Original Article

^{18}F-fluorodeoxyglucose positron emission tomography-compute tomography parameters for predicting the prognosis and toxicity in children and young adults with large B-cell lymphoma receiving chimeric antigen receptor T-cell therapy

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Background: Chimeric antigen receptor (CAR) T-cell therapy has been proven to be an effective choice for patients with relapsed or refractory large B-cell lymphoma (LBCL). Early identification of patients who may have a poor prognosis and develop severe side effects is necessary. In this study, we aimed to assess the value of ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) parameters in predicting the prognosis and toxicity of CAR T therapy for children and young adults with LBCL.

Methods: This retrospective cohort study included patients with LBCL under 30 years of age who underwent ^{18}F-FDG PET/CT at Beijing Friendship Hospital of Capital Medical University and Beijing GoBroad Boren Hospital before CAR T-cell infusion within 1 month. ^{18}F-FDG PET/CT metabolic parameters including maximum standardized uptake value (SUVmax), total metabolic tumor volume (TMTV), and total lesion glycolysis (TLG) were recorded. Clinical characteristics and laboratory indicators were also collected. The main endpoints were progression-free survival (PFS) and overall survival (OS) as estimated by the Kaplan-Meier method and log-rank test. We also assessed the relationship between these metabolic and clinical parameters and severe toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Results: Forty-five patients were recruited. The median duration of the follow-up period was 13.9 months. Patients with an age-adjusted international prognostic index (aaIPI) 2–3 (P=0.014) and TMTV >101.4 mL (P=0.026) had a shorter PFS. Patients with Eastern Cooperative Oncology Group (ECOG) performance status 2–3 (P=0.015) and TMTV >101.4 mL (P=0.011) had a shorter OS. Lactate dehydrogenase (LDH) > upper normal limit (UNL) (P=0.030) and TMTV >101.4 mL (P=0.042) were associated with grade 2–4 CRS, and C-reactive protein (CRP) > UNL (P=0.014) was associated with grade 2–4 ICANS.

Conclusions: aaIPI and TMTV were independent risk factors for PFS, and ECOG score and TMTV had independent prognostic value for OS. Higher LDH and TMTV were associated with grade 2–4 CRS, and higher CRP was associated with more severe ICANS. Thus, integrating these metabolic parameters of ^{18}F-FDG PET/CT and clinical-laboratory indicators can be valuable for managing children and young adults with B-cell lymphoma who have received CAR T-cell therapy.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT); chimeric antigen receptor T cell (CAR T cell); B-cell lymphoma; children; young adults

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Introduction

Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma (PMBCL) are common tumors among children and young adults (1). Although chemotherapy can significantly improve survival, with a 5-year event-free survival >80%, the prognosis is poor for patients who relapse or respond poorly to frontline chemotherapy [overall survival (OS) rate ≤25%] (2). Moreover, high-dose chemotherapy may induce delayed effects including secondary malignancies, chronic health conditions, and infertility (3,4).

As a novel immune therapy, chimeric antigen receptor (CAR) T-cell therapy has achieved remarkable results in many types of malignancies, especially in relapsed or refractory large B-cell lymphoma (LBCL), and the therapeutic effects can be enduring (5-7). However, the majority of patients do experience relapse (8,9). Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common immune-related adverse events that must be closely monitored, as they can be fatal (10). Therefore, it is important to identify patients with poorer prognoses and those at risk for severe adverse effects before CAR T-cell therapy is administered.

As a combination of morphologic and functional imaging, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) is critical to diagnosis, staging, evaluation of response, and prediction of long-term survival in patients LBCL (11-13). Studies have assessed the prognostic value of ^{18}F-FDG PET/CT metabolic parameters, such as total metabolic tumor volume (TMTV), maximum standardized uptake value (SUVmax), and total lesion glycolysis (TLG), before CAR T-cell infusion in patients with lymphoma (14-16). Clinical-laboratory characteristics such as Eastern Cooperative Oncology Group (ECOG) performance status and C-reactive protein (CRP) level have also been demonstrated to be associated with patient prognosis. Furthermore, a few studies have investigated the relationship between PET/CT metabolic parameters and the adverse effects caused by CAR T cells. However, these studies focused primarily on older adults, and thus studies on the relationship between metabolic parameters of pretreatment ^{18}F-FDG PET/CT and the prognosis and adverse effects in children and young adults with LBCL are lacking.

Therefore, in this study, we retrospectively collected clinical characteristics, laboratory examinations, and PET/CT metabolic parameters of patients under 30 years old who received CAR T-cell infusion and investigated the correlation of these indices with prognosis and treatment-related adverse events. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1737/rc).

Methods

Patients

This study was approved by the Institutional Review Board of Beijing Friendship Hospital of Capital Medical University (No. 2024-P2-259-01) and followed the Declaration of Helsinki (as revised in 2013). The other participating hospital, Beijing GoBroad Boren Hospital, was informed of and agreed with the study. The requirement of individual consent for this retrospective and observational analysis was waived. We analyzed PET data between January 2020 and September 2023 acquired from Beijing Friendship Hospital of Capital Medical University and Beijing GoBroad Boren Hospital. The inclusion criteria were as follows: (I) age ≤30 years; (II) diagnosis of relapsed/refractory B-cell non-Hodgkin lymphoma; (III) administration of second-generation CD19-directed CAR T-cell therapy (17,18); and (IV) ^{18}F-FDG PET/CT scan performed within 1 month before CAR T-cell infusion. Patients associated with other malignancies or lost to follow-up were excluded.

Clinical characteristics

The following characteristics were collected: age, gender, pathology type, stage (Ann Arbor staging system for adults and the international pediatric non-Hodgkin lymphoma staging system for children) (19), B symptoms, ECOG score, age-adjusted international prognostic index (aaIPI), therapy lines, bridging therapy, levels of lactate dehydrogenase (LDH) and ferritin, and CRP, CRS, and ICANS stage. Efficacy after 1 month of CAR T-cell infusion was evaluated and recorded. Laboratory data were collected within 1 week before CAR T-cell infusion.

PET/CT protocol and measurement

On average, ^{18}F-FDG PET/CT was carried out 17±6 days prior to the infusion of CAR T cells. Before the examination, informed consent was signed by all patients >18 years old or by the guardians of patients ≤18 years old. PET/CT examinations were performed using a uMI Vista scanner (United Imaging, Shanghai, China), and the ^{18}F-FDG had a ≥95% radiochemical purity. Patients were required to fast for at least 6 hours before injection of the tracer and to ensure that fasting blood glucose was ≤11.1 mmol/L. The active concentration of ^{18}F-FDG was 3.70–5.55 MBq/kg (0.10–0.15 mCi/kg). Scanning was performed approximately 60 minutes after injection. Two experienced nuclear physicians independently analyzed PET/CT scans using LIFEx v.7.5.12 software (20). When their opinions differed, senior nuclear medicine physicians made the final decision. As recommended, each lesion was measured individually and then segmented based on the threshold, which was 41% of the SUVmax (21). The following metabolic parameters were recorded: SUVmax, defined as the maximum SUVmax among all lesions; TMTV (mL), defined as the sum of all metabolic volumes; and TLG, defined as the sum of TLG of all lesions.

Follow-up

Patients were followed up via query of the medical record system or by telephone. Efficacy was assessed using PET/CT, CT, or MRI after 1 month of CAR T-cell infusion, and the objective response rate (ORR) included partial or complete response. The cut-ff date for follow-up was March 31, 2024. The main endpoint included progression-free survival (PFS) and OS. PFS was regarded as the period starting from CAR T-cell infusion and ending at the time of disease relapse, progression, death by any cause, or arrival of the follow-up cutoff date. PFS was defined as the time between CAR T-cell infusion and disease relapse, progression, death from any cause, or arrival of the follow-up cutoff date. OS was defined as the time between CAR T-cell infusion and death from any cause or follow-up cutoff date. The occurrence and severity of CRS and ICANS were also collected from the medical record system.

Statistical analysis

All statistical analyses were performed using SPSS 27.0, (IBM Corp., Armonk, NY, USA) and GraphPad Prism v. 10.2.3.347 (Dotmatics, Boston, MA, USA; www.graphpad.com). Qualitative data are expressed as percentages. Quantitative data that conformed to a normal distribution are expressed as mean ± standard deviation, while data that did not conform to a normal distribution are expressed as the median and interquartile range (IQR). Laboratory examination data were analyzed by transforming them into dichotomous variables using the upper limit of normal values as the threshold. According to the literature, the following prognostic clinical features were dichotomized [ECOG 2–3 *vs.* 0–1 (15,22,23), stage III–IV *vs.* I–II (23), aaIPI 2–3 *vs.* 0–1] (16). The CRS and ICANS were divided into grade 0–1 and grade 2–4. For PET parameters, the optimal cutoff values were calculated by receiver operating characteristic (ROC) curves for PFS, and these threshold values were also applied to the analysis of OS and toxicities. The Kaplan-Meier method was used to estimate PFS and OS, and the log-rank test was used to compare the prognostic value of clinical indicators and PET/CT metabolic parameters for PFS and OS. Univariate and stepwise multivariate analyses were performed using Cox proportional models to select prognostic characteristics for PFS and OS, and hazard ratios (HR) and 95% confidence intervals (CI) were recorded. The Spearman correlation coefficient (ρ) was determined for every pair of variables that had prognostic significance. Factors associated with CRS and ICANS were analyzed using univariate and multivariate logistic regression. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Forty-five patients were included in this study (*Figure 1*).

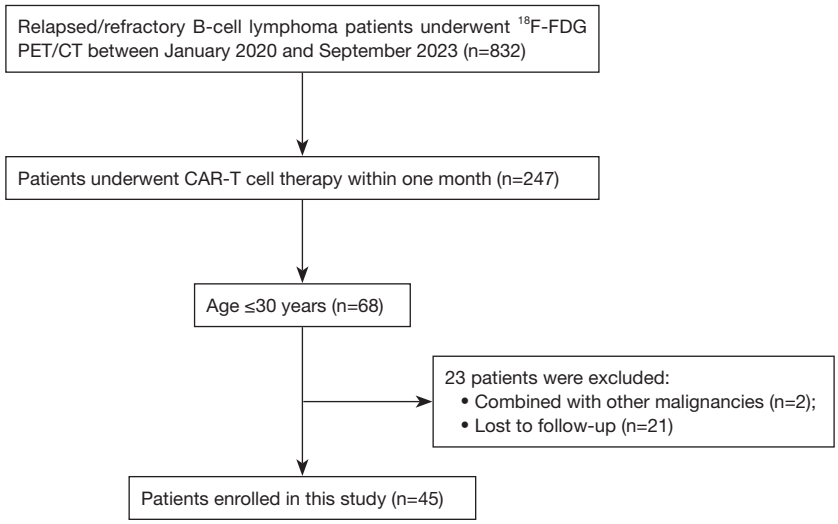

Figure 1 The workflow for the inclusion and exclusion of patients. ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography; CAR-T, chimeric antigen receptor T cell.

The detailed clinical and laboratory characteristics are shown in *Table 1*. The median SUVmax was 11.5 (IQR, 4.8–21.4). The median TMTV was 47.0 mL, with an IQR of 15.0–124.9 mL. Meanwhile, the median TLG was 214.1, and its IQR was 57.9–771.2. Among the patients, 27 (60%) achieved complete response, 9 (20%) achieved partial response, 3 (6.7%) experienced stable disease, and 6 (13.3%) experienced disease progression. The ORR was 80%. The median follow-up time was 13.9 months (95% CI: 6.613–24.687). Moreover, 21 (46.7%) patients experienced relapse or progression during the follow-up period, and 15 (33.3%) patients died. The median PFS was 15.6 months (95% CI, 7.497–20.303), and the 1-year PFS was 60%. The median OS was not reached (NR), and the 1-year OS was 73.3%.

Threshold values of ^{18}F-FDG PET/CT metabolic parameters

For the ROC curves for PFS, the area under the curve (AUC) of the SUVmax was 0.674 (95% CI: 0.515–0.832; P=0.047), the AUC for TMTV was 0.718 (95% CI: 0.568–0.869; P=0.012), and the AUC for TLG was 0.680 (95% CI: 0.552–0.837; P=0.039) (*Figure 2*). Therefore, the optimal threshold value was 13.8 for SUVmax, 101.4 mL for TMTV, and 333.6 for TLG.

Prognostic value

According to the univariate analysis, aaIPI 2–3, SUVmax >13.8, and TMTV >101.4 mL were significantly associated with shorter PFS. In the multivariate analysis, aaIPI 2–3 and TMTV >101.4 mL remained independent risk factors of PFS (*Table 2*). The median PFS was significantly longer for the aaIPI 0–1 group than for the aaIPI 2–3 group (NR *vs.* 6.6 months; P=0.014) (*Figure 3A*). When the two groups were compared, the median PFS was substantially longer for the group with TMTV ≤101.4 mL than for the group with TMTV >101.4 mL (NR *vs.* 6.2 months; P=0.026) (*Figure 3B*).

Regarding OS, statistically significant features in the univariate analysis included ECOG 2–3, SUVmax >13.8, TMTV >101.4 mL, and TLG >333.6. After performing multivariate analysis, we found that ECOG 2–3 and TMTV >101.4 mL had an independent correlation with OS (*Table 3*). The median OS in the ECOG 0–1 group was significantly greater than that of the ECOG 2–3 group (NR *vs.* 9.7 months; P=0.015) (*Figure 4A*). Similarly, the median OS was significantly longer in the TMTV ≤101.4 mL group than in the TMTV >101.4 mL group (NR *vs.* 10.9 months; P=0.011) (*Figure 4B*).

Significant pairwise correlations emerged among aaIPI, ECOG, TMTV, SUVmax, and TLG. The specific correlations were as follows: for aaIPI and ECOG, ρ=0.476 and P<0.001; for aaIPI and SUVmax, ρ=0.473 and P=0.003; for aaIPI and TMTV, ρ=0.372 and P=0.012; for aaIPI and TLG, ρ=0.486 and P<0.001; for ECOG and SUVmax, ρ=0.422 and P=0.004; for ECOG and TMTV, ρ=0.412 and P=0.005; for ECOG and TLG, ρ=0.488 and P<0.001; for

Table 1 Patient characteristics before chimeric antigen receptor T-cell infusion

Feature	Values (n=45)
Sex	
Male	31 (68.9)
Female	14 (31.1)
Age (years)	17.4±7.4
Lymphoma subtype	
BL	16 (35.6)
PMBCL	12 (26.7)
DLBCL	17 (37.8)
Bridging therapy	
Yes	35 (77.8)
No	10 (22.2)
Previous lines of systemic therapy	
2	17 (37.8)
≥3	28 (62.2)
B symptoms	
Yes	8 (7.8)
No	37 (82.2)
Stage	
No disease	2 (4.4)
I–II	14 (31.1)
III–IV	29 (64.4)
ECOG score	
0–1	38 (84.4)
2–3	7 (15.6)
aaIPI	
0–1	31 (68.9)
2–3	14 (31.1)
LDH	
Normal	30 (66.7)
> UNL	15 (33.3)
CRP	
Normal	31 (68.9)
> UNL	14 (31.1)
Ferritin	
Normal	10 (22.2)
> UNL	35 (77.8)
Adverse events	
CRS	
Grade 0–1	30 (66.7)
Grade 2–4	15 (33.3)
ICANS	
Grade 0–1	39 (86.7)
Grade 2–4	6 (13.3)

Data are presented as n (%) or mean ± standard deviation. BL, Burkett lymphoma; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; aaIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; UNL, upper normal limit; CRP, C-reactive protein; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

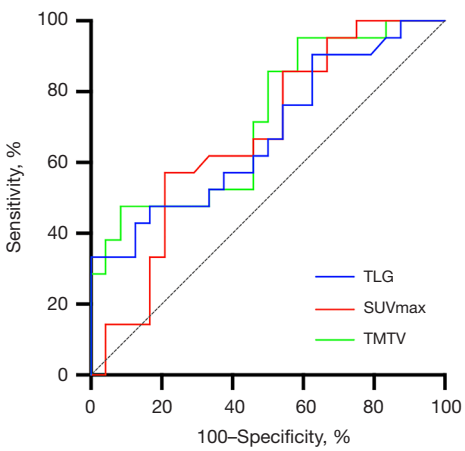

Figure 2 ROC curves of PFS. ROC, receiver operating characteristic; PFS, progression-free survival; TLG, total lesion glycolysis; TMTV, total metabolic tumor volume; SUVmax, maximum standardized uptake value.

SUVmax and TMTV, ρ=0.646 and P<0.001; for SUVmax and TLG, ρ=0.803 and P<0.001; and finally, for TMTV and TLG, ρ=0.933 and P<0.001.

Prediction of toxicity

Univariate and multivariate logistic regression analyses showed that a pretreatment LDH > upper normal limit (UNL) and TMTV >101.4 mL were significantly associated

Table 2 Univariate and multivariate Cox regression analyses of progression-free survival

Variable	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age >17.4 years	0.911	0.951 (0.395–2.290)		
Males	0.331	0.580 (0.194–1.739)		
Stage III–IV	0.212	2.180 (0.641–7.411)		
ECOG 2–3	0.093	2.432 (0.863–6.856)		
aaIPI 2–3	0.011*	3.057 (1.292–7.234)	0.014*	2.974 (1.249–7.083)
Ferritin > UNL	0.446	1.576 (0.463–5.360)		
LDH > UNL	0.179	1.799 (0.763–4.239)		
CRP > UNL	0.153	2.008 (0.772–5.223)		
SUVmax >13.8	0.012*	3.062 (1.279–7.335)		
TMTV >101.4 mL	0.020*	2.800 (1.172–6.689)	0.026*	2.726 (1.126–6.599)
TLG >333.6	0.187	1.791 (0.754–4.256)		

*, P<0.05. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; aaIPI, age-adjusted International Prognostic Index; UNL, upper normal limit; LDH, lactate dehydrogenase; CRP, C-reactive protein; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

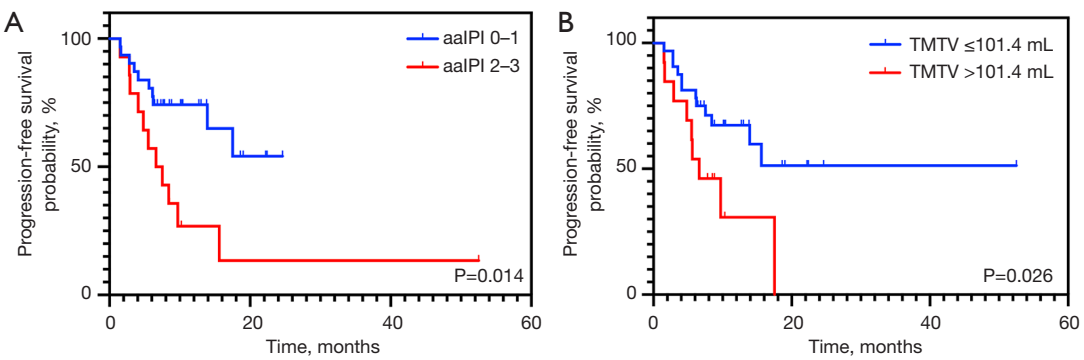

Figure 3 Progression-free survival curves for patients with (A) aaIPI 0–1 (blue) and aaIPI 2–3 (red) and (B) with TMTV ≤101.4 mL (blue) and TMTV >101.4 mL (red). aaIPI, age-adjusted International Prognostic Index; TMTV, total metabolic tumor volume.

with the emergence of grade 2–4 CRS. Meanwhile, a pretreatment CRP > UNL was an independent indicator for the occurrence of ICANS grade 2–4 (*Table 4*).

Discussion

BL, DLBCL, and PMBCL are common malignancies in children and young adults (1). Studies have confirmed the value of ^{18}F-FDG PET/CT in diagnosis, staging, efficacy assessment, and follow-up for this group of patients (24,25). However, there is scant literature regarding the prognostic value of ^{18}F-FDG PET/CT in children and young adults with B-cell lymphoma treated with CAR T cells. In this study, we retrospectively analyzed ^{18}F-FDG PET/CT features before CAR T-cell infusion in this patient population. We found that TMTV was significantly associated with PFS, OS, and grade 2–4 CRS. Furthermore, we analyzed the prognostic role of the clinical and laboratory indicators before CAR T therapy. aaIPI was associated with PFS, and ECOG score was associated with OS.

As a metabolic parameter of PET/CT, TMTV can

Table 3 Univariate and multivariate Cox regression analyses of overall survival

Variable	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age >17.4 years	0.633	1.288 (0.456–3.642)		
Males	0.694	0.773 (0.214–2.792)		
Stage III–IV	0.349	2.038 (0.459–9.055)		
ECOG 2–3	0.015*	3.970 (1.314–11.993)	0.015*	4.009 (1.315–12.222)
aaIPI 2–3	0.177	2.016 (0.729–5.572)		
Ferritin > UNL	0.141	4.635 (0.603–35.641)		
LDH > UNL	0.261	1.793 (0.647–4.967)		
CRP > UNL	0.056	2.933 (0.973–8.845)		
SUVmax >13.8	0.035*	3.066 (1.084–8.667)		
TMTV >101.4 mL	0.011*	3.966 (1.371–11.471)	0.011*	4.023 (1.372–11.796)
TLG >333.6	0.047*	2.296 (1.016–8.674)		

*, P<0.05. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; aaIPI, age-adjusted International Prognostic Index; UNL, upper normal limit; LDH, lactate dehydrogenase; CRP, C-reactive protein; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

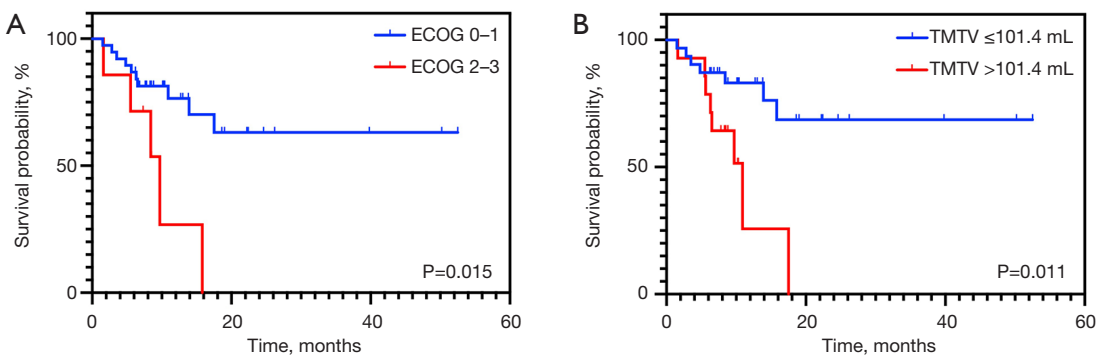

Figure 4 Overall survival curves for patients with (A) ECOG 0–1 (blue) and ECOG 2–3 (red), (B) TMTV ≤101.4 mL (blue) and TMTV >101.4 mL (red). ECOG, Eastern Cooperative Oncology Group; TMTV, total metabolic tumor volume.

reflect the systematic tumor burden and has already been confirmed to be one of the best prognostic indicators for patients with LBCL. Marchal *et al.* demonstrated that TMTV, at a cutoff value of 36 mL, serves as an independent predictor for PFS in patients with LBCL receiving CAR T-cell therapy (14). Dean *et al.* included 96 patients with LBCL who received anti-CD19 CAR T cells and found that the low-MTV group (cutoff value of 147.5 mL) had a better PFS and OS than did the high-MTV group (23). Other studies reported that TMTV was associated with prognosis in patients with LBCL treated with CAR T cells (26-31). In our study, the patients with low and high TMTV had different PFS and OS, as demonstrated in *Figures 5*,*6*, respectively. Although the conclusions were consistent, the cutoff values of the TMTV varied considerably, from 25 to 147.5 mL. Our study calculated the optimal threshold to be 101.4 mL, which was within the published range. However, the cutoff value of TMTV in our study was higher than that in most studies (14,26,31). The possible reasons are as follows: first, there were different time intervals between PET examinations and CAR T-cell infusion; second, there were differences in the study populations. Some studies also

Table 4 Univariate and multivariate logistic regressions of the correlation between severe adverse events and the preinfusion values of laboratory indicators and ^{18}F-FDG PET/CT metabolic parameters

Variable	CRS grade 2–4			ICANS grade 2–4		
	OR (95% CI)	P_{uni}	P_{multi}	OR (95% CI)	P_{uni}	P_{multi}
Ferritin > UNL	4.773 (0.531–42.888)	0.163		4.750 (0.507–44.483)	0.172	
LDH > UNL	6.389 (1.651–24.728)	0.007*	0.030*	2.000 (1.651–24.728)	0.433	
CRP > UNL	6.741 (1.430–31.773)	0.016		11.000 (1.633–74.083)	0.014*	0.014*
SUVmax >13.8	1.478 (0.423–5.157)	0.540		4.000 (0.646–24.768)	0.136	
TMTV >101.4 mL	6.171 (1.553–24.527)	0.01*	0.042*	2.545 (0.444–14.585)	0.294	
TLG >333.6	3.704 (1.028–13.346)	0.045		3.200 (0.521–19.668)	0.209	

*, P<0.05. OR, odds ratio; CI, confidence interval; ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography; UNL, upper normal limit; LDH, lactate dehydrogenase; CRP, C-reactive protein; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; uni, univariate; multi, multivariate.

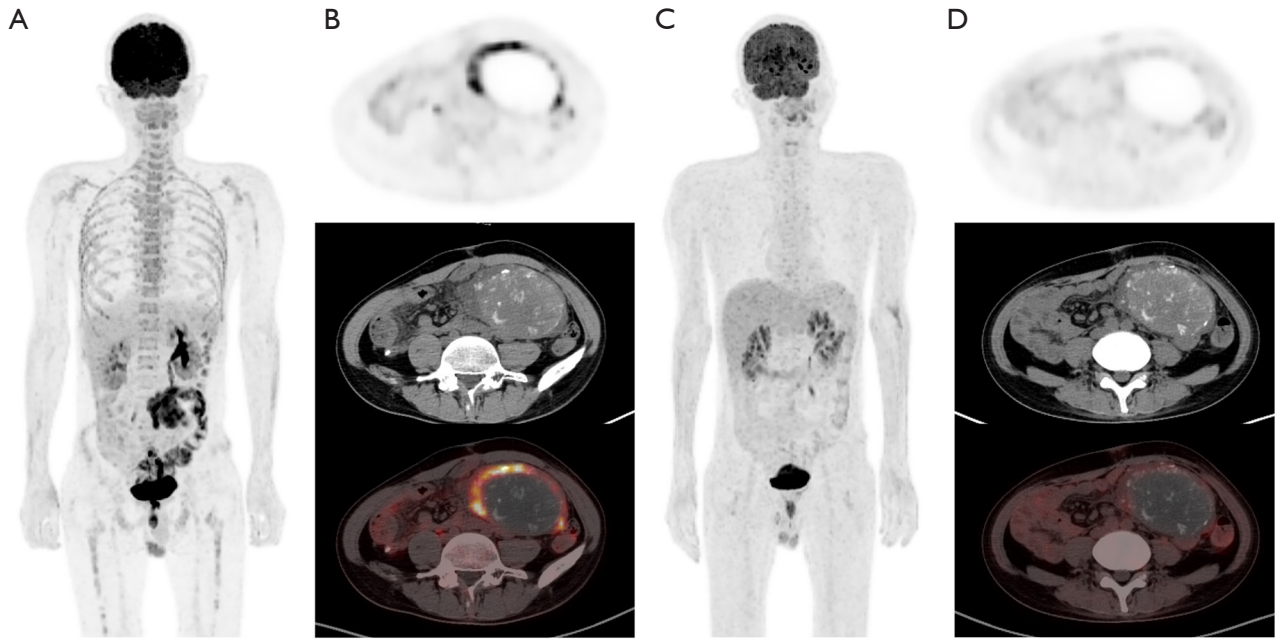

Figure 5 Representative ^{18}F-FDG PET/CT images of patients with low tumor burden. A 22-year-old man was diagnosed with refractory Burkitt lymphoma. (A) The pretreatment MIP image showed an FDG-avid mass in the abdomen. (B) On axial images, there were foci of calcification in the soft tissue mass, with ring-shaped hypermetabolism in the margin (SUVmax =11.4, TMTV =99.0 mL, and TLG =560.1). One month after CAR T-cell infusion, a follow-up PET/CT showed the previous hypermetabolic lesion had disappeared (C, MIP image; D, axial images). At follow-up more than 8 months later, the patient maintained complete response, without recurrence. ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography; MIP, maximum intensity projection; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; CAR, chimeric antigen receptor.

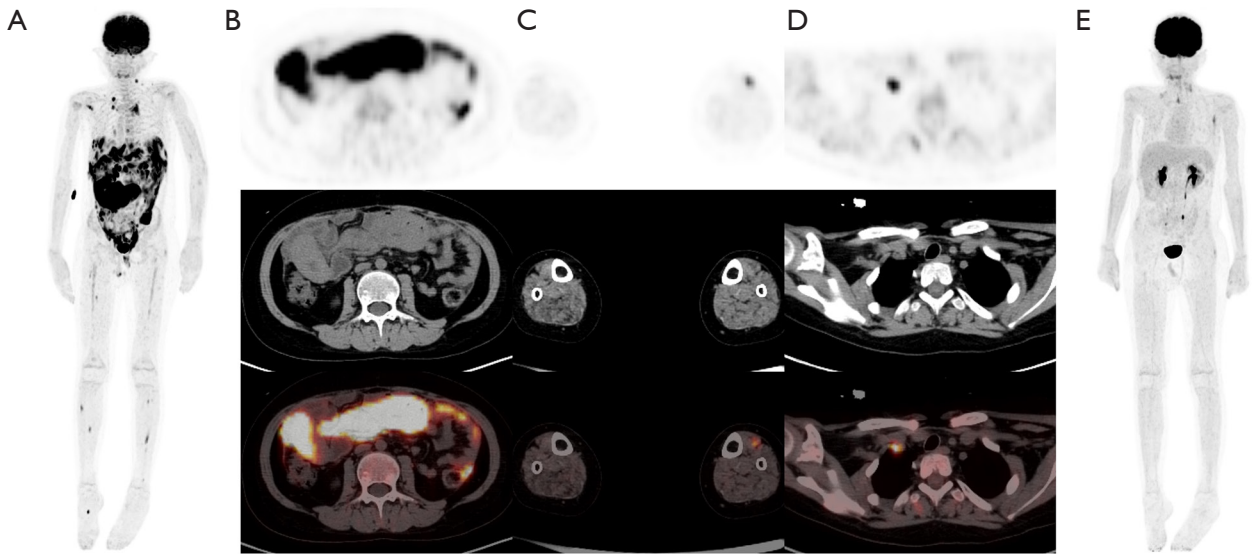

Figure 6 Representative ^{18}F-FDG PET/CT images of patients with high tumor burden. A 12-year-old boy was diagnosed with refractory diffuse large B-cell lymphoma. (A) The MIP image before CAR T-cell therapy demonstrated multiple hypermetabolic lesions in the left neck, chest, abdomen, bilateral calves, and right foot. On axial images, these lesions corresponded to intestines and the (B) peritoneum, (C) muscles, (D) and lymph nodes, with an SUVmax of 33.4, an TMTV of 327.6 mL, and a TLG of 4,559.6. A follow-up PET/CT scan was performed 1 month after CAR T-cell infusion, and the (E) MIP image showed that all previous hypermetabolic lesions had disappeared. Unfortunately, the boy relapsed at 4.8 months and died at 6.5 months. ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography; MIP, maximum intensity projection; CAR, chimeric antigen receptor; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

concluded that SUVmax and TLG of pretreatment PET/CT had prognostic value in patients with LBCL (15,29). Cohen *et al.* reported that an SUVmax >17.1 at the time of decision and SUVmax >12.1 at the time of transfusion were associated with shorter OS (15). Ababneh *et al.* found that high TLG was an independent prognostic factor for inferior PFS (29). In our study, univariate analysis indicated that higher SUVmax and TMTV were associated with worse PFS, whereas higher SUVmax, TLG, and TMTV were associated with poorer OS. However, in multivariate analysis, only TMTV was identified as an independent prognostic factor for PFS and OS, while SUVmax and TLG were not predictive of PFS or OS. This might be due to the moderate-to-strong correlation among these three factors (ρ=0.646–0.933), which might have obscured the independent prognostic values of SUVmax and TLG in multivariate analyses (32). Our study also found that aaIPI was a prognostic indicator for PFS, while ECOG score was a prognostic indicator for OS, which is in line with the literature (5,15,33).

Treatment-related adverse effects also should be examined, as they can occasionally be fatal. Our study showed that higher TMTV was significantly associated with grade 2–4 CRS, but there was no significant association between the metabolic indicators and ICANS. Other studies have examined the relationship between PET/CT parameters and toxicity. Wang *et al.* found that higher MTV and TLG were associated with more severe CRS (34), and Hong *et al.* reported a similar result (35). In 38 patients treated with CAR T cells for LBCL, Gui *et al.* found that SUVmax was correlated with the severity of CRS (16). Meanwhile, Ababneh *et al.* concluded that high TLG was correlated with CRS and that high TMTV and SUVmax were correlated with ICANS (29). Our study also found that elevated LDH was associated with CRS and that elevated CRP was an independent prognostic factor for grade 2–4 ICANS, which is consistent with previous results (36,37). Our study did not find there to be an association between any of the PET variables and ICANS, possibly because of the small number of high-grade ICANS cases (6/45, 13.3%). A few studies have examined the relationship between metabolic parameters, clinical-

laboratory characteristics, and toxicity, with the results being controversial, so the exact prognostic value of these parameters remains unclear. Recently, a study demonstrated that the occurrence of ICANS is associated with microglia activation and could be detected by translocator protein (TSPO) PET imaging (38), which might be a useful tool for the evaluation of ICANS.

This study involved several limitations which should be addressed. First, we employed a retrospective design, and selection bias was unavoidable. Therefore, prospective and large-sample studies are necessary. Second, the number of patients was limited while the pathology was relatively complex. Therefore, in the future, the relationship between PET/CT metabolic parameters and the prognosis of different types of LBCL should be analyzed in large-sample studies. Third, we only focused on the prognostic value of PET/CT before CAR T treatment. In our future studies, PET scans at different times and the inclusion of addition metabolic parameters should be adopted to enhance the value of PET/CT for patients undergoing CAR T therapy.

Conclusions

^{18}F-FDG PET/CT metabolic parameters have significant value for predicting prognosis and treatment-related adverse events for children and young adults with LBCL. TMTV was demonstrated to be predictive of PFS, OS, and severe CRS. aaIPI, a clinical indicator, was associated with PFS, while ECOG score was associated with OS. Furthermore, patients with higher LDH and CRP tended to have a greater severity of CRS and ICANS, respectively. Studies with larger samples should be performed to validate these results; nonetheless, we believe that the value of ^{18}F-FDG PET/CT metabolic parameters for prognosis and toxicity can be generalized and used for managing children and young adults with LBCL.

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Footnote

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