

Dear Editor and Reviewers,

Thank you for your questions and advice. We have revised our manuscript according to your comments. And the answers to the reviewers are listed below.

Round 1

Reviewer #1: Authors explored an intriguing aspect of a new topic in this field. The study is original and well designed. It adds to the current knowledge, although data derived from a small cohort of patients. My comments are listed below:

1. abstract: in the results section, percentage should be given.

Answer: Dear reviewer, thank you for your suggestion. We have given the percentage of each comparison group in the results section in the abstract.

2. introduction: Metabolic dysfunction should be defined accordingly to MAFLD criteria.

Answer: Dear reviewer, thank you for your suggestion. We have defined “metabolic dysfunction” according to MAFLD criteria in the introduction part.

3. discussion: both usefulness and effectiveness of MAFLD definition have been investigated in several recent studies. This should be added and discussed (e.g. PMIDs 33806784 and 32819754)

Answer: Dear reviewer, thank you for your recommended literature. We have added and discussed the usefulness, effectiveness and possible limitations of MAFLD definition in the 4th paragraph in the discussion part.

4. table 1: W/Hr (as adiposity measurement) should be given and compared between the groups.

Answer: Dear reviewer, thank you for your suggestion. Waist-to-Hip Ratio is an important index for adiposity measurement -- people with more weight around their waist are at greater risk of metabolic dysfunctions than those with weight around their

hips. Unfortunately, due to W-HR was not necessary in the diagnosis of MAFLD, we didn't collect the hip circumferences of the subjects, so we were unable to calculate the W-HR. We are very sorry and thank you very much for your good advice!

5. English language needs to be largely revised and polished throughout the paper.

Answer: Dear reviewer, we have polished the language throughout the paper and a language editing certificate by AJE has been provided. Thank you for your review!

Reviewer #2: Nonalcoholic fatty liver disease (NAFLD) has been suggested to rename to metabolic-associated fatty liver disease. However, there are many concerns about the new nomenclature. In this study, the authors further investigate the significant associated histological features with MAFLD in patients diagnosed with NAFLD, when compared to non-MAFLD patients but with diagnosed NAFLD. Study results showed that MAFLD patients have more severe NAS and hepatic steatosis than that in non-MAFLD patients, but not other histological features and the presence of NASH, the advanced form of NAFLD. Overall, the study was well-designed and performed. The data were well analyzed, with a limitation of case numbers. However, there are some concerns about enhancing the quality of the paper.

1. A major suggestion is that representative histological images should be added to give an overview of the pathological change, but not only with numbers in all the figures.

Answer: Dear reviewer, thank you for your suggestion. We have supplemented the representative histological images of the liver biopsy specimens in Figure 1.

2. All the words in the Figures are small, so the size should be increased. In addition, Figure 1H is suggested to be combined in one for all groups to have the same y-axis scale for easy comparison. Similar changes are suggested for Figure 2H, Figure 3H, and Figure 4H.

Answer: Dear reviewer, thank you for your suggestion. We have increased the size of

the words in the figures. And we have combined Figure 1h, Figure 2h, Figure 3h, Figure 4h in one for all groups to have the same y-axis scale for easy comparison. Actually, as suggested by another reviewer, we have combined all figures in one graph (Figure 2) to make the figures more expressive and less space occupying. Thank you!

3. For manuscript format, a Core Tip part is suggested except the abstract.

Answer: Dear reviewer, we have supplemented a Core Tip part in the manuscript. Thank you!

4. In addition, some minor changes are needed. Minors: On page 3, does NAFLD include cirrhosis and hepatocellular carcinoma (HCC)? Or NAFLD can lead to cirrhosis and HCC.

Answer: Dear reviewer, thank you for your critical question. As we know, NAFLD can lead to cirrhosis and HCC just like other chronic liver diseases. In this study, we aimed to compare the histologic features between MAFLD and non-MAFLD. Therefore, we should exclude those with already known cirrhosis or HCC. We have added this exclusion criterion in the “study design and patients” part in “Materials and Methods”. And we have revised the sentence in the “introduction” part on page 3 as “NAFLD covers a broad spectrum of disease severity, ranging from simple fatty liver to nonalcoholic steatohepatitis (NASH), and can even lead to cirrhosis and hepatocellular carcinoma.”

5. On page 4, 1.70 mmol/l should be 1.70 mmol/L. In addition, whether adding a space between $>$, $<$, or \geq and number or not should be consistent across the manuscript.

Answer: Dear reviewer, thank you for your careful review and corrections. We have revised the above minor points across the manuscript.

6. On page 5, with an alanine aminotransferase (ALT) ‘level was needed here’ <3 -fold

of the ULN. On page 9, a group of lean and metabolically healthy individuals are not included; 'are' changes to is. On page 10, that only fibrosis stage instead of other histologic features of NASH were related to; were > was.

Answer: Dear reviewer, thank you for your corrections. We have revised the above points according to your advice.

Reviewer #3: The manuscript addresses a hot topic of our time, the proposed change from NAFLD to MAFLD, and attempts to evaluate the differences that these two definitions have with regards to patients with liver steatosis. Although it is reasonable to research differences between NAFLD patients with and without MAFLD, the article does not have a sufficient sample to offer definitive conclusions, in a topic that is at the center of liver research, resulting in studies with bigger population samples.

Answer: Dear reviewer, thank you for your question. The sample size of this study was 83, with 61 MAFLD and 22 non-MAFLD. The study population was lopsided, as fatty liver with no metabolic dysfunction (non-MAFLD group) is relatively rare. Because liver biopsy is an invasive examination, only a small proportion of patients are willing to receive liver biopsy. We have acknowledged this issue as one of the limitations of this study. We hope this explanation is satisfactory and thank you very much for your review and valuable comments!

Reviewer #4: Non-MAFLD group is also a heterogenous population. It includes simple steatosis, NASH, advanced fibrosis and cirrhosis. The nomenclature has not changed to MAFLD from NAFLD. There are recommendations but still has unmet needs. The issue is still under debate. This should be noted.

1. The clinics • "Subjects with a BMI <23 kg/m² were defined as having lean NAFLD". Could be: "Asian subjects with a BMI <23 kg/m² were defined as having lean NAFLD." since BMI <25 is lean NAFLD for Western World.

Answer: Dear reviewer, thank you for your suggestion. Since all subjects in this study were Asian subjects from China, we have added "Asian" according to your suggestion.

Thank you!

2. “Analyze” can be preferred instead of “analyse”.

Answer: Dear reviewer, we have corrected the word throughout the manuscript.

Thank you!

3. How the sample size calculated? The sample size seems insufficient for reliable comparison according to “power analysis” as stated in limitations paragraph. Sample Size Calculator (clincalc.com)

Answer: Dear reviewer, thank you for your question. We used the Sample Size Calculator at clincalc.com as you suggested, and determined the minimum number of subjects for adequate study power was 68. In our study, a total of 83 participants were enrolled. Although the sample size was relatively small as stated in limitations paragraph, the size was sufficient for reliable statistical analysis. Thank you for your advice!

4. The graphs could be more expressive and less space occupying with segmented bars, all in one graph as coupled two bars for each criteria. The percentages may be more readable as a table.

Answer: Dear reviewer, thank you for your suggestion. We have combined the graphs in one figure (Figure 2) to make it more expressive and less space occupying. We hope the modifications are satisfactory and thank you very much for your advice!

5. Table 1: Please use widely accepted abbreviations in tables. Prefer “Neu” instead of “N” for Neutrophil. “N” is usually abbreviated for Nitrogen. ChE instead of CHE. Typographic error: CLU should be GLU.... Hs-CRP as hs-CRP,... “ALP” instead of “AKP”, etc... “Glycemia” instead of “glycometabolism.”

Answer: Dear reviewer, we have revised the above errors. Thank you for your careful review!

6. Table 2: “Correlations between steatosis and other hepatic histologic features” can be “Correlations between degree of steatosis and severity of other hepatic histologic features”

Answer: Dear reviewer, we have revised the issue according to your suggestion. Thank you!

7. The title focuses only on metabolic dysregulation lacks the diabete and obseity. MAFLD can be replaced.

Answer: Dear reviewer, thank you for your question. The definition of metabolic dysfunction includes obesity and T2DM, which is consistent to MAFLD criteria. We have stated the definition of “metabolic dysfunction” in the introduction part. Thank you!

Round 2

Reviewer’s code: 02536349

Reviewer’s comments: Thank you for revisions Still there are few grammar errors. e.g.

Core Tip: Non-obese and metabolically healthy patients with fatty liver is excluded >> “are” Non-obese and metabolically healthy patients with nonalcoholic fatty liver disease (NAFLD) is excluded from the definition >> “are” tHE TERM "non-MAFLD" Lacks indicating the presence of fatty liver or not.

The below link highlights the possible subgroups. non-MAFLD covers more clinical spectrum then authors' definition.

[https://pubmed.ncbi.nlm.nih.gov/32930521/#&gid=article-figures&pid=figure-1-uid-](https://pubmed.ncbi.nlm.nih.gov/32930521/#&gid=article-figures&pid=figure-1-uid-0)

0 The nomenclature change is still as a proposal. In manuscript it has been stated as NAFLD has totally removed to MAFLD and non-MAFLD. So it is early to use -formerly for NAFLD Metabolic dysfunction is associated with steatosis but no other histologic features in the formerly named NAFLD could it be? Metabolic dysfunction is associated with steatosis but no other histologic features in MAFLD and non-MAFLD subgroups of NAFLD

Answers:

1. Grammar errors have been modified. And an additional new language certificate has been provided.
2. In this study, we have defined “non-MAFLD” as NAFLD participants without obesity, T2DM or the above metabolic disorders (Page 6, Line 13). All subjects in this study are present with fatty liver and conform to the definition of NAFLD. Thank you for your reference about the clinical spectrum of non-MAFLD. We have modified the term “non-MAFLD” as “non-MAFLD subgroup of NAFLD” in the manuscript according to your advice.
3. The nomenclature change from “NAFLD” to “MAFLD” is still as a proposal. It is too early to use the “formerly-named NAFLD”. We have deleted the “formerly named” in the manuscript.
4. We have modified the conclusion as “Metabolic dysfunction is associated with steatosis but no other histologic features in the MAFLD and non-MAFLD subgroups of NAFLD”.

Thank you for your review and suggestions!