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Improving the international prognostic index score using peripheral blood counts: Results of a large multicenter study involving 520 patients with diffuse large B cell lymphoma

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Abstract

The main purpose of this study was to assess whether it is possible to improve the prognostic impact of international prognostic index (IPI) score by combining it with peripheral blood counts. Thus, we evaluated the prognostic power of lymphocyte, neutrophil, and monocyte counts in 520 patients with diffuse large B cell lymphoma treated with R-CHOP, confirming that these parameters have a strong impact on overall survival (OS). Using revised IPI (R-IPI), 44% of patients were categorized as poor-risk and showed an OS at 5 years of 46%. As OS at 5 years of the 520 patients is 67%, it is clearly evident that R-IPI tends to overestimate the proportion of patients with poor prognosis. Accordingly, in an attempt to improve the discriminating power of R-IPI, we evaluated and compared three different scores by combining the neutrophil lymphocyte ratio (NLR) and absolute monocyte count (AMC) with the following values: (a) IPI score 3-5, (b) age > 60 years and performance status, (c) age ≥ 65 years and LDH > ULN. The three indexes studied, had a similar 5 years OS for the high-risk group (46%-52%), but the proportion of patients classified as poor-risk were 37%,

Raffaella Marcheselli and Alessia Bari contributed equally to this study.

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20%, and 32%, respectively, which are lower than 44% identified with R-IPI. Thus, while R-IPI overestimates the number of high-risk patients, after applying our models, it is possible to recognize patients who are truly at high-risk. Of the three scores, the most accurate appears to be that based on NLR, AMC, LDH > ULN and age ≥ 65 years, which identifies 32% of high-risk patients, correlating well with what is seen in clinical practice.

KEYWORDS

DLBCL, IPI score, lymphocyte, monocyte, neutrophil, prognosis

1 | INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 25% of all NHL cases worldwide.[1] In Europe the incidence is approximately 3.13 cases per 100 000 persons per year.[2]

The international prognostic index (IPI) still remains a good model for risk stratification in patients with aggressive lymphomas.[3,4] However, in recent years the introduction of Rituximab and its addition to combination chemotherapy has led to meaningful improvement of survival in patients with DLBCL. Consequently, IPI needed to be reassessed to determine whether it still maintained its predictive value in the Rituximab era. In 2007, IPI was revised after a retrospective study of 365 patients treated with R-CHOP (rituximab combined with cyclophosphamide, doxorubicin, vincristine, prednisolone), which showed that IPI score could now only identify two major risk groups instead of the four originally reported. Accordingly, a revised IPI (R-IPI) was proposed, which restratified patients into three significantly different prognostic groups which provided a more useful prediction of clinical outcome.[5] In an attempt to further improve the prognostic power of R-IPI, Cox et al,[6] considered the absolute lymphocyte count (ALC) a surrogate marker of immunity and suggested combining it with R-IPI. They showed that ALC at diagnosis has prognostic impact independent of the R-IPI.[6] In this respect it should be stressed that the choice of considering low ALC as a surrogate marker for immunosuppression is purely empirical, as there is little data linking ALC to immunity. In 2010 based on the above findings, we then reported the results of another study performed on an Italian cohort of 831 patients with DLBCL, aiming to evaluate IPI scores after the introduction of Rituximab, as well as to apply R-IPI and validate ALC/R-IPI in an independent data set. We concluded that the standard IPI had lost much of its discriminative power after the introduction of rituximab.[7] In this respect new prognostic models, R-IPI and ALC/R-IPI, appeared to be more accurate, but both had difficulties defining truly high-risk patients. Using the National Comprehensive Cancer Network (NCCN) database, an enhanced international prognostic index (NCCN-IPI) for patients with DLBCL treated in the rituximab era was first reported in 2014. Compared with the IPI, the NCCN-IPI better discriminated low- and high-risk sub groups than the IPI. This index has been validated using an independent cohort from the British Columbia Cancer Agency and is widely used in North America.[8] Unfortunately, in this regard, in our database the LDH values are entered in a binary way (< or > at normal values). Furthermore, in some Italian centers normal values have been changed over time and because of this we have not been able to calculate the NCCN-IPI score in our cohort.

Based on the hypothesis that absolute neutrophil count (ANC) represents a measure of systemic inflammatory response to malignancy, while ALC is a biomarker of tumour infiltrating lymphocytes reflecting host immunity and that absolute monocyte count (AMC) serves as a surrogate biomarker of tumour-associated macrophages, we planned the present study attempting to establish whether levels of the peripheral blood counts alone or in combination with other clinical prognostic factors, could perhaps improve the discriminating power of R-IPI in patients with DLBCL.

2 | PATIENTS AND METHODS

2.1 | Inclusion criteria

This retrospective study included patients with DLBCL diagnosed according to WHO criteria during the time period January 2004-December 2012 and treated with R-CHOP or R-CHOP-like immunochemotherapy. We reviewed clinical and laboratory data of consecutive "therapy-naïve" patients, treated in different centers in Italy and Israel, after approval by local institutional review boards. Italian cases were collected from several sites, including academic/university and community centers belonging to the Gruppo Italiano Studio Linfomi, while data from Israeli patients were collected from two medical centers. The study was performed in accordance with the Declaration of Helsinki.

The inclusion criteria were: histopathological diagnosis of DLBCL, age > 18 years, HIV negativity, availability of data relating to clinical and laboratory features and treatment given, as well as long term follow-up and survival outcome.

The database contained a total of 534 patients who had received CHOP or CHOP-like regimes with rituximab (R). Analysis was performed on a final cohort of 520 patients, after exclusion of cases with missing data relating to IPI (n = 5), or hematological parameters (n = 9). Unfortunately, in our database there is very little collected

data on treatment dose intensity that could influence the survival outcomes.

Thus the primary goal of this study is to examine whether it is possible to increase the prognostic power of IPI by combining the peripheral blood cell count values with the strongest prognostic power with IPI or single factors contribuiting to IPI score. Prognostic robustness is assessed in terms of the ability to identify a group of patients with significantly worse overall survival (OS). Subsequently by empirically combining the most significant values with the IPI score we attempted to obtain new and meaningful prognostic models. The accuracy of the new models is determined by their ability to identify a number of high-risk patients of approximately 28%-38% bearing in mind that the OS at 5 years in this series of patients is 67%.

2.2 | Statistical analysis

Overall survival (OS) was defined as the time from study entry to the last observation or death from any cause. Patient baseline characteristics are expressed as absolute frequencies and percentages for categorical variables, and compared with the χ^2 test or exact Fisher's test. Continuous variables were reported as the median and 2.5-97.5 percentile.

Formal comparisons were performed with Mann-Whitney or Kruskal-Wallis test. Survival functions were evaluated with the Kaplan-Meier method.[9] Statistical comparisons by groups of risk were performed with the log-rank test and the Cox proportional hazard (PH) regression analysis,[10] with a confidence interval at 95% (CI 95%). The proportional hazard assumption was verified graphically by means of scaled Schoenfeld residuals.[11] The effect size was reported as hazard ratio (HR) with the associated CI 95%.

2.3 | Cutoff analysis

2.3.1 | Lymphocytes

In a previous retrospective study, we have already examined and compared ALC cutoff levels of 1, 0.84, and 0.65×10^9/L in a large multicentre database of DLBCL, with a median follow-up of 54 months. Results of this study showed that an ALC ≤ 0.65×10^9/L was the best cutoff point to define lymphopenia and we applied this cutoff in the study we report here.[12]

2.3.2 | Monocytes

In an earlier retrospective study we have already examined different cutoff values and arbitrarily chose an AMC of 0.63×10^9/L as a reference value, because this threshold selected more cases with poorer survival compared to higher cutoff levels.[13] Thus we applied this cutoff in the present study.

2.3.3 | Neutrophil/lymphocyte ratio

Here, we used the most frequently applied and recognized cutoff value of 3.5.[14]

TABLE 1 Overall survival by IPI factors and blood cell count for patients treated with regimens containing rituximab (520 patients)

Variable		N (%)	5-years OS% (95% CI)	HR (95% CI)	*P*-value
Age, years	≤60	177 (34)	81 (73-87)	1.00	
	>60	343 (66)	60 (53-66)	2.51 (1.66-3.79)	<.001
Age, years	<65	217 (42)	79 (71-85)	1.00	
	≥65	303 (58)	59 (52-65)	2.48 (1.70-3.63)	<.001
Stage	I-II	186 (36)	80 (72-86)	1.00	
	III-IV	332 (64)	59 (52-65)	2.23 (1.51-3.29)	<.001
LDH	≤ULN	246 (47)	79 (73-85)	1.00	
	>ULN	274 (53)	56 (49-62)	3.03 (2.10-4.37)	<.001
ENS	0-1	363 (70)	74 (69-79)	1.00	
	>1	157 (30)	49 (40-58)	2.19 (1.58-3.04)	<.001
ECOG-PS	0-1	438 (84)	71 (65-75)	1.00	
	>1	82 (16)	47 (35-59)	2.57 (1.78-3.71)	<.001
AMC, $\times 10^9$/L	≤0.63	331 (64)	73 (67-79)	1.00	
	>0.63	187 (36)	57 (48-65)	1.82 (1.31-2.51)	<.001
ALC, $\times 10^9$/L	≥0.65	444 (85)	70 (64-75)	1.00	
	<0.65	76 (15)	50 (38-62)	2.14 (1.47-3.14)	<.001
NLR	≤3.5	296 (56)	72 (65-78)	1.00	
	>3.5	224 (43)	60 (53-67)	1.79 (1.29-2.47)	<.001

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ECOG, Eastern Cooperative Oncology Group; ENS, extranodal sites; HR, Hazard ratio; IPI, international prognostic index; LDH, lactate dehydrogenase; N, number; NLR, neutrophil lymphocyte ratio; OS, overall survival; PS, performance status; ULN, upper limit of normality; %, percentage.

3 | RESULTS

3.1 | Patients characteristics

The median age of the 520 patients enrolled in the study was 67 years (range 25-95); 46% were females; 64% had clinical stages III-IV, 53% had lactate dehydrogenase (LDH) > upper limit of normality (ULN); 16% had ECOG-PS > 1; 30% had extranodal sites (ENS) > 1. The median values of ANC, ALC, AMC, and NLR were 4.80 (range 1.93-9.84) $\times 10^9$/L, 1.40 (range 0.42-3.2) $\times 10^9$/L, 0.53 (range 0.17-1.21) $\times 10^9$/L and 3.14 (range 1.11-14.8) $\times 10^9$/L, respectively.

Of the 520 patients, 87% (n = 454) were treated with CHOP or CHOP-like regimens plus R and 66 (13%) with mini-CEOP plus R. After a median follow-up of 47 months (range: 1-137 months), 147 patients have died (from any cause) and the estimated 5- and 10-years OS were 67% (95% CI, 62%-71%) and 50% (95% CI, 30%-67%), respectively.

On univariable analysis of 520 patients it was evident that all five factors contributing to IPI maintained a strong prognostic power (Table 1). In addition, after analyzing peripheral blood counts (ALC, AMC, and NLR) all had strong prognostic impact (Table 1).

Taking into account, that the OS at 5 years in this group of patients is 67%, it is clearly evident that R-IPI overestimates the

TABLE 2 Multivariable Cox proportional hazard regression for the three evaluated scores in patients treated with regimens containing rituximab

R-IPI	HR (95% CI)	Levels	N (%)	5-years OS (95% CI)	HR (95% CI)	*P*-value
	—	0	43 (8)	98 (84-99)	1.00	
	—	1-2	245 (48)	80 (73-86)	7.90 (1.08-57.5)	.041
	—	3–5	227 (44)	46 (38-54)	29.7 (4.13-213)	.001

Score 1	HR (95% CI)	Levels	N (%)	5-years OS (95% CI)	HR (95% CI)	*P*-value
AMC > 0.63	1.45 (1.05-2.02)	0-1	186 (36)	87 (79-92)	1.00	
NLR > 3.5	1.42 (1.02-1.98)	2	139 (27)	66 (55-75)	2.87 (1.65-5.00)	<.001
IPI 2	1.28 (0.68-2.40)	3-4	190 (37)	48 (40-56)	6.35 (3.87-10.4)	<.001
IPI 3-5	4.53 (2.72-7.54)					

Score 2	HR (95% CI)	Levels	N (%)	5-years OS (95% CI)	HR (95% CI)	*P*-value
AMC > 0.63	1.60 (1.15-2.22)	0-1	248 (48)	81 (74-86)	1.00	
NLR > 3.5	1.46 (1.04-2.04)	2	164 (32)	60 (50-68)	2.51 (1.66-3.79)	<.001
Age > 60 years	2.30 (1.52-3.48)	3-4	103 (20)	46 (35-56)	4.34 (2.86-6.57)	<.001
ECOG-PS > 1	2.00 (1.37-2.92)					

Score 3	HR (95% CI)	Levels	N (%)	5-years OS (95% CI)	HR (95% CI)	*P*-value
AMC > 0.63	1.56 (1.12-2.16)	0-1	189 (37)	86 (78-91)	1.00	
NLR > 3.5	1.47 (1.06-2.04)	2	159 (31)	60 (49-69)	3.61 (2.14-6.08)	<.001
Age ≥ 65 years	2.35 (1.60-3.44)	3–4	167 (32)	52 (43-60)	5.51 (3.36-9.03)	<.001
LDH > ULN	2.52 (1.74-3.66)					

Note: Score 1: AMC and NLR with weight = 1, IPI 3-5 weight 2; score was grouped 0-1, 2, and 3-4. Score 2 and Score 3: all covariates with weight = 1; score was grouped 0-1, 2, and 3-4.

Abbreviations: AMC, absolute monocyte count; ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; HR, hazard ratio; IPI, international prognostic index; R-IPI, revised IPI; LDH, lactate dehydrogenase; N, number; NLR, neutrophil lymphocyte ratio; OS, overall survival; ULN, upper limit of normality; %, percentage.

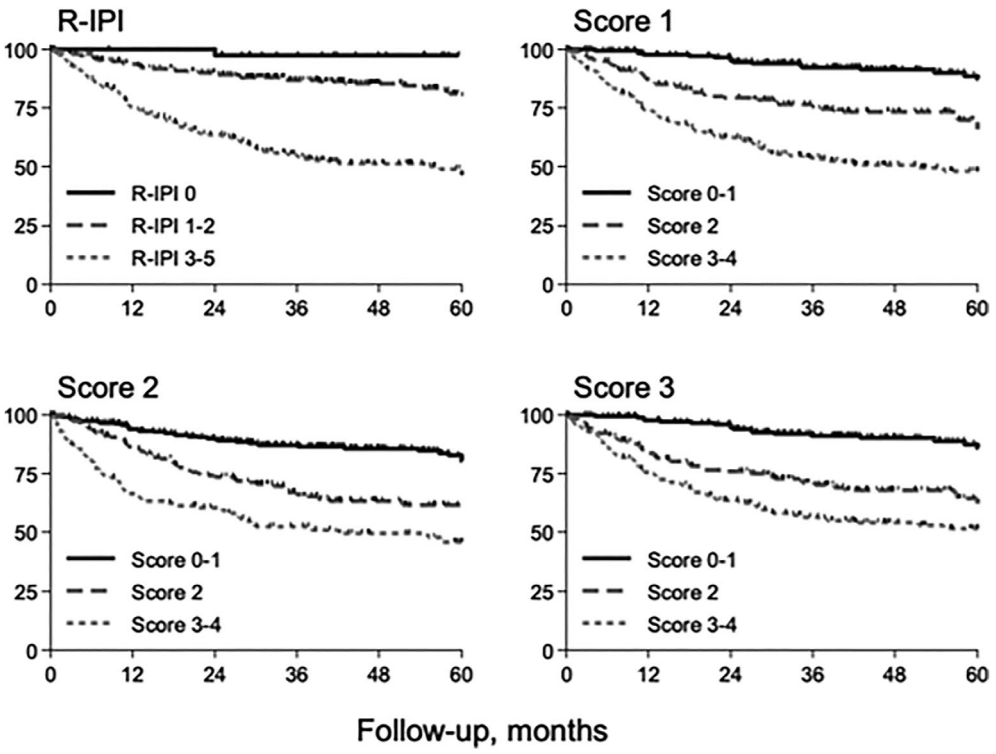

FIGURE 1 Comparison of R-IPI with the three evaluated scores in patients treated with regimens containing rituximab (n = 520). Score 1: AMC, NLR, and IPI score; Score 2: AMC, NLR, Age > 60 years, and ECOG-PS; Score 3: AMC, NLR, Age ≥ 65 years, and LDH. AMC, absolute monocyte count; ECOG-PS, Eastern Cooperative Oncology Group -Performance Status; R-IPI, revised-international prognostic index; LDH, lactate dehydrogenase; NLR, neutrophil lymphocyte ratio

proportion of patients with poor prognosis. Thus, using peripheral blood count, we attempted to define some prognostic scores which could identify patients with a bad prognosis at diagnosis.

In all cases we used AMC and NLR together with IPI 3-5 in score 1, with ECOG-PS and age > 60 years in score 2, and with age ≥ 65 years and LDH upper normal limit in score 3. In Table 2 and Figure 1, a comparison between the different scores is shown. The proportion of patients eventually defined as high-risk (5-year OS between 46% and 52%) varies from 44% when using R-IPI, to 37% using score 1, to 20% using score 2, and to 32% using score 3.

4 | DISCUSSION

At diagnosis the IPI[3,4] and its subsequent revision, R-IPI[5] serve as easy, reliable, and reproducible prognostic scores for DLBCL and remains the cornerstone to which all new prognostic factors must be compared to. However, until now no data are available to support escalation or de-escalation of treatment based on IPI score alone. Furthermore, the IPI is unable to predict the response to novel agents and fails to clearly identify or distinguish high and very high-risk groups.[15,16] Thus, there is a real need to improve its prognostic capabilities.

Despite the fact that in the last two decades molecular features such as cell of origin, MYC and BCL-2 protein overexpression and genetic alterations have been extensively studied, results obtained are contradictory and their true prognostic values are still unclear.[17-19] Furthermore, these tests are expensive to perform, time consuming and not equally accessible to all. As a result, it is not easy to combine them with the IPI score or to apply in routine clinical practice.

In recent years a growing amount of research has shown that tumour microenvironment, host immunity, and inflammatory responses all play an important role in determining survival outcome of lymphoma. In this respect some have considered AMC as a surrogate biomarker of tumour-associated macrophages within the tumour microenvironment[20] while others have regarded ALC as an important biomarker of tumour infiltrating lymphocytes (TILs) reflecting host immunity status,[21]and others have regarded ANC as a measure of the systemic inflammatory response to the tumor.[22] In this respect, inflammation is considered as a critical component of tumour progression, and it is evident that the tumour microenvironment, is largely coordinated by inflammatory cells, which play a central role in the neoplastic process by promoting proliferation, survival, and migration of tumour cells via activation of signaling pathways.[23-25]

As the aim of the current study was to establish whether the peripheral blood count could add discriminating power to IPI, we evaluated the prognostic impact of ALC, AMC, ANC and their respective ratios to one another. Using univariable and multivariable Cox PH regression analysis the results obtained here demonstrate that NLR is a robust and independent prognostic factor. In addition, we also confirm that in this group of patients, the AMC is also a valid and independent risk factor.

In an attempt to improve the discriminating capacity of IPI, we evaluated three different scores by combining AMC and NLR values with: (a) IPI score 3-5; (b) age > 60 years and ECOG-PS > 1; (c) LDH > ULN and age ≥ 65.

As seen in Figure 1, when R-IPI was used, 44% of patients were regarded as higher risk (score 3-5) with OS of 46% at 5 years. The three proposed indexes had a similar 5 years OS for the high-risk group (46%-52%), but the proportion of patients classified as poor-risk were 37%, 20%, and 32%, respectively—lower than the 44% identified with R-IPI. These proportions seem to us to be closer to "real life" clinical practice experience, where with current first line therapies, various salvage regimens and the best supportive therapies, about 25%-35% of patients were seen to have truly bad outcomes (5 years OS 48%).[26-29] Thus in the light of these observations, we believe that the R-IPI tends to overestimate the percentage of high-risk patients, while models 1, 2, and 3 are more likely to recognize patients who are truly at higher risk.

In conclusion, we believe that the best prognostic scores for DLBCL will eventually be based on molecular genetic factors but these still need to be assessed in detail and validated. Furthermore, like others,[30] we also believe that with the advent of increasingly sophisticated methods important and significant data can still be provided by standard laboratory tests, including routine blood cell counts and biological markers.

In addition, we should be aware of the fact that IPI and R-IPI do not accurately define true high-risk patients and that other scores may well perform better. Of the three scores we have proposed here, we believe the most accurate is the one based on AMC, NLR in association with LDH levels and age ≥ 65 years. This score which is based on four objective variables identifies the number of high-risk patients as 32% which correlates better with what is seen in routine clinical practice.

CONFLICT OF INTEREST

The authors have no competing interest.

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