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ORIGINAL ARTICLE

Clinicopathological features and survival outcomes of acral lentiginous melanoma: an 18-year retrospective cohort from a Colombian dermatopathology referral unit

Características clinicopatológicas y supervivencia del melanoma lentiginoso acral: una cohorte retrospectiva de 18 años de una unidad de referencia en dermatopatología colombiana

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Palabras clave

Melanoma; Neoplasias Cutáneas; Pronóstico; Análisis de Supervivencia; Colombia; América Latina.

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Abstract

Background

Acral lentiginous melanoma (ALM) is an uncommon cutaneous melanoma subtype worldwide but occurs more frequently in Latin American, Asian, and African populations. Despite its clinical relevance, evidence regarding its clinicopathological characteristics and prognosis in Latin America remains limited.

Objective

To describe the clinicopathological features and overall survival (OS) of patients with ALM diagnosed at a dermatopathology referral unit in Cali, Colombia.

Methods

Retrospective cohort of patients with histopathologically confirmed cutaneous melanoma diagnosed in 2003-2020. Five-year OS for invasive ALM was estimated using Kaplan-Meier, and prognostic factors were assessed using univariable and multivariable Cox proportional hazards regression.

Results

Of 285 cutaneous melanomas, 91 (31.9%) were ALM. The median age was 65 years (IQR: 54-77), 61.5% were females, and 92.3% of tumors arose on the foot. Clark levels IV-V were present in 54/90 (60.0%); the median Breslow thickness of invasive tumors was 1.7 mm (IQR: 0.8-3.4). Among the 63 invasive cases analyzed for survival, 24 died within five years of diagnosis. In the multivariable model (n= 60; 23 deaths), age was independently associated with poorer OS (aHR per year: 1.04; 95% CI: 1.00-1.08; *p*= 0.029), whereas Breslow thickness ≥2 mm showed a higher but imprecise hazard of death (aHR: 2.20; 95% CI: 0.87-5.56; *p*= 0.096).

Conclusions

ALM accounted for nearly one-third of cutaneous melanomas in this Colombian referral cohort. Older age independently predicted poorer OS, and the association with Breslow thickness, although imprecise, was consistent with its established prognostic value. These findings support early detection of acral lesions and the need for multicenter studies in Latin America.

Conflict of interest

None declared

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CRediT authorship contribution statement

R.A.R: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing, Supervision; **A.C.B:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing, Supervision; **E.K.G-A:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing, Supervision. All authors read and approved the final version of the manuscript.

Data availability statement

The data supporting the findings of this study are not publicly available because they derive from pathology records and the Cali Population-Based Cancer Registry and contain information that could compromise patient confidentiality. De-identified data are available from the corresponding author upon reasonable request, subject to approval by the RPCC and the Health Research Ethics Committee of Universidad del Valle.

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Resumen

Antecedentes

El melanoma lentiginoso acral (MLA), infrecuente a nivel mundial, es más frecuente en poblaciones latinoamericanas, asiáticas y africanas; sin embargo, en América Latina se sabe poco sobre sus características clinicopatológicas y su pronóstico.

Objetivo

Describir las características clinicopatológicas y la supervivencia global (SG) de pacientes con MLA en una unidad de referencia de dermatopatología en Cali, Colombia.

Métodos

Cohorte retrospectiva de melanomas cutáneos histopatológicamente confirmados entre 2003 y 2020. La SG a los 5 años del MLA invasivo se estimó mediante el método de Kaplan-Meier, y los factores pronósticos se evaluaron mediante regresión de Cox univariable y multivariable.

Resultados

De los 285 melanomas cutáneos, 91 (31.9%) fueron MLA; el 61.5% se presentó en mujeres y el 92.3% en el pie, con una mediana de edad de 65 años (RIC: 54-77). El 60.0% (54/90) presentaba un nivel de Clark IV-V, y la mediana del espesor de Breslow de los tumores invasivos fue de 1.7 mm (RIC: 0.8-3.4). De los 63 casos invasivos, 24 fallecieron en los primeros cinco años. En el modelo multivariable (n= 60; 23 defunciones), la edad se asoció independientemente con menor SG (HRa por año: 1.04; IC95%: 1.00-1.08; p= 0.029), y un espesor de Breslow ≥2 mm, con mayor riesgo de muerte, aunque impreciso (HRa: 2.20; IC95%: 0.87-5.56; p= 0.096).

Conclusiones

En esta cohorte, el MLA representó casi un tercio de los melanomas cutáneos. La edad avanzada predijo, de forma independiente, una menor SG, y la asociación con el espesor de Breslow, aunque imprecisa, concuerda con su valor pronóstico. Estos hallazgos respaldan la detección temprana de lesiones acrales y los estudios multicéntricos regionales.

Remark

1) Why was this study conducted?

ALM is proportionally more frequent in Latin American populations than in populations of European ancestry, yet clinicopathological and survival data from Colombia are scarce. This study characterizes ALM in an 18-year dermatopathology referral cohort in Cali, Colombia.

2) What were the most relevant results of the study?

ALM accounted for 31.9% (91/285) of cutaneous melanomas; 92.3% of cases arose on the foot, mainly on the heel and sole, and 60.0% had Clark level IV-V at diagnosis. In the multivariable analysis (n= 60), older age was independently associated with poorer overall survival, and Breslow thickness ≥2 mm with an approximately twofold, although imprecise, higher hazard of death.

3) What do these results contribute?

These data expand the limited Latin American evidence on ALM, document the frequent diagnosis of deeply invasive plantar lesions, and support early-detection strategies for acral sites and multicenter, population-based studies to refine prognostic estimates.

Introduction

Cutaneous malignant melanoma is a highly aggressive, heterogeneous tumor derived from melanocytes, which represents the leading cause of death from skin cancer [1,2]. In the last decade, incidence and mortality rates of invasive melanoma have been changing, with a downward trend in incidence in people under 50 years and stability after that age, as well as a 4% annual decrease in mortality associated with skin screening programs and the introduction of new therapies for advanced tumors [2,3].

Acral lentiginous melanoma (ALM) is one of the four major histological varieties of melanoma. ALM was first described as pigmented lesions located in the nail beds, palms, and soles, characterized by progression from a cancerous zone, a "radial" lentiginous growth phase, to a "vertical" invasive dermal phase over months to years [4,5]. Although ALM is the least frequent variety of malignant melanoma among Caucasians, with a proportion of less than 3% of cases, in African, Asian, and Latin American countries, such as Colombia, it represents a higher proportion of malignant melanomas [6-8].

The etiology of ALM remains controversial. Since lesions are predominantly located in anatomical areas susceptible to mechanical stress and protected from the sun, lack of ultraviolet ray exposure suggests a positive relationship with genetic factors (personal or family history of non-cutaneous malignancies) and trauma (friction, impact, or twisting) [9]. In addition to having an aggressive biological behavior, late diagnosis, which usually accompanies ALM due to its unusual anatomical location and clinical presentation, should make us consider it, for prognostic purposes, as a severe form of melanoma [8,10]. ALM clinical and histopathological diagnosis is essential. Measurement of Breslow thickness, mitotic rate, and presence of ulcerations are used as prognostic attributes that must be determined in each case [9-11]. In Colombia, epidemiological information on ALM is limited, heterogeneous, and does not capture the magnitude of the problem or enable comparison with the mestizo population elsewhere in the world. We explore the biological behavior and overall survival (OS) of ALM cases diagnosed in a specialized dermatopathology unit (SDPU) in Cali, Valle del Cauca, Colombia, during 2003-2020.

Materials and Methods

Background

The Specialized Dermatopathology Unit (SDPU) has collaborated with the Cali Population-Based Cancer Registry (RPCC, its Spanish acronym) for more than two decades. Since 1993, the SDPU has followed standardized diagnostic and reporting protocols that provide comparability with international melanoma registries [12]. Histopathological diagnoses are confirmed by expert dermatopathologists, and standardized information on prognostic variables, including Breslow thickness, ulceration, mitotic rate, Clark level, and growth pattern, is routinely reported to the RPCC.

Since 1962, the RPCC has conducted continuous cancer surveillance in accordance with internationally accepted procedures for cancer registration, follow-up, and quality control. The methodology, objectives, coverage, and procedures of the RPCC have been previously described [12,13]. The study was approved by the Health Research Ethics Committee of Universidad del Valle (IRB approval #E012-024). Given the retrospective design and the use of de-identified records, the committee waived the requirement for individual informed consent.

Study design and population

This retrospective clinicopathological cohort study included consecutive patients with histopathologically confirmed cutaneous melanoma diagnosed at the SDPU between 2003 and 2020.

Although the SDPU contributes standardized information to the RPCC, this investigation was conducted using a clinicopathological referral cohort. The study population included patients evaluated at the SDPU, including both Cali residents and non-residents. Patient flow through the study, including exclusions applied for the survival and multivariable analyses, is summarized in the flow diagram (Figure 1).

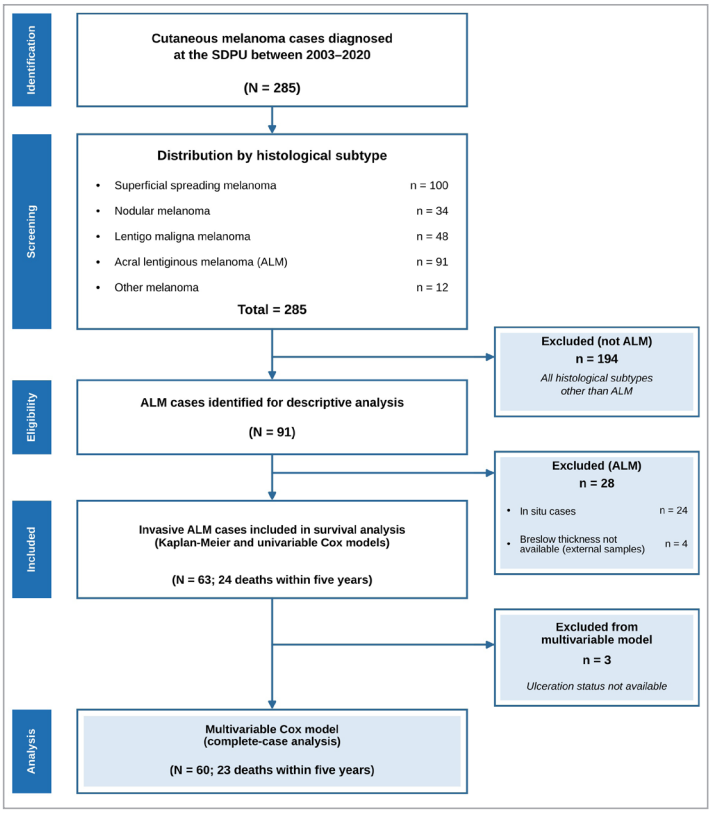

Figure 1. Flow diagram of the study cohort selection at the specialized dermatopathology unit, 2003-2020.

Participants and selection criteria

Patients of both sexes and all ages were included regardless of place of residence, with a new diagnosis of primary cutaneous melanoma confirmed by histopathology during the study period.

Melanomas were classified into the main histological subtypes: superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma (ALM), and lentigo maligna melanoma. Twelve melanomas of other or unspecified subtypes were retained in the descriptive analysis (Table 1) but, owing to their histological heterogeneity, were not analyzed as separate subtypes. ALM-specific analyses (Tables 2-4; Figures 2-4) included only ALM cases. The comparison of OS across histological subtypes was descriptive and limited to melanomas diagnosed between 2016 and 2020. OS of the 24 ALM *in situ* cases was estimated separately; these cases were excluded from the main survival analysis. Age was analyzed as a continuous variable and subsequently categorized into three groups: <45, 45-64, and ≥65 years [7].

For OS analyses, only invasive melanomas with available follow-up information and known vital status were included. Melanoma *in situ* and cases lacking essential prognostic or follow-up information were excluded to align with the analytical objective.

Histopathological assessment and follow-up

Cases were coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) [14]. Staging information was limited to the primary tumor. Breslow thickness, routinely recorded in each pathology report, was categorized according to the American Joint Committee on Cancer (AJCC) T-category thresholds (T1 ≤1.0 mm, T2 1.01-2.0 mm, T3 2.01-4.0 mm, T4 >4.0 mm), which remained unchanged from the sixth to the eighth edition [11]. Because regional nodal and distant metastasis status were not systematically available, AJCC stage groups were not assigned. Breslow thickness was analyzed both as a

continuous variable and categorized as follows: a. ≤1.00 mm, 1.01-2.00 mm, 2.01-4.00 mm, and >4.00 mm, and b. <2 mm vs ≥2 mm [5].

Additional histopathological variables included ulceration (present/absent), mitotic rate (absent, <1, 1-4, 5-9, and >9 mitoses/mm²), regression (present/absent), Clark level (I-V), tumor-infiltrating lymphocytes (absent, mild, moderate, or severe), and radial and vertical growth phases (present/absent) [15]. Although Clark level was evaluated because it was systematically recorded throughout the study period, Breslow thickness was considered the primary histopathological prognostic variable according to current AJCC recommendations [11].

For ALM cases, anatomical location and laterality were classified using an adaptation of the anatomical mapping system developed by the Study Group for Pigmented Lesions, a methodology previously applied in historical and contemporary studies of acral melanoma [8,16].

Vital status was determined through linkage between the SDPU and RPCC databases using death certificates provided by the Cali District Public Health Secretariat, pathology reports, and administrative databases from public and private health insurance systems. OS was defined as the time from the date of histopathological diagnosis to death from any cause, with the last follow-up on 31st December 2025. Patients alive or lost to follow-up were censored at the date of last known vital status. Kaplan-Meier and Cox analyses were restricted to the first five years after diagnosis. Median follow-up for the full cohort was estimated with the reverse Kaplan-Meier method. Deaths from any cause over the entire follow-up are reported descriptively.

Data quality control

Data management and quality assurance procedures adhered to standardized protocols established by the SDPU and the RPCC. Histopathological diagnoses and key prognostic variables, including melanoma subtype, Breslow thickness, ulceration, and mitotic rate, were verified by experienced dermatopathologists. Database completeness and internal consistency were evaluated in accordance with international cancer registration standards.

Missing data were assessed before statistical analysis. Given the low proportion of missing values, complete-case analyses were performed without imputation. Patient confidentiality was maintained throughout the study.

Statistical analysis

Statistical analyses were performed using Stata version 19. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, according to their distribution. Categorical variables were described using absolute and relative frequencies. Denominators shift slightly from one variable to the next, reflecting missing data on specific fields. We report the available n for each variable.

OS was estimated using the Kaplan-Meier method. Differences between survival curves were assessed using the log-rank test. Multivariable Cox proportional hazards regression models were used to evaluate independent prognostic factors for OS in ALM (excluding *in situ* cases and cases with missing Breslow information). Adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) were estimated. The multivariable model was specified *a priori* based on clinical relevance and prior evidence and included established prognostic factors for cutaneous melanoma: age, sex, Breslow thickness (≥2 mm vs. <2 mm), and ulceration, the latter two of which are the defining criteria for the AJCC T category [11]. To limit overfitting given the number of events, covariates representing overlapping constructs were not entered simultaneously; accordingly, vertical growth phase, which reflects the same biological dimension as Breslow thickness (tumorigenic dermal invasion), was not included. Collinearity among covariates was assessed before model fitting. The proportional hazards assumption was evaluated using Schoenfeld residuals and graphical methods. Univariable associations are reported descriptively. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

New melanoma cases (2003-2020)

Table 1 shows the number and distribution of cutaneous melanoma cases in the SDPU by histological subtype, sex, residence, and age group. Most cases occurred in females (54.7%), residents of Cali (69.1%), and those aged ≥65 years (48.4%). Twelve cases were classified as other melanomas. Superficial spreading melanoma and ALM represented the most common histological subtypes (35.1% and 31.9%, respectively).

ALM cases

Of the 221 ALM cases registered by the RPCC among Cali residents during 2003-2020, 44 (19.9%) were diagnosed at the SDPU. Tables 2 and 3 show the demographic, clinical, and pathological characteristics of ALM cases in the SDPU. Of the 285 melanoma cases, 91 were ALM. The median age of patients at diagnosis was 65 years (IQR: 54-77). Cases were equally distributed between Cali residents and non-residents (44/91 each, 48.4%; residence unknown in 3). Most patients were females (56/91, 61.5%) and aged ≥65 years (50/91, 54.9%). By anatomical region, the overall ALM group was distributed as follows: lower limb, 92% (n= 84); upper limb, 8% (n= 7). Most of the ALM cases were located on the right side (n= 48; 53%), specifically on the right foot; two cases lacked the necessary information for laterality-specific analysis: "foot, no information" (2%) (Table 2). The most frequently affected anatomical regions were the heel, n= 27; non-specific areas of the sole, n= 26; hallux, n= 7; lateral border of the foot, n= 7; and the forefoot, n= 7 (Figure 2).

At the time of diagnosis, 54 of 90 ALM cases with available Clark level (60.0%; 59.3% of all 91 cases) showed invasion into the reticular dermis and the subcutaneous cellular tissue (Clark levels IV-V). Breslow thickness was available for 63 cases (69.2%); it was not measured in 24 *in situ* cases (26.4%) and was unavailable for 4 external samples (4.4%). Twenty-seven cases of ALM had a Breslow thickness ≤1 mm (27/63, 42.9% of measurable invasive tumors; 29.7% of all 91 cases), and 13 had >4 mm (13/63, 20.6%; 14.3% of all cases); the median Breslow

Table 1. Distribution of skin melanoma cases in the specialized dermatopathology unit according to histological type during the period 2003-2020.

Demographic characteristics	Histological subtypes, n (%)					
	Superficial spreading	Nodular melanoma	Lentigo maligna melanoma	Acral lentiginous melanoma	Other melanoma	Total
Number of cases	100 (35.1)	34 (11.9)	48 (16.8)	91 (31.9)	12 (4.2)	285 (100.0)
Sex						
Female	59 (59.0)	7 (20.6)	27 (56.3)	56 (61.5)	7 (58.3)	156 (54.7)
Male	41 (41.0)	27 (79.4)	21 (43.8)	35 (38.5)	5 (41.7)	129 (45.3)
Residence						
Cali	85 (85.0)	26 (76.5)	34 (70.8)	44 (48.4)	8 (66.7)	197 (69.1)
Outside Cali	11 (11.0)	6 (17.6)	8 (16.7)	44 (48.4)	3 (25.0)	72 (25.3)
Missing data	4 (4.0)	2 (5.9)	6 (12.5)	3 (3.3)	1 (8.3)	16 (5.6)
Age groups (years)						
<45	28 (28.0)	2 (5.9)	2 (4.2)	5 (5.5)	1 (8.3)	38 (13.3)
45-64	44 (44.0)	9 (26.5)	20 (41.7)	36 (39.6)	0 (0.0)	109 (38.2)
≥65	28 (28.0)	23 (67.6)	26 (54.2)	50 (54.9)	11 (91.7)	138 (48.4)

Table 2. Sociodemographic and clinical characteristics of acral lentiginous melanoma cases of the specialized dermatopathology unit, 2003-2020.

Demographic and clinical characteristics	n= 91, n (%)
Demographic	
Sex	
Female	56 (61.5)
Male	35 (38.5)
Age (years)	
Median (IQR)	65 (54 - 77)
<45	5 (5.5)
45 - 64	36 (39.6)
≥65	50 (54.9)
Residence	
Cali	44 (48.4)
Outside Cali	44 (48.4)
Missing data	3 (3.3)
Clinical	
Anatomical region	
Upper limb	7 (7.7)
Lower limb	84 (92.3)
Laterality	
Right	48 (52.7)
Left	41 (45.1)
Missing data	2 (2.2)

IQR: interquartile range

Table 3. Pathological features of acral lentiginous melanoma cases of the specialized dermatopathology unit, 2003-2020.

Pathological features	n= 91, n (%)
Clark level	
I	24 (26.4)
II	3 (3.3)
III	9 (9.9)
IV	43 (47.3)
V	11 (12.1)
Missing data	1 (1.1)
Breslow thickness (mm)	
Median (IQR)	1.7 (0.8-3.4)
In situ	24 (26.4)
≤1.00	27 (29.7)
1.01 - 2.00	9 (9.9)
2.01 - 4.00	14 (15.4)
>4.00	13 (14.3)
Missing data	4 (4.4)
Growth phase	
Radial	
Absent	24 (26.4)
Present	60 (65.9)
Missing data	7 (7.7)
Vertical	
Absent	44 (48.4)
Present	40 (44.0)
Missing data	7 (7.7)

Continuation of Table 3

Pathological features	n= 91, n (%)
Mitotic rate (mitoses/mm²)	
<1	32 (35.2)
1 - 4	22 (24.2)
5 - 9	5 (5.5)
>9	0 (0.0)
Absent	21 (23.1)
Missing data	11 (12.1)
Regression	
Absent	81 (89.0)
Present	2 (2.2)
Missing data	8 (8.8)
Tumor-infiltrating lymphocytes (TILs)	
Absent (Not observed)	5 (5.5)
Mild	9 (9.9)
Moderate	54 (59.3)
Severe	16 (17.6)
Missing data	7 (7.7)
Ulceration	
Absent	63 (69.2)
Present	21 (23.1)
Missing data	7 (7.7)

Percentages are calculated over all 91 ALM cases; missing data are shown as a separate category, and *in situ* cases (n= 24) are included in all rows. In the text, percentages are calculated over cases with available information, and denominators are reported explicitly. A mitotic rate <1/mm² denotes mitoses present at a density below 1 per mm². IQR: interquartile range.

thickness of the 63 measurable tumors was 1.7 mm (IQR, 0.8 - 3.4). Radial and vertical growth phases were present in 71.4% (60/84) and 47.6% (40/84) of cases with available information, respectively. Mitotic rates were available for 80 of 91 cases (88%). Mitoses were present in 59/80 (73.8%). A mitotic rate of <1 mitosis/mm² was the most frequent, followed by 1-4 mitoses/mm² (32/80, 40.0%, and 22/80, 27.5%, respectively; 35.2% and 24.2% of all 91 cases in Table 3). Present ulceration was documented in 21 of 84 cases with available information (25.0%; 23.1% of all 91 cases in Table 3). Most ulcerations were located on the soles of the feet (n= 16/21, 76%). Regression was observed in only 2 of 83 cases with available information (2.4%; 2.2% of all 91 cases). Intensity of the inflammatory infiltrate, represented by tumor-infiltrating lymphocytes, was predominantly moderate (54/84, 64.3%), followed by severe infiltration (16/84, 19.0%).

At the end of follow-up (median follow-up by the reverse Kaplan-Meier method, 13.3 years; median observed time, 8.3 years), 113 of 285 patients (39.6%) had died from any cause. All-cause mortality over the entire follow-up was highest among patients with nodular melanoma (24/34, 70.6%) and ALM (46/91, 50.5%). Among the 63 invasive ALM cases included in the survival analysis, 37 (58.7%) had died by the end of follow-up, and 24 of these deaths occurred within five years of diagnosis. The remaining 9 ALM deaths (46 minus 37) occurred among the 28 cases excluded from the survival analysis (7 *in situ* and 2 without Breslow thickness). Of the 46 ALM deaths, 43 (93.5%) occurred in patients with ALM located on the foot, and 15 of the 44 with available information (34.1%) had ulceration.

Overall survival

In the last quinquennium (2016-2020), OS was 88% (95% CI: 39-98) for superficial spreading melanoma, 33% (95% CI: 1-77) for nodular melanoma, 100% for lentigo maligna melanoma, and 62% (95% CI: 38-79) for acral lentiginous melanoma.

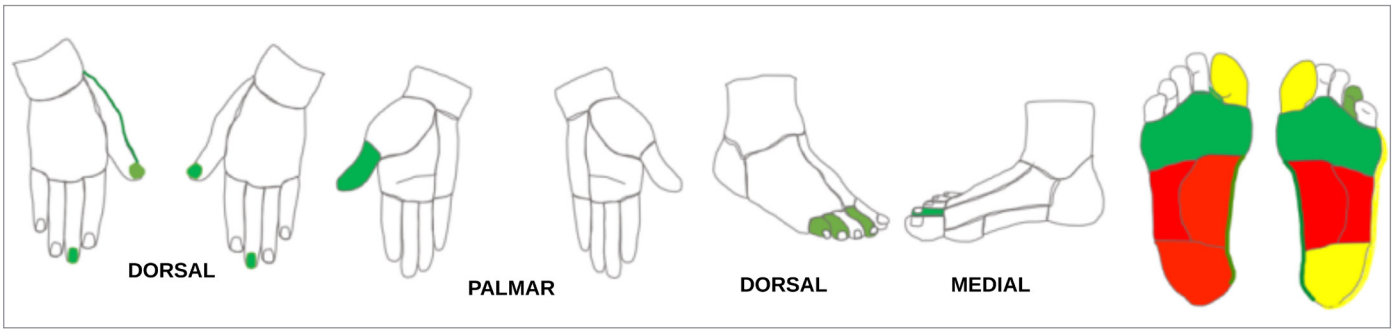

Figure 2. Frequency distribution of acral lentiginous melanoma according to anatomical region. Cases (n): white (0), green (1-2), yellow (3-5), orange (6-8), and red (≥9).

Figure 3 shows the 5-year OS of invasive ALM by sex and period of diagnosis. Of the total number of recorded ALM cases, 28 were excluded from the OS analysis: 24 because they were *in situ* and 4 because Breslow information was unavailable. Although overall survival was consistently lower among males than females, the observed differences were not statistically significant. The female-male OS gap decreased by 4.0 percentage points between 2003-2005, with a 75.0% (95% CI: 31.5-93.1) vs. 66.7% (95% CI: 19.5-90.4) and 2016-2020, with 64.3% (95% CI: 15.2-90.2) vs. 60.0% (95% CI: 12.6-88.2; p >0.05).

In situ ALM (n= 24) had a 5-year OS of 90.7% (95% CI: 67.6-97.6), with two deaths within five years. An OS reduction was observed among ALM with Breslow thickness ≥1.01 mm (51.4% (95% CI: 34.0-66.4)) compared with lesions ≤1.0 mm (69.6% (95% CI: 46.6-84.2)).

In univariable Cox regression analyses, increasing age was significantly associated with worse OS (HR per year: 1.04; 95% CI: 1.00-1.08; p= 0.030). A Breslow thickness ≥2 mm showed a non-significant trend toward poorer survival (HR: 2.07; 95% CI: 0.88-4.85; p= 0.094), whereas sex and ulceration were not significantly associated with mortality. The vertical growth phase also demonstrated a clinically relevant, although statistically non-significant, association with survival (HR: 2.71, 95% CI: 0.92-7.99; p= 0.070) (Table 4, Figure 4).

The multivariable model adjusted for age, sex, Breslow thickness, and ulceration; age remained independently associated with mortality (adjusted HR: 1.04 per year, 95% CI: 1.00-1.08, p= 0.029). Breslow thickness ≥2 mm remained associated with an approximately twofold higher hazard of death, although the confidence interval included the null value (adjusted HR: 2.20, 95% CI: 0.87-5.56, p= 0.096). Sex and ulceration were not independently associated with OS (p= 0.716 and p= 0.655, respectively). No evidence of violation of the proportional hazards assumption was observed (global Schoenfeld test p= 0.996).

Discussion

Melanoma, a malignant tumor derived from melanocytes, is a highly aggressive heterogeneous neoplasia [16]. Although in countries with a Caucasian population, ALM cases represent less than 5% of cutaneous melanomas [17], in our cohort, ALM represented 32% of all melanoma cases. Our results are similar to those reported in the black population of the United States (33%) and in other series from Latin American countries, such as Colombia, where nearly 40% of cases are ALM [8,16,18]. Regarding the distribution by sex, the proportion of ALM cases in females was consistent with that found by other studies, where more than half of the patients diagnosed with ALM are female [3,7]. The median age and the age group with the highest number of ALM cases in this study were similar to those reported in high- and middle-income countries, where the estimated median age of ALM cases is greater than 60 years [19].

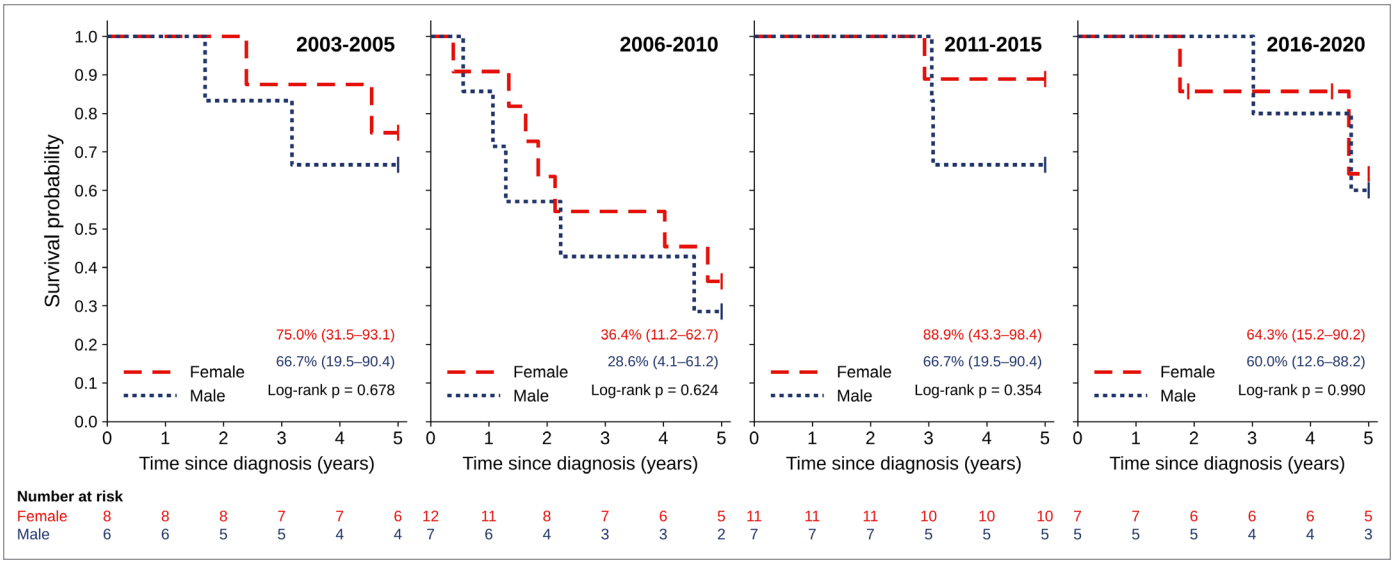

Figure 3. Five-year overall survival of invasive acral lentiginous melanoma by sex and period of diagnosis at the specialized dermatopathology unit. Values are Kaplan-Meier estimates at five years (95% CI); *p*-values correspond to the log-rank test.

With respect to the anatomical distribution of acral skin regions, ALM most frequently originated on the heel (30%), followed by non-specific areas of the sole (29%). These figures support the reports in the literature that propose trauma in pressure points (heel, forefoot) and torsional stress as a predisposing factor to the development of ALM [7,20,21]. Recent research into the genetic evolution of ALM has identified early chromosomal events involving *TERT* activation [22]. Previous studies have proposed mechanical stress as a potential biological mechanism; however, this hypothesis could not be evaluated in the present study.

More than half of the ALM cases with available information had invaded the reticular dermis or subcutaneous tissue at diagnosis (Clark IV-V; 54/90, 60.0%), and one in four presented with ulceration (21/84, 25.0%), supporting the hypothesis that a significant proportion of ALM patients are diagnosed late; therefore, the prognosis is poor [13,18].

The numerically lower survival observed in males in this cohort, although not statistically significant, is consistent with reports from Brazil and high-income countries, where lower survival has been observed in males regardless of lesion clinical stage [23]. This sex-based difference in survival is likely multifactorial, potentially reflecting diagnostic delay, differences in health-seeking behavior, stage at diagnosis, comorbidities, and possible biological factors [24]. Because estimating survival in cutaneous melanomas, and specifically in the ALM of the data presented, is a tangential measure of the effectiveness of oncological care in the city, it is necessary to continue prioritizing interventions focused on risk control and early detection of the disease [13].

The SDPU captured 19.9% of the ALM cases registered by the RPCC among Cali residents during the study period. This finding suggests that our cohort constitutes a referral population with a potential selection bias toward more complex, referred, or clinically more severe cases, which limits the population-level representativeness of the survival estimates presented in this study.

Although the adjusted association between Breslow thickness and OS did not reach conventional statistical significance, the estimated hazard ratio was greater than two. This effect size is clinically important, and its direction is consistent with the current understanding of melanoma biology. The imprecision of this estimate is expected given the limited effective sample size available for multivariable analysis. Taken together, these findings reinforce the importance of interpreting survival analyses in accordance with contemporary epidemiological recommendations that prioritize clinical relevance over *p*-values, and they align with the established prognostic value of Breslow thickness.

Table 4. Univariable and multivariable Cox proportional hazards regression analysis for overall survival in invasive acral lentiginous melanoma, follow-up truncated at five years.

Characteristic	Unadjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Age (years)	1.04 (1.00-1.08)	0.030	1.04 (1.00-1.08)	0.029
Sex (Male vs. Female)	1.45 (0.64-3.26)	0.370	1.18 (0.48-2.94)	0.716
Breslow thickness (≥2 mm vs. <2 mm)	2.07 (0.88-4.85)	0.094	2.20 (0.87-5.56)	0.096
Ulceration (Present vs. Absent)	1.59 (0.70-3.63)	0.280	1.21 (0.53-2.78)	0.655
Vertical growth phase (Present vs. Absent)	2.71 (0.92-7.99)	0.070	-	-

HR: Hazard ratio; CI: confidence interval.

Multivariable model: adjusted for age, sex, Breslow thickness, and ulceration. Reference categories: female sex, Breslow thickness < 2 mm, and absence of ulceration; robust standard errors; age was entered as a continuous variable (HR per year). The multivariable model included 60 patients (23 deaths).

Univariable models included 63 patients (24 deaths) for age, sex, and Breslow thickness, and 60 patients (23 deaths) for ulceration and vertical growth phase.

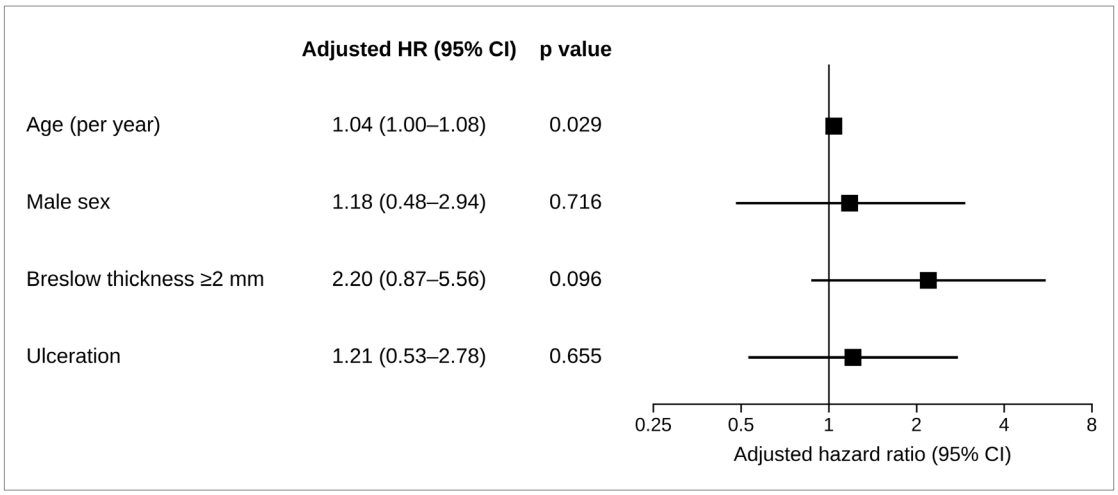

Figure 4. Forest plot of the multivariable Cox proportional hazards regression analysis for overall survival in invasive acral lentiginous melanoma.

Limitations

Because the referral-based retrospective cohort design captures only 19.9% of cases recorded in the RPCC, the survival estimates cannot be extrapolated to the general population. Breslow thickness, arguably the single most important prognostic variable in melanoma, was missing in some ALM cases, which is a real constraint on what the multivariable model can tell us. Related to that: the number of events available for adjusted analysis was small, so the 95% confidence intervals around our hazard ratios are wide, and some associations that look clinically meaningful did not reach statistical significance. OS was defined as the time from histopathological diagnosis to death from any cause; we did not have the data to separate melanoma-specific mortality or account for competing risks. Finally, the 18-year recruitment window (2003-2020) spans real changes in melanoma staging and treatment that we were unable to explicitly adjust for.

Conclusion

Acral lentiginous melanoma (ALM) accounted for nearly one-third of melanoma cases and 40.7% of all deaths in this Colombian referral cohort, a proportion higher than that reported in populations of predominantly European ancestry and largely consistent with other Latin American series. Advanced age at diagnosis was an independent predictor of poorer overall survival. Greater Breslow thickness was associated with an increased hazard of death, although the estimate was imprecise and did not reach conventional statistical significance. These findings underscore the need for enhanced early-detection strategies for ALM in Latin American populations, ideally through population-based, prospective studies to refine prognostic estimates and inform clinical and public health interventions.

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