SEMMELWEIS UNIVERSITY
*Division of Oncology, Department of Internal Medicine and Oncology*

Budapest, December 20, 2021

Dear Lian-Sheng Ma, Company Editor-in-Chief,
Dear Professor Dennis A Bloomfield, Professor Bao-Gan Peng, and Professor Sandro Vento, Editor-in-Chiefs,
Dear Managing Editors,
Dear Reviewers,

On behalf of my fellow authors, first of all, I would like to thank you for your attention and opinion on our original article entitled "*Longitudinal changes in personalized platelet count metrics are good indicators of initial 3-year outcome in colorectal cancer*". We are grateful that you have found it to be interesting and suitable for publication in World Journal of Clinical Cases.

Our answers to the comments raised in the reviews are given below.

**Reviewer 1**

*Authors retrospectively evaluated the value of the platelet count metrics in CRC patients. Authors the concluded the platelet count metrics is useful to follow the prognosis of CRC patients and helpful for therapy decisions. But its clinical usefulness was unclear due to its retrospective nature. In clinical setting, imaging studies are a key factor for decision making. The changes of tumor maker might be also useful to assess tumor growth. It is unclear whether the platelet count metrics are superior to imaging studies or tumor markers. Furthermore, the platelet count metrics can be largely affected by chemotherapies or surgical intervention. Indeed, the pattern of patients with death was different as shown in Fig. 4A and B.*

Thank you for your kind criticism. Considering that we have refined the Conclusion of the study and the following paragraph had been added to Discussion:

*"Routine follow-up of CRC patients is currently done according to the following scheme, recommended e.g. by the European Society for Medical Oncology (ESMO)[61,62] or by others[63]. In general, the current gold standards are the measurement of the tumor marker carcinoembryonic antigen (CEA) and imaging studies, which are recommended to be performed every 3-6 month and 3-6-12 months depending on the stage, presence of metastases, current treatment etc. of the disease, respectively. Although the superiority of tumor markers and*

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*imaging studies are not questioned, our results suggests that frequent CBC measurements may extend the current routine follow-up arsenal of medical tests. The application of CBC metrics is easy and cost-effective; however, a prospective clinical trial – similar to that of the COLOFOL randomized clinical trial[64] and its retrospective counterpart[65] – is required to properly address its everyday usefulness in routine CRC follow-up. The two aforementioned studies[64,65] have found that there is no connection between CEA/imaging surveillance intensity and overall survival or frequency of tumor recurrence for stage II and III CRC."*

Furthermore, Limitations of the study had been extended with a sentence about the retrospective design of the study.

**Reviewer 2**

*Good work, well done! This study involved 835 CRC patients with longitudinal data and multiple analysis methods. The results are interesting and convincing that demonstrated early detection of the pathological changes in $pPLT_D$, $pPLT_S$ (new metrics), LMR, NLR, or HPR can be useful for oncologists to make a therapeutic decision. The only problem I am concerned about is that I notice many parameters are not available for near half of the patients of this study, such as Neutrophyil-to-lymphocyte ratio and Platelet-to-lymphocyte ratio, which should be discussed properly in the limitation section. In addition, authors can improve their work's breadth by testing their findings in other published datasets.*

Thank you for your positive comment on our article. The idea of testing our results on publicly available datasets is very promising. Unfortunately, to the best of our knowledge, no such dataset is available that includes continuous complete blood count measurements of patients with colorectal tumors throughout the course of the disease and therefore we cannot confirm our results on a different dataset.

Thank you for bringing to our attention that the limitations of our work had to be further detailed. The following modification was performed:

*"Further limitation of the study was that some CBC indices were not available for every visit. LMR, NLR, PLR, HPR, RPR, pPLTD and pPLTS were available for 88.15% (n = 4062), 69.73% (n = 3213), 70.05% (n = 3228), 100% (n = 4608), 78.97% (n = 3639), 100% (n = 4608) and 78.84% (n = 3633) of all patient visits, respectively. To reduce the resulting biases, we chose statistical methods that can robustly address the problem of missing values. Both mixed effect models and Bayesian methods, including joint models, can perform better and can give more proper results with sufficient strength when missing values are present[66]."*

Yours sincerely,

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