

## PEER-REVIEW REPORT

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

**Manuscript NO:** 79445

**Title:** Alcohol use disorder and liver injury related to COVID-19 pandemic

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05382654

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Chief Physician

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

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

**Manuscript submission date:** 2022-08-21

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-08-24 09:31

**Reviewer performed review:** 2022-08-27 08:12

**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 type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" 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 Grade E: Do not publish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 type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

This manuscript mainly discussed alcohol and liver injury and SARS-CoV-2 effects on the liver. There is no more innovative information, no table/figures provided by the manuscript, and its context is too briefly. Therefore, "Rejection" is recommended. Specific suggestions for the authors: 1. Please refer to recent papers published in World Journal of Gastroenterology and correct the format. In page 1, "Marano G et al. Alcohol, liver and COVID-19" should be added. "Abstract", "Introduction", "Alcohol and liver injury", "SARS-CoV-2 effects on the liver", "Conclusions" and "References" should be changed to "ABSTRACT", "INTRODUCTION", "ALCOHOL AND LIVER INJURY", "SARS-COV-2 EFFECTS ON THE LIVER", "CONCLUSION" and "REFERENCES". In page 2, "Key words" should be changed to "Key Words". All "Covid-19" should be changed to "COVID-19" in the main text. Core Tip should be provided in the text according to the journal's requirements. 2. It is suggested that a table/figure should be added to the manuscript. 3. Some minor errors: In page 3, should "abuse or misure" be changed to "abuse or misuse"? In page 4, should "it cusesmalnutrition" be changed to "it causes malnutrition"? 4. In references, the first author should be bold, journal name should be italic, volume number should be bold, issues should be deleted. In reference 30, "PMCID: PMC7768217" should be deleted, PMID number should be added. In reference 38, "PsychiatrDanub. 2021 Spring;33(1):124-126." should be changed to "Psychiatr Danub 2021;33:124-126". In reference 1, 35-39, DOI number should be provided. Please check other references including content and format carefully according to the journal's requirements. Other suggestiones have been listed in the uploaded revised version.

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**Peer-review model:** Single blind

**Reviewer's code:** 06312209

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Assistant Professor, Research Dean

**Reviewer's Country/Territory:** United States

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

**Manuscript submission date:** 2022-08-21

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-08-22 20:32

**Reviewer performed review:** 2022-08-28 15:43

**Review time:** 5 Days and 19 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 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

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

A very well written and timely study I particularly appreciate the focus given to psychoanalysis of alcohol use disorder Very important article to bring home importance of uncontrolled alcohol abuse epidemic currently on going with covid 19 Suggestions - Fix spelling mistakes I found in 3-4 places and can use editing software to correct - Explain or paraphrase psychoanalytic section especially references 36-39 to be made more easily understandable or explain transitional states and conscious and unconscious masks in more detail.

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**Peer-review model:** Single blind

**Reviewer's code:** 05346682

**Position:** Peer Reviewer

**Academic degree:** BSc, MBChB, MRCP, MSc

**Professional title:** Doctor

**Reviewer's Country/Territory:** United Kingdom

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

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<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 type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

Many thanks for offering me the opportunity to review this manuscript. The authors present an interesting overview of the pathophysiological aspects of AUD, some of the consequent clinical data around alcohol misuse and hospitalisation during the pandemic. This mini-review whilst interesting, is lacking in a number of aspects, which I would expect to be addressed before being considered for publication. Whilst it is a mini-review, there are portions that are too generalized, with broad statements and a lack of contextualization. The insights are not novel, which one would not expect of a review, but some interrogation of the data presented by the authors would be helpful. As a general point, there are a number of spelling concerns, I would expect that the document is re-reviewed by a native English speaker, in addition to the use of a language suite on a word processor. Points to note: Abstract: "Alcohol is a hepatotoxin whose metabolism creates profound alterations in the liver cell " - This needs to be re-phrased; or say "within the hepatocyte" "Alcohol abuse is the most frequent cause of liver disease in the Western world, such as steatosis, steatohepatitis, fibrosis, cirrhosis, tumours " - Again, this sentence is poorly constructed and doesn't make sense - please rephrase. Introduction: "developing damage of multiple organs " - re-phrase The authors alternate between ALD and ArLD - I would use one; (ArLD - Alcohol-related Liver Disease) is probably preferable. "A large longitudinal population-based study conducted in the Unites States has demonstrated an alarming rise in 60-and 90-day mortality rates in patients with ALD who were admitted to emergency departments or were inpatients during the pandemic, due to the increase in alcohol use and stress, to the direct impact of Covid-19 but also to its indirect effect on the healthcare system (inadequate medical resources, delays in follow-up visits or

presenting to medical attention)" - This is a very monopolar perspective. There have been numerous studies on this and should be included here for balance (Gaspar, Digestive and Liver Disease (2020); Manship et al, BMJ Open Gastro -The Effect of COVID-19 on Presentations of Decompensated Liver Disease in Scotland (2022), and Mahmud et al. Gastroenterology Declining Cirrhosis Hospitalizations in the Wake of the COVID-19. Pandemic: A National Cohort Study 2020. The Marjot et al JHEP Registry study should also be included in balancing outcomes of various aetiologies and stages of liver disease. Similarly, it is important to not draw implausible parallels, clearly different SARS\_CoV2 variants had different effects as did the vaccination program in terms of severity and admissions. This also needs discussion. Is there any evidence that those with ArLD had less vaccine uptake, again these biases are important to note. "A simulation model of the long-term drinking patterns for people with lifetime AUD has revealed that if the increase in alcohol consumption observed in the United States in the first year of the pandemic continues with similar characteristics, alcohol-related mortality, morbidity and associated costs will increase substantially over the next 5 years" - Again these was a modelled paper and was not borne out universally, there are a myriad of papers on this (some I have already mentioned), these should be included to provide context and discussion which the authors should be careful to do. Alcohol and Liver Injury "The most frequent cause of acute damage of the liver is alcohol (in particular in the form of alcohol binge drinking) followed by hepatitis (A, B, E, autoimmune) and some drugs (i.e. antituberculosis ) [11]." Please rephrase this (e.g. acute liver injury); also anti-tuberculosis medications are very niche and rarely encountered, there are more common causes of DILI (please re-phrase this as DILI) - reference Brennan PN et al. Guideline review: EASL clinical practice guidelines: drug-induced liver injury (DILI) - Frontline Gastroenterology 2021. "These mechanisms together with other complex effects, some of which not yet fully understood, contribute to the

development of hepatic steatosis [12]. " - This needs to be expanded on more comprehensively. "It brings high levels of proinflammatory cytokines , so it reacts to Covid-19 infection with a massive inflammatory response (the so-called inflammatory "tsunami", " - numerous spelling mistakes and poor sentence construction. "Besides, since alcohol reduces oropharyngeal tone it can lead to increased risk of aspiration of microbes, may modify alveolar macrophage function and very often it causes malnutrition[14]. " Spelling needs correction. "It has been observed that a short-term increase in alcohol consumption during the Covid-19 pandemic can substantially increase long-term ALD-related morbidity, hospitalizations and mortality" Again, this needs more context and balance as the authors only reference a single paper here.

**SARS\_Cov2 Effect on the Liver** "Acute-on-chronic liver failure (ACLF) has been hypothesized as one of the possible explanations of higher mortality in liver disease patients with Covid-19: it is characterized by two types of liver injury in combination, one acute (liver-specific or systemic) and one chronic (often misunderstood ). " - This is not true, the cause of the decompensation can be nebulous, however, these persons have established parenchymal disease. In those with AUD, Alcoholic Hepatitis is often the singularly most significant cause. Again, there are many papers on this. "It has been demonstrated that patients with ACLF of alcoholic etiology have significantly prolonged hospital stay, severe Covid-19 illness, admission in intensive care unit and higher mortality" - Again this needs more balance as this was not universally encountered, for a myriad of reasons, which the authors can provide some nuance around. **Conclusion** "Furthermore, alcohol is a potential risk factor for pneumonia through other mechanisms: it reduces oropharyngeal tone, increasing the risk of microbial aspiration, and modifies the function of alveolar macrophages, alcohol often causes malnutrition, a condition that rises the risk of infections ." I would want a number of references to corroborate this. "individuals who daily consume high amount of alcohol or are obese should be





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monitored closely" - Spelling (Should) "immunology, psychiatry, internal medicine, hepatology, gastroenterology and pharmacology) interact and strictly collaborate through a multidisciplinary intervention " - Spelling (strictly) "Reaching general practitioners , stimulating them and training them for short-term intervention in this field, means obtaining an important ...." Why not propose alternative AHPs/interventional and addiction services that can be optimised in attempting to mitigate the risk of AUD here? This needs expanding.

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**Peer-review model:** Single blind

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**Professional title:** Doctor

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

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

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<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</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

## **SPECIFIC COMMENTS TO AUTHORS**

See the attached file.

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

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**Professional title:** Additional Professor

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

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<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
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<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

a. It would be better to use the term “COVID-19” uniformly throughout the manuscript, instead of using Covid-19 in some places and COVID-19 in some other places. b. The abstract is poorly organized. There is lack of proper flow. The authors may discuss about general things like “Alcohol abuse is the most frequent cause of liver disease in the Western world, such as steatosis, steatohepatitis, fibrosis, cirrhosis, tumours.” in the beginning and then may discuss about the context of COVID-19. c. Introduction: Kindly rephrase the sentence “Excessive alcohol consumption has a dual harmful effect: the development of alcohol dependence, withdrawal symptoms and psychosocial problems, on one side, and a significantly augmented risk of developing damage of multiple organs.” d. Introduction: Provide references for “It has been observed that lockdown due to Covid-19 pandemic has led to a notable increase in alcohol abuse and misuse.” And “In particular, psychological symptoms such as anxiety, fear and stress result to be correlated with a general increase in alcohol consumption and, in the case of patients with alcohol use disorder (AUD), it has been outlined that social isolation can favour psychological decompensation and increased drinking or relapse.” e. There are several typological errors, that need to be corrected. f. Introduction: “A simulation model of the long-term drinking patterns for people with lifetime AUD has revealed that if the increase in alcohol consumption observed in the United States in the first year of the pandemic continues with similar characteristics, alcohol-related mortality, morbidity and associated costs will increase substantially over the next 5 years[10]. These observations impose a red flag on the necessity of improvement of screening for high-risk alcohol use and optimization of early treatment of abuse or misuse and its physical and psychological consequences”. This paragraph seems less relevant. The

authors need to discuss about AUD in the context of COVID-19 in more details. Adding evidences about use of alcohol in COVID-19 patients and the subsequent risk of liver injury, will increase the importance of the paper. g. The authors also need to discuss about the risk of COVID-19 among patients with AUD and the outcome in these patients.