



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 05068976

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Spain

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-02-25 17:35

**Reviewer performed review:** 2021-03-17 08:37

**Review time:** 19 Days and 15 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

The manuscript by Losurdo et al. constitutes a critical and comprehensive review on the topic of liver involvement in inflammatory bowel disease (IBD). The authors herein provided a very complete state-of-the-art on the field, summarizing the most important findings related to the presence of liver diseases and IBD and also the occurrence of liver damage during the treatment of IBD. The information is very well-organized, in a clear structure and it is easy to follow. There are only minor concerns that should be addressed before publication. - Et al. should be in italics. - Please consider the inclusion of 2 tables in the manuscript: one with the IBD and liver comorbidities (summarizing the information displayed in the text) and another one with the liver-related effects (DILI) in patients with IBD. - Are there any data on the impact of IBD in liver transplantation? - The authors mention the risk for CCA development in patients with PSC-IBD. But is this risk higher when compared with patients with isolated PSC? This should be discussed. - Regarding NAFLD, the multiple theory hypothesis states that several hits, including the translocation of bacterial products, might trigger the progression from simple steatosis towards NASH. It might be possible that patients with IBD display an increase prevalence or risk for development of NASH and fibrosis? Furthermore, which of them comes first? NAFLD or IBD? And is it more often associated with CD or UC?



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 03658334

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Full Professor

**Reviewer's Country/Territory:** Croatia

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-17 20:49

**Reviewer performed review:** 2021-03-20 19:37

**Review time:** 2 Days and 22 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

To the Authors Thank you for the paper that will be very useful for the clinicians in everyday practice. But, there are some ambiguities, listed below that should be corrected. Second part of Introduction is written without cited references. In part 2.1. CSP is written instead of PSC. In part 2.4. is written „A non significant increase of risk for neoplasia was shown in patients with PSC-CD, in contrast to that found in patients with UC alone.” Do you men CD? In part 2.5. Reference about microbiota is missing. In part 5.2. “Sulfasalazine is overall used for mild CD”. Owing to the guidelines 5-ASA derivates are not effective in the CD. Furthermore, mesalamine and sulfasalazine can also be used in UC as well. In part 5.3. The doses of methotrexate used in IBD are higher than the doses in rheumatology. Methotrexate is used weekly. In part 5.4. Etanercept is not effective in IBD. In part 5.5. Natalizumab can cause serious neurological side effects so its use in IBD is limited. In order to make the paper clearer, my advice is to put the mean messages in one or two tables.



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 04091850

**Position:** Editorial Board

**Academic degree:** DSc, MD, PhD

**Professional title:** Adjunct Professor, Chief Doctor

**Reviewer's Country/Territory:** Denmark

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-17 04:29

**Reviewer performed review:** 2021-03-22 09:11

**Review time:** 5 Days and 4 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

The manuscript does not present new thoughts. Rather it provides the reader with a review of possible liver involvement in inflammatory bowel disease. In that sense it is very useful. In general the manuscript is well disposed and the subjects chosen for description are logic. However a major revision is needed before it can be recommended for publication. The major reason for that is that the quality of the language is rather bad. The language is uneven and here and there it leads to possible misunderstandings and for that reason it can be difficult to follow the thoughts and recommendations. Specific comments: Abstract: Many sentences are a direct copy of the introduction pg 3: line 2 IBD consists of the two separate disease entities ulcerative colitis and Crohn's disease Pg 3 section 2.1: If the endoscopic appearance is normal it should be noted that the diagnosis of UC in these cases is based on histology pg 4 section 2.1 line 11: What is meant by "colorectal involvement in PSC-UC seems to be less severe" Should be " the severity of the mucosal inflammation seems less pronounced" pg 5 section 2.4 line Contradictory statement regarding GBC compared with what is written in line 1 + 2 in the same section line 19 It is correct that it is suggested that mesalazine could have a cancer protecting effect but this is not specific for PSC-UC but has also been documented in UC without liver involvement pg 6 section 3 line 34. A study is mentioned in which three different cohorts were followed. In this context a prevalence figure is given for the occurrence of overall NAFLD in IBD patients. A prevalence cannot be depicted from a cohort study of patients known to suffer from NAFLD. Should be explained Section 3 pg 7 line 4: How would you treat NAFLD ? Section 4 pg 7 line 30: A general recommendation of hepatitis B vaccination is given for HBV negative patients. It should be discussed whether this is necessary in low-prevalent areas. Section 5.1 pg 9 line 29: The statement is given that the prevalence of NRH is the same in thiopurine treated and thiopurine-naive patients. This



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statement is not in line with what is written earlier that NRH is the most frequent liver injury causes by vascular endothelial lesions provoked by thiopurines. line 36: The information should be given that the dose of thiopurines should be reduced if allopurinol is co-administered section 5.3 pg 10: The section describing Methotrexate should be placed before section 5.2 Section 5.4 pg 11. The correct title would be TNF alpha inhibiting agents. This part of the manuscript is suffering from a very bad english and it should be heavily revised. pg 11 line 19: Prevalence of DILI is an incorrect term. Occurrence is better. pg 11 line 25: Elucidate whether it is really meant that liver affection was documented in 163 of 252 patients treated with IFX Section 5.5 pg 13 line 1: Vedolizumab was approved in 2014 and Natalizumab even before that. This is not "recent". It should be noted that Natalizumab is associated with the possible severe side effect of PML in JC virus positive patients. Even if a satisfactory response to the above mentioned specific points is given the manuscript cannot be recommended for publication unless it is heavily improved regarding the language



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 04737076

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Consultant Physician-Scientist, Doctor, Lecturer, Pediatric Gastroenterology Fellow, Professor, Senior Postdoctoral Fellow, Senior Researcher, Senior Scientist

**Reviewer's Country/Territory:** Russia

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-17 07:47

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<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input type="checkbox"/> ] Anonymous [ <input checked="" type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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### **SPECIFIC COMMENTS TO AUTHORS**

The title of the article fully reflects the main topic of the manuscript. Abstract and keywords reflects well the content of the manuscript. The introduction sufficiently reflects the current state of the problem described. A very good review and analysis of modern literature on the topic presented is presented, which allows to expand the knowledge of clinicians on the problem of a combination of inflammatory bowel diseases and liver diseases, including sclerosing cholangitis, non-alcoholic fatty liver disease, chronic viral hepatitis, and drug-induced liver damage. The effect of various drugs, which are used both in the treatment of liver diseases and in the treatment of inflammatory bowel diseases, is shown, as well as their interaction, which is very important in clinical practice. This manuscript is very useful not only for clinicians who prescribe treatment for patients with chronic liver diseases and inflammatory bowel diseases, as well as their combination, but also for researchers of the etiology and pathogenesis of these diseases. The manuscript has been prepared in accordance with the requirements. I read the manuscript with great pleasure!



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 04091933

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor, Senior Researcher

**Reviewer's Country/Territory:** Russia

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-17 08:41

**Reviewer performed review:** 2021-04-03 20:25

**Review time:** 17 Days and 11 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript deserves publication in the World Journal of Hepatology, since the authors professionally review the actual topic of liver involvement in IBD, which can worsen the course of the disease and its outcomes, and require additional therapy and careful monitoring. However, the manuscript requires revision. Not all liver lesions are carefully considered. Since the manuscript claims to be a comprehensive review, it is recommended to include information regarding the rarer liver lesions in patients with IBD, such as primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH). In addition, since there is a risk of HBV reactivation in patients with IBD who are receiving immunosuppressants, additional information on prophylaxis against HBV reactivation should be included based on ECCO and EASL guidelines. Even more rare variants of liver damage, such as secondary hepatic amyloidosis, pyogenic liver abscess, and PVT should be included in the review. They do not need to be discussed in detail, but they can be given in a table with relevant references. The manuscript can be accepted after revision.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 64950

**Title:** Liver involvement in inflammatory bowel disease: What should the clinician know?

**Reviewer's code:** 04091850

**Position:** Editorial Board

**Academic degree:** DSc, MD, PhD

**Professional title:** Adjunct Professor, Chief Doctor

**Reviewer's Country/Territory:** Denmark

**Author's Country/Territory:** Italy

**Manuscript submission date:** 2021-02-25

**Reviewer chosen by:** Li-Li Wang

**Reviewer accepted review:** 2021-07-18 07:32

**Reviewer performed review:** 2021-07-19 05:58

**Review time:** 22 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS



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The major questions and suggestions have been carefully addressed by the authors and required changes have been made in the manuscript where appropriate. I can therefore recommend the manuscript to be published.