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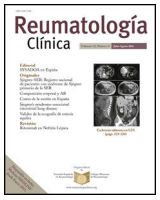

Original article

Exploring the link between inflammatory myopathies and cancer: A comprehensive retrospective analysis in a Colombian cohort

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ABSTRACT

Background: This study investigates the association between inflammatory myopathies (IM), and their correlation with cancer. There are several potential causes behind the association of cancer and inflammatory myopathies. The positivity of specific antibodies for myositis plays a significant role. Our objective is to describe cancer and inflammatory myopathies in Colombia, focusing on demographics, clinical characteristics, and laboratory data.
Methods: We retrospectively analyzed 112 IM patients diagnosed at Fundación Valle del Lili in Cali, Colombia, the cases met the EULAR/ACR criteria. Data included demographics, clinical signs, laboratory findings, and malignancy. Malignancy associations were explored using logistic regression. The survival analysis was assessed using Kaplan–Meier curves and the Log-Rank test.
Results: Dermatomyositis was the most common subtype (45.5%), with a female predominance (66.1%). Cancer diagnosis occurred in 11.6% of cases, predominantly thyroid cancer. The median time from myopathy onset to cancer diagnosis was 11 months, with 75% of cases within the first year. Bivariate analysis indicated associations between cancer and age, Gottron's papules, digital ulcers, and heliotrope rash. However, multivariate analysis identified age as the only significant malignancy risk factor. Survival analysis showed better rates in younger patients.
Conclusion: This study provides into the link between IM and cancer in the Colombian population. Thyroid cancer predominated, with a slightly higher proportion of female cancer diagnoses. Age emerged as a significant risk factor for malignancy. Understanding this association is crucial for early detection and improving patient outcomes related to IM-associated malignancies.

Exploración de la relación entre las miopatías inflamatorias y el cáncer: un análisis retrospectivo exhaustivo en una cohorte Colombiana

Palabras clave:
Dermatomiositis
Polimiositis
Neoplasias
Cáncer
Cáncer de tiroides

RESUMEN

Antecedentes: Este estudio investiga la asociación entre las miopatías inflamatorias (MI) y su correlación con el cáncer. Hay varias causas potenciales detrás de la asociación entre el cáncer y las miopatías inflamatorias. La positividad de anticuerpos específicos para la miositis desempeña un papel importante. Nuestro objetivo es describir el cáncer y las miopatías inflamatorias en Colombia, centrándonos en datos demográficos, características clínicas y laboratorios.

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Métodos: Analizamos retrospectivamente a 112 pacientes de MI diagnosticados en la Fundación Valle del Lili en Cali, Colombia, cuyos casos cumplían con los criterios EULAR/ACR. Incluyeron datos demográficos, signos clínicos, hallazgos de laboratorio y malignidad. Se exploraron las asociaciones con malignidad mediante regresión logística. El análisis de supervivencia se evaluó utilizando las curvas de Kaplan-Meier y la prueba de Log-Rank.
Resultados: La dermatomiositis fue el subtipo más común (45,5%), con predominio femenino (66,1%). El diagnóstico de cáncer ocurrió en el 11,6% de los casos, siendo predominantemente cáncer de tiroides. El tiempo mediano desde el inicio de la miopatía hasta el diagnóstico de cáncer fue de 11 meses, con el 75% de los casos dentro del primer año. El análisis bivariado indicó asociaciones entre el cáncer y la edad, las pápulas de Gottron, úlceras digitales y el rash de heliotropo. Sin embargo, el análisis multivariado identificó la edad como el único factor de riesgo significativo para la malignidad. El análisis de supervivencia mostró tasas más favorables en pacientes más jóvenes.
Conclusión: Este estudio proporciona información sobre la relación entre las MI y el cáncer en la población colombiana. Predominó el cáncer de tiroides, con una proporción ligeramente mayor de diagnósticos de cáncer en mujeres. La edad surgió como un factor de riesgo significativo para la malignidad. Comprender esta asociación es crucial para la detección temprana y la mejora de los resultados de los pacientes relacionados con las malignidades asociadas a las MI.

Background

Inflammatory myopathies (IM) constitute a diverse group of autoimmune muscle disorders, categorized into polymyositis (PM), dermatomyositis (DM), inclusion body myositis (MCI), and necrotizing myositis. They can present independently or coexist with autoimmune diseases, systemic disorders, or neoplastic processes. Characterized by acute or subacute onset, these conditions primarily exhibit proximal muscle weakness, along with cutaneous and systemic manifestations, elevated muscle enzymes, myopathic electromyographic patterns, and characteristic muscle biopsy findings.[1–3]

IM, being relatively rare, shows an annual incidence of 0.8–8 cases per million inhabitants and a prevalence of 5–8 cases per 100,000 individuals. Predominantly affecting women (2:1 ratio), onset can occur at any age, with prominent peaks in childhood (10–15 years) and adulthood (45–60 years), the latter including cases associated with malignancies.[1–3] Dermatomyositis (DM) has an incidence rate of 4.66, while polymyositis (PM) holds a rate of 1.75 for developing cancer. DM presents an increased risk of neoplastic comorbidities, with cancer frequency in DM/PM ranging from 6 to 60% across the literature.[4] Among adults with IM, cancer is the primary cause of mortality, but consensus on cancer screening in this group is lacking.[5]

The association between DM and cancer types aligns with gender and age expectations. In men, lung, stomach, and prostate cancers predominate, while women show a higher prevalence of lung, breast, and gynecological cancers, especially ovarian cancer. Associations with rarer neoplasms of diverse origins have also been documented.[6]

There are multiple genetic and epigenetic associations for cancer development. However, the pathogenesis of cancer-associated myositis remains incompletely understood. Specifically, in inflammatory myopathies, it has been determined that positivity for anti-TIF-1g, anti-NXP2 antibodies has a higher risk association with cancer, as well as anti-HMGCR, anti-Jo-1, and anti-PL-12 antibodies.[7]

Given the limited information in Colombia, this study aims to enhance our understanding of the intricate relationship between cancer and inflammatory myopathies. Conducted by Fundación Valle del Lili, a high-complexity center, this research explores the demographic, clinical, and laboratory profiles of our patient population and their associations with cancer.

Methods

Study design and patients

We conducted an observational, retrospective study on our inflammatory myopathies (IM) cohort, covering the period from 2011 to 2022. The patient population was sourced from a Rheumatology research center, namely the one from University Hospital Fundación Valle del Lili in Cali, Colombia. The inclusion criteria encompassed 112 patients who met the European League Against Rheumatism/American College of Rheumatology Classification Criteria (EULAR/ACR) for IM,[8] including dermatomyositis (DM), polymyositis (PM), inclusion body myopathy (IBM), juvenile dermatomyositis (JDM), and immune-mediated necrotizing myopathy (IMNM). Patients of all ages and genders meeting these criteria were included, while individuals with myopathies attributed to toxic, metabolic, infectious, or neuromuscular etiologies were excluded. The study focused on elucidating the demographic, clinical, and laboratory profiles of patients with IM and their association with cancer.

Ethical considerations

Approval for this study was obtained from Fundación Valle del Lili's Institutional Review Board (IRB) (Protocol #1960). The research adhered to the principles outlined in the Declaration of Helsinki. Since there is no risk associated with this study, it was exempt from obtaining informed consent in compliance with Resolution 8430 issued by the Ministry of Health of Colombia.

Variables and data collection

Data collection of demographics, clinical, laboratory variables, and mortality (in cases occurring during the study period), and the necessity for Intensive Care Unit (ICU) care, were also documented. The primary outcome variable was malignancy (cancer, yes/no), with a secondary outcome focusing on the elapsed time between the onset of myopathy and the development of cancer. Data were extracted through the review of medical records and laboratory reports. The information was then recorded within an institutional database by the study's co-investigators and subsequently exported to a statistical software package for in-depth analysis.

Sample size

A convenience sampling approach was utilized, we included all patients diagnosed with inflammatory myopathies according to the EULAR/ACR criteria, adding up to 112 individuals during the period 2011–2022.

Statistical analysis

Exploratory data analysis was carried out to confirm the data's completeness and rectify any missing information. Numerical variables were presented as either means and standard deviations or medians and interquartile ranges, depending on the distribution of the variables. Categorical variables were expressed as absolute numbers and percentages. Appropriate statistical tests, including Fisher's/Chi-square tests or Mann–Whitney *U*/Student's *t*-tests, were applied to compare relevant clinical and paraclinical variables. Variables exhibiting a p-value < 0.15 in bivariate analyses were selected for inclusion in the multivariate analysis model as considered to have a possible relationship with cancer. Multivariate analyses to identify predictors of malignancy in association with IM were conducted using logistic regression analyses. Adjusted odds ratios (ORs) along with their respective 95% confidence intervals were calculated. Variables with a p-value < 0.05 were considered significant and retained in the final model.

As a secondary analysis, patient survival was assessed, and survival probabilities were estimated using Kaplan–Meier curves, and subsequently compared via the log-rank test. Statistical analyses were executed using Stata® version 16 (StataCorp, College Station, TX, USA).

Results

General characteristics

A total of 112 patients were analyzed in this study. The mean age of patients at inclusion was 47.4 (± 18) years, with an onset of symptoms at 41.2 (± 19.4) years. Sixty-six-point one percent were females. The primary diagnoses among inflammatory myopathies were dermatomyositis (45.5%), followed by polymyositis (34.8%), juvenile dermatomyositis (8.1%), and other inflammatory myopathies (11.6%). The median duration of disease evolution was 48 (120–12) months. Predominant clinical characteristics included symmetric weakness (57%), upper limb weakness (56%), myalgias (50%), arthralgia (41%), dysphagia (28.6%), and respiratory distress (27.7%). Additionally, Gottron's papules were observed in 25% of patients, while a heliotrope rash and weight loss were present in (17.9%) each (see Supplementary Information 1).

Cancer

Thirteen patients (11.6%) received a cancer diagnosis, with thyroid cancer being the most prevalent (30.8%). Skin cancer and hematological cancer followed, each accounting for (15.4%). Dermatomyositis was the most prevalent IM in cancer patients (61.5%). The median time between the onset of myopathy and an oncologic diagnosis was 11 (13–12) months, with cancer manifesting within the first year of an IM diagnosis in (75%) of cases.

Diagnostic studies and treatment

Laboratory data were as follows: The median (interquartile range) values of Lactate Dehydrogenase (LDH) 267 (521.5–188) UI/L, Creatine Phosphokinase (CPK) 670.5 (3978.5–129) mcg/L, Aspartate Aminotransferase (AST) 40 (88.6–24) U/L, and Alanine Aminotransferase (ALT) 36.5 (102.1–18.8) U/L (see Supplementary Information 2). Muscle biopsy confirmation was obtained in 42 (37.5%) patients; myopathic patterns were observed in 59.8% through electromyography. Treatment approaches included corticosteroids in 79.5% of patients, with a mean weekly dose of 35 (70–5) mg of prednisolone. Other treatments encompassed rituximab (29.5%) with approximately 2 (3–1) cycles, azathioprine (35.7%), methotrexate (16.1%), cyclophosphamide (13.4%), mycophenolate (11.6%), and cyclosporine (11.6%) (see Supplementary Information 1).

Bivariate analysis

We examined the risk factors, and cancer and non-cancer status in patients with IM. Age ($p = 0.01$), Gottron's papules ($p = 0.017$), digital ulcers ($p = 0.036$), heliotrope rash ($p = 0.054$), steroid use ($p = 0.13$), platelets ($p = 0.087$), and Blood Urea Nitrogen (BUN) ($p = 0.097$) showed significant associations. No significant associations were found between other clinical characteristics in cancer-associated and non-cancer patients, including the type of myopathy ($p = 0.413$), weight loss ($p = 0.224$), and several laboratory parameters, including, CPK ($p = 0.713$), and Antinuclear Antibodies (ANAs) positivity ($p = 0.509$) (Table 1). Anti-TIF-1g, anti-NXP2, and anti-MDA5 were identified, the number of patients exhibiting these antibodies was not significant.

Multivariate analysis

Multivariate analysis revealed that age (adjusted odds ratio [aOR] = 1.05; 95% confidence interval [CI] = 1.01–1.10; $p = 0.015$) was the sole independent risk factor associated with malignancy. There were no statistically significant differences concerning heliotrope rash, the use of corticosteroids, and Gottron papules. However, the latter may suggest a potential relationship ($p < 0.10$) (Table 2).

Survival analysis

We conducted a survival analysis for the overall population, individuals with and without cancer. In our survival analysis, survival is defined as being free from cancer. Global survival rates were 92% at 12 months and 89% at 24 months (Fig. 1a). When comparing these rates across age groups, it was observed that individuals under 50 exhibited a first-year survival probability of 96% and 94% in a second year; in contrast, patients aged 50 or older demonstrated a first-year survival probability of 84% and 81% in a second year ($p = 0.009$) (Fig. 1b). No statistical differences were found in gender ($p = 0.25$) or treatment use ($p = 0.091$). However, there is a slightly lower survival for men and untreated patients (Fig. 1c and d). Additionally, four patients died during the follow-up period. One patient died due to polymyositis, another from pneumonia unrelated to the underlying IM, one from septic shock due to a severe urinary tract infection, and one from cardiac arrest.

Discussion

Our study analyzed 112 patients from 2011 to 2022, with a mean age of 47.4 years, and a mean age at symptoms' onset of 41.2 years. Most patients were females (66.1%). The mean duration of disease evolution was 48 months. Dermatomyositis is the predominant diagnosis among primary inflammatory myopathies (45.5%). Thirteen patients (11.6%) received a diagnosis of cancer, with thyroid cancer being the most prevalent (30.8%), followed by skin cancer and hematological malignancies. The median dura-

Table 1
Demographic, clinical and paraclinical characteristics of patients.

Variable	*N*	Cancer yes *n* = 13 (%)	Cancer no *n* = 99 (%)	*p*-Value
Demographics				
Female sex	112	7 (53.8)	67 (67.7)	0.359†
Age	112	58.8 (19.4)	45.9 (17.4)	**0.014**§
Mean (standard deviation)				
Type of myopathy				
Dermatomyositis	112	8 (61.5)	43 (43.4)	0.413†
Polymyositis		3 (23.1)	36 (36.4)	
Juvenile dermatomyositis		0 (0.0)	9 (9.1)	
Other inflammatory myopathies		2 (15.4)	11 (11.1)	
Treatment				
Use of corticosteroids	89	8 (61.54)	81 (81.82)	0.137†
Signs and symptoms				
Gottron's papules	112	7 (53.9)	21 (21.2)	**0.017**†
Digital ulcers	111	2 (15.4)	1 (1.0)	**0.036**†
Rash in heliotrope	112	5 (38.5)	15 (15.2)	**0.054**†
Weight loss	111	4 (33.3)	16 (16.2)	0.224†
Diagnostic studies				
Hemoglobin	107	14 (14.6–12.6)	13.2 (14.2–12)	0.931*
Hematocrit	99	40.65 (44–36)	41.3 (43.1–37.8)	0.805*
Leukocytes	109	7260 (9050–4640)	7320 (10155–6005.5)	0.471*
Neutrophils	101	3980 (7174.5–3085)	4880 (7726–3380)	0.355*
Lymphocytes	100	1745 (2275–1240)	1459 (1825–1175)	0.128*
Eosinophils	74	100 (220–59)	100 (240–31)	0.868*
Platelets	110	242,000 (303,000–205,000)	280,000 (344,000–248,000)	0.087*
LDH	72	270 (650–203)	267 (509–186)	0.621*
CPK	108	448 (2586–216.5)	787 (3978.5–129)	0.713*
RCP	101	0.61 (1.46–0.23)	0.3 (1.36–0.16)	0.5493*
ANAS' positivity	93	6 (60%)	38 (45.78%)	0.509†
C3	47	113 (32.7)	115.5 (26.8)	0.845§
C4	48	24 (31–21)	22 (30–17)	0.588*
AST	105	41.15 (71–27.5)	40 (92–23)	0.643*
ALT	104	25.5 (73.5–13.7)	39.3 (110–19.5)	0.511*
Creatinine	106	0.6 (0.8–0.5)	0.6 (0.8–0.4)	0.540*
BUN	82	17 (40–10)	11 (16–9)	0.097*

Categorical data *n* (%) and continuous values are mean ± SD or median (RIC).
† Fisher.
* Mann–Whitney.
§ *T*-Student.
LDH, lactate dehydrogenase; CPK, creatin phosphokinase; RCP, reactive C protein; ANAS, antinuclear antibodies; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

Table 2
Multivariate analyses; adjusted odds ratios (ORs) for risk of malignancy in 112 IM patients.

Variables	OR	95% CI	*p*-Value
Age (in years)	1.05	[1.01–1.10]	0.015
Use of corticosteroids	0.28	[0.057–1.44]	0.130
Gottron's papules	5.25	[0.82–33.08]	0.080
Rash in heliotrope	1.53	[0.21–10.89]	0.670
Lymphocytes	0.99	[0.99–1.00]	0.325

tion between the onset of myopathy symptoms and the subsequent oncologic diagnosis was approximately 11 months.

A review by Oldroyd et al. found a significant association between the male gender and an increased cancer risk compared to females.[5] In another study, the relative cancer risk remained higher in men but varied depending on the myopathy type. For instance, in dermatomyositis, the relative risk was 5.29 for men and 4.56 for women, while in polymyositis, it was 1.62 for men and 2.02 for women.[9] Unlike our study, which did not differentiate based on gender or myopathy type regarding cancer presence, a non-significant *p*-value indicated a slightly higher proportion of female patients receiving a cancer diagnosis.

In our study, 11.6% of patients received a cancer diagnosis, aligning with findings from a cohort of 309 inflammatory myopathy patients where 11.9% had neoplasms.[10] Nearly 25% of patients were diagnosed with cancer within three years of inflammatory myopathy onset.[11] The highest likelihood of tumor detection was two years post-inflammatory myopathy diagnosis, with 64.8% of cases presenting both conditions within the first year.[12] Our investigation recorded a median interval of 11 months (13 – 2), with 75% of patients receiving an oncologic diagnosis within the initial year.

Our study did not reveal a statistically significant association between different myopathy types and cancer incidence, despite a higher number of cancer cases in dermatomyositis patients. However, an analysis of five studies involving 4538 patients with dermatomyositis (DM) or polymyositis (PM) showed a notable connection, with a relative risk of 4.66 for DM and 1.75 for PM.[9]

Ovarian cancer was reported as the major cancer, followed by lung and pancreatic cancer. Histologically, adenocarcinomas predominated in DM patients, while neoplasms of hematopoietic–lymphatic origin were prevalent in PM patients.[13] In a multicenter study, 15% of DM patients had cancer, primarily breast (35%) and nasopharynx (25%), with a paraneoplastic course in 90% of cases.[14] A retrospective cohort in China found ovary and breast cancers to be the most frequent.[15] In our study, thyroid cancer was the predominant malignancy, followed by skin and hematological cancers. According to the latest update from the National Cancer Institute of Colombia in 2022, it is observed that

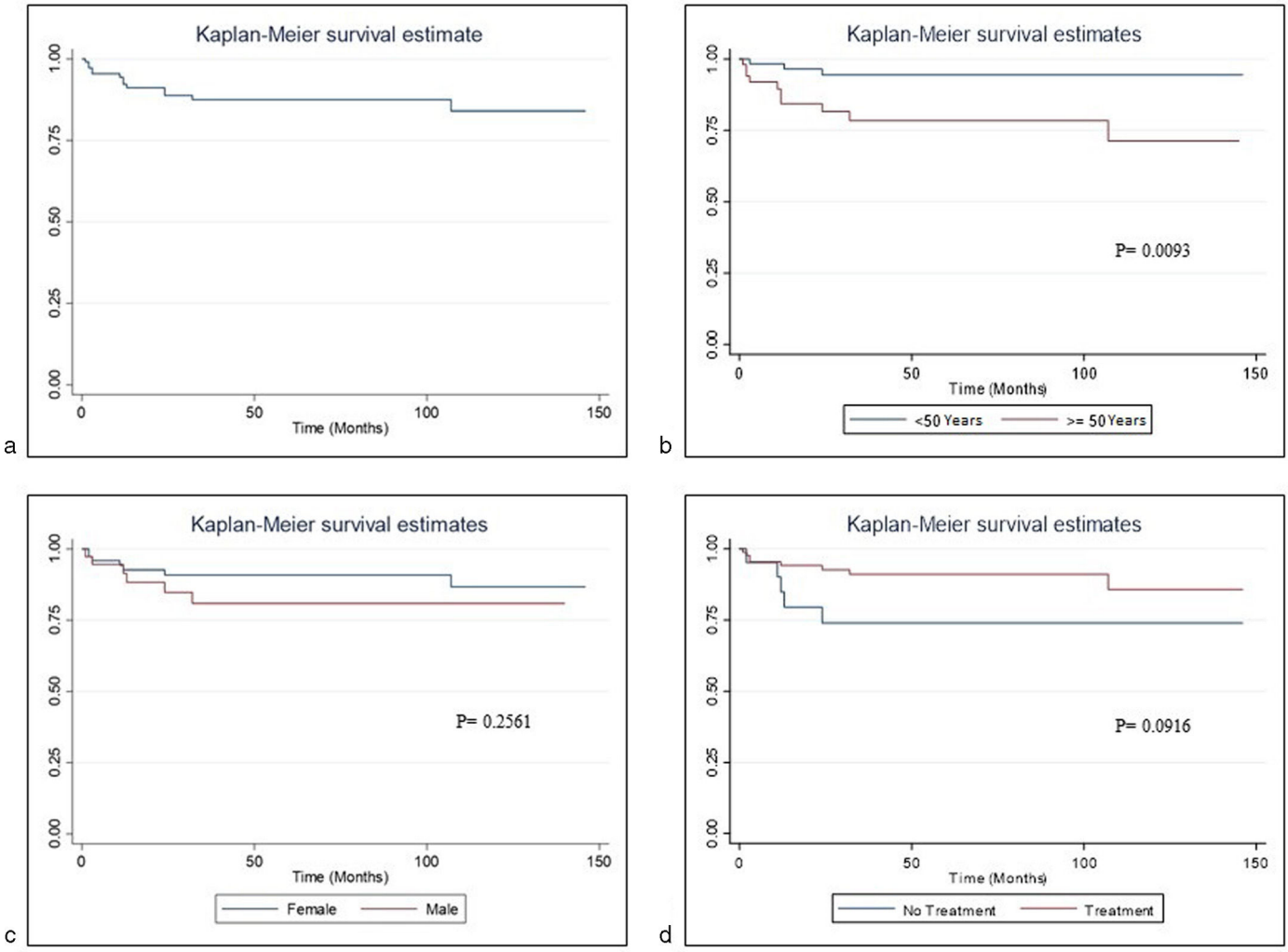

Fig. 1. Kaplan–Meier survival estimate: (a) The global survival rates. (b) Survival based on age. (c) Survival by gender. (d) Survival about treatment.

the incidence of cancer in men varies depending on its localization, with skin being the most common, followed by prostate and stomach. In women, the highest frequency is recorded in breast cancer, followed by skin and thyroid cancer. It is noteworthy that, in men, thyroid cancer ranks seventh in terms of frequency.[16]

The prevalence of cancer in women could serve as an explanatory factor for the findings associated with the increased incidence of thyroid cancer. This is attributed to a slightly higher proportion of women who received a cancer diagnosis in our study. However, the limitations inherent in our study preclude definitive conclusions regarding this potential explanation.

In our bivariate analysis, significant associations between cancer and age, Gottron's papules, corticoid use, and a heliotrope rash were identified. However, no statistically significant associations were found for other clinical characteristics, including myopathy type, weight loss, and creatine phosphokinase (CPK) levels. The potential association between cancer and Gottron's papules and a heliotrope rash, while indicative of a less favorable prognosis, did not reach statistical significance in the multivariate analysis. A study of 251 patients with myositis and malignancy found that dermatomyositis (DM) associated with cancer exhibited more severe skin and muscle symptoms, increased dysphagia prevalence, and greater diaphragmatic involvement.[17] Similarly, a study in China reported a higher incidence of heliotrope rash, shawl sign, and V sign in myositis patients associated with cancer.[15]

In our work, the multivariate analysis identified age as the sole risk factor, indicating a 5% increase in the odds of cancer per year. These results align with previous studies, supporting the concept that advancing age is associated with an elevated cancer risk. One study demonstrated a statistically significant association between individuals with dermatomyositis over the age of 52 and an increased cancer risk.[18] In a separate study focused on dermatomyositis, a relative risk of 2.79 was observed for patients aged 15–44 years, which increased to 3.3 for those older than 44 years.[19]

Chinese studies reported 83.1%, 78.9%, and 74.2% survival rates at 1, 2, and 5 years for inflammatory myopathy (IM) patients,[20] while another study showed rates of 88.8%, 83.2%, and 78.9%.[21] Our analysis found cumulative survival rates without malignancies of 99% at the first month, 92% at 12 months, and 89% at 24 months, with younger patients showing higher survival. In a Chinese study with 311 patients, 21.9% died, mainly due to infections for both dermatomyositis (DM) and polymyositis (PM).[12] Our cohort had a 3.6% fatality rate, with infections causing half, aligning with the Chinese study but showing variations in mortality rates.

Regarding the use of corticosteroids and the risk of cancer, the bivariate and multivariate analyses do not demonstrate statistical significance. The survival curve, indicating higher survival rates in patients with treatment in the first and second years (94% and 92%) compared to those without treatment (86% and 77%), showed a trend, although it did not reach statistical significance ($p = 0.091$). This difference could be attributed to the role of corticosteroids

in cytoreduction and inflammation, potentially delaying the cancer diagnosis.[22] However, it is crucial to note that these data did not achieve statistical significance. Furthermore, this study cannot establish causality.

International guidelines recommend assessing cancer risk in inflammatory myopathy patients with specific "high-risk" factors. Our study aligns with this, as most cancers occur in dermatomyositis patients aged over 50 with digital ulcers. High-risk patients should undergo enhanced and basic cancer screening, including various tests to facilitate early malignancy detection.[23]

Limitations

This study has a significant limitation due to its retrospective nature, which introduces the risk of selection bias and incomplete data. Additionally, data obtained from a single high-complexity referral hospital may not adequately capture the diversity of the entire Colombian population affected by inflammatory myopathy (IM), thus limiting the generalizability of our findings. The relatively small sample size of cancer patients may impact statistical power, limiting the ability to draw definitive conclusions on risk factors. Myositis-specific antibodies play a crucial role in cancer development. According to an international guideline, positivity for anti-TIF-1g and anti-NXP2 is identified as a high risk factor, while anti-SAE1 and anti-HMGCR present intermediate risks, and anti-SRP and anti-Jo1 are considered low risk.[23] Unfortunately, gaining access to these antibodies in Colombia is challenging, limiting their availability. However, this emphasizes the need for greater accessibility to these tests within our community.

Conclusions

Dermatomyositis and polymyositis were the predominant myopathies, showing slightly elevated cancer prevalence among females. Most tumors, primarily thyroid cancer, occurred within 11 months of myopathy diagnosis. No statistically significant association between specific inflammatory myopathies and cancer was found in multivariate analysis.

This retrospective study contributes valuable insights into the connection between inflammatory myopathies and cancer in the Colombian context. Considerations, including a relatively small sample size and potential biases, must be acknowledged. Further research is essential to validate and expand these findings, deepening our understanding and guiding clinical practices.

Authors' contributions

All authors declare having participated in (1) the conception and design of the study, or the acquisition of data, or the analysis and interpretation of data, (2) drafting the article or revising it critically to determine important intellectual content, (3) final approval of the submitted version.

Ethical standards

This study followed the ethical standards laid down in the 1964 Declaration of Helsinki. Approval for this study was obtained from Fundación Valle del Lili's Institutional review board (IRB) (Protocol #1960). Since there is no risk associated with this study, it was exempt from obtaining informed consent in compliance with Resolution 8430 issued by the Ministry of Health of Colombia.

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Conflict of interest

None.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.reuma.2024.04.002.

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