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Real-world clinical features and survival outcomes in diffuse large B-cell lymphoma patients with hepatitis B virus infection

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Abstract

Objective Hepatitis B virus (HBV) infection is associated with the incidence and prognosis of diffuse large B-cell lymphoma (DLBCL), and previous studies differ in terms of clinical characteristics and prognostic factors. In this study, we explored the clinical features and prognostic characteristics of real-world DLBCL patients infected with HBV.

Methods Patients with pathologically diagnosed primary DLBCL at West China Hospital of Sichuan University were enrolled. Patients with follicular lymphoma-transformed DLBCL, primary central nervous system DLBCL, and hepatitis C virus, hepatitis E virus, human immunodeficiency virus, or syphilis infections were excluded. Ultimately, a total of 941 patients were included in this study. All patients included in the study underwent HBV serum marker testing before treatment. The demographic features, clinical characteristics and treatments of patients with different HBV infection states were collected and analyzed comprehensively to identify prognostic factors for OS and PFS.

Results Statistical analysis of the data revealed that hepatitis B surface antigen positive (HBsAg +) DLBCL patients were younger and more likely to present with advanced disease, germinal center B cell-like subtype, B symptoms and splenic involvement. There were no significant differences in OS or PFS among patients with different HBV infection statuses ($\chi^2 = 0.139$, $P = 0.933$; $\chi^2 = 0.787$, $P = 0.675$); R-CHOP/R-CHOP-like regimens improved prognosis in HBsAg + DLBCL patients (OS: $\chi^2 = 7.679$, $P = 0.006$; PFS: $\chi^2 = 9.042$, $P = 0.003$); antiviral prophylaxis for HBsAg + DLBCL patients improved OS and PFS (HR: 0.336, $P = 0.012$, 95% CI [0.143, 0.788]; HR: 0.397, $P = 0.032$, 95% CI [0.171, 0.925]), with tenofovir treatment being particularly effective ($\chi^2 = 4.644$, $P = 0.031$; $\chi^2 = 4.554$, $P = 0.033$).

Conclusions HBsAg + DLBCL patients have unique clinical characteristics, and the use of CD20 monoclonal antibody based regimens significantly improves the outcome and prognosis of patients with HBsAg + DLBCL. Anti-HBV therapy, especially tenofovir, improves the prognosis of DLBCL patients with HBV presenting infection. Timely and sustained antiviral prophylaxis should be the standard strategy for treating DLBCL patients with HBV infection to optimize the efficacy of chemotherapy and immunotherapy.

Keywords Diffuse large B cell lymphoma, Hepatitis B virus, Prognosis, Clinical features

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 30.5%-41.2% of all NHL patients, with approximately 150,000 new patients diagnosed worldwide each year [1–4]. Previous studies have shown that hepatitis B virus (HBV) infection is associated with an increased risk of developing DLBCL, with a 1.24–2.69

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times greater risk compared to the general population [5–7]. Several reports suggest that patients with hepatitis B surface antigen positive (HBsAg+) DLBCL are characterized by a younger age, more advanced disease stage and B symptoms, high IPI scores, more splenic or retroperitoneal lymph node involvement, and reduced overall survival [8–12]. A high IPI score, MYC gene rearrangement, HBV-DNA concentration $\geq 2\times10^7$ IU/L and stage IV disease are currently considered risk factors in patients with HBsAg+DLBCL [13–15]. The clinical characteristics and prognostic factors of the patients varied in different studies, so we analyzed a large amount of real-world data in China, which better reflect actual clinical practice and enhances the external validity of the study. Additionally, this study retrospectively analyzed the impact of different antiviral drugs on patient outcomes, providing further reference for clinical practice.

Materials and methods

Patients and materials

We collected complete clinical data on a total of 941 patients with primary DLBCL pathologically diagnosed at West China Hospital of Sichuan University from January 2010 to December 2019. All patients included in this study were treated with CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone)/CHOP-like or R-CHOP (rituximab + CHOP)/R-CHOP-like regimens for ≥ 4 cycles. Prophylactic anti-HBV drugs mainly include lamivudine, entecavir and tenofovir.

Baseline information included age; sex; Ann Arbor stage of DLBCL; B symptoms; extranodal involvement; anti-HBV prophylaxis; frontline treatment regimens; Eastern Cooperative Oncology Group (ECOG) score; International Prognostic Index (IPI) score; liver, spleen and bone marrow involvement; Hans subtypes; BCL2 and MYC protein expression; and MYC, BCL2 and/or BCL6 gene rearrangement. We also collected laboratory data, including lactate dehydrogenase (LDH), β_2 microglobulin (β_2-MG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), HBV-DNA load, and serum hepatitis B virus marker levels.

Definition of HBV infection status and HBV reactivation

HBV infection status was classified into three groups based on the different status of HBV-related antibodies in the serum: HBsAg positive (HBsAg+), HBsAg negative and core antibody positive (HBsAg−/HBcAb+), and negative for both HBsAg and HBcAb (HBsAg−/HBcAb−). The HBsAg- group included patients who were HBsAg-/HBcAb+and HBsAg-/HBcAb-. HBsAg+patients are considered to be currently infected with HBV, while HBsAg-/HBcAb+patients are previously infected with HBV.

HBV reactivation (HBV-R) was defined as HBsAg+or HBsAg-/HBcAb+patients who experienced a more than 100-fold increase in the HBV DNA level after receiving therapy compared with the baseline value or who were negative for HBV DNA or HBsAg at baseline. HBV-R-related hepatitis was defined as a threefold or greater increase in the serum ALT level that exceeded the reference range (>50 U/L) during or after chemotherapy in the absence of other causes of hepatitis.

Assessment indicators

The efficacy of antitumor therapy was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the 2014 Lugano criteria. Overall survival (OS) was calculated from the date of diagnosis of DLBCL until death or censored at the last date of follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression.

Statistical analysis

Baseline characteristics were analyzed using the Pearson χ^2 test or Fisher's exact test for unordered categorical variables, and ordinal categorical variables were compared using the rank-sum test. Survival analysis was performed using the Kaplan–Meier method, and the log-rank test was used to compare the survival curves of the two groups. Univariate and multivariate Cox hazards proportional analyses were performed to determine potential risk factors for mortality. A P values < 0.05 were considered to indicate statistical significance. The data were analyzed using IBM SPSS 27.0.

Results

Clinical characteristics

All patients enrolled in the study were followed, the median follow-up time was 61.0 months (3.0–152.0 months). The median age of the 941 patients was 56.0 years (45.0–65.0 years), and 489 (52.0%) patients were male. HBsAg+patients were significantly younger at diagnosis (median age, 51.6 vs. 55.0), had an advanced stage (proportion of patients with stage III-IV disease: 60.9% vs. 47.5%, $P=0.021$), and had more GCB subtypes (37.0% vs. 26.8%, $P=0.041$), B symptoms (39.9% vs. 28.5%, $P=0.007$), spleen involvement (23.9% vs. 7.0%, $P<0.001$), elevated β_2-MG (60.1% vs. 55.0%, $P=0.008$) and AST levels (21.7% vs. 10.2%, $P<0.001$) (Table 1).

HBV-R

A total of 138 patients with HBsAg+DLBCL and 473 patients with HBsAg−/HBcAb+DLBCL were included in the study, and a total of 26 (4.3%, 26/611) patients developed HBV-R. The median time from

Table 1 Clinical characteristics of HBsAg positive and HBsAg negative diffuse large B-cell lymphoma patients

	HBsAg + (n = 138,%)	HBsAg- (n = 803,%)	P^*
Number of patients	138	803	
Age, y			**0.006**
≤ 60	102(73.9)	496(61.8)	
> 60	36(26.1)	307(38.2)	
Sex			0.429
Male	76(55.1)	413(51.4)	
Female	62(44.9)	390(48.6)	
Ann Arbor stage			**0.021**
I	20(14.5)	187(23.3)	
II	34(24.6)	235(29.3)	
III	36(26.1)	122(15.2)	
IV	48(34.8)	259(32.3)	
Cell of origin			**0.041**
GCB	51(37.0)	215(26.8)	
Non-GCB	83(60.1)	569(70.9)	
Not available	4(2.9)	19(2.4)	
ECOG score			0.178
0–1	118(85.5)	718(89.4)	
2–4	20(14.5)	85(10.6)	
IPI			0.455
0–1	61(44.2)	387(48.2)	
2–3	61(44.2)	324(40.3)	
4–5	16(11.6)	92(11.5)	
Symptoms B	55(39.9)	229(28.5)	**0.007**
Liver involvement	7(5.1)	26(3.2)	0.406
Spleen involvement	33(23.9)	56(7.0)	**< 0.001**
Bone marrow involvement	10(7.2)	54(6.7)	0.894
Extranodal involvement			0.755
0	18(13.0)	106(13.2)	
1	70(50.7)	419(52.2)	
≥ 2	50(36.2)	278(34.6)	
Elevated LDH	57(41.3)	288(35.9)	0.221
Elevated β2-MG	83(60.1)	442(55.0)	**0.008**
Elevated HBV-DNA	68(49.3)	3(0.4)	**< 0.001**
Elevated ALT	19(13.8)	77(9.6)	0.134
Elevated AST	30(21.7)	82(10.2)	**< 0.001**
double expression	25(18.1)	164(20.4)	0.662
Double/triple hit	2(1.4)	8(1.0)	1.000

HBsAg, hepatitis B virus surface antigen; GCB, germinal center B cell-like diffuse large B-cell lymphoma; non-GCB, non-germinal center B cell-like diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; LDH, lactate dehydrogenase; β2-MG, β2 microglobulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase

* χ^2 test and rank-sum test were used for comparison. Significant values ($P < 0.05$) are highlighted in bold

first chemotherapy to HBV-R was 12 months. Compared with HBsAg−/HBcAb + DLBCL patients, HBsAg + DLBCL patients had a greater rate of HBV-R (15.2% vs. 1.1%, $P < 0.001$). The use of CD20 monoclonal antibodies did not increase the HBV reactivation rate in HBsAg + DLBCL patients (16.1% vs. 7.1%, $P = 0.621$) or HBsAg−/HBcAb + patients (1.1% vs. 0%, $P = 1.000$). Anti-HBV prophylaxis did not decrease the HBV-R rate in HBsAg + /HBV DNA- patients (21.6% vs. 26.7%, $P = 0.949$) or HBsAg−/HbcAb + patients (1.1% vs. 1.0%, $P = 1.000$), but HBsAg + /HBV DNA- patients had more HBV-R than HBsAg−/HbcAb + patients despite receiving

anti-HBV prophylaxis (21.6% vs. 1.1%, $P<0.001$). Nine patients in the study developed HBV-R-related hepatitis, and all of these patients were treated with R-CHOP/R-CHOP-like regimens. The incidence of HBV-R-related hepatitis was greater in patients with HBsAg+DLBCL than in those with HBsAg−/HBcAb+DLBCL (5.1% vs. 0.4%, $P<0.001$).

In this study, 292 patients received prophylactic anti-HBV treatments. A total of 18 (6.2%, 18/292) patients developed HBV-R, of which 8 (8/114, 7.0%) patients were treated with Lamivudine, 7 (7/129, 5.4%) patients were treated with Entecavir, and 1 (1/42, 2.4%) patient was treated with Tenofovir. HBV-R developed in 1 of 6 patients who had received multi-drug anti-HBV therapy. Only 1 patient was treated with Adefovir, and that patient developed HBV- R. There is no significant difference in HBV-R when lamivudine, entecavir, or tenofovir was used for anti-HBV therapy ($P=0.605$). Additional analyses revealed tenofovir improved patients' OS and PFS more than did entecavir ($\chi^2=4.644$, $P=0.031$; $\chi^2=4.554$, $P=0.033$) (Fig. 1).

Efficacy and survival outcomes

Efficacy

A total of 637 patients (67.7%, 637/941) achieved CR, and 203 patients (21.6%, 203/941) achieved PR; the overall remission rate (ORR) was 89.3%. 29 patients (50.9%, 29/57) achieved CR, 15 patients (26.3%, 15/57) achieved PR among patients treated with CHOP/CHOP-like regimens, with an ORR of 77.2%; 608 patients (68.8%, 608/884) achieved CR, and 188 patients (21.3%, 188/884) achieved PR among patients treated with R-CHOP/R-CHOP-like regimens, with an ORR of 90.0%. The ORR was similar in HBsAg+DLBCL, HBsAg−/HBcAb+DLBCL, and HBsAg-/HBcAb-DLBCL patients (87.0% vs. 90.1% vs. 89.1%, $P=0.579$).

Treatment of HBsAg+DLBCL and HBsAg−/HBcAb-DLBCL patients with R-CHOP/R-CHOP-like regimens was more effective than treatment with CHOP/CHOP-like regimens, but there was no statistically significant difference in efficacy between these two chemotherapy regimens in HBsAg−/HBcAb+DLBCL patients (Supplementary Table S1). Relapse after treatment was more common in HBsAg+DLBCL patients than in HBsAg−/HBcAb+DLBCL and HBsAg−/HBcAb-DLBCL patients (10.9% vs. 5.3% vs. 5.8%, $P=0.052$).

Survival outcomes

At the end of follow-up, 243 patients (25.8%, 243/941) in this cohort had died—38 patients (27.5%, 38/138) in the HBsAg+group, 124 patients (26.2%, 124/473) in the HBsAg−/HBcAb+group, and 81 patients (25.4%, 81/330) in the HBsAg−/HBcAb− group—and the median OS and PFS of all patients were not reached.

The 5-year OS rates for DLBCL patients in the HBsAg+, HBsAg−/HBcAb+, and HBsAg-/HBcAb- groups were 76.0% versus 74.4% versus 77.4%, respectively; the median OS was 121 months in the HBsAg-/HBcAb+group and was not reached in either the HBsAg+or HBsAg−/HBcAb− group ($\chi^2=0.139$, $P=0.933$); the 5-year PFS rates in the three groups were 71.3% versus 73.9% versus 76.3%, respectively; and the median PFS was not reached in any of the three groups ($\chi^2=0.787$, $p=0.675$). Both the median OS and PFS were greater in the R-CHOP/R-CHOP-like group than in the CHOP/CHOP-like group (not reached vs. 68 months, $\chi^2=21.686$, $P<0.001$; not reached vs.48 months, $\chi^2=26.776$, $P<0.001$) (Fig. 2).

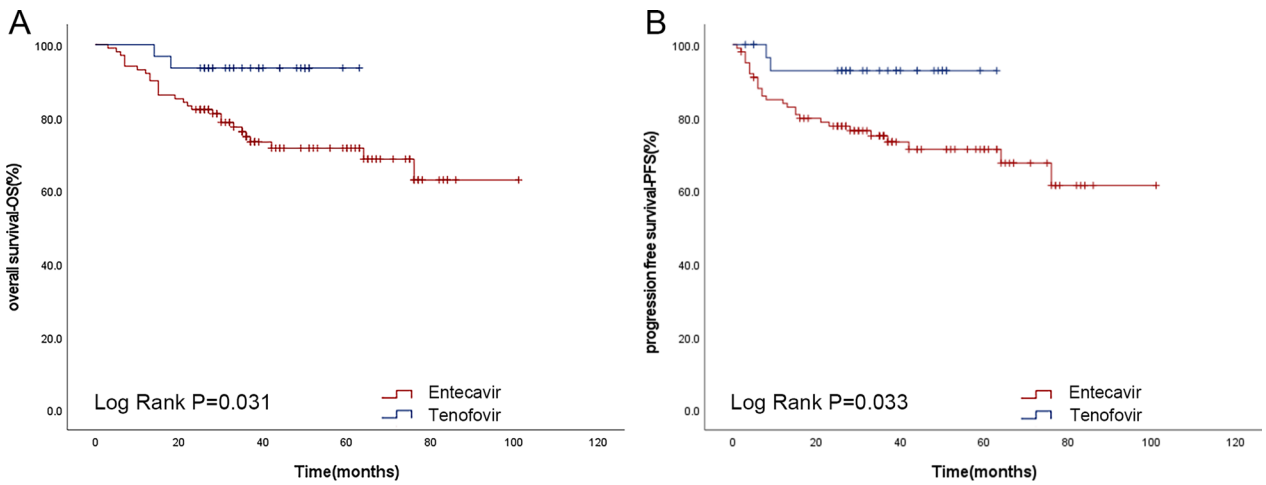

Fig. 1 Kaplan–Meier analysis of the OS (**A**) and PFS (**B**) in patients with primary DLBCL treated with prophylactic anti-HBV therapy with entecavir and tenofovir after June 17, 2014.OS: overall survival; PFS: progression-free survival; DLBCL: diffuse large B-cell lymphoma; HBV: hepatitis B virus

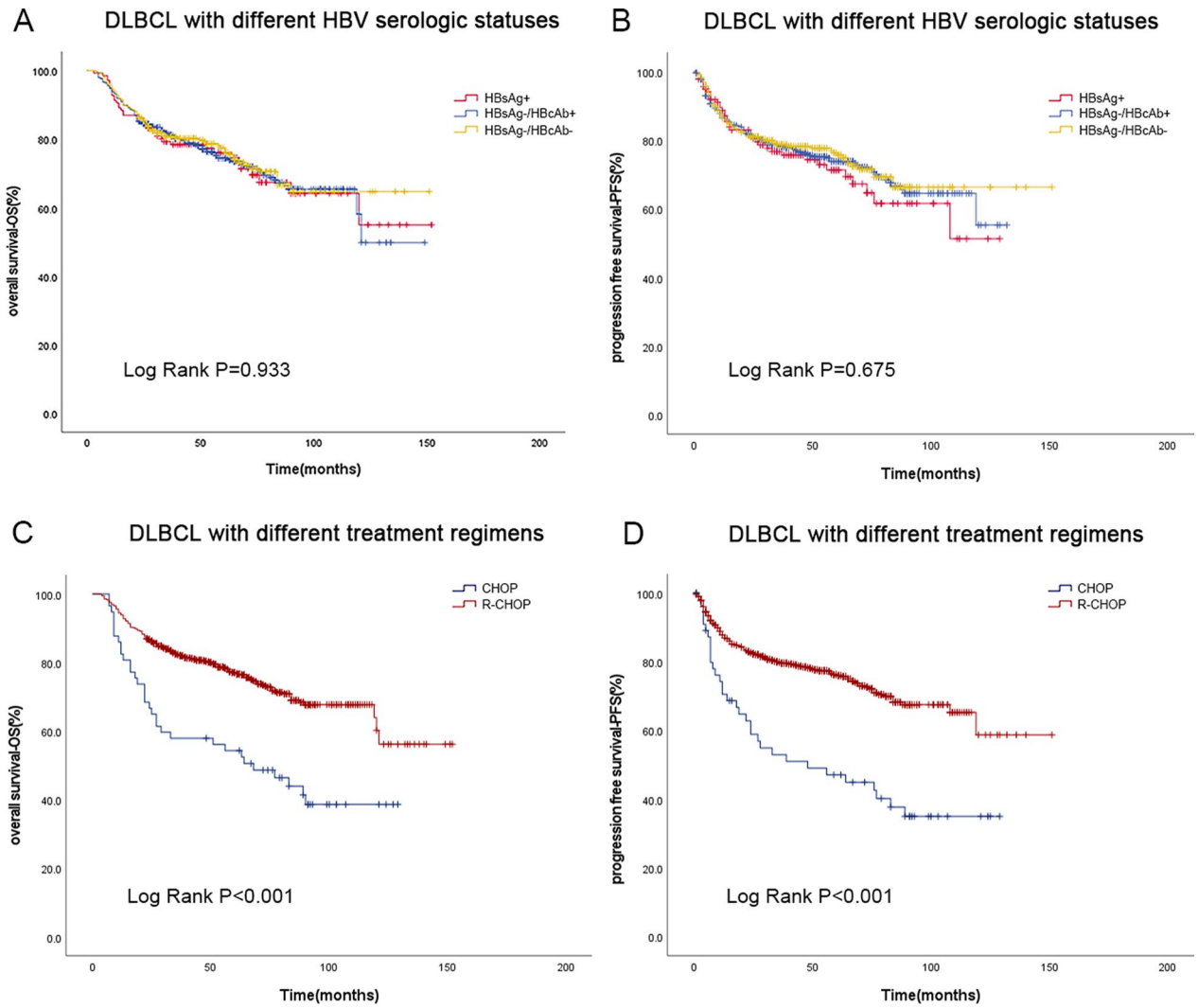

Fig. 2 Kaplan–Meier analysis of the OS and PFS in patients with different HBV serologic statuses and different chemotherapy regimens. OS (**A**) and PFS (**B**) in patients with different HBV serologic statuses. OS (**C**) and PFS (**D**) in patients treated with different chemotherapy regimens. OS: overall survival; PFS: progression-free survival; HBV: hepatitis B virus

Among the 138 HBsAg + DLBCL patients, 14 (10.1%) patients received CHOP/CHOP-like regimens, and 124 (89.9%) patients received R-CHOP/R-CHOP-like regimens. The 3- and 5-year OS rates were 57.1% versus 81.9% and 49.0% versus 79.6%, respectively, in the two groups, and the R-CHOP/R-CHOP-like group had a better median OS than did the CHOP/CHOP-like group (not reached vs. 56 months, $\chi^2 = 7.679$, $P = 0.006$); the 3- and 5-year PFS rates were 48.7% versus 79.6% and 29.2% versus 76.8%, respectively, in the two groups, and the median PFS was also better in the R-CHOP/R-CHOP-like group (not reached vs. 33 months, $\chi^2 = 9.042$, $P = 0.003$).

There were 473 HbsAg−/HbcAb + DLBCL patients, 30 (6.3%) in the CHOP/CHOP-like group and 443 (93.7%) in the R-CHOP/R-CHOP-like group; the 3- and 5-year OS rates were 60.0% versus 82.6% and 56.7% versus 75.3% in the two groups, respectively; the 3- and 5-year PFS rates were 53.6% vs 79.7% and 49.1% vs 75.1% in the two groups, respectively; and both OS and PFS were better in the R-CHOP/R-CHOP-like group (median OS: 121 months vs. 83 months, $\chi^2 = 7.146$, $P = 0.008$; median PFS: not reached vs. 77 months, $\chi^2 = 9.515$, $P = 0.002$).

Among the 330 HbsAg-/HbcAb-DLBCL patients, 13 patients (3.9%) were in the CHOP/CHOP-like group, and 317 patients (96.1%) were in the R-CHOP/R-CHOP-like

group; the 3-year and 5-year OS rates in the two groups were 46.2% versus 82.1% and 46.2% versus 78.7%, respectively; the 3-year and 5-year PFS rates were 46.2% versus 80.1% and 36.9% versus 76.8%, respectively; and the R-CHOP/R-CHOP-like group remained superior in terms of OS and PFS (median OS: not reached vs. 29 months, $\chi^2=8.039$, $P=0.005$; median PFS: not reached vs. 24 months, $\chi^2=8.317$, $P=0.004$) (Fig. 3).

After excluding 23 patients with missing information, we analyzed survival outcomes in 918 patients with different COO subtypes. In HBsAg+DLBCL patients, there was no significant difference between GCB and non-GCB subtypes in OS and PFS ($\chi^2=0.101$, $P=0.751$; $\chi^2=0.404$, $P=0.525$). GCB and non-GCB subtypes in HBsAg-/HBcAb+and HBsAg-/HBcAb- patients similarly did not show a significant difference (HBsAg−/ HBcAb+: OS: $\chi^2=0.415$, $P=0.520$; PFS: $\chi^2=0.454$, $P=0.500$; HBsAg-/HBcAb-: OS: $\chi^2=1.260$, $p=0.262$; PFS: $\chi^2=1.093$, $p=0.296$) (Supplementary Fig. 1).

Prognostic factors

Prognostic factors in HBsAg + DLBCL patients

According to the univariate analysis, female sex, age > 60 years, elevated LDH and ECOG score ≥ 2 were risk factors for OS; ECOG score ≥ 2, elevated LDH and IPI score > 3 were risk factors for PFS in HBsAg+DLBCL patients. Multivariate analysis revealed that female sex, age > 60 years, elevated LDH, rituximab used and anti-HBV prophylaxis were found to be independent prognostic factors affecting OS, and the above five factors with an ECOG score ≥ 2 were prognostic factors affecting PFS. The use of rituximab and anti-HBV prophylaxis were protective factors for OS and PFS in HBsAg+DLBCL patients (Table 2).

Prognostic factors in HBsAg-/HBcAb + DLBCL patients

Univariate analysis revealed that age > 60 years, advanced stage disease (stage III or IV), liver involvement, extranodal involvement ≥ 2, elevated LDH, and IPI ≥ 3 were associated with inferior OS and PFS in HBsAg-/HBcAb+DLBCL patients. Multivariate analysis revealed that age, rituximab used, and disease stage were prognostic factors affecting OS and PFS in patients, and the administration of rituximab improved the prognosis of HBsAg−/HBcAb+DLBCL patients (Table 3).

Prognostic factors in HBsAg-/HBcAb-DLBCL patients

According to the univariate analysis, advanced disease stage (stage III or IV), elevated LDH, an IPI ≥ 3 and rituximab were prognostic factors for OS in patients with HBsAg-/HBcAb-DLBCL, and the above four factors plus an ECOG score ≥ 2 were prognostic factors for PFS. Multivariate analysis revealed that prognostic factors for OS in HBsAg-/HBcAb-DLBCL patients included advanced disease stage, elevated LDH, and GCB type cell origin. Advanced disease stage, elevated LDH, GCB type cell origin and rituximab used affected PFS in HBsAg-/HBcAb-DLBCL patients (Supplementary Table S2).

Discussion

To our knowledge, this is one of the largest studies to investigate DLBCL patients with HBV infection. Our study included 138 HBsAg+DLBCL patients, 473 HBsAg-/HBcAb+DLBCL patients, and 330 HBsAg-/HBcAb-DLBCL patients in the same period of time in the real world and compared and analyzed their clinical features and prognostic characteristics from multiple perspectives. With an HBV incidence rate of 5.9% in 2019, the Western Pacific region is second to the African region [16], and in China, which is one of the countries in the Western Pacific region, HBV infection remains a major public health problem. The prevalence of HBV infection is significantly greater in patients with DLBCL than in the general population, and an association between HBV infection and an increased incidence of DLBCL has been demonstrated in previous studies [5–7]. Chronic stimulation by the HBV antigen, genetic mutations caused by HBV and integration of the HBV genome with host genes are possible mechanisms of HBV-related DLBCL [8, 11, 12].

The HBsAg+rate in the DLBCL patients included in the study was 14.7%, which was similar to that observed in previous retrospective studies (13.8–32.5%) [11, 13, 17, 18] but notably greater than that in the general population. Compared to HBsAg-DLBCL patients, HBsAg+DLBCL patients have the following characteristics: younger age, advanced clinical stage, higher

(See figure on next page.)

Fig. 3 Kaplan–Meier analysis of the OS and PFS of patients receiving different chemotherapy regimens. OS (**A**) and PFS (**B**) in HBsAg+DLBCL patients treated with CHOP/CHOP-like or R-CHOP/R-CHOP-like regimens; OS (**C**) and PFS (**D**) in HBsAg-/HBcAb+DLBCL patients treated with CHOP/CHOP-like or R-CHOP/R-CHOP-like regimens; OS (**E**) and PFS (**F**) in HBsAg-/HBcAb-DLBCL patients 28 treated with CHOP/CHOP-like or R-CHOP/R-CHOP-like regimens. OS: overall survival; PFS: progression-free survival; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP: CHOP plus rituximab; HBsAg+: hepatitis B virus surface antigen positive; HBsAg-/HBcAb+: hepatitis B virus surface antigen negative/core antibody positive; HBsAg-/HBcAb-: hepatitis B virus surface antigen negative/core antibody negative; DLBCL: diffuse large B-cell lymphoma

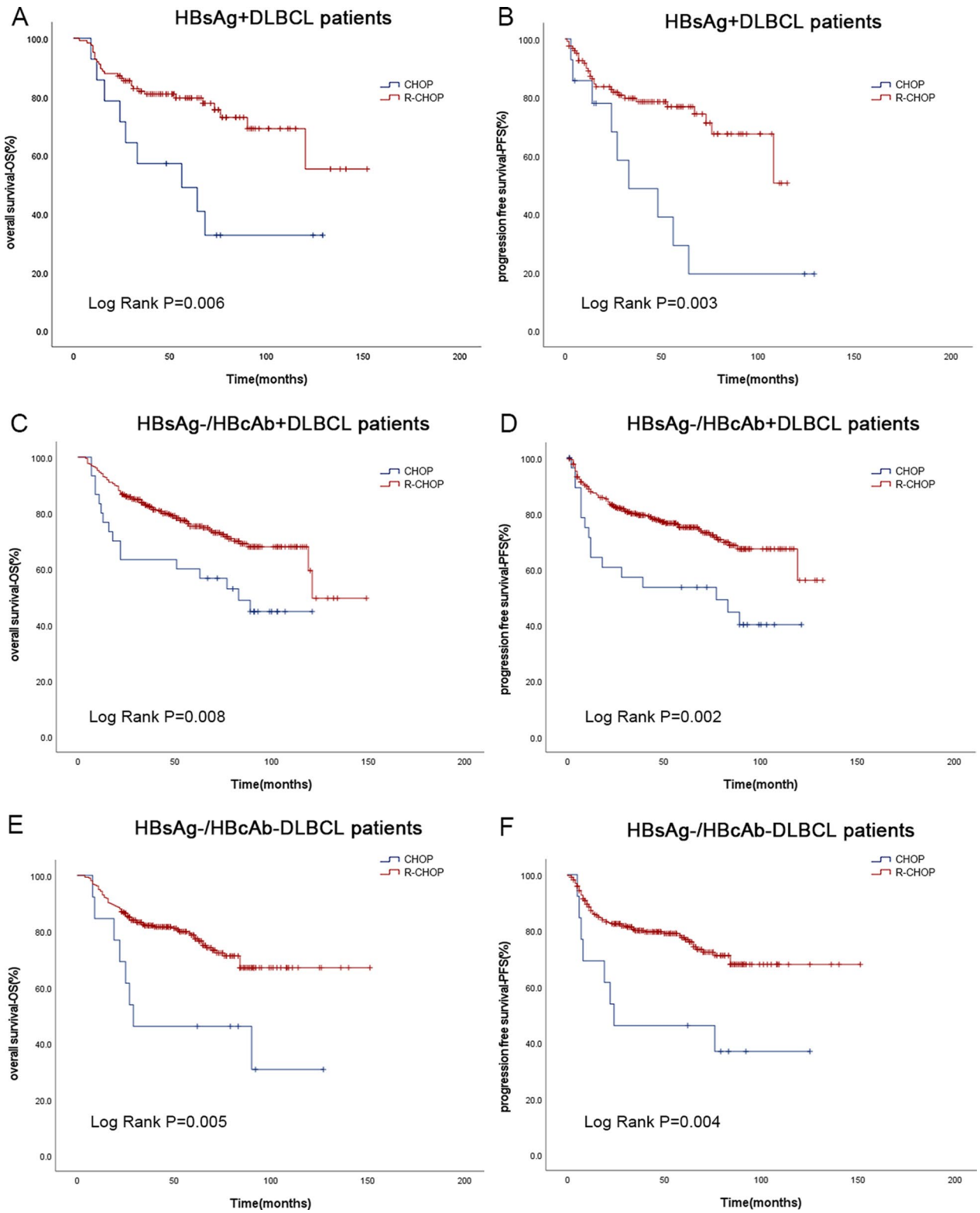

Fig. 3 (See legend on previous page.)

Table 2 Risk factors for OS and PFS in HBsAg + DLBCL patients

Parameters	OS				PFS			
	Univariant		Multivariant		Univariant		Multivariant	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P**
Females	1.989 (1.039–3.810)	**0.038**	2.035 (1.040–3.981)	**0.038**	1.743 (0.915–3.321)	0.091	2.137 (1.088–4.199)	**0.027**
Age > 60 years	2.016 (1.039–3.913)	**0.038**	2.496 (1.188–5.245)	**0.016**	1.831 (0.946–3.543)	0.073	2.281 (1.085–4.795)	**0.030**
Rituximab included	0.361 (0.170–0.766)	**0.008**	0.198 (0.081–0.485)	**< 0.001**	0.331 (0.155–0.706)	**0.004**	0.161 (0.065–0.398)	**< 0.001**
Ann Arbor stage III/IV	0.950 (0.494–1.826)	0.878	0.460 (0.179–1.183)	0.107	1.108 (0.577–2.125)	0.758	0.523 (0.211–1.293)	0.160
Positive B symptoms	1.167 (0.612–2.227)	0.639	/	/	1.247 (0.654–2.377)	0.503	/	/
Liver involvement	1.015 (0.244–4.224)	0.984	/	/	1.037 (0.249–4.317)	0.960	/	/
Spleen involvement	0.841 (0.385–1.836)	0.664	/	/	0.854 (0.390–1.872)	0.693	/	/
Extranodal involvement ≥ 2	0.988 (0.505–1.933)	0.973	/	/	1.112 (0.567–2.181)	0.757	/	/
ECOG score ≥ 2	2.689 (1.267–5.705)	**0.010**	2.157 (0.867–5.367)	0.098	3.595 (1.664–7.767)	**0.001**	2.934 (1.177–7.316)	**0.021**
GCB subtype	1.203 (0.623–2.323)	0.581	0.731 (0.323–1.658)	0.454	1.313 (0.681–2.533)	0.416	0.718 (0.300–1.719)	0.457
Elevated LDH	2.158 (1.137–4.095)	**0.019**	3.675 (1.342–10.059)	**0.011**	2.561 (1.342–4.888)	**0.004**	3.357 (1.234–9.130)	**0.018**
IPI ≥ 3	1.921 (0.992–3.719)	0.053	0.893 (0.268–2.631)	0.763	2.128 (1.100–4.119)	**0.025**	1.068 (0.352–3.242)	0.907
Anti-HBV	0.600 (0.288–1.248)	0.171	0.336 (0.143–0.788)	**0.012**	0.740 (0.356–1.535)	0.418	0.397 (0.171–0.925)	**0.032**

OS, overall survival; PFS, progression-free survival; HBsAg +, hepatitis B virus surface antigen positive; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell-like diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, international prognostic index; anti-HBV, prophylactic anti-hepatitis B virus therapy

* Cox hazards proportional analysis of prognostic factors for patients with diffuse large B-cell lymphoma. Significant values ($P < 0.05$) are highlighted in bold

percentage of the GCB subtype, elevated β2-MG and AST levels, common B-symptoms, and more frequent splenic involvement. The young age, advanced clinical stage, and frequent splenic involvement of HBsAg + DLBCL patients have been similarly reported in previous studies [8, 9, 11, 13, 19, 20]. The high proportion of the GCB subtype in HBsAg + DLBCL patients found in our data is different from that reported in prior studies [8, 9]; in addition, we found no difference in OS or PFS between GCB and non-GCB patients with HBsAg + DLBCL, which has been similarly reported in the past [11, 14], but there are also different findings of significantly shorter OS in GCB patients [13]. The generally smaller sample sizes and greater proportion of patients without cell of origin testing in previous studies may have contributed to the discrepancy in the results.

Cheng et al. [21] showed that compared with HBsAg- DLBCL patients, HBsAg + DLBCL patients had a lower ORR (76.5% vs. 85.5%, $p = 0.043$), 5-year OS rate (57.2% vs. 73.5%, $p < 0.001$) and PFS rate (47.2% vs. 60.7%, $p = 0.013$). HBsAg positivity is an independent risk factor for HBV-related DLBCL and is also an important factor contributing to the poor efficacy of cytotoxic chemotherapy or immunotherapy [9, 22]. Our study revealed no statistically significant differences in OS, PFS, or ORR among patients with different HBV serologic statuses. Since further analysis revealed that tenofovir was more prognostically favorable than entecavir, the differences in the results may be related to the low rate of entecavir use and the small sample size in the above study.

Analysis of the efficacy of different antitumor regimens revealed that R-CHOP/R-CHOP-like regimens had better efficacy in HBsAg + and HBsAg−/HBcAb- DLBCL patients than did CHOP/CHOP-like regimens, whereas the efficacy of the two regimens was similar in HBsAg−/HBcAb + DLBCL patients. It has been noted that HBV infection can make cells resistant to chemotherapeutic agents that induce S-phase arrest by

Table 3 Risk factors for OS and PFS in HBsAg-/HBcAb + DLBCL patients

Parameters	OS				PFS			
	Univariant		Multivariant		Univariant		Multivariant	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P**
Females	0.874 (0.612–1.249)	0.461	/	/	0.893 (0.625–1.276)	0.534	/	/
Age > 60 years	2.017 (1.407–2.893)	**< 0.001**	1.744 (1.173–2.593)	**0.006**	1.985 (1.384–2.846)	**< 0.001**	1.717 (1.156–2.549)	**0.007**
Rituximab included	0.494 (0.291–0.838)	**0.009**	0.406 (0.235–0.702)	**0.001**	0.446 (0.262–0.757)	**0.003**	0.382 (0.220–0.664)	**< 0.001**
Ann Arbor stage III/IV	2.402 (1.661–3.473)	**< 0.001**	2.369 (1.440–3.898)	**< 0.001**	2.518 (1.740–3.643)	**< 0.001**	2.520 (1.526–4.160)	**< 0.001**
Positive B symptoms	0.724 (0.628–1.382)	0.724	/	/	0.941 (0.634–1.396)	0.761	/	/
Liver involvement	2.898 (1.351–6.218)	**0.006**	1.898 (0.861–4.183)	0.112	2.660 (1.240–5.710)	**0.012**	1.520 (0.681–3.392)	0.307
Spleen involvement	1.313 (0.706–2.443)	0.390	/	/	1.412 (0.759–2.626)	0.276	/	/
Extranodal involvement ≥ 2	1.678 (1.177–2.393)	**0.004**	1.103 (0.721–1.687)	0.652	1.680 (1.178–2.396)	**0.004**	1.126 (0.736–1.725)	0.584
ECOG score ≥ 2	1.460 (0.873–2.443)	0.149	0.877 (0.477–1.611)	0.671	1.421 (0.851–2.373)	0.179	0.824 (0.449–1.515)	0.534
GCB subtype	1.140 (0.764–1.699)	0.521	0.947 (0.624–1.436)	0.797	1.146 (0.769–1.709)	0.502	0.963 (0.635–1.461)	0.860
Elevated LDH	1.678 (1.176–2.394)	**0.004**	1.262 (0.808–1.970)	0.306	1.637 (1.147–2.336)	**0.007**	1.159 (0.740–1.815)	0.518
IPI ≥ 3	2.146 (1.501–3.069)	**< 0.001**	0.956 (0.547–1.671)	0.873	2.122 (1.484–3.035)	**< 0.001**	0.938 (0.538–1.633)	0.820
Anti–HBV	0.914 (0.626–1.334)	0.641	/	/	0.891 (0.611–1.298)	0.547	/	/

OS, overall survival; PFS, progression-free survival; HBsAg−/HBcAb +, hepatitis B virus surface antigen negative/core antibody positive; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell-like diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, international prognostic index; anti-HBV, prophylactic anti-hepatitis B virus therapy

* Cox hazards proportional analysis of prognostic factors for patients with diffuse large B-cell lymphoma. Significant values ($P < 0.05$) are highlighted in bold

specifically inhibiting the activation of CHK2 response signaling in DLBCL or by upregulating the expression of lncNBAT1 in tumor cells [13, 23]. In this study, 78.3% of patients (108/138) in the HBsAg + group and 38.1% of patients (180/473) in the HBsAg−/HBcAb + group were treated with anti-HBV drugs prior to antitumor therapy ($P < 0.001$), and 30.0% of HBsAg-/HBcAb + DLBCL patients (88/293) who did not undergo anti-HBV treatment did not have their HBV-DNA loads tested, which may have resulted in HBV virus replication in the patient's body but not being recognized and prevented promptly, thus affecting the patient's response to chemotherapy regimens.

The use of rituximab and anti-HBV prophylaxis are associated with improved OS in HBsAg + DLBCL patients. Although the use of rituximab in HBsAg-/HBcAb-DLBCL patients did not significantly affect OS according to multivariate analysis, the survival analysis still indicated that patients treated with R-CHOP/R-CHOP-like regimens had a more favorable prognosis than those treated with CHOP/CHOP-like regimens. This discrepancy may be attributed to the limited sample size of the HBsAg-/HBcAb-DLBCL patient group in our study.

HBV-R is a serious complication after cytotoxic chemotherapy or immunotherapy in DLBCL patients with chronic HBV infection, with clinical outcomes varying from asymptomatic to acute liver failure or death [24]. CD20 monoclonal antibodies in combination with anthracycline-based chemotherapeutic agents have been reported to increase the risk of HBV-R in patients with DLBCL [25]. Our study revealed that HBsAg + DLBCL patients had a greater rate of HBV-R and a greater incidence of HBV-R-related hepatitis than HBsAg-DLBCL patients. Treatment with or without CD20 monoclonal antibody had no effect on HBV-R but may increase the risk of HBV-R-related hepatitis. The majority of patients who developed HBV-R-related hepatitis in this study

improved after receiving antiviral and hepatoprotective treatments. As R-CHOP/R-CHOP-like chemotherapy regimens have significant advantages in improving the prognosis of patients, more emphasis should be placed on the detection of serum hepatitis B markers and HBV-DNA levels before chemotherapy, and prophylactic anti-HBV drugs should be used as appropriate. Serum hepatitis B markers, HBV-DNA and liver function should also be regularly monitored both during and after chemotherapy, and early intervention should be implemented when HBV-R and related hepatitis are present. The common anti-HBV prophylaxes include entecavir, tenofovir, and lamivudine. Tenofovir was approved for the treatment of HBV in China on June 17, 2014, and survival analyses of patients after this date revealed that the use of tenofovir was more favorable for patient prognosis than the use of entecavi; however, the study was unable to collect patients' courses of anti-HBV treatment for analysis. The standardized criterion for the optimal course of anti-HBV prophylaxis has not been established and needs to be explored in prospective studies.

There are several limitations to our study. First, retrospective studies have inherent limitations, and confounding factors and bias may affect the accuracy of the results. Second, in our study, HBV-R was defined as a more than 100-fold increase in HBV DNA from baseline, a decrease in the percentage of patients who were negative for HBV DNA at baseline to positive, or a change from negative to positive for HBsAg after receiving immunosuppressive therapy or chemotherapy; however, some patients were not regularly monitored for HBsAg status and HBV DNA load, and the inability to determine their HBV-R status may have led to an underestimation of HBV-R rates in the study. In addition, this study was unable to collect the treatment course of patients receiving anti-HBV therapy, and some patients may discontinue the medication on their own before achieving treatment targets, which could affect the results of the efficacy analyses of anti-HBV prophylaxis, as well as prognostic analyses of patients.

Conclusions

In summary, the prevalence of HBsAg positivity in DLBCL patients is greater than that in the general population, and DLBCL patients with HBV infection have unique clinical features and prognosis factors. HBV infection may be associated with an increased risk of developing DLBCL as well as patient resistance to chemotherapeutic regimens. Further study on the function and mechanism of HBV in the pathogenesis of DLBCL is necessary to guide clinical practice and improve patient survival and prognosis. CD20 monoclonal antibody does not increase the risk of HBV reactivation in HBsAg + DLBCL patients, but does increase the risk of HBV reactivation-related hepatitis. Tenofovir used improves the prognosis of HBsAg + DLBCL patients.

Abbreviations

HBV	Hepatitis B virus
DLBCL	Diffuse large B-cell lymphoma
HBsAg+	Hepatitis B surface antigen-positive
HBsAg-	Hepatitis B surface antigen negative
HBcAb	Hepatitis B virus core antibody
HBsAg-/HBcAb+	Hepatitis B virus surface antigen negative/core antibody positive
HBsAg-/HBcAb-	Hepatitis B virus surface antigen negative/core antibody negative
NHL	Non-Hodgkin lymphoma
GCB	Germinal center B cell-like diffuse large B-cell lymphoma
non-GCB	Non-germinal center B cell-like diffuse large B-cell lymphoma
ECOG	Eastern cooperative oncology group score
IPI	International prognostic index score
LDH	Lactate dehydrogenase
β2-MG	β_2 Microglobulin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HBV-R	HBV reactivation
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
OS	Overall survival
PFS	Progression-free survival

Supplementary Information

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Additional file 1.

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Author contributions
WXY: Conceptualization, data curation, formal analysis, writing—original draft. XZ: Conceptualization, data curation, investigation. HBM: review and editing. CGX: Conceptualization, review and editing. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
This retrospective study protocol was conducted in conformity with the Declaration of Helsinki and was approved by the Ethics Committee of West China Medical College of Sichuan University (approval number: 2024–955). As this study is a retrospective study and patient anonymization, the Ethics Committee has determined to be exempt from signing informed consent forms.

Consent for publication
Not applicable.

Competing interests
All the authors declare no actual or potential conflict of interest with this study.

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