Dear Editor,

Thank you for reviewing our manuscript "**Alcohol-Related Hepatitis: A Review Article**". We have noted the comments by the reviewers and have made changes to our manuscript accordingly. The responses to reviewer's comments are below.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors comprehensively review the clinical and basical research about Alcohol-Related Hepatitis (ARH). The manuscript is well organized. The manuscript would provide insights into the latest progress on ARH.

Thank you for reviewing our manuscript. We appreciate your feedback.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This review summarized the epidemiology, genetics, pathogenesis, diagnosis and treatment of alcohol-related hepatitis. Some issues need to be addressed before publication. 1. The background in Introduction section needs to be detailed. 2. Some abbreviations should be described in the full names when they first appeared, such as AASLD. 3. The format of tables needs to be adjusted to three-line tables. 4. The authors claimed that the prevalence of ARH has been on a rise even prior to COVID-19 pandemic. But there is not much information about the association between COVID-19 and ARH. It is strongly suggested that authors should discuss more about it.

Thank you for reviewing our manuscript. We appreciate your feedback.

1. We have updated the introduction section and references. We have included all the pertinent information including prevalence, epidemiology, genetics and pathogenesis under relevant sections.

2. We have edited the abbreviations and described them in full names.

3. The format of all tables has been adjusted to three-line tables.

4. The increase in cases of ARH during and after COVID-19 has been published in multiple papers. We have described it in further detail and included references.

- Moon AM, Curtis B, Mandrekar P, Singal AK, Verna EC, Fix OK. Alcohol-Associated Liver Disease Before and After COVID-19-An Overview and Call for Ongoing Investigation. *Hepatol Commun*. 2021 Sep;5(9):1616-1621. Epub 2021 Jun 5. PMCID: PMC8239751.doi: 10.1002/hep4.1747
- Sohal A, Khalid S, Green V, Hagino J, Chaudhry H, Gulati A, Roytman M. Soaring rates of alcohol-related hepatitis in the latter phase of the COVID-19 pandemic: A new normal? *JGH Open*. 2023 Jan 13;7(2):148-151. PMID: 36852146 DOI: 10.1002/jgh3.12864.
- Gonzalez HC, Zhou Y, Nimri FM, Rupp LB, Trudeau S, Gordon SC. Alcohol-related hepatitis admissions increased 50% in the first months of the COVID-19 pandemic in the USA. Liver Int. 2022 Apr;42(4):762-764. doi: 10.1111/liv.15172. Epub 2022 Feb 24. PMID: 35094494.

We appreciate your time and consideration and look forward to hearing from you.

Regards,
Hunza Chaudhry, MD
Corresponding Author

The second Round Review

Specific Comments To Authors: The authos have revised the manuscript accordingly and they have comprehensively reviewed ARH. One minor problem still need to be addressed. 1. The titles of tables should be above the tables.

Response:
Dear Editor, Thank you for reviewing our manuscript. We have edited the tables. Please see the updated table file below. Regards, Hunza Chaudhry

Tables:

Table 1: Histological differences between non-alcoholic steatohepatitis (NASH) and alcohol-related hepatitis (ARH).

Histological Features	NASH	ARH
Canalicular cholestasis	Less common	More common
Mallory Denk Body (MDB)	Less common	More common
Ductular reaction	Less common	More common
Fibrosis in portal tract	Less common	More common
Sclerosing hyaline necrosis	Less common	More common
Veno-occlusive lesions	Less common	More common
Severe steatosis	More common	Less common
Glycogenated nuclei	More common	Less common
Lipogranulomas	More common	Less common
Fibrosis	Lattice pattern	Solid pattern

Table 2: Prediction models for alcohol-related hepatitis (ARH).

Score	Variables	Mortality Rate
Maddrey discriminant function (MDF)	PT, total bilirubin	50% at 30 days for score ≥32
Lille model	Age, albumin, change in total bilirubin, renal insufficiency, MDF score	75% at 6 months for score ≥0.45
Model for end-stage liver disease (MELD)	Creatinine, total bilirubin, INR	20% at 90 days for score >21
Glasgow alcoholic hepatitis score (GAS)	Age, white blood cell count, BUN, total bilirubin, PT	48% at 28 days for score ≥9
ABIC score	Age, total bilirubin, creatinine, INR	75% at 90 days for score >9

Table 3: Clinical trials under investigation.

Drugs	Mechanisms	Clinical Trials
Anakinra and Canakinumab	Reduce hepatic inflammation	NCT01809132[121], NCT04072822[122], NCT03775109[123]

N-acetyl cysteine, S-adenosyl methionine (SAM-E)	**Reduce oxidative stress**	**NCT03069300[124], NCT00851981[125], NCT02024295[126]**
DUR-928	**Epigenetic modulation of lipid homeostasis, inflammation, cell survival, tissue regeneration**	**NCT03432260[127], NCT03917407[128]**
Granulocyte colony stimulating growth factors, IL-22 and obeticholic acid	**Boosts liver regeneration**	**NCT02442180[129], NCT03703674[130], NCT04066179[131], NCT02655510[132], NCT01918462[133], NCT02039219[134]**
Rifaximin, zinc supplementation, bovine colostrum, probiotics, and fecal microbiota transplant (FMT)	**Targets the gut-liver axis**	**NCT02116556[135], NCT02485106[136], NCT01968382[137], NCT02473341[138], NCT01922895[139], NCT02335632[140], NCT02458079[141], NCT03091010[142], NCT03827772[143]**