



IMPACT OF NEUTROPHIL-LYMPHOCYTE RATIO IN ACRAL LENTIGINOUS MELANOMA

IMPACTO DEL ÍNDICE NEUTRÓFILO/LINFOCITO EN EL MELANOMA LENTIGINOSO ACRAL

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ORIGINAL PAPER

ABSTRACT

Introduction: Acral lentiginous melanoma (ALM) is the fourth type of cutaneous melanoma and is the most common subtype in some countries in Latin America and Asia. The neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that has been shown to be useful as a prognostic tool in several malignant neoplasms. **Objective:** The objective of the study was to evaluate whether NLR has prognostic value in ALM. A retrospective study was conducted that included patients with ALM between 2010 and 2015. **Methods:** An observational, analytical and retrospective cohort design was used. We worked with a total population of 69 patients with the diagnosis of acral lentiginous melanoma. For the statistical analysis, the SPSS statistical package version 26 was used. Univariate and multivariate Cox proportional regression models were performed. **Results:** A total of 69 patients with ALM were included. The median age was 68 years, with a predominance of females (55%). Most patients had T4 (34%), lymph node involvement (57.1%), and Clark III (34.4%). In univariate analysis, Clark level III/IV, anaplasia, lymphocytic infiltration, stage III-IV, and NLR were associated with prognoses. In the multivariate analysis, NLR >3.5 (HR 3.9, 95% CI 1.5-10.3, p=0.005) and Clark level III-IV (HR 3.5, 95% CI 1.6-7.8, p= 0.002) were associated with poor overall survival (OS). **Conclusions:** NLR is an independent prognostic factor for survival in ALM.

Keywords: Acral Lentiginous melanoma; Prognostic factor; Survival; Neutrophil-Lymphocyte Ratio. (Source: MESH-NLM)

RESUMEN

Introducción: El melanoma lentiginoso acral (MLA) es el cuarto tipo de melanoma cutáneo y es el subtipo más común en algunos países de América Latina y Asia. El índice neutrófilo-linfocito (NLR), es un marcador inflamatorio, que ha demostrado tener utilidad como herramienta pronóstica en varias neoplasias malignas. **Objetivo:** El objetivo del estudio fue evaluar si el NLR tiene valor pronóstico en la MLA. Se realizó un estudio retrospectivo que incluyó pacientes con MLA entre 2010 y 2015. **Métodos:** Se empleó un diseño observacional, analítico, y de tipo cohorte retrospectiva. Se trabajó con una población total de 69 pacientes con el diagnóstico de melanoma acral lentiginoso. Para el análisis estadístico se empleó el paquete estadístico SPSS versión 26. Se realizaron modelos de regresión proporcional de Cox univariados y multivariados. **Resultados:** Se incluyeron un total de 69 pacientes con MLA. La mediana de edad fue 68 años, con predominio del sexo femenino (55%). La mayoría de los pacientes tenían T4 (34%), compromiso ganglionar (57,1%) y Clark III (34,4%). En el análisis univariado, el nivel de Clark III/IV, la anaplasia, la infiltración linfocitaria, el estadio III-IV y el NLR se asociaron con el pronóstico. En el análisis multivariado, el NLR >3,5 (HR 3,9, IC 95% 1,5-10,3, p=0,005) y el nivel de Clark III-IV (HR 3,5, IC 95% 1,6-7,8, p= 0,002) se asociaron con mala supervivencia general (SG). **Conclusiones:** El NLR es un factor pronóstico independiente de supervivencia en la MLA.

Palabras clave: Melanoma Acral Lentiginoso; Factor pronóstico; Sobrevida; Radio Neutrófilo-Linfocito. (Fuente: DeCS- BIREME)

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INTRODUCTION

Malignant melanoma (MM) is the deadliest form of skin cancer worldwide⁽¹⁾. According to GLOBOCAN 2018, MM ranks thirteenth in global prevalence, with the highest number of cases reported in the United States, Germany, the United Kingdom, and Australia^(2,3). The main histological subtypes of cutaneous melanoma are superficial spreading melanoma, nodular melanoma, lentigo maligna, and acral melanoma. Acral melanoma is defined by its location and was first described by Reed in 1976, with the most common histological subtype being acral lentiginous melanoma (ALM)⁽⁴⁾.

While the genesis of non-acral melanoma is related to intermittent sun exposure, the pathogenesis of ALM is not fully defined⁽¹⁾. Some studies have associated it with traumatic injuries, ultraviolet light exposure, and chemical exposure as risk factors, while others do not find these associations⁽⁵⁻⁸⁾. Clinically relevant prognostic factors for malignant cutaneous melanoma include tumor depth, clear margins, sentinel lymph node biopsy, and ulceration. Mitosis count is no longer considered relevant for prognosis. For the ALM subtype, clinically relevant prognostic factors include tumor depth and clinical stage⁽⁹⁾.

From a pathophysiological perspective, the use of NLR (neutrophil-to-lymphocyte ratio) is supported by the roles of both cell populations. Neutrophils, with their pro-tumoral phenotype, promote tumor growth, angiogenesis, and invasion, while lymphocytes, particularly T lymphocytes, play a crucial role in immune surveillance and response against cancer. An elevated NLR suggests a pro-inflammatory environment that may favor tumor progression and exhibit an ineffective immune response against cancer. Recently, new prognostic parameters such as the NLR have emerged, widely used in other types of neoplasms. We previously reported that NLR is related to survival in patients with aggressive B-cell and T-cell lymphomas^(10,11). The clinical relevance of using NLR in Peruvian patients with ALM lies in its non-invasive and easily accessible nature, allowing for early prognosis estimation and risk

stratification. Therefore, this study aims to demonstrate the prognostic value of NLR in patients with ALM, the most common cutaneous melanoma in Peru.

METHODS

Study Design and Area

This study employed a quantitative, observational, retrospective cohort design. The STROBE checklist for cohort studies was applied⁽¹²⁾.

Population and Sample

The study population consisted of patients diagnosed with Acral Lentiginous Melanoma treated at the Hospital Edgardo Rebagliati Martins between 2010 and 2015. Inclusion criteria considered patients with a histopathological diagnosis of Acral Lentiginous Melanoma, age over 18 years, complete clinical information, and adequate follow-up. Patients with a second neoplasm and those with incomplete clinical information were excluded.

Variables and Instruments

Data for the study variables were collected from patients' medical records.

Patients' clinical characteristics were classified accordingly. The gender variable was assessed as a dichotomous qualitative variable. The primary tumor site was defined as a polytomous qualitative variable. Age was evaluated as a continuous quantitative variable and later divided into a dichotomous qualitative variable based on whether patients were considered elderly. Tumor pathological characteristics were evaluated as qualitative variables, including Clark levels (I-IV), Breslow thickness (0.01-1, 1.01-2, 2.01-4, >4), presence of anaplasia (present, absent, unknown), ulceration (present, absent, unknown), microsatellitosis (present, absent, unknown), perineural infiltration (present, absent, unknown), lymphocytic infiltration (present, absent, unknown), vascular invasion (present,

absent, unknown), nodal involvement (present, absent, unknown), number of affected nodes (1-2, 3-5, >6), pathological stage according to the 7th edition of the American Joint Committee on Cancer (AJCC 7th edition) (I, II, III, IV, unknown).

The neutrophil-to-lymphocyte ratio (NLR) was defined as the ratio of absolute neutrophil count to absolute lymphocyte count ($NLR = ANC/ALC$). Hematological variables (absolute counts of neutrophils, lymphocytes, monocytes, platelets) were measured using a Sysmex XN-1000 hematology analyzer, employing flow cytometry. Overall survival (OS) was calculated from the diagnosis of the disease (event) to the date of the last follow-up (censored).

Statistical Analysis

Data collected were entered into a database using SPSS version 26 for statistical analysis. Clinical-pathological information was analyzed using descriptive statistical tools, including absolute and relative frequencies for qualitative variables. An NLR cutoff of 3.5 was used for patient stratification according to the study by Vano Y et al^[13]. Inferential analysis employed survival analysis

using the Kaplan-Meier method to generate survival curves, compared using the log-rank test. Additionally, a Cox proportional hazards regression model was conducted to establish univariate and multivariate survival models. The results of the Cox proportional hazards regression model were reported with a hazard ratio (HR) and their respective 95% confidence intervals (Cis). A p-value was considered significant if it was less than 0.05.

Ethical Aspects

The research project was approved (Letter N° 387-GRPR ESSALUD-2023) by the Ethics Committee of the Hospital Edgardo Rebagliati Martins. Patient confidentiality and rights were respected according to bioethical principles and the Declaration of Helsinki.

RESULTS

A total of 69 patients were analyzed, with a significant predominance of females (51.1%). The mean age was 68 years, and 68% of patients were over 60 years old. The plantar location was the most frequently affected site in ALM, with 88.4%, followed by palmar location at 8.6%, and subungual location at only 2.9% of cases (Table 1).

Table 1. Clinical characteristics of the patients.

Characteristics	N	%
Patients	69	
Age		
Median (IQR)	68 (16.89)	
<60	22	31.9
>60	47	68.1
Gender		
Female	38	55.1
Male	31	44.9
Primary site		
Plantar	61	88.4
Palmar	6	8.6
Subungual	2	2.9

*IQR: Interquartile Range



In relation to the pathological characteristics, it was found that a Breslow thickness between 0.01 and 1 mm was present in 18.8% of the patients, 1.01-2 mm in 21.7%, 2.01-4 mm in 13% and more than 4 mm in 37.7% of patients. Ulceration was absent in more than half of the patients (58.0%) and most patients did not have perineural infiltration, lymphocyte infiltration and

vascular invasion (89.9%, 82.6%, and 89.9%, respectively). Anaplasia and microsatellitosis were present in 5.8% and 1.4%, respectively. No tumor regression was found. Nodal involvement was present in 17.4%. Pathological stage I was present in 28.9% of the patients, stage II in 34.8%, stage III in 24.6%, and stage IV in 5.8% (Table 2).

Table 2. Pathological characteristics of the tumor.

Características	N	%
Patients	69	
Clark levels		
I	7	10.1
II	14	20.3
III	21	30.4
IV	13	18.8
V	6	8.7
Unknown	8	11.6
Breslow		
0.01-1	13	18.8
1.01-2	15	21.7
2.01-4	9	13.0
> 4	26	37.7
Unknown	6	8.7
Anaplasia		
No	59	85.5
Yes	4	5.8
Unknown	6	8.7
Ulceration		
No	40	58.0
Yes	25	36.2
Unknown	4	5.8
Microsatellitosis		
No	64	92.8
Yes	1	1.4
Unknown	4	5.8

Perineural infiltration		
No	62	89.9
Yes	3	4.3
Unknown	4	5.8
Lymphocytic infiltration		
No	57	82.6
Yes	8	11.6
Unknown	4	5.8
Vascular invasion		
No	62	89.9
Yes	3	4.3
Unknown	4	5.8
Nodal involvement		
No	53	76.8
Yes	12	17.4
Unknown	4	5.8
Number of positive lymph nodes (+)		
1-2	7	58.3
3-5	4	33.3
>6	1	8.3
Regression		
No	65	94.2
Yes	0	0.0
Unknown	4	5.8
Stage (7th Edition AJCC)		
I	20	28.9
II	24	34.8
III	17	24.6
IV	4	5.8
Unknown	4	5.8

*AJCC: American Joint Committee on Cancer

82.6% of patients with clinical stage I to III underwent surgical intervention, and 76.9% of the patients had a complete lymph node dissection (CLND). Adjuvant treatment was performed in 32.3% of patients with stage IIB to IIIC.

All patients with stage IV received the best supportive care and no systemic treatment due to poor functional status. The overall 5-year survival rate was 54.3% with a median of 6.3 months.



Univariate analysis using a Cox proportional hazards regression model showed that the variables Clark levels IV-V (HR: 1.8, 95% CI, 1.1-3.2, $p = 0.016$), anaplasia (HR: 3.0, 95% CI, 1.5-5.7, $p = 0.022$), lymphocyte infiltration

(HR: 2.8, 95% CI, 1.6-5.0, $p = 0.035$), advanced clinical stage (HR: 2.5, 95% CI, 1.5-4.1, $p = 0.030$), and NLR > 3.5 (HR 2.1; 95% CI, 1.1-4.19, $p = 0.002$) were associated with poor prognosis. (Table 3).

Table 3. Univariate analysis using a Cox proportional hazards regression model to evaluate the utility of NLR in the prognosis of patients diagnosed with acral lentiginous melanoma.

Characteristics	Median	5 Year (%)	HR	p-value
Overall Survival	6.3	54.3	-	-
Age				
<60	NR	52.8	Reference	
>60	5.4	55.1	1.2 (0.7, 2.1)	0.867
Gender				
Female	6.8	63.6	Reference	
Male	3.5	45.1	2.1 (1.3, 3.5)	0.130
Clark levels				
I-III	6.7	58.7	Reference	
IV-V	2.5	32.3	1.8 (1.1, 3.2)	0.016
Breslow thickness				
<1	6.3	54.3	Reference	
>1	4.4	42.0	1.2 (0.6, 2.4)	0.644
Anaplasia				
No	5.4	53.6	Reference	
Yes	0.4	25.0	3.0 (1.5, 5.7)	0.022
Ulceration				
No	6.3	61.1	Reference	
Yes	3.2	41.8	1.8 (1.1, 3.0)	0.453
Lymphocytic infiltration				
No	6.3	57.4	Reference	
Yes	2.2	25.0	2.8 (1.6, 5.0)	0.035
Clinical stage				
I-II	6.7	65.2	Reference	
III-IV	2.5	30.9	2.5 (1.5, 4.1)	0.030
NLR				
<3.5	6.6	57.6	Reference	
>3.5	1.7	31.7	2.1 (1.1, 4.19)	0.002

LMR					
>0.2	6.8	62.5	Reference		
<0.2	4.4	49.6	1.7 (1.0, 3.1)	0.064	
PLR					
<170	6.6	58.7	Reference		
>170	4.3	43.6	2.1 (1.2, 3.4)	0.085	

*OS: Overall survival, NLR: Neutrophil-Lymphocyte Ratio, LMR: Lymphocyte-Monocyte Ratio, PLR: Platelet-Lymphocyte Ratio

The multivariate analysis using a Cox proportional hazards regression model showed that the variables Clark levels IV-V (HR 3.5; 95% CI, 1.6-7.8, $p = 0.002$) and NLR >3.5 were associated with lower overall survival (HR: 3.9, 95% CI, 1.5-10.3, $p = 0.005$) (Table 4).

Table 4. Multivariate analysis using a Cox proportional hazards regression model to evaluate the utility of NLR in the prognosis of patients diagnosed with acral lentiginous melanoma.

		CI 95%	p - value	HR Lower	Superior
Clark level					
I-III	Reference				
IV-V	1.2	0.002	3.5	1.6	7.8
NLR					
<3.5	Reference				
>3.5	1.4	0.005	3.9	1.5	10.3

*HR: Hazard Ratio, 95% CI: 95% Confidence Interval

The Kaplan-Meier survival curves for NLR levels according to the cutoff point of 3.5 to evaluate overall survival in patients diagnosed with acral lentiginous melanoma showed statistically significant differences between the high NLR and low NLR groups, according to the log-rank test ($p < 0.001$). (Figure 1)

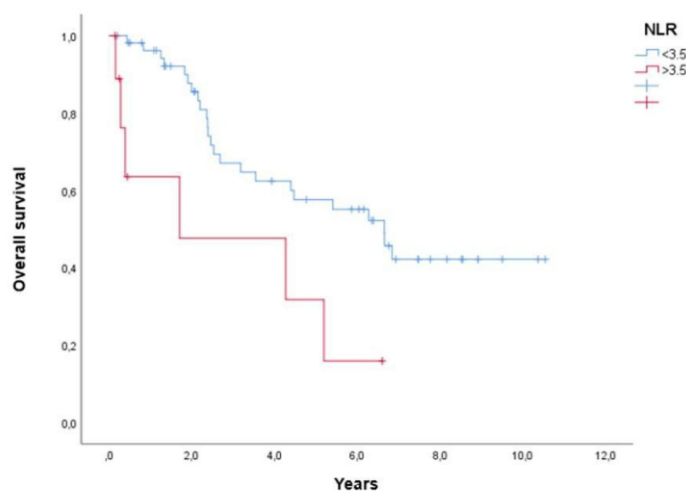


Figure 1. Kaplan-Meier curve for NLR with a cutoff point of 3.5 to evaluate prognosis in patients diagnosed with Acral Lentiginous Melanoma.



DISCUSSION

This is the first report in Latin America to study the role of NLR in ALM. In our cohort of 135 patients with cutaneous melanoma, 51.1% had ALM (69 cases). A previous Peruvian study found that ALM is the most frequent subtype of melanoma, accounting for 61.2% compared to non-acral melanomas⁽¹⁴⁾.

In non-acral cutaneous melanoma, some studies demonstrate the prognostic value of NLR, and three meta-analyses have confirmed its predictive role with checkpoint inhibitors or anti-BRAF treatment^(15,16,17). Recently, Cocorocchio et al. found that clinical stage, elevated serum LDH, and NLR > 5 were prognostic of OS in patients with advanced melanoma receiving BRAFi alone or combined with a MEK inhibitor (MEKi) at recommended doses. These data suggest an immunomodulatory effect of the therapy on the tumor microenvironment in addition to the direct treatment effect and could indicate some potential clinical biomarkers⁽¹⁸⁾. Finally, Bartlett et al. conducted a prospective study with metastatic cutaneous melanoma patients receiving anti-PD1 treatment, describing that patients with NLR>5 had a higher disease burden and poorer functional status, which correlated with worse OS in both univariate and multivariate analyses⁽¹⁹⁾.

The rationale for NLR is that it measures the tumor inflammatory response (neutrophilia) and the host immune response (lymphopenia). One of its strengths is its simplicity of calculation, defined as the number of absolute circulating neutrophils divided by the absolute lymphocyte count^(18,19,20,21). Neutrophils exhibit dual behavior in the tumor microenvironment. Two subtypes or phenotypes have been established: high-density neutrophils (HDN) and low-density neutrophils (LDN)⁽¹⁴⁾.

The HDN subtype has antitumor activity and directly affects tumor cells or indirectly stimulates T-cell-mediated immunity. Conversely, the LDN subtype exhibits pro-tumoral activity that promotes progression, mediated by two mechanisms. LDNs promote the activation of suppressor T cells by secreting Arginine, regulating angiogenesis through

the stimulation of vascular endothelial growth factors (VEGF). At the onset of inflammation, neutrophils have the HDN phenotype, but upon resolving this acute inflammation, the LDN phenotype accumulates. Chronic inflammation, as seen in cancer, results in the generation and accumulation of the LDN phenotype, leading to an unfavorable neutrophil phenotype. The proportion of LDN neutrophils increases with the tumor burden⁽¹⁴⁾.

On the other hand, lymphopenia is associated with reduced host immunity and indirectly with the stimulation of suppressor T cells⁽²⁰⁾. These cells contribute to the decreased antitumor immune activity, with the most well-known being CD4+ CD25+ FOXP3+ regulatory T cells (Tregs). These cells are involved in preventing the immune response and inhibiting antitumor immune responses, thus maintaining normal balance in the body. However, Treg accumulation in cancer has been linked to poor outcomes in some cancer types^(21,22).

The importance of NLR in ALM has not been well-studied. However, there are few studies in Asia investigating its prognostic value^(23,24). Yu et al. evaluated baseline peripheral blood biomarkers to predict early-stage ALM outcomes treated with IFN α -2b and found that NLR \geq 2.35 was associated with poor recurrence-free survival and OS⁽²⁵⁾. Conversely, Jung et al. conducted a retrospective study in an Asian population to evaluate the efficacy of Ipilimumab in melanoma, finding that 31% had advanced-stage ALM.

They found that NLR levels greater than 5 represented an independent poor prognostic factor for survival. Elevated NLR levels were observed in patients experiencing progressive disease, and low NLR predicted longer progression-free survival (PFS) and OS⁽²⁶⁾. Additionally, Lee et al. conducted a retrospective cohort of 152 patients, of which 58 (38%) had ALM. NLR levels > 2.1 were associated with poorer progression-free survival (median 6.9 vs. 2.4 months, $p = 0.015$) and OS (median not reached vs. 10.4 months, $p < 0.001$)^(27,28). Our study aligns with these findings, confirming the prognostic role of NLR in ALM survival in the South American population.



This study has limitations. Regarding the study design, being a retrospective cohort with a small population compared to other series, the power and external validity are limited. Moreover, it was a single-center study conducted in one institution where patients were referred for surgical, adjuvant, or first-line treatment, thus requiring careful extrapolation of the study results.

Additionally, data collection was based on the review of clinical records, posing a potential selection bias. This study reports that ALM is a frequent and aggressive subtype of cutaneous melanoma in our country. This is the first Latin American report investigating the

prognostic value of NLR in ALM, marking an initial step toward better understanding its tumor microenvironment. It also holds potential for targeting new therapeutic approaches in the future. Further research in prospective trials is needed.

CONCLUSION

The present study showed that NLR levels greater than 3.5 are associated with lower overall survival independently of other variables in patients with acral lentiginous melanoma, thus representing a notable prognostic marker in this population.

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