Burkitt Lymphoma: Advanced Stage Strongly Matters

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ABSTRACT

An ideal prognostic index in Burkitt lymphoma is lacking. Although recently developed Burkitt Lymphoma International Prognostic Index (BL-IPI) shows promise, the fact it doesn't include advanced stage is a matter of concern. We aimed to investigate advanced stage as a risk factor and propose a new prognostic score accordingly. This multicenter retrospective cohort study includes data of 101 adults. Advanced stage demonstrated poor prognosis along with age, lactate dehydrogenase (LDH), uric acid, and Eastern Cooperative Oncology Group Performance Score (ECOG PS). Even though BL- IPI performed well in the whole cohort, it wasn't efficient enough in the advanced stage subset. The alternative score consisted of age ≥ 55 years (1 point), LDH > 10 x ULN (1 point), hyperuricemia (1 point), ECOG PS ≥ 2 (2 points), and advanced stage (2 points). Low (≤1 point), intermediate (2-4 points), and high-risk (≥ 5 points) groups consisted of 18%, 59%, and 23% of the patients respectively. 3-year overall survival (OS) rates were 87.1%, 59.5%, and 0% (p< 0.001) whereas 3-year disease-free survival (DFS) rates were 83.3%, 53.5%, and 0% (p= 0.002). Advanced stage indicates poor prognosis independently. An ideal prognostic system should include it as a risk factor. Our risk score carves a path to the ideal risk score, however more studies with higher number of patients are needed to validate it.

Keywords: Burkitt lymphoma, Prognosis, Risk factor

INTRODUCTION

Burkitt lymphoma (BL) is a rare but aggressive subtype of non-Hodgkin lymphoma (NHL). It makes up 1-2% of adulthood lymphomas and nearly 40% of childhood lymphomas.[1] Relative improvement in prognosis has been observed with new treatment protocols developed in recent years. However, real-life studies and experience have shown that there are many patients who still have an unacceptably lower chance of survival with these regimens and in need of different treatment approaches.[2-4] An efficient disease risk assessment method is needed to identify these cases. However, we believe that a scoring system for BL that can be considered optimal for use in clinical practice still does not exist. Due to the high proliferative index (Ki-67 proliferative index is approximately 100%) and the need for urgent treatment, it is difficult to carry out prospective trials in BL patients and the lack of a good prognostic score makes it even more difficult.

Recently, BL International Prognostic Index (BL-IPI) has been developed by Olszewski et al.[5] Based on the data from a cohort of 633 patients; age ≥ 40 years, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, serum lactate dehydrogenase (LDH) > 3 x upper limit of normal (ULN), and central nervous system (CNS) involvement were identified as risk factors, and patients were grouped as low-risk (zero risk factors), intermediate-risk (one risk factor), and high-risk (≥ 2 risk factors).

The index was further validated in an international cohort of 457 patients. Even though this score seems to predict outcomes successfully, the fact that it does not include advanced stage as a risk factor is a topic of concern as it is regarded as one of the most important risk factors in clinical practice and advanced stage patients form the more difficult-to-treat group.[6-10]

In this multicenter study, we aimed to review the efficacy of the newly proposed BL-IPI, investigate whether advanced stage is an independent prognostic factor other than BL-IPI and BL-IPI parameters, and, if necessary, propose a new prognostic score that includes advanced stage.

PATIENTS AND METHODS

This is a multicenter retrospective cohort study that includes the data of 101 adult BL patients who were followed-up in three university hospitals in Turkey (specified in author affiliations) between 2001 and 2021. Patients diagnosed with BL in these centers were reviewed, and patients aged 18 years and older who could be confirmed to have BL according to the 2016 WHO criteria[11] were included in the study. Demonstration of myelocytomatosis oncogene (MYC) rearrangement was not mandatory. Patients who demonstrated typical morphological (medium-sized cells with round nuclei and dark basophilic cytoplasm -frequently containing vacuoles- which show a diffuse monotonous growth pattern, and starry sky appearance due to presence of numerous tangible body macrophages), and immunohistochemical (MYC, CD19, CD20, CD22, CD10, BCL6 positive; CD5, CD23, BCL2, TdT negative; Ki-67 proliferative index approximately 100%) findings of BL were also included in the study.

The prognostic effects of following variables were examined: age at diagnosis, gender, ECOG performance status, comorbidities, B symptoms, advanced (3 or 4) Ann Arbor stage[12], bone marrow involvement, CNS involvement, serum LDH, uric acid, creatinine and albumin levels, hemoglobin and platelet counts, first-line therapy regimen, and BL-IPI risk group. Primary endpoints were overall survival (OS) and disease-free survival (DFS). OS was defined as time from diagnosis until death from any cause. DFS was estimated in patients in whom remission was achieved and was defined as time from remission to relapse or death from any cause. Alive patients at the last follow-up visit were processed as censored data for OS analysis, and patients who were alive and did not relapse were processed as censored data for DFS analysis.

This study protocol was reviewed and approved by Hacettepe University Non-Interventional Clinical Researches Ethics Board, approval number 2022/03-02.

Statistical Analysis

Statistical analysis was conducted by IBM® SPSS® Statistics version 25. 2-tailed p values less than 0.05 were considered statistically significant. The categorical variables were shown as numbers of cases with percentages. Continuous variables were defined as mean ± standard deviation (SD) for parametric; and median with interquartile range (IQR) for nonparametric variables. Descriptive statistics were used to identify demographical, clinical and treatment-related characteristics of the cohort. Survival curves were estimated by Kaplan-Meier method. Log rank test was used for the univariable analyses of associations of various factors with survival. Factors that were found statistically significant in the univariable testing were further entered into multivariable analysis by Cox regression test to determine the independent predictors of survival. While evaluating the relationship between continuous variables and survival, repeated calculations were made to find the most predictive categorical forms of these variables. A scoring system for prediction of survival was developed depending on the results of Cox regression analysis as previously described.[13] Briefly, the lowest regression coefficient exponent, Exp(B), value of significant parameters in the multivariable analysis was scored with 1 point. Exp(B) values of other significant parameters were divided by the lowest one and the results were rounded to the nearest integer. Consequently, every significant parameter in the Cox regression analysis was scored with a point correlated with its impact on survival. These individual points were then added together to provide a total risk score for every patient. The relationship of each total score with survival was evaluated

visually in Kaplan-Meier analysis, and scores with similar relationships were grouped together. In this way, risk categories were determined.

RESULTS

Patient Characteristics

A total of 101 patients were included in the study. Median age at diagnosis was 39 (IQR: 27) and 70.3% of the patients were male. At the time of diagnosis, 75.2% of the patients had advanced stage disease (Ann Arbor stage 3 or 4). CNS involvement was present in 9.9% of the patients, whereas bone marrow involvement was present in 42.6%. Serum LDH was higher than ULN in 76.2% of the patients. MYC rearrangement investigated by break-apart fluorescent in situ hybridization probes was examined in 53 patients and found positive in 48 of them. First-line regimens received by the patients were as follows; hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternately with high-dose methotrexate and cytarabine (HyperCVAD) ± rituximab (R); dose-adjusted R, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA R-EPOCH); R, cyclophosphamide, doxorubicin, vincristine, methotrexate (R-CODOX-M); Cancer and Leukemia Group B (CALGB); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP). Patient numbers who received each regimen are shown in Table 1. Four patients died before treatment. Other important clinical characteristics are demonstrated in Table 1.

Median follow-up time of the patients was 11.1 months (IQR: 59) and OS rate at 1 year was calculated as 58.2%. Median OS duration was 83.8 months (95% CI: 0-177.9). DFS rate at 3 years was 56.2%. Mean DFS duration was 124.1 months (95% CI: 90.4-157.8) (median could not be reached).

Table 1. Characteristics of the patients included in the study

n	101
Age	
Median (IQR)	39 (27)
≥ 40 years, n (%)	50 (49.5)
≥ 55 years, n (%)	27 (26.7)
Gender, n (%)	
Female	30 (29.7)
Male	71 (70.3)
Any comorbidity, n (%)	31 (30.7)
B symptoms, n (%)	55 (54.5)
ECOG performance status ≥ 2, n (%)	35 (34.7)
Ann Arbor stage, n (%)	
1	15 (14.9)
2	10 (9.9)
3	4 (4.0)
4	72 (71.2)
CNS involvement, n (%)	10 (9.9)
Bone marrow involvement, n (%)	43 (42.6)
MYC rearrangement, n (%)	48/53[4] (90.6)
Hemoglobin, mean (±SD)	11.9 (2.36)
Anemia, n (%)	61 (60.4)
Platelet count, median (IQR)	261x10^3/µL (219)
Thrombocytopenia, n (%)	28 (27.7)
LDH, median (IQR)	628 (1709)
LDH, n (%)	
> ULN	77 (76.2)
> 3 x ULN	36 (35.6)
> 10 x ULN	14 (13.9)
Albumin, mean (±SD)	3.7 (0.67)
Hypoalbuminemia, n (%)	37 (36.6)
Uric acid, median (IQR)	6.8 (5.5)
Hyperuricemia, n (%)	45 (44.6)
Creatinine, median (IQR)	0.8 (0.4)
Renal dysfunction, n (%)	16 (15.8)
First-line regimen, n (%)	
HyperCVAD ± R	25 (24.8)
DA R-EPOCH	26 (25.7)
R-CODOX-M	4 (4.0)
CALGB 8811 ± R	8 (7.9)
CHOP ± R	34 (33.7)
Follow-up, median (IQR)	11.1 months (59)
OS at 1 year (%)	58.2
OS at 3 years (%)	53.1
DFS at 3 years (%)	56.2

Prognostic Factors

In univariable analysis; age, ECOG performance status ≥ 2, advanced stage, bone marrow involvement, LDH, anemia, thrombocytopenia, elevated serum uric acid and creatinine levels, hypoalbuminemia, and BL-IPI risk group had statistically significant effects on OS. Moreover, age ≥ 40 years, advanced stage, bone marrow involvement, thrombocytopenia, and BL-IPI risk group had statistically significant effects on DFS. Results of univariable analyses are shown in Table 2.

Table 2. Univariable analysis of prognostic factors, OS and DFS analyses

Variable	Median OS, months (95% CI)	p	Median DFS, months (95% CI)	p
Age				
≥ 40 years	11.2 (8.1-14.3)	0.02	8.6 (1.6-15.6)	0.04
< 40 years	152.4 (119.0-185.7)		160.5 (119.8-201.1)	
≥ 55 years	8.8 (5.6-12.1)		79.7 (0-189.9)	0.64
< 55 years	133.9 (103.4-164.5)	0.03	127.7 (91.1-164.2)	
Gender		0.90		0.91
Female	127.0 (80.3-173.8)		132.0 (72.8-191.2)	
Male	83.8 (0-186.0)		120.6 (81.8-159.4)	
ECOG performance status		<0.001		0.77
≥ 2	6.8 (2.4-11.1)		79.7 (0-189.9)	
< 2	146.2 (108.1-184.4)		126.9 (86.3-167.6)	
Any comorbidity		0.08		0.98
present	9.2 (5.4-13.0)		80.9 (43.3-118.5)	
absent	129.3 (96.7-161.8)		122.9 (84.4-161.3)	
B symptoms		0.10		0.08
present	13.1 (0-91.1)		11.9 (0-99.4)	
absent	151.2 (115.1-187.4)		163.5 (119.4-207.6)	
Advanced stage		0.003		0.01
present	11.2 (1.0-21.5)		10.5 (4.5-16.5)	
absent	166.5 (105.0-228.0)		172.2 (115.1-229.4)	
Bone marrow involvement		<0.001		0.008
present	8.9 (6.0-11.7)		7.5 (4.4-10.6)	
absent	155.3 (119.7-191.0)		161.9 (121.0-202.9)	
CNS involvement		0.06		0.12
present	4.9 (0-11.4)		7.1 (3.5-10.7)	
absent	125.8 (96.8-154.8)		128.8 (94.4-163.2)	
LDH				
> 3 x ULN	8.6 (4.4-12.9)	<0.001	7.5 (4.8-10.2)	0.05
≤ 3 x ULN	152.1 (118.7-185.6)		146.0 (107.6-184.4)	
> 10 x ULN	1.5 (0-9.3)	<0.001	8.6 (6.2-10.9)	0.24
≤ 10 x ULN	137.2 (109.0-165.5)		135.3 (101.2-169.5)[2]	
Anemia		0.004		0.07
present	11.2 (6.4-16.0)		11.9 (0-98.5)	
absent	167.7 (131.8-203.6)		160.2 (117.2-203.1)	
Thrombocytopenia		<0.001		<0.001
present	8.8 (4.2-13.3)		6.5 (3.1-9.8)	
absent	153.4 (122.8-183.9)		159.1 (122.3-195.9)	
Hypoalbuminemia		0.03		0.15
present	11.2 (0-60.3)		8.9 (0-90.7)	
absent	143.5 (113.4-173.7)		145.0 (108.6-181.3)	
Hyperuricemia		<0.001		0.10
present	8.8 (4.2-13.3)		9.0 (3.3-14.7)	
absent	158.4 (121.1-195.7)		142.9 (101.5-184.4)	
Renal dysfunction		0.008		0.63
present	1.8 (0-12.9)		159.2 (35.4-283.1)	
absent	127.1 (96.6-157.5)		100.2 (0-246.2)	
First-line regimen		0.55		0.09
HyperCVAD ± R	13.1 (0-71.0)		6.5 (4.2-8.7)	
DA R-EPOCH	50.7 (32.5-69.0)		47.2 (24.8-69.6)	
R-CODOX-M	58.7 (28.8-88.6)		38.3 (0-85.3)[2]	
CALGB 8811 ± R	178.6 (100.9-256.2)		201.5 (130.0-273.0)	
CHOP ± R	131.4 (89.0-173.9)		143.3 (96.3-190.3)	
BL-IPI		<0.001		0.04
Low-risk	192.8 (153.1-232.5)		176.7 (128.5-224.9)	
Intermediate-risk	107.4 (70,2-144,7)		103.8 (61.1-146.5)	
High-risk	6.9 (2.5-11.4)		8.6 (6.3-10.9)	

Table 3. Multivariable analysis of prognostic factors for OS (BL-IPI parameters separately)

Variable	Hazard ratio	95% CI	p
Age ≥ 55 years	2.4	1.2-5.1	0.02
ECOG performance status ≥ 2	4.3	2.1-8.8	<0.001
Advanced stage	4.2	1.4-13.0	0.01
Bone marrow involvement	2.6	0.9-7.6	0.09
CNS involvement	1.5	0.6-3.7	0.39
LDH > 10 x ULN	3.0	1.3-7.3	0.01
Anemia	1.9	0.8-4.3	0.12
Thrombocytopenia	2.1	0.8-5.7	0.14
Hypoalbuminemia	1.4	0.7-3.0	0.33
Hyperuricemia	3.3	1.6-6.9	0.002
Renal dysfunction	1.1	0.5-2.7	0.78

Variables which were shown to have statistically significant effects on OS in univariable analysis (including CNS involvement with borderline significance, p= 0.06) were further evaluated by multivariable analysis. Two different multivariable analyses were performed, with the parameters in BL-IPI separately or as a group. In both cases, advanced stage was statistically significant. In the first analysis, hyperuricemia and all BL-IPI parameters except CNS involvement (age, ECOG performance status, and serum LDH) were also significant, and in the second analysis, anemia was also significant other than BL-IPI risk group and advanced stage. Results are shown in Tables 3 and 4.

BL-IPI in our Cohort

The efficacy of the recently proposed BL-IPI was evaluated in our cohort. Low-risk group (28% of the patients) had a 3-year OS rate of 77.8%, intermediate-risk group (33% of the patients) had a 3-year OS rate of 61.1%, and high-risk group (39% of the patients) had a 3-year OS rate of 29.0% (Log Rank Chi-Square: 23.3, p< 0.001). 3-year DFS rates were also estimated and were as follows; 72.2% for the low-risk, 60.2% for the intermediate-risk, and 33.3% for the high-risk group (p= 0.04).

Efficacy of BL-IPI was further assessed in advanced stage patients in our cohort. Low-risk group had a 3-year OS rate of 64.8% whereas intermediate-risk group had 58.2%, and high-risk group had 22.6% (p< 0.001). On the other hand, 3-year DFS rates were as follows; 55.6% for the low-risk group, 57.1% for the intermediate-risk group, and 16.7% for the high-risk group and there was no statistically significant difference between the groups in terms of DFS (p= 0.06).

Table 4. Multivariable analysis of prognostic factors for OS (BL-IPI parameters as a group)

Variable	Hazard ratio	95% CI	p
Advanced stage	3.2	1.1-9.4	0.04
Bone marrow involvement	2.0	0.7-5.7	0.19
Anemia	2.4	1.1-5.2	0.02
Thrombocytopenia	1.8	0.7-4.6	0.20
Hypoalbuminemia	1.0	0.5-2.1	0.94
Hyperuricemia	2.1	1.0-4.4	0.06
Renal dysfunction	1.2	0.5-2.6	0.62
BL-IPI high-risk	2.7	1.3-5.7	0.01

Table 5. An alternative risk scoring system for BL patients

Risk factors	Assigned score	Total score (patient counts) and risk groups
Age ≥ 55 years	1	
LDH > 10 x ULN	1	≤ 1 (18): Low-risk
Hyperuricemia	1	2-4 (60): Intermediate-risk
ECOG performance status ≥ 2	2	≥ 5 (23): High-risk
Advanced stage (Stage 3 or 4)	2	

An Alternative Model

Advanced stage turned out to be a statistically significant risk factor in both univariable and multivariable analyses in our cohort; therefore, we proposed another prognostic model that includes advanced stage as a risk factor. As mentioned before, according to the results of multivariable analysis, risk factors that had significant effects on OS in our cohort were as follows; age ≥ 55 years, ECOG performance status ≥ 2, advanced stage, LDH > 10 x ULN, and hyperuricemia (serum uric acid > 7.2 mg/dl). These parameters were included in the alternative model and points were attained to each of them as described previously. Risk factors, points and risk groups that were determined according to survival curves are shown in Table 5.

When the alternative model was applied to our cohort; low, intermediate, and high-risk groups consisted of 18%, 59%, and 23% of the patients, respectively. 3-year OS rates were 87.1%, 59.5%, and 0% for low, intermediate, and high-risk groups, respectively (Log Rank Chi-Square: 51.1, p< 0.001) whereas 3-year DFS rates were 83.3%, 53.5%, and 0% (p= 0.002).

DISCUSSION

A successful prognostic risk assessment should also guide the treatment method apart from predicting survival. In a recent prospective, multicenter US study of a current BL treatment regimen, DA R-EPOCH, the protocol was equally effective across age groups, HIV status, and IPI risk groups.[14] However, treatment success was not satisfactory in advanced disease characterized by cerebrospinal fluid or bone marrow involvement. These findings indicate both the inadequacy of the IPI score[15] in determining the prognosis and treatment of BL, and the poor prognostic value of advanced disease in a current treatment platform and therefore the need for other prognostication methods and treatments.

In our multicenter retrospective cohort study, recently proposed BL-IPI was shown to be an efficient tool in risk stratification of adult BL patients, however when the subset of advanced stage patients was analyzed, it did not perform well. DFS analysis revealed that low-risk group had a lower survival rate than the intermediate-risk group and there was no statistically significant difference between the groups (p= 0.06). This is a matter of concern since advanced stage patients form approximately 70% of BL patients.[16]

The IPI risk score used in NHL and the dichotomous traditional risk classification of BL[17,18] both include advanced stage as a risk factor. In fact, a recent study by Lakhotia et al with 113 adult BL patients, who were treated by DA R-EPOCH, reported that patients who had CNS/bone marrow/peripheral blood involvement had lower survival rates than the patients who did not have any of these involvements and this trend was observed in both BL-IPI low/intermediate-risk and high-risk groups separately. They concluded that CNS/bone marrow/peripheral blood involvement, which indicated advanced stage disease, discriminated disease risk better than BL-IPI.[19] In similar, advanced stage resulted in inferior survival rates in our cohort. For all of these reasons, we believe that inclusion of only CNS involvement but not bone marrow/peripheral blood involvement or advanced stage is a weak aspect of BL-IPI score.

A study by Ribera et al reviewed the efficacy of BL-IPI in two prospective chemoimmunotherapy trials in Spain (BURKIMAB-08 and BURKIMAB-14,

a total of 277 patients) and showed that BL-IPI score effectively discriminated the risk groups in the whole group, however it did not predict the outcomes well in Burkitt's leukemia subgroup (n= 84).[20] Burkitt's leukemia patients form an important portion of advanced stage patients and they tend to develop CNS involvement early in the disease course.[11] Therefore, this finding is consistent with our and Lakhotia et al's findings that BL-IPI does not perform well enough in advanced stage patients.

Two recent retrospective studies, one by Chen et al from China[21] and another one by Sykorova et al from Czech Republic[22], also assessed the efficacy of BL-IPI score in cohorts of 336 and 101 adult BL patients, respectively, and they both concluded that the score discriminated the high-risk group successfully, however the low and intermediate-risk groups could not be distinguished. Moreover, Chen at al pointed out another prognostic index that consisted of the following biomarkers; platelets < 254×10^9/L, albumin < 40 g/L, LDH ≥ 334 U/L. The prognostic effects of high serum LDH and thrombocytopenia, which is an indirect sign of bone marrow involvement and hence advanced stage disease, are consistent with previous studies and our study; nonetheless they need to be supported by further studies.

As regards to the findings that support advanced stage is an important poor prognostic factor in BL, we tried to develop an alternative prognostic score that included advanced stage as a parameter. The alternative score consisted of the following parameters; age ≥ 55 years, ECOG performance status ≥ 2, advanced stage, LDH > 10 x ULN, and hyperuricemia (serum uric acid > 7.2 mg/dl) (Table 5). Even though it predicted outcomes successfully in our cohort, both in OS and DFS analyses, it needs to be validated by further studies.

The main limitations of this study are retrospective design and limited number of patients despite being a multicenter trial. Patients from a 20-year time window were included in order to increase the sample size, therefore the cohort is very heterogenous especially in terms of therapeutic approaches. In addition, MYC rearrangement was examined in nearly half (n= 53, 52,5%) of the patients, which is another limitation of the study. This is most probably caused by the fact that the test became popular after 2016 when WHO included the presence of MYC rearrangements as a diagnostic criterion for BL and an undeniably high proportion of our cohort had been diagnosed before this date.

Conclusion

Even though BL-IPI seems to be a useful prognostic index, it has its own limitations, especially in advanced stage patients. A risk score for BL patients including advanced stage as a risk factor, like ours, would be more suitable, however more studies with higher number of patients are needed to validate our model or develop alternative ones.

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