Insulin Resistance and the Prognosis in Diffuse Large B-cell Lymphoma

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ABSTRACT

Objective: To investigate whether insulin resistance (IR) affects the prognosis in patients with diffuse large B-cell lymphoma (DLBCL).

Place and Duration of the Study: The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, from September 2017 to December 2021.

Methodology: This study retrospectively analysed 324 patients with DLBCL who were divided into a non-IR group (251 cases) and IR group (73 cases) according to IR. The authors collected clinical data of the study population and calculated the overall survival (OS) of patients through inpatient case data or follow-up. The Cox regression method was used to assess the prognostic factors of the patients. The Kaplan–Meier method was used for drawing the survival curve of IR on OS of the DLBCL patients.

Results: The IR group had older age, higher international prognostic index (IPI), later stage, and higher insulin levels. The five-year OS rate was 46% in the IR group and 66% in the non-IR group. Compared with the non-IR group, the IR group showed a poor prognosis (OS: adjusted HR 1.23, 95% CI: 1.02–1.41, p = 0.031).

Conclusion: IR was one of the factors leading to poor prognosis in patients with DLBCL, and attention should be paid to this risk factor.

Key Words: *Insulin resistance, Diffuse large B-cell lymphoma, Overall survival, Prognosis.*

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL), with a global annual incidence rate of approximately 24% in NHL patients.[1] Insulin resistance (IR) refers to hyperinsulinemia caused by the excessive compensatory secretion of insulin by the body due to the reduction of glucose uptake and utilisation promoted by insulin. IR manifests as decreased insulin sensitivity, preprandial hypoglycaemia, and obesity. IR often causes diabetes, polycystic ovary syndrome, fatty liver, and dyslipidaemia. IR and endogenous hyperinsulinemia are key features in the development of metabolic syndrome.[2]

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The elevated concentrations of glucose, insulin, and free insulin like growth factor-1 that result from insulin resistance may generate a pro-inflammatory and protumourigenic state. These alterations may underlie an increased risk of developing various types of cancer; the worsening of cancer prognoses has also been observed in obese and diabetic patients.[3] Moreover, IR has been reported as an independent risk factor for colorectal cancer, breast cancer, endometrial cancer, and prostate cancer.[4-7] However, there have been few reports on the impacts of IR on the prognosis of DLBCL patients. Therefore, the aim of this study was to analyse patients with DLBCL, in order to explore the relationship between IR and DLBCL.

METHODOLOGY

This study was approved by the Medical Ethics Committee of the hospital and followed the principles of the Helsinki Declaration. All subjects provided informed consent. A total of 324 patients were definitely diagnosed with DLBCL in the haematology department of the Fourth Hospital of Hebei Medical University (Hebei Tumor Hospital), from September 2017 to December 2021. The exclusion criteria were fasting plasma glucose (FPG) >6.1 mmol/L after hospitalisation, diabetes mellitus, previous bariatric surgery, glucocorticoid therapy within

two weeks prior to hospitalisation, previous organ transplantation, end-stage cirrhosis or renal disease.

After patients fasted overnight, 5-mL venous blood samples from all 324 subjects were collected in tubes containing ethylene diamine tetraacetic acid anticoagulation, centrifuged to separate plasma, and then stored at -20°C until use in assays; no samples were thawed prior to the assays. Insulin was measured by electrochemiluminescence (Roche Diagnostics GmbH, Germany). Concentrations of serum glucose were measured using the glucose oxidase method (Makerbio, China). The IR was calculated using the homeostasis model assessment of IR (HOMA-IR) = (FPG [mmol/l]×fasting insulin [μU/ml])/22.5, which was defined as HOMA value >2.7.[8] The range of the fasting insulin was 2.6–24.9 uU/ml, while the range of the FPG was 3.9–6.1 mmol/L.

The clinical data included age, body mass index (BMI), gender, stage, pathological diagnosis, international prognostic index (IPI), B symptoms, FPG, hyperglycaemia, previous comorbidities, and treatment plan. According to the Hans classification system, the pathological diagnoses of the patients were divided into the following two groups: germinal non-GCB (Non-GCB) or centre B-cell source (GCB).[9] IPI was based on the following inclusion criteria: age >60 years, stage III/IV, performance status score ≥2 points, lactate dehydrogenase higher than normal, and number of extranodal involvement sites >1.[10] All enrolled patients received chemotherapy with R-CHOP regimen.

The deadline for follow-up was 30 December 2021. Overall survival (OS) was defined as the time from diagnosis to death for any reason, diagnosis to last follow-up, or loss to follow-up.

Data were analysed using SPSS 26.0 software. Continuous variables were expressed as mean ± standard deviation, while descriptive statistics were used to study variables and were expressed in terms of frequencies and percentages. Chi-square tests were used to assess the significance of differences in categorical variables between the two groups, and Student t-tests were used to analyse continuous variables. The Kaplan–Meier method was used to draw the survival curve of IR on the OS of the DLBCL patients. The value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Three hundred and twenty-four participants were included in the present study, of which 73 (22.5%) had IR and 251 (77.5%) had non-IR. The age of the population was 61.03±14.60 years, and the average age of the IR group was older ($p < 0.05$). There were 175 (54.0%) males and 149 (46.0%) females. The IR group had higher insulin, later Ann Arbor stages, and higher IPI scores (Table I).

At the end of follow-up period, 107 patients with DLBCL had died and 217 were alive. Age >60 years, late stage (III–IV), B symptoms, higher IPI score (3–5), Non-GCB and IR group, had higher mortality rate (Table II).

Univariate analysis of 324 patients indicated IR, age, stage, BMI, pathological diagnosis, IPI, and B symptoms related to the OS of the patients ($p < 0.05$). Multivariate analysis of these factors indicated that IR, BMI, stage III–IV, and IPI (3–5) were all related to worse prognosis ($p < 0.05$, Table III).

The longest OS was 128 months, and the shortest OS was one month (median OS: 37.3 ± 27.79 months). The five-year OS rate was 46% in the IR group and 66% in the non-IR group. IR reduced OS in the study population ($p = 0.009$, Figure 1).

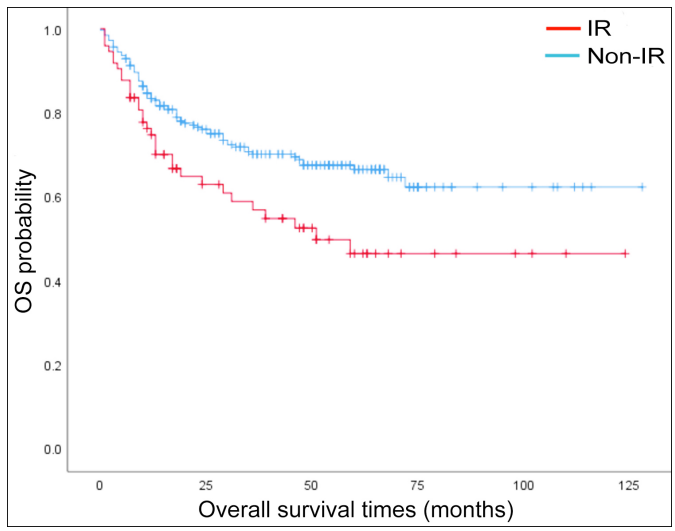

Figure 1: OS stratified by presence or absence of IR (Log Rank P=0.009).

DISCUSSION

IR can exist during pregnancy, fasting, exercise, acute stress, and other physiological conditions, as well as in a variety of chronic diseases, such as type 2 diabetes, obesity, and cancer.[11,12] The authors found that IR significantly reduced the OS of DLBCL patients in this study. In the IR group of this study, after excluding influencing factors, such as diabetes, prediabetes, glucocorticoid application, organ transplantation, end-stage renal disease, or liver cirrhosis, the IR of the enrolled population was considered to be caused by the disease itself, excluding the interfering factors, presenting in a particular way. As a surrogate for IR assessment, the HOMA-IR model was superior to hyperinsulinemia in diagnosing IR.[13] In a study of 10 male non–small cell carcinoma patients with weight loss, IR was related to the decreased protein anabolism and increased inflammatory marker C-reactive protein (CRP) but not weight loss.[14] This study found that the IR group was older on average, had later stage, and had higher IPI scores, but this group was not associated with higher BMI, partially similar to the above findings. Ning's study showed that under the premise of normal thyroid function, the incidence of IR in differentiated thyroid cancer was higher than that in benign thyroid nodules; in addition, high HOMA-IR was considered to be a potential risk factor for thyroid cancer.[15]

Table I: Clinicopathological characteristics of IR group and Non-IR group.

Factors	All (n=324)	IR (n=73)	Non-IR (n=251)	P
Age	61.03±14.60	65.34±13.18	59.78±14.77	0.004*
Gender				0.147
Male	175(54.0%)	34(46.6%)	141 (56.2%)	
Female	149 (46.0%)	39(53.4%)	110 (43.8%)	
BMI	24.21±3.97	24.58±4.49	24.11±3.81	0.370
Stage				0.017*
III-IV	178(54.9%)	49 (67.1%)	129 (51.4%)	
I-II	146(45.1%)	24(32.9%)	122 (48.6%)	
IPI score				
3-5	110 (34.0%)	37 (50.7%)	73 (29.1%)	0.001*
0-2	214 (66.0%)	36 (49.3%)	178 (70.9%)	
B symptoms				0.439
Yes	112 (34.6%)	28(38.4%)	84 (33.5%)	
No	212(65.4%)	45(61.6%)	167 (66.5%)	
Pathological diagnosis				0.932
GCB	139 (42.9%)	31(42.4%)	108 (43.0%)	
Non-GCB	185 (57.1%)	42(57.5%)	143 (57.0%)	
Insulin (uU/ml)	11.03±5.91	18.49±7.02	8.86±3.15	<0.001*
FPG (mmol/L)	4.78±0.63	4.74±0.73	4.80±0.60	0.525
HOMA-IR	2.28±1.09	3.77±1.14	1.85±0.57	<0.001*

Student t-tests was used for Age, BMI, Insulin, FPG, HOMA-IR; Pearson Chi-square test was used for others.

Table II: Survival analyses of patients with IR or Non-IR.

Factors	Survival (n=217)	Died (n=107)	X^2	p-value
Age			5.37	0.021*
>60y	121(55.8%)	74(69.2%)		
≤60y	96(44.2%)	33(30.8%)		
Gender			0.99	0.319
Male	113(52.1%)	62(57.9%)		
Female	104(47.9%)	45(42.1%)		
BMI			2.85	0.091
≥24Kg/m^2	121(55.8%)	49(45.8%)		
<24Kg/m^2	96(44.2%)	58(54.2%)		
Stage			20.81	<0.001*
III-IV	100 (46.1%)	78 (72.9%)		
I-II	117(53.9%)	29 (27.1%)		
IPI score			31.99	<0.001*
3-5	51(23.5%)	59 (55.1%)		
0-2	166(76.5%)	48 (44.9%)		
B symptoms			8.90	0.003*
Yes	63(29.0%)	49 (45.8%)		
No	154(71.0%)	58 (54.2%)		
Pathological diagnosis			4.52	0.034*
GCB	102 (47.0%)	37 (34.6%)		
Non-GCB	115(53.0%)	70(65.4%)		
HOMA-IR			4.98	0.026*
High	41(18.9%)	32(29.9%)		
Normal	176(81.1%)	75(70.1%)		

Pearson Chi-square test was used.

Table III: Cox analysis of OS in patients.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
IR (Yes, No)	1.75	1.20-2.54	0.004*	1.23	1.02-1.41	0.031*
Age (≤60y, >60y)	1.55	1.04-2.29	0.031*	1.30	0.86-1.96	0.221
Sex (Male, Female)	1.15	0.80-1.65	0.464	-	-	-
BMI (<24kg/m^2, ≥24kg/m^2)	0.64	0.45-0.92	0.015*	0.59	0.40-0.86	0.005*
IPI (3-5,0-2)	3.34	2.31-4.81	<0.001*	2.15	1.39-3.32	0.001*
Stage (I-II, III-IV)	2.78	1.83-4.24	<0.001*	1.71	1.05-2.79	0.031*
Pathological diagnosis (GCB, Non-GCB)	0.64	0.44-0.94	0.021*	0.77	0.52-1.14	0.193
B Symptoms (Yes, No)	1.71	1.19-2.45	<0.004*	1.34	0.93-1.95	0.120

A prospective study has suggested that elevated fasting serum insulin and IR appear to be related to an increased risk of developing lung tumour, and while quitting smoking was identified as the best way to prevent lung tumour, other lifestyle changes affected insulin concentrations and sensitivity (*e.g.*, avoiding excess weight, increasing physical activity, and changing to a healthy diet) that may also reduce lung-tumour risk.[16] For postmenopausal women, hyperinsulinemia was also an independent hazard factor for breast cancer.[17] Epidural anaesthesia has been found to cause less inflammation in the radical resection of colon cancer, with the insulin level and IR increasing after the surgeries based on fasting insulin and homeostasis model assessment.[18]

However, until now, the specific mechanism of IR in tumorigenesis has not been clarified due to a lack of in-depth research. The two diseases may share pathways and risk factors at an early-stage of development, such as immune deficiency and obesity. Insulin resistance has been associated with high oxidative stress, inflammatory states, and immune dysfunction, all of which have been associated with tumorigenesis in DLBCL.[19] Some studies had shown that endogenous hyperinsulinemia was associated with cancer progression, recurrence, and excessive mortality in patients with breast cancer.[20] High levels of insulin can increase free insulin-like growth factor 1 (IGF-1), which can induce tumour by promoting cell proliferation, differentiation, angiogenesis promotion, and the inhibition of tumour cell apoptosis, among other mechanisms, after binding with the corresponding receptors.[21] The importance of IGF-1 in DLBCL was verified by in-vitro IGF-1 inhibitor experiments, which were found to significantly inhibit the proliferation of DLBCL cell lines in a concentration-dependent manner.[22] Additionally, increased notch signalling lead to lipid accumulation and IR.[23] Since IR may lead to tumour cachexia, drugs that improve IR have the potential to improve cachexia in people with cancer.[24]

This study had significant limitations, including being a single-centre study, the presence of possible measurement error, and blood collection being done at only one time point. Furthermore, the authors acknowledge that IR was only one of many complicating factors contributing to the poor prognosis in DLBCL patients. Thus, more studies are needed to further verify this result and the possible mechanism of action.

CONCLUSION

Overall, this study found that IR was a factor in the poor prognosis of DLBCL patients. Therefore, in the DLBCL population, treatment should be comprehensive and IR must be considered.

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ETHICAL APPROVAL:
The study was approved by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University (Hebei Tumor Hospital) (Approval Number. 2022KY384) and followed the principles of the Declaration of Helsinki. All subjects gave informed consent.

PATIENTS' CONSENT:
Informed consents were obtained from the patients.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
WZ, XH, LL: Research idea and study design.
QG, LF: Data acquisition and analysis.
YW: Supervision and mentorship.
All the authors have approved the final version of the manuscript to be published.

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