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RESEARCH

Lymphocyte/monocyte to lactate dehydrogenase ratio prior to lymphodepletion impact the outcomes of patients with diffused large B cell lymphoma undergoing CAR-T cell therapy

Na Li[1] · Na An[1] · Sha Ma[1,2] · Jiang Cao[1,2] · Feng Zhu[1,2] · Kunming Qi[1,2] · Zhiling Yan[1,2] · Hai Cheng[1,2] · Wei Sang[1,2] · Wei Chen[1,2] · Depeng Li[1,2] · Zhenyu Li[1,2] · Kailin Xu[1,2] · Ying Wang[1,2]

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Abstract

Factors associated with outcomes of chimeric antigen receptor (CAR)-T cell therapy in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have not been fully elucidated. We explored the impact of the prelymphodepletion (pre-LD) lymphocyte to monocyte ratio (LMR) and its ratio to lactate dehydrogenase (LDH) (LMR/LDH) on the efficacy and prognosis of 60 patients with R/R DLBCL undergoing CAR-T cell therapy. The optimal cutoff values for pre-LD LMR and LMR/LDH were 3.583 and 0.0103, respectively. The overall response rate (ORR)s were higher in patients with high pre-LD LMR or LMR/LDH than those with low pre-LD LMR or LMR/LDH (ORR, 100% vs. 65.79%, $P=0.006$ and 96.15% vs. 38.24%, $P<0.0001$, respectively). Pre-LD LMR/LDH was an independent factor associated with ORR ($P=0.010$, odds ratio = 18.757; 95% confidence interval [CI] 2.046–171.975) by multivariate logistic regression analysis. Patients with high pre-LD LMR/LDH had significantly longer progression-free survival (PFS) (median PFS, 29.73 vs. 2.47 months, $P<0.0001$) and overall survival (OS) (median OS, not reached vs. 7.4 months, $P=0.0002$) than those with low pre-LD LMR/LDH. Multivariate Cox regression analysis showed that pre-LD LMR/LDH and ORR were independent factors affecting PFS ($P=0.030$, hazard ratio [HR] = 2.561; 95% CI 1.093–5.999 and $P=0.024$, HR = 2.202; 95% CI 1.22–4.369, respectively); pre-LD LMR/LDH was an independent factor affecting OS ($P=0.029$, HR = 3.331; 95% CI 1.131–9.807). In conclusion, the pre-LD LMR/LDH was an independent factor associated with ORR and an independent prognostic factor in patients with R/R DLBCL undergoing CAR-T cell therapy.

Keywords Diffuse large B-cell lymphoma · CAR-T cell therapy · Lymphocyte to monocyte ratio · Lactate dehydrogenase · Efficacy · Prognosis

Introduction

Chimeric antigen receptor (CAR) -T cell therapy has achieved significant efficacy for patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). CD19-targeted CAR-T cells have achieved a complete response (CR) rate of 40–60% and an overall response rate (ORR) of approximately 80% [1–3]. Dual targeting of CD19 and CD20 or CD22 CAR-T cells have also shown promising results in R/R DLBCL patients [4–7]. However, 20–30% of patients with R/R DLBCL have no response after CAR-T cell therapy, and more than one-third of patients eventually relapse. Exploring indicators to effectively predict the efficacy and outcome of CAR-T cell therapy and intervening in advance could help to improve prognosis.

It has been reported that the expansion and persistence or the immunophenotype of CAR-T cells were associated with the outcome of B-cell lymphoma patients undergoing CAR-T cell therapy [8]. Accumulated studied have confirmed the prognostic value of tumor burden at baseline or early response for CAR-T cell therapy in large B-cell lymphoma [9–11]. Vercellino et al. reported that extranodal

Na Li and Na An have contributed equally to this work.

✉ Ying Wang
ccwing28@163.com

[1] Blood Diseases Institute, Xuzhou Medical University, Xuzhou, Jiangsu, China

[2] Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, No. 99 West Huaihai Road, Xuzhou 221002, Jiangsu, China

involvement sites were risk factors for early progression in R/R DLBCL patients after CAR-T cell therapy [12]. However, effective predictors are still less, and some were debatable.

The tumor immune microenvironment has been proved to play a significant role in promoting the growth and survival of lymphoma cells in recent years [13, 14]. Lymphocyte/monocyte ratio (LMR), which may present host immune status, is an effective predictive indicator for prognosis in patients with DLBCL, classical Hodgkin's lymphoma and follicular lymphoma [15–17]. LMR to lactate dehydrogenase (LDH) ratio (LMR/LDH), which are related to host immune status and tumor burden, have been shown to be prognostic markers for various types of cancer, including DLBCL [18]. It is unclear whether prelymphodepletion (pre-LD) LMR and LMR/LDH levels impact the outcome of patients with R/R DLBCL that receiving CAR-T cell therapy. This study is aimed to explore the prognostic value of pre-LD LMR and LMR/LDH in patients with R/R DLBCL undergoing CAR-T cell therapy.

Study design and patients

We conducted a retrospective study of consecutive patients with R/R DLBCL who underwent CAR-T cell therapy at the Department of Hematology, the Affiliated Hospital of Xuzhou Medical University between January, 2017, and November, 2020 through participation in prospective clinical trials (Clinical Trial Registry: NCT02782351, NCT03207178, NCT02903810 and NCT02794961). Patients with primary central nervous system lymphoma was excluded. The data cutoff for the analysis was November 1, 2023. This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Informed consent were obtained from all patients.

Patients underwent leukapheresis to collect peripheral blood mononuclear cells (PBMCs) for the preparation of CAR-T cells about 14 to 21 days before CAR-T cell therapy. Patients received lymphodepletion chemotherapy consisting of fludarabine (30 mg/m^2 on days -5 to -3) and cyclophosphamide (750 mg/m^2 on day -5) before CAR-T cell infusion. On day 0, patients received infusions of CD19 CAR-T cells alone, or in combined with anti-CD22 or anti-CD20 CAR-T cells, or CD20 CAR-T cells alone at a median dose of 2 + 10E6 cells/kg (ranging from 0.8 to 6 + 10E6 cells/kg).

Clinical data involved patients' age, gender, Eastern Cooperative Oncology Group (ECOG) performance status score, Ann Arbor stage, B symptoms, International Prognostic Index (IPI) score, previous therapies, central nervous system invasion, bone marrow invasion, bulky disease, complete blood count and LDH before lymphodepletion preconditioning. Calculate the LMR as the ratio of absolute lymphocyte count (ALC) to absolute monocyte count (AMC), and LMR/LDH as the ratio of LMR to LDH.

Evaluation criteria for response and toxicity

Efficacy were evaluated according to 2014 Lugano efficacy evaluation criteria [19]. Responses were assessed as CR, partial response (PR), stable disease (SD), and disease progression (PD). The ORR includes the rates of CR and PR. Cytokine release syndrome (CRS) were graded according to the Lee criteria [20]. Progression-free survival (PFS) was defined as the time from the date of CAR T-cell infusion to disease progression or death due to any cause, or the end of follow-up. Overall survival (OS) was defined as the time from the date of CAR T-cell infusion to the death or the end of follow-up.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff values of LMR and LMR/LDH to predict a response, and patients were divided into high and low groups according to these cutoff values. The variance inflation factor (VIF) was introduced to assess the multi-collinearity among variables in the multivariate model, and the VIF values of these variables were less than 5. Continuous variables were analyzed using t-tests or Wilcoxon rank-sum tests, and the comparison of rates between groups was conducted using chi-square tests or Fisher's exact method. Logistic regression analysis was used to analyze factors affecting ORR. The inverse Kaplan–Meier method was used to calculate the follow-up time. Kaplan–Meier method and log-rank test to assess differences in PFS and OS between groups. Cox proportional hazards model was used for univariate and multivariate analysis to assess the prognostic factors. The variables with significant difference in univariate analysis were included in the multivariate analysis. *P* value less than 0.05 was considered statistically significant.

Results

Patients' clinical characteristics

A total of 60 patients with R/R DLBCL were enrolled, including 6 with transformed DLBCL. The baseline characteristics are listed in Table 1. The median age was 47 years (range 21 to 70). Fifty-four patients (90%) were in Ann Arbor stage III-IV status, and 32 patients (53.33%) had an IPI score of 3–5. Central nervous system involvement was observed in 6 patients (10%) and bone marrow

Table 1 Patients' characteristics and factors associated with pre-LD LMR and LMR/LDH

n (%)	Total	Pre-LD LMR ≤ 3.583 (n = 47)	Pre-LD LMR > 3.583 (n = 13)	*P*	Pre-LD LMR/LDH ≤ 0.0103 (n = 34)	Pre-LD LMR/LDH > 0.0103 (n = 26)	*P*
Gender				0.052			0.008
Male	41 (68.33)	35 (74.47)	6 (46.15.0)		28 (82.35)	13 (50.00)	
Female	19 (31.67)	12 (25.53)	7 (53.85)		6 (17.65)	13 (50.00)	
Age (years)				0.730			0.967
≤ 60	46 (76.67)	36 (76.60)	5 (38.26)		26 (76.47)	20 (76.92)	
> 60	14 (23.33)	11 (23.40)	8 (61.54)		8 (23.53)	6 (23. 0 8)	
Ann Arbor Stage				0.3835			0.931
I–II	6 (10.00)	5 (10.64)	1 (7.69)		4 (11.77)	2 (7.69)	
III–IV	54 (90.00)	42 (89.39)	12 (92.31)		30 (88.23)	24 (92.31)	
ECOG score				0.987			0.063
0–1	31 (51.67)	24 (51.06)	7 (53.85)		14 (41.18)	17 (65.38)	
2	29 (48.33)	23 (48.94)	6 (46.15)		20 (58.82)	9 (34.62)	
IPI score				0.503			0.134
0–2	28 (46.67)	23 (48.94)	5 (38.46)	0	13 (38.24)	15 (57.69)	
3–5	32 (53.33)	24 (51.06)	8 (61.54)		21 (61.76)	11 (42.31)	
Central nervous system invasion				0.403			0.931
No	54 (90.00)	41 (87.23)	13 (100)		31 (91.18)	23 (88.46)	
Yes	6 (10.00)	6 (12.77)	0 (0)		3 (8.82)	3 (11.54)	
Bone marrow invasion				0.856			0.133
No	15 (25.00)	12 (25.53)	10 (76.92)		23 (67.65)	22 (84.62)	
Yes	45 (75.00)	35 (74.47)	3 (23.08)		11 (32.35)	4 (15.38)	
Bulky disease*				0.552			0.668
No	41 (68.33)	33 (70.21)	8 (61.54)		24 (70.59)	17 (65.38)	
Yes	19 (31.67)	14 (29.79)	5 (38.46)		10 (29.41)	9 (34.62)	
Time since diagnosis to CAR-T (months)				0.779			0.414
≤ 24	50 (83.33)	39 (82.98)	11 (84.62)		30 (88.24)	20 (76.92)	
> 24	10 (16.67)	8 (17.02)	2 (15.38)		4 (11.76)	6 (23. 0 8)	
Previous therapy lines				0.108			0.623
< 3	21 (35.00)	14 (29.79)	7 (53.85)		11 (32.35)	10 (38.46)	
≥ 3	39 (65.00)	33 (70.21)	6 (46.15)		23 (67.65)	16 (61.54)	
CAR-T cell targets				0.459			0.954
CD19	19 (31.67)	14 (29.79)	5 (38.46)		4 (15.38)	4 (11.76)	
CD20	8 (13.33)	8 (17.02)	0 (0)		12 (35.29)	7 (26.92)	
CD19 + CD20	16 (26.67)	12 (25.53)	4 (30.77)		11 (42.31)	5 (19.23)	
CD19 + CD22	17 (28.33)	13 (27.66)	4 (30.77)		7 (20.59)	10 (38.46)	
Response				0.006			< 0.0001
CR + PR	38 (63.33)	25 (53.19)	13 (100.0)		13 (38.24)	25 (96.15)	
SD + PD	22 (36.67)	22 (46.81)	0 (0.00)		21 (61.76)	1 (3.85)	

CAR, chimeric antigen receptor; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LMR, lymphocyte/monocyte ratio; LMR/LDH, LMR to lactate dehydrogenase ratio; PD, progression; PR, partial response; pre-LD, prelymphodepletion; SD, stable disease

*Bulky disease was defined as a mass of at least 10 cm (largest diameter)

involvement in 15 patients (25%). Nineteen patients (31.67%) had bulky disease, which was defined as a mass of at least 10 cm in largest diameter. Thirty-nine patients (65%) had received at least three lines of prior therapy before CAR-T cell therapy. Nineteen patients (31.67%) received CD19 CAR-T cell infusion, 8 (13.33%) received

CD20 CAR-T cell infusion, 16 (26.67%) received CD19 and CD20 CAR-T cell infusion, and 17 (28.33%) received CD19 and CD22 CAR-T cell infusion.

Factors associated with pre-LD LMR and LMR/LDH

The cutoff value of pre-LD LMR and LMR/LDH was 3.583 (area under the curve [AUC], 0.709; 95% confidence interval [CI] 0.579 to 0.840; $P=0.007$) and 0.0103 (AUC, 0.760; 95% CI 0.635 to 0.884; $P=0.001$) with the optimum specificity and sensitivity, respectively. According to the optimal cut-off values, 47 patients were included in the low pre-LD LMR group (≤ 3.583), and 13 patients were included in the high pre-LD LMR group (>3.583). Thirty-four patients had a low pre-LD LMR/LDH (≤ 0.0103), and 26 patients had a high pre-LD LMR/LDH (>0.0103).

There were no significant differences in ECOG score, Ann Arbor stage, IPI score, B symptoms, central nervous system involvement, bone marrow invasion, bulky disease, etc. between patients with low pre-LD LMR and those with high pre-LD LMR. The ORR was higher in patients with high pre-LD LMR than in patients with low pre-LD LMR (100% [13/13] vs. 53.19% [25/47]; $P=0.006$). There were more males in patients with low pre-LD LMR/LDH, compared with patients with high pre-LD LMR/LDH (82.35% [28/34] vs. 50% [13/26], $P=0.008$). The other clinical characteristics were comparable between patients with low pre-LD LMR/LDH and those with high pre-LD LMR/LDH. Patients with high pre-LD LMR/LDH achieved higher ORR than patients with low pre-LD LMR/LDH (96.15% [25/26] vs. 38.24% [13/34]; $P<0.0001$; Table 1).

Impact of pre-LD LMR and LMR/LDH on response

On univariate analysis, the ORR was lower in patients with IPI score 3–5 than patients with IPI score 0–2 (50.00% [16/32] vs. 78.57% [22/28], $P=0.022$), higher in patients with high pre-LD LMR and LMR/LDH than in patients with low pre-LD LMR and LMR/LDH ($P=0.006$ and $P<0.0001$, respectively). There were no significant differences in gender, age, Ann Arbor Stage, ECOG score, central nervous system invasion, bone marrow invasion, bulky disease, time since diagnosis to CAR-T cell infusion, previous therapy lines, and CAR-T cell targets between patients who responded and those did not respond. Meanwhile, the severity of cytokine release syndrome (CRS) was not associated with ORR. Multivariate analysis results showed that pre-LD LMR/LDH was an independent factor associated with ORR ($P=0.010$, odds ratio [OR] = 18.757; 95% confidence interval [CI] 2.046–171.975; Table 2).

Survival analysis based on pre-LD LMR and LMR/LDH

Among all 60 patients, the median follow-up was 39.1 months. The median PFS was 4.93 months, and median OS was 25.87 months. The patients with high pre-LD LMR seemed to have a longer PFS and OS than those with low pre-LD LMR; however, there were no significant differences (Fig. 1A, B). Compared with patients with low pre-LD LMR/LDH, patients with high pre-LD LMR/LDH had longer PFS (median PFS: 29.73 months vs. 2.47 months, $P<0.0001$) and OS (median OS: not reached vs. 7.4 months, $P=0.0002$; Fig. 1 C, D).

The impact of pre-LD LMR/LDH on long-term outcomes

Univariate analysis showed that the time since diagnosis to CAR-T cell therapy ($P=0.025$), pre-LD LDH ($P=0.0003$), pre-LD LMR/LDH ($P<0.0001$), and ORR ($P<0.0001$) were associated with PFS after CAR-T cell therapy. However, gender, age, Ann Arbor stage, ECOG score, IPI score, central nervous system invasion, bone marrow invasion, bulky disease, previous lines of treatment, and pre-LD LMR level were not associated with PFS. There were no significant differences in PFS and OS among patients receiving different CAR-T cell products by log-rank test. Multivariate analysis results showed that pre-LD LMR/LDH and ORR were independent factors affecting PFS ($P=0.030$, hazard ratio [HR] = 2.561; 95% CI 1.093–5.999 and $P=0.024$, HR 2.202; 95% CI 1.22–4.369, respectively; Table 3).

Pre-LD LDH in peripheral blood ($P=0.011$), pre-LD LMR/LDH ($P=0.001$), and ORR ($P=0.008$) were associated with OS after CAR-T cell therapy by univariate analysis. And pre-LD LMR/LDH was an independent prognostic factor for OS by multivariate analysis ($P=0.029$, HR = 3.331; 95% CI 1.131–9.807; Table 3).

Discussion

Predictive biomarkers are currently lacking for CAR-T cell therapy in R/R DLBCL. The original IPI score and its modified versions, which are based primarily on clinical features and tumor burden, routinely used as a prognostic and predictive tool for patients with DLBCL. The molecular subtype, eg. germinal center B-cell and non-germinal center B-cell subtype of DLBCL are proved to be associated with prognosis [21]. The predict role of above indicators was explored in patients with R/R DLBCL undergoing CAR-T cell therapy, but the conclusion was debatable [12, 22, 23], which supports the needed of effective and convenient prognostic factors. In our study, high pre-LD LMR/LDH was associated

Table 2 Impact of pre-LD LMR and LMR/LDH on response

	Response, n (%) (n = 38)	Univariate	Multivariate	
		P	OR (95%CI)	*P*
Gender				
Male	24 (58.54)	0.257		
Female	14 (73.68)			
Age (years)				
≤ 60	30 (65.22)	0.583		
> 60	8 (57.14)			
Ann Arbor Stage				
I–II	2 (33.33)	0.346		
III–IV	36 (66.67)			
ECOG score				
0–1	23 (74.19)	0.071	1.085 (0.188–6.282)	0.927
2	15 (51.72)			
IPI score				
0–2	22 (78.57)	0.022	0.217 (0.037–1.254)	0.088
3–5	16 (50.00)			
Central nervous system invasion				
No	34 (62.96)	0.789		
Yes	4 (66.67)			
Bone marrow invasion				
No	28 (62.22)	0.757		
Yes	10 (66.67)			
Bulky disease*				
No	25 (60.98)	0.678		
Yes	13 (68.42)			
Time since diagnosis to CAR-T (months)				
≤ 24	30 (60.00)	0.402		
> 24	8 (80.00)			
Previous therapy lines				
< 3	12 (57.14)	0.350		
≥ 3	26 (66.67)			
CAR-T cell targets				
CD19	4 (50.00)	0.528		
CD20	12 (63.16)			
CD19 + CD20	9 (56.25)			
CD19 + CD22	13 (76.47)			
Pre-LD LMR				
≤ 3.583	25 (53.19)	0.006		0.998
> 3.583	13 (100)			
Pre-LD LMR/LDH				
≤ 0.0103	13 (38.24)	< 0.0001	18.757 (2.046–171.975)	0.010
> 0.0103	25 (96.15)			
CRS				
0–2	36 (64.29)	0.971		
≥ 3	2 (50.00)			

CAR, chimeric antigen receptor; CI, confidence interval; CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LMR, lymphocyte/monocyte ratio; LMR/LDH, LMR to lactate dehydrogenase ratio; pre-LD, prelymphodepletion; OR, odds ratio

*Bulky disease was defined as a mass of at least 10 cm (largest diameter)

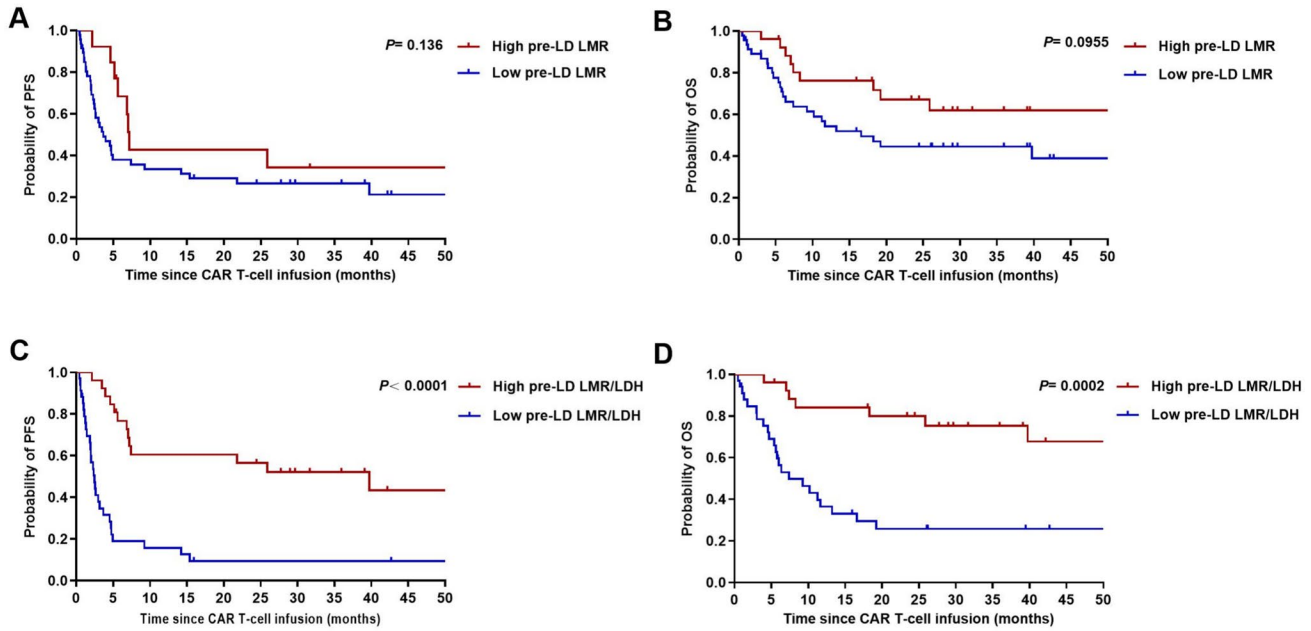

Fig. 1 Progression-free survival (PFS) and overall survival (OS) based on pre-LD LMR and LMR/LDH. Panel A shows Kaplan–Meier curves of PFS and Panel B shows Kaplan–Meier curves of OS, according to LMR. Panel C shows Kaplan–Meier curves of PFS and Panel D shows Kaplan–Meier curves of OS, according to LMR. Tick marks indicate the time of data censoring at the last follow-up

Table 3 Univariate and multivariate analysis of PFS and OS

	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Gender (female)	0.74 (0.384–1.434)	0.376			0.455 (0.196–1.060)	0.068		
Age > 60 years	1.020 (0.500–2.077)	0.957			1.120 (0.482–2.602)	0.792		
Ann-Arbor stage III–IV	1.689 (0.66004.321)	0.274			1.493 (0.522–4.273)	0.455		
ECOG score 2	0.747 (0.407–1.371)	0.347			0.556 (0.272–1.138)	0.108		
IPI score 3–5	0.617 (0.334–1.142)	0.094			0.824 (0.406–1.675)	0.194		
Central nervous system invasion	1.253 (0.49–3.204)	0.638			2.254 (0.859–5.917)	0.099		
Bone marrow invasion	1.312 (0.658–2.614)	0.440			0.688 (0.282–1.680)	0.412		
Bulky disease*	0.801 (0.420–1.526)	0.449			0.725 (0.346–1.520)	0.394		
Time since diagnosis to CAR-T > 24 months	3.868 (1.189–12.580)	0.025	0.408 (0.119–1.396)	0.153	6.602 (0.897–48.570)	0.064	4.791 (0.640–38.013)	0.138
Previous therapy lines ≥ 3	1.080 (0.578–2.017)	0.809			0.850 (0.407–1.776)	0.665		
Pre-LD LDH > ULN	0.247 (0.116–0.526)	0.0003	0.496 (0.198–1.246)	0.136	0.314 (0.128–0.770)	0.011	0.889 (0.285–2.769)	0.839
Pre-LD LMR > 3.583	1.787 (0.825–3.874)	0.141			2.044 (0.779–5.361)	0.146		
Pre-LD LMR/LDH > 0.0103	4.432 (2.256–8.707)	< 0.0001	2.561 (1.093–5.999)	0.030	4.192 (1.849–9.504)	0.001	3.331 (1.131–9.807)	0.029
Response	3.644 (1.946–6.824)	< 0.0001	2.202 (1.22–4.369)	0.024	2.603 (1.280–5.296)	0.008	1.272 (0.581–2.787)	0.547

CAR, chimeric antigen receptor; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LMR, lymphocyte/monocyte ratio; LMR/LDH, LMR to lactate dehydrogenase ratio; pre-LD, prelymphodepletion; PFS, progression-free survival; URL, upper reference limit; OS, overall survival

*Bulky disease was defined as a mass of at least 10 cm (largest diameter)

with longer survival, providing evidence that the pre-LD LMR/LDH is a prognostic marker for patients with R/R DLBCL undergoing CAR-T cell therapy.

Recent evidence shows that the tumor immune microenvironment plays a critical role in CAR-T cell resistance and relapse. The host immunity and circulating immune cell function participate in regulating tumor cell progression and associate with survival. Lymphocytes are involved in the immune surveillance against tumors and are characterized with functional roles in relation to the tumor microenvironment and host immune status in lymphoma patients [24–26]. Changes in lymphocyte counts before and after lymphodepletion are closely related to the efficacy of CAR-T cell therapy in patients with R/R large B-cell lymphoma [27], and patients with low pre-LD absolute lymphocyte count (ALC) have poor outcome [28]. Monocytes serve as a principal source of microenvironment infiltrating cells, thus contributing to cancer immune evasion by differentiating into immune regulatory cells [29–31]. Pretreatment circulating monocyte count associated with poor prognosis in tumor patients [32, 33]. The LMR, which reflects the degree of systemic inflammation, also reflects the host immune status and the degree of tumor progression [34], as well as the balance between immune-immune escape and anti-tumor immunity. LMR has recently been reported to correlate with survival and a low LMR is therefore associated with a poorer prognosis in various types of malignancies, including DLBCL, classical Hodgkin's lymphoma and follicular lymphoma [15–17, 35]. A low LMR is an independent poor prognostic factor for DLBCL patients treated with chemotherapy [26, 35]. In this study, pre-LD LMR count was associated with response rate by univariate analysis rather nor multivariate analysis. Furthermore, we did not find the prognostic value of LMR in survival in patients with R/R DLBCL treated with CAR-T cell therapy, which was suggested that the balance between the host immune system and TEM was not the independent factors affecting response and survival after CAR-T cell therapy. The reason may be that the synergistic effect of LMR pre-LD and some other factors, especially tumor burden, may play important role in the prognosis value.

Mounting evidence suggests that tumor burden assessed by tumor imaging not only represents a prognostic biomarker at baseline, but also a mean to dynamically assess disease response in the context of CD19 CAR-T cell therapy [36]. As a markers of tumor burden, LDH is one of the risk factors in the IPI score and has been proven to be associated with poor prognosis in DLBCL. It is reported that LDH is an independent factor for early relapse after CAR-T cell therapy [12], and is associated with PFS [37]. In our study, univariate analysis results showed that pre-LD LDH was associated with PFS and OS in patients after CAR-T cell therapy. However, LDH did not serve as a prognostic indicator by multivariate analysis. Nevertheless, our results, together with the previous studies, underscore the importance of tumor burden pre-LD in the efficacy of CAR-T cell therapy. Combining LMR with LDH together, which reflects the host immunity and tumor burden, respectively, may help to accurately assess the anti-tumor immunity.

Studies showed that LMR/LDH predicts survival in patients with DLBCL [38]. Whether there is a prognostic value of LMR/LDH for CAR-T cell therapy in patients with DLBCL is not reported yet. Here we present the preliminary results, focusing on the potential prognostic value of pre-LD LMR/LDH in CAR-T cell therapy. We found that low pre-LD LMR/LDH was an independent factor affecting the response rates of CAR-T cell therapy in 60 patients with R/R DLBCL, which may be due to the reason that patients with low LMR/LDH had weak anti-tumor immune response and high tumor burden. IPI score was associated with the response rate of CAR-T cell therapy without independent prognosis value, while Ann Arbor stage and bulky disease, did not affect the efficacy of CAR-T cell therapy as reported previously [39]. Pre-LD LMR/LDH is an independent prognostic factor affecting PFS and OS by both univariate and multivariate analysis in this study, emphasizing the importance role of host immune response to tumors on clinical outcomes and providing evidence for the potential value of pre-LD LMR/LDH as an immune-related prognostic marker for R/R DLBCL undergoing CAR-T cell therapy. In our study, IPI score was also not an independent predictor of PFS and OS. This is consistent with other studies that showed that IPI was not sufficient to distinguish DLBCL with different prognosis in the era of rituximab [40, 41]. In addition, the ORR is also an independent prognostic factor affecting patient PFS and OS, which could be attributed to the fact that responders exhibit better long-term outcomes to CAR-T cell therapy. Moreover, patients with clinical response had high pre-LD LMR/LDH, which reflect host anti-lymphoma immunity.

Our study has several limitations that should be considered. First, this is a retrospective study with a limited sample size from a single center, therefore the results may not be generalizable. Second, we did not analyze the impact of molecular heterogeneity on prognosis, including molecular, genetic, and microenvironmental factors, which are associated with clinical outcomes in DLBCL. Future larger sample size prospective studies are needed to validate the predictive role of pre-LD LMR/LDH in patients with R/R DLBCL undergoing CAR-T cell therapy.

In conclusion, pre-LD LMR/LDH was an independent factor associated with the response rate, and an independent factor affecting PFS and OS in patients with R/R DLBCL undergoing CAR-T cell therapy. Our study showed the promising prognostic value of pre-LD LMR/LDH on CAR-T cell therapy in patients with R/R DLBCL in clinical practice.

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Author contributions NL and NA were involved in conceptualization, investigation, methodology, formal analysis, supervision, writing-original, writing-revision and edits; SM and FZ contributed to formal analysis, investigation; JC and QK was involved in investigation, formal analysis, conceptualization, methodology; HC, ZY, WS, WC, TQ, DL and ZL contributed to resources, investigation, validation; YW, and KX were involved in conceptualization, funding acquisition, methodology, supervision, writing-review and edits. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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