



Research Article

EPIDEMIOLOGICAL ANALYSIS OF LYMPHOMA SUBTYPES IN A REFERENCE CENTER IN JOÃO PESSOA, PARAÍBA, BRAZIL

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ABSTRACT

A gradual increase in diagnosed cases of lymphoma has led to greater dissemination of relevant information and has simultaneously revealed a need to improve understanding of the pathology. The prevalence of lymphomas involves many factors that vary regionally, with regional differences in prognosis indeed playing a role in therapeutic decisions. This observational study aimed to retrospectively evaluate the prevalence of lymphoma subtypes diagnosed between 2011 and 2015. Immunohistochemistry findings and associated prognostic variables were analyzed. The most noteworthy findings include the large number of young people diagnosed with aggressive disease, with poor prognostic indexes but low mortality rates, confirming the technical strength of the institution as reflected in the improved prognosis associated with the disease. The prevalence of Hodgkin lymphoma was found to be high, contradicting a considerable part of the international literature but in agreement with some studies conducted with pediatric populations in Brazil. In addition, the most prevalent subtypes of non-Hodgkin lymphoma, already well discussed in the international literature, were also represented in the present sample. All cases of lymphoma registered at this center were catalogued, with their prognoses and anatomopathological and immunohistochemical diagnoses being analyzed, consequently providing a better database for this geographical region of Brazil.

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INTRODUCTION

Lymphomas can be defined as a neoplastic transformation of the normal lymphoid cells that reside predominantly in lymphoid tissues (Araújo *et al.* 2008). In 1994, the International Lymphoma Study Group drew up one of the first classifications of lymphoid tumors, referred to as the Revised European-American Classification of Lymphoid Neoplasms (REAL). This classification divides lymphomas into B-cell, T-cell and NK-cell neoplasms, i.e. non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (HL) (Nancy *et al.* 1994). The World Health Organization (WHO) classifies NHL in more than 20 subtypes with different clinical, morphological and immunogenetic features, reflecting the stage of maturation of the B- and T-lymphoid cells from which the neoplasm has originated. Nevertheless, to analyze the various subtypes over time, it is crucial to understand the effect of these complex malignancies on bone marrow, on the immune system and on

the cellular and genetic basis of the malignant transformation. Even now, rapid progress is being made in this area of oncology due to advances in genomics, in diagnostic techniques and in directed therapies, with the result that current definitions for lymphoma are continually subject to change (Smith *et al.* 2015).

Studies conducted both in North America and in Central and South America have shown that the incidence of NHL has been increasing over time, particularly in the elderly, with the incidence being higher in men and in white individuals (Müller *et al.* 2005; Chiu & Weisenburger 2003; Bassig *et al.* 2012; Clarke & Glaser 2002; Diumenjo *et al.* 2016; Excellence 2016). The subtypes that have increased most in frequency are diffuse large B-cell lymphoma, accounting for 30-40% of all cases of lymphoma (Chiu & Weisenburger 2003; Bassig *et al.* 2012; Clarke & Glaser 2002; Diumenjo *et al.* 2016; Excellence 2016), and immunoblastic lymphoma (Chiu & Weisenburger 2003), which, together with the other high-grade subtypes (poorly differentiated lymphocytic lymphoma, mantle cell

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lymphoma, peripheral T-cell lymphoma and anaplastic large cell lymphoma), is responsible for 50% of all cases of NHL (Araújo *et al.* 2008). In Brazil, the incidence of NHL in men can be as high as 9.1 cases per 100,000 inhabitants, with B-cell lymphomas being the most common subtype, accounting for 37% of NHL cases. Of these, diffuse large B-cell lymphomas are the most common (Diumenjo *et al.* 2016).

On the other hand, HL is a rare form of cancer, with an incidence rate in Canada of around 3 per 100,000 inhabitants. Although the outcome is often favorable, some patients fail to respond satisfactorily to standard treatment (Babashov *et al.* 2017). HL is much more common in children over ten years of age, and in those of 15-19 years of age its incidence is almost twice that of NHL (Ferreira *et al.* 2012). In Brazil, the incidence rate adjusted for age ≤ 19 years is 9.8 per million inhabitants. However, for the 15-19 year age group, the incidence rate increases to 18.5/million inhabitants (Ferreira *et al.* 2012). Cases of HL can be classified into two major groups: classic HL and nodular lymphocyte-predominant HL. Classic HL can be further subdivided into nodular sclerosis HL, mixed cellularity HL, lymphocyte-rich HL and lymphocyte-depleted HL. Of these, the most prevalent types in Brazil are nodular sclerosis HL and mixed cellularity HL, comprising 31% and 13%, respectively, of all cases of HL diagnosed in the country (Ferreira *et al.* 2012).

Therefore, HL are more specific and represent a very important group, accounting for up to 30% of all lymphomas diagnosed in Brazil (Gualco *et al.* 2010). A more accurate catalogue of this large specific group should be produced, identifying its local prevalence through a significant population-based study, particularly because a considerable number of cases of Hodgkin disease and many of the deaths resulting from this disease occur in countries at the lower end of the socioeconomic spectrum such as Brazil (Kusminsky *et al.* 2016).

Both diffuse large B-cell lymphomas, the most prevalent subtype of NHL, and HL are considered curable when early treatment, including chemotherapy, immunotherapy and radiation, is implemented (Sussman *et al.* 2016). Nevertheless, in view of the speed at which new scientific evidence is becoming available, together with the increased need for laboratory tests to enable a precise diagnosis to be reached, it becomes obvious that there is a scarcity of reliable, comprehensive, population based data on the underlying incidence and survival rates of the clinically significant subtypes of lymphoma, particularly with respect to Hodgkin disease.

Therefore, the need for reliable population-based data is not only to be able to identify the most prevalent subtypes of lymphoma, but also to define etiological hypotheses, to plan future healthcare services and to monitor the impact of alterations in treatment. This is particularly relevant in the field of hematological oncology in which treatment protocols are subject to rapid changes and the inclusion criteria for controlled and randomized studies require very specific subgroups of patients. Indeed, young patients with few comorbidities and few alterations are not uncommon (Smith *et al.* 2015).

The situation is much the same in northeastern Brazil and specifically in the state of Paraíba, which is characterized by poor life expectancy and peculiarities insofar as the

professional activities (contact with farming and cattle raising and excessive sun exposure) and education level of the population are concerned. Regarding socioeconomic conditions, which are also precarious for a considerable proportion of the population in this region, it is well known that the prognosis of those patients with better economic conditions is almost twice as likely to be good compared to those less privileged (Noor *et al.* 2013). Similar findings have been reported in the United Kingdom and in the United States, where 5-year survival rates are around 6% higher in those with better socioeconomic conditions (Excellence 2016). This may be due to the lesser ability of resource-poor patients to understand their comorbidities as a result of inequalities in education, for example, in addition to poorer access to different exams and treatments.

Other risk factors may also be associated with the presence of lymphomas in specific populations, including contact with solvents and pesticides in farming, greater exposure to ultraviolet radiation, a diet rich in saturated animal fats and the presence of certain pathologies that are locally more prevalent and are associated with both the development and the prognosis of lymphomas. The latter may be responsible for the higher incidence of cases in the young population despite the fact that advanced age has been identified as an important risk factor (Bassig *et al.* 2012; Noor *et al.* 2013; Orsi *et al.* 2009; Svec *et al.* 2005).

Recording the incidence of lymphoma subtypes adequately is associated with providing the best treatment choices for the various subtypes, ranging from a long period of expectant management to multiple sessions of chemotherapy. Since the lack of an adequate theoretical basis may also affect patients' survival, the need to conduct a better survey of the incidence of the principal subtypes of lymphoma, both Hodgkin and non-Hodgkin lymphomas, in northeastern Brazil is clear. The relationship between the epidemiology of the different subtypes and patients' prognosis needs to be analyzed, taking the peculiarities of this region into consideration.

The objective of the present study was to establish the prevalence of the principal subtypes of NHL and HL in a large oncological facility in the state of Paraíba, Brazil, with the aim of improving understanding of the demographic profile of the local population affected by the disease and to determine whether this profile alters the prognostic indexes for patients with lymphoma.

MATERIALS AND METHODS

This was a cross-sectional, descriptive prevalence study conducted within the referral facility for this micro-region, the Napoleão Laureano Hospital in the city of João Pessoa, Paraíba, Brazil. The study was conducted with the support of the Federal University of Paraíba Medical Sciences Center.

The sample population consisted of patients diagnosed with different subtypes of non-Hodgkin or Hodgkin lymphoma between January 2011 and December 2015, whether still alive or deceased. All the patients registered at the facility with an immunohistochemical diagnosis of one of the several subtypes of lymphoma were included. Those without immunohistochemical confirmation were excluded from the study. Therefore, this was a non-probabilistic convenience sample.

A digital form was used to record the data collected and to calculate the international prognostic index (IPI) (Shipp 1993). The exceptions were with regard to follicular lymphomas, mantle cell lymphomas and diffuse large B-cell NHL for which, respectively, the follicular lymphoma IPI (FLIPI) (Solal-céligny *et al.* 2011), the mantle cell lymphoma IPI for advanced stages (MIPI) (Hoster *et al.* 2012) and the National Comprehensive Cancer Network IPI (NCCN-IPI) (Zhou *et al.* 2015) for patients with diffuse large B-cell NHL treated with rituximab were used. In the case of patients over 60 years of age, the IPI was age-adjusted, as proposed in the International Non-Hodgkin's Lymphoma Prognostic Factors Project (Shipp 1993).

The selected patients with a positive immunohistochemical diagnosis were classified according to the latest classification proposed by the WHO for lymphoma subtypes (Swerdlow *et al.* 2016). Next, the patients' records were evaluated with respect to prognosis by calculating their IPI and Ann Arbor staging. Only high-grade lymphomas were included in the IPI calculation, with cases unclassifiable by immunohistochemistry (n=2) or with insufficient data in their records (n=2) being excluded. Patients with indolent subtypes were also excluded from the IPI calculation: small lymphocytic lymphoma (n=5), extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) (n=1), and primary cutaneous follicle center lymphoma (n=1). Data collection was performed using a Microsoft Excel 2010® spreadsheet and the descriptive statistical analysis was carried out using the R statistical computing system. The Kaplan-Meier nonparametric survival analysis was used to calculate the mean time until death in patients with different lymphoma subtypes. This study was conducted in compliance with Resolution 466/12 of the Brazilian National Health Council. The internal review board of the Lauro Wanderley Teaching Hospital approved the study protocol under reference CAAE 46337215.1.0000.5183.

RESULTS

Analysis was conducted on 125 cases selected from the records at the hematological oncology facility of the Napoleão Laureano Hospital. Cases had been diagnosed at physical examination and confirmed by anatomopathology and immunohistochemistry between January 2011 and December 2015. Of the different subtypes of lymphoma, 91 (72.8%) consisted of NHL and 34 (27.2%) of HL.

Table 1 shows the distribution of lymphoma cases according to age at diagnosis and the 2016 WHO classification. Overall, there were 78 males (62.4%) and 47 females (37.6%). With respect to age, 32 (25.6%) were > 60 years of age and 93 (74.4%) were < 60 years of age. The youngest of these patients was 4 years old and the oldest 85 years old, with a mean age of 45 years and a median of 44 years.

Most patients were < 60 years of age in both the NHL (69.23%; PR=1.20) and the HL (88.23%; PR=2.58) groups. Similarly, males were predominant in both groups, with 58 male patients having NHL (63.73%; PR=1.52) and 20 HL (58.82%; PR=0.86). Overall, 14 cases were diagnosed as Ann Arbor stage I, 30 as stage II, 39 as stage III and 42 as stage IV. The prevalence ratio for Ann Arbor stages III or IV (64.8%) among cases of NHL was 1.16 compared to 0.69 among the cases of HL. Graphic 1 describes the distribution of cases of lymphoma according to their subtype and Ann Arbor stage.

Fourteen deaths occurred: seven men (50%; PR=0.60) and seven women (50%; PR=1.66). Ten were < 60 years of age (71.41%; PR=0.86). Only one had a diagnosis of nodular sclerosis HL, while 13 had a diagnosis of one of the subtypes of NHL (92.85%; PR=4.85). Overall, these cases consisted of 11 B-cell lymphomas (78.57%; PR=0.39) and 3 T-cell lymphomas (21.43%; PR=2.57). There were 12 cases of Ann Arbor stage III or IV (85.71%; PR=3.74) and only 2 cases of Ann Arbor stage I or II (14.29%; PR=0.26).

Table 1 Distribution of the subtypes of lymphoma according to the World Health Organization classification in a population sample at the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil, 2011-2015 (n=125 patients).

	n (%)	Males (%)	Females (%)	% between cases of NHL/HL	<60 years (%)	Mean age at diagnosis (range)
All lymphomas	125 (100)	78 (62.4)	47 (37.60)	N/A	93 (74.4)	45 (4-85)
Diffuse large B-cell lymphoma	44 (35.20)	25 (56.81)	19 (43.19)	48.35	30 (68.18)	48 (20-87)
Hodgkin lymphomas	34 (27.20)	20 (58.82)	14 (41.18)	100	30 (88.23)	35 (17-85)
Classic nodular sclerosis HL	28 (22.40)	15 (53.57)	13 (46.43)	82.35	26 (92.85)	33 (17-79)
Classic mixed cellularity HL	5 (4.00)	4 (80)	1 (20)	14.70	3 (60)	52 (34-85)
Nodular lymphocyte-rich HL	1 (0.8)	1 (100)	0 (0)	2.95	1 (100)	20 (N/A)
Follicular lymphoma	7 (5.60)	5 (71.42)	2 (28.58)	7.70	4 (57.14)	57 (31-73)
Mantle cell lymphoma	6 (4.80)	4 (66.66)	2 (33.33)	6.59	2 (33.33)	62 (45-76)
Peripheral T-cell lymphoma with no other specifications	6 (4.80)	3 (50)	3 (50)	6.59	3 (50)	53 (18-71)
Small lymphocytic lymphoma	5 (4.00)	1 (20)	4 (80)	5.49	3 (50)	54 (36-80)
Burkitt lymphoma	5 (4.00)	3 (60)	2 (40)	5.49	5 (100)	18 (4-29)
Other B-cell lymphomas	12 (9.60)	9 (76.92)	3 (23.08)	13.20	10 (76.92)	55 (27-84)
Other T-cell lymphomas	6 (4.80)	6 (100)	0 (0)	6.59	6 (100)	31 (9-54)

NHL: Non-Hodgkin lymphoma; **HL:** Hodgkin lymphoma; **N/A:** not applicable.

Other B-cell lymphomas: T-cell/histiocyte-rich large B-cell lymphoma; nodal marginal zone lymphoma; B-cell lymphoma, unclassifiable; high-grade B-cell lymphoma; extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT); lymphoplasmacytic lymphoma; primary cutaneous follicle-center lymphoma.

Other T-cell lymphomas: T-cell lymphoblastic lymphoma; hepatosplenic T-cell lymphoma; extranodal NK/T-cell lymphoma, nasal type; ALK+ anaplastic large-cell lymphoma.

Table 2 Distribution of cases in relation to the international prognostic indexes in a population sample at the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil, 2011-2015 (n=125 patients).

	Alive (%)	Deceased (%)	Prevalence ratio (PR)
IPI (n= 23)	18 (78.26)	5 (21.74)	1.55
0-1 (low risk)	13 (72.23)	0 (0)	0
2 (low-intermediate risk)	2 (11.11)	3 (60)	5.4
3 (high-intermediate risk)	2 (11.11)	2 (40)	2.4
4-5 (high risk)	1 (5.55)	0 (0)	0
Age-adjusted IPI (<60 years; n= 20)	17 (85)	3 (15)	0.9
0 (low risk)	8 (47.06)	0 (0)	0
1 (low-intermediate risk)	5 (29.42)	0 (0)	0
2 (high-intermediate risk)	2 (11.76)	2 (66.66)	8
3 (high risk)	2 (11.76)	1 (33.33)	2.83
Age-adjusted IPI (≥60 years; n=3)	1 (33.33)	2 (66.66)	4.66
0 (low risk)	0 (0)	0 (0)	0
1 (low-intermediate risk)	0 (0)	1 (50)	2
2 (high-intermediate risk)	1 (100)	1 (50)	0.5
3 (high risk)	0 (0)	0 (0)	0
NCCN-IPI (n= 44)	38 (86.36)	6 (13.64)	0.7
0-1 (low risk)	15 (39.47)	0 (0)	0
2-3 (low-intermediate risk)	15 (39.47)	2 (33.33)	0.79
4-5 (high-intermediate risk)	8 (21.06)	3 (50)	3
6-8 (high risk)	0 (0)	1 (16.67)	8.6
MIPI (n= 6)	5 (83.33)	1 (16.66)	1.02
0-3 (low risk)	2 (40)	0 (0)	0
4-5 (intermediate risk)	0 (0)	1 (100)	5
6-11 (high risk)	3 (60)	0 (0)	0
FLIPI (n= 7)	6 (85.71)	1 (14.29)	0.87
0-1 (low risk)	1 (16.67)	0 (0)	0
2 (intermediate risk)	1 (16.67)	0 (0)	0
3-5 (high risk)	4 (66.66)	1 (100)	0

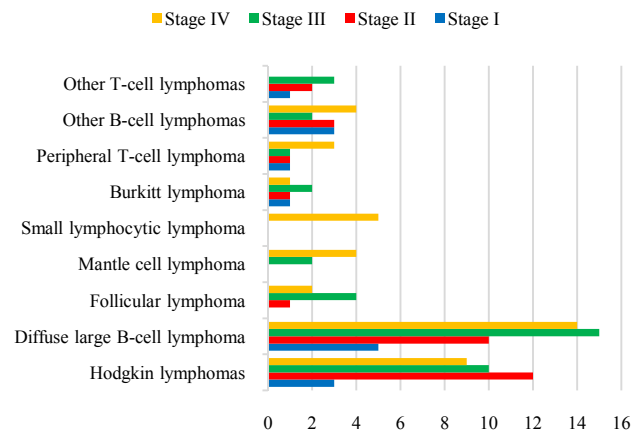
IPI: International Prognostic Index; **age adjusted IPI:** Age Adjusted International Prognostic Index; **NCCN-IPI:** National Comprehensive Cancer Network International Prognostic Index; **MIPI:** Mantle Cell Lymphoma International Prognostic Index; **FLIPI:** Follicular Lymphoma International Prognostic Index.

Of the subtypes of NHL (Graphic 2), diffuse large B-cell lymphoma was the most prevalent type, representing 44 of the 91 cases (48.35%). This was followed by the follicular subtype, with 7 cases (7.7%) and by the mantle cell subtype and peripheral T-cell subtype with no other specifications (n=6; 6.59% for each). Burkitt lymphoma was also one of the most prevalent subtypes, with 5 cases (5.2%). Similar prevalence was found for small lymphocytic lymphoma. Therefore, 113 cases of B-cell lymphoma were identified compared to only 12 cases of T-cell lymphoma (9.6%).

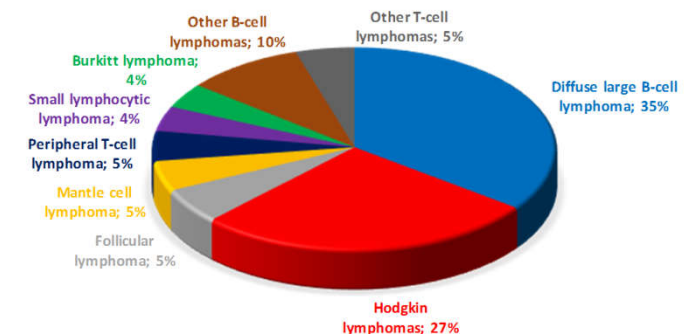
In relation to Hodgkin lymphoma, only three subtypes were catalogued: classic mixed cellularity HL (5 cases; 14.7%), nodular lymphocyte-predominant HL (1 case; 2.95%) and classic nodular sclerosis HL, which accounted for most of the cases (28 cases; 82.35%).

Six of the fourteen deaths were of patients with diffuse large B-cell NHL (PR=1.38; 42.85%), two classified as low-intermediate risk and 4 as high-intermediate risk (NCCN-IPI). Four of these patients (66.66%) were < 60 years of age. Five patients (35.71%) had one of the other subtypes of NHL whose prognostic indexes were calculated using the IPI, with one being classified as low-intermediate risk, three as high-

intermediate risk and one as high risk. Three of these patients (60%) were < 60 years of age. One case (7.15%) consisted of an indolent subtype (small lymphocytic lymphoma), Ann Arbor stage IV, while one (7.15%) consisted of a high-risk (FLIPI) follicular lymphoma, and one (7.15%) of a nodular sclerosis HL with Ann Arbor stage IV. Of the deaths resulting from NHL, 11 had been classified as Ann Arbor stage III or IV (78.57%; PR=3.13). Table 2 shows all the prognostic indexes calculated in this sample.



Graphic 1 Distribution of the subtypes of lymphoma according to Ann Arbor staging in the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil, 2011-2015 (n=125 patients).



Graphic 2 Prevalence of the subtypes of lymphoma in the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil, 2011-2015 (n=125 patients).

Of the deaths from diffuse large B-cell NHL, the mean time between diagnosis and death was 3 months and 16 days, whereas the mean time for the other subtypes with a prognostic index calculated using the IPI was 16 months and 11 days. According to the Kaplan-Meier survival, the mean time until death in patients with diffuse large B-cell NHL was found to be 41 months compared to a mean time until death of 61 months for the other subtypes, excluding the cases of follicular lymphoma (n=1) and classic nodular sclerosis HL (n=1). The overall survival in this sample was 81% at 16 months.

DISCUSSION

Epidemiological studies on lymphomas have been conducted around the world. However, with respect to developing countries with different socioeconomic, occupational, psychological, ethnic and even climatic conditions, prevalence and incidence rates, as well as the distribution of the subtypes, may vary, as can prognosis and survival (Noor *et al.* 2013; Excellence 2016; Anderson *et al.* 1998; Nair *et al.* 2016; Perry,

Diebold, *et al.* 2016; Perry, Perner, *et al.* 2016; Huh 2012; Skrabek *et al.* 2013).

The epidemiological profile of the current sample is in agreement with the existing literature regarding the greater prevalence of the subtypes of non-Hodgkin lymphoma and of male patients. Nevertheless, in this study, the prevalence of cases in patients under 60 years of age was much higher for the majority of the most prevalent subtypes of NHL. Although conflicting with some previous reports (Smith *et al.* 2015; Müller *et al.* 2005; Clarke & Glaser 2002; Diumenjo *et al.* 2016; Huh 2012; Combariza *et al.* 2015; Morton *et al.* 2006; Excellence 2016), these findings are in agreement with some major studies that have reported a greater incidence in individuals under 60 years of age in less developed countries of Central and South America, Africa and Asia (Nair *et al.* 2016; Perry, Diebold, *et al.* 2016; Perry, Perner, *et al.* 2016; Laurini *et al.* 2014; Mondal *et al.* 2013; Prakash *et al.* 2012; Mozaheb *et al.* 2011; Lee *et al.* 2005). In relation to Hodgkin lymphomas, a greater frequency of cases in individuals under 60 years of age was indeed expected, particularly for the classic mixed cellularity HL subtype that, according to the literature, tends to be more equally distributed among the different age groups at diagnosis (Smith *et al.* 2015; Ferreira *et al.* 2012; Kusminsky *et al.* 2016; Huh 2012; Combariza *et al.* 2015; Mozaheb *et al.* 2011; Swerdlow 2003). This was indeed the case, with 40% of cases occurring in individuals over 60 years of age compared to 7.15% for cases of the classic nodular sclerosis subtype.

As expected, the most prevalent subtypes were the diffuse large B-cell NHL (35.2% of all lymphomas and 48.35% of NHL) and the classic nodular sclerosis HL (22.4% of all lymphomas and 82.35% of HL) (Smith *et al.* 2015; Müller *et al.* 2005; Chiu & Weisenburger 2003; Ferreira *et al.* 2012; Kusminsky *et al.* 2016; Gualco *et al.* 2010; Anderson *et al.* 1998; Huh 2012; Combariza *et al.* 2015; Swerdlow 2003; Groves *et al.* 2000). However, cases of diffuse large B-cell NHL were not as predominant in some American studies, in which indolent lymphomas were catalogued as the most prevalent (Anderson *et al.* 1998; Morton *et al.* 2006). The percentage of cases of Hodgkin lymphoma in the present sample (22.4%) differs from rates reported in those studies, with rates reaching no higher than 15%, probably already reflecting the high incidence in younger patients (< 60 years of age) identified in the present study. Other expected findings were the prevalence rates of the subtypes already known to be more common such as follicular lymphomas, mantle cell lymphoma and peripheral T-cell lymphoma (Smith *et al.* 2015; Morton *et al.* 2006; Laurini *et al.* 2014; Mondal *et al.* 2013; Prakash *et al.* 2012; Lee *et al.* 2005; Groves *et al.* 2000). Some studies have already reported a similar prevalence of T-cell lymphomas (9.6%) in countries of Southeast Asia, South America, Europe and the United States, with a very similar distribution of subtypes to that found in the present study (Anderson *et al.* 1998; Combariza *et al.* 2015; Lee *et al.* 2005; Roman & Smith 2011; Shankland *et al.* 2012; Novelli *et al.* 2013; Gisselbrecht *et al.* 1998; Melnyk *et al.* 1997). Furthermore, some studies conducted in less developed nations of Africa and eastern Asia have shown a high prevalence of the small lymphocytic lymphoma/chronic lymphocytic leukemia subtype (Nair *et al.* 2016; Perry, Diebold, *et al.* 2016; Huh 2012), which was not the case in the present study,

possibly because cases of leukemia were clinically excluded from our calculations of prevalence to avoid any possible bias.

In relation to the prognosis of the patients at this hematology facility, death was more likely in those with non-Hodgkin lymphoma, T-cell lymphoma and Ann Arbor stage III or IV. Some studies have suggested that the T-cell or NK-cell immunophenotype could constitute an independent and significant factor associated with poor prognosis (Lee *et al.* 2005; Gisselbrecht *et al.* 1998; Melnyk *et al.* 1997). In addition, female patients (PR=1.66) and those over 60 years of age (PR=1.16) are also more likely to die, although in these cases this trend is less pronounced. A correlation was also found between a greater likelihood of death in patients with a diagnosis of one of the subtypes for which the IPI was used to estimate prognosis (PR=1.55), particularly in patients over 60 years of age (PR=4.66). Here, it is interesting to note that in the groups with the highest percentages in the sample (NCCN-IPI and IPI adjusted for age <60 years), even when the likelihood of death at diagnosis was small, there is a sudden increase in the prevalence ratio of deaths if risk is classified as high-intermediate (PR=3 and 8, respectively) or high (PR = 8.6 and 2.83, respectively), reflecting the importance of early diagnosis in these aggressive subtypes. Taking the prognostic indexes calculated for the patients during these five years into consideration, it is evident that, fortunately, the great majority is being diagnosed when their risk of death is still low, indicating, theoretically, that access to specialist healthcare services is satisfactory and provision of information on the disease has improved. Paradoxically, the large prevalence of NHL at Ann Arbor stage III or IV points to late-stage diagnosis. This unexpected association between poor prognostic indexes and low mortality rates could be explained by the composition of the sample that includes younger individuals. Indeed, prognosis is considered better in younger individuals even when they are diagnosed at advanced stages of the disease, consequently decreasing the likelihood of death in this group (PR = 0.9 versus PR = 4.66 for those over 60 years of age in age-adjusted IPI). On the other hand, even with a better prognosis at diagnosis, diffuse large B-cell NHL alone represented 42.85% of deaths in this sample (PR = 1.38).

The survival rates in this study sample could not be calculated over a longer follow-up time due to the few deaths recorded (n=14) over the five years analyzed. Nevertheless, of these deaths, mean survival was 44 months for the cases of diffuse large B-cell NHL, all of which were treated with rituximab, compared to 61 months for the other subtypes, reflecting the severity of the cases of lymphoma treated at this facility, with patients probably neglecting to seek medical help as a result of their poor education level and lack of social guidance. Despite the high possibility of cure when identified at an early stage, mortality is known to be greater with diffuse large B-cell NHL than with the other subtypes, even following the introduction of rituximab. Whereas the relative 5-year survival rate for NHL is 55% in the United States and 49% in Europe, rates for diffuse large B-cell NHL are around 45% (Sant *et al.* 2001; Swerdlow 2003; Smith *et al.* 2015). Nevertheless, the mortality rate from diffuse large B-cell NHL (13.95%) was similar to the rate for NHL in general and to the mortality rate for the other subtypes of NHL (13.2%).

The relative 5-year survival rate for Hodgkin lymphoma has been reported to be around 80%, supporting the finding of only one death in the present study and highlighting the very low

mortality rate (2.94%) associated with HL subtypes (Smith *et al.* 2015; Kusminsky *et al.* 2016; Combariza *et al.* 2015; Lee *et al.* 2005). This contrasts with NHL, for which the mortality rate in the present sample was 13.54%. This difference in aggressiveness is also obvious when the Ann Arbor stages at diagnosis are analyzed. Of the cases of HL, the prevalence ratio for stage III or IV was only 0.69.

CONCLUSION

The higher incidence of patients under 60 years of age with a diagnosis of lymphoma, both Hodgkin and non-Hodgkin lymphomas, in the population of Paraíba may reflect the greater exposure of the local population to risk factors such as greater contact with animal farming and agriculture, greater exposure to ultraviolet radiation and diets rich in saturated animal fats, characteristics of the region that may have accelerated the disease process. Case-control studies to be conducted in the region may investigate these factors further. This also affects the prognosis of cases identified in Paraíba where, despite diagnosis at an advanced stage, as in most economically and socially deprived regions of the world, mortality rates were found to be low.

Although diffuse large B-cell NHL mortality rates were comparable to those of the other subtypes of NHL, the diffuse large B-cell subtype is by nature aggressive, leading to death in a shorter treatment time and with lower survival estimates, even when patients are treated with rituximab.

The high prevalence ratio of higher Ann Arbor stages at diagnosis of NHL may be due to patients ignoring the characteristic symptoms of the disease, a fact that could be related to the socioeconomic and educational characteristics of the region. Further investigation is required to confirm this hypothesis. All cases of lymphoma registered at the Napoleão Laureano Hospital in Paraíba were catalogued, with their prognoses and anatomopathological and immunohistochemical diagnoses being analyzed, consequently providing a better database for this geographical region of Brazil. Some peculiarities of the region that could have affected the epidemiology and prognosis of lymphomas in the local population were identified.

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