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ORIGINAL RESEARCH

Prognostic Study of Inflammatory Markers in Nasopharyngeal Carcinoma Patients Receiving Intensity-Modulated Radiotherapy

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Purpose: Inflammatory markers in the blood have been linked to tumor prognosis, but their specific prognostic significance in nasopharyngeal carcinoma (NPC) patients undergoing intensity-modulated radiotherapy (IMRT) is not well established. This study aims to evaluate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) in this patient population.

Patients and Methods: A total of 406 non-metastatic NPC patients were included in the study. NLR, PLR, and LMR were stratified according to their average values. The Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Cox multivariate regression analysis was performed to evaluate the associations of NLR, PLR, and LMR with PFS and OS.

Results: Patients with NLR > 2.78 had worse PFS (P = 0.008) and OS (P < 0.001); PLR > 162.48 was related to lower PFS (P = 0.018) but not OS (P = 0.29); LMR > 5.05 showed no significant difference in PFS and OS compared to LMR ≤ 5.05 (P values were 0.13 and 0.94, respectively). Multivariate analysis indicated that NLR was an independent prognostic factor for PFS (HR, 1.674; 95% CI, 1.006–2.784; P = 0.047) and OS (HR, 4.143; 95% CI, 2.111–8.129; P = 0.000), while PLR and LMR did not demonstrate significant associations with PFS and OS.

Conclusion: This study identifies NLR as a novel and independent prognostic indicator for NPC patients receiving IMRT, offering valuable insights that could inform future clinical decision-making. In contrast, PLR and LMR did not demonstrate significant prognostic value in this context.

Keywords: nasopharyngeal carcinoma, inflammatory markers, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphocyte to monocyte ratio, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant epithelial tumor of the head and neck, with distinct geographical and ethnic distribution differences. The treatment of NPC requires a multidisciplinary team, including surgery, radiotherapy, and chemotherapy, to provide patients with more precise personalized treatment.[1] The choice of treatment depends on the location of the tumor and the stage of the disease.[2] Given the complexity of the anatomical location, surgery alone cannot cure NPC. The combined use of radiotherapy and chemotherapy has increased the cure rate for NPC. Additionally, targeted therapy or immunotherapy has also improved treatment outcomes for some NPC patients.[3] However, 10–20% of patients still experience recurrence, with a 5-year survival rate of only 27.5% to 57.2% following re-irradiation in cases of recurrent NPC.[4] The limitations of the traditional TNM staging system in the prognosis of NPC have become increasingly evident,[5] highlighting the urgent need to identify new predictive factors to distinguish high-risk populations for recurrence.

The relationship between inflammation and tumors is gaining increasing research attention. Initially observed in wounds and infections, inflammation is characterized by changes in blood vessels, the release of chemicals, and the accumulation of inflammatory cells.[6] Subsequent research has shown a close connection between inflammation and tumor development.[7,8] Tumor cells and stromal cells together constitute the tumor microenvironment. Inflammatory cells, including neutrophils, create

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a unique inflammatory microenvironment by releasing inflammatory mediators, which may play a role at different stages of tumor development.[9,10] Inflammation-induced changes in blood parameters represent a systemic manifestation of cancer.[11] Due to the minimally invasive nature, low cost, and easy accessibility of blood indicators, increasing research is focusing on analyzing the value of blood inflammatory cells in the prognosis of malignant tumors.

Neutrophils are the most abundant inflammatory cells in the blood. In addition to neutrophils, inflammatory cells in the blood also include lymphocytes, monocytes, and platelets. Studies have found that an increased neutrophil-to-lymphocyte ratio (NLR) is associated with poor prognosis in head and neck tumors.[12,13] Additionally, according to literature reports, the platelet-to-lymphocyte ratio (PLR) and the lymphocyte-to-monocyte ratio (LMR) are also associated with the prognosis of certain malignant tumors.[14,15] However, comprehensive analysis of the above-mentioned blood inflammatory markers in NPC remains limited. Therefore, we conducted this retrospective study to determine their prognostic value in NPC, providing a basis for future clinical decisions involving patient risk stratification and personalized treatment implementation.

Materials and Methods

The present study design followed the international regulations based on the Declaration of Helsinki and was approved by the Ethics Committee of the Longyan First Affiliated Hospital of Fujian Medical University (LYREC2023-k091-01). Consent from patients was waived owing to the retrospective study nature.

Study Populations

This study enrolled patients with NPC who were diagnosed and treated at our hospital from January 2012 to December 2021. The inclusion criteria were: (1) pathologically confirmed NPC; (2) treatment with intensity-modulated radiation therapy (IMRT); (3) completion of the entire treatment protocol. The exclusion criteria were: (1) Patients with a history of other malignancies who have received anti-tumor treatments such as radiotherapy and chemotherapy; (2) severe liver or kidney dysfunction; (3) distant metastasis at initial diagnosis.

Treatment Methods

All patients received definitive IMRT, targeting the nasopharyngeal tumor and neck metastatic lymph nodes (GTV), the subclinical lesion region (CTV1), and the lymph drainage area (CTV2). The prescribed doses were 68–69.3 Gy for GTV over 30–33 fractions, 60 Gy for CTV1, and 54 Gy for CTV2. Post-radiotherapy MRI was conducted to identify any residual lesions, and an additional dose was given required. For patients with stage II or higher, initial treatment involved platinum-based dual-agent chemotherapy followed by concurrent chemoradiotherapy, using a chemotherapy regimen of either cisplatin or nedaplatin. During radiotherapy, weekly blood tests were conducted to monitor and assess any treatment-related complications.

Follow-Up and Statistical Analysis

After completing treatment, patients regularly returned to the hospital for follow-up examinations, including nasopharyngeal and cervical MRI, chest CT, and abdominal ultrasound. Clinical and pathological characteristics (including age, tumor stage, radiation dose, pathological type, etc) and hematological indicators (including pre-treatment neutrophil count, lymphocyte count, platelet count, and monocyte count) were collected. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were calculated and stratified based on their mean values. The primary endpoint was progression-free survival (PFS), defined as the period from diagnosis to tumor recurrence, metastasis, or death from any cause. The secondary endpoint was overall survival (OS), defined as the period from diagnosis to death from any cause.

Statistical analyses were performed using SPSS 25.0 and R 4.0.5. The Kaplan-Meier method was used to calculate PFS and OS, and differences were assessed using the Log−rank test. Hematological indices, including NLR, PLR, and LMR, were converted into categorical variables for analysis based on their mean values. A multivariate prognosis analysis was performed using the Cox proportional hazards model, calculating hazard ratios (HR) and 95% confidence intervals (95% CI) to determine the relationship between hematological markers and PFS and OS. A two-sided p-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

This study included 406 patients with NPC, comprising 299 males (73.6%) and 107 females (26.4%), with a median age of 51 years (range 20–85 years). The majority of patients had non-keratinizing undifferentiated carcinoma. Patients were restaged according to the 8th edition of the AJCC (American Joint Committee on Cancer) staging standards, with 80.3% classified as having locally advanced NPC, as detailed in Table 1. Based on pre-treatment blood counts of neutrophils, platelets, lymphocytes, and monocytes, the average NLR was 2.78, PLR was 162.48, and LMR was 5.05.

Survival Outcomes

As of the last follow-up date on October 30, 2023, the median follow-up duration in this study was 58.3 months (range 2.5–154.7 months). A total of 71 patients (17.5%) experienced tumor recurrence or distant metastasis, and 42 patients (10.3%) died. The overall 5-year progression-free survival (PFS) rate was 80.8%, and the 5-year overall survival (OS) rate was 90.9%. For patients with NLR ≤2.78 and >2.78, the 5-year PFS rates were 83.3% and 77.0%, respectively (P<0.01), and the 5-year OS rates were 94.8% and 84.9%, respectively (P<0.01) (Figure 1). Patients with PLR ≤162.48 had a 5-year PFS of 83.2% versus 77.6% for those

Table 1 Baseline Characteristics of 406 Patients with Nasopharyngeal Carcinoma

Characteristic	Grouping	No. (%)
Gender	Female	107 (26.4)
	Male	299 (73.6)
Age(y)	≤51	204 (50.2)
	>51	202 (49.8)
Pathology	WHO type I	13 (3.2)
	WHO type II–III	393 (96.8)
T category	T1-2	186 (45.8)
	T3-4	220 (54.2)
N category	N0-1	159 (39.2)
	N2-3	247 (60.8)
Overall stage	I–II	80 (19.7)
	III–IV	326 (80.3)
Radiation dose	≤68Gy	138 (34.0)
	>68Gy	268 (66.0)
NLR	≤2.78	247 (60.8)
	>2.78	159 (39.2)
PLR	≤162.48	235 (57.9)
	>162.48	171 (42.1)
LMR	≤5.05	273 (67.2)
	>5.05	133 (32.8)

Abbreviations: NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

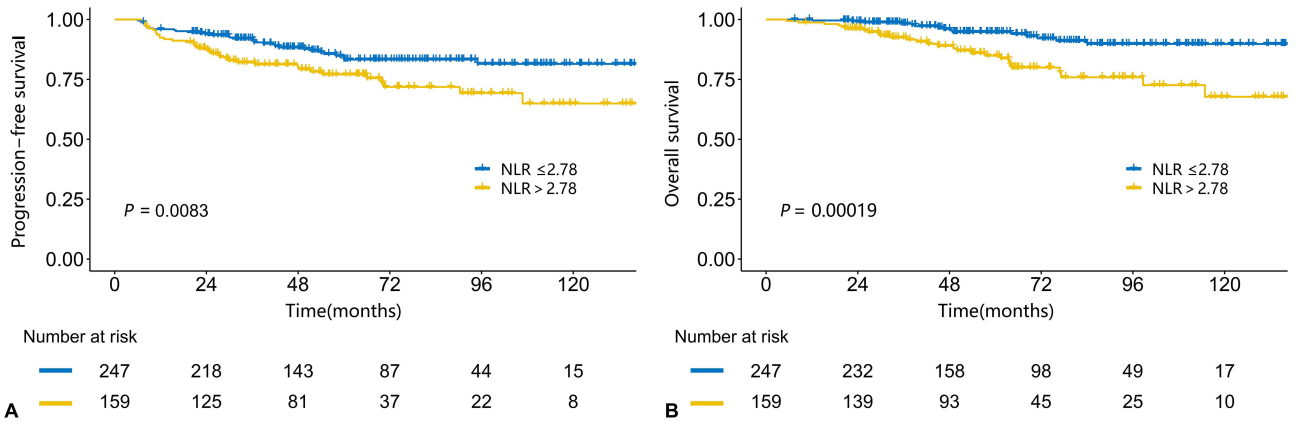

Figure 1 Kaplan-Meier curves for progression-free survival (**A**) and overall survival (**B**) of patients with nasopharyngeal carcinoma based on neutrophil−to−lymphocyte ratio (NLR).

with PLR >162.48 (P=0.018), and the 5-year OS rates were 91.2% and 90.5%, respectively (P=0.29) (Figure 2). For patients with LMR ≤5.05 and >5.05, the 5-year PFS rates were 79.3% and 83.9%, respectively (P=0.13), and the 5-year OS rates were 89.9% and 93.0%, respectively (P=0.94) (Figure 3).

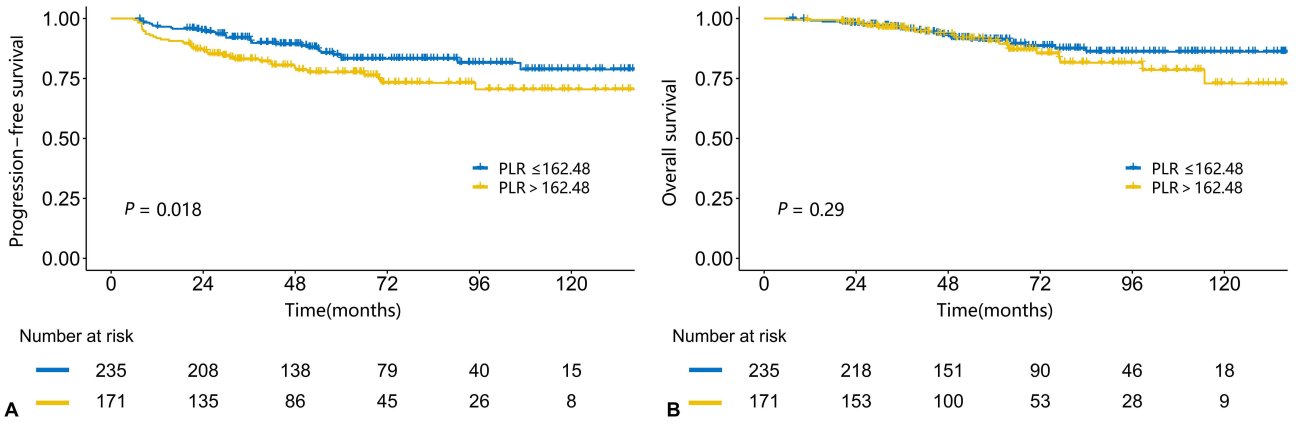

Figure 2 Kaplan-Meier curves for progression-free survival (**A**) and overall survival (**B**) of patients with nasopharyngeal carcinoma based on platelet−to−lymphocyte ratio (PLR).

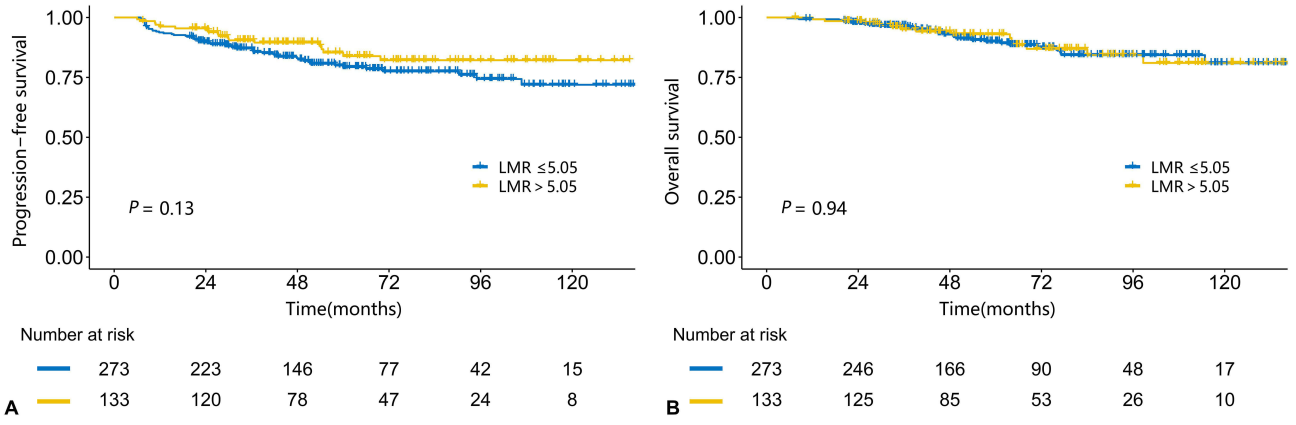

Figure 3 Kaplan-Meier curves for progression-free survival (**A**) and overall survival (**B**) of patients with nasopharyngeal carcinoma based on lymphocyte-to-monocyte ratio (LMR).

Prognostic Analysis

Univariate analysis revealed that an NLR > 2.78 correlated with decreased PFS (HR, 1.854; 95% CI, 1.163–2.955; P = 0.009) and OS (HR, 3.135; 95% CI, 1.666–5.898; P = 0.000). A higher PLR (>162.48) suggested a reduced PFS (HR, 1.743; 95% CI, 1.093–2.780; P = 0.020); however, it did not reach statistical significance for OS. No significant associations were observed between LMR and either PFS or OS, as detailed in Table 2.

After adjusting for factors such as age, gender, and tumor staging in multivariate analysis, only NLR emerged as an independent prognostic factor for both PFS (HR, 1.674; 95% CI, 1.006–2.784; P = 0.047) and OS (HR, 4.143; 95% CI, 2.111–8.129; P = 0.000), while PLR and LMR did not show statistical significance. Additionally, T stage (HR, 1.808; 95% CI, 1.089–3.003; P = 0.022) and N stage (HR, 1.980; 95% CI, 1.157–3.389; P = 0.013) were also independent prognostic factors for PFS, and age (HR, 8.718; 95% CI, 3.642–20.873; P = 0.000) was an independent prognostic factor for OS, as detailed in Table 3.

Subgroup Analysis

Of the 326 patients (80.3%) with locally advanced NPC, univariate analysis showed that high NLR and low LMR were correlated with lower PFS (P values of 0.002 and 0.043, respectively). Moreover, a high NLR significantly correlated with reduced OS (P = 0.007), but PLR and LMR did not show significant correlations with OS. Multivariate analysis indicated that NLR independently predicts PFS (HR, 1.870; 95% CI, 1.084–3.225; P = 0.024) and OS (HR, 3.344; 95% CI, 1.621–6.898; P = 0.001), whereas PLR and LMR showed no significant relationships with PFS or OS.

Table 2 Outcomes of Univariate Analysis

Variable	Progression-free survival		Overall survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (male vs female)	0.956(0.570–1.604)	0.864	1.092(0.548–2.174)	0.803
Age (>51y vs ≤51y)	1.422(0.890–2.272)	0.141	7.801(3.282–18.540)	0.000
T category (T3-4 vs T1-2)	2.026(1.231–3.333)	0.005	1.554(0.833–2.900)	0.166
N category (N2-3 vs N0-1)	1.969(1.154–3.362)	0.013	1.105(0.588–2.078)	0.757
Radiation dose (>68Gy vs ≤68Gy)	0.835(0.518–1.346)	0.459	0.671(0.358–1.260)	0.215
NLR (>2.78 vs ≤2.78)	1.854(1.163–2.955)	0.009	3.135(1.666–5.898)	0.000
PLR (>162.48 vs ≤162.48)	1.743(1.093–2.780)	0.020	1.388(0.757–2.544)	0.289
LMR (>5.05 vs ≤5.05)	0.661(0.387–1.128)	0.129	0.975(0.513–1.852)	0.938

Abbreviations: NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

Table 3 Multivariate Analysis of Prognostic Factors for NPC Patients

Endpoint	Variable	HR (95% CI)	*P*
PFS	T category (T3-4 vs T1-2)	1.808 (1.089–3.003)	0.022
	N category (N2-3 vs N0-1)	1.980 (1.157–3.389)	0.013
	NLR (>2.78 vs ≤2.78)	1.674 (1.006–2.784)	0.047
OS	Age (>51y vs ≤51y)	8.718 (3.642–20.873)	0.000
	NLR (>2.78 vs ≤2.78)	4.143 (2.111–8.129)	0.000

Abbreviations: NPC, nasopharyngeal carcinoma; PFS, progression-free survival; OS, overall survival; NLR, neutrophil–to–lymphocyte ratio.

Discussion

It is commonly accepted that inflammation plays a critical role in cancer development. Tumor cells interact with non-cancer cells in the extracellular matrix, such as inflammatory and immune cells, to secrete inflammatory factors, creating a unique tumor inflammatory microenvironment that significantly influences the malignancy of the tumor.[16] Inflammatory cells in the blood include neutrophils, lymphocytes, and monocytes. This study comprehensively assessed the prognostic significance of the NLR, PLR, and LMR in NPC patients. The results showed that patients with a high NLR have worse PFS and OS, with an NLR > 2.78 being an independent prognostic factor for both PFS and OS in patients with NPC. For patients with a PLR > 162.48, a significant decrease in PFS was observed, though this significance was not evident in multivariate analysis. Additionally, LMR showed no association with PFS or OS.

Inflammatory cells in the blood affect the occurrence and progression of tumors through various pathways.[17,18] Compared to single blood cells, composite blood inflammatory parameters have higher sensitivity and stability, making them more suitable as prognostic factors. Jiang et al's study analyzed 618 patients with locally advanced NPC treated with IMRT. Using the X-tile program, the NLR cutoff was set at 2.7, showing correlations with PFS and OS, but unfortunately, no significant associations were found in multivariate analysis.[19] In a multicenter cohort study that enrolled 1102 patients with non-metastatic NPC, it was found that patients with an NLR ≥ 3 had significantly lower OS compared to those with an NLR < 3.[20] However, the study did not report on the relationship between NLR and disease progression. Given that patients with NPC generally have long survival periods, this indicator of disease progression is also of significant value. Song et al[21] analyzed 111 patients with untreated non-metastatic NPC, obtaining an optimal NLR cutoff value of 2.02 via the receiver operating characteristic (ROC) curve. The results showed that the low NLR group had mortality and tumor progression rates of 20.6% and 32.4%, respectively, whereas the high NLR group had rates of 55.8% and 62.3%, both reaching statistical significance. Multivariate analysis indicated that NLR is an independent prognostic factor for OS, but not significantly for PFS, possibly due to the small sample size of the study. Liao et al[22] conducted a retrospective analysis of 180 patients with NPC, dividing them into high and low NLR groups based on the average value. The study found significantly lower rates of progression-free survival, overall survival, and disease-specific survival in the high NLR group. In another retrospective analysis involving patients with locally advanced NPC, researchers divided NLR at a cutoff of 7.05 based on the ROC curve. Multivariate analysis showed that NLR > 7.05 is a poor prognostic factor for OS, with PFS approaching statistical significance.[23] It should be noted that the NLR cutoff value of 7.05 in this study differs significantly from the range reported in current literature (2 to 5). In our study, only about 1.7% of patients had an NLR > 7.05, thus, caution is needed regarding the clinical significance of these results. In this study, we analyzed 406 patients with non-metastatic NPC, dividing them based on the average NLR value into two groups. The findings indicate that patients with an NLR > 2.78 had significantly worse PFS and OS compared to those with NLR ≤ 2.78. Multivariate analysis confirmed NLR as an independent prognostic factor for both PFS and OS, similar to other reported results.[22,24,25] However, our study had a larger sample size and a sufficiently long follow-up period. After adjusting for age and tumor stage, the results still indicated that NLR is an independent prognostic factor for NPC, providing a prognostic factor beyond TNM staging in clinical decision-making for NPC.

The PLR is another promising blood inflammatory composite marker for tumor prognosis. A single-center retrospective study analyzed the prognostic value of PLR in NPC, finding that patients with PLR > 203.3 had significantly lower three-year overall survival rates, local recurrence-free survival rates, and distant metastasis-free survival rates compared to those with PLR < 203.3.[26] Peng et al carried out a large retrospective study with 1661 patients, where multivariate regression analysis revealed PLR as an independent prognostic factor for both PFS and OS.[27] Li et al[24] analyzed 342 NPC patients undergoing intensity-modulated radiation therapy, determining an optimal PLR cutoff of 184.91 via the ROC curve. Results showed that higher PLR groups had worse PFS and OS, but PLR was not an independent prognostic factor for PFS and OS in multivariate analysis. In our study, patients with PLR > 162.48 had significantly lower PFS compared to those with PLR ≤ 162.48, but the OS was similar between the two groups. Additionally, PLR did not achieve significance for PFS or OS in multivariate analysis, which aligns with other research findings,[28,29] suggesting that further research is needed to establish PLR as a prognostic marker for NPC.

There is limited reporting on the prognostic significance of the LMR in NPC. Chen et al reported that patients with a low LMR had worse distant metastasis-free survival than those with high LMR, but there were no significant differences in overall survival or local recurrence-free survival between the groups.[30] The study's limitation was its small sample size, involving only 216 patients. In this study, no differences in PFS or OS were observed between groups with LMR > 5.05 and ≤ 5.05, and LMR was not an independent prognostic factor for PFS or OS, consistent with some reports.[21,31] Only in a subgroup analysis did patients with

locally advanced NPC and an LMR > 5.05 show better PFS than those with an LMR ≤ 5.05, indicating that LMR as a prognostic marker for NPC still requires more evidence.

While blood inflammation markers have significant potential in cancer prognosis, their limitations should not be overlooked. These blood inflammation markers do not have internationally recognized thresholds, and researchers often determine cutoff values based on the characteristics of their own data. A commonly used method in studies is based on the receiver operating characteristic curve (ROC). It's important to note the limitations of the ROC curve, such as its capacity to handle censored data, time-dependency, and potential for information loss, which constrain its usefulness.[32] Moreover, using ROC to optimize cutoff points can lead to biased or overly ideal results. For instance, in some studies, researchers used the ROC curve to determine optimal cutoffs for patient stratification. While this showed survival rate differences between groups, the uneven distribution of patients across these groups significantly diminishes the clinical significance. Thus, establishing standardized levels for blood inflammation markers is particularly important.

It should be noted that this study has certain limitations: First, as a retrospective analysis with all samples coming from a single institution, selection bias is inevitable Secondly, according to recent literature, the blood biomarker EB-DNA is an important prognostic factor for NPC. Since EB-DNA was not a routine test for NPC in the past, this study did not include EB-DNA in the analysis. Therefore, our study results still need to be further confirmed by multi-center prospective studies.

Conclusion

In summary, our analysis of the NLR, PLR, and LMR in NPC prognosis found that patients with NLR > 2.78 have significantly lower PFS and OS than those with NLR ≤ 2.78. Therefore, an NLR > 2.78 can be considered an adverse prognostic factor for PFS and OS in patients with NPC, while PLR and LMR are not significant prognostic factors for PFS and OS.

Data Confidentiality

All patient data used in this study were de-identified to ensure confidentiality. The data were collected and analyzed in a manner that fully protects the privacy of the patients. No identifiable information was used, and all analyses were performed on anonymized datasets to maintain strict confidentiality in compliance with ethical guidelines.

Ethical Statement

The present study design followed the international regulations based on the Declaration of Helsinki and was approved by the Ethics Committee of the Longyan First Affiliated Hospital of Fujian Medical University (LYREC2023-k091-01).

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Disclosure

The authors declare that they have no competing interests.

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