

**Prognostic indices in diffuse large B-cell lymphoma in the rituximab era: an analysis of the UK NCRI R-CHOP 14 versus 21 phase 3 trial**

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**Word count:**

Total 1,600

Summary 100

Manuscript 1,500

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**Key Words**

Diffuse large B-cell lymphoma

International Prognostic Index

Rituximab

Clinical trials

## **Summary**

We compared the International Prognostic Index (IPI), Revised (R)-IPI and age-adjusted (aa)-IPI as prognostic indices for patients with diffuse large B-cell lymphoma in the UK NCRI R-CHOP 14 versus 21 trial (N=1080). The R-IPI and aa-IPI showed no marked improvement compared to the IPI for overall and progression-free survival, in terms of model fit or discrimination. Similar results were observed in exploratory analyses incorporating the GELTAMO-IPI, where baseline Beta-2 microglobulin data were available (N=655). Although our findings support current use of the IPI, a novel prognostic tool to better delineate a high-risk DLBCL group in the rituximab era is needed.

## Introduction

The International Prognostic Index (IPI) (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993), the most widely used prognostic index in diffuse large B-cell lymphoma (DLBCL), was first reported by Shipp and colleagues in a pivotal study in the pre-rituximab era. Patients with aggressive non-Hodgkin lymphoma (NHL) (N=2,031) were evaluated to identify five independent risk factors for survival: age ( $\leq 60$  versus  $> 60$  years), stage (I/II versus III/IV), number of extranodal (EN) sites (0-1 versus  $\geq 2$ ), performance status (PS) (0-1 versus  $\geq 2$ ) and serum lactate dehydrogenase (LDH) (normal versus elevated). Four risk categories were determined: low (score 0-1), low-intermediate (2), high-intermediate (3), and high (4-5)–risk with corresponding 5-year overall survival (OS) rates of 73%, 51%, 43% and 26%. As patients aged  $\leq 60$  years had significantly better outcomes, an age-adjusted (aa)-IPI model, which also excluded presence of  $> 1$  EN site, was proposed for this subgroup.

With the advent of rituximab the IPI was re-assessed in a retrospective cohort of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)-treated patients (N=365) (Sehn *et al*, 2007). Although the IPI remained predictive, only 2 prognostic groups for OS and progression-free survival (PFS) were identified; hence a redistribution of the risk factors was recommended in the Revised (R)-IPI: very good (score 0) good (1-2) and poor (3-5). By contrast, in an analysis of pooled data from 3 prospective clinical trials enrolling patients with aggressive CD 20 positive lymphoma treated with R-CHOP +/- etoposide (N=1,062), the IPI remained prognostic (Ziepert *et al*, 2010).

More recently, the National Comprehensive Cancer Centre (NCCN)-IPI which utilizes refined age and LDH categorisation and involvement of pre-defined EN sites (Zhou *et al*, 2014) demonstrated superior discrimination versus the IPI, although its value has been found to be inconsistent by investigators (Melchardt *et al*, 2015; El-Galaly *et al*, 2015; Bishton *et al*, 2016; Nakaya *et al*, 2016; Montalbán *et al*, 2017). The Grupo Español de Linfomas/Transplante de Médula ósea (GELTAMO) group subsequently developed the GELTAMO-IPI, incorporating Beta-2 microglobulin ( $\beta 2M$ ) (normal versus elevated), which showed better discrimination than the NCCN-IPI and identified a very high-risk subgroup of DLBCL patients (Montalbán *et al*, 2017).

Here, we report a comparison of prognostic indices in the UK NCRI R-CHOP 14 versus 21 trial cohort which recruited 1,080 previously untreated patients with DLBCL from March 2005 to November 2008 (Cunningham *et al*, 2013).

## Methods

The primary aim of this retrospective analysis was to compare existing prognostic indices in DLBCL in a uniformly R-CHOP-treated population, including the younger patient subgroup aged  $\leq 60$  years. It was not possible to assess the NCCN-IPI due to missing data on local LDH normal ranges; the GELTAMO-IPI was investigated in the subset of patients where baseline  $\beta 2M$  data was available.

The association between prognostic indices and OS and PFS was described using the Kaplan-Meier method, calculated from the date of randomisation and censored at the date last seen. Exploratory Cox regression analyses were used to compare risk groups and individual risk factors. Performance of the prognostic indices was compared using the Concordance Probability Estimate (CPE) and Akaike's Information Criterion (AIC). CPE evaluates discriminatory power to assess the strength of statistical models (higher values indicate better discrimination), and AIC estimates the quality of statistical models relative to each other in terms of fitting the data (lower values indicate a better model fit).

The data analysis was generated using SAS software version 9.4 (SAS Institute Inc.) and SPSS version 23 (IBM Corp.).

## Results

Baseline characteristics for the main study cohort (N=1080) and for patients aged  $\leq 60$  years (N=515) are displayed in Supplementary Table I. Patients in the younger subgroup were generally similar to the main study cohort, with the exception of age and lower IPI score.

OS and PFS are described by IPI, R-IPI and aa-IPI in Figure 1 & Table I. After a median follow-up of 6.5 years, 5-year OS for the entire cohort was 85.5% (95%CI: 81.6-89.4), 76.9% (95%CI: 72.0-81.8), 67.2% (95%CI: 61.5-72.9) and 58.7% (95%CI: 51.3-66.1) in the low, low-intermediate, high-intermediate and high-risk IPI groups respectively. The prognostic indices performed similarly in terms of statistical significance, discrimination and model fit for both OS and PFS. The IPI had the lowest p-value (lower values indicate stronger probability of a real effect), highest CPE (higher values indicate better discrimination) and lowest AIC (lower values indicate a better model fit) for OS in all patients and the younger patient subgroup.

In exploratory analysis of the contributing risk factors (Supplementary Table II), there was strong evidence of an association with OS for each of the individual IPI variables

(patient age, PS, stage, EN disease, elevated serum LDH) and for B symptoms. All except for disease stage remained statistically significant in multivariable analyses after adjusting for all other risk factors. For the younger patient subgroup all IPI risk factors except disease stage remained independently significant in multivariable analyses of OS.

For patients where baseline  $\beta$ 2M data were available (655 in total, 303 aged  $\leq 60$  years), the GELTAMO-IPI was compared with other prognostic indices (Supplementary Figure 1 & Supplementary Table III). The indices again performed similarly in terms of statistical significance, discrimination and model fit, with the IPI having the lowest p-value, highest CPE and lowest AIC for OS in this subset of patients. Supplementary Table IV shows the cross-tabulation of the IPI with other indices.

## **Discussion**

A robust prognostic tool is needed to accurately predict clinical outcomes in DLBCL and to identify high-risk patients who might benefit from more intensive therapeutic approaches. Furthermore, it is essential for prospective trial design to ensure that the patients are well-balanced between arms in terms of risk.

In our analysis the IPI, R-IPI and aa-IPI demonstrated meaningful prognostic groups for both OS and PFS, with clear separation between the curves by risk category. Furthermore, these indices performed similarly in terms of statistical significance, discrimination and model fit; neither the R-IPI nor the aa-IPI (including for patients aged  $\leq 60$  years) showed a material improvement compared to the IPI which actually performed slightly better than the other indices. Despite successfully stratifying patients by risk, none of the indices could identify a particularly high-risk group with very poor overall survival. When exploring individual IPI risk factors, with the exception of DLBCL stage, all remained significant in multivariable analyses of OS for all patients and those aged  $\leq 60$  years.

In exploratory analyses investigating the GELTAMO-IPI in the subset of patients with available baseline data, the prognostic indices again performed similarly in terms of statistical significance, discrimination and model fit. These results were consistent for all patients and for those aged  $\leq 60$  years, with the newer indices performing no better than the established IPI risk stratification.

We evaluated prognostic indices in a large unselected prospective trial population of uniformly R-CHOP-treated patients with DLBCL with a long duration of follow-up (median of 6.5 years); however, the inherent limitations of this type of post-hoc analysis are acknowledged. Furthermore, we were unable to evaluate the recently described NCCN-IPI, due to missing data on the local normal ranges for LDH.

The role of the IPI as a prognostic tool in the rituximab era is controversial in the literature (Sehn *et al*, 2007; Ziepert *et al*, 2010), however we found no evidence that the other indices evaluated provided any material improvement in stratifying DLBCL patients. The failure to identify a very high-risk patient subgroup is consistent with the findings of others investigating rituximab-treated DLBCL populations (Sehn *et al*, 2007; Ziepert *et al*, 2010) and contrasting those of Shipp *et al* where a high-risk IPI score for patients with aggressive NHL equated to a 5-year OS of just 26% (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). Although we were not able to assess the NCCN-IPI in our cohort, application of the recently described GELTAMO-IPI, which is reported to be superior to the NCCN-IPI, did not surpass the standard IPI. The GELTAMO-IPI may distinguish a very poor prognosis group, particularly in younger patients, however only a small number of R-CHOP 14 versus 21 patients were stratified into the higher GELTAMO-IPI risk categories, thus limiting interpretation.

Several investigators have reported a lack of prognostic significance for the presence >1 EN site in the rituximab era (Ziepert *et al*, 2010; Zhou *et al*, 2014). In our analysis, involvement of >1 EN site as determined by computed tomography, was an independent risk factor for both OS and PFS, for all patients and within the younger subgroup. This contrasts the original report by Shipp *et al* where >1 EN site was not an independent risk factor for younger patients, and thus excluded from the aa-IPI (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993).

In conclusion, our results call into question preferential use of the R-IPI and aa-IPI versus the standard IPI to predict outcome in DLBCL, whilst the GELTAMO-IPI and NCCN-IPI require further evaluation. Nevertheless, our findings highlight the lack of precision of the traditional prognostic indices in identifying poor-risk DLBCL patients treated in the rituximab era. Incorporation of molecular biomarkers with clinical risk factors within novel prognostic indices has the potential to enhance prognostication in DLBCL and warrants future exploration.

## **Acknowledgements**

Cancer Research UK provided endorsement and funding and the National Health Service (NHS) provided funding to the National Institute for Health Research (NIHR) Biomedical Research Centres at both University College London and the Royal Marsden Hospital/Institute of Cancer Research, London, UK. Chugai Pharmaceuticals provided an educational grant and lenograstim for the R-CHOP 14 versus 21 trial.

### **Author Contributions**

M.G., N.C., D.C., and D.L. designed the study; M.G., N.C., D.C. and D.L. interpreted the data, performed literature searches and wrote the report. N.C., A.L., L. C-H., N.C., J.G., P.S. and P.M. gathered and interpreted the data; N.C. analysed and interpreted the data, produced figures and wrote the report; M.G., D.C., E.A.H., A.M., K.M.A., C.B., C.P., J.A.R, J.D., D.T., A.K., P.J., D.L. gathered and interpreted the data. All authors reviewed and approved the final manuscript.

### **Disclosures of Conflicts of Interest**

D.C. has received research funding from Amgen, Astra Zeneca, Bayer, Celgene, Medimmune, Merrimack, Merck Serono and Sanofi. E.A.H. has received research funding from Astra Zeneca, Celgene, Merck KgA, BMS and Merck Sharpe and Dohme, honoraria for advisory boards or educational events from Roche, Takeda, BMS, Janssen, Celgene and travel expenses from Takeda and Bristol-Myers Squibb. K.M.A. has received research funding, conference expenses and honoraria for attending or chairing advisory boards from Roche. P.J has received research funding from Janssen and Epizyme. All other authors declare that they have no conflicts of interest to report.



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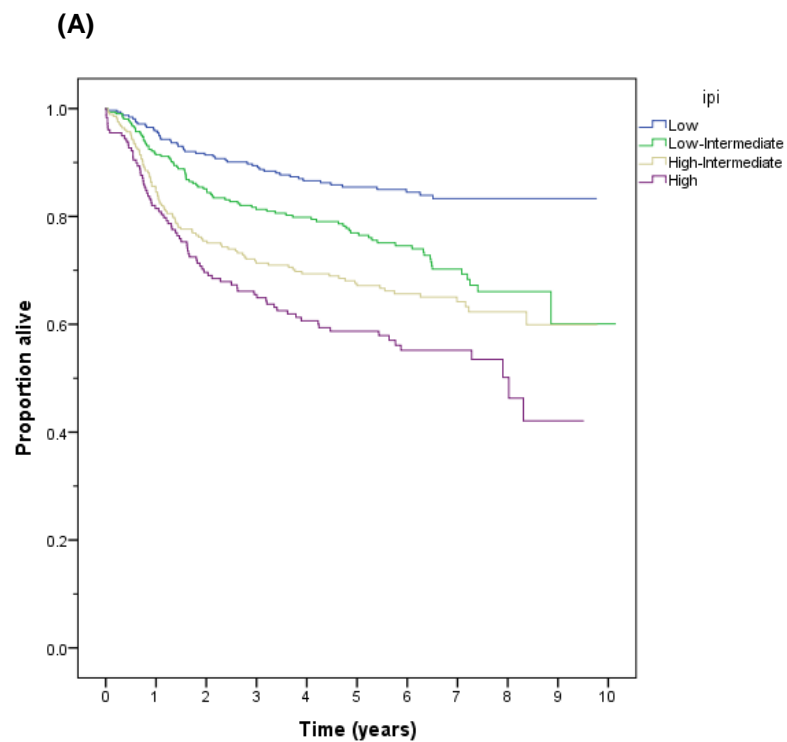
**Table I:** IPI, R-IPI, aa-IPI with 5-year overall survival, progression-free survival and prognostic performance.

<i>All patients (N=1,080)</i>									
<b>Index</b>	<b>Group (n, %)</b>	<b>5-yr OS (95% CI)</b>	<b>p-value</b>	<b>CPE</b>	<b>AIC</b>	<b>5-yr PFS (95% CI)</b>	<b>p-value</b>	<b>CPE</b>	<b>AIC</b>
<b>IPI</b>	Low (316, 29.3%)	85.5% (81.6-89.4)	<b>&lt;0.001</b>	<b>0.624</b>	<b>4081</b>	79.9% (75.4-84.5)	<b>&lt;0.001</b>	<b>0.600</b>	<b>5042</b>
	Low-intermediate (306, 28.3%)	76.9% (72.0-81.8)				68.9% (63.6-74.3)			
	High-intermediate (279, 25.8%)	67.2% (61.5-72.9)				59.1% (53.2-65.0)			
	High (179, 16.6%)	58.7% (51.3-66.1)				55.6% (48.3-63.0)			
<b>R-IPI</b>	Very good (83, 7.7%)	89.1% (82.4-95.8)	<0.001	0.606	4090	86.4% (78.9-93.9)	<0.001	0.588	5046
	Good (539, 49.9%)	80.1% (76.6-83.6)				72.7% (68.8-76.6)			
	Poor (458, 42.4%)	63.8% (59.3-68.3)				57.7% (53.1-62.3)			
<i>Patients ≤60 years (N=515)</i>									
<b>Index</b>	<b>Group (n, %)</b>	<b>5-yr OS (95% CI)</b>	<b>p-value</b>	<b>CPE</b>	<b>AIC</b>	<b>5-yr PFS (95% CI)</b>	<b>p-value</b>	<b>CPE</b>	<b>AIC</b>
<b>IPI</b>	Low (241, 46.8%)	87.1% (82.8-91.4)	<b>&lt;0.001</b>	<b>0.648</b>	<b>1323</b>	81.3% (76.3-86.3)	<b>&lt;0.001</b>	<b>0.627</b>	<b>1819</b>
	Low-intermediate (149, 28.9%)	80.2% (73.7-86.7)				71.5% (64.3-78.8)			
	High-intermediate (89, 17.3%)	71.5% (62.1-80.9)				57.5% (47.0-68.0)			
	High (36, 7.0%)	45.8% (29.1-62.5)				47.1% (30.7-63.4)			

<b>R-IPI</b>	Very good (83, 16.1%)	89.1% (82.4-95.8)	<0.001	0.626	1330	86.4% (78.9-93.9)	<b>&lt;0.001</b>	0.616	1819
	Good (307, 59.6%)	83.3% (79.0-87.6)				75.1% (70.3-80.0)			
	Poor (125, 24.3%)	64.2% (55.6-72.8)				54.4% (45.5-63.3)			
<b>aa-IPI</b>	Low (93, 18.1%)	90.3% (84.2-96.4)	<0.001	0.631	1328	87.9% (81.2-94.6)	<0.001	0.620	<b>1818</b>
	Low-intermediate (191, 37.1%)	82.6% (77.1-88.1)				74.9% (68.6-81.1)			
	High- intermediate (194, 37.7%)	76.8% (70.7-82.9)				66.3% (59.5-73.1)			
	High (37, 7.2%)	51.2% (35.1-67.3)				45.9% (29.9-62.0)			

Abbreviations: OS: overall survival; CI: confidence interval; PFS: progression-free survival; CPE: concordance probability estimate; Akaike's information criteria; IPI: International Prognostic Index; R-IPI: Revised-IPI; aa-IPI: age-adjusted IPI

**Figure 1:** Overall survival for all patients (N=1,080) by IPI (A) and R-IPI (B) and for patients aged ≤ 60 years (N=515) by IPI (C), R-IPI (D) and aa-IPI (E)

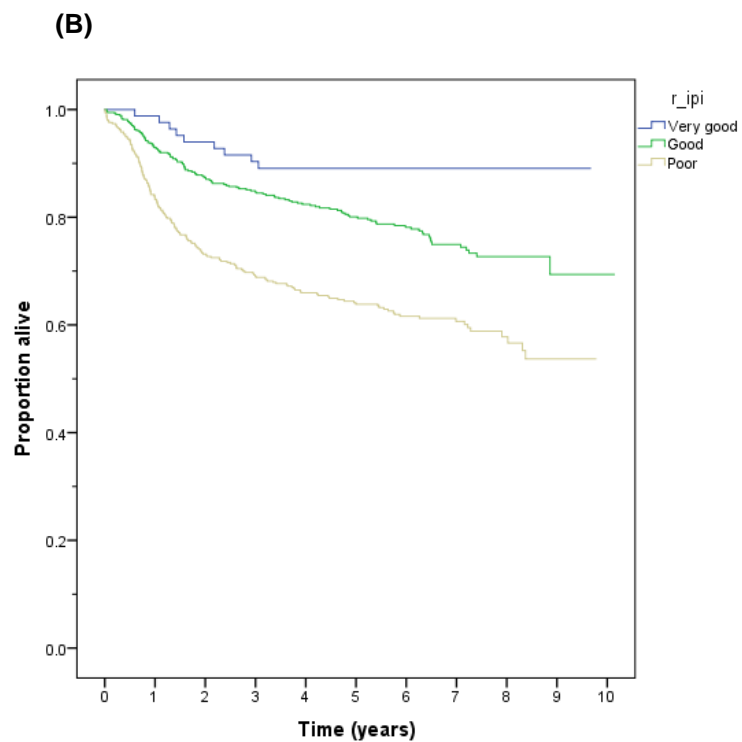


IPI ( $p < .01$ , reference category 'Low')

'Low-Intermediate' versus 'Low': HR=1.95 (95% CI: 1.37-2.78;  $p < .01$ )

'High-Intermediate' versus 'Low': HR=2.61 (95% CI: 1.85-3.69;  $p < .01$ )

'High' versus 'Low': HR=3.67 (95% CI: 2.56-5.25;  $p < .01$ )

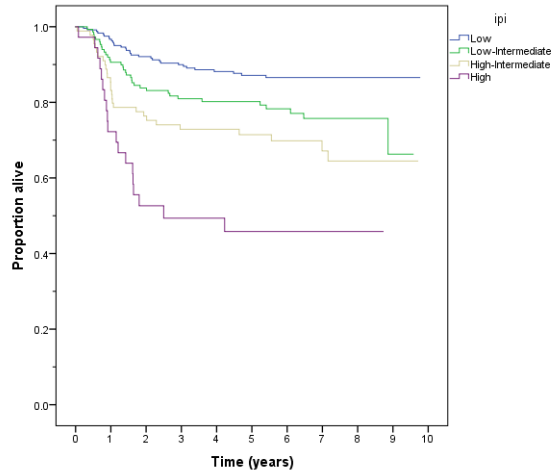


R-IPI ( $p < .01$ , reference category 'Very Good')

'Good' versus 'Very Good': HR=2.29 (95% CI: 1.17-4.51;  $p = .02$ )

'Poor' versus 'Very Good': HR=4.37 (95% CI: 2.24-8.54;  $p < .01$ )

(C)



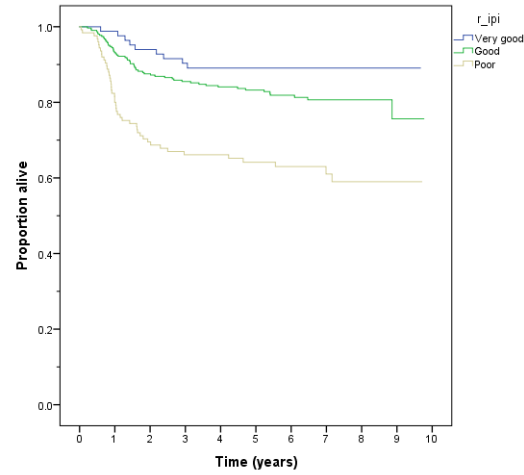
IPI ( $p < .01$ , reference category 'Low')

'Low-Intermediate' versus 'Low': HR=1.91 (95% CI: 1.17-3.1)

'High-Intermediate' versus 'Low': HR=2.82 (95% CI: 1.69-4.7)

'High' versus 'Low': HR=5.88 (95% CI: 3.31-10.43;  $p < .01$ )

(D)

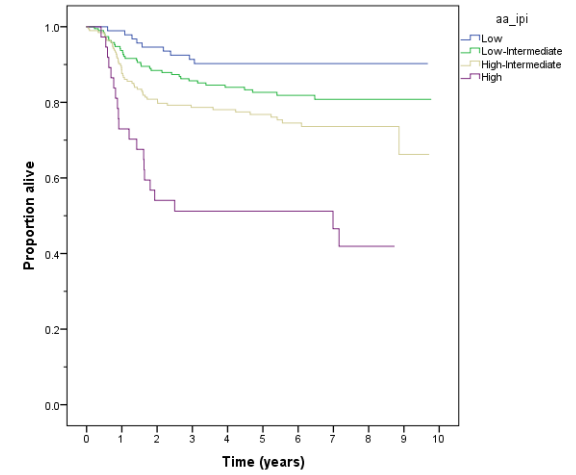


R-IPI ( $p < .01$ , reference category 'Very Good')

'Good' versus 'Very Good': HR=1.79 (95% CI: 0.89-3.62;  $p = .10$ )

'Poor' versus 'Very Good': HR=4.32 (95% CI: 2.12-8.82;  $p < .01$ )

(E)



aa-IPI ( $p < .01$ , reference category 'Low')

'Low-Intermediate' versus 'Low': HR=1.98 (95% CI: 0.95-4.13;  $p = .07$ )

'High-Intermediate' versus 'Low': HR=2.98 (95% CI: 1.46-6.06;  $p < .01$ )

'High' versus 'Low': HR=7.69 (95% CI: 3.50-16.90;  $p < .01$ )