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**Abstract**

**Purpose:** This study aimed at describing prognosis of pediatric B-NHL patients treated with FAB LMB-96 based protocol without dose modification, and to identify possible prognostic factors influencing the outcome and the treatment related toxicities.

**Methodology:** Through a retrospective study design, the researchers traced 48 pediatric cases who had been diagnosed with Mature B-NHL and treated at Prince Nora Oncology Center (PNOC) in the period from January 2007 to December 2016. Data were retrieved from the medical records, radiology images and pathology specimen for cases who met the inclusion criteria. For operational definition, cases were defined according to WHO classification, while staging was performed according to Murphy's classification. Kaplan Meier survival function analysis was used to determine overall survival and Event Free Survival; and Chi Square test was used to verify significance in the differences according to characteristics of the cases.

**Findings:** Out of all cases (n=48), Saudis formed (85.4%) and male to female ratio was 2.4:1, with a median age at diagnosis of 5.6 years. Most of the cases were diagnosed as Burkitt's lymphoma (87.5%), mainly in stage III (37.5%) and stage IV (39.6%), chiefly as primary abdominal retro-peritoneal tumors (47.9%). Almost all cases (97.9%) developed chemotherapy related hematologic toxicity and fever neutropenia, and one third (34.8%) had septic shock. At the end of follow-up (median=112 months), there were 40 patients (83.3%) achieved remission, out of them, 6 (12.5%) relapsed. Death was attributed to disease recurrence (3 cases) and treatment related toxicities (4 patients). No statistically significant difference detected in the overall and Event Free survival rates according to their age, gender, histology, biochemical markers, disease locations, staging and FAB group classifications (P >0.05).

**Conclusion and recommendations:** Childhood non-Hodgkin lymphomas are almost all high grade and frequently extranodal. They fall mainly into the categories Burkitt lymphoma, lymphoblastic lymphoma and anaplastic large cell lymphoma. Our findings are comparable with those reported in other international trials.

**Keywords***: Survival, Pediatric, Lymphomas, Non Hodgkin lymphoma.*

## 1. Introduction.

According to Saudi Cancer Registry, non-Hodgkin's lymphoma (NHL) has been reported to be the third most common malignancy among children younger than 14 years in the Kingdom of Saudi Arabia (KSA) (Saudi Health Council, 2015). Mature B-cell non-Hodgkin lymphomas (B-NHL) account for more than one half of the NHL occurring in children, adolescents, and young adults (CAYA) (Hochberg et al., 2009). Burkitt lymphoma (BL) is the most common, representing approximately 40% of NHL in CAYA throughout the world, and diffuse large B-cell lymphoma (DLBCL) accounts for nearly 20% (Gurney JC, Smith MA, Bunin GR, 1999; Sandlund et al., 1996; Swerdlow et al., 2017).

In pediatrics, Burkitt, Burkitt-like lymphoma/leukemia and DLBCL are treated using the same protocols. The French Society of Pediatric Oncology and French-American-British (FAB) studies have treated completely resected stage I and abdominal stage II (group A) patients with two cycles of multiagent chemotherapy, without intrathecal chemotherapy (COG-C5961 [FAB/LMB-96]) and recommended follow up for an average of 50.5 months, the 4 year event-free survival is 98.3% and overall survival is 99.2% (Gerrard et al., 2008). For unresected stage I through IV disease (group B), the 3-year EFS was 90% for stage III and 86% for stage IV (CNS-negative) patients (Patte et al., 2007). Group C, patients with leukemic disease, and no CNS disease, had a 3-year EFS of 90%, while patients with CNS disease at presentation had a 70% 3-year EFS. Patients who were CNS-positive but marrow-negative did better, with an EFS of 82%, while those with combined marrow and CNS disease at diagnosis had an EFS of only 61% (Cairo et al., 2007).

The excellent outcome rates of mature B-NHL in the developed countries (approaching 90s %), is higher than those seen in developing countries. The low survival rate in such countries could be related to many factors, but mostly related to treatment related toxicities and mortalities which frequently necessitated treatment modification or interruption to overcome the encountered challenges (Sandlund & Martin, 2016). Nevertheless, in resource rich developing countries like KSA, where income may be high but the healthcare and demographic changes are more redolent of low-middle-income countries (LMIC), create a challenge situation. Unfortunately, a considerable proportion of pediatric patients come from low socio-economic background; they presented at advanced stage due to limited financial resources and this delay could affect their clinical outcome (Mobark et al., 2015).

Scarce data is available in literature to describe the behavior of B-NHL among pediatric age group in our region. This study looked into outcomes of pediatric B-NHL patients using international protocol (FAB LMB 96).The researchers aimed at describing the clinical and epidemiological characteristics of this cohort of patients, in addition to identify the possible prognostic factors that influenced the outcome.

## 2. Subjects and Methods:

This is a retrospective study included 48 consecutive pediatric patients, aged 14 years and below, newly diagnosed with Mature B-NHL treated at Prince Nora Oncology Center (PNOC), King Abdulaziz Medical City (KAMC), Jeddah, KSA, between January 2007 and December 2016. The study was approved by King Abdullah International Medical

Research Center (KAIMRC) and hospital Ethics Review Committee. (KAIMRC ref. no. RJ17/091/J). The researchers, retrospectively, reviewed the medical records, radiology images & pathology specimen of the cases. The collected information included: age at diagnosis, gender, clinical presentation, tumor location, disease characteristics that included pathological subtypes. In Princess Norah Oncology Center (PNOC), KSA, we treated patients on FAB LMB-96 based protocol without dose modification. Treatment plan, treatment toxicity and outcome of treatment including relapse, death from all causes and occurrence of second malignancies were also recorded.

Primary objectives include, Overall Survival (OS), Event Free Survival (EFS). Secondary objectives include the association of clinical factors such as disease location, histology, stage, tumor burden & response to initial chemotherapy on the final outcomes and determine significant treatment related toxicities.

Diagnosis was based according to the WHO classification and included Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), Diffuse large B cell lymphoma (DLBCL) (Swerdlow et al., 2017). Staging was performed according to Murphy's classification (Swerdlow et al., 2017).

Patients with previous chemotherapy, congenital or acquired immunodeficiency, prior organ transplantation, secondary malignancies, or known HIV positivity were excluded.

*Statistical Methods***:** Using SPSS ver21, Kaplan Meier survival function analysis was used to determine overall survival as well as Event Free Survival; and Chi Square test was used to verify significance in the differences of mortalities and EFS of the patients according to their characteristics. P value <0.05 was considered an indication for significance.

**3. Results:**

*Characteristics of the cases*: The majority of the patients were Saudis (85.4%) and male to female ratio was 2.4:1. Almost one third of the cases (35.4%) were diagnosed before reaching their 5th birthday, while one half (50%) were diagnosed between 5-10 years old. Median age at diagnosis was 5.6 years ranging between 1.2 and 13.8 years.

*Histopathology types*: Most of the cases were diagnosed as Burkitt's lymphoma (87.5%), while (10.4%) as DLBCL and one case (2.1%) was classified as high grade B cell Burkitt like pathology.

*Diseases site, staging and stratification:* According to *"Murphy" staging classification*: 11 cases (22.9%) were in stage II, 18 (37.5%) in stage III and 19 (39.6%) in stage IV. According to FAB risk classification: 2 patients (4.2%) were classified as Group A, 27 (56.3%) as Group B and 19 (39.6%) as Group C. Almost two thirds of the cases (69.7%) had Ki67 level >95% and slightly more than one third (38.6%) had LDH ≥1000. **[Table1]** Primary abdominal retro-peritoneal tumors were the most common, affecting 23 patients (47.9%) followed by head and neck 19 patients (39.5%) and bone marrow infiltration was the most common site of metastasis by 5 patients (10.4%).

**Table 1: Characteristics of the cases (n=48).**

| Characteristics | No. | Percentage |
|---|---|---|
| *Nationality:* | | |
| *Saudi* | 41 | 85.4 |
| *Non Saudi* | 7 | 14.6 |
| *Gender:* | | |
| Males | 34 | 70.8 |
| Females | 14 | 29.2 |
| *Age at diagnosis:* | | |
| <5 years | 17 | 35.4 |
| 5-10 years | 24 | 50.0 |
| >10 years | 7 | 14.6 |
| *Histopathology:* | | |
| Burkitt's | 42 | 87.5 |
| DLBCL | 5 | 10.4 |
| High grade B cell Burkitt like | 1 | 2.1 |
| *Diagnosis specimen:* | | |
| Tissue biopsy | 40 | 83.3 |
| Body fluid | 2 | 4.2 |
| BM | 6 | 12.5 |
| *Stage:* | | |
| II | 11 | 22.9 |
| III | 18 | 37.5 |
| IV | 19 | 39.6 |
| *Group:* | | |
| A | 2 | 4.2 |
| B | 27 | 56.3 |
| C | 19 | 39.6 |
| *Ki67 level (n=33):* | | |
| ≤95% | 10 | 30.3 |
| >95% | 23 | 69.7 |
| *LDH level (n=44):* | | |
| <1000 | 27 | 61.4 |
| ≥1000 | 17 | 38.6 |

*Adverse events*. Tumor lysis syndrome (TLS) was recognized in a total of 25 patients (54.3%), 18 (39.1%) developed only laboratory abnormalities, 7 patients (15.2%) had clinical manifestations. All TLS cases had bulky abdominal disease, BM involvement and elevated LDH. Five (10.9%) patients developed acute renal impairment, 3 patients (6.4%) underwent hemodialysis for a short period. One third of the cases (31.9%) required Rasburicase use, six cases (12.8%) used Sevelamer. **[Table 2]** None of the cases died by TLS.

**Table 2: Frequency of Tumor Lysis Syndrome (TLS), possible consequences and management (n=48).**

| | No. | Percentage |
|---|---|---|
| *TLS (n=46):* | | |
| No | 21 | 45.7 |
| Lab only | 18 | 39.1 |
| Clinical | 7 | 15.2 |
| *Acute renal impairment (n=46):* | | |
| Yes | 5 | 10.9 |
| No | 41 | 89.1 |
| *Rasburicase use (n=47):* | | |
| Yes | 15 | 31.9 |
| No | 32 | 68.1 |
| *Sevelamer use (n=47):* | | |
| Yes | 6 | 12.8 |
| No | 41 | 87.2 |
| *hemodialysis (n=47):* | | |
| Yes | 3 | 6.4 |
| No | 44 | 93.6 |

Almost all cases (97.9%) had chemotherapy related hematologic toxicity and fever neutropenia. One third of cases (34.8%) developed septic shock and one quarter (26.1%) diagnosed with typhlitis. Two thirds of patients (62.5%) had bacterial infection and (41.7%) had proven fungal infection. Eighty percent developed grade II-IV mucositis. Rare complications included neurologic toxicity (10.4%), hyperglycemia (8.3%), and one patient had cardiac toxicity. **[Table 3]**

**Table 3: Treatment related toxicities (n=48).**

| | No. | Percentage |
|---|---|---|
| Hematologic toxicity | 47 | 97.9 |
| Fever neutropenia | 47 | 97.9 |
| Mucositis (n=46) | 37 | 80.4 |
| Bacterial infection | 30 | 62.5 |
| Fungal infection | 20 | 41.7 |
| Septic shock (n=46) | 16 | 34.8 |
| Typhlitis (n=46) | 12 | 26.1 |
| Neurologic toxicity | 5 | 10.4 |
| Hyperglycemia | 4 | 8.3 |
| Cardiac toxicity | 1 | 2.1 |

*Survival outcome.* The median follow-up in patients not experiencing an adverse event was 112 months. At the end of follow-up, there were 40 patients (83.3%) achieved remission. Of the patients who achieved remission, 6 (12.5%) developed relapse, 3 patients were treated and survived, 2 patients post ABMT, and 1 patient (only chemotherapy). Death was

attributed to disease recurrence in 3 cases, treatment related toxicities in 4 patients. Unfortunately, one "relapsed" patient died in a car accident (in complete remission for 5 years), was not considered as disease related mortality. The total 3-year overall survival (OS) and event free survival (EFS) rate was 83.3%. and 79.2% respectively. **[figure 1]**

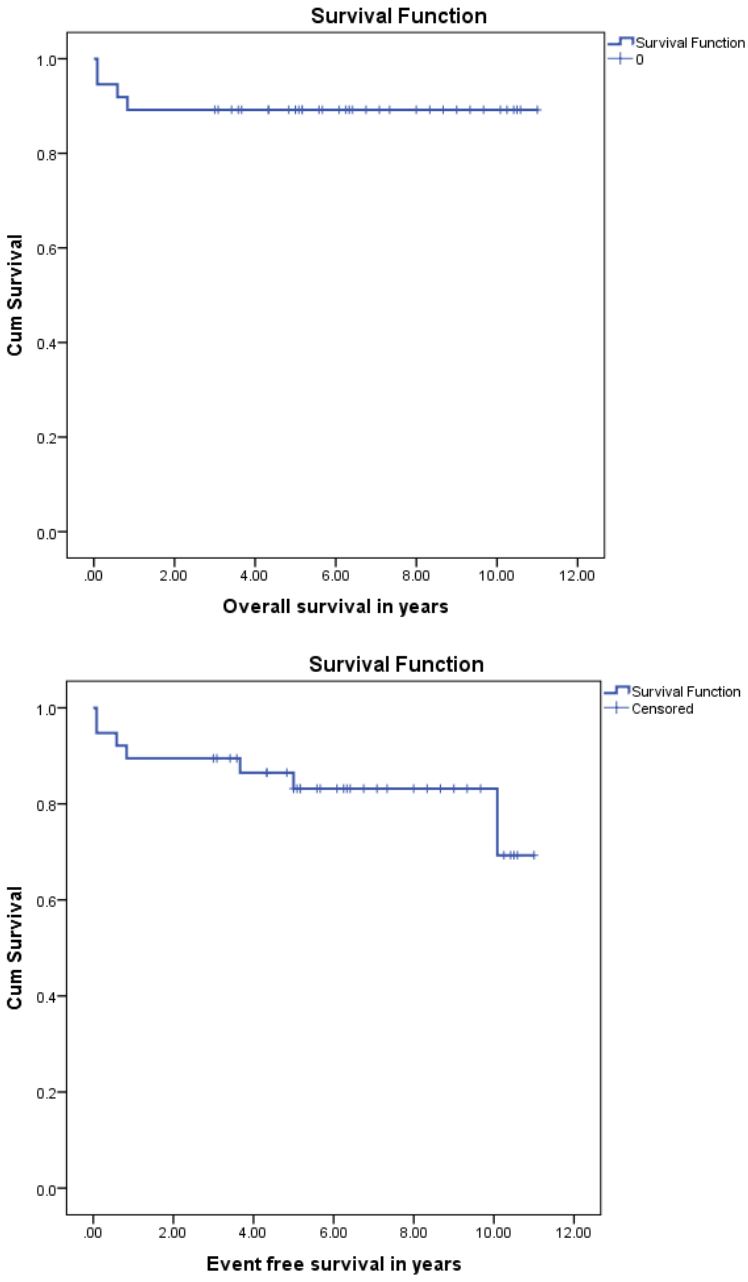


*Figure 1: Three-year overall survival (OS) and event-free survival (EFS) of non-Hodgkin lymphoma (NHL).*

There was no statistically significant difference in the OS and EFS rates of the cases according to their age, gender, histology, biochemical markers, disease locations, staging and FAB group classifications (P >0.05). **[Table 4, 5] [figure 2].** However, a border line significance was observed in OS difference encountered in subgroup of patients from other nationalities (P = 0.057). **[Table 4] [Figure 3]** Although it didn't reach a statistical significant differences, mortality rates were relatively higher among females (28.6%), non-Saudis (42.9%), older age more than 10 years (28.6%), advanced FAB risk group C (15.8%), DLBCL pathology (20%), higher LDH level ≥1000 (25%), Ki67 level >95% (22.7%) and primary tumor site in head and neck (21.1%). **[Table 4]**

**Table 4: Mortality rates according to patients' clinical characteristics.**

| Characteristics | Mortality | | | | $X^2$ | P* |
|---|---|---|---|---|---|---|
| | Yes | | No | | | |
| | No | % | No | % | | |
| *Gender*: | | | | | | |
| Male | 3 | 9.1% | 30 | 90.9% | | |
| Female | 4 | 28.6% | 10 | 71.4% | Fisher | 0.173 |
| *Nationality:* | | | | | | |
| *Saudi* | 4 | 10.0% | 36 | 90.0% | | |
| *Non Saudi* | 3 | 42.9% | 4 | 57.1% | Fisher | 0.057 |
| *Age at diagnosis:* | | | | | | |
| <5 years | 3 | 17.6% | 14 | 82.4% | | |
| 5-10 years | 2 | 8.7% | 21 | 91.3% | 1.751 | 0.417 |
| >10 years | 2 | 28.6% | 5 | 71.4% | | |
| *Stage:* | | | | | | |
| II | 2 | 18.2% | 9 | 81.8% | | |
| III | 2 | 11.8% | 15 | 88.2% | 0.240 | 0.887 |
| IV | 3 | 15.8% | 16 | 84.2% | | |
| *Histopathology:* | | | | | | |
| Burkitt's | 6 | 14.6% | 35 | 85.4% | | |
| DLBCL | 1 | 20.0% | 4 | 80.0% | | |
| High grade B cell Burkitt like | 0 | 0.0% | 1 | 100.0% | 0.419 | 0.811 |
| *Group:* | | | | | | |
| A | 0 | 0.0% | 2 | 100.0% | | |
| B | 4 | 15.4% | 22 | 84.6% | 0.662 | 0.718 |
| C | 3 | 15.8% | 16 | 84.2% | | |
| *Ki67 level:* | | | | | | |
| ≤95% | 1 | 10.0% | 9 | 90.0% | | |
| >95% | 5 | 22.7% | 17 | 77.3% | Fisher | 0.637 |
| *LDH level:* | | | | | | |
| <1000 | 3 | 11.1% | 24 | 88.9% | | |
| ≥1000 | 4 | 25.0% | 12 | 75.0% | Fisher | 0.394 |
| *Primary site:* | | | | | | |
| Abdominal/Retro abdominal | 2 | 8.7% | 21 | 91.3% | | |
| Head and neck | 4 | 21.1% | 15 | 78.9% | 1.410 | 0.494 |
| Leukemia | 1 | 20.0% | 4 | 80.0% | | |

* Based on Chi Square ** Statistically significant

**Table 5: Event Free Survival for three years or more.**

| Characteristics | Event free survival for ≥3 years | | | | $X^2$ | P* |
|---|---|---|---|---|---|---|
| | Yes | | No | | | |
| | No | % | No | % | | |
| *Gender*: | | | | | | |
| Male | 21 | 84.0% | 4 | 16.0% | | |
| Female | 10 | 76.9% | 3 | 23.1% | Fisher | 0.672 |
| *Nationality:* | | | | | | |
| *Saudi* | 28 | 84.8% | 5 | 15.2% | | |
| *Non Saudi* | 3 | 60.0% | 2 | 40.0% | Fisher | 0.223 |
| *Age at diagnosis:* | | | | | | |
| <5 years | 7 | 77.8% | 2 | 22.2% | | |
| 5-10 years | 19 | 82.6% | 4 | 17.4% | 0.111 | 0.946 |
| >10 years | 5 | 83.3% | 1 | 16.7% | | |
| *Stage:* | | | | | | |
| II | 6 | 85.7% | 1 | 14.3% | | |
| III | 12 | 80.0% | 3 | 20.0% | 0.240 | 0.887 |
| IV | 13 | 81.3% | 3 | 18.8% | | |
| *Histopathology:* | | | | | | |
| Burkitt's | 28 | 82.4% | 6 | 17.6% | | |
| DLBCL | 2 | 66.7% | 1 | 33.3% | | |
| High grade B cell Burkitt like | 1 | 100.0% | 0 | 0.0% | 0.800 | 0.670 |
| *Group:* | | | | | | |
| B | 18 | 81.8% | 4 | 18.2% | | |
| C | 13 | 81.3% | 3 | 18.8% | Fisher | 1.000 |
| *Ki67 level:* | | | | | | |
| ≤95% | 7 | 87.5% | 1 | 12.5% | | |
| >95% | 12 | 75.0% | 4 | 25.0% | Fisher | 0.631 |
| *LDH level:* | | | | | | |
| <1000 | 18 | 90.0% | 2 | 10.0% | | |
| ≥1000 | 10 | 71.4% | 4 | 28.6% | Fisher | 0.202 |
| *Primary site:* | | | | | | |
| Abdominal/Retro abdominal | 16 | 88.9% | 2 | 11.1% | | |
| Head and neck | 11 | 73.3% | 4 | 26.7% | 1.347 | 0.510 |
| Leukemia | 4 | 80.0% | 1 | 20.0% | | |

* Based on Chi Square ** Statistically significant

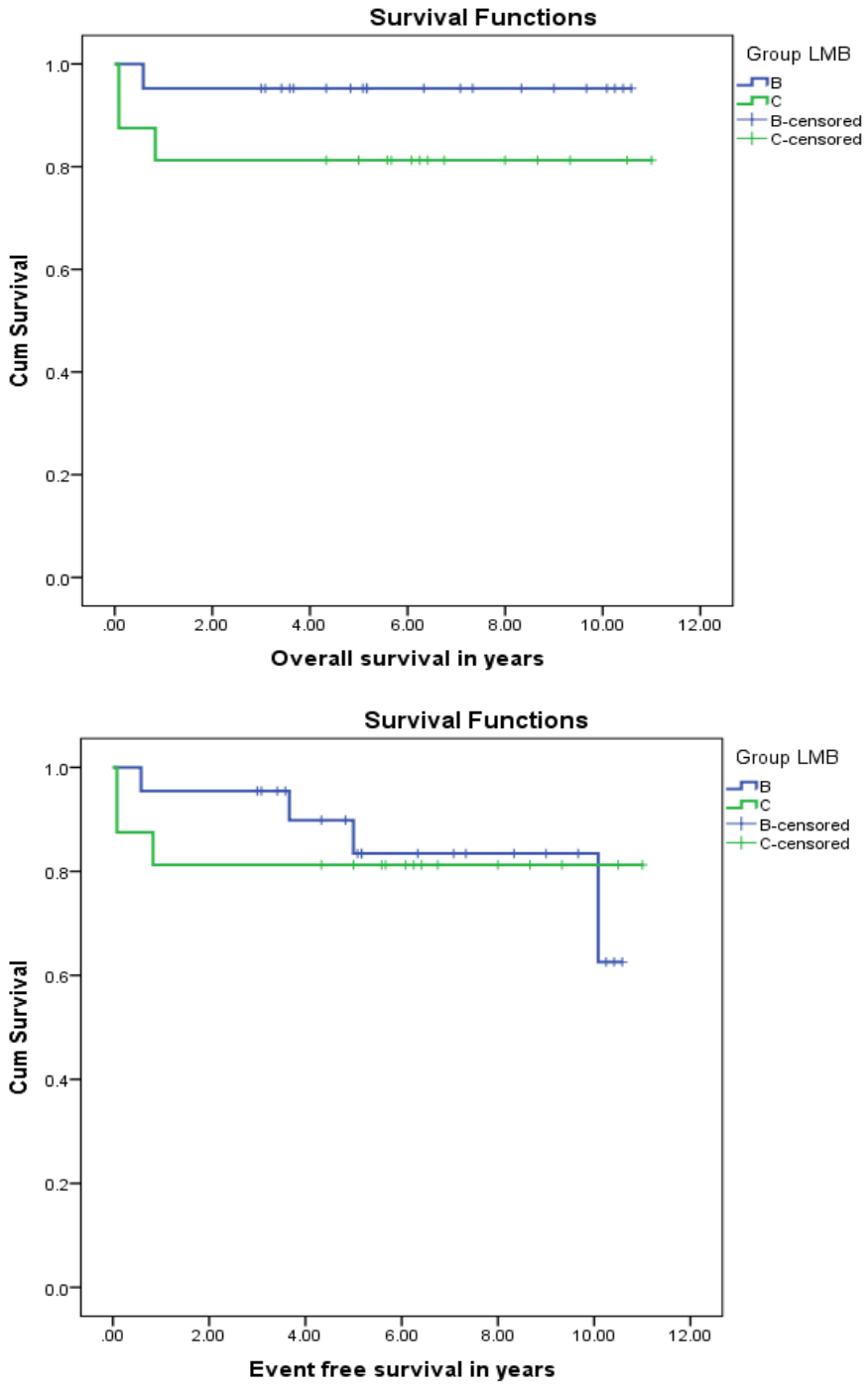


*Figure 2: OS & EFS according to FAB/LMB group*

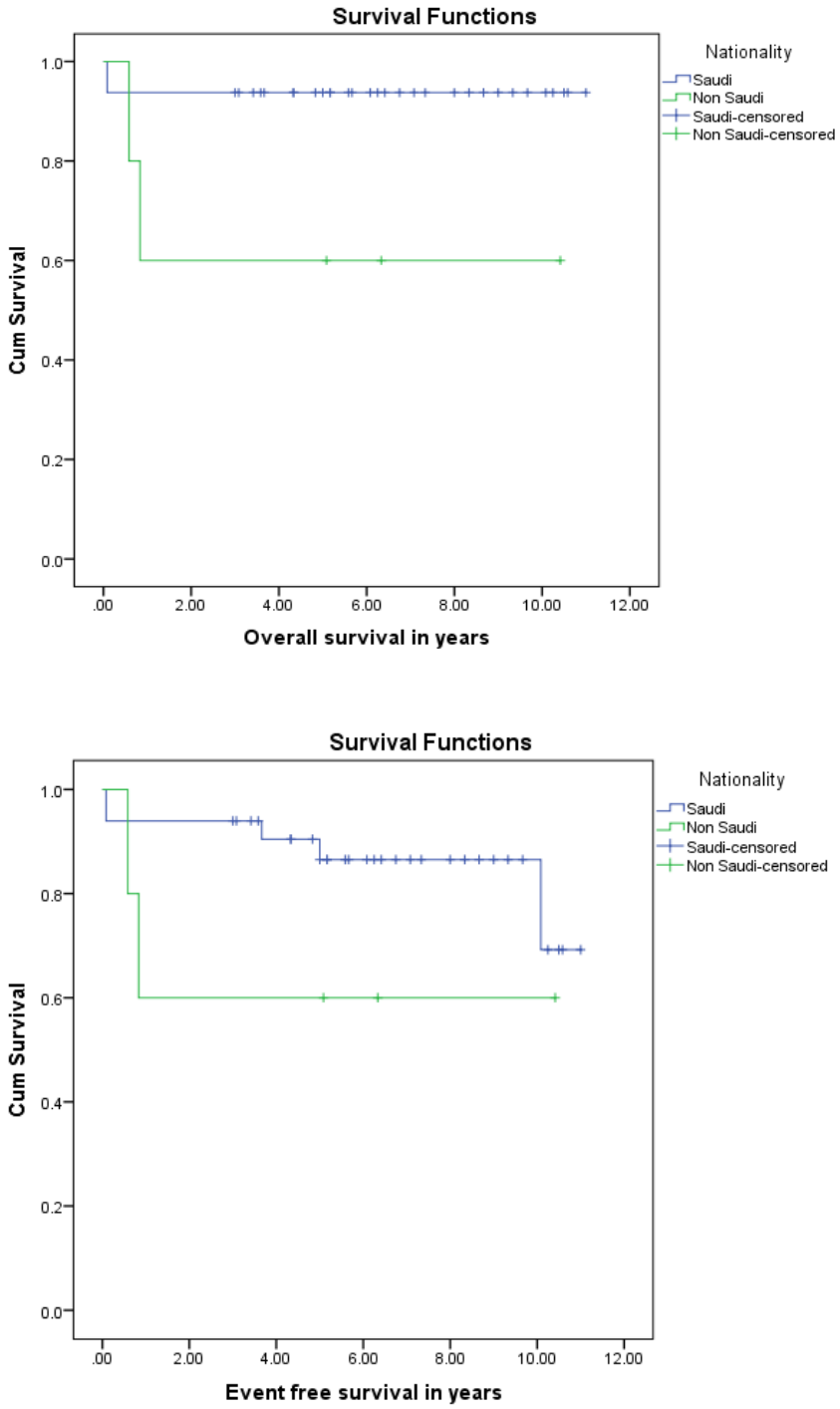


*Figure 3: OS & EFS according to nationality*

**4. Discussion:**

NHL is a heterogeneous group of highly malignant neoplasia with a distinct pathological immune context and clinical features. In this retrospective cohort study, the researchers described the demographic, histopathology pattern and clinical outcomes of 48 pediatric patients with NHL enrolled in a single tertiary center in Western region of Saudi Arabian. The annual age-specific incidence rate (ASR) of cancer in children aged 0 to 14 years in Saudi Arabia is 99.83 per million children, and pediatric lymphoma comes second in the list of all childhood cancer with a prevalence of (17.3%), and the ASR of pediatric NHL is 8.02 per million (Belgaumi et al., 2019). This study showed marked male preponderance especially in children above five years old which was comparable to worldwide series (Belgaumi et al., 2019; Cairo et al., 2012; Ferreira et al., 2012); that can be considered as a consequence of the typical dominance of lymphoid tumor in male children (Mbulaiteye et al., 2009); nevertheless, there was no significant difference in the OS between males and females similar with what was reported by Cairo and his colleagues (Cairo et al., 2012). Burkitt's lymphoma (BL) constituted 87.5 % of all our cases; which comes in accordance with what had been reported in other Arabic and Western countries (Burkhardt et al., 2005; Pedrosa et al., 2007; Wright et al., 1997); in contrast, BL was reported at a relatively lower frequency (10-12%) in East and South of Asia (Nakagawa et al., 2004; Srinivas et al., 2002); which needs further researches to explore reasons behind this difference. In the present cohort analysis, no precursor T-cell lymphoblastic lymphoma (TLL) was recorded among the 48 patients, that could be explained by the fact that our cases were immunocompetent. In general, TLL frequency in Saudi Arabia is as low as 8% (Akhtar et al., 2009). Abdominal involvement was the commonest presentation (47.9%) in our cases, followed by head and neck involvement, while BM infiltration was the most common site of metastasis (10.4%); which comes in congruence with what had reported in other studies (Naresh et al., 2004; Temmim et al., 2004), on the other hand, no jaw involvement was seen in our cases, in contrast to reports of endemia BL in a previous research (Mwanda et al., 2005).

Regarding management of our cases, the use of prophylactic recombinant urate oxidase for high risk TLS (Rasburicase) cases significantly decreased incidence of acute renal failure and dialysis to 6.4% during early course of intensive chemotherapy, this finding is similar to other reports (Coiffier et al., 2003; Wössman et al., 2003). During infusion of Rituximab, no complications occurred, therefore, there was no need to stop or modify dosage. While there was no statistically significant difference in OS and EFS according to age, gender, histopathology and staging of the cases, a border line significance was found in OS among non-Saudi children; their shorter OS could be attributed to late presentation of the cases due to financial problems of their families, belief and dependence on alternative medicine.

**5. Conclusion and recommendations:**

Pediatric NHLs are extra-nodal highly grade tumors, that fall in three main categories: Burkitt lymphoma, lymphoblastic lymphoma and anaplastic large cell lymphoma. Most of our cases presented in advanced stage of the disease. Rutixmab is safe and efficient medication for intermediate and high risk groups. Although that the outcome and survival of our cases are comparable with those in other international centers, better outcome could

be achieved by establishing discipline for early detection of the cases and ensuring easy access to childhood cancer care center. For patients who are resistant and refractory to conventional and second line therapy, more prospective studies are needed to explore potential therapeutic agents to improve outcome.

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