



# Metabolic tumor burden on baseline $^{18}\text{F}$ -FDG PET/CT improves risk stratification in pediatric patients with mature B-cell lymphoma

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## Abstract

**Purpose** In order to better identify patients most at risk of treatment failure and disease progression in pediatric mature B-cell non-Hodgkin lymphoma (B-NHL), the prognostic role of metabolic tumor burden measured on baseline  $^{18}\text{F}$ -FDG PET/CT scan, including total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG), was investigated.

**Methods** Pretreatment  $^{18}\text{F}$ -FDG PET/CT scans from 46 consecutive pediatric patients (median age 7 years; range 2–18 years) with newly diagnosed B-NHL were retrospectively analyzed. Clinicopathological parameters and imaging characteristics, including TMTV, TLG, and bone marrow (BM) involvement detected by PET/CT were compared to predict progression-free survival (PFS) and overall survival (OS).

**Results** The median follow-up time was 31 months. Areas under the curve of TMTV and TLG to predict events were 0.820 and 0.816, respectively. The 2-year PFS and OS were 29% and 43% in 7 patients with high TLG ( $> 5797$  g) vs. 93% and 96% in those with low TLG ( $P < 0.001$ ). High TMTV ( $> 524$  cm<sup>3</sup>) was present in ten patients and predicted a significantly inferior outcome (PFS: 50% vs. 92%,  $P = 0.001$ ; OS: 60% vs. 96%,  $P = 0.002$ ). In multivariate analysis, TMTV and TLG outperformed other clinicopathological factors, including serum lactate dehydrogenase and BM involvement on biopsy, and remained the most robust predictors of survival. Furthermore, TLG sub-stratified patients with distinct outcomes efficiently within high- or intermediate-risk groups, with the negative predictive value of 100% and 92% and the positive predictive value of 100% and 50% for high-risk and intermediate-risk patients, respectively. On the other hand, BM involvement identified only by PET demonstrated an inferior prognostic value in comparison with BM biopsy.

**Conclusions** Baseline TMTV and TLG are both strong independent prognostic factors for pediatric B-NHL and provide a potential approach to aid in risk sub-stratification, especially in patients with high-risk disease.

**Keywords**  $^{18}\text{F}$ -FDG PET/CT · TMTV · TLG · Pediatric · Mature B-cell non-Hodgkin lymphoma · Survival

## Introduction

Mature B-cell non-Hodgkin lymphoma (B-NHL) is the most frequent subtype of non-Hodgkin lymphoma (NHL) in children

and adolescents, accounting for about 60% of all pediatric NHL cases. Different from adulthood NHL, it is characterized by almost exclusively high-grade histology and an aggressive behavior. The outcome of pediatric B-NHL has significantly improved over the past decades because of the introduction of intensive multi-agent chemotherapy regimens, with long-term survival rates now exceeding 80% [1, 2].

However, about 10% of patients will not respond to first-line treatment or will experience disease relapse, and their outcome is dismal [3, 4]. These patients are not easily identified by existing risk stratification criteria used by standard chemotherapy regimens such as French-American-British mature lymphoma B (FAB/LMB) protocols and Berlin-Frankfurt-Münster protocols. Such criteria are typically based on extent of disease, resection status, bone marrow (BM) involvement, central nervous system (CNS) involvement and

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serum lactate dehydrogenase (LDH) level. The International Prognostic Index, which shows significant value in adulthood NHL, has limited utility in pediatric NHL because of common extranodal involvement and a different staging system. Therefore, improving the ability of identifying patients most at risk of treatment failure will facilitate the development of better risk-adapted treatment strategies in pediatric B-NHL.

$^{18}\text{F}$ -FDG PET/CT is one of the most well developed clinical applications in adulthood lymphoma and is increasingly used in pediatric lymphomas. Intensive  $^{18}\text{F}$ -FDG uptake has been shown in most pediatric NHL subtypes [5, 6]. Nonetheless, the role of  $^{18}\text{F}$ -FDG PET/CT in the management of pediatric NHL has yet to be established [7, 8]. To address this issue, we have previously shown that PET/CT accurately detected BM involvement and has a higher sensitivity than BM biopsy (BMB) in pediatric NHL [5]. However, the prognostic impact of BM involvement identified by PET is uncertain.

Metabolic volumetric parameters obtained from baseline PET, including total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG), allow measurement of the whole-body tumor burden. They have been recently proposed as significant prognostic factors for adult patients with diffuse large B-cell lymphoma (DLBCL) [9], follicular lymphoma [10], peripheral T-cell lymphoma [11] and Hodgkin lymphoma [12]. However, there are major differences in clinical presentation, distribution of histologic type, genetic alteration, staging system and therapeutic approach between pediatric and adulthood NHL [13]. Currently, prognostic impact of TMTV and TLG in pediatric NHL and whether they have added value to existing risk stratification systems have not been determined.

In the present study, our key objectives were to evaluate whether metabolic parameters on pretreatment PET reflecting whole-body tumor burden could be used to further risk-stratify pediatric patients with B-NHL, and to investigate whether BM involvement identified by PET was of prognostic value.

## Materials and methods

### Patients

This retrospective study was approved by the Institutional Review Board (Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), which waived the requirement for informed consent. This study included consecutive pediatric patients with histologically proven B-NHL between May 2010 and December 2017, with the following inclusion criteria: a baseline  $^{18}\text{F}$ -FDG PET/CT, newly diagnosed mature B-lineage NHL, including either Burkitt/Burkitt-like lymphoma (BL), DLBCL, or aggressive mature B-cell NHL non-other specified. Patients were excluded if they had indolent NHL or had received chemotherapy prior to

PET/CT imaging. Clinicopathological prognostic indices, such as stage, BM involvement on biopsy, LDH, and other laboratory data were evaluated. Clinical stage was determined according to the Murphy classification [8]. Two risk classification systems, FAB/LMB 96 and Chinese Children Cancer Group (CCCCG)-BNHL-2015, were utilized in this study. FAB/LMB 96 risk classification criteria was defined as: low-risk (Group A) with resected stage I and abdominal completely resected stage II; high-risk (Group C) with BM involvement  $\geq 25\%$  blasts and/or CNS disease; intermediate-risk (Group B), all others. CCCC-BNHL-2015 risk classification was defined as follows: R1 with completely resected stage I or II disease; R2 with non-resected stage I or II and LDH  $< 2$  upper normal limit (NL); R3 with stage I or II and LDH  $\geq 2$  NL but  $< 4$  NL, Stage III and LDH  $< 4$  NL; R4 with stage III and LDH  $\geq 4$  NL or stage IV.

### $^{18}\text{F}$ -FDG PET/CT acquisition

All patients were fasting for at least 4 h before the injection of a body weight-adapted dose of  $^{18}\text{F}$ -FDG (5.18 MBq/Kg). Chloral hydrate was administered at a dose of 50 mg/kg 30 min before PET/CT for sedation in children who were unable to follow instruction. PET/CT scans from the vertex of the skull to the proximal thigh were acquired about 60 min after injection on a Biograph mCT-64 scanner (Siemens, Erlangen, Germany). When the tumor occurred in the extremities, vertex-to-toe scans were performed. Noncontrast-enhanced CT images used for attenuation correction and diagnostic purposes were acquired with 3-mm slice thickness and pitch of 1.5.

### Identification of BM involvement

Patterns of  $^{18}\text{F}$ -FDG uptake in BM has been described in our previously published study [5]. Similarly, four patterns of BM uptake were categorized (Online Resource 1): normal BM as no visible increased  $^{18}\text{F}$ -FDG uptake within BM; homogeneously increased  $^{18}\text{F}$ -FDG uptake higher than liver within the axial skeleton while sparing the distal portion of extremities; focal/multifocal as one or more circumscribed area(s) of intense  $^{18}\text{F}$ -FDG uptake within the skeleton; increased  $^{18}\text{F}$ -FDG uptake involving both the axial skeleton and distal portion of extremities homogeneously and diffusely.

Undirected unilateral BM trephine aspiration and biopsy at the iliac crest was performed routinely at the time of diagnosis of B-NHL in our institution. Patients were considered to have BM involvement if they had positive BMB or focal/multifocal intense  $^{18}\text{F}$ -FDG uptake in BM on PET, which was confirmed by concomitant CT findings or supplementary magnetic resonance imaging, or resolution of the BM lesions in parallel with other lymphoma lesions during or after treatment on follow-up PET scans or radiological studies, as previously described [14, 15].

## Quantitative PET-derived parameters

PET scans were reviewed blinded to patients' clinical parameters and outcomes. Metabolic indices were obtained on semiautomatic software Beth Israel Fiji20 (<http://petctviewer.org>). The maximum standardized uptake value ( $SUV_{max}$ ) of the lesion with the highest  $^{18}F$ -FDG uptake was measured for analysis. TMTV and TLG were obtained in patients with no history of tumor resection. TMTV was calculated by summing the metabolic volumes of all lesions, with a threshold of 41%  $SUV_{max}$  as recommended by the European Association of Nuclear Medicine (EANM) [16]. Briefly, volumes of interest (VOIs) were drawn manually around each lymphomatous lesion. Some bulky masses were made of contiguous lymph nodes or lesions, which may have SUV lower than 41% of the mass, and resulted in underestimation of the whole volume. To account for this, we first drew a VOI engulfing the bulky region, then additional VOIs were drawn upon the components left out by the initial VOI, as previously described [17, 18]. The shape and size of the VOIs were adjusted to ensure that areas of increased physiological uptake, such as bladder, myocardium or thymus, were excluded. An example of VOI placement can be found in Online Resource 2. BM involvement was included in TMTV and TLG measurement when there was focal/multifocal uptake. TLG was calculated as the product of MTV and the mean SUV in the contoured region.

## Statistical analysis

PFS and OS were calculated as the time from the date of histological diagnosis to the date of disease progression or death. Differences between groups were compared using the Mann-Whitney U test for continuous variables, chi-square test and Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to define the optimal cutoff values of TMTV and TLG for survival prediction. The univariate and multivariate Cox proportional hazards regression analyses were used to compare the prognostic impact of metabolic indices on PET and clinicopathological parameters. Kaplan-Meier survival analysis and log-rank test were utilized to determine median follow-up time and 2-year PFS and OS rates. Statistical analysis was carried out using SPSS 22.0 software (IBM, Chicago, IL, USA). All tests were two-sided, and a  $P$  value less than 0.05 was considered statistically significant.

## Results

### Patient characteristics

A total of 46 pediatric patients who met the inclusion criteria were identified. Patient baseline characteristics are

summarized in Table 1. There were 36 males (median age 7 years; range 2–18 years) and ten females (median age 7.5 years; range 2–18 years). Twenty-four patients had BL, 11 had DLBCL and 11 had B-NHL non-other specified. Most of the patients had advanced-stage disease (34/46, 74%). Thirty-six patients were treated with CCG-BNHL-2009/2015 chemotherapy protocol. Five were treated with R-EPOCH regimen, four with R-Hyper-CVAD and one with R-CHOP regimen. With a median follow-up time of 31 months, 2-year PFS and OS rates were 84% and 89%, respectively. Relapse or progression occurred in seven patients at a median of 5 months after diagnosis.

### BM involvement and survival

Of the 46 patients, 18 were judged to have BM involvement. Seven of them were identified by BMB and all of them had a positive PET (two had diffusely increased uptake in both the axial skeleton and distal portion of the extremities; 16 had focal/multifocal BM lesions). Eleven patients with focal/multifocal BM lesions on PET had a negative BMB. Seven of them had bone changes (osteolysis or osteosclerosis) on concomitant CT compatible with BM infiltration of lymphoma. Supplementary magnetic resonance imaging was performed in two patients and showed abnormal alterations compatible with malignancy. Response assessment showed resolution of the BM lesions in ten patients on follow-up PET scans and one on follow-up magnetic resonance imaging in parallel with other lymphoma lesions. Thirteen patients with normal  $^{18}F$ -FDG uptake in BM and 15 with homogeneously increased uptake only in BM of axial skeleton were considered to have a negative BM PET. All of them had no lymphoma infiltrate in marrow specimens. Sensitivity was 100% for PET/CT and 39% for BMB. Specificity were both 100%. PET/CT had a higher overall accuracy than BMB.

Kaplan Meier analysis revealed that patients with BM involvement had a poorer survival outcome than those without, with 2-year PFS and OS rates of 71% vs. 93% ( $P = 0.055$ ) and 76% vs. 96% ( $P = 0.02$ ), respectively. Next, patients were stratified into three groups according to BMB status and PET positivity in BM as follows: BMB+: patients with positive BMB ( $n = 7$ ); PET+/BMB-: patients with focal/multifocal increased  $^{18}F$ -FDG uptake in BM but negative BMB ( $n = 11$ , Online Resource 3); PET-/BMB-: patients with both negative BMB and PET ( $n = 28$ ). Kaplan-Meier analysis demonstrated that 2-year PFS rates for the three groups were 57%, 78% and 93% ( $P = 0.033$ ), respectively. Two-year OS rates were 57%, 88% and 96% ( $P = 0.004$ ), respectively. As shown in Fig. 1, PFS and OS were significantly different between patients with BMB+ and those with no BM involvement ( $P = 0.008$  and 0.002, respectively). However, there was no statistically significant difference between group of PET+/BMB- and group of PET-/BMB- or BMB+. Univariate analysis revealed that

**Table 1** Patient characteristics and stratification according to TLG with the cutoff of 5,797 g

Characteristic	Total population N = 46		Low TLG N = 31		High TLG N = 7		<i>P</i> value
	No.	%	No.	%	No.	%	
Age (range), years	7 (2–18)		5 (2–12)		12 (5–14)		<b>0.001</b>
Gender							1.000
Female	10	22	7	23	1	14	
Male	36	78	24	77	6	86	
Murphy stage							0.309
I-II	12	26	7	23	0	0	
III-IV	34	74	24	77	7	100	
BMB status							0.101
Negative	39	85	27	87	4	57	
Positive	7	15	4	13	3	43	
LDH (U/L)	350 (173-3842)		350 (173-2443)		1113 (488-3842)		<b>0.008</b>
Increased	39	85	27	87	7	100	1.000
≥ 2 UL	21	46	14	45	7	100	<b>0.011</b>
WBC (10 <sup>9</sup> /L)	8.1 (3.2-18.7)		8.5 (3.2-18.7)		6.5 (4.8-10.7)		0.200
RBC (10 <sup>12</sup> /L)	4.6 (2.1-5.9)		4.7 (3.5-5.9)		4.3 (2.1-4.8)		<b>0.033</b>
Hemoglobin (g/L)	126.5 (59-157)		126 (84-157)		111 (59-128)		<b>0.025</b>
Platelet count (10 <sup>9</sup> /L)	286.5 (75-631)		279 (75-631)		336 (116-441)		0.985
Protein (g/L)	64.3 (49.1-76.6)		64.0 (50-76.6)		63.5 (49.1-69.6)		0.243
Albumin (g/L)	39.7 (28.5-47.3)		39.7 (28.5-47.3)		37.1 (32.6-40.0)		0.152
SUV <sub>max</sub>	16.2 (4.4-36.7)		16.5 (4.4-36.7)		15.1 (6.8-24.9)		0.693
FAB/LMB 96							0.146
Group B	30	65	26	87	4	62.5	
Group C	8	17	5	13	3	37.5	
CCCG-BNHL-2015							0.198
R3	20	43	15	62.5	2	29	
R4	14	30	9	37.5	5	71	
Progression or death							<b>0.001</b>
No	39	85	29	93.5	2	29	
Yes	7	15	2	6.5	5	71	

*P*-values in italics are considered statistically significant

*BMB* bone marrow biopsy, *LDH* lactate dehydrogenase, *RBC* red blood cell count, *SUV<sub>max</sub>* maximum standardized uptake value, *TLG* total lesion glycolysis, *WBC* white blood cell count

patients with a positive BMB had an inferior outcome (HR: 5.432, 95% CI: 1.211-24.367, *P* = 0.027 for PFS; HR: 7.327, 95% CI: 1.472-36.477, *P* = 0.015 for OS).

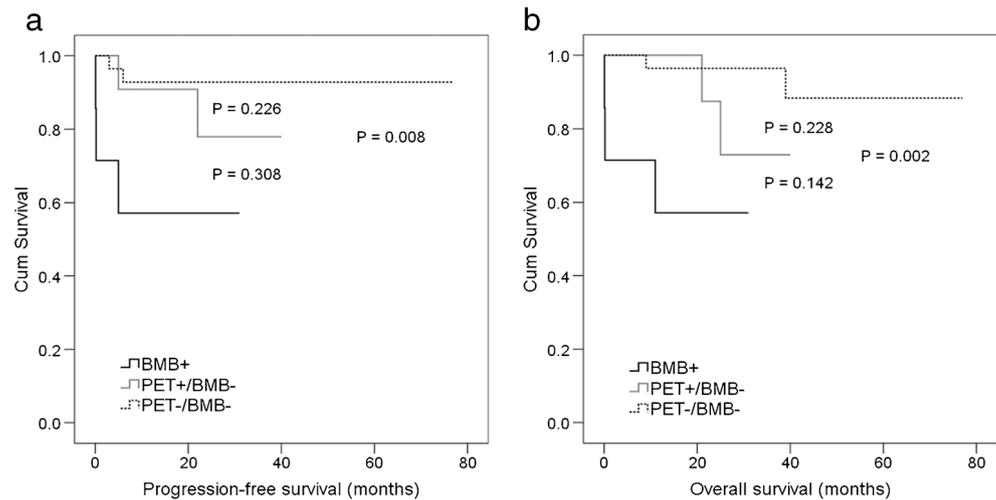
In addition, patients with BM involvement were divided into two groups: patients with limited BM lesions (< 10 lesions); patients with extensive BM lesions (≥ 10 lesions or increased <sup>18</sup>F-FDG uptake involving both the axial skeleton and distal portion of extremities homogeneously and diffusely). All of the seven patients with BMB+ had an extensive BM involvement, whereas only two of the 11 patients with PET+/BMB- had BM lesions more than 10. Therefore, there were nine patients with extensive BM lesions and nine with limited BM lesions. As shown in Online Resource 4, patients with an extensive BM

involvement on PET tended to have worse prognosis. However, no statistical significance was reached either for PFS (*P* = 0.468) or for OS (*P* = 0.396).

### Quantitative PET-derived parameters

Eight patients received tumor resection and four of them presented no residual disease on PET/CT. In all, 38 patients with baseline scans suitable for TMTV and TLG calculation were included. Median TMTV and TLG were 142 cm<sup>3</sup> and 1231 g, respectively. In univariate Cox regression analysis of TMTV and TLG as continuous variables, a significant increase of risk was associated with an increase in TMTV (for every 100 cm<sup>3</sup> increase, HR: 1.104, 95% CI: 1.040-1.171, *P* = 0.001 for PFS;

**Fig. 1** Kaplan-Meier curves of progression-free survival (a) and overall survival (b) according to bone marrow biopsy (BMB) status and PET positivity in bone marrow. *BMB+* patients with positive BMB, *PET+/BMB-* patients with focal/multifocal increased  $^{18}\text{F}$ -FDG uptake in bone marrow but negative BMB, *PET-/BMB-* patients with both negative BMB and PET



and HR: 1.099, 95% CI: 1.037–1.166,  $P=0.002$  for OS, respectively) and TLG (for every 1000 g increase, HR: 1.160, 95% CI: 1.047–1.284,  $P=0.004$  for PFS; and HR: 1.151, 95% CI: 1.039–1.275,  $P=0.007$  for OS, respectively). Patients with progression or death had significantly higher TMTV of 1078  $\text{cm}^3$  contrasting with 94  $\text{cm}^3$  ( $P=0.009$ ) and higher TLG of 6703 g versus 826 g ( $P=0.01$ ).

Areas under the curve of TMTV and TLG to predict disease progression or death were 0.820 ( $P=0.009$ ) and 0.816 ( $P=0.01$ ) by ROC analysis (Fig. 2), respectively. The optimal TMTV cutoff of 524  $\text{cm}^3$  and TLG cutoff of 5797 g were identified using the Youden index for both PFS and OS. Sensitivity and specificity were 71% and 84% for TMTV and 71% and 93% for TLG, respectively. Using 50  $\text{cm}^3$  as the cutoff threshold for TMTV or 611 g as the cutoff threshold for TLG, sensitivity was improved to 100%. Using cutoff value of 987  $\text{cm}^3$  for TMTV or 12,604 g for TLG, specificity was improved to 97%.

A high TMTV ( $> 524 \text{ cm}^3$ ) was present in 10 (26%) out of 38 patients. Half (5/10) of them progressed, as compared with 7% (2/28) progressed in groups of patients with a low TMTV. The presence of a high TMTV was significantly associated with older age, higher LDH level, lower level of red blood cell count (RBC), hemoglobin, serum protein and albumin (Online Resource 5). The 2-year PFS and OS rates for patients with high or low TMTV were 50% vs. 92% ( $P=0.001$ ) and 60% vs. 96% ( $P=0.002$ ), respectively (Fig. 3).

A high TLG ( $> 5797 \text{ g}$ ) was present in 7 (18%) patients. Five (71%) of them progressed, as compared with 6.5% (2/31) that progressed in patients with a low TLG. A high TLG ( $> 5797 \text{ g}$ ) was associated with older age, higher LDH level and lower level of RBC and hemoglobin (Table 1). As shown in Fig. 4, patients with a high TLG experienced a significantly inferior 2-year PFS and OS compared with those with a low TLG (PFS: 29% vs. 93%,  $P<0.001$ ; OS: 43% vs. 96%,  $P<0.001$ ).

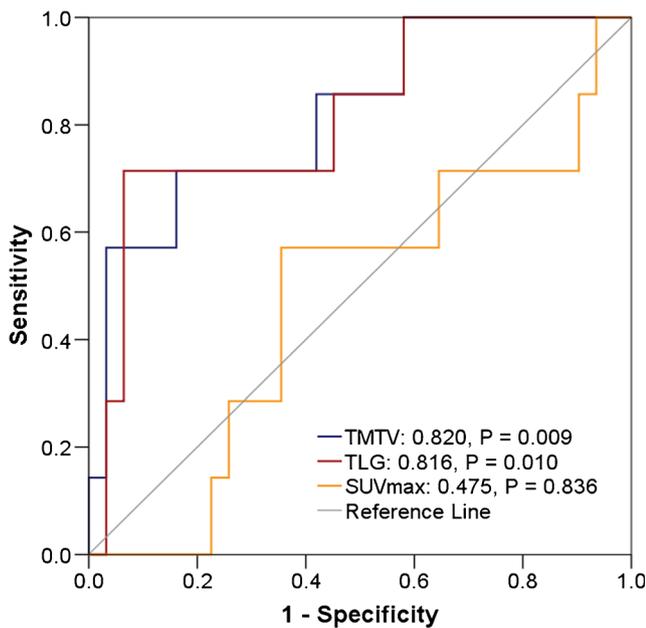
$\text{SUV}_{\text{max}}$  of the most intense lesion, with a median of 16.2 (range 4.4–36.7), was not predictive of survival outcome (Fig. 2). There was no significant difference of  $\text{SUV}_{\text{max}}$  between patients with a high metabolic tumor burden and those without.

### Multivariate survival analysis

In univariate analysis, *BMB+*, RBC, LDH, TMTV, and TLG were significantly associated with both PFS and OS, whereas age, white blood cell count, platelet count, protein, and albumin level failed to predict outcome (Table 2). As TMTV and TLG highly correlated ( $r=0.922$ ,  $P<0.001$ ), they were analyzed separately in multivariate Cox proportional hazard analyses. As shown in Table 3, both TMTV and TLG remained the most robust prognostic factors for survival outcome after adjusting for other factors. BM involvement identified by BMB retained its marginal significance in the model incorporating TLG but not in the model incorporating TMTV. Multivariate Cox analyses of TMTV and TLG as continuous variables are provided in Online Resource 6.

### Risk stratification based on metabolic tumor burden

Because FAB/LMB 96 classification has been used in daily clinical practice and numerous clinical trials to assess the risk of treatment failure in pediatric B-NHL, we next evaluated whether adding TMTV or TLG improved the predictive accuracy for clinical outcome. There were 30 patients identified as intermediate-risk (Group B) and eight as high-risk (Group C). As shown in Table 4, patients with different outcomes among Group C were distinguished by TLG efficiently. All of the three patients who had a high TLG relapsed and died, contrasting with none of the five patients with a low TLG who progressed ( $P=0.018$ ) (Fig. 5). Despite belonging to Group C, none of the four



**Fig. 2** Receiver operating characteristic curve analysis of PET-derived parameters to predict disease progression or death. Areas under the curve were 0.820 for TMTV ( $P=0.009$ ), 0.816 for TLG ( $P=0.01$ ), and 0.475 for  $SUV_{max}$  ( $P=0.836$ ), respectively. TMTV total metabolic tumor volume, TLG total lesion glycolysis,  $SUV_{max}$  the maximum standardized uptake value

patients with a low TMTV relapsed while three of four patients with a high TMTV experienced relapse ( $P=0.143$ ). Among patients in Group B, patients with a low TLG had a higher survival rate than those with a high TLG (92% vs. 50%), although the significance was marginal ( $P=0.075$ ).

Fourteen patients were stratified as high-risk (R4) by CCCG-BNHL-2015 regimen. None of the patients with low TMTV or TLG relapsed, contrasting with a higher proportion of patients with high metabolic tumor burden who

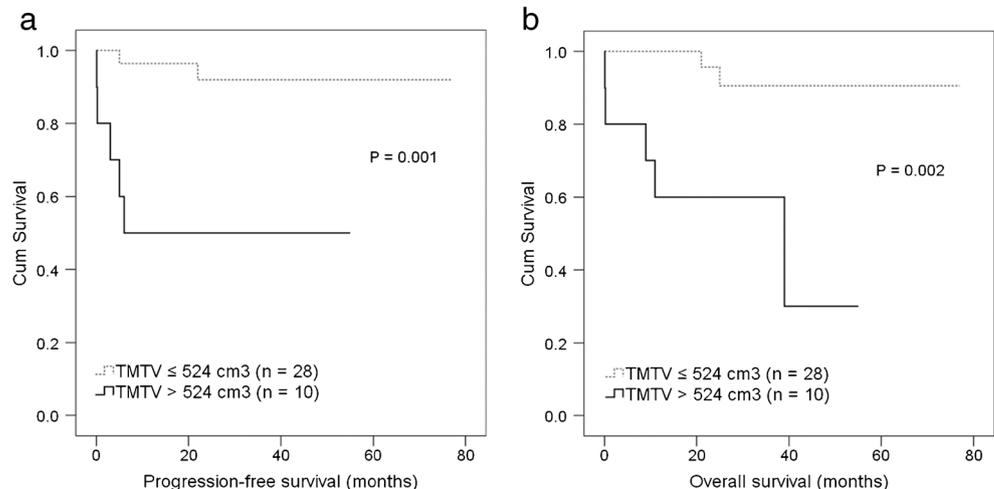
experienced events (4 of 5 with high TLG,  $P=0.005$ ; 4 of 8 with high TMTV,  $P=0.085$ ).

### Discussion

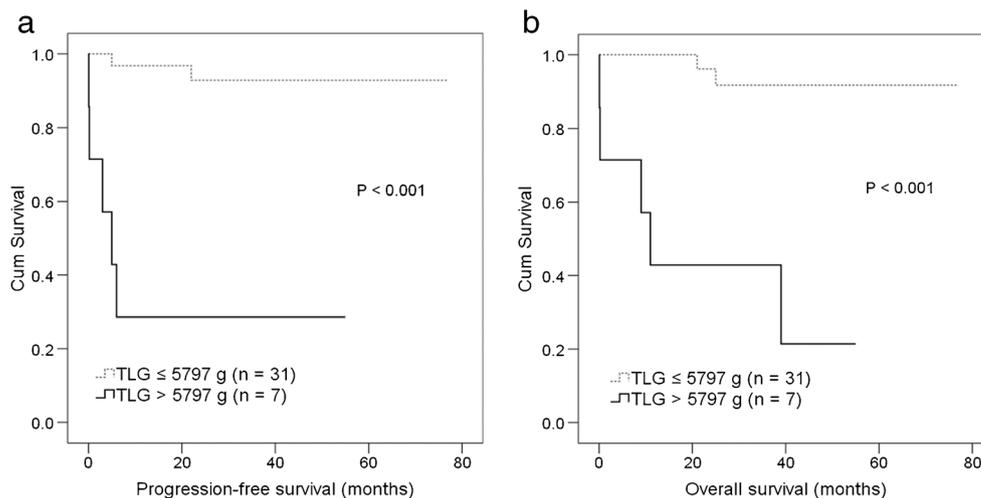
To our knowledge, this is the first study evaluating the prognostic role of metabolic volumetric parameters obtained from baseline PET in pediatric patients with mature B-cell NHL. The present study confirms that metabolic parameters reflecting whole-body tumor burden, namely, TMTV and TLG, were the most robust pretreatment predictors in pediatric B-NHL. Patients with a high metabolic tumor burden was associated with a dismal outcome. PET was more sensitive to detect BM involvement than BMB. However, BM involvement identified only by PET demonstrated an inferior prognostic impact as compared with BMB.

Pretreatment surrogate markers of tumor burden in pediatric B-NHL, including stage, LDH level, BM or CNS involvement, are routinely incorporated into risk stratification. A report from the FAB/LMB 96 study group showed that LDH level  $\geq 2$  UL at diagnosis was the only baseline parameter independently associated with OS in children with refractory or relapsed mature B-NHL [4]. Different from these conventional prognostic factors, TMTV and TLG derived from baseline PET allow a direct measure of whole-body tumor burden. There is growing evidence of the prognostic importance of TMTV and TLG in adults with different types of lymphoma [9–12] and in pediatric HL [19]. We confirmed these findings in pediatric B-NHL and showed that TLG and TMTV both outperformed other clinical parameters, including LDH level and BM involvement on biopsy, remained the most robust predictors for survival. In our study, patients with a high metabolic tumor burden had a markedly inferior survival outcome with 2-y

**Fig. 3** Progression-free survival (a) and overall survival (b) according to baseline TMTV with a cutoff value of 524  $cm^3$ . TMTV total metabolic volume



**Fig. 4** Kaplan-Meier curves of progression-free survival (**a**) and overall survival (**b**) according to TLG with a cutoff value of 5797 g. *TLG* total lesion glycolysis



PFS of 29% vs. 93% for TLG and 50% vs. 92% for TMTV. The optimal threshold was 524 cm<sup>3</sup> for TMTV and 5797 g for TLG, respectively, showing a high specificity and a moderate sensitivity. When using lower cutoff value of 50 cm<sup>3</sup> for TMTV and 611 g for TLG, sensitivity was improved to 100%. Various cutoff values for TMTV and TLG to predict survival in mature B-cell NHL have been

reported. In patients with DLBCL, cutoff values for TMTV ranged from 281 to 550 cm<sup>3</sup> [9, 20–22], and TLG ranged from 1703 g to 4541 g [21, 22]. Albano et al. [23] reported the optimal cutoff values of TMTV and TLG in adulthood BL were 231 cm<sup>3</sup> and 2891 g with 3-y PFS of 27% vs. 89% and 30% vs. 84%, respectively. The cutoff values in our study are similar with that reported by Sasanelli et al. [22],

**Table 2** Univariate analysis of clinicopathological parameters and metabolic tumor burden on PET

Parameter	Progression-free survival			Overall survival		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age	1.113	0.955–1.296	0.170	1.114	0.951–1.305	0.181
Murphy stage						
III–IV vs. I–II	33.449	0.030–37,250.261	0.327	33.476	0.030–37,368.819	0.327
BMB status						
Positive vs. Negative	5.432	1.211–24.367	0.027	7.327	1.472–36.477	<b>0.015</b>
LDH (U/L)	1.001	1.000–1.002	0.010	1.001	1.000–1.002	<b>0.008</b>
WBC (10 <sup>9</sup> /L)	0.825	0.616–1.105	0.196	0.846	0.634–1.130	0.259
RBC (10 <sup>12</sup> /L)	0.342	0.165–0.705	0.004	0.262	0.107–0.641	<b>0.003</b>
Hemoglobin (g/L)	0.971	0.941–1.001	0.057	0.967	0.934–1.002	0.063
Platelet count (10 <sup>9</sup> /L)	0.994	0.986–1.003	0.183	0.994	0.985–1.002	0.162
Protein (g/L)	0.941	0.842–1.051	0.279	0.942	0.842–1.053	0.292
Albumin (g/L)	0.978	0.842–1.136	0.767	0.975	0.839–1.134	0.746
FAB/LMB 96						
Group C vs. Group B	3.367	0.752–15.075	0.112	4.651	0.934–23.150	0.060
CCCG-BNHL-2015						
R4 vs. R3	2.224	0.497–9.956	0.296	2.134	0.477–9.556	0.322
TMTV						
High vs. low	9.328	1.802–48.291	0.008	8.987	1.734–46.580	<b>0.009</b>
TLG						
High vs. low	18.594	3.540–97.667	0.001	15.665	3.012–81.478	<b>0.001</b>

*BMB* bone marrow biopsy, *CI* confidence interval, *HR* hazard ratio, *LDH* lactate dehydrogenase, *RBC* red blood cell count, *TLG* total lesion glycolysis, *TMTV* total metabolic tumor volume, *WBC* white blood cell count

**Table 3** Multivariate Cox analysis for survival prediction

Parameter	Progression-free survival			Overall survival		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Positive BMB status				5.385 <sup>a</sup>	0.920-31.522	0.062
TMTV >524 cm <sup>3</sup>	9.328	1.802-48.291	<b>0.008</b>	8.987	1.734-46.580	<b>0.009</b>
TLG > 5797 g	18.594	3.540-97.667	<b>0.001</b>	15.378	2.798-84.510	<b>0.002</b>

<sup>a</sup> Model incorporating TLG

BMB bone marrow biopsy, CI confidence interval, HR hazard ratio, TLG total lesion glycolysis, TMTV total metabolic tumor volume

while higher than other studies. The differences could be attributed to better outcome of pediatric B-NHL than of adult patients after standard treatment strategies [24].

Furthermore, we evaluated whether adding TMTV or TLG could give added prognostic value on existing risk stratification systems. Our results suggested that metabolic tumor burden distinguished patients with distinct outcomes, especially among the unfavorable groups (Group C of FAB/LMB 96 and R4 of CCCG-BNHL-2015). The negative predictive values were extremely high (92–100% in FAB/LMB96; 85–100% in CCCG-BNHL-2015), as there was low or no progression among patients with low TMTV or TLG, even among the unfavorable groups. TLG exhibited a higher positive predictive power than TMTV, with 50% vs. 33% in Group B and 100% vs. 75% in Group C. These findings may aid in sub-stratification of pediatric B-NHL patients for risk-adapted treatment approaches in the future. As the most dismal outcome occurred in the patients with unfavorable risk group and a high TLG, clinical trials that evaluate more novel treatment approaches should be considered for this subset of patients.

The second objective of this study was to evaluate whether BM involvement identified only by PET had prognostic value in pediatric B-NHL. BM involvement is one of the most important prognostic indices in lymphoma and is more common in pediatric patients than in adulthood NHL. Although a higher sensitivity of <sup>18</sup>F-FDG PET than BMB to detect BM infiltration in pediatric NHL has been demonstrated [5, 25], its clinical significance and

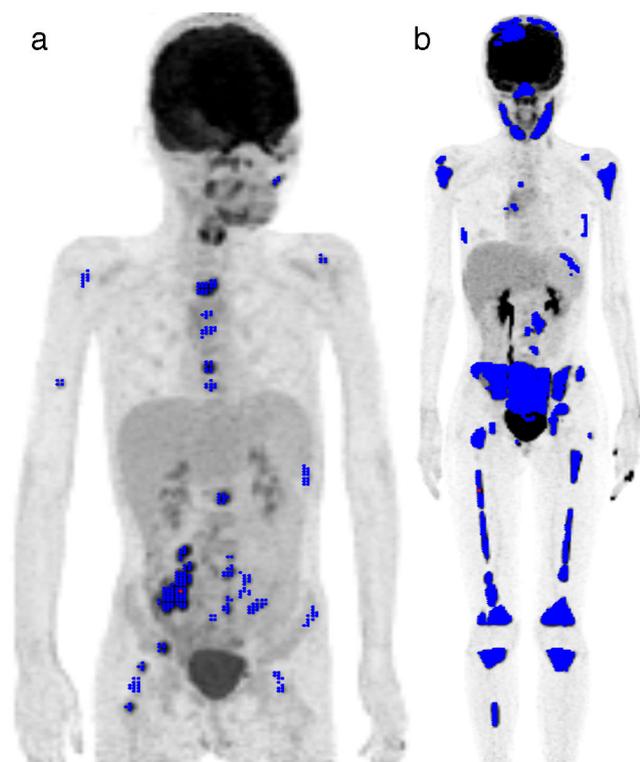
prognostic impact is yet to be addressed. In this study, we confirmed that pediatric patients with lymphomatous infiltration in BM had a worse outcome. After further stratification, a tendency of shorter survival outcome was observed in patients with marrow deposits identified only by PET than in those without BM involvement (2-year PFS rates of 57%, 78% and 93% and 2-year OS rates of 57%, 88% and 96% for patients with BMB+, PET+/BMB- and PET-/BMB-, respectively). However, no statistical significance could be reached. This is in line with the previous reports regarding the prognostic value of BM PET in adulthood DLBCL [26–29], showing that BM involvement based on PET, without positive BMB, did not significantly impact survival outcome. The most plausible explanation for weak or lacking of prognostic value of detection of marrow involvement only by PET could be due to the high sensitivity of PET to detect limited lymphomatous deposits in BM, in contrast to BMB it detects only the most extensive BM involvement.

Our study had certain limitations. First, it was a retrospective study and the small number of events limited our analyses and underpowered the statistical significance. Nevertheless, this is the first study highlighting the significant prognostic value of TMTV and TLG in pediatric mature B-NHL and may offer a tool to identify patients at highest risk of treatment failure early. Second, the determination of cutoff values of TMTV and TLG was based on the ROC analysis and Youden index, which might overestimate or underestimate the predictive performance in certain patients. Hence, a lower

**Table 4** Number of patients (%) who experienced progression or death according to baseline metabolic tumor burden in patients with intermediate or high risk

Risk groups	TLG ≤ 5797 g	TLG > 5797 g	<i>P</i> value	TMTV ≤ 524 cm <sup>3</sup>	TMTV > 524 cm <sup>3</sup>	<i>P</i> value
FAB/LMB 96						
Group B (n = 30)	2/26 (8%)	2/4 (50%)	0.075	2/24 (8%)	2/6 (33%)	0.169
Group C (n = 8)	0/5 (0%)	3/3 (100%)	<b>0.018</b>	0/4 (0%)	3/4 (75%)	0.143
CCCG-BNHL-2015						
R3 (n = 15)	2/13 (15%)	1/2 (50%)	0.331	2/13 (15%)	1/2 (50%)	0.331
R4 (n = 14)	0/9 (0%)	4/5 (80%)	<b>0.005</b>	0/6 (0%)	4/8 (50%)	0.085

TMTV total metabolic tumor volume, TLG total lesion glycolysis



**Fig. 5** Examples of Group C patients with low or high metabolic tumor burden. **a** An 8-year-old boy with Burkitt lymphoma had blasts in bone marrow of 28% and LDH of 306 U/L. TMTV was 39 cm<sup>3</sup> and TLG was 221 g. After a follow-up of 31 months, he did not experience relapse. **b** An 11-year-old girl with Burkitt lymphoma had 45% blasts in bone marrow and LDH of 2261 U/L. TMTV was 632 cm<sup>3</sup> and TLG was 7102 g. This patient progressed 5 months after diagnosis and died 6 months later. LDH lactate dehydrogenase, TMTV total metabolic tumor volume, TLG total lesion glycolysis

threshold, such as 50 cm<sup>3</sup> for TMTV or 611 g for TLG, could achieve higher sensitivity. Vice versa, a higher threshold, such as 987 cm<sup>3</sup> for TMTV or 12,604 g for TLG, could provide higher specificity. An additional limitation was that there is no standard technique or consensus for calculating TMTV and TLG. A threshold of 41% of SUV<sub>max</sub> was employed in this study as suggested by the EANM. We also evaluated SUV<sub>max</sub> threshold of 2.5, which showed results similar to 41% of SUV<sub>max</sub>. Additional data are given in Online Resource 7. Nevertheless, this method has been proven to have high reproducibility between observers and centers even when different software was used [30]. Validation of these findings in larger cohorts is needed.

In conclusion, this study shows that TMTV and TLG at diagnosis are the most robust prognostic factors and offer a promising advance on existing surrogates for tumor burden. Combining with current risk classification systems, TLG enables early identification of a minority of pediatric B-NHL patients with a very high risk of progression who might benefit from treatment escalation or more novel treatment approaches.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This retrospective study was approved by the Institutional Review Board (Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, XHEC-D-2019-012, 2019). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study, the requirement for informed consent is waived.

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