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ORIGINAL RESEARCH

Prognostic Impact of Advanced Lung Cancer Inflammation Index (ALI) on Immunotherapy Outcomes in Recurrent or Metastatic Nasopharyngeal Carcinoma: A Multicenter Post Hoc Analysis

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Purpose: The Advanced Lung Cancer Inflammation Index (ALI) is a newly introduced index that integrates inflammatory and nutritional statuses to assess malignancies. This study investigates the association between pre-immunotherapy ALI levels and clinical outcomes in recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) patients receiving immune checkpoint inhibitors (ICIs) therapy.

Patients and Methods: We conducted an exploratory post hoc analysis of a multicenter, single-arm Phase 2 trial enrolling 153 patients with R/M NPC. This study evaluated the prognostic utility of the pretreatment ALI for overall survival (OS) and progression-free survival (PFS), along with its association with treatment response to ICIs. The optimal ALI cutoff was empirically derived from this cohort. Propensity score matching (PSM) was also applied to assess the independent association between pretreatment ALI and clinical outcomes.

Results: Patients with low ALI scores demonstrated shorter OS and PFS compared to the high ALI group (OS: HR=4.07, p<0.001; PFS: HR=2.17, p<0.001). Low ALI was also associated with a lower disease control rate (DCR) (25.0% vs 58.7%, p=0.002), but showed no significant correlation with objective response rate (ORR) (15.6% vs 23.1%, p=0.361). In multivariate analysis incorporating propensity score-matched cohorts (n=62), ALI retained prognostic value for OS (HR=3.74, p=0.001) and PFS (HR=1.84, p=0.049).

Conclusion: Our findings suggest that pretreatment ALI as a promising prognostic biomarker for R/M NPC patients treated with ICIs. Given the exploratory post hoc nature of this analysis, the use of an empirically derived cutoff without external validation and the modest sample size of the matched cohort, these results warrant validation in future prospective studies.

Keywords: ALI, nutrition, ICIs, prognosis

Introduction

Nasopharyngeal carcinoma (NPC), endemic to Southeast Asia and southern China,[1] is tightly linked to Epstein-Barr virus (EBV) infection, which plays a crucial role in its oncogenesis. A key feature of NPC is its unique tumor microenvironment, which is heavily infiltrated by lymphocytes, making it a classic example of an "inflamed" cancer.[2] NPC is primarily treated with radiotherapy or chemo-radiotherapy for early-stage and locoregionally advanced disease, achieving

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a 5-year survival rate of approximately 85%.[3] Nevertheless, distant metastasis drives therapeutic failure in 20–30% of locoregionally advanced cases.[4–6] For recurrent or metastatic (R/M) NPC, cisplatin plus fluorouracil remains the first-line platinum-based regimen, with response rates ranging from 40% to 65%.[4] However, no consensus exists on salvage therapies for patients who fail initial platinum-based treatment.

Immune checkpoint inhibitors (ICIs) have shown clinically meaningful activity in R/M NPC.[7–9] In our prior multi-center study,[10] which evaluated PD-L1 blockade, KL-A167, in previously treated R/M NPC, demonstrated a median overall survival (OS) of 16.2 months (95%CI 13.4−21.3). However, the Phase III KEYNOTE-122 trial demonstrated no statistical OS improvement with pembrolizumab monotherapy versus platinum-based chemotherapy in R/M NPC.[11] Consequently, the identification of novel predictive biomarkers is essential for optimizing immunotherapy in R/M NPC patients, enabling more precise treatment strategies.

Inflammation and nutrition status exert a dual role in cancer progression and treatment response.[12–15] Indeed, while established inflammation-based scores like the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have shown prognostic value in NPC, they primarily reflect systemic inflammation. The Advanced Lung Cancer Inflammation Index (ALI) offers a potentially more comprehensive assessment by integrating both inflammatory status (via NLR) and crucial nutritional markers (body mass index (BMI), serum albumin levels).[16] This composite nature may provide a more holistic view of the patient's physiological resilience and capacity to respond to therapy. This index was an independent prognostic indicator for lung cancer initially.[17–19] Interestingly, this composite biomarker has demonstrated utility across hematologic and solid tumors, including B-cell lymphoma,[20] gastric,[21] esophageal,[22] and colorectal cancers.[23] Especially, retrospective comparative analyses in advanced non-small cell lung cancer (NSCLC) have identified the ALI as superior to PD-L1 expression for predicting ICI monotherapy efficacy.[18] Nevertheless, the role of pretreatment ALI in predicting oncological outcomes for R/M NPC patients who received the immunotherapy has never been clarified.

Therefore, we conducted a post-hoc analysis to explore the effect of pre-immunotherapy ALI levels on survival outcomes and treatment response in R/M NPC patients who have failed platinum-based treatment and are now undergoing anti-PD-L1 (KL-A167) therapy.

Materials and Methods

Patients and Data Collection

The study utilized data from 153 participants enrolled in a multicenter, single-arm Phase II trial (NCT03848286) conducted across 42 Chinese hospitals. All patients had histologically confirmed stage IVb R/M NPC according to the AJCC/UICC 8th edition staging system with progression after at least two prior chemotherapy lines, including a platinum-based first-line regimen. Additional criteria were age ≥ 18 years, ECOG performance status 0–1, at least one measurable lesion per RECIST v1.1, life expectancy ≥ 12 weeks, and adequate organ function. Key exclusions were prior therapy with anti–PD-1, anti–PD-L1, anti–PD-L2, or anti–CTLA-4 antibodies; chimeric antigen receptor T-cell therapy; or other agents targeting T-cell costimulatory or checkpoint pathways. The detailed inclusion and exclusion criteria published previously.[9] The study protocol adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants before enrollment.

Laboratory Measurements

Baseline anthropometric measurements (height and weight) and fasting venous blood samples were obtained before treatment initiation for all participants. The ALI was calculated as: ALI = BMI × Alb/NLR, where BMI is defined as weight (kg) divided by height squared (m^2), Alb refers to serum albumin (g/dL), and NLR was derived from complete blood count data (neutrophils/lymphocytes, both $\times 10^9$/L). The receiver operating characteristic (ROC) curve was used to identify an optimal ALI cutoff (Supplementary Figures 1 and 2). Based on this cutoff, patients were subsequently stratified into ALI-low and ALI-high subgroups for comparative analyses. The baseline characteristics including age (p=0.423), sex (p=0.667), ECOG status (p=0.293) were balanced across ALI groups before PSM. (Supplementary Table 1) The ALI cutoff

values were derived empirically using ROC curve analysis, and different thresholds were used for survival and therapeutic response. These cutoffs were not prespecified or validated, which introduces a high risk of overfitting.

Statistical Methods

Continuous variables exhibiting non-normal distributions were summarized as median values with interquartile range (IQR). For group comparisons, non-parametric tests were employed: the Mann–Whitney *U*-test for comparisons between two groups, and the Kruskal–Wallis test with Dunn's post hoc correction for multi-group comparisons. ROC curve analysis, adjusted for Youden's index, was used to determine optimal ALI cutoff thresholds for survival outcomes (OS and PFS: ALI = 35.82026; Supplementary Figure 1) and therapeutic efficacy (objective response rate (ORR) and disease control rate (DCR): ALI = 11.92918; Supplementary Figure 2). Survival distributions were estimated using the Kaplan-Meier method, with between-group differences evaluated by the Log rank testing. Cox proportional hazards regression modeling was employed to calculate hazard ratios (HRs) for mortality or recurrence. Prognostic determinants were identified through multivariable logistic regression analysis. All analyses were executed in R 4.4.1 with two-tailed α=0.05 defining statistical significance.

Propensity Score Matching

To address potential confounding, propensity score matching (PSM) was implemented. Patients were stratified into high-ALI and low-ALI cohorts based on pretreatment ALI thresholds established through time-dependent ROC analysis. Propensity scores were estimated via multivariable logistic regression incorporating six clinically relevant covariates: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor stage, node stage, and liver metastasis. One-to-one nearest neighbor matching with caliper width set to 0.20 of the propensity score standard deviation achieved balanced cohorts.[24] The small sample size in the matched cohort (n=62) limits the power of the multivariable analysis and that the models may be overfitted.

Study Outcomes

The primary endpoint evaluated the association between pretreatment ALI levels and survival outcomes, including OS and PFS. OS was defined as the time from KL-A167 initiation to death from any cause. PFS was defined as the time from treatment initiation to radiological progression (RECIST v1.1) or death. Secondary endpoints assessed ALI's predictive value for tumor response, with ORR defined as the proportion of patients achieving a complete response (CR) or partial response (PR), and DCR as the proportion with CR, PR, or stable disease (SD). The treatment response was assessed by RECIST v1.1. Radiographic tumor assessments were conducted at 6-week intervals during the initial 24 months, transitioning to 12-week intervals thereafter. Assessments continued until confirmed disease progression per RECIST v1.1, independent of treatment discontinuation status.

Results

Baseline Characteristics

This study enrolled 153 patients with R/M NPC treated with KL-A167 between February 26, 2019, and January 13, 2021. The cohort had a median age of 49 years (range: 20.0–68.0) with male predominance (81.7%, 125/153). ECOG performance status distribution showed 38.6% (59/153) as 0. The median pretreatment ALI for the entire cohort was 21.0 (IQR: 1.69–94.4). Subgroup analyses revealed significantly higher ALI levels in patients with ECOG PS 0 compared to ECOG PS 1 (p = 0.039). No significant differences in ALI were observed across other subgroups, as shown in Table 1.

Pretreatment ALI Was Associated with Survival Outcomes in R/M NPC Patients

Kaplan-Meier analysis stratified by ALI thresholds revealed markedly inferior survival outcomes in the ALI-low cohort versus ALI-high patients. R/M NPC patients with a lower pretreatment ALI exhibited worse OS (HR=4.07 95%CI: 2.11–7.87, p<0.001, Figure 1A) and PFS (HR=2.17, 95%CI: 1.39–3.39, p<0.001, Figure 1B). Multivariate analysis showed that ALI is a promising prognostic factor for both OS (HR = 3.99, 95% CI: 2.02–7.87, p < 0.001) and PFS (HR = 2.02, 95% CI: 1.28–3.19,

Table 1 Demographics of Patients

	Overall (N=153)	ALI median (IQR)	P-value
Age (years)			
Median (range)	49 (20.0–68.0)		
≤50	95 (62.1%)	21.0 (1.69–94.4)	0.557
51–65	53 (34.6%)	21.1 (5.64–74.3)	
>65	5 (3.3%)	18.8 (6.28–55.8)	
Gender			
Female	28 (18.3%)	20.9 (5.64–94.4)	0.257
Male	125 (81.7%)	21.0 (1.69–73.4)	
ECOG PS			
0	59 (38.6%)	23.7 (5.23–94.4)	0.039*
1	94 (61.4%)	19.9 (1.69–62.0)	
Tumor Stage			
T0-T2	52 (34.0%)	23.9 (1.97–62.0)	0.385
T3-T4	50 (32.7%)	19.2 (1.69–94.4)	
Tx	51(33.3%)	20.7 (4.83–74.3)	
Node Stage			
N0-N2	84 (54.9%)	22.5 (1.69–62.0)	0.833
N3	26 (17.0%)	18.4 (3.63–94.4)	
Nx	43 (28.1%)	20.3 (4.83–74.3)	
Liver Metastasis			
Yes	71 (46.4%)	20.1 (1.69–55.8)	0.094
No	82 (53.6%)	22.1 (3.63–94.4)	

Note: *P < 0.05.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

p = 0.003). (Tables 2 and 3). In addition to ALI, liver metastasis (HR = 2.45, 95% CI: 1.61–3.74, p < 0.001) and higher ECOG scores (HR = 2.74, 95% CI: 1.65–4.56, p < 0.001) were identified as independent prognostic factors for OS. These findings highlight the potential of ALI as a prognostic marker in clinical outcomes.

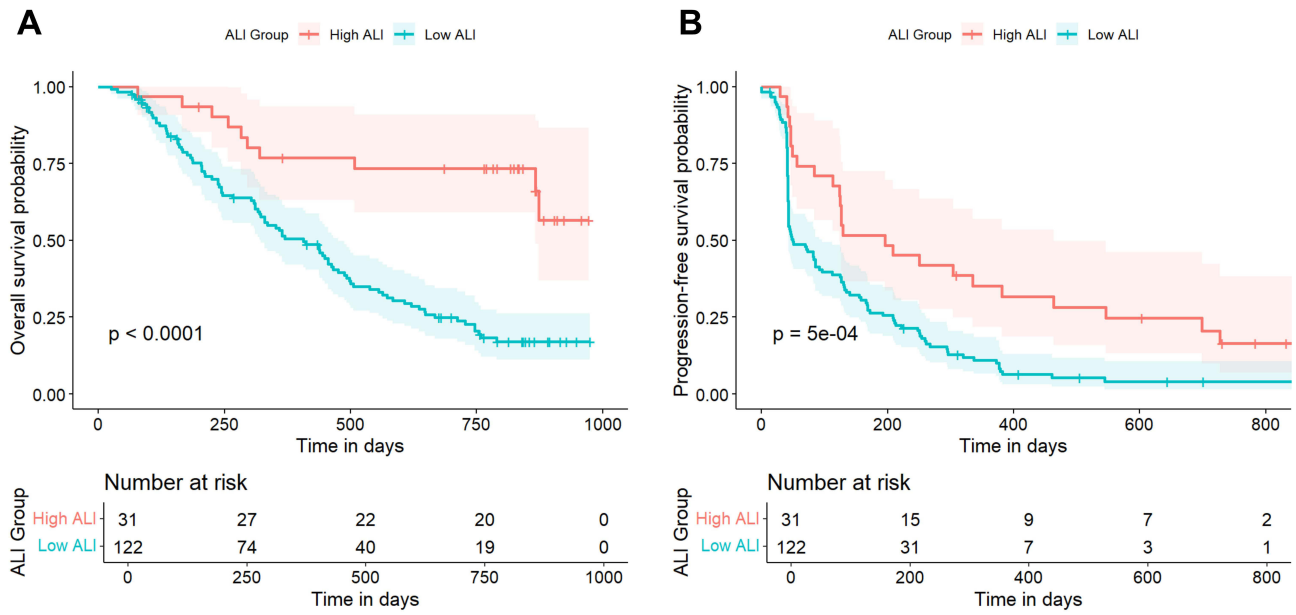

Figure 1 (**A**) Prognostic significance of ALI for overall survival (OS); (**B**) Prognostic significance of ALI for progression-free survival (PFS).

Table 2 Multivariate Analysis for Overall Survival

	Univariate		Multivariate	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age	0.81 (0.56–1.16)	0.412	0.76 (0.51–1.14)	0.179
Gender (Female)	0.83 (0.50–1.38)	0.462	0.83 (0.49–1.40)	0.484
Tumor Stage (T3-T4)	1.12 (0.71–1.78)	0.617	0.91 (0.57–1.45)	0.691
Node Stage (N3)	1.24 (0.75–2.06)	0.402	1.12 (0.66–1.90)	0.677
Liver Metastasis (present)	2.57 (1.73–3.82)	<0.001*	2.45 (1.61–3.74)	<0.001*
ECOG PS (1)	2.79 (1.79–4.33)	<0.001*	2.74 (1.65–4.56)	<0.001*
ALI (low)	4.07 (2.11–7.87)	<0.001*	3.99 (2.02–7.87)	<0.001*

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for survival.
Abbreviations: ALI, advanced lung cancer inflammation index; HR, hazard ratio; CI, confidence interval.

Table 3 Multivariate Analysis for Progression-Free Survival

	Univariate		Multivariate	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age	0.76 (0.55–1.04)	0.088	0.77 (0.55–1.07)	0.118
Gender (Female)	0.88 (0.58–1.35)	0.570	0.90 (0.58–1.41)	0.647
Tumor Stage (T3-T4)	0.81 (0.53–1.21)	0.297	0.76 (0.49–1.16)	0.195
Node Stage (N3)	1.07 (0.67–1.70)	0.788	1.30 (0.80–2.10)	0.292
Liver Metastasis (present)	1.99 (1.42–2.79)	<0.001*	1.84 (1.29–2.64)	<0.001*
ECOG PS (1)	1.61 (1.14–2.28)	0.007*	1.50 (1.02–2.21)	0.037*
ALI (low)	2.17 (1.39–3.39)	<0.001*	2.02 (1.28–3.19)	0.003*

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for survival.
Abbreviations: ALI, advanced lung cancer inflammation index; HR, hazard ratio; CI, confidence interval.

Exploratory Analysis of the Association Between Pretreatment ALI and Treatment Response

In an exploratory analysis of treatment response, univariate logistic regression analysis showed the association between low ALI and DCR (low vs high: 25% vs 58.7%, OR=0.235, 95% CI: 0.097–0.566, p=0.001) in R/M NPC patients receiving immunotherapy, which remained significant in multivariable models adjusted for clinical covariates (OR=0.21, 95% CI: 0.08–0.57, p=0.002). However, no associations were found between ALI and ORR in either univariate (p=0.361) or multivariable analyses (p=0.548) (Table 4). Given the non-significant association with ORR, these findings regarding treatment response should be interpreted with caution and are considered exploratory.

Table 4 Multivariate Analysis for Disease Control Rate and Objective Response Rate

	DCR Multivariate		ORR Multivariate	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Age	1.72 (0.88–3.38)	0.115	1.90 (0.92–3.93)	0.084
Gender (Female)	1.69 (0.62–4.59)	0.301	1.64 (0.60–4.49)	0.335
Tumor Stage (T3-T4)	2.00 (0.80–5.02)	0.137	2.46 (0.81–7.44)	0.111
Node Stage (N3)	0.45 (0.15–1.34)	0.151	0.61 (0.16–2.30)	0.463
Liver Metastasis (present)	0.23 (0.11–0.50)	<0.001*	0.53 (0.22–1.28)	0.160
ECOG PS (1)	0.54 (0.23–1.26)	0.154	0.38 (0.15–0.95)	0.038*
ALI (low)	0.21 (0.08–0.57)	0.002*	0.71 (0.23–2.18)	0.548

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for therapeutic efficacy.
Abbreviations: ALI, advanced lung cancer inflammation index; OR, Odds Ratio; CI, confidence interval.

Validation of ALI's Prognostic Value in a Propensity Score-Matched Cohort

PSM was an established method to minimize confounding in nonrandomized studies and was implemented to assess the prognostic utility of pretreatment ALI in R/M NPC. After 1:1 nearest-neighbor matching (caliper=0.2) with six clinical covariates (age, gender, ECOG PS, tumor stage, nodal stage, liver metastasis), we derived balanced cohorts of 62 patients (31 per ALI-high/low group), achieving standardized mean differences <0.10 for all baseline characteristics (Supplementary Table 2). The small sample size in the matched cohort (n=62) limits the power of the multivariable analysis and that the models may be overfitted.

In the matched cohort, low ALI remained a strong independent predictor of worse OS in multivariable analysis (HR=3.74, 95% CI: 1.67–8.36, p=0.001). However, its association with PFS reached only marginal statistical significance (HR=1.84, 95% CI: 1.00–3.38, p=0.049). Univariate analysis demonstrated significant OS association (HR=3.03, 95%CI 1.42–6.50, p=0.004) but only marginal PFS significance (HR=1.66, 95%CI 0.94–2.95, p=0.080) (Tables 5 and 6; Figure 2A and B). No statistically significant associations emerged between ALI and tumor response metrics (DCR: p=0.229; ORR: p=0.206) (Table 7). Notably, the loss of a significant association for DCR and the marginal p-value for PFS in this smaller matched cohort suggest that these particular findings may be underpowered due to the limited sample size and should be interpreted cautiously as potentially unstable.

Table 5 Multivariate Analysis for Overall Survival in Propensity-Score Matched Cohort

	Univariate		Multivariate	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age	0.72 (0.38–1.38)	0.328	0.82 (0.38–1.78)	0.620
Gender (Female)	0.96 (0.39–2.34)	0.926	1.46 (0.47–4.54)	0.514
Tumor Stage (T3-T4)	0.56 (0.22–1.46)	0.237	0.72 (0.23–2.26)	0.572
Node Stage (N3)	0.91 (0.36–2.29)	0.834	0.83 (0.29–2.39)	0.731
Liver Metastasis (present)	2.35 (1.15–4.78)	0.018*	2.71 (1.14–6.49)	0.025*
ECOG PS (1)	3.04 (1.39–6.66)	0.006*	3.03 (1.22–7.53)	0.017*
ALI (low)	3.03 (1.42–6.50)	0.004*	3.74 (1.67–8.36)	0.001*

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for survival.
Abbreviations: ALI, advanced lung cancer inflammation index; HR, hazard ratio; CI, confidence interval.

Table 6 Multivariate Analysis for Progression-Free Survival in Propensity-Score Matched Cohort

	Univariate		Multivariate	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age	0.73 (0.44–1.21)	0.226	0.71 (0.40–1.27)	0.248
Gender (Female)	0.75 (0.38–1.50)	0.418	0.85 (0.36–2.01)	0.708
Tumor Stage (T3-T4)	0.50 (0.22–1.09)	0.081	0.50 (0.19–1.28)	0.147
Node Stage (N3)	0.84 (0.38–1.88)	0.675	1.70 (0.66–4.38)	0.274
Liver Metastasis (present)	1.77 (0.99–3.19)	0.055	1.63 (0.78–3.38)	0.193
ECOG PS (1)	1.75 (1.00–3.07)	0.050*	2.47 (1.24–4.94)	0.010*
ALI (low)	1.66 (0.94–2.95)	0.080	1.84 (1.00–3.38)	0.049*

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for survival.
Abbreviations: ALI, advanced lung cancer inflammation index; HR, hazard ratio; CI, confidence interval.

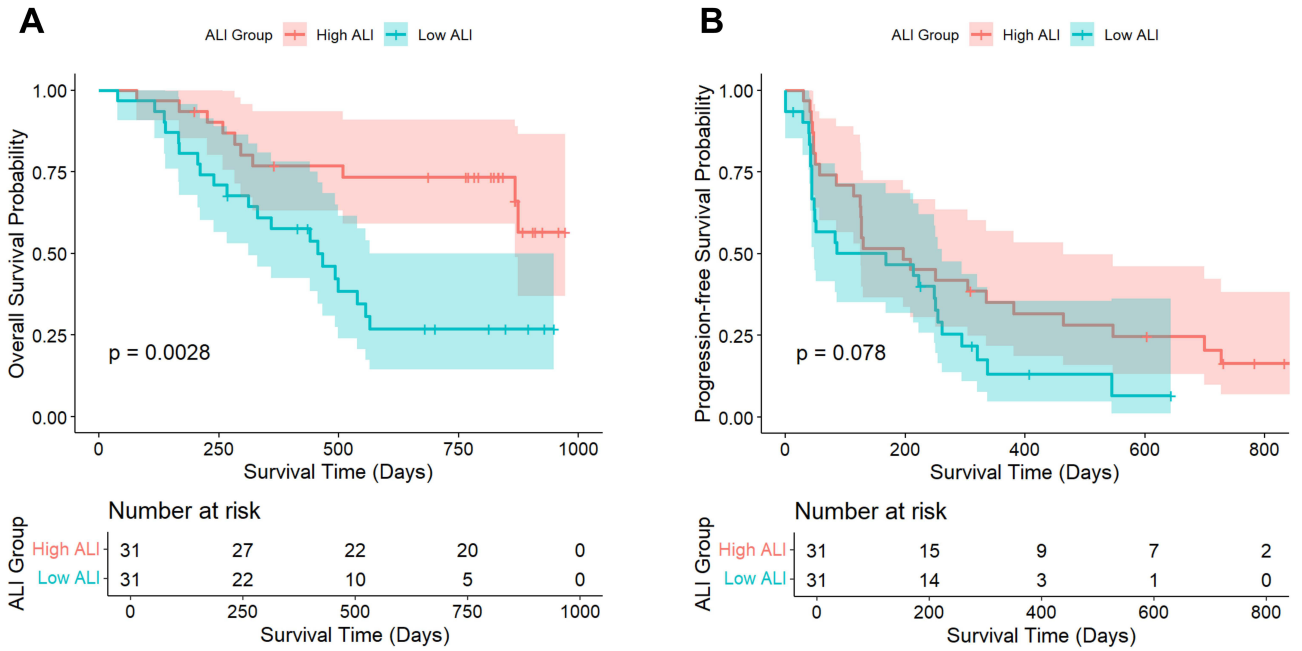

Figure 2 (**A**) Prognostic significance of ALI for overall survival (OS) in the PSM cohort; (**B**) Prognostic significance of ALI for progression-free survival (PFS) in the PSM cohort.

Discussion

This post-hoc analysis of our prior multicenter, single-arm, phase 2 study established potential prognostic effects of pretreatment ALI on the oncological outcomes of patients with R/M NPC receiving immunotherapy. Univariate and multivariable Cox regression suggested lower ALI as a negative prognostic factor for OS and PFS. Also, ALI-low patients showed worse DCR versus ALI-high counterparts. Furthermore, PSM analysis was conducted to minimize confounding, highlighting the prognostic value of ALI in R/M NPC patients. To our knowledge, this study is the first to assess the prognostic utility of pretreatment ALI in patients with R/M NPC receiving immunotherapy.

The development of ICIs has established a promising treatment strategy for R/M-NPC, with increasing emphasis on efficacy and safety outcomes. Notably, the KEYNOTE-122 trial revealed that pembrolizumab monotherapy did not improve OS over chemotherapy (PFS HR = 1.31, $p = 0.04$; ORR RR = 0.69, $p = 0.25$),[11] underscoring the limited clinical benefit of ICIs in unselected R/M NPC patient populations and the critical need to identify predictive biomarkers for immunotherapy. Peripheral blood biomarkers, which can be obtained without invasive procedures, are ideal prognostic markers.

Table 7 Multivariate Analysis for Disease Control Rate and Objective Response Rate in Propensity-Score Matched Cohort

	DCR Multivariate		ORR Multivariate	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Age	1.33 (0.46–3.85)	0.593	2.19 (0.68–7.05)	0.191
Gender (Female)	1.04 (0.21–5.25)	0.961	1.74 (0.35–8.66)	0.499
Tumor Stage (T3-T4)	4.29(0.67–27.56)	0.125	4.61 (0.56–37.89)	0.155
Node Stage (N3)	0.34 (0.06–1.86)	0.216	1.27 (0.16–10.21)	0.821
Liver Metastasis (present)	0.53 (0.12–2.31)	0.395	0.99 (0.19–5.07)	0.987
ECOG PS (1)	0.60 (0.18–2.05)	0.416	0.21 (0.05–0.88)	0.031*
ALI (low)	0.29 (0.04–2.14)	0.229	0.20 (0.02–2.36)	0.206

Notes: *P < 0.05. The cutoff value of ALI determined by ROC curve analysis for therapeutic efficacy.
Abbreviations: ALI, advanced lung cancer inflammation index; OR, Odds Ratio; CI, confidence interval.

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To our knowledge, systemic inflammation and malnutrition were found to promote tumorigenesis and therapeutic resistance through multifaceted mechanisms. A low ALI, reflecting both heightened systemic inflammation and poor nutritional status, provides a powerful biological rationale for predicting ICI outcomes. Chronic inflammatory mediators not only initiate oncogenic mutations but also sustain tumor progression via epithelial-mesenchymal transition (EMT) and angiogenesis.[13] Systemic inflammation fosters an immunosuppressive tumor microenvironment by promoting the accumulation of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs). Tumor-associated neutrophils (TANs) further facilitate immune evasion and reactive oxygen species (ROS) secretion, directly suppressing CD8+ T cell cytotoxicity.[25–27] Accumulating evidence demonstrated the correlation between systemic immune-inflammation index (SII) and the prognosis of NPC.[28–31] Malnutrition is a common complication in oncology, particularly prevalent in head and neck cancers due to tumor localization and treatment sequelae.[32,33] Malnutrition has been observed in previous studies to compromise immune function and treatment tolerance, with nutritional biomarkers such as BMI and serum ALB serving as prognostic indicators.[34,35] Several studies demonstrated that hypoalbuminemia independently predicts OS across malignancies.[36–38] Malnutrition aggravates immune suppression by inhibiting lymphocyte proliferation and function, which undermines the antitumor immune responses induced by ICIs and the combined effects of systemic inflammation and malnutrition establish a profound immunosuppressive state that correlates with both primary and acquired resistance to immunotherapy. Furthermore, ALI may not solely be a proxy for aggressive tumor biology but could also be an indicator of underlying patient frailty or reduced tolerance to treatment-related toxicities, which in turn affects outcomes.

The ALI demonstrates prognostic utility across multiple malignancies. A study analyzed 16 nutrition or systemic inflammation-based indicators and found that ALI (C-index: 0.611) had the best predictive ability on the OS in patients with lung cancer.[19] High ALI values were significantly associated with longer OS (HR = 0.402, $P < 0.0001$) for advanced NSCLC patients receiving ICI monotherapy, but not chemo-immunotherapy.[18] Also, our study suggests that pretreatment ALI may be a potential prognostic factor for OS and PFS in patients with R/M NPC undergoing ICI monotherapy, and the PSM analysis supported these findings. After PSM, ALI retained its prognostic significance, suggesting its potential stability as a prognostic marker against confounders like liver metastasis and ECOG performance status. However, it is important to interpret these findings with caution, given the retrospective and exploratory nature of this work. An additional finding of this study is that pre-treatment ALI can serve as a potentially predictor for DCR in R/M NPC patients. The high ALI correlates with improved DCR but not ORR suggests that a favorable host status (high ALI) may facilitate disease stabilization rather than significant tumor regression. Consequently, patients with elevated ALI levels may derive greater benefit from sustained disease control rather than immediate tumor shrinkage, an outcome especially relevant in the palliative management of R/M-NPC. Clinically, ALI could be integrated as a simple, cost-effective tool for risk stratification. A low ALI could prompt early nutritional or anti-inflammatory interventions to improve patient fitness for therapy and aid in setting realistic prognostic expectations. Our findings suggest the potential role of ALI in identifying patients who may benefit from interventions targeting nutritional and inflammatory pathways to improve treatment outcomes.

Finally, this study offers mechanistic insights into the unique biology of NPC. This EBV-driven inflammation may exhibit bidirectional immunomodulatory effects: while promoting immune cell infiltration, it simultaneously induces T-cell exhaustion and adaptive immune tolerance. Therefore, the ALI may indirectly reflect this complex interplay. A low ALI could signify an exhausted or dysfunctional immune state that is less responsive to ICI. Future studies could benefit from exploring the direct correlation between EBV DNA load, specific inflammatory cytokine profiles, ALI, and the efficacy of ICIs in R/M-NPC to further elucidate these mechanisms. Furthermore, our findings align with a broader trend emphasizing the integration of both tumor-intrinsic and host-derived biomarkers. ALI's prognostic value is complementary to established tumor-centric biomarkers in NPC, such as circulating EBV DNA load and PD-L1 expression. While these markers reflect tumor burden and direct therapeutic targets, ALI captures the host's systemic immune fitness—a critical determinant for treatment tolerance and response. Therefore, integrating a host-factor biomarker like ALI with tumor-specific markers could create a more robust prognostic model, offering a more holistic assessment of patient prognosis. Furthermore, studies on tumor-tissue markers like CK18 and GDF5 have demonstrated their prognostic power in other head and neck cancers.[39] Our work on ALI, a systemic host-factor index, provides a parallel line of evidence

from the host perspective. The convergence of these approaches highlights that a comprehensive understanding, combining both tumor biology and host fitness, is essential for advancing personalized cancer therapy.

This study suggests that pretreatment ALI may be a potential independent prognostic factor in R/M NPC patients treated with ICIs. To our knowledge, this study is the first to investigate ALI's prognostic role in R/M NPC, utilizing prospectively collected data from a multicenter phase II trial (NCT03848286), and the prognostic utility of ALI was supported by PSM analysis. However, this study has its limitations. Firstly, despite PSM adjustment, the retrospective analysis design and moderate sample size (pre-PSM N=153) warrant validation in larger prospective cohorts to confirm generalizability. Secondly, the ALI cutoff values were derived empirically using ROC curve analysis, and were not prespecified or validated, which introduces a high risk of overfitting. Additionally, as a composite index (ALI = [BMI×albumin]/NLR), ALI may be influenced by nutritional status, chronic inflammation, medicine used, and physiologic circumstances. Also, the small sample size in the matched cohort (n=62) limits the power of the multivariable analysis and that the models may be overfitted. Key confounders (eg, PD-L1, EBV DNA load, and tumor burden) not included in the matching process may compromise the accuracy of our findings. Future research should investigate the biological mechanisms of ALI components, providing deeper insights into the role of nutritional and inflammatory status in cancer therapy.

Conclusions

This study suggests that pretreatment ALI may be a potential prognostic factor for R/M NPC patients with ICIs and low pretreatment ALI may be associated with poorer outcomes. The findings of our study require prospective validation in larger cohorts.

Abbreviations

AUC-ROC, Area under the receiver operating characteristic curve; BMI, Body Mass Index; CR, Complete response; CNS, Central nervous system; DCR, Disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EBV, Epstein-Barr virus; EMT, Epithelial-mesenchymal transition; HR, Hazard ratios; ICIs, Immune checkpoint inhibitors; IQR, Interquartile range; MDSCs, Myeloid-derived suppressor cells; NPC, Nasopharyngeal carcinoma; NLR, Neutrophil-to-lymphocyte ratio; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PD-L1, Programmed cell death ligand 1; PR, Partial response; PLR, Platelet-to-lymphocyte ratio; PSM, Propensity score matching; R/M NPC, Recurrent or metastatic nasopharyngeal cancer; ROC, Receiver operating characteristic; ROS, Reactive oxygen species; SII, Systemic immune-inflammation index; SD, Stable disease; ALI, The Advanced Lung Cancer Inflammation Index; TANs, Tumor-associated neutrophils; Tregs, Regulatory T-cells.

Data Sharing Statement

Participants of this study did not agree to share their data publicly, so supporting data is not available.

Ethical Guidelines Statement

The study adhered to the principles of the Declaration of Helsinki and the International Council for Harmonisation's guidelines for Good Clinical Practice. Each participating center's independent ethics committee granted approval for the study protocol. Before enrollment, all participants provided written informed consent. Ethical approval was obtained from the West China Hospital Institutional Review Board (HX-IRB-AF-12-V4.0).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Junyou Ge, Yan Qing, and Youneng Wei declare affiliations with Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. The authors report no other conflicts of interest in this work.

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