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Statistical Challenges in Development of Prognostic Models in Diffuse Large B-Cell Lymphoma: Comparison Between Existing Models – A Systematic Review

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Background and Aim: Based on advances in the diagnosis, classification, and management of diffuse large B-cell lymphoma (DLBCL), a number of new prognostic models have been proposed. The aim of this study was to review and compare different prognostic models of DLBCL based on the statistical methods used to evaluate the performance of each model, as well as to analyze the possible limitations of the methods.

Methods and Results: A literature search identified 46 articles that proposed 55 different prognostic models for DLBCL by combining different clinical, laboratory, and other parameters of prognostic significance. In addition, six studies used nomograms, which avoid risk categorization, to create prognostic models. Only a minority of studies assessed discrimination and/or calibration to compare existing models built upon different statistical methods in the process of development of a new prognostic model. All models based on nomograms reported the c-index as a measure of discrimination. There was no uniform evaluation of the performance in other prognostic models. We compared these models of DLBCL by calculating differences and ratios of 3-year overall survival probabilities between the high- and the low-risk groups. We found that the highest and lowest ratio between low- and high-risk groups was 6 and 1.31, respectively, while the difference between these groups was 18.9% and 100%, respectively. However, these studies had limited duration of follow-up and the number of patients ranged from 71 to 335.

Conclusion: There is no universal statistical instrument that could facilitate a comparison of prognostic models in DLBCL. However, when developing a prognostic model, it is recommended to report its discrimination and calibration in order to facilitate comparisons between different models. Furthermore, prognostic models based on nomograms are becoming more appealing owing to individualized disease-related risk estimations. However, they have not been validated yet in other study populations.

Keywords: diffuse large B-cell lymphoma, discrimination, calibration, prognosis, models, nomograms

Introduction

The most commonly used prognostic index for risk stratification of patients with diffuse large B-cell lymphoma (DLBCL) is the International Prognostic Index (IPI).[1,2] Since the introduction of rituximab in DLBCL therapy, the discriminative abilities of the IPI have been challenged in many studies.[2–6] Predominantly, based on the new insights into the pathobiology of disease, the predictive power of different

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biomarkers for prognosis has been extensively investigated and this has led to numerous attempts at incorporating clinical, biological, laboratory, immunohistochemical, and genetic markers in prognostic scores.[7–15] However, none of the newly developed models has been as widely used as the IPI.

Despite the standard treatment with chemoimmunotherapy, approximately 30% of patients experience disease relapse or are refractory to therapy.[16] Therefore, the utilization of selected group of patients' characteristics through a statistical model is important to identify high-risk patients who could potentially benefit from more intensive immuno-chemotherapy and/or molecular-targeted agents.[17] Prognostic risk models, which are a mathematically precise way to summarize properties of measurements and their associations, are created to predict events.[18] When developing a model, it is important to provide some evaluation of its performance in comparison to an existing model.[19] The usefulness of a prognostic test in clinical practice depends mainly on the ability of the test to stratify patients into different risk groups and to provide accurate predictions about their future outcome. However, when biomarkers are included in statistical models for predicting a clinical outcome, two problems can occur, namely "error in discrimination" and "error in calibration".[20] To achieve accurate risk prediction, validation of the specific prediction model is needed. For that task, various statistical methods have been suggested in the literature.[20–22]

In our previous systematic review, we described the studies that reported different prognostic models for newly diagnosed DLBCL with a focus on clinical, laboratory, molecular, and/or imaging parameters included in each model. However, the analysis of statistical methods used to compare the novel models in DLBCL with the previously reported models, to the best of our knowledge, has never been performed. Therefore, this study aims to investigate the statistical instruments that have been used to develop, compare, and evaluate the performance of prognostic models for DLBCL. Another aim is to analyze possible limitations of each statistical method that can restrict the wide usage of the derived model.

Materials and Methods
Search Strategy
Similarly to our previous research, this review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-

analysis.[23] A comprehensive search was conducted in PubMed and Embase to identify original publications that proposed prognostic scores for newly diagnosed DLBCL.[24] Only studies in English published between 1993 and 15 July 2019 were considered.

The relevant Medical Subject Headings (MeSH) were used where possible and the following search terms were used in our analysis: lymphoma, large B-cell, diffuse/DLBCL, index/indices, model, score, prognosis/prognostic, outcome, survival, and comparison. The additional eligible studies were retrieved through secondary references.[24] The search results were independently double-screened by the research team (JJ, MM, BA) according to inclusion/exclusion criteria at the abstract and the full-text screening. All the studies included in the final list were checked for data availability by BA and underwent full statistical analysis, performed by ZB.

Selection Criteria and Data Extraction
This analysis included studies that developed a new risk model for newly diagnosed DLBCL patients by combining at least two parameters, of which one must be a clinical or a laboratory parameter with or without imaging or a molecular prognostic marker. The studies evaluated overall survival (OS) using the Kaplan–Meier method and/or expressed the outcome as the percentage of surviving patients. The exclusion criteria referred to all articles that did not provide a new prognostic model (eg case reports, commentaries, meeting reports, reviews), as well as those that analyzed only one subtype of DLBCL, proposed an index based exclusively on histopathological or molecular data, and/or lacked sufficient data for estimating OS. Moreover, we excluded studies that only tested scores previously developed on patient populations other than newly diagnosed DLBCL.[24]

After exclusion of the irrelevant studies based on the titles and abstracts, the full texts of the selected articles were analyzed. We also reviewed the full text of the studies from which a decision could not be made on the abstract alone. All studies included in the final list were reviewed for their data accuracy.[24] The data extracted from each study were all of the following whenever reported: author and publication year, index name, risk categories, number of patients per group of new index and previously reported index (eg IPI, revised IPI), model performance, and OS expressed as the 3-year percentage of surviving patients. If missing, the 3-year OS for newly created models and previously reported models (used to compare

with the newly developed model) was estimated from the survival curves using GetData Graph Digitizer 2.26. Three-year OS was chosen because the majority of studies report this endpoint.

For the studies that compared performance of a new score and previously tested scores, the statistical methods of comparison were recorded. Additional statistics included c-index, Bayesian information criterion (BIC), concordance probability estimate (CPE), Akaike's information criterion (AIC), Hosmer–Lemeshow goodness of fit, and receiver operating characteristics (ROC) curves. The difference between c-index was calculated in the studies that reported the c-index. For each new score, the difference and proportion between high- and low-risk groups were calculated. We first extracted 3-year OS measures, then these values were compared between high-risk and low-risk groups using calculations of differences and proportions. Proportion was assessed by dividing 3-year OS estimates in high-risk patients by those in low-risk patients, while the difference was calculated by subtraction of 3-year OS of the low-risk group from the high-risk group. This value was expressed in percentages. Furthermore, similar calculations were performed if the studies reported 3-year OS survival for previously reported indices (eg IPI). If the 3-year OS was not reached because of censored patients, or if the OS was 0%, the proportion was labeled as not applicable (NA) for mathematical reasons. The scores with the highest values of the difference and proportion were regarded as those with better differentiation between risk categories.

Results

The initial search strategy identified 5239 articles, but after the inclusion/exclusion criteria were used, of 418 potentially relevant articles, 46 studies were included in the final list. Among these, seven additional articles were retrieved through the references included in the eligible studies and relevant reviews (Figure 1). Although the IPI was developed based on a broad cohort of patients with aggressive lymphoma subtypes, this model was included in the current study because it is widely used for prognostication in DLBCL.[1,24] Furthermore, the search strategy identified six additional studies that used nomograms to develop prognostic models.[25–30] Although these studies did not meet the inclusion criteria regarding OS and risk stratification, they are briefly discussed later owing to their individualized approach for risk prediction. In total, 52 studies were analyzed.

In 46 studies, a total of 55 prognostic models were proposed for DLBCL patients. From 1993 until 2019,

a significant increase in the number of proposed prognostic models for DLBCL patients has been observed (Figure 2). In all, 40 studies proposed one prognostic model, while four studies proposed two models,[10,31-33] one proposed three,[1] and one study proposed four prognostic models.[11]

In total, 26 prognostic models used a four-category risk stratification with recognition of low-, low–intermediate-, high–intermediate-, and high-risk groups (Tables 1–4). Three-category risk stratification (low-, intermediate-, and high-risk groups) was proposed in 20 studies. Two-category risk stratification with high- and low-risk groups was reported in six studies, while five-category risk stratification was proposed in three studies.

Each of six studies that developed nomograms proposed just one prognostic model based on the individual risk prognostication. Additional data regarding each study are provided in the supplementary table.

Statistical Analysis

Twelve of 46 studies analyzed populations with more than 400 patients (range 403–2031), while 32 studies included fewer patients (range 45–391). Among studies based on nomograms, three of six included more than 400 patients.

The majority of studies lacked the splitting of the analyzed population into training and validation sets as well as a comparison to previously proposed models.[24] Seven studies of 46 used training and validation sets to develop a prognostic index and to validate it.[1,2,16,31,34-36] Among the studies using nomograms, three used both internal and external validation,[26–28] one used internal validation only,[25] and two did not assess the performance through validation.[29,30]

Model performance was evaluated using different methods, which are discussed in the following subsections.

C-Statistics

As a measure of discrimination, the area under the receiver operating characteristics (ROC) curve for survival outcomes (the c-index) was used in seven of 46 studies.[7,16,32,34,37-39] Higher values of the c-index indicated better discrimination. The value of the c-index for the novel prognostic models ranged from 0.708 for the comorbidity National Comprehensive Cancer Network-IPI (cNCCN-IPI) to 0.830 for the lipoprotein prognostic index (Lipo-PI). The c-index was also calculated for the indices that were previously reported, such as IPI (range 0.67–0.76), revised IPI (c-index 0.642), and NCCN-IPI (range 0.6950.791). Two studies pointed to the use of Harrell's c-index/modified
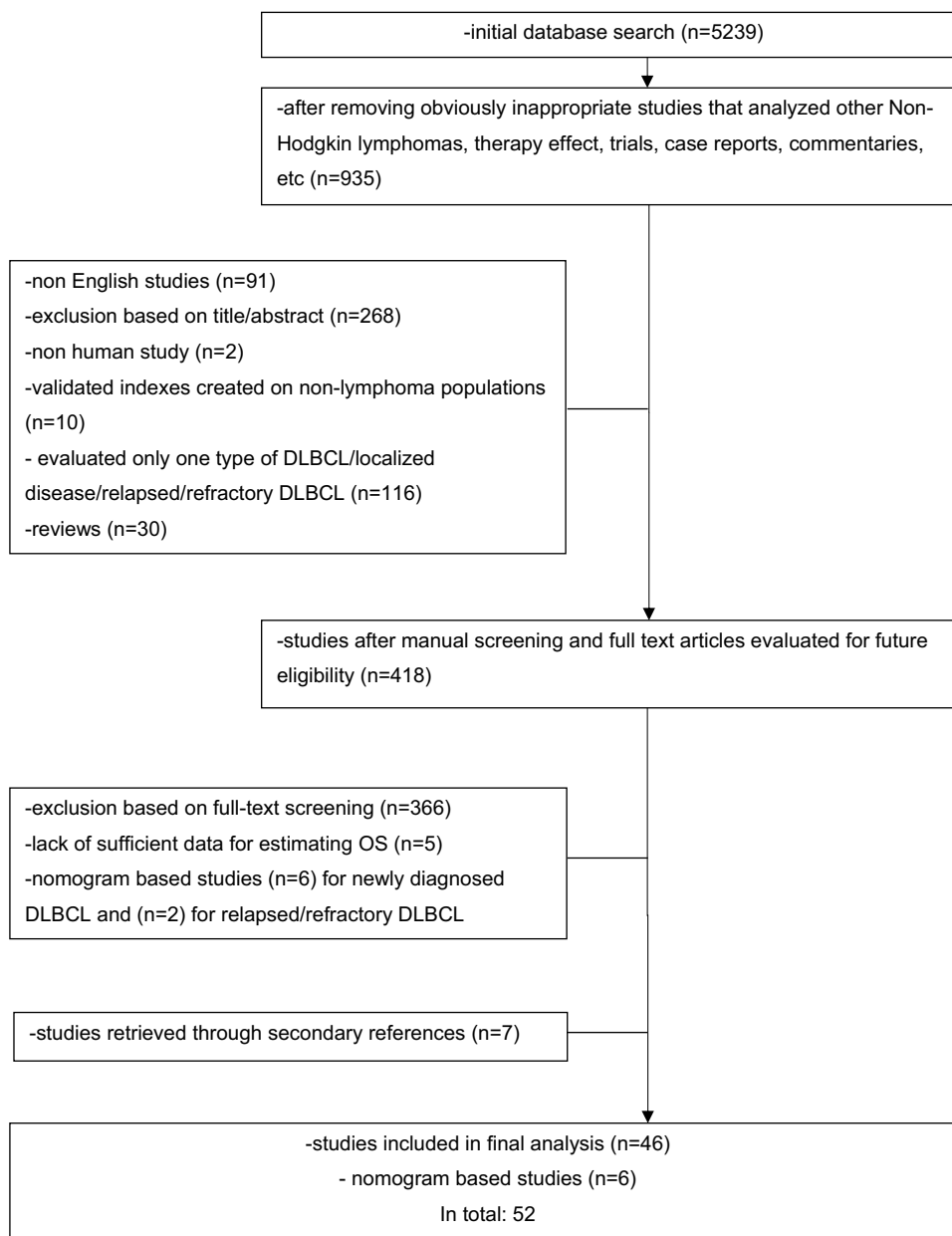
-initial database search (n=5239)

-after removing obviously inappropriate studies that analyzed other Non-Hodgkin lymphomas, therapy effect, trials, case reports, commentaries, etc (n=935)

-non English studies (n=91)

-exclusion based on title/abstract (n=268)

-non human study (n=2)

-validated indexes created on non-lymphoma populations (n=10)

- evaluated only one type of DLBCL/localized disease/relapsed/refractory DLBCL (n=116)

-reviews (n=30)

-studies after manual screening and full text articles evaluated for future eligibility (n=418)

-exclusion based on full-text screening (n=366)

-lack of sufficient data for estimating OS (n=5)

-nomogram based studies (n=6) for newly diagnosed DLBCL and (n=2) for relapsed/refractory DLBCL

-studies retrieved through secondary references (n=7)

-studies included in final analysis (n=46)

- nomogram based studies (n=6)

In total: 52

Figure 1 Flowchart representing the selection process of including studies published between 1993 and July 2019.

method as a discrimination method,[16,32] while one reported the use of the c-index according to Uno et al.[22]

Concordance Probability Estimate (CPE)

The discrimination of the newly developed prognostic models and previously developed models was measured by CPE along with its 95% confidence intervals (CI) in four of 46 studies.[2,3,10,40] A higher CPE indicated better discrimination. The CPE value was 0.66 for E-IPI,[3] 0.781 for a new risk model,[40] 0.783 for modified NCCN-IPI,[10] and 0.8 for NCCN-IPI. For the compared models, the lowest CPE value was 0.59 for R-IPI,[3] while the highest was 0.76 for NCCN-IPI.[40]

Bayesian Information Criterion (BIC)

A global measure of fit, the BIC was assessed in two studies, where lower values of BIC indicate a better fit.[7,32]

Akaike's Information Criterion (AIC)

The performance of indices was compared by a measure of global fit (AIC) in five studies, in which a lower value indicated a better fit.[2,3,9,31,40] The lowest AIC of 662.5 was
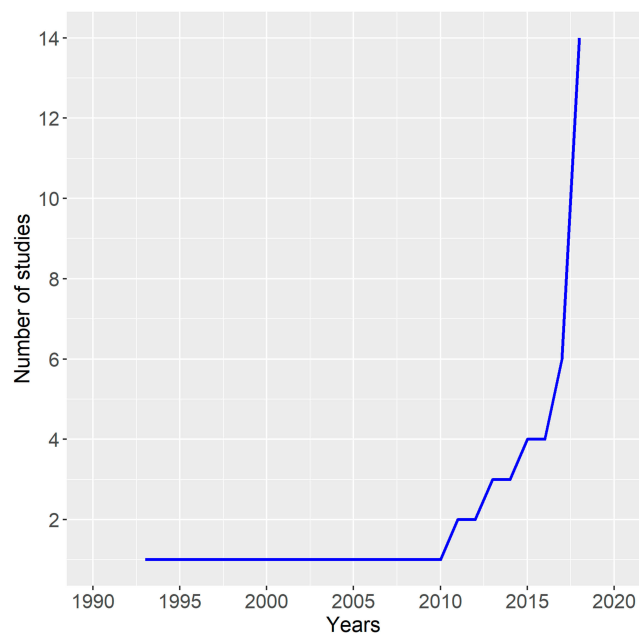
Figure 2 Graph showing an increasing number of reported studies over the past two decades.

observed in a new risk model,[40] while the highest value was 4566 in NCCN-IPI.[2] Of the compared models, the highest AIC value was observed in the IPI[2] and the lowest in NCCN-IPI.[40]

Hosmer–Lemeshow Goodness of Fit

One study used Hosmer–Lemeshow goodness of fit to assess calibration, by comparing the proportions of patients whose estimated risk shifted in the correct and wrong directions on the basis of a χ^2-test within reclassified categories for each score separately.[36]

Relative Brier Score Reduction (RBSR)

One study reported RBSR, which represents a measure of the overall model performance. The lower the Brier score for a set of predictions, the better the predictions are calibrated.[34]

Receiver Operating Characteristics (ROC) Curves

In 11 of 46 studies, the cut-off of a continuously distributed measurement for OS prediction was defined as the point at which the sensitivity plus the specificity were maximized in the ROC curves.[15,35,37,40-47] One study each used ROC curves to select the best cut-off of beta-2 microglobulin (B2M),[40] C-reactive protein (CRP),[44] lymphocyte to monocyte ratio,[44] platelet to lymphocyte ratio (PLR),[45] tumor-infiltrating

T-lymphocyteproportion and ratio between CD4-positive and CD8-positive T-lymphocytes,[48] age,[35] maximum standardized uptake value,[47] and ratio Deauville score.[46] In two studies, ROC was used to assess the albumin level,[35,44] and in two the absolute monocyte count and absolute lymphocyte count.[42,43] One study used X-tile software to calculate the optimal cut-off value for the albumin to globulin ratio.[41]

Regarding the absolute monocyte count, absolute lymphocyte count, and platelet level, previously reported cut-off points were used in five studies.[9,33,49-51] However, the majority of studies used institutional upper/lower limits of normal (ULN/LLN) for the continuously distributed measurements, including hemoglobin levels, platelet counts,[52] absolute monocyte count, absolute neutrophil count, B2M, LDH,[37] B2M,[36,45,53,54] and lipid levels.[16]

Three studies used other statistical techniques (eg percentile value, medians) for testing different cut-off points of continuous measurements.[8,33,55]

Difference and Ratio in 3-Year Overall Survival Between Risk Groups

Fifteen of 46 studies reported 3-year OS for novel prognostic models, while OS was calculated from Kaplan–Meier curves for the rest[3,9,10,16,31,34,35,39,40,44,52,56-59] (Tables 1–3). Only the minority of studies (six of 46) reported 3-year OS for compared indices.[9,10,31,39,44,52] Regarding 3-year OS of the novel models, the highest ratio between the low- and high-risk groups was 6,[53] while the lowest was 1.31.[41] These studies included 71 and 335 patients, respectively. In six articles the ratio in 3-year OS between low-risk and high-risk groups was not applicable owing to the short follow-up of high-risk patients or there being no surviving patients at 36 months.[35,45,47,56,60,61] The difference in 3-year OS ranged from 18.9%[41] to 100%[56] with335 and 105 patients, respectively, being analyzed.

Regarding the IPI, the ratio between risk groups ranged from 1.38 to 7.73, and the difference from 22.9% to 68.8%. The lowest age-adjusted IPI (aaIPI) ratio score between the low-risk and high-risk groups was 2.05 and the highest was 2.48, while the lowest difference was 42.0% and the highest was 53.4%. Regarding NCCN-IPI, the ratio ranged from 1.75 to 3.70, and the difference from 40.9% to 72.9%. Additional information regarding differences and the ratios of other indices are provided in Tables 1–4.

Figure 3A and B shows the graphical presentation of the ratio and difference, with preferable position close to the upper right point, which indicates better model power. Both

Table 1 Summary of Characteristics (Number of Patients, 3-Year OS Per Risk Category, Difference/Ratio Between High- and Low-Risk Groups, and Additional Statistics Used to Compare Novel Model and Previously Developed Models) of Studies that Reported Four-Risk Categorization Prognostic Model

Four-Category Models		IPI1	aaIPI ≤60 Years1	aaIPI >601	B2M IPI[53]	E-IPI[3]	Salles et al[7]	Huang et al[9]	NCCN-IPI[2]
No of pts[24]		2031	1274	761	71	267	284	274	1650
No of pts/3-year OS (%) per group	L	711/(~77.4)	280/(~88.9)	137/NA	28/(~72.0)	72/(86.0)	56/(~94.7)	52/(~97.5)	88/(95.0)
	LI	548/(~58.0)	408/(~76.0)	236/NA	6/(~50.0)	75/(74.0)	84/(~86.9)	115/(~87.2)	93/(79.0)
	HI	447/(~45.5)	408/(~53.1)	266/NA	6/(~37.0)	77/(58.0)	58/(~64.0)	85/(~69.5)	69/(40.0)
	H	325/(~27.4)	178/(~35.5)	122/NA	31/(~12.0)	43/(36.0)	86/(~49.4)	22/(~49.3)	25/(18.0)
Additional statistics[24]		NA	NA	NA	NA	AIC=1147 CPE=0.66	c-index=0.69 BIC=1145	AIC=771.102	AIC 4566 CPE=0.8
Ratio (L/H)		2.83	2.48	NA	6.0	2.39	1.92	5.28	1.98
Difference (L – H)		50.0	53.4	NA	60.0	50.0	45.3	77.0	48.2
Total no of pts in compared index		NA	NA	NA	IPI =104	IPI=267 R-IPI=267 aaIPI=267	IPI=347	IPI=274 R-IPI=274 ALC/R-IPI=274	IPI=1650
3-year OS (%) per L/H group	L, H	NA	NA	NA	IPI: ~75.8/~9.8 aaIPI: NA	IPI: 83.0/43.0 R-IPI: NA/57.0 aaIPI: 83.0/35.0	IPI: ~84.0/~51.0	IPI: 95.0/45.0 R-IPI: 100.0/47.0 ALC/R-IPI: 94.0/29.0	IPI: ~93.8/~61.7
Additional statistics		NA	NA	NA	NA	IPI: AIC=1155; CPE=0.63 R-IPI: AIC=1168; CPE=0.59 aaIPI: AIC=1163; CPE=0.62	c-index=0.67 BIC=1153	IPI: AIC=798.715 R-IPI: AIC=791.263 ALC/R-IPI: AIC=780.935	AIC=4627 CPE=0.74
Ratio (L/H) of compared index		NA	NA	NA	IPI=7.73	IPI=1.93 aaIPI=2.37	IPI=1.65	IPI=2.11 R-IPI=2.13 ALC/R-IPI=3.24	IPI=1.52
Difference (L – H) of compared index		NA	NA	NA	IPI=66.0	IPI=40.0 aaIPI=48.0	IPI=33.0	IPI=50.0 R-IPI=53.0 ALC/R-IPI=65.0	IPI=32.1

	ABE4[31]	Nols et al[60]	Melchardt et al[10]	DLBCL-PI[32]	aaDLBCL-PI[32]	Kong et al[56]	Kanemasa et al[40]	M-IPI-R[11]
Difference in c-statistic	NA	NA	NA	NA	NA	0.02	NA	NA
Four-Category Models								
No of pts[24]	379	73	403	1803	1169	105	274	471
No of pts/3-year OS (%) per group — L	51/(94.0)	NA/(~90.0)	99/(97.8)	596/(~92.4)	318/NA	65/(100.0)	26/((100.0)	78/(~90.2)
LI	125/(77.0)	NA/(~75.6)	75/(82.7)	471/(~76.8)	360/NA	23/(91.3)	162/(87.0)	201/(~82.3)
HI	149/(63.0)	NA/(~50.0)	198/(65.9)	417/(~58.9)	296/NA	9/(55.6)	50/(57.2)	163/(~53.1)
H	54/(35.0)	NA/(~0.0)	31/(44.2)	319/(~44.8)	147+48/NA	8/(0.0)	36/(23.4)	29/(~18.1)
Additional statistics[24]	MoC 0.686 AIC 1304	NA	CPE=0.783	c-index=0.77	c-index=0.79	NA	CPE=0.781 AIC=662.5	NA
Ratio (L/H)	2.69	NA	2.21	2.07	NA	NA	4.27	4.99
Difference (L – H)	59.0	90.0	53.6	47.6	NA	100	76.6	72.1
Total no of pts in compared index	IPI=374 aaIPI=372 E-IPI=372	IPI=73	IPI=499 NCCN-IPI =499	IPI=1990	IPI=NA	IPI=105	NCCN-IPI=274	IPI=499 L 197/(~86.7) H 76/(~43.3)
3-year OS (%) per L/H group — L / H	IPI: 83.0/51.0 aaIPI 82.0/40.0 E-IPI: 82.0/41.0	NA	IPI: 90.9/45.0 NCCN-IPI: 97.7/39.5	NA	NA	NA	NCCN-IPI: 100.0/27.1	IPI: ~86.7/~43.3
Additional statistics	IPI: AIC=1336; MoC=0.635 aaIPI: AIC=1325; MoC=0.650 E-IPI: AIC=1292; MoC=0.665	NA	IPI: CPE=0.713 NCCN-IPI: CPE=0.753	c-index=0.73	c-index=0.76	NA	CPE=0.760 AIC=678.1	NA
Ratio (L/H) of compared index	IPI=1.63 aaIPI=2.05 E-IPI=2.0	NA	IPI=2.02 NCCN-IPI =2.47	NA	NA	NA	NCCN-IPI =3.69	IPI=2.0
Difference (L – H) of compared index	IPI=32.0 aaIPI=42.0 E-IPI=41.0	NA	IPI=45.9 NCCN-IPI =58.2	NA	NA	NA	NCCN-IPI =72.9	IPI=43.4

(Continued)

Table 1 (Continued).

Four-Category Models		IPI1	aaIPI ≤60 Years1	aaIPI >601	B2M IPI53	E-IPI3	Salles et al7	Huang et al9	NCCN-IPI2	
									Li et al47	Toledano et al46
Difference in c-statistic		NA	NA	NA	0.04	0.03	IPI=499	NA	NA	
Four-Category Models		KPI34	ACA35	GELTAMO-IPI36	Kang et al38	ICPS44	cNCCN-IPI39	LIPO-PI16	Li et al47	Toledano et al46
No of pts24		323	555	1672	621	564	958	367	NA	181
No of pts/3-year OS (%) per group	L	105/(96.4)	181/(86.0)	190/(~96.6)	146/(~96.4)	202/(95.6)	33/(100.0)	NA/(98.0)	NA/ ~83.7	80/(~87.8)
	LI	138/(84.7)	224/(72.0)	972/(~84.6)	153/(~89.4)	144/(88.2)	330/(86.0)	NA/(82.8)	NA/ ~43.2	63/(~63.4)
	HI	36/(63.8)	132/(51.0)	284/(~69.6)	233/(~71.3)	99/(76.0)	475/(63.0)	NA/(50.0)	NA/ ~38.0	9/(~43.7)
	H	44/(33.3)	18/(0.0)	226/(~46.3)	89/(~54.4)	119/(62.2)	120/(27.0)	NA/(34.3)	NA/ NA/ NA	29/(~29.0)
Additional statistics24		c-index=0.740 RBSR=30.5%	NA	χ²=9.54; p=0.299	c-index=0.739	NA	c-index=0.708	c-index=0.830	NA	NA
Ratio (L/H)		2.89	NA	2.09	1.77	1.54	3.7	2.86	NA	2.71
Difference (L – H)		63.1	86	50.3	42.0	33.4	63.0	63.7	NA	55.4
Total no of pts in compared index		R-IPI=NA NCCN-IPI=NA	IPI=NA	IPI=1764 NCCN-IPI=1777	IPI=621 NCCN-IPI=621	IPI=564	IPI=962 NCCN-IPI=962	NCCN-IPI=NA	IPI=77	IPI=181
3-year OS (%) per L/H group	L	NA	NA	IPI: ~91.9/~54.7 NCCN-IPI: ~95.3/~54.4	IPI: ~90.2/~53.3 NCCN-IPI: ~95.6/~39.3	IPI: 87.6/51.5	IPI: 84.0/39.0 NCCN-IPI: 91.0/27.0	NCCN-IPI: 100.0/31.9	NA	NA
	H									
Additional statistics		R-IPI: c-index=0.642 RBSR=13.5% NCCN-IPI: c-index=0.736 RBSR=25.1%	NA	χ²=16.4; p=0.037	IPI: c-index=0.705 NCCN-IPI: c-index=0.710	NA	IPI: c-index=0.687 NCCN-IPI: c-index=0.695	c-index=0.791	NA	NA

Ratio (L/H) of compared index	NA	NA	IPI=1.68 NCCN-IPI =1.75	IPI=1.69 NCCN-IPI=2.43	IPI=1.7	IPI=2.15 NCCN-IP=3.37	NCCN-IPI =3.13	NA
Difference (L − H) of compared index	NA	NA	IPI=37.2 NCCN-IPI =40.9	IPI=36.9 NCCN-IPI=56.3	IPI=36.1	IPI=45.0 NCCN-IPI=64.0	NCCN-IPI =68.1	NA
Difference in c-statistic	KPI vs R-IPI=0.098 KPI vs NCCN-IPI =0.004	NA	NA	New index vs IPI=0.034 New index vs NCCN-IPI=0.029	NA	cNCCN-IPI vs NCCN-IPI=0.013 cNCCN-IPI vs IPI=0.021	0.039	NA

Abbreviations: aaDLBCL-PI, age-adjusted DLBCL-PI; aalPI, age-adjusted IPI; ABE4, age, bulk, Eastern Cooperative Oncology Group (ECOG); ACA, age, comorbidity, albumin; AIC, Akaike's information criterion; ALC, absolute lymphocyte count; B2M, beta-2 microglobulin; BIC, Bayesian information criterion; c-index, concordance index; cNCCN-IPI, comorbidity NCCN-IPI; CPE, concordance probability estimate; DLBCL-PI, diffuse large B-cell lymphoma prognostic index; E-IPI, elderly IPI; H, high; HI, high-intermediate; I, intermediate; ICPS, inflammation-based cumulative prognostic score system; IPI, International Prognostic Index; KPI, Kyoto Prognostic Index; L, low; LI, low–intermediate; LIPO-PI, lipoprotein prognostic index; M-IPI-R, molecularly adjusted IPI for R-CHOP; MoC, measure of concordance; NA, not applicable; NCCN-IPI, National Comprehensive Cancer Network; no, number; OS, overall survival; pts, patients; RBSR, relative Brier score reduction; R-IPI, revised IPI.

parts of the figure allow the visual comparison of different models owing to their position with the identical range on the X and Y axes. The studies with a larger number of patients had lower variability than the studies with a limited number of patients (Figure 3A, B). Furthermore, it was observed that the IPI in different studies tends to have a lower difference and ratio (Figure 3B).

Prognostic Models Based on Nomograms

A total of six studies proposed prognostic models for DLBCL patients based on calculated individual risk using nomograms (Table 4).[25–27,29,30] In all studies, the predictive accuracy of the nomogram was evaluated using discrimination and/or calibration. Three studies used splitting of the analyzed population into training and validation sets.[26–28] One study combined the machine learning method, known as a stacking algorithm, with clinical data obtained from nationwide lymphoma registries in order to develop a stacking-based prognostic model, which was superior to both IPI and NCCN-IPI.[28]

All nomogram-based studies reported the c-index[25–30] and one study also applied integrated Brier score (IBS).[28] Two studies reported the c-index for estimating progression-free survival.[25,30] The nomogram and other prognostic indices were compared with the 2 log likelihood (2LL) and the AIC in terms of goodness of fit in one study.[29] Calibration plots were reported in three nomogram studies[26,27,29], while one study applied Hosmer–Lemeshow goodness of fit to assess calibration .[25] New models were typically compared with established indices such as IPI, NCCN-IPI, and R-IPI.

Discussion

Our review shows that a large number of new prognostic models for patients with DLBCL have been proposed, aiming at improving the discriminative power compared to the IPI. However, general application of the majority of these new prognostic models has been prevented because of a lack of validation, limited number of analyzed patients, and other statistical difficulties regarding model development. The most commonly validated models used for prognostication as well as for the comparison with other novel models were IPI, R-IPI, and NCCN-IPI.[24] Among these, NCCN-IPI had the highest performance values, although the performance of models based on nomograms was superior to the NCCN-IPI. However, these models are relatively new and have not been validated in other study populations.

Table 2 Summary of Characteristics (Number of Patients, 3-Year OS Per Risk Category, Difference/Ratio Between High- and Low-Risk Groups, and Additional Statistics Used to Compare Novel Model and Previously Developed Models) of Studies that Reported Three-Risk Categorization Prognostic Model

Three-Category Models		Barrans et al[13]	R-IPI[4]	ALC/R-IPI[55]	ALC/AMC[42]	IMI[49]	AMPLI[50]	ABE3[31]	Melchardt et al[10]	L-GPS[14]
No of pts[24]		155	365	88	366	229	245	379	353	213
No of pts/3-year OS (%) per group	L	75/(~77.0)	37/(~94.2)	39/(~90.4)	119/(~88.5)	128/(~86.8)	105/(~92.0)	87/(92.0)	42/(94.2)	76/~91.8
	I	24/(~50.5)	164/(~79.8)	31/(~65.0)	186/(~71.2)	89/(~61.5)	119)/~76.0)	231/(67.0)	246/(69.3)	108/~74.3
	H	56/(~18.2)	164/(60.9)	18/(~52.6)	61/(~41.2)	12/(~28.1)	21/(~60.0)	61/(36.0)	65/(39.5)	29/~39.8
Additional statistics[24]		NA	NA	NA	NA	NA	NA	NA	NA	NA
Ratio (L/H)		4.23	1.55	1.72	2.15	3.09	1.53	2.55	2.38	2.31
Difference (L – H)		58.8	33.3	37.8	47.3	58.7	32.0	56.0	54.7	52.0
Total no of pts in compared index		IPI=143	IPI=365	R-IPI=88	IPI=366	IPI=229	IPI=244	R-IPI=374 ALC/R-IPI=374	The same as Table 4	IPI=213
3-year OS (%) per L/H group	L	IPI: ~76.7/	IPI: ~83.0/	R-IPI: ~100.0/	IPI: ~86.0/	IPI: ~86.5/	IPI: ~86.7/NA	R-IPI: 80.0/58.0		IPI: ~91.5/~30.5
	H	~7.9	~60.1	58.1	~42.4	~51.8		ALC/R-IPI: 80.0/50.0		
Additional statistics		NA	NA	NA	NA	NA	NA	R-IPI: AIC 1340; MoC=0.605 ALC/R-IPI: AIC 1337; MoC=0.619	NA	NA
Ratio (L/H) of compared index		IPI=9.71	IPI=1.38	R-IPI=1.72	IPI=2.03	IPI=1.67	NA	R-IPI=1.38 ALC/R-IPI=1.6		IPI=3.0
Difference (L – H) of compared index		IPI=68.8	IPI=22.9	R-IPI=41.9	IPI=43.6	IPI=34.7	NA	R-IPI=22.0 ALC/R-IPI=30.0		IPI=61.6
Difference in c-statistic		NA	NA	NA	NA	NA	NA	NA	NA	NA

Three-Category Models	ALC/ AMC PS[43]	Saygin et al[6]	PA index[51]	Candelaria et al[54]	IACA[61]	Matsumoto et al[58]	Zhao et al[45]	Chen et al[48]	Keane et al[33]	HP index[52]	DM-PI[59]
No of pts[24]	148	312	391	131	99	185	309	66	141	89	553

Measure		1	2	3	4	5	6	7	8	9	10	11
No of pts/3-year OS (%) per group	L	39/(~94.3)	111/(~88.7)	243/(~88.9)	58/(80.0)	39/NA	79/(94.6)	NA/(~88.0)	206/(96.1)	NA/(~48.1)	42/(79)	NA/(~97.2)
	I	79/(~72.5)	174/(~69.6)	125/(~54.4)	43/(55.5)	44/NA	81/(82.0)	NA/(~54.5)	266/(74.8)	NA/(~40.4)	39/(52)	NA/(~57.8)
	H	30/(~50.3)	27/(~43.5)	23/(26.7)	30/(19.8)	16/NA	25/(61.4)	NA/(0.0)	81/(49.4)	NA/(~16.9)	8/(30)	NA/(~41.1)
Additional statistics[24]		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	AUC=0.752
Ratio (L/H)		1.87	2.04	3.39	4.04	NA	1.54	NA	2.85	2.36	2.63	1.94
Difference (L − H)		44.0	45.2	62.2	60.2	NA	33.2	88.0	31.2	56.1	49.0	46.7
Total no of pts in compared index		IPI=148	IPI=413	IPI=391 NCCN-IPI=391	IPI=141	ACA=99	NA	IPI=309 aaIPI=NA	R-IPI=55	NA	IPI=89	IPI=553
3-year OS (%) per L/H group	L / H	NA	NA	IPI: ~90.4/~56.8 NCCN-IPI: ~100.0/~49.6	NA	NA	NA	IPI: ~59.9/NA aaIPI: ~90.0/~38.1	NA	NA	IPI: 87.0/38.0	IPI: 92.8/51.8
Additional statistics		NA	NA	NA	NA	NA	NA	NA	NA	NA	AUC=0.732	NA
Ratio (L/H) of compared index		NA	NA	IPI=1.59 NCCN-IPI=2.0	NA	NA	NA	aaIPI=2.36	NA	NA	IPI=2.29	IPI=1.79
Difference (L − H) of compared index		NA	NA	IPI=33.6 NCCN-IPI=50.4	NA	NA	NA	aaIPI=51.9	NA	NA	IPI=49.0	IPI=41.0
Difference in c-statistic		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	AUC=0.02

Abbreviations: aalPI, age-adjusted IPI; ABE3, age, bulk, Eastern Cooperative Oncology Group (ECOG); ACA, age, comorbidity, albumin; AIC, Akaike's information criterion; ALC, absolute lymphocyte count; ALC/AMC PS, ALC/AMC prognostic index; AMC, absolute monocyte count; AMPLI, absolute monocyte and lymphocyte prognostic index; AUC, area under the curve; c-index, concordance index; DM-PI, diabetes mellitus prognostic index; H, high; HP index, hemoglobin platelet index; I, intermediate; IACA, IADL (instrumental activities of daily living) and age, comorbidity, albumin; IMI, immunological index; IPI, International Prognostic Index; L, low; L-GPS, lactate dehydrogenase (LDH) plus Glasgow Prognostic Index; MoC, measure of concordance; NA, not applicable; NCCN-IPI, National Comprehensive Cancer Network IPI; no, number; OS, overall survival; PA index, platelet albumin index; pts, patients; R-IPI, revised IPI.

Table 3 Summary of Characteristics (Number of Patients, 3-Year OS Per Risk Category, Difference/Ratio Between High- and Low-Risk Groups, and Additional Statistics Used to Compare Novel Model and Previously Developed Models) of Studies that Reported Two- and Five-Risk Categorization Prognostic Model

Two-Category Models		SIL[8]	Lanic et al[12]	Pardal et al[57]	AGR[15]	AGR[41]	LAR[33]	Five-Category Models	Chen et al[37]	IPI +CD37+ABC[11]	IPI+IHC[11]
No of pts[24]		366	45	108	232	335	210		817	471	453
No of pts/3-year OS (%) per group	L	245/(~92.4)	24/(~91.0)	NA/(58.0)	139/ (~75.2)	188/ (~78.9)	NA/ (~86.4)	L	106/(~98.9)	54/(~94.3)	88/(~94.2)
								LI	196/(~93.8)	157/(~86.1)	126/(~82.1)
								HI	172/(~88.9)	97/(~70.5)	149/(~66.4)
	H	121/(~68.5)	21/(~37.0)	NA/(25.0)	93/ (~46.6)	147/ (~60.0)	NA/ (~57.9)	H	310/(~71.4)	135/(~49.8)	74/(~34.0)
								VH	33/(~38.5)	28/(~19.9)	16/NA
Additional statistics[24]		NA	NA	NA	NA	NA	NA		c-index=0.75	NA	NA
Ratio (L/H)		1.35	2.46	2.32	1.61	1.31	1.48		2.79	4.7	NA
Difference (L − H)		23.9	54.0	33.0	28.6	18.9	57.9		60.4	74.4	NA
Total no of pts in compared index		IPI=366 R-IPI=366	aaIPI=57	R-IPI=245	IPI=93	IPI=335	IPI=206		IPI=817	IPI=499	The same as previous
3-year OS (%) per L/H group	L	IPI: NA R-IPI: ~95.9/ ~71.3	NA	NA	NA	NA	NA		IPI: ~95.8/ ~66.0	IPI: ~86.7/~43.3	NA
	H										
Additional statistics		NA	NA	NA	NA	NA	NA		c-index=0.71	NA	NA
Ratio (L/H) of compared index		R-IPI=1.34	NA	NA	NA	NA	NA		IPI=1.45	IPI=2.0	NA
Difference (L − H) of compared index		R-IPI=24.6	NA	NA	NA	NA	NA		IPI=29.8	IPI=43.4	NA
Difference in c-statistic		NA	NA	NA	NA	NA	NA		NA	NA	NA

Abbreviations: aaIPI, age-adjusted IPI; ABE, age, bulk, Eastern Cooperative Oncology Group (ECOG); AGR, albumin to globulin ratio; c-index, concordance index; H, high; IPI, International Prognostic Index; IPI+IHC, IPI + immunohistochemistry; L, low; LAR, lactate dehydrogenase (LDH) to absolute lymphocyte count ratio; NA, not applicable; no, number; OS, overall survival; pts, patients; R-IPI, revised IPI; SIL, soluble interleukin.

Table 4 Summary of Characteristics (Number of Patients, Additional Statistics Used to Compare Novel Model and Previously Developed Models) of Studies that Used Nomograms

Nomogram	Han et al[27]	Biccler et al[28]	Zhong et al[26]	Chow et al[25]	Go et al[29]	Go et al[30]
No of pts	1070	5173	538	76	187	232
Test/validation group	748/322	2759/2414	228/310	Internal validation (PFS)		
Additional statistics	c-index=0.77 (5-year) Calibration plot/curve	c-index=0.756 IBS=0.131 Time-varying AUC	c-index=0.81 (2-year) Calibration plot/curve	c-index=0.81 Hosmer and Lemeshow	c-index=0.80 AIC=599.77–611.77 Calibration plot	c-index=0.79
Ratio/difference	NA	NA	NA	NA	NA	NA
Total no of pts in compared index	IPI=748 R-IPI=748 NCCN-IPI=748	IPI: NA NCCN-IPI: NA	IPI=228 NCCN-IPI=228 ICPS=228 Inflammatory IPI=179	IPI=76	IPI=187 R-IPI=187 NCCN-IPI=187	IPI=232 R-IPI=232 NCCN-IPI=232
3-year OS (%) per L/H group — L / H	IPI: 78.6/37.8 R-IPI: 91.5/43.5 NCCN-IPI: 85.1/38.7	NA	IPI: 92.6/59.2 NCCN-IPI: 93.7/60.1 ICPS: 97.1/66.2 Inflammatory IPI: 95.9/54.7	NA	NA	NA
Additional statistics	IPI: c-index=0.73 R-IPI: c-index=0.70 NCCN-IPI: c-index=0.71	IPI: IBS=0.150 c-index=0.662 NCCN-IPI: IBS=0.144 c-index=0.681	IPI: c-index=0.72 NCCN-IPI: c-index=0.72 ICPS: c-index=0.69 Inflammatory IPI: c-index=0.69	c-index=0.75	IPI: −2LL 613.41, AIC 615.41, c-index=0.77 R-IPI: −2LL=630.47; AIC=632.47; c-index=0.74 NCCN-IPI:-2LL 614.18; AIC 616.18; c-index 0.77	IPI: c-index=0.74 R-IPI: c-index=0.71 NCCN-IPI: c-index=0.75
Ratio	IPI=2.08; R-IPI=2.1; NCCN-IPI=2.2	NA	IPI=1.56; Inflammatory IPI=1.75, NCCN-IPI=1.56; ICPS=1.47	NA	NA	NA
Difference	IPI=40.8; R-IPI=48.0; NCCN-IPI=46.4	NA	IPI=33.4; Inflammatory IPI=41.2; NCCN-IPI=33.6; ICPS=1.47	NA	NA	NA
Difference in c-statistic	N vs IPI=0.04 N vs R-IPI=0.07 N vs NCCN-IPI =0.06	N vs IPI=0.094 N vs NCCN-IPI =0.075	N vs IPI=0.09 N vs NCCN-IPI=0.09 N vs Inflammatory IPI=0.12 N vs ICPS=0.12	N vs IPI=0.06	N vs IPI=0.03 N vs R-IPI=0.06 N vs NCCN-IPI=0.03	N vs IPI=0.05 N vs R-IPI=0.08 N vs NCCN-IPI =0.04

Abbreviations: AIC, Akaike's information criterion; AUC, area under the curve; c-index, concordance index; H, high; IBS, integrated Brier score; ICPS, inflammation-based cumulative prognostic score system; IPI, International Prognostic Index; L, low; 2LL, 2 log likelihood; N, nomogram; NA, not applicable; NCCN-IPI, National Comprehensive Cancer Network-IPI; no, number; OS, overall survival; PFS, progression-free survival; pts, patients; R-IPI, Revised IPI.
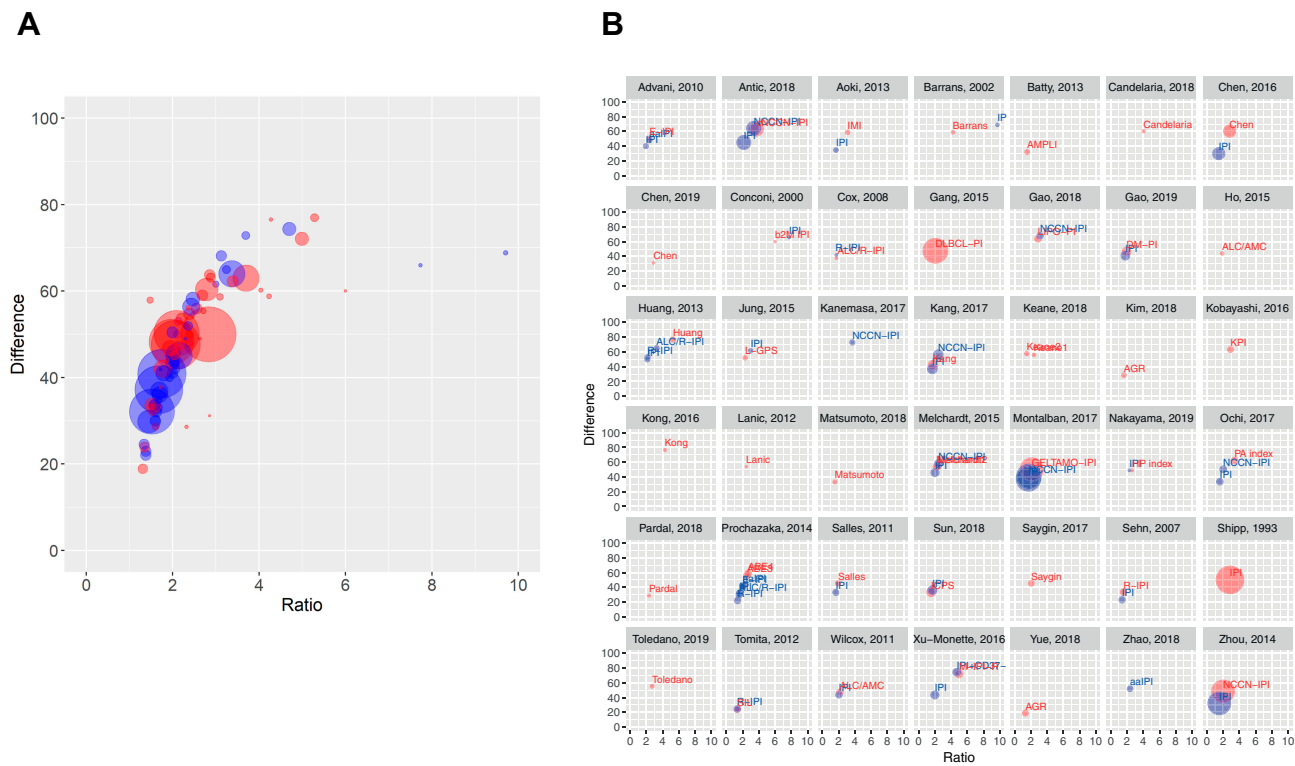
Figure 3 Graphical presentation of difference and ratio between high- and low-risk groups of novel models (red circles) and previously reported (compared) models (blue circles). (**A**) Difference/ratio presentation of all models and (**B**) each study. Ratio is presented on the x-axis, while difference is presented on the y-axis and is expressed in percentages. Larger circles indicate a larger study population, while the closeness to the right upper point indicates a bigger difference and ratio between compared groups.

The traditional splitting of data into the training and validation data sets when developing a new model was used in only 19% of studies. Using the training data set, it is possible to construct an initial prediction model, the accuracy of which is then assessed using the validation set. However, the usefulness of any model actually depends on its accuracy, ie the ability of the model to correctly identify each patient's outcome.[17] To report the discrimination (accuracy) value of the model, seven studies plus all studies based on nomograms used the concordance (c) statistic, which is conceptually similar to the ROC curve.[17] The c-index scores between 0.5 (no discrimination) and 1.0 (perfect discrimination).[20] The value of the c-index for novel prognostic models ranged from 0.708, indicating a good model, to 0.830, indicating a strong model. However, the c-index for the widely applied indices such as IPI, R-IPI, and NCCN-IPI had the lowest value of only approximately 0.6, which defines low discrimination powers. In the analyzed studies the c-index refers to time-to-event outcome (OS). In such analyses, the c-index and its interpretation are less well established than a binary outcome, since some patients had not experienced an event at the time of analysis.[17] There is no consensus on how to handle time-to-event data, because this

requires exclusion of censored patients or using indirect estimates of survival, based on the regression model, with a tendency to give lower c-statistics than other methods.[17,62] Another issue with the c-statistic is that it measures discrimination and not calibration, which is the agreement between observed outcomes and predictions.[17] The c-statistic is not a good measure of the actual probability of events if only a small number of patients experience the event of interest.[17] In addition, four studies reported CPE in order to evaluate the discriminatory power and the predictive accuracy of non-linear statistical models.[2,3,10,40] An early estimate of the concordance probability, which was the predominant discrimination statistic adapted for survival analysis, was Harrell's c-index, used in three studies.[16,25,32,63] However, Harrell's c-index was influenced by the rate of patient accrual and the length of the study. To avoid this limitation, Uno et al introduced inverse probability censoring weights to the c-index. This method was used in one study.[22,33,39]

In six studies, the performance of indices was compared using the AIC.[2,3,9,29,40,64] To compare the quality of a set of statistical models (to perform model comparisons) with each other, two studies used another criterion for model selection – the BIC, which measures the trade-off between model fit and

complexity of the model.[7,18,32] Both BIC and AIC balance the level of fit (based on the log-likelihood, a basic estimate of fit) with model complexity. Furthermore, the formula for the BIC is similar to the formula for the AIC, but with a different penalty for the number of parameters.[18] Lower AIC and BIC values are preferred, and indicate a more explanatory and informative model.[64] The AIC is the commonly used model selection tool for choosing between alternative models and has a preference for more complex models compared to the BIC, owing to its ability to eliminate unnecessarily complicated models, which contain too many parameters for accurate estimation on a given data set.[64] However, the AIC takes into account each model and ranks them from the best to worst, then it chooses between the models based on the goodness of fit using the lowest number of variables that explains the outcome best. This means that if all models are poor, it will choose the best of these, because quality is not taken into account.[65] Furthermore, when the sample size is small, there is a high probability that the AIC will select models that have too many parameters, leading to overfitting. To address such potential overfitting, alternative versions of the AIC have been proposed to make it easier to compare models estimated on different data sets of varying sizes.[66]

Two studies used the Hosmer–Lemeshow test goodness of fit to assess calibration.[25,36,67] Models are well calibrated if expected and observed event rates in subgroups of risk models are similar. The main limitations of this test are that it is based on an arbitrary grouping of observations, it has poor power in small data sets, and the result is expressed only in a *p*-value.[68] In addition, three models used a calibration plot, described as a graphical illustration of the Hosmer–Lemeshow test, which is another method to assess calibration in which the observed event status is plotted against the predicted risk estimates. The plot is often supplied with a calibration curve to help to diagnose a lack of fit, and will lie on the 45-degree line in a well-calibrated model.[68,69] Some authors have suggested the use of the calibration slope, which, in addition to the *p*-value, provides a confidence interval and a measure of size of effect, since the estimated slope is obtained from the regression model and does not require the patients to be grouped. Therefore, the calibration slope does not suffer from the limitations of the Hosmer–Lemeshow test.[68]

To determine the optimal cut-off point for continuous measurements for predicting OS, 11 of 46 studies used the ROC curve, which maximizes the likelihood ratio.[15,35,37,40–47] The ROC curve analysis has earned a place in biomedical studies when interpreting the results of diagnostic accuracy of a continuous marker. The performance of a marker is evaluated by the area under the ROC curve (AUC), an indicator of overall "accuracy", in which a higher AUC value indicates a better performance. However, there is variation in the sensitivity and specificity from point to point along the ROC curve and therefore it is important to consider the aims of diagnostic tests with respect to the significance and costs of a false-positive or negative interpretation.[70] Regarding the cut-off points of continuous variables used in prognostic models in DLBCL, it is obvious that different thresholds based on ROC results were incorporated in the models, where an additional five studies used cut-off points that had already been reported.[9,33,49–51] However, in ROC, one's choice of the value based on specificity and sensitivity can largely depend on the data set, meaning that the optimal cut-off value in one population might not be the optimal value in another.

Because of the lack of comparisons between prognostic models and the use of a variety of statistical methods for model comparison, it was not possible to make a universal comparison. Therefore, we have chosen to compare models by using very simple tools: the difference and proportion between scores among low-risk and high-risk groups. The bigger the observed value between the low- and high-risk groups, the better the model's power. However, the number of patients in the high-risk group has a major impact on the results. Hence, it is not surprising that the highest ratio was observed in a study including just 73 patients, while the highest difference was observed in a study that analyzed 337 patients. However, these tools have pointed to the rather limited power of the IPI, as well as the lower prognostic value of models developed in a limited number of patients. Although these are simple methods of comparison, they can give a false impression of superiority of one model, possibly due to a limited number of patients in high-risk groups or relatively short follow-up. Thus, they should be used as an addition to other performance measures and not as the primary method of comparison owing to these limitations. The studies that used nomograms presented a visual representation of a statistically predictive model that estimates the probability of a clinical event by calculating the cumulative effect of weighted independent variables.[71] Although these models cannot be compared by the ratio or difference because they do not use risk categories, they provide the discrimination and/or calibration to compare different prognostic models. Irrespective of the fact that that

these complex models did not entirely fulfill our inclusion criteria, their recognition indicates the current trend towards more individualized prognostication. This is mainly due to the fact that grouping of patients into risk categories results in an ineffective use of the data and tends to reduce the predictive accuracy of a prognostic model. In addition, the complexity of nomograms can be offset by using electronic versions.[72] Still, there are no guidelines regarding which value could be used in decision making when nomograms are used for prognostication. However, it would advance clinical application if future studies evaluated nomograms in the risk-adapted therapeutic strategies.[26] Nevertheless, due to other limitations of nomograms, the focus of future studies, besides developing new models, should be validation of the existing prognostic models.[73]

In addition, one study developed a prognostic model by combining data from a clinical database with machine learning techniques.[28] The stacking algorithm, used in the study, is a way of ensembling multiple regression models to obtain survival curves, eliminating the need for the specification of one prognostic modeling approach.[74] Although the machine learning technique is not a new concept, it is gaining more attention in the classification, prognostication, and genetic analysis of DLBCL.[28,75,76] It is evident that the clinical and genetic heterogeneity of DLBCL, as well as overlapping of DLBCL subgroup classifications, represent significant challenges for accurate outcomes prediction.[74] To provide a prediction of clinically relevant outcomes for patients with DLBCL, future studies will likely have to combine different factors (clinical, sociodemographic, tumor microenvironment, genetic, etc), possibly with the aid of the machine learning and high-dimensional data analysis or other statistical methods in order to develop comprehensive, multilevel prognostic models that should be easily applicable in clinical care.[74]

Conclusion

Although an increasing number of prognostic models for DLBCL has emerged in the past two decades, there is no universally accepted statistical method of reporting prognostic models in DLBCL. When reporting a new prognostic model, we would recommend assessing the discrimination and calibration of the prognostic model. Other measures of its performance may be used when adding a novel predictor to an established model.[19] In addition, comparisons of different available prognostic models based on the same population should be provided. This is needed in order to avoid the vagueness that currently exists in the literature, owing to an inability to compare current prognostic models in DLBCL.

Furthermore, to adapt models to a more individualized approach, an increasing number of models based on nomograms has been published. These models generally report the discrimination and calibration in order to compare the novel model with previous models, and tend to have higher predictive accuracy by avoiding potential loss of information due to the omission of risk categorization. However, future prognostication studies that integrate advances in statistics with growing knowledge on the diagnostics, pathology, and therapy of DLBCL are necessary.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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