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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
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Academic degree:
Professional title:
Reviewer's Country/Territory: Spain
Author's Country/Territory: Italy

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Reviewer #1: 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.

The expression “et al” has been italicized. As suggested, we have enclosed two tables in order to summarize the concepts regarding liver co-morbidities and DILI that have been described in the text.

- Are there any data on the impact of IBD in liver transplantation?

As regards this point, some papers found that IBDs do not worsen the survival in patients with liver transplantation for PSC. Only the exposure to azathioprine seems to increase post-transplant mortality, while IBD *“per se”* increases the risk of Citomegalovirus infection (*Irlès-Depé M, et al. Impact of Preexisting Inflammatory Bowel Disease on the Outcome of Liver Transplantation for Primary Sclerosing Cholangitis. Liver Transpl. 2020*). These sentences have been enclosed in the text of revised manuscript.

- 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.

IBD could be an additional risk factor that further increases the hazard of CCA in PSC. In particular, a long duration of IBD is associated with CCA with a hazard ratio of 1.37 (*Gulamhusein AF et al. Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD. Am J Gastroenterol. 2016*). This concept has been enclosed in the text of revised manuscript.

- 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?

There are no studies that evaluate the progression of NASH in IBD. However, since IBD induce gut barrier perturbation and an increase in toxin and bacterial translocation, it is possible that in patients with NAFLD, the coexistence of IBD can trigger the progression from a simple steatosis towards NASH. On the other hand, a single study has shown that the progression of fibrosis, estimated by NAFLD fibrosis score, is quite rare in IBD (*Ritaccio G et al. Nonalcoholic Fatty Liver Disease Is Common in IBD Patients However Progression to Hepatic Fibrosis by Noninvasive Markers Is Rare. Dig Dis Sci. 2020*)

It has been demonstrated that there are no differences in the prevalence of NAFLD between patients

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with CD and UC. (*Principi M, et al. Non alcoholic fatty liver disease in inflammatory bowel disease: prevalence and risk factors. Inflamm Bowel Dis. 2018; Sourianarayanane A et al. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease.J Crohns Colitis. 2013*)

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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?

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Position: Peer Reviewer
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Professional title: Full Professor

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Author's Country/Territory: Italy

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] 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.

We have enclosed additional references in the second part of Introduction.

In part 2.1. CSP is written instead of PSC.

We are sorry for the mistake, it was corrected in the revised version.

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?

We are sorry for the mistake, which was corrected in the revised version: of course, we meant CD

In part 2.5. Reference about microbiota is missing.

We have added a dedicated reference in the revised manuscript (*Shah A, et al.Targeting the Gut Microbiome as a Treatment for Primary Sclerosing Cholangitis: A Conceptional Framework. Am J Gastroenterol 2020*)

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.

That statement was justified by a meta-analysis showing that Sulfasalazine may have a trend towards a benefit over placebo (two RCTs, RR of failure to achieve remission=0.83; 95% CI=0.69-1.00), as stated by *Ford AC, et al .Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol. 2011*

However, we rephrased the sentence regarding the effectiveness of both mesalamine and sulfasalazine on UC in revised manuscript.

In part 5.3. The doses of methotrexate used in IBD are higher than the doses in rheumatology. Methotrexate is used weekly.

In the revised manuscript, we underlined that in CD, methotrexate is administered intramuscularly at the dose of 25 mg/week for inducing and 15 mg/week for maintaining remission. Considering that this dose is higher than that used for rheumatologic patients, this detail could explain the more frequent liver adverse events.

In part 5.4. Etanercept is not effective in IBD.

We agree that etanercept is not indicated in IBD, so we enclosed this detail in revised manuscript. Nevertheless, the aim of the sentence was to assert that liver involvement is common in all anti-TNF drugs.

In part 5.5. Natalizumab can cause serious neurological side effects so its use in IBD is limited.

As also suggested by reviewer 3, we underlined that Natalizumab is poorly used in IBD, especially for its potential neurologic adverse events such as PML (*Bellizzi A, et al. Early years of biological agents therapy in Crohn's disease and risk of the human polyomavirus JC reactivation. J Cell Physiol 2010)*.

In order to make the paper clearer, my advice is to put the mean messages in one or two tables.

Two tables have been added, as also suggested by reviewer 1.

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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
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] 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. It 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.

We thank the reviewer for the comment. Indeed, the aim of our review was to present an updated guide about liver involvement in IBD that could be useful for the clinician, even for a non gastroenterology audience. We performed a supplementary linguistic revision of the article, as requested.

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

We have re-formulated part of the content of the Abstract.

pg 3: line 2 IBD consists of the two separate disease entities ulcerative colitis and Crohn´s disease

As suggested, we have rephrased the sentence.

Pg 3 section 2.1: If the endocopic appearence is normal it should be noted that the diagnosis of UC in these cases is based on histology

We have rephrased the sentence, as suggested.

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"

We changed the sentence, as suggested.

pg 5 section 2.4 line Contradictory statement regarding GBC compared with what is written in line 1 + 2 in the same section

In the revised manuscript, we removed GBC from the list, since, as reported in paragraph 2.4, no study has been performed in order to demonstrate an increased risk for gallbladder carcinoma in PSC-IBD patients

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

We agree with the comment of the reviewer, therefore we underlined that the chemopreventive effect of mesalazine has been documented for patients with UC alone so far.

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 ?

In the study of Glassner, the prevalence of NAFLD was estimated only in the IBD group, and not in the group of patients known to suffer from NAFLD. Regarding NAFLD treatment, so far only diet and physical exercise have been proved to be effective (*Franco I, et al. Physical Activity and Low Glycemic Index Mediterranean Diet: Main and Modification Effects on NAFLD Score. Results from a Randomized Clinical Trial. Nutrients. 2020*).

Section 4 pg 7 line 30: A general recommendation of hepatitis B vaccination is given for HBV negative patients.

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It should be discussed whether this is necessary in low-prevalent areas.

In the revised manuscript, we enclosed a statement confirming that HBV vaccination is strongly advised by guidelines, possibly before starting any immunosuppressive treatment and preferably at the moment of diagnosis, if anti-HBs title is not protective. This approach should be followed in any region, irrespectively from HBV prevalence.

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 statement is not in line with what is written earlier that NRH is the most frrequent liver injury causes by vascular endothelial lesions provoked by thiopurines.

NRH is a quite rare and poorly investigated condition. Therefore, the results of the studies are often conflicting. However, in revised manuscript, we enclosed a sentence supporting the hypothesis that thiopurines are associated with NRH when the dose is high (tioguanine >40 mg/day) or when administered to male patients with small bowel resection > 50 cm (*Musumba CO. Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. Aliment Pharmacol Ther 2013; Seksik P, et al. Incidence of nodular regenerative hyperplasia in inflammatory bowel disease patients treated with azathioprine. Inflamm Bowel Dis 2011*).

line 36: The information should be given that the dose of thiopurines should be reduced if allopurinol is co-administered

We performed the suggested change.

section 5.3 pg 10: The section describing Methotrexate should be placed before section 5.2

Metotrexate is a conventional drug that is used less frequently than AZA or mesalazine and, for this reason, we decided to place it after the paragraphs regarding drugs with a more common utilization.

Section 5.4 pg 11. The correct title would be TNF alpha inhibiting agents.

We changed the title of the paragraph accordingly.

This part of the manuscript is suffering from a very bad english and it should be heavily revised.

A deep revision of that paragraph has been performed

pg 11 line 19: Prevalence of DILI is an incorrect term. Occurrence is better.

We performed the requested change

pg 11 line 25: Elucidate whether it is really meant that liver affection was documented in 163 of 252 poatients treated with IFX

We want to elucidate that among 252 patients, 163 were under infliximab. Therefore the percentage of DILI events reported in the following sentences was calculated only on IFX patients.

Section5.5 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.

We changed “recently” into “from several years”. Moreover, we added a statement about PML occurrence in Natalizumab treated 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

We have performed an additional linguistic revision of the article.

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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
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Academic degree: MD, PhD
Professional title: Consultant Physician-Scientist, Doctor, Lecturer, Pediatric Gastroenterology Fellow, Professor, Senior Postdoctoral Fellow, Senior Researcher, Senior Scientist
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Author's Country/Territory: Italy
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Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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!

We thank the reviewer for the kind appreciation of our manuscript.

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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?

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Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor, Senior Researcher
Reviewer's Country/Territory: Russia
Author's Country/Territory: Italy

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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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).

Thank you for this suggestion. In the revised version of our manuscript, we added an additional paragraph dedicated to PBC and AIH.

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by inflammatory cell infiltration of intralobular biliary ducts, with consequent biliary duct damage, which can progress towards fibrosis. Currently, there is no hint about a solid link between IBD and PBC, since only few "case reports" have been published. The most consistent case series reports about six PBC patients in a cohort of IBD subjects in the period 2006-2016 (3 CD and 3 UC). All PBC diagnosis by liver biopsy and then were responders to ursodeoxycholic acid therapy (*Liberal R, et al. Clin Res Hepatol Gastroenterol. 2020*). A genetic association study showed that TNFSF15 and ICOSLG-CXCR5 might be a shared pathogenic pathway in the development of PBC and CD (*Aiba Y et al. Disease susceptibility genes shared by primary biliary cirrhosis and Crohn's disease in the Japanese population. J Hum Genet 2015*).

Similarly, only some case reports about the association between IBD and autoimmune hepatitis (AIH) have been published. A systematic review found about 109 cases, which were mostly overlap syndrome with PBC. Authors reported that jaundice was the most common onset sign and that response to steroids was good, with a low mortality rate

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(*Ballotin VR, et al. Primary sclerosing cholangitis and autoimmune hepatitis overlap syndrome associated with inflammatory bowel disease: A case report and systematic review. World J Clin Cases 2020*). Interestingly, a case report of AIH onset after starting adalimumab has been described, to underline the possibility that an immunogenic drug may alter the equilibrium in immune system (*Miranda-Bautista J et al. Adalimumab-induced autoimmune hepatitis in a patient with Crohn's disease. Gastroenterol Hepatol 2019*).

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.

As suggested also by another reviewer, we added a paragraph reporting the statement about HBV vaccination as suggested by 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.

We thank the reviewer for the suggestion. Hepatic amyloidosis and pyogenic liver abscess are very rare in IBD, therefore we presumed that they did not deserve to be discussed herein. On the other hand, we added a paragraph about portal vein thrombosis (PVT), which is a quite common event in IBD. Indeed, IBD patients have a high risk of thromboembolism due to systemic inflammation and alterations in the levels of some coagulation factors, such as high factors V and VIII or low antithrombin III (*Rojas-Feria M et al. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. World J Gastroenterol. 2013*).

In a retrospective study, the incidence of thromboembolic events in patients with IBD rose from 5.65% in 2000 to 7.17% in 2009 (*Kuy S, et al. The increasing incidence of*

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thromboembolic events among hospitalized patients with inflammatory bowel disease. Vascular 2015). In particular, the prevalence of PVT in IBD has been estimated to be about the 0.17% (*Maconi G et al. Portal vein thrombosis in inflammatory bowel diseases: a single-center case series. J Crohns Colitis 2012*). The causes of PVT are various, including inflammation, immobilization, major extent of colon disease, disease severity, surgery, use of corticosteroids and smoking. For that reason, guidelines recommend to start heparin for PVT prophylaxis, when facing an acute flare of UC (*Zezos P et al. Inflammatory bowel disease and thromboembolism. World J Gastroenterol. 2014*).

After the onset of PVT, complications such as portal hypertension, bleeding or even death are not common, but an early anticoagulation is safe and associated with a better outcome, and the use of novel direct oral anticoagulants was associated with particularly favorable outcomes in this setting (*Naymagon L, et al. The Natural History, Treatments, and Outcomes of Portal Vein Thrombosis in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2021*).