

# Epidemiology and Clinical Characteristics of Non-Hodgkin Lymphoma in Mexico

Eleazar Hernandez-Ruiz<sup>a, b, c</sup>, Martha Alvarado-Ibarra<sup>b, p</sup>, Lourdes Esthela Juan Lien-Chang<sup>c</sup>,  
Luisa Banda-Garcia<sup>d</sup>, Jorge Luis Aquino-Salgado<sup>a</sup>, Gabriel Barragan-Ibanez<sup>a</sup>,  
Eva Fabiola Ramirez-Romero<sup>e</sup>, Cesar Nolasco-Cancino<sup>f, g</sup>, Wilfrido Herrera-Olivares<sup>h</sup>,  
Javier de Jesus Morales-Adrian<sup>i</sup>, Eugenia Patricia Paredes-Lozano<sup>j</sup>, Maria Eugenia Espitia-Rios<sup>b</sup>,  
Maria de Monserrat Gonzalez Lopez-Elizalde<sup>k</sup>, Jose Luis Lopez-Arroyo<sup>l</sup>, Jorge Enrique Trejo-Gomora<sup>m</sup>,  
Jose Antonio De la Pena-Celaya<sup>b</sup>, Jose Luis Alvarez-Vera<sup>b</sup>, Luara Luz Arana-Luna<sup>b</sup>, Annel Martinez-Rios<sup>n</sup>,  
Rodrigo Resendiz-Olea<sup>n</sup>, Lucero Jazmin Rodriguez-Velasquez<sup>a</sup>, Nidia Zapata-Canto<sup>o</sup>,  
Juan Manuel Perez-Zuniga<sup>b, n, p</sup>

## Abstract

**Background:** There is no epidemiological registry in Mexico. The information about the epidemiology in our country is obtained by

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<sup>a</sup>Servicio de Hematología, Hospital Regional de Alta Especialidad, de Oaxaca, Oaxaca, Mexico

<sup>b</sup>Servicio de Hematología, Centro Medico Nacional “20 de Noviembre”, ISSSTE, Mexico City, Mexico

<sup>c</sup>Servicio de Hematología, Unidad de Oncología y Servicios de Salud del Estado de Puebla, Puebla, Mexico

<sup>d</sup>Servicio de Hematología, Hospital General de Zona No. 11 de Xalapa, Veracruz, Mexico

<sup>e</sup>Servicio de Hematología, Hospital Regional Presidente Juarez de Oaxaca, ISSSTE, Oaxaca, Mexico

<sup>f</sup>Servicio de Hematología, Hospital Regional Doctor Juan Graham Casaus de Villahermosa, Tabasco, Mexico

<sup>g</sup>Servicio de Hematología, Hospital CERACOM, Villahermosa, Tabasco, Mexico

<sup>h</sup>Servicio de Hematología, Hospital Regional de Puebla, ISSSTE, Puebla, Mexico

<sup>i</sup>Servicio de Hematología, Hospital Regional de Merida, ISSSTE, Yucatan, Mexico

<sup>j</sup>Servicio de Hematología, Hospital Regional 1° de Octubre ISSSTE, Mexico City, Mexico

<sup>k</sup>Servicio de Hematología, Hospital H+ de Queretaro, Queretaro, Mexico

<sup>l</sup>Servicio de Hematología, Hospital General B de Ciudad Juarez, Chihuahua, Mexico

<sup>m</sup>Servicio de Hematología, Hospital San Angel Inn Universidad, Mexico City, Mexico

<sup>n</sup>Servicio de Hematología, Hospital Regional Ignacio Zaragoza ISSSTE, Mexico City, Mexico

<sup>o</sup>Instituto Nacional de Cancerología, Mexico City, Mexico

<sup>p</sup>Corresponding Authors: Juan Manuel Perez Zuniga and Martha Alvarado Ibarra, Servicio de Hematología, Centro Medico Nacional “20 de Noviembre”, ISSSTE, Mexico City, Mexico. Emails: kbzaz@hotmail.com and normoblasto@gmail.com

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these types of studies, such as multicentric studies. A lot of improvements in the survival in non-Hodgkin lymphoma patients had occurred in the last 20 years. The access to treatment in these types of pathology could change the prognostic factors in Mexican Mestizos patients. The primary objective of the study was to learn what the most frequent histological varieties of non-Hodgkin lymphoma in Mexico are. The secondary objectives included clinical characteristics, treatments used, treatment response, disease-free survival and overall survival.

**Methods:** A retrospective, descriptive study of consecutive cases was carried out in 14 hospitals across 14 Mexican states with patients diagnosed with non-Hodgkin lymphoma using the World Health Organization (WHO) 2008 criteria. Inclusion criteria included:  $\geq 18$  years of age, male or female, any clinical stage at diagnosis, who had received any chemotherapy regimen, with a known outcome. Descriptive statistics was performed for all variables, and survival was assessed using Kaplan-Meier curves.

**Results:** Totally, 609 patients were enrolled, of which 545 were B-cell lymphomas and 64 were T-cell lymphomas. Median ages were 61 and 50, respectively. B-cell lymphomas were more common in males with 52.1%, and 65.5% of T-cell lymphomas occurred in females. For B-cell lymphomas, the two most frequent histological subtypes were diffuse large B-cell lymphoma in 63.9%, followed by follicular lymphoma at 18%. Meanwhile, 50% of T-cell lymphomas were of the T/natural killer (NK) subtype, and 87.1% of the patients received a CHOP-like regimen. Radiotherapy was given to 31% of B-cell Lymphomas and 46.9% of T-cell lymphomas. Overall survival at 9 years was 84.6% for B-cell lymphomas, and 73.4% for T-cell lymphomas.

**Conclusions:** Diffuse large B-cell lymphoma constitutes the most frequent subtype for B-cell lymphomas in Mexico. The most frequent T-cell lymphoma is the NK/T histological subtype.

**Keywords:** Non-Hodgkin lymphoma; Histological subtype; B-cell lymphomas; NK/T-cell lymphoma; Chemotherapy regimen

## Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid tissue neoplasms [1], usually characterized by an increase in proliferation [2] and/or reduction of apoptosis [3], with a subsequent accumulation of lymphoid tissue at a nodal or extra nodal site [4]. Tumor micro-environment plays a pivotal role in disease development, and at least three mechanisms have been described for this group of lymphoid neoplasms. The first mechanism is proliferation, like in the case of Burkitt's lymphoma, which generates a "deletion" of cells from the micro-environment; the second and third mechanisms are "re-education", observed in follicular lymphoma, and "recruitment" of various cells into the tumor, like in the case of Hodgkin lymphoma [5]. These mechanisms condition countless molecular and cellular environments for this disease [6].

NHLs correspond to 90% of all lymphoid tissue neoplasms, with the remaining 10% belonging to Hodgkin lymphoma [7]. NHLs frequently are B lineage in almost in 95% of the cases, and only 5% are of T lineage [8]. Being a heterogeneous group in lineage, molecular characteristics, ontogeny, clinical stage and affected sites, treatment approaches are usually different, ranging from watch and wait to chemotherapy, immunotherapy, targeted therapy, radiotherapy, and bone marrow transplant [9]. Survival in each type of lymphoma has been clarified due to the great heterogeneity of this disease as well as the identification of prognostic factors related to survival, with the most widespread one being the International Prognostic Index (IPI) [10]. Over time, new histological and molecular classifications, such as those proposed by the World Health Organization (WHO) [11], have helped to discriminate the diagnosis, clinical stage and ideal treatment for each subtype of the disease.

In Mexico, NHL is the ninth cause of cancer, making up 3.1% of all cancers. In 2012 there was a prevalence of 8,700 cases; there were 4,632 new reported cases and 2,558 deaths attributed to this disease [12]. Based on the information from various public and private institutions that treat these kinds of patients, gaining better insight of the epidemiology of this disease in Mexico must be of the utmost importance, and this is the first effort to obtain nation-wide statistics on this disease.

## Patients and Methods

### Design

A retrospective, observational, descriptive, multi-center study was carried out in 14 hospitals in 14 states of the country, between January 2008 and December 2016. The protocol of this study was approved by the Ethics Committee; the study complies with the Declaration of Helsinki, and was in accordance with the guidelines of good clinical practice and compliance with the regulations of the general health law in the field of health research in Mexico.

### Inclusion and exclusion criteria

Patients with a diagnosis of NHL were included. Diagnosis of histological subtype, with the use of immunohistochemistry, was made by the department of pathology of each institution, and was based on WHO 2008 [13] criteria for classification of lymphoma. Adult patients over the age of 18, of any gender, clinical stage, with any treatment received and known were included. Response was determined by Cheson's 1999 criteria [14] for standardization of lymphoid neoplasms. Patients without complete data were excluded for the study.

### Objectives

The primary objective of the study was to learn what the most frequent histological varieties of NHL in Mexico are. The secondary objectives included clinical characteristics, treatments used, treatment response, disease-free survival and overall survival.

### Statistical analysis

The statistical analysis was performed in SPSS version 23 of IBM, performing descriptive statistics. For treatment response, intention to treat was conducted in all cases. Survival was determined by the Kaplan-Meier method.

## Results

From January 2008 to December 2017, 643 patients were registered; 34 were excluded because they lacked complete data for this study. Median age was 59 years, 50.2% of patients were females, and 89.5% of cases were B-cell lymphomas. Clinical stage III - IV as per modified Ann Arbor was documented in 54.4% of the cases. Performance status, determined by Eastern Cooperative Oncology Group (ECOG) scale, was 0 - 2 in 94.7% of the cases. Complete clinical characteristics are presented in Table 1.

Regarding the histological varieties identified, diffuse large B-cell lymphoma was the most frequent subtype. Natural killer (NK)/T-cell lymphoma was the most frequent histological subtype when it came to T-lineage lymphomas. Table 2 describes the main histological varieties for each group.

When analyzing the most used treatment in this group of patients, the CHOP-21 regimen was applied to 87.1% of the patients; 91.3% of patients with B-cell lymphoma received the CHOP-21 chemotherapy regimen, while 53.2% of patients with T-cell lymphoma also received this same treatment. Rituximab was applied in 74.7% of B-cell lymphomas. Radiotherapy was applied in 32.7% of cases. Only 31% of B-cell lymphomas received radiotherapy, whereas in T-cell lymphomas it was applied to 46.9% of cases.

The overall response in the group analyzed was 88%, with 74.9% complete responses. When analyzing overall response by lineage, B-cell lymphomas had an overall response rate of

**Table 1.** Clinical Characteristics and Disease Stage Classification

	Total (n = 609)	Type B (n = 545)	Type T (n = 64)	P
Age (years)	59 (48 - 70)	61 (50 - 70)	50 (39 - 63)	< 0.05
Gender (female/male) (%)	50.2/49.8	47.9/52.1	65.6/34.4	< 0.05
Ann Arbor (%)				
I - II	45.6	44.9	51.6	NS
III - IV	54.4	55.1	48.4	
ECOG (%)				
0 - 2	94.7	95	92.3	NS
≥ 3	5.3	5	7.7	
Symptoms B (%)	23.3	23.5	21.9	NS
Bulky (%)	27.1	28.6	14.1	< 0.05
IPI				
Low	32.9	31.5	41.6	NS
Intermediate low	21.2	21.9	16.7	
Intermediate high	16.1	16.9	11.7	
High	29.8	29.8	30	

Age is reported as a median, with 25th and 75th percentiles. Age differences were conducted by median comparison with Mann-Whitney U. For the other variables, a Chi-squared test was conducted. ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; NS: not significant.

89.9%, of which 77% reached a complete response. In T-cell lymphomas, the overall response rate achieved was 71.9% with only 51.6% of these being complete responses.

Overall survival, determined at 9 years, was observed in

83.4% of the cases. When an analysis of survival based on the lineage was done, 84.6% overall survival was seen in B-cell lymphomas, and 73.4% in T-cell lymphomas (Fig. 1).

**Table 2.** Pathological Classification of Non-Hodgkin Lymphoma by Cell Type and Percentage

Type B (n = 545)	
Diffuse large cell lymphoma	63.9
Follicular	18
Small lymphocytes	4.2
Mantle cell	3.9
MALT	3.1
Lymphoblastic	1.7
Marginal zone	1.1
Burkitt	0.9
Others	3.2
Type T (n = 64)	
T/NK	50
Mycosis fungoides	10.9
T peripheral	6.3
Anaplastic	3.1
Lymphoblastic	3.1
Unspecified T	16.6
Others	10

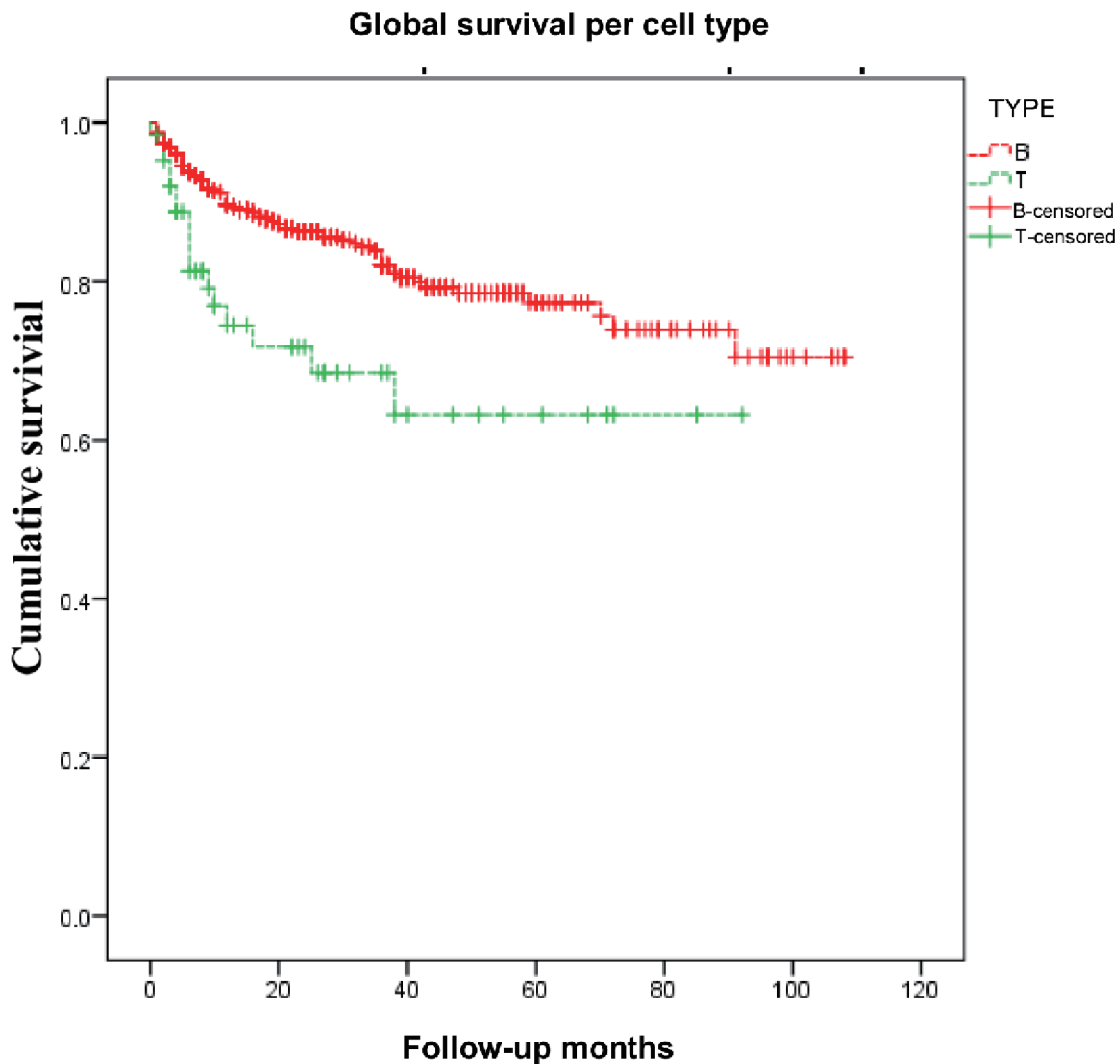
MALT: mucosa-associated lymphoid tissue; NK: natural killer.

## Discussion

In the present study, diffuse large B-cell lymphoma occurred in 63.9% of all diagnosed cases of NHL. This is in contrast with what has been published in numerous studies, where approximately 40% of the cases correspond to this histological subtype [15]. Even in developed countries in different continents, as reported by Perry et al [16], diffuse large B-cell lymphomas account for 42.5% of all cases. On the other hand, there was a reduction in the prevalence of follicular lymphoma, which was of 18% in this study, lower than in international reports, where its reported frequency is of up to 30% [17].

Meanwhile, the most frequent T-cell lymphoma corresponded to the NK/T variety, accounting for 50% of the cases, higher than the average reported elsewhere. In their review, Aozasa et al [18] reported a frequency of 8-40%.

One of the limitations of this study was that cases were classified in each institution using the 2008 WHO's classification criteria, and there was no centralized review of the cases. This might have impacted the difference in frequencies we reported in this study when compared to international data. In summary 4,727 presented at ASH 2018, Solano et al [19] stated that in up to half the cases of diagnosed NHL; there were inconsistencies between the local pathologists and hematopathologists located in Mexico. This presents an opportunity for future collaboration for the standardization of diagnostic processes for NHL.



**Figure 1.** Overall survival curves by cell type, B-cell non-Hodgkin lymphoma and T-cell non-Hodgkin lymphoma.

Treatment with CHOP-like regimens was the most frequently used, which is consistent with the descriptions of Kumar et al [20], Hu et al [21] in advanced disease, and Schmitz et al [22], in aggressive T-cell lymphomas.

Only 74.7% of patients with B-cell lymphomas received rituximab, a smaller number than the average in other reports. Jo et al [23] reported in 2010 that only 4% of B-cell lymphomas are negative for CD20, so rituximab is used in 96% of these patients. This study included institutions with no access to rituximab, which might explain the reduced percentage of patients that did receive treatment with this drug.

Radiotherapy was used in one out of every three cases of B-cell lymphomas, consistent with the current international average. However, Zimmermann et al [24] stated in 2016 that there exists a downward tendency when it comes to the use of radiotherapy (47% since the year 2000), which might play a deleterious role in overall and disease-free survival.

Overall survival in our study at 9 years was 83.4%, higher than reported in consolidated surveillance programs [25].

These results can be attributed to the fact that the patients we included had different histological varieties, as reported by Ji et al [26]; half of the patients were in early stages and one-third were low risk for IPI, additionally, 90% had ECOG less than 2, important factors for survival as reported by the International Non-Hodgkin's Lymphoma Prognostic Factors Projects [10, 27] in favor of low risks, early stages and better functional status; finally, in our study, patients with poor functional status who did not receive treatment for NHL were excluded.

This study has its limitations: its retrospective design, from different medical centers with diagnosis being made by local pathologists; its registered consecutive cases with local incidences and no restrictions, which might lead to biases in reporting the frequency of NHL. However, it is also the first effort made to have better knowledge of the epidemiology of this disease in Mexico. There is no doubt this must progress and generate more solid and systematic prospective studies. With these new studies, a centralized review of each case should be implemented, improving classification, reproducibility and

consistency, and, most important of all, enabling the optimization of diagnosis so as to individualize therapy for NHL patients in Mexico.

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## Financial Disclosure

None to declare.

## Conflict of Interest

The authors have no potential conflict of interest to disclose.

## Informed Consent

Informed consent was obtained.

## Author Contributions

All authors contributed by providing the data of their patients and completing the database. Doctor Eleazar Hernandez Ruiz was the main author since he headed the project; he invited all the colleagues from the country; and together with Doctor Martha Alvarado Ibarra and Doctor Juan Manuel Perez Zuniga carried out the statistical analysis, as well as the final revision and the translation of the text. All authors reviewed and approved the final text.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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