Scientific section: LYMPHOID NEOPLASIA

Title: Classification of Non-Hodgkin Lymphoma in Central and South America: a Review of 1028 Cases

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Abstract

The distribution of non-Hodgkin lymphoma (NHL) subtypes differs around the world but a systematic study of Latin America has not been done. Therefore, we evaluated the relative frequencies of NHL subtypes in Central and South America (CSA). Five expert hematopathologists classified consecutive cases of NHL from five CSA countries using the WHO classification and compared them to 400 cases from North America (NA). Among the 1028 CSA cases, the proportions of B- and T-cell NHL and the sex distribution were similar to NA. However, the median age of B-cell NHL in CSA (59 years) was significantly lower than in NA (66 years; p<0.0001). The distribution of high-grade (52.9%) and low-grade (47.1%) mature B-cell NHL in CSA was also significantly different from NA (37.5% and 62.5%; p<0.0001). Diffuse large B-cell lymphoma was more common in CSA (40%) than in NA (29.2%; p<0.0001), whereas the frequency of follicular lymphoma was similar in Argentina (34.1%) and NA (33.8%), and higher than the rest of CSA (17%; p<0.001). Extranodal NK/T-cell NHL was also more common in CSA (p<0.0001). Our study provides new objective evidence that the distribution of NHL subtypes varies significantly by geographic region and should prompt epidemiological studies to explain these differences.
Introduction

Neoplasms of the lymphoid system are very diverse with different clinical presentations, morphological appearances, and biological behaviors\(^1\). Furthermore, the non-Hodgkin lymphoma (NHL) category includes numerous different subtypes. The incidence of NHL is increasing worldwide and, although this increase began to slow in the 1990’s, significant variations in temporal trends have been noted for individual NHL subtypes\(^2,3\).

Epidemiological studies of risk factors for NHL have contributed significantly to our understanding of the pathogenesis of these neoplasms\(^2-5\). Numerous epidemiologic studies have also analyzed the distribution of NHL subtypes in North America (NA), Europe, the Far East, and Middle East\(^3,6-12\). These studies have shown substantial differences in the relative frequencies of NHL subtypes in different geographic regions. Furthermore, it has become clear that subtype-specific NHL frequency patterns in different geographic regions may be indicative of environmental or host risk factors in a particular region\(^2-4,7\). Moreover, comparison of the incidence rates and frequency patterns of specific NHL subtypes may provide critical clues to guide future epidemiological studies\(^3\).

Although studies of individual NHL subtypes have been conducted in several Central and South American (CSA) countries\(^13-16\), only a few epidemiological studies have looked at the distribution of NHL subtypes in individual countries\(^17-19\). However, to our knowledge, a large-scale, well-organized, systematic study of the distribution of NHL subtypes in CSA has not
been done. The aim of this study was to assess the clinical features and
distribution of NHL subtypes in different countries in CSA, and to compare the
findings to a cohort of similarly-accrued NHL cases from NA.
**Materials and Methods**

*International NHL Classification Project*

Institutions from five countries in CSA including Argentina, Brazil, Chile, Guatemala, and Peru were invited to participate in the current study by submitting cases of NHL that were representative of each country. Among the participating institutions, four are academic medical centers with cancer expertise and one is a private pathology laboratory in Guatemala (see Acknowledgements). Each institution was instructed to collect 200 consecutive, newly-diagnosed and untreated cases of NHL. These cases were accrued between the years 2000 and 2009. The design of the current study is the same as to that of the original study by the International NHL Classification Project. Briefly, hematoxylin and eosin (H&E) stained slides, immunostains, pathology reports, clinical data, and the results of ancillary studies were organized for review at each institution. A panel of five expert hematopathologists (J.D., K.A.M., H.K.M-H, B.N.N. and D.D.W) then reviewed all of the collected cases using the 2001 World Health Organization (WHO) classification. Each expert independently reviewed all of the material available for each case, including the clinical data, at the same time and recorded his diagnosis. A consensus diagnosis was reached when at least four of the experts agreed on the diagnosis. However, a consensus on the grade of follicular lymphoma was reached when at least three experts agreed on the grade. For cases in which a consensus diagnosis could not be reached, a specific diagnostic algorithm for each case was developed and agreed upon by
the group of experts. Requested clinical data and materials, either paraffin-embedded blocks or unstained slides, were then sent to the University of Nebraska Medical Center where additional ancillary testing was performed by D.D.W., who then assigned the case to a diagnostic category based upon the algorithm. For cases in which a specific NHL subtype could not be established due to suboptimal morphology, or inadequate or insufficient material, the diagnostic categories of unclassifiable low-grade or high-grade NHL were used. The data from CSA was then compared to a cohort of 400 previously-published NA cases accrued in Omaha, Nebraska, and Vancouver, British Columbia. The data from two of the CSA countries, Guatemala and Chile, has been previously published. Approval for this study was obtained from the Institutional Review Board at the University of Nebraska Medical Center and at each of the participating institutions as required by individual institutional policies. This study was conducted in accordance with the Declaration of Helsinki.

For this analysis, only information on age and sex is included because the clinical data collected at the various institutions was often incomplete and quite variable. By convention, cases of composite lymphoma were classified according to the low-grade component. Mature B-cell NHL was further subdivided into low- and high-grade subgroups, with the low-grade subgroup including cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), lymphoplasmacytic lymphoma (LPL), mantle cell lymphoma (MCL), follicular lymphoma (FL, all grades), marginal zone lymphoma (MZL, all types), and cases of unclassifiable low-grade B-cell lymphoma. The high-grade B-cell lymphoma
subgroup included cases of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), Burkitt lymphoma (BL), unclassifiable B-cell lymphoma with features intermediate between BL and DLBCL (Burkitt-like), and cases of unclassifiable high-grade B-cell lymphoma. For statistical analysis of FL, two subgroups were defined: FL grades 1 and 2 were combined into one group, and FL grade 3 comprised the other group. Furthermore, due to the low number of cases of T-cell lymphoma, cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma, anaplastic large T/null-cell lymphoma, hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma and enteropathy-associated T-cell lymphoma were all grouped together under the category of PTCL.

Statistical analysis

Data analysis was done using SAS software version 9.2 (SAS Institute Inc, Cary, NC). Comparisons of medians for continuous variables were conducted using the Wilcoxon rank sum test. Comparisons of categorical variables were done using Chi-square or Fisher's exact tests; the latter was used when the Chi-square test may not have been valid due to small numbers. P-values for pairwise comparisons were adjusted using the Bonferroni method, and P-values less than 0.05 were considered statistically significant.
Results

Of the 1028 cases reviewed, including 198 cases from Argentina, 227 from Brazil, 207 from Chile, 224 from Guatemala, and 172 from Peru, 927 cases (90.2%) were confirmed to be NHL by the expert review. However, 74 cases (7.2%) were found to have a diagnosis other than NHL and, therefore, were excluded from further analysis. Among the latter cases, one case (0.1%) was thought to be a lymphoid neoplasm but could not be further classified, 18 (1.8%) were Hodgkin lymphomas, 29 (2.8%) were reclassified as non-lymphoid malignant neoplasms, and 26 cases (2.5%) were considered unclassifiable due to inadequate diagnostic material. There was a statistically significant difference between CSA and NA when comparing the relative frequency of cases that were reclassified by expert review (7.2% vs. 1%; p<0.001). Finally, 27 cases of multiple myeloma (2.6%) were excluded from the CSA cohort, as in our previous publications.6,7

The overall distribution of NHL subtypes in CSA, as well as the distribution by individual country, is shown in Table 1. Of the 927 cases, 809 (87.3%) were B-cell lymphomas and 118 (12.7%) were T-cell lymphomas. Overall, the distribution of B- and T-cell NHL was similar in CSA (87.3% vs. 12.7%) and NA (90.4% vs. 9.6%; p=0.1). However, among mature B-cell NHL, the frequency of high-grade lymphomas was significantly higher in CSA (52.9%) compared to NA (37.5%; p<0.0001; Table 2). Further comparison of individual CSA countries with NA revealed a significantly increased frequency of high-grade B-cell NHL in Brazil.
significant differences were observed in the relative frequencies of low-grade and high-grade B-cell NHL in Argentina, Guatemala and Peru when compared with the rest of CSA. More precisely, a predominance of low-grade B-cell NHL was observed in Argentina (p<0.001), whereas the reverse was true in Guatemala and Peru where high-grade B-cell NHL was more common (p<0.001 for both countries).

Among the B-cell lymphomas (Table 1), diffuse large B-cell lymphoma (DLBCL) was the most common subtype (40.0%), and it was the most common B-cell lymphoma in all of the CSA countries except Argentina, where follicular lymphoma (FL) was the most common (34.1%). Follicular lymphoma was also relatively frequent in Chile (25.4%), but was less common in the other countries, especially Guatemala (10.4%) and Peru (11.6%). Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type was common in Brazil (9.4%) and Chile (10.4%), where it was the third most common subtype, whereas mantle cell lymphoma (MCL) was common in Argentina (8.1%) and rare in Peru (0.6%). Guatemala had a relatively high frequency of Burkitt lymphoma (BL; 6.7%) and precursor B-lymphoblastic leukemia/lymphoma (PB-ALL; 6.2%).

When comparing individual lymphoma subtypes, DLBCL was more common in CSA than in NA (40% vs. 29.2%, respectively; p<0.0001; Table 1). Analysis of DLBCL among individual CSA countries showed that the frequency of this subtype was similar to NA in Argentina, and higher in Brazil and Chile, whereas Guatemala (p=0.01) and Peru (p<0.001) had significantly higher frequencies of DLBCL. However, when compared to the other CSA countries, the
relative frequency of DLBCL was significantly lower in Argentina (p<0.001) and higher in Peru (p=0.02).

In contrast to DLBCL, FL was more common in NA than in CSA (33.8% vs. 20.4%, respectively; p<0.0001; Table 1). When analyzing FL among individual countries, the frequencies of this subtype in Brazil (p=0.005), Guatemala (p<0.0001) and Peru (p<0.0001) were significantly lower than in NA, whereas Argentina and Chile were similar to NA. Moreover, the relative frequency of FL in Argentina was significantly higher than in the other CSA countries (p<0.001). The opposite was observed in Guatemala (p=0.001) and Peru (p=0.02), where the frequency of FL was significantly lower when compared to the other CSA countries. The frequency of low-grade FL was also significantly lower in CSA (14.3%) than in NA (25.3%; Table 2). Among individual countries, the frequency of low-grade FL was significantly lower in Brazil (p=0.015), Guatemala (p<0.0001) and Peru (p<0.0001) than in NA, whereas Argentina and Chile had a frequency similar to NA. When compared to the other CSA countries, the frequency of low-grade FL was significantly higher in Argentina (p<0.0001) and lower in Guatemala (p=0.003) and Peru (p=0.006). No significant differences were observed in the frequency of high-grade FL between CSA and NA or among the individual CSA countries.

The frequency of MCL was particularly low in Peru (p=0.002), whereas the remaining CSA countries had a frequency similar to NA (Table 1). Although MZL of MALT type was more common in Chile, the difference was not statistically significant. Precursor B-lymphoblastic leukemia/lymphoma was more common in
CSA than in NA (p<0.0001), with both Guatemala (p<0.0001) and Peru (p=0.03) having a significantly higher frequency than NA. Burkitt lymphoma was also more common in CSA than in NA, with most of the cases seen in Guatemala (p<0.001). No significant differences were observed between CSA and NA in the frequencies of CLL or MZL of the nodal/splenic types.

Among the T-cell lymphomas, peripheral T-cell lymphoma (PTCL) was the most common subtype in all of the countries except Guatemala, where extranodal NK/T-cell lymphoma, nasal type (ENKTL; 7.8%), was the most common T-cell NHL. Moreover, ENKTL was more common in CSA (p<0.0001) than in NA, with most of the cases seen in Guatemala (p<0.0001), Chile (p=0.04) and Peru (p=0.07). The frequency of adult T-cell leukemia/lymphoma (ATLL) was also significantly higher in CSA than in NA (p<0.0001), and was largely restricted to Peru where it represented 5.5% of all NHL. No significant differences between NA and CSA were observed in the distribution of precursor T-cell lymphoblastic leukemia/lymphoma or PTCL.

The distribution of NHL by sex and age is shown in Table 3. The age of the patients in CSA ranged from one to 100 years, and 50.9% were male. No significant differences were observed in the sex distribution between NA and CSA (p=0.5), or among the individual CSA countries. Overall, the median age of patients with NHL was significantly lower in CSA than NA (58 years vs. 65 years, respectively; p<0.001), with this difference being most significant in Argentina, Guatemala and Peru. Furthermore, the median age of NHL patients in Chile (63 years) was significantly higher than in the other CSA countries (p=0.003). The
median age of patients with B-cell NHL in CSA was 59 years, which was significantly lower than in NA where the median age was 66 years (p<0.0001). The countries in which this difference was most significant were Argentina (p<0.001), Brazil (p=0.01) and Guatemala (p<0.001). When compared to the other CSA countries, the median ages of patients with B-cell NHL in Chile and Guatemala were significantly different (p=0.047 and p=0.009, respectively). The median age of patients with low-grade B-cell lymphoma in CSA was 60 years, which was significantly lower than in NA where the median age was 64 years (p=0.01). This difference was most evident in Argentina, where the median age for low-grade B-cell lymphomas was significantly lower than in NA (57 years vs. 64 years, respectively; p=0.002) or the other CSA countries (p=0.003). Similarly, the median age of patients with high-grade B-cell lymphoma in CSA was 59.5 years, which was significantly lower than in NA (68.5 years; p<0.0001). The countries in which this difference was most significant included Argentina (p=0.006), Brazil (p=0.02) and Guatemala (p<0.001). There were no significant differences in the median age of patients with high-grade B-cell lymphoma among the individual CSA countries. There was also no significant difference when comparing the median age of T-cell NHL patients between CSA and NA, or among the individual CSA countries.
Discussion

The current study of 1028 consecutive cases initially diagnosed as NHL from five different countries represents the first large study of the distribution of NHL subtypes in CSA. Of these, 927 (90.2%) cases were confirmed to be NHL following the expert panel review. Also, 74 (7.2%) cases were found to have a diagnosis other than NHL and, therefore, were excluded from further analysis. The most common reasons for exclusion were a diagnosis other than lymphoma (29 cases, 2.8%), inadequate material for diagnosis (26 cases, 2.5%) and a diagnosis of Hodgkin lymphoma (18 cases, 1.8%). These findings suggest that technical improvements and better diagnostic training are needed in these CSA countries to decrease the number of misdiagnosed cases.20

As a region, CSA has a distribution of NHL subtypes that is different from that observed in NA and Western Europe,1,3,6,7 with a predominance of DLBCL (40%) in CSA. Even though the distribution of B- and T-cell NHL was similar in CSA and NA, significant differences were observed when comparing data from individual countries to NA or to the rest of CSA. As individual countries, Argentina and Chile have NHL distributions which are somewhat similar to NA. In contrast to NA, Guatemala and Peru had much lower frequencies of low-grade B-cell NHL, particularly FL and CLL. The relative frequency of MCL in Guatemala was similar to NA, but a much lower frequency was observed in Peru. On the other hand, the frequencies of DLBCL, ENKTL, BL, and PB-ALL were much higher in Guatemala and Peru compared to NA. Moreover, in Guatemala and Peru, the
relative frequencies of T-cell NHL approached those observed in the Middle East and Asia.\textsuperscript{1,6,8,10,21} Interestingly, compared to NA, Guatemala had a high frequency of ENKTL and a low frequency of PTCL, whereas Peru had a higher frequency of PTCL and ATLL. Although it is possible that the high European population in Argentina and Chile may partially explain the observed differences, it is likely that environmental factors also play a role in the distribution of NHL subtypes in CSA. Additional epidemiological studies by NHL subtype are clearly required to understand these differences.

The frequency of mature high-grade B-cell NHL was significantly higher in CSA than in NA, with this difference mainly due to a high frequency of high-grade B-cell NHL in Brazil, Guatemala and Peru. Furthermore, a predominance of low-grade mature B-cell NHL was observed in Argentina and Chile, whereas high-grade mature B-cell NHL was more common than low-grade mature B-cell NHL in Guatemala and Peru. These differences are most likely multifactorial in origin. However, differences in socioeconomic factors, as well as differences in the patterns of medical practice, in these developing countries may have influenced the relative frequencies of low- and high-grade mature B-cell lymphomas in CSA. Interestingly, the pattern of income per capita and life expectancy in the CSA countries (Table 4) appear to correlate with the pattern of B-cell lymphomas. Argentina and Chile are the most similar to NA, whereas Guatemala and Peru are the least similar, and Brazil is somewhat intermediate.

No statistically significant differences were observed in the distribution of NHL subtypes by sex in NA and CSA, or among the individual CSA countries.
However, the median age of patients with B-cell NHL in CSA was significantly lower compared to NA, with this difference being most significant in Argentina, Brazil and Guatemala. Regarding high-grade mature B-cell NHL, a significance difference was observed in the median age for Argentina, Brazil and Guatemala when compared with NA. A study from the United States comparing the mean ages at diagnosis by race showed that DLBCL in African-Americans occurred approximately a decade earlier than in other racial groups. These findings suggest that both environmental and host risk factors, such as race, play a role in the development of NHL.

Our study showed that FL was more common in NA than in CSA. However, interesting regional differences were observed when analyzing the distribution of FL among the individual countries. The relative frequencies of FL in Argentina and Chile were similar to NA. Moreover, the frequency of FL in Argentina was significantly higher than in the other CSA countries, representing the most common NHL subtype in that country. Furthermore, the frequency of low-grade FL was significantly higher in Argentina compared with the rest of the CSA countries. Previous studies have shown that FL is common in NA and Western Europe with lower rates observed in Asian populations and developing countries. Although the reasons for these differences are not well understood, some studies suggest that environmental risk factors and socioeconomic status may be more important than host factors in the etiology of FL.
Pesticide exposures and dietary habits are environmental risk factors for NHL.\textsuperscript{5,25-27} Exposure to some pesticides including 2,4-diphenoxoacetic acid (2,4-D), organophosphates, carbamates, and organochlorine insecticides has been associated with an increased risk for the development of NHL.\textsuperscript{27,28} Moreover, the use of pesticides in agricultural populations has been associated with the t(14;18)(q32;q21) chromosomal translocation, a common abnormality in NHL and especially FL and DLBCL.\textsuperscript{25,26} On the other hand, dietary factors have been extensively investigated as risk factors for NHL with variable results.\textsuperscript{5,29-35} A positive association between the intake of dairy products and NHL risk has been reported, with the risk being highest for DLBCL.\textsuperscript{29,34} Interestingly, a positive association between milk intake and the risk of t(14;18)-positive NHL and, to a lesser extent, t(14;18)-negative NHL was observed by a group of investigators.\textsuperscript{31} Numerous epidemiological studies have also assessed the association of meat and saturated fat intake with risk of NHL. Several studies have found positive associations \textsuperscript{29,30,33,35}, but others failed to demonstrate a significant association.\textsuperscript{32,34} In a large case-control study of NHL in Nebraska, an increased risk of DLBCL was associated with a high intake of red meat, whereas the risk of FL was associated with a high intake of total fat, particularly animal fat (DDW, manuscript in preparation). Moreover, a Western dietary pattern characterized by the high intake of red meat, processed meat, salty snacks, fat, and French fries was associated with an increased risk of NHL overall, and particularly FL and DLBCL (DDW, manuscript in preparation). Therefore, high fat intake from red meat may explain, at least in part, the high frequency of FL in both NA and
Argentina. Given the importance of the agricultural activity and high meat intake in Argentina, additional epidemiological studies looking at these potential risk factors for the development of FL are warranted.

Overall, the frequency of MZL of MALT type was similar in CSA (6.9%) and NA (6.3%). However, this NHL subtype represented the third most common NHL in Chile (10.4%) and Brazil (9.4%). Chronic inflammatory disorders such as Helicobacter pylori gastritis and autoimmune conditions are the main risk factors for the development of MZL of MALT type. Infection with H. pylori is particularly common in the developing world where an inverse relationship between socioeconomic status and the prevalence of infection has been noted. The prevalence of H. pylori infection ranges from 36 to 90% in Chile and 30 to 82% in Brazil, which is significantly higher than the rates observed in USA (30%) and Canada (23.1%). However, the prevalence of this infection also ranges from 51 to 65% in Guatemala, but we did not observe a relative increase in the frequency of MZL of MALT type in that country. Interestingly, H. pylori infection in developing countries is more prevalent at younger ages than in the developed world, suggesting that early infection may play a role in the etiology of gastric MZL of MALT type.

A high frequency of ENKTL was observed in CSA when compared to NA. Furthermore, this subtype was the most common T-cell NHL in Guatemala (7.8%), with high frequencies also observed in Chile (2.6%) and Peru (2.9%). An increased frequency of ENKTL has also been reported in Hong Kong and other Asian countries, and studies have demonstrated a strong association.
between this lymphoma and Epstein-Barr virus infection.\textsuperscript{1,7,8,13,42} Furthermore, Morton \textit{et al.} \textsuperscript{3} have reported a higher incidence of ENKTL among Asian Americans, and other epidemiologic studies have demonstrated little difference in the incidence of this subtype among foreign-born and USA-born Asians, supporting the role of host susceptibility in this disease.\textsuperscript{23,44-46} The higher frequency of ENKTL in both the Far East and CSA countries is due to the fact that both populations have a common genetic background.\textsuperscript{3,18} Evidence from genetic studies, including mitochondrial DNA and Y chromosome haplotypes, indicates that native Americans came from a single Siberian population that migrated across the Bering land bridge to Alaska and moved south around 13,000 to 30,000 years ago.\textsuperscript{47} The Asian ancestry of the native population in CSA, especially in the countries located along the west coast, correlates with the observed high frequency of ENKTL.

Our data also showed a higher frequency of ATLL in CSA when compared with NA. Moreover, the cases of ATLL were largely restricted to Peru (5.5%), representing the second most common T-cell NHL and the fourth most common NHL subtype in that country. Although only a single additional case was observed in our series in Chile, previous reports from that country have shown that ATLL represents 40\% of the T-cell lymphoproliferative processes.\textsuperscript{14} Moreover, cases of ATLL have also been reported in native Americans in the northwest region of Argentina, an area near the Andes and close to Peru and Chile.\textsuperscript{15} Cases of ATLL have also been described in Brazil, mostly in the center of the country and along the northeastern coast, areas where the population is largely of African
descent.\textsuperscript{48} ATLL is endemic in several areas of the world including Japan, the Caribbean basin, central Africa, Iran and South America.\textsuperscript{21,49,50} The distribution of this subtype is closely related to the seroprevalence of the human T-cell leukemia virus, type 1 (HTLV-1), in the population.\textsuperscript{1,21,49,50} The Asian origin of the native American population has been postulated as a mechanism for introduction of HTLV-1 into CSA.\textsuperscript{47,49} Other authors have postulated an origin from Africa through the slave trade.\textsuperscript{48,49} In the case of Peru, significant Japanese immigration in the distant and recent past could also explain the increased frequency of ATLL.\textsuperscript{49} Additional studies, including human leukocyte antigen (HLA) typing and virus serotyping, should be performed to further understand these relationships.

One of the strong features of our study is the participation of an expert panel of hematopathologists to review all of the cases. Although the participating institutions in each country provided consecutive cases representative of their geographical region during a specific time period, it was not possible to calculate the actual incidence rates by subtype for each country due to the lack of centralized and comprehensive population-based cancer registries. Only limited incidence data from local or regional cancer registries is available for four of the five CSA countries (Table 4), and this may not be accurate or representative of each country as a whole. When comparing the distribution of NHL subtypes among regions and individual countries, it is important to realize that the actual incidence of a given subtype depends on accurate diagnosis and the true incidence of NHL in that geographical region.
In summary, our study represents the first large and systematic study to address the distribution of NHL subtypes in CSA. We found that the regional distribution of NHL subtypes was very different from that seen in NA. The differences in NHL subtype distribution among the individual countries, as well as between CSA and NA, suggest etiologic heterogeneity by NHL subtype and support the active pursuit of epidemiological studies by subtype in CSA.
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Authorship

Contribution: J.A.L. analyzed the data and wrote the manuscript; A.M.P. analyzed the data; E.B. performed the statistical analysis; J.D., K.A.M., H.K.M., B.N.N. and D.D.W. reviewed the cases; and J.O.A. and D.D.W. designed the research project. All coauthors read and reviewed the manuscript.

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References


Tables
Table 1: Frequency of non-Hodgkin lymphoma subtypes by country and region

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Argentina % (N)</th>
<th>Brazil % (N)</th>
<th>Chile % (N)</th>
<th>Guatemala % (N)</th>
<th>Peru % (N)</th>
<th>CSA Total % (N)</th>
<th>North America % (N)</th>
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<tr>
<td><strong>B-cell Neoplasms</strong></td>
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<td>Diffuse large B-cell lymphoma</td>
<td>25.9* (48)</td>
<td>40.6 (78)</td>
<td>38.9 (75)</td>
<td>45.1† (87)</td>
<td>50.6**† (83)</td>
<td>50.6† (189)</td>
<td>40.0† (134)</td>
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<td>Follicular lymphoma, all grades</td>
<td>34.1* (63)</td>
<td>19.8† (38)</td>
<td>25.4 (49)</td>
<td>10.4**† (20)</td>
<td>11.6**† (19)</td>
<td>10.4**† (64)</td>
<td>20.4† (25)</td>
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<td>Marginal zone B-cell lymphoma, MALT type</td>
<td>5.9 (11)</td>
<td>9.4 (18)</td>
<td>10.4 (20)</td>
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<td>4.3 (7)</td>
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<td>Mantle cell lymphoma</td>
<td>8.1 (15)</td>
<td>3.6 (7)</td>
<td>5.7 (11)</td>
<td>6.2 (12)</td>
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<td>0.6**† (12)</td>
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<td>Chronic lymphocytic leukemia/ small B-cell</td>
<td>5.4 (13)</td>
<td>6.3 (12)</td>
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<td>1.6 (3)</td>
<td>2.1 (4)</td>
<td>2.1 (4)</td>
<td>6.7**† (13)</td>
<td>1.8 (5)</td>
<td>1.8 (3)</td>
<td>2.9 (3)</td>
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<td>Precursor B-lymphoblastic leukemia / lymphoma</td>
<td>4.3 (8)</td>
<td>2.1 (4)</td>
<td>1.6 (4)</td>
<td>2.1 (3)</td>
<td>3.0 (5)</td>
<td>3.0 (24)</td>
<td>2.6 (7)</td>
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<tr>
<td>High-grade B-cell lymphoma, Burkitt-like</td>
<td>0.0 (0)</td>
<td>0.5 (0)</td>
<td>0.5 (0)</td>
<td>0.5 (0)</td>
<td>0.6 (0)</td>
<td>0.6 (0)</td>
<td>0.5 (0)</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>0.0 (0)</td>
<td>2.1 (0)</td>
<td>0.0 (0)</td>
<td>0.5 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>0.5 (1)</td>
<td>0.5 (1)</td>
<td>0.0 (0)</td>
<td>1.6 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.5 (0)</td>
</tr>
<tr>
<td>Unclassifiable low-grade B-cell lymphoma</td>
<td>1.1 (2)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.2 (0)</td>
</tr>
<tr>
<td>Unclassifiable high-grade B-cell lymphoma</td>
<td>0.5 (1)</td>
<td>1.0 (2)</td>
<td>0.5 (0)</td>
<td>1.0 (0)</td>
<td>0.6 (0)</td>
<td>0.6 (0)</td>
<td>1.3 (0)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>88.1 (163)</td>
<td>90.6 (174)</td>
<td>88.6 (171)</td>
<td>87.0 (168)</td>
<td>81.1 (133)</td>
<td>87.3 (809)</td>
<td>90.4 (359)</td>
</tr>
<tr>
<td><strong>T-cell Neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphomas</td>
<td>9.2 (17)</td>
<td>5.7 (11)</td>
<td>6.7 (13)</td>
<td>3.1 (6)</td>
<td>9.8 (16)</td>
<td>9.8 (63)</td>
<td>6.8 (21)</td>
</tr>
<tr>
<td>Extramedullary NK/T-cell</td>
<td>0.5 (0)</td>
<td>1.0 (0)</td>
<td>0.0 (0)</td>
<td>0.5 (0)</td>
<td>0.5 (0)</td>
<td>0.5 (0)</td>
<td>0.5 (0)</td>
</tr>
<tr>
<td>Precursor T-lymphoblastic leukemia / lymphoma</td>
<td>1.6 (3)</td>
<td>1.6 (3)</td>
<td>1.6 (3)</td>
<td>2.1 (4)</td>
<td>0.6 (1)</td>
<td>0.6 (14)</td>
<td>1.5 (8)</td>
</tr>
<tr>
<td>Adult T-cell leukemia / lymphoma</td>
<td>11.9 (22)</td>
<td>9.4 (18)</td>
<td>11.4 (22)</td>
<td>13.0 (25)</td>
<td>18.9 (31)</td>
<td>18.9 (118)</td>
<td>12.7 (38)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>185</td>
<td>192</td>
<td>193</td>
<td>198</td>
<td>164</td>
<td>927</td>
<td>397</td>
</tr>
</tbody>
</table>
CSA: South America, NA: North America; * p<0.05 compared with the rest of CSA; † p<0.05 compared with North America
Table 2: Comparison of the frequencies of mature B-cell non-Hodgkin lymphomas according to grade

<table>
<thead>
<tr>
<th></th>
<th>Argentina % (N)</th>
<th>Brazil % (N)</th>
<th>Chile % (N)</th>
<th>Guatemala % (N)</th>
<th>Peru % (N)</th>
<th>CSA % (N)</th>
<th>NA % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell NHL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade</td>
<td>67.9* (110)</td>
<td>48.8† (81)</td>
<td>52.6 (90)</td>
<td>31.6*† (48)</td>
<td>29.4*† (37)</td>
<td>47.1† (366)</td>
<td>62.5 (223)</td>
</tr>
<tr>
<td>High-grade</td>
<td>32.1* (52)</td>
<td>51.2† (85)</td>
<td>47.4 (81)</td>
<td>68.4*† (104)</td>
<td>70.6*† (89)</td>
<td>52.9† (411)</td>
<td>37.5 (134)</td>
</tr>
<tr>
<td><strong>Follicular NHL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade</td>
<td>28.2* (46)</td>
<td>13.2† (23)</td>
<td>17.5 (30)</td>
<td>5.9*† (10)</td>
<td>5.3*† (7)</td>
<td>14.3† (116)</td>
<td>25.3 (91)</td>
</tr>
<tr>
<td>High-grade</td>
<td>10.4 (17)</td>
<td>8.6 (15)</td>
<td>11.1 (19)</td>
<td>5.9 (10)</td>
<td>9.0 (12)</td>
<td>9.0 (73)</td>
<td>12.0 (43)</td>
</tr>
</tbody>
</table>

NHL: non-Hodgkin lymphoma; CSA: Central and South America; NA: North America; * p<0.05 compared with the rest of CSA; † p<0.05 compared with NA.
Table 3: Sex distribution and median age (years) by country and region for non-Hodgkin lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>Argentina % (N)</th>
<th>Brazil % (N)</th>
<th>Chile % (N)</th>
<th>Guatemala % (N)</th>
<th>Peru % (N)</th>
<th>CSA % (N)</th>
<th>NA % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54.1 (87)</td>
<td>49.7 (93)</td>
<td>46.1 (89)</td>
<td>53.9 (104)</td>
<td>51.2 (84)</td>
<td>50.9 (457)</td>
<td>52.9 (210)</td>
</tr>
<tr>
<td>Female</td>
<td>45.9 (74)</td>
<td>50.3 (94)</td>
<td>53.9 (104)</td>
<td>46.1 (89)</td>
<td>48.8 (80)</td>
<td>49.1 (441)</td>
<td>47.1 (187)</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>57.0†</td>
<td>59.0†</td>
<td>64.0*</td>
<td>54.0*†</td>
<td>62.0</td>
<td>59.0†</td>
<td>66.0</td>
</tr>
<tr>
<td>Low-grade</td>
<td>57.0*†</td>
<td>59.0</td>
<td>64.0</td>
<td>63.0</td>
<td>60.0</td>
<td>60.0†</td>
<td>64.0</td>
</tr>
<tr>
<td>High-grade</td>
<td>57.0†</td>
<td>58.0†</td>
<td>62.0</td>
<td>53.0†</td>
<td>62.0</td>
<td>59.5†</td>
<td>68.5</td>
</tr>
<tr>
<td>T-cell NHL</td>
<td>51.0</td>
<td>51.0</td>
<td>47.5</td>
<td>41.0</td>
<td>41.0</td>
<td>46.0</td>
<td>43.5</td>
</tr>
<tr>
<td>Totals</td>
<td>57.0†</td>
<td>58.0</td>
<td>63.0*</td>
<td>53.0*†</td>
<td>59.0†</td>
<td>58.0†</td>
<td>65.0</td>
</tr>
</tbody>
</table>

NHL: non-Hodgkin lymphoma, CSA: Central and South America, NA: North America; * p<0.05 compared with the rest of CSA; † p<0.05 compared with NA
Table 4: Reported incidence rates of non-Hodgkin lymphoma, income per capita and life expectancy by country.

<table>
<thead>
<tr>
<th>Age standardized incidence rates (per 100,000)*</th>
<th>Argentina (Bahia Blanco)</th>
<th>Brazil (Sao Paulo)</th>
<th>Chile (Valdiva)</th>
<th>Guatemala</th>
<th>Peru (Trujillo)</th>
<th>USA</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>11.2/9.1</td>
<td>14.6/10.4</td>
<td>7.4/6.2</td>
<td>NA</td>
<td>14.4/9.0</td>
<td>22.4/15.3</td>
<td>20.9/1</td>
</tr>
<tr>
<td>Income per capita (in US dollars)†</td>
<td>8,450</td>
<td>9,390</td>
<td>9,940</td>
<td>2,740</td>
<td>4,710</td>
<td>47,140</td>
<td>41,95</td>
</tr>
<tr>
<td>Life expectancy (years)‡</td>
<td>77.1</td>
<td>72.8</td>
<td>78.1</td>
<td>71.2</td>
<td>72.7</td>
<td>78.5</td>
<td>81.5</td>
</tr>
</tbody>
</table>

Classification of non-Hodgkin lymphoma in Central and South America: a review of 1028 cases

Javier A. Laurini, Anamarija M. Perry, Eugene Boilesen, Jacques Diebold, Kenneth A. MacLennan, H. Konrad Müller-Hermelink, Bharat N. Nathwani, James O. Armitage and Dennis D. Weisenburger