Comparison of International Prognostic Indices and Validation Study for Patients with Diffuse Large B-Cell Lymphoma in the Rituximab Era

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ABSTRACT

In diffuse large B-cell lymphoma (DLBCL), patients needing new alternative regimens in first-line treatment should be selected with better risk classification. After International Prognostic Index (IPI), Revised-IPI (R-IPI), National Comprehensive Cancer Network (NCCN)-IPI, and Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO)-IPI, have been developed to improve risk predictions. This study compared performances of four prognostic indices concerning differentiation of overall survival (OS), the most critical endpoint. The study was conducted on 116 patients diagnosed with DLBCL. Patients with primary nervous system and testicular DLBCL, and post-transplant lymphoproliferative disorders, were excluded. The fitting of prognostic indices for database and the prediction of patient discrimination were compared using Akaike's information criterion and concordance index. Of the study cohort, 63.8% were male, the median age was 56 (18-88), and median follow-up term was 45.6 (0.3-75.2) months. All factors, constituting IPI and R-IPI scores, demonstrated a significant difference in OS. Involvements of the extranodal regions specified in NCCN-IPI and elevated serum beta-2 microglobulin levels in GELTAMO-IPI had prognostic significance (p= 0.005 and p= 0.040, respectively). Each of the four prognostic indices, resulted in risk groups with significantly different OS. R-IPI provided the best fit for database, while NCCN-IPI provided the best discrimination between patients with high and low OS. Although NCCN-IPI provides the best discrimination between patients with short and long OS, using original IPI still seems acceptable in the rituximab era. Integration of tumor molecular characteristics into NCCN-IPI may better characterize high-risk group in new treatment approaches.

Keywords: International Prognostic Index, National Comprehensive Cancer Network, Validation, Diffuse Large B-Cell Lymphoma, Rituximab

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of B-cell lymphoma, demonstrating significant heterogeneity when newly diagnosed patients are evaluated according to their respective survival status.[1] Therefore, identification of prognostic markers and a more correct risk classification are essential. International Prognostic Index (IPI) is the first prognostic scoring system, developed in 1993 and is still being widely used.[2] IPI identifies four independent patient groups (low, low-intermediate, high-intermediate and high risk) and has constituted a standard and practical prognostic tool for DLBCL patients. Despite advances in understanding the molecular genetic characteristics of DLBCL, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or similar regimens continue to be the standard therapeutical regimen for DLBCL.[3] While the addition of rituximab to the chemotherapy protocol has greatly improved overall survival (OS), IPI has failed in the identification of patients with poor outcomes despite being a useful prognostic model.[4]

Revised IPI (R-IPI) has been developed for better risk classification of newly diagnosed patients, who are treated particularly with the R-CHOP regimen.[5] R-IPI uses the same risk variables and the same scoring model for each risk variable with IPI yet redistributes scores to constitute three risk groups (Very good, good, and poor risk).

For DLBCL patients, who are treated with R-CHOP, the National Comprehensive Cancer Network (NCCN)-IPI score, aiming to define a subgroup with 5-year OS < 50%, has been developed using the NCCN database as an improvement on IPI and R-IPI.[6] Using NCCN-IPI, the patients were also similarly divided into four groups, as in the original IPI. Instead of the conventional "> 1 extranodal area involvement" definition, NCCN-IPI has included the localization of extranodal disease (bone marrow, central nervous system, liver/gastrointestinal system, and lung). In addition, NCCN-IPI allows more robust stratification of age and serum lactate dehydrogenase (LDH) levels, compared to IPI. Subsequently, Grupo Español de Linfomas y Trasplante de Médula Ósea (GELTAMO) have developed the improved GELTAMO-IPI, comprising beta-2 microglobulin (β2M) as a novel prognostic factor.[7]

An important issue is that the patients in different ethnic groups were not homogeneously represented in the creation of such prognostic models. To this day, it is not known which prognostic model better differentiates different ethnic populations of DLBCL patients, treated with chemoimmunotherapy. This study, by using an independent clinical database, aimed to present real-life data and to compare the performances of four clinical scoring systems, in terms of the differentiation of OS, the most critical endpoint, in a homogeneous cohort of Turkish DLBCL patients.

PATIENTS and METHODS

Patients and Inclusion Criteria

The study was conducted on 116 patients, who had been diagnosed with DLBCL in Bursa Uludag University, Faculty of Medicine Hospital between January 2015 and December 2019. Patients, who were over 18 years of age, who had been diagnosed with de novo DLBCL and had received induction therapy with R-CHOP or R-CHOP-like regimens, were included. R-CHOP-like regimens include different attenuated immunochemotherapy regimens, aiming to prevent excessive toxicity. In our study, rituximab, together with cyclophosphamide, vincristine, and prednisone (R-CVP), were administered as an anthracycline-free treatment regime. Induction therapy consisted of R-CHOP or R-CHOP-like regimens, administered every 21 days for 6 to 8 cycles. DLBCL diagnosis was reported in accordance with World Health Organization 2016 Classification.[8] Due to unique biological characteristics, patients with the primary DLBCL of the central nervous system and primary testicular DLBCL and post-transplant lymphoproliferative disorders, were excluded. In addition, patients with missing data to assess any prognostic score, were excluded. Response to treatment was evaluated with positron emission tomography/computerized tomography (PET/CT) with ^{18}F-Fluorodeoxyglucose. Response to treatment assessment was based on Lugano criteria.[9] Ethics committee approval was obtained for the study (Bursa Uludag University date, 10 June 2021; Nr. 2011-KAEK-26/354). All ethical issues were conducted strictly in accordance with the Declaration of Helsinki. All patients granted informed consent during their admission to Bursa Uludag University, Faculty of Medicine Hospital.

Assessment of Prognostic Models

Using our study cohort, we compared IPI, R-IPI, NCCN-IPI and GELTAMO-IPI with each other. Variables and risk classification in each prognostic index were retrospectively assessed by considering original studies.[2,5-7] LDH and serum β2M levels were normalized on the basis of local laboratory results.

Statistical Analysis

Descriptive statistics were reported for baseline characteristics, such as frequency and percentage values in categorical variables. The primary variable of interest and endpoint was the OS, defined as the time from diagnosis to death for any cause. Surviving cases were censored on the last control date. In the comparison of OS on the basis of risk

groups, Kaplan-Meier (Log-Rank test) analysis was used. COX regression analysis was used in the evaluation of risk factors, affecting OS. Agreement between prognostic indices was examined using Kappa statistics. Using Akaike's information criterion (AIC) and concordance index (C-index), stratified models were compared for each risk point. AIC value showed the consistency of the data with the model. Models with small AIC values showed better fit compared to models with large AIC values on the same data. The C-index value was between 0 and 1. A C-index value for the models that close to 1 showed that the model makes good discrimination among patients. Data related to prognostic models was analyzed using IBM SPSS V23 and R version 4.2.1 program. The significance level was taken as $p< 0.05$.

RESULTS

Patient Characteristics

In the study, 116 patients, who had been diagnosed with DLBCL between January 2015 and December 2019 and who had been administered rituximab-based induction treatment regimen, were included. Of these patients, 63.8% were male the median age was 56 (18-88) and 42.2% were over 60 years of age. 95.7% of patients had been administered R-CHOP as induction therapy. The basic characteristics of patients are given in Table 1.

Table 1. Patient characteristics

	n	%
Age (years)		
≤ 60	67	57.8
> 60	49	42.2
Age (years)		
≤ 40	24	20.7
41 - 60	43	37.1
61 - 75	43	37.1
> 75	6	5.2
Age (years)		
< 65	76	65.5
65 - 79	38	32.8
≥ 80	2	1.7
Gender (male)	74	63.8
ECOG performance status		
0 - 1	71	61.2
2	32	27.6
3 - 4	13	11.2
Ann Arbor staging (III-IV)	75	64.7
LDH (normalized ratio)		
≤ 1	51	44
> 1 to ≤ 3	47	40.5
> 3	18	15.5
Extranodal involvement areas (>1)	31	26.7
Distinct extranodal sites for NCCN-IPI	44	37.9
Beta-2 microglobulin (normalized ratio >1)	50	43.1
Induction therapy		
R-CHOP	111	95.7
R-CVP	5	4.3

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, NCCN: National Comprehensive Cancer Network, IPI: International Prognostic Index, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CVP: Rituximab with cyclophosphamide, vincristine, and prednisone.

Outcome According to Clinical Scoring Systems

All patients were grouped according to the four clinical risk scoring systems. In line with the design, patients with high-intermediate and high-risk groups in IPI, belonged to poor risk in R-IPI and those in the low-intermediate risk category in IPI, belonged to good risk in R-IPI. Patients in low-risk in IPI, were divided between good risk and very good risk groups in R-IPI (70% and 30%, respectively). A moderate agreement was found between IPI and NCCN-IPI classifications ($\kappa= 0.472$; $p< 0.001$); while 69 out of 116 cases (59.5%) were in similar risk categories, 47 (40.5%) were in adjacent risk categories. A minimal agreement was found between IPI and GELTAMO-IPI classifications ($\kappa= 0.386$; $p< 0.001$). While 61 cases (52.6%) were in similar risk categories, 51 (44%) were in adjacent risk categories. Risk categories were drastically different only in 3.4% of patients (4 patients, designated as high-risk according to IPI and low-intermediate risk according to GELTAMO-IPI). A moderate agreement was found between NCCN-IPI and GELTAMO-IPI classifications ($\kappa= 0.498$; $p< 0.001$); while 77 cases (66.4%) were in similar risk categories, 38 (32.8%) were in adjacent risk groups. Risk categories were drastically different only in 1 patient (designated as high-risk

Table 2. Comparison of risk groups of prognostic models

	IPI n (%)	NCCN-IPI n (%)	GELTAMO-IPI n (%)
Low	40 (34.5)	15 (12.9)	14 (12.1)
Low-intermediate	24 (20.7)	49 (42.2)	70 (60.3)
High-intermediate	26 (22.4)	36 (31)	15 (12.9)
High	26 (22.4)	16 (13.8)	17 (14.7)
		R-IPI [n (%)]	
Very Good		12 (10.3)	
Good		52 (44.8)	
Poor		52 (44.8)	
	Kappa Value	p-value	
IPI vs. R-IPI	0.396	< 0.001	
IPI vs. NCCN-IPI	0.472	< 0.001	
IPI vs. GELTAMO-IPI	0.386	< 0.001	
R-IPI vs. NCCN-IPI	0.594	< 0.001	
R-IPI vs. GELTAMO-IPI	0.490	< 0.001	
NCCN-IPI vs. GELTAMO-IPI	0.498	< 0.001	

IPI: International Prognostic Index, R-IPI: Revised IPI, NCCN: National Comprehensive Cancer Network, GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula ósea.

by NCCN-IPI and low-intermediate risk by GELTAMO-IPI). The best agreement between prognostic models was between revised R-IPI, which is recommended for patients, treated with rituximab, and recently used NCCN-IPI ($\kappa = 0.594$; $p < 0.001$) (Table 2).

Prognostic Significance of Each Risk Factor Used in IPI, R-IPI, NCCN-IPI, and GELTAMO-IPI

All prognostic factors, constituting IPI and R-IPI scores, demonstrated a significant difference in terms of OS. Although more excellent categorization of age and serum LDH levels in NCCN-IPI resulted in a more effective risk classification, no statistical significance was detected between age ≤40 years vs. 41-60 years and ≤40 years vs. 61-75 years (p values, 0.139, 0.716, respectively). In addition, there was no significant difference between LDH normalized ratio ≤ 1 vs. 1-3 ($p = 0.221$). The involvement of extranodal regions, specified by NCCN-IPI, had prognostic significance ($p = 0.005$). In GELTAMO-IPI, cases with elevated serum β2M levels, showed substantially lower OS ($p = 0.040$) (Table 3).

Overall Survival Outcomes

The median follow-up term was 45.6 (0.3-75.2) months. Thirty-two out of 116 enrolled patients (27.6%), died during follow-up failing to achieve median OS term. The median survival for 32 patients, who passed away during follow-up, was 8.5 (0.3-51.7) months. Survival rates for patients in different groups by each prognostic index and Cox regression analysis, are shown in Table 4. Each of the four prognostic indices resulted in risk categories with substantially different OS (for IPI, R-IPI, and NCCN-IPI, $p < 0.001$, for GELTAMO-IPI $p = 0.001$, Figure 1). NCCN-IPI had the most significant absolute difference between the highest and lowest risk categories in terms of mortality percentage (Table 4). Although R-IPI, compared to IPI, provided better identification of patient subgroup with a more favorable long-term survival, it created a poor-risk group, consisting of patients with heterogeneous results. NCCN-IPI improved IPI by identifying a less heterogenous high-risk category. A common but clinically significant weakness of clinical scoring systems, including R-IPI and NCCN-IPI, is their inability to adequately identify a subset of patients with very poor survival.

Table 3. Stratified models for OS of individual risk factors, including IPI, R-IPI, NCCN-IPI, and GELTAMO-IPI

	Mortality			
	Living (n = 84)	**Dead (n = 32)**	**Hazard Ratio (95% CI)**	**p**
Age (IPI, R-IPI)				
≤ 60 years	54 (80.6)	13 (19.4)	Reference	
> 60 years	30 (61.2)	19 (38.8)	2.2 (1.08-4.45)	0.029
Age (NCCN-IPI)				
≤ 40 years	17 (70.8)	7 (29.2)	Reference	
41-60 years	37 (86)	6 (14)	0.44 (0.15-1.31)	0.139
61-75 years	28 (65.1)	15 (34.9)	1.18 (0.48-2.9)	0.716
> 75 years	2 (33.3)	4 (66.7)	3.83 (1.12-13.12)	0.033
Age (GELTAMO-IPI)				
< 65 years	58 (76.3)	18 (23.7)	Reference	
65-79 years	26 (68.4)	12 (31.6)	1.35 (0.65-2.81)	0.419
≥ 80 years	0 (0)	2 (100)	19.61 (4.01-95.97)	< 0.001
Ann Arbor staging				
I-II	35 (85.4)	6 (14.6)	Reference	
III-IV	49 (65.3)	26 (34.7)	2.79 (1.14-6.78)	0.024
ECOG performance status (IPI, R-IPI, NCCN-IPI)				
0 - 1	61 (85.9)	10 (14.1)	Reference	
≥ 2	23 (51.1)	22 (48.9)	4.75 (2.24-10.07)	< 0.001
ECOG performance status (GELTAMO-IPI)				
0 - 1	61 (85.9)	10 (14.1)	Reference	
2	18 (56.3)	14 (43.8)	4.07 (1.80-9.19)	< 0.001
3 - 4	5 (38.5)	8 (61.5)	6.74 (2.65-17.16)	< 0.001
Extranodal involvement areas (IPI, R-IPI)				
≤ 1	67 (79.8)	17 (20.2)	Reference	
> 1	16 (51.6)	15 (48.4)	2.66 (1.33-5.33)	0.006
Distinct extranodal sites* (NCCN-IPI)				
Absent	59 (81.9)	13 (18.1)	Reference	
Present	25 (56.8)	19 (43.2)	2.75 (1.36-5.57)	0.005
LDH normalized ratio (IPI, R-IPI, GELTAMO-IPI)				
≤ 1	42 (82.4)	9 (17.6)	Reference	
> 1	42 (64.6)	23 (35.4)	2.25 (1.04-4.88)	0.039
LDH normalized ratio (NCCN-IPI)				
≤ 1	42 (82.4)	9 (17.6)	Reference	
1 - 3	34 (72.3)	13 (27.7)	1.7 (0.73-3.98)	0.221
> 3	8 (44.4)	10 (55.6)	3.97 (1.60-9.84)	0.003
Beta-2 microglobulin (GELTAMO-IPI)				
Not increased	53 (80.3)	13 (19.7)	Reference	
Increased	31 (62)	19 (38)	2.1 (1.04-4.25)	0.040

*IPI: International Prognostic Index, R-IPI: Revised IPI, NCCN: National Comprehensive Cancer Network, GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula ósea, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, *Bone marrow, central nervous system, liver, gastrointestinal system or lung involvement.*

The AIC estimates each prognostic model's quality compared to other models. AIC uses a model's maximum likelihood estimation (log-likelihood), which deals with the goodness of fit. AIC scores for models with high log-likelihood are low. This means that the lower AIC scores represent better models. In prognostic models, classified in line with the study, R-IPI provided the best fit for data, followed by NCCN-IPI, IPI and then GELTAMO-IPI (as shown with the lowest AIC value: 236, 238.8, 239.2, 242.3, respectively; Table 5). NCCN-IPI provided the best discrimination between patients

Table 4. Cox regression analysis results for OS in risk groups by prognostic models

	Mortality			
	Living (n = 84)	**Dead (n = 32)**	**Hazard Ratio (95% CI)**	**p**
IPI				
Low	37 (92.5)	3 (7.5)	Reference	
Low-intermediate	20 (83.3)	4 (16.7)	2.45 (0.55 - 10.96)	0.242
High-intermediate	17 (65.4)	9 (34.6)	5.95 (1.61 - 21.99)	0.008
High	10 (38.5)	16 (61.5)	11.92 (3.46 - 41.1)	< 0.001
R-IPI				
Very Good	12 (100)	0 (0)	Reference*	
Good	45 (86.5)	7 (13.5)		
Poor	27 (51.9)	25 (48.1)	5.77 (2.49 - 13.36)	< 0.001
NCCN-IPI				
Low	14 (93.3)	1 (6.7)	Reference	
Low-intermediate	43 (87.8)	6 (12.2)	1.99 (0.24 - 16.49)	0.526
High-intermediate	21 (58.3)	15 (41.7)	8.51 (1.11 - 64.6)	0.038
High	6 (37.5)	10 (62.5)	13.94 (1.78 - 109.1)	0.012
GELTAMO-IPI				
Low	14 (100)	0 (0)	Reference**	
Low-intermediate	54 (77.1)	16 (22.9)		
High-intermediate	8 (53.3)	7 (46.7)	3.12 (1.28 - 7.59)	0.012
High	8 (47.1)	9 (52.9)	3.65 (1.61 - 8.29)	0.002

IPI: International Prognostic Index, R-IPI: Revised IPI, NCCN: National Comprehensive Cancer Network, GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula ósea.
* Very good-risk and good-risk patient groups were combined, due to mortality was not observed in very good-risk patients.
** Low-risk and low-intermediate risk patient groups were combined, due to no deaths were observed in those with low-risk patients.

with high and low OS, followed by IPI, R-IPI, and then GELTAMO-IPI (as shown with the highest C-index: 0.696, 0.694, 0.676, 0.673, respectively; Table 5).

DISCUSSION

This study showed that, NCCN-IPI, which is one of the scoring systems, developed to improve IPI, provided the best discrimination between patients with short and long OS. In some studies, it has been reported that the effectiveness of distinguishing risk groups in DLBCL patients, diminished with the addition of rituximab to treatment.[10] However, in support of other studies, our study also confirmed that the original IPI was still valid in the age of rituximab-based therapy.[11] However, the predictive power of all these indices for risk groups in different ethnic populations, is still uncertain. Our study analyzed all prognostic indices in a homogeneous cohort of Turkish DLBCL patients, treated with R-CHOP or similar regimens.

All of the four prognostic models were calculated using clinical and laboratory characteristics, which are parts of standard diagnostic procedures and which may easily be obtained. In addition, there are no significant differences in terms of difficulty of calculation of scores and the effort; because all four indices mainly require the measurement of the same characteristics. The disadvantages of NCCN-IPI are that it has not been used for as long as IPI and lack of accessibility in analyses, requiring comparison of data between studies. Therefore, it is recommended to collect information that is suitable for the calculation of NCCN-IPI and IPI scores.[1] Minor differences between the NCCN-IPI and the original IPI may not be sufficient to assign patients to a better treatment option. Consequently,

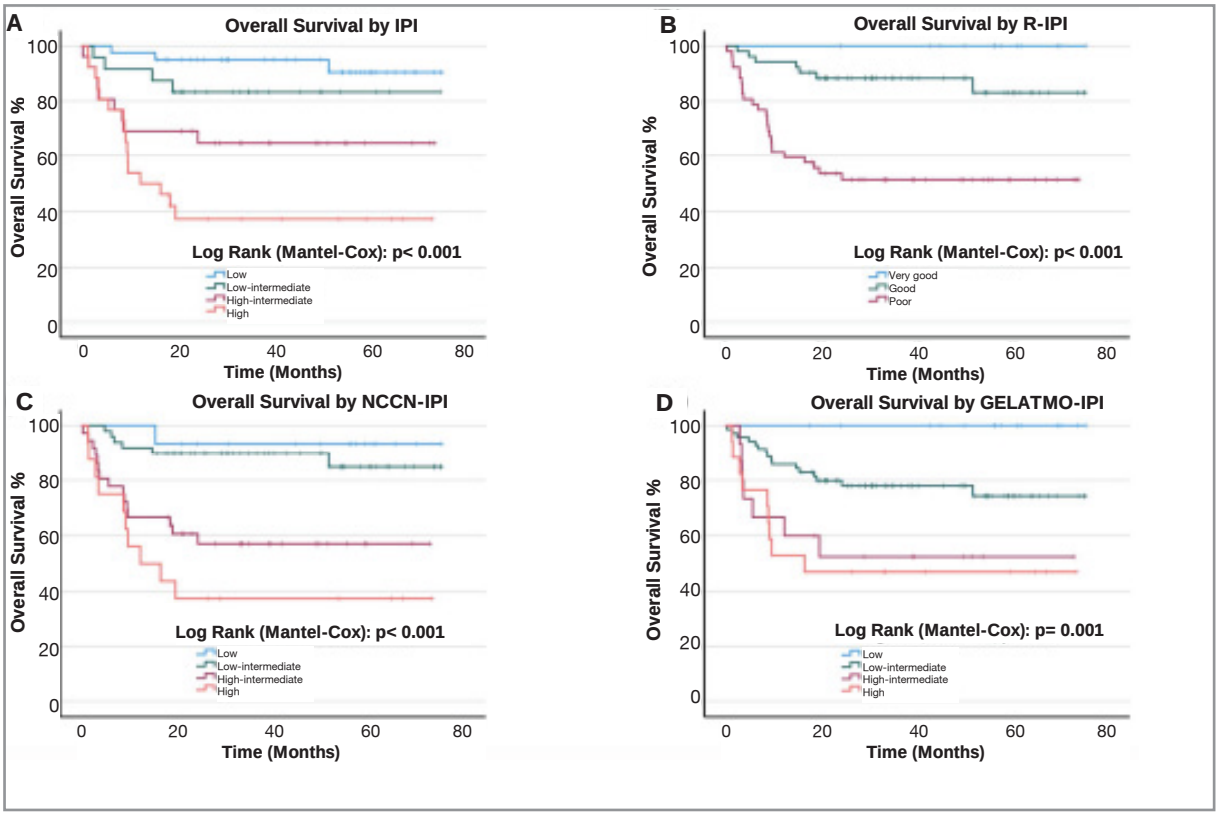

Figure 1. Overall survival for risk groups, identified by prognostic indices

(A) Overall survival by IPI, **(B)** Overall survival by R-IPI, **(C)** Overall survival by NCCN-IPI, **(D)** Overall survival by GELTAMO-IPI

using the original IPI in the rituximab era appears acceptable.

NCCN-IPI classified our study cohort under two independent risk groups and specified an OS value of 37.5% in the high-risk category. The characteristics of our study cohort and these outcomes did not significantly deviate from the outcomes in the NCCN series. In our study, the involvement of major extranodal areas, identified by NCCN, had prognostic importance. Although some studies have claimed that there were no correlations, there are some studies, presenting positive outcomes.[12,13] According to the GELTAMO group's validation study for NCCN-IPI, it has been concluded that extranodal involvement, specified in NCCN-IPI, lost its prognostic value in multivariate analysis.[7] Therefore, the extranodal involvement specified in NCCN-IPI was not included in GELTAMO-IPI. However, in the Danish-Canada study, the involvement of three or more extranodal areas was associated with poor outcomes and was reported to be an independent risk factor.[12] The prognostic effect of the number or anatomical locations of extranodal areas, is still controversial.

In the development of GELTAMO-IPI, in particular serum β2M has been included as an IPI factor. It has been asserted that β2M was an indicator of high cellular turnover and heavy tumor load,[14] and

Table 5. Predictive accuracy of prognostic indices for overall survival, and results of relative model quality

	AIC	C-index (95% CI)
IPI	239.2	0.694 (0.608 - 0.779)
R-IPI	236	0.676 (0.593 - 0.758)
NCCN-IPI	238.8	0.696 (0.610 - 0.782)
GELTAMO-IPI	242.3	0.653 (0.562 - 0.743)

IPI: International Prognostic Index, R-IPI: Revised IPI, NCCN: National Comprehensive Cancer Network, GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula ósea, AIC: Akaike's information criterion, C-index: Concordance index.

it has been reported that it was a strong prognostic indicator in DLBCL.[15,16] In our study, although serum β2M elevation had prognostic significance, the power of GELTAMO-IPI to distinguish patients was not higher than other prognostic indices. In the comparison of results, it is essential to note the sampling sizes of the risk groups in our study.

A better risk classification is required for patients, who have the greatest need for the new alternative first-line therapy regimens must be identified. Therefore, a continuous effort to improve prognostic scoring systems, is required. A clinically significant weakness of all examined prognostic scoring indices, including NCCN-IPI, is their failure to detect the patient subgroup with very poor survival. Integration of the molecular and other characteristics of the tumor and its micro-frame, into the existing prognostic scoring indices may be a viable approach. In order to characterize the biological features for prognosis in DLBCL, various gene expressions with prognostic importance, such as double-hit and triple-hit rearrangement (MYC and BCL2 and/or BCL6) and CD30 protein expression, have been identified.[17-21] In a recently published study it has been found that overexpression of K-ras and C-myc in patients with DLBCL, did not affect OS. It has been reported that, in contrast, C-myc overexpression played a harmful role in complete remission.[22] However, it is occasionally possible to integrate the use of variables, based on immunohistochemical techniques, into daily clinical practice. In addition, these techniques have been standardized for repeatability only in a limited number of centers. The risk model, recently published by Bento et al., has comprised the presence of bulky mass, together with absolute lymphocyte/monocyte ratio and red blood cell distribution volume.[23] Compared to R-IPI, it provided a better high-risk assessment and risk distinction in terms of OS. Since it employs clinical and laboratory characteristics, which may be easily obtained in clinical practice during diagnosis, this risk score is more appropriate compared to others, yet it requires more external validation.

The size of our study cohort and the retrospective nature of our study may be deemed as principal limitations of our research. In addition, in this study, we did not integrate any biological prognostic indicators, such as gene expressions, in DLBCL and biomarkers. However, since the current objective was to validate and compare IPIs in a different ethnic group, the prognostic indicators, given above, are excluded from the study.

Consequently, while R-IPI is the best fit for data, NCCN-IPI provides the best discrimination between patients with short OS and patients with long OS. In addition, the use of the original IPI seems acceptable in the era of rituximab. All these indices are based on clinical and laboratory parameters and these parameters may easily be integrated into daily clinical practice. The integration of molecular characteristics of tumor into NCCN-IPI, may provide improved identification of the high-risk group, in which has the greatest need for new treatment approaches.

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