

Dear editor,

thank you for giving me the possibility of submitting a revised version of the review paper entitled "Gastrointestinal dysfunction in liver cirrhosis" (ESPS Manuscript NO: 6749). I would also like to thank the reviewers for their comments and suggestions as through their efforts I feel that I have been able to improve the paper significantly. Changes made to the paper are indicated as highlighted text. The fact that the author's doctoral thesis has been an important source for this paper has been re-added in the title page of the paper (removed since last version presumably during copy-editing). My point-to-point response to the reviewers is as follows:

Reviewer 1 (00003629)

*The review article by Kalaitzakis E et al entitled "Gut dysfunction in patients with liver cirrhosis", is a well written and documented report on the stated subject. The author and his co-workers are well known from their work on the pathophysiology of cirrhosis and the GI tract and this review includes aspects of their group experience on the subject. Following are some more detailed comments on the paper. Major comments: 1. The text could be shortened by 2-3 pages. 2. A more appropriate title of the review should have been: "Gastrointestinal dysfunction in liver cirrhosis". The present title as it is, my mislead the reader, that the review refers only to intestinal disturbances of cirrhosis. 3. (Page 3, "Malnutrition in liver cirrhosis"): Some consideration must be given to the role of reduced synthetic ability of the liver for the development of sarcopenia of chronic liver failure. 4. (Page 5, 2nd paragraph, 15th line from bottom): The range 11-94% is too wide. Please give some explanation and refer to a more recent bibliography. 5. (Page 12, Conclusion): "GI symptoms are common in patients with liver cirrhosis": The reader would expect a more detailed description of the type and frequency of GI symptoms present in cirrhosis. Before referring to pathophysiology of motility, function and disturbances of the GI tract in cirrhosis, a short section of common GI symptoms in cirrhosis appears necessary. Minor Comments: 1. A few grammatical and typing errors throughout the text. Please use shorter sentences. It makes reading easier. 2. (Page 3, "GI symptoms in patients with liver cirrhosis"): The phrase "as well as to patients with chronic renal failure on hemodialysis [26]" is irrelevant. 3. (Page 3, 5th line from bottom): "Satiety". 4. (Page 5, 3rd line from bottom): "in cirrhotics compared to those..."*

I would like to thank the reviewer for finding the paper "well-written and documented report" on the subject.

#### Major Comments

1. As per the invitation from the editorial team, there would not be a word limit for this review. However, an attempt has been made to reduce the length of the paper somewhat and further attempts can be made should the editorial team request it.

2. The title has been changed as per the reviewer's suggestion.

3. The potential role of poor synthetic capacity of the cirrhotic liver in the development of malnutrition in cirrhosis has been added in the revised version of the paper (under the subheading "Malnutrition in liver cirrhosis").

4. The wide variation in the reported prevalence of portal hypertensive gastropathy, confirmed in a recent review on the subject (Cubillas R, et al. Liver Int 2010; 30: 1094-102), could probably be related to the wide variation in study quality (prospective vs. retrospective, etc) and the cirrhotic cohorts studied. The reference mentioned by the reviewer has been exchanged with a more recent one in the revised version of the paper. This potential explanation has also been added to the paper. The prevalence of portal hypertensive gastropathy in patients with cirrhosis without a history of variceal bleeding, medium or large esophageal varices, previous endoscopic therapy, or propranolol treatment (reported in a study cited in the previous version of the paper) has been highlighted in the revised version of the paper.

5. The most common GI symptoms and their frequency has been added in the revised version of the paper (under the subheading "GI symptoms in patients with liver cirrhosis").

#### Minor Comments

1. A grammatical check has been performed with a text editor and a few typos have been corrected. An attempt has been made to shorten sentences throughout the paper as per the reviewer's suggestion.

2. This phrase has been removed from the text in the revised version of the paper.

3-4. Changes have been made as per the reviewer's suggestions.

#### Reviewer 2 (02529109)

*The clinical problem is common, the pathophysiology of the disorders is complex and not fully elucidated. The subject of the article is very interesting, however rather difficult to "digest" for non-physiologists. I have found several physiological parameters or terminology, which should be additionally explained in the article, e.g. intestinal vasculopathy in portal hypertension, gut hypersensitivity, epithelial barrier. The changes in gut microbiota in liver cirrhosis are very important, but not explained in the text based on the current knowledge e.g. J Gastroenterol Hepatol. 2014 Feb 18. doi: 10.1111/jgh.12556). Majority of references were published before 2010. We could find in Pub Med many papers dealing with the gut dysfunction in liver cirrhosis published after 2011 y. Therefore, I suggest that the Author has improved and modernized the manuscript.*

1. The term intestinal vasculopathy is explained page 5, second paragraph under the subheading "Structural changes in the GI tract in liver cirrhosis". Hypersensitivity is defined in the second paragraph under the subheading "Gastric sensitivity to distension". The epithelial barrier, as part of the gut barrier, is defined under the subheading "Intestinal permeability".

2. The author agrees with the referee on the importance of gut microbiota changes in liver cirrhosis. The importance of bacterial overgrowth as well as that of permeation of

bacterial products (such as endotoxin) has been mentioned in the paper (under the subheading "Intestinal permeability"). In the revised version of the paper, the role of alterations in the gut bacterial flora for the development of minimal hepatic encephalopathy has been mentioned, together with the beneficial effect of modulation of the gut flora by means of probiotics, prebiotics, and symbiotics (3rd paragraph under the subheading ""Intestinal permeability").

3. It is correct that several of the references are older as the subject of gut dysfunction in liver cirrhosis, in particular sensorimotor function of the stomach and the small bowel, is a neglected one. The author is confident that regarding gastric sensorimotor function, small bowel transit and gastric sensitivity all relevant recent papers have been included in the reference list. Concerning gut barrier dysfunction older but still valid data have been discussed together with newer studies -reference 116 (2013), 117 (2010), ref 119 (2011), ref 120 (2013), ref 123 (2013), ref 124 (2011), ref 127 (2013), ref 133 (2013), ref 137 (2012), ref 138 (2012)- and a recent extensive review of the topic (ref 118 - 2013). Although there may be several more papers published on the topic of gut barrier function, the author feels that the subject is covered in a relevant way and in accordance with the comments of 4 previous reviewers. Finally, this review was not meant to be a systematic or extensive review of the literature. However, should the editorial team consider that further changes in the reference list are required the author would be happy to proceed to them.

Kind regards,

Evangelos Kalaitzakis MD, PhD, FEBGH  
Associate professor of medicine