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RESEARCH ARTICLE

Hodgkin and non-Hodgkin lymphomas in pediatric-age patients of Northeast Mexico: 18-year outcomes and survival rates at an academic center

José C. Jaime-Pérez, Ana L. Beltrán-López, Valentina Jiménez-Antolínez, Renata Barragán-Longoria, Julia E. Colunga-Pedraza, Óscar González-Llano, and David Gómez-Almaguer*

Department of Hematology, Dr. José Eleuterio González University Hospital, School of Medicine, Universidad Autónoma de Nuevo León, Monterrey, Mexico

Abstract

Background: *Hodgkin lymphoma (HL) and non-HL (NHL) are the third and fourth most common malignancies during childhood, with limited information available from Latin America.* **Method:** *We retrospectively studied patients with HL and NHL from a single academic center in Northeast Mexico between 2002 and 2020. Data included treatment regimens, staging, and survival outcomes. Survival was determined by Kaplan–Meier analysis, and features of lymphomas were compared using the X^2 test.* **Results:** *The study included 75 patients, 36 (48%) with HL and 39 (52%) with NHL. Males predominated (70%); the median age was 9 years. Stages III and IV were detected in 59% and median follow-up reached 50 months. Relapse occurred in 16 (21%) patients, 9 (12%) in the HL group and 7 (9%) in the NHL group. Thirteen (17.3%) patients underwent transplantation, 12 (85%) in the HL group; 11 are alive. Most deaths, 10/11 (91%), occurred in NHL patients. Five-year overall survival rates were 96% (95% confidence interval [CI] 95.6-97) for HL and 75% (95% CI 74.9-76.3) for NHL (p = 0.004). Five-year disease-free survival was 70% for HL (95% CI 69-72.5) and 69% (95% CI 67.7-71) for NHL (p = 0.672).* **Conclusion:** *Pediatric-age HL and NHL had similar frequency in the study population; most patients presented with advanced disease at diagnosis. A high success rate was documented for HL, while NHL outcomes were suboptimal.*

Keywords: *Pediatric lymphomas. Non-Hodgkin lymphoma. Hodgkin lymphoma. Transplantation in pediatric lymphomas. Survival in pediatric lymphomas.*

Linfomas Hodgkin y no Hodgkin en pacientes en edad pediátrica del noreste de México: resultados y tasas de supervivencia a 18 años en un centro académico

Resumen

Introducción: *Los linfomas Hodgkin (LH) y no Hodgkin (LNH) son la tercera y cuarta neoplasia maligna durante la infancia, con escasa información sobre sus características y evolución en Latinoamérica.* **Método:** *Se incluyeron pacientes ≤ 18 años con LH y LNH de un centro académico en el noreste de México entre 2002 y 2020. Los datos analizados incluyeron modalidades de tratamiento, estadificación y supervivencia. La supervivencia se determinó por análisis de Kaplan–Meier y las características de los linfomas se compararon mediante X^2.* **Resultados:** *Se incluyeron 75 pacientes, 36 (48%) con HL y*

***Correspondence:**
José C. Jaime-Pérez
E-mail: carjaime@hotmail.com

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39 (52%) con LNH. Predominaron los varones (70%); la edad media fue de 9 años. Se detectaron estadios III y IV en el 59%, la mediana de seguimiento alcanzó los 50 meses. La recaída se produjo en 16 (21%) pacientes, 9 (12%) HL y 7 (9%) LNH. Trece (17.3%) pacientes fueron sometidos a trasplante, 12 (85%) en el grupo HL, 11 vivos actualmente. La mayoría de las muertes, 10/11 (91%), ocurrieron en pacientes con LNH. La sobrevida general (SG) a cinco años fue 96 % para LH y 75 % para LNH, (p = 0,004). La sobrevida libre de eventos (SLE) fue del 70 % para HL (IC del 95 %: 69-72,5) y del 69 % (IC del 95 %: 67,7-71) para LNH (p = 0,672). **Conclusión:** *Los LH y LNH en edad pediátrica tuvieron una frecuencia similar en la población del estudio. Se documentó una alta tasa de curación para LH, mientras que para LNH los resultados fueron subóptimos.*

Palabras clave: *Linfomas pediátricos. Linfoma de Hodgkin. Linfoma no Hodgkin. Trasplante en linfomas pediátricos. Supervivencia en linfomas de la infancia.*

Introduction

In patients of pediatric age, lymphoma is the third most frequent neoplasia, with a prevalence of 15%[1]. In 2021, the incidence in this age group was approximately 25/million, with 2,000 new cases diagnosed yearly[2]. Lymphoma makes up 12% (ages < 15 years) to 19% (ages 15-19) of childhood cancers in the United States[1]. The incidence of Hodgkin lymphoma (HL) and non-HL (NHL) varies according to gender, age, geographic location, and socioeconomic conditions[3]. HL is the third most common malignancy in this age group, and eight percent of all cancers at this age correspond to HL, with a higher incidence in adolescents.

Non-HL in children accounts for 7% of children and teens diagnosed annually in the United States. As in HL, the NHL incidence has increased, with a higher number seen in white children compared to other ethnic groups and a male predominance 2-3 times greater than in girls[2]. Between 1975 and 2010, the 5-year survival rate for pediatric NHL in the United States increased from 45% to 87% in children < 15 years and from 48% to 82% in adolescents aged 15-19[4].

In addition to classical chemotherapy, monoclonal antibodies, such as rituximab, have contributed significantly to increasing response rates in B-cell lymphomas[5].

Limitations for improvement in lymphoma outcomes in low- and middle-income countries and consequent betterment needs have been identified, including those on standards for diagnosis and classification, treatment affordability, long-term sustainability of cooperative programs, and development of clinical research projects, among others[6].

We report and compare the distribution of lymphomas by type, main diagnostic features, treatment modalities, and survival in an open-population pediatric Hispanic cohort diagnosed in a public hospital in Northeast Mexico over 18 years.

Method

A longitudinal and retrospective analysis from 2002 to 2020 in pediatric patients 18 years of age and younger diagnosed with any lymphoma at the Hematology Department of the Dr. Jose Eleuterio Gonzalez University Hospital and School of Medicine of the *Universidad Autónoma de Nuevo León* in Monterrey, Mexico, was performed. The hospital is an academic reference center for low-income, uninsured open population from the country's Northeast region. Electronic databases and clinical files were scrutinized, and age, sex, initial complete blood count, treatment regimen, Ann Arbor stage, date of birth, date of diagnosis, date to relapse, last visit/death, cause of death, transplantation, and survival data were accrued. Advanced disease was defined as a bulky disease or an Ann Arbor stage III-IV; no radiotherapy was used as part of the treatment. Due to the retrospective design of the study, informed consent was not required.

Statistical analysis

Data were analyzed using Statistical Packages for the Social Sciences Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Overall survival (OS) was calculated from the date of diagnosis until the date of death or the past follow-up. Disease-free survival (DFS) was calculated from the date of diagnosis until relapse, death, or last visit. OS and DFS were calculated using the Kaplan-Meier method; the groups were compared using the log-rank test with a 95% confidence interval (CI). Categorical variables were displayed as absolute numbers and percentages. Comparisons were made with the Pearson X^2 test. Quantitative variables were analyzed with descriptive statistics, including median and ranges. A $p < 0.05$ was considered statistically significant.

Table 1. Principal characteristics of 75 pediatric lymphoma patients diagnosed in a single academic center in Northeast Mexico

Variable	All patients, n = 75 (%)	HL, n = 36 (48%) (%)	NHL, n = 39 (52%) (%)	p
Age, years median (range)	9 (2-18)	11 (3-17)	9 (2-18)	0.796
Follow-up, months, median (range)	50 (0.2-163)	62 (1-153)	38 (0.2-163)	0.361
Gender				0.465
Male	53 (70)	24 (67)	29 (74)	
Female	22 (30)	12 (33)	10 (26)	
Stage				0.003
I	12 (16)	8 (22)	4 (10)	
II	13 (17)	8 (22)	5 (13)	
III	23 (31)	8 (22)	15 (38)	
IV	21 (28)	9 (25)	12 (31)	
Missing	6 (8)	3 (8)	3 (8)	
Clinical finding				
Adenopathy	61 (81)	35 (97)	26 (67)	0.002
Mediastinal mass	12 (16)	6 (17)	6 (15)	0.880
Cough or dyspnea	8 (11)	4 (11)	4 (10)	0.905
Hepatomegaly	17 (23)	10 (28)	7 (18)	0.310
Splenomegaly	11 (15)	5 (14)	6 (15)	0.855
HSCT	14 (19)	12 (33)	2 (5)	0.004
Autologous	11 (15)	11 (31)	0	
Allogeneic	3 (4)	1 (3)	2 (5)	
Relapse	16 (21)	9 (25)	7 (18)	0.456
Progression	10 (13)	1 (3)	9 (23)	0.012
Death	11 (15)	1 (3)	10 (26)	0.005
TRM	1	0	1 (2.5)	0.333
5-year OS	85	96	75	0.004
5-year DFS	70	70	69	0.672

*DFS: disease-free survival; OS: overall survival; TRM: transplant related mortality.

Results

Data from 75 pediatric patients aged 2-18 years with histologically and immunohistochemically confirmed lymphoma from a single tertiary care hospital in Northeast Mexico over 18 years were analyzed. General demographic data, clinical stages, B symptoms, physical findings, and histopathologic diagnosis are displayed in tables 1 and 2. Of the total, 36 patients (48%) were diagnosed with HL and 39 (52%) with NHL. Male gender predominated (n = 52, 70%) with a median age at diagnosis of 9 years. Advanced stages (III and IV) were diagnosed in 47% and 69% of the patients, respectively. The median follow-up was 50 months (range: 2-163). A total of 16 (23%) patients experienced relapse, 9/36 (25%) in the HL group versus 7/39 (18%) in the NHL group, p = 0.467. Fourteen (18.7%) patients underwent transplantation, with HL patients receiving a higher proportion, 85.7% (12/14). Eleven transplants (78.6%) were autologous, all in the HL group, while 3 were allogeneic, 1 in the HL and 2 in the NHL group, respectively. Most deaths occurred in the NHL group, 10 (26%), compared to 1 (3%) in the HL group (p = 0.005). All patients with HL were treated with ABVD, while different protocols were used over time for NHL patients, as described in table 2. The 5-year OS was 96% (95% CI 95.6-97) in patients with HL and 75% (95% CI 74.9-76.3) in patients with NHL (p = 0.004), (Fig. 1), while the 5-year DFS was 70% (95% CI 69-72.5) in HL and 69% (95% CI 67.7-71) in NHL (p = 0.672), (Fig. 2).

HL

The median age at HL diagnosis was 11 years (range: 3-17). According to histopathological classification, nodular sclerosis was the most frequent subtype, with 25/36 (69%) cases reported. According to the Ann Arbor classification, the most frequent stage in the entire study group was IV, with 9 (25%) cases, and B symptoms were present in 15 (42%) patients at diagnosis. Lymphadenopathy was the main clinical sign in 35/36 (97%) patients, with a mediastinal mass observed

Table 2. Salient findings and treatment schemes administered to 75 pediatric lymphoma patients diagnosed at a single academic center in Northeast Mexico

Variable	n (%)
Hodgkin lymphoma	n = 36
Histological subtype	
Mixed cellularity	4 (11)
Nodular sclerosis	25 (69)
Lymphocyte depletion	0
Lymphocyte predominance	5 (14)
Missing	2 (6)
Treatment	
ABVD	36 (100)
Non-Hodgkin lymphoma	n = 39
Histological subtype	
Lymphoblastic lymphoma	23 (59)
Burkitt lymphoma	8 (20.5)
Anaplastic large cell lymphoma	4 (10.3)
Large cell lymphoma	2 (5)
Primary CNS lymphoma	1 (2.6)
Hydroa Vacciniforme	1 (2.6)
Treatment	
BFM	13 (33)
COG5971	10 (26)
Hyper-CVAD	7 (18)
LMB-89	6 (15)
CHOP	2 (5)
De Angelis	1 (2.5)

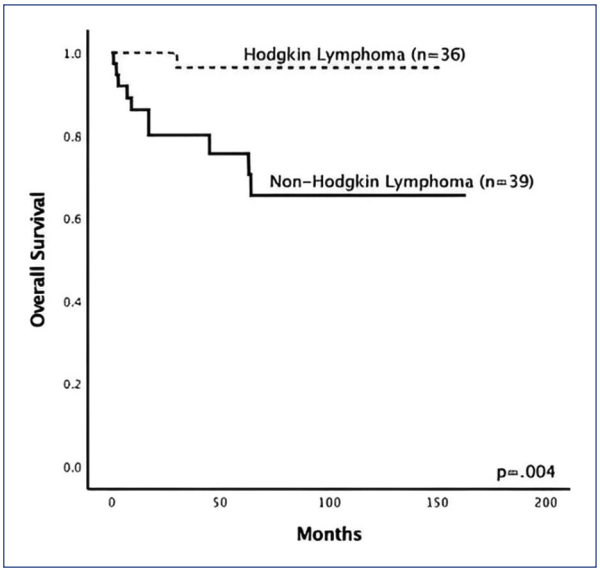

Figure 1. Overall survival for children with Hodgkin lymphoma (n = 36) and non-Hodgkin lymphoma (n = 39) treated at a reference center in Northeast Mexico from 2002 to 2020.

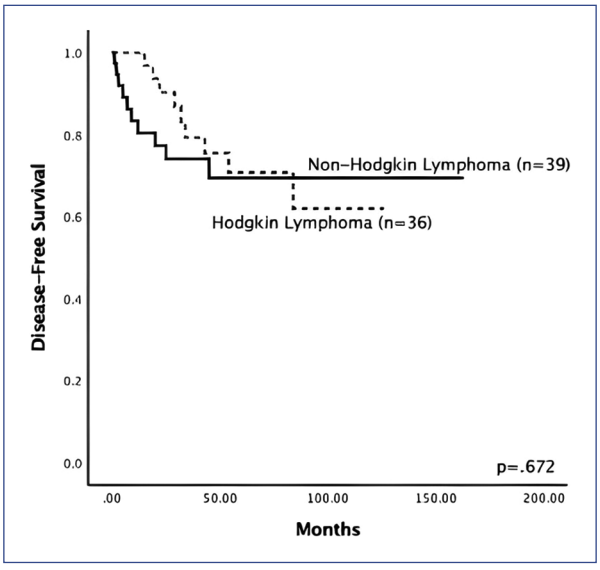

Figure 2. Disease-free survival for children with Hodgkin lymphoma (36) and non-Hodgkin lymphoma (39) treated at a reference center in Northeast Mexico from 2002 to 2020.

in 6 (17%) cases. Relapse developed in 9 (25%) patients. The median time from diagnosis to relapse was 32 months (range: 15-84), with 50% occurring in groups II and III/IV. Among relapsed patients, 4 (44.4%) experienced a second relapse. Autologous transplantation was performed in 11/36 (30.5%), and allogeneic transplantation was performed in 1 HL patient. One patient in this group died due to disease progression. He experienced a relapse 15 months after diagnosis and received additional chemotherapy. Subsequently, the patient was consolidated with an autologous transplant, experienced a second relapse 7 months later, and died 1 year post-transplant due to disease progression.

NHL

The median age for NHL at presentation was 9 years (range: 2-18). In this group, the anatomopathological diagnosis was compatible with lymphoblastic lymphoma in 23/39 cases (59%), followed by Burkitt lymphoma (BL) in 8 (21%) patients. Staging was classified according to the Murphy Staging System, with 27 patients (69%) in stage III/IV. The most frequently reported clinical manifestation was lymphadenopathy in 67% of patients. Visceromegaly was detected in 33% of patients during the initial evaluation, and 15% had a mediastinal mass. Eight patients (21%) experienced a relapse, with 50% occurring in the bone marrow, two patients in the central nervous system, and one patient in the testicle. The median time from diagnosis to relapse was 20 months

Table 3. Characteristics of 13 pediatric patients diagnosed with lymphoma and undergoing hematopoietic stem cell transplantation in a single academic center in Northeast Mexico

Patient	Age	Sex	Variety of lymphoma	DFS (months)	OS (months)	Second transplant	Status
1	15	F	HL	32	32	No	Alive
2	15	M	HL	19	91	No	Alive
3	6	M	HL	54	148	No	Alive
4	8	F	HL	22	153	No	Alive
5	13	M	HL	15	30	No	Dead
6	16	M	HL	43	73	No	Alive
7	17	M	HL	34	108	No	Alive
8	7	M	HL	90	90	No	Alive
9	14	M	HL	62	62	Yes	Alive
10	5	F	HL	79	79	No	Alive
11	10	F	HL	51	51	No	Alive
12	6	M	NHL	25	152	No	Alive
13	7	M	NHL	34	63	No	Dead

DFS: disease-free survival; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; OS: overall survival.

(range: 5-61). Two of these eight patients are currently alive following an allogeneic transplant.

In this group, 10/39 (25.6%) patients died: nine (90%) due to disease progression. Among these patients, seven were diagnosed with lymphoblastic lymphoma, one with BL, and one with refractory *hydroa vacciniforme*. One patient suffered a treatment-related death while in complete response.

Hodgkin and NHL differences

When comparing data between the two lymphoma types, no difference in median age or follow-up was found, whereas males predominated 2:1 in HL and 3:1 in NHL groups; advanced stages were more frequent in the NHL group (p = 0.003, table 1). Except for adenopathy (p = 0.002), no differences between HL and NHL for physical findings, including mediastinal mass, hepatomegaly, splenomegaly, cough, or dyspnea were found (Table 1).

Histological subtype diagnoses for both lymphomas and their treatment modalities are displayed in table 2.

Hematopoietic stem cell transplantation

Thirteen (17.3%) children received an autologous hematopoietic stem cell transplant; 11 (84.6%) were diagnosed with HL and 2 (15.4%) with NHL; one HL patient received two transplants after the first procedure resulted in graft failure and is currently alive. The median age for the transplant group was 10 years (range: 5-17), with a median DFS of 34 months (range: 15-90) and median OS of 79 months (range: 30-152). Two patients in the transplant group died, one of each lymphoma type; the longest post-transplant survival reported was 152 months (Table 3).

Discussion

HL ranks as the third, and NHL as the fourth most common childhood malignancy, with survival rates exceeding 90% in high-income countries[7]. Nevertheless, challenges persist in low-income populations, characterized by delayed diagnosis, restricted treatment access, limited therapy options, and elevated treatment-associated mortality[8]. Late-stage diagnoses remain prevalent, resulting in heightened tumor burdens and complications. Emerging therapeutic modalities, including immunotherapy and targeted treatments, are promising options but face considerable accessibility barriers in disadvantaged populations like the one in this report. The results of this study underscore the need for early diagnosis and referral, delivery of risk-adapted treatment, and targeted research endeavors to

improve outcomes for pediatric lymphoma patients, especially NHL, in high-risk groups.

Progress in the prognosis of this group of childhood cancers is principally due to the administration of intensive chemotherapy regimens, with toxicity-related deaths at 2% or lower; hence, 90% of children with HL and NHL are cured with first-line therapy[9,10]. Our HL pediatric group reached this standard, while those with NHL lagged considerably. In this respect, the administration of intensified chemotherapy schemes requires hospitalization, specialized nurse personnel, and advanced nutrition support, which is lacking in most public institutions of low-income populations, like ours.

In comparison with industrialized nations, the landscape in resource-limited areas of the world is less optimistic due to delayed diagnosis, lack of access to appropriate treatment and support, high rates of treatment-related mortality at 9%, treatment abandonment of 15%, and relapse associated with less intensive chemotherapy[8]. We documented only one patient with treatment-related mortality in complete response, accounting for 2.5% of the NHL group, while none occurred in the HL group.

Different authors describe diagnostic delay as contributing to all-cause treatment failure[11]. Lack of resources in the health system in our country may prevent the opportune detection and treatment of hematologic diseases; also, socioeconomic limitations in the general population can lead to delayed diagnosis and treatment, and be major contributors to childhood cancer death rates, including lymphoma[12]. Patients with a late diagnosis have a higher tumor burden and a higher risk for malnutrition, tumor lysis syndrome, comorbid infections, and early treatment-related death, with the associated higher costs of treatment for the main disease and its complications[13]. Diagnosis in advanced stages is the most frequent presentation in low to middle-income countries in > 70% of the cases, as observed in multiple studies[11-14]. This finding is related to greater difficulty in effective treatment due to more tumor burden, worse clinical condition at presentation, and more complications, such as tumor lysis syndrome, organic dysfunction, and infections[15].

In our cohort, almost 60% of patients were diagnosed with advanced stages at presentation, and stages III and IV were reported in around 70% of patients in the NHL group. Within this group, visceromegaly was present in a third of cases and a mediastinal mass in 15%. In contrast, advanced-stage HL was found in 47% of patients at diagnosis, and the main clinical manifestations were lymphadenopathy in 97% and B symptoms in 42%.

It is reported that 33% of childhood NHLs correspond to lymphoblastic lymphomas (LL), 40% BL, 20-30% diffuse large B-cell lymphoma (DLBCL), and 10-20% anaplastic large cell lymphoma[16,17]. The distribution of the different varieties in our patients differed considerably, with a predominance of LL of 59%, almost twice that reported; the second most frequent entity was BL, with 21%, considerably < 37% in Brazil[16]. Furthermore, it has been described that the most common type of HL in children under 10 years of age in developing countries is mixed cellularity, often associated with Epstein-Barr virus infection; remarkably, in our study group, the most frequent subtype was nodular sclerosis, being 69%, close to 76% reported in Brazil[18].

Our overall results for the NHL are inferior to the reported outcomes in high-income countries. However, compared to other low-to-middle-income countries, our results are equal or superior; in those populations, cure rates are below 50% for NHL and around 90% for HL[11,15]. In one study, the same treatment regimen for NHL was used in 6 different countries of Central America, reporting challenges like those mentioned previously. With a cohort of 405 patients, the 3-year OS was 70%, while in our group, it was 80%, and DFS was comparable at 66% versus 68%, using treatment protocols without dose reductions[14]. In a single-center study from Northern Brazil, results, such as ours were reported, with 5-year OS and DFS rates of 70% and 68%, respectively[17]. Interestingly, our single-center report included 39 children, compared with 76 contributed from Guatemala and 70 from Nicaragua in the Association of Pediatric Hematology Oncology of Central America (AHOPCA) report[14].

In a previous study, the AHOPCA group implemented a uniform protocol for the treatment of HL in four of its member institutions from January 1999 to December 2004. A total of 216 newly diagnosed HL patients were included, staged according to the Ann Arbor classification, and divided into favorable (stages I, IIA, and IIIA) and unfavorable (stages IIB, IIIB, and IV) groups. Subjects in the favorable group received six cycles of 28-day chemotherapy (COPP/COPP ABV), while subjects in the unfavorable cohort received eight cycles of 28-day chemotherapy with COPP/ABV. Event-free survival (EFS) at 5 and 10 years was 71% and 68%, comparable to 70% in our cohort[19]. A recent report from Greece included 93 children with HL over 25 years; the most common subtype was nodular sclerosis in 50.5%, while in our patients it accounted for 69%; B symptoms were present in 16.1% versus 42% in our patients, corresponding to more advanced states at presentation.

The OS and EFS were 95.7% and 83.9%, in comparison to 96% and 75% in our study, with our lower EFS explained by a relapse rate of 25%, compared to 7.5% in that study[20].

It is estimated that 90% of pediatric lymphomas worldwide occur in low-to-middle-income countries; hence, even modest improvements in EFS and OS could significantly reduce the burden of pediatric NHL[21].

Although new first-line treatments offer promising results, these options represent a challenge for low-middle-income countries due to the lack of access and high cost.

In this respect, rituximab was not part of the routine treatment regimen during the study period in our center; this biological agent is currently incorporated for treating Burkitt and DLBCL s in this age group.

It is important to note that there is an ongoing international collaboration to improve lymphoma outcomes, like the one fostered by the Pediatric Cancer Data Commons for developing the HL data collaboration (NODAL) to advance pediatric HL research[22].

Earlier diagnosis, referral to specialized centers, contemporary therapeutic approaches including biological agents, and incorporation of radiotherapy to the treatment protocols, as well as advanced imaging follow-up methods, are required in disadvantaged populations to close the gap with developed nations.

Survivors of pediatric lymphoma are at risk for second primary malignancies, with 40-year cumulative incidence rates up to 22.2% for HL and 12.6% for NHL in a recent report[23]; thus, long-term follow-up of these patients is critical to assure the best quality of life.

Conclusion

Comparable frequencies for HL and NHL were documented in our cohort of open-population pediatric-age patients in Northeast Mexico; survival rates for HL were similar to those in high-income countries, while for NHL lagged considerably.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The Sex and Gender Equity in Research guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript (SCISPACE, in introduction, data search in discussion).

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