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Low pretreatment prognostic nutritional index predicts unfavorable survival in stage III-IVA squamous cervical cancer undergoing chemoradiotherapy

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Abstract

Background To investigate potential predictive factors and assess the utility of systemic inflammatory and nutritional indexes as prognostic indicators for survival in patients with FIGO stage III-IVA squamous cervical cancer (squamous HR-LACC) treated with concurrent chemoradiotherapy.

Methods We included consecutive patients with PET-CT diagnosed squamous HR-LACC undergoing curative chemoradiotherapy from November 2016 to April 2024. We systematically reviewed data pertaining to pretreatment clinicopathologic characteristics, hematological parameters, and treatment specifics. A range of composite inflammatory and nutritional indices were calculated, including the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, systemic immune-inflammation index, systemic inflammation response index, pan-immune-inflammation value, and prognostic nutritional index (PNI). X-Tile software was utilized to establish optimal cut-off values based on progression-free survival (PFS). Both univariate and multivariate Cox regression analyses were conducted to identify factors associated with PFS and overall survival (OS).

Results Among 157 patients (median age 55) included, 136 had lymph node involvement, and 45 had para-aortic metastasis. After a median follow-up of 35 months, 47 patients had disease progression, and 22 died, yielding 3-year PFS and OS rates of 66.2% and 82.0%, respectively. Multivariate analysis revealed that low SCC-Ag (HR: 1.518, 95% CI: 1.067–2.159, $p=0.020$), para-aortic lymph node involvement (HR: 1.864, 95% CI: 1.020–3.408, $p=0.043$), and low PNI (HR: 1.477, 95% CI: 1.105–1.975, $p=0.009$) were independently associated with worse PFS, whereas low PNI emerged as the sole independent risk factor for diminished OS (HR = 1.525, 95% CI: 1.002–2.323, $p=0.049$).

Conclusions PNI, a readily obtainable metric based on albumin and lymphocyte count, can serve as a predictor of survival in HR-LACC patients undergoing concurrent chemoradiotherapy. Further research is necessary to ascertain

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whether optimizing pretreatment nutritional status, a modifiable factor, can enhance outcomes in these high-risk patients.

Keywords Cervical cancer, Advanced stage, Chemoradiotherapy, Biomarker, Prognostic nutritional index

Background

Cervical cancer continues to be the fourth most prevalent cancer among women globally [1]. Since the late 20th century, platinum-based concurrent chemoradiotherapy (CRT) has been established as the standard treatment for locally advanced cervical cancer (LACC) without distant metastasis [2]. Despite advancements in radiotherapy techniques and the introduction of MRI-guided adaptive brachytherapy, patients with high-risk LACC (HR-LACC, FIGO stage 2018 III-IVA) still face a 41–53% chance of recurrence or progression within five years, with a 5-year survival rate of only 52–64% [3, 4]. Consequently, there is an urgent need to enhance therapeutic outcomes for these high-risk patients.

The recent international phase 3 OUTBACK trial demonstrated that the addition of adjuvant carboplatin and paclitaxel chemotherapy following standard CRT did not improve progression-free survival (PFS) or overall survival (OS) in LACC patients [5]. Meanwhile, a recent meta-analysis has demonstrated that neoadjuvant chemotherapy followed by radical hysterectomy is associated with inferior PFS and an increase in severe acute toxicity, without any improvement in OS [6]. Therefore, this treatment strategy is recommended only as an alternative in situations where radiotherapy resources are limited [7]. Conversely, the phase 3 GCIG INTERLACE trial showed that short-course induction chemotherapy prior to CRT significantly improved survival in LACC patients, although it is noteworthy that 70% of participants had stage IIB disease and those with para-aortic lymph node involvement were excluded [8]. Encouragingly, the phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial has demonstrated that the incorporation of pembrolizumab into chemoradiotherapy (CRT) significantly enhances survival outcomes in patients with HR-LACC, particularly in those classified under FIGO 2014 stage III-IVA [9, 10]. However, 32% of patients treated with CRT plus pembrolizumab experienced disease progression within two years, and 39% encountered immune-mediated adverse events [10]. Given the emergence of these novel therapies, it is imperative to identify patients who may exhibit resistance to CRT and to accurately stratify HR-LACC patients who are likely to benefit from the addition of immunotherapy.

The role of systemic inflammation and malnutrition in tumor development and progression is increasingly acknowledged. Biomarkers indicative of these conditions have been linked to poor prognoses in various cancers, including cervical cancer [11]. Hematological parameters, due to their accessibility and cost-effectiveness, are extensively studied. Circulating indices such as hemoglobin [12, 13], fibrinogen [14], neutrophil count [15], lymphocyte count [16, 17], and the neutrophil-to-lymphocyte ratio (NLR) [18–22], platelet-to-lymphocyte ratio (PLR) [14, 18, 21, 23, 24], lymphocyte-to-monocyte ratio (LMR) [25], systemic immune-inflammation index (SII) [25, 26], prognostic nutritional index (PNI) [20, 23, 27, 28], and geriatric nutritional risk index (GNRI) [29] have been identified as prognostic biomarkers in patients with LACC undergoing CRT. Meanwhile, recent subgroup analyses from a meta-analysis [11] and a large retrospective study [24] have indicated a stronger correlation between systemic haemato-immunological indices and advanced FIGO stages. However, the majority of these studies have focused on patients with various FIGO stage IB-IVA, and no study has specially addressed on the stage III-IVA HR-LACC.

Consequently, we conducted this retrospective study to evaluate the prognostic significance of systematic inflammatory and nutritional indices in patients with squamous HR-LACC diagnosed via PET-CT and treated with CRT.

Methods

Participants

The study cohort was derived from a prospectively maintained database, encompassing patients treated between November 2016 and April 2024 at the Cancer Institute and Hospital, Chinese Academy of Medical Sciences. The inclusion criteria were: (1) histologically confirmed squamous cell carcinoma of the cervix (SCC); (2) stage III-IVA confirmed by ^{18}F-FDG PET/CT according to the 2018 FIGO staging guidelines; (3) receipt of curative CRT using volumetric-modulated arc therapy (VMAT). The exclusion criteria included: (1) prior systemic therapy, immunotherapy, definitive surgery, or radiation before CRT; (2) presence of other malignancies; (3) incomplete CRT regimen or follow-up data less than three months.

The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences (approval number: 24/290–4570). Informed consent was obtained from all participants.

Data collection and definition

The demographic features, clinical characteristics, and laboratory findings of the patients were extracted from their medical records. Hematological assessments were

conducted prior to the commencement of CRT. Two experienced gynecologists (S. J. and J. A.), independently evaluated the pretreatment PET/CT and MRI scans, determining the clinical tumor stage in accordance with the 2018 FIGO criteria.

Inflammatory markers were quantified as the ratios of neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte. Composite indexes were calculated as follows: prognostic nutritional index (PNI) = serum albumin (g/L) + 5 × lymphocyte count (10^9/L); systemic immune-inflammation index (SII) = absolute platelet count × NLR; systemic inflammation response index (SIRI) = absolute neutrophil count × monocytes/lymphocytes; and pan-immune-inflammation value (PIV) = absolute neutrophil count × platelet count × monocyte count/lymphocyte count.

Table 1 Baseline characteristics of 157 patients with squamous HR-LACC

Characteristics	Values
Age (years)	55 (26–88)
≤55	83 (52.9%)
>55	74 (47.1%)
BMI (Kg/m^2)	23.6 (16.5–37.2)
≤23.9	82 (52.2%)
>23.9	75 (47.8%)
SCC-Ag (ng/ml)	21.7 (0.5 -448.4)
≤ 3.8	19 (12.1%)
>3.8	138 (87.9%)
Tumor differentiation	
Well to moderate	99 (63.1%)
Poorly	58 (36.9%)
Tumor size (cm)	5.5 (2.2–10.1)
≤ 4	17 (10.8%)
>4	140 (89.2%)
FIGO 2018 stage	
IIIB	20 (12.7%)
IIIC1R	91 (58.0%)
IIIC2R	40 (25.5%)
IVA	6 (3.8%)
LNM	
≤ 1	40 (25.5%)
>1	117 (74.5%)
Treatment modality	
CRT	139 (88.5%)
Radiotherapy	18 (11.5%)
Baseline index	
NLR, median (range)	2.7 (0.9–12.1)
PLR, median (range)	164.7 (49.7 -411.1)
LMR, median (range)	5.1 (1.9–9.1)
PNI, median (range)	51.0 (39.1–61.8)
SII, median (range)	839.7 (250.4 -5434.9)
SIRI, median (range)	1.0 (0.2–6.9)
PIV, median (range)	281.9 (52.6 -2880.5)

N number, BMI body mass index, LNM lymph node metastasis, CRT chemoradiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR, platelet to lymphocyte ratio, LMR lymphocyte to monocyte ratio, PNI prognostic nutrition index, SII systemic immune-inflammation index, SIRI systemic inflammation response index, PIV pan-immune-inflammation value

Treatment and follow-up

All patients were treated with platinum-based chemotherapy combined with image-guided beam radiotherapy and high-dose-rate brachytherapy, achieving an equivalent total dose of 85–90 Gy. The external beam radiotherapy was administered in 25 fractions of 1.8–2.0 Gy/fraction for a total dose of 45–50 Gy, using the VMAT technique with 6-MV photon beams. Positive lymph nodes received an additional simultaneous boost of 10–20 Gy, while the administration of para-aortic external beam radiotherapy was left to the discretion of the attending physician. Concurrent chemotherapy involved weekly cisplatin or carboplatin for 5 weeks.

Following the completion of therapy, patients were monitored every three months for the first two years, every six months for the subsequent three years, and annually thereafter. Follow-up evaluations included pelvic examinations, radiological imaging, and biopsies as necessary.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 26.0). The primary endpoint of the study was PFS, defined as the duration from diagnosis to disease progression, death from any cause, or the last visit. OS was defined as the interval between diagnosis and death from any cause. Furthermore, in light of the COVID-19 pandemic, we classified COVID-related deaths as censored at the time of death [30]. Baseline characteristics of the study participants were described using median (range) and frequency (percentage), as appropriate. X-Tile software was utilized to determine the optimal cut-off values based on PFS [31]. Survival analysis was conducted using the Kaplan–Meier method and comparisons were made using the log-rank test. Variables with a p-value of less than 0.20 in the univariate analysis were subsequently included in the multivariate Cox regression analysis. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 presents a summary of the baseline characteristics of the 157 patients enrolled in the study. The median age of the participants was 55 years (range, 26–88), and the median tumor size was 5.5 cm (range, 2.2–10.1). The majority of patients (86.6%, $n = 136$) exhibited lymph node involvement, with pelvic involvement in 91 patients (58.0%) and both pelvic and para-aortic involvement in 45 patients (28.7%). Furthermore, 88.5% ($n = 139$) of the

patients received CRT. The median overall treatment duration was 53 days, with 33.8% ($n = 53/157$) of patients completing their treatment within 7 weeks.

The median pretreatment total leukocyte count was 7.21 × 10^9/L, with absolute neutrophil, lymphocyte, and monocyte counts of 4.74 × 10^9/L, 1.74 × 10^9/L, and 0.36 × 10^9/L, respectively. The median baseline hemoglobin (HGB) level was 12.5 g/dL, the median platelet count was 290 × 10^9/L, and the albumin level was 42.4 g/L. At baseline, the median values for the NLR, PLR, LMR, SII, SIRI, PNI, and PIV were 2.73 (range: 0.92–12.15), 164.66 (range: 49.69–411.11), 5.09 (range: 1.91–9.13), 839.70 (range: 250.38–5434.89), 1.03 (range: 0.19–6.92), 51.00 (range: 39.05–61.80), and 281.92 (range: 52.58–2880.49), respectively.

Over a median follow-up period of 35 months (range: 3–96 months), 47 patients (29.9%) experienced disease progression, and 22 patients (14.0%) died, yielding 3-year PFS and OS rates of 66.2% and 82.0%, respectively (Fig. 1).

Optimal cut off values

Utilizing X-Tile software, the optimal cut-off values based on PFS for BMI, SCC-Ag, NLR, PLR, LMR, SII, SIRI, PNI, and PIV were determined to be 23.9, 3.8, 3.2, 133.0, 6.2, 1181.2, 2.0, 49.1, and 143.2, respectively. The corresponding survival curves are depicted in Fig. 2a and i, respectively.

Factors associated with survival for HR-LACC treated with CRT

Tables 2 and 3 present factors associated with survival in patients with HR-LACC treated with CRT. Univariate analysis identified SCC-Ag ≤ 3.8 ng/mL (reference: 0–1.5 ng/mL), para-aortic lymph node involvement, and low PNI as significant prognostic factors for poor PFS (Fig. 2b and j, and 2i). In multivariate analysis, low SCC-Ag levels (HR: 1.518, 95% CI: 1.067–2.159, $p = 0.020$), para-aortic lymph node involvement (HR: 1.864, 95% CI: 1.020–3.408, $p = 0.043$), and low PNI (HR: 1.477, 95% CI: 1.105–1.975, $p = 0.009$) were identified as independent factors associated with PFS (Table 2). The 3-year PFS rates were 36.4% versus 69.8%, 54.3% versus 70.3%, and 52.1% versus 72.6%, respectively.

The same threshold settings were applied for OS as for PFS. Univariate analysis indicated that para-aortic lymph node involvement and low PNI were correlated with poorer OS (Fig. 2k and l). In multivariate analysis, low PNI emerged as the sole independent parameter associated with diminished OS (Table 3), with 3-year OS rates of 63.5% versus 87.8%.

Relationship between pretreatment PNI and clinicopathologic factors

We also compared the clinicopathological factors between pretreatment low and high PNI groups. As shown in Table 4, there was no significant difference between the two groups.

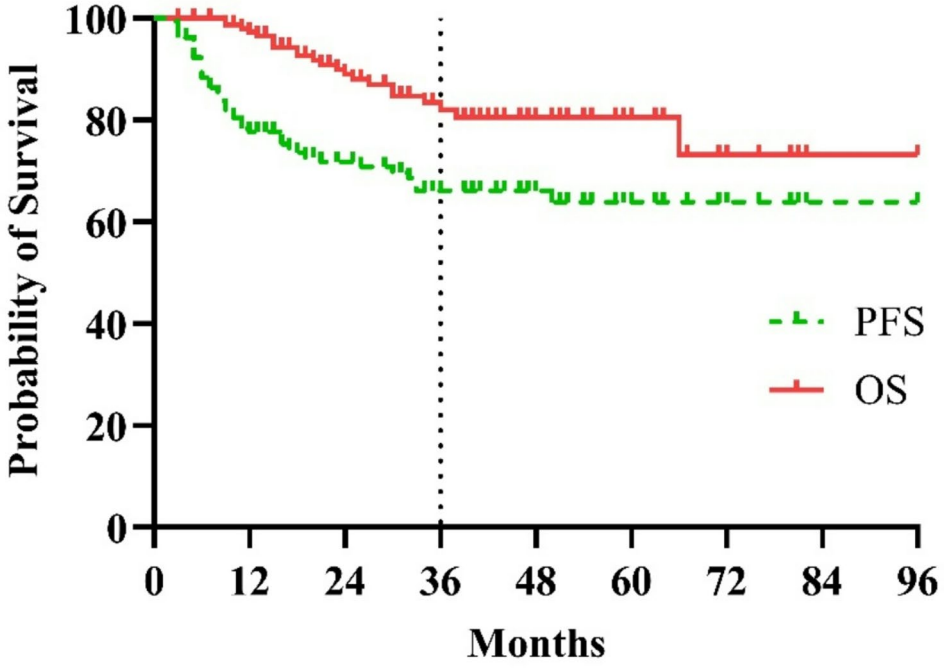
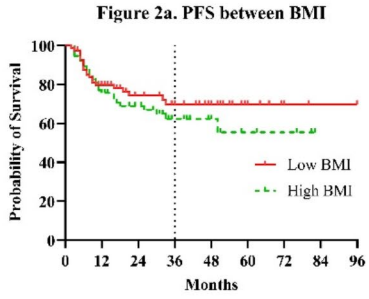
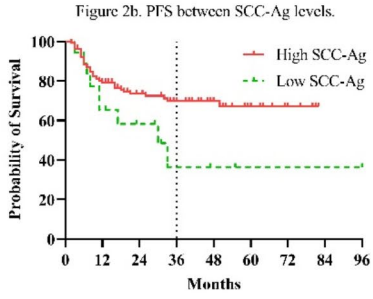
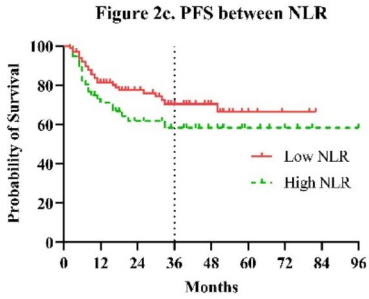
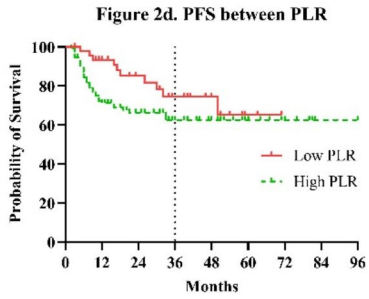


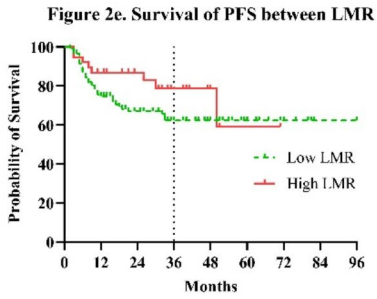
Fig. 1 Kaplan-Meier plot for survival of the whole cohort

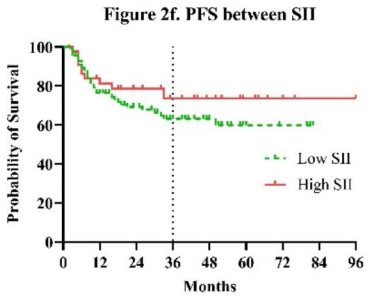


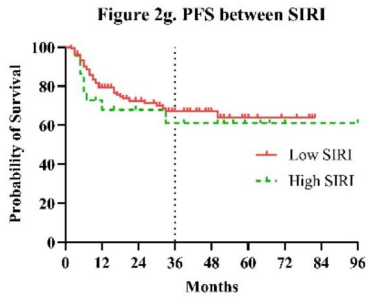


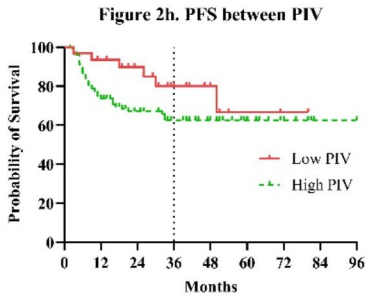


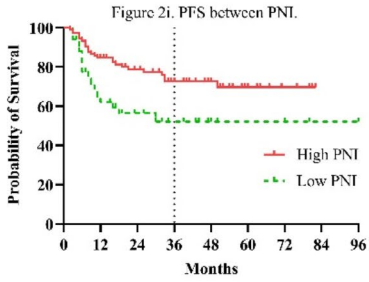


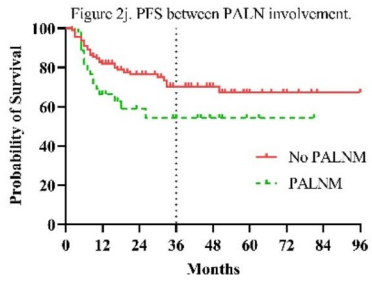


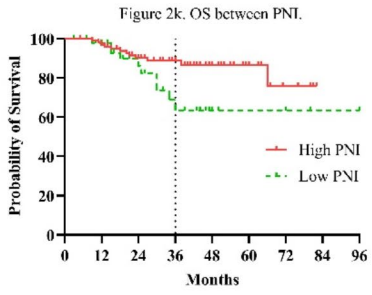












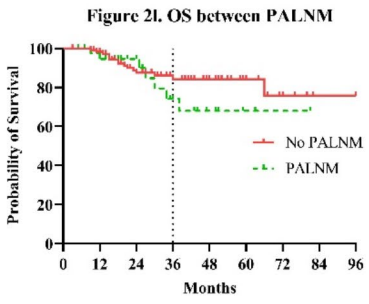


Fig. 2 (See legend on next page.)

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Fig. 2 Kaplan–Meier plots of survival in different subgroups for squamous HR-LACC. **a** Progression-free survival (PFS) between different BMI subgroups. **b** PFS between different SCC-Ag subgroups. **c** PFS between different neutrophil-to-lymphocyte subgroups. **d** PFS between different platelet-to-lymphocyte subgroups. **e** PFS between different lymphocyte-to-monocyte subgroups. **f** PFS between different systemic immune-inflammation index subgroups. **g** PFS between different ystemic inflammation response index subgroups. **h** PFS between different pan-immune-inflammation value subgroups. **i** PFS between different prognostic nutritional index subgroups. **j** PFS between different para-aortic lymph node status subgroups. **k** Overall survival (OS) between different prognostic nutritional index subgroups. **l** OS between different para-aortic lymph node status subgroups

Discussion

In this study, we conducted a comprehensive investigation into the potential predictive factors for women with squamous HR-LACC undergoing CRT. We specifically evaluated the prognostic utility of systemic inflammatory and nutritional indices for PFS and OS. This study constitutes a significant contribution to the understanding of squamous HR-LACC, with all participants diagnosed using PET-CT and treated with modern VMAT technology. Our findings indicate that low pretreatment PNI, para-aortic lymph node involvement, and low baseline SCC-Ag levels are independently associated with poorer PFS. Regarding long-term prognosis, pretreatment PNI emerged as the sole factor related to OS. These results strongly support the integration of PNI into risk stratification protocols for squamous HR-LACC patients undergoing CRT and highlight the critical need to optimize nutritional status in preparation for treatment in these high-risk individuals.

Malnutrition was prevalent in nearly two-thirds of HR-LACC patients receiving CRT [32], and it was associated with deteriorated survival outcomes [33, 34]. Serum albumin and lymphocyte levels are key indicators of nutritional and immune status in cancer patients. Low albumin suggests malnutrition, while reduced lymphocytes indicate weakened immunity. Therefore, the PNI, calculated from circulating albumin and lymphocyte levels, may function as a quantitative biomarker reflecting the nutritional and immune status of cancer patients. A low PNI is hypothesized to be associated with cancer-related malnutrition and immune deficiency. Our study, aligning with previous research [20, 23, 27, 29], shows that a lower pretreatment PNI is associated with worse PFS and OS in HR-LACC patients undergoing CRT. Lower PNI is also documented to be related to older age, larger tumor size, advanced FIGO stage, lymph node involvement, parametrial extension, and vaginal invasion [20, 23, 27]. However, only 31.4-55% of the patients in these studies were in FIGO stage III-IV HR-LACC, with limited sample sizes [20, 23, 24, 27, 29]. Recent research suggests that PNI is more significant in HR-LACC patients than in early-stage LACC [20, 24]. Kumar et al. have conducted the most extensive study to date on HR-LACC patients, investigating the correlation between hematological parameters and clinical outcomes [24]. However, only 12.4% of the patients in their study received treatment with modern IMRT/VMAT radiotherapy, and the PNI cut-off value used was substantially lower than the standard values (41.05 versus 48.3 to 49.5) [20, 23, 27, 29], which may limit the applicability of their findings. Despite this, their findings and ours suggest pretreatment PNI is a strong risk stratification tool for HR-LACC.

Notably, our study identified that patients with low pretreatment SCC-Ag levels exhibited reduced PFS. Elevated pretreatment SCC-Ag levels have been associated with advanced FIGO stage [35, 36], increased primary tumor volume [35, 37], regional lymph node metastasis [35, 36], lymphovascular invasion [36], and deep stromal infiltration [36] in cervical squamous carcinoma. Elevated pretreatment SCC-Ag levels have been associated with poorer survival outcome [35, 38–40], increased local-regional recurrence [35], para-aortic lymph node relapse [41], and distant failure [35, 42] in LACC patients undergoing CRT. Furthermore, in vitro studies have shown that overexpression of SERPINB3, an SCC-Ag isoform, increases radio-resistance, while its knockout enhances radiosensitivity in cervical tumor cells [38]. Unlike previous studies, our research exclusively focused on squamous HR-LACC. In contrast, earlier studies included 10.6-16.6% of patients with adeno- or adenosquamous carcinoma of the cervix [40, 42], employed varying cut-off values for SCC-Ag, and notably, only half of the patients were high-risk or node-positive [35, 38, 39, 42, 43]. Our study found 95.5% of squamous HR-LACC ($n = 150/157$) exhibited elevated pretreatment SCC-Ag levels, surpassing the previously reported rates of 71.4-71.9% for LACC patients [38, 39]. Therefore, it is crucial not to be misled by the apparent low SCC-Ag levels in these radiologically high-risk subjects, as they may not accurately reflect the true tumor burden.

It was not surprising to find that para-aortic lymph node involvement is associated with inferior PFS. PALNM is a strong predictor of worse prognosis [44–47], and is incorporated in the new FIGO 2018 staging system, highlighting the importance of evaluating PALN status [48]. Despite this recognition, therapeutic advancements for these ultra high-risk patients remain limited, and patients with para-aortic node involvement were all excluded for recent phase III chemoradiation trials [3–5]. In a retrospective analysis involving 59 patients with PALNM treated with extended-field IMRT, the 3-year PFS and OS rates were only 41.3% and 52.8%, respectively [49]. And the phase I GOG study

Table 2 Factors associated with PFS for high-risk locally advanced squamous cervical cancer treated with chemoradiotherapy

Characteristics	*n*	Univariable		Multivariable	
		HR, 95% CI	*p*-value	HR, 95% CI	*p*-value
Age (years)			0.497		
≤55	83	1			
> 55	74	0.819 (0.459–1.461)			
BMI (Kg/m^2)			0.302		
≤23.9	82	1			
> 23.9	75	1.342 (0.757–2.379)			
SCC-Ag (ng/ml)			0.018		0.020
> 3.8	138	1		1	
≤3.8	19	2.267 (1.126–4.567)		1.518 (1.067–2.15)	
Tumor differentiation			0.206		
Well to moderate	99	1			
Poorly	58	1.491 (0.802–2.772)			
Tumor size (cm)			0.557		
≤5.5	81	1			
> 5.5	76	1.187 (0.669–2.107)			
FIGO 2018 stage			0.328		
IIIB	20	1			
IIIC1R	91	0.943 (0.386–2.303)			
IIIC2R-IVA	46	1.531 (0.598–3.921)			
LNM			0.515		
≤1	40	1			
> 1	117	1.251 (0.636–2.459)			
PALNM			0.040		0.043
No	112	1		1	
Yes	45	1.851 (1.018–3.368)		1.864 (1.020–3.408)	
Chemotherapy cycles			0.291		
≤ 4	92	1			
> 4	65	0.857 (0.643–1.142)			
NLR			0.124		
≤ 3.2	100	1			
> 3.2	57	1.565 (0.880–2.782)			
PLR			0.085		0.368
≤133.0	46	1			
> 133.0	111	1.832 (0.911–3.687)			
LMR			0.164		
≤6.2	119	1			
> 6.2	38	0.587 (0.274–1.256)			
PNI			0.004		0.009
> 49.1	51	1		1	
≤ 49.1	106	1.513 (1.132–2.022)		1.477 (1.105–1.975)	
SII			0.280		
≤1181.2	114	1			
> 1181.2	43	0.682 (0.339–1.372)			
SIRI			0.503		
≤ 2.0	135	1			
> 2.0	22	1.297 (0.605–2.780)			
PIV			0.093		0.231
≤143.2	31	1			
> 143.2	126	2.050 (0.870–4.834)			

N number, BMI body mass index, LNM lymph node metastasis, PALNM para-arotic lymph node metastasis, CRT chemoradiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR, platelet to lymphocyte ratio, LMR lymphocyte to monocyte ratio, PNI prognostic nutrition index, SII systemic immune-inflammation index, SIRI systemic inflammation response index, PIV pan-immune-inflammation value

Table 3 Factors associated with OS for high-risk locally advanced squamous cervical cancer treated with chemoradiotherapy

Characteristics	*n*	Univariable		Multivariable	
		HR, 95% CI	*p*-value	HR, 95% CI	*p*-value
Age (years)			0.918		
≤55	83	1			
> 55	74	0.974 (0.637–1.491)			
BMI (Kg/m^2)			0.190		
≤23.9	82	1			
> 23.9	75	1.315 (0.565–3.061)			
SCC-Ag (ng/ml)			0.151		
> 3.8	138	1			
≤3.8	19	1.494 (0.907–2.461)			
Tumor differentiation			0.228		
Well to moderate	99	1			
Poorly	58	1.149 (0.621–2.125)			
Tumor size (cm)			0.740		
≤5.5	81	1			
> 5.5	76	1.456 (0.625–3.392)			
FIGO 2018 stage			0.107		
IIIB	20	1			
IIIC1R	91	1.210 (0.271–5.403)			
IIIC2R-IVA	46	1.992 (0.413–9.604)			
LNM			0.963		
≤1	40	1			
> 1	117	1.191 (0.437–3.243)			
PALNM			0.038		0.306
No	112	1		1	
Yes	45	1.665 (0.676–4.099)		1.604 (0.649–3.961)	
Chemotherapy cycles			0.221		
≤ 4	92	1			
> 4	65	1.328 (0.573–3.078)			
NLR			0.313		
≤ 3.2	100	1			
> 3.2	57	1.180 (0.503–2.769)			
PLR			0.214		
≤133.0	46	1			
> 133.0	111	1.966 (0.663–5.828)			
LMR			0.526		
≤6.2	119	1			
> 6.2	38	0.705 (0.238–2.088)			
PNI			0.043		0.049
> 49.1	51	1		1	
≤ 49.1	106	1.525 (1.002–2.323)		1.525 (1.002–2.323)	
SII			0.213		
≤1181.2	114	1			
> 1181.2	43	0.508 (0.172–1.503)			
SIRI			0.927		
≤ 2.0	135	1			
> 2.0	22	0.975 (0.566–1.680)			
PIV			0.160		
≤143.2	31	1			
> 143.2	126	2.716 (0.635–11.625)			

BMI body mass index, LNM lymph node metastasis, PALNM para-aortic lymph node metastasis, CRT chemoradiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR, platelet to lymphocyte ratio, LMR lymphocyte to monocyte ratio, PNI prognostic nutrition index, SII systemic immune-inflammation index, SIRI systemic inflammation response index, PIV pan-immune-inflammation value

Table 4 Relationship between baseline PNI and clinicopathologic characteristics

Variable	*n*	Low PNI	High PNI	*P* value
Age (years)				0.312
≤55	83	24 (28.9%)	59 (71.1%)	
> 55	74	27 (36.5%)	47 (63.5%)	
BMI (Kg/m^2)				0.420
≤23.9	82	29 (35.4%)	53 (64.6%)	
> 23.9	75	22 (29.3%)	53 (70.7%)	
SCC-Ag (ng/ml)				0.665
> 3.8	138	44 (31.9%)	94 (68.1%)	
≤3.8	19	7 (36.8%)	12 (63.2%)	
Tumor differentiation				0.446
Well to moderate	99	30 (30.3%)	69 (69.7%)	
Poorly	58	21 (36.2%)	37 (63.8%)	
Tumor size (cm)				0.141
≤5.5	81	22 (27.2%)	59 (72.8%)	
> 5.5	76	29 (38.2%)	47 (61.8%)	
FIGO 2018 stage				0.291
IIIB	20	5 (25.0%)	15 (75.0%)	
IIIC1R	91	27 (29.7%)	64 (70.3%)	
IIIC2R-IVA	46	19 (41.3%)	27 (58.7%)	
LNM				0.694
≤1	40	14 (35.0%)	26 (65.0%)	
> 1	117	37 (31.6%)	80 (68.4%)	
PALNM				0.099
No	112	32 (28.6%)	80 (71.4%)	
Yes	45	19 (42.2%)	26 (57.8%)	
Chemotherapy cycles				0.759
≤4	139	29 (31.5%)	63 (68.5%)	
> 4	18	22 (33.8%)	43 (66.2%)	

BMI body mass index, LNM lymph node metastasis, PALNM para-arotic lymph node metastasis, PNI: prognostic nutrition index

demonstrated the safe tolerability of extended-field CRT followed by adjuvant chemotherapy in HR-LACC patients with [50]. Importantly, the global, randomized, phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial established that the addition of pembrolizumab to CRT significantly enhances PFS and OS in patients with HR-LACC, including those with PALNM [9]. Consequently, there is a pressing need for the continued investigation of innovative treatment strategies, such as consolidation systemic therapy combining chemotherapy and immunotherapy in these ultra high-risk subjects.

Our study has several limitations. Firstly, as a retrospective analysis, it is subject to selection bias. Secondly, our investigation focuses solely on squamous HR-LACC from a single center and ethnicity, thereby limiting the generalizability of our findings. External validation in multi-center trials is needed. Thirdly, the optimal PNI cut-off value is undetermined, with studies using varying methods. We used X-Tile software [31] to set it at 49.1, aligning with previous research that reported values ranging from 48.3 to 49.5 in LACC patients [20, 23, 27, 29]. Fourthly, recent studies have demonstrated that the high-sensitivity modified Glasgow Prognostic Score (HS-mGPS) is capable of reflecting the status of cancer-associated cachexia and serves as a reliable prognostic biomarker for cancer patients [51]. However, its applicability in HR-LACC remains uncertain. Lastly, recent research indicates that dynamic changes in nutritional status during cancer treatment may more accurately predict tumor prognosis than static pretreatment measurements [17, 34, 52]. Regrettably, our study lacked data on these dynamic changes. Further research is necessary to evaluate these aspects comprehensively.

In conclusion, this study may be among the first to demonstrate the PNI as an independent pretreatment indicator for PFS and OS in patients with squamous HR-LACC undergoing CRT. Our findings advocate for the integration of these simple, readily accessible, and cost-effective standard laboratory parameters into routine management of squamous HR-LACC, thereby aiding clinicians in developing individualized therapeutic strategies for these patients. Nevertheless, multi-center and large-scale prospective studies are necessary to validate the optimal PNI cut-off value and its prognostic significance.

Abbreviations

CRT	chemoradiotherapy
LACC	locally advanced cervical cancer
HR-LACC	high-risk locally advanced cervical cancer
PFS	progression-free survival
OS	overall survival
NLR	neutrophil-to-lymphocyte ratio
PLR	platelet-to-lymphocyte ratio
LMR	lymphocyte-to-monocyte ratio
SII	systemic immune-inflammation index
PNI	prognostic nutritional index
GNRI	and geriatric nutritional risk index
SCC	squamous cell carcinoma
VMAT	volumetric-modulated arc therapy

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Author contributions
Shuang-Zheng Jia: Data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); writing– original draft (lead). Xue-Jiao Yang: Data curation (equal); formal analysis (equal); writing– original draft (equal). Duan Yang: Data curation (equal). Rui Wang: Data curation (equal). Xi Yang: Data curation (equal). Man-Ni Huang: Data curation (equal). Ju-Sheng An: formal analysis (equal); investigation (equal); project administration (equal); writing– review and editing.All authors reviewed the manuscript.

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

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences (approval number: 24/290–4570). Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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