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Chirurgia

Dipartimento di
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Naples, 19th December 2023

Dear Editor,

first and foremost, we want to express our gratitude for inviting us to contribute a manuscript to *World Journal of Gastroenterology* (**ID 04124587**).

Please, enclosed you'll find the revised form of the original article *"RDW/Platelet ratio estimates the 3-year risk of decompensation in patients with MASLD-related compensated advanced chronic liver disease"*, by Dallio et al., which we would like to submit for consideration in *World Journal of Gastroenterology (WJG)*.

We are thankful to the reviewers for dedicating time in revising our manuscript. We really appreciate their suggestions and recommendations that will certainly enhance rigor and significance of the article.

According to the referee reports, we have revised the manuscript and addressed each critical remark providing a point-by-point response. We sincerely hope that the uploaded version can meet both yours and reviewers' expectations.

Thank you very much for your kind attention and consideration of our manuscript.

We do hope it might be acceptable for publication in the *WJG*.

Best Regards,

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Point-by-Point Response

First, we would kindly remark on the aim of our research. In our study, red blood cell distribution width-to-platelet ratio (RPR) was not assessed (and consequently not revealed) as a predictor of hepatic fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), differently from large evidence already supporting this result. Rather, to investigate a still unexplored scenario, we assessed and revealed RPR as a non-invasive tool that accurately predicts decompensation (timing and modalities) in MASLD cirrhotic individuals: this represented the real novelty with new potentially relevant consequences in the clinical management of such patients.

In the resubmitted version of our manuscript, according to the Reviewer's suggestions, we supplemented and clarified all the requested information.

- The medical records of enrolled patients were incomplete, such as information on medications received before the laboratory indicator test needed to be supplemented.
  We thank the Reviewer for this observation. As already reported in the "2.2 Patients" subsection of the Methods section, at the baseline, a complete clinical evaluation for each patient including, among several others (the assessment of alcohol consumption, smoking, and drug abuse) the complete medical history collection with the recording of comorbidities and concomitant therapies represented a crucial moment preceding the collection of venous blood samples for the lab assessments (including RDW and PLT count). However, to fulfill the Reviewer's request more deeply, we've realized a supplementary file ("Supplementary Table 3") detail reporting the "ongoing" therapies/medications received by each patient before the enrolment/the assessment of laboratory and other parameters. As appreciable, none of the medications administered appear potentially able to influence results of the laboratory and non-laboratory tests performed after the enrollment and thus the outcomes supporting the evidence of this study, except for statins.
  However, despite a growing interest in clinical use of statins in cirrhotic patients, given their several pleotropic effects, the emerging evidence supporting the association between statin use and reduction in risk for hepatic decompensation is still not sufficiently robust with a lack of well-designed prospective randomized clinical trial (doi: 10.1097/HEP.0000000000000278). Contrariwise, more robust evidence exists on nonselective beta blockers and a paramount trial recently revealed how long-term treatment with β blockers could increase decompensation-free survival in patients with compensated cirrhosis and CSPH (doi: 10.1016/S0140-6736(18)31875-0). Based on this status of the art, without losing sight of the concrete objectives of our study, only non-selective beta-blockers, whose administration was assessed also semiannually (during the follow-up medical examinations) were considered "disease-modifying drugs" and was included in our logistic regression analysis evaluating the variables influencing the outcome. These features have entirely been reported and explained in the Methods, Results, and Discussion sections.
- Is there a difference in diagnostic efficiency between male and female patients with RPR?
  We thank the Reviewer for this suggestion. To fulfill this request, data were gender-based split and RPR predictive accuracy was assessed by separately performing ROC curve analysis in male and female MASLD individuals. AUC resulted in quite similar for males and females and, by adequately comparing these results, RPR predictive accuracy resulted in no statistically significant difference between male MASLD patients and female MASLD subjects. We included all these new findings in the "Results" and "Discussion" sections of the resubmitted manuscript. Furthermore, regarding gender issue, we kindly remark that: 1) Chi-square test analysis has not revealed a statistically significant difference between the frequency distribution of males and females remaining

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compensated versus patients progressing to decompensation (table 2); 2) for both outcomes (i.e. first transition to decompensation and Acute Decompensation), we've also performed a multinomial logistic regression analysis properly including in our model "sex" as a confounding variable.

- Since MASLD is a chronic disease that progresses gradually, is the change of RPR related to the course of the disease? The above information is recommended to be supplemented in the table and discussed where necessary.

  We thank the Reviewer for this very interesting suggestion. Since fibrosis and clinically significant portal hypertension (CSPH) represent the two crucial key drivers fueling MASLD progression to advanced chronic liver disease and decompensation, we've already investigated the relationship between baseline RPR values and Liver Stiffness Measurement (LSM), as well as between baseline RPR values and CSPH severity: relevantly, a positive correlation between RPR and LSM (R:0.94; figure 3), as well as between RPR and CSPH severity (R:0.80) (Supplementary figure 4A, B) was highlighted. However, to assess "more dynamically" the correlation between RPR and disease progression and to fulfill the precious Reviewer's suggestion, since RPR data on the occasion of the first DE were fortunately available (considering that MASLD subjects were all inpatients in our department when LREs occurred) as well as LSM values (assessed to non-invasively reevaluate CSPH, as already reported in the Methods and subsection "2.8" of the paper), we furtherly investigated the relationship between "RPR values variations" (expressing this as D%RPR) and "LSM variations" (expressing this as D%LSM) during the study period. In detail, as reported also in the Methods section, D% was determined by using the following formula: for RPR: {[D% RPR= (RPR on the first DE - baseline RPR)/baseline RPR*100]}, for LSM: {[D% LSM= (LSM on the first DE - baseline LSM)/baseline LSM*100]}. Consistently, a direct positive correlation between D%RPR and D%LSM was highlighted, properly reported in the "Results" (subparagraph 3.3), and adequately described in "Discussion" in this resubmitted new version of our manuscript. In the newly added Supplementary Figure 1, this relationship is illustrated as well as the LSM and RPR (Mean ± DS) variations (baseline vs on first DE).
- In addition, the number of enrolled patients and controls was relatively small, so it is recommended to increase the number of enrolled patients as much as possible.

  We thank the Reviewer for this observation. As précised in the statistical analysis section in the resubmitted version of our manuscript, sample size estimation, based on the primary end-point, was determined by performing a Logistic Regression analysis model (p0:0.15; p1:0.23; alfa:0.05; power:0.8) testing whether a predictor variable is a significant predictor of the binary (0/1) outcome (y= decompensation) by using the wp. logistic function of STATA18 for macOS software.
  Anyway, as already largely reported in the "Discussion", our population, even if a representative MASLD cohort, could represent a relatively small sample size and this constitutes a limitation of our study. However, in the currently available scientific literature, this last feature frequently recurs in many other studies (for example DOI: 10.3748/wjg.v29.i32.4873; doi: 10.1016/j.cgh.2019.01.042) having a similar experimental design and exploring the same research topic.

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