Independent Prognostic Value of Serum Markers in Diffuse Large B-Cell Lymphoma in the Era of the NCCN-IPI

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Abstract

Background: Several serum parameters have been evaluated for adding prognostic value to clinical scoring systems in diffuse large B-cell lymphoma (DLBCL), but none of the reports used multivariate testing of more than one parameter at a time. The goal of this study was to validate widely available serum parameters for their independent prognostic impact in the era of the National Comprehensive Cancer Network–International Prognostic Index (NCCN-IPI) score to determine which were the most useful. **Patients and Methods:** This retrospective bicenter analysis includes 515 unselected patients with DLBCL who were treated with rituximab and anthracycline-based chemoimmunotherapy between 2004 and January 2014. **Results:** Anemia, high C-reactive protein, and high bilirubin levels had an independent prognostic value for survival in multivariate analyses in addition to the NCCN-IPI, whereas neutrophil-to-lymphocyte ratio, high gamma-glutamyl transferase levels, and platelets-to-lymphocyte ratio did not. **Conclusions:** In our cohort, we describe the most promising markers to improve the NCCN-IPI. Anemia and high C-reactive protein levels retain their power in multivariate testing even in the era of the NCCN-IPI. The negative role of high bilirubin levels may be associated as a marker of liver function. Further studies are warranted to incorporate these markers into prognostic models and define their role opposite novel molecular markers. (J Natl Compr Canc Netw 2015;13:1501–1508)

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of all non-Hodgkin's lymphomas (NHLs) and comprises approximately 20% of newly diagnosed lymphoid neoplasms.[1] Although an increasing knowledge of biology in DLBCL has led to the proposal of molecular tools for risk stratification, such as cell of origin (COO) assignment or analysis of Myc or Bcl2 status, relevant problems in the definitions of technical aspects in both COO and "double-hit lymphoma" definitions have led to a delay in translating this knowledge into clinical cohorts outside of clinical trials. Thus, most risk assessments in everyday clinical practice are still performed using clinically available parameters. To this end, an enhanced National Comprehensive Cancer Network–International Prognostic Index (NCCN-IPI) was recently proposed in patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in North America. The NCCN-IPI incorporates the impact of very high lactate dehydrogenase levels as the only laboratory value in the list of parameters, in addition to very old age, and outperforms the traditional IPI.[2,3]

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We recently validated this superior risk score in a European cohort.[4] In the past, a number of laboratory markers have been proposed for prognostication in DLBCL. We have previously shown the additional independent value of serum albumin and β2-microglobulin,[4] but both parameters are not routinely available in large registries of patients with DLBCL.

We thus set out to define which more commonly available laboratory parameters may be suitable to help improve the prognostication in DLBCL. Markers such as C-reactive protein (CRP), lymphocytes, and neutrophils are available in most patients with DLBCL in clinical practice. These markers of inflammation are among the most frequently reported and published laboratory parameters in prognostication for malignant diseases. Persistent inflammation with increased acute phase protein, such as CRP or granulocytes, is a well-known cause of anemia, and overall is associated with a worse prognosis in lymphoma and other malignancies.[5–10] In addition, liver function tests are generally available at baseline, but although lymphoma treatment efficiency or toxicity may be relatively determined by liver performance, no analyses on DLBCL prognosis have been reported.

Importantly, the best choice of laboratory markers in clinical practice was not clear in the past, because such markers were never included in multivariate analysis alongside each other.

The goal of this work was to assess the independent prognostic role of these serum parameters, and to determine a possible correlation between them in the era of the NCCN-IPI. Markers with an independent and reproducible influence on the clinical outcome may further improve the NCCN-IPI.

Patients and Methods

This retrospective analysis was approved by the Ethics Committee of the provincial government of Salzburg, Austria (415-EP/73/127-2012), and the local ethical committee of the Medical University of Graz (No. 25-434 ex 12/13). All patients included for this analysis were diagnosed with de novo DLBCL between 2004 and January 2014. Patients were HIV-negative and treated with R-CHOP or R-CHOP–like chemoimmunotherapy as first-line treatment at the Third Medical Department of the Paracelsus Medical University Salzburg, Austria, and the Division of Hematology of the Medical University of Graz, Austria. Clinical data, including the ECOG performance status, B symptoms, stage according to the Ann Arbor staging system, overall survival (OS), and progression-free survival (PFS), were retrospectively analyzed through chart-based review. All included laboratory parameters were routinely assessed prior to the start of chemotherapy. For patients who did not attend follow-up visits, clinical follow-up data were obtained via telephone interviews with the patients' general practitioner. All statistical analyses were performed using IBM SPSS statistics software, version 21. Mann-Whitney U test, Spearman rank order correlation, and Pearson chi-square test were used for univariate analyses, where appropriate. Survival was estimated using Kaplan-Meier curve analysis, with statistical comparison using the log-rank statistic. A 2-tailed significance level of 0.05 was considered statistically significant. Only statistically significant factors were included in multivariate Cox-regression analyses. Cutoff values in our cohort were determined using the receiver operating characteristic (ROC) calculation and Youden index analysis for OS.

Results

Patient Characteristics

We included 515 patients consecutively diagnosed with DLBCL treated between 2004 and January 2014 in this retrospective analysis (Table 1). In detail, the mean age of the whole cohort was 65.3 years (range, 20–92 years) and 52.4% of the patients were male. Ann Arbor stage III and IV were present in 47.6%, and nonpegylated liposomal doxorubicin (NPLD) was used in 26% of the cases. The median follow-up for all patients alive was 53 months.

Prognostic Impact of the NCCN-IPI

Applying the NCCN-IPI in our patient cohort resulted in 9.3% of patients classified as low risk, 39.8% as low-intermediate, 37.3% as high-intermediate, and 13.2% as high risk (Table 1). As expected, the NCCN-IPI identified 4 prognostic groups of patients with highly different clinical outcomes (3-year PFS: 88.9%, 73.8%, 62.8%, 38.9, respectively; $P<.001$, and 3-year OS: 97.7%, 84.4%, 66.8%, 41.0%, respectively; $P<.001$).

Serum Markers in DLBCL

Several serum markers have been separately analyzed for their influence on the prognosis of patients with

Table 1 Patient Characteristics Treated in 2 Austrian Academic Cancer Centers With First-Line Chemoimmunotherapy

	Overall (n=515)
Center (%)	
Salzburg	45.6% (n=235)
Graz	54.4% (n=280)
Sex (%)	
Male	52.4% (n=270)
Female	47.6% (n=245)
Age (y)	
Mean +/– SD	65.3 +/– 14.5
Range	20–92
>60 y (%)	70.4
Stage (%)	
Stage 1–2	52.4% (n=270)
Stage 3–4	47.6% (n=245)
ECOG (%)	
0–1	85.2% (n=439)
>1	14.8% (n=76)
IPI (%)	
Low (0–1)	34.2% (n=176)
Low-intermediate (2)	30.3% (n=156)
High-intermediate (3)	22.9% (n=118)
High (4–5)	12.6% (n=65)
NCCN-IPI (%)	
Low (0–1)	9.3% (n=48)
Low-intermediate (2–3)	39.8% (n=205)
High-intermediate (4–5)	37.3% (n=194)
High ≥6	13.2% (n=68)
B symptoms (%)	
Yes	28.5% (n=147)
Extranodal involvement (%)	
Yes	53.6% (n=276)
Serum hemoglobin (%)	
>11.85 g/dL	63.9% (n=329)
<11.85 g/dL	35.1% (n=181)
Missing	1% (n=5)
C-reactive protein (%)	
>2.94 mg/dL	28.2% (n=145)
<2.94 mg/dL	66.6% (n=343)
Missing	5.2% (n=27)
Serum bilirubin (%)	
>0.52 mg/dL	44.7% (n=230)
<0.52 mg/dL	52.0% (n=268)
Missing	3.3% (n=17)
Neutrophil-to-lymphocyte ratio (%)	
>5.54	19.8% (n=102)
<5.54	73.8% (n=380)
Missing	6.4% (n=33)
Serum gamma-glutamyl transferase (%)	
>31.5 U/L	47.8% (n=246)
<31.5 U/L	49.9% (n=257)
Missing	2.3% (n=12)
Platelets-to-lymphocyte ratio (%)	
>435.4	15.1% (n=78)
<435.4	78.3% (n=403)
Missing	6.6% (n=34)
First-line treatment (%)	
Liposomal doxorubicin	26.0% (n=134)
Conventional doxorubicin	74.0% (n=381)
Vinorelbine instead of vincristine	7.9% (n=41)

DLBCL and possible improvement of the IPI and NCCN-IPI in the past. Nevertheless, multivariate testing for an independent prognostic impact of these markers has not been reported so far. To determine the components for our multivariate analysis, available serum markers were first analyzed in univariate fashion.

Markers of Inflammation and Their Influence on OS

We and others[10–12] have already shown the negative prognostic value of anemia in patients with lymphoma. In our cohort, an interpretable hemoglobin level before treatment was available in 510 patients (99%; Table 1). A cutoff value of 11.85 g/dL was determined to be optimal to discriminate the OS. Median PFS and OS were significantly lower in patients with low hemoglobin levels compared with patients with higher values (median PFS, 42 months vs not reached; $P<.001$; median OS, 55 months vs not reached; $P<.001$; Figure 1A).

High levels of CRP, an acute phase protein, are associated with worse clinical outcome in lymphoid and solid malignancies.[7,8,13,14] Pretherapeutic CRP levels were available in 488 patients (94.8%; Table 1). A cutoff value of 2.94 mg/dL was determined by ROC and Youden analysis for discrimination of OS. Higher CRP levels were significantly associated with worse PFS and OS (median PFS, 23 months vs not reached; $P<.001$; median OS, 50 months vs not reached; $P<.001$; Figure 1B).

The negative effect of a high neutrophil-to-lymphocyte ratio (NLR) was previously reported in smaller single-center cohorts.[6,15] Pretherapeutic NLR was available in 482 patients (93.6%; Table 1) and a cutoff value of 5.54 was found to be optimal to discriminate the OS. A higher ratio was associated with worse PFS (median PFS, 64 months vs not reached; $P=.017$) and worse OS (median OS, 65 months vs not reached; $P=.004$).

Platelets-to-lymphocyte ratio (PLR) is reported to be a prognostic factor in several solid malignancies,[16–21] but no data yet exist about patients with lymphoma. PLR was available in 481 patients (93.4%; Table 1). A cutoff value of 435.4 was determined by ROC and Youden analysis to be optimal to discriminate OS. Nevertheless, this cutoff had no significant effect on PFS (median PFS, 91 vs 96 months; $P=.115$) and OS (median OS, 115 months vs not reached; $P=.096$).

Liver Serum Markers in DLCBL

Despite its wide availability during routine assessment, there are only small reports about the role

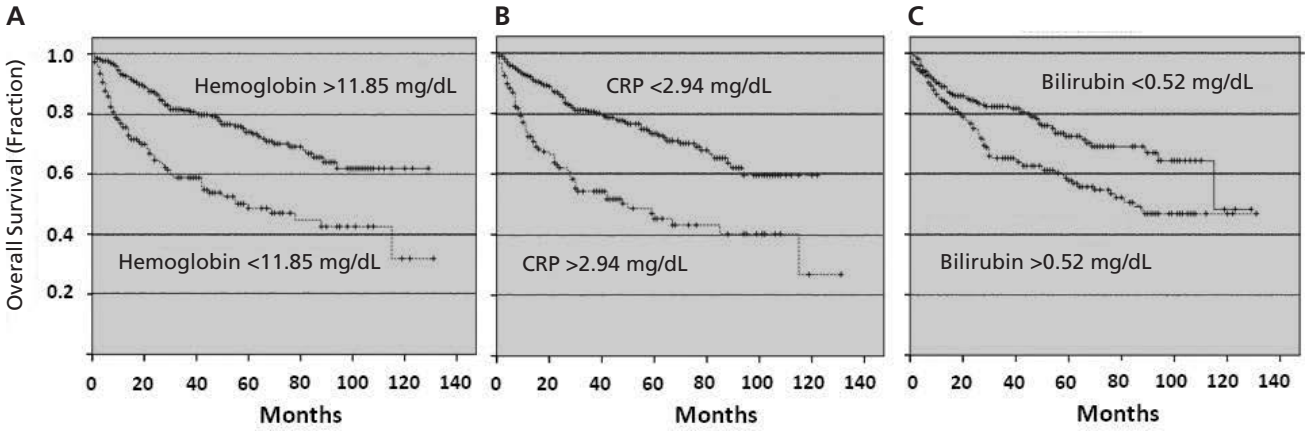

Figure 1 Outcome according to serum parameters assessed during clinical routine. (A) Anemia with a cutoff value of 11.85 mg/dL was associated with a lower overall survival ([OS] median OS: 55 months vs not reached; *P*<.001). (B) High C-reactive protein (CRP) levels with a cutoff value of 2.94 mg/dL were associated with a lower OS (median OS: 50 months vs not reached; *P*<.001). (C) High bilirubin levels with a cutoff value of 0.52 mg/dL were associated with a lower OS (median OS: 85 vs 115 months; *P*=.001).

of hyperbilirubinemia in patients with hematologic malignancies.[22–25] Serum bilirubin levels were available in 96.7% of our patients (n=498; Table 1). A cutoff value of 0.52 mg/dL was found to be optimal by ROC analysis to discriminate the OS. Higher values were associated with a worse OS (median OS, 85 vs 115 months; *P*=.001; Figure 1C), and a trend for worse PFS that did not reach statistical significance (median PFS, 65 vs 115 months; *P*=.078).

Serum levels of the gamma-glutamyl transferase (GGT) were available in 503 patients (97.7%; Table 1). A cutoff value of 31.5 U/L was determined to be optimal to discriminate the OS. Higher GGT levels were associated with a worse PFS (median PFS, 65 vs 115 months; *P*=.018) and worse OS (median OS, 88 vs 115 months; *P*=.011).

Independent Value of Serum Markers in Patients Assessed With the NCCN-IPI

Upon analyzing already described inflammation markers, we detected statistically significant, but at best moderate correlations, between CRP and hemoglobin levels (Spearman's correlation coefficient [r_s]; 0.472; *P*<.0001), CRP and NLR (r_s, 0.32; *P*<.0001), and NLR and hemoglobin levels (r_s, 0.207; *P*<.0001). Correlation between GGT and bilirubin serum levels was also weak but statistically significant (r_s, 0.118; *P*<.009).

To elucidate the additional value of the described parameters in the era of the NCCN-IPI, we performed a multivariate analysis in 450 patients with all tested parameters available on OS. Multivariate testing of all significant parameters in univariate testing revealed an independent prognostic role of hemoglobin, CRP, and bilirubin in addition to the NCCN-IPI. PLR failed to show any prognostic information in the preceding univariate testing, and GGT levels and NLR failed to show correlation with OS (Table 2) in multivariate testing.

We also analyzed the influence of these markers on PFS. High bilirubin level and PLR had no influence on PFS in univariate testing, and hemoglobin and CRP levels retained their prognostic impact on PFS compared with GGT level and NLR in multivariate testing in addition to the NCCN-IPI.

We also tested the value of anemia and increased CRP levels to refine the prognostic accuracy of the NCCN-IPI. Both variables could not significantly refine the prognosis of patients with very good prognosis according to the NCCN-IPI (low and low-intermediate risk groups) or of patients with poor survival (high-risk group). Nevertheless, within the high-intermediate risk group, the presence of none, one, or both variables could determine more precisely the prognosis (median PFS and OS: 94 months and not reached, respectively, for no anemia and no increased CRP vs 55 and 67 months, respectively, for anemia or increased CRP vs 16 and 23 months, respectively, for anemia and increased CRP; *P*<.001 for both; Figure 2).

Discussion

Risk prognostication in patients with DLBCL has been based on clinical parameters for more than 20 years. This practice has been challenged by prognostic tools based on new molecular insights in the

Table 2 Cox Regression Analysis of Routine Labor Parameters as an Independent Factor for Overall Survival in Diffuse Large B-Cell Lymphoma

	Univariate				Multivariate			
	HR	95% CI	*P* Value	n	HR	95% CI	*P* Value	n
Sex								
Female vs male	0.828	0.603–1.136	.242	515	NA			
NCCN-IPI								
Low vs high	3.180	2.237–4.521	<.001	515	2.063	1.379–3.088	<.001	450
Hemoglobin								
>11.85 vs <11.85 g/dL	2.415	1.759–3.316	<.001	510	1.577	1.082–2.299	.018	450
C-reactive protein								
>2.94 vs <2.94 mg/dL	2.518	1.817–3.488	<.001	488	1.679	1.137–2.453	.009	450
Bilirubin								
>0.52 vs <0.52 mg/dL	1.719	1.239–2.385	.001	498	1.517	1.066–2.159	.021	450
Neutrophil-to-lymphocyte ratio								
>5.54 vs <5.54	1.623	1.167–2.258	.004	482	1.141	0.796–1.635	.474	450
Gamma-glutamyl transferase								
>31.5 vs <31.5 U/L	1.512	1.097–2.084	.011	503	1.247	0.873–1.782	.224	450
Platelets-to-lymphocyte ratio								
>435.4 vs <435.4	1.387	0.940–2.048	.099	481	NA			

Abbreviations: HR, hazard ratio; IPI, International Prognostic Index; NA, not applicable; NCCN, National Comprehensive Cancer Network.

pathobiology of DLBCL.[26–29] Because of problems in standardization or reproducibility of tests or the lack of universally accepted definitions of risk, or as a result of simple lack of availability, these tools, such as COO or double-hit lymphoma assessment, are not regularly incorporated into clinical practice in most parts of the world, and their influence on treatment stratification is unclear.

Various algorithms of immunohistochemical staining used for COO analyses have been proposed, but their concordance with functional microarray analyses and their influence on clinical outcome differs in the literature.[30–32] Despite combined assessment of microarray and immunohistochemical data the COO definition added no additional prognostic value to the IPI in the largest cohort study published so far.[33] New techniques such as the nanostring technology may enhance reproducibility and efficacy of these analyses, as suggested in a cohort published by the British Columbia Cancer Agency. This approach added further information to the IPI assessment with the latter still remaining the most powerful prognostication tool, but no significant clinical influence of the immunohistochemical assessment of c-Myc and Bcl-2 was found in multivariate analyses.[34]

Because of these limitations, there is a relevant clinical need for a more accurate prognostication in patients with DLBCL. The recently established NCCN-IPI risk score, including no molecular information, has been shown to be superior to the conventional IPI[2,4] and may be implemented as novel standard risk prediction tool in patients with newly diagnosed DLBCL. However, although high and low risk are assessed very accurately, there remains a large intermediate group with statistically highly significant fates but a low power to predict the outcome of an individual, limiting the usable information for most patients. An improvement in this group would be worthwhile. We and others have investigated the role in risk prediction of serum markers of chronic inflammation in addition to the IPI in the past, but one major limitation of these reports was the missing multivariate testing within these markers.

We assessed an array of such parameters for their independent impact on prognosis in multivariate analyses in a large bicenter analysis of 515 patients. We could confirm the previously reported prognostic impact of elevated CRP and anemia.[7,10,35] Despite a weak correlation, they were significantly associated with a shorter OS and proved to have independent

power from each other in multivariate analysis. Both parameters may indicate inflammation caused by the lymphoma or individual comorbidity, and the tumor-promoting effect of inflammatory cytokines has already been described. As an example, high IL-6 serum levels, a major factor for the development of anemia in lymphoma, have been described to be associated with poor outcome in patients with DLBCL.[36] Furthermore, our results suggest a relatively smaller prognostic role of the NLR in DLCBL in contrast to findings of previous reports when analyzed in multivariate testing.[6,15]

As stated earlier, the NCCN-IPI provides very clear prognostic information in high- and low-risk situations, but the relative large intermediate-high risk group, especially, follows a course that is still highly variable. As judged from our cohort, elevated CRP and anemia may be used to refine the prognosis of patients within this high-intermediate NCCN-IPI group. This patient group has an intermediate prognosis (median PFS and OS: 65 and 85 months, respectively) as a whole, but adding these variables separated 3 groups of patients with highly different PFS and OS. Patients with anemia and increased CRP are lined up with the high-risk NCCN-IPI group, and those with normal hemoglobin and low CRP followed a similar course to that of the low-intermediate group. This may be of clinical importance, because this group with an intermediate risk may include the most patients, who may benefit from more intensive or novel therapy approaches.

We also assessed liver function parameters for their prognostic power, and found a negative prognostic role of higher bilirubin levels in patients with DLBCL treated with R-CHOP. This effect may seem expected in patients with high levels of bilirubin caused by overt liver damage, but we detected a highly significant cutoff value of 0.52 mg/dL, which is still in the normal range of the average population. When we tested the prognostic impact of the upper level of the normal range, 1.2 mg/dL, this cutoff lost its independent influence on OS during multivariate analyses. Additionally, when excluding all patients with bilirubinemia associated with local infiltration of DLBCL and all those with bilirubin higher than 2.0 mg/dL, both significance and cutoff held up, suggesting that a variation within the normal range of bilirubin was responsible for our finding. A similar phenomenon was observed regarding GGT in univariate testing. It is thus possible that variations in normal liver function may result in different efficacy of the glucuronidation system, determining the outcomes of chemoimmunotherapy in DLBCL. Furthermore, because of a significant association of higher bilirubin levels with OS, but not PFS, a role as a sur-

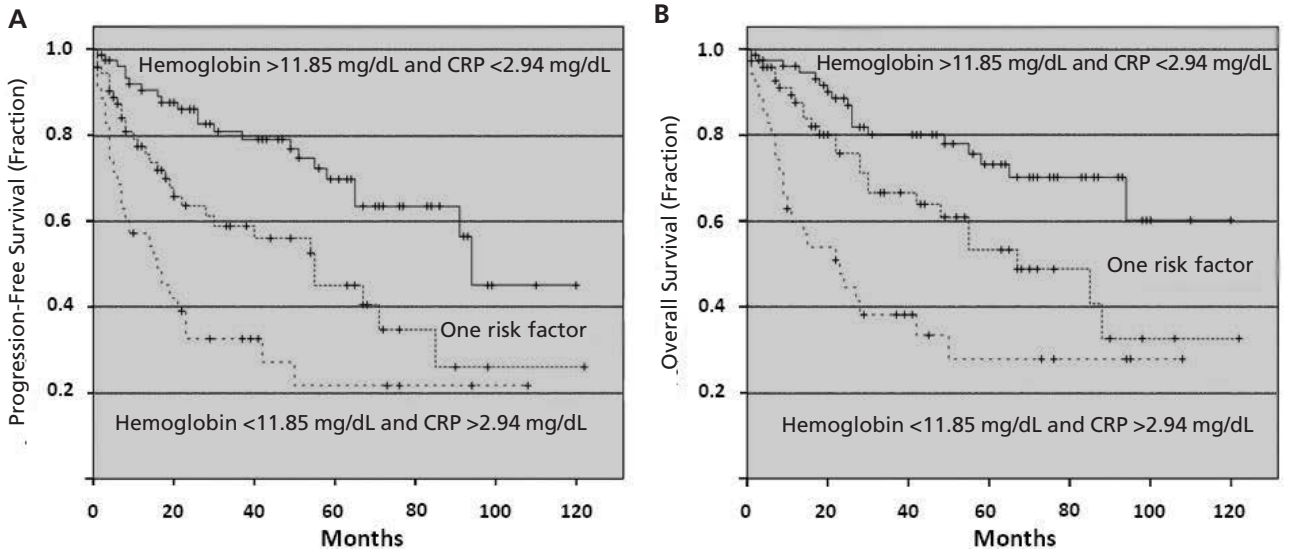

Figure 2 Outcome in patients with high-intermediate National Comprehensive Cancer Network–International Prognostic Index (NCCN-IPI). Anemia and increased C-reactive protein (CRP) levels improved the prognostic accuracy within the high-intermediate NCCN-IPI group. The presence of none, one, or both variables could state more precisely the progression-free survival (PFS; Figure 2A) and overall survival (OS; Figure 2B): median PFS and OS: 94 months and not reached, respectively, for no anemia and no increased CRP vs 55 and 67 months, respectively, for anemia or increased CRP vs 16 and 23 months, respectively, for anemia and increased CRP; *P*<.001 for both.

rogate parameter of general health and comorbidity instead of tumor control is also possible. Although we can only speculate about this, our work may inspire further analyses in this setting. A better understanding of these parameters is needed, because it would clearly be difficult to counsel patients regarding their risk using variations of normal laboratory values. Our data on liver function tests are thus hypothesis-generating, rather than easily clinically applicable. Overall, our results confirm the importance of multivariate testing during evaluation of the additional prognostic value of new biomarkers.

Our report is not without limitations, because retrospective analyses are always prone to bias factors. Nevertheless, we consider a possible selection bias as relatively small because both participating cancer centers are responsible for the care of almost all patients with lymphoma in their districts. In addition, lymphoma treatment is not offered in smaller hospitals in their region and there are no hematologists and oncologists in private practice in Austria. Therefore, we think that the described cohort is relatively close to patients with DLBCL found in the "real-life setting."

It will be very important to validate such parameters opposite molecularly defined risk factors, and future cohorts will possibly need to include clinical and laboratory values and molecular markers in their multivariate models.

Conclusions

In this study, we show that CRP, hemoglobin, and bilirubin levels have an independent prognostic effect in patients with DLBCL treated with R-CHOP. Anemia and increased CRP levels seem to be the most promising markers to improve the prognostic accuracy of the NCCN-IPI, especially in patients with intermediate risk. Further efforts may show whether the incorporation of these markers may be able to further improve clinical prognostication.

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