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Prognostic clinical and serum biomarkers in diffuse large B-cell lymphoma.

Biomarcadores clínicos y séricos de pronóstico en linfoma difuso de células B grandes

Alejandro Aranda-Gutiérrez,[1] José A Hernández-Hernández,[1] Rosa del Carmen López-Sánchez,[1] Luis Villela[2,3,4]

Abstract

Diffuse large B-cell lymphoma (DLBCL) is an aggressive malignancy with significant rates of relapse despite first-line treatment with anthracycline-based chemotherapy regimens and rituximab. Various indexes are available to estimate survival rates in patients with DLBCL. The most commonly employed are the International Prognostic Index (IPI), Revised-IPI (R-IPI), and National Comprehensive Cancer Network-IPI (NCCN-IPI). However, these indexes fail to recognize a subgroup of patients with very poor outcomes in the rituximab era. Modern technologies have allowed for the identification of molecular prognostic factors not contemplated in IPI, R-IPI, or NCCN-IPI that can identify patients with dismal outcomes. However, these technologies are usually expensive, technically challenging, and require further validation and standardization. Hence, while molecular prognostic factors become more readily available, it is important to consider other simpler and cheaper tools that can complement known prognostic indices. This review will focus on prognostic laboratory biomarkers obtained at diagnosis in patients with DLBCL treated with rituximab-containing regimens.

KEYWORDS: Diffuse large B-cell lymphoma; Prognosis; Biomarker.

Resumen

El linfoma difuso de células B grandes (LDCBG) es una neoplasia maligna agresiva con tasas significativas de recaída a pesar del tratamiento de primera línea con regímenes de quimioterapia basados en antraciclinas y rituximab. Hay varios índices disponibles para estimar las tasas de supervivencia en pacientes con linfoma difuso de células B grandes. Los que se usan más comúnmente son el Índice de pronóstico internacional (IPI), el IPI revisado (R-IPI) y la Red nacional integral del cáncer-IPI (NCCN-IPI). Sin embargo, estos índices no reconocen un subgrupo de pacientes con resultados muy deficientes en la era del rituximab. Las tecnologías modernas han permitido la identificación de factores de pronóstico molecular no contemplados en IPI, R-IPI o NCCN-IPI que pueden identificar a pacientes con resultados desalentadores. Sin embargo, estas tecnologías suelen ser caras, técnicamente desafiantes y requieren mayor validación y estandarización. Por tanto, si bien los factores de pronóstico molecular se vuelven más fácilmente disponibles, es importante considerar otras herramientas más simples y económicas que puedan complementar los índices de pronóstico conocidos. Esta revisión se centrará en los biomarcadores de laboratorio de pronóstico obtenidos en el momento del diagnóstico en pacientes con linfoma difuso de células B grandes tratados con regímenes que contienen rituximab.

PALABRAS CLAVE: Linfoma difuso de células B grandes; pronóstico; biomarcador.

[1] Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo León, Mexico.
[2] Universidad del Valle de México, Escuela de Ciencias de la Salud, Campus Hermosillo, Sonora, México.
[3] Centro Médico Dr. Ignacio Chávez, ISSSTESON, Hematology and Blood Bank Service, Hermosillo, Sonora, México.
[4] Hospital Fernando Ocaranza, ISSSTE, Hermosillo, Sonora, México.

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Correspondence
Luis Villela
luisvillela@yahoo.com

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BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL), accounting for 30-58% of cases in different regions of the world.[1] Despite its clinical aggressiveness, long-term survival is possible following treatment with anthracycline-based chemotherapy regimens and the anti-CD20 monoclonal antibody rituximab. However, approximately 40% of patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) will have refractory disease or relapse.[2]

Various methods exist to predict survival outcomes in patients with DLBCL. The most commonly employed prognostic tools are the International Prognostic Index (IPI), Revised-IPI (R-IPI), and National Comprehensive Cancer Network-IPI (NCCN-IPI), which are scored using five parameters: age, lactate dehydrogenase (LDH), Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance status, and extranodal involvement.[3] Although these indexes have proven their value in different clinical contexts, they fail to recognize a subgroup of patients with very poor outcomes (long-term overall survival [OS] < 50%) in the rituximab era.[4]

The use of next-generation sequencing and comprehensive genomic analysis technologies has allowed for the identification of molecular prognostic factors not contemplated in IPI, R-IPI, or NCCN-IPI.[5] The integration of these molecular factors into known prognostic indices could better characterize a high-risk group for which more aggressive and targeted treatment strategies are necessary.[4] However, these technologies are usually expensive, technically challenging, and require further validation and standardization. Hence, while molecular prognostic factors become more readily available, it is important to consider other simpler tools that can complement known prognostic indices in the rituximab era and that can be employed across academic and community centers, especially those found in resource-constrained settings.

This review will focus on prognostic laboratory biomarkers obtained at diagnosis in patients with DLBCL treated with rituximab-containing regimens. Studies performed on specific subtypes of lymphoma such as primary DLBCL of the central nervous system are not contemplated. A synthesis of the most relevant prognostic models based on laboratory biomarkers is presented in **Table 1**.

HEMOGLOBIN

Anemia is a frequent finding in patients with DLBCL. Several factors contribute to this, including inadequate erythropoietin synthesis, excessive interleukin 6 production, and poor utilization of apparently adequate iron stores.[6] In general, it appears that hemoglobin (Hb) levels below the population mean are associated with an inferior 5-year OS and event-free survival (EFS), even when found in the non-anemic range.[7]

The prognostic significance of Hb on patients with DLBCL has also been explored in combination with other laboratory parameters. For example, Candelaria et al. reported that ECOG performance status > 2, elevated β_2-microglobulin (B2M), bulky disease, and Hb <10.0 g/dL were all independent prognostic factors for OS in patients > 65 years.[8] Using these four parameters, they constructed a prognostic score, which successfully identified three groups with significantly different OS rates. In another study, Nakayama et al. computed the Hb-platelet (HP) index by assigning 1 point to Hb < 12.0 g/dL and another to platelet (PLT) count < 135 x 10^9/L.[9] Patients with higher HP scores had a significantly inferior 3-year OS than patients with lower HP scores. Notably,

Table 1. Prognostic models in DLBCL that incorporate laboratory biomarkers not contemplated in IPI, R-IPI, or NCCN-IPI (continued on next page)

Prognostic model	Scoring	Interpretation	Outcome	Reference
Score to predict survival in +65-year patients with DLBCL	*ECOG performance status* 1 = 1 point 2 = 2 points 3 = 3 points *B2M* Normal = 1 point Elevated = 2 points *Bulky disease* No = 1 point Yes = 2 points *Hb* >10.0 g/dL = 1 point <10.0 g/dL = 2 points	Low risk (< 5)	1-year OS: 87.9% 5-year OS: 80.1%	Candelaria et al.[8]
		Intermediate risk (6)	1-year OS: 62.7% 5-year OS: 55.5%	
		High risk (> 6)	1-year OS: 38.6% 5-year OS: 19.8%	
HP index	Hb < 12.0 g/dL = 1 point PLT count < 135 x 10^9/L = 1 point	Low (0)	3-year OS: 79.0%	Nakayama et al.[9]
		Intermediate (1)	3-year OS: 52.0%	
		High (2)	3-year OS: 30.0%	
Stratification by CBC	LMR < 1.6 = 1 point Hb < 10.0 g/dL = 1 point PLT count < 150 x 10^9/L = 1 point	CBC Group 1 (0)	5-year OS: 78.2%	Shimono et al.[3]
		CBC Group 2 (1-2)	5-year OS: 60.9%	
		CBC Group 3 (3)	5-year OS: 10.1%	
PA score	PLT count ≥ 100 x 10^9/L and SA ≥ 3.5 g/dL	Low	5-year OS: 81.5% 5-year EFS: 65.1%	Ochi et al.[11]
	PLT count < 100 x 10^9/L and SA ≥ 3.5 g/dL OR PLT count ≥ 100 x 10^9/L and SA < 3.5 g/dL	Intermediate	5-year OS: 48.6% 5-year EFS: 36.3%	
	PLT count < 100 x 10^9/L and SA < 3.5 g/dL	High	5-year OS: 20.2% 5-year EFS: 11.3%	
PLR and B2M with IPI or aaIPI	PLR < 170 and Normal B2M levels and IPI < 2 or aaIPI = 0	Low risk	5-year OS: 86.4% 5-year PFS: 81.4%	Zhao et al.[12]
	-	Intermediate risk	5-year OS: 54.1% 5-year PFS: 47.0%	
	PLR ≥ 170 and High B2M levels and IPI ≥ 4 or aaIPI = 3	High risk	5-year OS: 21.1% 5-year PFS: 21.1%	
AMC/ALC PS	AMC < 0.63 x 10^9/L and ALC > 1 x 10^9/L	Low risk	5-year OS: N/A 5-year PFS: 83.0%	Wilcox et al.[13]
	AMC ≥ 0.63 x 10^9/L or ALC ≤ 1 x 10^9/L	Intermediate risk	5-year OS: N/A 5-year PFS: 59.0%	
	AMC ≥ 0.63 x 10^9/L and ALC ≤ 1 x 10^9/L	High risk	5-year OS: 32.0% 5-year PFS: 30.0%	

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Table 1. Prognostic models in DLBCL that incorporate laboratory biomarkers not contemplated in IPI, R-IPI, or NCCN-IPI (continued on next page)

Prognostic model	Scoring	Interpretation	Outcome	Reference
ALC/R-IPI	R-IPI very good or good and ALC ≥ 0.84 x 10^9/L	Low risk	22-month OS: 92.0% 22-month EFS: 90.0% 22-month PFS: 95.0%	Cox et al.[23]
	R-IPI poor or ALC < 0.84 x 10^9/L	Intermediate risk	22-month OS: 81.0% 22-month EFS: 45.0% 22-month PFS: 58.0%	
	R-IPI poor and ALC < 0.84 x 10^9/L	High risk	22-month OS: 56.0% 22-month EFS: 17.0% 22-month PFS: 33.0%	
Modified three-factor prognostic model	ECOG performance status > 1 = 1 point Ann Arbor stage III or IV = 1 point ALC < 1 x 10^9/L = 1 point	Score 0	3-year OS: 94.8% 3-year PFS: 78.4%	Huang et al.[25]
		Score 1	3-year OS: 79.2% 3-year PFS: 59.6%	
		Score 2	3-year OS: 40.3% 3-year PFS: 33.7%	
		Score 3	3-year OS: 18.4% 3-year PFS: 10.0%	
Prognostic model based on ANC, AMC, B2M, ECOG performance status, and number of extranodal disease sites	*B2M* > 1-1.5 x normal = 1 point > 1.5-2 x normal = 2 points > 2 x normal = 3 points *ANC* > 1 x normal = 1 point *AMC* > 1 x normal = 1 point *ECOG performance status* > 1 = 1 point *Extranodal involvement* > 1 site = 1 point	Low1 risk (0)	5-year OS: 98.0% 5-year PFS: 95.0% 10-year OS: 98.0% 10-year PFS: 90.0%	Chen et al.[28]
		Low2 risk (1)	5-year OS: 92.0% 5-year PFS: 86.0% 10-year OS: 85.0% 10-year PFS: 74.0%	
		Intermediate risk (2)	5-year OS: 82.0% 5-year PFS: 68.0% 10-year OS: 66.0% 10-year PFS: 57.0%	
		High1 risk (3-5)	5-year OS: 66.0% 5-year PFS: 56.0% 10-year OS: 47.0% 10-year PFS: 38.0%	
		High2 risk (6-7)	5-year OS: 21.0% 5-year PFS: 18.0% 10-year OS: 8.0% 10-year PFS: 7.0%	

Table 1. Prognostic models in DLBCL that incorporate laboratory biomarkers not contemplated in IPI, R-IPI, or NCCN-IPI (continued on next page)

Prognostic model	Scoring	Interpretation	Outcome	Reference
DLBCL-IPI	Age (70 years) ECOG performance status SA LDH Stage	Low (0-1)	5-year OS: 87.0%	Gang et al.[36]
		Low-intermediate (2)	5-year OS: 69.0%	
		High-intermediate (3)	5-year OS: 53.0%	
		High (4-5)	5-year OS: 37.0%	
NCCN-IPI with SA	*NCCN-IPI* 5 parameters with a maximum of 8 points *SA* < 3.5 g/dL = 2 points	Low risk (0-2)	3-year OS: 97.8% 5-year OS: 93.5%	Melchardt et al.[37]
		Intermediate-low risk (3)	3-year OS: 82.7% 5-year OS: 78.0%	
		Intermediate-high risk (4-7)	3-year OS: 65.9% 5-year OS: 55.7%	
		High risk (8-10)	3-year OS: 44.2% 5-year OS: 36.8%	
KPI	*LDH* 1-3 = 1 point ≥ 3 = 2 points *ECOG performance status* ≥ 2 = 1 point *SA* < 3.5 g/dL = 1 point *Extranodal involvement* Bone marrow, skin and/or lung/pleura = 1 point	Low risk (0)	3-year OS: 96.4% 3-year PFS: 84.4%	Kobayashi et al.[38]
		Low-intermediate risk (1-2)	3-year OS: 84.7% 3-year PFS: 70.2%	
		High-intermediate risk (3)	3-year OS: 63.8% 3-year PFS: 53.4%	
		High risk (4-5)	3-year OS: 33.3% 3-year PFS: 24.1%	
ACA index	*Age* > 75 years = 1 point *SA* < 3.7 g/dL = 1 point *CCI score* ≥ 3 = 1 point	Excellent (0)	3-year OS: 86.0%	Miura et al.[39]
		Good (1)	3-year OS: 72.0%	
		Moderate (2)	3-year OS: 51.0%	
		Poor (3)	3-year OS: 0%	
IACA index	*IADL score* 6-7= 1 point ≤ 5 = 2 points *ACA index* Good = 1 point Moderate to poor = 2 points	Low risk (0)	2-year OS: 96.0% 2-year PFS: 80.6%	Liu et al.[40]
		Intermediate risk (1-2)	2-year OS: 70.1% 2-year PFS: 46.4%%	
		High risk (3-4)	2-year OS: 24.1% 2-year PFS: 16.7%	
PNI	PNI was calculated as 10 x serum levels of albumin (g/dL) + 0.005 x ALC (/mm^3)	< 40	Median OS: 15.6 months Median PFS: 11.2 months	Go et al.[43]
		≥ 40	Median OS: not reached Median PFS: not reached	

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Table 1. Prognostic models in DLBCL that incorporate laboratory biomarkers not contemplated in IPI, R-IPI, or NCCN-IPI (continued on next page)

Prognostic model	Scoring	Interpretation	Outcome	Reference
CONUT	*SA (g/dL)* 3.00-3.49 = 2 points 2.50-2.59 = 4 points < 2.50 = 6 points *Total lymphocyte counts (/µL)* 1200-1599 = 1 point 800-1199 = 2 points < 800 = 3 points *Serum total cholesterol (mg/dL)* 140-179 = 1 point 100-139 = 2 points < 100 = 3 points	Low CONUT score (≤ 3)	5-year OS: 83.2% 5-year PFS: 73.1%	Nagata et al.[44]
		High CONUT score (≥ 4)	5-year OS: 49.0% 5-year PFS: 46.1%	
GELTAMO-IPI	*Age* ≥ 65 to ≤ 79 = 1 point > 80 = 2 points *Ann Arbor stage* III-IV = 1 point *LDH, normalized* > 1 = 1 point *ECOG performance status* 2 = 1 point 3-4 = 2 points *B2M, normalized* > 1 = 1 point	Low risk (0)	5-year OS: 93.0%	Montalbán et al.[46]
		Low-intermediate risk (1-3)	5-year OS: 79.0%	
		High-intermediate risk (4)	5-year OS: 66.0%	
		High risk (≥5)	5-year OS: 39.0%	
B2M with age, LDH, ECOG performance status, and Ann Arbor stage	*Age* > 60 = 1 point *LDH ratio* > 1 = 1 point *ECOG performance status* ≥ 2 = 1 point *Ann Arbor stage* 3 or 4 = 1 point *B2M ratio* > 2.5 = 1 point	Low (0)	5-year OS: 95.2% 5-year PFS: 93.3%	Kang et al.[48]
		Low-intermediate (1)	5-year OS: 86.4% 5-year PFS: 88.7%	
		High-intermediate (2-3)	5-year OS: 69.2% 5-year PFS: 71.0%	
		High (4-5)	5-year OS: 47.8% 5-year PFS: 64.8%	
B2M with age, ECOG performance status, and Ann Arbor stage	*Age* > 60 = 1 point *ECOG performance status* ≥ 1 = 1 point *Ann Arbor stage* 3 or 4 = 1 point *B2M* ≥ 3.2 mg/L = 1 point	Low (0)	3-year OS: 100.0% 3-year PFS: 92.0%	Kanemasa et al.[49]
		Low-intermediate (1-2)	3-year OS: 87.0% 3-year PFS: 77.3	
		High-intermediate (3)	3-year OS: 57.2% 3-year PFS: 47.6%	
		High (4)	3-year OS: 23.4% 3-year PFS: 24.4%	

Table 1. Prognostic models in DLBCL that incorporate laboratory biomarkers not contemplated in IPI, R-IPI, or NCCN-IPI (continued)

Prognostic model	Scoring	Interpretation	Outcome	Reference
Lipo-PI	*NCCN-IPI* 5 parameters with a maximum of 8 points *Cholesterol levels* HDL-C < 1.03 mmol/L or LDL-C < 2.60 mmol/L = 1 point HDL-C < 1.03 mmol/L and LDL-C < 2.60 mmol/L = 2 points	Low risk (0-2)	3-year OS: 98.0% 3-year PFS: 91.3% 5-year OS: 96.9% 5-year PFS: 88.6%	Gao et al.[50]
		Low-intermediate risk (3-4)	3-year OS: 82.8% 3-year PFS: 72.4% 5-year OS: 79.6% 5-year PFS: 65.0%	
		High-intermediate risk (5-6)	3-year OS: 50.0% 3-year PFS: 35.1% 5-year OS: 45.0% 5-year PFS: 29.5%	
		High risk (≥ 7)	3-year OS: 34.3% 3-year PFS: 20.0% 5-year OS: 22.5% 5-year PFS: 10.0%	
ICPS	SA < 4.15 g/dL = 1 point LMR ≤ 2.7 = 1 point CRP > 8.6 mg/L = 1 point	ICPS 0 (0)	3-year OS: 95.6% 3-year PFS: 84.8%	Sun et al.[56]
		ICPS 1 (1)	3-year OS: 88.2% 3-year PFS: 84.8%	
		ICPS 2 (2)	3-year OS: 76.0% 3-year PFS: 71.6%	
		ICPS 3 (3)	3-year OS: 62.2% 3-year PFS: 54.5%	
GPS	CRP ≤ 10 mg/L and SA ≥ 3.5 g/dL	GPS-0	5-year OS: 90.8% 5-year PFS: 86.2%	Li et al.[57]
	CRP > 10 mg/L or SA < 3.5 g/dL	GPS-1	5-year OS: 76.6% 5-year PFS: 66.0%	
	CRP > 10 mg/L and SA < 3.5 g/dL	GPS-2	5-year OS: 38.5% 5-year PFS: 15.4%	

aaIPI: age-adjusted IPI; ACA: age, comorbidities and albumin; ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophil count; B2M: β_2-microglobulin; CBC: complete blood count; CCI: Charlson Comorbidity Index; CONUT: controlling nutritional status; CRP: C-reactive protein; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula Ósea; GPS: Glasgow Prognostic Score; Hb: hemoglobin; HDL-C: high-density lipoprotein cholesterol; HP: Hb-platelet; IACA: IADL ACA; IADL: instrumental activities of daily living; ICPS: inflammation-based cumulative prognostic score; IPI: International Prognostic Index; KPI: Kyoto Prognostic Index; LDH: lactate dehydrogenase; LDL-C: low-density lipoprotein cholesterol; Lipo-PI: lipoprotein prognostic index; LMR: lymphocyte-to-monocyte ratio; NCCN-IPI: National Comprehensive Cancer Network-IPI; OS: overall survival; PA: PLT-albumin; PFS: progression-free survival; PLR: platelet-to-lymphocyte ratio; PLT: platelet; PNI: prognostic nutritional index; PS: prognostic score; R-IPI: Revised-IPI; SA: serum albumin.

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the HP index was independent of the IPI, but not of clinical stage. Shimono et al. similarly established a prognostic model by using cutoff values of < 1.6, < 10.0 g/dL, and < 150 x 10^9/L for lymphocyte-to-monocyte ratio (LMR), Hb, and PLT count, respectively, to stratify patients into three different risk groups.[3] Those in complete blood count (CBC) Group 1 (none of the factors present) had a 5-year OS rate of 78.2%, which was significantly superior to the 5-year OS rate of 10.1% seen in CBC Group 3 (all factors present).

PLATELETS

Thrombocytopenia is common in patients with DLBCL. Various factors can contribute to this, including bone marrow infiltration, infection, splenic sequestration, myelodysplasia, and immune-mediated PLT destruction.[10] Chen et al. reported that thrombocytopenia was an independent adverse prognostic factor for OS and progression-free survival (PFS).[10] Ochi et al. also explored the prognostic value of a low PLT count, identifying both a PLT count < 100 x 10^9/L and serum albumin (SA) < 3.5 g/dL as predictors of a poor OS, independently of the NCCN-IPI.[11] Utilizing both parameters, they constructed the PLT-albumin score, which identified three groups with significantly different 5-year OS and EFS rates. Notably, Zhao et al. found no statistically significant association between the PLT count and OS or PFS in a multivariate analysis.[12] Nevertheless, they reported that patients with a platelet-to-lymphocyte ratio (PLR) ≥ 170 experienced a significantly decreased OS and PFS compared with those with PLR <170. Based on this, they formulated a novel prognostic model combining PLR with B2M and IPI or age-adjusted IPI. The score divided patients into three groups, with 5-year OS rates significantly differing between them.

WHITE BLOOD CELLS

Given the roles of the systemic inflammatory response and host immunity in lymphoma biology, several immune-related biomarkers can serve as prognostic tools in DLBCL. The most notable examples are the absolute lymphocyte count (ALC) and absolute monocyte count (AMC), which have been associated with worse outcomes when decreased and increased, respectively.[13,14] Nevertheless, similar to IPI, AMC and ALC as single variables are unable to identify truly high-risk patients.[13] Hence, ALC and AMC have been combined with one another to potentiate their prognostic value. For example, Wilcox et al. explored the AMC/ALC prognostic score (PS), which allowed them to stratify patients into three risk categories.[13] Those in the highest-risk category had an especially poor OS and PFS when compared with the other two groups. Others have also studied the AMC/ALC PS and related scores, with similar results.[14-18] The ALC/AMC ratio, also known as the LMR, is another combination of ALC and AMC that has demonstrated prognostic significance in DLBCL. Several meta-analyses regarding the prognostic utility of LMR on patients with DLBCL are available in the literature, with three supporting that a low LMR is associated with worse survival outcomes.[19,20,21]

ALC and AMC have also been combined with other parameters to create prognostic scores. For instance, Cox et al. combined ALC with IPI to develop a dichotomous score known as the ALC/IPI, which proved to be highly significant for EFS and PFS, but not OS.[22] They subsequently built a new trichotomous score known as ALC/R-IPI, which proved highly significant for EFS, PFS, and OS.[23] Bari et al. validated the ALC/R-IPI score and determined that it could be used to design clinical trials.[24] However, they did highlight that the ALC/R-IPI score had difficulty recognizing a high percentage of poor prognosis patients. Huang

et al. also reported that the ALC/R-IPI score was useful for discriminating between risk groups.[25] However, in their analysis, the ALC/R-IPI score was slightly inferior to a modified 3-factor model that incorporated ECOG performance status, Ann Arbor stage, and ALC. Another model combining ALC with IPI was reported by Maurer et al.[26] This model, known as IPI24, estimated the probability of failing to achieve EFS at 24 months. In their study, the IPI24 model had a superior discriminatory ability compared to IPI and NCCN-IPI. ALC has also been combined with LDH to create the LDH to ALC ratio (LAR). Keane et al. reported that a high LAR was associated with an inferior 5-year OS and PFS, independently of cell of origin and IPI.[27]

Neutrophils have also been studied as prognostic factors in DLBCL. For instance, Chen et al. reported that an elevated absolute neutrophil count (ANC) was associated with a worse OS.[28] They combined the ANC with AMC, B2M, ECOG performance status, and extranodal involvement to develop a new prognostic model, which divided patients into five risk groups with significantly different 5-year and 10-year OS and PFS rates. In another study, Porrata et al. reported that patients with a neutrophil-to-lymphocyte ratio (NLR) < 3.50 had a superior OS and PFS compared with those ≥ 3.50.[29] Similarly, Troppan et al. found a significant association between a high derived NLR (calculated by dividing the neutrophil count by the subtraction of the neutrophil count from the leukocyte count) and a worse OS and disease-free survival (DFS).[30]

Beltrán and Villela et al. validated the prognostic value of the NLR in two cohorts of Latin American patients with DLBCL. In both cohorts (learning and validation), patients with NLR ≥ 4.0 had lower odds of achieving a complete response with immunochemotherapy and had significantly worse 5-year OS rates than patients with NLR < 4.0.[31] Most recently, Go et al. reported that the five components of the NCCN-IPI and the NLR were independent prognostic factors for OS and PFS (except for extranodal disease in PFS).[32] Based on this, they constructed nomograms using NLR to improve the prognostic value of NCCN-IPI. The nomograms showed a good discriminating ability for OS and PFS. Of note, this model had a higher c-index than a similar model based on NLR and IPI reported by Keam et al., suggesting that the combination of NLR with NCCN-IPI has a superior prognostic value than its combination with IPI.[32,33]

SERUM ALBUMIN

SA has been extensively studied as a prognostic biomarker in DLBCL. For example, in a study of patients ≥80 years receiving R-miniCHOP, SA ≤ 3.5 g/dL was the only parameter associated with an adverse OS in a multivariate analysis.[34] Similarly, a study by Dalia et al. found that SA < 3.7 g/dL was associated with worse outcomes after controlling for R-IPI and initial lymphocyte count.[35] The relationship between low SA and adverse survival outcomes could be explained by the former's association with poor nutritional status, cytokine secretion, advanced disease stage, and comorbid status.[34,35,36]

SA has also been combined with other factors to improve its prognostic value. For instance, Gang et al. proposed two new modified models that incorporated SA <4.0 g/dL as an adverse prognostic factor.[36] The first was the DLBCL prognostic index (DLBLCL-PI), which incorporated age (70 years), performance status, SA, LDH, and stage. The second one was the age-adjusted DLBCL-IPI for patients ≤ 70 years, which incorporated performance status, SA, LDH, and extranodal involvement. Both models identified four risk groups with significantly different 5-year OS rates. Similarly, Melchardt et al. combined SA with NCCN-IPI to create a new prognostic score.[37] Using this score, four distinct groups

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with significantly different 3-year and 5-year OS rates were identified. Notably, this modified NCCN-IPI score including SA was superior to the conventional NCCN-IPI.

Kobayashi et al. evaluated various potential prognostic variables, including elevated serum C-reactive protein (CRP) and hypoalbuminemia.[38] Although both were significant in a univariate analysis, only SA retained its prognostic impact on OS in a multivariate analysis. A new prognostic index called the Kyoto Prognostic Index incorporating SA, LDH, ECOG performance status, and extranodal involvement allowed them to classify patients into four distinct risk groups with significantly different 3-year OS and PFS rates. Similarly, Miura et al. reported that in patients with DLBCL ≥ 65 years, the following were independently associated with worse survival outcomes: age > 75 years, SA < 3.7 g/dL, and Charlson Comorbidity Index score ≥ 3.[39] Based on these findings, a new index comprising these three factors, known as the Age, Comorbidities, and Albumin (ACA) index, was established. The ACA index was able to discriminate 3-year OS, tolerability to cytotoxic drugs, adherence to treatment, febrile neutropenia, and treatment-related deaths. Liu et al. combined the ACA index with the instrumental activities of daily living (IADL) scale to create the IADL ACA index, creating a three-category system that could effectively discriminate response and OS and PFS rates.[40]

Kim et al. evaluated the prognostic implications of the SA to globulin ratio (AGR).[41] The low AGR group (< 1.22) had significantly worse complete response and OS and PFS rates than the high AGR group (≥ 1.22), as well as an increase in treatment-related mortality. Yue et al. reported similar results with an AGR cutoff of 1.3.[42]

The prognostic value of SA in DLBCL has also been studied in the context of nutritional status. For example, Go et al. explored the effect of the prognostic nutritional index (PNI), which is calculated using SA and ALC.[43] Patients in the low-PNI group had diminished complete response rates, increased treatment-related toxicity, and more frequent treatment discontinuation rates. Furthermore, the OS was shorter in the low-PNI group than in the high-PNI group. Similarly, Nagata et al. tested the prognostic role of the controlling nutritional status (CONUT) score on patients with DLBCL.[44] This score, calculated using SA, total cholesterol, and lymphocyte counts, was able to statistically stratify 5-year OS and PFS rates. Namely, patients with high CONUT scores had a worse OS and PFS than those with low CONUT scores.

β_2-MICROGLOBULIN

Elevated B2M (seen in approximately 40% of patients with DLBCL) is a known predictor of worse outcomes.[45] Montalbán et al. developed the Grupo Español de Linfomas y Trasplantes de Médula Ósea (GELTAMO)-IPI score by combining NCCN-IPI parameters and B2M.[46] The GELTAMO-IPI score distinguished four risk groups with significantly different 5-year OS rates and was able to more accurately discriminate the high-risk group than NCCN-IPI. The effectiveness of GELTAMO-IPI was then compared by Hong et al. with IPI and NCCN-IPI.[47] The estimated 5-year OS of patients classified as high risk was 45.7% using IPI, 31.4% using NCCN-IPI, and 21.9% using GELTAMO-IPI. This indicates that both NCCN- and GELTAMO-IPI are superior to IPI in predicting poor prognosis, with a slight advantage when using GELTAMO-IPI.

Kang et al. developed a new prognostic model by integrating age, LDH, ECOG performance status, Ann Arbor stage, and B2M.[48] This model identified 4 risk groups with significantly different 5-years OS and PFS rates and showed better discriminative power than the classic IPI. Similarly, Kanemasa et al. created a prognostic

model incorporating age, ECOG performance status, Ann Arbor stage, and B2M, which showed better risk discrimination than NCCN-IPI.[49]

SERUM LIPIDS

Gao et al. explored the prognostic significance of serum lipid levels on patients with DLBCL.[50] Their results showed that low high-density lipoprotein cholesterol (HDL-C) together with low-density lipoprotein cholesterol (LDL-C) was an independent prognostic factor for PFS and OS. Based on this, they postulated the lipoprotein prognostic index (Lipo-PI), which combined NCCN-IPI and the cholesterol status of synchronously low HDL-C and LDL-C. In their analysis, Lipo-PI was superior to NCCN-IPI in predicting 3-year and 5-year OS and PFS.

SERUM ASPARTIC TRANSAMINASE

Lu et al. studied the prognostic effect of baseline aspartic transaminase (AST) on patients with DLBCL.[51] AST levels of 33.3 U/L were considered as the optimal threshold value for predicting prognosis. Those with a higher AST level had more aggressive clinicopathological features and a shorter 2-year OS than those with lower levels.

VITAMIN D

Drake et al. tested the prognostic effect of 25-hydroxyvitamin D [25(OH)D] on patients with DLBCL and other NHLs.[52] After adjusting for known prognostic factors, patients with DLBCL and 25(OH)D insufficiency had an inferior OS and EFS. Moreover, in patients with higher levels of 1,25-hydroxycholecalciferol, there was an improved OS and EFS.

Bittenbring et al. explored the impact of vitamin D deficiency (VDD) on the outcome of elderly patients with DLBCL.[53] Patients with VDD (≤ 8 ng/mL) had significantly decreased 3-year OS and EFS rates compared with patients with vitamin D > 8 ng/mL. Moreover, rituximab-mediated cellular cytotoxicity increased significantly in those with VDD after substitution and normalization of their vitamin D levels.

Hohaus et al. prospectively assessed 25(OH)D in a cohort of patients with aggressive B-cell lymphoma (most of which had DLBCL).[54] 25(OH)D levels below 20 ng/mL and IPI were independently associated with a worse EFS. Furthermore, those with normalized levels of 25(OH)D after supplementation had a superior EFS than those with persistently deficient/insufficient 25(OH)D levels.

C-REACTIVE PROTEIN

Elevated CRP levels have also been associated with worse DFS and OS in patients with DLBCL.[55] Sun et al. evaluated the prognostic significance of six systemic inflammatory parameters: CRP, SA, LMR, NLR, PLR, and fibrinogen. In a multivariate analysis, CRP, SA, and LMR were independent prognostic factors for OS. They constructed a new prognostic model utilizing these three parameters, known as the inflammation-based cumulative prognostic score (ICPS). An advanced multivariate analysis confirmed that the ICPS model served as a prognostic factor independent of IPI for both 3-year PFS and OS.[56]

Li et al. explored the prognostic value of the Glasgow Prognostic Score (GPS), which combines serum CRP and SA.[57] Those with higher GPS had a worse OS and PFS. Hao et al. determined that amongst several inflammation-based prognostic scores such as GPS, NLR, and PNI, GPS was the most powerful predictor for survival in patients with DLBCL.[58]

CONCLUSIONS

Currently, the use of molecular-based prognostic tools in DLBCL is limited by elevated costs, tech-

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nological obstacles, and insufficient validation and standardization. Therefore, until they become widely available, it is necessary to consider other simpler yet effective prognostic tools to predict poor survival outcomes in the rituximab era. Fortunately, many of these prognostic tools can be easily obtained from CBC and other routine laboratory tests. These laboratory biomarkers can be used independently and combined with one another to develop prognostic models that yield important data that is not always provided by the IPI, R-IPI, or NCCN-IPI.

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