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RESEARCH ARTICLE

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Construction and validation of prognostic scoring models to risk stratify patients with acquired immune deficiency syndrome-related diffuse large B cell lymphoma

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Abstract

Acquired immune deficiency syndrome (AIDS)-related diffuse large B cell lymphoma (AR-DLBCL) is a rare disease with a high risk of mortality. There is no specific prognostic model for patients with AR-DLBCL. A total of 100 patients diagnosed with AR-DLBCL were enrolled in our study. Clinical features and prognostic factors for overall survival (OS) and progression-free survival (PFS) were evaluated by univariate and multivariate analyses. Central nervous system (CNS) involvement, opportunistic infection (OI) at lymphoma diagnosis, and elevated lactate dehydrogenase (LDH) were selected to construct the OS model; CNS involvement, OI at lymphoma diagnosis, elevated LDH, and over four chemotherapy cycles were selected to construct the PFS model. The area under the curve and C-index of GZMU OS and PFS models were 0.786/0.712; 0.829/0.733, respectively. The models we constructed showed better risk stratification than International Prognostic Index (IPI), age-adjusted IPI, and National Comprehensive Cancer Network-IPI. Furthermore, in combined cohort, the Hosmer–Lemeshow test showed that the models were good fits (OS: $p = 0.8244$; PFS: $p = 0.9968$) and the decision curve analysis demonstrated a significantly better net benefit. The prognostic efficacy of the proposed models was validated independently and outperformed the

Han Zhao, Rongqiu Liu, Yu Tao, and Luca Bertero contributed equally to this work.

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currently available prognostic tools. These novel prognostic models will help to tackle a clinically relevant unmet need.

KEYWORDS
acquired immune deficiency syndrome, diffuse large B cell lymphoma, human immunodeficiency virus, prognostic model, risk stratification

1 | INTRODUCTION

Human immunodeficiency virus (HIV) infection significantly increases the risk of malignancy. More than 28% of HIV-related deaths are due to malignant tumors and more than 40% of HIV-infected people are eventually diagnosed with acquired immunodeficiency syndrome (AIDS)-related lymphoma (ARL).[1] Before the era of combined antiretroviral therapy (cART), the incidence of AIDS-related tumors was significantly higher in this population compared to the non-AIDS population, particular for lymphoma.[2] Incidence of ARL was over 100 times greater among patients with AIDS.[3]

With the introduction of cART, the incidence of ARL and AIDS-related deaths have significantly decreased, but AIDS-related tumors remain an important health problem among patients with HIV.

AIDS-related diffuse large B cell lymphoma (AR-DLBCL) is one of the most common ARL subtype, accounting for approximately 45% of these tumors.[4–6] A previous study showed that the 2-year overall survival (OS) of AR-DLBCL increased to 60%–70% thanks to the use of cART, achieving survival rates similar to HIV-negative patients.[7] However, ARL remains one of the leading causes of the death in AIDS patients.[8–10] Compared with DLBCL patients without HIV infection, AR-DLBCL often presents at an advanced disease stage, with extra-nodal (EN) involvement, high risk of infection and the overall prognosis remains unsatisfactory.[11] Therefore, early diagnosis and treatment of AR-DLBCL is critical.

The International Prognostic Index (IPI) was first proposed in 1993 to provide a model for predicting outcome in patients with aggressive NHL on the basis of clinical characteristics before treatment.[12] IPI score consists of five variables: age over 60 years, advanced stage, elevated lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2–4, and more than one EN location. While age-adjusted IPI (aaIPI) includes LDH, ECOG PS, and stage only, and is suitable for patients under 60 years old. Compared with IPI, National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) further stratifies the age and LDH to better discriminate patients in low- and high-risk subgroups especially among DLBCL patients in the rituximab era.[13]

The above models have been applied to the overall population of DLBCL patients showing a good prognostic efficacy of non-AIDS patients. Some studies revealed that IPI or aaIPI is strongly correlated with the prognosis of AR-NHL, and its components have previously been shown as prognostic factors of OS and progression-free survival (PFS) in NHL patients with HIV infection.[14–17] However, studies focusing on AR-DLBCL are relatively small and data regarding prognostic factors and outcomes in patients with AR-DLBCL treated in the cART era remains scarce and specific prognostic model for these patients was still missing. In this study, through a retrospective clinical data analysis of a large series of patients with AR-DLBCL, we tried to develop a simple and accessible prognostic model for risk stratification of these patients.

2 | METHODS

2.1 | Patients and study design

We collected data on patients with AR-DLBCL diagnosed from January 2011 to January 2022 in the Guangzhou Eighth People's Hospital, Guangzhou Medical University. The entire cohort was composed of two series: a training cohort of 84 patients and a validation cohort of 16 patients, depending on two searches with different ICD codes from patients' electronic medical records. Briefly, in the first time of search, ICD code B24.x01 (AIDS patients) and ICD code M96803/3 or C83.306 (DLBCL patients) were used; in accordance with inclusion and exclusion criteria, 84 patients were enrolled in the training cohort. Due to the variations of ICD code filings by different doctors, we conducted a second search as a supplement. In addition to ICD code B24.x01 (AIDS patients), we searched ICD code M95910/3 or C85.900 (NHL patients) and ICD code M95900/3 or C83.811 (lymphoma patients); in accordance with inclusion and exclusion criteria, 16 patients were enrolled in the validation cohort. The flowchart of patient selection is shown on Supporting Information: Figure S1. All adults >18 years diagnosed with AR-DLBCL were included. All patients had a definite diagnosis of DLBCL by pathological examination after a review by two independent pathologists who re-evaluated hematoxylin-eosin slides, immunohistochemical staining, and fluorescence in situ hybridization results in accordance with the diagnostic criteria provided by the 2016 revision of the World Health Organization classification of lymphoid neoplasms.[18] The diagnosis of AIDS met the standards of the 2021 Chinese guidelines for diagnosis and treatment of HIV/AIDS.[19] Patients with other active malignancies were excluded.

Demographic information, clinical characteristics, and outcome data were obtained from patients' electronic medical records, including the age, gender, HIV infection route, the number and site of EN lesion, ECOG PS, Ann Arbor stage, B symptoms, bulky disease, coinfection, Hans classification algorithm, LDH, HIV RNA, $CD4^+$ T cell

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count, and treatment pattern of the patients. Patients were classified into four levels of risk according to IPI, aaIPI, and NCCN-IPI. Lymphoma staging was performed according to the Ann Arbor system and included physical examination, routine laboratory tests, computed tomography, or positron emission tomography.[20]

Variables identified as significant factors in the univariate Cox analysis were selected into the multivariate Cox proportional hazards regression analysis to identify the independent prognostic factors using the Forward Stepwise (conditional LR) method; the screened factors were introduced into the logistic regression equation to calculate the prediction probability of an outcome and to draw the receiver operating characteristic curve. The area under the curve (AUC) and Harrell's concordance index (C-index) were compared. The Hosmer–Lemeshow test was used to assess the goodness of fit of the model. The decision curve analysis (DCA) was used to reflect the net benefit of the model.

2.2 | Outcomes and definitions

The primary outcomes of interest of this study were OS and progression-free survival (PFS). The last follow-up data was August 31, 2022. OS was defined as the time from DLBCL diagnosis to last follow-up or death from any cause. PFS was defined as the time from DLBCL diagnosis to disease progression, relapse or death from any cause.

2.3 | Statistical analysis

Continuous variables were presented as the medians and interquartile ranges (IQR), and categorical variables were presented as frequencies and percentages (%). χ^2 test was used for categorical variables, and the Mann–Whiney *U* test or *t*-test for continuous variables. The survival curves were plotted using the Kaplan–Meier method, and the log-rank test was used to compare the difference between curves. The Cox hazards model was performed for the univariate and multivariate analyses, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated. The optimal cutoff values were determined by using X-tile 3.6.1 software. A detailed variable importance analysis was conducted by coxphERR package in R. SPSS version 25.0, GraphPad Prism 8 and R software were used for statistical analyses. Differences were considered statistically significant when $p < 0.05$.

3 | RESULTS

3.1 | Baseline characteristic of AR-DLBCL patients

A total of 100 AR-DLBCL patients were enrolled in the present retrospective study. In the training cohort, the median age of the patients was 46 (IQR: 39–55) years old, and 72 (85.71%) were male. Among these patients, 11 cases (13.1%) were older than 60 years old; in 58 cases (69.05%), HIV and AR-DLBCL diagnoses were synchronous; 39.29% ($n = 33$) of the patients had ≥2 EN sites of disease; 3.57% ($n = 3$) had central nervous system (CNS) involvement and 7 cases (8.33%) had bone marrow involvement; 51 cases (60.71%) had advanced stage disease; 46 cases (54.76%) had an ECOG PS 2–4; 27.38% ($n = 23$) of patients had evidence of B symptoms at diagnosis, including fevers, weight loss, and night sweats, and 24 cases (28.58%) had bulky disease. 23.81% ($n = 20$) of AR-DLBCL patients were diagnosed with an opportunistic infection (OI) at the time of lymphoma diagnosis; LDH was evaluated in 76.19% of the patients ($n = 64$). The median time between HIV diagnosis and lymphoma diagnosis was 45 months, ranging between 8 and 124 months. The main route of HIV infection was through sexual transmission in 36 cases (42.86%). Using the Hans algorithm, 51 cases (60.71%) were classified as GCB, 13 cases (15.48%) were classified as non-GCB, and 20 cases (23.81%) were unclassified. Regarding HIV characteristics, the median $CD4^+$ T cell count was 89 cells per microliter (range: 4–2084 cells per microliter) with 59 patients (70.24%) presenting with $CD4^+$ T cell count <200 cells per mL. At the time of AR-DLBCL diagnosis, HIV viral load was detectable in 60.72%, undetectable in 28.57%, not examined in 10.71%. Baseline characteristics of the training cohort and the validation cohort were compared as described on Table 1.

3.2 | Treatment and survival analysis

The median PFS and OS for AR-DLBCL patients received chemotherapy were 36 and 42 months, and the overall 2-year PFS and OS rates were 52.75% and 56.65%, respectively (Supporting Information: Figure S2A,B), and the median OS was 33 months, in the training cohort. Among the 100 AR-DLBCL patients, most patients received chemotherapy and cART treatment. Sixty-nine patients (82.14%) received cART treatment and 70 (83.33%) patients received chemotherapy in the training cohort. Fifteen patients (93.75%) received cART treatment, and 14 (87.5%) patients received chemotherapy in the validation cohort. No significant difference was observed in terms of OS between patients who received chemotherapy (Supporting Information: Figure S2C, $p = 0.23$), or cART (Supporting Information: Figure S2D, $p = 0.69$) and those who did not.

In the whole cohort, when the relationship between treatment regimens and clinical outcomes were evaluated, no significance differences in terms of OS and PFS were observed between AR-DLBCL patients who received a CHOP based regimen, an EPOCH based regimen or other regimens (Figure 1A, $p = 0.094$; Figure 1B, $p = 0.079$). The rituximab-containing regimen was not associated with a different outcome considering either OS (Figure 1C, $p = 0.19$) or PFS (Figure 1D, $p = 0.16$). According to the numbers of therapy cycles, the median OS in patients who received 1–4 cycles and >4 cycles were 9 months and not reached, respectively (Figure 1E, $p < 0.0001$) and the median PFS in 1–4 cycles and >4 cycles were 7 months and not reached, respectively (Figure 1F, $p < 0.0001$).

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TABLE 1 Demographic and clinical features at AR-DLBCL patients in the training cohort and validation cohort.

	Combined N = 100 (%)	Training cohort N = 84 (%)	Validation cohort N = 16 (%)	p Value
Age				
Median, IQR	47 (39–56)	46 (39–55)	49 (37–59)	0.880
≤60	87 (87.00%)	73 (86.90%)	14 (87.50%)	1.000
60	13 (13.00%)	11 (13.10%)	2 (12.50%)	
Gender				
Male	84 (84.00%)	72 (85.71%)	12 (75.00%)	0.484
Female	16 (16.00%)	12 (14.29%)	4 (25.00%)	
HIV infection route				
Heterosexual	40 (40.00%)	32 (38.10%)	8 (50.00%)	0.261
Homosexual	5 (5.00%)	4 (4.76%)	1 (6.25%)	
Bisexual	3 (3.00%)	2 (2.38%)	1 (6.25%)	
Intravenous drug use	8 (8.00%)	6 (7.14%)	2 (12.50%)	
Unknown	44 (44.00%)	40 (47.62%)	4 (25.00%)	
AIDS before lymphoma diagnosis (>6 months)				
Yes	31 (31.00%)	26 (30.95%)	5 (31.25%)	1.000
Concurrent	69 (69.00%)	58 (69.05%)	11 (68.75%)	
Extra-nodal sites				
<2	63 (63.00%)	51 (60.71%)	12 (75.00%)	0.278
≥2	37 (37.00%)	33 (39.29%)	4 (25.00%)	
CNS involvement	4 (4.00%)	3 (3.57%)	1 (6.25%)	0.508
BM involvement	10 (10.00%)	7 (8.33%)	3 (18.75%)	0.413
Histologic subtype				
GCB	63 (63.00%)	51 (60.71%)	12 (75.00%)	0.296
Non-GCB	16 (16.00%)	13 (15.48%)	3 (18.75%)	
Unclassified	21 (21.00%)	20 (23.81%)	1 (6.25%)	
ECOG PS				
0–1	47 (47.00%)	38 (45.24%)	9 (56.25%)	0.419
2–4	53 (53.00%)	46 (54.76%)	7 (43.75%)	
Ann Arbor stage				
Stage I–II	41 (41.00%)	33 (39.29%)	8 (50.00%)	0.425
Stage III–IV	59 (59.00%)	51 (60.71%)	8 (50.00%)	
B symptoms				
No	72 (72.00%)	61 (72.62%)	11 (68.75%)	0.990
Yes	28 (28.00%)	23 (27.38%)	5 (31.25%)	
Bulky disease (≥7.5 cm)				
No	71 (71.00%)	60 (71.43%)	11 (68.75%)	1.000
Yes	29 (29.00%)	24 (28.57%)	5 (31.25%)	
Opportunistic infection at lymphoma diagnosis				
No	76 (76.00%)	64 (76.19%)	12 (75.00%)	1.000
Yes	24 (24.00%)	20 (23.81%)	4 (25.00%)	

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TABLE 1 (Continued)

	Combined *N* = 100 (%)	Training cohort *N* = 84 (%)	Validation cohort *N* = 16 (%)	*p* Value
IPI				
0–1	35 (35.00%)	26 (30.95%)	9 (56.25%)	0.341
2	16 (16.00%)	14 (16.67%)	2 (12.50%)	
3	19 (19.00%)	17 (20.24%)	2 (12.50%)	
4–5	30 (30.00%)	27 (32.14%)	3 (18.75%)	
aaIPI				
0	14 (14.00%)	12 (14.28%)	2 (12.5%)	0.336
1	25 (25.00%)	18 (21.43%)	7 (43.75%)	
2	22 (22.00%)	19 (22.62%)	3 (18.75%)	
3	39 (39.00%)	35 (41.67%)	4 (25.00%)	
NCCN-IPI				
0–1	11 (11.00%)	8 (9.52%)	3 (18.75%)	0.277
2–3	36 (36.00%)	28 (33.34%)	8 (50.00%)	
4–5	42 (42.00%)	38 (45.24%)	4 (25.00%)	
≥6	11 (11.00%)	10 (11.90%)	1 (6.25%)	
LDH				
Normal	24 (24.00%)	20 (23.81%)	4 (25.00%)	1.000
Elevated	76 (76.00%)	64 (76.19%)	12 (75.00%)	
HIV RNA (copies/mL)				
<1 × 10^5	37 (37.00%)	34 (40.48%)	3 (18.75%)	0.045
≥1 × 10^5	19 (19.00%)	17 (20.24%)	2 (12.50%)	
Undetectable	29 (29.00%)	24 (28.57%)	5 (31.25%)	
Not examined	15 (15.00%)	9 (10.71%)	6 (37.50%)	
$CD4^+$ T cell count (/uL)				
Median (range)	135 (4–2084)	89 (4–2084)	174 (20–579)	0.484
<200	71 (71.00%)	59 (70.24%)	12 (75.00%)	0.933
≥200	29 (29.00%)	25 (29.76%)	4 (25.00%)	
cART				
Yes	84 (84.00%)	69 (82.14%)	15 (93.75%)	0.430
No	16 (16.00%)	15 (17.86%)	1 (6.25%)	
Chemotherapy				
Yes	84 (84.00%)	70 (83.33%)	14 (87.50%)	0.964
No	16 (16.00%)	14 (16.67%)	2 (12.50%)	
	***n* = 84**	***n* = 70**	***n* = 14**	
Chemotherapy regimen				
CHOP based regimen	42 (50.00%)	41 (58.57%)	1 (7.14%)	0.000
EPOCH based regimen	28 (33.33%)	18 (25.72%)	10 (71.43%)	
Other regimens	14 (16.67%)	11 (15.71%)	3 (21.43%)	
Rituximab-containing regimen	61 (72.62%)	49 (70.00%)	12 (85.71%)	0.381

(Continues)

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TABLE 1 (Continued)

	n = 84	*n* = 70	*n* = 14	
Chemotherapy cycle				
0	16 (16.00%)	14 (16.67%)	2 (12.50%)	0.705
1–4	33 (33.00%)	29 (34.52%)	4 (25.00%)	
>4	51 (51.00%)	41 (48.81%)	10 (62.50%)	
Status at the end of the follow-up				
Alive	58 (58.00%)	45 (53.57%)	13 (81.25%)	0.040
Dead	42 (42.00%)	39 (46.43%)	3 (18.75%)	

Abbreviations: aaIPI, age-adjusted IPI; AR-DLBCL, AIDS-related diffuse large B cell lymphoma; BM, bone marrow; cART, combined antiretroviral therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CNS, central nervous system; ECOG PS, Eastern cooperative oncology group performance status; EPOCH, etoposide, prednisone, oncovin, cyclophosphamide, and hydroxydaunorubicin; IPI, international prognostic index; IQR, interquartile range; LDH, lactate dehydrogenase; NCCN-IPI, national comprehensive cancer network IPI.

3.3 | Prognostic factors associated with AR-DLBCL patients in the training cohort

We conducted univariate and multivariate analysis for risk factors of OS and PFS in patients with AR-DLBCL. In univariate analysis, CNS involvement (hazard ratio [HR] = 4.278, 95% CI: 1.293–14.157, $p = 0.017$), ECOG PS 2–4 (HR = 2.208, 95% CI: 1.131–4.312, $p = 0.02$), OI at lymphoma diagnosis (HR = 2.833, 95% CI: 1.493–3.572, $p = 0.001$), elevated LDH (HR = 5.500, 95% CI: 1.685–17.95, $p = 0.005$), and not exceeding 4 chemotherapy cycles (HR = 0.372, 95% CI: 0.145–0.952, $p = 0.039$) were associated with shorter OS; CNS involvement (HR = 5.300, 95% CI: 1.566–17.932, $p = 0.007$), OI at lymphoma diagnosis (HR = 2.916, 95% CI: 1.423–5.975, $p = 0.003$), elevated LDH (HR = 4.564 95% CI; 1.381–15.08, $p = 0.013$), and no more than 4 chemotherapy cycles (HR = 0.267, 95% CI: 0.130–0.549, $p = 0.000$) were associated with shorter PFS in univariate analysis. In multivariate analysis, our analysis suggested that CNS involvement (HR = 7.97, 95% CI: 2.161–29.391, $p = 0.002$), OI at lymphoma diagnosis (HR = 2.671, 95% CI: 1.404–5.080, $p = 0.003$), and elevated LDH (HR = 7.766, 95% CI: 2.161–27.908, $p = 0.002$) were independent prognostic variables of OS; CNS involvement (HR = 8.341, 95% CI: 2.166–32.110, $p = 0.002$), OI at lymphoma diagnosis (HR = 4.063, 95% CI: 1.834–9.002, $p = 0.001$), elevated LDH (HR = 4.745, 95% CI: 1.291–17.432, $p = 0.019$), and over 4 chemotherapy cycles (HR = 0.208, 95% CI: 0.092–0.471, $p = 0.000$) were independent prognostic variables of PFS as shown on Table 2.

3.4 | Construction of new prognostic models in the training cohort

Then, we developed a novel prognostic model for OS termed GZMU OS model, based on three independent adverse factors including CNS involvement, OI at lymphoma diagnosis, and elevated LDH; while CNS involvement, OI at lymphoma diagnosis, elevated LDH, and over 4 chemotherapy cycles consisted of a novel prognosis model for PFS, which called GZMU PFS model. Cox proportional hazards regression analysis was performed to assess the association between survival and the independent factors in the training dataset. The risk score was calculated for each patient using the formula from the multivariable Cox regression, which was expressed as follow:

$$\begin{aligned}&\text{Risk score of GZMU OS model}\\&= (2.076 \times \text{CNS involvement})\\&\quad + (0.982 \times \text{OI at lymphoma diagnosis})\\&\quad + (2.05 \times \text{elevated LDH});\end{aligned}$$

$$\begin{aligned}&\text{Risk score of GZMU PFS model}\\&= (2.121 \times \text{CNS involvement})\\&\quad + (1.402 \times \text{OI at lymphoma diagnosis})\\&\quad + (1.557 \times \text{elevated LDH})\\&\quad + (-1.571 \times \text{over 4 chemotherapycycle}).\end{aligned}$$

We then conducted a detailed variable importance analysis of GZMU OS model and GZMU PFS model, which were showed in Supporting Information: Figure S3A,B. According to the explained relative risk (ERR) and standard error of ERR (se ERR), it is noticed that elevated LDH is the dominant factor in the GZMU OS model, while >4 chemotherapy cycles is the dominant factor in the GZMU PFS model.

Patients were divided into different risk groups with the new prognostic models using X-tile (Supporting Information: Figure 4–5A-C; D-F). As for OS, two groups stratification performed better in terms of AUC and C-index compared to a stratification based on three groups (Figure 2A,B); whereas, three risk groups showed better AUC and C-index than two risk groups for PFS (Figure 2C,D). Therefore, patients were divided into two risk groups with GZMU OS model for OS and three risk groups with GZMU PFS model for PFS.

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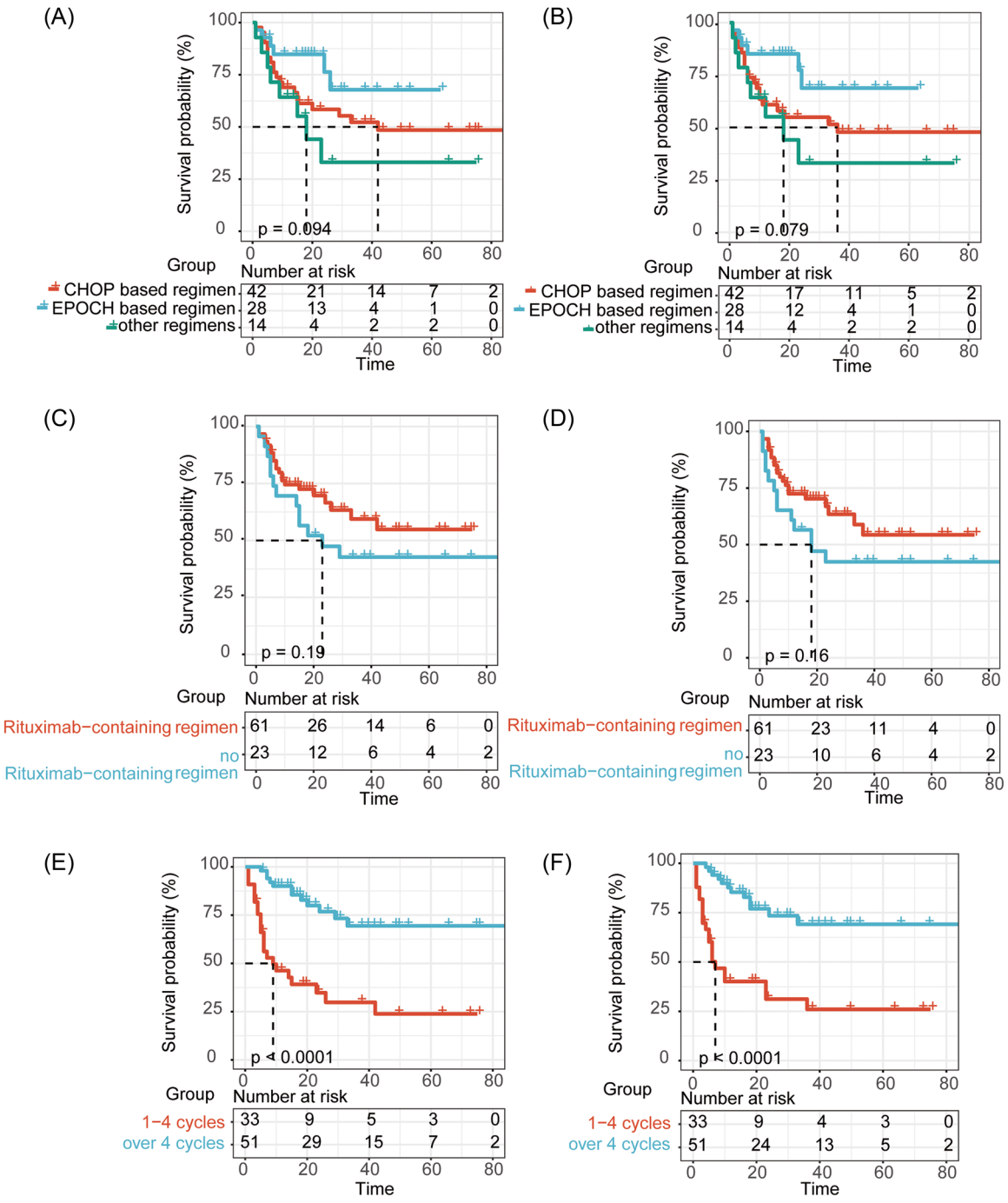

FIGURE 1 Survival by chemotherapy regimens and cycles. Kaplan–Meier curves of different chemotherapy regimens and cycles for OS and PFS in AR-DLBCL patients. (A) OS and (B) PFS for AR-DLBCL patients with EPOCH based regimen, CHOP based regimen and other regimen (OS, $p = 0.094$; PFS, $p = 0.079$); (C) OS and (D) PFS for AR-DLBCL patients with rituximab-containing regimen and without rituximab-containing regimen (OS, $p = 0.19$; PFS, $p = 0.16$); (E) OS and (F) PFS for AR-DLBCL patients with 1–4 cycles and >4 cycles (OS, $p < 0.0001$; PFS, $p < 0.0001$). AR-DLBCL, diffuse large B cell lymphoma; OS, overall survival; PFS, progression-free survival.

3.5 | Comparation of Kaplan–Meier curves with different prognostic models in the training cohort and the validation cohort

The Kaplan–Meier curves with different risk groups stratified by GZMU OS model, IPI, aaIPI, and NCCN-IPI for OS were showed in Figure 3A-D. The GZMU OS model could clearly distinguish different risk groups for OS better than IPI, aaIPI, and NCCN-IPI. According to the GZMU OS model, the median OS for the high- and the low-risk group patients were 6 months and not reached ($p < 0.0001$) as shown on Figure 3A. Due to the optimal cutoff values of the GZMU OS model were determined by X-tile, we also reorganized risk groups

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TABLE 2 Univariable and multivariable Cox regression analysis for OS and PFS in the training cohort.

	OS						PFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age												
≤60 & 60	0.757	0.269–2.132	0.599				0.514	0.123–2.152	0.362			
Gender												
Male & female	0.649	0.23–1.827	0.413				0.576	0.175–1.896	0.364			
Extra-nodal involvement												
No & yes	1.254	0.644–2.441	0.506				1.184	0.569–2.462	0.651			
Extra-nodal involved site												
<2 & ≥2	1.172	0.613–2.243	0.631				0.907	0.428–1.922	0.298			
CNS involvement												
No & yes	4.278	1.293–14.157	**0.017**	7.970	2.161–29.391	**0.002**	5.300	1.566–17.932	**0.007**	8.341	2.166–32.110	**0.002**
BM involvement												
No & yes	1.054	0.375–2.968	0.920				1.079	0.378-3.079	0.887			
Histologic subtype												
Non-GCB & GCB	1.365	0.522–3.570	0.526				1.164	0.434–3.120	0.763			
ECOG PS												
0–1 & 2–4	2.208	1.131–4.312	**0.020**				1.97	0.942–4.119	0.072			
Ann Arbor stage												
I–II & III–IV	1.334	0.692–2.571	0.389				1.305	0.635–2.683	0.469			
B symptoms												
No & yes	1.008	0.501–2.026	0.983				0.894	0.413–1.935	0.777			
Bulky disease												
No & yes	1.650	0.835–3.259	0.149				1.835	0.878–3.837	0.107			
Opportunistic infection at lymphoma diagnosis												
No & yes	2.833	1.493–5.372	**0.001**	2.671	1.404–5.080	**0.003**	2.916	1.423–5.975	**0.003**	4.063	1.834–9.002	**0.001**
IPI			0.503						0.408			
0–1	Ref						Ref					

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TABLE 2 (Continued)

Variable	OS						PFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
2	1.597	0.815–4.143	0.336				1.941	0.700–5.380	0.202			
3	1.718	0.679–4.344	0.253				2.264	0.839–6.109	0.107			
4–5	1.903	0.810–4.471	0.140				1.522	0.545–4.256	0.423			
aaIPI			0.089						0.203			
0	Ref						Ref					
1	7.846	0.993–61.986	0.051				7.946	0.977–64.616	0.053			
2	7.007	0.884–55.562	0.065				7.735	0.975–61.372	0.053			
3	11.300	1.511–84.518	**0.018**				9.218	1.210–70.248	**0.032**			
NCCN-IPI			0.303						0.425			
0–1	Ref						Ref					
2–3	4.270	0.558–32.685	0.162				3.824	0.493–29.654	0.199			
4–5	5.599	0.747–41.953	0.094				5.036	0.666–38.112	0.117			
≥6	6.684	0.803–55.641	0.079				5.234	0.577–47.455	0.141			
LDH												
Normal & elevated	5.500	1.685–17.95	**0.005**	7.766	2.161–27.908	**0.002**	4.564	1.381–15.08	**0.013**	4.745	1.291–17.432	**0.019**
HIV RNA (copies/mL)												
<1 × 10^5 & ≥1 × 10^5	0.582	0.242–1.400	0.227				0.561	0.226–1.389	0.211			
CD4 cell count (/uL)												
<200 & ≥200	0.678	0.329–1.397	0.292				0.580	0.260–1.293	0.183			
cART												
No & yes	1.124	0.471–2.686	0.792				1.707	0.519–5.618	0.379			
Chemotherapy												
No & yes	0.699	0.307–1.591	0.393									
Chemotherapy regimen			0.355						0.336			
CHOP based regimen	Ref						Ref					
EPOCH based regimen	0.639	0.239–1.704	0.370				0.579	0.217–1.546	0.276			
Other regimens	1.482	0.624–3.517	0.373				1.373	0.579–3.254	0.471			

(Continues)

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TABLE 2 (Continued)

Variable	OS						PFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Chemotherapy cycle			**0.010**									
0	Ref											
1–4	1.407	0.593–3.338	0.439				Ref					
>4	0.372	0.145–0.952	**0.039**				0.267	0.130–0.549	**0.000**	0.208	0.092–0.471	**0.000**

Note: The bold values mean $p < 0.05$. Differences were considered statistically significant when $p < 0.05$.

Abbreviations: aaIPI, age-adjusted IPI; B symptoms, consisting of fever >38°C, night sweats and/or unintentional weight loss of >10% the body weight over a period of up to 6 months; cART, combined antiretroviral therapy; CI, confidence interval; CNS, central nervous system; ECOG, Eastern cooperative oncology group; HIV, human immunodeficiency virus; HR, hazard ratio; IPI, international prognostic index; LDH, lactate dehydrogenase; NCCN-IPI, national comprehensive cancer network-IPI; OS, overall survival; PFS, progressive free survival; Ref, reference.

based IPI, aaIPI, and NCCN-IPI scores using X-tile. Then the Kaplan–Meier curves with different risk groups based on IPI, aaIPI, and NCCN-IPI for OS were showed in Supporting Information: Figure S6A-C. Because patients were divided into two risk groups by GZMU OS model for OS, patients were also divided into two risk groups by IPI, aaIPI, and NCCN-IPI scores and the Kaplan–Meier survival analysis were performed on Supporting Information: Figure S6D-F. In the validation cohort, the Kaplan–Meier curves with different risk groups stratified by GZMU OS model, IPI, aaIPI, and NCCN-IPI for OS with the cutoffs defined by training cohort were showed in Figure 3E–H.

The Kaplan–Meier curves with different risk groups stratified by GZMU PFS model, IPI, aaIPI, and NCCN-IPI for PFS were showed in Figure 4A–D. The GZMU PFS prognostic model could clearly distinguish different risk groups for PFS better than IPI, aaIPI, and NCCN-IPI. According to the GZMU PFS model, the median PFS for the high-, the intermediate,- and the low-risk group patients were 4 months, 18 months, and not reached, respectively ($p < 0.0001$) as shown on Figure 4A. Then the Kaplan–Meier curves with different risk groups based on IPI, aaIPI, and NCCN-IPI scores using X-tile for PFS were showed in Supporting Information: Figure S7A-C. Because patients were divided into three risk groups by GZMU PFS model for PFS, patients were also divided into three risk groups by IPI, aaIPI, and NCCN-IPI scores and the Kaplan–Meier survival analysis were performed on Supporting Information: Figure S7D-F. The Kaplan–Meier curves with different risk groups stratified by GZMU PFS model, IPI, aaIPI, and NCCN-IPI for PFS in the validation cohort were showed in Figure 4E–H.

3.6 | Comparation of Kaplan–Meier curves with different risk groups in subgroup analysis

We performed subgroup analyses for age, clinical stage, and molecular subtypes. Taking the overall cohort as the analysis object, it is seen that both GZMU OS and GZMU PFS models were suitable for patients at age ≤60 years (Supporting Information: Figure S8A-B left panel); for the group of age >60 years, there was a tendency between different risk groups (Supporting Information: Figure S8A right panel), and GZMU PFS model was suitable for age >60 years group (Supporting Information: Figure S8B right panel). In addition, GZMU OS model was found suitable for Ann Arbor stage III–IV (Supporting Information: Figure S9A right panel), and there was a tendency that low risk group had better OS than high risk group for Ann Arbor I–II (Supporting Information: Figure S9A left panel), while GZMU PFS model was suitable for Ann Arbor stage I–II and III–IV (Supporting Information: Figure S9B). Furthermore, GZMU OS model was suitable for non-GCB subtype (Supporting Information: Figure S10A right panel), and a tendency was shown for non-GCB subtype that low risk group had better OS than high risk group (Supporting Information: Figure S10A left panel), while GZMU PFS model was suitable for GCB and non-GCB subtype (Supporting Information: Figure S10B).

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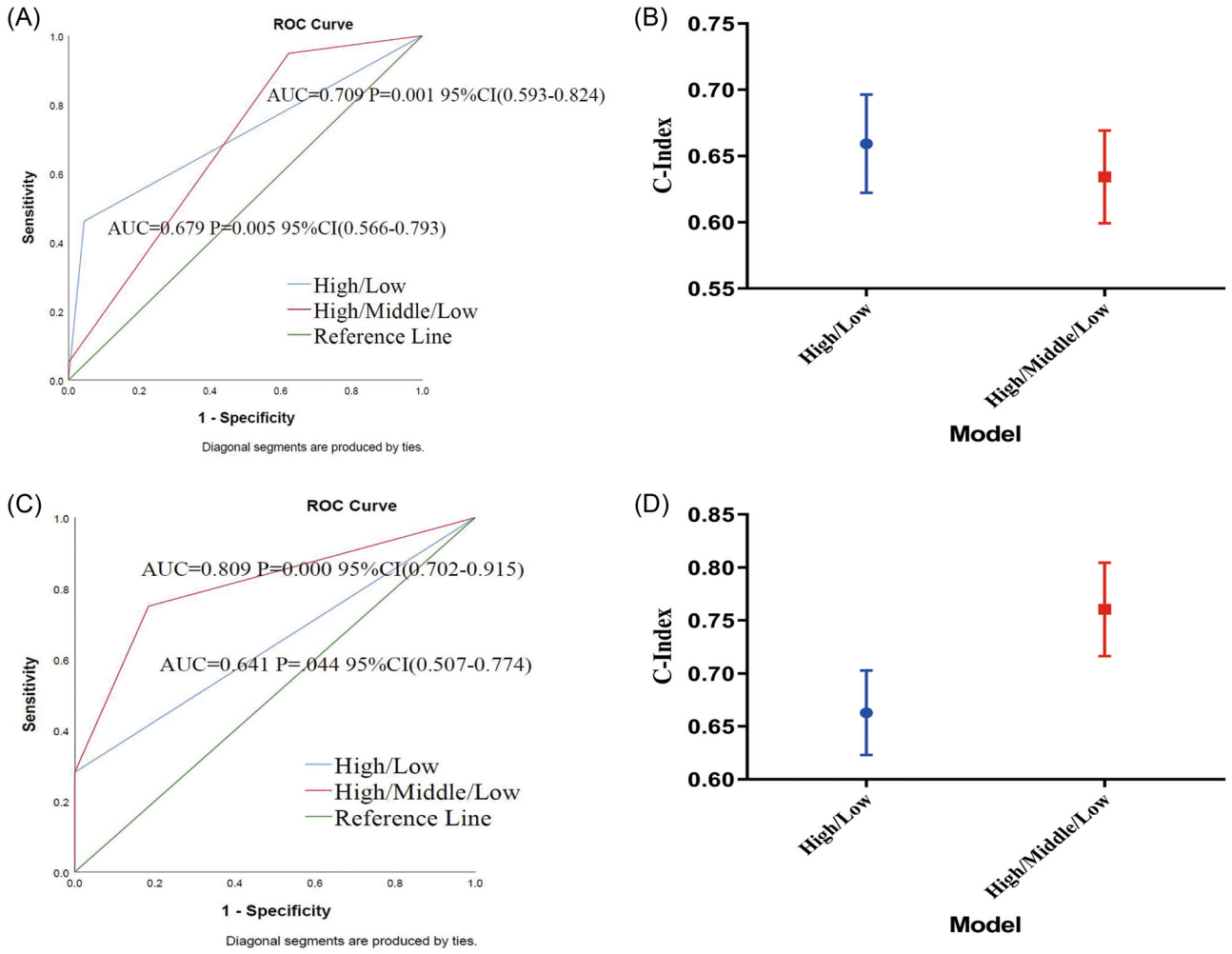

FIGURE 2 The comparison of AUC and C-index between two risk groups and three risk groups for OS and PFS by X-tile. The comparison of (A) AUC and (B) C-index between two risk groups (AUC = 0.709, 95% CI: 0.593–0.824, $p = 0.001$; C-index: 0.659) and three risk groups (AUC = 0.679, 95% CI: 0.566–0.793, $p = 0.005$; C-index: 0.634) for OS, two risk groups >three risk groups; the comparison of (C) AUC and (D) C-index between two risk groups (AUC = 0.641, 95% CI: 0.507–0.774, $p = 0.044$; C-index: 0.663) and three risk groups (AUC = 0.809, 95% CI: 0.702–0.915, $p = 0.000$; C-index: 0.76) for PFS, two risk groups <three risk groups. AUC, area under the curve; OS, overall survival; PFS, progression-free survival.

3.7 | Predictive accuracy of different prognostic models

Patients were classified into different risk stratification groups according to IPI, aaIPI, and NCCN-IPI scores, which were demonstrated on Supporting Information:Table 1 and the population distribution of different risk groups were shown on Supporting Information: Figure S11A-B. Then the AUC and C-index were compared between the novel models and these existing models. Both GZMU OS model and GZMU PFS model were the best model among these models. The predictive accuracy of prognostic model for OS, as measured by AUC was 0.786 (95% CI: 0.69–0.883), compared with 0.555 (95% CI: 0.431–0.678) of risk stratified by IPI, 0.638 (95% CI: 0.521–0.756) of risk stratified by aaIPI and 0.597 (95% CI: 0.447–0.718) of risk stratified by NCCN-IPI (Figure 5A). The C-index values based on GZMU OS model, IPI, aaIPI, and NCCN-IPI were 0.712, 0.577, 0.649, and 0.587, respectively (Figure 5B). The predictive accuracy of prognostic model for PFS, as measured by AUC was 0.829 (95% CI: 0.731–0.926), compared with 0.519 (95% CI: 0.382–0.655) of risk stratified by IPI, 0.609 (95% CI: 0.478–0.741) of the risk stratified by aaIPI, and 0.572 (95% CI: 0.438–0.706) of risk stratified by NCCN-IPI (Figure 5C). The C-index values based on GZMU PFS model, IPI, aaIPI, and NCCN-IPI were 0.733, 0.536, 0.591, and 0.563, respectively (Figure 5D).

In the validation cohort, the predictive accuracy of prognostic model for OS, as measured by AUC was 0.859, compared with 0.487 of risk stratified by IPI, 0.526 of risk stratified by aaIPI, and 0.641 of risk stratified by NCCN-IPI (Figure 5E). The C-index values based on GZMU OS model, IPI, aaIPI, and NCCN-IPI were 0.845, 0.512, 0.548, and 0.655, respectively (Figure 5F). The predictive accuracy of prognostic model for PFS, as measured by AUC was 0.958, compared with 0.583 of risk stratified by IPI, 0.583 of risk stratified by aaIPI,

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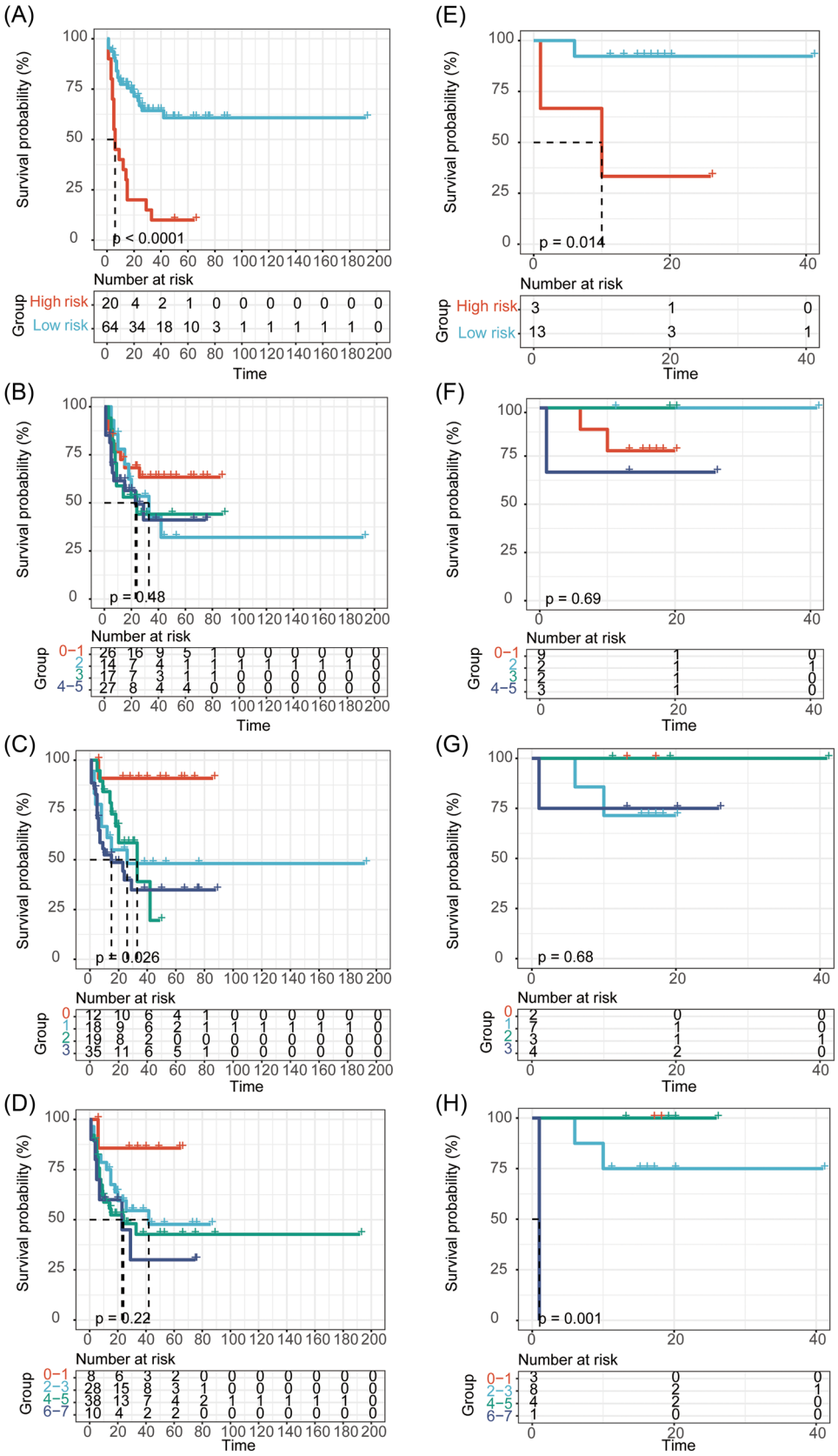

FIGURE 3 Overall survival (OS) analysis with different prognostic stratification models. Kaplan–Meier curves of (A) GZMU OS model ($p < 0.0001$), (B) IPI ($p = 0.48$), (C) aaIPI ($p = 0.026$), and (D) NCCN-IPI ($p = 0.22$) for OS in patients with AR-DLBCL in the training cohort; Kaplan–Meier curves of (E) GZMU OS model ($p = 0.014$), (F) IPI ($p = 0.69$), (G) aaIPI ($p = 0.68$), and (H) NCCN-IPI ($p = 0.001$) for OS in patients with AR-DLBCL in the validation cohort. AR-DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; NCCN-IPI, national comprehensive cancer network-IPI.

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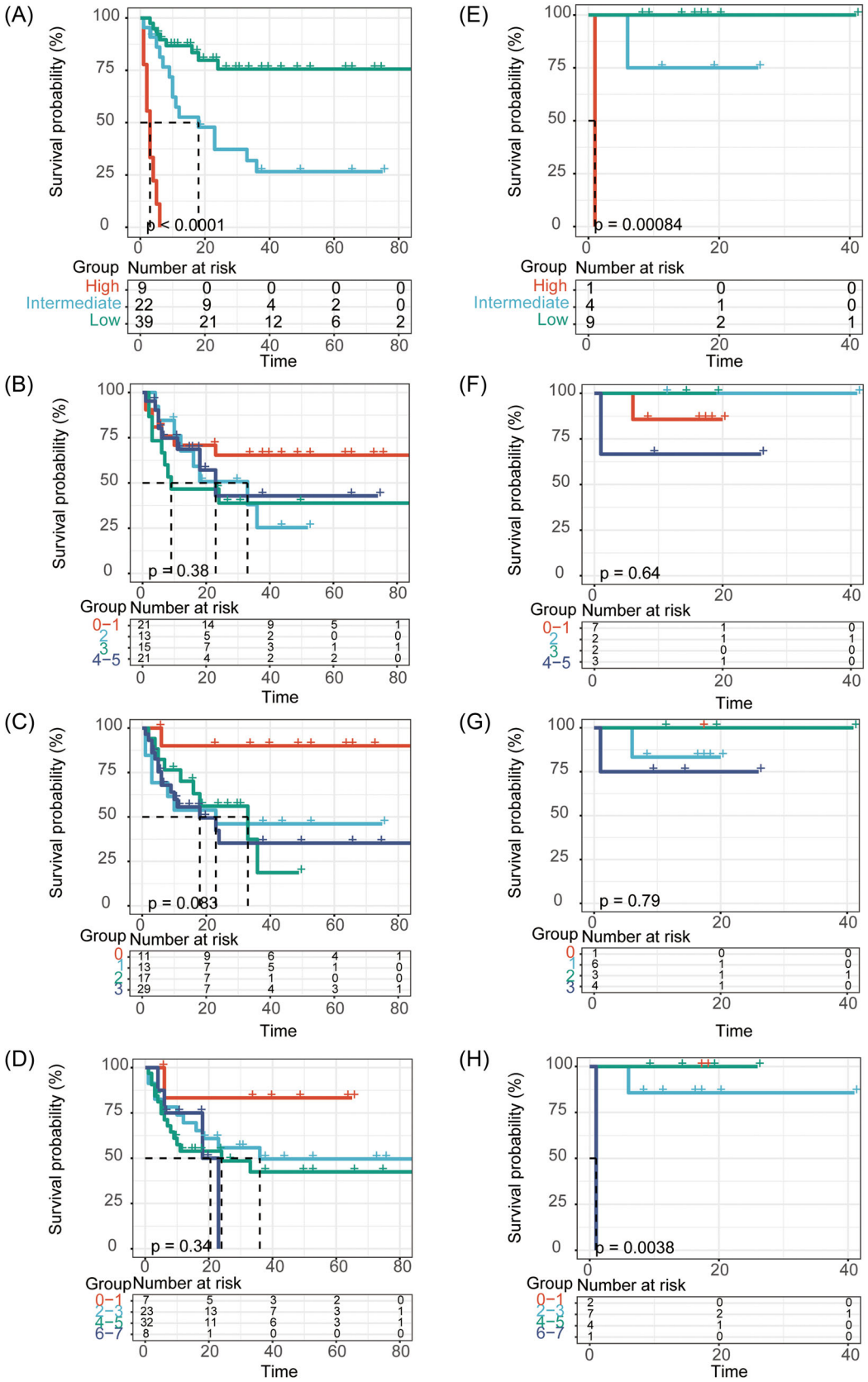

FIGURE 4 Progression free survival (PFS) analysis with different prognostic stratification models. Kaplan–Meier curves of (A) GZMU PFS model ($p < 0.0001$), (B) IPI ($p = 0.38$), (C) aaIPI ($p = 0.083$), and (D) NCCN-IPI ($p = 0.34$) for PFS in patients with AR-DLBCL in the training cohort; Kaplan–Meier curves of (E) GZMU PFS model ($p = 0.00084$), (F) IPI ($p = 0.64$), (G) aaIPI ($p = 0.79$), and (H) NCCN-IPI ($p = 0.0038$) for PFS in patients with AR-DLBCL in the validation cohort. aaIPI, age-adjusted IPI; AR-DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; NCCN-IPI, national comprehensive cancer network-IPI; PFS, progression-free survival.

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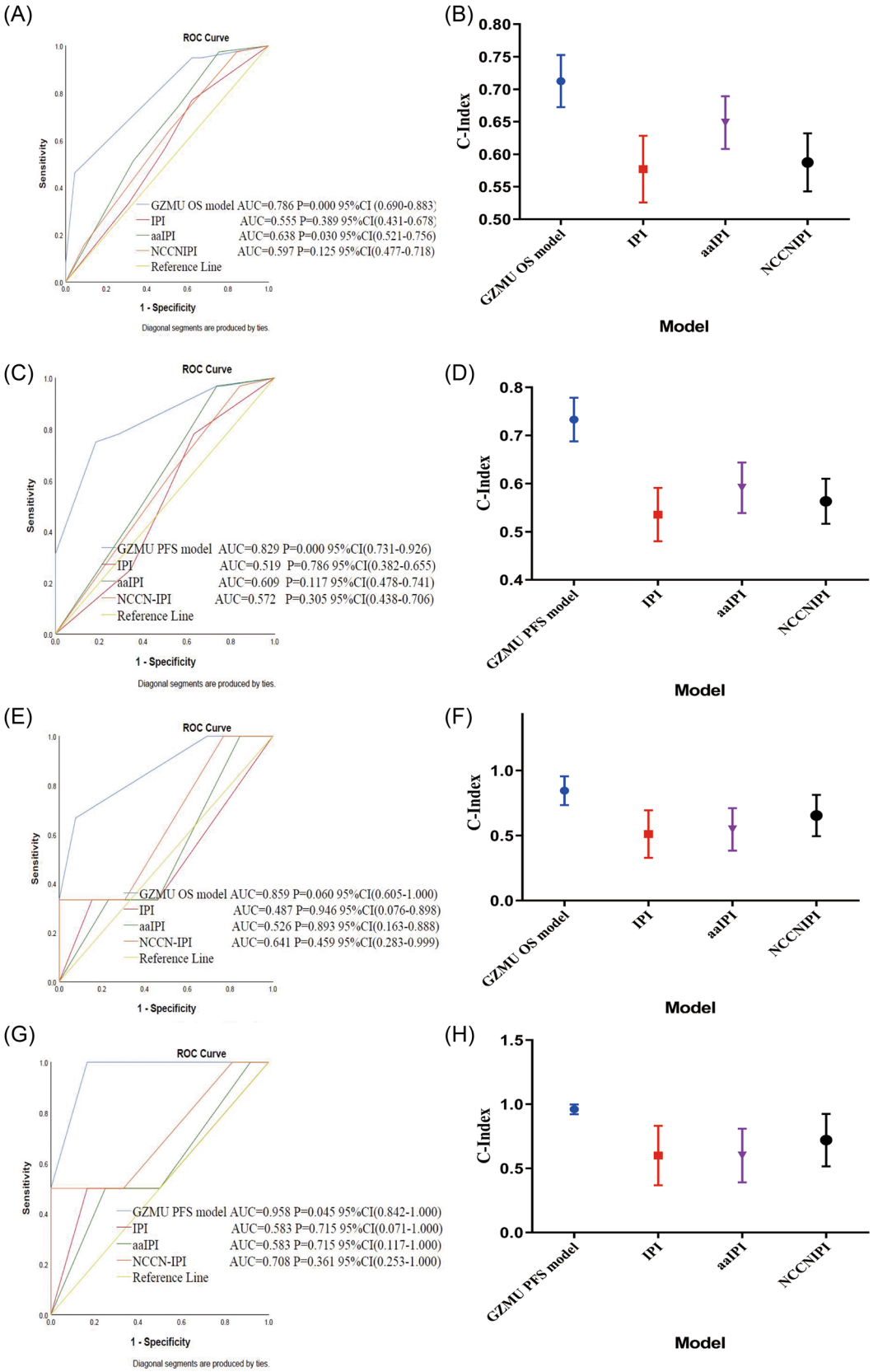

FIGURE 5 Prognosis of GZMU OS model and GZMU PFS model. Comparation of (A) AUC and (B) C-index in different prognostic risk stratification models for OS in the training cohort; comparation of (C) AUC and (D) C-index in different prognostic risk stratification models for PFS in the training cohort; comparation of (E) AUC and (F) C-index in different prognostic risk stratification models for OS in the validation cohort; comparation of (G) AUC and (H) C-index in different prognostic risk stratification models for PFS in the validation cohort. In all Figures, (AUC)s and C-index values are the highest in GZMU models. AUC, area under the curve; OS, overall survival; PFS, progression-free survival.

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and 0.708 of risk stratified by NCCN-IPI (Figure 5G). The C-index values based on GZMU PFS model, IPI, aaIPI, and NCCN-IPI were 0.96, 0.6, 0.6, and 0.72, respectively (Figure 5H). Generally, the AUC at 1-, 3,- and 5-year of different prognostic risk models for OS and PFS were compared as shown in Figure 6A-B and the AUC at 1-, 3,- and 5- year of each prognostic risk model for OS and PFS were shown on Supporting Information:Table 2 and Supporting Information: Figure S12A-D; E-H. In addition, the Hosmer–Lemeshow test demonstrated that the models were good fits (GZMU OS model: $p = 0.8244$; GZMU PFS model: $p = 0.9968$) and the DCA also showed significant net benefit of the predictive models in the entire cohort (Figure 6C,D).

4 | DISCUSSION

To our knowledge, the present study provided an important real-world data on the clinical features and prognostic factors of AR-DLBCL patients in China, which was the largest study reported thus far in the world. AR-DLBCL is characterized with young, at advanced stage, hyper-EN lesions and rare disease,[21] which is a fast-growing, highly aggressive malignancy that can occur if not treated as early as possible and can deteriorate into death over weeks or months even if treated with chemotherapy and cART therapy. Due to the poor prognosis, early recognition and treatment is very necessary.[22] Therefore, novel and practical models should be constructed to guide the risk stratification and clinical management of patients with AR-DLBCL. In the study, two prognostic risk stratification models were created to predict OS and PFS for AR-DLBCL based on clinicopathological variables that easily accessible from clinical practice, which showed better prediction accuracy than IPI, aaIPI, and NCCN-IPI according to the comparations of C-index values and (AUC)s. What's more, the models conducted in the training cohort were verified by the validation cohort, which showed robust ability and utility in survival prediction and risk stratification.

There is no suitable prognostic risk stratification model for patients with AR-DLBCL, so HIV-negative DLBCL prognostic models are mostly used for risk stratification for patients with AR-DLBCL. In the general population, the widespread use of rituximab in combination with chemotherapy poses a great challenge to the prognostic stratification ability of IPI for DLBCL in rituximab era. Ngo et al. study showed that both the IPI and aaIPI were less useful as prognostic models in patients receiving R-CHOP compared to CHOP, confirming that the use of rituximab led to previously recognized prognostic factors to be re-assessed and re-evaluated.[23] A survey of 570 newly diagnosed DLBCL patients showed that lower IPI or NCCN-IPI scores were independent favorable prognostic factors for OS and PFS, while IPI and NCCN-IPI have limited prognostic values in high-risk DLBCL patients.[24] What's more, the 5-year OS and PFS rates according to IPI, aaIPI, R-IPI, and NCCN-IPI did not show statistically significant differences between the subgroups when the subjects were stratified by each prognostic risk model in DLCBL treated with R-CHOP followed by autologous transplantation.[25] Ruppert et al. study showed that NCCN-IPI had the greatest absolute difference in OS estimates between the highest- and lowest-risk groups and best discriminated OS when compared with IPI and R-IPI.[26]

The research on the prognostic factors of OS and PFS in AR-DLBCL was scarce. Besson et al. study showed that ECOG PS 2–4 (HR = 3.3, 95% CI: 1.2–8.9, $p = 0.02$) and an advanced aaIPI (HR = 3.7, 95% CI: 1.0–13.1, $p = 0.04$) was associated with progression or death in univariate analysis.[27] Wu et al. showed that ECOG PS 2–4 (HR = 10.54, 95% CI: 4.45–24.96, $p = 0.003$) and IPI ≥ 3 (HR = 2.72, 95% CI: 0.55–13.46, $p = 0.004$) were associated with worse OS in univariate analysis.[28] In our study, ECOG PS 2–4 was also the adverse factor of OS in univariate analysis. Previous studies showed that IPI or aaIPI, and its components as prognostic factors of OS and PFS in patients with AR-NHL.[14–17] However, in the present study, no correlation was found between IPI or aaIPI and survival in either univariate or multivariate analysis. The possible reason was that only the DLBCL type was included in the present study, while previous studies included other NHL pathological types, such as Burkitt lymphoma (BL) and plasmablastic lymphoma.

Among AIDS patients, the relevant features of HIV infection (such as $CD4^+$ T cell count, HIV viral load, etc.) in the previous study have been repeatedly proven to be effective prognostic factors for ARL,[29] but some scholars believe that the influence of $CD4^+$ T cell count on the prognosis of ARL patients in the cART era is gradually weakening. According to a pooled analysis of 1546 patients, it was found that the use of cART not only effectively improved the OS of patients with AR-DLBCL, but also weakened the impact of HIV-related influencing factors on the prognosis, such as viral load, $CD4^+$ T cell count.[30] In our analysis, $CD4^+$ T cell count was not statistically different, suggesting that HIV infection is no longer a critical risk factor in the current era. IPI is still important in predicting the prognosis in the R-CHOP era in AR-DLBCL, while obtaining complete remission (CR) after four cycles of R-CHOP and presence of bulky disease might be new prognostic indices which should be considered together with IPI factors.[31] aaIPI was proved to be a significant predictor on survival of patients with AR-NHL according to a previous study, while HIV-related factors such as low $CD4^+$ T cell count and prior history of AIDS were no longer associated with poor outcomes in the contemporary era.[7] Chao et al. analysis showed that increasing IPI scores and failure to attain CR were associated with decreased survival, whereas $CD4^+$ T cell count <100/uL predicted shorter survival in only the pre-cART era.[32] Compared with IPI, aaIPI, and NCCN-IPI, our models are better able to identify high-risk patients with AR-DLBCL with poor survival in the cART and Rituximab era.

CNS involvement has been recognized to be common in ARL.[33] In the cART era, the incidence of CNS involvement has reportedly decreased in patients with AR-NHL.[34] In addition, compared with HIV-negative DLBCL patients, the incidence of CNS involvement in AR-DLBCL is higher.[35] CNS involvement at diagnosis was identified as a prognostic factor associated with poor OS and PFS in our study. In a prospective cohort analysis, it was found that the addition of high-dose methotrexate to the R-CHOP regimen was effective in

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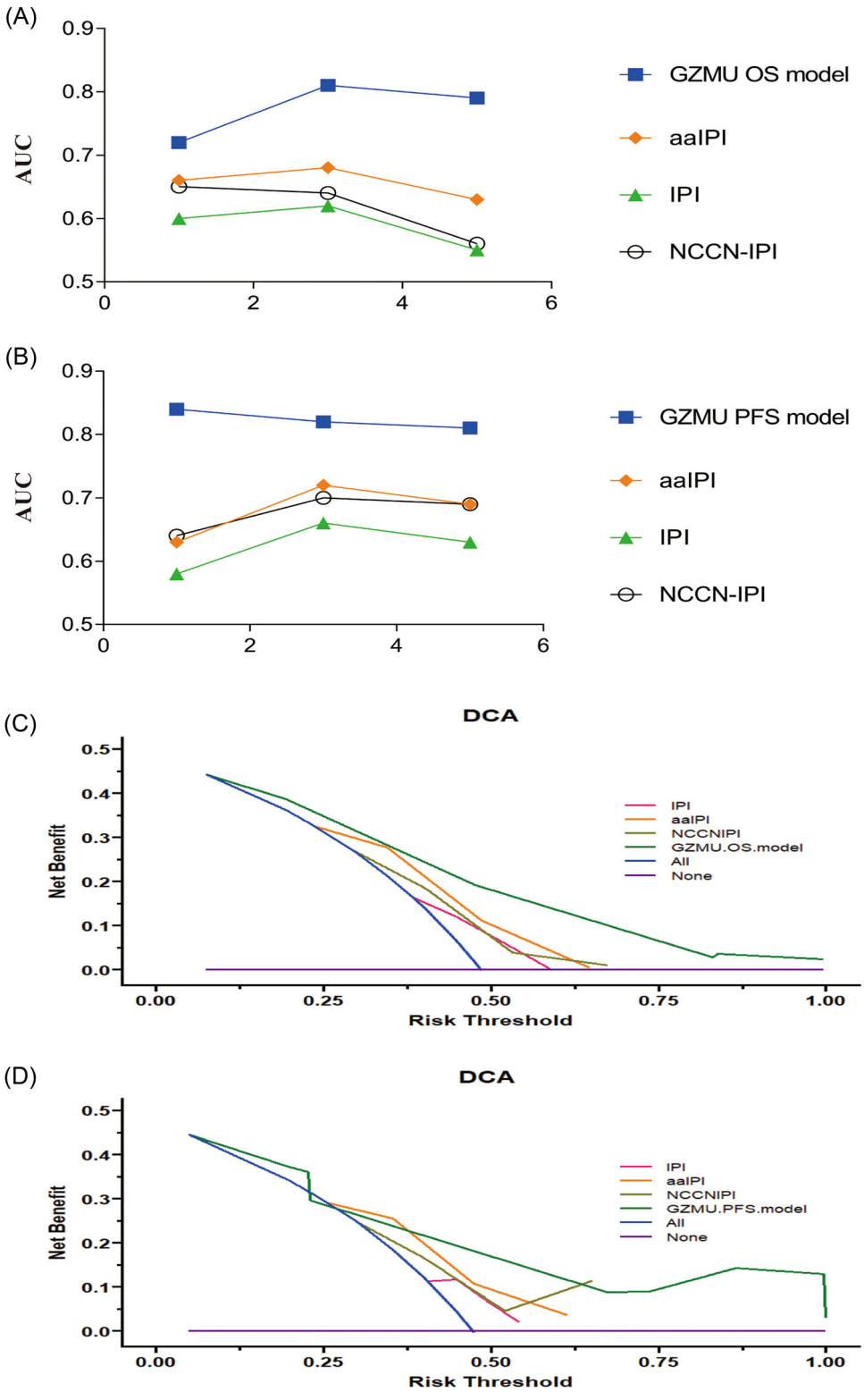

FIGURE 6 Predictive accuracy of GZMU OS model and GZMU PFS model. The difference of different prognostic models with the comparison of AUC at 1-, 3-, 5-year for (A) OS and (B) PFS in the training cohort; Decision curve analysis (DCA) in prediction of (C) OS and (D) PFS in the entire cohort. AUC, area under the curve; OS, overall survival; PFS, progression-free survival.

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improving PFS and OS in patients, but did not prevent recurrence of the patient's CNS involvement.[36] Therefore, the intrathecal injection of methotrexate and cytarabine as a protective measure is particularly essential. Few studies have evaluated coinfections in ARL and the impact on clinical outcomes, although the infection is common among the patients with AIDS. In our study, OI at the lymphoma diagnosis mainly included candidiasis, fungal infection, tuberculosis, and cryptococcosis, which were similar to what has been reported in CCASAnet in Latin America.[37] Previous studies showed that infection was an independent predictor of survival in NHL patients,[38,39] which was consistent with our result.

LDH, as a factor among the five indicators of IPI, has been studied sufficiently to support its role in lymphoma monitoring, which shows the importance of lymphoma assessment.[40] In many tumor cells, regardless of oxygen availability, metabolism shifts to high glucose uptake, and increased lactate production, a phenomenon known as the Warburg effect, which is one of the fundamental metabolic processes that occur during malignant transformation.[41] This is because tumor cells rely on a series of glucose metabolism involved in the synthesis of nucleic acids, fatty acids and lactic acid to promote intracellular signaling, angiogenesis in the microenvironment as well as tumor growth.[42] Furthermore, LDH, as one of the key enzymes in the glycolysis pathway, catalyzes the conversion of pyruvate into lactic acid and produces the energy, which is in the cytoplasm of tissue cells, mainly in the kidneys. When malignant lesions occur in the body, especially in lymphoma, the level of LDH is elevated,[43] which indicates a high disease burden, while in AR-DLBCL patients, may be caused by OI of HIV/AIDS itself.

Some studies have found that R-EPOCH has a higher response rate and survival rate compared to R-CHOP in AR-DLBCL.[44,45] However, there are also studies that show no significant difference between R-EPOCH and R-CHOP in improving survival in AR-NHL.[28] In our cohort, there was no statistical significance between different treatment regimens, but there is a tendency that EPOCH regimen better than CHOP regimen for both OS and PFS in our study. Most likely, no significant difference was observed because this was not the study aim and thus the study lacked an adequate power to detect differences between therapeutic regimens. Yang et al. study found that completing four courses of chemotherapy ($p = 0.000$) was correlated with OS and DFS rate significantly in the patients with DLBCL in an era of R-CHOP.[31] Our result also showed that patients who received over 4 chemotherapy cycle had better prognosis of OS and PFS, which revealed the importance of standardized treatment.

The prognostic models for AR-DLBCL that we developed here using clinically relevant parameters can be applied to other types of lymphoma, such as AIDS-related BL (AR-BL) (data not shown). However, the GZMU OS and GZMU PFS models require further validation in larger cohort of patients with different ARL types.

It is important to note that several limitations are present in our study. First, while our proposed prognostic models based on "real-world" data are valuable given the rarity of AR-DLBCL, external validation with larger datasets is necessary to assess their applicability to a broader patient population. Second, due to the limited sample size of our single-center data and the evolving nature of treatment protocols, future refinement of the models is essential with larger patient cohorts receiving a single treatment protocol.

AUTHOR CONTRIBUTIONS

Hua You designed the research and contributed the manuscript revision. Haolan He guided on clinical data collection and paper review. Han Zhao participated in data collection, data review, and interpreted the data. Rongqiu Liu performed the research, collected the data, analyzed the data, and wrote the manuscript. Yu Tao provided the data analysis methods and manuscript revision. Luca Bertero provided new analytical ideas and participated in manuscript revision. Lizhi Feng, Bo Liu, Zhimin Chen, Jialong Guan, Baolin Liao, and Linghua Li provided clinical suggestions. All authors contributed to the article and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The research protocols received ethical approval from the Ethics Committee of Guangzhou Eighth People's Hospital, Guangzhou Medical University (No. 202210222). We guaranteed the privacy of patient information and the date access procedures conformed to the data and privacy regulations of Declaration of Helsinki. The registration number is ChiCTR2200063651 in Chinese Trial Registry.

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