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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 85901

Title: Baseline Neutrophil-Lymphocyte Ratio & Platelet-Lymphocyte Ratio Appear Predictive of Immune Treatment Related Toxicity in Hepatocellular Carcinoma

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03537453
Position: Editorial Board
Academic degree: MD
Professional title: Chief Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2023-05-21
Reviewer chosen by: Geng-Long Liu
Reviewer accepted review: 2023-07-29 04:49
Reviewer performed review: 2023-07-31 07:52
Review time: 2 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Strength: It's an interesting subject. Data from multicenter and the general sample is relatively large. Weakness: A retrospective study, the study design was not sufficent, and the results of statistical analyses were not precision. There were no correlative study of the therapeutic effects with the immune-related adverse events (IrAEs). The immune-related adverse events (IrAEs) may be a part of the therapy response, and mechanism had better be discussed. If a patient with HCC has poor respose to the immune treatment, what is the immune-related adverse events? Some specific concerns:

The title should be rephrased to be better consistent to the central findings of this study (objectively and accurately). The abstract needs to be rewritten, making the purpose, methods, results and conclusion consistency, adequate and clear. Of 'in a subset of patients with aHCC' should be " in a subset of patients with advanced hepatocellular carcinoma (aHCC)". In this study, important information were enrolled in the Table 1, however, there were absence of the details and matching analysis (e.g., propensity score matching) of the different patients, so the study design was not sound and rigorous. Patients with advanced hepatocellular carcinoma usually have various conditions,

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including underlying diseases and complications, the neutrophil-lymphocyte ratio (NLR) & platelet-lymphocyte ratio (PLR) are subjected to many confounding factors, which influence the study outcome and reliability of the results and conclusion. Other necessary materials had better be added. Of 'METHODS'. In this section there is other 'methods', please specific. Of 'A total of 361 patients had documented IrAE data and were included in the final analysis, of whom 242 (67%) were treated in the USA, 51 (14%) in Asia and 68 (19%) in Europe (Figure 1). ' These should be in the 'Methods' section in this retrospective study. Of 'Figure 1 Study Flow Chart'. It is not a standard one. Number and reason of study sample inclusion and exclusion should be listed out. Please refer to some other articles to revise the "Study Flow Chart". Without decibel, the percentages of 19% and 10% in the Results that "NLR was ≤5 in 184 (51%) patients and >5 in 70 (19%) patients. The proportion of patients with an NLR < 5 or > 5 did not differ significantly between the IrAE groups. PLR was ≤ 300 in 217 (60%) and >300 in 37 (10%) patient" were not consistent with the figures in the Table 1. So do some other variables in the Table 1, please verify and revise. Of "Antibiotics use was not associated with IrAE incidence (OR = 1.02; p=0.954) (Tables 3)." Tables 3 should be Table 3. Of 'conducting such an analysis would not be feasible, and the results would not be statistically meaningful' may be 'conducting such an analysis would not be adequate, and the results would not be statistically meaningful. ' Of 'Table 2', 'IrAEs incidence by groups' and 'IrAE by organ system N = 167'. Note may be given to make the variables more clear. Of 'References'. The styles should be consistent and met the requirement of the present Journal. Of 'Reference 1'. It should be replced with an updated one. Reference 9 and10 are not complete.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02534290
Position: Editorial Board
Academic degree: MD, MSc, PhD
Professional title: Doctor, Professor, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: Romania
Author's Country/Territory: United States

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Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Congratulatioms! excellent work and huge effort to collect data from center on 3 continents. The work is signaling an importamt issue in forecast of imune related adverse effects by simple laboratory data. Work of high practical importance!

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Peer-review model: Single blind

Reviewer's code: 05723533
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Associate Professor, Doctor, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2023-05-21
Reviewer chosen by: Geng-Long Liu
Reviewer accepted review: 2023-07-30 16:00
Reviewer performed review: 2023-08-08 03:20
Review time: 8 Days and 11 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Human neutrophils and platelets produce a host of cytokines and growth factors relevant to tumor growth and progression. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported as predictive factors in several cancer types. Elevated NLR and PLR were also found to be associated with poor response to transarterial chemoembolization (TACE) and sorafenib treatment in HCC. As for immunotherapy in HCC, the same predictive effect has also been reported. In a subcohort of 242 patients in the CheckMate 040 trial (J Hepatol,2020,73:1460–9), patients with NLR in the low tertile showed better OS than those with medium or high tertile. A similar result was observed in PLR. Patients with complete response or partial response (CR/PR) had lower PLR than those with progressive disease. In another cohort of 194 HCC patients treated with nivolumab (Liver Int,2021,41:2189–99), those with baseline NLR≥3 presented poorer progression-free survival (PFS) and OS. Moreover, a dynamic increase of NLR at 4 weeks was associated with an increased risk of death. Interestingly, in this study, NLR increased at 4 weeks also had a role in predicting hyperprogressive disease, which may guide treatment plan in an early phase. In a cohort of 362 HCC

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patients treated with mono or combination immunotherapy (Cancers,2021,14:186), patients with higher NLR and PLR at baseline were reported to have a higher incidence of portal vein thrombosis (PVT), higher Eastern Cooperative Oncology Group (ECOG) performance status, and more advanced Barcelona Clinic Liver Cancer (BCLC) stage. Significantly shorter OS and PFS were observed in patients with NLR≥5 and PLR≥300. Therefore, I don't believe Dharmapuri's article tell us new information. However, it is a qualified multicenter clinical study. Please cite the above published paper in the manuscript and compare your results with them.

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Peer-review model: Single blind

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Position: Editorial Board
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: United States

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Review time: 36 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

By collecting clinical data of patients receiving immune checkpoint inhibitors for HCC in the international database, this study analyzed the relationship between NLR, PLR and clinically significant immune-related adverse events in ICI treatment of HCC, as well as the relationship between antibiotics, steroid exposure, the choice of ICI combined treatment regimen and IrAEs. It was concluded that lower baseline NLR and PLR could predict IrAEs in ICI treatment of HCC. Statistical methods were properly used in the study, and the conclusion has certain guiding value for clinical practice. However, the discussion content is slightly superficial, and the manuscript may be fuller if the following contents could be added: 1. There were few content about possible mechanisms by which baseline NLR could predict the occurrence of IrAEs in ICI treatment of HCC, and the possible relationship between baseline inflammation and IrAEs was not clearly explained; 2. It was mentioned in the paper that the possible mechanism by which baseline PLR could predict the occurrence of IrAEs was the hypercortisolemic state in chronic inflammatory diseases, and steroid exposure was associated with the occurrence of IrAEs, although 74% of patients were exposed to

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steroids for the treatment of IrAEs, what do you think about the relationship between PLR level and cortisol level in patients receiving ICI treatment for liver cancer? 3. It is mentioned in the article that "there is no significant difference in NLR and PLR levels between steroid exposed and non-exposed patients". Are the NLR and PLR levels here at baseline or after exposure?