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Association of the Neutrophil-to-Lymphocyte Ratio (NLR) with Survival in Locally Advanced and Metastatic Cervical Cancer: A Longitudinal, Retrospective Study

Asociación del índice neutrófilos/linfocitos con la supervivencia en cáncer de cérvix uterino localmente avanzado y metastásico: estudio retrospectivo

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ABSTRACT

Introduction: Cervical cancer is one of the gynecological tumors with the highest mortality rates. Inflammation plays a crucial role in its initiation and metastatic progression. The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between the tumor and the antitumoral immune response, positioning it as a relevant prognostic factor. Given the high lethality of this cancer, the evaluation of NLR allows for proper patient stratification, facilitating personalized treatment and, consequently, optimizing healthcare resources and costs. **Materials and Methods:** Observational, descriptive study of historical cohorts at the SOLCA Oncology Hospital, Quito, in patients diagnosed with locally advanced (IB2 - IVA) and metastatic (IVB) cervical cancer from January 2010 to 2018. These were anonymized according to current and updated legal regulations. **Results:**The study population included 672 patients with a 180-month follow-up, and the neutrophil-to-lymphocyte ratio was assessed before treatment. Values less than 2.5 were associated with longer overall survival and late recurrence, with data of 37 months (95% CI 26.3–47.6; p < 0.05) and 30 months (95% CI 9.4–50.5; p < 0.05), respectively. Furthermore, a neutrophil-to-lymphocyte ratio ≥ 2.5 is a predictor of recurrence. The hazard ratio (HR) for mortality is 3.09 (95% CI 2.42 to 3.94; p < 0.05) and for recurrence, HR = 3.16 (95% CI 2.47 to 4.05; p < 0.05). Similarly, the Moore criteria, in the intermediate-high risk group, mortality HR 5.39 and recurrence HR 10.66, both p 0.000. **Conclusions:** NLR less than 2.5 is associated with better overall survival and shorter time to recurrence. NLR ≥2.5 is associated with more aggressive tumor behavior with a tendency toward early recurrence and higher mortality.

Keywords: Cervical cancer, lymphocytes, neutrophils, survival, index.

RESUMEN

Introducción: El cáncer de cérvix uterino es uno de los tumores ginecológicos con mayor mortalidad. La inflamación desempeña un papel clave en su iniciación y progresión metastásica. El índice neutrófilo/linfocitos refleja el equilibrio entre el tumor y la respuesta inmunológica antitumoral, por lo que se ha propuesto como un factor pronóstico relevante. Dada la alta mortalidad de este cáncer, evaluarlo permite estratificar adecuadamente a los pacientes, lo que facilita personalizar el tratamiento y, en consecuencia, optimiza los recursos y costos en salud. **Materiales y métodos:** Se llevó a cabo un estudio observacional y descriptivo de cohortes históricas en el Hospital Oncológico de SOLCA, núcleo Quito. Participaron pacientes con diagnóstico de cáncer de cérvix localmente avanzado (IB2-IVA) y metastásico (IVB) desde enero del 2010 hasta enero del 2018. Los datos fueron anonimizados según las normativas legales vigentes y actualizadas. **Resultados:** La población de estudio incluyó a 672 pacientes con un seguimiento de 180 meses y se evaluó el índice neutrófilo/linfocitos antes del tratamiento. Los valores menores a 2,5 se asociaron con un mayor tiempo de sobrevida global y una recurrencia tardía,

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con datos de 37 meses (IC 95 % de26,3-47,6; p < 0,05) y 30 meses (IC 95 % de 9,4-50,5; p < 0,05), respectivamente. Además, un índice neutrófilo/linfocitos ≥ 2,5 es un factor que predice la recurrencia. La razón de riesgos (Hazard ratio, HR) para la mortalidad es de 3,09 (IC95% de 2,42 a 3,94; p< 0,05) y para la recurrencia, HR = 3,16 (IC 95 % de 2,47 a 4,05; p < 0,05). Igualmente, los criterios de Moore, en el grupo de riesgo intermedio-alto, HR mortalidad 5,39 y HR recurrencia 10,66, ambos p 0,000. **Conclusiones:** Un índice neutrófilo/linfocitos menor a 2,5 está relacionado con una mejor sobrevida global y menor tiempo de recurrencia; un índice neutrófilo/linfocitos ≥ 2,5 está relacionado con un comportamiento tumoral más agresivo con tendencia a la recurrencia temprana y mayor mortalidad.

Palabras Clave: cáncer de cérvix uterino, linfocitos, neutrófilos, supervivencia, índice..

1. Introduction

Cervical cancer (CC) is the second most common type of gynecological cancer worldwide, with approximately 528,000 new cases and 266,000 deaths annually [1,2]. Although its incidence and mortality have declined in developed countries, it remains a leading cause of death in developing regions. It accounts for 84% of cases, with high rates reported in Africa, Central America, Latin America, and the Caribbean. The average age at diagnosis is 48 years, with lower prevalence among women under 20 and over 85 years old [1,2,3]. In Ecuador, it ranks second in incidence and first in mortality, according to data from SOLCA-Quito and GLOBOCAN [4,5,6].

Key prognostic factors include tumor stage (FIGO, International Federation of Gynecology and Obstetrics), lymph node status, tumor size (TNM), and histologic grade. However, clinical staging has limitations, especially in advanced stages, highlighting the need for additional methods such as the neutrophil-to-lymphocyte ratio (NLR) [7]. Inflammation plays a crucial role in tumorigenesis, and NLR has been proposed as a useful marker to predict prognosis in solid tumors [8,9,10]. Several studies have shown that chemotherapy can normalize NLR, which is associated with better treatment responses [11–14].

Human papillomavirus (HPV) is detected in 99.7% of cases, with its persistence being the main factor in cancer development [15–17]. In locally advanced stages (IB2–IVA), recurrence rates reach 50–70%, and metastatic disease occurs in 15–61% of cases [18,19,20]. The standard treatment involves platinum-based chemotherapy combined with radiotherapy. Risk stratification using Moore criteria is essential to individualize treatment [18,19,21–25]. Mizunuma [26] demonstrated that a high pretreatment NLR is associated with poorer overall and progression-free survival [27]. This underscores the importance of this marker in optimizing resource use and improving patients' quality of life.

2. Materials and Methods

This study was conducted as an observational, descriptive, historical cohort study with a longitudinal, retrospective, and analytical approach to survival. It was carried out at the SOLCA Oncology Hospital in Quito, and included patients diagnosed with locally advanced cervical cancer (stages IB2 to IVA) and metastatic disease (stage IVB), treated between January 2010 and January 2018. Inclusion criteria encompassed the availability of complete blood count data, measurable disease on imaging, histologic subtype determination, and having received cancer treatment in accordance with clinical stage.

Prior to its implementation, the study was approved by the Ethics and Human Research Committee (CEISH) of SOLCA Quito. Data were anonymized through a de-identification process that irreversibly removed any information that could identify individuals, using coded identifiers to mask patient identity. Given the retrospective nature of the study, no interventions were performed that could affect patient care, and informed consent was therefore not required.

Statistical analysis was conducted using IBM-SPSS software, which facilitated the application of various statistical tests to examine the relationship between the neutrophil-to-lymphocyte ratio (NLR) and survival in patients with cervical cancer. First, descriptive analyses were performed to obtain measures of central tendency (mean, median) and dispersion (standard deviation) for quantitative variables, as well as frequency distributions for categorical variables.

Overall survival (OS) was defined as the time from the initiation of cancer treatment to the date of death from any cause or the last follow-up visit in censored patients. Recurrence-free survival (RFS) was defined as the interval from treatment initiation to the clinical or radiological detection of the first tumor recurrence. Both variables were analyzed using the Kaplan-Meier method to estimate cumulative survival probability over time. OS and RFS curves were compared between risk groups based on NLR (<2.5 vs. ≥2.5). The log-rank test was used to assess whether differences between groups were statistically significant.

Additionally, a Cox proportional hazards regression model was applied for multivariate analysis, enabling the identification of independent prognostic factors for survival, adjusted for potential confounders. This model calculated hazard ratios (HRs) and their confidence intervals, providing an estimate of the relative risk of survival events. The proportional hazards assumption was verified using the Schoenfeld residuals test. All p-values were two-sided, and a p-value <0.05 was considered statistically significant.

2.1 Inclusion criteria

- Age: between 18 and 80 years.
- Patients diagnosed with cervical cancer, FIGO 2009 clinical stages IB2 to IVB.
- Patients treated at the SOLCA Oncology Hospital – Quito, from 2010 to 2018, with concurrent chemoradiotherapy or chemotherapy alone.
- Measurable oncologic disease according to RECIST 1.0 criteria.

2.2 Exclusion criteria

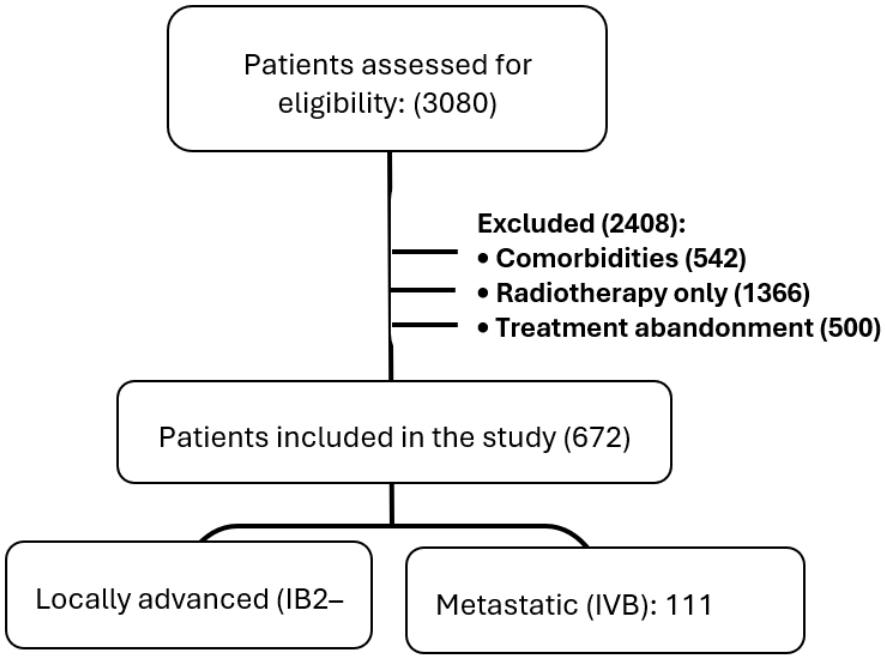
- Non-cancer-related conditions that could alter the NLR, such as pre-existing cardiovascular disease (e.g., hypertension), diabetes mellitus, acute or chronic kidney disease, or infection-related processes (e.g., sepsis, superimposed infection prior to treatment initiation).
- Patients who underwent non-oncologic surgery as treatment.
- Use of alternative therapies or treatment discontinuation.
- Diagnosis of a second primary malignancy.
- Patients who received radiotherapy alone as treatment.

A total of 3,080 patients were initially evaluated. After applying the exclusion criteria, 2,408 were excluded, including patients with comorbidities: 542 (history of cardiovascular disease, acute or chronic kidney disease, metabolic diseases such as diabetes mellitus, and autoimmune disorders), 1,366 (treated with radiotherapy alone), and 500 (treatment discontinuation) (Fig. 1).

All patients had their white blood cell counts assessed before treatment initiation, at treatment completion, and at the time of recurrence. Differential white blood cell counts (neutrophils, lymphocytes, among others) were measured using automated hematology analyzers.

Treatment response was evaluated after the third cycle in patients with metastatic disease, and after the fifth week in patients with locally advanced disease, using full body computed tomography and assessed according to RECIST 1.0 criteria, which were in use at the institution at the time of analysis.

Figure 1. Patient selection process



2.3 Results

A total of 672 patients met the inclusion criteria, representing 21.81% of the initial cohort. The final study population was stratified into two groups according to clinical stage: 561 patients (IB2–IVA) with locally advanced disease, and 111 patients (IVB) with metastatic disease.

The mean age was 48.7 years (SD ±11.4). The mean white blood cell count was 9,049/µL, with a mean lymphocyte count of 2,453/µL and neutrophil count of 5,438/µL. The mean neutrophil-to-lymphocyte ratio (NLR) was 2.39 (SD ±1.43). Regarding histopathological subtypes, squamous cell carcinoma predominated (85.6%), followed by adenocarcinoma (10%) and adenosquamous carcinoma (4.5%).

Among the 672 patients analyzed, 229 (34.1%) had a high-risk NLR, while 443 (65.9%) had a low-risk NLR. Based on Moore criteria, applied to patients with disease progression and metastasis, two risk groups were identified: an intermediate-to-high-risk group comprising 268 patients (39.9%), and a low-risk group with 34 patients (5.1%) (Table 1).

We conducted a contingency analysis of NLR in relation to vital status (alive, deceased) and disease status (recurrence, no recurrence), using a cutoff value of 2.5 based on previous literature and further supported by the mean NLR observed in our patient population (2.39 ± 1.43). Patients with a low-risk NLR exhibited a mortality rate of 32.7% and a recurrence rate of 32.4%. In comparison, those with a high-risk NLR showed a mortality rate of 35.8% and a recurrence rate of 54.9%. These differences were statistically significant (Table 2).

Table 1. Descriptives of the study population

Variables	Frequency (%)
Clinical stage (FIGO)	
IIB	246 (36,6)
IIIA	1 (0,1)
IIIB	303 (45,1)
IVA	11 (1,6)
IVB	111 (16,5)
Leukocytosis	
> 13000	55 (8,2)
≤ 13000	617 (91,8)
INL risk	
High	229 (34,1)
Low	443 (65,9)
Moore criteria (risk)	
Lowo	34 (5,1)
Intermediate-high	268 (39,9)
Vital status	
Alive	402 (59,8)
Dead	270 (40,2)

*__ECOG__, Eastern Cooperative Oncology Group; **INL, Neutrophil/lymphocyte ratio.**
Source: Medical records from the SOLCA-Quito Cancer Hospital

Table 2. Analysis of recurrence and mortality (Chi-square)

Variables		Recurrence (%)	Mortality (%)	p-value
Neutrophil-to-Lymphocyte Ratio (NLR)	High Risk ≥ 2.5	125 (54,9)	129 (35,8)	0,000
	Low Risk < 2.5	144 (32,7)	143 (32,4)	0,000
Moore Criteria	Intermediate and High Risk	265 (98,9)	249 (92,9)	0,000
	Low Risk	4 (11,4)	5 (14,7)	0,000
Leukocytosis	>13000	33 (60)	33 (60)	0,002
	≤ 13000	237 (38,4)	239 (38,7)	0,002
Neutrophils	> 7500	58 (54,7)	58 (54,7)	0,001
	≤ 7500	212 (37,5)	214 (37,8)	0,001
Lymphocytopenia	> 1000	265 (39,9)	267 (40,2)	0,195
	≤ 1000	5 (62)	5 (62,5)	0,202

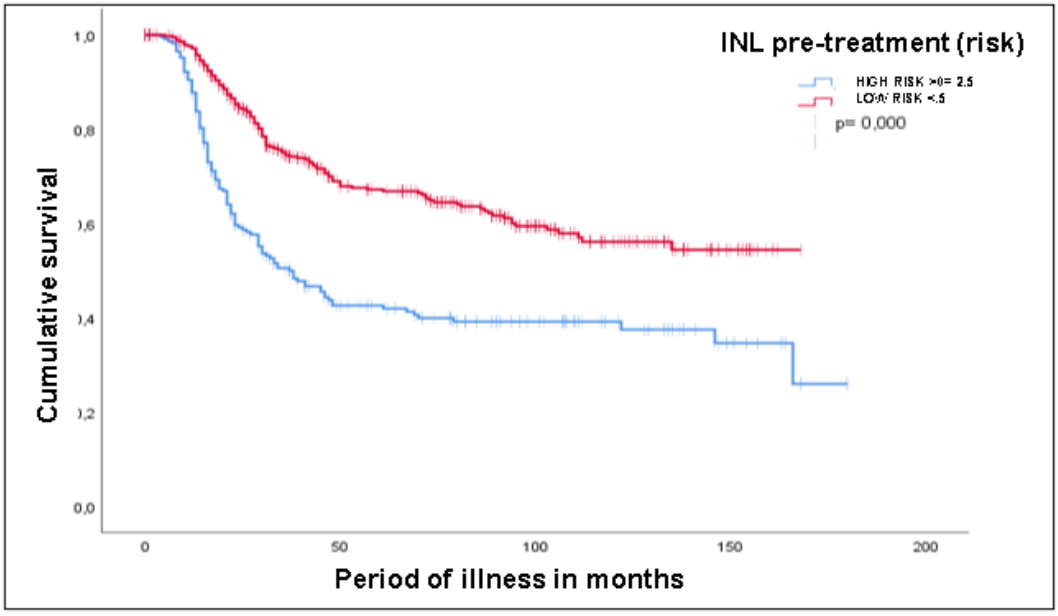
Source: Medical records from the SOLCA-Quito Cancer Hospital

An association analysis using Moore criteria revealed that women classified as intermediate-to-high risk exhibited a recurrence rate of 98.9% and a mortality rate of 92.9% (p = 0.000).

Survival analysis comparing high- and low-risk NLR groups among patients classified as intermediate-to-high versus low risk according to Moore criteria was conducted using the Kaplan–Meier method, with statistical significance evaluated via the log-rank test. The follow-up period extended up to 180 months. Regarding overall survival and NLR, the median survival for patients with NLR ≥ 2.5 was 37 months, with a 95% confidence interval (CI) of 26.3 to 47.6 (p < 0.05) (Figure 2).

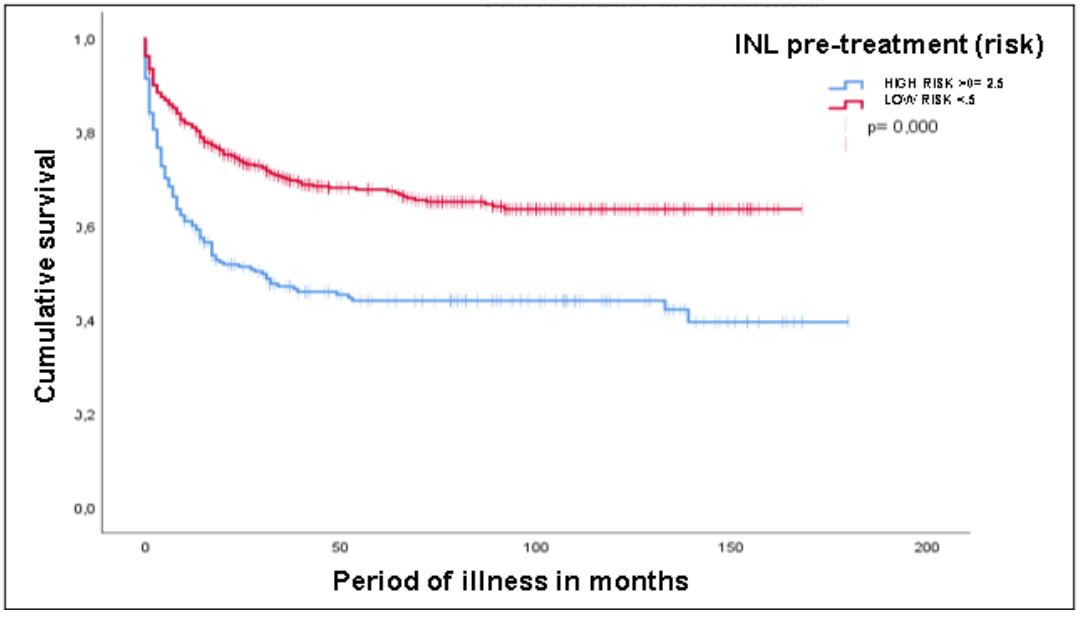
Recurrence-free survival in relation to NLR showed a median of 30 months for patients with NLR ≥ 2.5 (95% CI: 9.4–50.5; p < 0.05) (Figure 3).

Figure 2. Pre-treatment INL Overall Survival



Source: Medical records from the SOLCA-Quito Cancer Hospital

Figure 3. Recurrence-free survival



Source: Medical records from the SOLCA-Quito Cancer Hospital

The analysis of recurrence and mortality revealed significant associations with several prognostic factors. A high-risk NLR (≥2.5) was strongly associated with increased risk of disease recurrence (HR: 3.16, 95% CI: 2.47–4.05, p < 0.000) and mortality (HR: 3.09, 95% CI: 2.42–3.94, p < 0.000). Moore criteria (intermediate and high risk) showed a markedly higher risk, particularly for recurrence (HR: 10.66, 95% CI: 3.97–28.64, p < 0.000) and mortality (HR: 5.39, 95% CI: 2.00–14.48, p = 0.001). Leukocytosis (>13,000) and elevated neutrophil counts (>7,500) were also associated with increased risk in both outcomes, with hazard ratios of 2.11 and 1.79, respectively (p < 0.000). Finally, lymphocytopenia (≤1,000) was significantly associated with both recurrence and mortality risk (HR: 2.43, p < 0.000). These findings highlight the prognostic value of these hematologic biomarkers as predictors of poor outcomes (Table 3).

Table 3. Hazard Ratio

	Recurrence			Mortality		
VARIABLES	**HR**	**IC 95%**	**p-value**	**HR**	**IC 95%**	**p-value**
High-risk NLR ≥ 2.5	3,16	2,47-4,05	0,000	3,09	2,42-3,94	0,000
Moore criteria (Intermediate and High)	10,66	3,97-28,64	0,000	5,39	2,00-14,48	0,001
Leukocytosis (>13,000)	2,14	1,48-3,08	0,000	2,11	1,48-3,08	0,000
Neutrophils (>7,500)	1,79	1,34-2,40	0,000	1,79	1,34-2,40	0,000
Lymphocytopenia (≤ 1,000)	2,43	1,00-5,90	0,000	2,43	1,00-5,90	0,000

Source: Medical records from the SOLCA-Quito Cancer Hospital

3. Discussion

This study assessed the prognostic value of hematological and inflammatory markers in patients with cervical cancer (CC). The main findings indicate that a pre-treatment neutrophil-to-lymphocyte ratio (NLR) ≥ 2.5 is associated with a higher risk of early recurrence and reduced overall survival (OS), with medians of 30 and 37 months, respectively, and a significant hazard ratio (HR) for recurrence (3.16) and OS (3.09).

These results are consistent with those reported by Mizunuma et al. [13], who identified NLR ≥ 2.5 as a prognostic factor for both OS and progression-free survival (PFS), although with slightly longer periods (PFS of 35.9 months and OS of 37.7 months). Wang et al. [27] also reported differences in OS for NLR ≥ 2.5 values, while Onal et al. [28] confirmed the relevance of NLR as a predictor for both OS and PFS.

Other markers, such as leukocytosis and neutrophilia, were also associated with worse prognosis [29]. In this study, leukocytosis doubled the risk of recurrence and mortality (HRs of 2.14 and 2.11), in line with Cho et al. [30] and Mabuchi et al. [31], who reported significantly reduced OS in patients with tumor-associated leukocytosis. Neutrophilia was associated with earlier recurrence (HR 1.79) and shorter OS (38 months, HR 2.43), similar to findings by Matsumoto et al. [32] in granulocyte-colony stimulating factor (G-CSF)-producing tumors.

Regarding lymphocytopenia, although it did not show statistical significance on its own, it was associated with early recurrence and reduced OS when combined with other factors. This aligns with findings from studies such as that of Clark et al. [33] in pancreatic cancer.

The validity of the Moore risk model was also highlighted. This model stratifies patients into low-, intermediate-, and high-risk categories, showing a direct correlation between increased risk and worse prognosis. These findings are supported by the study by Tewari [34], in which patients in the intermediate- and high-risk groups derived significant OS benefit from treatment with bevacizumab.

Systemic inflammatory response is characterized by an imbalance in white blood cell populations, mainly neutrophilia with relative lymphocytopenia [35–37]. Although isolated counts of lymphocytes or neutrophils may hold prognostic value in CC [38,39], their variability limits their standalone utility; therefore, it is recommended to combine them with other parameters to enhance their accuracy as prognostic indicators.

Finally, it is emphasized that elevated NLR is associated with impaired antitumor immune response. Lymphocytes play a crucial role in immune surveillance, while tumor-associated neutrophils promote tumor progression by inducing an inflammatory and immunosuppressive microenvironment. Moreover, chronic systemic inflammation mediated by cytokines such as IL-6, TNF-α, and G-CSF is believed to contribute to CC progression [40,41].

The results of this study should be validated in larger, multicenter prospective studies. Since the study was conducted in a single institution, there is a potential risk of selection bias, which may limit the generalizability of the findings to other populations. Including multiple centers could yield a more diverse and representative sample and improve the external validity of the results.

4. Conclusions

This study demonstrated that a low-risk NLR (< 2.5) is associated with higher survival rates and fewer cases of recurrence across all stages of cervical cancer. This evaluation enables a more precise

stratification of patients, facilitating the personalization of treatment and optimizing healthcare costs related to this pathology. In contrast, an NLR ≥ 2.5 was associated with more aggressive tumor behavior, as evidenced by a higher probability of early recurrence and increased mortality.

Moreover, the importance of applying Moore criteria as a routine practice for prognostic evaluation in patients with recurrent and metastatic cervical cancer was highlighted. The study also revealed that leukocytosis has significant prognostic value in terms of survival and recurrence. Since the presence of infections was an exclusion criterion, it is concluded that treatment delays due to these conditions increase complications and accelerate disease progression.

5. Abbreviations

CC: cervical cancer

SD: standard deviation

ECOG: Eastern Cooperative Oncology Group

FIGO: International Federation of Gynecology and Obstetrics

HR: hazard ratio

CI: confidence interval

NLR: neutrophil-to-lymphocyte ratio

OS: overall survival

RFS: recurrence-free survival

HPV: human papillomavirus

6. Administrative Information

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6.2 Author Contributions

Edison A. Carrasco-Rubio: Conceptualization, validation, visualization, methodology, project management, writing: review and editing. Henry Caballero: Conceptualization, validation, visualization, methodology Statistics: SPSS Institutional. Edison A. Carrasco-Rubio

6.3 Funding

Self-funded

7. Declarations

7.1 Conflicts of Interest

None declared

7.2 Ethics Approval

The study was approved by the Ethics and Research Committee for Human Beings at SOLCA – Quito (Code: CEISHSOLCAQ.OBS.18.060).

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