency anemia", Infusino et al. "Soluble transferrin receptor (sTFR) and sTFR/ \log ferritin index for the diagnosis of iron-deficiency anemia a meta-analysis", Koulaouzidis et al. "Soluble transferrin receptors and iron deficiency, a step beyond ferritin. A systematic review".

Response: Thank you for pointing this out. We have re-written this part of the manuscript and we have included all the suggested references. We have also included a phrase in the Methods and in the Results sections highlighting the introduction of the new references after the peer review process.

Comment 3. Figure 2 does not address the scenario what to do when oral iron therapy results with poor achievement of treatment targets (which occurs for example in IDA during GI bleeding accompanied with heart failure).

Response: Thank you very much for this suggestion. We agree with the Reviewer and accordingly, we have incorporated this idea in Figure 2.

Comment 4. A table which details the pharmacological characteristics of oral and IV iron preparations, their advantages and disadvantages should be added.

Response: Thank you very much for this suggestion. We agree with the Reviewer and the suggested table (Table 4) was included in the manuscript.

Comment 5. Authors have not discussed the potential role of ascorbic acid in increasing iron absorption. Role of ascorbic acid is discussed in “Joint recommendations on management of anaemia in patients with gastrointestinal bleeding in Hong Kong” and “Guidelines for the management of iron deficiency anaemia from British Society of Gastroenterology”. For further recent details please consult “Iron deficiency anemia: A comprehensive review on iron absorption, bioavailability and emerging food fortification approaches” by Shubham et al.

Response: Thank you very much for this suggestion. We have included this idea and all the suggested references on the manuscript (p.17).

Editorial Office’s comments

The author must revise the manuscript according to the Editorial Office’s comments and suggestions, which listed below:

Science Editor comments:

Comment 1: Scientific quality: The manuscript describes a systematic review of the anemia in gastrointestinal bleeding. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This is an important work which should be helpful for clinicians (gastroenterologists and other fields of internal medicine) in their everyday work with patients. However, there are some issues should be addressed.

Response: We thank very much for the positive and encouraging comments.

Comment 2: A table which details the pharmacological characteristics of oral and IV iron preparations, their advantages and disadvantages should be added. The questions raised by the reviewers should be answered.

Response: Thank you very much for this suggestion. We agree with the Science Editor and the suggested table (Table 4) was included in the manuscript.

Comment 3: Format: There are 4 tables and 2 figures. A total of 42 references are cited, including 5 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form, and the PRISMA checklist form. The authors need to provide the Copyright License Agreement signed by all authors. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by OM Pharma. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. This manuscript is the resubmission of Manuscript No. 36605 (Rejected).

5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Response: The approved grant application form(s) or funding agency copy of any approval document(s) were uploaded, we have provided the original figure documents, and we have included the “article highlights” section at the end of the main text.