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RESEARCH

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictive biomarkers for treatment response in primary advanced hypopharyngeal squamous cell carcinoma treated with chemoimmunotherapy

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Abstract

To evaluate the predictive value of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in peripheral blood for assessing the treatment response to chemoimmunotherapy in primary advanced hypopharyngeal squamous cell carcinoma (HPSCC), we retrospectively reviewed the medical records of patients treated with neoadjuvant taxane–platinum (TP) chemotherapy plus an anti-programmed cell death-1 (PD-1) inhibitor at Wuhan Union Hospital from Jan 2020 to Dec 2022. We collected data on absolute neutrophil, lymphocyte, and platelet counts from routine blood tested at baseline and within a week after the first treatment. A total of 35 patients were included in this study. Post-treatment NLR ($r_s = -0.445$, $p = 0.007$) and PLR ($r_s = -0.475$, $p = 0.004$) demonstrated negative correlations with treatment response assessed by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). NLR and PLR were significantly lower in patients achieving a complete response than those not achieving it (with p values of 0.04 and 0.02 for NLR and PLR, respectively). Among the 27 patients who underwent radical surgery following three cycles of chemoimmunotherapy, a high PLR after the first treatment was negatively correlated with attaining a pathological complete response (pCR) ($r_s = -0.424$, $p = 0.028$). For predicting pCR, the receiver operating characteristic (ROC) curve of PLR after the first treatment yielded an area under the curve (AUC) of 0.759 (95% confidence interval [CI]: 0.572–0.946, $p = 0.031$), with a sensitivity of 77.8% and a specificity of 72.2%. This research underscores the predictive value of the NLR and PLR in appraising not only the treatment response, as gauged by the RECIST 1.1, but also the pathological response to chemoimmunotherapy in patients with HPSCC.

Keywords Hypopharyngeal squamous cell carcinoma · Immunotherapy · Treatment response · Neutrophil-to-lymphocyte ratio · Platelet-to-lymphocyte ratio

Introduction

Head and neck cancer is the sixth most common malignancy worldwide [1]. Among these, hypopharyngeal squamous cell carcinoma (HPSCC) is typically diagnosed at advanced stage [2, 3]. It is associated with a poor prognosis, characterized by a low 5-year overall survival (OS) rate [4]. Over the past decade, immune checkpoint inhibitors (ICIs) have achieved great progress in solid tumor and higher treatment efficacy in head and neck squamous cell carcinoma [5]. However, it is only about only 15–20% of patients with HNSCC achieve a durable response to immunotherapy [6]. High PD-L1 expression in tumor is an important predictor of immunotherapy efficacy and is associated with better prognosis [7, 8]. Nevertheless, studies have shown that patients with PD-L1 CPS < 1% or no PD-L1 expression can also benefit from anti-PD-1 or anti-PD-L1 inhibitors [9–11]. Therefore, it is vital to find other markers to predict treatment response in patients who received immunotherapy.

Chronic inflammation is known to play a crucial role in tumorigenesis, progression, and metastasis [12, 13]. Neutrophils contribute to tumor development and metastasis through promoting angiogenesis and weakening the immune response [14, 15]. Platelets, in turn, can mediate

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the proliferation of tumor cells in micrometastases by protecting tumor cells from natural killer cell attacks and releasing platelet-derived growth factor [16, 17].. Recently, some studies have found that peripheral blood markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are associated with the efficacy and prognosis of tumor immunotherapy. T. Ueda et al. [18] found that an NLR > 5 was associated with shorter OS (HR: 4.88; $p = 0.045$) and disease progression (HR: 5.0, $p = 0.046$) in patients with R/M HNSCC treated with nivolumab. Pre-treatment peripheral blood NLR and PLR have demonstrated predictive value regarding the efficacy of immunotherapy. For instance, an NLR ≥ 3.65 suggests a poor prognosis in advanced gastric cancer (GC) treated with immunotherapy [19]. Similarly, in metastatic colorectal cancer patients treated with immunotherapy, both a low baseline NLR ($P = 0.014$) and a decreased NLR after 2 cycles of immunotherapy ($P < 0.001$) were significantly correlated with better OS [20]. The longest median OS (29.63 months) was observed in patients with both a low baseline NLR and an early reduction in NLR [20]. Furthermore, elevated NLR and PLR have been significantly associated with worse OS and PFS in patients with advanced GC/gastroesophageal junction cancer (GEJC) treated with immunotherapy [21]. Post-treatment increases in NLR and PLR were also strongly associated with poor OS and event-free survival in patients with surgically resectable non-small cell lung cancer (NSCLC) [22].

However, currently, it remains unknown whether the peripheral blood NLR and PLR measured at baseline and shortly after the first chemoimmunotherapy can predict the treatment response assessed by RECIST1.1 and pathological response in patients with locally advanced HNSCC receiving chemoimmunotherapy. We retrospectively collected the absolute neutrophil count (ANC), absolute lymphocyte count (ANC), and absolute platelet count (APC) of the peripheral blood tested prior to the initial chemoimmunotherapy and within seven days following the treatment in order to explore the relationship between peripheral blood NLR and PLR and treatment response to chemoimmunotherapy in primary HPSCC. Additionally, we calculated NLR and PLR to examine the relationship between them and the pathological and treatment response of the patients.

Materials and methods

Clinical data

A retrospective analysis was conducted on the clinical data of all patients with histologically confirmed primary HPSCC who received TP based chemotherapy combined with anti-PD-1 inhibitors between January 2020 and December 2022. Patients were included if they met the following criteria: (1) histologically confirmed HPSCC; (2) stage IIIA-IVB according to the American Joint Committee on Cancer (AJCC) 8th edition; (3) Taxane, platinum (TP) combined with anti-PD-1 inhibitors regimens administered at least every three weeks for at least three cycles since diagnosis; (4) complete imaging data, such as CT or MRI; and (5) complete peripheral blood counts at baseline and within seven days following initial neoadjuvant chemoimmunotherapy. The patient who had a concurrent combination of other malignancies or have received antibiotic treatment during neoadjuvant therapy was excluded.

Methods

The following information was collected from the patients' medical records: gender, age, history of smoking and alcohol use, baseline tumor TNM stage, therapies, routine blood tests at baseline and within a week following the first chemoimmunotherapy, and images obtained from CT or MRI scans before the first treatment and after the finish of the third chemoimmunotherapy. RECIST 1.1 was used to evaluate treatment response. Histologic examination results after radical surgery were collected from patients to assess whether they had achieved a pathologically complete response (pCR). pCR is defined as the disappearance of tumor cells in both the primary lesion and the cervical lymph nodes.

Statistical analysis

All data were statistically analyzed and presented using SPSS 26.0.0 and GraphPad Prism 5. Continuous variables were summarized as means, minimums, and maximums, while categorical variables were described using frequencies and percentages. Spearman's rank correlation analysis was conducted to evaluate the relationships between ANC, ALC, APC, NLR, and PLR, and the pathological or therapeutic responses assessed by RECIST 1.1. Differences in means were assessed using either the independent samples t-test or one-way ANOVA. For non-normal or unevenly distributed data, the nonparametric Mann–Whitney U test was applied. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was used to evaluate the sensitivity and specificity of NLR and PLR in diagnosing pCR. Statistical significance was defined as $P < 0.05$, and all P values were two-tailed.

Results

Basic characteristics of patients

This study encompassed a total of 35 patients with HPSCC. All of them were male, with a mean age of 60.62 years

Table 1 Basic characteristics of all patients

Overall clinical characteristics	Subgroups	All patients (%)
Age (years)	60.62 (47–72)	
	≤60	16 (45.7)
	>60	19 (54.35)
Gender	Male	35 (100)
	Female	0
Smoking	No	0
	Yes	35 (100)
Alcohol consumption	No	6 (17.1%)
	Yes	29 (82.9%)
T stage	T2	8 (22.9)
	T3 + T4	27 (77.1)
N stage	N0 + N1	19 (54.3)
	N2 + N3	16 (45.7)
cTNM	III	6 (100)
	IV_{A+B}	29 (100)
RECIST1.1	CR	12 (34.3)
	PR	15 (42.8)
	SD	8 (22.9)
	PD	0 (0)
pCR	pCR	9 (25.7)
	Non-pCR	18 (51.4)
	Non-operated	8 (22.9)

(ranging from 47 to 72 years). Specifically, 16 patients were 60 years old or younger, whereas 19 patients were older than 60 years. Every participant had a smoking history, and 29 patients reported a history of alcohol consumption. In terms of treatment outcomes, the overall objective response rate (ORR) reached 77.1%. Among those who underwent radical surgery, 33.3% of the patients achieved a pCR (Table 1).

Post-treatment NLR and PLR are negatively correlated with treatment response

We analyzed the changes in blood test parameters between pre-treatment and post-treatment. As shown in Fig. 1, ANC, ALC, APC, NLR, and PLR exhibited significant changes after the completion of the first cycle of chemoimmunotherapy.

According to the RECIST 1.1, 12 patients achieved complete response (CR), 15 patients achieved partial response (PR), 8 patients experienced stable disease (SD), and no patients developed progressive disease (PD). For all 35 patients who underwent their first TP chemotherapy combined with an anti-PD-1 inhibitor, blood routine parameters, including ANC, ALC, APC, NLR, and PLR, were analyzed both pre-treatment and post-treatment to assess their rank correlation with treatment efficacy. The analysis showed that gender, alcohol consumption, T stage, N stage, ANC1,

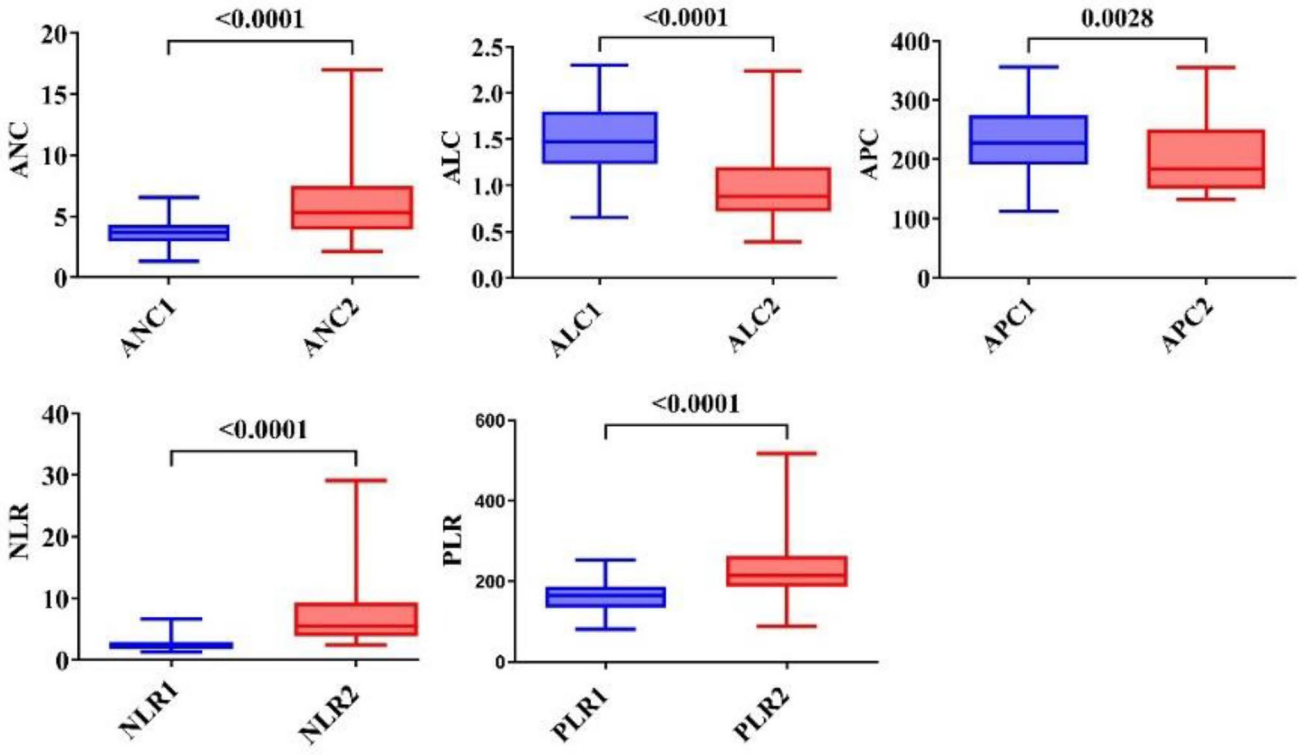

Fig. 1 Changes of peripheral blood routine between pre-treatment and post-treatment

ALC1, APC1, NLR1, and PLR1 (pre-treatment values) as well as ANC2, ALC2, and APC2 (post-treatment values) had no significant correlation with treatment response (supplement Table 1). However, post-treatment NLR2 was negatively correlated with treatment response ($r_s = -0.445$, $P = 0.007$), suggesting that higher NLR2 values were associated with poorer responses (Fig. 2). Similarly, post-treatment PLR2 was also negatively correlated with patient outcomes ($r_s = -0.474$, $P = 0.004$).

Subsequently, we separated SD and PR into one group (group $_{SD+PR}$), while CR was considered as another group (group $_{CR}$). An independent samples *t*-test showed that the mean NLR2 was significantly lower in the group $_{CR}$ (4.80) than in group $_{SD+PR}$ (8.35), with a p-value of 0.04 (Fig. 2C). Similarly, the mean PLR2 was 185.92 in the group $_{CR}$ and 251.43 in the group $_{SD+PR}$, and the mean PLR2 in the group $_{CR}$ was significantly lower than in the group $_{SD+PR}$ ($p = 0.02$) (Fig. 2D). No significant differences were observed in the mean values of ANC, ALC, APC, NLR1, or PLR1 between the two groups (Supplement Fig. 1).

ROC curves for NLR2 and PLR2 were plotted in group $_{SD+PR}$ and group $_{CR}$, respectively (Fig. 3A and B). The optimal cutoff values were determined to be 5.20 for NLR2 and 221.66 for PLR2. In the context of evaluating treatment response according to RECIST 1.1, when NLR2 and PLR2 values exceeded their respective optimal cutoffs, patients had a lower probability of achieving a CR. The area under the curve (AUC) for the NLR2 ROC curve was 0.79 (95% CI 0.62–0.95), with $p < 0.05$, indicating a moderate diagnostic value. Similarly, the AUC for the PLR2 ROC curve was 0.77 (95% CI 0.62–0.93), with $p < 0.05$, also reflecting a moderate diagnostic value.

PLR2 is negatively correlated with pathological response in HPSCC

A total of 27 patients underwent radical surgery following 3 cycles of chemoimmunotherapy. Among these patients, 9 achieved pathological complete response (pCR), whereas 18 did not (non-pCR). For both pCR and non-pCR patients, paired-sample t-tests were employed to analyze the alterations in ANC, ALC, APC, NLR, and PLR before and after treatment. The results showed significant differences in all observed parameters before and after treatment, except for APC and PLR in the pCR group (Supplement Table 2).

We analyzed the differences between peripheral blood ANC, ALC, APC, NLR, and PLR between patients who achieved pCR (pCR group) and those who did not (non-pCR group). The mean value of PLR2 was 186.99 in the pCR group and 239.24 in the non-pCR group, indicating a substantial, yet non-statistically significant difference ($p = 0.06$). Furthermore, no significant differences were observed for the other indicators (Supplement Fig. 2). The relationship between age, drinking, T stage, N stage, ANC, ALC, APC, NLR, and PLR in peripheral blood and pathological response was analyzed (Supplement Table 3). Analysis revealed that PLR2 was negatively correlated with pathological response ($r_s = -0.424$, $p = 0.028$), while the remaining indicators showed no significant correlation with pathological response. ROC curves for PLR2 and pathological response were plotted (Fig. 3C). The AUC of the ROC curve was 0.759 (95% CI 0.572–0.946), with $p = 0.03$. The optimal cutoff for PLR2 was 203, with a

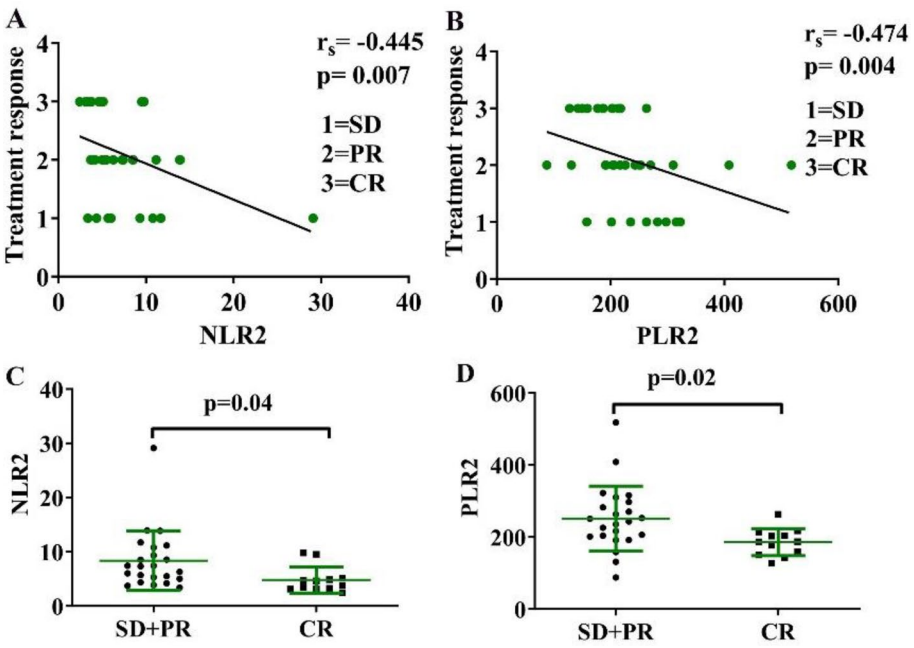

Fig. 2 NLR2 and PLR2 are negatively associated with treatment response. **A** and **B** The relationship between NLR and PLR, respectively, and treatment response assessed by RECIST 1.1. **C** and **D** Comparison of differential means of NLR2 and PLR2 between group $_{SD+PR}$ and group $_{CR}$

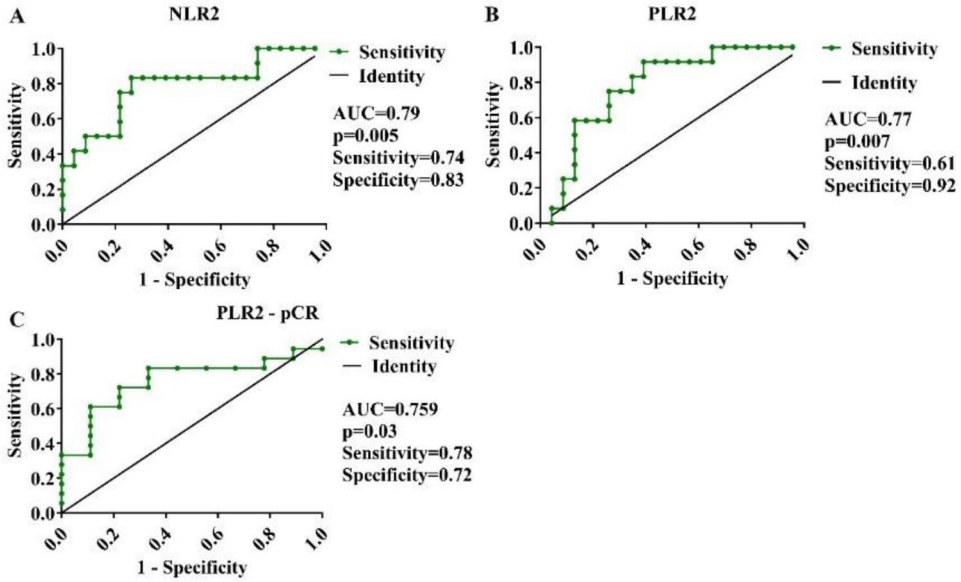

Fig. 3 ROC curves. **A** and **B**, ROC curves for NLR2 and PLR2 for treatment response assessed by RECIST 1.1. **C**, ROC curves for pCR

sensitivity of 0.78 and specificity of 0.72. These results suggest that PLR2 has moderate predictive value for identifying patients who achieve pCR after treatment.

Discussion

In this study, we investigated the relationship between treatment response and the counts of ANC, ALC, APC, NLR, and PLR in peripheral blood of patients with HPSCC who underwent neoadjuvant chemoimmunotherapy. These blood parameters were measured before and within 1 week after the first treatment. Analysis results showed that the baseline blood routine values of NLR, PLR, and other statistical indices were not associated with treatment response. Nevertheless, patients with higher NLR and PLR levels measured within 1 week after the first treatment demonstrated poorer treatment responses in terms of treatment response assessed by RECIST1.1. Moreover, routine blood measurements of NLR and PLR within 1 week after the first treatment were found to be potentially predictive of treatment response. The study also indicated that patients with a PLR > 203 after the first neoadjuvant chemoimmunotherapy had a lower likelihood of achieving pCR.

In the context of our study, we then explored the relationship between NLR, PLR, and treatment response. Interestingly, we found that baseline NLR and PLR were not correlated with treatment response. This result is consistent with the findings of a study that evaluated the association between NLR, PLR, and immunotherapy efficacy in hepatocellular carcinoma patients prior to anti-PD-1 inhibitor treatment [23]. Notably, Y. Takenaka et al. [24] reported that high pretreatment NLR was associated with poor treatment response in patients with R/M HNSCC. The observed discrepancy might be attributed to differences in gene mutations and the immune microenvironment between primary and recurrent malignancies. For example, a study on hepatocellular carcinoma discovered significant differences in the microenvironment between early recurrent and primary tumors [25].

In our study, we discovered that peripheral blood NLR2 ($r_s = -0.445$, $P = 0.007$) and PLR2 ($r_s = -0.474$, $P = 0.004$) following the first chemoimmunotherapy were negatively correlated with treatment response. Specifically, the higher the values of NLR2 and PLR2, the worse the treatment response in patients. In contrast with our findings, most previous studies have explored the relationship between peripheral blood NLR and PLR at baseline and the efficacy and prognosis of patients with various tumors [26, 27]. Additionally, some of these studies measured NLR and PLR 2–8 weeks after the completion of three cycles of immunotherapy [28, 29]. These studies have demonstrated that elevated NLR and PLR are associated with a poor prognosis in immunotherapy. An increase in NLR and PLR after treatment may reflect an elevation in neutrophils and platelets or a decline in lymphocytes. Neutrophils and platelets are associated with tumor proliferation, metastasis, and immune escape, while lymphocytes contribute to anti-tumor immunity. However, the exact mechanisms through which elevated NLR and PLR after treatment might promote tumor proliferation and metastasis while suppressing anti-tumor effects remain unclear. Some studies have indicated that patients with high NLR and PLR levels have fewer CD8 + T lymphocytes compared to those with low levels [30]. Both CD8 + T lymphocytes and PD-L1 expression are favorable indicators of good efficacy and prognosis in tumor immunotherapy. Therefore, further exploration of the relationship between

peripheral blood inflammatory cells, CD8 + T cells, PD-L1, and the underlying mechanisms may help validate the reliability of NLR and PLR as predictors of chemoimmunotherapy outcomes.

Neutrophils can have both pro-tumor and anti-tumor functions. For instance, antigen-presenting neutrophils can induce both (neo)antigen-specific and antigen-independent T cell responses, which are correlated with improved survival in many cancers [31]. In a gene-modified mouse model of lung adenocarcinoma, tumor-associated neutrophils (TANs) exhibit tumor-supportive functions and have an extended lifespan. Furthermore, researchers have found that tumor cell-derived GM-CSF induces the expression of the anti-apoptotic protein Bcl-xL, enhancing neutrophil survival through JAK/STAT signaling [32]. Bcl-xL blockade reduces TAN senescence and tumor growth in mouse models. Serum amyloid A (SAA), a peripheral inflammation-related biomarker, has been linked to anti-PD-1 resistance in hepatocellular carcinoma (HCC) [33]. Further study has shown that SAA induces neutrophils to express PD-L1 through glycolytic activation via the LDHA/STAT3 pathway and to release oncostatin M, thereby impairing cytotoxic T cell function [33]. Differences in neutrophil function are associated with their various subtypes in the tumor microenvironment. Therefore, additional studies are needed to investigate the differences in neutrophil activity between patients who respond well to immunotherapy and those who do not, as well as the underlying mechanisms.

In addition, our team was the first to discover that a higher peripheral blood PLR2, measured within 1 week after the first chemoimmunotherapy, was associated with a lower likelihood of achieving pCR ($r_s = -0.424$, $p = 0.028$), which suggests that post-treatment peripheral blood PLR is a possible predictor of achieving pCR. This study revealed that post-treatment PLR was elevated in both patients who achieved pCR and those who did not. However, post-treatment PLR was not significantly elevated in the pCR group ($p = 0.14$), whereas it was significantly elevated in the non-pCR group ($p < 0.001$). Platelets play a crucial role in tumor metastasis, and a significant elevation in PLR after treatment may indicate an increased risk of promoting tumor metastasis [34]. Therefore, **further exploration of the underlying mechanisms** may provide insights for predicting tumor treatment responses and optimizing treatment strategies.

However, the present study has several limitations. First, as a single-center study, it only included HPSCC patients with a small sample size. This reduces statistical power and limits representativeness. To address this, future research should expand the sample size, involve multiple centers, and include other HNSCC types for validation and more comprehensive analysis. Second, relying on retrospective data analysis may introduce bias due to incomplete records, recall issues, and confounding factors. **Well-designed multicenter prospective studies** are needed to obtain more reliable results, minimizing these potential biases. Third, the underlying molecular mechanisms and immune features remain largely unexplored. A deeper understanding of these aspects is crucial for uncovering novel therapeutic targets. A multicenter, large-sample prospective studies both involves in clinical and basic study are needed. Despite these limitations, our study offers a potential simple, cost-effective, non-invasive method for early prediction of treatment response in HPSCC patients receiving TP chemotherapy and anti-PD-1 immunotherapy. This can assist in personalized treatment decisions and improve patient outcomes.

In summary, our study found that peripheral blood NLR and PLR following the first cycle of TP chemotherapy combined with anti-PD-1 immunotherapy for primary HPSCC hold promise as factors for predicting treatment response and pathological remission, demonstrating moderate predictive value. High NLR or PLR values might signal an inflammatory or imbalanced immune state, prompting treatment plan adjustments, like dosage modification or treatment option changes. This offers an early-stage, non-invasive biomarkers and straightforward approach for both patients and clinicians to identify suitable candidates for chemoimmunotherapy or to have a dosage modification or treatment option changes in time. Nevertheless, further multicenter prospective studies are essential. These studies should aim to comprehensively assess the accuracy of NLR and PLR as response biomarkers in chemoimmunotherapy and to thoroughly explore the underlying molecular mechanisms specific to HPSCC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-025-01675-2.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Shi Yueyue. Tumor stage and treatment response were evaluated by Zhao Xueyan, Zhou Yan, and Zhang Xiaomeng. The first draft of the manuscript was written by Zhang Xiaomeng, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflicts of interest The authors declare no competing interests.

Ethics approval This study was approved by the Ethics Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China (Date 2023/ No 0089).

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