Original Article

The association of the hepatitis B virus infection and diffuse large B-cell lymphoma

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ABSTRACT

الأهداف: لاستطلاع الخصائص الأساسية للسكان المصابين بـ DLBCL، لنبحث ما إذا كانت HBsAg(+) تؤثر على بقاء الأفراد.

المنهجية: شملت الدراسة 602 فرداً يعانون من DLBCL خلال الفترة من يناير 2011م إلى ديسمبر 2021م. قمنا بتحليل البيانات السريرية العامة للمرضى. تم تطبيق تحليل COX متعدد المتغيرات وأحادي المتغيرات لتقييم العوامل التي تؤثر على فترة البقاء للمرضى الذين يعانون من DLBCL.

النتائج: تم جمع 602 حالة من الأفراد المصابين بـDLBCL في هذه الدراسة، بما في ذلك 154 مريضًا (25.6%) في مجموعة HBsAg(+) و448 مريضًا (74.4%) في مجموعة HBsAg(–). بالمقارنة مع حالات HBsAg(–)، فإن السكان في مجموعة HBsAg(+) يميلون إلى أن يكونوا في مرحلة لاحقة (المرحلة III–IV)، ويحصلون على نقاط IPI أعلى (3–5 نقاط)، ويميلون إلى وجود أعراض B، وظهور تأثير على وظائف الكبد، والتكرار (جميع القيم $p<0.05$). بعد المتابعة، توفي 194 مريضًا (32.2%). كانت المتوسطة العامة للبقاء في مجموعتي HBsAg(+) و 16.5 شهرًا و HBsAg(–) 35 شهرًا على التوالي. كان معدل البقاء العام لمدة 5 سنوات في السكان المصابين بـ HBsAg(+) و 42% HBsAg(–) و 63% على التوالي. أظهر تحليل COX أن HBsAg(+) يؤثر على توقعات مرضى DLBCL (HR 1.46، 95%CI 1.07–1.99، $p=0.017$)

الخلاصة: يبدو أن HBsAg(+) عامل خطر مستقل لسوء توقعات سكان DLBCL، لذا يجب أن نركز على هؤلاء المرضى في العمل السريري.

Objectives: To investigate the basic characteristics of patients with diffuse large B-cell lymphoma (DLBCL) and whether hepatitis B surface antigen positive (HBsAg [+]) affects the survival of patients with DLBCL.

Methods: The study was carried out at Affiliated Hospital of Hebei University, Baoding, China, including 602 DLBCL cases from January 2011 to December 2021. We analyzed patients' general clinical data and applied multivariate and univariate Cox analyses to assess the factors influencing their survival times.

Results: The HBsAg(+) and HBsAg(-) groups comprised 154 (25.6%) and 448 (74.4%) of the 602 cases, respectively. HBsAg(+) cases tended to be later-stage (III–IV) with higher international prognostic index (IPI) points (3–5) and a greater tendency toward B symptoms, impaired liver function, and recurrence than HBsAg(-) cases (all $p<0.05$). After follow-up, 194 (32.2%) patients died. The median overall survival (OS) and 5-year OS rates in the HBsAg(+) and HBsAg(-) groups were 16.5 months (42%) and 35 months (63%), respectively. Cox analyses indicated that HBsAg(+) affected the prognosis of DLBCL cases (HR=1.46, 95%CI=1.07-1.99, $p=0.017$).

Conclusion: The HBsAg(+) seems to be an independent hazard factor for the worse prognosis of DLBCL patients; hence, a focus on these patients in clinic is required.

Keywords: hepatitis B virus, diffuse large b-cell lymphoma, overall survival, prognosis

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Lymphoma is a complex lymphopoietic system tumor that can be divided into 2 major categories: Hodgkin lymphoma and non-Hodgkin lymphoma. An aging population, environmental factors, viral infection, and genetic factors may be related to its pathogenesis. Hepatitis B virus (HBV) has been recognized as a global health problem. According to statistics, approximately 30% of the global population has chronic HBV infection, China has a high incidence area of HBV infection, and the positive rate of hepatitis B surface antigen (HBsAg) in the general population is 4–8%.[1-3] Hepatitis B virus is not only a hepatocellular virus, but also has the properties of lymphocyte affinity. Its ability to replicate and proliferate in lymphocytes has a certain correlation with the occurrence and development of lymphoma, especially B-cell-derived lymphoma. Studies have found that HBV infection increased the risk of non-Hodgkin lymphoma and that the positive rate of HBsAg in non-Hodgkin lymphoma was 2–3 times higher than in the healthy population.[4,5] Some research data has suggested that HBV infection may affect patient outcomes,but other researchers have proposed different views.[6,7] Lemaitre's study suggested that HBsAg(-) cases and HBsAg (+) cases had a similar survival time, and viral infection did not affect the prognoses of patients.[8] Considering the small sample sizes in previous studies and the large number of cases with diffuse large B-cell lymphoma (DLBCL) complicated with HBV in clinical work, the current study retrospectively analyzed 602 patients with DLBCL to investigate the relevance between HBV infection and survival situation of DLBCL.

Methods. Data were collected from 602 individuals with DLBCL admitted to the Affiliated Hospital of Hebei University, Baoding, China from January 2011 to December 2021. The inclusion criterion was as follows: i) all individuals were confirmed to have DLBCL by histopathology and immunohistochemistry. The exclusion criteria were as follows: ii) complicated by other malignant tumors, iii) viral hepatitis infection other than HBV, iv) cirrhosis or liver cancer, v) incomplete clinical case data. This research followed the principles of the Helsinki Declaration and was approved by the Medical Ethics Committee of the hospital.

Basic clinical data were recorded by consulting the electronic medical record system, including age, gender, international prognostic index (IPI), pathology, stage, B symptoms, hepatitis history, HBsAg serology results, and liver function (alanine transaminase, aspartate transaminase, and serum bilirubin), extranodal involvement, and therapy.

This study was conducted by telephone from the follow-up center of our hospital or by consulting electronic medical records until November 2022. The OS refers to the definitive diagnosis time of DLBCL patients to loss, last time of follow-up, or death for any reason.

Statistical analysis. data were statistically analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). The categorical variables were represented by percentages, and the comparison was realized by carrying out a Chi-square test. Continuous variables were represented by mean±standard deviation, and group comparisons used T-tests. The Cox regression risk model was applied to assess independent risk predictors of DLBCL. $P<0.05$ was considered to indicate statistically significant differences.

Results. *Basic clinical data of 602 patients with DLBCL.* In total, 602 cases of DLBCL were collected in our study and divided into HBsAg(+) (n=154) and HBsAg(-) (n=448) groups on the basis of HBV serological results. The age of the patients considered was 59.72±14.14 years. There were no differences in gender or age between the 2 groups ($p>0.05$). In addition, 122 (79.2%) cases in the HBsAg(+) group were at stages III–IV, 95 (61.7%) cases had an IPI score of 3–5, and 75 (48.7%) cases had B symptoms (all $p<0.05$). However, there was no difference between the HBsAg(+) and HBsAg(-) groups in terms of Hans classification, extranodal involvement, and therapy (all $p>0.05$). Moreover, a total of 6 cases of spleen involvement were found in the data, with 3 cases in the HBsAg(+) group and 3 in the HBsAg(-) group. No liver involvement was found in this study. By the end of data collection, a total of 102 (16.9%) patients was found to have hepatic impairment, of whom 39 (25.3%) were in the HBsAg(+) group and 63 (14.1%) in the HBsAg(-) group, showing the difference between the groups (all $p<0.05$). In addition, this study found that the disease recurrence rate of the HBsAg(+) group was higher than that of the HBsAg(-) group ($p<0.05$) (Table 1).

*Univariate analysis of the prognosis of 602 patients with DLBCL.*The follow-up period continued until November 2022. The follow-up time was 30 (1–210) months, and 194 (32.2%) patients died during follow-up. The median OS in the HBsAg(+) and HBsAg(-) groups was 16.5 months and 35 months, respectively. The 5-year OS rates of HBsAg(+) and HBsAg(-) patients were 42% and 63%, respectively. A univariate Cox analysis showed that in the HBsAg(+) group, age, stage, IPI score, and B symptoms all

decreased the survival time of DLBCL patients (all $p<0.05$) (Table 2).

Multivariate analysis of the survival time of 602 patients with DLBCL. A multivariate Cox analysis indicated that DLBCL patients with HBsAg(+) (HR=1.46, 95% CI=1.07–1.99, $p=0.017$) and an IPI score of 3–5 (HR=2.40, 95% CI=1.67–3.32, $p<0.001$) had poorer prognosis than HBsAg(-) group (Table 3).

Discussion. In this study, a retrospective analysis of 602 patients with DLBCL was conducted, and the outcomes indicated that 25.6% of the patients were HBsAg(+). In terms of clinical characteristics, HBV infection in patients with hepatitis could cause the disease to accelerate more rapidly than in patients without hepatitis, as shown by such patients being at a later stage and having a higher IPI score and a rapid progression, as other authors have also found.[6] The current study suggested that the 5-year survival time rate of HBsAg(-) cases was 63%, while that of HBsAg(+) cases was 42%. HBV infection may cause a certain negative prognosis in DLBCL patients, which is consistent with Zhan's study.[6] Diffuse large B-cell lymphoma is a subtype of non-Hodgkin lymphoma that accounts for about 30% to 40% of non-Hodgkin lymphoma, and China has a high incidence of HBV infection, which contributes to the large number of patients who have DLBCL combined with HBV infection. [9,10]

Hepatitis B virus infection is the production of a large number of viral proteins and a strong and sustained antibody response.[11] The lymphatic system is considered to be an important reservoir for HBV.[12] In recent years, more and more studies have shown a link between non-Hodgkin lymphoma and HBV, and chronic persistent HBV infection may improve the risk of non-Hodgkin lymphoma.[13] In addition to the potential role of occult HBV infection in the progression of B-cell lymphoma, preventative care strategies could certainly reduce the incidence of HBV-mediated DLBCL, thereby reducing the burden of these

Table 1 - Basic clinical data of 602 patients with diffuse large B-cell lymphoma.

Factors	AII (n=602)	HBsAg(+) group (n=154)	HBsAg(-) group (n=448)	*P*-value
Age	59.72 ±14.14	61.57 ± 12.45	59.09 ± 14.61	0.060
Gender				0.955
Male	310(51.5%)	79(51.3%)	231(51.6%)	
Female	292(48.5%)	75(48.7%)	217(48.4%)	
Stage				<0.001*
I–II	248(41.2%)	32(20.8%)	216(48.2%)	
III–IV	354(58.8%)	122(79.2%)	232(51.8%)	
IPI score				<0.001*
0–2	389(64.6%)	59(38.3%)	330(73.7%)	
3–5	213(35.4%)	95(61.7%)	118(26.3%)	
B symptoms				<0.001*
Yes	217(36.1%)	79(51.3%)	138(30.8%)	
No	385(64.0%)	75(48.7%)	310(69.2%)	
Hans classification				0.635
GCB	256(45.5%)	68(41.2%)	188 (42.0%)	
Non-GCB	346(57.5%)	86(58.8%)	260 (58.0%)	
Extranodal involvement				0.473
Yes	197(32.7%)	54(35.1%)	143 (31.9%)	
NO	405(67.3%)	100(64.9%)	305 (68.1%)	
Therapy				0.399
CHOP	74(12.3%)	22 (14.3%)	52 (11.6%)	
R-CHOP	336(55.8%)	89 (57.8%)	247 (55.1%)	
Other	192(31.9%)	43 (27.9%)	149 (33.3%)	
Hepatic impairment				0.001*
Yes	102(16.9%)	39 (25.3%)	63 (14.1%)	
NO	500(83.1%)	115 (74.7%)	385 (85.9%)	
Recurrence				
Yes	164(27.24%)	46(29.87%)	103(23.0%)	0.035*
NO	438(72.76%)	108(70.1%)	345(77.0%)	

IPI: international prognostic index, GCB: germinal center B cell. Hepatic impairment is defined as ALT/AST or blood bilirubin > the upper limit of normal. *$P<0.05$ was considered statistically significant.

Table 2 - Univariate analysis of the survival time of 602 patients with diffuse large B-cell lymphoma.

Factors	B	SE	HR	95% CI	*P*-value
HBsAg(+) group (Yes, No)	0.80	0.15	2.21	1.65–2.98	<0.001*
Age (≥60 years, <60 years)	0.39	0.15	1.48	1.10–1.99	0.010*
Gender (Male, Female)	0.02	0.14	1.02	0.77–1.35	0.915
Stage (I–II, III–IV)	0.92	0.17	2.50	1.80–3.47	<0.001*
IPI score (0–2, 3–5)	1.24	1.15	3.44	2.58–4.58	<0.001*
B symptoms (Yes, No)	0.52	0.14	1.68	1.26–2.23	<0.001*
Hans classification (GCB, Non-GCB)	-0.29	0.15	0.75	0.56–1.01	0.055
Extranodal involvement (Yes, No)	0.18	0.16	1.19	0.87–1.63	0.272
Therapy (CHOP, R-CHOP, Other)	-0.06	0.08	0.94	0.81–1.10	0.462

*P<0.05 was considered statistically significant. IPI: international prognostic index; GCB: germinal center B cell, HR: hazard ratio, CI: cinfidence interval

Table 3 - Multivariate analysis of the survival time of 602 patients with diffuse large B-cell lymphoma .

Factors	B	SE	HR	95%CI	*P*-value
HBsAg(+) group (Yes, No)	0.38	0.16	1.46	1.07–1.99	0.017*
Age (≥60years, <60years)	0.19	0.16	1.20	0.88–1.64	0.242
Stage (I–II, III–IV)	0.34	0.20	1.40	0.95–2.07	0.092
IPI score (0–2, 3–5)	0.88	0.19	2.40	1.67–3.32	<0.001*
B symptoms (Yes, No)	0.23	0.15	1.26	0.94–1.07	0.122

*P<0.05 was considered statistically significant. IPI: international prognostic index, HR: hazard ratio, CI: confidence interval

seemingly "non-infectious" cancers.[14] The occurrence and development of lymphoma require long-term chronic antigenic stimulation; such stimulation has usually been associated with infection or autoimmune diseases, which partly explains the high number of patients with HBV infection complicated with DLBCL seen in clinical work.[15]

Antiviral treatment of hepatitis C virus (HCV)-associated non-Hodgkin lymphoma has been shown to increase the rate of complete response, confirming that HCV contributes to the development of lymphoma.[16] In addition, a study that collected data from 128 patients with HBsAg(+) with DLBCL, all of whom received immunochemotherapy and prophylactic antiviral therapy, found that the prognosis for HBsAg(+) patients was no worse than that for DLBCL patients.[17] Another study showed that approximately 50% of DLBCL patients receiving R-CHOP or CHOP-like chemotherapy had their therapeutic dose reduced due to active HBV infection, while 66.7% had to abandon first-line therapy due to HBV infection.[18] Therefore, in order to improve patient prognoses, early preventive intervention with antiviral drugs should be used for HBV-positive patients with relapsed refractory DLBCL.

Negara's study included 129 patients with lymphoma, of whom 15 (11.6%) were diagnosed with HBV infection and 21 (16.3%) with HCV infection, showing that the presence of the hepatitis B/C virus was not related to the specific clinical and pathological characteristics of lymphoma,19 contrary to the conclusion of our study. However, another study indicated that HBV infection was an independent risk of poor survival time (HR=2.85; 95% CI 1.80–4.52) in chronic lymphocytic leukemia patients.[20] We collected 602 patients with DLBCL from the last decade, and this relatively large number gives a certain credibility to our findings.

Study limitations. The research was a single-center study and did not consider either the double-strike/triple-strike lymphoma models or the effects of comorbidities. In addition, due to the large time span of the study, the number of HBV replicates in patients was not detailed, and we had no data concerning treatment responses and transplantation. Larger sample sizes are needed to further verify the conclusion.

In conclusion, this study showed that HBsAg(+) patients had later stages (III–IV), a higher IPI score (3-5 points), and a tendency to have B symptoms and impaired liver function and were associated with worse prognosis in DLBCL. Therefore, in clinical work, it is necessary to pay more attention to the virus replication and liver function impairment in this part of the population and ensure timely drug intervention to improve the survival of patients.

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