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Evaluation of the MD Anderson tumor score for diffuse large B-cell lymphoma in the rituximab era

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Abstract

Objectives: Diffuse large B-cell lymphoma (DLBCL) is an aggressive heterogeneous lymphoma with standard treatment. However, 30%-40% of patients still fail, so we should know which patients are candidates for alternative therapies. IPI is the main

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prognostic score but, in the rituximab era, it cannot identify a very high-risk (HR) subset. The MD Anderson Cancer Center reported a score in the prerituximab era exclusively considering tumor-related variables: Tumor Score (TS). We aim to validate TS in the rituximab era and to analyze its current potential role.

Methods: From GELTAMO DLBCL registry, we selected those patients homogeneously treated with R-CHOP (n = 1327).

Results: Five-years PFS and OS were 62% and 74%. All variables retained an independent prognostic role in the revised TS (R-TS), identifying four different risk groups, with 5-years PFS of 86%, 71%, 50%, and very HR (28%). With a further categorization of three variables of the original TS (Ann Arbor Stage, LDH and B2M), we generated a new index that allowed an improvement in HR assessment.

Conclusions: (a) All variables of the original TS retain an independent prognostic role, and R-TS remains predictive in the rituximab era; (b) R-TS and additional categorization of LDH, B2M, and AA stage (enhanced TS) increased the ability to identify HR subsets.

KEYWORDS
diffuse large B-cell lymphoma, international prognostic index, prognosis, score, tumor score

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of aggressive lymphomas, considering their biologic, pathological, and clinical backgrounds. Treatment of DLBCL is relatively homogeneous and standard, mainly based on the R-CHOP regimen that produces complete remission (CR) rates of around 70%-90%[1,2] and 5-years progression-free survival (PFS) and overall survival (OS) of around 60%-70%.[3] However, 30%-40% of patients are still failing this standard therapy, so efforts to improve outcomes by new approaches or adding new drugs are needed. For this purpose, the most important point is how we can identify those patients at high risk of failure with standard therapy.

The most important and widely used clinical prognostic score is the International Prognostic Index (IPI) proposed in 1993[4] and lately validated in the rituximab era (R-IPI).[5] However, despite being a good prognostic score, it cannot identify a very high-risk (HR) subset in the rituximab era: The HR group of R-IPI has a 4-years OS and PFS higher than 50%. Several attempts have been made to try to improve: the NCCN-IPI and the GELTAMO-IPI.[6-8]

In 1992, the MD Anderson Cancer Centre (MDACC) reported a score exclusively considering variables related to the tumor: the Tumor Score (TS).[9] Two of them were already in IPI: LDH and Ann Arbor stage, but three were different: beta-2 microglobulin (B2M), bulky mass, and B symptoms. The study was performed in 144 intermediate lymphomas treated frontline with CHOP-bleo plus radiotherapy, if localized, and CHOP-Bleo/CMED, in advanced stage. The result was a simple prognostic model that identified in the prerituximab era two prognostic groups: low-risk (3-years failure-free survival [FFS] of 83%) vs high-risk (3-years FFS of 24%). This index has not been studied in the rituximab era. We aim to evaluate and validate the TS in the rituximab era, analyzing its current potential role in DLBCL.

Novelty statement

- The manuscript evaluates the Tumor Score (TS), revised in the rituximab era (R-TS) and provides an evolution of the score (Enhanced TS).
- We describe two ways (R-TS and Enhanced TS) that improve high-risk assessment in DLBCL, with a more precise identification of a very high-risk subset.
- TS may be used in standard clinical practice and inside clinical trials.

2 | METHODS

2.1 | Patients

This study is a nationwide retrospective analysis of an unselected population of patients with DLBCL treated in Spain from November 2000 to April 2014. We selected from the original final GELTAMO DLBCL[8] database (n = 2156) and those cases that received frontline induction with R-CHOP had all variables of IPI and TS available and

a minimum follow-up of 1 year (n = 1327). The study was approved by the Ethics Committee (EC) of the Hospital Ramon y Cajal (Madrid, Spain), which is the reference EC.

Standard clinical characteristics with prognostic value in DLBCL were registered at the time of diagnosis. LDH and B2M levels were normalized and presented as normal (ratio to the normal level in the local center ≤ 1) or high (ratio > 1).

2.2 | Statistical methods

The primary endpoint was PFS, defined as the time from diagnosis to refractoriness (lack of CR at the end of induction or early progression), relapse, or death from any cause. As an evaluation of CR may differ between the participating hospitals or the period of time, including Cheson or Lugano criteria,[10-12] we excluded those cases with <12-month follow-up to avoid sensitivity or specificity bias related to different response criteria in terms of progression identification. OS was calculated from the date of diagnosis until death from any cause. PFS and OS were analyzed with the Kaplan-Meier method and compared with the log-rank test. Multivariate analysis with the variables that appeared to be significant in the univariate analysis was carried out according to the Cox proportional hazard regression model. The validity of proportional hazard assumption was verified by adding a time-dependent variable to each model to confirm that HR for each covariate did not increase or decrease over time. Comparisons between scores were performed using the C index.

2.3 | Enhanced TS design

To develop the enhanced TS (enhanced TS), the series was non-randomly split into training and validation cohorts, representing 85% (all series excluding centers in the validation cohort; n = 1124) and 15% (Hospital del Mar, Son Espases and Dr Negrin; n = 203) of the whole series, respectively. To further improve the ability

TABLE 1 Main characteristics of patients (n = 1327)

Characteristics	Whole series (N = 1327)	Training cohort (N = 1124)	Validation cohort (N = 203)	*P*
Age				
18-60	580 (44%)	489 (44%)	91 (45%)	.76
>60 y	747 (56%)	635 (56%)	112 (55%)	
Sex				
Male	658 (50%)	559 (50%)	99 (49%)	.76
Female	663 (50%)	559 (50%)	104 (51%)	
LDH				
Normal	611 (46%)	521 (46%)	90 (44%)	.65
Elevated	716 (54%)	603 (54%)	113 (56%)	
AA stage				
I-II	518 (39%)	442 (39%)	76 (37%)	.64
III-IV	809 (61%)	682 (61%)	127 (63%)	
# extranodal sites				
0-1	1087 (82%)	933 (83%)	154 (76%)	.017
>1	238 (18%)	189 (17%)	49 (24%)	
ECOG PS				
0-1	916 (70%)	785 (70%)	131 (66%)	.27
>1	394 (30%)	328 (29%)	66 (33%)	
B symptoms				
Yes	504 (38%)	412 (37%)	92 (45%)	.023
No	823 (62%)	712 (63%)	111 (55%)	
Bulky mass				
Yes	385 (29%)	319 (28%)	66 (32%)	.24
No	942 (71%)	805 (72%)	137 (67%)	
B2M				
Normal	657 (50%)	565 (50%)	92 (45%)	.2
Elevated	670 (50%)	559 (50%)	111 (55%)	

Abbreviations: AA, Ann Arbor; B2M, beta-2 microglobulin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase.

of finding a very HR subset with the variables included in TS, we tested the possibility of analyzing a further categorization of several of the original TS variables (AA state, LDH, and B2M). In the last two, we examined the linearity assumption concerning their effects on PFS using MAXTAT and restricted cubic splines,[13] followed by refined categorization in the CoX model, minimizing Martingale residuals.[14] B symptoms or bulky mass were included as the original binary ones.

3 | RESULTS

3.1 | Characteristics of patients

The main characteristics of patients included in the study (n = 1327) are shown in Table 1. Regarding R-IPI, 12%, 45%, and 43% pertained to the low, intermediate and high-risk groups, respectively. Considering the original TS, 53% and 47% were scored as low or high risk.

TABLE 2 Univariate and multivariate analysis of single variables for PFS and OS

Univariate analysis	5-y PFS (IC95%)	*P*	5-y OS	*P*
Age				
0-60	67% (63-71)	<.001	81% (78-85)	<.001
>60	57% (54-61)		69% (65-72)	
Sex				
Male	58% (54-62)	.006	71% (67-74)	.01
Female	66% (62-69)		78% (75-81)	
LDH				
Normal	72% (68-76)	<.001	84% (80-87)	<.001
Elevated	53% (49-56)		66% (63-70)	
AA stage				
I-II	77% (73-81)	<.001	86% (83-89)	<.001
III-IV	52% (48-55)		67% (63-70)	
Extranodal sites				
0-1	65% (62-68)	<.001	77% (74-79)	<.001
>1	46% (39-53)		63% (56-69)	
ECOG PS				
0-1	69% (66-72)	<.001	81% (78-84)	<.001
>1	45% (40-50)		58% (52-63)	
B symptoms				
Yes	47% (42-52)	<.001	62% (58-67)	<.001
No	70% (67-74)		81% (79-84)	
Bulky mass				
Yes	53% (48-58)	<.001	67% (62-72)	<.001
No	65% (62-68)		77% (74-80)	
B2M				
Elevated	52% (48-56)	<.001	65% (61-69)	<.001
Normal	71% (67-75)		83% (80-87)	
Multivariate analysis	**PFS HR (95% CI)**	***P***	**OS HR (95% CI)**	***P***
Age > 60 y	1.22 (1.01-1.47)	.036	1.64 (1.3-2.06)	<.001
III-IV AA stage	1.75 (1.4-2.19)	<.001	1.52 (1.16-2)	.002
Elevated LDH	1.29 (1.06-1.58)	.011	1.30 (1.02-1.66)	.032
ECOG PS > 1	1.47 (1.22-1.78)	<.001	1.78 (1.42-2.22)	<.001
>1 extranodal site	1.09 (0.88-1.36)	.41	1.07 (0.83-1.38)	.62
B symptoms	1.28 (1.06-1.56)	.012	1.35 (1.07-1.71)	.01
Bulky mass	1.32 (1.1-1.59)	.003	1.32 (1.06-1.64)	.013
Elevated B2M	1.23 (1.01-1.5)	.044	1.45 (1.14-1.86)	.003

Abbreviations: AA, Ann Arbor; B2M, beta-2 microglobulin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

3.2 | Response rates, PFS and OS according to the TS in the rituximab era

In our series, 1080 (81%) achieved a CR to frontline R-CHOP. Median follow-up was 59 months (12-176). Five-years PFS and OS were 62% (95% confidence interval [95% CI]: 59-64) and 74% (95% CI: 72-77), respectively. At last follow-up, 338 (26%) had relapsed/progressed and 364 (27%) had died. In the univariate and multivariate survival analyses of PFS and OS, all the variables of the original TS retained an independent prognostic role in our series as well as all the IPI except for more than 1 extranodal site (Table 2).

The original MDCC TS categorization identifies two risk groups in our sample that represent near half the patients with a very different outcome (low and high risk). However, as in the case of original IPI, this original categorization does not identify in the rituximab era a very HR group, as the original HR subset has 61% 5-years OS, 46% 5-years PFS, and a CR rate of 69% (Table 3). For this reason, considering current survival curves, we changed TS categorization to a revised one (Figure 1). The revised TS in the rituximab era (R-TS) remains predictive. R-TS clearly identifies four different risk groups of 5-years PFS (86%, 71%, 50%, and 28%) and OS (93%, 83%, 64%, and 40%) (Figure 1A and B). There is an HR subset with a worse outcome (5-years PFS of 28% and a median PFS of only 4 months). These figures compare favorably with the HR group of R-IPI and NCCN-IPI: 5-years PFS of 47% and 38%, respectively (Figure 1C and D); and are like GELTAMO-IPI with 29% 5-years PFS (Figure 1E). These four risk groups of the R-TS represented 15%, 38%, 40%, and 7% of our series, while the HR groups in the R-IPI, NCCN-IPI, and GELTAMO-IPI were 45%, 8%, and 14% of their original series.[5,6]

TABLE 3 Outcome according to scores

Risk groups	N (%)	5-y PFS (%)	5-y OS (%)	CR (%)
R-IPI				
0	158 (12%)	86	92	94
1-2	596 (45%)	69	83	88
3-5	559 (43%)	47	60	70
Original TS				
0-2	705 (53%)	75	86	92
3-5	624 (47%)	46	61	69
R-TS				
0	198 (15%)	86	93	95
1-2	508 (38%)	71	84	91
3-4	536 (40%)	50	64	73
5	90 (7%)	28	40	47
NCCN-IPI				
0-1	168 (13%)	85	94	92
2-3	471 (36%)	70	83	89
4-5	476 (36%)	55	69	78
6-8	200 (15%)	38	48	62
GELTAMO-IPI				
0	161 (12%)	87	93	95
1-3	754 (57%)	65	80	86
4	224 (17%)	57	68	77
5-7	176 (13%)	29	40	55

Regarding response, these four groups also show decreasing CR rates from 95% in low risk to 47% for the HR subgroup, which compares favorably to the CR rates observed in the HR groups of IPI (70%), NCCN-IPI (62%), or GELTAMO-IPI (55%). Even considering OS, R-TS could improve HR assessment with a 5-years OS of 40% compared with 60% in R-IPI and 48% for NCCN-IPI, and like GELTAMO-IPI (40%).

Comparison between TS and the other indexes (IPI, NCCN-IPI, or GELTAMO-IPI) showed similar C indexes for PFS in our series: 0.67 vs 0.66, 0.66 and 0.67, respectively (p = NS) (Figure 1). However, TS had better discrimination of the high-risk subgroup than IPI and NCCN-IPI, both concerning PFS, OS, and CR rate (Table 3). Table 4 shows a comparative analysis of cases considering R-IPI and R-TS scores, in which we can see that R-TS more precisely may subcategorize the risk inside the larger R-IPI groups.

3.3 | Outcome according to an enhanced TS

To improve the R-TS, we split the original series in training and validation cohorts. Table 1 shows the clinical characteristics of both cohorts that are similar in most clinical variables, except for the number of extranodal sites and the presence of B symptoms. These differences between cohorts are acceptable in the context of independent samples.

In the training cohort, the abovementioned variables were subcategorized in three categories as shown in Figure 2A-F: AA stage (I, II, and III-IV) (Figure 2A and B), normalized B2M (0-1.13, >1.13-2.43, and >2.43) (Figure 2C and D), and normalized LDH (0-0.82, 0.82-2.67, and >2.67) (Figure 2E and F). The model obtained in the training cohort was confirmed in the validation set (Figure 3A and B).

With these changes, the new enhanced TS could identify an HR group with a 5-years PFS of 23% and 22%, respectively, in the training and validation cohorts. Low, low-intermediate, and high-intermediate risk groups had a 5-years FFS of 85%, 69%, and 50%, respectively (Figure 3A and B). Furthermore, the HR group of the enhanced TS has a very poor outcome in terms of OS with a 5-years OS of 35% that also improves HR identification compared with the HR subsets of R-IPI with 5-years OS of 60% in the same patients. Comparison between enhanced TS and the other indexes (IPI, TS, and NCCN-IPI) showed significantly better risk discrimination measured by C index for PFS in our training cohort: 0.67 vs 0.65 (P = .026), 0.67 vs 0.65 (P < .001), and 0.67 vs 0.64 (P = .007), respectively.

4 | DISCUSSION

Our analysis was performed in a large multicentric nationwide DLBCL series (GELTAMO) that represents a real-life population, as patients were recruited from academic and smaller community hospitals, unselected and not systematically included in trials. To generate or

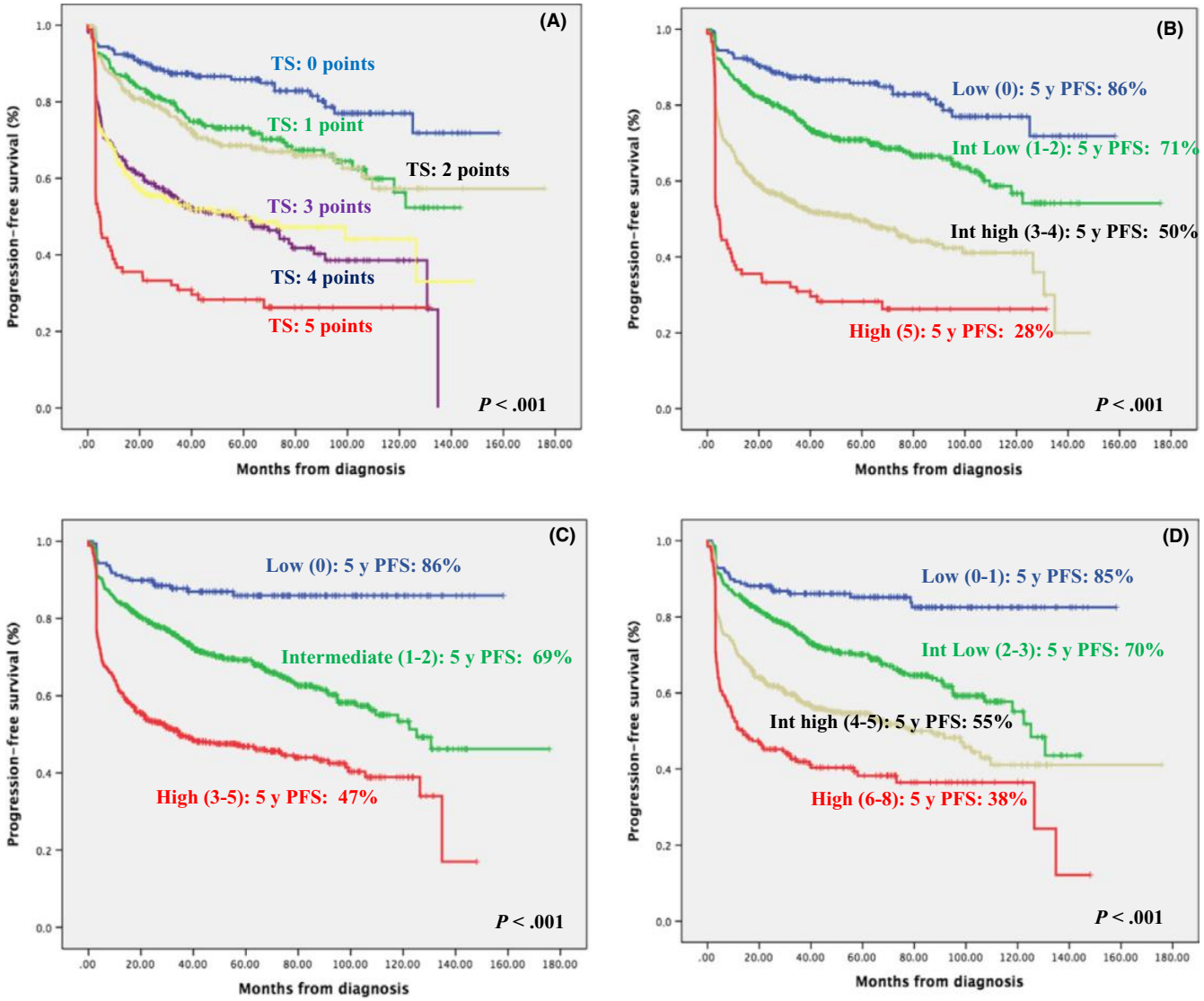

FIGURE 1 PFS using TS (A), R-TS (B), R-IPI (C), and NCCN-IPI (D)

TABLE 4 Analysis of the differences between R-IPI and R-TS

R-IPI Risk groups	N (%)	5-y PFS (%)	5-y OS (%)	CRR (%)	R-TS	N (%)	5-y PFS (%)	5-y OS (%)	CRR (%)
Low (0)	158 (12%)	86	92	94	Low (0)	109 (69%)	90	95	95
					Int low (1-2)	49 (31%)	77	87	90
Intermediate (1-2)	596 (45%)	69	83	88	Low (0)	87 (15%)	81	93	94
					Int low (1-2)	355 (60%)	72	85	91
					Int high (3-4)	145 (24%)	56	72	78
					High (5)	9 (1%)	44	78	67
High (3-5)	559 (43%)	47	60	70	Int low (1-2)	95 (17%)	64	76	89
					Int high (3-4)	386 (69%)	47	61	71
					High (5)	78 (14%)	26	36	44

evaluate a prognostic score in an aggressive lymphoma with a standard therapy as DLBCL, we believe that not only is it essential to consider death from any cause and disease progression, but also not achieving a CR. In an aggressive lymphoma, this last situation is also considered a failure because it will be followed by a short progression-free period, compared with indolent lymphoma where a partial response or even a stable disease could be acceptable to prolong survival. But on the other hand, information provided by OS may be influenced by several treatment lines or different approaches that may bias the analysis and make it sample-dependent. Therefore, to increase accuracy our main

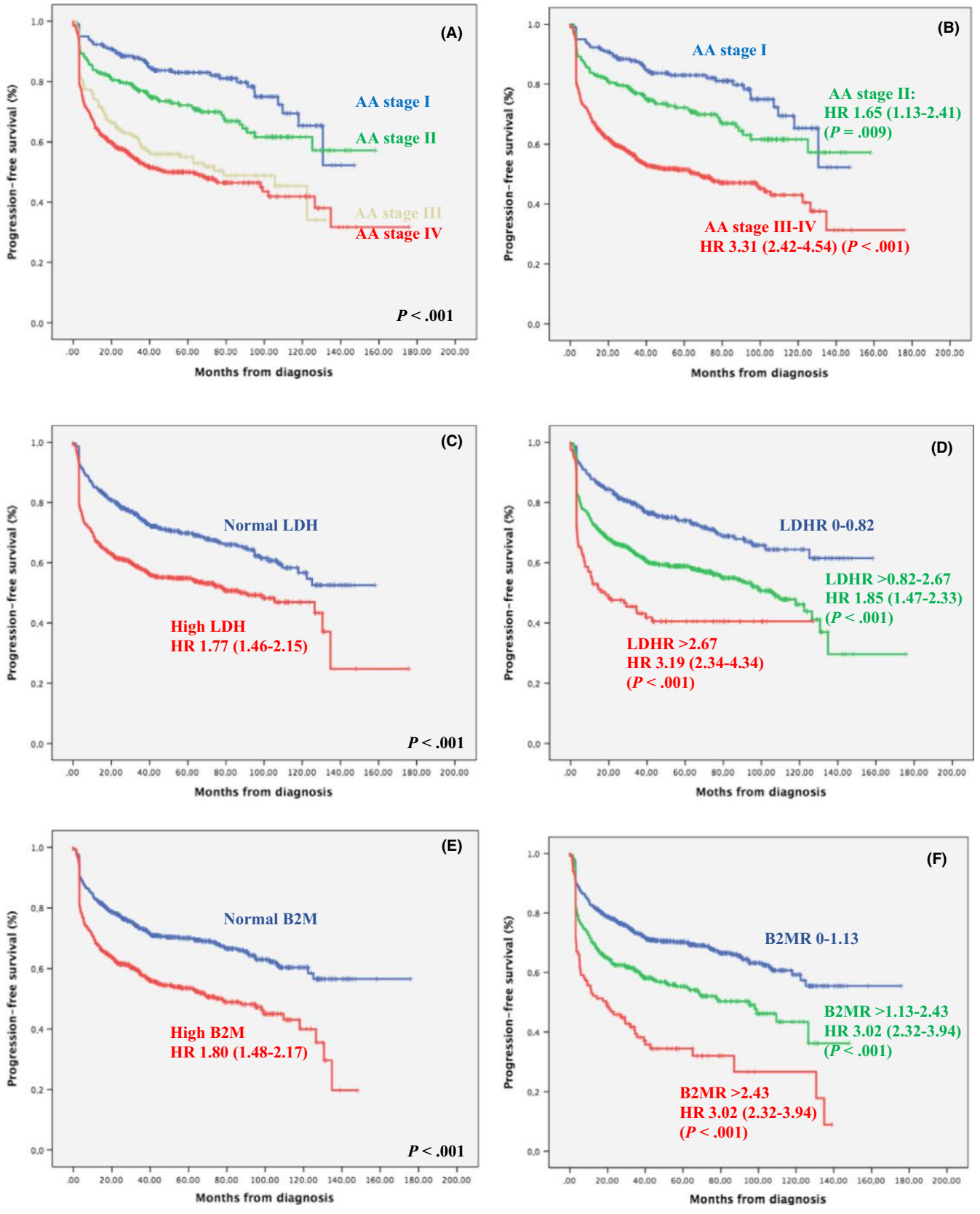

FIGURE 2 Original and further refined categorization of three variables of the original TS in the training sample: AA stage (A and B), LDH (C and D), and B2M (D and E)

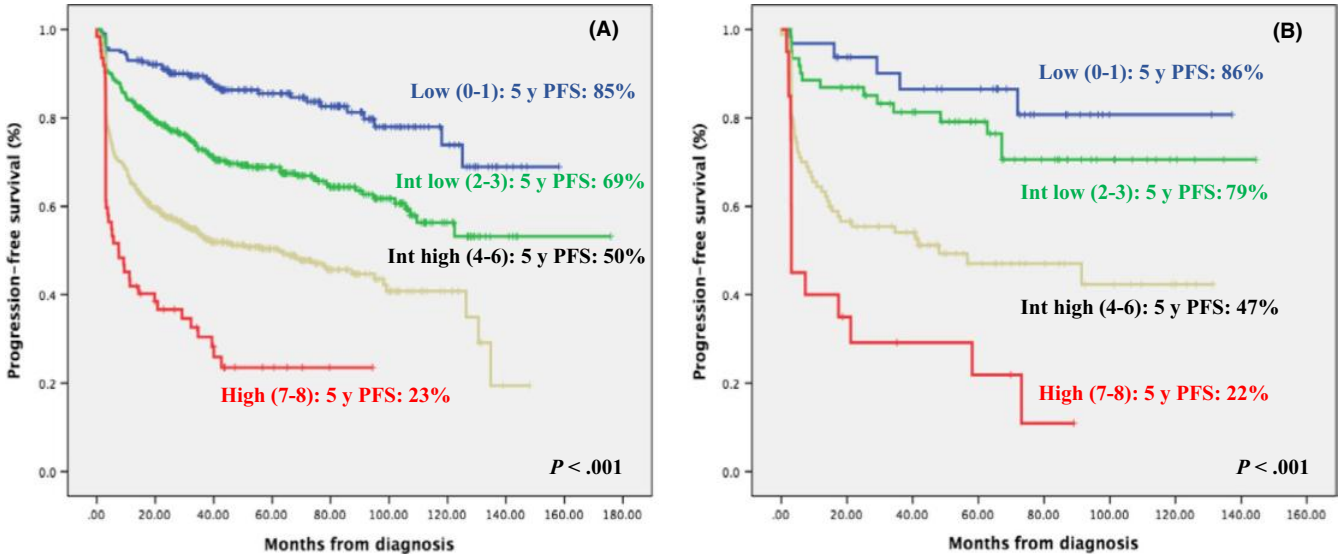

FIGURE 3 PFS using enhanced TS in the training (A) and validation (B) samples

endpoint was PFS, also including not achieving a CR as progression event, in a homogeneously treated with R-CHOP series, in contrast to most other scores reported in DLBCL.[6,8,15]

Tumor Score is enriched with three tumor-related variables not present in the IPI: B2M, bulky mass, and B symptoms. B2M is a small polypeptide light chain that forms part of the major histocompatibility complex (MHC) class I antigens. Several works have shown its prognostic role in DLBCL both in the pre-[9,16] and postrituximab eras.[17,18] As white blood cell membrane is the main source of serum B2M, lymphoid malignancies with great tumor burden and high rates of cellular turnover have been associated with elevated B2M levels. As B2M is mainly excreted by the kidneys, renal failure might be a cause of serum elevation[17] as well as in inflammation or the elderly.[18] The addition of B2M to the primary variables of IPI clearly improves risk assessment as we recently reported in the GELTAMO-IPI,[8] recently confirmed in an independent series.[19] The presence of B symptoms (fever > 38°C, weight loss > 5%, or night sweats) is a known adverse prognostic factor in patients with non-Hodgkin lymphoma (NHL). They are related to increased levels of inflammatory proteins such as C-reactive protein (CRP)[20] and cytokines as interleukin-6 (IL-6).[21,22] Also, patients with higher levels of inflammatory markers have a worse outcome in terms of response rates and survival.[23] Several studies both pre- and postrituximab have shown the adverse prognostic role of bulky disease.[9,24] This was analyzed in the MabThera International Trial (MInT), where this adverse prognostic effect was shown to be decreased but not overcome when receiving Rituximab in young patients with good prognosis DLBCL. The original TS considered 7 cm as the cutoff for bulky mass, but MInT study defined 10 cm in the maximum tumor diameter as the optimal cutoff for bulky disease consideration in the rituximab era.[24] In fact, in our series, most of the centers used the 10-cm cutoff and this variable remained with an independent significance for PFS and OS.

In this series, we found that all variables of the original TS and all but one (more than one extranodal site) in the IPI retained their independent significance both for PFS and OS. This coincides with several other series reported in the rituximab era, particularly when the other relevant variables of IPI are present in the model.[6,8,25,26] Rituximab generated a significant improvement in patients with B-cell lymphomas. Any change in the outcome may modify the risk assessment. This occurred with the IPI when re-evaluated postrituximab where the categorization changed from 4 to 3 risk groups[5] in the R-IPI. However, the main problem was that the HR patients had a PFS or OS higher than 50%, and so in the rituximab era, there is a need to identify patients with much worse prognosis candidates to receive alternative treatments.

In our study, R-TS showed a change from the two original to four identifiable prognostic groups (Figure 1A and B). But the most critical point is that we can see a fully differentiated HR subgroup with a 28% 5-years PFS and only 4 months of median PFS, obtaining an important improvement in the HR identification (47% and 38% 5-years PFS for R-IPI and NCCN-IPI, respectively). This better HR assessment may also be observed when considering OS and CR rates (Tables 3 and 4). Only GELTAMO-IPI (also proposed by our group) has similar results in terms of PFS and OS but with a more complicated design that includes subcategorization of two variables (age and ECOG PS). R-TS is easier to calculate in the daily clinical practice and better predicted an HR subpopulation with lower CR rates (Table 3).

Furthermore, we present an enhanced TS obtained through a refined categorization of three variables of the original TS. With this new index, we can identify a HR subgroup of 22% that highly improves risk assessment in DLBCL. And the most important point is that we obtain this HR information with easily available variables at the time of diagnosis, without the need for more complex and time-consuming, translational biomarkers. However, new tumor-related translational prognostic factors such as cell-of-origin or myc/bcl-2 expression, between others, should be tested for a role inside clinical prognostic scores to guide DLBCL treatment decisions, and we plan to use R-TS or enhanced TS as backbones for this purpose.

From our study, we may conclude that (a) all variables included in the original MDACC TS retain an independent prognostic role in the rituximab era; (b) TS remains predictive of PFS and OS in the rituximab era with a similar discrimination when compared to previously reported prognostic scores; (c) TS and enhanced TS showed a better identification of patients with HR prognosis compared to IPI or NCCN-IPI; and (d) R-TS and enhanced TS may be backbones for including new tumor-related molecular or translational prognostic factors.

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