scientific reports

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# Prognostic significance of POD24 in primary central nervous system diffuse large B-cell lymphoma: a retrospective study

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**Primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL) is a rare form of non-Hodgkin lymphoma with a notably poor prognosis. This study aimed to identify new prognostic factors for improved prognostic stratification in PCNS-DLBCL. A total of 85 PCNS-DLBCL cases from three hospitals were retrospectively analyzed. Disease progression within 24 months (POD24) and its risk factors were investigated, and a prognostic model for predicting POD24 was constructed. The median overall survival (mOS) and median progression-free survival (mPFS) for the entire cohort were 48.54 months and 39.09 months, respectively. Survival analysis indicated that age ≥ 65 years (HR = 4.05, *P* = 0.008), non-responsive disease (HR = 4.43, *P* = 0.004), and POD24 (HR = 25.22, *P* = 0.002) were independent poor prognostic factors for OS in PCNS-DLBCL. Further analysis revealed that independent risk factors for POD24 included elevated serum lactate dehydrogenase (LDH) levels (OR = 12.00, *P* = 0.03), elevated triglycerides (TG, OR = 4.88, *P* = 0.047), and non-responsive disease (OR = 9.39, *P* = 0.003). Subsequently, an "LDH-TG-Efficacy (LTE)" prognostic model for PCNS-DLBCL was constructed. The incidence of POD24 was significantly higher in the "LTE" high-risk group (≥ 1 point) compared to the low-risk group (0 points) (81.8% vs. 35%, *P* < 0.001). The receiver operating characteristic (ROC) curve determined that the area under the curve (AUC) for the "LTE" model was 0.828 (95% CI: 0.7282–0.927), with a sensitivity and specificity of 79.4% and 79.3%, respectively. Additionally, the prognosis of the "LTE" high-risk group was significantly worse. These findings demonstrated that POD24 might serve as an independent prognostic indicator for PCNS-DLBCL, and the "LTE" prognostic index may provide a reference for better identifying populations at risk for POD24.**

**Keywords** Primary central nervous system diffuse large b-cell lymphoma, POD24, Prognosis, "LTE" prognostic model

Primary central nervous system lymphoma (PCNSL) is a rare subtype of non-Hodgkin lymphoma (NHL), it is usually confined to the brain, eyes, spinal cord or pia mater without other systemic infiltration. Diffuse large B-cell lymphoma (DLBCL) account for about 95% of PCNSL (also known as PCNS-DLBCL). The prognosis of PCNS - DLBCL is far worse than that of systemic DLBCL[1]. In the past few decades, intruduction of a series of treatment strategies, such as Whole Brain Radiation Therapy (WBRT), combination chemotherapy based on high dose methotrexate (HD-MTX), and autologous Hematopoietic Stem Cell Transplantation (ASCT), have significantly improved the survival of PCNS-DLBCL. However, relapse is common and long - term survival remains poor.

International Extranodal Lymphoma Study Group (IELSG) score[2] and Memorial Sloan Kettering Cancer Center (MSKCC) score[3] were routine prognostic models for PCNS-DLBCL in clinic. IELSG scoring system based on five factors: age, Eastern Cooperative Oncology Group Performance Status (ECOG) score, serum lactate dehydrogenase (LDH) level, the total protein concentration of cerebrospinal fluid (CSF), and involvement of

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deep brain structures. The MSKCC scoring system assessed outcomes of PCNS-DLBCL by age and the Karnofsky Performance Status (KPS) score. However, both the IELSG and MSKCC models had insufficient discriminative ability for either progression-free survival (PFS) or overall survival (OS) prognostic in asian population[4]. Some factors beyond these models were validated to affect survival, such as treatment patterns and response, should also be taken into account. Therefore, new risk stratification systems according to therapy changes over time are still needed to tailor therapeutic approaches in PCNS-DLBCL to date.

Disease progress within 24 months (POD24) is first proposed in follicular lymphoma (FL) and defined as primary - refractory disease (less than partial response), progression, transformation, or relapse within 24 months after diagnosis. Observational studies indicated that patients with FL who experience POD24 of front-line chemoimmunotherapy have unfavorable outcomes[5]. POD24 was subsequently shown to portend poor outcomes in marginal zone lymphoma (MZL)[6]. Except for indolent NHLs, early disease progression is also associated with dismal outcomes in aggressive lymphomas[7]. Previous studies showed event-free survival at 24 months (EFS24) predicted longer survival in DLBCL[8]. Above all, early disease progression is important prognostic factor in various subtype of NHLs, however, the specific role of POD24 in PCNS-DLBCL is still unclear.

Herein, based on retrospective analysis of PCNS-DLBCL cases from three chinese hospitals, we observed POD24 was a potent prognostic factor in predicting OS and PFS. In addition, we constructed a new prognostic model in order to identify high-risk POD24 population, it might help to optimize stratified treatment and improve long-term survival in the future.

## Materials and methods

### Study population and enrollment

In this retrospective study, we included cases with newly diagnosed PCNS-DLBCL admission from June 1, 2016 to September 30, 2023, in Huai'an First People's Hospital, Yancheng No.1 People's Hospital, and Affiliated Hospital of Xuzhou Medical University. The inclusion criteria were as follows: (1) The final histopathological and immunohistochemical (IHC) stain confirmed DLBCL. (2) Isolated central nervous system involvement, without systemic evidence of disease was confirmed by chest, abdominal and pelvic CT/MRI or systemic PET/CT and bone marrow tests (aspiration and biopsy). The exclusion criteria were as follows: (1) Confirmation of systemic DLBCL by imageological examinations or bone marrow tests. (2) With histories of immunodeficiency disorders (such as HIV infection) or organ transplantation. (3) Untreated cases. All the cases were divided into two groups based on whether they experienced disease progression within 24 months (POD24). 86 cases of central nervous system lymphoma (58 cases of PCNSL and 28 cases of secondary central nervous system lymphoma) from the MSK dataset of the cBioPortal database were used for validation. Informed consent was obtained from all subjects and/or their legal guardian(s). The use of data in this study has been approved by the ethics committee of Huai'an First People's Hospital, and ethical approval has been obtained from all participating institutions. All methods we used were performed in accordance with the relevant guidelines and regulations.

### Treatments and assessments

All the patients were treated with combination chemotherapy regimen based on high-dose methotrexate (HD-MTX). The response to therapies was evaluated by imaging examinations after 3 to 4 courses of induction therapy. IPCG criteria was used for efficacy evaluation. Achieving partial remission (PR) or better in the first-line treatment was defined as responsive disease (which includes PR and complete remission, abbreviated as CR), while the remainder was defined as non-responsive disease (which includes stable disease and progressive disease, abbreviated as SD and PD, respectively).

### Prognostic model development

R software was employed to ascertain the weights of key prognostic factors for POD24, based on the results of the logistic regression model. A simplified model was formulated, incorporating the three identified factors. The discriminatory capacity of this simplified model was assessed using a receiver operating characteristic (ROC) curve. A nomogram was subsequently developed to quantify the prognostic value.

### Statistical analyses

All patients were followed until January 10, 2024. Variables that adhered to a normal distribution were represented as mean ± standard deviation ($\bar{x} \pm s$) and tested using the unpaired t-test, whereas non-normally distributed continuous data were represented as median (interquartile range) and tested using the Mann-Whitney U test. The chi-squared test or Fisher's exact test were used to evaluate relationships between categorical variables. Kaplan-Meier curves (the log-rank test) and Cox proportional hazards regression were used for survival analysis. A binary logistic regression model was constructed to examine the predictors of POD24. The ROC curve was applied to assess the "LTE" prognostic index. SPSS (version 26.0) was used for data analysis. Statistical significance was defined as a $P$ value of 0.05 or less.

## Results

### Baseline characteristics

In this study, we meticulously reviewed the medical records of 85 patients diagnosed with primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL), of which 50.6% were male, with an average age of 58.00 years (interquartile range: 50.00 to 66.00 years). The baseline demographic and clinical features were delineated in Table 1. A preponderance of the patients exhibited a robust Ki-67 proliferation index, with 53.85% demonstrating a rate of 80% or greater. Additionally, 78.6% of patients presented with elevated protein

| Attributions | Total ($n=85$) | POD24 arm ($n=50$) | non-POD24 arm ($n=34$) | *P* |
|---|---|---|---|---|
| Gender, male/female (%) | 43 (50.6)/42 (49.40) | 28 (56.00)/22 (44.00) | 15 (44.12)/19 (55.88) | 0.37 |
| Age, Median (interquartile) | 58.00 (50.00, 66.00) | 57.00 (49.00, 66.00) | 59.50 (54.00, 65.75) | 0.52 |
| B symptom, n (%) | | | | > 0.99 |
| No | 84 (98.80) | 49 (98.00) | 34 (100.00) | |
| Yes | 1 (1.20) | 1 (2.00) | 0 (0) | |
| Elevated β2M, n (%) | | | | 0.13 |
| No | 66 (89.20) | 35 (83.33) | 30 (96.77) | |
| Yes | 8 (10.80) | 7 (16.67) | 1 (3.23) | |
| NA | 11 | 8 | 3 | |
| D - Dimer (μg/mL), Median (interquartile) | 0.57 (0.29, 1.19) | 0.56 (0.30, 0.56) | 0.59 (0.26, 1.32) | 0.51 |
| KPS scores | 70 (60–90) | 70 (60–82.5) | 80 (60–90) | 0.05 |
| MSKCC | | | | 0.46 |
| LR | 19 (22.35) | 13 (26.00) | 6 (17.60) | |
| IR | 42 (49.41) | 22 (44.00) | 20 (58.80) | |
| HR | 24 (28.24) | 15 (30.00) | 8 (23.50) | |
| ECOG score > 2, n (%) | | | | 0.22 |
| No | 73 (85.89) | 40 (80.00) | 31 (91.18) | |
| Yes | 13 (15.29) | 10 (20.00) | 3 (8.80) | |
| GCB subtype, n (%) | | | | 0.19 |
| No | 47 (67.14) | 25 (60.98) | 22 (78.57) | |
| Yes | 23 (32.86) | 16 (39.02) | 6 (21.43) | |
| NA | 15 | 9 | 6 | |
| Ki 67 ≥ 80%, n (%) | | | | 0.64 |
| No | 36 (46.15) | 23 (50.00) | 13 (41.90) | |
| Yes | 42 (53.85) | 23 (50.00) | 18 (58.10) | |
| NA | 7 | 4 | 3 | |
| Elevated LDH (u/L), n (%) | | | | 0.04 |
| No | 70 (82.40) | 38 (76.00) | 32 (94.12) | |
| Yes | 15 (17.60) | 12 (24.00) | 2 (5.88) | |
| TG (mmol/L), Median (interquartile) | 1.20 (0.83, 1.75) | 1.26 (0.81, 1.90) | 1.20 (0.86, 1.46) | 0.42 |
| CHOL (mmol/L), Median (interquartile) | 4.46 (3.90, 5.18) | 4.49 (3.91, 5.24) | 4.38 (3.76, 5.19) | 0.81 |
| CREA (μmol/L), Median (interquartile) | 58.00 (48.00, 68.15) | 58.00 (48.00, 66.00) | 59.45 (48.00, 71.00) | 0.50 |
| Elevated protein levels in CSF, n (%) | | | | > 0.99 |
| No | 9 (21.40) | 5 (23.81) | 4 (19.05) | |
| Yes | 33 (78.60) | 16 (76.19) | 17 (80.95) | |
| NA | 43 | 29 | 13 | |
| Albumin (g/L), Median (interquartile) | 40.70 (36.80, 44.05) | 40.30 (35.80, 44.30) | 40.80 (37.60, 43.93) | 0.64 |
| HbsAg positive, n (%) | | | | 0.19 |
| No | 74 (87.10) | 42 (84.00) | 32 (94.12) | |
| Yes | 11 (12.90) | 8 (16.00) | 2 (5.88) | |
| Excision of intracranial tumor, n (%) | | | | 0.01 |
| No | 16 (18.80) | 14 (28.00) | 2 (5.88) | |
| Yes | 69 (81.20) | 36 (72.00) | 32 (94.12) | |
| Residual parenchymal central system lymphoma, n (%) | | | | 0.01 |
| no | 25 (29.40) | 9 (18.00) | 16 (47.06) | |
| yes | 60 (70.60) | 41 (82.00) | 18 (52.94) | |
| WBRT, n (%) | | | | > 0.99 |
| No | 73 (89.02) | 42 (89.36) | 31 (91.18) | |
| Yes | 9 (10.98) | 5 (10.64) | 3 (8.82) | |
| NA | 3 | 3 | 0 | |
| Regimens without RTX, n (%) | | | | 0.23 |
| No | 56 (69.14) | 29 (63.00) | 26 (37.00) | |
| Yes | 25 (30.86) | 17 (34.00) | 8 (23.53) | |
| NA | 4 | 4 | 0 | |
| ASCT, n(%) | | | | > 0.99 |
| Continued | | | | |

| Attributions | Total ($n=85$) | POD24 arm ($n=50$) | non-POD24 arm ($n=34$) | $P$ |
|---|---|---|---|---|
| No | 76 (89.40) | 45 (90.00) | 30 (88.24) | |
| Yes | 9 (10.60) | 5 (10.00) | 4 (11.76) | |
| Non-responsive diseases, n (%) | | | | 0.002 |
| No | 51 (68.00) | 22 (52.40) | 28 (87.50) | |
| Yes | 24 (32.0) | 20 (47.60) | 4 (12.50) | |
| NA | 10 | 8 | 2 | |

**Table 1**. Baseline characteristics of of patients with DLBC - PCNSL. NA: not available; n: numbers; ASCT: auto-hematopoietic stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; GCB: germinal center B-cell-like lymphoma; TG: triglyceride; CHOL: cholesterol; CREA: creatinine; LDH: lactate dehydrogenase; CSF: Cerebrospinal fluid; WBRT: whole brain radiotherapy; RTX: Rituximab; LR: low risk; IR: intermediate risk; HR: high risk; POD24: Disease progress within 24 months.

concentrations in the cerebrospinal fluid (CSF). Only a minority of cases, 1.2%, 10.8%, and 17.6% respectively, were complicated by B symptoms, elevated β2-microglobulin (β2M), and elevated lactate dehydrogenase (LDH) levels. The GCB subtype was identified in 32.86% (42/78) of the cohort, while 12.9% were found to be infected with the hepatitis B virus (HBV). The median Karnofsky Performance Status (KPS) score for the entire patient population was 70. Risk stratification according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria allocated 17.6%, 58.8%, and 23.5% of patients to the low, intermediate, and high-risk categories, respectively. Despite the strong recommendation for stereotactic biopsy as a diagnostic gold standard, the majority of patients (81.2%) underwent surgical resection for diagnosis, with 70.6% exhibiting residual lymphoma within the central nervous system prior to induction therapies. As for the primary treatment approach, 30.86% of patients received Rituximab - containing regimens, For consolidation, 9/82 (10.98%) cases underwent WBRT, autologous hematopoietic stem cell transplantation (ASCT) was employed in 10.6% (9/85) of cases. Following induction therapy, 28.24% of the patients (24 out of 75) experienced refractory disease.

Except for one patient whose PFS event could not be evaluated, the other 84 patients were divided into the POD24 group ($n=50$) and the non-POD24 group ($n=34$). Compared with the non-POD24 group, the proportion of patients with an elevated serum LDH level at baseline was significantly higher in the POD24 group (24.00% vs. 5.88%, $P=0.04$), and the proportion of patients with residual parenchymal central nervous system lymphoma before systemic therapies was significantly higher (82.00% vs. 52.94%, $P=0.01$). In the non-POD24 group, the proportion of patients receiving surgical resection was significantly higher (94.12% vs. 72.00%, $P=0.01$), and the proportion of patients who failed first-line treatment was significantly lower (12.50% vs. 47.60%, $P=0.002$). No statistical differences in other baseline variables between the two groups were observed.

## Survival analysis

In our study, the median OS (mOS) and the median PFS (mPFS) for the entire cohort were 48.54 and 39.09 months, respectively. The 1-year, 3-year, and 5-year OS rates were 63.5%, 24.7%, and 15.3%, respectively. The 1-year, 3-year, and 5-year PFS rates were 49.4%, 16.5%, and 8.2%, respectively. There was no significant difference in OS among the three risk groups of PCNSL patients stratified by the MSKCC prognostic system. The PFS of patients in the intermediate-risk group was superior to that of patients in the low-risk group, while there was no statistically significant difference in PFS between the other groups (Fig. 1A-B). However, compared to patients who experienced POD24, those who did not (non-POD24) had both better OS in our cohort and the validation cohort (Fig. 1C-D, $P<0.001$).

To further analyze the effects of various factors on OS in PCNS-DLBCL, we included them in univariate analyses. The results indicated that the following were adverse prognostic factors for OS: triglycerides (TG) > 1.7 mmol/L, hepatitis B surface antigen (HbsAg) positive, non-responsive disease, POD24, and residual parenchymal central nervous system lymphoma before systemic therapies. Subsequently, age, sex, factors with a $P$ value ≤ 0.1 in univariate analyses, elevated LDH levels (a significant difference was observed between the two groups at baseline), first-line therapies without Rituximab (RTX), and ASCT (although our results did not show statistical significance, previous study[9] have observed benefits from upfront ASCT in PCNSL) were included in Cox proportional hazards regression analyses. The results revealed that age ≥ 65y (HR = 4.05, $P$ = 0.008), non-responsive disease (HR = 4.43, $P$ = 0.004) and POD24 (HR = 25.22, $P$ = 0.002) were independent inferior prognostic factors for OS in PCNS-DLBCL (Table 2).

## Analysis of risk factors for POD24

Since POD24 was a potent inferior prognostic factor for PCNS-DLBCL, further analyses were conducted to identify clinical predictors of early progression. Univariate analyses revealed that elevated LDH and TG at baseline, not undergoing excision of the intracranial tumor, residual parenchymal central nervous system lymphoma, and non-responsive diseases were risk factors for POD24. Gender, age, all significant factors identified by univariate analyses, KPS scores, regimens without RTX, and ASCT were further included in the multivariate analysis. The results revealed that elevated LDH (OR = 12.00, $P=0.03$) and TG (OR = 4.88, $P=0.047$) at baseline, and non-responsive diseases (OR = 9.39, $P=0.003$) were independent risk factors for POD24 (as shown in Table 3).

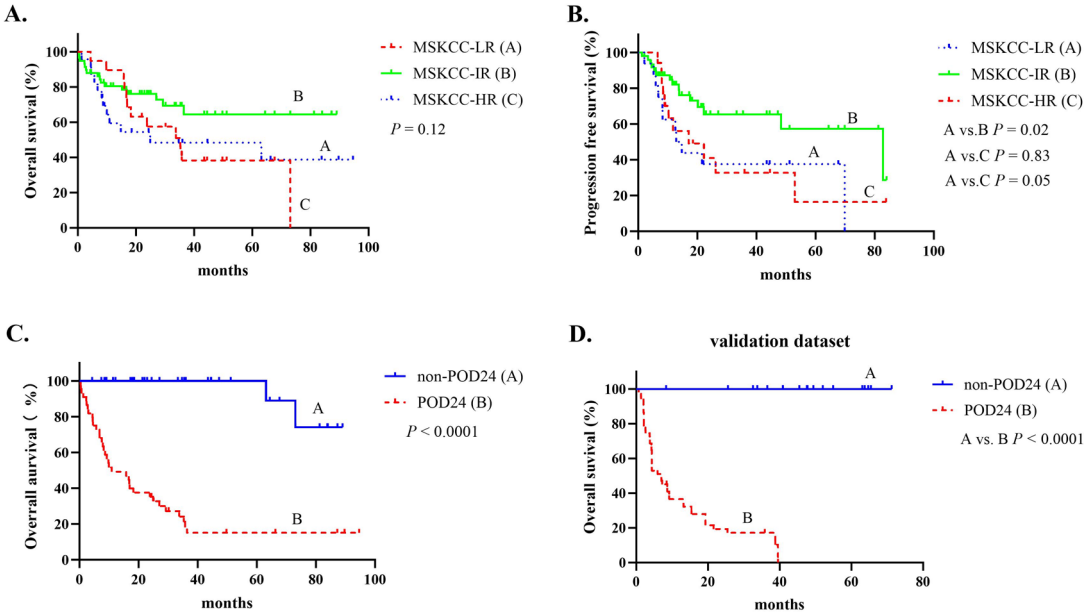


**Fig. 1**. Survival of primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL) patients stratified by the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic system and by POD24 status. (**A**) and (**B**) Overall survival (OS) and Progression-free survival (PFS) curves for PCNSL patients stratified by the MSKCC prognostic system. (**C**) and (**D**) Comparison of OS between non-POD24 and POD24 groups within the study cohort and the validation dataset (the MSK dataset of the cBioPortal database).

| | OS | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| Factors | HR (95%CI) | *P* value | HR | *P* value |
| Age ≥ 65y | 1.20 (0.62–2.34) | 0.58 | 4.05 (1.45–11.31) | 0.008 |
| Gender, female | 1.10 (0.59–2.05) | 0.77 | | |
| β2M > 2.7 μg/mL | 1.13 (0.34–3.71) | 0.84 | | |
| D-Dimer > 2 mg/L | 1.38 (0.65–2.95) | 0.40 | | |
| KPS scores | 0.99 (0.97–1.01) | 0.37 | | |
| MSKCC | 1.01 (0.67–1.53) | 0.95 | | |
| GCB subtype | 1.80 (0.89–3.64) | 0.10 | | |
| Ki 67 ≥ 80% | 1.39 (0.71–2.72) | 0.33 | | |
| ECOG > 2 | 1.08 (0.48–2.45) | 0.85 | | |
| LDH > 225 u/L | 1.03 (0.47–2.24) | 0.94 | | |
| TG > 1.7 mmol/L | 2.74 (1.37–5.50) | < 0.01 | | |
| CHOL > 5.2 mmol/L | 1.00 (0.45–2.23) | 0.99 | | |
| CREA | 1.00 (0.98–1.03) | 0.68 | | |
| Elevated protein levels in CSF | 1.26 (0.36–4.47) | 0.72 | | |
| Albumin < 40 g/L | 1.09 (0.58–2.02) | 0.80 | | |
| HbsAg positive | 2.85 (1.29–6.27) | 0.01 | | |
| WBRT | 0.84 (0.33–2.18) | 0.73 | | |
| Excision of intracranial tumor | 0.89 (0.41–1.94) | 0.78 | | |
| Residual parenchymal central system lymphoma | 2.37 (1.09–5.16) | 0.03 | | |
| Regimens without RTX | 0.97 (0.48–1.94) | 0.92 | | |
| ASCT | 0.48 (0.15–1.57) | 0.22 | | |
| Non-responsive diseases | 4.31 (2.11–8.83) | < 0.001 | 4.43 (1.59–12.32) | 0.004 |
| POD24 | 23.28 (5.59–96.88) | < 0.001 | 25.22 (3.22–197.85) | 0.002 |

**Table 2**. Univariate and multivariate analyses of risk factors for OS in DLBC - PCNSL.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Factors** | **OR (95%CI)** | ***P* value** | **OR (95%CI)** | ***P* value** |
| Age | 1.13 (0.44–2.91) | 0.80 | | |
| Gender, female | 0.62 (0.26–1.49) | 0.29 | | |
| β2M > 2.7 μg/mL | 6.00 (0.70–51.58) | 0.103 | | |
| D-Dimer > 2 mg/L | 1.05 (0.39–2.85) | 0.92 | | |
| KPS scores | 0.97 (0.94–1.00) | 0.05 | | |
| MSKCC | 0.96 (0.52–1.79) | 0.90 | | |
| GCB subtype | 2.35 (0.79–7.05) | 0.13 | | |
| Ki 67 ≥ 80% | 0.72 (0.29–1.81) | 0.49 | | |
| ECOG score > 2 | 2.58 (0.66–10.20) | 0.18 | | |
| LDH > 225 u/L | 5.05 (1.05–24.26) | 0.04 | 12.00 (1.27–113.58) | 0.03 |
| TG > 1.7 mmol/L | 3.89 (1.14–13.29) | 0.03 | 4.88 (1.02–23.33) | 0.047 |
| CHOL > 5.2 mmol/L | 1.11 (0.37–3.33) | 0.86 | | |
| CREA | 0.99 (0.97–1.02) | 0.59 | | |
| Elevated protein levels in CSF | 0.75 (0.17–3.31) | 0.71 | | |
| Albumin < 40 g/L | 1.04 (0.43–2.49) | 0.93 | | |
| HbsAg positive | 3.05 (0.61–15.34) | 0.18 | | |
| WBRT | 1.23 (0.27–5.54) | 0.79 | | |
| Excision of intracranial tumor | 0.16 (0.03–0.76) | 0.02 | | |
| Residual parenchymal central system lymphoma | 4.05 (1.51–10.86) | 0.005 | | |
| Regimens without RTX | 1.91 (0.71–5.14) | 0.20 | | |
| ASCT | 0.83 (0.21–3.36) | 0.80 | | |
| Non-responsive diseases | 6.36 (1.90–21.34) | 0.003 | 9.39 (2.16–40.87) | 0.003 |

**Table 3**. Univariate and multivariate analyses of risk factors for POD24 in DLBC - PCNSL.

## Construction of POD24 risk prediction model

Furthermore, this study developed a risk prediction model named "LDH-TG-Efficacy" ("LTE" for short) for predicting the occurrence of POD24 in PCNSL patients, based on the aforementioned multivariate logistic regression model. The nomogram, illustrated in Fig. 2, encompasses three variables: LDH, TG, and Efficacy, each assigned corresponding weights (elevated TG assigned 64 points, elevated LDH assigned 100 points, and non-responsive disease assigned 90 points). By summing the scores of each variable, the total score for a patient can be obtained, which corresponds to the probability of POD24. The ROC curve analysis determined that the area under the curve (AUC) for the "LTE" model was 0.828 (95% CI: 0.7282–0.927, Fig. 3A), with a sensitivity and specificity of 79.4% and 79.3%, respectively, indicating its good predictive performance. The ROC curve identified the optimal cutoff value for the model as 0.436, and all patients were categorized into a low-risk group (LR, predicted probability < 0.436) and a high-risk group (HR, predicted probability ≥ 0.436) based on whether their values exceeded this cutoff. Patients in the HR group exhibited a significantly higher risk of POD24 compared to those in the LR group (81.8% vs. 23.3%, $P < 0.001$, Table 4). Additionally, the prognosis for the "LTE" high-risk group was significantly worse ($P < 0.001$, Fig. 3B-C).

## Survival analysis of OS in POD12, POD12-24, and Non-POD groups

To further analyze whether there were differences in the prognosis of PCNSL patients who progressed within 12 months and those who progressed between 12 and 24 months, we further divided the patients into three groups: POD12, POD12-24, and Non-POD (no progression within 24 months). The median OS for these groups was 8.2 months, 33.77 months, and undefined, respectively. The OS of the Non-POD group was significantly better than that of the POD12-24 group, and the OS of the POD12-24 group was also better than that of the POD12 group, with *P*-values of 0.01 and 0.0007, respectively (Fig. 4A). In the cBioPortal validation dataset, the median OS for POD12, POD12-24, and Non-POD patients was 4.333 months, 18.48 months, and undefined, respectively. The OS of the Non-POD group was significantly better than that of the POD12-24 group and the POD12 group (both *P*-values < 0.0001). However, there was no statistically significant difference in OS between the POD12-24 group and the POD12 group ($P = 0.44$, Fig. 4B).

## Discussion

In this collaborative retrospective study, conducted across three Chinese institutions, we elucidated that the median age for the diagnosis of PCNS-DLBCL was 58 years. Our findings revealed a male to female ratio akin to that observed in the SEER database, which encompasses over 5000 cases of PCNSL. However, our patient cohort was diagnosed at a younger age, contrasting with the SEER database median diagnosis age of 63.1 ± 14.9 years[10]. Consistent with prior research, the predominant subtype of PCNSL in our study was non-GCB, and baseline LDH levels were generally unremarkable[11]. Furthermore, In non-GCB subtype PCNSL patients, high Ki-67 index was an adverse independent prognostic marker[12]. Regarding the induction therapy, all patients

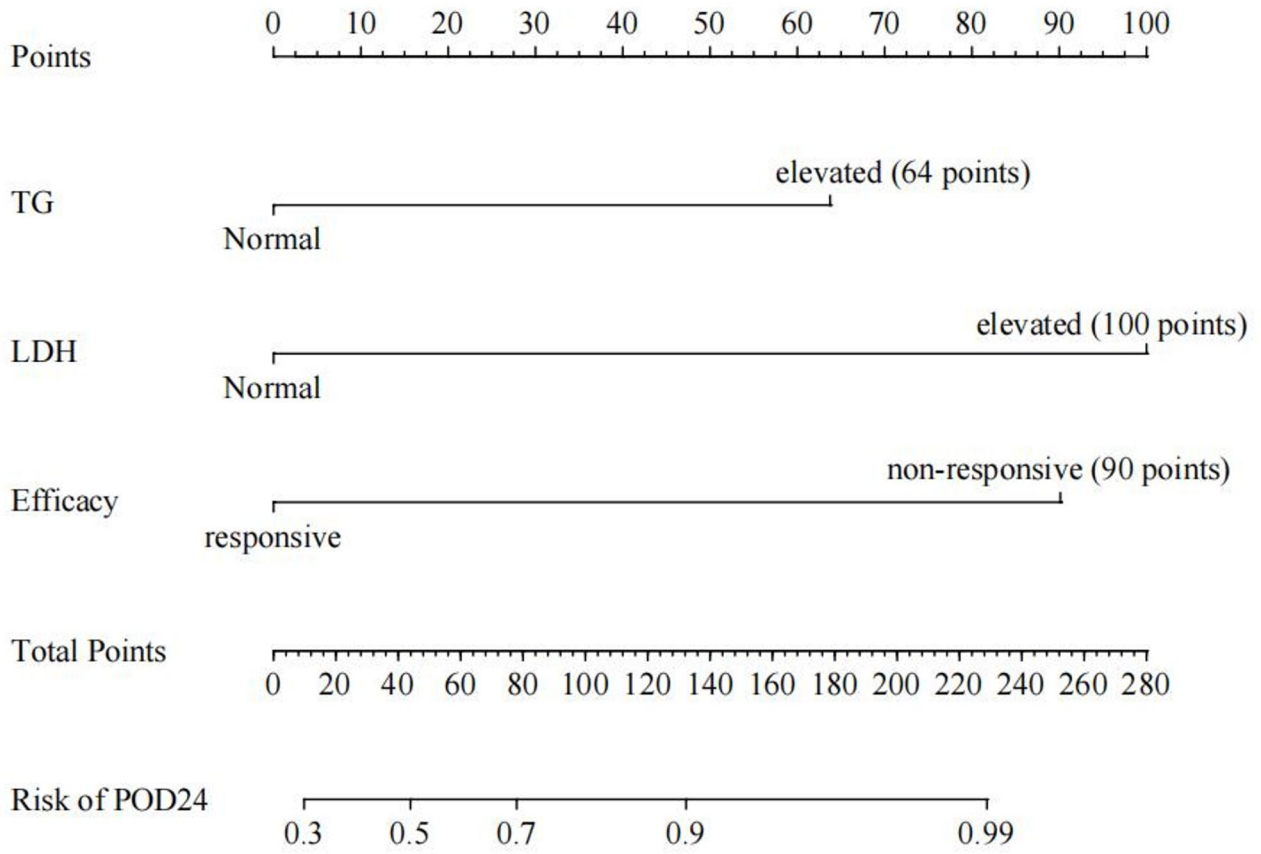


**Fig. 2**. The "LTE" POD24 predictive model for PCNS-DLBCL was constructed through a multivariate logistic regression analysis which included TG, LDH, and first-line efficacy.

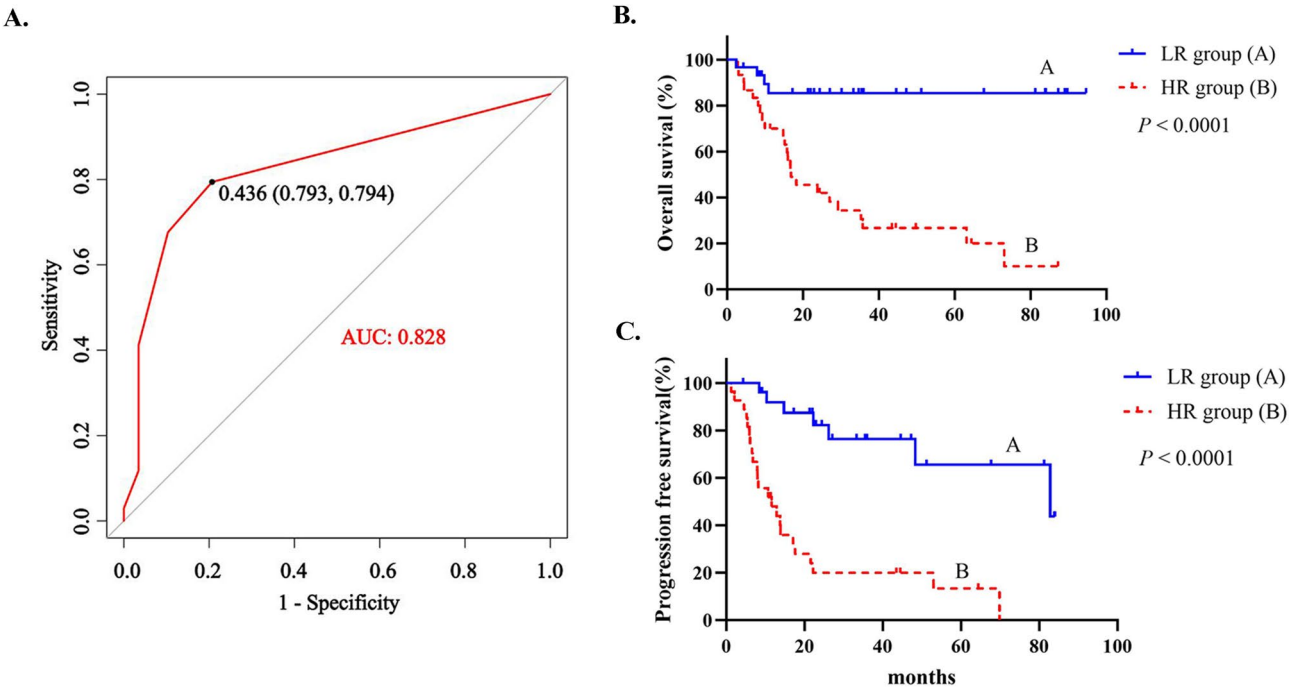


**Fig. 3**. (**A**) The ROC curve of the "LTE" POD24 predictive model. (**B**) and (**C**) Kaplan-Meier plot comparing OS and PFS between the "LTE" LR and HR groups.

| The "LTE" prognostic model | | Incidence of POD24 | *P* value |
|---|---|---|---|
| LDH > 225 U/L | The LR group | 23.3% (7/30) | < 0.001 |
| TG>1.7 mmol/L | The HR group | 81.8% (27/33) | |
| Non - responsive diseases | | | |

**Table 4**. The "LTE" prognostic model for POD24 in DLBC - PCNSL.

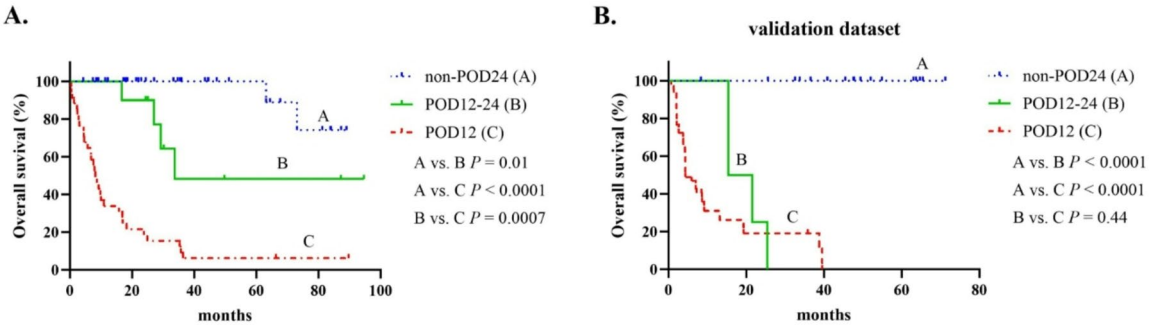


**Fig. 4**. Comparison of OS among PCNS-DLBCL patients categorized into non-POD24 (Disease does not progress within 24 months), POD12-24 (Disease progression between 12 and 24 months), and POD12 (Disease progress within 12 months) groups using Kaplan-Meier analysis. (**A**) Our cohort. (**B**) The validation dataset (the MSK dataset of the cBioPortal database).

in our cohort were administered HD-MTX, with 30.86% of the patients also receiving Rituximab. As one of the limited agents capable of traversing the blood-brain barrier (BBB), HD-MTX (3–8 mg/m²) and HD-MTX-based combination therapies have emerged as the standard induction protocols for patients newly diagnosed with PCNSL[13]. In the era of HD-MTX, the median survival for PCNSL in the United States has significantly improved, rising from 12.5 months in the 1970s to 26 months in the 2010s[14]. Consistent with prior reports[15], our findings revealed a mPFS of 39.1 months and a mOS of 48.54 months, respectively, with a 12-month overall survival rate of 63.5%.

Although recent advancements in radiotherapy and chemotherapy have led to improved efficacy and survival rates for patients with PCNS-DLBCL compared to a decade ago, these improvements are often not sustained, with up to 50% of cases eventually recurring[16]. The prognosis for recurrent/refractory PCNSL is exceptionally poor, with a median survival time of approximately 2 months[17]. Therefore, effectively predicting lymphoma recurrence remains a critical challenge in the management of PCNS-DLBCL. The conventional Ann Arbor staging system is not applicable to PCNSL, and to date, no specific staging system for PCNSL has been established. Clinically, the prognostic assessment frameworks proposed by the IELSG and the MSKCC are predominantly utilized. Nevertheless, these pre-rituximab-era systems, which have been in use for two decades or more, exhibit considerable limitations in their clinical application. Previous studies have indicated that the traditional IELSG score has limited discriminatory value in stratifying PCNSL within the Chinese population[4]. In our cohort, the MSKCC scoring system also failed to effectively differentiate the prognostic outcomes for PCNSL patients, underscoring the necessity for a more instructive prognostic stratification system to guide the management of PCNSL in this new era of therapeutic advancements.

Our univariate analysis revealed that TG > 1.7 mmol/L, HbsAg positivity, residual parenchymal central nervous system lymphoma, non-responsive disease, and POD24 were adverse prognostic factors for OS in patients with PCNSL. Multivariate analysis identified non-responsive disease, age, and POD24 as independent adverse prognostic factors for OS. In recent years, the incidence of PCNSL has increased among the elderly population, with patients over 60 years accounting for more than 50% of all PCNSL cases. Consistent with our findings, age has been established as an independent adverse prognostic factor for PCNSL, potentially due to the diminished organ function and reduced tolerance to chemotherapy in older patients compared to younger ones. Patients over 50 years with a KPS < 70 have the poorest prognosis, with a median survival of only 1.1 years[18]. Therefore, as a unique subgroup of PCNSL, elderly patients require more effective and less toxic treatment regimens.

In our cohort, 11 patients (12.9%) tested positive for HbsAg. A study from the affiliated cancer hospital of Fudan university, involving 199 PCNSL patients, reported an HBV infection prevalence of 16.1% in PCNSL, higher than that in a control group based on the national population[19]. A retrospective study found that 127 of systemic DLBCL patients (30.2%) were HbsAg positive, and HbsAg-positive DLBCL exhibited distinct clinicopathological features (such as more advanced disease). Additionally, in the context of antiviral prophylaxis, HBV infection was not an independent prognostic factor for OS in DLBCL[20]. In line with these findings, our univariate analysis suggested that HbsAg positivity might be an adverse prognostic factor for OS, however, it was not an independent prognostic factor in PCNS-DLBCL. In summary, although the prevalence of HBV infection

is lower in PCNS-DLBCL than in systemic DLBCL, it remains higher than in the general population. The role of HBV infection in the pathogenesis of PCNS-DLBCL warrants further investigation.

In our PCNS-DLBCL cohort, a significant proportion of patients in the non-POD24 group underwent surgical resection. Although multivariate analysis showed that surgical resection and residual parenchymal central nervous system lymphoma were not independent prognostic factors for OS, univariate analysis indicated that residual parenchymal central nervous system lymphoma was an adverse prognostic factor for OS in PCNSL. Given that 44% of PCNSL cases are multifocal, most tumors cannot be completely resected surgically. Considering previous studies indicating that surgical resection offers no survival benefit for PCNSL and significantly increases the risk of postoperative neurological deficits and other complications, and that PCNSL is highly sensitive to chemotherapy and radiotherapy, surgical resection is not a standard treatment for PCNSL[13,21,22]. Current consensus recommends surgery only for emergency decompression of brain herniation or treatment of a single superficial tumor[23,24]. Despite the fact that stereotactic biopsy has largely replaced surgical resection for the diagnosis of PCNSL, a considerable proportion of patients still receive a diagnosis through surgical resection. In our study, 81.2% of patients underwent surgical resection, which, in addition to providing a diagnosis, also offered more rapid reduction of intracranial pressure. A retrospective study based on the SEER database showed that PCNSL patients who underwent surgical resection had better overall survival, especially those with complete resection, compared to those who did not undergo surgical resection[10]. Similarly, Schellekes et al. found that patients with a single lesion of PCNSL might benefit from resection in terms of survival compared to those who received only diagnostic biopsy[23]. Furthermore, with advancements in neurosurgical techniques, an increasing number of studies have shown that craniotomy is safe for patients[25,26]. These findings suggest that complete tumor resection might offer greater survival benefits for PCNSL if more neurological function can be preserved. Our results indicated that surgical tumor resection was not a favorable factor for OS, considering that 70.6% of patients had residual central nervous system lymphoma before systemic treatment. It is plausible that the lack of complete tumor resection limited the survival benefit after surgery. The therapeutic and prognostic significance of surgery in PCNSL requires further prospective studies to evaluate.

Currently, although the NCCN guidelines recommend HD-MTX +/- RTX as the first-line induction therapy for PCNSL, followed by ASCT consolidation, the clinical benefit of RTX remains uncertain. In a recent meta-analysis including 13 studies (2 randomized controlled trials and 11 retrospective cohort studies)[27], the results showed that PCNSL patients receiving RTX treatment had significantly better objective response rate (ORR), complete response (CR) rate, and PFS than those who did not receive RTX. However, there was no statistically significant difference in OS ($P = 0.06$). The phase III large randomized controlled clinical trial HOVON 105/ALLG NHL 24 showed that the addition of RTX to the treatment regimen for newly diagnosed PCNSL did not improve efficacy[28]. Similarly, in this study, multivariate analysis showed that induction therapy without RTX was not an independent prognostic factor for survival. Furthermore, our study indicated that WBRT and ASCT were not independent predictors of OS in PCNSL, which might be due to the bias caused by the small number of patients who received ASCT or WBRT consolidation. A recent study reported an 8-year OS of 69% with the application of ASCT as a first-line consolidation regimen for newly diagnosed PCNSL, along with a significantly lower risk of relapse[29]. Two randomized controlled trials (IELSG32 study[30] and ANOCEF-GOELAMS study[31]) compared the efficacy of WBRT or ASCT as consolidations in patients who achieved remission after induction therapy. The results showed that both therapies achieved good disease control, with the ANOCEF-GOELAMS study showing a certain advantage of PFS in the ASCT group. Both studies observed more pronounced long-term neurological adverse effects in the WBRT group. To mitigate the cognitive impairment associated with WBRT, recent studies have focused on reduced-dose WBRT (rdWBRT) as consolidation therapy for PCNSL, with results showing good PFS and OS rates. rdWBRT combined with HD-MTX showed no statistically significant difference in OS and PFS compared to high-dose WBRT and suggested that patients under 60 years might benefit from rdWBRT[18]. A recent study showed that 5 years of HD-MTX maintenance was not inferior to ASCT consolidation[32]. Additionally, the emergence of new drugs (such as BTK inhibitors, bispecific antibodies, CAR-T cells, and IMiDs) will further challenge the authoritative status of ASCT in PCNSL[18].

Our results indicated that POD24 was an independent adverse prognostic factor for OS. Previous studies have shown that POD24 is not only an adverse prognostic factor for indolent NHLs (such as follicular lymphoma and marginal zone lymphoma)[5,6] but also for aggressive NHLs[7,8]. Current guidelines recommend classifying relapsed/refractory systemic DLBCL into two categories: patients with progression within 12 months are advised to receive second-line CAR-T therapy, while those with relapse/progression after 12 months consider second-line salvage chemotherapy followed by ASCT consolidation. Therefore, the prognostic and therapeutic significance of POD12 in systemic DLBCL patients is well established. Previous studies have shown that EFS24 is an important prognostic factor for systemic DLBCL[8]. However, the prognostic and therapeutic significance of progression between 12 and 24 months (POD12-24) and beyond 24 months in systemic DLBCL and PCNSL remains unclear. Our results indicated that not only was POD24 an adverse prognostic factor for OS in PCNSL, but patients with POD12-24 might also differ from those with POD12 and beyond 24 months, warranting treatment as a unique subgroup in clinical practice. However, the results of the validation dataset differed from our study, showing no statistically significant difference in survival between the two subgroups of POD12 and POD12-24. This discrepancy might be due to the following two factors: (1) our patients received HD-MTX-based regimens, while patients in the validation dataset were treated with BTK inhibitor ibrutinib, which might overcome the adverse prognosis associated with short-term progression; (2) the validation dataset included a small number of patients with secondary central nervous system diffuse large B-cell lymphoma, which might have affected the results. However, POD24 was also an adverse prognostic factor for OS in the validation dataset. In summary, the prognostic significance of POD24 and POD12-24 in PCNSL needs to be further clarified by large-sample prospective clinical trials. Additionally, our results indicated that elevated LDH, elevated TG, and non-responsive disease were independent adverse prognostic factors for POD24. Previous studies have shown

that lipid metabolism abnormalities exist in various tumors. In systemic DLBCL, univariate analysis showed that serum TG levels was associated with OS and PFS, and multivariate analysis confirmed the adverse effect of TG on PFS ($P = 0.013$)[33]. In our cohort, elevated TG was an adverse prognostic factor for OS in univariate analysis and was closely related to POD24. Moreover, a higher proportion of cases with elevated LDH was observed in the POD24 group. Previous studies have shown that serum LDH levels do not have a prognostic effect in PCNSL cases under 70 years[34]. Similarly, in our cohort, serum LDH levels were not an adverse prognostic factor for OS in PCNSL. It was reported that 10–15% of PCNSL were refractory to initial treatment[18]. Our results indicated that non-responsive disease was an independent adverse prognostic factor for OS in PCNS-DLBCL. This is consistent with previous studies, in PCNSL who treated with HD - MTX - based induction regimens, after a median follow-up of 27.5 months, there was no statistically significant difference in OS and PFS between patients with interim positive and negative diseases assessed by PET - CT. However, at the end of treatment, PET - CT - negative patients had significantly longer PFS than PET - CT - positive patients ($P = 0.892$)[35]. Moreover, multivariate analysis found that incomplete remission before high-dose therapy/ASCT was an independent adverse prognostic factor for OS[18]. Based on these above three factors, we constructed the POD24 prediction model "LTE". The risk of POD24 was significantly higher in the high-risk "LTE" group compared to the low-risk group. The ROC curve determined the AUC for POD24 prediction to be 0.828, with a sensitivity and specificity of 79.4% and 79.3%, respectively. This model might helps to identify high-risk groups for POD24 early and may guide the adjustment of treatment strategies.

In summary, we observed that POD24 was an independent adverse predictor for OS, and, elevated LDH, elevated TG, and non-responsive disease were independent adverse prognostic factors for POD24 in PCNS-DLBCL. The "LTE" prediction model, which included these above three factors, might serve as a strong predictor of POD24. Additionally, the "LTE" prediction model was an adverse prognostic indicator for OS and PFS in PCNS-DLBCL. Several limitations of our study should be noted. The modest sample size may affect the robustness of our conclusions. Furthermore, our prognostic model lacks contemporary molecular biomarkers, a significant oversight given their clinical relevance. The model's predictive accuracy also remains untested in the context of novel therapies, such as BTK inhibitors and pomalidomide, which are changing the treatment paradigm for PCNSL. Therefore, large-scale prospective trials are essential to validate our findings and define the role of the "LTE" model in this new therapeutic era.

## Data availability

The datasets analysed during the current study available from the corresponding author on reasonable request.

Received: 11 July 2025; Accepted: 31 December 2025
Published online: 24 January 2026

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## Author contributions

Yuye Shi, Chunling Wang, and Yuqing Miao were primarily responsible for the conception and writing of the article. Yuye Shi was in charge of providing financial support. Yunjie Li, Xiaohu Xu, and Jingjing Ma was responsible for data organization and chart preparation. Yuan Deng, Tingting Ji, Zhengyuan Liu and Hong Tao were involved in data organization. The authors declare that they have no conflict of interest.


## Funding

The authors declare that no specific grant was received from any funding agency in the public, commercial, or not-for-profit sectors to support this work. The authors declare no conflict of interest.


## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

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