Construction and validation of a nomogram for predicting recurrence of diffuse large B cell lymphoma

Yuxi Gong
The First Affiliated Hospital of Nanjing Medical University
Haitao Yan
The First Affiliated Hospital of Nanjing Medical University
Yefan Yang
The First Affiliated Hospital of Nanjing Medical University
Boya Zhai
The First Affiliated Hospital of Nanjing Medical University
Zhendong Huang
The First Affiliated Hospital of Nanjing Medical University
Zhihong Zhang (zhangzh@njmu.edu.cn)
The First Affiliated Hospital of Nanjing Medical University

Research Article

Keywords: Diffuse Large B cell Lymphoma (DLBCL), recurrence, risk stratification, nomogram

Posted Date: May 31st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1672289/v1

Abstract

Purposes: To explore recurrence-risk factors of diffuse large B cell lymphoma (DLBCL) and construct a risk nomogram for predicting recurrence and risk stratification.

Materials and Methods: A retrospective analysis was performed on 228 DLBCL patients who achieved complete remission after initial treatment between January 2015 and December 2019. Univariate and multivariate analyses were applied to identify recurrence-related risk factors from the pretreatment evaluation factors covering patients' demographic characteristics, clinical manifestations, serological indicators, pathological and immunohistochemical results. A nomogram was developed based on the above results and validated by the concordance index (C-index), the receiver operating characteristic (ROC) curve, and the calibration curve.

Results: Fifty of 228(21.9%) cases recurred during follow-up. Three recurrence-risk factors including BCL2 expression (P=0.013), Ann Arbor stage (P=0.011), LDH level (P=0.038) were identified from multivariate analysis and entered the final nomogram "ABL-nomogram". The C-index of the ABL-nomogram was 0.808, higher than that of IPI system (0.717) and NCCN-IPI system (0.714). And the 1-year, 2-year, 3-year, and 4-year areas under ROC(AUC) were 0.851, 0.859, 0.843, and 0.791, respectively. The calibration curves also showed a good discrimination capability and accuracy. DLBCL could be divided into four subgroups (G1, G2, G3, G4) with significant differences in recurrence risk based on the total points calculated from ABL-nomogram.

Conclusions: ABL-nomogram incorporating the three independent risk factors (BCL2 expression, Ann Arbor stage and LDH level) for DLBCL recurrence, had a better ability to assist risk stratification and identify DLBCL patients with high recurrence risk than IPI system or NCCN-IPI system.

Introduction

Diffuse Large B cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, with significant biological and clinical heterogeneity. Most patients can benefit from the first-line treatment – R-CHOP and achieve complete remission (CR), but 30%-40% of patients will experience relapse, progression or even death[1]. As the salvage regimen for these relapsed patients, high-dose cytarabine-based chemotherapy or ifosfamide-based chemotherapy combined with Auto Stem Cell Transplantation (ASCT) can only guarantee a 3-year progression-free survival rate of 55%[2, 3]. And there are cases that failed in stem cell collection due to advanced age or complications. Therefore, early identification of DLBCL patients with high relapse risk is of great significance for formulating personalized treatment and improving prognosis.

Efforts have been made to find suitable prognostic markers. Since 1993, the International Prognostic Index (IPI), which is based on age, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance status, number of extranodal sites, and serum lactate dehydrogenase (LDH) levels, has been widely used for risk stratification and prognosis prediction[4], and further refined into Revised IPI(R-IPI)

and National Comprehensive Cancer Network IPI (NCCN-IPI) in the rituximab era[5, 6]. However, the IPI system only contains clinical indicators and cannot fully reveal the biological heterogeneity of DLBCL. Patients with same IPI scores still show different outcomes. Recent studies attempt to incorporate numerous biological markers into prognostic scores, including pathological markers such as cell-of-origin classification, CD5 expression and BCL2 expression, serological indicators such as β2 -microglobulin (β2-MG), hemoglobin[7, 8]. However, the discriminative abilities of these prognostic risk markers for relapsed DLBCL patients still need further exploration.

The utilization of a simple and accurate recurrence-risk predictive model is important to identify high-risk patients. Nomogram, a statistical predictive tool, can be used to calculate the probability of a clinical event by integrating diverse risk factors[9]. We wish to develop a specific risk stratification nomogram incorporating clinical and pathological factors that can predict recurrence of DLBCL. In the present study, we performed a retrospective study on 228 DLBCL cases, 50 of which experienced relapses. Clinical manifestations, pathological features, and laboratory indicators at the initial diagnosis were collected to explored recurrence-risk factors. We further conducted and validated a nomogram model predicting recurrence, which may provide insight for individualized clinical chemotherapy and targeted therapy.

We present the following article in accordance with the TRIPOD reporting checklist.

Materials And Methods

The use of samples in this study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2020-SR-097).

Sample selection and follow up

According to the WHO classification of Tumors of Hematopoietic and Lymphoid Tissue (2016), 573 patients were diagnosed with DLBCL (including consultation) by the Department of Pathology and received standard R-CHOP-like treatment in the Department of Hematology between January 2015 and December 2019 at the First Affiliated Hospital of Nanjing Medical University. The exclusion criteria were as follows: (1) transformed from indolent lymphoma or other lymphohematopoietic system diseases; (2) merged with other malignant tumors at the same time; (3) originated in the mediastinum or central nervous system; (4) with positive EBER expression; (5) high-grade B-cell lymphoma confirmed by FISH (with MYC rearrangement, BCL2 and/or BCL6 rearrangement). In total, 228 patients achieved complete remission after initial treatment, and all patients did not receive any treatment at the time of initial diagnosis. A flowchart of the enrolled patients was shown in Fig. 1.

After achieving CR, patients were followed up through hematologic examination and Computed Tomography (CT) examination at the outpatient clinic. Telephone interviews were also used for later outcomes. Relapse referred to disease reappearance after obtaining CR for more than one month. The deadline for follow-up was May 2021, and progression-free survival (PFS) was defined as the time interval from the date of diagnosis to the end of follow-up without progression or recurrence or death. All

228 patients were divided into two groups: RE group (with recurrence), and CR group (with recurrence-free).

Clinical and pathological indicators

Pretreatment evaluation factors covered patients' demographic characteristics, clinical manifestations, serological indicators, pathological and immunohistochemical results, including age, sex, HBV infection, B symptoms (fever, night sweats, weight loss), primary site of origin, extranodal involvement, Ann Arbor stage, ECOG score, IPI score, NCCN-IPI score, total protein (abnormal: <65g/L), albumin (abnormal: <30g/L), hemoglobin (abnormal: <110g/L(female) or 120g/L(male)), LDH (abnormal: >271U/L), β2-MG (abnormal: >2.53mg/L), C-reaction protein (CRP, abnormal: >8mg/L), cell of origin (COO) subtypes, the expressions of CD10, BCL-6, MUM1, BCL-2 and Ki-67 index. The response assessment was based on the Cheson (2014) classification[10].

Nomogram construction and validation

Univariate analysis was applied to identify recurrence-related risk factors with P value < 0.1, and then independent relapsed parameters were evaluated by multivariate Cox regression analysis for further constructing a nomogram for recurrence. The receiver operating characteristic (ROC) curve and the calibration curve constructed by means of 1000 bootstrap resamples were used for model internal validation. The area under ROC curve (AUROC) and the concordance index (C-index) could evaluate the discrimination of the model, and the calibration curve was a useful tool for showing the concordance between predicted and observed probabilities for recurrence.

Statistical analysis

Statistical analysis was performed using the *rms, survival, survival ROC* package in R 4.0.5 software (http://www.r-project.org). Chi-square test was used to compare the differences in clinicopathological characteristics between the relapse group and the CR group. Kaplan-Meier curves were used for evaluation of PFS, and Log-rank test was used for univariate analysis. Multivariate Cox regression analysis was performed to identify independent relapsed factors for risk nomogram construction, and calculate the hazard ratio and the 95% confidence interval (CI). P < 0.05 was considered significant.

Results

Baseline characteristics of DLBCL patients

In the whole cohort, the median age at diagnosis was 56 (15–84) years, and the median PFS was 36 (6–77) months, the average PFS was 37.2 months. Fifty patients relapsed during follow-up, accounting for 21.9%. The accumulative recurrence rates of 1-year, 2-year, 3-year, and 4-year are 7.5% (17/228), 16.2% (37/228), 16.7% (38/228), and 19.3% (44/228), respectively. The majority of the relapses occurred within the first 2 years. The baseline characteristics of all 228 DLBCL patients were summarized in Table.1.

Comparison of the characteristics between the RE group and CR group

There were significant differences between the two groups in terms of primary site of origin, Ann Arbor stage, ECOG score, numbers of extranodal involvement, IPI score, NCCN-IPI score, LDH level, β2-MG level, CRP level, COO subtypes, CD10 expression, BCL6 expression, and BCL2 expression, but no statistical differences were found in terms of age, sex, HBV infection status, B symptoms, total protein level, albumin level, hemoglobin level, MUM1 expression and Ki-67 index. The clinicopathological characteristics of the RE group and the CR group were summarized in Table.1.

Construction of risk nomogram for recurrence and internal validation

The univariate analysis revealed that primary site of origin, Ann Arbor stage, NCCN-IPI score, numbers of extranodal involvement, LDH level, β2-MG level, CRP level, COO subtype, CD10 expression, MUM1 expression, BCL6 expression and BCL2 expression were factors affecting recurrence. The multivariate analysis indicated advanced Ann Arbor stage(P = 0.011), positive BCL2 expression(P = 0.013) and elevated LDH level(P = 0.038) were independent risk factors associated with recurrence. (Table.2)

We then developed a new nomogram model (Fig. 2A), including the three independent factors (BCL2 expression, Ann Arbor stage and LDH level), for predicting recurrence based on the results of the multivariate analysis. This nomogram had a C-index of 0.808 (95%CI, 078-0.836). And the calibration plots showed a significant correlation between predicted and observed probabilities for recurrence (Fig. 2B). The time-dependent ROC curves and the corresponding 1-year, 2-year, 3-year and 4-year AUROC shown in Fig. 2C also indicating that the nomogram had advantages in predicting recurrence.

Comparison of the predictive accuracy for recurrence among the nomogram, IPI system and NCCN-IPI system

The current IPI system was widely applied for prognostic evaluation, and the enhanced IPI score (NCCN-IPI) was developed for newly diagnosed patients with DLBCL and treated with R-CHOP. Univariate analysis suggested that both IPI score and NCCN-IPI score could affect recurrence and clearly distinguish low-risk and high-risk patients. We wondered if IPI score and NCCN-IPI score had the same ability to predict recurrence as the new nomogram? The time-dependent ROC curves and the corresponding 1-year, 2-year, 3-year and 4-year AUROC of IPI system and NCCN-IPI system were shown in Fig. 3. While all AUROC of the two classic predicting systems were significantly less than that of the constructed nomogram. The nomogram also had a higher C-index of 0.808 than that of IPI system (0.717, 95%CI, 0.684–0.75) and NCCN-IPI system (0.714, 95%CI, 0.678–0.75). It indicated that the new nomogram was more satisfactory for recurrence risk assessment than the IPI system and NCCN-IPI system.

Analysis of subgroups with different recurrence risk

We finally chose the new nomogram as the recurrence prediction model and named it “ABL-nomogram”. In ABL-nomogram, a DLBCL patient with positive BCL2 expression, Ann Arbor stage III-IV, elevated LDH level (1–3× ULN) or elevated LDH level (> 3× ULN) could obtain 92 points, 100 points, 48 points and 97 points, respectively. According to the possible total points, we divided DLBCL into four subgroups with different recurrence risks: G1 (low recurrence risk, total points = 0), G2 (low-intermediate recurrence risk, total points = 48/92/97/100), G3 (high-intermediate recurrence risk, total points = 140/148/189/192/197), G4 (high recurrence risk, total points = 240/289), and the cumulative recurrence rate was 0, 12.2%, 25%, 62.5%, respectively. The Kaplan Meier curves (Fig. 4) showed a significant difference in cumulative recurrence rate among the four subgroups($P < 0.001$), indicating the ABL-nomogram had a good ability to stratify the recurrence risk.

Discussion

Some DLBCL patients would relapse within the first two or three years after diagnosis, and late relapse that occurred after five years was less common[11]. To screen out patients prone to relapse at the first diagnosis was a hot spot in clinical research. Although significant achievements had been made in studying prognostic markers of novel DLBCL, and the nomogram had been validated as a useful tool for predicting overall survival (OS) with higher sensitivity and accuracy than IPI system[7] the recurrence-related risk factors of DLBCL and the nomogram models for recurrence risk assessment needed to be further explored.

In this study, we focused on those widely concerning parameters in daily clinical and pathological work and found that relapsed DLBCL had some special characteristics. Patients with relapsed DLBCL were more likely to be of non-GCB type, and have advanced Ann Arbor stage (III-IV), advanced IPI score (3–5), advanced NCCN-IPI score, higher ECOG score (2–4), elevated LDH, β2-MG and CRP level. The lesions tended to originate from nodal, with IHC showed CD10-negative, BCL6-negative and BCL2-positive.

We further identified two independent predictors: positive BCL2 expression, advanced Ann Arbor stage and elevated LDH level. Ann Arbor stage, a member of IPI system using for prognostic evaluation, could affect the PFS and OS of DLBCL. There were also many previous studies to explore the relationship between Ann Arbor stage and lymphoma recurrence. Yusuke Kanemasa *et al.* [12]found that advanced Ann Arbor stage (III-IV) was significantly associated with central nervous system (CNS) relapse, and could distinguish the low- and high-risk groups when combined with albumin level, number of extranodal sites, and involvement of retroperitoneal lymph node. Kerry J Savage[13] once again emphasized the significance of Ann Arbor stage in predicting CNS recurrence in 2017. In Philipp Schommers’s study[14], advanced Ann Arbor stage was also an independent risk factor for relapses in HIV-associated non-Hodgkin lymphoma. Our research further confirmed the role of advanced Ann Arbor stage in DLBCL recurrence.

As a key regulator in cell apoptosis, dysregulation of BCL2 caused by chromosome translocation, gene amplification, or activation of the NF-κB signal pathway could promote the occurrence and development

of B-cell lymphoma[15]. BCL2 overexpression was associated with drug resistance and poor prognosis[16], and could be inhibited by Venetoclax in many hematological cancers[17]. Naoko Tsuyama *et al.* [18]found that DLBCL patients with BCL2 overexpression had a lower rate to obtain CR, a higher probability of recurrence after CR, and a worse 3-year PFS rate. What's more, DLBCL with coexpression of MYC and BCL2 protein (so-called double-expressor lymphoma, DEL) was considered to have adverse outcomes and increased risk of CNS recurrence[19]. Since there was little information regarding the MYC protein expression in consultation cases in our study, the relationship between the co-expression of BCL2 and MYC and the recurrence of DLBCL was unknown. But we did find that positive BCL2 expression was a significant independent risk factor for DLBCL recurrence, which was consistent with that in previous studies.

The elevated LDH level could also promote the relapse of DLBCL in this study. LDH, a valuable biomarker, could be easily measured in clinical and hospital laboratories. As its elevation was mostly associated with high tumor burden and adverse clinical behavior, LDH level was of great prognostic effect on solid tumors, in particular melanoma, prostate and renal cell carcinomas[20], and was also widely used as one of the independent prognostic factors in IPI system and other prognostic nomogram models in aggressive B-cell lymphomas[7, 21, 22]. In terms of DLBCL, elevated LDH level at initial diagnosis was found to be related to the increased risks of CNS relapse[23, 24]. Compared with patients with late relapses, patients with early relapses were more likely to have a higher LDH level, higher IPI score and adverse stage (III-IV)[25]. In Huang's study, univariate analysis also indicated that LDH > 1000U/L was one of the relapse risk factors of pediatric mature B cell lymphoma[26].

The final nomogram consisted of 3 predictors: Ann Arbor stage, BCL2 expression, and LDH level, so we called it "ABL-nomogram". Based on the data in our study, this newly recurrence-risk predicted nomogram had a higher C-index than IPI system and NCCN-IPI system. And the ROC curves and calibration plots also demonstrated that ABL-nomogram had a good level of discriminative ability and accuracy. What's more, according to the points calculated from ABL-nomogram, DLBCL patients could be well divided into four subgroups with significant differences in recurrence risk ($P < 0.001$). Patients in G4 subgroup with adverse Ann Arbor stage (III-IV), elevated LDH level and positive BCL2 expression had the highest recurrence risk, while patients in G1 subgroup with none of these three risk factors had the lowest recurrence risk. It meant that ABL-nomogram had a good ability to assist risk stratification.

As far as we know, the ABL-nomogram was the first nomogram model constructed for predicting DLBCL recurrence based on clinical and pathological characteristics. The model not only performed better than IPI and NCCN-IPI, but also used economically accessible indicators for risk stratification. It could be used to assess the recurrence risk of each DLBCL patient before treatment, so as to formulate personalized treatment to improve the prognosis. However, this study had some limits. Firstly, as a retrospective study, there was a certain bias in patients' selection. Secondly, due to the sample size limitation, this study lacked external validation. Thirdly, although patients received R-CHOP-like chemotherapy, the effects of dosage and other adjuvant treatments on the prognosis were not explored. Lastly, this model had not yet included molecular factors. We would try to realize multi-center prospective research to expand the

sample size and control confounding factors, and incorporate more novel biomarkers for further improving this nomogram model and verifying its feasibility in future studies.

Conclusions

In summary, our study explored the significant clinicopathological characteristics and recurrence-risk factors of relapsed DLBCL. Additionally, we constructed the first nomogram for predicting DLBCL recurrence incorporating the expression of BCL2 protein with Ann Arbor stage and LDH level, which had a good ability to assist risk stratification.

Abbreviations

DLBCL diffuse large B cell lymphoma

CR complete remission

ASCT Auto Stem Cell Transplantation

IPI International Prognostic Index

ECOG Eastern Cooperative Oncology Group

LDH serum lactate dehydrogenase

NCCN-IPI National Comprehensive Cancer Network IPI

β2-MG β2 -microglobulin

PFS progression-free survival

ROC curve the receiver operating characteristic curve

AUROC the area under ROC curve

C-index the concordance index

CI confidence interval

Declarations

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The use of samples in this study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2020-SR-097). Since this study was a retrospective study and the patient had signed the informed consent for the remaining tissue

samples for scientific research before surgery, the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2020-SR-097) waived the need of repeated informed consent.

Data Sharing Statement: The datasets are available from the corresponding author on reasonable request.

Declaration of interest statement All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Funding: None.

Authors' contributions: Z. Zhang designed research; Y. Gong, H. Yan, Y. Yang, Z. Huang collected data; Y. Gong, H. Yan and B. Zhai analyzed data; Y. Gong and H. Yan wrote the paper; Z. Zhang supported administratively; Z. Zhang revised the paper. All authors contributed to and have approved the final manuscript.

Acknowledgements: We are very grateful to all the haematologists and pathologists who assisted in the collection of clinical data. We thank G. Song and J. Tang for immunohistochemical staining.

Consent to Publish: Not applicable.

References

1. Li S, Young KH, Medeiros LJ. Diffuse large b-cell lymphoma. Pathology. 2018;50(1):74-87. doi:10.1016/j.pathol.2017.09.006.
2. Lignon J, Sibon D, Madelaine I, Brice P, Franchi P, Briere J, et al. Rituximab, dexamethasone, cytarabine, and oxaliplatin (r-dhax) is an effective and safe salvage regimen in relapsed/refractory b-cell non-hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2010;10(4):262-9. doi:10.3816/CLML.2010.n.055.
3. Gisselbrecht C, Glass B, Mounier N, Singh GD, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large b-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90. doi:10.1200/JCO.2010.28.1618.
4. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-94. doi:10.1056/NEJM199309303291402.
5. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, 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(5):1857-61. doi:10.1182/blood-2006-08-038257.
6. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, 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(6):837-42. doi:10.1182/blood-2013-09-524108.

7. Han Y, Yang J, Liu P, He X, Zhang C, Zhou S, et al. Prognostic nomogram for overall survival in patients with diffuse large b-cell lymphoma. Oncologist. 2019;24(11):e1251-e1261. doi:10.1634/theoncologist.2018-0361.
8. Jelicic J, Larsen TS, Frederiksen H, Andjelic B, Maksimovic M, Bukumiric Z. Statistical challenges in development of prognostic models in diffuse large b-cell lymphoma: comparison between existing models - a systematic review. Clin Epidemiol. 2020;12:537-555. doi:10.2147/CLEP.S244294.
9. Balachandran VP, Gonen M, Smith JJ, Dematteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173-80. doi:10.1016/S1470-2045(14)71116-7.
10. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: the lugano classification. J Clin Oncol. 2014;32(27):3059-68. doi:10.1200/JCO.2013.54.8800.
11. Friedberg JW. Relapsed/refractory diffuse large b-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:498-505. doi:10.1182/asheducation-2011.1.498.
12. Kanemasa Y, Shimoyama T, Sasaki Y, Tamura M, Sawada T, Omuro Y, et al. Central nervous system relapse in patients with diffuse large b cell lymphoma: analysis of the risk factors and proposal of a new prognostic model. Ann Hematol. 2016;95(10):1661-9. doi:10.1007/s00277-016-2744-5.
13. Savage KJ. Secondary cns relapse in diffuse large b-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. Hematology Am Soc Hematol Educ Program. 2017;2017(1):578-586. doi:10.1182/asheducation-2017.1.578.
14. Schommers P, Gillor D, Hentrich M, Wyen C, Wolf T, Oette M, et al. Incidence and risk factors for relapses in hiv-associated non-hodgkin lymphoma as observed in the german hiv-related lymphoma cohort study. Haematologica. 2018;103(5):857-864. doi:10.3324/haematol.2017.180893.
15. Warren C, Wong-Brown MW, Bowden NA. Bcl-2 family isoforms in apoptosis and cancer. Cell Death Dis. 2019;10(3):177. doi:10.1038/s41419-019-1407-6.
16. Delbridge AR, Grabow S, Strasser A, Vaux DL. Thirty years of bcl-2: translating cell death discoveries into novel cancer therapies. Nat Rev Cancer. 2016;16(2):99-109. doi:10.1038/nrc.2015.17.
17. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting bcl2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):311-22. doi:10.1056/NEJMoa1513257.
18. Tsuyama N, Sakata S, Baba S, Mishima Y, Nishimura N, Ueda K, et al. Bcl2 expression in dlbcl: reappraisal of immunohistochemistry with new criteria for therapeutic biomarker evaluation. Blood. 2017;130(4):489-500. doi:10.1182/blood-2016-12-759621.
19. Qualls D, Abramson JS. Advances in risk assessment and prophylaxis for central nervous system relapse in diffuse large b-cell lymphoma. Haematologica. 2019;104(1):25-34. doi:10.3324/haematol.2018.195834.
20. Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V, et al. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. Acta Oncol. 2015;54(7):961-70. doi:10.3109/0284186X.2015.1043026.

21. Jurisic V, Radenkovic S, Konjevic G. The actual role of ldh as tumor marker, biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:115-24. doi:10.1007/978-94-017-7215-0_8.
22. Zhong H, Chen J, Cheng S, Chen S, Shen R, Shi Q, et al. Prognostic nomogram incorporating inflammatory cytokines for overall survival in patients with aggressive non-hodgkin's lymphoma. Ebiomedicine. 2019;41:167-174. doi:10.1016/j.ebiom.2019.02.048.
23. Zhang J, Chen B, Xu X. Impact of rituximab on incidence of and risk factors for central nervous system relapse in patients with diffuse large b-cell lymphoma: a systematic review and meta-analysis. Leuk Lymphoma. 2014;55(3):509-14. doi:10.3109/10428194.2013.811239.
24. Nazir A, Fawad, Siddique N, Hameed A. Cns relapse of diffuse large b cell lymphoma a single centre experience. Pak J Med Sci. 2017;33(6):1454-1458. doi:10.12669/pjms.336.13812.
25. Kang J, Chae H, Hong JY, Yoon DH, Kim S, Park JS, et al. Distinct clinical characteristics at diagnosis in patients with late relapses compared with early relapses of diffuse large b-cell lymphoma treated with r-chop. Leuk Lymphoma. 2020;61(5):1119-1125. doi:10.1080/10428194.2019.1709831.
26. Huang S, Jin L, Yang J, Duan YL, Zhang M, Zhou CJ, et al. [clinical pathologic characteristics and treatment outcomes of 19 relapsed pediatric b-cell lymphoma]. Zhonghua Er Ke Za Zhi. 2017;55(10):748-753. doi:10.3760/cma.j.issn.0578-1310.2017.10.007.

Tables

Table 1

The clinical characteristics, laboratory indicators and pathological features of 228 DLBCL patients.

Parameters	Total	RE group	CR group	P value
Sex				0.150
male	114（50.0）	20（40.0）	94（52.8）	
female	114（50.0）	30（60.0）	84（47.2）	
Age				0.757
≤40	34（14.9）	6（12.0）	28（15.7）	
41-60	95（41.7）	23（46.0）	72（40.4）	
61-74	86（37.7）	18（36.0）	68（38.2）	
≥75	13（5.7）	3（6.0）	10（5.6）	
HBV				0.804
Present	54（23.7）	13（26.0）	41（23.0）	
Absent	174（76.3）	37（74.0）	137（77.0）	
Primary site				**0.000***
nodal	124（54.4）	39（78.0）	85（47.8）	
extranodal	104（45.6）	11（22.0）	93（52.2）	
Ann Arbor stage				**0.000***
I-II	126（55.3）	9（18.0）	117（65.7）	
III-IV	102（44.7）	41（82.0）	61（34.3）	
ECOG				**0.047***
0-1	199（87.3）	39（78.0）	160（89.9）	
2-4	29（12.7）	11（22.0）	18（10.1）	
Extranodal involvement				**0.000***
<2	163（71.5）	23（46.0）	140（78.7）	
≥2	65（28.5）	27（54.0）	38（21.3）	
IPI score				**0.000***
0-2	159（69.7）	19（38.0）	140（78.7）	
3-5	69（30.3）	31（62.0）	38（21.3）	
NCCN-IPI score				**0.000***
0-1	68（29.8）	6（12.0）	62（34.8）	

2-3	96（42.1）	16（32.0）	80（44.9）	
4-5	52（22.8）	22（44.0）	30（16.9）	
6-8	12（5.3）	6（12.0）	6（3.4）	
B symptoms				0.685
present	167（73.2）	15（30.0）	46（25.8）	
absent	61（26.8）	35（70.0）	132（74.2）	
Total protein				1
normal	141（61.8）	32（64.0）	109（61.2）	
decreased	87（38.2）	18（36.0）	69（38.8）	
Albumin				1
normal	101（44.3）	22（44.0）	79（44.4）	
decreased	127（55.7）	28（56.0）	99（55.6）	
Hemoglobin				1
normal	112（49.1）	25（50.0）	87（48.9）	
decreased	116（50.9）	25（50.0）	91（51.1）	
LDH ratio				**0.000***
<1× ULN	152（66.7）	18（36.0）	134（75.3）	
1-3× ULN	65（28.5）	26（52.0）	39（21.9）	
>3× ULN	11（4.8）	6（12.0）	5（2.8）	
β2-MG				**0.029***
normal	146（65.2）	25（51.0）	121（69.1）	
elevated	78（34.8）	24（49.0）	54（30.9）	
CRP				
normal	142（65.7）	23（46.9）	119（71.3）	**0.003***
elevated	74（34.3）	26（53.1）	48（28.7）	
COO subtype				**0.010***
GCB	83（36.4）	10（20.0）	73（41.0）	
non-GCB	145（63.6）	40（80.0）	105（59.0）	
CD10				**0.010***

negative	160（70.2）	43（86.0）	117（65.7）	
positive	68（29.8）	7（14.0）	61（34.3）	
BCL6				**0.001***
negative	33（14.7）	15（30.0）	18（10.3）	
positive	192（85.3）	35（70.0）	157（89.7）	
MUM1				0.176
negative	34（15.0）	4（8.0）	30（17.0）	
positive	192（85.0）	46（92.0）	146（83.0）	
Ki67 index				0.893
<75%	63（27.8）	13（26.0）	50（28.2）	
≥75%	164（72.2）	37（74.0）	127（71.8）	
BCL2				
negative	77（37.2）	8（17.0）	69（43.1）	**0.002***
positive	130（62.8）	39（83.0）	91（56.9）	
ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; NCCN-IPI: National comprehensive cancer network International Prognostic Index; LDH: lactate dehydrogenase; β2-MG: β2 -microglobulin (β2-MG); CRP: C-reaction protein; COO: cell of origin; GCB: germinal center B-cell.				

Table 2

Univariate and multivariate analysis of 228 DLBCL patients.

Parameters		Average PFS(m)	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value
Sex	female	37.5	Ref.			
	male	36.8	0.668 (0.379-1.176)	0.162		
Age	≤40	37.3	Ref.			
	41-60	39.3	1.058 (0.740-1.512)	0.757		
	61-74	35.9				
	≥75	30.3				
HBV	Absent	38.3	Ref.			
	Present	33.4	1.050 (0.535-2.061)	0.888		
Primary site	nodal	34.2	Ref.			
	extranodal	40.7	0.287 (0.145-0.561)	**0.000***	0.933 (0.396-2.195)	0.873
Ann Arbor stage	I-II	40.5	Ref.			
	III-IV	33.0	6.746 (3.275-13.890)	**0.000***	4.360 (1.398-13.597)	**0.011***
ECOG	0-1	37.5	Ref.			
	2-4	34.9	1.804 (0.909-3.582)	0.092	0.956 (0.360-2.541)	0.928
Extranodal involvement	<2	39.6	Ref.			
	≥2	31.2	3.526 (2.014-6.175)	**0.000***	0.652 (0.284-1.495)	0.312
NCCN-IPI score	0-1	41.7	Ref.			
	2-3	39.1	4.087 (2.327-7.181)	**0.000***	0.972 (0.437-2.161)	0.944
	4-5	31.8				
	6-8	20.3				
B symptoms	absent	35.6	Ref.			
	present	37.7	1.186 (0.646-2.181)	0.582		
Total protein	normal	37.2	Ref.			

	decreased	37.1	0.878 (0.486-1.587)	0.667		
Albumin	normal	37.5	Ref.			
	decreased	36.9	0.996 (0.542-1.687)	0.876		
Hemoglobin	normal	38.2	Ref.			
	decreased	36.2	1.093 (0.620-1.926)	0.758		
LDH ratio	<1× ULN	40.7	Ref.			
	1-3× ULN	31.5	3.331 (2.235-4.963)	**0.000***	1.952 (1.038-3.669)	**0.038***
	>3× ULN	22.3				
β2-MG	normal	40.1	Ref.			
	elevated	31.1	2.349 (1.328-4.154)	**0.003***	1.326 (0.646-2.719)	0.441
CRP	normal	38.8	Ref.			
	elevated	32.4	2.641 (1.495-4.665)	**0.001***	1.512 (0.753-3.035)	0.246
COO subtype	GCB	39.4	Ref.			
	non-GCB	35.9	2.550 (1.274-5.105)	**0.008***	0.651 (0.157-2.702)	0.555
CD10	negative	36.4	Ref.			
	positive	39.0	0.346 (0.156-0.772)	**0.009***	0.445 (0.102-1.936)	0.280
BCL6	negative	36.9	Ref.			
	positive	37.0	0.437 (0.236-0.808)	**0.008***	0.582 (0.279-1.214)	0.149
MUM1	negative	42.3	Ref.			
	positive	36.2	2.652 (0.943-7.460)	0.065	1.260 (0.270-5.888)	0.769
Ki67 index	<75%	45.0	Ref.			
	≥75%	34.2	1.601 (0.814-3.151)	0.173		
BCL2	negative	37.5	Ref.			
	positive	34.2	3.266 (1.525-6.994)	**0.002***	3.235 (1.285-8.146)	**0.013***

PFS: progress-free survival; HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; NCCN-IPI: National comprehensive cancer network International Prognostic Index; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin; CRP: C-reaction protein; COO: cell of origin; GCB: germinal center B-cell.

Figures

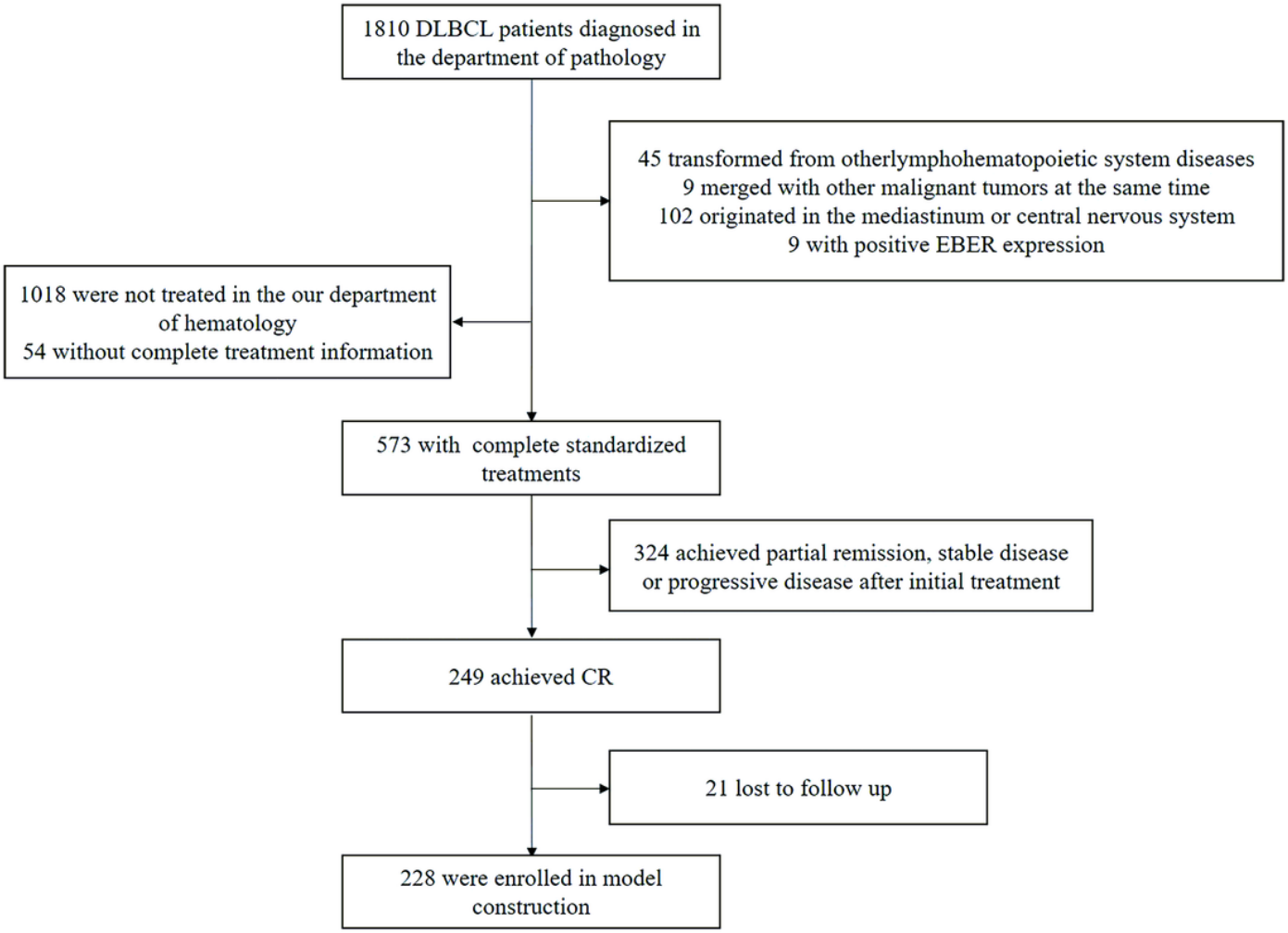

Figure 1

Patient selection.

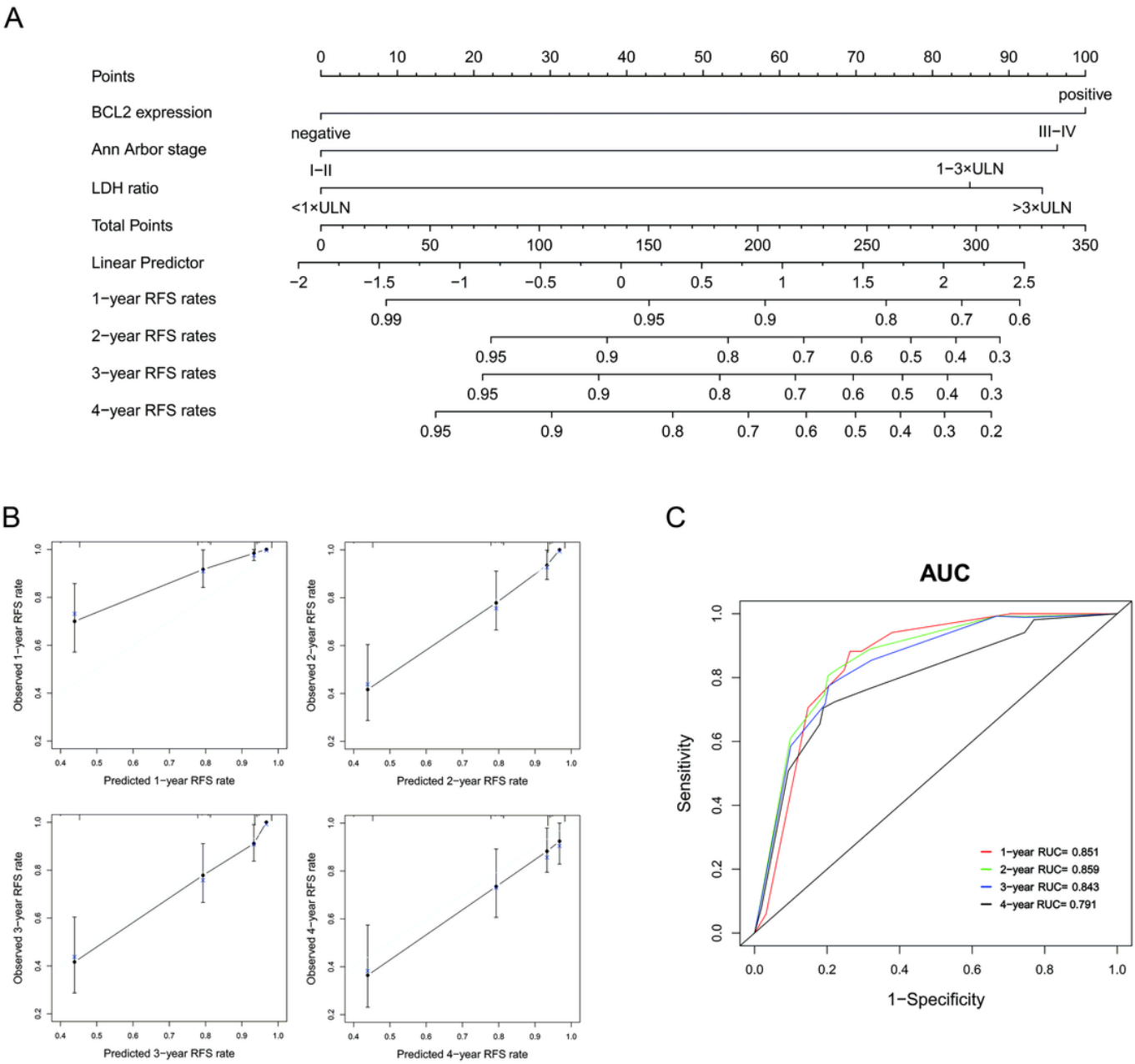

Figure 2

The ABL-nomogram and its predictive efficiency.

A. Nomogram (ABL-nomogram) incorporating BCL2 expression with Ann Arbor stage and LDH level for DLBCL. B. The calibration plots of nomogram.1 showing the predicted RFS rate on the x axis and the observed RFS on the y axis. C. The 1-year, 2-year, 3-year and 4-year AUROC was 0.851, 0.859, 0.843, and 0.791, respectively. RFS: recurrence-free survival; AUROC: area under receiver operating characteristic curves.

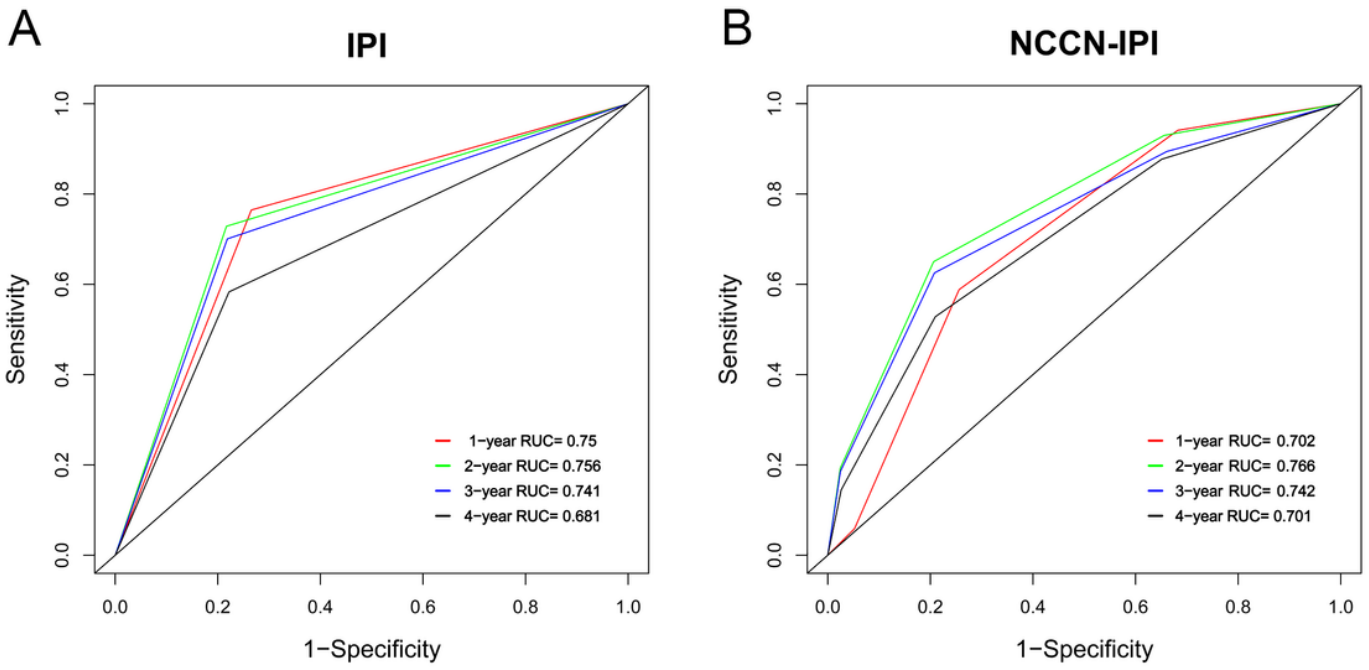

Figure 3

The predictive effectiveness of IPI system and NCCN-IPI system.

A. The 1-year, 2-year, 3-year and 4-year AUROC of IPI system was 0.75, 0.756, 0.741, and 0.681, respectively. B. The 1-year, 2-year, 3-year and 4-year AUROC of NCCN-IPI system was 0.702, 0.766, 0.742, and 0.701, respectively. RFS: recurrence-free survival; AUROC: area under receiver operating characteristic curves.

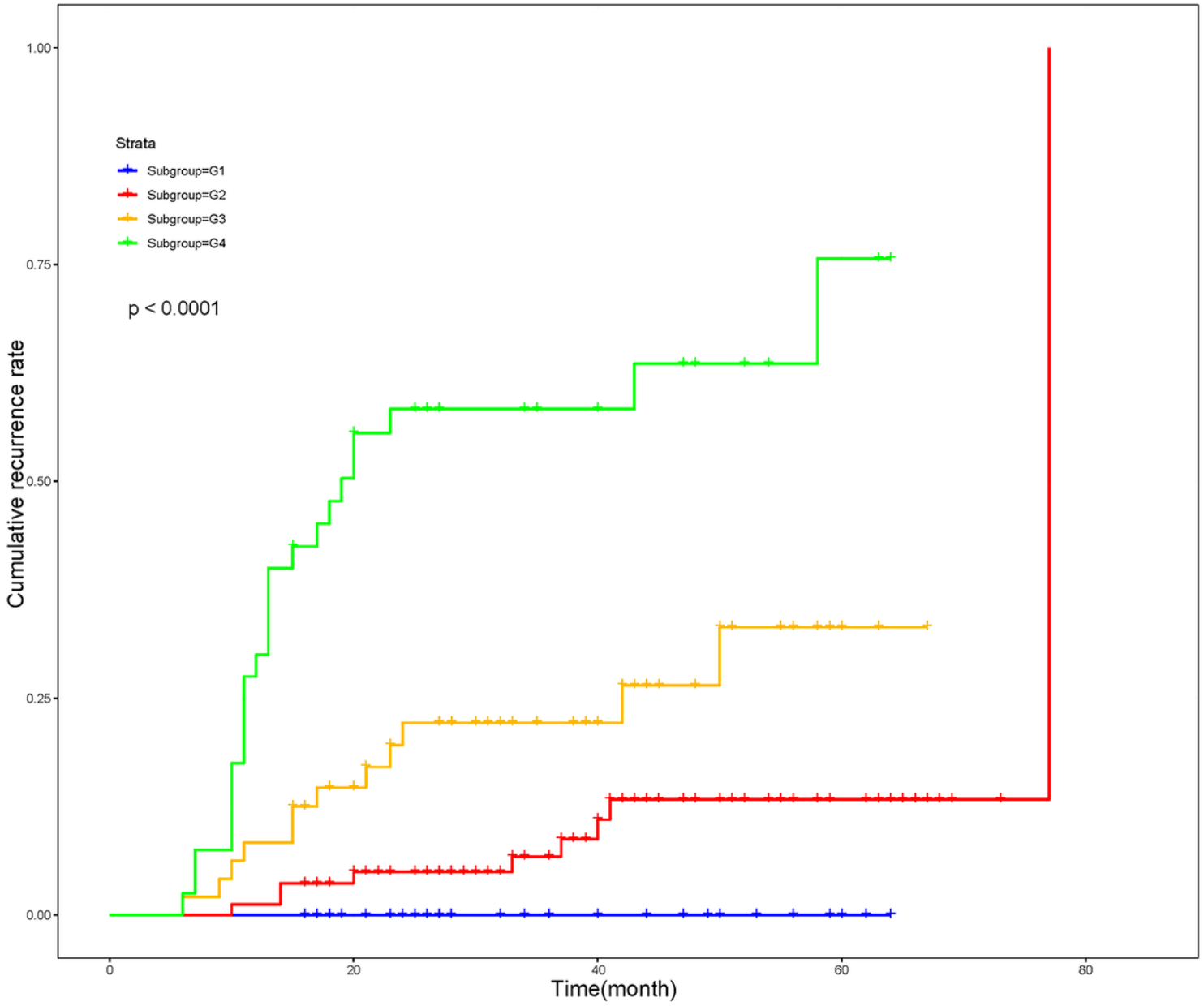

Figure 4

Kaplan-Meier cumulative recurrence curves of the DLBCL cohort. The cumulative recurrence rate of the four subgroups was 0, 12.2%, 25%, 62.5%, respectively. G1 subgroup: low recurrence risk, and total points =0; G2 subgroup: low-intermediate recurrence risk and total points =48/92/97/100; G3 subgroup: high-intermediate recurrence risk and total points =140/148/189/192/197; G4 subgroup: high recurrence risk and total points =240/289.