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ORIGINAL RESEARCH

Influence of Hyperglycemia on the Prognosis of Patients with Diffuse Large B-Cell Lymphoma

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Purpose: To explore the effects of primary and secondary hyperglycemia and the application of the hypoglycemic drug metformin on the prognosis of patients with diffuse large B-cell lymphoma (DLBCL).

Methods: We performed a retrospective analysis of 1767 DLBCL patients.Cox regression method was used for analysis to evaluate the prognostic factors, and the Kaplan-Meier method was used to draw a survival curve to analyze the effect of hyperglycemia and the hypoglycemic drug metformin on the progression-free survival (PFS) and overall survival (OS) of DLBCL patients.

Results: Our study showed that patients with hyperglycemia tend to have higher age (age>60 years), high body mass index (BMI) (≥24kg/m^2), late Ann Arbor stage (III–IV), high international prognostic index (IPI) (3–5 score), high lactic dehydrogenase (LDH) level (>250U/L), bulky disease and comorbidity. Hyperglycemia affects the survival time of the DLBCL population (PFS: adjusted HR 1.41, 95% CI: 1.16–1.70, P <0.001, OS: adjusted HR 1.33, 95% CI:1.09–1.61, P=0.004).Compared with the non-hyperglycemia group, the secondary hyperglycemia increase affects the prognosis of the DLBCL population (P<0.001). Compared with the secondary hyperglycemia group, the primary hyperglycemia group has a poor prognosis (P<0.05). For patients with DLBCL and hyperglycemia (732 patients in total), the use of metformin can improve their PFS and OS (PFS: adjusted HR 0.69, 95% CI: 0.49–0.96, P=0.028, OS: adjusted HR 0.68, 95% CI: 0.49–0.95, P=0.024).

Conclusion: Hyperglycemia and secondary hyperglycemia are related to the poor prognosis of DLBCL population.For patients with DLBCL combined with hyperglycemia, the application of metformin can improve survival rate.

Keywords: hyperglycemia, diffuse large B-cell lymphoma, metformin, recrudescence, death, prognosis

Introduction

Lymphoma is a malignant tumor of the immune system that originates in lymph nodes and lymph node tissues. According to histopathological changes, it can be divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, with an annual incidence of approximately 24% of NHL.[1] Diabetes mellitus (DM) is a metabolic syndrome mainly manifested by chronic blood glucose elevation caused by the combined action of genetic and environmental factors. The number of people aged 20–79 years with diabetes worldwide has already reached 537 million in 2021 according to International Diabetes Federation, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045.[2] Studies have shown that diabetes is associated with an increased risk of multiple tumors in the liver, pancreas, endometrium, colorectal, breast, and bladder.[3–9] Diabetes is associated with a higher risk of hematological malignancies, and is an independent risk factor for all-cause and specific cause mortality.[10] Studies have shown that DM is associated with an increased risk of NHL.[11,12] Metformin is a common hypoglycemic drug. Many studies have shown that the use of metformin in diabetic patients can reduce the incidence of cancer or reduce the mortality rate associated with cancer.[13–17] Metformin inhibits tumor growth, proliferation, invasion and metastasis by decreasing blood glucose levels, attenuating insulin resistance, reducing inflammation

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and improving the tumor microenvironment.[14] However, whether hyperglycemia, especially secondary hyperglycemia, affects the prognosis of DLBCL has not yet been reported, and there are few reports on whether metformin can help improve the prognosis of DLBCL patients.We aim to clarify the impact of hyperglycemia and the application of the hypoglycemic drug metformin on the prognosis of patients with DLBCL.

Methods

Cases

A retrospective collection of 1767 patients diagnosed with DLBCL in the Department of Hematology, the Fourth Hospital of Hebei Medical University from January 1, 2010 to June 1, 2020, all met the diagnostic criteria for DLBCL. Informed consent was obtained before data collection. Those who did not have complete clinical information or immunohistochemistry data, or who were lost to follow-up immediately after treatment were excluded from this study. The study was approved by the medical ethics committee of the the Fourth Hospital of Hebei Medical University (Hebei Tumor Hospital),(approval number, 2022KY384) and followed the principles of the Declaration of Helsinki.

Clinical Information

The collected clinical data include age, gender, height, weight, pathological diagnosis, Ann-Arbor staging, B symptoms, IPI score, LDH, β2 micro-globulin, blood glucose level, immunohistochemistry, therapy proposal, extranodal involvement, bulky disease, comorbidities (hypertension, cerebrovascular disease, hepatitis, tuberculosis, other malignant tumors) and whether taking metformin, Among them, pathological diagnosis is divided into germinal center B cell source (GCB type) and non-GCB (Non-GCB) type according to the Hans classification system.[18] According to the results of PET-CT or CT, DLBCL patients were staged according to the Ann-Arbor staging system [19] B symptoms are defined as unexplained fever (body temperature above 38°C), night sweats, weight loss (unexplained weight within 6 months Reduce by more than 10%);IPI score according to the adverse factors (age> 60 years old, disease stage III/IV, LDH higher than normal, ECOG performance status score ≥ 2 points, number of extranodal involvement sites>1).[20] Immunohistochemistry mainly includes whether or not Ki-67, BCL-2, BCL-6, C-MYC are positive and the positive ratio; Therapy proposal: All patients received CHOP or R-CHOP regimen, and some received radiotherapy and operation, CHOP regimen: cyclophosphamide 750 mg/m^2 on day 1; doxorubicin 50 mg/m^2 on day 1; vincristine 1.4 mg/m^2 (maximum dose 2 mg/m^2), on the 1st day; prednisone 60 mg/m^2, on the 1st to 5th days.R-CHOP regimen: rituximab 375 mg/m^2, day 1; cyclophosphamide 750 mg/m^2, day 1; doxorubicin 50 mg/m^2, day 1; vincristine 1.4 mg/m^2 (maximum dose 2 mg/m^2), on day 1; prednisone 60 mg/m^2, on days 1 to 5. The specific drug dose is adjusted according to the patient's body surface area, general condition and patient tolerance;Hyperglycemia mainly includes: ①The type 2 diabetes is clearly diagnosed according to the medical records of the previous outpatient or hospitalization (Dry mouth, polydipsia, and polyphagia and weight loss + Fasting plasma glucose (FPG)≥7.0mmol/L or random blood glucose≥11.1mmol/L or oral glucose tolerance test 2-hour blood glucose≥11.1mmol/L); ②FPG≥ 6.1 mmol/L during the evaluation before DLBCL treatment.[21] Secondary hyperglycemia mainly includes: ①No previous history of DM and FPG <6.1 mmol/L at the time of evaluation before DLBCL treatment; ②During the treatment, At least two time's of the first day of hospitalization FPG≥6.1mmol/L. Metformin group refers to taking single-drug metformin or metformin combined with other hypoglycemic drugs, non-metformin group refers to never taking metformin (other hypoglycemic drugs are not excluded).

The follow-up was be conducted by the telephone of our hospital's follow-up center, outpatient review and inpatient review. The deadline for follow-up is August 15, 2021.Primary endpoint: Overall survival (OS) period is defined as the time from initial diagnosis to death, last follow-up or loss to follow-up due to any reason; progression-free survival (PFS) period is defined as the period from initial diagnosis to tumor recurrence, progression or last follow-up time.

Statistical Analysis

All data were statistically analyzed using SPSS for Windows (version 26.0, Armonk, NY: IBM Corp). Continuous variables were presented by mean±standard deviation. Categorical variables were presented as numbers and percentage.

Group comparisons used *t*-tests on continuous, and x^2 tests on categorical variables. The Cox regression risk model was used for univariate and multivariate analysis to evaluate independent risk predictors of DLBCL. The Kaplan-Meier method was used to draw the survival curve, and the Log rank test was used to compare differences between groups. P<0.05 indicates that the difference is statistically significant.

Results

1. A total of 1767 DLBCL patients were enrolled in this study. The mean age was 60.71 ± 14.66 years (17–96 years). 335 cases (19.0%) had hyperglycemia before the diagnosis of DLBCL (including 291 for type 2 diabetes and 44 for pre-diabetes), and 131 patients (7.4%) had high blood glucose before the pre-DLBCL assessment. 266 cases (15.1%) had secondary hyperglycemia,1035 patients (58.6%) had non-hyperglycemia. Patients with hyperglycemia are more likely to have higher age (age>60 years), higher BMI, late Ann-Arbor staging, high IPI score, high LDH level, bulky disease and comorbidities. (all P<0.05).(Table 1).

2. Those with DLBCL and hyperglycemia who are older than 60 years old mostly have primary hyperglycemia. Compared with secondary hyperglycemia, primary hyperglycemia had significant differences in age, β2 micro-globulin, C-MYC and metformin (P < 0.05).Compared with non-hyperglycemia group, the patients with secondary hyperglycemia tended to have higher age, higher BMI, late Ann Arbor stage, high IPI, high LDH level, bulky disease and comorbidities (P < 0.05). (Table 2).

3. Cox univariate analysis of 1767 cases showed that hyperglycemia, age, BMI, Ann-Arbor staging, IPI, B symptoms, pathological diagnosis, LDH level, β2 micro- globulin, bulky disease,BCL-2 and C-MYC positive were all associated with OS and PFS (all P<0.05).Multivariate analysis of these factors showed that hyperglycemia, age, high BMI, late Ann-Arbor staging, high IPI, B symptoms, high LDH level,highβ2 micro-globulin, extranodal involvement, bulky disease,BCL-2 positive were all associated with worse prognosis (all P<0.05).(Tables 3 and 4).

Cox univariate analysis of 732 patients with hyperglycemia showed that secondary hyperglycemia, metformin application, age,BMI, Ann-Arbor staging,IPI score, B symptoms,LDH level,β2 micro-globulin,C-myc were related to OS and PFS (all P<0.05).Multivariate analysis of these factors showed that secondary hyperglycemia no metformin application, high BMI,high IPI score, C-MYC positive were associated with poor prognosis (all P<0.05). (Tables 5 and 6).

4. Survival analysis: the follow-up time for 1767 patients ended on August 5, 2021. The shortest follow-up time was 1 month, the longest time was 281 months, and the follow-up time was 35.8±33.4 months. 494 (28.0%) patients died and 875 (49.5%) patients experienced disease progression.The 5-year OS rate in hyperglycemia group was 57%, the 5-year OS rate in non-hyperglycemia group was 73%, the 5-year PFS rate in hyperglycemia group was 55%, and the 5-year PFS in non-hyperglycemia group was 72%. The median survival time in the hyperglycemia group was 109 months, and the median survival time in the non-hyperglycemia group was 184 months.

Compared with the non-hyperglycemia group, the hyperglycemia group were associated with worse prognosis, the differences in OS and PFS were statistically significant (all P<0.001) (Figure 1).

Compared with the secondary hyperglycemia group, the primary hyperglycemia group had a worse prognosis (all P <0.05);Compared with the non-hyperglycemia group, the secondary hyperglycemia also affected the prognosis of DLBCL patients (all P<0.001) (Figure 2).

The application of the hypoglycemic drug metformin can increase the PFS and OS of people with DLBCL and hyperglycemia (all P <0.05) (Figure 3).

Discussion

With the increase in the incidence of diabetes, the impact of diabetes on the prognosis of cancer has attracted more and more attention. This study retrospectively analyzed the prognosis of 1767 cases of DLBCL. Our study showed that the prevalence of type 2 diabetes with diffuse large B-cell lymphoma was 26.4%, of which 19.0% of patients had hyperglycemia before the diagnosis of DLBCL, and 7.4% of patients had hyperglycemia during the evaluation before DLBCL treatment. Among people over 60 years old, 20.3% of DLBCL patients had hyperglycemia, which was similar to the results of the Lam study.[22] In our study, hyperglycemia significantly affected the PFS and OS of DLBCL patients (P <0.001), and the 5-year PFS and OS of DLBCL patients with hyperglycemia were significantly lower than non-

Table 1 Baseline Clinical Characteristics of 1767 DLBCL Patients with or Without Hyperglycemia

Clinical Characteristics	DLBCL and Hyperglycemia (n=732)	DLBCL and Non-Hyperglycemia (n=1035)	F/ *X*2	P value
Age	64.38± 12.45	58.11± 15.54	57.97	<0.001*
Gender			0.11	0.741
Male	369(50.4%)	530(51.2%)		
Female	363(49.6%)	505(48.8%)		
BMI	24.92± 3.76	24.05± 3.84	0.61	<0.001*
Ann-Arbor Staging			28.46	<0.001*
III–IV	486(66.4%)	556(53.7%)		
I–II	246(33.6%)	479(46.3%)		
IPI score			98.40	<0.001*
3–5 score	349(47.7%)	258(24.9%)		
0–2 score	383(52.3%)	777(75.1%)		
LDH			12.44	<0.001*
>250U/L	335(45.8%)	387(37.4%)		
≤250U/L	397(54.2%)	648(62.6%)		
β2 micro-globulin			3.80	0.051
>2.8ug/mL	274(37.4%)	341(32.9%)		
≤2.8ug/mL	458(62.6%)	694(67.1%)		
B symptoms			3.62	0.057
Yes	308(42.1%)	389(37.6%)		
No	424(57.9%)	646(62.4%)		
Pathological diagnosis			0.02	0.897
GCB	316(43.2%)	450(43.5%)		
Non-GCB	416(56.8%)	585(56.5%)		
Extranodal involvement			2.38	0.120
Yes	470(64.2%)	701(67.7%)		
No	262(35.8%)	334(32.3%)		
Bulky disease			61.64	<0.001*
Yes	238(32.5%)	171(16.5%)		
No	494(67.5%)	864(83.5%)		
Comorbidities			30.42	<0.001*
Yes	307(41.9%)	303(29.3%)		
No	425(58.1%)	732(70.7%)		
Ki-67			1.99	0.370
≥90%	140(19.1%)	198(19.1%)		
0–90%	566(77.3%)	812(78.5%)		
Negative	26(3.5%)	25(2.4%)		
BCL-2			0.01	0.919
Positive	526(71.8%)	746(72%)		
Negative	206(28.2%)	289(28%)		

(*Continued*)

Table 1 (Continued).

Clinical Characteristics	DLBCL and Hyperglycemia (n=732)	DLBCL and Non-Hyperglycemia (n=1035)	F/ $X2$	P value
BCL-6			2.55	0.111
Positive	521(71.1%)	772(74.6%)		
Negative	211(28.9%)	263(25.4%)		
C-MYC			1.21	0.547
≥40%	239(32.6%)	313(30.2%)		
0–40%	264(36.1%)	382(36.9%)		
Negative	229(21.3%)	340(32.9%)		

Notes: Categorical variables were compared by Pearson chi-square and represented by X^2 value, continuous variables were compared by analysis of variance and represented by F value. *P value less than 0.05 was considered statistically significant.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; BMI, body mass index; IPI, international prognostic index; LDH, lactate dehydrogenase; GCB, germinal center B cell.

Table 2 Baseline Clinical Characteristics of 732 Patients with DLBCL with Hyperglycemia and 1035 Patients with DLBCL and Non-Hyperglycemia

Clinical Characteristics	DLBCL with Primary Hyperglycemia (n=466)	DLBCL with Secondary Hyperglycemia (n=266)	DLBCL with Non-Hyperglycemia (n=1035)	F/ X^2	P value
Age	65.94±12.53	61.65±11.83	58.11± 15.54	*0.11 #29.41	*<0.001† #0.001†
Gender				*0.20	*0.655
Male	232(49.8%)	137(51.5%)	530(51.2%)	#0.01	#0.931
Female	234(50.2%)	129(48.5%)	505(48.8%)		
BMI	24.97±3.82	24.83± 3.66	24.05± 3.84	*0.05 #0.54	*0.641 #0.003†
Ann-Arbor Staging				*0.18	*0.672
III–IV	312(67.0%)	174(65.4%)	556(53.7%)	#11.75	#0.001†
I–II	154(33.0%)	92(34.6%)	479(46.3%)		
IPI score				*3.31	*0.069
3–5 score	234(50.2%)	115(43.2%)	258(24.9%)	#34.67	#<0.001†
0–2 score	232(49.8%)	151(56.8%)	777(75.1%)		
LDH				*0.00	*0.967
>250U/L	213(45.7%)	122(45.9%)	387(37.4%)	#6.38	#0.012†
≤250U/L	253(54.3%)	144(54.1%)	648(62.6%)		
β2 micro-globulin				*7.78	*0.005†
>2.8ug/mL	192(41.2%)	82(30.8%)	341(32.9%)	#0.43	#0.510
≤2.8ug/mL	274(58.8%)	184(69.2%)	694(67.1%)		
B symptoms				*0.09	*0.765
Yes	198(42.5%)	110(41.4%)	389(37.6%)	#1.27	#0.260
No	268(57.5%)	156(58.6%)	646(62.4%)		
Pathological diagnosis				*0.56	*0.454
GCB	206(44.2%)	110(41.4%)	450(43.5%)	#0.39	#0.532
Non-GCB	260(55.8%)	156(58.6%)	585(56.5%)		

(*Continued*)

Table 2 (Continued).

Clinical Characteristics	DLBCL with Primary Hyperglycemia (n=466)	DLBCL with Secondary Hyperglycemia (n=266)	DLBCL with Non-Hyperglycemia (n=1035)	F/ X^2	P value
Extranodal involvement				*0.99	*0.320
Yes	293(62.9%)	177(66.5%)	701(67.7%)	#0.14	#0.710
No	173(37.1%)	89(33.5%)	334(32.3%)		
Bulky disease				*1.14	*0.290
Yes	145(31.1%)	93(35.0%)	171(16.5%)	#44.49	#<0.001†
No	321(68.9%)	173(65.0%)	864(83.5%)		
Comorbidities				*3.24	*0.070
Yes	207(44.4%)	100(37.6%)	303(29.3%)	#6.85	#0.009†
No	259(55.6%)	166(62.4%)	732(70.7%)		
Ki-67				*1.05	*0.591
≥90%	90(19.3%)	51(19.2%)	198(19.1%)	#0.04	#0.979
0–90%	357(77.6%)	208(78.2%)	812(78.5%)		
Negative	19(4.1%)	7(2.6%)	25(2.4%)		
BCL-2				*1.37	*0.241
Positive	328(70.4%)	198(74.4%)	746(72%)	#0.59	#0.442
Negative	138(29.6%)	68(25.6%)	289(28%)		
BCL-6				*0.00	*0.956
Positive	332(71.2%)	189(71.1%)	772(74.6%)	#1.37	#0.242
Negative	134(28.8%)	77(28.9%)	263(25.4%)		
C-MYC				*6.69	*0.035†
≥40%	164(35.2%)	75(28.2%)	313(30.2%)	#2.1	#0.350
0–40%	152(32.6%)	111(41.7%)	382(36.9%)		
Negative	150(32.2%)	80(30.1%)	340(32.9%)		
Metformin				*40.41	*<0.001†
Yes	126(27.0%)	20(7.5%)	–	–	–
No	340(73%)	246(92.4%)	–		

Notes: Categorical variables were compared by Pearson chi-square and represented by X^2 value, continuous variables were compared by analysis of variance and represented by F value. *DLBCL with primary hyperglycemia VS DLBCL with secondary hyperglycemia. #DLBCL with secondary hyperglycemia VS DLBCL with non-hyperglycemia. †P value less than 0.05 was considered statistically significant.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; BMI, body mass index; IPI, international prognostic index; LDH, lactate dehydrogenase;GCB, germinal center B cell.

hyperglycemia group (P <0.001), and Drozd-Sokolowska research was similar.[23] Therefore, it is necessary to pay attention to people with hyperglycemia when diagnosing and treating DLBCL, especially those with unknown hyperglycemia. Yang and other studies found that compared with patients without diabetes, patients with T2DM had a higher risk of NHL, with a hazard ratio of 2.00 (95% CI: 1.32–3.03), which was consistent with the conclusions of this study.[24] In addition, 12.1% of the population experienced increased blood glucose during DLBCL treatment. Compared with patients with non-hyperglycemia, secondary hyperglycemia also affected the prognosis of DLBCL patients (P <0.001), which was contrary to the results of Lamar.[25] The sample size needs to be increased to further evaluate the relationship between the two.Compared with the secondary hyperglycemia group, the primary hyperglycemia group had a worse prognosis. The consideration of secondary hyperglycemia may be related to the application of hormones,[26] excluding weight factors: This study found that compared with the non-hyperglycemia group, the secondary hyperglycemia had a higher BMI, indicating that overweight people are more likely to have secondary hyperglycemia, which in turn affects the prognosis of DLBCL people. So in the process of diagnosis and treatment, we need to pay attention to the weight management of overweight people.Through retrospective analysis, Anil showed that metformin combined with first-line

Table 3 Univariate and Multivariate Analysis of PFS in 1767 Patients with DLBCL

	Univariate Analysis	Multivariate Analysis
	HR (95% CI) P value	HR (95% CI) P value
Hyperglycemia (Yes, No)	1.83 (1.53–2.18) <0.001*	1.41 (1.16–1.70) <0.001*
Gender (Male, Female)	1.21 (1.01–1.44) 0.036*	1.18 (0.99–1.41) 0.071
Age (>60,≤60)	1.97 (1.62–2.41) <0.001*	1.48 (1.19–1.82) <0.001*
BMI (≥24kg/m2,<24kg/m2)	0.74 (0.62–0.88) 0.001*	0.76 (0.63–0.91) 0.003*
Ann-Arbor Staging (III˜ V, I˜II)	2.77 (2.24–3.42) <0.001*	1.54 (1.20–1.98) 0.001*
IPI score (3˜5,0˜2)	3.35 (2.80–4.01) <0.001*	1.74 (1.39–2.19) <0.001*
B symptoms (Yes, No)	1.65 (1.38–1.97) <0.001*	1.23 (1.02–1.48) 0.032*
Pathological diagnosis (GCB, Non-GCB)	0.77 (0.64–0.92) 0.005*	0.90 (0.75–1.08) 0.261
LDH (>250 U/L,≤250 U/L)	2.93 (2.00–2.86) <0.001*	1.42 (1.15–1.75) 0.001*
β2 micro-globulin (>2.8ug/mL,≤2.8ug/mL)	2.32 (1.94–2.77) <0.001*	1.36 (1.12–1.66) 0.002*
Extranodal involvement (Yes, No)	1.04 (0.86–1.25) 0.710	1.35 (1.11–1.64) 0.002*
Bulky disease (Yes, No)	1.26 (1.04–1.54) 0.020*	1.13 (0.93–1.39) 0.026*
Comorbidities (Yes, No)	0.99 (0.82–1.19) 0.932	–
Ki-67(≥90%,<90%)	1.02 (0.82–1.28) 0.840	–
BCL-2(Positive, Negative)	1.39 (1.34–1.71) 0.002*	1.26 (1.02–1.55) 0.035*
BCL-6(Positive, Negative)	0.94 (0.78–1.14) 0.550	–
C-MYC (≥40%,<40%)	1.30 (1.08–1.57) 0.006*	1.12 (0.92–1.35) 0.264

Note: *P value less than 0.05 was considered statistically significant.
Abbreviations: PFS, progression-free survival; HR, hazard ratio; BMI, body mass index; GCB, germinal center B cell; IPI, international prognostic index; LDH, lactate dehydrogenase.

Table 4 Univariate and Multivariate Analysis of OS in 1767 Patients with DLBCL

	Univariate Analysis	Multivariate Analysis
	HR (95% CI) P value	HR (95% CI) P value
Hyperglycemia (Yes, No)	1.75 (1.46–2.09) <0.001*	1.33 (1.09–1.61) 0.004*
Gender (Male, Female)	1.19 (1.00–1.43) 0.051	1.16 (0.97–1.39) 0.106
Age (>60,≤60)	1.93 (1.58–2.35) <0.001*	1.48 (1.20–1.83) <0.001*
BMI (≥24kg/m2,<24kg/m2)	0.74 (0.62–0.88) 0.001*	0.76 (0.64–0.92) 0.004*
Ann-Arbor Staging (III˜IV, I˜II)	2.64 (2.14–3.27) <0.001*	1.46 (1.13–1.87) 0.003*
IPI score (3˜5,0˜2)	3.30 (2.76–3.95) <0.001*	1.76 (1.40–2.21) <0.001*
B symptoms (Yes, No)	1.68 (1.41–2.01) <0.001*	1.25 (1.04–1.50) 0.020*
Pathological diagnosis (GCB, Non-GCB)	0.78 (0.65–0.93) 0.006*	0.92 (0.76–1.10) 0.361
LDH (>250 U/L,≤250 U/L)	2.43 (2.03–2.91) <0.001*	1.48 (1.21–1.83) <0.001*
β2 micro-globulin (>2.8ug/mL,≤2.8ug/mL)	2.33 (1.95–2.78) <0.001*	1.39 (1.14–1.70) 0.001*
Extranodal involvement (Yes, No)	1.06 (0.88–1.29) 0.526	1.39 (1.15–1.70) 0.001*
Bulky disease (Yes, No)	1.28 (1.05–1.55) 0.016*	1.16 (0.95–1.42) 0.153
Comorbidities (Yes, No)	0.95 (0.79–1.14) 0.588	–
Ki-67(≥90%,<90%)	0.98 (0.79–1.23) 0.862	–
BCL-2(Positive, Negative)	1.38 (1.13–1.70) 0.002*	1.24 (1.00–1.53) 0.047*
BCL-6(Positive, Negative)	1.03 (0.85–1.26) 0.749	–
C-MYC (≥40%,<40%)	1.39 (1.15–1.68) 0.001*	1.21 (1.00–1.47) 0.055

Note: *P value less than 0.05 was considered statistically significant.
Abbreviations: OS, overall survival; HR, hazard ratio; BMI, body mass index; GCB, germinal center B cell; IPI, international prognostic index; LDH, lactate dehydrogenase.

Table 5 Univariate and Multivariate Analysis of PFS in 732 Patients with DLBCL and Hyperglycemia

	Univariate Analysis	Multivariate Analysis
	HR (95% CI) P value	HR (95% CI) P value
Metformin (Yes, No)	0.71 (0.52–0.99) 0.044*	0.69 (0.49–0.96) 0.028*
Secondary hyperglycemia (Yes, No)	1.35 (1.04–1.75) 0.026*	1.31 (1.00–1.72) 0.046*
Gender (Male, Female)	1.01 (0.79–1.28) 0.968	–
Age (>60,≤60)	1.38 (1.04–1.83) 0.026*	1.12 (0.83–1.51) 0.479
BMI (≥24kg/m2,<24kg/m2)	0.71 (0.56–0.91) 0.006*	0.79 (0.62–1.02) 0.070
Ann-Arbor Staging (III˜IV, I˜II)	2.25 (1.67–3.04) <0.001*	1.31 (0.92–1.86) 0.137
IPI score (3˜5,0˜2)	2.82 (2.18–3.65) <0.001*	2.06 (1.49–2.85) <0.001*
B symptoms (Yes, No)	1.44 (1.13–1.83) 0.003*	1.09 (0.84–1.43) 0.506
Pathological diagnosis (GCB, Non-GCB)	0.81 (0.64–1.04) 0.097	0.86 (0.67–1.11) 0.250
LDH (>250 U/L,≤250 U/L)	1.84 (1.44–2.31) <0.001*	1.15 (0.86–1.53) 0.349
β2 micro-globulin (>2.8ug/mL,≤2.8ug/mL)	1.71 (1.34–2.17) <0.001*	1.19 (0.91–1.56) 0.199
Extranodal involvement (Yes, No)	1.09 (0.84–1.40) 0.528	–
Bulky disease (Yes, No)	1.20 (0.94–1.54) 0.151	1.25 (0.97–1.61) 0.090
Comorbidities (Yes, No)	1.92 (0.86–1.39) 0.474	–
Ki-67(≥90%,<90%)	1.18 (0.88–1.58) 0.263	–
BCL-2(Positive, Negative)	1.12 (0.85–1.46) 0.423	–
BCL-6(Positive, Negative)	0.84 (0.65–1.08) 0.170	0.86 (0.65–1.12) 0.265
C-MYC (≥40%,<40%)	1.34 (1.03–1.73) 0.027*	1.33 (1.02–1.74) 0.038*

Note: *P value less than 0.05 was considered statistically significant.
Abbreviations: PFS, progression-free survival; HR, hazard ratio; BMI, body mass index; IPI, international prognostic index; GCB, germinal center B cell; LDH, lactate dehydrogenase.

Table 6 Univariate and Multivariate Analysis of OS in 732 Patients with DLBCL and Hyperglycemia

	Univariate Analysis	Multivariate Analysis
	HR (95% CI) P value	HR (95% CI) P value
Metformin (Yes, No)	0.70 (0.51–0.97) 0.034*	0.68 (0.49–0.95) 0.024*
Secondary hyperglycemia (Yes, No)	1.36 (1.05–1.77) 0.021*	1.35 (1.03–1.77) 0.030*
Gender (Male, Female)	0.99 (0.78–1.26) 0.910	–
Age (>60,≤60)	1.37 (1.03–1.82) 0.029*	1.15 (0.86–1.56) 0.348
BMI (≥24kg/m2,<24kg/m2)	0.69 (0.54–0.89) 0.003*	0.75 (0.59–0.97) 0.026*
Ann-Arbor Staging (III˜IV, I˜II)	2.12 (1.57–2.86) <0.001*	1.24 (0.87–1.77) 0.277
IPI score (3˜5,0˜2)	2.69 (2.08–3.48) <0.001*	1.94 (1.41–2.68) <0.001*
B symptoms (Yes, No)	1.49 (1.17–1.89) 0.001*	1.13 (0.87–1.48) 0.351
Pathological diagnosis (GCB, Non-GCB)	0.87 (0.68–1.11) 0.245	–
LDH (>250 U/L,≤250 U/L)	1.86 (1.46–2.37) <0.001*	1.24 (0.93–1.66) 0.144
β2 micro-globulin (>2.8ug/mL,≤2.8ug/mL)	1.73 (1.36–2.20) <0.001*	1.23 (0.93–1.61) 0.143
Extranodal involvement (Yes, No)	1.06 (0.82–1.36) 0.665	–
Bulky disease (Yes, No)	1.14 (0.88–1.46) 0.318	–
Comorbidities (Yes, No)	1.07 (0.84–1.36) 0.610	–
Ki-67(≥90%,<90%)	1.15 (0.86–1.54) 0.355	–
BCL-2(Positive, Negative)	1.10 (0.84–1.44) 0.476	–
BCL-6(Positive, Negative)	0.93 (0.72–1.20) 0.563	–
C-MYC (≥40%,<40%)	1.44 (1.11–1.86) 0.006*	1.39 (1.07–1.80) 0.014*

Note: *P value less than 0.05 was considered statistically significant.
Abbreviations: OS, overall survival; HR, hazard ratio; BMI, body mass index; IPI, international prognostic index; GCB, germinal center B cell; LDH, lactate dehydrogenase.

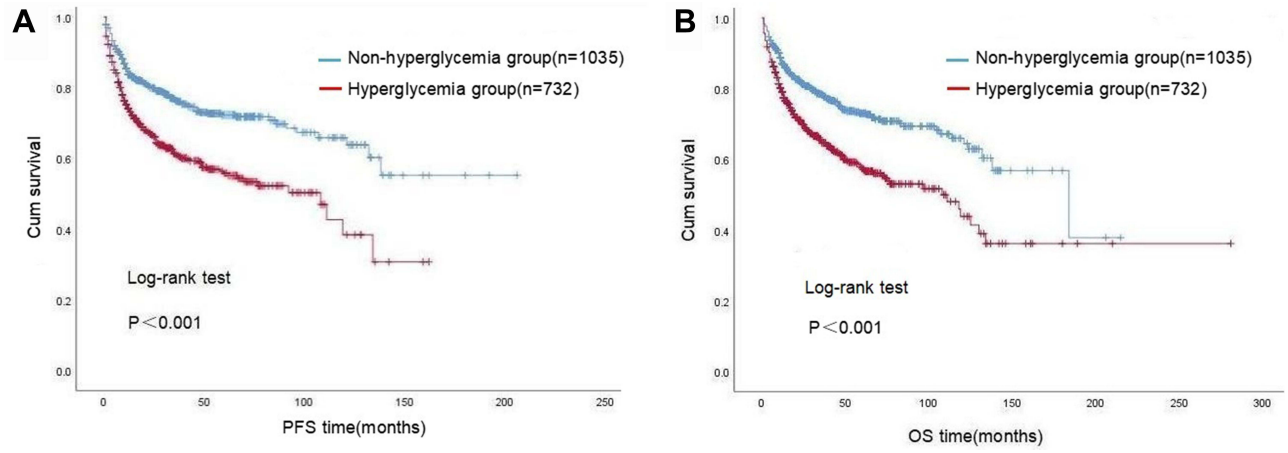

Figure 1 Kaplan–Meier survival curve of the two cohorts. Description: (**A**) PFS regarding non-hyperglycemia group and hyperglycemia group. (**B**) OS regarding non-hyperglycemia group and hyperglycemia group.

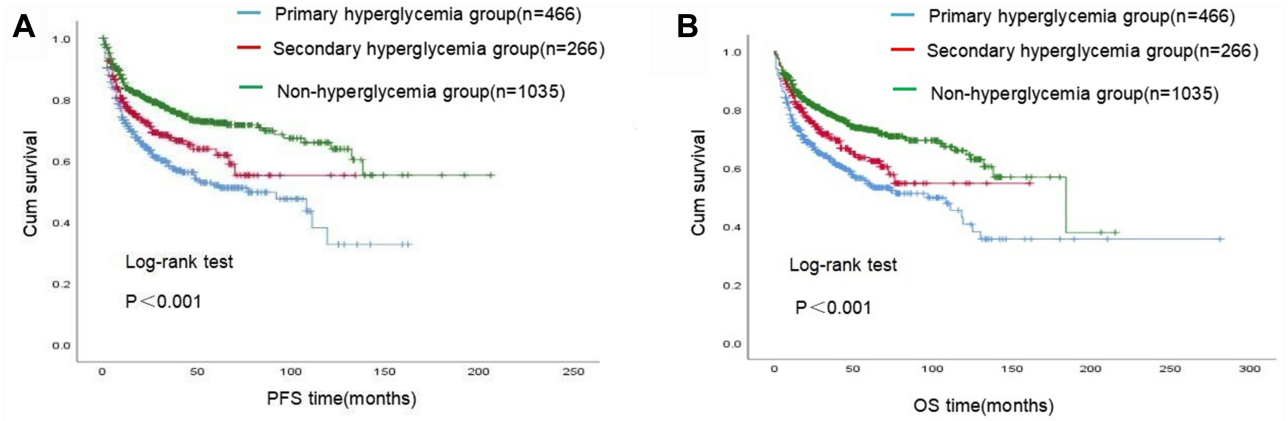

Figure 2 Kaplan–Meier survival curve of the three cohorts. Description: (**A**) PFS regarding primary hyperglycemia group, secondary hyperglycemia group and non-hyperglycemia group. (**B**) OS regarding primary hyperglycemia group, secondary hyperglycemia group and non-hyperglycemia group.

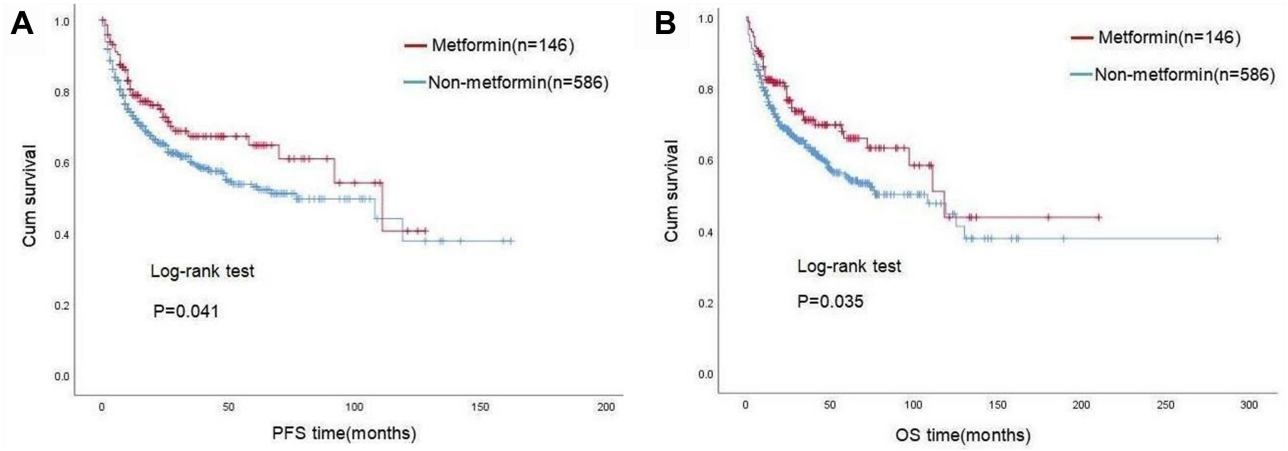

Figure 3 Kaplan–Meier survival curve of the two cohorts. Description: (**A**) PFS regarding the metformin group and the non-metformin group. (**B**) OS regarding the metformin group and the non-metformin group. Metformin group refers to taking single-drug metformin or metformin combined with other hypoglycemic drugs, non-metformin group refers to never taking metformin (other hypoglycemic drugs are not excluded).

chemotherapy can improve PFS and OS in diabetic patients, preclinical studies had shown metformin had the potential to re-sensitize drug-resistant lymphoma to chemoimmunotherapy.[27] This study shows that for people with DLBCL and hyperglycemia, the use of the hypoglycemic drug metformin can increase the population's PFS and OS (PFS: adjusted HR 0.69, 95% CI: 0.49–0.96, P=0.028, OS: adjusted HR 0.68, 95% CI: 0.49–0.95, P=0.024).Therefore, for people with DLBCL and hyperglycemia, if there is no obvious contraindication, metformin is the first choice for hypoglycemic therapy.

This is a large-scale clinical retrospective study with a large number of enrolled cases and a long follow-up time, which is representative to a certain extent. Moreover, this study is the first to suggest that secondary hyperglycemia also affects the prognosis of DLBCL patients. However, because this is a single-center study with a large time span, large-scale chromosome or FISH examination of lymphoma cells was not performed, and double-hit and triple-hit lymphoma models were not included. At the same time, this study did not exclude end-stage diabetes patients, multicenter and larger sample sizes are required to validate this result.

Conclusions

In short, our data suggested hyperglycemia was related to the poor prognosis of DLBCL population, and secondary hyperglycemia also affected the prognosis of DLBCL population, and hyperglycemia was an independent risk factor affecting the prognosis of DLBCL.This study also found that overweight people were more likely to have secondary hyperglycemia, and clinical attention should be paid to DLBCL patients with overweight.In addition, this study showed that the application of metformin could improve the survival rate of patients with DLBCL and hyperglycemia.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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