Perspective

# Beyond international prognostic index: risk stratification in diffuse large B-cell lymphoma

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*Comment on:* Xu-Monette ZY, Li L, Byrd JC, *et al.* Assessment of CD37 B-cell antigen and cell of origin significantly improves risk prediction in diffuse large B-cell lymphoma. Blood 2016;128:3083-100.

**Abstract:** Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). Both the clinical behavior and the underlying biological process are very heterogeneous in DLBCL, suggesting the necessity of utilizing individualized and risk adapted therapy. The international prognostic index (IPI) has been widely used for risk evaluation in DLBCL. Although IPI could successfully differentiate DLBCL patients into four groups with different outcome in the era of conventional chemotherapy, the efficacy of the IPI has declined in the era of rituximab. Newer prognostic systems, including the revised IPI (R-IPI) and the enhanced IPI (NCCN-IPI), have shown superiority over the traditional IPI in predicting outcome in DLBCL patients treated with rituximab based therapy. Risk stratification system based solely on clinical factors is feasible in daily practice, but they can not necessarily reflect the underlying biological process, and it's very hard to tailor targeted therapy based on solely clinical information. Over the past decade, numerous biomarkers were shown to be prognostic or predictive. However, incorporating biomarkers and clinical factors in one risk stratification system remains challenging.

**Keywords:** Diffuse large B-cell lymphoma (DLBCL); international prognostic index (IPI); risk stratification

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## Background

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for more than 30% of all cases (1). The standard treatment for patients with DLBCL had been CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) for many years until the introduction of the anti-CD20 monoclonal antibody rituximab, which has dramatically improved the outcome of DLBCL patients (2-5). Novel agents, including monoclonal antibody, epigenetic therapeutic agents, and small-molecule kinase inhibitors, are also under development.

The clinical course of DLBCL is rather diverse, ranging from a relatively indolent course to an extremely aggressive one. In addition to the diversity in clinical outcome, the biological features of DLBCL are also very heterogeneous, suggesting that DLBCL may comprise several distinct disease entities that might ultimately benefit from different therapeutic approaches. Under current treatment strategy, most DLBCL patients could achieve an optimal response and experience a relatively long overall survival (OS). However, a small proportion of patients do not respond

well or experience early relapse. To better identify high risk patients and eventually develop better treatment strategy, identifying risk factors and developing risk stratification system become crucial.

## IPI and other clinical parameters

For decades, clinicians have been using the revised IPI (R-IPI) to predict outcome of DLBCL patients. The IPI, using five clinical and laboratory parameters including age >60 years, stage III/IV disease, Eastern Cooperative Oncology Group (ECOG) performance status score ≥2, more than one extranodal site of disease and elevated lactate dehydrogenase (LDH) level, defines four distinct outcome groups with different 5-year OS ranging from 26% to 73%. However, the efficacy of the IPI has declined in the era of rituximab therapy. Several prognostic scoring systems have been developed to refine the traditional IPI. The R-IPI identified three distinct prognostic groups instead of four groups, with the exact same parameters but different grouping criteria as in the traditional IPI do (6). The enhanced IPI (NCCN-IPI) further refined the categorization of age and normalized LDH and defined four risk groups (7). Both the R-IPI and the NCCN-IPI are more powerful than the IPI for predicting survival in the rituximab era.

Recent studies have identified additional clinical prognostic markers other than those included in the traditional and R-IPI. Male sex appears to have a negative impact on outcome of elderly patients, due to a faster rituximab clearance in elderly males compared with elderly females (8). Elevated serum free light chains and C-reactive protein level are also identified as independent prognostic markers that indicate less favorable outcome (9-11). Low absolute lymphocyte/absolute monocyte counts ratio was shown to counteract the beneficial effect of rituximab on survival, which might be related to host adaptive immunity and the tumor microenvironment (12,13). Concordant bone marrow involvement portends a poorer prognosis in DLBCL patients treated with rituximab, whereas discordant bone marrow involvement does not (14). Additionally, increased body mass index (BMI) has been reported to be a favorable prognostic factor, but it remains controversial (15-17).

Using additional clinical parameters allows further risk assessment beyond the traditional and R-IPI. The clinical data required could be easily obtained, making it very applicable in daily practice. However, as clinical parameters are only surrogates of the underlying biological features, risk stratification based solely on clinical factors can not necessarily reflect the biological process of disease. Furthermore, although the clinical factors could be useful in guiding risk adapted therapy to some extent, it remains very difficult, if not impossible, to direct targeted therapy.

## Cell of origin (COO) and molecular markers

With the advent of genome-wide expression profile (GEP) technology, DLBCL has been categorized into at least two subgroups based on their similarities with putative COO: the germinal center B-cell (GCB) subtype and the activation B-cell (ABC) subtype, with a small proportion of patients remaining unclassifiable (18). What's more, the COO classification based on GEP was shown to be predictive of OS in DLBCL, and the ABC subtype had a less favorable outcome in both pre-rituximab and rituximab era (19-22). However, GEP is not suitable for the clinical routine due to the high requirement of sample preparing and huge expense. Alternatively, several immunohistochemistry (IHC) based algorithms, are routinely used to determine COO in DLBCL. Nevertheless, the reproducibility of them remains doubtable and challenged (23,24), due to high variability of this technique (25) and failure to identify the unclassifiable subgroup. More recently, GEP based assay performed on paraffin embedded tissue is used to classify DLBCL and predict clinical outcome, exhibiting high consistency with the traditional GEP classifier (26,27). This new method is likely to make it more convenient and accurate to apply COO classification to stratifying DLBCL and predicting prognosis.

Besides COO classification, numerous molecular prognostic markers have been identified. Here, we focus on several robust biomarkers among them.

TP53 mutation is probably the very first genetic variation to be reported in the prognosis of patients with DLBCL, the importance of which was demonstrated as early as 1997 (28). TP53 mutations indicate unfavorable prognosis in patients treated with or without rituximab (28-31), and mutations in the DNA-binding domains are the strongest predictor of poor OS (29-31). In the era of conventional chemotherapy, TP53 mutations were shown to be adverse prognostic indicators only in patients with GCB subtype DLBCL, but not in those with ABC subtype. In contrast, when it comes to the era of R-CHOP therapy, TP53 mutations regain the efficacy in stratifying R-CHOP treated patients with either GCB or ABC subtype (31). Furthermore, IHC analysis showing >50% cells expressing

 

p53 protein could serve as a useful surrogate, when gene mutation analysis is not available (31).

MYC rearrangement (MYC-R) was reported to be a strong adverse prognostic factor in the era of rituximab in most studies (32-35), and the adverse impact of MYC-R was shown to be correlated with the MYC translocation partner gene: only GCBs with IG genes, but not with other partner genes, have an adverse prognostic impact in DLBCL patients (36). MYC break may occur as a sole genetic event or in combination with BCL2 and/or BCL6 translocations defining "double-hit" lymphoma (DHL) or "triple-hit" lymphomas (THL) (37), which generally tends to have a very poor survival (38,39). As expected, MYC/BCL2 protein coexpression also contributes to the inferior survival of DLBCL patients treated with rituximab (40,41), but neither MYC nor BCL2 protein expression alone significantly impacts survival (40). Regarding the prognostic impact of BCL2 expression alone, several previous studies revealed inconsistent results (42,43), due to small patient cohorts and confounding effects of MYC expression.

Immune escape is a critical gateway to malignancy, representing the defeat of immune surveillance. Tumor cells escape immune destruction, at least partially, by exploiting the inhibitory programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) immune checkpoint. The presence of a large number of PD-1$^{+}$ tumor-infiltrating lymphocytes (TILs) in DLBCL is associated with favorable survival (44). Patients with tumors expressing PD-L1 (45,46) and high level of soluble PD-L1 in plasma (47) demonstrate inferior survival upon long term follow-up. Therefore, identification of DLBCL cases that express PD-L1 may contribute to targeted immunotherapy in this distinct subgroup.

CD5, a pan-T-cell surface marker, is rarely expressed in DLBCL, but recently *de novo* CD5$^{+}$ DLBCL is increasingly recognized as a subtype of DLBCL with an aggressive disease course in the era of rituximab (48-50). CD30 originally identified as a cell surface marker of Reed-Sternberg and Hodgkin cells in classic Hodgkin lymphoma (HL) is also expressed in DLBCL. The CD30 expression is associated with favorable outcome in R-CHOP treated patients, but indicates extremely poor survival in those who are positive for Ebstein-Barr virus (EBV) (51).

In addition to the factors mentioned above, other genetic aberrations, including MYD88 mutations (52), FOXP1 overexpression (49,53), loss of PRDM1/BLIMP-1 function (54), RCOR1 deletions (55), and HLA specificities (56) have been identified as relevant prognostic factors of DLBCL. Despite the significant improvement brought by rituximab, the outcome remains dismal in a portion of patients. Although R-CHOP-21therapy remains to be the standard of care, many clinical trials are investigating alternative treatments for high risk patients. As it remains difficult to direct targeted therapy based on the IPI, R-IPI or NCCN-IPI, the opportunity of providing individualized care lies in the discovery and utilization of molecular prognostic markers.

## Integrating prognostic factors

Currently, there is no universally accepted way to combine various prognostic factors to predict the outcome of patients with DLBCL. Recently, Xu-Monette *et al.* provided us a good mode of integrating molecular markers to the current IPI, and the leading role in this study is CD37 B-cell antigen, which is widely expressed on normal and malignant mature B-cells (57,58). Earlier, their study group reported that mice lacking CD37 developed GCB cell lymphoma spontaneously through constitutive activation of the IL6-AKT-STAT3 pathway, and that loss of CD37 directly correlated with a poorer survival in patients with DLBCL (59).

Based on these results, Xu-Monette *et al.* assessed CD37 status and its prognostic effects in larger cohorts of patients with DLBCL (58): first of all, they found that DLBCL patients with CD37 loss had significantly worse outcome, and that CD37 loss was associated with adverse prognostic factors, including TP53 mutation, NF-κB activation and MYC translocation. Subsequently, to examine whether the unfavorable effect of CD37 loss relied on its associated genetic abnormalities, they incorporated all of them into the survival analysis and confirmed that predictive value of CD37 expression was robust, especially in GCB subtype. In fact, this predictive value completely abolished the prognostic significance of TP53 mutation, p50$^{high}$, MYC$^{high}$, p-STAT3$^{high}$, and GCET1$^{high}$ expression inCD37$^{+}$GCB DLBCL. Similarly, CD37 loss predicted significantly worse survival with or without p50$^{high}$, survivin$^{high}$, RelB$^{+}$, p63$^{-}$, CXCR4$^{high}$, PI3K$^{high}$, FOXP1$^{high}$, MUM1$^{high}$, and BCL6 translocation in ABC DLBCL. Afterwards, multivariate survival analysis showed that CD37 status remained to be an independent prognostic factor in overall DLBCL, GCB DLBCL and ABC DLBCL. Impressively, the hazard ratio (HR) of CD37 was even higher than that of IPI >2, and the IPI lost prognostic significance in CD37$^{+}$ GCB DLBCL. Ultimately, based on the pivotal prognostic role of CD37 status, two risk stratification models were

 

established. The "molecular adjusted IPI for R-CHOP" (M-IPI-R) model combined the CD37 status and COO with the IPI, and the "IPI-plus-immunohistochemistry" (IPI+IHC) model incorporating CD37 status, $MYC^{high}$ and BCL-$2^{high}$ risk factors into the IPI. Both risk stratification systems successfully defined several groups of patients with distinct outcome.

Their finding added a robust biomarker to our current knowledge and made significant progress on integrating the IPI and various prognostic factors.

## Discussion and conclusion

Despite the progresses we have made, there are several major challenges we may face when integrating biomarkers to the IPI. First, IHC is the most commonly applied method for evaluating biomarkers, but the variability in sample preparing, staining, cut point selection and results interpretation significantly limits its usage. In a previous study, significant inconsistency among pathologists was observed when assessing routine lymphoma biomarkers (24). Furthermore, studies investigating the prognostic impact of IHC detected biomarkers usually reveal conflicting results, making it even more complicated to establish a clear method to apply IHC results in risk evaluation (60-62). More advanced techniques, including next generation sequencing and microarray detection, may offer a better choice. However, more data are needed to validate the prognostic impact of the biomarkers defined by those new techniques.

Second, the prognostic impact of a certain biomarker is often affected by other concurrent factors. A well-known example is "DHL". The synergistic effect of concurrent MYC and BCL-2 rearrangement leads to an extremely poor prognosis (38). Another example is "CD30 expression". CD30 expression is a favorable prognostic marker in R-CHOP treated patients, but indicates an unfavorable outcome in EBV+ patients (51). Such non-linear correlation should be evaluated with more sophisticated statistical model, rather than a simple additive score system.

Third, the constantly evolving treatment strategy has a huge impact in the significance of risk stratification system. In the era of rituximab, while the IPI remains predictive, it distinguishes two risk groups instead of four risk groups: the two low-risk and two high-risk groups exhibit similar outcome (6). More importantly, novel agents are being developed at a quick pace and will fundamentally change the significance of a prognostic marker (42,43). Thus, it will be more complicated to establish a universal risk stratification system for all DLBCL patients treated with different regimens.

In conclusion, the discovery of new clinical and biological prognostic markers has greatly improved the risk stratification in DLBCL. However, no consensus was reached on which of the prognostic markers should be routinely assessed in clinical practice and how the results should be interpreted. To better assess patients risk, guide individualized therapy and eventually optimize patient outcome, a comprehensive risk stratification system incorporating both clinical and biological parameters needs to be developed.

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## Footnote

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## References


1. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 2015;90:790-5.
2. Martelli M, Ferreri AJ, Agostinelli C, et al. Diffuse large B-cell lymphoma. Crit Rev Oncol Hematol 2013;87:146-71.
3. Kubuschok B, Held G, Pfreundschuh M. Management of diffuse large B-cell lymphoma (DLBCL). Cancer Treat Res 2015;165:271-88.
4. Chen R, Yu Z, Zhang H, et al. Primary malignant lymphoma of the uterus and broad ligament: a case report and review of literature. Onco Targets Ther 2015;8:265-8.
5. Bachy E, Salles G. Treatment approach to newly diagnosed diffuse large B-cell lymphoma. Semin Hematol 2015;52:107-18.
6. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;109:1857-61.
7. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-42.
8. Pfreundschuh M, Müller C, Zeynalova S, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood 2014;123:640-6.
9. Maurer MJ, Micallef IN, Cerhan JR, et al. Elevated serum free light chains are associated with event-free and overall survival in two independent cohorts of patients with diffuse large B-cell lymphoma. J Clin Oncol 2011;29:1620-6.
10. Witzig TE, Maurer MJ, Stenson MJ, et al. Elevated serum monoclonal and polyclonal free light chains and interferon inducible protein-10 predicts inferior prognosis in untreated diffuse large B-cell lymphoma. Am J Hematol 2014;89:417-22.
11. Troppan KT, Schlick K, Deutsch A, et al. C-reactive protein level is a prognostic indicator for survival and improves the predictive ability of the R-IPI score in diffuse large B-cell lymphoma patients. Br J Cancer 2014;111:55-60.
12. Song MK, Chung JS, Seol YM, et al. Influence of low absolute lymphocyte count of patients with nongerminal center type diffuse large B-cell lymphoma with R-CHOP therapy. Ann Oncol 2010;21:140-4.
13. Wilcox RA, Ristow K, Habermann TM, et al. The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large-B-cell lymphoma. Leukemia 2011;25:1502-9.
14. Sehn LH, Scott DW, Chhanabhai M, et al. Impact of concordant and discordant bone marrow involvement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol 2011;29:1452-7.
15. Carson KR, Bartlett NL, McDonald JR, et al. Increased body mass index is associated with improved survival in United States veterans with diffuse large B-cell lymphoma. J Clin Oncol 2012;30:3217-22.
16. Hong F, Habermann TM, Gordon LI, et al. The role of body mass index in survival outcome for lymphoma patients: US intergroup experience. Ann Oncol 2014;25:669-74.
17. Li T, Liu ZG, Liang PQ, et al. Can body mass index predict the outcome of diffuse large B-cell lymphoma? A single-center retrospective study in China. Leuk Lymphoma 2016:1-6. [Epub ahead of print].
18. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
19. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937-47.
20. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 2008;359:2313-23.
21. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol 2011;29:4079-87.
22. Molina TJ, Canioni D, Copie-Bergman C, et al. Young patients with non-germinal center B-cell-like diffuse large B-cell lymphoma benefit from intensified chemotherapy with ACVBP plus rituximab compared with CHOP plus rituximab: analysis of data from the Groupe d'Etudes des Lymphomes de l'Adulte/lymphoma study association phase III trial LNH 03-2B. J Clin Oncol 2014;32:3996-4003.
23. Gutiérrez-García G, Cardesa-Salzmann T, Climent F, et al. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Blood 2011;117:4836-43.
24. Coutinho R, Clear AJ, Owen A, et al. Poor concordance among nine immunohistochemistry classifiers of cell-of-origin for diffuse large B-cell lymphoma: implications for


 

therapeutic strategies. Clin Cancer Res 2013;19:6686-95.
25. de Jong D, Rosenwald A, Chhanabhai M, et al. Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2007;25:805-12.
26. Barrans SL, Crouch S, Care MA, et al. Whole genome expression profiling based on paraffin embedded tissue can be used to classify diffuse large B-cell lymphoma and predict clinical outcome. Br J Haematol 2012;159:441-53.
27. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood 2014;123:1214-7.
28. Ichikawa A, Kinoshita T, Watanabe T, et al. Mutations of the p53 gene as a prognostic factor in aggressive B-cell lymphoma. N Engl J Med 1997;337:529-34.
29. Young KH, Weisenburger DD, Dave BJ, et al. Mutations in the DNA-binding codons of TP53, which are associated with decreased expression of TRAILreceptor-2, predict for poor survival in diffuse large B-cell lymphoma. Blood 2007;110:4396-405.
30. Young KH, Leroy K, Møller MB, et al. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood 2008;112:3088-98.
31. Xu-Monette ZY, Wu L, Visco C, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2012;120:3986-96.
32. Klapper W, Stoecklein H, Zeynalova S, et al. Structural aberrations affecting the MYC locus indicate a poor prognosis independent of clinical risk factors in diffuse large B-cell lymphomas treated within randomized trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Leukemia 2008;22:2226-9.
33. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009;114:3533-7.
34. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-5.
35. Valera A, López-Guillermo A, Cardesa-Salzmann T, et al. MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematologica 2013;98:1554-62.
36. Copie-Bergman C, Cuillière-Dartigues P, Baia M, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study. Blood 2015;126:2466-74.
37. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood 2011;117:2319-31.
38. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273-9.
39. Niitsu N, Okamoto M, Miura I, et al. Clinical features and prognosis of de novo diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations. Leukemia 2009;23:777-83.
40. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. Blood 2013;121:4021-31; quiz 4250.
41. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-9.
42. Iqbal J, Neppalli VT, Wright G, et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J Clin Oncol 2006;24:961-8.
43. Iqbal J, Meyer PN, Smith LM, et al. BCL2 predicts survival in germinal center B-cell-like diffuse large B-cell lymphoma treated with CHOP-like therapy and rituximab. Clin Cancer Res 2011;17:7785-95.
44. Ahearne MJ, Bhuller K, Hew R, et al. Expression of PD-1 (CD279) and FoxP3 in diffuse large B-cell lymphoma. Virchows Arch 2014;465:351-8.
45. Kiyasu J, Miyoshi H, Hirata A, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. Blood 2015;126:2193-201.
46. Xing W, Dresser K, Zhang R, et al. PD-L1 expression in EBV-negative diffuse large B-cell lymphoma: clinicopathologic features and prognostic implications. Oncotarget 2016;7:59976-86.
47. Rossille D, Gressier M, Damotte D, et al. High level

 

of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-Cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28:2367-75.
48. Xu-Monette ZY, Tu M, Jabbar KJ, et al. Clinical and biological significance of de novo CD5+ diffuse large B-cell lymphoma in Western countries. Oncotarget 2015;6:5615-33.
49. Tzankov A, Leu N, Muenst S, et al. Multiparameter analysis of homogeneously R-CHOP-treated diffuse large B cell lymphomas identifies CD5 and FOXP1 as relevant prognostic biomarkers: report of the prospective SAKK 38/07 study. J Hematol Oncol 2015;8:70.
50. Alinari L, Gru A, Quinion C, et al. De novo CD5+ diffuse large B-cell lymphoma: Adverse outcomes with and without stem cell transplantation in a large, multicenter, rituximab treated cohort. Am J Hematol 2016;91:395-9.
51. Hu S, Xu-Monette ZY, Balasubramanyam A, et al. CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2013;121:2715-24.
52. Fernández-Rodríguez C, Bellosillo B, García-García M, et al. MYD88 (L265P) mutation is an independent prognostic factor for outcome in patients with diffuse large B-cell lymphoma. Leukemia 2014;28:2104-6.
53. Wong KK, Gascoyne DM, Brown PJ, et al. Reciprocal expression of the endocytic protein HIP1R and its repressor FOXP1 predicts outcome in R-CHOP-treated diffuse large B-cell lymphoma patients. Leukemia 2014;28:362-72.
54. Xia Y, Xu-Monette ZY, Tzankov A, et al. Loss of PRDM1/BLIMP-1 function contributes to poor prognosis of activated B-cell-like diffuse large B-cell lymphoma. Leukemia 2016. [Epub ahead of print].
55. Chan FC, Telenius A, Healy S, et al. An RCOR1 loss-associated gene expression signature identifies a prognostically significant DLBCL subgroup. Blood 2015;125:959-66.
56. Alcoceba M, Sebastián E, Marín L, et al. HLA specificities are related to development and prognosis of diffuse large B-cell lymphoma. Blood 2013;122:1448-54.
57. Barrena S, Almeida J, Yunta M, et al. Aberrant expression of tetraspanin molecules in B-cell chronic lymphoproliferative disorders and its correlation with normal B-cell maturation. Leukemia 2005;19:1376-83.
58. Xu-Monette ZY, Li L, Byrd JC, et al. Assessment of CD37 B-cell antigen and cell of origin significantly improves risk prediction in diffuse large B-cell lymphoma. Blood 2016;128:3083-100.
59. de Winde CM, Veenbergen S, Young KH, et al. Tetraspanin CD37 protects against the development of B cell lymphoma. J Clin Invest 2016;126:653-66.
60. Culpin RE, Sieniawski M, Angus B, et al. Prognostic significance of immunohistochemistry-based markers and algorithms in immunochemotherapy-treated diffuse large B cell lymphoma patients. Histopathology 2013;63:788-801.
61. Dawod M, Gomez-Gelvez J, Mattour A, et al. Prognostic Significance of Cell of Origin Subclassification in Diffuse Large B Cell Lymphoma. Blood 2012;120:5081.
62. Nandikolla AG, Wang Y, Shah UA, et al. Cell of Origin By Immunohistochemistry Is Not Prognostic of Overall Survival in HIV Associated DLBCL- Analysis of Clinical Pathological Markers in HIV DLBCL. Blood 2016;128:1867.

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