Peer Review File
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Reviewer A

Thank you for requesting my review of the article titled: "Prognostic role of dynamic changes in inflammatory indicators in patients with non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors."
Overall, the article is well-written, but significant limitations in its design need to be addressed. There are already numerous publications on the subject, with no significant new findings presented in this article.
Thanks for the positive comments. Like most literature, we first investigated the usefulness of the NLR and PLR in predicting the clinical outcomes of NSCLC patients undergoing treatments with PD-1 inhibitors. Next, we constructed a predictive model based on hematological inflammatory parameters for assessing the prognostic markers of NSCLC patients treated with ICIs, which demonstrates our innovation.
Changes in the text: None

The authors mention the prognostic role, but no overall survival data is provided.
Thank you very much for the comments. Due to limited follow-up time, we only provided the PFS data.
Changes in the text: None

The baseline levels of circulating immune markers are not associated with the response, which contradicts previous publications. This brings me to another point: the authors have included a highly heterogeneous population treated in the first line (38%), second line (27%), and even beyond. These patient populations are entirely different, and it would be more interesting to compare if the markers NLR/dNLR/PLR have distinct roles between the lines of treatment where immunotherapy is administered. However, I am concerned that the sample sizes may not allow for this analysis.
Thanks for the crucial comments. In our study, we really did not find the correlation between the baseline levels of circulating immune markers and clinical results. As you suggested, this may be attributed to the highly heterogeneous population, but regardless, under the same conditions, the dynamic changes in the circulating immune markers were significantly associated with the clinical outcomes, which emphasized its greater clinical significance.
Changes in the text: None

Reviewer B

1. First, the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study.
   Thanks, we did.
   Changes in the text:
   Prognostic role of dynamic changes in inflammatory indicators in patients with non-small cell lung cancer treated with immune checkpoint inhibitors- A

retrospective cohort study.

2. Second, in the abstract, the background did not explain why the authors focused on inflammatory indicators and what the current knowledge gap is. The methods need to describe the inclusion of subjects, follow up procedures, and measurements of prognosis outcomes. The results need to briefly summarize the baseline clinical characteristics of the patient sample, as well as to quantify the findings on the prognostic roles such as HR and accurate P values.

Thanks, we did as suggested.

Changes in the text:

As effective biomarkers, programmed cell death ligand 1 (PD-L1) expression, microsatellite instability (MSI), the tumor mutation burden (TMB) and tumor-infiltrating lymphocytes (TILs) require invasive procedures that place heavy physical and psychological burdens on patients.

This retrospective study comprised 95 patients with metastatic NSCLC who were treated with ICIs either as the standard of care or in a clinical trial. The following data were extracted from the medical records. The baseline and dynamic neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated in the present study. Responses were assessed by computed tomography (CT) imaging and classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 every 6–12 weeks during treatment.

In total, 95 patients were included in the present study. The median age of patients was 61 years, (83.2%, 79/95) patients were male, 62.1% (59/95) were former or current smokers, 66.3% (63/95) had adenocarcinoma, 93.7% (89/95) had stage IV disease, and 87.4% were without molecular alterations.

A higher overall response rate (ORR) and prolonged median progression-free survival (PFS) was observed in patients with a lower cycle 3 (C3) NLR (7.7 versus 5.5 months, HR: 1.70, 95% CI: 0.90–3.22; P=0.12) and dNLR (8.2 versus 5.6 months, HR: 1.67, 95% CI: 0.94–2.97; P=0.08). After two cycles of ICI treatment, patients who had an increased NLR, dNLR, and PLR had a lower ORR and an inferior median PFS than those with a decreased NLR (5.5 versus 8.5 months, HR: 1.87, 95% CI: 1.09–3.21; P=0.02), dNLR(5.6 versus 8.4 months, HR: 1.49, 95% CI: 0.87–2.57; P=0.15), and PLR(11.8 versus 5.5 months, HR: 2.28, 95% CI: 1.32–3.94; P=0.003). Moreover, patients with both an increased NLR and PLR had a worse ORR and median PFS than those with either an increased NLR or PLR, or both an increased NLR and PLR (11.8 versus 5.5 versus 5.6 months, P=0.003). In addition, the dynamic changes in the PLR could serve as an independent predictive factor of PFS in NSCLC patients treated with

ICIs.

3. Third, in the introduction, it is necessary to review what has been known on the prognostic factors of non-small cell lung cancer treated with immune checkpoint inhibitors, in articular biological markers, and analyze the limitations and knowledge gaps. It is also necessary to analyze the knowledge gaps on the prognostic roles of NLR and PLR.
   Thanks, as suggested, we have added.
   Changes in the text:

   However, most of studies only indicated the prognostic effect of the static level, they fail to show the real-time association of survival with dynamic changes in these markers over time, which potentially reflects a combined time- and treatment-dependent variation in the underlying disease process.
4. Fourth, in the methodology, please describe the clinical research design, sample size estimation, follow up procedures, and measurements of prognosis outcomes. In statistics, please indicate the P value for statistical significance and details of the multiple regression analysis on the independent prognostic role of the inflammatory indicators.
   We added.
   Changes in the text:
   The sample size was calculated using the Raosoft calculator. In total, 95 patients were included in the present study

   Responses were assessed by computed tomography (CT) imaging and classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 every 6–12 weeks during treatment.

   We reported 95% confidence intervals with two-sided $p < 0.05$ being set as a threshold for significance.

5. Finally, please consider to review and cite several related papers: 1. Xu M, Xu L, Hao Y, Shao K, Song Z. Clinical characteristics and prognostic implications of immune-related hepatitis in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors: a retrospective study. J Thorac Dis 2024;16(3):1900-1910. doi: 10.21037/jtd-23-1684. 2. Tang J, Fu Y, Song Y, Yin J, Wang J, Arasanz H, Zhang B. Increasing serum complement component 1q is associated with worse prognosis in advanced non-small cell lung cancer treated with immune checkpoint inhibitors: a single-center, retrospective study. J Thorac Dis 2024;16(5):3251-3259. doi: 10.21037/jtd-24-304. 3. Li Y, Gong B, Lou J, Guo Y, Liang B, Liu W, You Z, Chen C, Chai B, Jiang S, Zhang H, Pan F, Yang L, Zhou G. Association between thymus density loss and efficacy in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Transl Lung

Cancer Res 2024;13(7):1544-1558. doi: 10.21037/tlcr-24-203. 4. Weng J, Huang J, Yu W, Zhao Z, Zhu B, Lin J, Cai Y, Zhang J, Su W, Chen X, Zhu K, Lin S. Combination of albumin concentration and neutrophil-to-lymphocyte ratio for predicting overall survival of patients with non-small cell lung cancer. J Thorac Dis 2021;13(9):5508-5516. doi: 10.21037/jtd-21-1320.

As suggested, we have added.

Changes in the text:

It may also lead to an increase in the incidence and severity of treatment-related adverse events[4-6].

In addition, a previous study revealed that thymic density changes were observed in nearly all NSCLC patients undergoing immunotherapy, with decreased density associated with longer OS[15].

Similarly, hematological inflammatory parameters can also reflect the immune status of patients and have been established as important predictive markers associated with the prognosis of tumors [23,24,25,26,27].