

1.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Agata et al retrospectively explored the value of RDW, RPR and RLR in 142 ALC patients and 92 MAFLD. They concluded that RDW with its derivatives appear to be valuable diagnostic markers in patients with ALC. Compared with their previous published papers (doi:10.3748/wjg.v26.i47.7538 and doi:10.1155/2021/8867985), this manuscript seems used the similar clinical data and studied different indices. In general, this manuscript has certain novelty, and the English writing is well. But there were some concerns need to be addressed. 1. My major concern is the bias caused by the clinical confounders that affect the levels of RDW with its derivatives, since the authors has showed other hematological indices (NLR, PLR and MPR) associated with ALC and MAFLD patients, I suggested that they performed the comparison of RDW, RPR and RLR with other hematological indices to reduce the influence of potential clinical confounders. 2. Is it the data of Table 2, Table 3 and Table 4 correctly present, why each data presented separately, shouldn't they present as Table 1? 3. The text of Figures were overlapped with the square frame of AUC, could they be separated from the curve. 4. There remains several spell mistakes in the manuscript. For example, in the "Procedures" section, "NAFLD" was used instead of "MAFLD", "Conentrations" was misspelling in the first paragraph of Discussion section.

Thank you for a detailed review. We really appreciate your comments.

1. Basically, we considered the comparison of the greater number of hematological indices performed by us; including the data from two previous papers (doi:10.3748/wjg.v26.i47.7538 and doi:10.1155/2021/8867985), nonetheless, because of the quite large diversity of assess hematological markers we decided do divide them into subgroups; in the current manuscript we focused on RDW-derivatives. Due to the complexity of these markers it is hard to discuss all of them in a single study. Furthermore, it is even quite challenging to find similar investigations in the literature. The inflammation and anemia are potential pathological states that may influence the result of values of hematological indices measured by our team. Thus, we excluded from the survey patients with noticeable features of the inflammatory process and subjects with anemia - it was included in the manuscript, in the section of Materials. Undoubtedly, a further exploration of this topic in details is crucial here. But we still think that the data obtained in the current manuscript are quite promising and encouraging to continue this direction of investigations.

2. Table 2 presents a different type of data in comparison to Tables: 3 and 4 and from a graphical point of view it looks in a more clear way as a separate table. The content of Tables: 3 and 4 was connected into Table 3., according to the suggestion.

3. Graphic issues were corrected and modified Figures 1-3 were placed in the manuscript.

4. Misspellings were corrected in the manuscript.

2.

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The study investigated the values of RDW, RPR and RLR in ALC patients and MAFLD patients, and the correlations were analyzed between the value and the parameter of liver fibrosis, respectively. The results indicate that RDW derivatives can be as diagnostic markers for ALC or MAFLD patients. Some issues in this paper, however, should be raised. 1. About the title, it is not suitable for use of “liver disorders” in the title. The role of RDW derivatives should be discussed in a certain disease rather than a broad one. In addition, the RDW derivatives were studied in ALC and MAFLD patients, but there was no association presented about the RDW derivatives between the two illnesses. So, the data provided in this paper cannot provide a meaningful and a clear conclusion. 2. About the so-called “indirect and direct indices of liver fibrosis”. Actually, all the serological markers, including the assessing models (APRI, FIB-4, etc), are the indirect indices. Liver biopsy is still the gold-standard approach for the assessment of liver fibrosis or cirrhosis. Due to the lack of pathological data in these patients, the analyses on the RDW derivatives as well as their association with the serological markers cannot provide compelling and reliable evidences to support the conclusions in the study. 3. This study is a retrospective one, so the authors should explain how to keep or obtain the serum samples for detecting the serological markers of liver fibrosis in the section of method. 4. In the section of discussion, the authors mentioned “HEV infection”. Hepatitis E is an acute liver disease, so it is not meaningful to discuss the indicators of liver fibrosis assessment in HEV infection. 5. MAFLD has a broad spectrum of disease, so the results suggest that the RDW derivatives have high diagnostic accuracy in ALC patients, but what the results will be if the majority of MAFLD are NASH patients. This is also a defect of the study.

Thank you for your comprehensive assessment of our paper and valuable pieces of advice.

1. The title was modified and now concerns disorders discussed in the manuscript: *Red blood cell distribution width derivatives in alcohol-related liver cirrhosis and metabolic-associated fatty liver disease*. We evaluated a relatively small sample of patients and our main aim was an independent assessment of RDW-derived markers in ALC and MAFLD without a detailed comparison between these pathologies (what was mentioned in the section of Discussion). ROC curves were used in the current study as tools differentiating diagnostic accuracy of evaluated parameters in examined two groups of patients and it appears to us that particularly these results are crucial here in the context of their potential usefulness.

Moreover, we came to the conclusion that the two groups of investigated patients are not heterogeneous and the comparison of hematological markers between them from scientific and clinical point of view will not be adequate.

2. The term of indirect indices of liver fibrosis concerned: AAR, APRI, FIB-4 and GPR. But we also assessed direct parameters of liver fibrosis, related to the changes taking place within an extracellular matrix: procollagen I carboxyterminal propeptide (PICP), procollagen III aminoterminal propeptide (PIIINP), platelet-derived growth factor AB (PDGF-AB), transforming growth factor- α (TGF- α) and laminin. Our study was a pilot one and the obtained data suggest a potential usefulness of RDW-derivatives in the course of ALC and MAFLD. Nevertheless, a further analysis of the patients with presented disorders should take place, including liver biopsy. The lack of this procedure in our study might be perceived as a significant disadvantage and limitation, but during the continuation of the exploration of this issue, we will measure the concentration of direct markers of liver fibrosis in liver biopsy samples, as well and compare the results with serological findings. We will also evaluate RDW-derivatives in the context of the morphological severity of liver fibrosis. For now, the results seem to us still valuable, because they indicate a potential role of RDW in ALC and MAFLD patients.

3. The description of the storage of serum samples was described in the section of Methods: *The remaining part of blood samples without an anticoagulant was centrifuged at the speed of 2000 x g for 10 minutes within 15 minutes from blood collection. The obtained serum was stored then in 1 mL Eppendorf test tubes at the temperature of -80° Celsius until the evaluation of direct markers of liver fibrosis with ELISA.*

4. In the current study we tried to present already known liver pathologies which were already explored in the context of RDW-derivatives. Our goal was not to compare HEV to ALC or MAFLD, but to present possibly the widest spectrum of liver disorders which could be linked to RDW-derivatives abnormalities. On the other hand, inflammation constitutes an inseparable part of both: ALC and NaFLD, so it can not be excluded that this phenomenon (characteristic for HEV, too) is the background of observed hematological aberrations. But one again - to verify this issue, liver biopsy should be performed in examined by us ALC and MAFLD patients. In the future we will continue this investigation.

5. We would like to emphasize one more time that the lack of liver biopsy constitutes the limitation of the current study (what was mentioned in the section of discussion) and its application will become the element of our further investigation.

3.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Title: Red blood cell distribution width derivatives in liver disorders Ref number: 78584 First author: Agata Michalak This is a very interesting

study, which aimed to evaluate a group of peripheral inflammatory biomarkers [red blood cell distribution width (RDW), RDW-to-platelet ratio (RPR) and RDW-to-lymphocyte ratio (RLR)] and liver fibrosis in 142 patients with alcoholic liver cirrhosis (ALC) and 92 with metabolic associated fatty liver disease (MAFLD); 68 persons were included as controls. The results showed that peripheral inflammatory biomarkers were obviously higher in patients with ALC and MAFLD. Further, these peripheral factors showed an excellent performance to predict ALC, judged by AUC values. The paper was well written. However, some concerns need to be further addressed. 1. Inflammation was believed to be involved in the development of liver fibrosis in both alcoholic and non-alcoholic status. The most common factor to evaluate systemic inflammation was high-sensitivity CRP. Did the author collect the data? 2. The advantage of these peripheral inflammatory biomarkers were easily to be obtained; however, it might be affected by many diseases such as anemia. How to exclude the potential effects of these confounding? 3. A flow chart for enrolling the participants might be necessary. 4. As Spearman Correlation did not take confounding into consideration, it might be appropriate to analyze the data by multi-variables linear regression. For example, BMI was a important factor contributing liver fibrosis in both alcoholic and non-alcoholic liver diseases. 5. Did these peripheral inflammatory biomarkers differ in different sex or age groups? 6. The description of baseline characteristics was helpful to get a general impression of study population. 7. Are there any limitations in the current study? The study design might be a cross-sectional study with small sample size. We did not know whether peripheral inflammatory biomarkers or liver fibrosis appeared first.

Thank you for your valuable and practical comments on our paper.

1. Inflammation could be a potential factor influencing the character of obtained results. However, we assessed the concentration of high sensitivity in examined patients, indeed and its values in all study participants remained in the reference range.
2. A potential impact of various systemic states on the values of RDW-derived markers is an essential issue to be raised. We excluded the presence of a detectable inflammation in our patients, they did not take steroids; anemia was also excluded - as it was written in the manuscript, in the section of Materials. However, even in such circumstances it is hard to eliminate with complete certainty the presence of other potential factors influencing the results of RDW-related markers. This topic requires further analysis.
3. We included a flow chart demonstrating the enrollment of the study participants into the section of Methods. It was described as Figure 1 in the section of Figures.
4. We thought about the implementation of multivariate linear regression, too, nevertheless it did not bring any new significant data to be presented. BMI did not have any impact on the achieved results.
5. We looked for relevant relationships between the values of hematological markers and patient' age and sex, but we did not obtain any statistically significant differences. Thus we did not include this information in the manuscript.
6. We tried to present these data in the most clear way, thank you for your approval.

7. The main limitation is connected with the lack of liver biopsy as a used diagnostic tool. We did not differentiate MAFLD patients according to the presence of hepatitis. In addition, we did not evaluate the severity of liver fibrosis in ALC patients. Thus, in the future we would like to broaden the spectrum of the current survey. We considered the possibility of cross-sectional study concerning this study, as well. However, taking into consideration a similar previously published paper by our team and the point of view of our statistics, we chose a retrospective study. In the investigated population of patients liver fibrosis seems to be the first baseline phenomenon and hematological indices were obtained from patients with already developed ALC and MAFLD.

All the changes introduced in the manuscript were written in red colour.