

The standard, revised and a simplified International Prognostic Index reliably predict outcome in patients with PET/CT-staged diffuse large B-cell lymphoma treated with R-CHOP

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Background

- The standard, revised International Prognostic Index (IPI and R-IPI, respectively) estimate prognosis in diffuse large B-cell lymphoma (DLBCL) using 5 factors: age, LDH, performance status, stage and number of extranodal sites.
- The National Comprehensive Cancer Network IPI (NCCN-IPI) defines categories of age and LDH, as well as specific extranodal sites.
- However, these indexes were developed before the introduction of staging 18F-FDG positron-emission combined with computed tomography scanning (PET/CT).
- Because PET/CT assesses the number and sites of extranodal involvement in DLBCL more accurately than traditional staging investigations, it may more accurately predict outcomes (by refining stage and extranodal involvement in the IPI).

Objective

To analyze the prognostic performance of different versions of the IPI in a contemporary cohort of DLBCL patients staged with PET/CT and treated with R-CHOP.

Methods

- **Patients**
 - 443 patients with biopsy-proven DLBCL staged with PET/CT and bone marrow biopsy were retrospectively identified in institutional databases in Aalborg (n=155, 2007-2012), Copenhagen (n=202, 2009-2012), and British Columbia (n=87, 2011-2012).
 - Original staging PET/CT reports were reviewed to determine stage and sites of extranodal involvement.
 - Patient, disease, treatment, and outcome data were collected from each participating center and combined for analysis.
- **Treatments**
 - All patients were treated with CHOP (or CHOP-like) chemotherapy with rituximab.
- **Statistical Analysis**
 - The prognostic impact of IPI and R-IPI prognostic subgroups were evaluated using the Kaplan-Meier method, and compared using the log-rank test.
 - A multivariate analysis was used to evaluate the impact of the number of extranodal sites on PFS and OS, adjusted for IPI risk factors.

Results

Table 1. Patient characteristics

Characteristics	N (%)
Median age, years (range)	65 (16-90 years)
Male	251 (57)
Ann Arbor Stage	
I	98 (22)
II	72 (16)
III	68 (15)
IV	205 (46)
Elevated LDH	223 (50)
ECOG Performance Status > 1	74 (17)
B Symptoms	181 (41)
Bulky mass (≥10 cm)	113 (26)
Extranodal organs by PET/CT	
Bone/bone marrow	127 (29)
Gastrointestinal	56 (13)
Soft tissue	46 (10)
Liver	34 (8)
Lung	33 (7)
Pleura	16 (4)
Testicular	13/251 (5)
Gynecologic	10/192 (5)
Bone Marrow Biopsy	
Negative	370 (83)
DLBCL	43 (10)
DLBCL + low grade NHL	2 (1)
Low-grade NHL	28 (6)

Table 2. Outcomes according to number of extranodal sites in univariate analysis using the Kaplan-Meier (KM) method and Cox regression.

Extra-nodal sites	N (%)	PFS		OS	
		3-yr (KM)	HR, 95% CI (Cox)	3-yr (KM)	HR, 95% CI (Cox)
None	147 (33%)	79%	Reference	82%	Reference
1	161 (36%)	71%	1.75 (1.06, 2.88), P=0.03	75%	2.04 (1.16, 3.58), P=0.01
2	73 (17%)	70%	1.82 (1.01, 3.29), P=0.05	75%	1.98 (1.01, 3.88), P=0.05
3	34 (8%)	52%	3.51 (1.86, 6.61), P<0.001	60%	3.53 (1.69, 7.32), P<0.001
≥4	28 (6%)	25%	7.81 (4.34, 14.06), P<0.001	36%	7.41 (3.81, 14.39), P<0.001

- In multivariate analysis, involvement of >2 extranodal sites was associated with worse PFS (HR 2.11 [95% CI 1.34, 3.33], p=0.001) and OS (HR 2.68 [95% CI 1.81, 3.97], p<0.001) adjusted for the other four IPI risk factors.

- Because >2 extranodal sites = stage IV, a simplified index was created (see Table 3).

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Figure 1. Outcomes according to the standard IPI

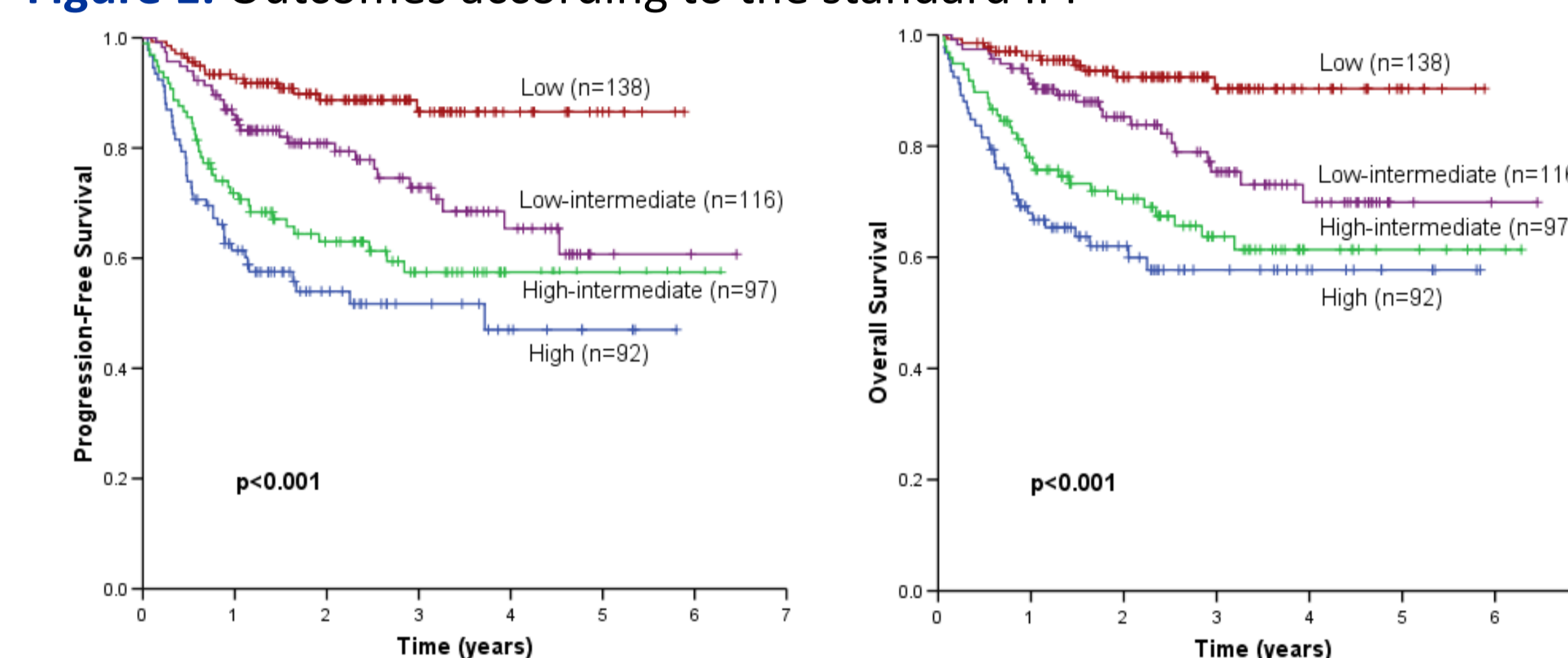


Figure 2. Outcomes according to a simplified version of the standard IPI

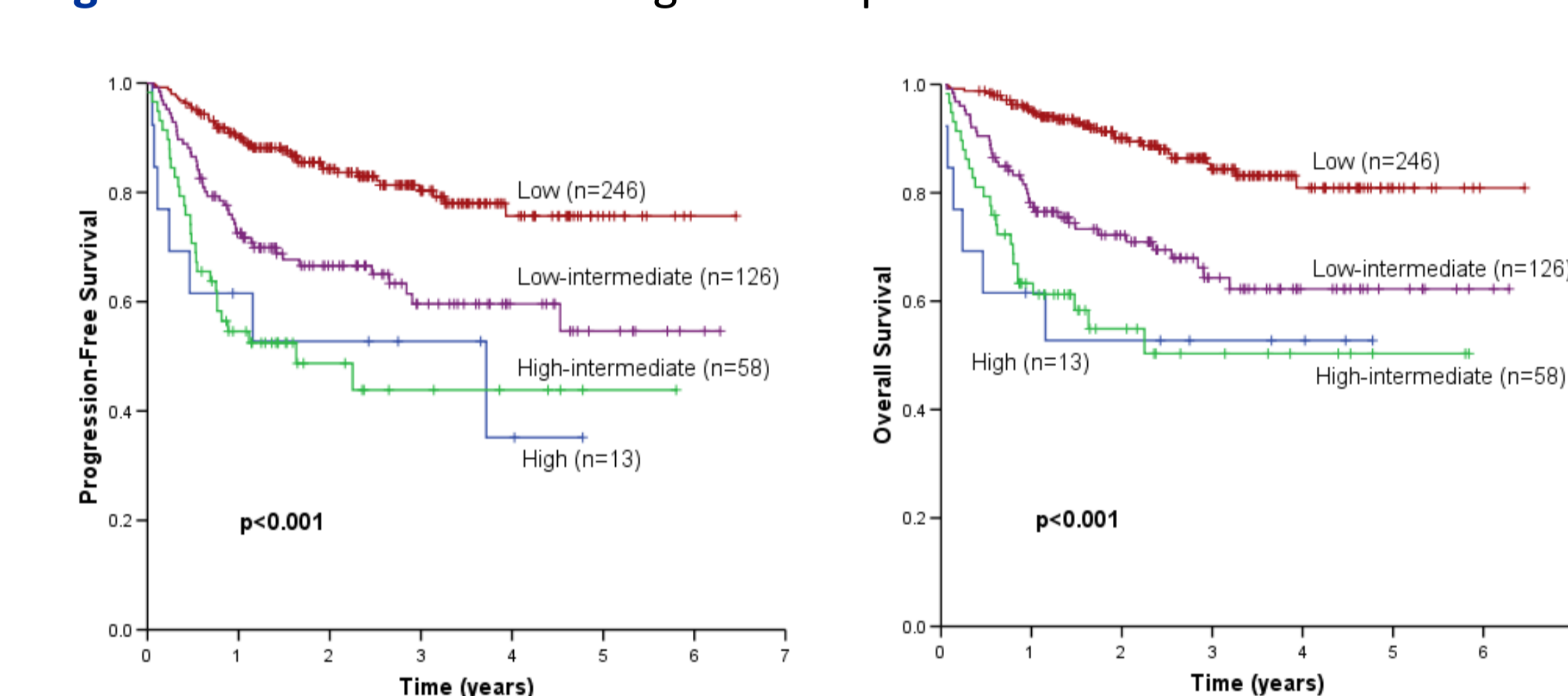


Figure 3. Outcomes according to the revised IPI (R-IPI)

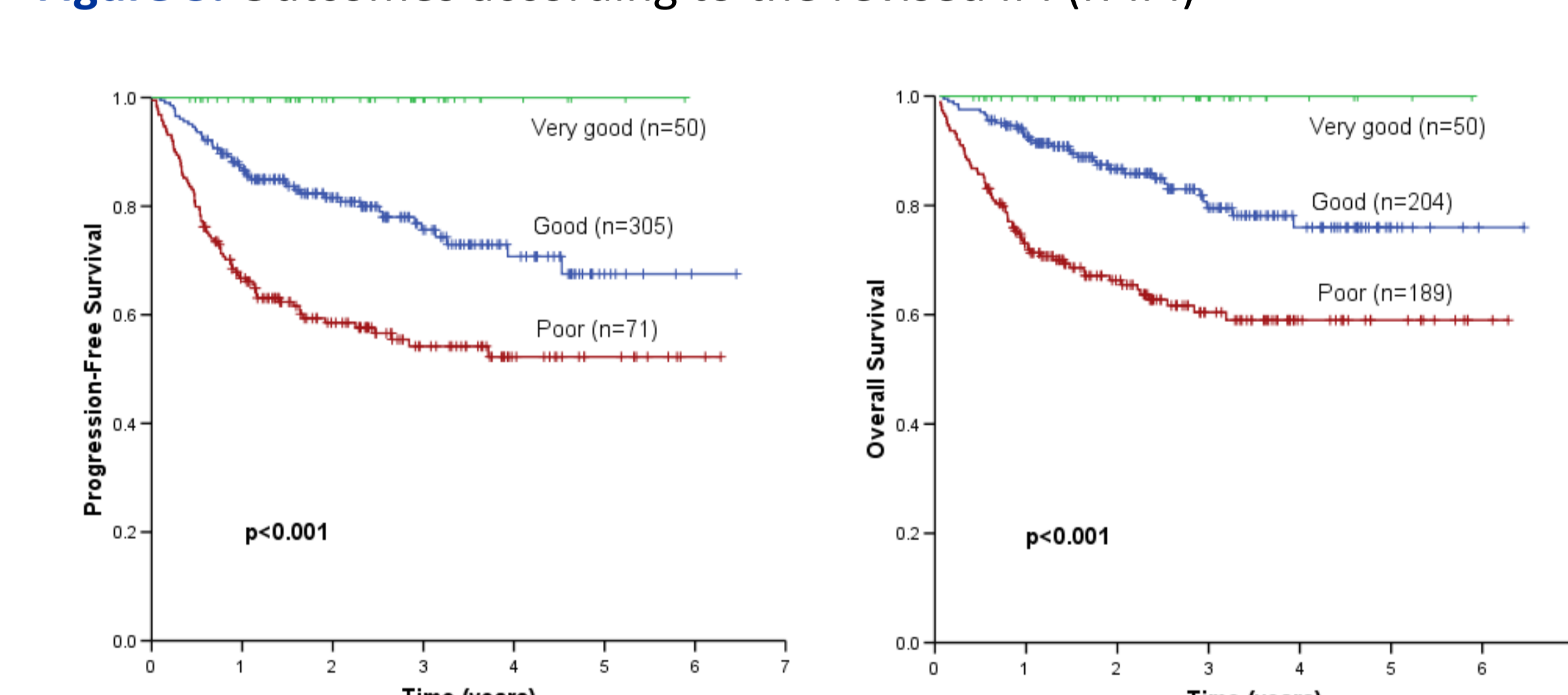


Figure 4. Outcomes according to a simplified version of the R-IPI

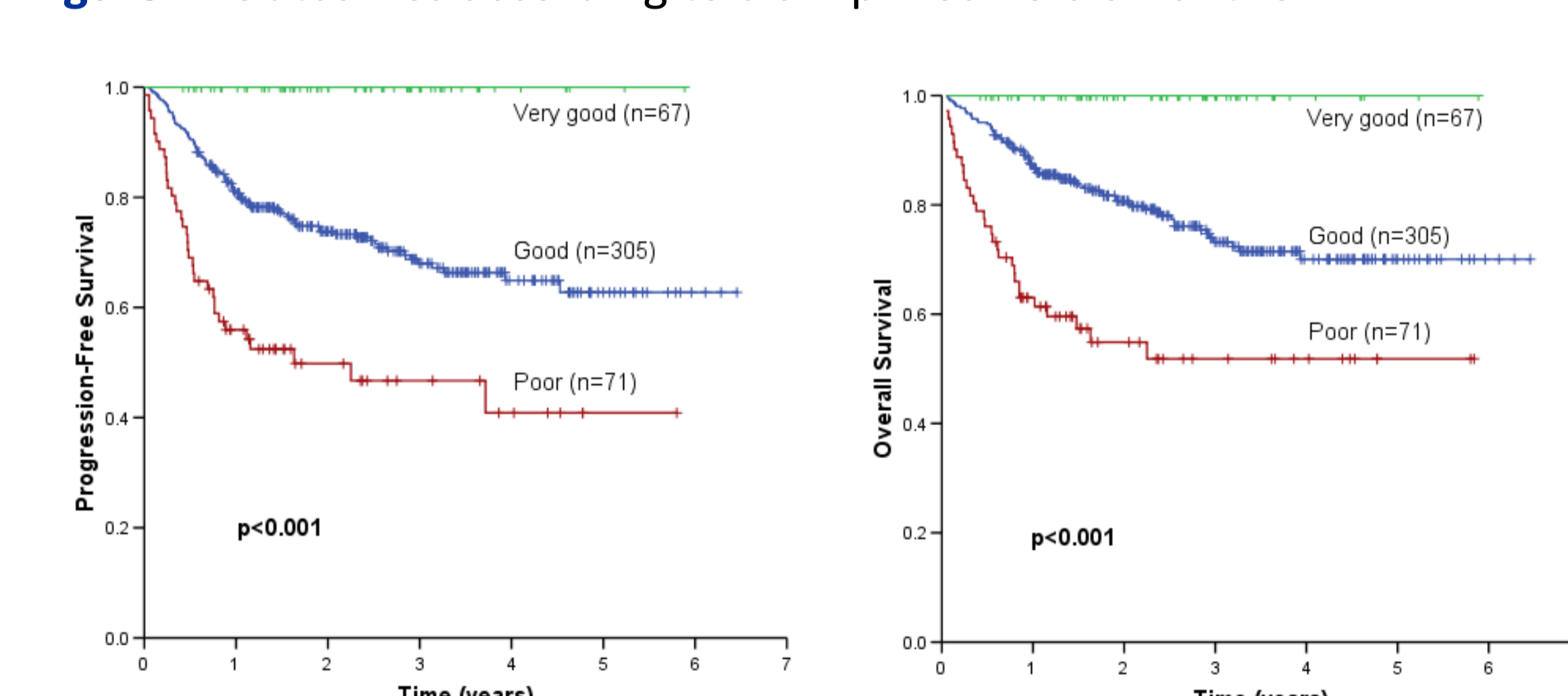


Figure 5. Outcomes according to the NCCN-IPI

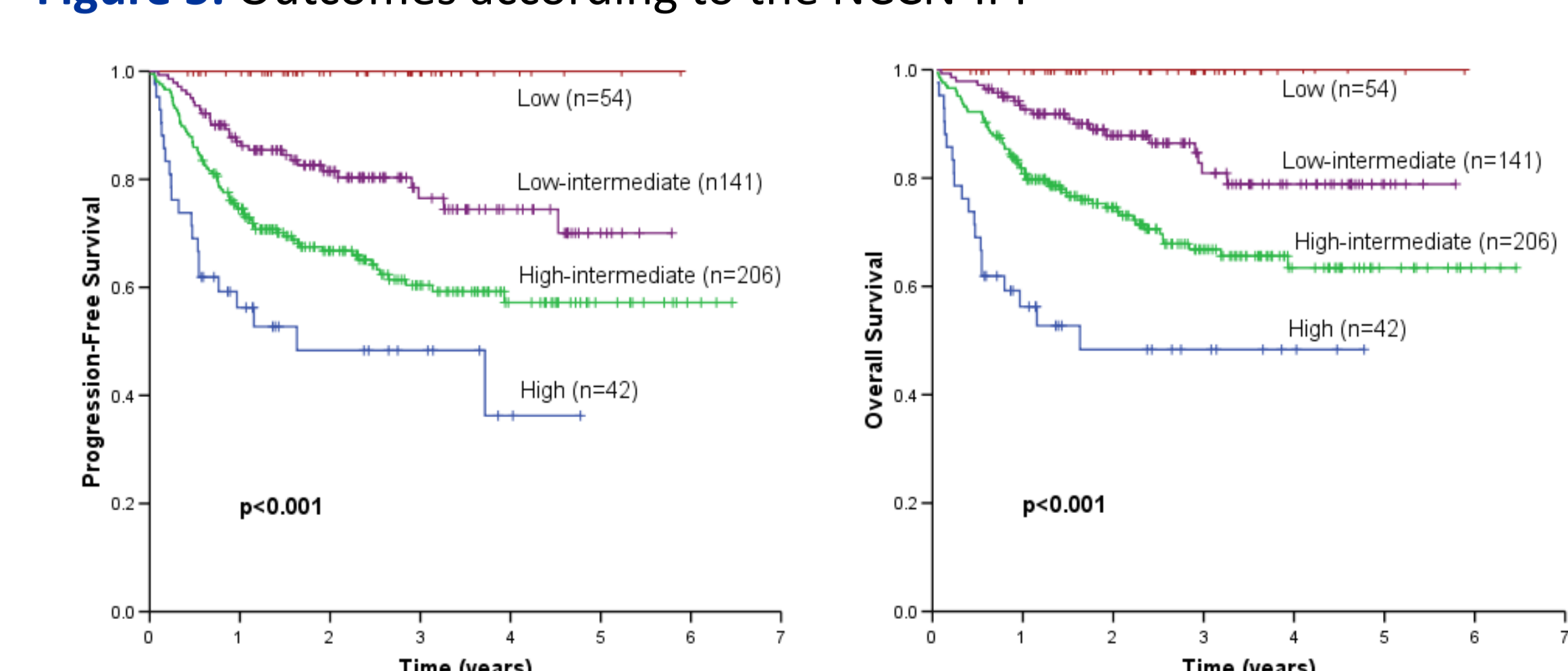


Table 3. Definition of IPI versions.

Variable	IPI and R-IPI	Simplified IPI and R-IPI	NCCN-IPI
Age	>60	>60	41-60 (1 point) 61-75 (2 points) >75 (3 points)
LDH	Elevated	Elevated	2-3x (1 point)* >3x (2 points)*
Performance status	>1	>1	>1
Ann Arbor Stage	III or IV		III or IV
Extranodal sites	>1	>2	Bone marrow, CNS, liver, GI, or lung

*LDH ratio was not available. For the present study, LDH was coded as elevated (1 point) vs. normal.

Table 4. Outcomes according to different IPI versions.

IPI	# of factors	N (%)	3-year PFS % (95% CI)	3-year OS % (95% CI)
IPI				
Low	0, 1	138 (31)	87 (79, 95)	90 (84, 96)
Low-intermediate	2	116 (26)	73 (63, 83)	75 (65, 85)
High-intermediate	3	97 (22)	58 (46, 70)	64 (54, 74)
High	4, 5	92 (21)	52 (40, 64)	58 (46, 70)
Simplified IPI				
Low	0, 1	246 (56)	80 (74, 84)	84 (78, 90)
Low-intermediate	2	126 (28)	60 (50, 70)	64 (54, 74)
High-intermediate	3	58 (13)	44 (28, 60)	50 (34, 66)
High	4	13 (3)	35 (2, 68)	53 (26, 80)
R-IPI				
Very good	0	50 (11)	100 (88, 100)	100 (88, 100)
Good	1, 2	204 (46)	76 (68, 84)	79 (71, 87)
Poor	3, 4, 5	189 (43)	54 (46, 62)	60 (52, 68)
Simplified R-IPI				
Very good	0	67 (15)	100 (88, 100)	100 (88, 100)
Good	1, 2	305 (69)	68 (62, 74)	73 (67, 79)
Poor	3, 4	71 (16)	47 (33, 61)	52 (38, 66)
NCCN-IPI				
Low	0, 1	54 (12)	100 (88, 100)	100 (88, 100)
Low-intermediate	2, 3	141 (32)	77 (69, 85)	81 (73, 89)
High-intermediate	4, 5	206 (46)	60 (52, 68)	67 (59, 75)
High	6, 7	42 (10)	48 (30, 66)	48 (30, 66)

Conclusions

- In this cohort of PET/CT-staged patients with DLBCL treated with R-CHOP, the IPI, R-IPI, and NCCN-IPI identified distinct prognostic subgroups.
- Patients with very good R-IPI and low-risk IPI-NCCN experience 3-year PFS and OS 100%.
- A simplified version of the IPI and R-IPI provides very similar prognostic estimates.

