

The Editor,

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We appreciate your helpful comments and kind words. We feel that the manuscript is now greatly improved. Revisions based on the comments/suggestions of Reviewers #1, 2, 3, 4 and 5 were made. The comments of each reviewer are numbered below, followed by a response indicating the modifications made.

**Reviewer #1:** Comments: Overall, i would like to congratulate the whole team for great effort to bring this manuscript. I feel that some recent advances scientific study should be included in the study. Also i have some points made in the manuscript. please kindly find it. also the limitation of these tests should be mentioned.

- Thank you for your revision and suggestions, we think they improved our review substantially. 1. In our review, we tried to emphasize on the general approach of interpreting liver biochemical markers which are commonly ordered on a daily basis by primary care providers hence we did not delve deeper into the more detailed tests and scores available as they are less likely to be used by primary care physicians or in the inpatient setting on a daily basis. The relevant concepts of interpreting liver biomarkers were explained with examples of different etiologies discussed. We have added the ALT proposed lowering of the cut-off values in addition discussed the possible inaccuracies of these tests.

**Reviewer #2:** Comments: 1. In line 60, Keywords: Words no abbreviations "LFT" 2. In line 61: Hyperbilirubinemia, with capital letter, and I between b and n. 3. In line 76: Without space between study\_ of 4. In line 80: with space next to "unexplained" 5. In line 148: to use "U" instead of "units" 6. In line 160: The correct unit is "g/dL" instead to "g/dl" 7. In line 338: to put "Pi\*ZZ "genotype or "Pi\*Z" mutation don't "Pi\*ZZ mutation" In the abstract they only mention to aminotransferases, I suggest incorp other enzymes since the title mentioned "liver enzymes" or to incorporate Liver biochemical tests in the title with above observation on the abstract. It is correct a space before number reference? In line 99: describe: What are the enzymes, Markers of liver synthetic function, etc. to follow coherent way the next paragraphs In the table 1: title, doesn't describe their content. For example, interpretation, site and function of Liver biochemical studies. In table 2: needs a description title of the table. For example: Interpretation of..... R-value In table 3: "Common condition with abnormal liver biochemical tests" in the title is repeated in the table. In table 4: Title in each column is needed and abbreviations at the foot of the table. Verify similar format in tables

- Thank you for your comments. 1. We added the abbreviations required. 2, 3, 4, 5, 6. Mistakes in spelling and punctuation have been addressed. 7. PiZ mutation have been edited as suggested as it is more appropriate as mentioned by the reviewer. 8. Additions of the different tests was addressed and

added in the abstract as suggested. Table titles have been modified for increased clarity as recommended.

These comments have helped improve our paper and we appreciate the added insight.

**Reviewer #3:** Comments: The Authors performed an interesting and well-written review on LFTs. Some comments may be raised at improving the quality of the manuscript. SPECIFIC COMMENTS - The Authors may mean NAFL instead of NALFD when they state: "NAFLD and Nonalcoholic steatohepatitis (NASH) are diseases in the same spectrum where NAFLD can progress to NASH and subsequently liver cirrhosis if no intervention or modification of risk factors was done.....". "The difference between the two is primarily seen on histology as NAFLD has only fatty infiltration without inflammation whereas NASH has marked inflammation." - Liver function tests have been combined in specific scores for assessing liver fibrosis (serum biomarkers of liver fibrosis such as NFL, HFS, FIB-4...). Although serum biomarkers of liver fibrosis perform much better to exclude advanced fibrosis rather than to identify it, they may be useful to select patients for further assessment of liver fibrosis by transient elastography or liver biopsy in selected cases (Loomba R, Gut. 2020 Jul;69(7):1343-1352.). In addition, serum biomarkers of liver fibrosis are also correlated with cardiovascular risk scores therefore allowing the stratification of both hepatological and cardio-metabolic risks (Ballestri S, et al. Diagnostics (Basel). 2021 Jan 9;11(1):98.). Please comment and update literature. - The need to lower the cut-off of aminotransferases has long been suggested (Prati D, Ann Intern Med. 2002 Jul 2;137(1):1-10.). Please comment.

- Thank you for your revision and suggestions, we think they improved our review substantially. The NAFLD was switched to NAFL as suggested as we agree that it is more accurate and will decrease any possible confusion. The need to lower the cut off for aminotransferases have been added and elaborated upon to give the reader a deeper and more accurate understanding of these values interpretation.

Regarding the scores associated with fibrosis and cardiovascular risk, we believe that the purpose of this review is more geared towards physicians who are not necessarily hepatologists and that the addition of that might steer away from the main purpose of the paper as these scores are still being further investigated.

**Reviewer #4:** Comments: Liver function tests (LFTs) are commonly ordered routine tests and the results provide lots of information for the clinicians to make further decision for either treatment or referral. The authors first introduced the contents and characteristics of each item in the LFT, then explained the pattern and interpretation of abnormalities in LFTs. Importantly, the authors depicted the typical pattern of LFTs to differentiate NAFLD/NASH, viral hepatitis, inherited metabolic liver diseases, autoimmune hepatitis, DILI, etc. The manuscript is well prepared and written. I only have a few minor suggestions. 1, p4, lines 28-29, "The normal range for ALT in males between 29-33 IU/L and 19-25 IU/L for females" should be the normal range adopted in the USA. Other countries/regions use different normal range. Please specify this point. 2, p6, lines 23-25, "The liver is involved in the synthesis of multiple clotting factors including, factors I, II, V, VII, IX, X, XI, and XIII. In addition to protein C, protein S, and anti-thrombin." Did the authors add an unnecessary full stop before "In addition to" (do the authors

mean that all the factors mentioned above are synthesized by liver?) 3, p8, lines 21-22, "GGT x2 the ULN is suggestive of alcohol abuse specifically when paired with AST: ALT > 2". What do the authors mean by saying "GGT x2 the ULN"? Do they mean that GGT >2 xULN? 4, p11, paragraph 1, if the authors could add some information about the LFT pattern in acute/chronic hepatitis E, that will be awesome. 5, p12, line 16, "AST: ALT > 2.2, and ALP: Bilirubin < 4": I don't understand the calculation here. When the authors say AST:ALT, do they use the direct measurement of AST and ALT to calculate the ratio of AST/ALT, or instead they calculate the (AST/ULN)/(ALT/ULN)? And for the statement of ALP: bilirubin< 4, I feel even more confused. The measurement unit of ALP is IU/L, while the unit of bilirubin is mg/dl. How can these 2 parameters be calculated like this? Or do the authors still mean that they are using the ALP/ULN to be divided by bilirubin/ULN? And what is the rationale to make this calculation? 6, p13, line 26, "ALP: AST/ALT < 3", similar comment as in #5, are they calculating the ratio of (ALP/ULN)/[(AST/ULN)/(ALT/ULN)]? And there are 2 division symbols (: and /), what is the calculation order? Do they first divide AST by ALT, then divide ALP by the ratio of AST/ALT? If this is the case, then it should be presented as ALP : (AST/ALT). I have an example here: A subject who was autoimmune hepatitis (decompensated) had a LFT result as follows: ALT=87 (ULN 64), AST=213 (ULN 40), ALP=172 (ULN 126). The result is way too much different by the 2 calculation methods. Please clarify this. 1) ALP: (AST/ALT)=172:(213/87)=70.26 2) ALP/ULN:((AST/ULN)/(ALT/ULN))=(172/126):((213/40)/(87/64))=0.35

- Thank you for your revision and suggestions, you brought good points and we think this improved our manuscript substantially. 1.The normal range mentioned is as per the reference range by the American Gastroenterology Association. In addition, we updated our paper and mentioned that these values are variable between different countries and different centers. 2. We specified the point mentioned in your comment and corrected the punctuation error. 3. We modified the phrases regarding GGT > 2x ULN for increased clarity for the readers as suggested. 4. Regarding hepatitis E, we did not go into more details as it is less commonly seen in addition to the similar pattern it has with acute viral hepatitis generally. 5. Regarding the AST: ALT > 2.2, we have re-reviewed the reference mentioned and verified that it is the ratio which is used without any upper limits (similar to the alcohol induced elevation in liver enzymes). We went back through the results of the study mentioned in the reference and verified that the ALP: bilirubin ratio is calculated directly despite having different units. 6. Your point was astute and we have modified the ratio after reviewing the literature which involved incorporating the ULN in the calculation and we have clarified that the AST/ALT is AST or ALT rather than the division of these variables.

**Reviewer #5:** Comments: This is a concise summary of liver biochemical tests which is very useful for medical students but not so much for hepatologist. To be more informative, the authors may add the following content: (1) discuss the challenge of current upper limit of normal (ULN) of serum ALT and AST levels for detecting chronic liver disease and the proposed new thresholds; (2) discuss the significance of laboratory parameters in the liver biochemical tests in stratifying risk of unfavorable outcome such as significant fibrosis, cirrhosis, HCC and death;

- Thank you for your revision and suggestions, we think they improved our review substantially. 1. The challenge of the current cut offs for ALT have been added and discussed to provide more insight into

this lab value. 2. We believe that going into details about the significance of liver biochemical functions for the prediction of fibrosis and other complications is not completely relevant to our paper which is more geared towards the day-to-day ordering of these labs. Such a topic would need a separate review to be addressed appropriately.