

28th of January, 2022

Prof. Andrzej S Tarnawski
Editor-in-Chief

Dear Editor-in-Chief,

We greatly appreciate the positive evaluation and comments of the Editors and Reviewers for our work. The Reviewers' comments were helpful in the revision of our manuscript that now contains numerical data about the performance of the different markers, and information about the role of PSC related HLA alleles in acute rejection after liver transplantation.

The manuscript has also been proofread by a native English speaker co-worker.

Below we provide point-by-point responses to the comments and concerns of the editors and reviewers.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In the present review article Tornai et al discussed about scores and biological markers that may be useful in the management of primary sclerosing cholangitis (PSC), especially in terms of prognosis. This is an outstanding review that covers most of the treated topics. I have only few minor suggestions:

1) Page 8: what do Authors mean when affirming that "both UK-PSC risk scores performed better than MRS and APRI"? Please be more precise, and report some figures.

We thank the reviewer for the careful evaluation of our manuscript and for pointing out the lack of precision in the mentioned sentence. We changed the sentence to the following:

"Both short and long-term UK-PSC risk scores had better performance than MRS and AST-to-platelet ratio index (APRI) when predicting outcomes (C-statistics for 2-year survival (short term) were 0.81 vs. 0.75 and 0.63, respectively; for 10-year survival (long term) were 0.80 vs. 0.79 and 0.59, respectively)."

We also added figures on other markers.

2) Is there some evidence about the role of HLA haplotypes in PSC? (see for example Fosby B et al, World J Gastroenterol 2014).

We thank the reviewer for bringing this article to our attention. We incorporated the information found in the paper into our manuscript (at the end of the section about the relationship of ANCA formation and HLA genotypes) as follows:

“Interestingly, association between presence of PSC related HLA alleles (B*08, C*07, DRB1*03) and increased risk of acute rejection syndrome in liver transplant recipients has also been reported (while DRB1*04 was found to be a protecting factor) [30].”

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Recent advances in biomarker research may help clinicians identifying relevant subgroups of primary sclerosing cholangitis (PSC) and assist everyday clinical work-up. However, a diagnostic biomarker is still an unmet need. On the other hand, several biomarkers have been reported to predict outcome in PSC, however most of them have not been validated by subsequent studies. IgA type anti-glycoprotein 2 antibody (anti-GP2 IgA) is the first one to be supported by a satisfactory number of clinical studies and could be incorporated in the clinical practice. These discoveries also reveal different aspects of PSC providing with potential therapeutic targets. The manuscript is well, concisely and coherently organized and presented.

We thank the reviewer for the careful evaluation of our manuscript and the positive feedback. We have addressed the grammatical issues in the paper.

(1) Science editor:

This is a good mini-review to help the field. Please revise according to the reviewers' comments.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

We thank the editor for the careful evaluation of our manuscript and the positive feedback. We have addressed the linguistic issues of the paper.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures

are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

We thank the editor for the careful evaluation of our manuscript. We revised the manuscript according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision.

The figures in the paper are the original artwork by our team. However, a different version of Figure 1 has been published in Tornai D, Papp M. Editorial: serologic antibodies in primary sclerosing cholangitis - a tell-tale sign of compromised gut-liver immunity? *Aliment Pharmacol Ther* 2021; 53: 350-351.

The policy of Alimentary Pharmacology & Therapeutics on reusing authors' own work can be found at:

<https://onlinelibrary.wiley.com/page/journal/13652036/homepage/permissions.html>

and it says: "If you wish to reuse your own article (or an amended version of it) in a new publication of which you are the author, editor or co-editor, prior permission is not required (with the usual acknowledgements)."

Of note, the figure has been modified and has not been used in present form. The figure legend includes the citation as required. We also added "Copyright ©The Author(s) 2022" to Figure 2.

We are very much grateful for the possibility to submit this revision of our work and hope that the paper in its present form will meet the high standards of *World Journal of Gastroenterology*.

Yours sincerely,

Maria Papp, MD, PhD, DSc, FEBG
Department of Gastroenterology,
Clinical Center,
University of Debrecen
Nagyerdei krt. 98, Debrecen
H-4032 Hungary
Phone: (+36) 52-258-598

Mobil: (+36) 30-405-4993
e-mail: papp.maria@med.unideb.hu

Peter Lakatos, MD, PhD, DSc, FEBG, AGAF
Director of IBD Centre, Professor of Medicine
McGill University Health Centre, Montreal General Hospital,
1650 Ave. Cedar, D7-201, Montreal, QC, H3G 1A4
Tel: +1-514-9341934 x ext 45567
Fax: +1-514-934-4452
Tel: +1-514-4317994
e-mail: Peter.Lakatos.med@ssss.gouv.qc.ca
e-mail: peter.lakatos@mcgill.ca
email: kislakpet99@gmail.com

1st Department of Medicine
Semmelweis University
Koranyi S 2A, Budapest
H-1083, Hungary
Tel: +36-1-4591500 / 51500, 51520
Fax: +36-1-313-0250
e-mail: lakatos.peter_laszlo@med.semmelweis-univ.hu

David Tornai, MD, PhD
Department of Gastroenterology,
Clinical Center,
University of Debrecen
Nagyerdei krt. 98, Debrecen
H-4032 Hungary
e-mail: tornai.david@med.unideb.hu

Dear Editor, We would like to thank you your effort to evaluate our manuscript. We made the required modifications: we deleted or changed the references listed below. The maximum number of citations from a particular journal is now 3. Please note that we needed to renumber the references due to deletion. References that are no longer cited are: Rupp C, Rössler A, Halibasic E, Sauer P, Weiss KH, Friedrich K, Wannhoff A, Stiehl A, Stremmel W, Trauner M, Gotthardt DN. Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther* 2014; 40: 1292-1301 [PMID: 25316001 DOI: 10.1111/apt.12979] Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009; 50: 808-814 [PMID: 19585548 DOI: 10.1002/hep.23082] Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009; 50: 808-814 [PMID: 19585548 DOI: 10.1002/hep.23082] Terjung B, Söhne J, Lechtenberg B, Gottwein J, Muennich M, Herzog V, Mähler M, Sauerbruch T, Spengler U. p-ANCA in autoimmune liver disorders recognise human

beta-tubulin isotype 5 and cross-react with microbial protein FtsZ. Gut 2010; 59: 808-816 [PMID: 19951907 DOI: 10.1136/gut.2008.157818] Seidel D, Eickmeier I, Kühl AA, Hamann A, Loddenkemper C, Schott E. CD8 T cells primed in the gut-associated lymphoid tissue induce immune-mediated cholangitis in mice. Hepatology 2014; 59: 601-611 [PMID: 24038154 DOI: 10.1002/hep.26702] Quraishi MN, Sergeant M, Kay G, Iqbal T, Chan J, Constantinidou C, Trivedi P, Ferguson J, Adams DH, Pallen M, Hirschfield GM. The gut-adherent microbiota of PSC-IBD is distinct to that of IBD. Gut 2017; 66: 386-388 [PMID: 27196590 DOI: 10.1136/gutjnl-2016-311915] Wannhoff A, Hov JR, Folseraas T, Rupp C, Friedrich K, Anmarkrud JA, Weiss KH, Sauer P, Schirmacher P, Boberg KM, Stremmel W, Karlsen TH, Gotthardt DN. FUT2 and FUT3 genotype determines CA19-9 cut-off values for detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 2013; 59: 1278-1284 [PMID: 23958938 DOI: 10.1016/j.jhep.2013.08.005] We also attached a written confirmation of the grant EFOP-3.6.1-16-2016-00022. Since this grant was won by our university (University of Debrecen) including many groups besides our own, we cannot provide the application form. However, the provided document includes the following information: grant number; donor of the financial support (Emberi Erőforrások Minisztériuma Európai Unió Fejlesztések Végrehajtásáért Felelős Helyettes Államtitkárság); recipient (Debreceni Egyetem); end date of the project; and in the last sentence it confirms that Maria Papp is a contributor to the project. We hope that this document will meet your expectations. Sincerely, Maria Papp, MD, PhD, DSc, FEBG Department of Gastroenterology, Clinical Center, University of Debrecen Nagyterdei krt. 98, Debrecen H-4032 Hungary Phone: (+36) 52-258-598 Mobil: (+36) 30-405-4993 e-mail: papp.maria@med.unideb.hu Peter Lakatos, MD, PhD, DSc, FEBG, AGAF Director of IBD Centre, Professor of Medicine McGill University Health Centre, Montreal General Hospital, 1650 Ave. Cedar, D7-201, Montreal, QC, H3G 1A4 Tel: +-1-514-9341934 x ext 45567 Fax: +1-514-934-4452 Tel: +1-514-4317994 e-mail: Peter.Lakatos.med@sss.gov.qc.ca e-mail: peter.lakatos@mcgill.ca email: kislakpet99@gmail.com 1st Department of Medicine Semmelweis University Koranyi S 2A, Budapest H-1083, Hungary Tel: +36-1-4591500 / 51500, 51520 Fax: +36-1-313-0250 e-mail: lakatos.peter_laszlo@med.semmelweis-univ.hu