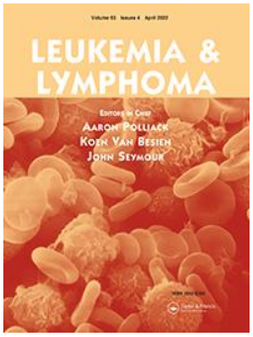

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LETTER TO THE EDITOR

Validation of the Burkitt Lymphoma International Prognostic Index in patients treated with two prospective chemoimmunotherapy trials in Spain

Josep-Maria Ribera[a], Olga García[a], Buenaventura Buendía-Ureña[b], Maria-José Terol[c], Ana Vicent[d], Ferran Vall-Llovera[e], Juan Bergua[f], Irene García-Cadenas[g], Jordi Esteve[h], Jordi Ribera[a], Evelyn Acuña-Cruz[i], Pilar Herrera[j], Jesus-Maria Hernández-Rivas[k], Pau Abrisqueta[l], José González-Campos[m], Carlos Rodríguez[n], Mariana Bastos-Oreiro[o], Eulàlia Genescà[a], Nerea Caminos[p], Maria-Paz Queipo de Llano[q], Antònia Cladera[r], Juan-Manuel Sancho[a] and on behalf of the Members of PETHEMA: Josep-Maria Ribera[a], Olga García[a], Ferran Vall-Llovera[e], Juan Bergua[f], Irene García-Cadenas[g], Jordi Esteve[h], Jordi Ribera[a], Evelyn Acuña-Cruz[i], Jesus-Maria Hernández-Rivas, José González-Campos[m], Eulàlia Genescà[a], Maria-Paz Queipo de Llano[q], Antònia Cladera[r] Members of GELTAMO: Buenaventura Buendía-Ureña[b], Maria-José Terol[c], Ana Vicent[d], Pilar Herrera[j], Pau Abrisqueta[l], Carlos Rodríguez[n], Mariana Bastos-Oreiro[o], Nerea Caminos[p], Juan-Manuel Sancho[a] Groups

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KEYWORDS
Burkitt lymphoma; prognosis; International Prognostic Index; validation

Chemoimmunotherapy including rituximab and high-dose or infusional chemotherapy constitute the standard treatment for patients with Burkitt's lymphoma (BL) or Burkitt's lymphoma and leukemia (BLL) [1–3]. Until recently, no specific prognostic index was available for patients with BL and BLL. The Burkitt Lymphoma (BL) International Prognostic Index (BL-IPI) identified four variables (age $\geq$40 years, performance status (PS) $\geq$2, serum lactate dehydrogenase (LDH) $>3\times$ upper limit of normal (ULN), and central nervous system (CNS) involvement) with independent prognostic value for progression-free survival (PFS) [4]. The BL-IPI was validated in an external data set of 457 patients treated in Europe, Canada, and Australia between 2004 and 2019.

As the BL-IPI was obtained from patients treated with various chemotherapy regimens suggested by the National Comprehensive Cancer Network guidelines (90% including rituximab), our objective was to validate this score in two prospective sequential chemoimmunotherapy trials for patients with BL and BLL conducted in Spain by the PETHEMA (Programa Español de Tratamientos en Hematología) and GELTAMO (Grupo Español de Linfomas y Trasplante de Medula Osea) groups.

From 2008 to 2020, two consecutive prospective trials of chemoimmunotherapy for patients with sporadic and immunodeficiency-related BL/BLL (BURKIMAB-08 and BURKIMAB-14, Clinicaltrials.gov Identifier: NCT00388193 and NCT05049473, respectively) were conducted in Spain [5,6]. The diagnosis of BL was performed according to the 2016 World Health Organization Classification and specific cytogenetic or *MYC* rearrangements were

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Supplemental data for this article can be accessed here.

Table 1. Comparison of the main clinical and biologic characteristics of patients from the two BURKIMAB trials with those from the BL-IPI cohort.

	BURKIMAB-08 and BURKIMAB-14 ($n = 277$)	BL-IPI series derivation cohort ($n = 633$)
Gender, male, *n* (%)	206/277 (74%)	479/633 (76%)
Age, years, median (min; max)	47 (15; 83)	47 (IQR: 33–59)
Diagnosis, *n* (%)		
BLL	84/277 (30%)	NS
BL	193/277 (70%)	NS
HIV-infected, *n* (%)	74/277 (27%)	140 (22%)
Extranodal involvement ≥2, *n* (%)	121/275 (44%)	270 (43%)
Ann Arbor stage, *n* (%)		
I–II	63/262 (24%)	139 (22%)
III–IV	199/262 (76%)	494 (78%)
ECOG ≥2, *n* (%)	105/272 (39%)	141 (22%)
CNS involvement, *n* (%)	39/276 (14%)	118 (19%)
LDH >3x ULN, *n* (%)	129/220 (59%)	268 (42%)
BL-IPI score, *n* (%)		
Low (0 factors)	22/230 (10%)	18%
Intermediate (1 factor)	65/230 (28%)	36%
High (2–4 factors)	143/230 (62%)	46%

BL: Burkitt lymphoma; BLL: Burkitt lymphoma and leukemia; BL-IPI: Burkitt Lymphoma International Prognostic Index; HIV: human immunodeficiency virus; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; LDH: lactic dehydrogenase; ULN: upper limit normal; IQR: interquartile range; NS: not specified.

required for inclusion of patients in both trials. Burkitt's leukemia was considered when infiltration by Burkitt's cells in bone marrow was greater than 20%. Both trials were based on the same blocks of dose-intensive chemo-immunotherapy including rituximab, high-dose methotrexate, high-dose cytarabine, and cyclophosphamide/ifosfamide, among other drugs (Supplemental Table 1). CNS prophylaxis included triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) in the pre-phase and in every treatment block, for a total of nine doses. Patients with non-bulky stages I–II BL received four blocks of therapy whereas patients in stages I–II with bulky mass or in stages III–IV received six blocks followed by two additional doses of rituximab. A 50% reduction of doses of methotrexate and cytarabine was scheduled for patients over 55 years. As an excess of toxicity (especially mucositis and infections) was observed in patients in complete response (CR) from the BURKIMAB-08 trial [5], a 33% reduction of doses of methotrexate and cytarabine was performed in patients with CR in the ongoing BURKIMAB-14 trial [6]. Response was assessed by clinical, morphologic, and imaging techniques (computed tomography (CT) scan in the BURKIMAB-08 trial and positron emission tomography (PET)-CT scan in the BURKIMAB-14 trial) at the end of the second block of treatment.

Both trials showed similar rates of CR and overall survival (OS) (CR 85% vs. 80%, 5-year OS 72% vs. 68%), allowing us to consider them together for validation of the BL-IPI. Although the median follow-up of patients in both trials was 5.4 years (range, 0.1–15.5), the follow-up of the patients was truncated at 5 years for this study to ensure full comparability with the results of the BL-IPI.

A total of 277 patients were included (BURKIMAB-08: 185, BURKIMAB-14: 92). The median age (range) was 47 (15–83) years, and 181 (65%) were over 40 years of age. One hundred and ninety-three patients (70%) had BL, and the remaining 84 (30%) BLL. Seropositivity for human immunodeficiency virus (HIV) was detected in 74 (27%) patients. The PS was ≥2 in 105/272 (39%), serum LDH levels were ≥3 × upper age limit in 129/220 (59%) and CNS involvement at diagnosis was present in 39/276 (14%). Table 1 shows the comparison of the main clinical and biologic characteristics of patients from the two BURKIMAB trials with those of the BL-IPI cohort. The distribution of patients according to the number of risk factors was: 0: 22 (10%), 1: 65 (28%), 2: 85 (37%), 3: 44 (19%), and 4: 14 (6%). The 3-year PFS (95% confidence interval (CI)) for the whole series was 70% (64%, 75%), and the 3-year OS (95% CI) was 72% (66%, 77%). The 3-year PFS according to risk groups was: low-risk (0 risk factors; 10% of patients) 100% (NA), intermediate risk (one risk factor; 28% of patients) 78% (66%, 87%), and high-risk (≥2 factors; 62% of patients) 56% (47%, 63%) ($p < .001$, Figure 1(A)). In turn, the 3-year OS (95% CI) according to risk groups was: low-risk (0 risk factors; 10% of patients) 100% (NA), intermediate risk (one risk factor; 28% of patients) 82% (69%, 89%), and high-risk (≥2 factors; 62% of patients) 56% (47%, 64%) ($p < .001$, Figure 1(B)).

We further tried to validate the BL-IPI in patients with Burkitt's leukemia ($n = 84$). As expected, the distribution according to IPI score was different: low-risk ($n = 1$, 1%), intermediate-risk ($n = 6$, 8%), and high-risk ($n = 68$, 91%). The OS and PFS probabilities (95% CI) were of 100% (NA) in patients with low and intermediate-risk vs. 100% (NA), 53% (41–64%) and 53% (41–65%), respectively, for high-risk cases (Supplemental Figure 1). The same approach was performed for the 74 HIV-positive patients, in 57 of whom all variables of BL-IPI were available for analysis. The distribution of BL-IPI categories showed: low-risk ($n = 5$, 9%), intermediate-risk ($n = 19$, 33%), and high-risk ($n = 33$, 58%). This distribution was not significantly different from that of the non-HIV-infected patients

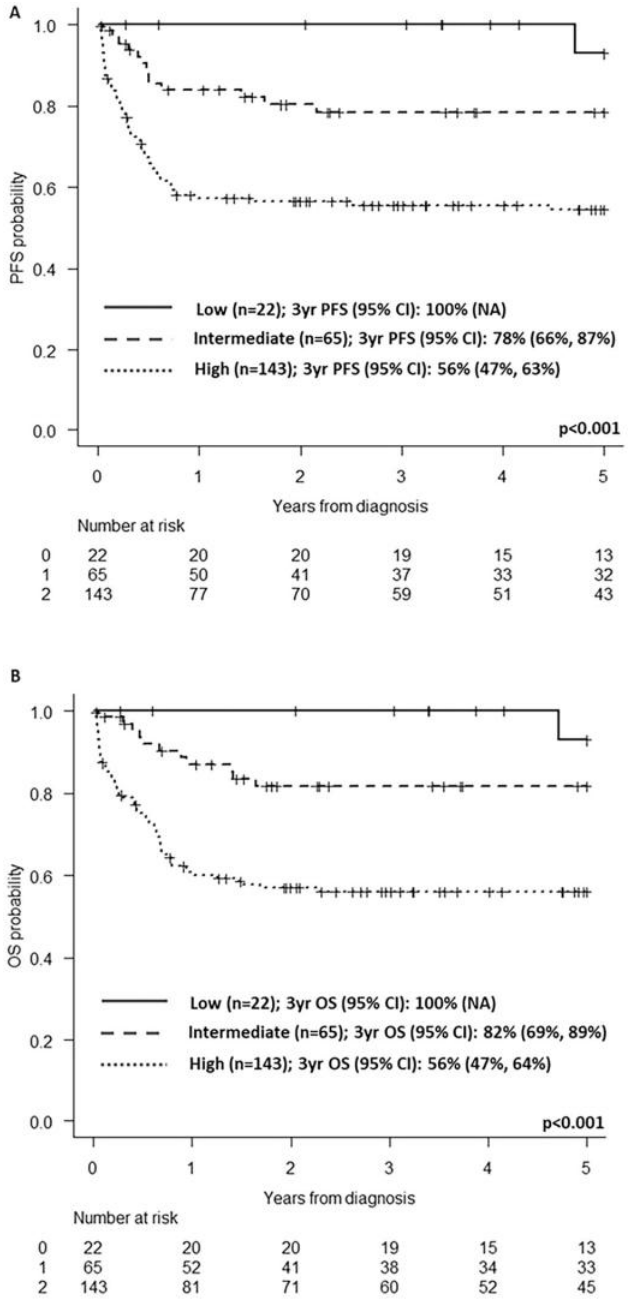

Figure 1. Progression-free survival (panel A) and overall survival (panel B) according to the BL-IPI derived groups for patients included in the BURKIMAB-08 and BURKIMAB-14 trials.

(p=.618). The OS and PFS probabilities (95% CI) according to each category were: low-risk 100% (NA) and 100% (NA), intermediate-risk 50% (25–70%) and 50% (25–70%), and high risk 46% (28–61%) and 42% (25–58%), respectively (Supplemental Figure 2).

This study shows that the clinical and biologic characteristics of adult patients with BL and BLL were similar to those of patients from the BL-IPI cohort. The distribution of patients according to the number of risk factors was similar, although the proportion of patients with high-risk scores was higher in our series, because of a higher percentage of cases with an Eastern Cooperative Oncology Group (ECOG) score $\geq$2 and high LDH levels. The 3-year PFS and OS probabilities were very similar to those from the BL-IPI series. Harrell's *C*-index, a concordance measurement for the validation, was similar to that from the BL-IPI cohort (0.64 and 0.67, respectively). Consequently, the BL-IPI was validated in our series of patients with BL and BLL. The BL-IPI derived groups could not discriminate adequately the three risk groups when the analysis was performed exclusively in patients with Burkitt's leukemia or with HIV-infection.

In the original publication, the BL-IPI was externally validated by pooling data from patients treated with standard immunochemotherapy from multi-institutional registries from Australia, Canada, Denmark, Norway, and Sweden (2004–2017) and from a specifically collected data set from eight hospitals in the UK (2008–2019) [4]. Most patients in the validation cohort received the CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine) regimen ± rituximab. However, the data collected in both the derivation and the validation cohorts were retrospective, and the treatment schedules given to patients were not homogeneous. The present study is based on data from two prospective sequential trials including the same drugs and schedules, only differing in the dose-intensity of methotrexate and cytarabine in patients who achieved CR in the second trial. For that reason, we think that the validation performed with patients from the BURKIMAB-08 and BURKIMAB-14 trials reinforces the value of BL-IPI for prognostication in patients with BL and BLL.

Disclosure statement

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