

Disease patterns of pediatric non-Hodgkin lymphoma: A study from a developing area in Egypt

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Abstract. Non-Hodgkin lymphoma (NHL) accounts for 8-10% of all childhood cancers. NHL collectively represents various lymphoid malignancies with diverse clinicopathological and biological characteristics. In this study, we aimed to describe the epidemiological and clinicopathological characteristics and treatment outcomes of pediatric NHL patients treated at the Pediatric Oncology Unit of Zagazig University Hospital and the Benha Specialized Pediatric Hospital. We conducted a cross-sectional retrospective study by reviewing the medical records of 142 patients admitted with a diagnosis of NHL over a period of 8 years (February, 2004 to February, 2012) in these two Oncology Units. The age at presentation ranged between 2 and 15 years, with a mean $\pm$ standard deviation (SD) of 6.1 ± 2.8 years and a male:female ratio of 1.7:1. Abdominal involvement was the most common presentation (73.2%). Burkitt's lymphoma (BL) was the most common NHL subtype (69%), followed by lymphoblastic lymphoma, diffuse large B-cell lymphoma and anaplastic large-cell lymphoma, accounting for 18.3, 10.6 and 2.1% of the cases, respectively. The majority of the patients (88.7%) had been diagnosed with advanced disease (Murphy stage III/IV). Complete remission was achieved in 120 cases (84.5%). A total of 16 patients (11.3%) succumbed to the disease during the first few months and 6 patients (4.2%) remained alive following relapse. The mean follow-up duration $\pm$ SD was 34.6 ± 25.1 months (range, 3-84 months). The 5-year overall survival (OS) and event-free survival (EFS) rates were 88.7 and 85.1%, respectively. None of the clinical, epidemiological or pathological variables exhibited a statistically significant association with the OS or EFS. In conclusion, NHL occurs at a younger age, with a higher incidence of BL and advanced-stage disease.

The outcome of NHL in our two centers was satisfactory, approaching the international rates.

Introduction

Non-Hodgkin lymphoma (NHL) accounts for 8-10% of all childhood malignancies (1). NHL is a heterogeneous group of diseases, as malignant clonal proliferation may occur at any stage during lymphocyte proliferation. Four NHL subtypes comprise 90% of the NHL cases in children, namely Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (precursor T- and precursor B-cell lymphoma) and anaplastic large-cell lymphoma (ALCL) (2-5). The remaining 10% include marginal zone, cutaneous, follicular and peripheral T-cell lymphomas, which are the NHL subtypes common in the adult population (6-8). There has been a significant improvement in the overall survival (OS) of children and adolescents with NHL. The reported disease-free survival for pediatric NHL, independent of subtype, is currently $\sim 80\%$ (3). The most significant prognostic determinants are type of treatment and the extent of the disease, as determined by pretreatment staging (9,10). There is geographic variation in the incidence of NHL, particularly regarding BL, which is endemic in Equatorial Africa and accounts for 50% of all childhood cancers, affecting 50 children per million diagnoses (11). However, in other areas of the world, BL occurs sporadically and is less common, affecting ~ 2 per million children (1). Depending on the geographic region investigated, there are major differences in terms of the clinical and epidemiological characteristics of NHLs diagnosed during childhood (1,12). The scarcity of data available in the literature on the behavior of NHL among children in our region prompted us to conduct this study, with the aim of describing the clinical and epidemiological characteristics of NHL patients, assessing their survival and identifying possible prognostic associations with the variables under analysis.

Patients and methods

Patients and inclusion criteria. We retrospectively reviewed the records of children and adolescents with NHL treated consecutively between February, 2004 and February, 2012 at

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the Pediatric Oncology Unit of Zagazig University Hospital and the Benha Specialized Pediatric Hospital. The study was approved by the Research and Ethics Committees of the contributing hospitals. Patient records from the Pediatric Oncology Department containing oncological details on diagnosis, treatment course and follow-up were analyzed for this study. The inclusion criteria were as follows: i) children and adolescents aged ≤ 18 years with pathologically confirmed NHL; ii) the diagnosis of NHL was established in all the cases by pathology in conjunction with immunophenotype studies and subclassified according to World Health Organization (WHO) criteria (13); and iii) all the anticancer treatments and follow-up examinations were completed at the abovementioned two centers. Disease staging was performed according to the St. Jude staging system (14).

Diagnosis and staging. Diagnostic investigations included biopsy of a clinically involved lymph node or mass, computed tomography (CT) scan of the chest, abdominopelvic ultrasonography and CT scan, bone marrow aspirates and biopsies and bone scintigraphy in selected cases. Diagnosis, staging and treatment planning for all the patients were performed by the center's multidisciplinary Pediatric Oncology Group. Laboratory tests included a complete blood count, liver and renal function tests, serum electrolyte, uric acid and lactate dehydrogenase levels and cerebrospinal fluid analysis. The clinical and laboratory findings evaluated for prognostic significance on event-free survival (EFS) and OS were age, gender, stage (I/II vs. III/IV) and pathology.

Treatment protocols. The therapeutic regimen was prescribed depending on histological type and immunophenotype of the lymphoma. BL and large B-cell lymphomas were treated with a chemotherapy protocol based on LMB-96. A therapeutic protocol based on modified CCG-1991 and CCG-1961 high-risk protocols was used for lymphoblastic lymphoma. A therapeutic protocol based on BFM-NHL 90 was used for ALL. An ifosamide, caboblatin, etoposide (ICE) protocol was used for relapsed cases.

Statistical analysis. Data were statistically described as means $\pm$ standard deviation (SD) and range, or frequencies (number of cases) and percentages where appropriate. A survival analysis was performed for the different outcome measures using Kaplan-Meier statistics, calculating the mean and median survival time for each group with their 95% confidence intervals and corresponding survival graphs. $P < 0.05$ was considered to indicate a statistically significant difference. All the statistical calculations were performed using the Statistical Package for the Social Sciences software, version 15 (SPSS, Inc., Chicago, IL, USA) for Microsoft Windows.

Results

Patients. Between February, 2004 and February, 2012, 142 patients with NHL were admitted to our Pediatric Oncology Units. The age at presentation ranged between 2 and 15 years, with a mean $\pm$ SD of 6.1 ± 2.8 years. The majority of the cases (59.2%) of BL were diagnosed in children aged 2-5 years, followed by children aged 5-10 years (32.6%); only 8.2% of the

Table I. Clinical and demographic characteristics of patients.

Characteristics	Patient no. (%) (n=142)
Age (years)	
<5	58 (40.8)
5-10	65 (45.8)
>10	19 (13.4)
Gender	
Female	52 (36.6)
Male	90 (63.4)
Residence	
Rural	89 (62.7)
Urban	53 (37.3)
Consanguinity	
Positive	33 (23.2)
Negative	109 (76.8)
Histological type	
Burkitt's lymphoma	98 (69.0)
Lymphoblastic lymphoma	26 (18.3)
Large-cell lymphoma	15 (10.6)
Anaplastic large-cell lymphoma	3 (2.1)
Primary site	
Abdomen	104 (73.2)
Mediastinum	23 (16.2)
Peripheral lymph nodes	9 (6.4)
Other	6 (4.2)
Stage	
I	2 (1.4)
II	14 (9.9)
III	95 (66.9)
IV	31 (21.8)
LDH (IU/dl)	
≤ 500	41 (28.9)
> 500	101 (71.1)
Protocol	
LMB-96	113 (79.6)
CCG-1961	26 (18.3)
BFM-NHL 90	3 (2.1)
Outcome	
Alive in CR	120 (84.5)
Alive following relapse	6 (4.2)
Deceased	16 (11.3)

LDH, lactate dehydrogenase; CR, complete remission.

BL cases occurred in children aged > 10 years. The majority of the patients with lymphoblastic lymphoma (78.6%) were aged 5-10 years and only 14.2% were aged < 5 years. However, all the cases of large-cell lymphoma were diagnosed at an age of > 5 years, with 72.2% aged 5-10 and 27.7% > 10 years. The NHL patient population included 90 male and 52 female patients (male:female ratio, 1.7:1). A total of 89 patients resided

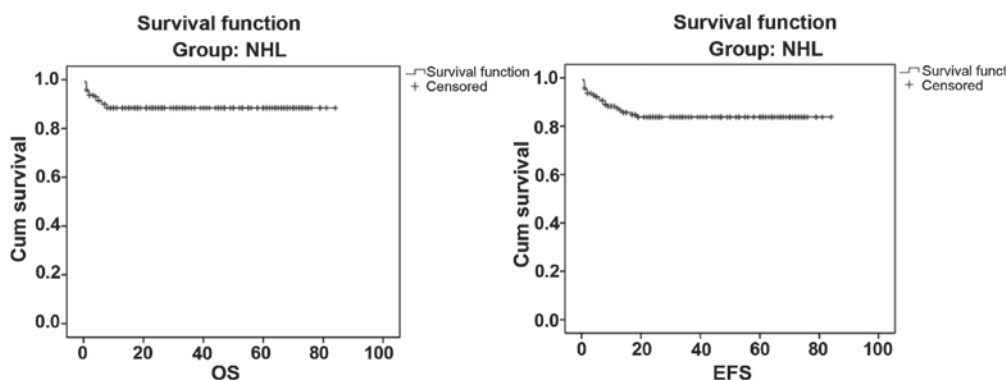


Figure 1. Five-year overall survival (OS) and event-free survival (EFS) of non-Hodgkin lymphoma (NHL).

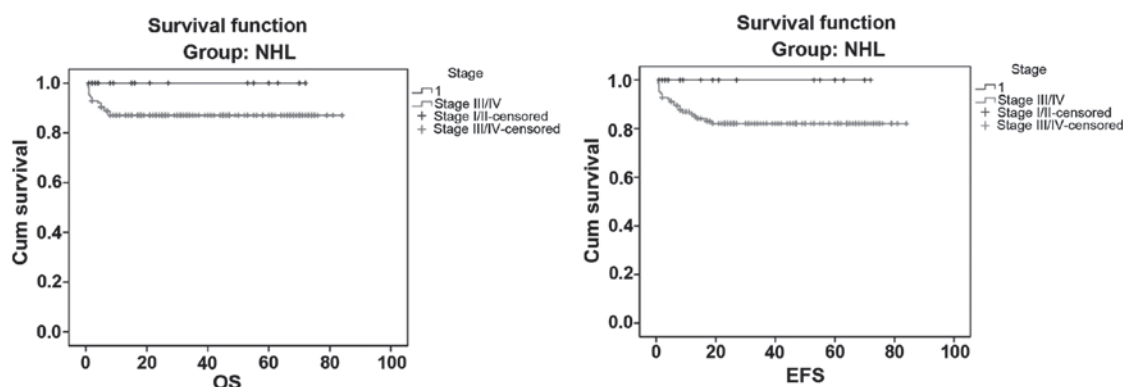


Figure 2. Five-year overall survival (OS) and event-free survival (EFS) according to stage. NHL, non-Hodgkin lymphoma.

Table II. Results of statistical tests for associations between overall survival and event-free survival and the study variables in non-Hodgkin lymphoma patients.

Variables	Overall survival		Event-free survival	
	Log-rank	P-value	Log-rank	P-value
Age	0.71	0.70	0.45	0.80
Gender	0.30	0.59	1.78	0.18
Pathology	2.43	0.49	3.02	0.39
Stage	1.94	0.16	2.50	0.11

in a rural and 53 in an urban area. A total of 33 patients (23.2%) were born to consanguineous parents (Table I).

Types of NHL. Based on the WHO 2008 classification for hematolymphoid neoplasms (13), NHL was classified into two main groups, namely precursor and mature B- and T-cell hematolymphoid neoplasms.

Mature-cell NHL corresponded to 116 (81.7%) of all NHL cases, including 113 (79.6%) B- and 3 (2.1%) T-cell lymphomas. BL included 98 cases (84.5% of all mature lymphomas and 86.7% of all mature B-cell lymphomas). BL is the most common NHL subtype, affecting 98 (69%) of all NHL patients, followed by lymphoblastic lymphoma with 26 (18.3%), DLBCL with 15 (10.6%) and ALCL with 3 (2.1%) patients (Table I).

Disease localization and staging. Primary abdominal tumors were the most common, affecting 104 (73.2%) of our patients and bone marrow infiltration was the most common site of metastasis, affecting 31 (21.8%) patients, followed by the central nervous system in 5 (3.5%) and bone infiltration in 2 (1.4%) patients.

Only 16 (11.3%) patients had localized disease (stage I/II) and 126 (88.7%) presented with advanced disease (stage III/IV). The majority of advanced-stage patients (95/126; 66.9%), had stage III lymphoma. LMB-96 was the most used protocol, as BL and large-cell lymphoma predominated in our patients, accounting for 113 (79.6%) of the cases (Table I).

Survival outcomes. The mean follow-up period $\pm$ SD was 34.64 ± 25.14 months (range, 3-84 months). A total of 126 patients achieved remission and 16 (11.3%) patients succumbed to the disease. Death was attributed to tumor lysis syndrome in 2 and infection in 14 patients. Of the patients who achieved remission, 6 (4.2%) developed a relapse, were treated and survived. The 5-year OS and EFS for all NHL cases were 88.7 and 85.1%, respectively (Fig. 1). The 5-year OS and EFS for stage I/II cases were both 100%, whereas for stage III/IV cases they were 87.3 and 83.2%, respectively (Fig. 2). There was no statistically significant difference in the OS and EFS rates between the four stages (log-rank test, $P > 0.5$; Table II). The 5-year OS and EFS for BL were 90.8 and 87.8%, respectively, whereas for lymphoblastic lymphoma they were 80.7 and 80%, respectively (Fig. 3). None of the clinical, epidemiological or pathological variables exhibited a statistically significant

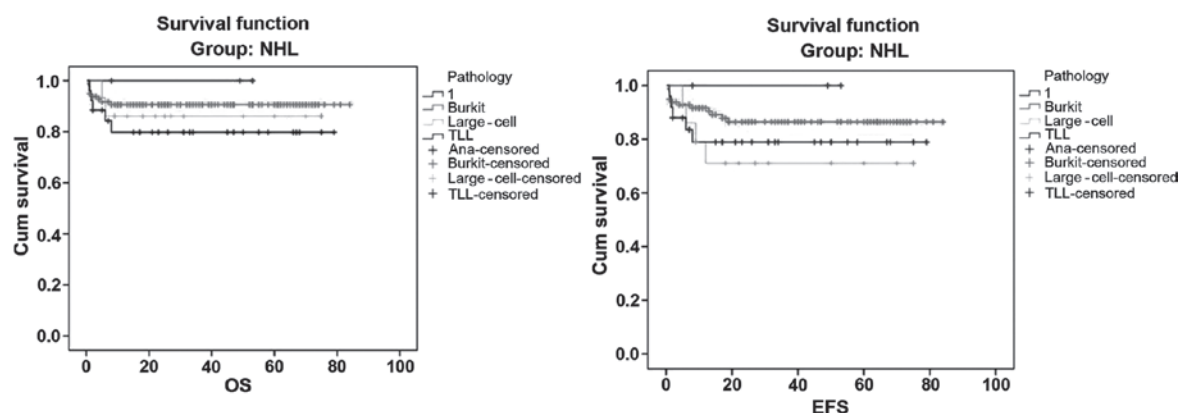


Figure 3. Five-year overall survival (OS) and event-free survival (EFS) of non-Hodgkin lymphoma (NHL) according to pathological subtypes. TLL, T-cell lymphoblastic lymphoma.

association with global survival or EFS, i.e., age, gender, stage and pathology were not significantly associated with patient outcome ($P>0.05$) (Table II).

Discussion

Lymphoma in children and adolescents comprises a heterogeneous group of malignant diseases of lymphoid tissues. The various lymphoma diagnoses present with distinctive biological and epidemiological characteristics. There are significant variations worldwide in the incidence of childhood malignancies, among which lymphomas are the dominant type (15). The present study describes the epidemiological and clinical characteristics of 142 Egyptian pediatric NHL patients admitted to two Pediatric Oncology Units. Patients aged <10 years constituted $>88.5\%$ of our study sample and there was a trend toward a decrease of the relative incidence with increasing age, with 88.5 and 11.5% for the age groups of 0-10 and >10 years, respectively, which was consistent with previously reported findings (16-18). Sandlund *et al* (1) and Manipadam *et al* (19) reported that the incidence of NHL increases uniformly with age and is rarely diagnosed before 2 years of age. The possibility of an infectious etiology, principally associated with Epstein-Barr virus (EBV) (12), being involved in the pathogenesis of NHL may be a partial explanation of the emergence of this disease in younger patients in our region, as populations of lower socioeconomic status are presumably exposed to infectious agents earlier in life. The incidence of childhood NHL was generally higher in male (63.4%) compared to female (36.6%) patients and this male predominance of childhood lymphoma mirrors the reported general pattern of male predominance exhibited by lymphoid malignancies, but not by all types of cancer (16,18). Although the majority of lymphomas in adults are of low or intermediate grade, $>90\%$ of childhood NHLs are of high grade and may be classified into one of four main categories (20).

BL was the most common NHL subtype (69%) in our series. Furthermore, BL accounted for 78.2, 77.2, 68, 48.2, 42.2 and 39% of the cases in studies conducted in Brazil, Kuwait, Saudi Arabia, Germany, UK and Egypt, respectively (16,21-25). By contrast, BL was encountered at a surprisingly low frequency (9-12%) in India, Pakistan and Shanghai (21,26).

There is evidence that the incidence of BL varies markedly worldwide, being particularly high in Equatorial Africa, which is likely due to early infection by EBV (almost all cases in Africa are EBV-related) and chronic exposure to malaria. As early exposure to EBV is associated with a lower socioeconomic status and BL is commonly associated with EBV worldwide, the variability in the incidence of BL is likely to be, at least in large part, a function of the epidemiology of EBV (27).

Our analysis revealed that the proportion of precursor T-cell lymphoblastic lymphoma (TLL) was 18.3% of all NHLs, which is lower among children in Egypt compared to other Asian countries. The proportion of T-cell NHL is significantly higher in the Korean pediatric and young adult population (28), Japan (29) and India (19,26), while the frequency of TLL was found to be low in Saudi Arabia (8%), Pakistan (8%) and nearly the same results were obtained from the UK (19%) and Germany (16.1%) (23,24).

Overall, DLBCL accounted for 10.6% of all pediatric NHLs. This finding was similar to that reported in the English literature. Burkhardt *et al* (24) found that DLBCL constituted 13% of pediatric NHLs. Wright *et al* (23) reported that B-cell NHLs other than lymphoblastic lymphoma and BL constituted 7.8% of the cases and comprised centroblastic lymphoma, high-grade B-cell NHL not otherwise specified, T-cell-rich B-cell lymphoma and primary mediastinal large B-cell lymphoma. The frequency of DLBCL was higher in Korea (28) and Japan (29). Pediatric DLBCL is considered to be biologically different from its adult counterpart and is associated with an excellent prognosis. In this study, ALCL was the fourth most common NHL subtype and constituted only 2.1% of all pediatric NHLs. In previous studies, ALCLs accounted for 15% of pediatric NHLs in the UK (23), 11.5% in India (19), 10.3% in Germany (24) and 20.5% in Korea (28). However, the possible reasons of geographic differences in the spectrum of lymphoma remain unknown, mainly due to the etiology of lymphoma being largely unknown, although certain risk factors were recently documented, including genetic factors, immune abnormalities, individual susceptibility, lifestyle, environmental exposures, as well as various infections caused by bacteria, viruses, mycoplasma and chlamydia (30). Epidemiologic studies suggested that

the distribution of lymphoma subtypes exhibits significant geographic variation (31). However, research regarding such information in Egypt is limited.

NHL in children is generally considered to be widely disseminated from the outset, even when apparently localized (32). In the present study, 88.7% of NHL patients had Murphy stage III/IV disease and only 11.3% had stage I/II disease; similar results were reported by several previous studies (1,14,29,33). The high prevalence rates of advanced tumor stage in our series was possibly associated with, among other factors, the large number of patients with voluminous abdominal lymphomas, late diagnosis and the predominance of primary mediastinal tumors within the lymphoblastic histological type, and with the low frequency of NHL with more superficial primary sites, such as tumors of the head neck and primary nodal disease, making it difficult to detect the disease at an earlier stage.

Tumors in pediatric NHL cases are frequently found extranodally and are difficult to diagnose, clinically as well as histopathologically (14,34,35). In our analysis of 142 patients with NHL, abdominal involvement was the most common presentation (73.2%), followed by mediastinal involvement, while bone marrow infiltration was the most common site of metastasis; similar results was reported by many authors (21,36). In Turkey, abdominal involvement was the most common presentation (>75%), followed by the jaw and the central nervous system (21). As regards identifying prognostic factors, no statistically significant associations were observed between age, gender, histopathology and staging and either OS or EFS in our study. The 5-year OS and EFS in the present study were 88.7 and 85.1%, respectively (Figs. 1 and 2). The survival of our patients is consistent with the results presented by the major collaborative childhood cancer treatment groups, reporting a survival rate of ~80-90% for patients with NHL (37-41).

In conclusion, NHL occurs at younger age among pediatric patients in Egypt, with a higher incidence of BL and advanced-stage disease. The outcome of NHL in our two centers was satisfactory, approaching the international rates.

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