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Burkitt lymphoma-a retrospective analysis of data from the Registry of the Czech Lymphoma Study Group with external validation of the Burkitt lymphoma International Prognostic Index

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Burkitt lymphoma (BL) is a rare subtype of non-Hodgkin's lymphoma with an aggressive course. To refine the individual patient's prognosis, the International Prognostic Index for BL (BL-IPI) was recently developed and 4 risk factors (RF) were determined as optimal prognostic cut-off by multivariate analysis: age ≥40 years, lactate dehydrogenase >3× upper limit of normal, ECOG performance status ≥2, and central nervous system involvement. The BL-IPI distinguishes 3 prognostic groups, low (without RF), intermediate (1 RF), and high risk (2–4 RF), with significant differences in survival. The aim of the current project was to perform an external validation of the BL-IPI in 101 patients from the Registry of Czech Lymphoma Study Group diagnosed between 1999 and 2016 (median age, 45 years). The median follow-up was 50.4 months. The induction treatment included rituximab plus chemotherapy in 82% and chemotherapy alone in 18%. The overall response rate was 78% and the complete remission rate was 73%. According to BL-IPI, low/intermediate/high risk was present in 21/35/45% of patients, showing high similarity to the training BL-IPI US (United States) dataset (18/36/46%). There were significant differences in progression-free survival (PFS) and overall survival (OS) between patients with high vs. intermediate risk (PFS: hazard ratio 0.16, 95% confidence interval 0.08-0.31, p<0.0001; OS: hazard ratio 0.17, 95% confidence interval 0.09–0.35, p<0.0001) but not between patients with low vs. intermediate risk. The 3-year OS probability according to BL-IPI with low/intermediate/high risk was 96/76/59% in the BL-IPI training dataset vs. 95/85/45% in our external validation cohort; the 3-year PFS probability with low/intermediate/high risk was 92/72/53% in the BL-IPI training dataset vs. 95/85/42% in our cohort. In summary, our external validation of the BL-IPI confirmed a good separation of high-risk patients, who have a poor prognosis and for whom the new therapeutic approaches are needed; patients with low and intermediate risk had favorable clinical outcomes, and differences between these groups were not significant, likely due to a small number of patients.

Key words: Burkitt lymphoma, prognosis, treatment, survival

Burkitt lymphoma (BL) is a rare subtype of mature B-cell lymphoproliferative disorders with aggressive behavior [1]. The literature specific for BL is relatively scarce because of the rarity of the disease and the numbers of patients are usually small in published studies on this topic. Despite being typically diagnosed at an advanced stage, the disease is potentially curable [2, 3]. The principle of BL treatment is the administration of dose-intensive polychemotherapy with incorporated prophylaxis of the central nervous system (CNS). A modified combination of cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate with a combination of ifosfamide, vincristine, etoposide, high-dose cytosine-arabinoside (CODOX-M/IVAC,) and combination of cyclophosphamide, vincristine, doxorubicin,

and dexamethasone given as hyperfractionated therapy (hyperCVAD) is usually used for BL treatment [4, 5]. The dmCODOX-M/IVAC protocol for BL is an iteration of the original multiagent regimen designed by Magrath et al. in 1996 with the intention of developing a dose-intensive regimen while maintaining the efficacy of the therapy with reduced treatment-related toxicity [2, 6]. Low-intensity treatment approaches with dose-adjusted polychemotherapy of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (DA-R-EPOCH), and short course (SC)-EPOCH-R have been studied and are highly curative and well tolerated [7–9]. The benefit of rituximab administration in BL has been confirmed in several studies [10-12]. Elderly patients >60 years (y) do not usually tolerate intensive chemotherapy (CMT), and the therapeutic approach is rather palliative [13–16]. Many studies have contributed to the identification of negative risk factors for a worse prognosis, such as response to treatment, age, sex, lactate dehydrogenase (LDH) value, CNS/bone marrow involvement, and cytogenetic abnormalities [17, 18].

BL has a unique biology and clinical course and lacks a standardized prognostic model. The traditional International Prognostic Index used for diffuse large B-cell lymphoma is not suitable for use in BL patients, because BL is present at a younger age, the disease is usually diagnosed at an advanced stage, and most patients have elevated LDH. For predicting lymphoma prognosis, patients are usually stratified into high-risk and low-risk groups according to their LDH levels and the extent of the disease [2, 3]. However, this definition varies between studies, leaving 80–90% of patients in a large and heterogeneous "high-risk" group.

To refine the individual patient's prognosis, the International Prognostic Index for BL (BL-IPI) was recently developed and validated using an external dataset of patients [19, 20]. Age ≥40 y, ECOG performance status (PS) ≥2, Ann Arbor stage III/IV, bone marrow (BM) involvement, CNS involvement, LDH >3× upper limit of normal (ULN), low value of hemoglobin (<11.5 g/dl) and albumin (<3.5 g/dl) were associated with inferior progression-free survival (PFS) in univariate analysis. Four risk factors (RF) were determined as the optimal prognostic cut-off for PFS and overall survival (OS) by multivariate analysis: age ≥40 y, LDH >3× ULN, ECOG PS ≥2, and CNS involvement [19, 20].

The aims of the study were to assess outcomes for patients with Burkitt's lymphoma treated between 1999 and 2016 in the Czech Republic and to externally validate the BL-IPI.

Patients and methods

The Registry of CLSG (Czech Lymphoma Study Group) is a nationwide prospectively operated registry that has been collecting data about patients with newly diagnosed non-Hodgkin's lymphoma (NHL) from hemato-oncological centers throughout the Czech Republic since 1999 [21]. This project is a part of an Observational Epidemiological and Clinical Study (NiHiL) registered at clinicaltrials.gov (NCT03199066). All registered patients in the CLSG registry signed informed consent forms for the NiHiL project, which was approved by the multicentric ethics committee at University General Hospital, Prague, and the local ethics committee. The registry gathers anonymized data that consist of detailed clinical and laboratory data in newly diagnosed patients with NHL with regular follow-ups being carried out.

All of the pathology reports were reviewed centrally by an experienced hematopathologist who serves as a

Table 1. Baseline characteristics of BL patients from the Registry of CLSG-(n = 101)-external validation dataset (Column 1), BL-IPI training US dataset (Column 2).

Characteristics	External validation dataset n=101 (%)	BL-IPI training dataset [19] n=633 (%)
Median age (range), years	45 (18-84)	47 (33-59)
Male gender	75 (74)	479 (76)
Ann Arbor stage		
I–II	32	NA
III–IV	68 (67)	494 (78)
Missing	2	0
B-symptoms present	54 (53)	NA
LDH >3× ULN	40 (40)	268 (42)
ECOG PS >1	41 (41)	141 (22)
"Bulky disease" ≥5 cm		
Yes	57 (63)	NA
Missing	11	
EN involvement	85 (84)	NA
EN ≥2	54 (53)	270 (43)
CNS involvement	16 (16)	118 (19)
Missing	1	0
BM involvement		
Present	34 (35)	NA
Missing	5	
Groups according to BL-IPI		
Low-risk	21 (21)	114 (18)
Intermediate-risk	35 (35)	228 (36)
High-risk	45 (45)	291 (46)
Intensive chemotherapy	82 (84)	
Rituximab-containing therapy	81 (80)	578 (91)
First line regimen		
CODOX-M/IVAC +-R	68 (69)	194 (31)
HyperCVAD/HD MTX_ARA-C+-R	10 (10.5)	195 (31)
Other	20 (20.5)	244 (38)
Median follow-up (months)	50.4	45
PFS at 3 years	67%	65%
OS at 3 years	69%	70%

Abbreviations: BL-Burkitt lymphoma; CLSG-Cooperative Lymphoma Study Group; n-number; LDH-lactate dehydrogenase; ECOG PS-Eastern Cooperative Oncology Group Performance status; EN-extranodal; CNS-central nervous system; BM-bone marrow; ULN-upper limit of normal; CMT-chemotherapy; R-rituximab; CODOX-M/IVAC+-R-cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, vincristine, etoposide, high-dose cytosine-arabinoside with or without rituximab; hyperCVAD/HD MTX_ARA-C+-R-cyclophosphamide, vincristine, doxorubicin, dexamethasone/high dose methotrexate and cytarabine with or without rituximab; BL-IPI-The Burkitt Lymphoma International Prognostic Index; PFS-progression-free survival; OS-overall survival; NA-not availableç

national lymphoma expert. The histological diagnosis of BL was reviewed according to the World Health Organization Classification criteria of 2008 [22]. The initial staging included physical examination, computed tomography (CT) or fluorodeoxyglucose positron emission tomography combined with CT scan (FDG-CT/PET), bone marrow aspirate and biopsy, and examination of c-MYC (by immunohistochemistry and/or cytogenetics/FISH-fluorescence in situ hybridization).

Patients with a completely resected abdominal disease or extra-abdominal disease without elevation of serum LDH, with ECOG PS 0-1 and Ann Arbor stage I and II were considered as low-risk. All other patients fulfilled the criteria for having high-risk (HR) disease [2, 5, 23].

The treatment response was evaluated based on the criteria of the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma which was published in 1999 and later revised and updated in Lugano in 2014 [24–26].

The toxicity of treatment was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 4.0).

We carried out a retrospective analysis of the treatment results and outcomes of consecutive BL patients who were entered into the Registry of CLSG between 1999 and 2016. We externally validated the BL-IPI index in 101 (0.77%) patients with BL of 13,001 patients with NHL entered into the registry. The basic characteristics of the patients are summarized in Table 1.

Statistics. Overall survival and progression-free survival curves were estimated using the Kaplan-Meier method with differences compared using the stratified log-rank test. The data were analyzed using the statistical software MedCalc (MedCalc Software, Mariakerke, Belgium). PFS was defined as the time interval from the start of treatment until the first relapse/progression or death from any cause. OS was defined from the date of diagnosis until death from any cause.

The Fisher test was used to analyze differences in the categorical variables. Multivariate analysis was performed by the Cox regression analysis method using the backward stepwise selection process. All point estimates were presented with an appropriate 95% confidence interval. A p-value <0.05 was considered to be statistically significant; all p-values are double-sided.

Results

Treatment, response, and clinical outcome. Overall, 101 patients were included in the intention-to-treat (ITT) analysis of the results. First-line treatment is shown in Table 2.

Overall, 51 high-risk patients in our cohort were treated with high-dose CMT, which was modified to dm (dose modified) CODOX-M/IVAC with/without rituximab. Nine low-risk patients, who tolerated intensive treatment, were treated with the CODOX-M regimen with/without rituximab. The anthracyclines-based regimen CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), no-anthracycline regimen COP (cyclophosphamide, vincristine, prednisone), and administration of high-dose methotrexate monotherapy (HD MTX) were considered to be insufficient for BL treatment and were defined as nonintensive chemotherapeutic regimens.

The overall response rate (ORR) was 78%, and complete responses (CR) were achieved in 73% of patients in our cohort. Stable disease (SD) was present in 1% of the patients,

Table 2. First-line treatment (n=101).

	Number of patients (%)	Patients ≤60 y (number)	Patients >60 y (number)
CMT +/– Rituximab	98 (98)	79	19
CMT only	18 (18)	15	3
R-CMT	80 (80)	82	16
Intensive CMT	82 (82)	72	10
Main intensive CMT:			
dmCODOX-M	17 (17)	16	1
dmCODOX-M/IVAC	51 (51)	48	3
Other intensive CMT:	14 (14)	8	6
HyperCVAD without HD MTX_ARA-C	3 (3)	0	3
HyperCVAD-HD MTX_ARA-C	6 (6)	6	0
HD MTX_ARA-C	1 (1)	0	1
GMALL	4 (4)	2	2
Non-intensive CMT (CHOP, HD MTX, COP)	16 (16)	7	9
No CMT	3 (3)	0	3

Abbreviations: CMT-chemotherapy; R-rituximab; CODOX-M-cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate; IVAC-ifosfamide, vincristine, etoposide, high-dose cytosine-arabinoside; hyper-hyperfractionated; CVAD-cyclophosphamide, vincristine, doxorubicin, dexamethasone; HD MTX-high-dose methotrexate; CHOP-cyclophosphamide, doxorubicin, vincristine, prednisone; COP-cyclophosphamide, vincristine, prednisone, dm-dose-modified; ARA-C-cytosina-rabinoside; GMALL-German Multicentre Study Group for adult Acute Lymphoblastic Leukaemia

and primary progressive disease (PPD) was present in 13% of the patients. The response rate was higher in younger patients, with an 81% ORR (CR 77%). In the older patients (>60 y), the ORR was 66.6% (CR 57%), the SD was 0% and the PPD was 14%.

At the median follow-up of 50.4 months, 33 patients had died; more deaths were observed in older patients (n=14.6%) than in younger patients (n=19.2%), p=0.002. The main cause of death was disease progression in 22 patients.

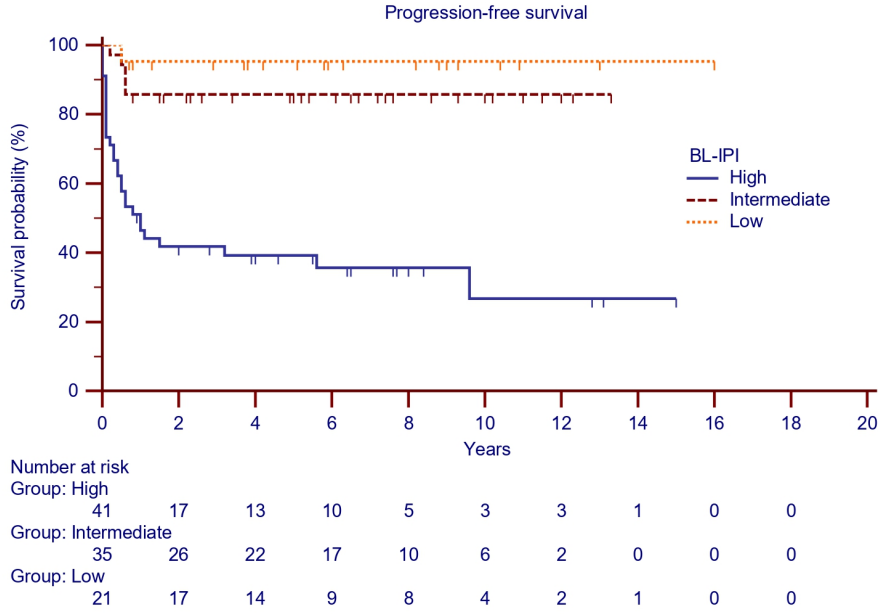

Figure 1. Progression-free survival according to BL-IPI risk groups in the external validation dataset.

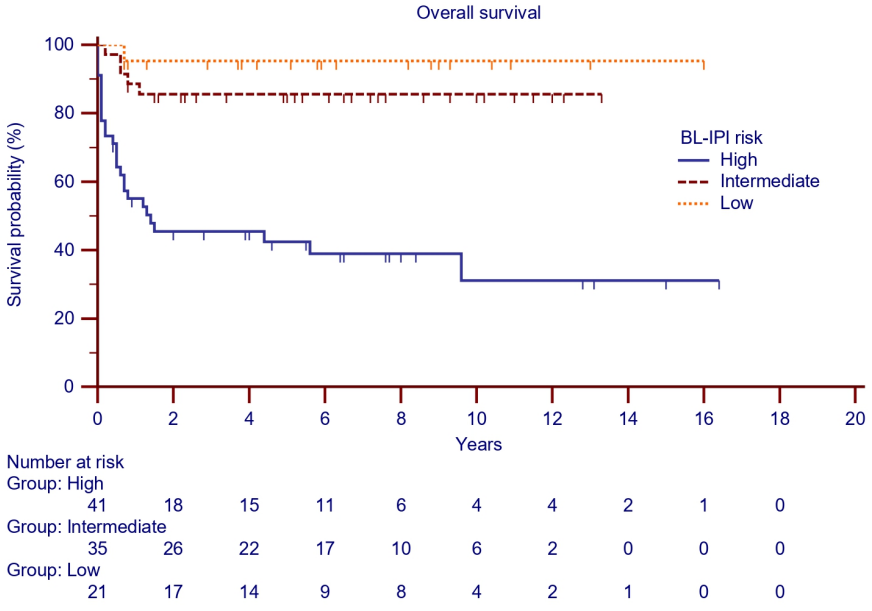

Figure 2. Overall survival according to BL-IPI risk groups in the external validation dataset.

The estimated 3-y PFS and OS were 67% and 69%, respectively. The median PFS and OS were not reached in all patients (n=101) and in patients ≤60 y (n=79). The median PFS in patients >60 y was 7.2 months (p=0.003), and the median OS was 14 months (p=0.001). The survival of low-risk patients was significantly better than that of HR patients in which the 3-y OS was 100% for low-risk and 66% for high-risk patients (p=0.04). The 3-y PFS was 100% for low-risk and 64% for high-risk patients (p=0.039).

Administration of dmCODOX-M/IVAC with/without rituximab did not result in significant improvement of PFS or OS in comparison to other CMT regimens in our cohort: dmCODOX-M/IVAC with/without rituximab with a 2-y OS 76%, 2-y PFS 72% vs. other CMT regimens (n=47) with a 2-y OS 68% and a 2-y PFS 66% (OS p=0.10, PFS p=0.23).

Multivariate Cox regression analysis for the external validation cohort. The failure to achieve CR, extranodal (EN) involvement, and advanced Ann Arbor stage IV-were independent risk factors for a shorter PFS in multivariate analysis. CNS involvement and failure to achieve CR were independent factors for OS (Table 3).

Toxicity. The most common grade ≥3 hematological toxicities included neutropenia (97.5%) with febrile neutropenia in 14.8%, thrombocytopenia in 80%, and anemia in 77.5% of the patients, who were treated with intensive CMT. Serious (grade ≥3) infections occurred in 48 (59%) of 82 patients. Nonhematological grade ≥3 toxicity consisted of gastrointestinal toxicity (GIT) in 29.6% of the patients; mucositis and colitis were the most common GIT adverse events. Hepatotoxicity grade ≥3 was present in 18.5% and renal toxicity in 16% of the patients. Tumor lysis syndrome was observed in 12.3% of the patients and 6% of them required hemodialysis. Cardiac toxicity occurred in 5 patients. We observed

five treatment-related deaths (4 of them were patients >60 y; one younger patient died of sepsis).

External validation of the BL-IPI. Low/intermediate/high risk according to BL-IPI was present in 21/35/45% of our cohort of patients. There were significant differences in PFS and OS between patients with low vs. high risk and intermediate vs. high risk but not between low and intermediate risk. Stratification according to BL-IPI enabled the identification of the high-risk group with a dismal prognosis (estimated 3-y OS of 49%). On the other hand, low- and intermediate-risk patients had favorable prognoses, with 3-y OS rates of 95% and 85%, respectively. There were no significant differences between these subgroups, likely due to the low number of patients (low-risk subgroup, n=21). The results of external validation of the BL-IPI are summarized in Table 4.

Using the BL-IPI scoring system, the estimated OS at 3 years for low/intermediate/high risk was 96/76/59% in the training US dataset (n=633) and 95/85/45% in our external validation cohort; the estimated PFS at 3 years was 92/72/53% vs. 95/85/42% (Table 5). Survival curves for PFS and OS in our external validation cohort (NiHiL project) are shown in Figure 1 and Figure 2.

Discussion

Here, we retrospectively analyzed a cohort of 101 cases of sporadic BL, who were entered into the CLSG registry between 1999 and 2016. With regard to the epidemiology of BL, our study represents a relatively large group of patients. The epidemiological data of BL in our study are in agreement with published data, in the USA, BL comprises <1% of NHL in adults [1]. The baseline characteristics of the patients (median age of 45 y, 74% male predominance, the presence of CNS disease in 16%, advanced stage at diagnosis in 68%, EN involvement in 84%, and the presence of B-symptoms in 53% of patients are comparable with those in the literature [13, 19, 22, 27–35]. We observed a higher incidence of BM involvement (35%) compared with previously published studies (10% of patients) [13]. Extranodal/CNS involvement, Ann Arbor stage, and failure to achieve CR appear to be significant for unfavorable clinical outcomes. Published studies reported a 47–91% CR in BL patients who were treated with rituximab in combination with CMT, with outcomes depending on the intensity of the treatment and the age of the patients [5, 7, 29–32, 36–39].

Overall, 51 patients in our cohort were treated with dmCODOX-M/IVAC with/without rituximab, with modifications according to LaCasce et al. [6, 23, 31] Administration of dmCODOX-M/IVAC with/without rituximab did not result in significant improvement of PFS or OS in comparison to other CMT regimens. This may be explained by the heterogeneity of CMT regimens, selection bias, and a relatively low number of patients in each subgroup. The importance of adding rituximab in combination with CMT dmCODOX-M/IVAC could not be evaluated due to the small number of patients in the chemotherapy-only group.

Intensive CMT administration was frequently complicated by hematological grade 3–4 toxicity in which anemia

Table 3. Multivariate analysis for overall survival (OS) and progression-free survival (PFS) in our external validation cohort (n = 101).

Multivariate analysis	Overall survival (OS)			Progression-free survival (PFS)		
Variable	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Failure of CR achievement	19.21	6.56–56.27	<0.0001	98.74	18.22–535.07	<0.0001
CNS involvement	5.76	1.61–20.58	0.0073	–	–	–
EN involvement	–	–	–	0.036	0.0027–0.51	0.014
Ann Arbor stage IV	–	–	–	0.14	0.025–0.76	0.023

Abbreviations: CNS-central nervous system; CR-complete remission; EN-extranodal; CI-Confidence Interval

Table 4. Progression-free survival and overall survival according to BL-IPI risk groups in our external validation cohort.

BL-IPI	Low vs. intermediate risk			Intermediate vs. high risk			Low vs. high risk		
Variable	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Overall survival	0.32	0.06–1.68	0.277	0.17	0.09–0.35	<0.0001	0.03–0.12	0.06	0.0001
Progression-free survival	0.33	0.06–1.71	0.279	0.16	0.08–0.31	<0.0001	0.03–0.11	0.05	<0.0001

Abbreviations: BL- IPI-The Burkitt Lymphoma International Prognostic Index; CI-Confidence Interval

Table 5. Progression-free survival and overall survival according to BL-IPI risk groups in our external validation cohort and BL-IPI training dataset.

BL-IPI risk groups	External validation dataset (n=101)		BL-IPI training dataset (n = 633) [19]	
	3-y PFS	3-y OS	3-y PFS	3-y OS
Low risk (0 factors)	95%	95%	92%	96%
Intermediate risk (1 factor)	85%	85%	72%	76%
High risk (2-4 factors)	42%	45%	53%	59%

Abbreviations: BL-IPI-The Burkitt Lymphoma International Prognostic Index; y-year; PFS-progression-free survival; OS-overall survival

was seen in 77.5%, neutropenia in 97.5%, thrombocytopenia in 80%, and febrile neutropenia in 14.8% of the patients. These observations are from data gathered after the administration of CODOX-M/IVAC [2] and dmCODOX-M/IVAC [5, 23, 40–42].

In patients treated with intensive CMT, we observed that acute renal failure due to tumor lysis syndrome (TLS) developed in 10 patients (12.3%), and half of them required hemodialysis. The most common manifestations of grade 3–4 GIT toxicity were mucositis and colitis.

A worse treatment response was seen in patients >60 y (a CR rate of 57% in elderly patients compared to 77% in younger patients). The more aggressive behavior of BL in elderly individuals, a worse tolerance of intensive therapy, or the impossibility of its administration due to comorbidities were the probable reasons for a decreased response rate and OS in the elderly population. CNS involvement in our study proved to be a significant risk factor for OS in multivariate analyses, which confirmed the reported data [19, 31, 43–47]. Clinical stage IV and EN disease (mostly BM involvement) were risk factors for a shorter PFS in multivariate analyses in which the data are comparable with other published works [28, 44, 48].

We confirmed better outcomes for low-risk patients in our analysis (3-y OS was 100% for low-risk and 66% for HR patients (p=0.04)), which is consistent with published data [9, 23]. Our low-risk group of patients with BL included 9 patients (9%) only and this incidence was lower than in other studies [2, 6, 23, 40, 41].

The BL-IPI is a novel prognostic index, that was recently developed from a large real-world evidence cohort of US adult patients, who were treated in the US between 2009 and 2018 (training dataset, n=633) [19]. The index was validated by an external international cohort (n=457) treated with standard intensive immunochemotherapy from multicentric registries from Australia, Canada, Denmark, Norway, and Sweden between 2004 and 2017 [20]. According to the BL-IPI model, 3 prognostic groups emerged with significantly different clinical outcomes: low- (without RF) risk patients had a significantly better prognosis than intermediate- (1 RF), and high-risk (2–4 RF) patients; BL-IPI was similarly prognostic for OS [19, 20]. Limitations of both studies included their retrospective design, heterogeneous induction treatment, and lack of formal central pathology review. In the external international validation cohort (n=457), most patients were treated with the CODOX-M/IVAC regimen with/without rituximab (65%) compared to the patients in the training US dataset (31%). On the other hand, the BL-IPI was validated by the study based on data from two prospective sequential trials BURKIMAB-08 and BURKIMAB-14, where the patients with BL and Burkitt leukemia were treated with consistent therapy between 2008 and 2020. Both trials showed similar rates of CR (CR 85% vs. 80%, 5-y OS 72% vs. 68%) allowing to consider them together for validation of the BL-IPI [49].

The distribution of risk groups was very similar in the BL-IPI training US dataset and in our external validation cohort. Using the BL-IPI scoring system, the OS probability was significantly different for these 3 risk groups in the training US dataset (n=633). The low-risk group showed significantly better outcomes than the high-risk group in our external validation cohort (NiHiL project). In our analysis, the BL-IPI efficiently separated the high-risk group, while the differences in PFS and OS between low- and intermediate-risk were not significant, likely due to the limited number of patients, especially in the low-risk subgroup (n=21). Several other factors may have contributed to these results: retrospective design of our analysis; in our external validation cohort, more patients were treated with intensive CMT but fewer patients received rituximab; in addition, more patients in our external validation cohort had worse ECOG PS and more frequent EN involvement against training the US cohort. The 3-year PFS and OS in all patients were very similar with a similar median follow-up. The value of the simplified BL-IPI index was therefore reinforced by our study to determine and refine the prognostication of untreated BL patients. Finally, it should be noted, that the intensity of treatment is considered depending on the age of patients (age is an important risk factor for the clinical outcome of patients with BL), and the BL-IPI index is valid only for patients treated with multiagent chemotherapy.

In conclusion, our real-world data focusing on the outcome of Burkitt lymphoma patients treated in the Czech Republic support the use of rituximab + intensive CODOX-M/IVAC chemotherapy in younger patients due to its high efficacy. Our external validation of the BL-IPI index in a cohort of unselected, consecutive patients with BL in the Czech Republic confirmed that BL-IPI is able to identify a subgroup of high-risk patients with dismal prognosis. For these patients, novel treatment strategies (such as currently investigated specific inhibitors of c-MYC, inhibition of CCND3, TCF3, CDK6, or the PI3 kinase) are needed.

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