

September 10, 2015

Dr. Ze-Mao Gong
Scientific Editor
World Journal of Gastroenterology

Dear Dr. Gong:

Thank you for your careful review and constructive criticisms of the manuscript entitled, “Distinctive aspects of peptic ulcer disease, Dieulafoy’s lesion, and Mallory-Weiss syndrome in patients with advanced alcoholic liver disease or cirrhosis” by Borko Nojkov, M.D., and Mitchell S, Cappell, M.D., Ph.D. submitted as a systematic review to the World Journal of Gastroenterology. This paper is entirely revised in accord with the reviewers’ comments and the editorial specifications as follows:

Reviewer 1: 03022475

Reviewer comments: The manuscript, ESPS, No. 21765, provides a comprehensive review of the recent literature data on the association between PUD, DL, and MWS and aALD or cirrhosis. It is also well supported by the quoted references. This is well written and interesting contribution of considerable interest to the readership of the Journal.

Author responses: No changes necessary in manuscript.

Reviewer 2: 00008736

Reviewer’s comments: This is an excellent review of the current knowledge about UGI bleeding in patients with ALD. The authors give a comprehensive overview over the various disease conditions associated with bleeding and highlight controversies around these topics. The paper could be improved by giving the actual number of papers that was analyzed here.

Authors responses: As per the reviewer’s comments, we have added the following to the Methods section:

“Of about 1,200 articles initially identified by computerized review, about 825 articles were eliminated as not relevant to the subject of this paper after briefly reviewing the articles, including thoroughly reviewing the abstracts. The remaining 375 articles were thoroughly

reviewed, and 165 articles were selected for incorporation and citation in this systematic review.”

Reviewer 3: 02440657

Reviewers comments: This review manuscript comprehensively analyzes the association between PUD, DL, and MWS and aALD or cirrhosis, and also discussed the clinical consequences in terms of treatment and prognosis, which is quite good, but several issues need to be clarified: 1. The title is rather confusing, it emphasized “acute upper gastrointestinal bleeding”, whereas the aALD and the correlation are the main topic through the manuscript;

Author response: This manuscript is revised entirely according to the reviewer’s criticism by:
CHANGE OF TITLE TO:

Distinctive aspects of peptic ulcer disease, Dieulafoy’s lesion, and Mallory-Weiss syndrome in patients with advanced alcoholic liver disease or cirrhosis

CHANGE OF TITLE FROM:

Acute upper gastrointestinal bleeding associated with alcoholic liver disease or cirrhosis, but not directly related to portal hypertension: peptic ulcer disease, Dieulafoy’s lesion, and Mallory-Weiss syndrome.

Reviewer’s comments 2. As indicate in the manuscript, “While the majority of acute gastrointestinal (GI) bleeding with aALD is related to portal hypertension, about 30-40% of acute GI bleeding in patients with ALD is unrelated to portal hypertension”, it seems the authors should focus on these “30-40% of acute GI bleeding ...” and to discuss the related influencing factors other than portal hypertension, so the short title “Gastrointestinal bleeding unrelated to portal hypertension in alcoholic liver disease ”might be not proper; 3.. The content of the manuscript include all the liver cirrhosis trials, and not that ALD specific

CHANGE OF SHORT TITLE TO:

PUD, Dieulafoy’s lesion, & MWS in alcoholic hepatitis & cirrhosis

CHANGE OF SHORT TITLE FROM:

Gastrointestinal bleeding unrelated to portal hypertension in alcoholic liver disease

As suggested, the manuscript includes many liver cirrhosis trials and is not that ALD specific.

Editor's comments:

1. Title: Too long

CHANGE OF TITLE TO SHORTEN IT TO:

Distinctive aspects of peptic ulcer disease, Dieulafoy's lesion, and Mallory-Weiss syndrome in patients with advanced alcoholic liver disease or cirrhosis

CHANGE OF TITLE FROM:

Acute upper gastrointestinal bleeding associated with alcoholic liver disease or cirrhosis, but not directly related to portal hypertension: peptic ulcer disease, Dieulafoy's lesion, and Mallory-Weiss syndrome.

2. Author affiliations are changed as per editorial style to the following:

Nojkov B, M.D.
Gastroenterology Fellow
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3. Author contributions are changed as per editorial style to the following:

Author contributions: Nojkov, B: Designed research, performed research, analyzed data, and wrote the paper. Cappell MS: Designed research, performed research, analyzed data, and wrote the paper. Both authors read and approved the final manuscript. Both authors contributed equally to the paper.

4. As per editorial style the following Biostatistics statement is added:

Biostatistics statement: The statistical analysis in this manuscript was reviewed by a biostatistician (see Methods section). The name and affiliation of the biostatistician is to be

supplied. The article is now out for the biostatistician's review and the letter from the biostatistician will be forwarded to the journal as soon as this review is completed.

5. As per editorial style the following Data sharing statement is added:

Data sharing statement: No additional data available for this systematic review.

6. As per editorial style the first letter of the first word of each key word is capitalized, as follows:

Key words: Alcoholic liver disease; Alcoholic hepatitis; Cirrhosis; Portal hypertension; Peptic ulcer disease; Mallory-Weiss syndrome; Dieulafoy lesion; Endoscopic therapy.

7. As per editorial style the Core Tip is shortened to 100 words, as follows:

Core Tip

Alcoholism is highly prevalent worldwide and can cause advanced-alcoholic-liver-disease (aALD) from alcoholic hepatitis or cirrhosis. This work systematically reviews the literature on acute-upper-gastrointestinal-bleeding not directly related to portal hypertension in patients with aALD. Such patients have markedly increased risks of peptic ulcers, and worse outcomes from peptic ulcer bleeding than other patients, including refractory bleeding, rebleeding, and mortality. Such patients apparently have increased frequency and mortality of bleeding from Dieulafoy-lesions. Such patients have more frequent, more severe, and more rebleeding from Mallory-Weiss-syndrome than non-cirrhotics. Prompt endoscopy, after resuscitation, is essential to diagnose and appropriately treat these patients, using endoscopic therapy when necessary.

8. As per editorial style, the following audio core tip will be forwarded separately to the journal.

9. The level of titles has been distinguished as per editorial style.

10. The references have been rechecked and numerous references have been corrected as necessary.

11. The tables have been corrected, as per editorial policy,

A. The table titles have been typed in bold font.

B. The entries in the top row of the tables have been centered.

C. The tables have been renumbered as 1 to 10 instead of I to X.

12. As per editorial policy all the abbreviations in Figure 1 have been clarified.

CHANGE TO:

Frequency distribution of the etiologies of upper gastrointestinal bleeding in patients with cirrhosis. Varices include esophageal or gastric varices. PUD – peptic ulcer disease. PHG – portal hypertensive gastropathy, MWS – Mallory-Weiss syndrome, Other – other etiologies of upper gastrointestinal bleeding . Based on: [39,44-47].

CHANGE FROM:

Frequency distribution of the etiologies of upper gastrointestinal bleeding in patients with cirrhosis. Varices include esophageal or gastric varices. PUD – peptic ulcer disease. PHG – portal hypertensive gastropathy, MWS – Mallory-Weiss syndrome. Based on: [39,44-47].

Please inform us if further changes are required which we will gladly perform. Please note that you will receive separately the Biostatistics Statement and the audio core tip. The revised manuscript has been forwarded to you without these 2 items in order not to delay the review process.

Thank you for your interest in this manuscript.

Warm regards,

Mitchell S. Cappell, M.D., Ph.D.

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