Research Square

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Dyslipidemia in diffuse large B cell lymphoma based on the genetic subtypes: a single-center study of 259 Chinese patients

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) is a kind of highly heterogeneous non-Hodgkin lymphoma both in clinical and genetic terms. DLBCL is admittedly categorized into 6 subtypes by genetics, which contains MCD, BN2, EZB, N1, ST2 and A53. Dyslipidemia is relevant to a multitude of solid tumors and has recently been reported associated with hematologic malignancy. We aim to present a retrospective study investigating dyslipidemia in DLBCL based on the molecular subtypes.

Results: This study concluded 259 patients with newly diagnosed DLBCL and their biopsy specimens were available for molecular typing. Results show that the incidence of dyslipidemia (87.0%, p<0.001) is higher in the EZB subtype than in others, especially the hypertriglyceridemia (78.3%, p=0.001) in the EZB subtype. Based on the pathological gene-sequencing, patients with BCL2 gene fusion mutation are significantly correlative with hyperlipidemia (76.5%, p=0.006) and hypertriglyceridemia (88.2%, p=0.002). Nevertheless, the occurrence of dyslipidemia has no remarkable influence on prognosis.

Conclusion: In summary, dyslipidemia connects with the genetic heterogeneity in DLBCL while without significant influence on survival.

Introduction

Diffuse large B cell lymphoma (DLBCL) is characterized by aggressive and heterogeneous both epigenetically and genetically. Besides, DLBCL accounts for approximately 35% of non-Hodgkin lymphoma (NHL) and is the most common lymphoma in adults[1]. In 2018, the definition of molecular typing was initially propounded. Shipp MA et al. classified DLBCL into clusters 1 ~ 5 by genetic abnormality[2]. Staudt LM. et al. implemented molecular typing by analyzing genetic alterations and proposed 4 prominent subtypes, termed MCD (featured as the co-occurrence of MYD88. L265p and CD79B mutations), BN2 (featured as BCL6 fusion mutations and NOTCH2 mutations), EZB (featured as EZH2 mutations and BCL2 fusion mutations) and N1 (featured as NOTCH1 mutations). Later other 2 types were added, including ST2 (featured as SGK1 and TET2 mutations) and A53 (featured as TP53 mutations)[3, 4]. Researchers had considered the influence of MYC mutations, therefore divided the EZB subtype into MYC positive EZB isoform and MYC negative EZB isoform furthermore[4]. While the prior simple algorithm of 6 subtypes is more frequently being applied in clinical. Dyslipidemia has been considered correlative with multitudes of solid tumors, like breast cancer, prostate cancer, thyroid cancer, colorectal cancer and lung cancer[5–9]. Recently, researchers have found that a portion of hematologic malignancies is relative to the incidence of dyslipidemia, for instance, chronic leukemia and acute promyelocytic leukemia[10, 11]. Ma J et al. recently found that cholesterol biosynthesis relative axis may have an oncogenic function in DLBCL with BCL2-IGH translocations[12]. While the correlation between dyslipidemia and DLBCL has not been reported, especially on the genetic aspect. Therefore, we purpose to investigate dyslipidemia in DLBCL in the context of molecular typing and to explore the correlation between dyslipidemia and gene mutation.

In this retrospective study, we analyzed 259 DLBCL patients with gene sequencing finished to assess dyslipidemia in newly diagnosed DLBCL.

Methods

Patients and samples collection

Totally 259 newly diagnosed DLBCL patients were selected with indispensable pathological issues to analyze molecular typing. All patients were admitted to the clinic center affiliated with the First Affiliated Hospital of Zhejiang University School of Medicine from April 2014 to November 2022. A total of 121 genes covering exon, fusion-relevant intron and alternative splicing are analyzed. Six typing method was applied in this study, which contains MCD, BN2, EZB, N1, ST2 and A53. In terms of dyslipidemia, we collected lipid indices including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). According to the category of dyslipidemia, we defined dyslipidemia as hypertriglyceridemia, hypercholesterolemia, hypoalbuminemia and mixed hyperlipidemia[13]. Lipid profiles were stratified according to The Guidelines on Prevention and Treatment of Blood Lipid Abnormality in Chinese Adults (Version 2016)[14].

All patients were initially treated with the first-line therapy recommended by National Comprehensive Cancer Network (NCCN)[15]. Patients with CD20 positive were primely treated with rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or R-CHOP-like regimens. Older patients were medicated by a dose-decreased R-CHOP regimen. The R-DA-EPOCH regimen was administrated in patients with poor left ventricular patients.

Diagnosis and prognosis indicators related to DLBCL were collected that concluded: B symptoms, Ann Arbor stage, international prognosis index (IPI), Eastern Cooperative Oncology Group stage (ECOG stage) and results of immunohistochemistry (IHC). We also collected demographic and other clinical data from medical records that concluded: age, sex, height, weight, body mass index (BMI), white blood count (WBC), hemoglobin count, platelet counts, albumin, alanine transaminase (ALT), serum creatinine, lactate dehydrogenase(LDH), ferritin, C-

reactive protein (CRP), β micro-globulin (β-MG), fibrinogen, Prothrombin time (PT), activates prothrombin time (APTT), thrombin time (TT), International normalized ratio (INR), D-dimer and cytokine including Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin-17α (IL-17α), Tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). We collected 22375 samples totally.

The study was approved by the institutional Ethics Committee and it was conducted in accordance with the Declaration of Helsinki.

Classification of abnormality

According to the Guidelines on Prevention and Treatment of Blood Lipid Abnormality in Chinese Adults (Version 2016), we defined dyslipidemia as hypertriglyceridemia, hypercholesterolemia, hypoalbuminemia and mixed hyperlipidemia, which meets both hypertriglyceridemia and hypercholesterolemia.

The upper limits of normal TG, TC and LDL were 1.70 mmol/L (150 mg/dL), 5.86 mmol/L (226.6 mg/dL) and 3.29 mmol/L (127.2 mg/dL), respectively. The lower limit of normal HDL was 0.78 mmol/L (30.2 mg/dL).

Statistical Analysis

Data are presented as median and absolute range or frequencies. The Kruskal-Wallis H test was used to compare the distribution of numerical variables. The χ^2 test was used in qualitative variables. The relationships between clinical factors and dyslipidemia were assessed using univariable and multivariable logistic regression models. All multivariable analyses were adjusted by sex and age. The Kaplan-Meier method was used to estimate univariate survival curves and the differences between curves were calculated via the log-rank test. Multivariable Cox proportional hazard regression models were used to assess the prognostic impact of hypertriglyceridemia with regard to OS and PFS. Statistical analyses were performed using SPSS software, version 23.0. P values below 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 259 newly diagnosed DLBCL patients are categorized into 6 genetic subtypes and the proportion of each type is 21.6% MCD subtype, 19.3% BN2 subtype, 8.9% EZB subtype, 3.5% N1 subtype, 4.2% ST2 subtype and 12.4% A53 subtype, respectively (Fig. 1). Besides, 30.1% of patients are unclassified and this isoform is defined as black control. In order to investigate the concrete genes influencing the lipid, meanwhile, we considered the familiar decisive genes of molecular typing such as BCL2, BCL6, TP53, MYD88, MYC, NOTCH2 and EZH2. More details regarding genetic typing and gene translocation are shown in Fig. 2.

We recorded and analyzed the initial concentration of lipids before DLBCL patients receiving any treatment. Results show that TG in the EZB subtype was higher than the unclassified subtype (Kruskal-Wallis H test, $p = 0.001$). The median concentration of TG in these two groups is 2.01 mmol/L (range 1.76 ~ 2.48 mmol/L) and 1.16 mmol/L (range 0.84 ~ 1.58 mmol/L), respectively. More importantly, results show that in the EZB subtype the incidence of hypertriglyceridemia is 78.3% compared with 19.2% in the unclassified subtype, 36.0% in the MCD subtype and 18.2% in the ST2 subtype (chi-square test and Fisher's exact test, $p < 0.001$, $= 0.001$, < 0.001). In addition, dyslipidemia is discovered more commonly in the EZB subtype than the unclassified subtype with a significant statistical difference (87% vs 39.7%, $p < 0.001$). The other 3 types of lipids including TC, HDL-C and LDL-C, whereas, demonstrated no significant differences in the 7 types.

According to the World Health Organization (WHO) classification of lymphoma, researchers put forward the concept of high-grade B cell lymphoma on the basis of three types of gene translocation that are BCL2, BCL6 and MYC. Thus, we also analyzed the correlation between dyslipidemia and gene translocation. Based on the pathological gene-sequencing, patients with BCL2 gene fusion mutation are significantly correlative with dyslipidemia (chi-square test, 76.5%, $p = 0.006$) and hypertriglyceridemia (chi-square test, 88.2%, $p = 0.002$) than patients without rearrangement of these 3 genes.

Other demography and clinical characteristics are demonstrated in Table 1.

Table 1
Characteristics of democracy and clinical factors in different types of DLBCL.

	Genetic typing							
	MCD n = 50	BN2 n = 56	EZB n = 23	N1 n = 9	ST2 n = 11	A53 n = 32	Unclassified n = 78	P value
Age(years), range	66(47–90)	62(23–87)	60(39–81)	70(60–79)	69(31–87)	64(18–90)	58(19–87)	0.001*
Gender								0.747
Male	30(20.7)	29(20.0)	15(10.3)	5(3.4)	8(5.5)	18(12.4)	40(27.6)	
Female	20(17.5)	27(23.7)	8(7.0)	4(3.5)	3(2.6)	14(12.3)	38(33.3)	
Height(cm), range	165(149–180)	165(147–184)	167(151–182)	158(145–170)	165.5(156–177)	164.5(155–180)	166(150–186)	0.482
Weight (Kg), range	60(44–87)	61(40–86)	65(46–84)	55(46–70)	58.75(50–84)	61(47–83)	61(42–99)	0.530
BMI(Kg/m^2), range	22.0(17.0-22.4)	23.5(14.7–29.4)	23.7(16.5–29.0)	22.9(17.1–25.1)	22.0(18.7–26.8)	22.0(18.4–29.3)	22.4(16.2–33.9)	0.860
B symptoms, No. (%)	14(20.0)	16(22.9)	8(11.4)	4(5.7)	3(4.3)	11(15.7)	14(20.0)	0.390
Hans typing, No. (%)								0.001*
Non-GCB	38(22.2)	43(25.1)	5(2.9)	6(3.5)	6(3.5)	24(14.0)	49(28.7)	
GCB	11(13.4)	12(14.6)	18(22.0)	2(2.4)	5(6.1)	1(16.7)	2(33.3)	
Unclassified	1(16.7)	1(16.7)	0(0.0)	1(16.7)	0(0.0)	1(16.7)	2(33.3)	
BM involvement, No. (%)	14(28.0)	9(18.0)	3(6.0)	3(6.0)	5(10.0)	5(10.0)	11(22.0)	0.119
Ann Arbor stage, No. (%)								0.277
I-II	10(17.5)	14(24.6)	4(7.0)	0(0.0)	0(0.0)	9(15.8)	20(35.1)	
III-IV	40(20.0)	41(20.5)	18(9.0)	9(3.5)	11(4.3)	32(12.5)	58(29.0)	
IPI score, No. (%)								0.175
0–1	8(14.5)	11(20.0)	5(9.1)	0(0.0)	2(3.6)	7(12.7)	22(40.0)	
2–3	18(14.9)	30(24.8)	11(9.1)	3(2.5)	6(5.0)	16(13.2)	37(30.6)	
4–5	20(27.4)	14(19.2)	7(9.6)	3(2.5)	6(8.2)	16(13.2)	15(20.5)	
WBC (10×10^9/L), range	5.2(0.9–11.9)	6.7(2.2–17.4)	7.0(1.5–17.3)	3.7(2.2–14.6)	7.1(4.2–12.0)	6.6(2.7–19.2)	5.6(2.1–30.9)	0.093
Hb(g/L), range	123.5(46–160)	129(69–162)	123(93–174)	123(57–148)	123(51–153)	110(57–156)	128(54–166)	0.265
PLT (10×10^9/L), range	171(29–367)	202.5(40–404)	229(59–428)	155(52–264)	218(93–541)	227(20–486)	225(41–434)	0.163

	Genetic typing							
	MCD n = 50	BN2 n = 56	EZB n = 23	N1 n = 9	ST2 n = 11	A53 n = 32	Unclassified n = 78	P value
Ab(g/L), range	39.5(23–51)	42.1(24–50)	40.8(32–48)	41.1(30–47)	41.3(29–47)	40.1(27–53)	41.9(23–52)	0.292
ALT(U/L), range	17.5(6–53)	17.5(6–56)	12(7–59)	23(11–65)	15(7–37)	17(4-157)	17(5–60)	0.616
Scr(μmol/L), range	69(34–168)	75(32–152)	75(49–285)	64(36–133)	77(55–110)	74(37–266)	69(42–193)	0.296
LDH(IU/L), range	291(94-2752)	329(139–2259)	352(131–772)	556(215–1429)	248(149–630)	280(145-10540)	224(118–2220)	0.034
Ferritin(ng/mL), range	462.6(35-5102)	429.4(24-40000)	355.8(34-1224)	699.9(80-12555)	333.9(12-4533)	288.8(5-3177)	182.6(4-1616)	< 0.001*
CRP (mg/L), range	10.0(0-167)	12.7(0-160)	19.4(0-120)	27.3(2-167)	41.3(2-230)	19.5(1-118)	5.9(0–80)	0.082
β2-MG	2665(0-7460)	2795(1160–10980)	2470(1150–16790)	4190(1990–6500)	3550(1450–12330)	2470(1329–14400)	2070(230–7700)	0.008*
IL-6(kU/L), range	14.1(1.5-716.6)	9.0(1.5-416.3)	10.5(0.7-174.6)	10.3(0.1-136.9)	26.4(4.0-1436.1)	10.1(2.9-378.6)	6.0(0.4-424.3)	0.027*
IL-10(kU/L), range	10.0(0.7-1046.7)	3.9(0.7-2226.2)	4.6(0.1–54.8)	39.9(1.8–6007.0)	5.9(0.1–49.2)	4.6(0.1-512.6)	3.5(0.1-475.9)	< 0.001*
TG (mmol/L), range	1.3(0.6–6.2)	1.5(0.5–3.7)	2.0(0.5–5.3)	1.2(0.5–2.6)	1.3(0.7–2.7)	1.5(0.6–22.0)	1.1(0.4–5.4)	0.003*
TC (mmol/L), range	3.6(2.2–7.4)	4.1(1.6–5.7)	4.3(2.3–6.9)	4.9(2.5–5.6)	4.2(2.5–6.2)	4.1(2.3–6.3)	4.1(2.1–8.1)	0.177
HDL (mmol/L), range	0.9(0.2–2.7)	1.1(0.2–1.6)	0.9(0.6–1.8)	1.1(0.3–2.2)	0.9(0.6–1.4)	0.9(0.2-2.0)	1.0(0.2-2.0)	0.092
LDL (mmol/L), range	2.1(1.0-4.6)	2.2(0.1–3.7)	2.3(0.6–4.3)	2.7(1.7–3.9)	2.2(1.0-4.4)	2.3(0.9–3.5)	2.4(0.3–5.7)	0.285

BMI: Body Mass Index; Non-GCB: non-Germinal Center B-cell; GCB: Germinal Center B-cell; BM: bone marrow; IPI: International Prognostic Index; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; Ab: albumin; ALT: alanine aminotransferase; Scr: serum creatinine; LDH: lactate dehydrogenase; CRP: C-reaction protein; β2-MG: β2-microglobulin; IL-6: Interleukin-6; IL-10: Interleukin-10; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

* Significantly different.

Continuous variables are presented as median with range and categorical variables are shown as frequency and percentage (No, %).

Other clinical factors about dyslipidemia

Binary logistic regression is used to analyze other clinical elements related to hypertriglyceridemia and dyslipidemia. In univariable analysis, molecular typing, BCL2 fusion translation, ferritin and BMI were risk factors in hypertriglyceridemia ($p < 0.05$). In terms of dyslipidemia, B symptoms, molecular typing, BCL2 fusion translation, ferritin, CRP and IL-6 have influenced dyslipidemia ($p < 0.05$).

In multivariable analysis, results indicate that being the EZB subtypes ($p = 0.002$, OR 34.524, 95% CI 3.700-322.120) is correlative with hypertriglyceridemia. Besides, the level of BMI affects triglyceride ($p = 0.002$, OR 1.183, 95% CI 1.064–1.315). As for dyslipidemia, the EZB

subtype is significantly associated with dyslipidemia (p = 0.020, OR 14.931, 95% CI 1.532-145.477). The influence of ferritin level is familiar (p = 0.026, OR 1.001, 95% CI 1.000-1.001). Detailed results of the logistic regression model are shown in Table 2.

Table 2
Logistic regression models evaluating the associations between clinical variables and hypertriglyceridemia and dyslipidemia in DLBCL patients.

		Univariable analysis		Multivariable analysis	
Dependent variable	**Independent variable**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
	B symptoms	1.738(0.989–3.053)	0.054	1.291(0.627–2.661)	0.488
HTG	MCD subtype	3.150(1.454–6.822)	0.004*	3.751(0.721–19.507)	0.116
	BN2 subtype	2.362(1.055–5.292)	0.037*	2.386(0.907–6.272)	0.078
	EZB subtype	15.120(4.387–47.260)	< 0.001*	34.524(3.700-322.120)	0.002*
	A53 subtype	2.520(1.014–6.265)	0.047*	2.741(0.977–7.692)	0.055
	BCL2 fusion mutation	4.104(1.309–12.866)	0.015*	0.403(0.034–4.814)	0.473
	ferritin	1.000(1.000-1.001)	0.009*	1.000(1.000-1.001)	0.167
	IL-10	1.001(1.000-1.002)	0.096	1.001(1.000-1.003)	0.135
	BMI	1.156(1.058–1.265)	0.001*	1.183(1.064–1.315)	0.002*
Dyslipidemia	B symptoms	2.178(1.226–3.871)	0.008*	1.579(0.764–3.264)	0.218
	MCD subtype	1.880(0.938–3.768)	0.075	2.041(0.405–10.287)	0.387
	BN2 subtype	1.642(0.802–3.363)	0.175	1.261(0.524–3.031)	0.605
	EZB subtype	10.108(2.767–36.919)	< 0.001*	14.931(1.532-145.477)	0.020*
	A53 subtype	2.216(0.958–5.126)	0.063	1.937(0.732–5.123)	0.183
	BCL2 fusion mutation	7.232(1.603–32.628)	0.010*	0.559(0.041–7.714)	0.664
	ferritin	1.001(1.000-1.002)	0.001*	1.001(1.000-1.001)	0.026*
	IL-6	1.006(1.000-1.009)	0.048*	1.002(0.998–1.005)	0.306
	CRP	1.013(1.011–1.019)	0.013*	1.000(0.991–1.010)	0.979
	BMI	1.079(0.992–1.172)	0.075	1.080(0.975–1.195)	0.140

OR: odd ratio; CI: confidence interval; HTG: hypertriglyceridemia; IL-10: Interleukin-10; BMI: Body Mass Index; IL-6: Interleukin-6; CRP: C-reactive protein.

* Significantly different.

Relation between dyslipidemia and survival

The median follow-up time is 12.3 months (range 1.1 ~ 105.0 months) among 235 surviving patients. A total of 21 patients died, three of whom died of complications and 18 patients died of disease progress. Significantly, only 2 patients died during the induction treatment. Moreover, up to the cut-off time disease progress occurred in 57 patients and in 35 patients occurred disease progress at the first assessment during therapy. Three patients were lost to follow-up. The 2-year OS and 2-year PFS rates were 81.7% and 61.3%, respectively. We construed the influence between lipids and survival. Neither hypertriglyceridemia nor dyslipidemia significantly affected OS and PFS in DLBCL patients (Hypertriglyceridemia: OS hazard ratio [HR] 0.855, 95% CI 0.353–2.075, p = 0.7336; PFS HR 0.824, 95% CI 0.482–1.407, p = 0.4730. Dyslipidemia: OS hazard ratio [HR] 0.637, 95% CI 0.270–1.504, p = 0.3012; PFS HR 0.692, 95% CI 0.408–1.176, p = 0.1490, Fig. 3). OS and PFS in different genetic subtypes appeared no significant statistical divergence (Fig. 4). While interestingly, OS in A53 subgroup showed differences. The 32 patients who are defined as A53 subgroup were divided into HTG group and non-HTG group by the level of triglyceride, and divided into dyslipidemia group and non-dyslipidemia group familiarly. Although the small number of samples precludes achieving significant difference in PFS, the OS showed significant results. The non-HTG group revealed better survival than HTG group while contrarily non-dyslipidemia showed

worse survival than dyslipidemia group (Fig. 5). Relative parameters significantly influenced survival did not discovered neither in univariable nor multivariable Cox regression models.

Discussion

In our study, hypertriglyceridemia and dyslipidemia are associated with molecular typing of DLBCL and the most relevant is the EZB subtype. The other clinical factors also connect with dyslipidemia including B symptoms, BCL2 fusion translation, ferritin and BMI. Whereas the incidence of hypertriglyceridemia and dyslipidemia has not influenced OS and PFS. We demonstrated the correlation of dyslipidemia with the genetic type of DLBCL at the genetic level.

Dyslipidemia is featured with abnormal serum triglycerides, cholesterol, low-density lipoprotein and high-density lipoprotein. Frederickson model was raised to systematically categorize dyslipidemia with 5 phenotypes. Type 2 is characterized by elevated levels of LDL and the rest types are featured with increased levels of various triglyceride-rich lipoprotein subfractions[16]. A more practical model of dyslipidemia defines as hypertriglyceridemia, hypercholesterolemia, hypo-HDL and hyper-LDL. The recommended levels of TG, LDL and HDL are 2-9.9mmol/L, 3.4-4.9mmol/L and 0.7-0.9mmol/L[17]. Exorbitant levels of lipids express an increased risk of pancreatitis[18]. In our retrospective study, two patients have high levels of triglycerides with 28.02 and 22.00 mmol/L, respectively. While there occurred no events of acute pancreatitis. elevated plasma LDL-cholesterol levels being the 8th leading risk factor for death in 2019 worldwide[19]. A large study conducted in China indicated that the most common dyslipidemia subtypes are hypo-HDL type (20.4%) and HTG type (13.8%)[20]. The mechanism related to primary dyslipidemia has not been proved definitely. According to the genome-wide association studies (GWASes), TMEM57, DOCK7, CELSR2, APOB, ABCG5, HMGCR, TRIB1, FADS2/S3, LDLR, NCAN and TOMM40-APOE appears to be related with increased TC levels. Similarly, CELSR2-PSRC1-SORT1, PCSK9, NCAN-CILP2-PBX4, LDLR and APOC1-APOE are associated with variations in LDL levels[21]. D9N and N291S variants have been seen correlative with elevated TG, while the S447X variant appears to be related to depressed TG. Moreover, APOA5-related abnormality performs to be potentially correlative with TG[22, 23]. Besides, pre-B-cell leukemia transcription factor 4 (PBX4/CILP2 locus) and B-cell CLL/lymphoma 3 genes are considered to be the association factor of dyslipidemia[24, 25]. Secondary hyperlipidemia has been acknowledged as associated with obesity, smoking, metabolic syndrome, proinflammatory and prothrombotic biomarkers, and type 2 diabetes[26]. Recently, the interaction between dyslipidemia-related genes and hematologic malignancy genes are reported, for instance, PML/RARα fusion protein and peroxisome proliferator-activated receptor-α have a synergy effect on Acute promyelocytic leukemia[27].

Dyslipidemia has been reported associated with a multitude of solid tumors such as breast cancer, prostate cancer, thyroid cancer, colorectal cancer and lung cancer[5–9]. In terms of hematologic malignancy, chronic lymphocyte leukemia and acute promyelocytic leukemia are reported associated with dyslipidemia and hypertriglyceridemia[11, 28]. Whereas, the correlation between dyslipidemia and lymphoma or multiple myeloma has not been reported. More recently, studies aimed at lipids in DLBCL patients appeared to indicate prognosis[29–31]. Fundamental experiments investigated cholesterol and DLBCL. SYK inhibits cholesterol biosynthesis by modulating PI3K/AKT- dependent survival pathways[32]. SOX9-DHCR24-cholesterol biosynthesis axis in IGH-BCL2 fusion translation positive DLBCL makes an oncogenic role via upregulating cholesterol synthesis[12, 33]. Based on molecular typing, the EZB subtype is characterized by IGH-BCL2 fusion translation and EZH2 mutation. Jiao M et al. proposed the SOX9-DHCR24-cholesterol biosynthesis axis, which may interpret the association between the EZB subtype and dyslipidemia to some extent.

The concept of genetic typing was raised to provide potential nosology for precision medicine strategies in DLBCL. According to the research containing 574 DLBCL biopsy samples identified genes, the BN2 subtype is dominated by NOTCH pathway aberrations and the NF-κB pathway. Besides, the MCD subtype is characterized by BCR and NF-κB pathway aberrations. EZB subtype is enriched for BCL2 translocation, EZH2 mutation, and REL amplification, involving Janus-associated kinase–signal transducers and activators of transcription (JAK-STAT) signaling and PI3K pathway. BCR has been shown to directly promote cholesterol biosynthesis through intermediate kinases downstream of the BCR to maintain cell membrane integrity and BCR signaling[3, 34–38]. Aimed at this, targeting cellular cholesterol provides new precise treatment strategies. Thaxton CS et al. investigated functional lipoprotein nanoparticles in DLBCL via targeting both cellular cholesterol uptake and BCR-associated de novo cholesterol synthesis and achieved cellular cholesterol reduction and induced apoptosis in otherwise resistant ABC DLBCL cell lines[39].

We analyzed 259 DLBCL patients in the lipid aspect based on genetic typing and deduced the association between dyslipidemia and EZB subtype without prognosis discrepancy. This study has some deficiencies. Firstly, it is a retrospective study with limitations in patient selection and analysis. Secondly, follow-up times are not long enough because 121 types of gene sequencing analysis conducted in the clinical institution stated just in recent years. Thirdly, the role of dynamic alterations of blood biomarkers during and after treatment was not taken into consideration during the analysis. Further prospective and multicenter research are needed to investigate dyslipidemia in DLBCL to instruct prognosis evaluation and treatment.

Conclusion

A total of 259 newly diagnosed DLBCL patients were categorized by genetic typing and analyzed with dyslipidemia. Significant differences were found in the EZB subtype that dyslipidemia and hypertriglyceridemia occurred in this isoform without influence on survival. In summary, the EZB subtype is exposed to more risks of dyslipidemia and hypertriglyceridemia, which may guide clinical treatment strategies.

Declarations

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the first affiliated Hospital, College of Medicine, Zhejiang University. Written informed consent was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Availability of data and materials

All relevant data and materials have been involved in the article. Further inquiries can be directed to the corresponding author.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Author contributions

WX contributed to the conception and design of the article. YX, HS, YS and YZ wrote the manuscript. XZ, JS, XL, DZ, CY, JW, XH, JW, JH, HM, WY, HT and JJ revised the manuscript. All authors contributed to article revision, read, and approved the submitted version.

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Figures

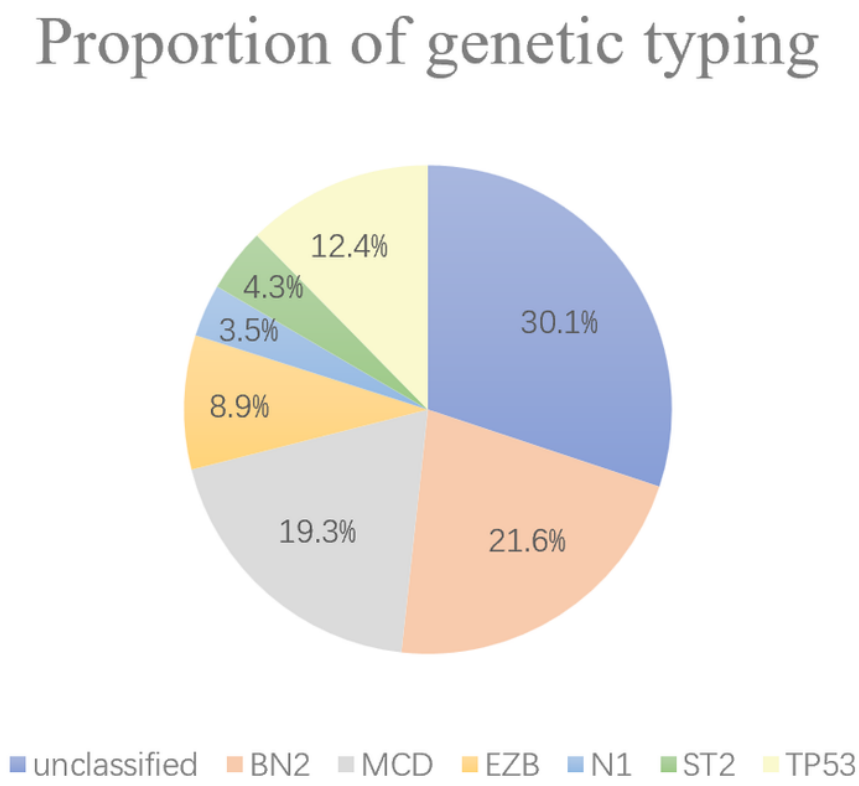


Figure 1

Proportion of genetic typing. In the 6 subgroups divided by genetic, the BN2 subtype, MCD subtype, EZB subtype account for most while the N1 and ST2 subtype account for no more than 10% totally.

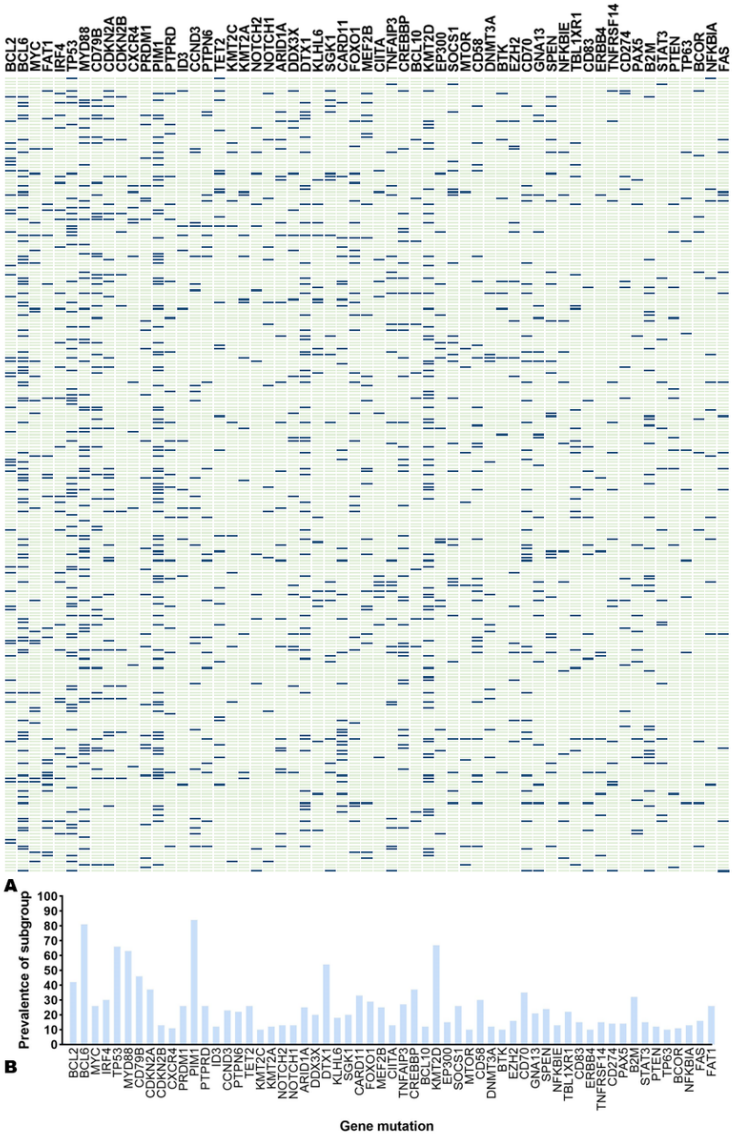


Figure 2

Panel A shows detail gene mutation in total 259 patients and panel B indicates the prevalence of gene mutation. A total of 121 genes covering exon, fusion-relevant intron and alternative splicing are analyzed and we selected 60 types of gene mutation which occurred rather frequent or molecular typing-related like BCL2, BCL6, MYC, MYD88, CD79B, PIM1, KMT2D, DTX1, TET2, SGK1.

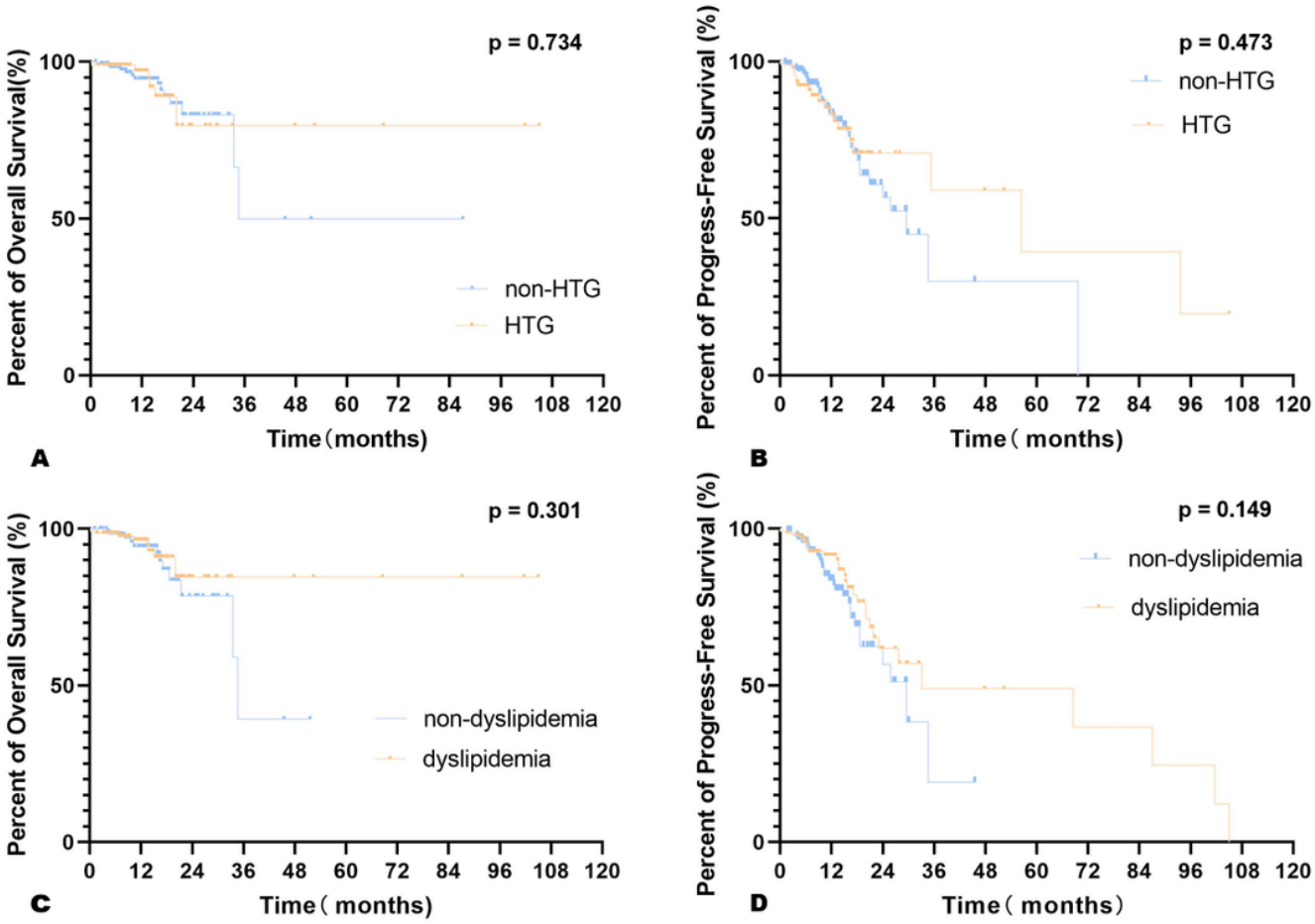


Figure 3

OS and PFS in patients. (A) percent of OS and (B) progress-free survival in patients with or without HTG. (C) percent of overall survival and (D) progress-free survival in dyslipidemia patients and non-dyslipidemia patients. OS: overall survival; PFS: progress-free survival; HTG: hypertriglyceridemia.

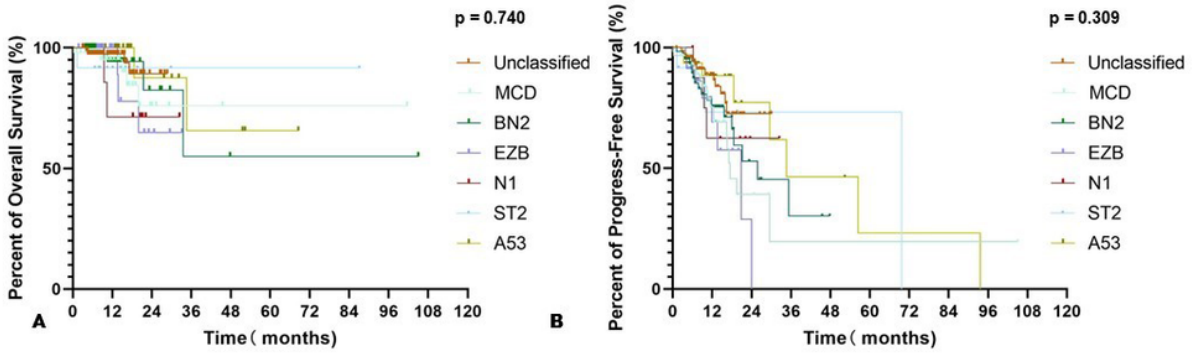


Figure 4

OS (A) and PFS (B) in different subtypes including MCD, BN2, EZB, N1, ST2, A53 and unclassified subtypes. OS: overall survival; PFS: progress-free survival.

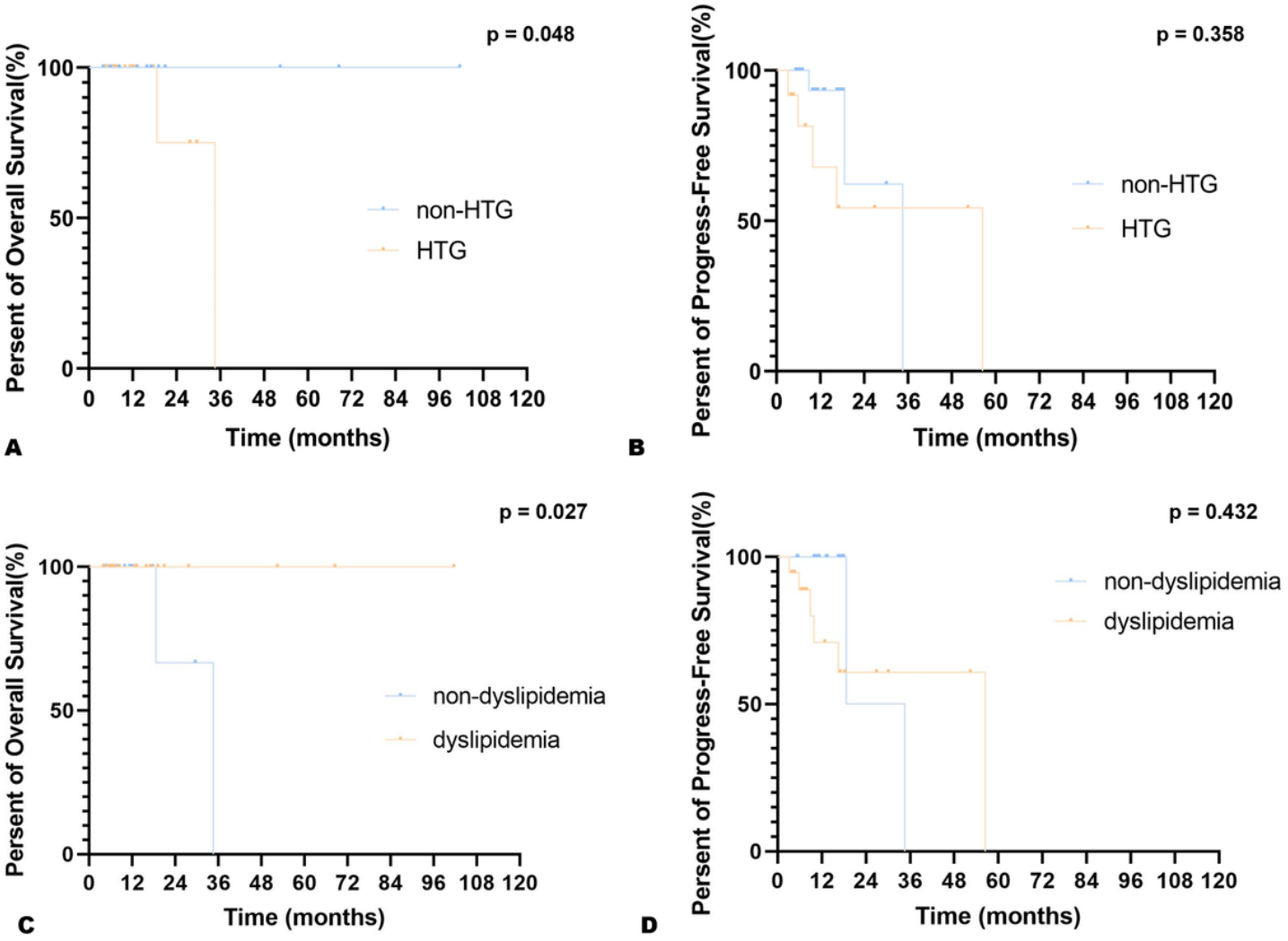


Figure 5

OS and PFS in A53 subgroup. Panel A illustrates OS in HTG group and non-HTG group with significant statistical difference. Panel B shows PFS in these two groups without significant statistical difference. Panel C and Panel D indicate OS and PFS in dyslipidemia group and non-dyslipidemia group with significant statistical difference only in OS. OS: overall survival; PFS: progress-free survival. HTG: hypertriglyceridemia.