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ORIGINAL RESEARCH

Predictive Value of Advanced Lung Cancer Inflammation Index and Development of a Nomogram for Prognosis in Patients with Cervical Cancer Treated with Radiotherapy

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Purpose: As an assessment tool of nutritional status and inflammation, the advanced lung cancer inflammation index (ALI) is associated with survival in various cancers. We aimed to investigate the association between the ALI's prognostic value and survival time in patients with the stage IIB–III cervical cancer treated with radiotherapy.

Patients and Methods: We retrospectively screened patients diagnosed with cervical cancer and underwent radiotherapy in a single institution between September 2013 to September 2015. The ALI was calculated as body mass index * serum albumin/neutrophil-to-lymphocyte ratio. The cut-off value of ALI was determined by the receiver operating characteristic (ROC) curves. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan–Meier method and Cox proportional hazards models. A nomogram was developed using prognostic factors based on multivariate analyses.

Results: A total of 178 patients with cervical cancer were included. The cutoff value of ALI was set at 310.6 by ROC analyses. Kaplan Meier survival curves indicated that patients with low ALI had a significantly poorer OS (log-rank P<0.001) and PFS (log-rank P=0.0056) than those with high ALI. The association between ALI and OS was significant in the patients with obese/overweight and low/normal weight. The Cox regression analysis indicated that patients with low ALI were associated with a decreased OS (Hazard Ratio (HR) = 2.56, 95% Confidence Intervals (CI), 1.35–4.83; P= 0.004) and PFS (HR = 1.83; 95% CI, 1.06–3.17; P = 0.031). The nomogram on OS was created based on ALI with C-index of 0.81. Patients with high nomogram points had worse OS than those with low nomogram points (log rank P<0.0001).

Conclusion: Pretreatment ALI is an independent negative prognostic factor in patients with cervical cancer treated with radiotherapy. The ALI based nomogram can help to identify patients who may have unfavorable outcomes.

Keywords: cervical cancer, prognosis, survival, advanced lung cancer inflammation index

Introduction

Cervical cancer ranks as the fourth leading malignancy among women worldwide, with an estimated 660,000 new cases and approximately 350,000 deaths occurring in the year 2022.[1] It was estimated 110,000 new cases were diagnosed in China in the year 2020.[2] Although cervical cancer is preventable by routine HPV vaccination and widely used screening tests, the 5-year survival rate was still not satisfied.[3] Based on data from the Surveillance, Epidemiology, and End Results (SEER) program 22, the 5-year relative survival rate was only 67.4%.[4] The mortality and number of deaths from cervical cancer are

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also higher in low- and middle-income countries, such as China, South Africa, Brazil and India.[5] Moreover, cervical cancer diagnosed in these countries is often too late for radical or surgical resection.[6] Radiotherapy and chemotherapy are the recommended treatments for patients with stage II–III cervical cancer.[7] However, the prognosis of different patients ar significantly different. Generally, the International Federation of Gynecology and Obstetrics (FIGO) stage and pathological type of cervical cancer can well predict the survival of patients.[8,9] However, many patients have the same stage and pathological type, the prognosis is quite different in clinical practice.[10] Therefore, in clinical setting, it is necessary and essential to find an appropriate predictive model to predict the prognosis of patients with cervical cancer.

Nutritional status and inflammatory status are two important factors affecting the survival time and treatment effect of patients with cancer.[11,12] Patients with cancer are particularly prone to developing malnutrition.[13] Studies have confirmed that malnutrition is an independent risk factor for the prognosis of cancer patients.[13,14] Systemic inflammation within the host environment is recognized as a hallmark of cancer, which is implicated in the stimulation of proliferative signaling, consequently promoting the spread, proliferation, and metastasis.[15,16] Inflammatory cells and mediators constitute pivotal elements within the tumor microenvironment, playing a significant role in supporting cancer progression and response to anti-cancer therapy.[17,18] Inflammation has also been shown to be a factor affecting the prognosis of cervical cancer patients.[19,20] Advanced lung cancer inflammation index (ALI) is an index that integrates nutritional status and inflammatory status.[21] It was calculated as body mass index (BMI) * serum albumin (ALB)/Neutrophil-to-Lymphocyte Ratio (NLR). In 2013, the ALI was verified as a significant prognostic factor in metastatic non-small cell lung cancer.[22] Many studies have found that ALI is closely related to the prognosis of cancer patients.[23,24] Qi et al's study found that patients with low ALI had a 1.43-fold increased risk of death compared with patients with high ALI in extensive-stage small-cell lung cancer.[25] The results from previous meta-analyses suggested that ALI was one of the factors predicting the prognosis of patients with gastric cancer[26] and lung cancer.[27] Previous studies found that the incidence of malnutrition in patients with cervical cancer is not low, and malnutrition is also an independent risk factor for the prognosis of patients with cervical cancer.[28,29] Systemic inflammation had also been found to affect the prognosis of cervical cancer patients.[30,31] Therefore, we hypothesized that ALI would affect the prognosis of patients with cervical cancer. To our knowledge, no literature has reported the relationship between ALI and the prognosis of patients with cervical cancer. Thus, this study aimed to explore the relationship between ALI and prognosis in FIGO IIB–III cervical cancer receiving radiotherapy. As ALI was calculated by the BMI and some studies have shown that patients with cancer and a high BMI had better outcomes than patients with normal BMI,[32] we also aimed to investigate the predictive value of ALI in patients with obesity and overweight. In addition, a nomogram was also created to predict the survival time in patients with cervical cancer treated with radiotherapy. The nomogram for cervical cancer patients treated with radiotherapy can help clinicians identify high-risk patients who may benefit from treatment strategies or closer monitoring. Additionally, the nomogram helps to assist in treatment decision-making.

Material and Methods

Study Patients

The medical records of patients with cervical cancer who received radiotherapy in Hubei Cancer Hospital from September 2013 to September 2015 were extracted and analyzed. Of these, 178 patients were included in the study. The inclusion criteria were as follows: (1) The patient was pathologically diagnosed as cervical cancer; Cervical cancer was diagnosed based on pathological results. The definitive diagnosis was made through the examination of cervical tissue obtained via biopsy or conization. This pathological examination confirmed the presence of malignant cells and determines the type of cervical cancer, such as squamous cell carcinoma or adenocarcinoma. (2) The patient received radiotherapy; (3) 18–80 years old. Participants were excluded based on the following criteria: individuals with a diagnosis of other malignancies or diseases that had a significant impact on the nutritional status, including severe infections, acquired immunodeficiency syndrome, chronic kidney failure, and severe hepatic cirrhosis, and those lacking complete clinical records. The Ethics Committee of the Hubei Cancer Hospital of Huazhong University of Science and Technology approved the study (LLHBCH2021YN-049). The study was conducted in compliance with the ethical standards as delineated in the Declaration of Helsinki. Given the retrospective nature of the investigation, the requirement for informed consent was waived. All personal identifiers, including names and hospital admission numbers, were removed prior to analysis to ensure patient confidentiality. Data were securely stored and managed in compliance with institutional guidelines.

Data Collection and Variables

Clinicopathological information including age, height, weight, number/size of metastatic lymph nodes, pathological type, FIGO stage and therapy methods were obtained from the medical records of patients. Clinical data including ALB, squamous cell carcinoma antigen, peripheral blood related indicators were also collected within 2 weeks before treatment. Neutrophil to Lymphocyte Ratio was calculated as Neutrophil/ Lymphocyte. ALI was calculated as BMI * ALB/NLR.

Radiotherapy Regimen

In this study, patients with FIGO stage IIB - III cervical cancer were treated with radiotherapy (RT) as part of their treatment regimen. A total of 106 patients were treated with intensity - modulated radiotherapy (IMRT), which was delivered at a dose rate of 1.8 Gy per fraction, five days a week, with a total dose ranging from 45.0 to 50.4 Gy. Another 72 patients received conventional radiotherapy (CRT), also with a total dose of 45.0–50.4 Gy, using anterior and posterior opposing techniques. A computed tomography (CT) scan was conducted to generate a three - dimensional map of the tumor. Subsequently, a multidisciplinary team of radiation therapy experts, including physicians and medical physicists, employed advanced computer software to precisely calculate and deliver radiation directly to the tumor from multiple angles. Concurrent chemotherapy with cisplatin at a dose of 40 mg/m^2 was considered for eligible patients (n=170), initiated after the start of RT. Following whole-pelvic irradiation, all patients received high-dose ^{192}Ir brachytherapy, with a maximum dose of 36 Gy. For patients who require further treatment after radiotherapy, the expert team will continue to administer treatments such as chemotherapy.

Follow-up

The follow-up strategy involved regular follow-up, conducted either through outpatient visits or by phone, with a final follow-up deadline of September 2019. Overall survival (OS) was measured from the start of RT to the date of death or the last follow-up, while progression-free survival (PFS) was calculated from the start of RT to the first sign of tumor progression, death from any cause, or the last follow-up. The treatment and follow-up procedures were in line with the Radiation Therapy Oncology Group guidelines, ensuring a standardized approach to care.

Data Analysis

Data analysis was conducted using R software, with version 4.1.3 employed depending on the study. Statistical significance was set at a P-value of less than 0.05. In the analysis, continuous variables were reported as the mean with standard deviation or the median with interquartile range. For categorical variables, the presentation was in terms of frequencies and percentages. Statistical comparisons of continuous variables were performed using a *t*-test, whereas categorical variables were assessed using either a chi-square test or Fisher's exact test, depending on the data distribution and sample size. Additionally, receiver operating characteristic (ROC) curves were used to determine the optimal cutoff value for ALI and nomogram points. The cumulative survival curves were created by the Kaplan-Meier (K-M) method, and the Log rank test was used to analyze differences in OS and PFS between high ALI and low ALI groups. Both univariate and multivariate analyses were performed using the Cox proportional hazard model to assess the impact of ALI on OS and PFS. All the factors with P-values less than 0.20 in the univariate analysis were selected for inclusion in the subsequent multivariate Cox regression models. A Least Absolute Shrinkage and Selection Operator (LASSO) regression were also used to select factors. The selected variables used in the multivariable Cox regression models were utilized to construct the nomograms to predict OS and PFS. The C-index, serving as a measure of model discrimination, was employed to assess the performance of the nomogram developed for overall survival (OS) based on ALI.

Results

Baseline Characteristics of Study Participants

A total of 178 diagnosed patients with cervical cancer were enrolled in this retrospective study after screening (Figure S1). Table 1 presented the baseline characteristics of the 178 patients. In the enrolled study population, the mean age was 55

Table 1 The Baseline Characteristics of Patients With Cervical Cancer

		High ALI (n=116)	Low ALI (n=62)	*P*
Age (median [IQR])		54.0 [49.0, 60.0]	51.0 [46.0, 61.8]	0.381
Age (n, (%))	≤ 55	64 (55.2)	37 (59.7)	0.663
	> 55	52 (44.8)	25 (40.3)	
No. of MLN (n, (%))	> 2	17 (14.7)	11 (17.7)	0.747
	≤ 2	99 (85.3)	51 (82.3)	
Size of MLN (n, (%))	≤ 1cm and MLN	60(51.7)	26 (41.9)	0.277
	> 1cm	56 (48.3)	36 (58.1)	
Vaginal invasion (%)	No	58 (50.0)	22 (35.5)	0.09
	Yes	58 (50.0)	40 (64.5)	
Pathology (n, (%))	Squamous cell carcinoma	107 (92.2)	55 (88.7)	0.61
	Adenocarcinoma	9 (7.8)	7 (11.3)	
FIGO stage (n, (%))	II	70 (60.3)	25 (40.3)	**0.017**
	III	46 (39.7)	37 (59.7)	
SCC antigen (n, (%))	≤ 1.5	35 (30.2)	14 (22.6)	0.366
	> 1.5	81 (69.8)	48 (77.4)	
Height (median [IQR])		156.5 [155.0, 160.0]	157.0 [156.0, 160.0]	0.317
Weight (median [IQR])		58.0 [54.0, 62.0]	54.0 [50.3, 59.8]	**0.001**
ALB (median [IQR])		42.3 [40.1, 44.8]	40.00 [37.5, 42.3]	**<0.001**
BMI (median [IQR])		23.3 [22.2, 25.1]	22.0 [20.8, 23.8]	**<0.001**
BMI (n, (%))	≤ 23.9	66 (56.9)	47 (75.8)	**0.02**
	> 23.9	50 (43.1)	15 (24.2)	
Chemoradiotherapy (n, (%))	No	5 (4.3)	3 (4.8)	0.999
	Yes	111 (95.7)	59 (95.2)	
Type of Radiotherapy (n, (%))	IMRT	75 (64.7)	31 (50.0)	0.082
	Conventional radiotherapy	41 (35.3)	31 (50.0)	
ALI (mean (SD))		601.5 (281.6)	191.7 (72.1)	**<0.001**

Note: Bold values indicate statistical significance (*P* <0.05).
Abbreviations: MLN, metastatic lymph nodes; IQR, interquartile range; ALI, advanced lung cancer inflammation index; ALB, albumin; BMI, body mass index; IMRT, intensity-modulated radiotherapy; SCC, squamous cell carcinoma.

years, and the mean BMI was 23.2. At the time of diagnosis, there were 95 individuals at FIGO stage II and 83 at FIGO stage III. One hundred and sixty-two patients had squamous cell carcinoma, while the rest were diagnosed with adenocarcinoma. According to the ROC curve, the optimal cutoff value for ALI was 310.6 (Figure S2). The study population was divided into two groups based on the cutoff value for ALI: the low ALI group (n=116) and the high ALI group (n=62). Among these study participants, the 5-year overall survival rate was 76.4%, with an average follow-up period of 50.88 months. In the entire population, the median follow-up for the entire cohort was 59 months, with a 95% CI of 56 to 62 months. There were 42 deaths during the follow-up.

The Association Between ALI and Survival Times in Cervical Cancer

Figure 1A presented the results of the K-M survival analysis, indicating that the overall survival time of patients with low ALI was significantly shorter than that of patients with high ALI. (Log rank test, P<0.001, Figure 1A). Additionally, the 1-year estimated overall survival rate for the low ALI group was 91.9%, the 3-year estimated overall survival rate was 67.7%, and the 5-year overall survival rate was 60.9%. For the high ALI group, the estimated 1-year, 3-year, 5-year overall survival rate was 96.6%, 85.3% and 84.5% respectively. As shown in the Figure 1B, the K-M survival analysis results showed that patients with low ALI had shorter PFS compared with patients with high ALI. (Log rank test, P<0.01, Figure 1B) Additionally, the 1-year estimated PFS rate for the low ALI group was 66.1%, the 3-year estimated PFS survival rate was 62.9%, and the 5-year PFS survival rate was 55.3%. For the high ALI group, the estimated 1-year, 3-year, 5-year PFS survival rate was 87.9%, 78.4% and 73.4% respectively.

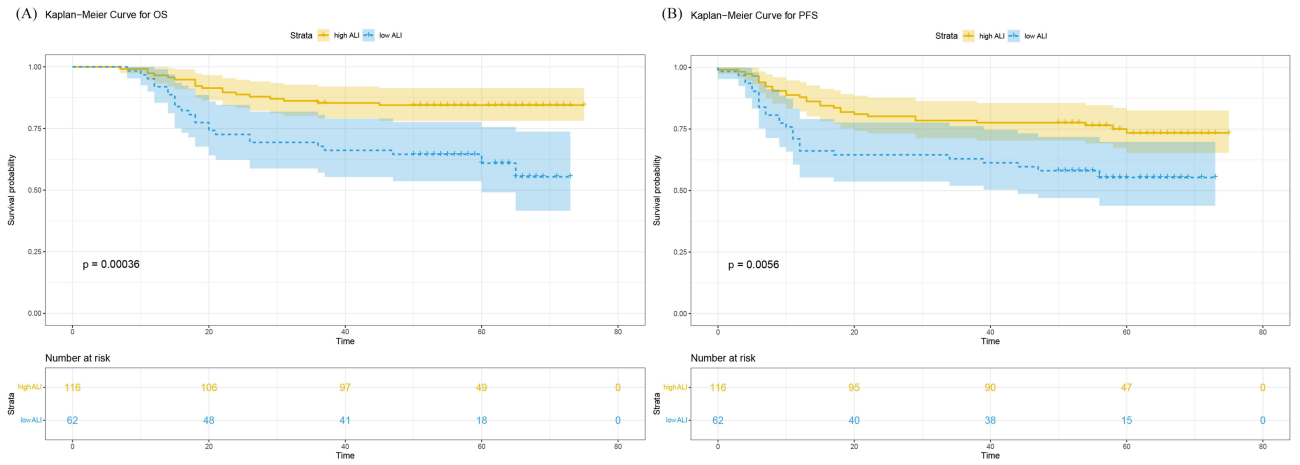

Figure 1 Kaplan–Meier curves of survival time according to the advanced lung cancer inflammation index (ALI) for overall survival (OS) (**A**) and progression-free survival (PFS) (**B**).

Subgroup Analysis Based on the Body Weight

In order to further explore the predictive efficacy of ALI across different BMI, we conducted a subgroup analysis. The results of the K-M analysis suggested that for patients who were overweight and obese, the patients with high ALI had significantly better overall survival and progression-free survival times compared to the patients with low ALI (Log rank test, OS, P<0.001, Figure 2A; PFS, P<0.001, Figure 2B). For patients with normal weight and underweight, the group with high ALI had a significantly longer overall survival time than the group with low ALI (Log rank test, P = 0.041). (Figure 2C) Patients with low ALI had shorter progression-free survival times than those with high ALI, but the difference was not statistically significant (Log rank test, P = 0.2). (Figure 2D) Further analysis was conducted to compare the OS among multiple groups based on the Chinese BMI reference standard. The results showed that there was no significant association between BMI and OS (BMI < 18.5 vs 18.5–23.9, p=0.73; BMI < 18.5 vs > 24, p=0.73; BMI 18.5–23.9 vs 18.5–23.9, p=0.9) (Figure S3).

Univariable and Multivariable Analyses

In our retrospective analysis, we performed univariable and multivariable analyses to identify potential predictors of OS and PFS in patients with cervical cancer. Several factors demonstrated significant relationships with OS and PFS in the univariate analysis. Notably, several factors demonstrated significant associations with OS, including No. of metastatic lymph nodes, size of metastatic lymph nodes, size of tumor, type of pathology, FIGO stage and ALI (Table 2). On the other hand, parameters such as type of radiotherapy and SCC antigen did not reach statistical significance in the analysis, suggesting that they may not be independent prognostic factors for OS in this cohort. In the terms of PFS, No. of metastatic lymph nodes, size of metastatic lymph nodes, size of tumor, type of pathology, FIGO stage and ALI were significantly associated with PFS (Table 2). A LASSO regression was also used to screen the variables (Figure S4). Finally, No. of metastatic lymph nodes, Size of metastatic lymph nodes, Size of tumor pathology, FIGO stage and ALI were selected. In the multivariable analyses, which factors were selected by P <0.2 in the univariate Cox analyses, low ALI was significantly associated with poorer OS, yielding a Hazard Ratio (HR) of 2.56 (95% CI, 1.35, 4.83; P = 0.004). (Table 3) Low ALI showed a markedly increased HR of 1.83 (95% CI, 1.06–3.17; P = 0.031) on PFS, indicating that patients with low ALI had a significantly high risk of progression compared to patients with high ALI. (Table 3) In the multivariable analyses (LASSO regression analyses model), low ALI was also associated with decreased OS and PFS.

Prognostic Model on OS Based on ALI

To visualize the Cox regression model, we constructed two nomograms that incorporated several variables, including type of pathology, ALI, and the number of lymph nodes. One nomogram used the factors identified in the Univariate Cox analyses model with P <0.2. (Figure 3) Another nomogram used the factors identified in the LASSO regression analyses model.

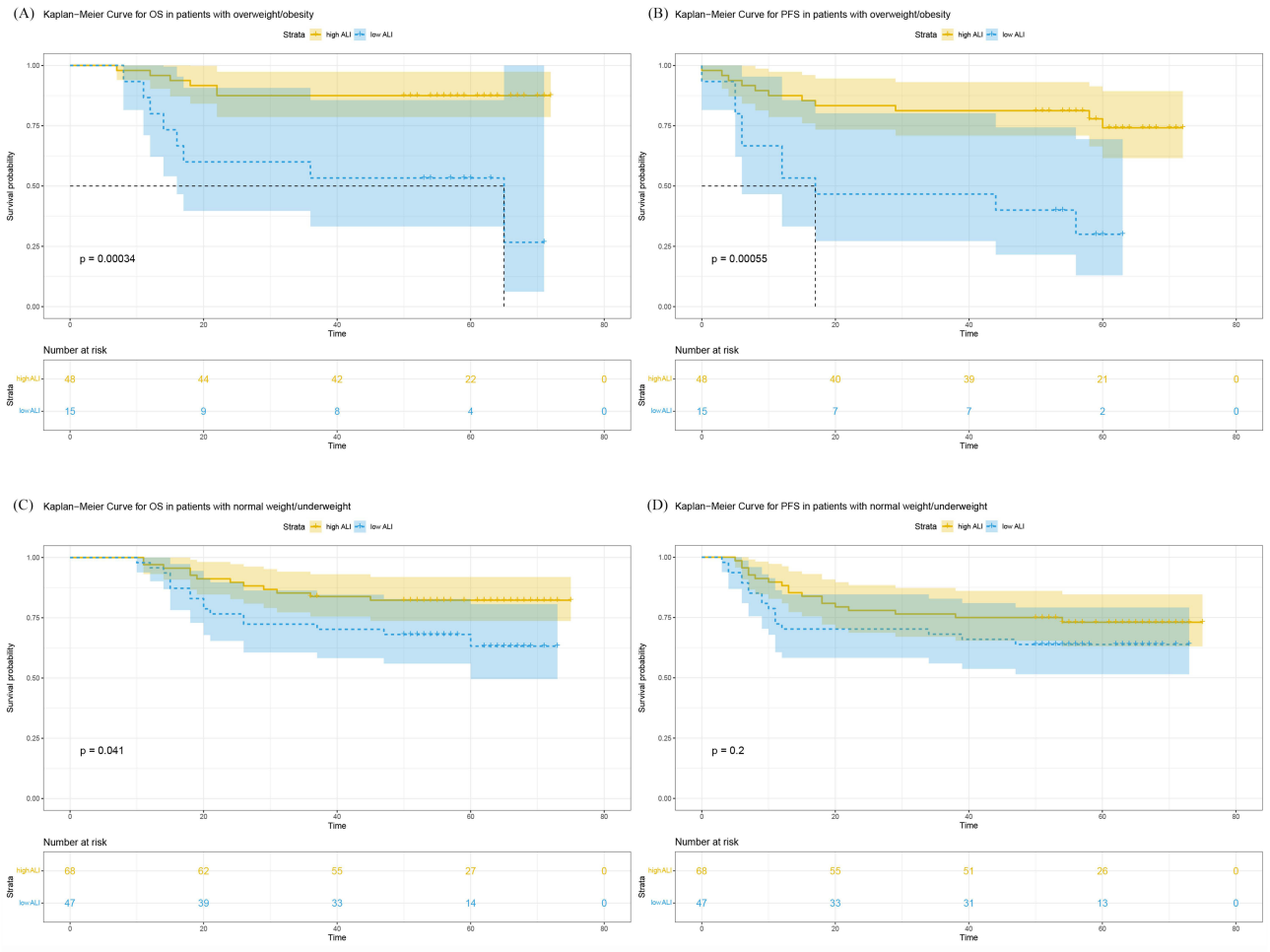

Figure 2 Kaplan–Meier curves of survival time according to advanced lung cancer inflammation index (ALI) for overall survival (OS) in patients with overweight/obesity (**A**), progression-free survival (PFS) in patients with overweight/obesity (**B**), OS in patients with normal weight/underweight (**C**) and PFS in patients with normal weight/underweight (**D**).

(Figure 4) Based on the contribution of each influencing factor to the outcome variable in the model, as indicated by the hazard ratio (HR), points were assigned to each level of the influencing factors. The points were then summed to obtain a total score. Finally, using the conversion relationship between the total score and mortality rate, the predicted value for the mortality rate for that individual can be calculated. The nomograms were presented in Figures 3A and 4A. The C-index, serving as a measurement to assess the performance of the nomogram, was found to be 0.81 for Univariate Cox analyses model. The nomograms, designed for estimating 5-year OS, showed good agreement between their predictions and the actual results in all the included patients by using calibrate plots, as illustrated in Figures 3B and 4B. By using the ROC curves, the optimal cutoff values for nomogram scores were 124.86 (Univariate Cox analyses model) and 111.94 (LASSO regression analyses model). (Figures 3C and 4C) All patients were classified into two groups: the high point group and the low point group. The K-M survival analysis results showed that patients with high nomogram points had worse OS than those with low nomogram points (log-rank P<0.0001) in both models. (Figures 3D and 4D).

Discussion

This study was mainly designed to access the prognostic significance of the ALI in patients with FIGO IIB–III cervical cancer treated with radiotherapy. The findings revealed a substantial correlation between ALI and clinical outcomes. Eventually, 178 patients were included and divided into two groups based on the ALI. ALI was verified as an independent prognostic factor in patients with cervical cancer. According to the results of the Cox regression multivariate

Table 2 Univariate Analyses of Overall Survival and Progression-Free Survival

	Overall Survival		Progression-Free Survival	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age ≤ 55	1.46 (0.78–2.75)	0.238	0.98 (0.58–1.67)	0.954
BMI ≤ 23.9	1.14 (0.6–2.16)	0.694	0.95 (0.56–1.64)	0.867
BMI Continuous	0.93 (0.83–1.05)	0.224	0.95 (0.86–1.05)	0.33
No. of metastatic lymph nodes ≤ 2	0.27 (0.15–0.52)	**<0.001**	0.34 (0.19–0.61)	**<0.001**
Size of metastatic lymph nodes ≥ 2cm	4.27 (2.32–7.83)	**<0.001**	3.00 (1.77–5.11)	**<0.001**
Size of tumor ≥ 4cm	3.04 (1.53–6.05)	**0.002**	1.94 (1.12–3.36)	**0.017**
Invasion of vagina Yes	1.82 (0.96–3.45)	0.069	1.67 (0.96–2.88)	0.067
Type of radiotherapy IMRT	0.96 (0.52–1.78)	0.902	0.94 (0.55–1.6)	0.819
Pathology squamous cell carcinoma	0.26 (0.13–0.54)	**<0.001**	0.27 (0.14–0.52)	**<0.001**
FIGO stage III	3.19 (1.63–6.23)	**0.001**	2.39 (1.38–4.13)	**0.002**
SCC antigen >1.5	1.28 (0.63–2.6)	0.498	1.42 (0.75–2.69)	0.283
Chemoradiotherapy Yes	0.58 (0.18–1.87)	0.36	0.51 (0.18–1.41)	0.194
ALI low	2.9 (1.57–5.35)	**0.001**	2.07 (1.23–3.5)	**0.007**
WBC ≤ 10	0.76 (0.27–2.13)	0.604	0.82 (0.36–2.04)	0.663
PLT ≤ 125	1.19 (0.37–3.84)	0.775	1.57 (0.63–3.92)	0.339
MON ≤ 0.6	0.84 (0.41–1.71)	0.626	0.74 (0.41–1.36)	0.338
ALB ≤ 40	1.59 (0.86–2.95)	0.139	1.68 (0.98–2.85)	0.057
NLR ≤ 3.53	0.36 (0.20–0.66)	**0.001**	0.49 (0.28–0.84)	**0.009**

Note: Bold values indicate statistical significance (*P* <0.05).
Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; IMRT, intensity-modulated radiotherapy; SCC, squamous cell carcinoma; ALI, advanced lung cancer inflammation index. WBC, White Blood Cell Count; PLT, Platelet Count; MON, Monocyte Count; ALB, Albumin; NLR, Neutrophil-to-Lymphocyte Ratio.

Table 3 Multivariate Analyses of Overall Survival and Progression-Free Survival

	Overall Survival		Progression-Free Survival	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
ALI low (Univariate Cox analyses model)	2.07 (1.23–3.5)	**0.007**	1.83 (1.06, 3.17)	**0.031**
ALI low (LASSO regression analyses model)	2.56 (1.35–4.76)	**0.004**	1.82 (1.06–3.13)	**0.030**

Notes: Univariate Cox analyses model: ALI was adjusted for No. of metastatic lymph nodes, Size of metastatic lymph nodes, Size of tumor, invasion of vagina, pathology, FIGO stage. Lasso regression analyses model: ALI was adjusted for No. of metastatic lymph nodes, Size of metastatic lymph nodes, Size of tumor, pathology, FIGO stage.
Abbreviations: HR, hazard ratio; CI, confidence interval; Bold values indicate statistical significance (*P* <0.05).

analysis, patients with low ALI exhibit a 2.56-fold increased risk of mortality and a 1.83-fold increased risk of recurrence compared to those with high ALI. Two nomograms were also created and verified to predict the OS and PFS for individual patients with cervical cancer.

The mechanisms by which ALI predicted the prognosis of patients with cervical cancer can be explained from these two aspects. Emerging evidence has further refined our understanding of the critical role of inflammation in the development and progression of cancer.[33] Inflammation has been recognized as one of the hallmarks of cancer.[34] By inducing immune suppression and producing anti-tumor immune responses, inflammation directly affects the tumor microenvironment.[35] Numerous inflammatory indices to a certain extent reflect the body's inflammatory status, such as the NLR, C-reactive Protein (CRP), and the Systemic Immuno-Inflammation Index (SII) were associated with prognosis in cancer.[36,37] The NLR had been identified as a promising biomarker for predicting cancer prognosis, demonstrating significant clinical utility due to its ease of assessment and derivation from routine complete blood count analyses. The findings from one umbrella review of systematic reviews and meta-analyses showed that the evidence was strong for associations between NLR and OS in many types of cancer.[38] Many studies have also confirmed the relationship between the NLR and prognosis in cervical cancer.[39] Chen's study demonstrated that pretreatment NLR was an independent factor

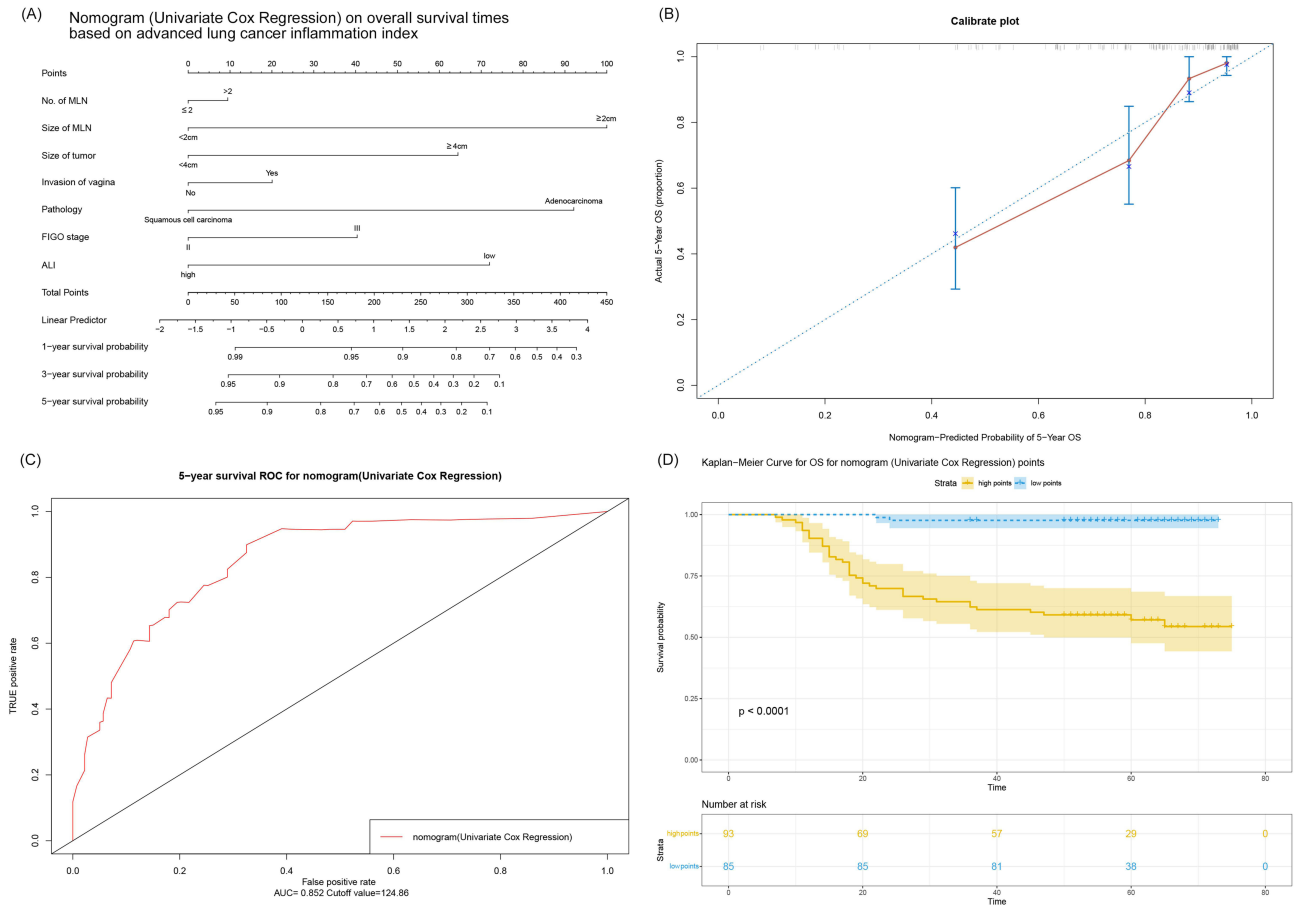

Figure 3 Prognostic nomogram (Univariate Cox Regression) for overall survival (OS) time prediction based on advanced lung cancer inflammation index (ALI). Nomogram on OS based on ALI (**A**). Calibrate plot (**B**). ROC for nomogram points (**C**). Kaplan–Meier curve of OS for nomogram points (**D**).

of survival in patients with metastatic cervical cancer.[40] Other studies have also found that NLR served as a predictor of overall survival for patients with cervical cancer treated with combination immunotherapy.[40] The incorporation of the NLR as a component of the ALI suggests that ALI partially mirrors the inflammatory status in patients with cancer.

As ALI is determined by multiplying the BMI by the serum albumin level and then dividing by the NLR, ALI is a composite marker that reflects nutritional status. Malnutrition has been identified as an independent risk factor that significantly impacts the prognosis of cancer patients, including those with cervical cancer.[28,41] Patients who were malnourished tend to have poorer responses to antitumor treatments, experience more severe side effects from therapy, and have reduced survival times, as well as a decrease in quality of life.[42] Previous research has also suggested that undernourished patients with cervical cancer were at a significantly increased risk of mortality and experienced a marked reduction in survival time.[29] BMI is a widely recognized parameter for diagnosing underweight and overweight conditions in clinical practice. It serves as a critical indicator that is directly associated with nutritional status. Current research indicated that low BMI values had a significant impact on the survival time of patients with cervical cancer. A retrospective cohort study showed that underweight patients had worse OS than normal weight patients with cervical cancer.[43] However, the finding termed the "obesity paradox" also indicated that overweight and obese states predicted improved survival in cancer.[44] The potential reasons for the obesity paradox in cancer may be attributed to the early tumor staging, as well as their enhanced response to anti-cancer treatments. Additionally, patients with obesity tend to have better nutritional status and greater nutrient reserves.[45] To further analyze the prognostic efficacy of ALI in patients with cervical cancer across different BMI categories, subgroup analyses were conducted in this study. The findings revealed that for obese/overweight patients, those with higher ALI levels exhibited significantly longer overall survival and PFS times compared to those with lower ALI levels. For patients with low/normal weight, high ALI predicted long

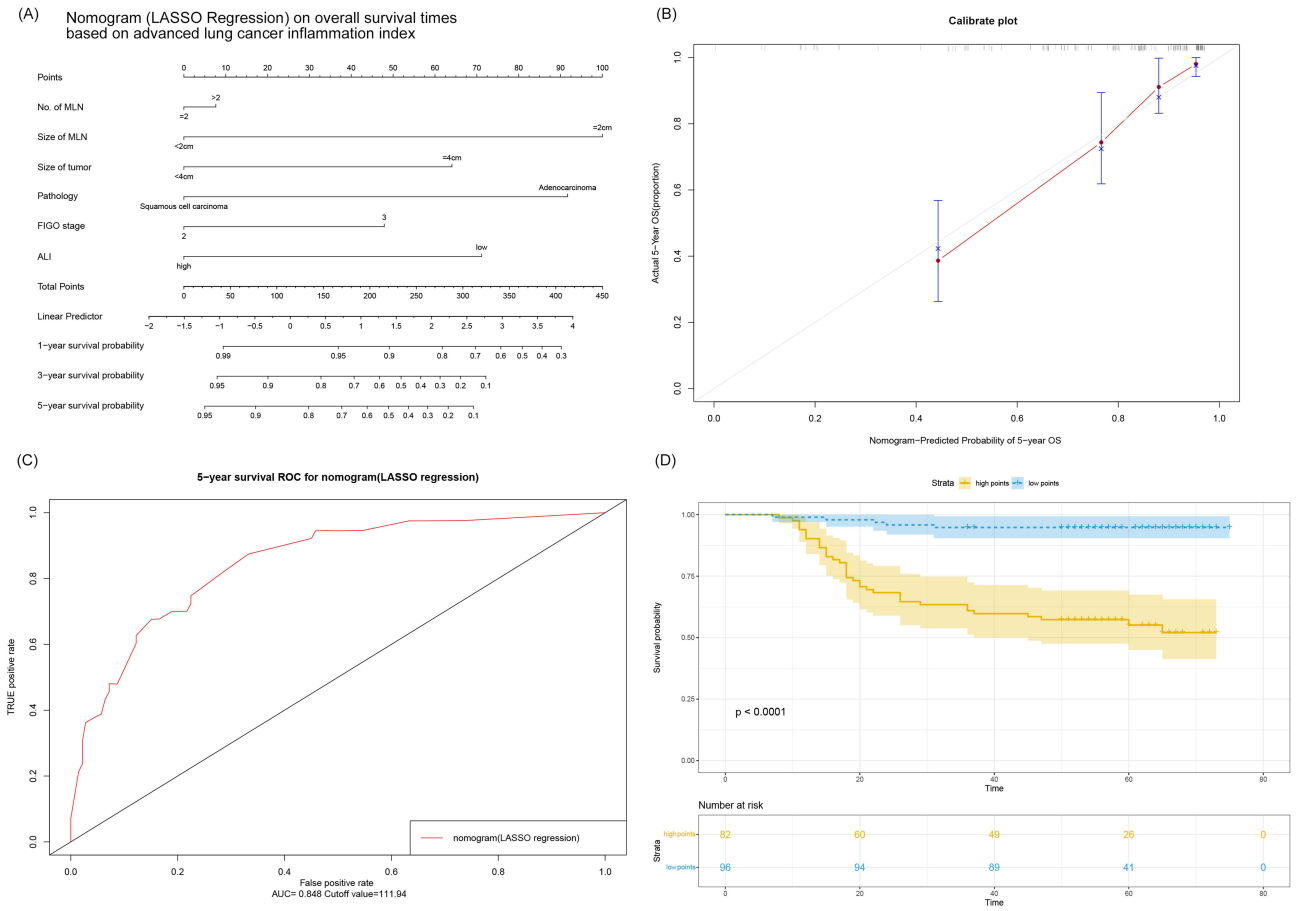

Figure 4 Prognostic nomogram (LASSO regression) for overall survival (OS) time prediction based on advanced lung cancer inflammation index (ALI). Nomogram on OS based on ALI (**A**) Calibrate plot (**B**) ROC for nomogram points (**C**) Kaplan–Meier curve of OS for nomogram points (**D**).

OS times in cervical cancer. However, the results indicated that the difference was not significant in PFS. The possible explanation was that for obese patients, the poorer the nutritional status, the more severe the loss of skeletal muscle mass, and the higher the risk of developing sarcopenic obesity, leading to poorer prognosis. For patients with normal weight and underweight, although the nutritional status had no significant impact on the risk of recurrence, it may result in reduced treatment efficacy, increased adverse events, and higher incidence of complications, which directly affected the overall prognosis, thus leading to a worse overall prognosis for the patients with cervical cancer.

Despite being influenced by many factors in the body, such as capillary permeability, drugs and impaired liver function, albumin is still considered to be related to nutritional status. Serum albumin is a relatively abundant plasma protein in the body, with only 5% being synthesized daily by the liver.[46] The majority of the body's albumin reserves are distributed between the vascular and extravascular compartments, with over 50% located extravascularly. Since the proportion of newly synthesized albumin in the total albumin pool is quite small, daily protein intake has minimal impact on the overall albumin pool, making albumin one of the indicators that reflect long-term nutritional status. Numerous studies have also found a close relationship between hypoalbuminemia and the prognosis of cancer patients.[47,48] For patients with cervical cancer, a low albumin to globulin ratio had been found to be a negative factor in patients treated with surgery and radiation-based therapy.[49–51] On the other hand, ALB was also influenced by the inflammation.[52] As a results, incorporating albumin into the calculation of the ALI also takes into account the patient's inflammatory and nutritional status.

To our knowledge, this study is the first study to evaluate the relationship of the ALI and prognosis among patients with cervical cancer. The ALI was initially designed as an immunonutritional index for patients with lung cancer, intended to predict patients' prognosis. The predictive efficacy of ALI has also been studied and verified in many types of

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cancer.[53] To build prognostic models for predicting treatment outcomes in FIGO IIB–IIIB cervical cancer, we created two ALI based nomograms. The nomograms based models had also been verified in this cohort. The results showed that ALI-based nomograms demonstrated satisfactory predictive efficacy in forecasting the prognosis of patients with cervical cancer undergoing radiotherapy.

In our previous work, we investigated the prognostic role of the controlling nutritional status score (CONUT) and modified CONUT scores in cervical cancer patients undergoing radiotherapy.[28] The CONUT score, a widely used diagnostic tool for malnutrition, is calculated based on albumin levels, total lymphocyte counts, and cholesterol levels. This score categorizes nutritional status into normal, mild malnutrition, moderate malnutrition, and severe malnutrition. Our findings in BMC Cancer highlighted the predictive value of the CONUT score for survival in cervical cancer patients receiving radiotherapy. In this work, we explored the prognostic implications of another inflammatory index, ALI. The calculation methods for the ALI and CONUT indices differ. Unlike the CONUT score, the ALI is a novel index that reflects both nutritional status and inflammatory levels. It offers a more convenient calculation in clinical settings. This is also the innovative aspect of this article.

This study has certain limitations. First, the sample size was insufficient, with only 178 participants included, which prevented us from conducting separate subgroup analyses for underweight individuals. The small sample size may also affect the reliability of the results. Second, as a retrospective study, we were unable to collect further information that could impact patient prognosis, such as treatment methods, which could affect the accuracy of the results. Third, the follow-up in this study was conducted through regular clinic visits and telephone calls, which may introduce bias. Fourth, the study did not collect data on treatment-related adverse reactions and events, preventing a comprehensive understanding of the impact of ALI on the prognosis of cervical cancer patients. Fifth, the cutoff values for ALI vary across different studies, which to some extent limits the application of ALI. Finally, it should be noted that this study did not include an independent internal validation cohort or an external cohort to verify the predictive model. The strength of our study lies in being the first to explore the predictive role of ALI in FIGO IIB–III cervical cancer and in establishing the nomogram models based on the Cox model to predict the survival time of individual cervical cancer patients. In the future, more prospective large-sample studies are needed to verify the predictive role of ALI in cervical cancer and to conduct more nutritional intervention studies based on ALI to improve prognosis.

Conclusion

This study revealed that ALI was an independent factor to predict survival in patients with cervical cancer receiving radiotherapy. The ALI based nomogram was an effective tool to predict survival time for patients with FIGO IIB–III cervical cancer. The ALI based nomogram can help to identify patients who are likely to have unfavorable outcomes and make clinical decisions to conduct nutrition therapy during the radiotherapy. In future, more prospective studies are needed to confirm these findings.

Data Sharing Statement

The data that supports the findings of this study are available on request from the corresponding author.

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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

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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