

Detailed response to reviewers

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I would like to thank authors for extensive review of assessment of liver disease in chronic hepatitis C patients with alcohol use. They have reviewed the literature in an elaborative manner and rightly said that association of alcohol results in faster progression of liver disease in CHC patients. They have also raised the important issue of association of HCV infection in alcohol abuse. They may include criteria of significant alcohol intake as described in different guidelines like AASLD, EASL etc. And they may also explain the unhealthy alcohol use in terms of amount, type and duration etc.

- *We thank the reviewer for this comment. We agree that information around alcohol use assessment was scarce in the prior version of the manuscript. In order to address all Reviewer#1 comments, we have included a new section entitled "**Assessment of alcohol use in patients with liver disease**" in the updated version of the manuscript. The section reads as follows: "The American (AASLD) and European (EASL) guidelines for the treatment of alcohol-related liver disease suggest the use of the Alcohol Use Disorders Identification Test (AUDIT) to identify patients with alcohol use disorder ^[14], ^[15]. AUDIT includes 10 questions and explores consumption, dependence and alcohol-related problems according to the number of positive answers ^[16]. For patients with an AUDIT>7, Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) is an appropriate tool used for the assessment of clinical, personal and social alcohol-related problems ^[17]. The severity of AUD, that encompasses both alcohol dependence and alcohol abuse, is based on the number of criteria that the patient meets [mild AUD: 2-3 criteria, moderate AUD: 4-5 criteria and severe AUD >6). AUD represents the more extreme form of unhealthy alcohol use, a term that will be used throughout the manuscript ^[17].*
- *In terms of amount, unhealthy alcohol use means drinking more than the recommended amount of alcohol by the *National Institute of Alcohol abuse and Alcoholism* (2 drinks per day or 14 drinks per week for men and 1 drink per day or 7 drinks per week for women or men aged >65), what includes the spectrum from risky alcohol use to AUD ^[18].*
- *It is important to note that for those who already have HCV infection there is no safe threshold of alcohol consumption and abstinence from alcohol should be the main treatment goal ^[12]."*

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Page 9-page 11 **【Transient elastography】** These newest references could be added : 1) Serra-Burriel M, Graupera I, Torán P, et al . Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia. J Hepatol. 2019 Dec;71(6):1141-1151. 2)Clin Gastroenterol Hepatol : .2021 Feb 12;S1542-3565(21)001. doi: 10.1016/j.cgh.2021.02.021. Online ahead of print. Transient Elastography Accurately Screens for Compensated Advanced Chronic Liver Disease in Patients with Ongoing or Recent Alcohol Withdrawal 3. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. Liver Int. 2020 Jul 30. doi: 10.1111/liv.14625 4) Transient Elastography Accurately Screens for Compensated Advanced Chronic Liver Disease in Patients with Ongoing or Recent Alcohol Withdrawal. Clin Gastroenterol Hepatol. 2021 Feb

- *We have added the references that the reviewer suggests in a paragraph that reads as follows: "Other researchers have confirmed that elastography is a good predictor of clinical events [64]. Transient elastography has also been proven to be cost-effective in primary care [65], and other authors have used it to detect chronic alcohol-related liver disease after alcohol cessation [66] or to detect improvements in liver fibrosis after successful HCV antiviral therapy [67]."*

Studies have shown that there is a good correlation between Virtual Touch Quantification (VTQ), and the degree of liver fibrosis! Many references can be added ,such as : 1)Bâldea V, Sporea I, Tudor A, et al Virtual Touch Quantification using Acoustic Radiation Force Impulse Imaging Technology versus Transient Elastography for the Noninvasive Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B or C using Liver Biopsy as the Gold Standard. J Gastrointestin Liver Dis. 2020 Jun 3;29(2):181-190. 2) Sporea I, Mare R, Lupusoru R, et al Comparative study between four ultrasound Shear Waves Elastographic methods for liver fibrosis assessment. Med Ultrason. 2018 Aug 30;20(3):265-271. 3) Summers JA, Radhakrishnan M, Morris E, et al . Virtual Touch™ Quantification to Diagnose and Monitor Liver Fibrosis in Hepatitis B and Hepatitis C: A NICE Medical Technology Guidance. Appl Health Econ Health Policy. 2017 Apr;15(2):139-154 Elastography can also be used to judge the curative effect! For example , the fibrosis score (IQR) declined to 5.2 kPa by week 12 after HCV treatment in patients with HIV-HCV Coinfection. The reference is following: Doyle MA, Lee T, Singer J, Crawley A, Klein M, Cooper C. Evaluation of Safety and Effectiveness of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Switch Followed by Ledipasvir/Sofosbuvir HCV Therapy in HIV-HCV Coinfection. Open Forum Infect Dis. 2019 Jul 1;6(7):ofz318. doi: 10.1093/ofid/ofz318.

- *Following this reviewer comment, we have included all the suggested references. We have also included a sentence addressing Virtual Touch Quantification. The updated version of the paragraph now reads: "Virtual touch quantification is a point shear wave elastography technique, using Acoustic radiation force impulse technology also offers also good diagnostic accuracy for liver*

fibrosis assessment [74]. It has been used in patients with chronic liver disease of different origins, mainly due to viral hepatitis [75], [76]."

- *In addition, the reference by Doyle and colleagues has also been added in a sentence that reads: "Transient elastography has also been proven to be cost-effective in primary care [65], and other authors have used it to detect chronic alcohol-related liver disease after alcohol cessation [66] or to detect improvements in liver fibrosis after successful HCV antiviral therapy [67]."*

Although ultrasonic elastography has advantages, its disadvantages cannot be ignored! Ultrasound elastography also has its limitations. Many factors, such as thickness of subcutaneous fat, width of intercostal space, ascites and the patients' breathing will affect the results of transient elasticity measurement. Moreover, a lot of research is to explore the relationship between the transient elasticity of liver in puncture area and liver fibrosis. However, because the degree of liver fibrosis may exist uneven distribution between different hepatic segments, so it can not represent the degree of liver fibrosis of the whole liver. In addition, elastography measures the change of liver stiffness caused by fibrosis, not fibrosis itself, which are not completely the same thing. Therefore, non fibrosis diseases such as liver congestion, acute hepatitis, fatty liver and so on, maybe cause the change of liver stiffness, so they will influence judgment which is the real cirrhosis.

- *We thank the reviewer for this comment. We have added the following sentences to the revised version of the manuscript: "It is important to note that transient elastography results may be affected by the thickness of subcutaneous fat, width of intercostals effect, by the presence of ascites, by the patients' breathing or by an uneven distribution of liver fibrosis. In addition, the presence of hepatic congestion or steatosis may also distort transient elastography results [28], [56]."*

Page 11 **【Controlled attenuation parameter】** This new reference could be added: Aynur Unalp-Arida , Constance E Ruhl .Transient elastography assessed hepatic steatosis and fibrosis are associated with body composition in the United States. Clin Gastroenterol Hepatol . 2021 Feb 4;S1542-3565(21)00110-5.

- *We have added the reference that the reviewer suggests in a sentence that reads: "A study by Unalp-Arida and colleagues measured liver stiffness and CAP in 4870 participants in the National Health and Nutrition Examination Survey (NHANES) cohort. Liver stiffness in the highest quartile was associated, among others, with HCV infection, increased age and body mass index and CAP [73]."*

Table 1. Studies that have used transient elastography in patients with alcohol-related liver disease. Author, year Number of patients Advanced liver fibrosis (≥ 3) Sensitivity Specificity

How could "transient elastography" diagnose alcohol-related liver disease? Where does "Specificity" come from? For example: how to differentiate the hyperechoic area in liver on ultrasound between alcohol-drinking and high-fat diet? Compared with hepatitis C, hepatitis B is more common in some eastern countries. How to make differential diagnosis with elastography? So, the author needs to provide more references!!

- *The specificity and sensitivity that appear in the table refer to advanced liver fibrosis detected by transient elastography and by liver biopsy. All the information provided in the table has been extracted from the individual references and from the two meta-analyses referenced in the manuscript. We have added a footnote that reads "Sensitivity and specificity are calculated using liver biopsy as the gold standard." in order to avoid any misinterpretation.*

【Table 2. Studies that used non-patented indices to estimate liver fibrosis in patients with HCV infection and unhealthy alcohol use.】 APRI* What is APRI? What does the asterisk indicate?

- *We thank the reviewer for pointing this typo. APRI stands for "Platelet to AST ratio", a non-invasive index to estimate liver fibrosis described in 2003 by Wai and colleagues (reference #83). This information has now been added to the foot of the table, and the asterisk indicates what APRI, FIB-4 and AUDIT-C stand for. The footnote reads as follows:
**APRI: $\text{AST to platelet ratio Index} = ((\text{patient AST} / \text{AST upper limit of normal [IU/L]}) / \text{platelet count [10}^9/\text{L]}) \times 100$.
**FIB-4 = $\text{age} \times \text{AST (IU/L)} / \text{platelet count (10}^9/\text{L)} \times \text{ALT (IU/L)}^{1/2}$.
***AUDIT-C: Alcohol Use Disorders Identification Test."*

Scientific editor:

1 Scientific quality: The manuscript describes a review of the assessment of liver disease in patients with chronic hepatitis C and unhealthy alcohol use. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: Authors reviewed the assessment of liver disease in chronic hepatitis C patients with alcohol use. They have reviewed the literature in an elaborative manner and rightly said that association of alcohol results in faster progression of liver disease in CHC patients. The questions raised by the reviewers should be answered; (3) Format: There are 2 tables; (4) References: A total of 93 references are cited, including 26 references published in the last 3 years; (5) Self-cited references: There are 8 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Two Grades B. A language editing certificate issued by San Francisco Edit was provided. 3 Academic norms and rules: No

academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Institute of Health Carlos III, National Plan on Drugs, Spain, Autonomous Government of Catalonia, Spain. The topic has not previously been published in the WJG.

- *We thank the scientific editor for the suggestion provided. We have responded all the questions raised by the reviewers (see above).*
- *The current number of references is 106.*
- *In terms of self-cited references, we have kept all 8 references in the updated version of the manuscript. In the revised version of the manuscript, self-cited references account for 7.5% of total references.*

5 Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. 6 Recommendation: Conditional acceptance.

1.- We have provided an author contributions section that reads as follows:

"DF and X G-C performed the literature review.

DF drafted the initial version of the manuscript.

RM and X G-C revised the initial version of the manuscript and provided feed-back and suggestions.

All authors revised and approved the final version of the manuscript."

2.- We have uploaded the approved grant application forms.

3.- PMID and DOI numbers have been included to all references. In addition, all authors have been included in the reference list.