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Lymphoblastic lymphoma in children seven years' experience of children welfare teaching hospital

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Abstract
Background: Lymphoblastic lymphoma (LBL) is an aggressive neoplasm originating from lymphoblasts of either B-cell (B-LBL) or T-cell origin (T-LBL). Classified alongside acute lymphoblastic leukemia (ALL) in the 2008 WHO classification of hematopoietic malignancies, LBL is marked by rapid progression and high aggressiveness. Aim: To investigate the clinicopathological features, treatment outcomes, and survival rates of pediatric LBL cases.
Methods: From January 1, 2014, to December 31, 2020, 23 newly diagnosed cases of LBL in patients under 14 years were admitted to the Children Welfare Teaching Hospital, Medical City. One patient who had previously received treatment elsewhere was excluded, leaving 22 patients for evaluation. Data on patient demographics, clinical presentation, diagnosis, and treatment outcomes were extracted from inpatient and oncology clinic records. Follow-up was conducted every three months for patients who completed chemotherapy.
Results: The median age was 8.3 years (range 3.4–13.3), with a male-to-female ratio of 4.5:1. Cervical lymphadenopathy and mediastinal masses were observed in 36.4% and 72.7% of patients, respectively. Advanced stages (III & IV) were present in 95% of patients. T-cell LBL was diagnosed in 86% of cases, with diagnostic tissue obtained mainly from lymph nodes (45.4%) and mediastinal masses (27.3%). Nineteen patients (90.5%) achieved remission, with an overall survival and event-free survival rate of 51.4% at three years.
Conclusion: The clinicopathological profiles and treatment outcomes align with previous studies from the same hospital, and Italian pathology review was consistent with local findings, supporting diagnostic accuracy in our setting.

Keywords: Lymphoblastic, lymphoma, children, seven years

Introduction
Childhood non-Hodgkin lymphoma (NHL) significantly differs from adult NHL in terms of disease sites, staging, treatment, and subtypes [1]. The World Health Organization (WHO) classification identifies distinct subtypes in childhood NHL, each with unique morphological, immunophenotypic, and genetic characteristics, emphasizing the importance of an accurate diagnosis that integrates these factors. The primary subtypes of NHL in children include Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), T or B lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL) [2]. Lymphoblastic lymphoma (LBL) is an aggressive neoplasm originating from lymphoblasts, which may be of B-cell (B-LBL) or T-cell origin (T-LBL). In the 2008 WHO classification of hematopoietic malignancies, LBL is grouped with acute lymphoblastic leukemia (ALL) due to their close biological relationship, though they are not identical [3]. In LBL, bone marrow involvement is minimal or partial, with fewer than 25% (or 20% by WHO recommendations) of infiltrating blast cells. Cases with overlapping features are not uncommon, indicating leukemic spread in patients who may present late to the hematologist-oncologist. These and other distinctions in disease biology, clinical presentation, risk profiling, optimal treatment approaches, and outcomes warrant a focused examination of LBL as a distinct clinical entity [4]. The aim of study is to study clinical and pathological feature of Lymphoblastic lymphoma in children and to study outcome of treatment.

Method
Between January 1, 2014, and December 31, 2020, 23 cases of lymphoblastic lymphoma

(LBL) were registered among 225 non-Hodgkin lymphoma (NHL) cases in the pediatric oncology unit at Children Welfare Teaching Hospital. One patient was excluded due to prior treatment elsewhere, leaving 22 patients for analysis. Data on age, sex, residence, clinical presentation, diagnostic procedures, staging, treatment, and outcomes were collected from patient files and oncology clinic records. Staging was based on the International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) [5]. Diagnosis relied on tissue biopsy with immunohistochemistry, bone marrow aspirate/biopsy, cerebrospinal fluid (CSF) analysis, and pathology review. CSF analysis classified CNS involvement into CNS-1 (no identifiable blasts), CNS-2 (low leukocytes with blasts), and CNS-3 (high leukocytes with blasts or cranial nerve palsy) [6]. Patients received supportive care, including hydration and Allopurinol, to manage tumor lysis syndrome. Specific therapy followed the UKALL 2011 Group C protocol, modified in 2019 for certain patients (appendix). Sixteen patients were treated under UKALL 2011, two with UKALL 2019, two initially with COP protocol, and one under BFM protocol (IRAN) before switching to UKALL 2011; one patient died before treatment began. Response criteria included complete response (CR), relapse (RL), progressive disease (PD), and treatment failure [5]. Follow-up was conducted at three-month intervals with evaluations such as physical exams, imaging, and event-free survival (EFS) assessments. EFS included all events leading to remission failure, while overall survival tracked time from diagnosis to death [6]. Statistical analysis was performed using SPSS [7].

Results

Table 1: Geographical Distribution of Patients

Of the 22 patients, the majority (65.2%) were from Baghdad, with the rest distributed across other regions.

Table 2: Patient Characteristics

- Median age: 8.3 years (range 3.4 to 13.3 years).
- Gender distribution: 18 males (81.8%) and 4 females (18.1%), with a male-to-female ratio of 4.5:1.
- Median symptom duration: 8 weeks (range 5 days to 12 months).
- Main presentations: respiratory symptoms (54.5%), cervical lymphadenopathy (36.4%), with other symptoms including fever, pallor, cheek swelling, proptosis, and scalp mass.

Table 3: Laboratory and Radiological Findings

- Hemoglobin range: 3.1–15.1 g/dL (mean 11.6 g/dL).
- Leukocyte count: 1.3–22.16 × 10^9/L (mean 11.6 × 10^9/L).
- Platelet count: 40–665 × 10^9/L (mean 372.5 × 10^9/L).
- Mediastinal mass observed in 72.7% of patients; respiratory distress and pleural or pericardial effusions in 50% of those with mediastinal masses.
- Initial bone marrow involvement: 23.8%; initial CNS involvement: 14.3%.

Table 4: Clinical Staging

- Stage IV: 36.3% of patients.
- Stage III: 59.1%.
- Stage I-II: 4.5%.

Table 5: Diagnostic Tissue Sources

- Lymph nodes: 45.4%.
- Mediastinal mass: 27.3%.
- Maxillary sinus, scalp mass, and bone marrow: smaller percentages.

Table 6: Immunohistochemistry (IHC) and Pathology Results

- T-cell Lymphoblastic Lymphoma diagnosed in 19 patients.
- Most IHC samples positive for CD3 and TdT, negative for CD20, with significant Ki-67 levels.
- Of 18 patients with available IHC, 83.3% were immature T-cell LBL, 2 pre-B LBL, and 1 peripheral T LBL.

Fig 1 and 2: Survival Outcomes

1. Three-year event-free survival and overall survival rates were both 51.4%.
2. Relapses resulted in a 100% mortality rate for those who relapsed.

Causes of Death

One patient died before treatment from respiratory compromise, four from sepsis/hepatic complications, and three post-relapse.

Table 1: Referral pattern of 22 patients with lymphoblastic lymphoma to CWTH

Residence	Frequency	(%)
Baghdad	14	65.2
Wasit	3	13
Maysan	2	8.7
Salah Aldeen	2	8.7
Najaf	1	4.3
Total	22	99.9

Table 2: Demographic and clinical data*

Item	No.	%
Age (years)		
1-5	2	9
6-10	8	36.4
11-14	12	54.5
Gender		
Male	18	81.8
Female	4	18.2
Duration of onset		
< 6 weeks	7	31.8
6 weeks – 6 months	14	63.6
> 6 months	1	4.5
Presentation		
Respiratory distress	12	54.5
Cervical LAP	8	36.3
Cheek/facial swelling	2	9.1
Fever and pallor	2	9.1
Scalp lesion/masses	1	4.5
Eye proptosis	1	4.5
Abdominal distension	1	4.5

*Some patients have more than one clinical presentation

Table 3: Initial laboratory and radiological results

Item	No.	%	Valid %
Hb (g/dl)			
< 5	1	4.5	5.3
5-10	2	9.1	10.5
>10 g/dl	16	72.7	84.2
NV	3	13.6	
WBC ($\times 10^9$/L)			
< 5	4	18.2	
5-10	15	68.2	
>10	3	13.6	
Platelet ($\times 10^9$/L)			
< 20	1	4.5	
20-99.99	2	9.1	
≥100000	19	86.3	
Uric acid <7.5mg /dl	13	59	
>7.5 mg/dl	1	4.5	
Not done	8	36.3	
Mediastinal mass**			
Yes	16	72.7	
No	7	31.8	
Bone marrow			
Involvement	5	22.7	23.8
No involvement	16	72.7	76.2
Not done*	1	4.5	
CNS status			
Involved	3	13.6	14.2
Not involved	18	81.8	85.7
Not assessed*	1	4.5	

NV: Not Valid 3 patients received blood transfusion before referral to (CWTH) *One patient died before having BM and CNS assessment.
**Eleven patients (50%) has respirotery distress.

Table 4: Staging of the patients

Stages	Frequency	%
I-II	1	4.5
III	13*	59
IV	8	36.4
Total	22	100

*One patient died before having BM evaluation, he was otherwise stage III.

Table 5: Diagnostic procedures

	Frequency	%
Tissue Biopsy	18	81.8
Lymph node	(10)	(45.4)
Mediastinal mass	(6)	(27.3)
Maxillary sinus	(1)	(4.5)
scalp mass	(1)	(4.5)
BM*	4	18.2
Total	22	100

*Diagnosis only by BM examination.

Table 6: Details of Anatomical pathology reports for 22 patients with LBL:

N.	sex	Age	Diagnostic site	Stage	Diagnosis	Iraqi details	Italian pathology review
1	M	11	BMA	4	LBL	LBL	
2	F	4	BMA	4	LBL	LBL	
3	M	14	BMA	4	LBL	LBL	
4	M	11	Cervical	3	T-LBL	CD3+, TdT+	
5	M	11	Mediastinum	3	T-LBL	CD3+, TdT+	+ve TdT, CD3, CD1a, CD10. -ve CD20, CD79a. Ki67 60%.
6	M	12	Cervical	3	T-LBL	CD3+, TdT+, CD20-, Ki high	+ve TdT, CD3, CD1a -ve CD20, CD79a, Ki67 >80%.
7	M	11	Mediastinum	3	T-LBL	Morphology	+ve CD3, CD1a. -ve CD20, CD79a.
8	M	8	Cervical	4	T-LBL	CD3+, TdT+	+ve TdT, CD3, CD5. -ve CD1a, CD34, CD20, CD79a. Ki67 70%

9	M	13	Cervical	4	T-LBL	CD3+, TdT+	+ve TdT, CD3. -ve CD1a, CD10, CD20, CD79a, BCL2. Ki67 80%.
10	M	10	Mediastinum	3	LL	Morphology	
11	M	12	Mediastinum	3	T-LBL	CD3+, TdT+	+ve TdT, CD3. -ve CD1a, CD20, CD79a. Ki67 >90%.
12	M	5	Cervical	3	T-LBL	Morphology	+veCD3,-ve CDla,CD20,CD -ve CD1a, -CD20, CD79a
13	M	9	Scalp mass	4	B LBL	CD10+, TdT+, CD3-, CD20-	+ve TdT, CD79a. -ve CD20, CD1a, CD3.
14	M	12	Supraclavicular	3	T-LBL	CD3+, TdT+	+ve TdT, CD3. -ve CD1a, Ki67 80%.
15	F	10	Cervical	4	Peripheral T-LBL	CD3+, CD20-	+ve CD3, CD8. -ve CD30, CD15, TdT, ALK. Ki67 60-70%
16	M	14	Supraclavicular	3	T-LBL	CD3+, TdT+	+ve CD3, CD1a. -ve TdT, CD34, CD20, CD79a, CD10.
17	F	6	Cervical	3	T-LBL	CD3+, TdT+	
18	M	10	BMB	4	T-LBL	CD3+, TdT+	+ve CD3. -ve TdT, CD34, CD1a, CD20, CD79a, CD10.
19	F	11	Maxilla	1-2	B LBL	CD10+, TdT+, CD20-, CD30-, KI85%	+ve TdT, CD10, CD79a, Ki67 60%. -ve CD20, CD3,CD1a
20	M	13	Mediastinum	3	T-LBL	CD3+, CD20-	
21	M	9	Mediastinum	3	T-LBL	CD3+, TdT+,Ki 90%	
22	M	8	Cervical	3	T-LBL	CD3+, TdT+, Ki 90%	

Table 7: Outcome of 22 patients with Lymphoblastic lymphoma

	No.	**%**
Total patient No.	22	100
Pre-induction		
Died	1	4.5
Induction phase	21	95.5
Complete remission	19	
Died	1	4.5
Not in remission--lost	1	4.5
Post induction phase	19	
CCR	11	50
Died	3	13.6
Lost	2	9.1
Relapse*	3	13.6

*three patient with relapse are died

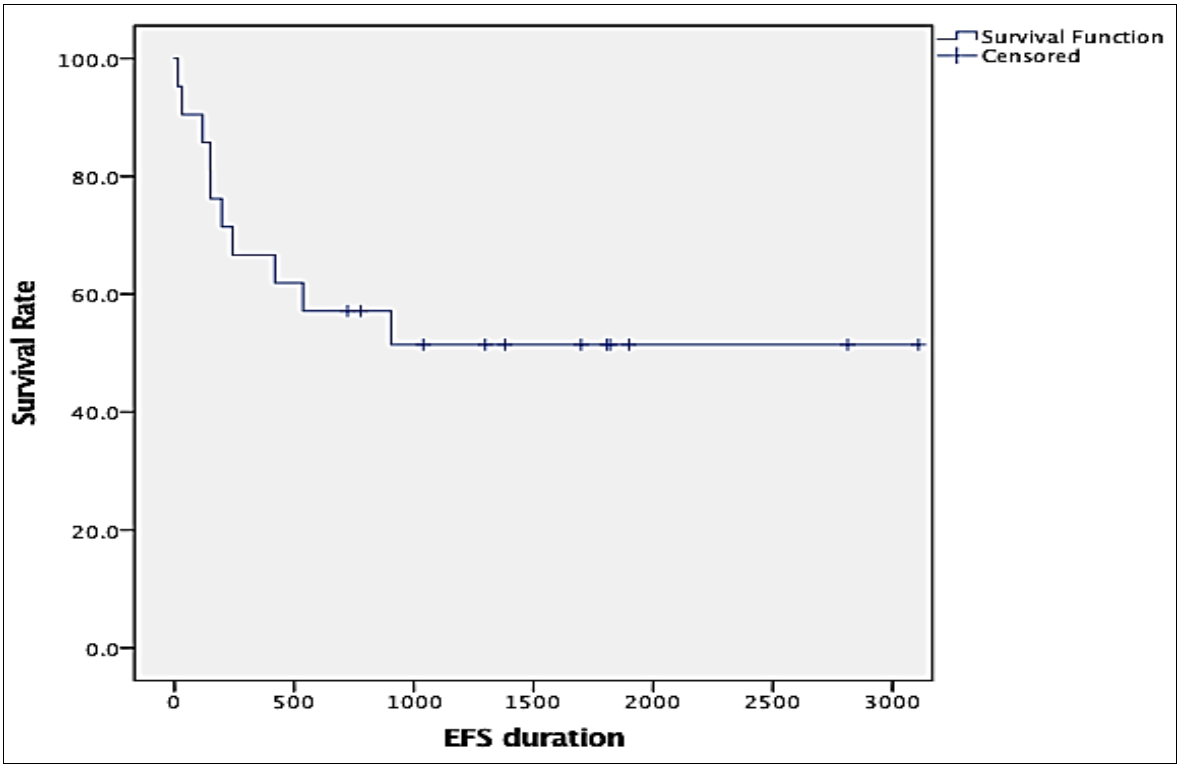

Fig 1: 3 years of EFS = 51.4%

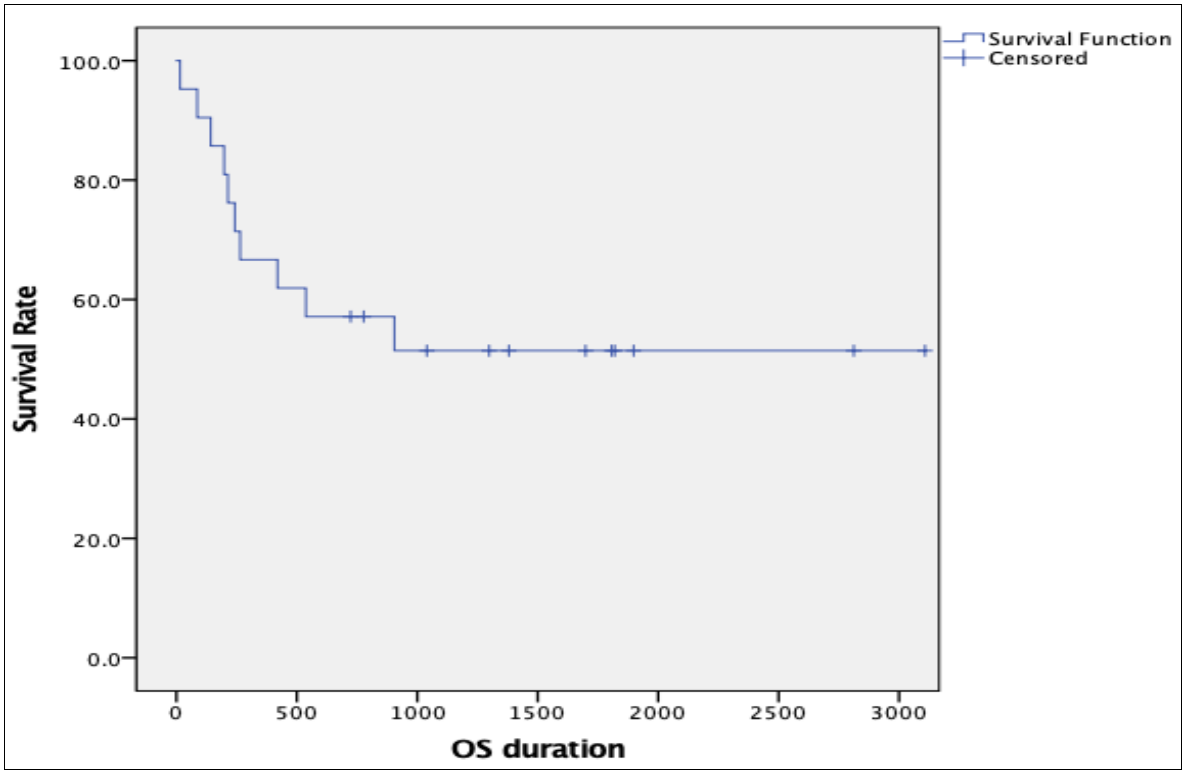

Fig 2: 3 years of OS = 51.4%

Discussion

In this study, lymphoblastic lymphoma (LBL) accounted for 10.2% (23/225) of all non-Hodgkin lymphoma (NHL) cases diagnosed at Children Welfare Teaching Hospital (CWTH) during the study period, with Burkitt's lymphoma being the most common subtype. This incidence is higher than prior CWTH studies (7.1% in 2000-2005 [9] and 8% in 2000-2007 [10] but lower than the 14.9% reported from 2008-2013 [11]. In comparison, studies in other regions recorded higher LBL percentages: 21.8% in Morocco [12], 35.6% in Lahore [13], and 27.2% in the UK [14]. Lower LBL rates in Iraq could reflect the higher incidence of Burkitt's lymphoma in the Middle East and Africa, as well as potential limitations in pathology classifications [8, 15]. The median age was around 8 years, consistent with other studies [7, 9, 10, 15]. A mediastinal mass was found in 72.7% of patients, higher than the 48.9% observed in the 2008-2013 CWTH study (12) but lower than the 82.1% reported in 2000-2007 [10]. International studies showed higher detection rates, such as 86.2% in Korea [41] and 86.3% in Morocco [16]. The median duration of symptoms was 8 weeks, shorter than previous CWTH studies but longer than the 69% presenting within 35 days in a study by Mora *et al.* [17]. Most patients (95%) presented with advanced stages, a trend consistent with other CWTH studies (96%) [9, 10] and reports from Brazil, Korea, Morocco, and Pakistan, where advanced stages were common [12, 15, 16, 18]. T-cell LBL was identified in 83.3% of patients, in line with the literature [2-4], though higher than CWTH's previous study at 67.6% [10] and Korea's study at 61.9% [18], but lower than Egypt's 87% [11], Morocco's 91% [16], and Pakistan's 91% [13]. Bone marrow involvement at diagnosis was found in 23.8% of patients, though this may be underestimated. Studies suggest that more sensitive methods like flow cytometry could improve risk classification [19]. Treatment followed protocols similar to acute lymphoblastic leukemia, supporting survival outcomes comparable to ALL [20]. The current study's survival rate (51.7%) has improved compared to previous CWTH studies (37.8% and 46.4%) [10, 11], yet remains lower than rates of 65% [12], 68% [15], 78% [18], and 79% [17] reported internationally. The relatively small sample size in this study limited the ability to compare outcomes based on specific prognostic factors.

Conclusion

Presentations, staging, and pathological subtypes were similar to other studies in the same hospital. Final pathology review abroad supported Iraqi findings. The survival results of the current and previous studies conducted at Children Welfare Teaching Hospital have shown improvement over time yet fail to reach the survival figures from other studies as well as the literature.

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