Answering Reviewers

We thank the Reviewers and the Editor for the time spent in reviewing our manuscript and for the opportunity to resubmit it after appropriate revision.

Rev 1

This minireview describes the relevance of genetic factors, inflammation, fat distribution, and microbial alterations to metabolic disorders in MAFLD patients, and compares the differences between MAFLD and NAFLD. It highlights that using the definition of MAFLD allows for better identification of liver fibrosis, metabolic disorder diseases, and kidney injury diseases compared to NAFLD. This review provides an overview of the latest findings in this field of research in humans, summarizes the progress of research on MAFLD in adults as well as in children, and raises the thorny issues that remain to be addressed. On the one hand, I found the paper to be overall well written and much of it to be well described. I felt confident that the authors performed careful and thorough literature search and information collection, which reflects the current status of MAFLD in a more comprehensive way. On the other hand, I found some of the description of the paper not to be too detailed, while the description of some very important points were inadequate or completely missing. Therefore, I recommend that a minor revision is warranted. I explain my concerns in more detail below.

1. This article describes the latest diagnostic criteria for MAFLD in adults, but is inadequate for the diagnosis of metabolic disorders.

Answer: following your valuable suggestion, we added an explanation about diagnosis of metabolic disorders. Please see lines 83-92 and 101-105 of the revised manuscript.

2. The title of the article is about MAFLD in children and adults, but the manuscript lacks a definition of age-appropriate MAFLD in children based on sex and age percentiles.

Answer: according to your comment, we added the pediatric MAFLD definition. Please see lines 232-240 of the revised version of the text.

3. There are similarities and differences in the etiology, natural history and prognosis of fatty liver in children compared to adults. This article does not described in sufficient detail and rigorously.

Answer: according to your comment, we described more in depth similarities and differences between adults and children on these aspects of fatty liver. Please see lines 216-219 and 244-255 of the revised text.

4. Page 8, lines 24. How do you define significant fibrosis?

Answer: Significant fibrosis was defined by FIB-4 index ≥1.3 and liver stiffness ≥6.6 kPa using Shear wave elastography (SWE). We added this explanation in the revised version of the manuscript. Please see lines 202-203 of the revised version of the text.

5. Page 5, lines 5-9. I suggest adjusting this sentence to use a transitive logical relationship to emphasize the higher cardiovascular risk of MUO compared with MHO.

Answer: we modified the sentence accordingly. Please see lines 97-100 of the revised manuscript.

6. It is suggested to add statistical data at the main findings in the table to more visually represent the strength of the association.

Answer: following your suggestion, the main findings in the table were enriched with statistical data. Please see the revised Table 1.

7. There are not enough comments on the outlook for future research in children and adults with MAFLD, and I suggest enriching the insights into this aspect.

Answer: thank you for your comment. Future perspectives for adult and pediatric MAFLD have been further discussed. Please see lines 254-318 of the revised version of the text.

Rev 2

The manuscript (#72515) entitled “MAFLD from childhood to adulthood: state of art and future directions" is a manuscript by Francesca Lanzaro, et al. The authors aimed to investigate the proposed replacement of the term of Non-alcoholic fatty liver disease (NAFLD) with metabolic associated fatty liver disease (MAFLD). Main comments

1. The abstract does not really reflect what the authors have done. Please describe what and how you have summarized the current state of MAFLD.

Answer: we have re-edited it accordingly. Please see the abstract in the revised version of the manuscript (lines 3-24).

2. Please differentiates MAFLD and metabolic syndrome (MetS). What are their similarities and what are the differences?

Answer: we described differences and similarities between MAFLD and MetS in the revised version of the manuscript. Please see lines 83-92 of the revised text. We also added a table on diagnostic MetS criteria. Please see table 3 of the revised version of the text.

3. Section two (PATHOPHYSIOLOGY) contains many paragraphs with only one sentence. Please summarize those genes in a table and describe them according to their functions or pathways.

Answer: according to your valuable comment, we summarized the genes in a table and described them accordingly. Please see lines 117-148 and table 1 of the revised text.

4. In the third paragraph of the third section (EVIDENCE ON MAFLD: FROM CHILDHOOD TO ADULTHOOD), please define older and younger in terms of age in years before you use them and conclude that MAFLD patients are older.
Answer: we specified it and modified the text accordingly. Please see line 161 of the revised text.

5. NAFLDD has stages. Does MAFLD leads to hepatoma or tumorigenesis?
Answer: to date, no studies examined the influence of MAFLD on the progression of fatty liver to hepatocellular cancer. Please see lines 211-213 of the revised text.

6. Please use a table or graph to compare NAFLD and MAFLD.
Answer: we added a table comparing MAFLD to NAFLD diagnostic criteria. Please see Table 2 in the revised version of the text.

7. Please include a section to describe the treatment options and strategies for MAFLD if any.
Answer: following your comment, we discussed this aspect. Please see lines 251-253 and 316-321 of the revised version of the manuscript.

Rev 3
The authors intended to interpret the differences of MAFLD and NAFLD in both children and adults. However, I don't think there are much information for children, I suggest that authors should considered to delete those about children. And the whole manu need to completely re-edit. and the authors need to more conclusive than just see this study and that study so so. There are too many paragraphs in the manu and may be the authors should try to combine those tell the same topic.

Answer: thank you for your comments. We modified the manuscript accordingly. In particular, we shortened and combined the paragraph of the same topic.
We agree with you about limited evidence on pediatric MAFLD, but we think that a topic as relevant for public health should be also include data on children, although if they are still scarce. Noteworthy, as a result of the considerable scientific attention gained by MAFLD also in childhood, a recent pediatric MAFLD definition has been proposed. In the revised version of the manuscript, we added and discussed this aspect and specified in a clearer manner that pediatric MAFLD evidence is still limited. Please see lines 109-110, 211, and 235-243 of the revised version of the text.

Rev4

In the present study, the authors reviewed the roles of several factors (including genetics, inflammation, metabolic abnormalities, insulin resistance, obesity, prenatal determinants, and gut liver axis) in MAFLD pathophysiology, the adaptability of MAFLD diagnostic criteria for children, and current available data on the feasibility of MAFLD definition in clinical practice. This review is interesting. However, several aspects need to be modified as follows,

1.The key words should reflect the focus of the manuscript.

Answer: we modified the keywords accordingly . Please see the new keywords in the revised version of the text (lines 30-31).

2.The statement of diagnostic criteria in Page 4 needs to be more closely aligned with the original guidelines. For example, 1) MAFLD diagnosis is based on histological (biopsy), imaging or blood biomarker evidence of fat accumulation in the liver (hepatic steatosis), but not only the radiological evidence. Actually, for detection of steatosis, ultrasound is the most widely used first-line diagnostic modality and is recommended by the guidelines. 2) The standard of waist circumference is varied in Caucasian men and Asian men. 3) It's the plasma high-sensitivity C-reactive protein (hs-CRP) level instead of C-reactive protein (CRP) level is recommended in the guidelines for metabolic at-risk criteria. These subtle differences have very different meanings in the clinical practice of diagnostic criteria.

Answer: thank you for your comment. We clarified MAFLD diagnostic criteria according to guidelines. Please see lines 58,59, 62-63 and 67-68 of the revised text.

3.In Page 8, in regard to the Yamamura et al. studies (in reference 64), the results should be stated. Actually, Yamamura et al concluded in this report that in patients with MAFLD, even mild alcohol intake was associated with an increase in the prevalence of significant fibrosis (25.0% vs 15.5%; P = .0181). 4.In Page 9, in regard to the study in a large cohort of 954 of Italian children with obesity (in reference 16), the results of the article deserve a more accurate explanation. Actually, Sessa et al showed that that the MAFLD diagnosis based on "overweight/obesity" criteria in obese children were less accurate in identifying patients at higher cardiometabolic risk compared with the diagnosis of MAFLD based on "evidence of metabolic dysregulation" and "overweight/obesity" criteria. Sessa et al emphasized the usefulness of MAFLD diagnostic criteria in adequately stratifying young patients in a specific context such as obesity having an intrinsic greater cardiometabolic risk.

Answer: following your valuable comment, we explained in a clearer manner the results of the aforementioned studies. 2 Please see line 187-205 and 223-234 of the revised version of the text.

5.The statement of previous research results can be more concise and more logical.

Answer: we shortened and clarified them accordingly. Please see lines 175-194 of the revised text.

Rev 5
Thank you for compiling the recent status of MAFLD in children. I will recommend for publishing. Two minor typographic errors (comma after Similarly-Similarly, ... or Similar to...) and change coline to choline "phosphatidylcholine instead of phosphatidylcoline)

Answer: thank you for your appreciation. We corrected the typographic errors accordingly. Please see lines 293, 296 of the revised manuscript.