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Prognostic significance of systemic inflammatory indices in squamous cell carcinoma of the anal canal: A retrospective cohort study

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Abstract

Background: Squamous cell carcinoma of the anal canal is a rare gastrointestinal malignancy with heterogeneous outcomes despite standardized chemoradiotherapy. Systemic inflammation has been implicated in tumor progression, and hematological indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation score (SII) have emerged as potential prognostic markers. This study aimed to assess the prognostic significance of pre-treatment inflammatory indices (NLR, PLR, SII) for disease-free survival (DFS) and overall survival (OS). **Methods:** This retrospective cohort study included 243 adult patients treated between 2006 and 2023 with combined chemoradiotherapy (5-fluorouracil and mitomycin C). Inflammatory indices were calculated from baseline laboratory values. Optimal cut-offs were determined using ROC analysis. Survival was evaluated using Kaplan–Meier curves and log-rank tests. Independent prognostic factors were identified through multivariate Cox regression. **Results:** Elevated indices were frequent (NLR ≥4: 56.8%; PLR ≥250: 47.7%; SII ≥980: 52.3%). Higher NLR, PLR, and SII were significantly associated with reduced DFS and OS ($p < 0.05$). In multivariate analysis, lymph node involvement (HR 1.94; $p = 0.003$), SII ≥980 (HR 2.01; $p = 0.013$), and absence of complete response (HR 5.67; $p < 0.001$) independently predicted poorer DFS. For OS, ECOG ≥1 (HR 2.70; $p = 0.005$), lymph node involvement (HR 3.45; $p = 0.001$), absence of complete response (HR 4.21; $p < 0.001$), NLR ≥4 (HR 2.47; $p = 0.049$), and PLR ≥250 (HR 3.28; $p = 0.006$) were independent predictors. **Conclusion:** Pre-treatment inflammatory indices provide significant prognostic information in squamous cell carcinoma of the anal canal and may enhance baseline risk stratification alongside established clinical factors.

Keywords

anal cancer, NLR, PLR, systemic inflammation, survival, prognosis

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Introduction

Squamous cell carcinoma of the anal canal is a rare but increasingly recognized gastrointestinal malignancy.[1,2] With an estimated 4.8 million new cases and 3.4 million deaths, cancers of the gastrointestinal tract account for more than a quarter (26%) of the global cancer incidence and more than a third (35%) of all cancer-related deaths.[3,4]

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Anal canal carcinoma accounts for approximately 1% of all gastrointestinal cancers. The majority are squamous cell carcinomas, and adenocarcinoma represents <10% of all anal tumors.[5,6] Histology varies by tumor location. Tumors of the anal margin are squamous cell carcinomas (accounting for about three-quarters of tumors in this location) and, less frequently, basal cell carcinomas, Bowen's disease, and Paget's disease. Approximately 20% of patients present with metastatic disease at diagnosis, and another 20% of early-stage patients will develop metastases.[5,7]

Risk factors such as HPV, HIV, anal intercourse, smoking, and immunosuppression are also cited. HPV infection, particularly serotypes 16, 18, and 31, has been associated with squamous cell carcinoma of the anus. Similarly, the presence of chronic inflammatory changes is identified in fistulous processes, hidradenitis suppurativa, or chronic inflammatory bowel disease.[5,6] Smoking appears to play a significant role in the development of anal cancer, independent of other risk factors.[5,6] Clinical diagnosis is difficult, with nonspecific symptoms that appear late and are often confused with a benign perianal fistula. The most frequent clinical manifestation is rectal bleeding in 45% of patients; this is usually attributed to hemorrhoidal disease, thus delaying diagnosis. Up to 35% of patients report pain or a mass in the rectum.[5,6]

Tumor staging is performed using pelvic magnetic resonance imaging and, if the patient tolerates it, transanal ultrasound.[8,9] Despite advances in the diagnosis and treatment of squamous cell carcinoma of the anal canal, patients with this tumor have a poor therapeutic response and survival rate.[5,7] Therefore, biomarkers with predictive value for prognosis and survival are being sought.

Cancer progression and development are related to the host's inflammatory response. Studies demonstrate that the systemic inflammatory response is a good independent predictor of tumor stage.[10] The role of the systemic inflammatory response in cancer recurrence and death is increasingly recognized. It is evident that, in both advanced and recently diagnosed localized cancer, host factors such as weight loss, poor functional status, and systemic inflammatory response are related, with the latter being an important predictor of prognosis independent of tumor stage.[7,10] Elevated systemic inflammatory response is one of the key indicators of the tumor microenvironment status, which corresponds to a poor prognosis.[10]

Approximately 25% of neoplasms are associated with chronic inflammation, which causes DNA damage or failures in the mechanisms for resolving the immune response, thus contributing to the development of neoplastic cells. This occurs through the convergence of intrinsic and extrinsic inflammation, resulting in the activation of transcription factors, which in turn generates the production of inflammatory mediators such as cytokines, chemokines, and cyclooxygenase-2.[10,11] In cancer, adaptive immune responses are suppressed and other pathways are activated. Among the markers of the acute phase response are C-reactive protein and albumin; these are sensitive and correlate with systemic inflammation in cancer patients.[10] The modified Glasgow Prognostic Score, which is based on a combination of these acute-phase proteins, has been validated in a variety of clinical settings and demonstrates prognostic value, independent of tumor-based factors.[10,11]

In recent years, the role of hematological indices in the systemic inflammatory response has been analyzed for their use in predicting prognosis in patients with anal cancer.[12–14] Among these indices, the following have been identified: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammation score (SII), and lymphocyte-C-reactive protein index.[13,15] Currently, the neutrophil-to-lymphocyte ratio is known to be a highly sensitive marker of acute, subacute, and/or chronic inflammation associated with infectious diseases, non-infectious diseases, and diseases of mixed etiology. Accordingly, more than 140 studies have been published on the clinical utility of this index in predicting prognosis in various types of cancer.[12,16]

Furthermore, the association between platelets and tumors has been known since 1865. In the tumor microenvironment, platelets promote angiogenesis and metastasis through the release of vascular endothelial growth factor and transforming growth factor-β.[17,18] Solid tumors can increase platelet production by increasing the production of thrombopoietin and interleukin-6, leading to secondary thrombocytosis.[17,18] The systemic immune-inflammation index integrates neutrophils, platelets, and lymphocytes and reflects the balance between inflammation and immune status. Among the advantages of these indices is that they are robust and reliable biomarkers of systemic inflammation; they are available, easy to obtain, and economically affordable; and they have an independent prognostic role with respect to overall survival and disease-free survival.[12,14,15]

Despite their importance, there are insufficient studies evaluating inflammatory indices as a prognostic factor in patients with squamous cell carcinoma of the anal canal in our setting.

Aim and objectives

The aim of this study is to identify the prognostic value of inflammatory indices in patients with squamous cell carcinoma of the anal canal treated between January 2006 and December 2023 and to evaluate whether NLR, PLR, and SII independently predict disease-free survival and overall survival.

Methods

Study design

A retrospective, quantitative, observational study was conducted. The study followed a cohort design, as it analyzed previously recorded clinical and pathological data of patients diagnosed with anal carcinoma and assessed their outcomes over time. This design was appropriate because it enabled the evaluation of prognostic inflammatory markers and their association with survival and therapeutic response using existing medical records. The retrospective cohort approach allowed for long-term follow-up and survival analysis while ensuring feasibility and cost-effectiveness.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19]

Setting

The study was carried out at the Oncology Service of the Hermanos Ameijeiras Clinical Surgical Hospital. This tertiary care institution provides specialized oncological treatment and follow-up for patients with malignant diseases. The chemo-radiotherapy protocol (5-fluorouracil and mitomycin C with concurrent radiotherapy) remained consistent throughout the 2006-2023 study period, with no major changes in drug doses, radiation total dose (45-54 Gy), or fractionation schedule. All eligible patients diagnosed and treated during the defined study period were identified through hospital medical records.

Population and sampling

The target population consisted of all patients diagnosed with primary anal carcinoma. The accessible population included all patients with a confirmed primary diagnosis of anal carcinoma who were treated at the Oncology Service of the Hermanos Ameijeiras Clinical Surgical Hospital between January 2006 and December 2023.

A non-probabilistic convenience sampling technique was used because the study aimed to include all eligible patients with complete medical records over the 18-year period, rather than random selection. This approach maximized sample size for survival analysis given the rarity of anal cancer. Initially, 265 patients with a primary diagnosis of anal carcinoma were identified from hospital records. Of these, 22 patients were excluded: 12 had incomplete medical records, 6 received palliative-only treatment, and 4 had documented acute infection or systemic steroid use within 7 days of the pre-treatment blood draw. After applying inclusion and exclusion criteria, the final sample consisted of 243 patients aged 18 years and older.

Inclusion and exclusion criteria

Inclusion criteria

Patients aged $\geq$18 years.
Confirmed primary diagnosis of anal carcinoma.
Received combined chemoradiotherapy using the 5-fluorouracil (5-FU) and mitomycin C (MMC) regimen with radiotherapy.
Adequate clinical follow-up and complete medical records.

Exclusion criteria

Patients with incomplete medical records or insufficient clinical information.
Patients with T1N0 tumors of the anal margin treated only with surgery $\pm$ radiotherapy.
Patients who received exclusively palliative treatment or who did not complete the prescribed therapeutic course.
Patients with documented acute infection (e.g., fever, leukocytosis, antibiotic prescription) or systemic steroid use within 7 days prior to the pre-treatment blood draw.

These criteria ensured homogeneity of the sample and reliability of outcome assessment.

The number of patients excluded for each criterion was as follows: incomplete records (n=12), palliative-only treatment (n=6), acute infection or steroid use (n=4), and T1N0 anal margin tumors treated with surgery alone (n=0, as none met this criterion).

Instrumentation

Data were collected using a structured data extraction form specifically developed for this study. The instrument was designed by the principal investigator in collaboration with the co-author, both of whom have expertise in oncology and clinical research. The development process was guided by the study objectives, a comprehensive review of the literature on inflammatory biomarkers in oncology, and the operational definitions of the study variables. The final version of the instrument was reviewed and approved by oncology specialists within the institution before implementation.

It was necessary to tailor the data collection form to the specific objectives of evaluating inflammatory indices (NLR, PLR, and SII) and their prognostic value in squamous cell carcinoma of the anal canal within the institutional context. The data extraction form included locally relevant clinical variables, treatment protocols (5-FU/MMC with radiotherapy), and survival outcomes based on available medical records.

The data collection form consisted of four main sections:

1. Sociodemographic and baseline clinical variables: Included age, sex, and functional status (ECOG classification). These variables were obtained from medical records at the time of diagnosis.
2. Clinicopathological characteristics: Included primary tumor site (anal canal, anal margin, or both), degree of differentiation (good, moderate, poor, undifferentiated), tumor stage (T1–T4), lymph node involvement, presence of metastasis, and clinical stage (I–IV). These variables are detailed in Table 1.
3. Inflammatory indices (independent variables):
   Neutrophil-to-Lymphocyte Ratio (NLR): calculated as total neutrophil count divided by total lymphocyte count; categorized as < 4 and ≥ 4.
   Platelet-to-Lymphocyte Ratio (PLR): platelet count divided by total lymphocyte count; categorized as <250 and ≥ 250.
   Systemic Immune-Inflammation Index (SII): calculated using the formula (neutrophil count $\times$ platelet count)/ lymphocyte count; categorized as <980 and ≥ 980.

Medical records were systematically reviewed for evidence of acute infection (defined as fever $>38.0°C$, white blood cell count $>11{,}000/\mu L$, or documented antibiotic prescription) or systemic steroid use (any dose of oral or intravenous corticosteroids) within 7 days prior to blood sampling. Patients meeting these criteria were excluded (see Exclusion Criteria). No additional statistical adjustment was performed, as the exclusion was designed to remove identifiable non-cancer drivers of inflammation.

4. Outcome variables:
   Overall Survival (OS): time from diagnosis to death.
   Disease-Free Survival (DFS): time from diagnosis to documented recurrence.
   Therapeutic response: evaluated according to RECIST v1.1 criteria.[20] Response assessment was performed at 3 months after completion of chemoradiotherapy using pelvic MRI and/or CT imaging, with confirmation at 6 months. Complete response (CR) was defined as disappearance of all target lesions; partial response (PR) as $\geq 30\%$ decrease in sum of diameters; stable disease (SD) as neither sufficient shrinkage nor progression; progressive disease (PD) as $\geq 20\%$ increase or new lesions.
   Relapse and recurrence status (yes/no) was assessed at 1, 2, and 3 years. Although clinical follow-up extended beyond this period, the Kaplan–Meier survival curves and associated numbers at risk are presented up to 36 months (Figures 2 and 3) due to a marked reduction in the number of patients at risk beyond this time point.

Validity and reliability

Content validity was assessed through expert review. The instrument was evaluated by three experienced research professors and oncology specialists with expertise in clinical oncology, hematological biomarkers, and survival analysis. Suggestions provided by the experts led to: Refinement of operational definitions, improved alignment between inflammatory indices and survival endpoints, and clarification of recurrence and relapse definitions. After revision, the instrument was re-evaluated and confirmed to have satisfactory content validity.

Construct validity was further supported statistically by ROC curve analysis to confirm discriminatory ability of inflammatory index cut-off points; significant hazard ratios (HRs) were also observed in univariate and multivariate Cox regression models, demonstrating the prognostic value of NLR, PLR, and SII.

Data collection process

Data collection was conducted retrospectively at the Clinical Oncology Service of the Hermanos Ameijeiras Clinical Surgical Hospital for the period from January 2006 to December 2023. A list of all patients diagnosed with primary anal carcinoma during the study period was obtained from hospital registries. Medical records were subsequently screened according to the predefined inclusion and exclusion criteria. Eligible records were reviewed systematically using a structured data extraction form. Hematological parameters were recorded from laboratory results obtained prior to the initiation of chemoradiotherapy. The inflammatory indices (NLR, PLR, and SII) were calculated using predefined formulas. Survival data were obtained from follow-up records and hospital registries.

Data were collected in person through direct review of both physical and electronic medical records available in the hospital archives and the oncology department database.

Data collection was performed by the principal investigator, a medical oncologist with clinical experience in gastrointestinal malignancies, with the assistance of a co-author who is a PhD candidate in oncology and palliative care. Both researchers are trained in clinical data abstraction, oncology research methodology, and survival analysis. Prior to data extraction, a standardized review protocol was established to ensure consistency and to reduce inter-observer variability.

The primary investigation tool was a structured data extraction sheet. This instrument included closed-ended categorical variables such as sex, tumor stage, and lymph node involvement; continuous variables including age and survival time; calculated indices (NLR, PLR, and SII); and binary outcome variables such as recurrence and mortality. The tool focused on clinicopathological characteristics, inflammatory markers, and survival outcomes relevant to prognostic assessment. A copy of the data collection instrument is provided in the Appendices for reference.

Statistical analysis

The statistical analysis was conducted using SPSS version 20.0. Descriptive statistics were used to summarize the data, with quantitative variables reported as means, standard deviations, medians, and ranges, while qualitative variables were summarized as frequencies and percentages. Survival outcomes, including overall survival (OS) and disease-free survival (DFS), were analyzed using the Kaplan--Meier method. Differences between survival curves were assessed with the log-rank test, and both median and mean survival times were calculated along with their corresponding 95% confidence intervals. To investigate prognostic factors influencing survival, univariate analysis was performed initially using the log-rank test to assess the relationship between each independent variable (e.g., age, sex, ECOG performance status, tumor characteristics, NLR, PLR, SII, and clinical stage) and survival outcomes. Variables with a p-value of less than 0.05 were then included in multivariate analysis using the Cox proportional hazards regression model to identify independent prognostic factors. Hazard ratios with 95% confidence intervals were estimated to quantify the strength of associations. Prior to final model interpretation, the proportional hazards assumption was verified. To assess multicollinearity among the inflammatory indices (NLR, PLR, and SII) in the multivariate Cox regression models, we calculated variance inflation factors (VIFs). A VIF value exceeding 5 was considered indicative of significant multicollinearity.

A p-value of less than 0.05 was considered statistically significant throughout the analysis.

No a priori sample size calculation was performed. This was a retrospective cohort study that included all eligible patients from a single institution over the 18-year study period (2006-2023). The final sample size (n = 243) was determined by the availability of complete medical records meeting the inclusion criteria, rather than by a statistical power calculation.

Ethical considerations

This study was approved by the Direction of the Hospital Clínico Quirúrgico "Hermanos Ameijeiras" and the Head of the Department of Clinical Oncology, under the supervision of the institutional Ethics Committee (approval date: March 3, 2022). The protocol complies with the ethical principles for research involving human subjects, including autonomy, beneficence, non-maleficence, and justice, as outlined in the Declaration of Helsinki (1975, as revised in 2024). Confidentiality and appropriate handling of clinical data were ensured, with all data anonymized to protect participant privacy. Because this was a retrospective cohort study using only pre-existing medical records and all data were anonymized prior to analysis, the institutional Ethics Committee granted a waiver of informed consent (written or verbal). No direct patient contact or prospective data collection occurred. No conflicts of interest were declared by the authors.

Results

Patient characteristics

A total of 243 patients with histologically confirmed squamous cell carcinoma of the anal canal were included in the final analysis. The majority of patients were older than 50 years (87.7%), and females constituted 84.4% of the cohort. Most patients presented with preserved functional status (ECOG 0 in 71.2%).

Primary tumors were predominantly located in the anal canal (84.4%), while 11.5% arose from the anal margin. According to T classification, T2 tumors were the most frequent (48.1%), followed by T1 and T3 lesions (21.8% each). Lymph node involvement was present in 23.9% of patients, whereas distant metastases at diagnosis were uncommon (2.1%; n = 5). These 5 patients had oligometastatic disease (≤3 metastases, single organ) and received the same curative-intent chemoradiotherapy regimen as non-metastatic patients, rather than palliative-only treatment. Their inclusion was therefore consistent with the study's aim to evaluate outcomes following curative chemoradiotherapy. Stage II disease represented the largest subgroup (53.1%).

Elevated baseline inflammatory markers were common. NLR ≥4 was observed in 56.8% of patients, PLR ≥250 in 47.7%, and SII ≥980 in 52.3%.

Detailed clinicopathological characteristics and inflammatory indices are presented in Table 1.

Table 1. Baseline clinicopathological characteristics and inflammatory indices (n = 243).

Characteristic		n	%
Age	≤50 years	30	12.3
	>50 years	213	87.7
Sex	Male	38	15.6
	Female	205	84.4
ECOG Performance Status	0	173	71.2
	1	67	27.6
	≥2	3	1.2
Tumor Location	Anal canal	205	84.4
	Anal margin	28	11.5
	Both	10	4.1
T Classification	T1	53	21.8
	T2	117	48.1
	T3	53	21.8
	T4	20	8.2
Lymph Node Involvement	Yes	58	23.9
	No	185	76.1
Degree of differentiation	Well differentiated	45	18.5
	Moderately differentiated	128	52.7
	Poorly differentiated	60	24.7
	Undifferentiated	10	4.1
Metastasis at Diagnosis	Yes	5	2.1
	No	238	97.9
Clinical Stage	I	40	16.6
	II	129	53.1
	III	69	28.4
	IV	5	2.1
Inflammatory Indices	NLR ≥4	138	56.8
	PLR ≥250	116	47.7
	SII ≥980	127	52.3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte Ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation score.

Treatment response

After completion of chemoradiotherapy, 189 patients (77.8%) achieved a complete response (CR), 28 patients (11.5%) had a partial response (PR), 16 patients (6.6%) had stable disease (SD), and 10 patients (4.1%) had progressive disease (PD). Response rates by clinical stage are presented in Table 2.

Univariate Cox regression analysis was performed for all variables listed in Table 3. Both significant and non-significant variables are reported to ensure transparency. The complete univariate results, including hazard ratios (HRs), 95% confidence intervals (CIs), and p-values for each variable, are presented in Table 3.

Prognostic discrimination of inflammatory indices

Receiver operating characteristic (ROC) curve analysis demonstrated that all three inflammatory markers showed discriminatory ability for predicting recurrence. NLR yielded the highest area under the curve (AUC = 0.694), followed by SII (AUC = 0.686) and PLR (AUC = 0.684), though the AUC values were closely clustered. The optimal cut-off values derived from this cohort were NLR ≥4, PLR ≥250, and SII ≥980, which were used for subsequent survival analyses. The ROC curves are presented in Figure 1.

During follow-up, patients with elevated inflammatory markers experienced significantly higher rates of recurrence.

Kaplan–Meier analysis demonstrated significantly reduced disease-free survival (DFS) in patients with NLR ≥4, PLR ≥250, and SII ≥980 compared with those below the respective thresholds (log-rank $p < 0.05$ for all comparisons). The separation between survival curves was most pronounced for SII, suggesting a stronger prognostic gradient for this composite inflammatory score. Kaplan–Meier survival curves for DFS are illustrated in Figure 2.

In univariate Cox regression analysis, advanced T classification, lymph node involvement, elevated inflammatory indices, and lack of complete response (CR) were significantly associated with poorer DFS. After adjustment for age, sex, ECOG performance status, T classification, nodal status, and CR status, only lymph node involvement, SII ≥980, and absence of CR retained independent prognostic significance. Lymph node positivity was associated with a 1.94-fold increased risk of recurrence (95% CI 1.26–2.98; $p = 0.003$). SII ≥980 independently increased the risk of disease relapse (HR 2.01; 95% CI 1.15–3.52; $p = 0.013$). Patients who did not achieve CR had a substantially higher risk of recurrence (HR 5.67; 95% CI 3.21–10.02; $p < 0.001$). Multivariate Cox regression results for DFS are summarized in Table 4.

Model adjusted for: age, sex, ECOG status, T classification, lymph node status, CR status, and inflammatory indices.

Overall survival

Kaplan–Meier analysis revealed significantly reduced overall survival (OS) among patients with elevated inflammatory markers, particularly NLR ≥4 and PLR ≥250. The divergence of survival curves became more evident over time, especially among patients with nodal involvement and impaired performance status. Kaplan–Meier survival curves for OS are presented in Figure 3.

In multivariate Cox regression analysis (excluding stage IV patients), ECOG ≥1, lymph node involvement, and lack of complete response (CR) were strong independent predictors of mortality. ECOG ≥1 was associated with a 2.70-fold increased risk of death (95% CI 1.35–5.40; $p = 0.005$). Lymph node involvement conferred a 3.45-fold increased mortality risk (95% CI 1.68–7.08; $p = 0.001$). Absence of CR was associated with a 4.21-fold increased risk of death (95% CI 2.45–7.23; $p < 0.001$). Among inflammatory markers, NLR ≥4 independently predicted poorer OS (HR 2.47; 95% CI 1.05–6.11; $p = 0.049$), as did PLR ≥250 (HR 3.28; 95% CI 1.40–7.68; $p = 0.006$). SII did not retain independent significance in the final OS model. Multivariate results for overall survival are presented in Table 5.

Model adjusted for: age, sex, ECOG status, T classification, lymph node status, CR status, and inflammatory indices.

Table 2. Treatment response by clinical stage (n = 243).

Response	Stage I (n=40)	Stage II (n=129)	Stage III (n=69)	Stage IV (n=5)	Total (n=243)
CR	38 (95.0%)	108 (83.7%)	41 (59.4%)	2 (40.0%)	189 (77.8%)
PR	2 (5.0%)	15 (11.6%)	10 (14.5%)	1 (20.0%)	28 (11.5%)
SD	0 (0%)	4 (3.1%)	10 (14.5%)	2 (40.0%)	16 (6.6%)
PD	0 (0%)	2 (1.6%)	8 (11.6%)	0 (0%)	10 (4.1%)

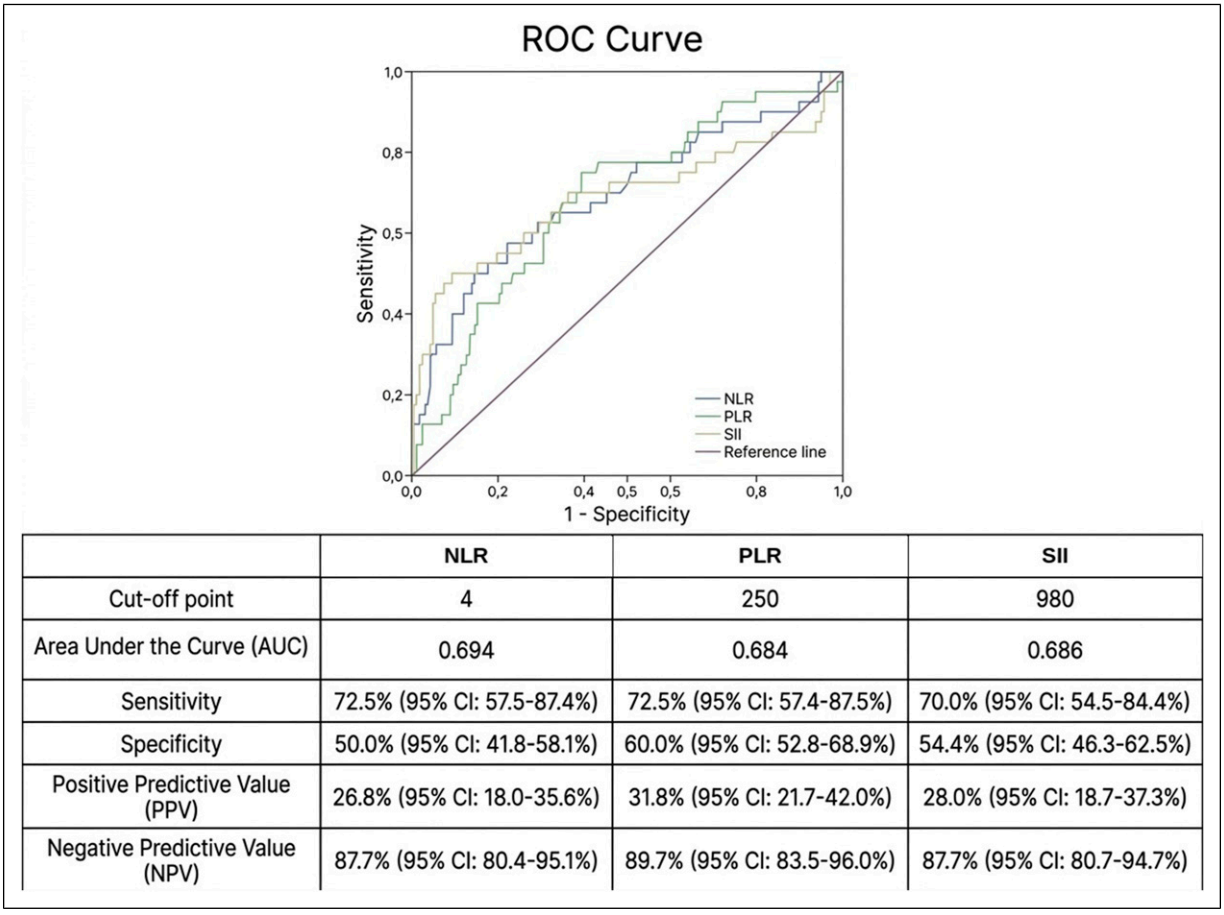
Table 3. Univariate Cox regression analysis for disease-free survival (DFS) and overall survival (OS).

Variable	DFS HR (95% CI)	DFS p-value	OS HR (95% CI)	OS p-value
Age (>50 vs ≤50)	1.12 (0.65–1.93)	0.68	1.08 (0.58–2.01)	0.81
Sex (Female vs Male)	0.89 (0.54–1.47)	0.64	0.92 (0.51–1.66)	0.78
ECOG (≥1 vs 0)	1.78 (1.12–2.83)	0.015	2.45 (1.45–4.14)	0.001
T classification (T3-T4 vs T1-T2)	2.15 (1.38–3.35)	0.001	1.98 (1.18–3.32)	0.009
Lymph node involvement (Yes vs No)	2.45 (1.62–3.71)	<0.001	3.12 (1.94–5.02)	<0.001
NLR ≥4 (Yes vs No)	1.89 (1.23–2.90)	0.004	2.34 (1.44–3.80)	0.001
PLR ≥250 (Yes vs No)	1.76 (1.14–2.72)	0.010	2.56 (1.58–4.15)	<0.001
SII ≥980 (Yes vs No)	2.21 (1.42–3.44)	<0.001	2.02 (1.24–3.29)	0.005

Note. HR = hazard ratio; CI = confidence interval. Non-significant variables (tumor location, clinical stage, metastasis) not shown for brevity; full data available upon request.

Variance inflation factors (VIFs) for NLR, PLR, and SII in the multivariate models ranged from 1.12 to 1.48, all well below the conventional threshold of 5. This indicates no significant multicollinearity among the inflammatory indices, confirming that each index contributes independent prognostic information.

The primary OS multivariate model excluded 5 stage IV patients (2.1% of the cohort), given the small subgroup size. In a post-hoc sensitivity analysis, these 5 patients were added back into the model; hazard ratios and p-values for the remaining predictors (ECOG, lymph node involvement, CR status, NLR, PLR) remained nearly identical, confirming that their exclusion did not materially affect the primary findings.



	NLR	PLR	SII
Cut-off point	4	250	980
Area Under the Curve (AUC)	0.694	0.684	0.686
Sensitivity	72.5% (95% CI: 57.5-87.4%)	72.5% (95% CI: 57.4-87.5%)	70.0% (95% CI: 54.5-84.4%)
Specificity	50.0% (95% CI: 41.8-58.1%)	60.0% (95% CI: 52.8-68.9%)	54.4% (95% CI: 46.3-62.5%)
Positive Predictive Value (PPV)	26.8% (95% CI: 18.0-35.6%)	31.8% (95% CI: 21.7-42.0%)	28.0% (95% CI: 18.7-37.3%)
Negative Predictive Value (NPV)	87.7% (95% CI: 80.4-95.1%)	89.7% (95% CI: 83.5-96.0%)	87.7% (95% CI: 80.7-94.7%)

Figure 1. ROC curve analysis of the prognostic capacity of inflammatory indices disease-free survival.

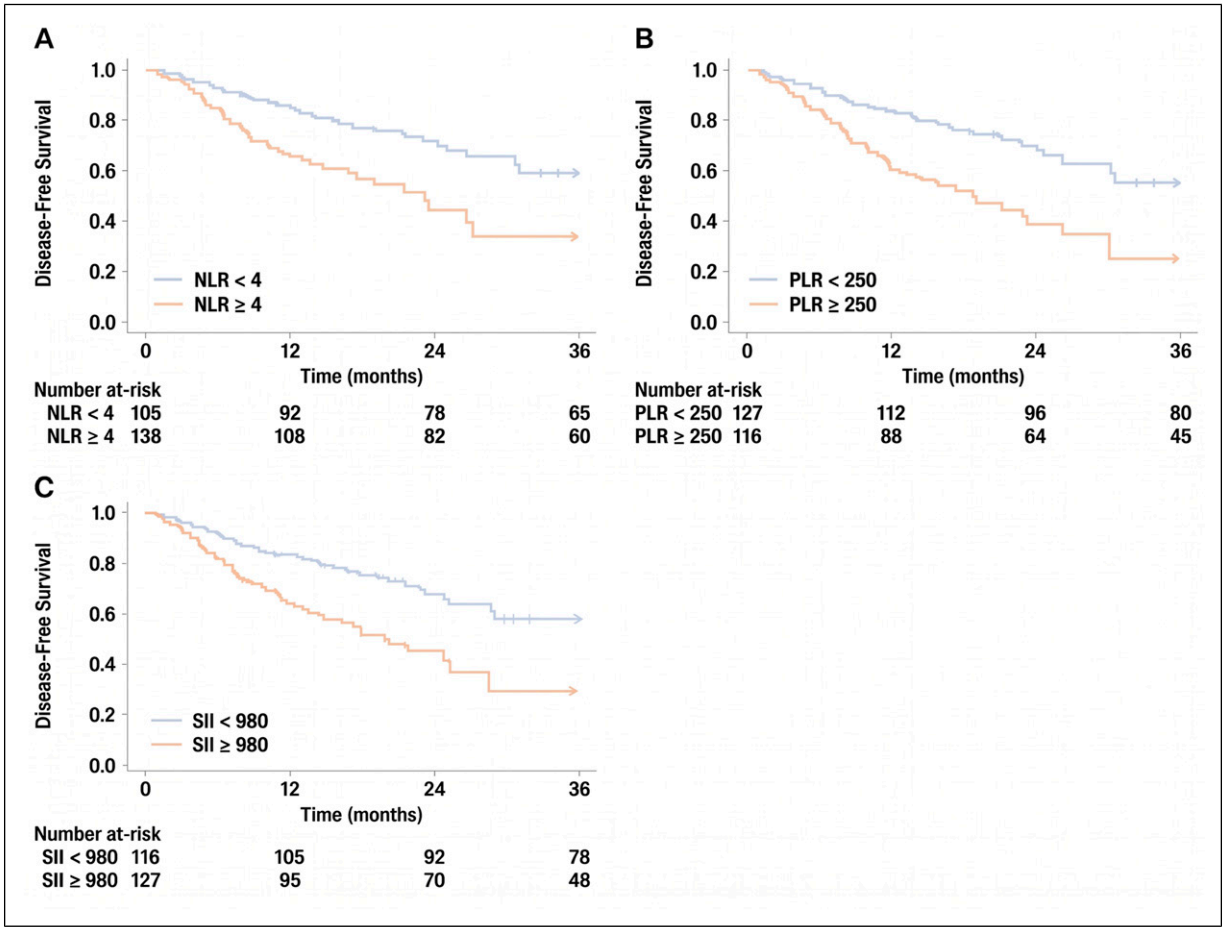


Figure 2. Kaplan-Meier curves for disease-free survival. (A) Neutrophil/lymphocyte ratio, (B) platelet/lymphocyte ratio, (C) systemic inflammation index.

Discussion

The search for biomarkers in squamous cell carcinoma of the anal canal is driven by the need to identify a subgroup of patients who may have a worse prognosis regardless of the stage of their disease. Systemic inflammation associated with cancer has been identified as one of the phenomena that facilitates tumor invasion, angiogenesis, and metastasis.[18,21]

In the present investigation, the highest incidence of this disease was found in patients over 50 years of age, a result consistent with that reported by Grabenbauer et al.[22] who found that 54% of patients with anal squamous carcinoma were in their fifth and sixth decades of life. Other recent studies have also shown that the mean age of diagnosis is typically between 56 and 63 years.[23–25] The predominance of female patients in this cohort aligns with the literature, where female sex is identified as a risk factor for anal cancer. This is likely related to higher exposure to risk factors such as sexually transmitted diseases and HPV infection.[9]

The majority of patients in this study presented with a good general condition at diagnosis (ECOG 0), as expected in a hospital-based series. Most patients were diagnosed at an early stage, predominantly stage II (53.1%), which is somewhat contradictory to what is found in the literature, where more than 85% of patients are diagnosed with locally advanced

Table 4. Multivariate Cox regression analysis for disease-free survival.

Variable	Hazard ratio (HR)	95% CI	p-value
Lymph node involvement (Yes vs No)	1.94	1.26–2.98	0.003
SII ≥980 (Yes vs No)	2.01	1.15–3.52	0.013
No complete response (CR) vs CR	5.67	3.21–10.02	<0.001

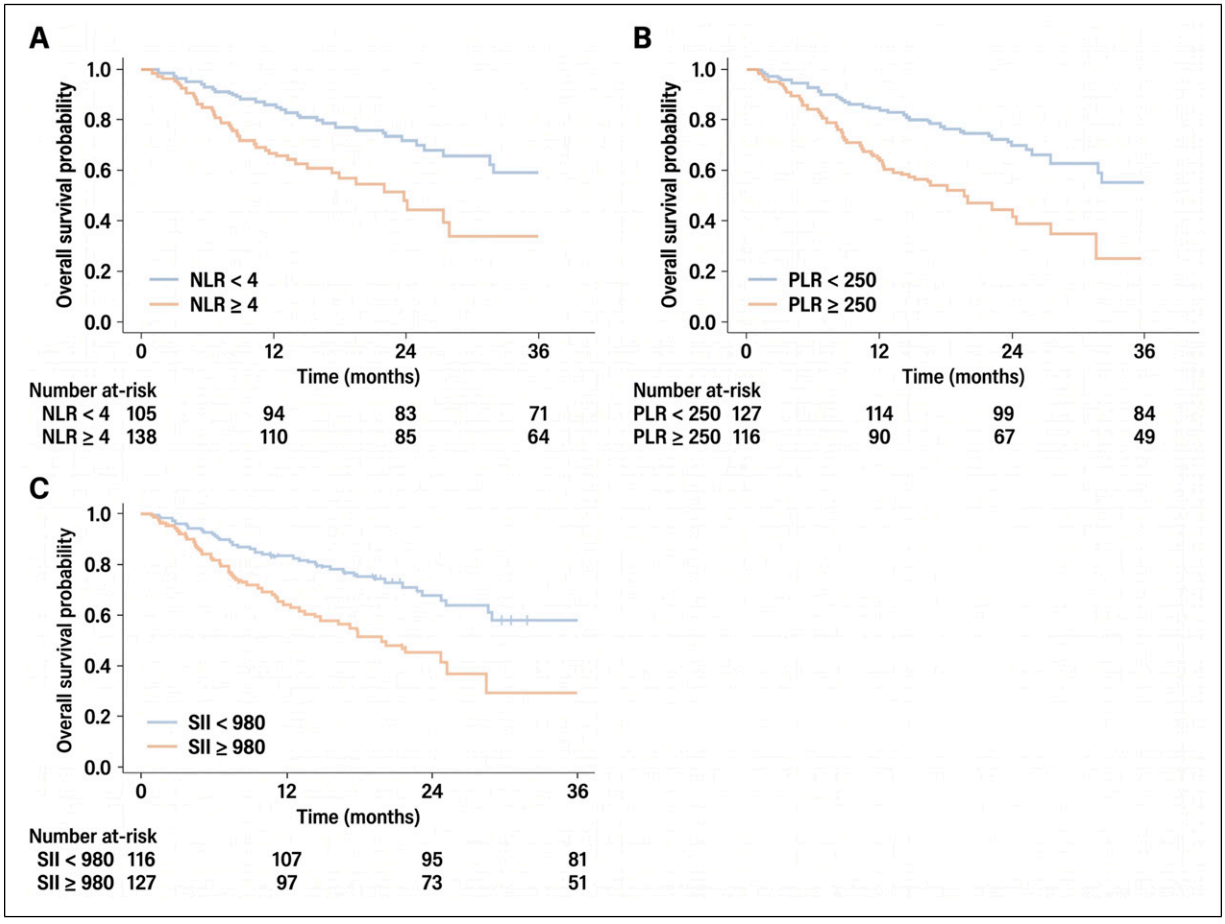


Figure 3. Kaplan-Meier curves for overall survival. (A) Neutrophil/lymphocyte ratio, (B) platelet/lymphocyte ratio, (C) systemic inflammation index.

disease.[26] However, similar frequencies have been reported in other studies, such as Lord et al.[27] who reported 54% of patients at stage II.

Regarding tumor location, most cases were located in the anal canal, with few involving the anal margin or presenting with distant metastases at diagnosis. These findings are consistent with previous studies, where 80–84% of squamous cell carcinomas are confined to the anal canal.[7] The current series also found moderately to poorly differentiated histology in most tumors, a finding similar to that described by Eng et al.[28] and Glynne-Jones et al.[7]

One of the most important findings of this study is the significant association between elevated inflammatory indices and poorer oncologic outcomes, both in terms of disease-free and overall survival. Elevated values of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation score (SII) were all linked to higher recurrence and mortality rates. These results are consistent with other studies conducted in patients with different types of neoplasms.[16,29–31] An important finding of this study is the discordant prognostic pattern observed among the three inflammatory indices: SII independently predicted disease-free survival (DFS) but not overall survival (OS), whereas NLR

Table 5. Multivariate Cox regression analysis for overall survival.

Variable	HR	95% CI	p-value
ECOG ≥1 (vs 0)	2.70	1.35–5.40	0.005
Lymph node involvement (Yes vs No)	3.45	1.68–7.08	0.001
No complete response (CR) vs CR	4.21	2.45–7.23	<0.001
NLR ≥4 (Yes vs No)	2.47	1.05–6.11	0.049
PLR ≥250 (Yes vs No)	3.28	1.40–7.68	0.006

and PLR independently predicted OS but not DFS. Several biologically plausible explanations may account for this discrepancy. First, SII uniquely integrates platelets, neutrophils, and lymphocytes, whereas NLR and PLR are simpler two-component ratios. Platelets play a critical role in early metastatic dissemination by promoting epithelial-mesenchymal transition, protecting circulating tumor cells from immune surveillance, and facilitating extravasation.[17,18] These mechanisms are particularly relevant to early recurrence (DFS endpoint) rather than late mortality. Conversely, the prognostic impact of isolated neutrophilia (NLR) or thrombocytosis (PLR) on long-term survival (OS endpoint) may be mediated through chronic inflammation-driven cachexia, immune exhaustion, and resistance to subsequent therapies – processes that unfold over a longer time horizon. Second, the differential predictive value may reflect the timing of outcomes. DFS events (recurrence) typically occur earlier in follow-up, whereas OS events (deaths) accumulate over a longer period. SII, as a composite score, may be more sensitive to early events, while simpler ratios like NLR and PLR may capture ongoing inflammatory processes that influence late mortality. This pattern has been observed in other malignancies, including colorectal and pancreatic cancers.[14,15] Third, the loss of SII significance in the OS model may be attributable to the competing effects of post-recurrence treatments. Patients who recur (captured by DFS) receive salvage therapies that can alter the natural history of disease and attenuate the prognostic impact of pre-treatment SII on ultimate OS. In contrast, NLR and PLR may better reflect the host inflammatory reserve that influences tolerance of and response to salvage therapies, thus retaining predictive value for OS.

The systemic inflammatory response promoted by tumor cells leads to infiltration of inflammatory cells in the tumor microenvironment, promoting progression through the production of pro-inflammatory cytokines, such as interleukin-2, IL-6, IL-10, TNF, and vascular endothelial growth factor, which contribute to angiogenesis and metastasis.[32,33] Elevated systemic inflammatory markers are associated with neutrophilia, lymphopenia, and altered T lymphocyte response, all of which are linked to a higher risk of recurrence and worse prognosis.[34,35]

In the present study, patients with elevated NLR showed higher recurrence rates at 1, 2, and 3 years, although NLR was not an independent prognostic factor for disease-free survival after multivariate adjustment. However, for overall survival, elevated NLR and PLR were found to be independent prognostic factors, consistent with the findings of De Felice et al.[13] and Casadei-Gardini et al.[15] The use of ROC curve analysis to determine the cut-off points for each inflammatory index reduced overestimation bias and identified the most favorable values for stratifying the patient sample, as recommended in recent literature.[12]

Regarding the platelet-to-lymphocyte index, recurrence and mortality rates at 2 and 3 years were higher in patients with elevated values, and PLR was also an independent predictor of poor overall survival. These findings are in line with Casadei-Gardini et al.[15] who found that elevated PLR was associated with lower overall and progression-free survival and suggested that this may be due to the activation of TGF-beta and NF-κB pathways by circulating platelets.[17]

The systemic immune-inflammation score (SII) proved to be an independent prognostic factor for disease-free survival but not for overall survival. This is similar to findings by Knight et al.[14] who reported that SII is an independent prognostic factor for progression-free survival but not for overall survival. The advantage of SII is its integration of neutrophils and platelets as elements of the inflammatory response and lymphocytes as the main cellular element of the immune response, thus reflecting the balance between inflammation and immune status.

In our cohort, 189 patients (77.8%) achieved a complete response after chemoradiotherapy. As expected, lack of CR was the strongest predictor of poor outcomes, with a 5.67-fold increased risk of recurrence (95% CI 3.21–10.02; $p < 0.001$) and a 4.21-fold increased risk of death (95% CI 2.45–7.23; $p < 0.001$) in multivariate analyses. These findings align with established literature confirming CR as a critical endpoint in anal cancer.[7] Importantly, the prognostic significance of NLR, PLR, and SII remained independent of CR status, indicating that pre-treatment inflammatory indices provide additional prognostic information beyond treatment response. Patients with elevated NLR or PLR who achieved CR still had worse OS than those with normal indices (data not shown), suggesting that systemic inflammation may influence post-response outcomes through mechanisms independent of tumor response, such as persistent immune dysfunction or pro-metastatic microenvironment.

The optimal cut-off values identified in our cohort (NLR ≥4, PLR ≥250, SII ≥980) are broadly consistent with previously reported thresholds in anal cancer. For NLR, De Felice et al.[13] reported an optimal cut-off of 3.5, while Knight et al.[14] used 4.0. For PLR, Casadei-Gardini et al.[15] identified a cut-off of 230, similar to our 250. For SII, Knight et al.[14] reported a cut-off of 980, identical to our finding. This consistency suggests that these thresholds may have reasonable external validity despite being derived from a single-center cohort. However, our cut-offs were determined using ROC analysis within this specific population and are therefore cohort-dependent. External validation in independent, preferably multicenter, cohorts is necessary before these thresholds can be recommended for routine clinical use.

Regarding model stability and potential overfitting, our multivariate Cox regression models included 6-8 independent variables. With a total of 243 patients and approximately 60-80 events (recurrences and deaths), the events-per-variable ratio ranged from 12 to 15, exceeding the recommended minimum of 10 and arguing against significant overfitting.[36] Furthermore,

alternative model selection procedures (stepwise and backward elimination) yielded identical predictor sets, confirming the robustness of our findings. The low VIFs (<2.0) also indicate that the inflammatory indices are not collinear and provide independent prognostic information.

Limitations

This study has several important limitations. Its retrospective, single-center design limits causal inference and generalizability. Although a standardized data extraction protocol was used, reliance on medical records introduces potential information bias and missing data, and the non-probabilistic convenience sample may have introduced selection bias.

No a priori sample size calculation was performed; the sample size (n = 243) was determined by data availability, which may underpower subgroup analyses and affect precision, as exemplified by the limited number of metastatic cases (n = 5).

Inflammatory indices were calculated from a single pre-treatment laboratory measurement. We excluded patients with documented acute infection or systemic steroid use within 7 days of blood draw, but subclinical infections, chronic inflammatory conditions, and over-the-counter medication use could not be fully ascertained. Moreover, a single measurement does not capture dynamic changes during therapy, and the optimal timing of assessment remains unclear.

Key clinical confounders (HIV status, HPV subtype, smoking history) were not routinely recorded in medical records, making retrospective collection impossible. If HIV-positive patients or smokers were disproportionately represented in elevated inflammatory index groups, the observed associations could be overestimated; if evenly distributed, bias would be minimal and likely attenuate true associations. However, consistent associations across three indices (NLR, PLR, SII) make residual confounding alone unlikely to explain the results.

Our cut-off values were derived internally via ROC analysis and are therefore cohort-specific. Although they align with published values, external validation in independent, multicenter cohorts is needed before clinical application. The cohort included 5 stage IV patients with oligometastatic disease who received curative-intent chemoradiotherapy; their small proportion (2.1%) makes their exclusion unlikely to materially alter the results, but our findings may not generalize to patients with extensive metastatic disease.

The study spanned 18 years (2006-2023), during which diagnostic imaging, radiotherapy techniques, supportive care, and follow-up practices may have evolved. While the core chemoradiotherapy protocol remained unchanged, era-based stratified analysis was not feasible due to limited sample size per period, though we adjusted for key prognostic variables and found no significant interaction between year of diagnosis and inflammatory index effects.

Finally, the discordant prognostic patterns between DFS and OS, while biologically plausible, should be interpreted with caution given the limited statistical power for certain subgroups. External validation in larger cohorts is needed to confirm the differential roles of SII versus NLR/PLR in anal cancer.

Implications and recommendations

The results suggest that baseline inflammatory indices may serve as practical adjunctive prognostic markers in anal squamous cell carcinoma. Given their low cost and availability from routine blood tests, NLR, PLR, and SII could be integrated into baseline risk assessment alongside TNM stage and ECOG performance status.

At the institutional level, it is feasible to standardize automatic calculation of inflammatory indices at diagnosis and incorporate them into structured oncology records. Patients with elevated indices may benefit from closer surveillance during early follow-up, when recurrence risk is highest.

Future research should prioritize prospective, multicenter validation studies to confirm reproducibility. Longitudinal assessment of inflammatory markers during and after treatment is needed to determine whether dynamic changes improve prognostic accuracy. Integration with molecular and immunologic tumor markers may further refine risk stratification. Development of validated composite prognostic models or nomograms represents a logical next step toward personalized management.

Conclusion

Elevated pre-treatment inflammatory indices (NLR, PLR, and SII) are associated with poorer outcomes in patients with squamous cell carcinoma of the anal canal. SII independently predicted disease-free survival, while NLR and PLR independently predicted overall survival, supporting the prognostic relevance of systemic inflammatory status. Given their availability, low cost, and reproducibility, these markers may complement established clinicopathological factors in baseline risk stratification. However, prospective multicenter validation and integration with molecular and immunologic biomarkers

are required before routine clinical implementation. Future research should focus on validating standardized cut-offs and exploring dynamic changes in inflammatory indices to refine individualized prognostic models.

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Ethical considerations

This study was approved by the Direction of the Hospital Clínico Quirúrgico "Hermanos Ameijeiras" and the Head of the Department of Clinical Oncology, under the supervision of the institutional Ethics Committee (approval date: March 3, 2022; no formal approval number was assigned by the committee). The protocol complies with the ethical principles for research involving human subjects, including autonomy, beneficence, non-maleficence, and justice, as outlined in the Declaration of Helsinki (1975, as revised in 2024). Confidentiality and appropriate handling of clinical data were ensured, with all data anonymized to protect participant privacy. Because this was a retrospective cohort study using only pre-existing medical records and all data were anonymized prior to analysis, the institutional Ethics Committee granted a waiver of informed consent (written or verbal). No direct patient contact or prospective data collection occurred. No conflicts of interest were declared by the authors.

Consent to participate

Informed consent was obtained where applicable; for secondary data analysis, duly anonymized data were used without requiring additional consent, in accordance with institutional and national regulations.

Consent for publication

This manuscript does not contain any individual person's data in any form (including individual details as name, images, or videos).

Authors contributions

YA: Conception and design of the study, data collection, manuscript drafting (introduction and discussion sections), critical revision for important intellectual content. FF: Data analysis and interpretation, statistical analysis, manuscript writing (methods, results, discussion, and conclusion), corresponding author, critical revision of the entire manuscript. BA: Data collection, clinical data verification, contribution to results interpretation, critical revision of the manuscript. IC: Data analysis and interpretation, Conception and design of the study, critical revision for important intellectual content, data collection.

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Declaration of conflicting interests

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Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Trial registration

(Note: This is a retrospective cohort study, not a clinical trial).

Disclaimer

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