Prognostic value of pre- and post-treatment neutrophil-to-lymphocyte, platelet-to-lymphocyte and lymphocyte-to-monocyte ratios in nasopharyngeal carcinoma

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Received January 27, 2026; Accepted July 9, 2026

DOI: 10.3892/mco.2026.2968

Abstract. Blood cell count ratios are useful prognostic indicators in cancer. The present retrospective study evaluated the levels of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) across different treatment phases and their potential prognostic value in nasopharyngeal carcinoma. A total of 99 patients were treated with induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT). Biomarkers were assessed at three separate time points: Pre-IC, pre-CCRT and post-radiation therapy (RT). Results indicated that the NLR and PLR values were higher, while the LMR values were lower at later chronological time points, particularly post-RT. Post-RT, higher NLR and PLR levels and a lower LMR level were observed in non-survivors. Being ≥60 years old was associated with lower odds of elevated PLR post-RT and experiencing weight loss ≥7.5% predicted increased NLR post-RT. Elevated pre-IC and post-RT PLR was associated with reduced 5-year overall survival. Multivariate analysis, although limited by the small number of events (n=15), identified PLR pre-IC and advanced nodal stage (N3) as independent mortality predictors. PLR pre-IC and N3 stage may therefore serve as preliminary independent predictors of poor prognosis, supporting the use of inflammatory biomarkers for risk stratification. Despite this, prospective external validation in larger cohorts is required.

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Abbreviations: CCRT, concurrent chemoradiotherapy; HR, hazard ratio; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; LMR, lymphocyte-to-monocyte ratio; NPC, nasopharyngeal carcinoma; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; TME, tumor microenvironment

Key words: nasopharyngeal carcinoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, prognosis

Introduction

The incidence of nasopharyngeal carcinoma (NPC), a head and neck malignancy for which >76% of cases are concentrated in East and Southeast Asia, remains high in Taiwan and Eastern China (1). The pathogenesis of NPC, which arises from the epithelial cells in the nasopharynx situated behind the nasal cavity adjacent to the oropharynx, is attributed to a number of factors, including environmental factors, hereditary susceptibility and Epstein-Barr virus (EBV) infection (2). Owing to the deep-seated anatomical position of this carcinoma, surgical resection is technically challenging and chemoradiotherapy is the primary treatment modality. The majority of NPCs are histologically classified as non-keratinizing undifferentiated carcinomas that are highly sensitive to chemoradiotherapy; thus, favorable treatment outcomes can be achieved. Recent progress in radiotherapy, particularly the widespread adoption of intensity-modulated radiotherapy (IMRT) (3), has improved the prognosis of patients with NPC. Combined modality treatment involving induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT) has further improved the 5-year overall survival (OS) rate to 85-90% (4,5) specifically within these endemic regions of Taiwan and Southern China.

Treatment failure in NPC is primarily driven by the persistent risk of distant metastasis and local relapse. In addition, the fact that patients with identical TNM stages may experience considerably different clinical trajectories reflects the underlying biological diversity of the disease. Previously, researchers have

begun to increasingly emphasize the effects of the tumor microenvironment (TME), inflammatory status and immune modulation on tumor behavior and metastatic potential (6,7). Components of the TME, including stromal and immune cells, extracellular structures and vascular networks, intricately interact with tumor cells and are closely linked to angiogenesis and tumor expansion. Inflammatory cells, such as neutrophils, monocytes and platelets, contribute to numerous oncogenic processes, including immune suppression, angiogenesis and metastasis (8-13).

Inflammatory biomarkers derived from standard hematological tests are being recognized for their prognostic relevance. Ratios such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are associated with clinical outcomes in certain malignancies, including non-small cell lung cancer, breast cancer and gastric cancer, as well as NPC, offering insights into the balance between systemic inflammation and host immunity. Despite this, prior investigations have largely focused on pre-treatment levels, while the prognostic impact of these ratios when measured at subsequent treatment phases remains insufficiently characterized (14,15). Therefore, the present study aimed to determine whether NLR, LMR and PLR measured across different treatment phases could predict outcomes in NPC and whether the biomarker levels at these specific time points were associated with OS.

Materials and methods

Study population. The present study was conducted at Chi Mei Medical Center (Tainan, Taiwan). Data was retrospectively collected from the Center's cancer registry database covering the period from January 2012 to December 2022. The treatment protocol followed a prospective regimen of IC followed by CCRT. Patients aged 25-84 years were included and disease staging was based on the American Joint Committee on Cancer TNM classification, 8th edition (16). The present study involved patients who met the following inclusion criteria: i) Histopathologically confirmed NPC; and ii) complete blood sample data available, including samples collected within 3 days before the start of IC (pre-IC), within 3 days before the start of CCRT (pre-CCRT) and within 1 week after the completion of radiotherapy (post-RT). The exclusion criteria were as follows: i) Patients who had not received induction chemotherapy (IC) and lacked pre-IC baseline hematological data (n=26; Fig. 1); and ii) patients with a history of other malignancies, hematologic disorders, active infections or febrile illness at baseline.

Treatment. All patients with NPC received IC followed by definitive CCRT. Radiotherapy was administered using the IMRT technique. The IC and CCRT protocols were implemented according to established clinical guidelines in Taiwan and China (17-19). The IC regimen followed the TPF protocol, comprising docetaxel (60-75 mg/m^2), cisplatin (50-75 mg/m^2) and 5-fluorouracil (600-1,000 mg/m^2/day), administered every 3 weeks for two or three cycles. Following IC, the patients underwent definitive radiotherapy concurrently with cisplatin (100 mg/m^2), administered every 3 weeks for two cycles.

All patients underwent either IMRT or tomotherapy at Chi Mei Medical Center. For radiotherapy, the radiation dose for the gross tumor volume in the nasopharynx and involved cervical lymph nodes was 70-72 Gy. The first clinical target volume was treated with a radiation dose of ~60 Gy, and the second clinical target volume was treated with 45-54 Gy. Conventional fractionation was performed with daily doses of 1.80 and 2.12 Gy. Concurrent cisplatin chemotherapy was administered at 100 mg/m^2 every 3 weeks for a total of two cycles, as previously described (20).

Measurements. Information regarding patient characteristics, including age, sex, histological type, disease stage, weight changes before and after treatment and treatment modalities (including radiotherapy prescription and chemotherapy regimen), was collected from the registry database. Complete blood count data were obtained at three specific time points: i) Pre-IC; ii) pre-CCRT and; iii) post-RT. NLR, PLR and LMR were calculated at each time point.

Blood specimens (3 ml per collection) were collected in plastic vacuum tubes and analyzed using a Sysmex XR-9000 fully automated hematology analyzer (Sysmex Corporation) to obtain information on routine hematological parameters, including absolute neutrophil, lymphocyte, monocyte and platelet counts. Based on these values, the following hemogram ratios were calculated: i) NLR=neutrophil count/lymphocyte count; ii) PLR=platelet count/lymphocyte count and; iii) LMR=lymphocyte count/monocyte count.

Receiver operating characteristic (ROC) curve analysis was conducted to examine the prognostic utility of the nine inflammatory markers (including NLR, PLR and LMR pre-IC, pre-CCRT and post-RT) and determine the optimal cut-off values for predicting survival outcomes.

Statistical analysis. Descriptive statistics are presented as frequencies and percentages for categorical variables and as the mean ± SD for continuous variables. A two-sided significance (α) level of 0.05 was predefined, and exact P-values are reported for all statistical tests. Comparisons of hematological biomarkers, including NLR, PLR and LMR, across the three time points (pre-IC, pre-CCRT and post-RT), were conducted using one-way repeated-measures ANOVA since these measurements were obtained from the same patients. When the overall repeated-measures ANOVA exhibited a statistically significant difference, post hoc pairwise comparisons were performed using the Bonferroni correction. Independent samples t-tests were used to compare NLR, PLR and LMR between the survivor and non-survivor groups at the three time points. Variables with significant differences ($P<0.05$) were analyzed using binary logistic regression to investigate their association with mortality. Additional covariates included in the regression model were patient characteristics, such as sex, age, cancer stage, weight loss percentage and pretreatment EBV status (classified as positive, negative or missing).

The χ^2 test was used to compare survival status (alive vs. deceased) across categorical variables. Optimal cutoff values for NLR, PLR and LMR at each treatment phase were determined using ROC curve analysis based on the maximum Youden index, with diagnostic metrics detailed in Table SI. Kaplan-Meier analysis was used to estimate survival probabilities, and the log-rank test was used to evaluate differences between survival curves. OS was defined as the period from confirmed diagnosis

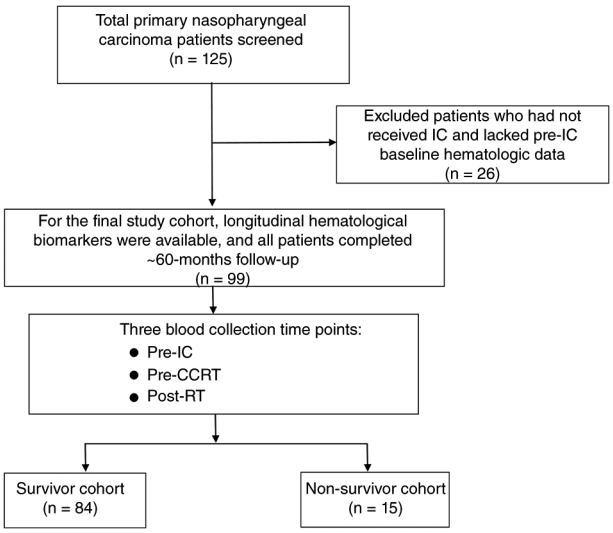

Figure 1. Patient selection flowchart. IC, induction chemotherapy; CCT concurrent chemoradiotherapy, RT; radiation therapy.

to mortality or the last follow-up. Cox proportional hazards modeling was performed to explore survival determinants. Owing to the limited number of mortality events, the multivariable model was restricted to variables that were statistically significant in the univariate analysis (P<0.05) to reduce the risk of overfitting and unstable estimates. To address small-sample bias, Firth's penalized likelihood correction was applied in both univariate and multivariable Cox regression analyses. In addition, to evaluate the robustness of the present findings and address potential information loss from dichotomization, sensitivity analyses were performed by treating inflammatory biomarkers as continuous variables in the Cox regression models (Table SII). All analyses were performed using SPSS (version 25.0; IBM Corp.) P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics describe the study cohort. A total of 125 patients with histologically determined NPC were initially screened for eligibility. Of these, 26 patients were excluded as they did not receive IC and lacked the required pre-IC baseline hematologic data. Ultimately, a final cohort of 99 patients met all inclusion criteria and were enrolled in the present retrospective analysis (Fig. 1). Complete data regarding histology, clinical characteristics and follow-up were available for all patients. The demographic and clinical details of the patients are summarized in Table I. The present study comprised 76 male (76.8%) and 23 female patients (23.2%). The average patient age was 50 (range: 25-84) years. Among the patients, 1 (1.0%) had stage I, 12 (12.1%) had stage II, 38 (38.4%) had stage III and 48 (48.5%) had stage IV disease. With regard to pre-treatment viral load, EBV status was detected in 52 patients (52.5%), undetected in 20 (20.2%) and remained unknown in 27 (27.3%). All patients received at least two cycles of IC, followed by definitive CCRT. The median follow-up period was 60 (range: 11-209) months. During the follow-up period, 11 patients experienced local recurrence, 10 had distant metastases and 15 were deceased. The overall 5-year OS rate for the entire cohort was 84.8%.

Table I. Patient characteristics (n=99).

Characteristic	Patients, n (%)
Age, median (range) years	50 (25-84)
Age, years	
<60	76 (76.8)
≥60	23 (23.2)
Sex	
Male	76 (76.8)
Female	23 (23.2)
Tumor classification	
T1	25 (25.3)
T2	20 (20.2)
T3	30 (30.3)
T4	24 (24.2)
Nodal classification	
N0	3 (3.0)
N1	16 (16.2)
N2	51 (51.5)
N3	29 (29.3)
AJCC clinical stage[a]	
I	1 (1.0)
II	12 (12.1)
III	38 (38.4)
IV	48 (48.5)
Treatment	
Induction chemotherapy + CCRT	99 (100.0)
RT, Gy	
<70	9 (9.1)
≥70	90 (90.9)
KPS	
<80	25 (25.3)
≥80	74 (74.7)
Pre-treatment EBV status	
Undetected	20 (20.2)
Detected	52 (52.5)
Unknown	27 (27.3)
Median weight loss, %	
During RT (<7.5)	42 (42.4)
During RT (≥7.5)	57 (57.6)

[a]AJCC Staging Manual, 8th edition. AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; EBV, Epstein-Barr virus; KPS, Karnofsky Performance Scale; RT, radiation therapy.

ROC curve-derived cutoff values across the three treatment phases. Optimal pre-IC cut-off values used to stratify patients with NPC into high- and low-level groups were as follows: i) NLR=4.02; ii) PLR=248.67 and; iii) LMR=3.17. These thresholds effectively differentiated patients with poorer vs.

Table II. Comparison of hematological biomarkers measured at three separate treatment phases (pre-IC, pre-CCRT and post-RT).

Hematological marker	Pre-IC (n=99)			Pre-CCRT (n=99)			Post-RT (n=99)			Multiple comparison P-value
	Mean	SD	P-value[a]	Mean	SD	P-value[a]	Mean	SD	P-value[a]	
NLR										
Overall cohort	3.31	3.29		3.93	10.60		10.74	11.13		<0.001[b,c]
Survivors	3.35	3.53	0.62	4.20	11.49	0.17	9.84	10.68	0.05	<0.001[b,c]
Non-survivors	3.09	1.29		2.42	1.11		15.76	13.49		<0.001[b,c]
PLR										
Overall cohort	166.01	67.37		176.04	106.95		574.55	593.68		<0.001[b,c]
Survivors	163.34	67.11	0.37	180.19	111.40	0.25	516.93	414.20	0.02	<0.001[b,c]
Non-survivors	180.95	69.17		152.76	76.21		897.21	1,148.29		0.03[b,c]
LMR										
Overall cohort	4.93	4.40		5.41	12.36		1.62	3.15		0.06[b,c]
Survivors	4.77	4.01	0.42	5.82	13.37	0.07	1.73	3.41	0.05	0.02[b,c]
Non-survivors	5.78	6.29		3.09	1.44		0.98	0.50		0.03[b,c]

[a]Independent t-test for comparing the difference between survivors and non-survivors (P≤0.05). [b]One-way repeated-measures ANOVA for comparing the difference among the three time points (P<0.05). [c]Post hoc pairwise comparisons were conducted using the Bonferroni correction and P<0.05 compared with pre-IC or pre-CCRT. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; RT, radiation therapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

better outcomes. Subsequently, the cut-off values were adjusted at the pre-CCRT phase to; i) NLR=1.91; ii) PLR=212.16 and; iii) LMR=2.80, distinguishing the high- and low-risk cohorts. Finally, post-RT, the cut-off values were; i) NLR=9.51; ii) PLR=296.36 and; iii) LMR=1.06, providing a final stratification point. These time-specific cut-off values (Table SI) were determined through ROC curve analyses performed at each treatment phase (pre-IC, pre-CCRT and post-RT) to examine the prognostic performance of NLR, PLR and LMR, and identify the most informative thresholds for predicting survival outcomes.

Biomarkers measured in different treatment phases. Table II outlines hematological biomarker values at the three investigated time points: Pre-IC, pre-CCRT and post-RT. Repeated-measures ANOVA revealed significant longitudinal variations throughout the therapeutic course for NLR and PLR (both P<0.001), while a marginal trend was observed for LMR (P=0.06). Specifically, higher mean NLR and PLR values were observed at later time points, whereas LMR values were lower post-RT. Notably, at the post-RT evaluation, non-survivors exhibited higher NLR (P=0.05) and PLR (P=0.02) levels, alongside lower LMR levels (P=0.05), compared with survivors.

The logistic regression analysis showed that being ≥60 years old was significantly associated with a reduced likelihood of elevated PLR post-RT [odds ratio (OR)=0.27; 95% CI: 0.09-0.76; P=0.01]. In addition, patients who experienced weight loss of ≥7.5% body weight exhibited significantly higher odds of elevated NLR post-RT compared with those who lost <7.5% (OR=2.44; 95% CI: 1.02-5.86; P=0.05). No other variables, including sex, tumor stage, nodal stage, pretreatment EBV status and LMR, showed significant associations with inflammatory markers after radiotherapy (Table III).

Association of hematologic biomarkers pre-IC, pre-CCRT and post-RT with clinical outcomes. Patients with PLR pre-IC ≥248.67 exhibited significantly poorer 5-year OS compared with those with PLR pre-IC <248.67 (66.7 vs. 87.4%; P=0.03; Fig. 2D). Similarly, patients with PLR post-RT ≥296.3 exhibited poorer 5-year OS compared with those with PLR post-RT <296.3 (79.7 vs. 96.7%; P=0.02; Fig. 2F).

Table IV presents the results of the univariate and multivariate Cox regression analyses with Firth's correction to evaluate the risk factors associated with mortality in patients with NPC. Advanced nodal stage (N3) and high PLR pre-IC were significantly associated with a poor OS (both P<0.05) in the univariate analysis. In the multivariate analysis, high PLR pre-IC [hazard ratio (HR): 3.81; 95% CI: 1.21-12.00; P=0.02] and advanced nodal stage (N3; HR: 2.91; 95% CI: 1.01-8.38; P=0.05) were found to be independent predictors of mortality.

Furthermore, sensitivity analyses, with NLR, PLR and LMR evaluated as continuous variables using Cox regression models with Firth's correction, yielded results that were not entirely identical to those obtained by the primary ROC-dichotomized analyses. In the univariate analysis, an advanced nodal stage (N3; P=0.04) and an elevated NLR post-RT (P=0.02) were significantly associated with poor OS. However, in the present multivariable continuous model, both advanced nodal stage (N3; HR=2.75; 95% CI: 0.91-8.29; P=0.07) and NLR post-RT (HR=1.02; 95% CI: 0.99-1.04; P=0.12) were not statistically significant (Table SII).

Subgroup analysis by sex. To evaluate the prognostic stability of the hematologic biomarkers, a sex-stratified subgroup analysis was conducted (Table SIII). In male patients (n=76), an elevated PLR pre-IC was notably associated with poorer survival in both univariate (HR, 4.31; 95% CI, 1.22-15.23; P=0.02) and multivariable analyses (HR, 4.21; 95% CI,

Table III. Factors associated with elevated post-radiotherapy inflammatory markers based on logistic regression analysis.

	NLR post-RT (n=99)		PLR post-RT (n=99)		LMR post-RT (n=99)	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years						
<60	1.00		1.00		1.00	
≥60	0.77 (0.27-2.14)	0.61	0.27 (0.09-0.76)	0.01[a]	0.75 (0.28-2.00)	0.56
Sex						
Male	1.00		1.00		1.00	
Female	1.20 (0.43-3.34)	0.73	0.73 (0.24-2.24)	0.58	0.87 (0.33-2.31)	0.78
T stage						
T1-T3	1.00		1.00		1.00	
T4	0.29 (0.07-1.27)	0.10	0.21 (0.04-1.07)	0.06	2.27 (0.54-9.64)	0.27
N stage						
N0-N2	1.00		1.00		1.00	
N3	1.60 (0.32-7.90)	0.57	0.40 (0.07-2.30)	0.30	1.05 (0.22-4.96)	0.95
Pre-treatment EBV status						
Undetected	1.00		1.00		1.00	
Detected	2.00 (0.61-6.55)	0.25	1.77 (0.49-6.34)	0.38	0.42 (0.13-1.40)	0.16
Unknown	2.16 (0.82-5.68)	0.12	1.45 (0.54-3.89)	0.46	0.95 (0.34-2.61)	0.92
Weight loss, %						
<7.5	1.00		1.00		1.00	
≥7.5	2.44 (1.02-5.86)	0.05[a]	2.15 (0.83-5.60)	0.12	0.73 (0.32-1.67)	0.45

[a]Statistically significant (P<0.05) determined by binary logistic regression analysis. EBV, Epstein-Barr virus; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio.

1.17-15.13; P=0.03), demonstrating the role of PLR pre-IC as a robust prognostic indicator within this sub-cohort. Although a decreased LMR pre-IC was notably associated with mortality in the univariate analysis (HR, 5.97; 95% CI, 1.02-34.83; P=0.05) for males, this effect was attenuated and lost statistical significance after multivariable adjustment (HR, 5.61; 95% CI, 0.92-34.41; P=0.06). Conversely, no marked prognostic factors were identified among female patients (n=23), including PLR pre-IC in univariate analysis (HR, 14.48; 95% CI, 0.15-1363.45; P=0.25). Notably, the statistical estimates within the female subgroup exhibited wide CIs, reflecting limited statistical precision driven by the smaller sample size and fewer clinical events in the present cohort.

Discussion

Throughout the present study, the levels of hematologic biomarkers, including NLR, PLR and LMR, across different treatment phases in patients with NPC and their associations with survival outcomes were comprehensively examined. The present findings indicate that PLR may serve as a valuable prognostic indicator of OS. Specifically, elevated PLR pre-IC (≥248.67) and PLR post-RT (≥296.3) were notably associated with poorer 5-year OS. The present findings also indicate that elevated PLR, a marker of systemic inflammation, is an important contributor to NPC progression and prognosis (21). These results align with those of a previous comprehensive meta-analysis of nine studies (n=3,459), wherein elevated PLR was found to predict worse OS, progression-free survival and distant metastasis-free survival in NPC (22).

In the present cohort, higher NLR and PLR, as well as lower LMR rates were observed at later chronological time points, particularly post-RT. These differences were more notable in non-survivors, highlighting the potential relevance of the post-treatment inflammatory status as a possible marker for poor outcomes. The present finding aligns with that of an additional previous study, which reported that inflammation-based markers reflect tumor burden, host immune response and treatment-induced stress, all of which can influence the disease trajectory in NPC (23).

The present logistic regression analysis revealed that weight loss of ≥7.5% body weight during treatment was markedly associated with an elevated NLR post-RT, indicating a potential pathophysiological interplay among nutritional status, systemic inflammation and treatment-related toxicities. These findings are consistent with clinical observations that acute side effects such as oral mucositis and esophagitis tend to worsen with increased cumulative radiation doses during CCRT, thereby triggering inflammatory responses that restrict oral intake, leading to weight loss and subsequent malnutrition (24). By contrast, older patients (≥60 years) were found to be less likely to exhibit elevated PLR post-RT, which

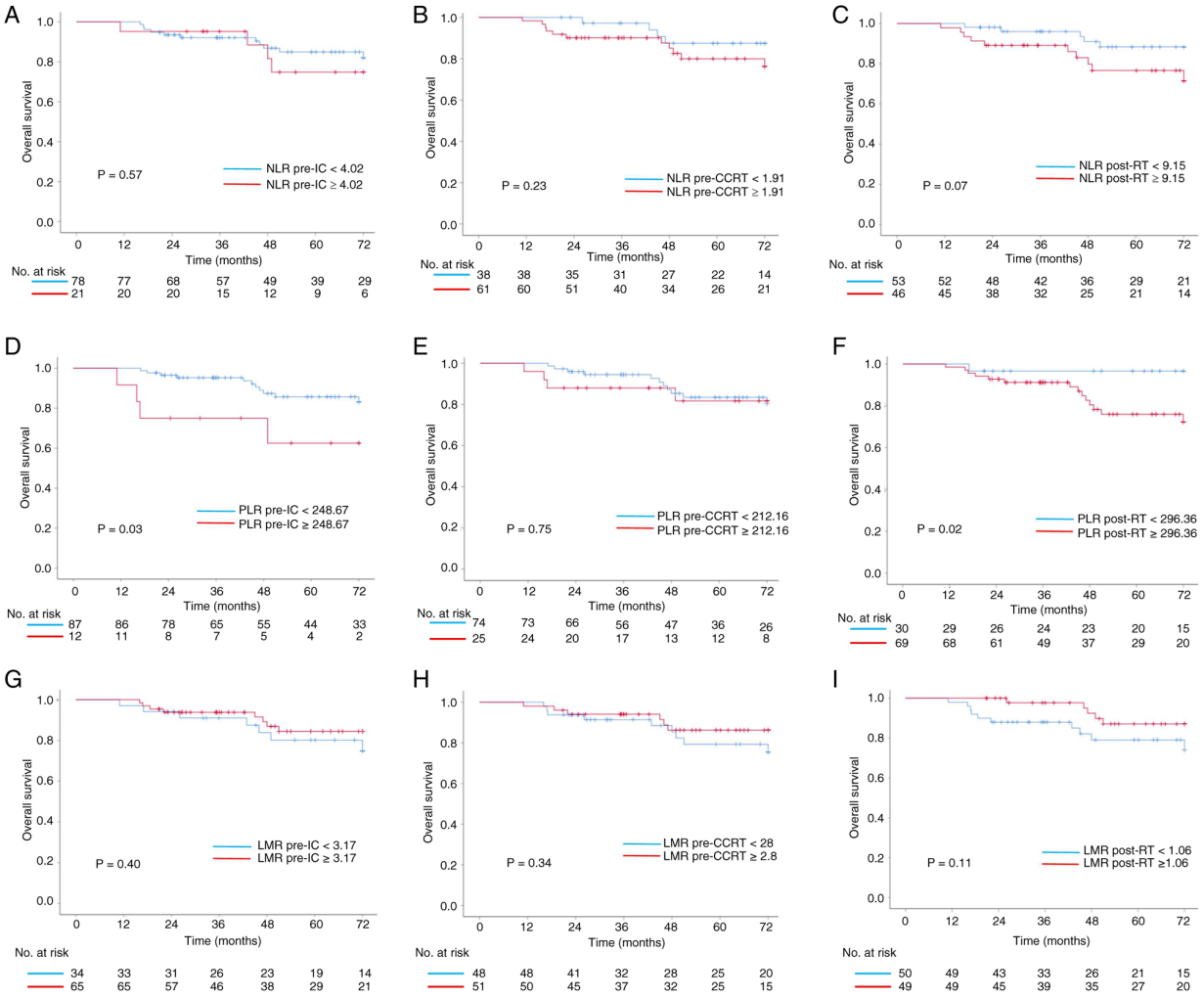

Figure 2. Kaplan-Meier curves of overall survival by (A-C) NLR, (D-F) PLR and (G-I) LMR pre-IC (A, D and G), pre-CCRT (B, E and H) and post-RT (C, F and I) in patients with nasopharyngeal carcinoma (log-rank test, P<0.05). The number of patients at risk is displayed below each survival plot. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RT, radiation therapy.

may reflect age-related differences in immune responses or treatment tolerance (25).

Notably, the present multivariate analysis showed that both elevated PLR pre-IC and advanced nodal stage (N3) remained independent predictors of mortality even after adjusting for tumor stage and other covariates. To further analyse potential confounders, pretreatment EBV status and longitudinal clinical parameters were also incorporated, including treatment-associated weight loss percentage, into the multivariate Cox regression models. Furthermore, neither EBV status nor weight loss percentage retained independent statistical significance in the final model. While this attenuation may partly stem from the statistical power limitations associated with missing data in the present EBV records, it does not diminish their clinical importance but implies a potential mediation effect.

In the present cohort, the distinct prognostic signals of NLR and PLR post-RT statistically overshadowed baseline tumor activity (EBV status) and physical wasting (weight loss). Clinically, this suggests that severe, treatment-induced inflammatory crisis and subsequent host tissue damage may act as important downstream drivers of long-term survival in NPC, eclipsing the independence of baseline tumor load and progressive nutritional depletion. However, these post-RT biomarkers must be interpreted with caution. Given that blood samples were collected within 1 week following the completion of radiotherapy, they are inherently and heavily confounded by acute radiation toxicities, such as severe hematological toxicity (profound lymphopenia), acute mucositis leading to temporary nutritional decline and concurrent subclinical infections, as well as supportive clinical interventions, including the transient use of corticosteroids or granulocyte-colony stimulating factor (G-CSF) (26-28). Consequently, rather than reflecting true tumor-specific biology, elevated NLR or PLR post-RT likely represents a composite indicator of severe treatment-associated systemic stress, tissue damage and impaired host hematological recovery, all of which are associated with compromised long-term survival.

The prognostic impact of PLR pre-IC suggests that systemic inflammation before IC may reflect a tumor growth-promoting microenvironment and impaired host immunity, thereby contributing to adverse outcomes (29). Similarly, an advanced nodal stage (N3) indicates increased tumor burden and the likelihood of micrometastasis, which have been consistently associated poor survival in patients with NPC (30-33). The

Table IV. Cox regression analysis with Firth's correction to evaluate risk factors for mortality.

	Mortality			Univariate analysis		Multivariate analysis	
Characteristic	Negative	Positive		HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years							
<60	65 (77.40)	11 (73.30)	0.73	1.00			
≥60	19 (22.6)	4 (26.70)		1.43 (0.46-4.49)	0.54		
Sex							
Male	63 (75.00)	13 (86.70)	0.32	1.00			
Female	21 (25.00)	2 (13.30)		0.58 (0.14-2.34)	0.44		
T stage							
T1-T3	61 (72.60)	13 (86.70)	0.25	1.00			
T4	23 (27.40)	2 (13.30)		0.56 (0.14-2.28)	0.42		
N stage							
N0-N2	63 (75.00)	7 (46.70)	0.03[a]	1.00		1.00	
N3	21 (25.00)	8 (53.30)		2.99 (1.04-8.63)	0.04[b]	2.91 (1.01-8.38)	0.05[b]
Pre-treatment EBV status							
Undetected	18 (21.40)	2 (13.30)	0.45	1.00			
Detected	45 (53.60)	7 (46.70)		2.57 (0.40-16.30)	0.32		
Unknown	21 (25.00)	6 (40.00)		3.20 (0.49-20.75)	0.22		
Weight loss, %							
<7.5	36 (42.90)	6 (40.00)	0.84	1.00			
≥7.5	48 (57.10)	9 (60.00)		1.27 (0.45-3.56)	0.65		
NLR pre-IC	67 (79.76)	11 (73.33)	0.73	1.00			
	17 (20.24)	4 (26.67)		1.64 (0.52-5.13)	0.40		
PLR pre-IC	76 (90.48)	11 (73.33)	0.08	1.00		1.00	
	8 (9.52)	4 (26.67)		3.96 (1.26-12.43)	0.02[b]	3.81 (1.21-12.00)	0.02[b]
LMR pre-IC	27 (32.10)	7 (47.70)	0.28	1.00			
	57 (67.90)	8 (53.30)		0.69 (0.25-1.92)	0.48		
NLR pre-CCRT	34 (40.48)	4 (26.67)	0.31	1.00			
	50 (59.52)	11 (73.33)		1.70 (0.54-5.33)	0.37		
PLR pre-CCRT	63 (75.00)	11 (73.33)	1.00	1.00			
	21 (25.00)	4 (26.67)		1.43 (0.46-4.48)	0.54		
LMR pre-CCRT	39 (46.43)	9 (60.00)	0.33	1.00			
	45 (53.57)	6 (40.00)		0.68 (0.24-1.96)	0.48		
NLR post-RT	48 (57.14)	5 (33.33)	0.09	1.00			
	36 (42.86)	10 (66.67)		2.37 (0.81-6.93)	0.11		
PLR post-RT	29 (34.52)	1 (6.67)	0.03[a]	1.00			
	55 (65.48)	14 (93.33)		5.05 (0.89-28.77)	0.07		
LMR post-RT	40 (47.62)	10 (66.67)	0.17	1.00			
	44 (52.38)	5 (33.33)		0.47 (0.16-1.37)	0.17		

[a]χ^2 test for comparing the difference between survivors and non-survivors (P≤0.05). Variables with P<0.05 in the univariate analysis were included in the multivariate model. HRs with 95% CIs and the corresponding P-values are reported. [b]Statistically significant associations. CCRT, concurrent chemoradiotherapy; EBV, Epstein-Barr virus; IC, induction chemotherapy; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio.

coexistence of these two risk factors may synergistically exacerbate disease progression, indicating that patients with high PLR pre-IC and advanced nodal stage (N3) may require intensified surveillance and closer monitoring of the inflammatory status. The present sex-stratified subgroup analysis demonstrated that the predictive strength of PLR pre-IC was preserved within the male sub-cohort. Conversely, no statistically significant prognostic factors reached significance among female patients, suggesting potential sex-dependent variations in baseline tumor ecology or treatment tolerability (34).

The present study exhibited a number of limitations. The retrospective design and modest cohort size may restrict the generalizability of the findings. Most notably, the small number of OS events (n=15) severely limited the statistical power of the present multivariate analyses and restricted the statistical precision of the present sub-cohort models (35). This constraint was particularly evident in the sex-stratified subgroup analysis, where the skewed sex distribution, with only two mortalities occurring in female patients, resulted in wide CIs. In addition, peripheral inflammatory markers could be influenced by unmeasured clinical dynamics or transient conditions, such as baseline CRP/lactate dehydrogenase levels or the aforementioned acute toxicities and supportive treatments (including the transient use of corticosteroids or G-CSF), which were not fully documented in the present retrospective dataset.

Furthermore, despite the ROC-derived cutoff values for NLR, PLR and LMR being determined and evaluated within the same cohort, overfitting cannot be excluded (36). An external validation cohort was unavailable in the present study and splitting the present modest dataset into derivation and validation sets was statistically unfeasible owing to the low event size (n=15); for instance, partitioning few events risks creating underpowered, unstable models in both subsets that can lead to overoptimistic performance (37). Therefore, these cut-off values must be interpreted cautiously as exploratory and cohort-specific rather than definitive clinical thresholds. Future large-scale prospective studies are required to externally validate these cut-off values before broad clinical implementation. Furthermore, while the present study focused on biomarker levels in three specific treatment phases, future prospective studies incorporating continuous, high-frequency longitudinal sampling are warranted to fully capture the dynamic changes of these markers throughout the entire therapeutic course.

In conclusion, the present single-center retrospective study suggests that treatment-associated variations in NLR, PLR and LMR may be associated with survival outcomes in patients with NPC. Notably, elevated PLR before IC and advanced nodal stage (N3) were identified as potential independent prognostic indicators of poor 5-year OS in the present cohort. Furthermore, the present findings highlight the possible influence of patient-specific factors, revealing that a weight loss of 7.5% correlated with elevated NLR post-RT, while being aged ≥60 years old was associated with reduced odds of elevated PLR post-RT. Given the present modest sample size, the results for these accessible, non-invasive biomarkers should be interpreted cautiously. While the biomarkers offer preliminary clinical utility for risk stratification and treatment monitoring, rigorous external validation in larger prospective cohorts is required before they can be used to guide personalized clinical decision-making.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Chi Mei Medical Center, Liouying (Tainan, Taiwan) in July 2025 (grant no. CLFHR11428).

Availability of data and materials

The data generated in the present study are not publicly available due to institutional review board restrictions and the need to protect patient privacy but may be requested from the corresponding author.

Authors' contributions

SCY, SYH, CHH, SWL, JQC and LTS conceptualized and designed the study. SCY, SYH, CHH, SWL, JQC and LTS contributed to patient selection and clinical coordination. SCY, SYH and CHH collected and assembled data. SCY, SYH and CHH contributed to data analysis and interpretation. SCY and CHH confirm the authenticity of all the raw data. All authors contributed to manuscript writing. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Chi Mei Hospital (Tainan, Taiwan; approval no. 11303-L08).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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