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Implications of Sarcopenia and Glucometabolism Parameters of Muscle Derived From Baseline and End-of-Treatment ^{18}F-FDG PET/CT in Diffuse Large B-Cell Lymphoma

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Objective: We previously found that the incidence of sarcopenia increased with declining glucose metabolism of muscle in patients with treatment-naïve diffuse large B-cell lymphoma (DLBCL). This study aimed to investigate the relationship between sarcopenia and muscle glucometabolism using ^{18}F-FDG PET/CT at baseline and end-of-treatment, analyze the changes in these parameters through treatment, and assess their prognostic values.

Materials and Methods: The records of 103 patients with DLBCL (median 54 years [range, 21–76]; male:female, 50:53) were retrospectively reviewed. Skeletal muscle area at the third lumbar vertebral (L3) level was measured, and skeletal muscle index (SMI) was calculated to determine sarcopenia, defined as SMI < 44.77 cm^2/m^2 and < 32.50 cm^2/m^2 for male and female, respectively. Glucometabolic parameters of the psoas major muscle, including maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean), were measured at L3 as well. Their changes across treatment were also calculated as ΔSMI, ΔSUVmax, and ΔSUVmean; Δbody mass index was also calculated. Associations between SMI and the metabolic parameters were analyzed, and their associations with progression-free survival (PFS) and overall survival (OS) were identified.

Results: The incidence of sarcopenia was 29.1% and 36.9% before and after treatment, respectively. SMI (P = 0.004) was lower, and sarcopenia was more frequent (P = 0.011) at end-of-treatment than at baseline. The SUVmax and SUVmean of muscle were lower (P < 0.001) in sarcopenia than in non-sarcopenia at both baseline and end-of-treatment. ΔSMI was positively correlated with ΔSUVmax of muscle (P = 0.022). Multivariable Cox regression analysis showed that sarcopenia at end-of-treatment was independently negatively associated with PFS (adjusted hazard ratio [95% confidence interval], 2.469 [1.022–5.965]), while sarcopenia at baseline was independently negatively associated with OS (5.051 [1.453–17.562]).

Conclusion: Sarcopenic patients had lower muscle glucometabolism, and the muscular and metabolic changes across treatment were positively correlated. Sarcopenia at baseline and end-of-treatment was negatively associated with the prognosis of DLBCL.

Keywords: Diffuse large B-cell lymphoma; ^{18}F-FDG PET/CT; Sarcopenia; Glucometabolic parameters of muscle; Prognosis

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin's lymphoma, accounting for approximately 35% of newly diagnosed cases [1]. Although the first-line regimen rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has significantly improved DLBCL outcomes, over 25% of patients still experience disease recurrence or progression after treatment [2]. For patients with DLBCL treated with CHOP, the international prognostic index (IPI) is the most common tool for initial risk stratification, treatment planning, and prognostication; however, with the advent of rituximab, the clinic value of IPI has significantly decreased [3].

Sarcopenia, defined as a reduction in skeletal muscle mass or strength, has been recognized as an independent risk factor in patients with a variety of malignancies [4,5]; for DLBCL specifically, sarcopenia diagnosed before treatment was found to be associated with decreased survival [6,7]. To date, reduced skeletal muscle index (SMI) is the only well-accepted imaging criteria for the diagnosis of sarcopenia, and it requires the measurement of skeletal muscle area (SMA) at the third lumbar vertebral (L3) level on CT and normalization using patient height [8]. However, the downside of this method is that CT images require exportation to a separate workstation to be analyzed using designated software, a process which is time-consuming and unfeasible in routine clinical practice [9].

^{18}F-FDG PET/CT has been proven to play an important role in the prognostic evaluation of patients with DLBCL [10,11]. It can offer both anatomic information derived from CT and metabolic information derived from PET, thus simultaneously obtaining the SMA and glucose metabolic parameters of muscle such as the maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) at L3. Our previous studies [12-15] have confirmed that the SUVmax of muscle at L3 was lower in sarcopenic patients compared with non-sarcopenic patients before treatment, and the incidence of sarcopenia increased with declining SUVmax in patients with malignancy. Moreover, compared with SMI, the SUVmax offers a more straightforward and convenient way to predict sarcopenia [14,15].

At present, literature about sarcopenia after treatment and its changes through treatment was rarely investigated in patients with malignancy. Therefore, this study aimed to explore the relationship between sarcopenia and the glucometabolic parameters of muscle in patients with DLBCL at end-of-treatment and the changes before and after treatment. Additionally, the prognostic role of sarcopenia, PET-derived metabolic parameters of muscle, and other clinical factors were also studied in patients with DLBCL treated with standard R-CHOP.

MATERIALS AND METHODS

Patients

From December 2012 to November 2021, a total of 103 consecutive patients with pathologically confirmed DLBCL in our hospital were retrospectively enrolled using the following criteria: 1) underwent both baseline and end-of-treatment ^{18}F-FDG PET/CT scan, 2) received a standard R-CHOP regimen, and 3) no prior or synchronous malignancy (Fig. 1). Clinical data including sex, age, serum lactate

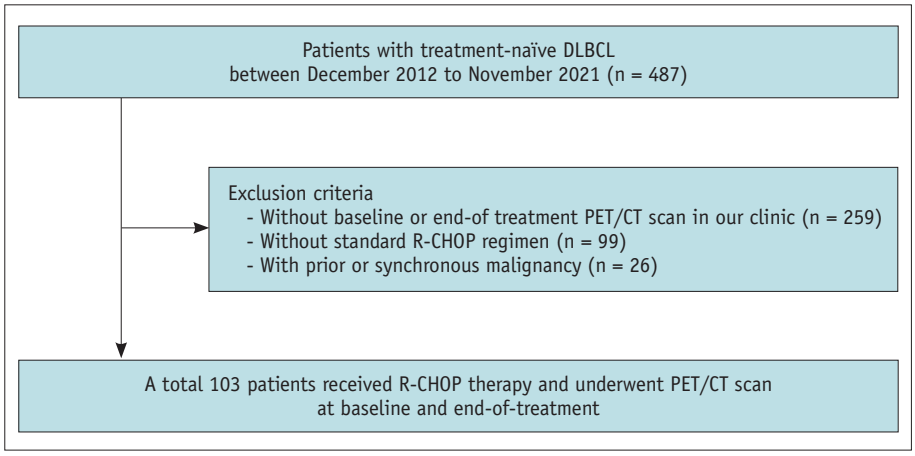

Fig. 1. Flowchart showing the inclusion and exclusion criteria. DLBCL = diffuse large B-cell lymphoma, R-CHOP = regimen rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

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dehydrogenase and β^2 microglobulin levels, body mass index (BMI), B symptoms, performance status (PS), Ann Arbor stage, extranodal sites, and IPI were collected. Moreover, ΔBMI was calculated as follows: ΔBMI = baseline BMI - end-of-treatment BMI.

The study was approved by the ethics committee of Guangdong Provincial People's Hospital (IRB No. KY2023-869-02) and conducted following the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The need for informed consent was waived due to the retrospective nature of the study and proper anonymization.

^{18}F-FDG PET/CT Scan

All enrolled patients underwent baseline and end-of-treatment PET/CT examinations after six cycles of standard R-CHOP chemotherapy. Both baseline and end-of-treatment PET/CT scans were performed using Biograph 16 (Siemens Healthineers, Erlangen, Germany). All patients were required to fast for at least 6 h and avoid strenuous exercise 24 h prior to imaging. ^{18}F-FDG was injected intravenously at a body weight-adjusted dose (3.7 MBq/kg) when fasting blood glucose level was confirmed to be no more than 11.0 mmol/L, and image acquisition started approximately 60 ± 5 min thereafter. PET images were acquired using 5–7 bed positions with 2.5 min per bed position from the skull base to the middle thigh. Low-dose CT images were obtained using the same scanner and the following parameters: 120 kV, 75 mA (with auto mA), 0.75 mm pitch, 0.5 s tube rotation, and an axial slice thickness of 5 mm. PET image reconstructions were performed with the ordered subset expectation maximization algorithm, incorporating a CT-based attenuation correction.

Sarcopenia Measurement

Sarcopenia measurements were calculated from the CT component of the baseline and end-of-treatment PET/CT images [16]. Hounsfield units (HU) were used to identify skeletal muscle using a threshold ranging from -29 to 150 HU. The total SMA (cm^2) was calculated at the L3 level using ImageJ (version 2.0, National Institutes of Health, Bethesda, MD, USA) and subsequently normalized as SMI (cm^2/m^2) for height (m^2) [8]. The change of SMI (ΔSMI) was calculated as follows: ΔSMI = baseline SMI - end-of-treatment SMI. Sarcopenia was defined as SMI < 44.77 cm^2/m^2 for males and SMI < 32.50 cm^2/m^2 for females according to a previous study [17].

PET Metabolic Parameters of Muscle

PET metabolic parameters of muscle were analyzed through Syngo station (Siemens Healthineers). A three-dimensional circular volume of interest (VOI) was manually drawn on the bilateral psoas muscle at the L3 level, and the VOI diameter was kept to 1 cm as previously described [13,14]. The SUVmax and SUVmean of the psoas major muscle (SUVmax_M and SUVmean_M) were measured on both baseline and end-of-treatment PET/CT images. Changes in the glucose metabolism of muscle were calculated as follows: ΔSUVmax_M = baseline SUVmax_M - end-of-treatment SUVmax_M, and ΔSUVmean_M = baseline SUVmean_M - end-of-treatment SUVmean_M.

Follow-Up

All enrolled patients underwent routine clinical follow-up which assessed clinical symptoms, laboratory tests, imaging data, and histopathological findings. The survival endpoints included progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval between the diagnosis and the date of post-treatment progression, relapse, death, or date of censor. OS was defined as the interval from the diagnosis to the date of death from any cause or date of censor.

Statistical Analysis

SPSS (version 26.0, IBM Corp., Armonk, NY, USA) and R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. Continuous variables were presented as median and range, and categorical variables were presented as frequencies. Continuous variables were compared using the independent *t*-test or Mann-Whitney U test, while categorical variables were compared using Pearson's Chi-square test. The Wilcoxon paired test was used to compare the SMI and metabolic parameters of muscle at baseline and end-of-treatment. The correlation between variables was calculated using the Spearman correlation coefficient. Univariable followed by multivariable Cox proportional hazards regression using a stepwise protocol was utilized to identify independent prognostic factors. Variables with $P < 0.05$ in the univariable Cox regression analysis were selected and sequentially entered into the multivariable Cox regression analysis to determine independent predictors. We tested the Cox proportional hazard assumption using Schoenfeld residuals and the linear assumption using Martingale residuals. A two-sided *P*-value less than 0.05 was considered

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to be statistically significant.

RESULTS

Clinical Characteristics and Metabolic Parameters of Muscle at Baseline

A total of 103 patients (50 male, 53 female) with a median age of 54 years (range, 21–76 years) were enrolled in this study. Patient demographics at baseline are tabulated in Table 1. The median BMI was 21.5 kg/m^2 (range, 11.3–34.1 kg/m^2) at disease onset. The majority of patients (92/103, 89.3%) had a good ECOG status (PS = 0 or 1). Among the patients, 30 (29.1%) were diagnosed with sarcopenia. Sarcopenic patients had a lower BMI (P = 0.001) and higher IPI (P = 0.019) compared with non-sarcopenic patients. The median interval between diagnosis and start of treatment was 15 days (range, 5–35 days), while the interval between baseline PET/CT and start of treatment was 10 days (range, 2–16 days). A lower SUVmax (P < 0.001) and SUVmean (P < 0.001) were observed in sarcopenia than non-sarcopenia (Figs. 2A, B, 3). No significant differences in other clinical characteristics were found between the two groups.

Clinical Characteristics and Metabolic Parameters of Muscle at the End-of-Treatment

The clinical characteristics and PET/CT parameters of

Table 1. Clinical characteristics and PET/CT parameters of muscle at baseline

Characteristics	All patients (n = 103)	Sarcopenia at baseline (n = 30)	Non-sarcopenia at baseline (n = 73)	P
Age, yr	54 (21–76)	61 (21–75)	54 (22–76)	0.195
Sex				0.136
Male	50	18	32	
Female	53	12	41	
BMI, kg/m^2	21.5 (11.3–34.1)	20.2 (11.3–27.9)	21.8 (16.8–34.1)	0.001
Performance status				1.000
0 or 1	92	27	65	
≥ 2	11	3	8	
B symptoms				0.412
Present	19	7	12	
Absent	84	23	61	
LDH				0.222
Elevated	42	15	27	
Normal	61	15	46	
β^2 microglobulin*				0.050
Elevated	22	10	12	
Normal	79	19	60	
Extranodal sites				0.060
0–1	72	17	55	
≥ 2	31	13	18	
Ann Arbor stage				0.586
I–II	42	11	31	
III–IV	61	19	42	
IPI				0.019
0–2	69	15	54	
≥ 3	34	15	19	
PET/CT parameters				
SUVmax_M	1.28 (0.68–2.22)	0.92 (0.68–1.49)	1.41 (0.86–2.22)	< 0.001
SUVmean_M	0.78 (0.31–1.23)	0.64 (0.31–1.10)	1.82 (0.52–1.23)	< 0.001

Data are presented as number of patients or median (range).
*101 patients had serum β^2 microglobulin examination.
BMI = body mass index, LDH = lactate dehydrogenase, IPI = international prognostic index, SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle

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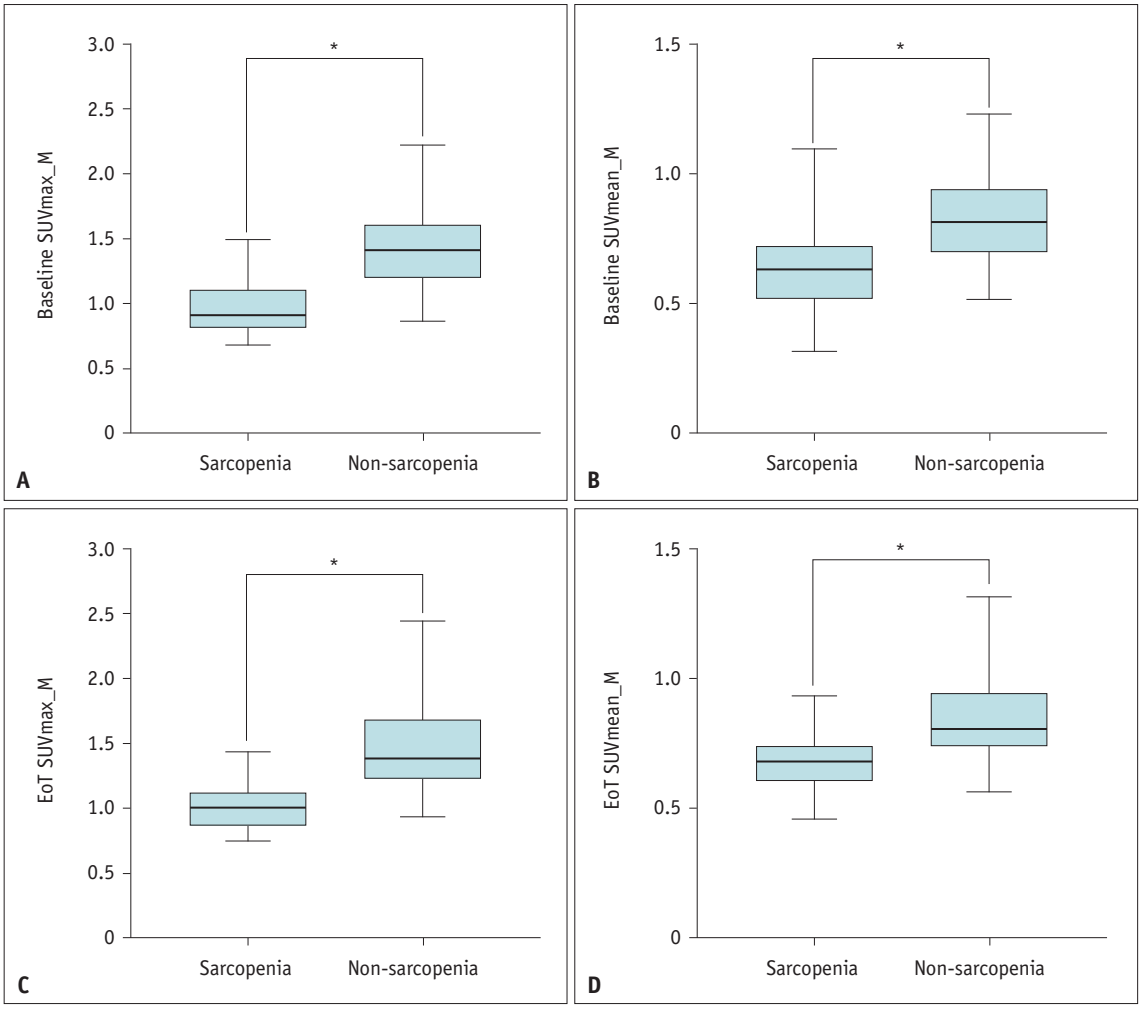

Fig. 2. The differences between SUVmax_M and SUVmean_M in patients with and without sarcopenia at baseline **(A, B)** and EoT **(C, D)**. *P < 0.001. SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle, EoT = end-of-treatment

muscle at the end-of-treatment are shown in Table 2. The median BMI was 22.1 kg/m^2 (range, 15.1–30.1 kg/m^2). The median interval between the last treatment course and end-of-treatment PET/CT was 39 days (range, 22–60 days). Of the 30 patients diagnosed with sarcopenia at baseline, 1 recovered after chemotherapy; however, 9 patients developed sarcopenia at end-of-treatment, resulting in a total of 38 patients (36.9%) having sarcopenia after treatment. Compared with non-sarcopenic patients, advanced age (P = 0.033), male sex (P = 0.007), lower BMI (P = 0.027), and lower SUVmax (P < 0.001) and SUVmean (P < 0.001) were observed more often in sarcopenic patients (Figs. 2C, D, 3).

In addition, compared with the disease onset, more people presented with sarcopenia (P = 0.011) and lower SMI (P = 0.004) at the end-of-treatment (Table 3, Fig. 4). No significant differences in BMI, SUVmax, and SUVmean were found between the baseline and end-of-treatment groups (Table 3).

Correlations among ΔBMI, ΔSMI and ΔSUV of Muscle

The median interval between baseline and end-of-treatment PET/CT examinations was 179 days (range, 140–259 days). As shown in Figure 5, ΔBMI had a positive correlation with ΔSMI (R_s = 0.51, P < 0.001), ΔSUVmax of muscle (R_s = 0.31, P = 0.002), and ΔSUVmean of muscle (R_s = 0.25, P = 0.013). In addition, ΔSMI had a positive correlation with ΔSUVmax of muscle (R_s = 0.23, P = 0.022) but no correlation with ΔSUVmean of muscle (P = 0.321). The ΔSUVmax of muscle also had a positive correlation with ΔSUVmean of muscle (R_s = 0.69, P < 0.001).

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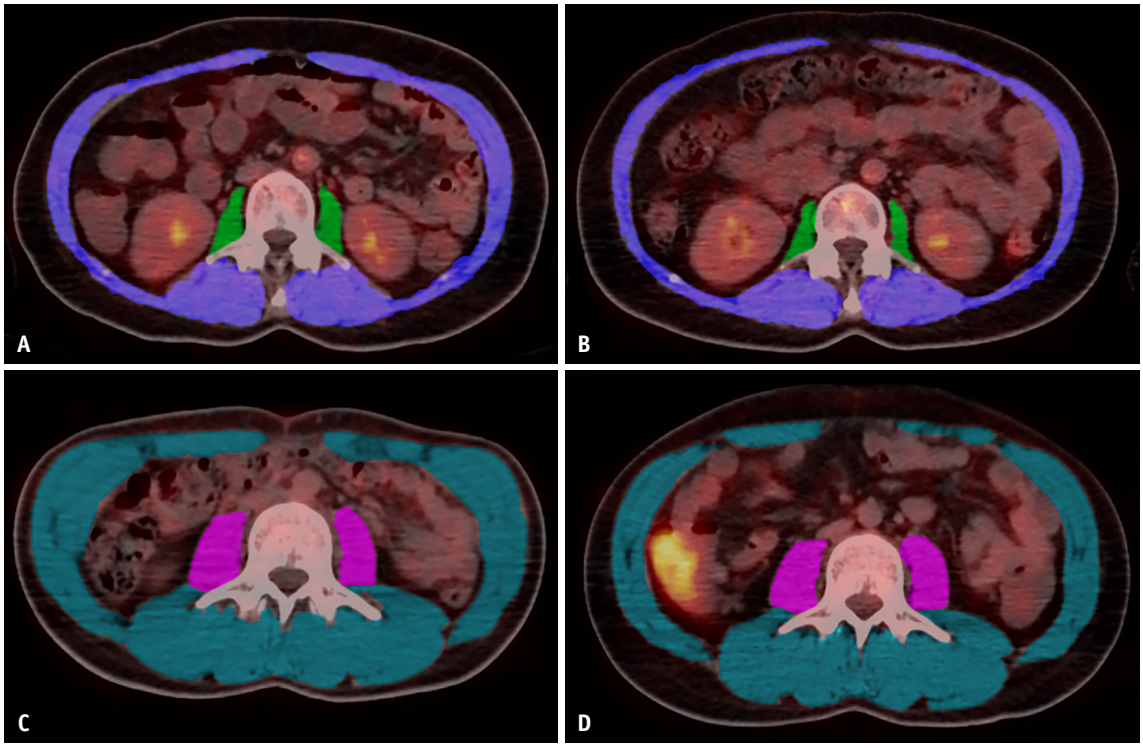

Fig. 3. Example of SMI and SUVmax_M measured on PET/CT fused image at the L3 level. **A, B:** Baseline **(A)** and EoT **(B)** PET/CT fused images in a sarcopenic patient (baseline SMI [purple and green] of 30.04 cm^2/m^2 and SUVmax_M [green] of 0.90; EoT SMI of 27.40 cm^2/m^2 and SUVmax_M of 0.89). **C, D:** Baseline **(C)** and EoT **(D)** PET/CT fused images in a non-sarcopenic patient (baseline SMI [blue and pink] of 51.42 cm^2/m^2 and SUVmax_M [pink] of 1.01; EoT SMI of 49.66 cm^2/m^2 and SUVmax_M of 1.35). SMI = skeletal muscle index, SUVmax_M = maximum standardized uptake value of muscle, EoT = end-of-treatment

Table 2. Clinical characteristics and PET/CT parameters of muscle at the EoT

Characteristics	All patients (n = 103)	Sarcopenia at EoT (n = 38)	Non-sarcopenia at EoT (n = 65)	*P*
Age, yr	54 (21–76)	62 (21–75)	53 (22–76)	0.033
Sex				0.007
Male	50	25	25	
Female	53	13	40	
BMI, kg/m^2	22.1 (15.1–30.1)	21.7 (15.1–27.1)	22.5 (15.6–30.1)	0.027
PET/CT parameters				
SUVmax_M	1.23 (0.74–2.45)	0.99 (0.74–1.43)	1.38 (0.92–2.45)	< 0.001
SUVmean_M	0.86 (0.45–1.31)	0.68 (0.45–0.93)	0.80 (0.56–1.31)	< 0.001

Data are presented as number of patients or median (range).
EoT = end-of-treatment, BMI = body mass index, SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle

Survival Analysis

The median follow-up time was 53 months (range, 17–126 months). During the follow-up period, disease progression was observed in 21 patients, including 14 deaths. The median PFS was 42.8 months in this cohort, and the 1-, 2-, and 5-year PFS rates were 90.3%, 76.7%, and 25.2%, respectively. The median OS was 43.8 months, and the 1-, 2-, and 5-year OS rates were 98.1%, 82.5%, and 26.2%, respectively.

Univariable Cox regression analysis showed that sex (P = 0.018), ΔBMI (P = 0.039), B symptoms (P = 0.025), and sarcopenia at baseline (P = 0.012) and end-of-treatment (P = 0.036) were associated with PFS (Table 4). As sarcopenia at baseline heavily correlated with sarcopenia at end-of-treatment, we entered them into the multivariable Cox regression analysis one at a time. Therefore, two multivariable Cox regression models were established. The model entering sarcopenia at baseline identified sex (P =

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0.010) and B symptoms (P = 0.025) to be independently associated with PFS. In comparison, the model entering sarcopenia at end-of-treatment identified sex (P = 0.010), ΔBMI (P = 0.035), B symptoms (P = 0.011), and sarcopenia at end-of-treatment (P = 0.045) to be independently associated with PFS. Moreover, univariable Cox regression analysis showed that sex (P = 0.018), BMI at end-of-treatment (P = 0.045), serum β^2 microglobulin (P = 0.039), and sarcopenia at baseline (P = 0.016) were associated with OS (Table 5). Furthermore, multivariable Cox regression analysis showed that BMI at end-of-treatment (P = 0.021) and sarcopenia at baseline (P = 0.011) were independently associated with OS.

DISCUSSION

Sarcopenia is common in patients with malignancy and is associated with an increased risk of treatment-related side effects and poorer survival. It is defined as a gradual decrease in both the mass and/or strength of the skeletal muscle. At present, the diagnosis of sarcopenia mainly relies on the measurement of SMA at the L3 level using a single-slice CT image which needs to be subsequently normalized as SMI [18]. The whole-body PET/CT scan is a routine examination for diagnosing, staging, and evaluating treatment response in malignancies, including DLBCL. Hence, sarcopenia can be analyzed using the CT component of PET/CT images, which has been proven safe and accurate [16]. Moreover, our previous studies found that the SUVmax of muscle at L3 was lower in sarcopenia than in non-sarcopenia [12-15]. Thus, we have used ^{18}F-FDG PET/CT to conduct many studies on sarcopenia and glucose

Table 3. Comparison of BMI, SMI, and SUV of muscle between before and after treatment

Characteristics	Baseline	End-of-treatment	P
BMI, kg/m^2	21.5 (11.3–34.1)	22.1 (15.1–30.1)	0.656
SMI, cm^2/m^2	41.3 (24.4–60.2)	39.1 (26.2–59.4)	0.004
Sarcopenia			0.011
Present	30	38	
Absent	73	65	
PET/CT parameters			
SUVmax_M	1.28 (0.68–2.22)	1.23 (0.74–2.45)	0.505
SUVmean_M	0.78 (0.31–1.23)	0.86 (0.45–1.31)	0.287

Data are presented as number of patients or median (range).
BMI = body mass index, SMI = skeletal muscle index, SUV = standardized uptake value, SUVmax_M = maximum SUV of muscle, SUVmean_M = mean SUV of muscle

	ΔSMI	ΔBMI	ΔSUVmax_M	ΔSUVmean_M
ΔSMI	1.00	0.51	0.23	0.10
ΔBMI	0.51	1.00	0.31	0.25
ΔSUVmax_M	0.23	0.31	1.00	0.69
ΔSUVmean_M	0.10	0.25	0.69	1.00

Fig. 5. Correlation analysis of ΔSMI, ΔBMI, ΔSUVmax_M, and ΔSUVmean_M in the enrolled patients. Data in the figure are correlation coefficients. SMI = skeletal muscle index, BMI = body mass index, SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle

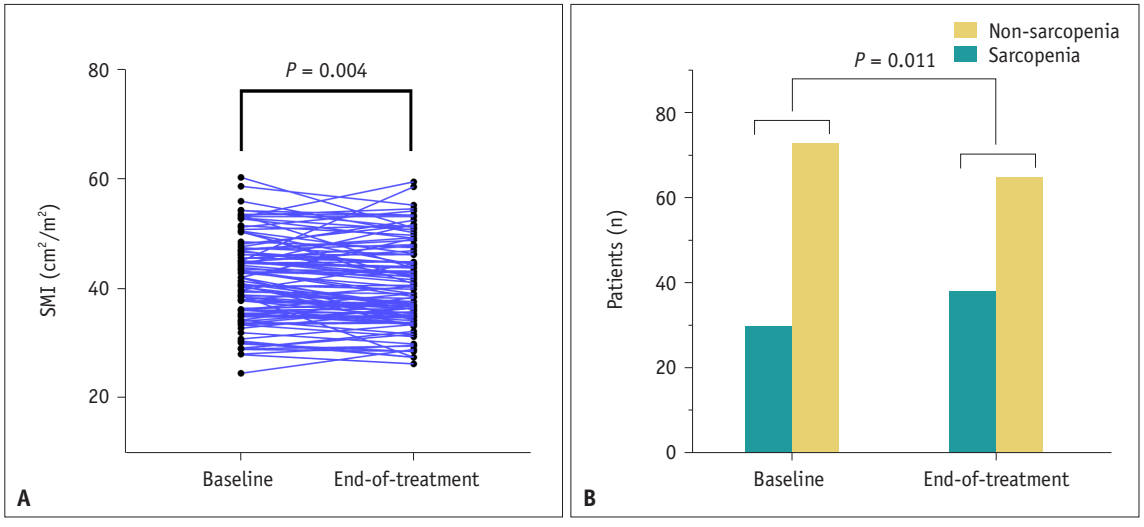

Fig. 4. Changes in SMI **(A)** and sarcopenia **(B)** before and after treatment. SMI = skeletal muscle index

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Table 4. The univariable and multivariable Cox regression analysis of PFS in 103 DLBCL patients

Variables	Univariable Cox regression		
	HR	95% CI	*P*
Age, yrs*	1.022	0.989–1.057	0.198
Sex (male vs. female)†	3.137	1.214–8.106	0.018
BMI at baseline, kg/m²*	1.028	0.914–1.156	0.643
BMI at EoT, kg/m²*	1.110	0.979–1.258	0.103
ΔBMI, kg/m²*	0.771	0.603–0.986	0.039
PS (≥ 2 vs. 0 or 1)†	2.279	0.766–6.779	0.138
B symptoms (present vs. absent)†	2.837	1.143–7.039	0.025
LDH (elevated vs. normal)†	1.633	0.693–3.847	0.262
β² microglobulin (elevated vs. normal)†	1.493	0.578–3.857	0.407
Extranodal sites (≥ 2 vs. 0 and 1)†	0.896	0.348–2.311	0.821
Ann Arbor stage (III–IV vs. I–II)†	1.141	0.473–2.755	0.769
IPI (≥ 3 vs. 0–2)†	1.992	0.845–4.692	0.115
Sarcopenia at baseline (present vs. absent)†	3.018	1.279–7.119	0.012
Sarcopenia at EoT (present vs. absent)†	2.525	1.063–5.998	0.036
ΔSMI, cm²/m²*	0.998	0.891–1.118	0.972
SUVmax_M at baseline, ratio*	0.563	0.151–2.101	0.392
SUVmean_M at baseline, ratio*	0.448	0.041–4.851	0.509
SUVmax_M at EoT, ratio*	0.592	0.041–4.851	0.436
SUVmean_M at EoT, ratio*	0.357	0.022–5.879	0.471
ΔSUVmax_M, ratio*	0.950	0.220–4.107	0.945
ΔSUVmean_M, ratio*	0.965	0.080–11.654	0.977
Variables	Multivariable Cox regression: including sarcopenia at baseline		
	Adjusted HR	95% CI	*P*
Sex (male vs. female)†	3.660	1.368–9.793	0.010
ΔBMI, kg/m²*	0.839	0.661–1.065	0.150
B symptoms (present vs. absent)†	3.015	1.146–7.932	0.025
Sarcopenia at baseline (present vs. absent)†	2.329	0.964–5.629	0.060
Variables	Multivariable Cox regression: including sarcopenia at EoT		
	Adjusted HR	95% CI	*P*
Sex (male vs. female)†	3.778	1.381–10.339	0.010
ΔBMI, kg/m²*	0.788	0.631–0.983	0.035
B symptoms (present vs. absent)†	3.534	1.336–9.348	0.011
Sarcopenia at EoT (present vs. absent)†	2.469	1.022–5.965	0.045

*For continuous variables with reference units, an increase by 0.01 unit was considered when calculating HRs and 95% CIs with the Cox regression analysis, †For categorical variables with categories in parentheses, the former was compared with the latter (the reference) to calculate HRs and 95% CIs with the Cox regression analysis.
PFS = progression-free survival, DLBCL = Diffuse large B-cell lymphoma, HR = hazard ratio, CI = confidence interval, BMI = body mass index, EoT = end-of-treatment, PS = performance status, LDH = lactate dehydrogenase, IPI = international prognostic index, SMI = skeletal muscle index, SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle

metabolism of muscle in patients with malignancies such as T-cell lymphoblastic lymphoma, non-small cell lung cancer, and pancreatic cancer [12-15].

The present study showed that the incidence of sarcopenia was 29.1% at baseline and 36.9% at the end-of-treatment, which is in accordance with prior studies reporting a sarcopenia incidence of 23.9%–55.6% in DLBCL patients [18]. Although there was no significant difference in BMI before and after treatment, SMI was found to significantly decrease at end-of-treatment compared with baseline. Similarly, Xiao et al. [19] concluded that patients with DLBCL experienced further muscle loss during chemotherapy, with SMA decreasing by 2.8% after treatment. Lucijanic et al. [20] observed psoas muscle area loss in 57.7% of DLBCL patients during the immunochemotherapy period and demonstrated that higher body surface area, number of

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Table 5. The univariable and multivariable Cox regression analysis of OS in 103 DLBCL patients

Variables	Univariable Cox regression		
	HR	95% CI	*P*
Age, yrs*	1.038	0.993–1.085	0.101
Sex (male vs. female)†	4.679	1.302–16.822	0.018
BMI at baseline, kg/m²*	1.068	0.927–1.230	0.360
BMI at EoT, kg/m²*	1.172	1.004–1.370	0.045
ΔBMI, kg/m²*	0.766	0.574–1.022	0.070
PS (≥ 2 vs. 0 or 1)†	1.373	0.307–6.142	0.679
B symptoms (present vs. absent)†	1.272	0.355–4.560	0.712
LDH (elevated vs. normal)†	1.511	0.529–4.310	0.441
β² microglobulin (elevated vs. normal)†	3.058	1.060–8.823	0.039
Extranodal sites (≥ 2 vs. 0 and 1)†	0.588	0.164–2.111	0.416
Ann Arbor stage (III–IV vs. I–II)†	2.713	0.757–9.726	0.126
IPI (≥ 3 vs. 0–2)†	2.175	0.762–6.204	0.146
Sarcopenia at baseline (present vs. absent)†	3.697	1.279–10.687	0.016
Sarcopenia at EoT (present vs. absent)†	2.507	0.869–7.236	0.089
ΔSMI, cm²/m²*	0.995	0.866–1.144	0.948
SUVmax_M at baseline, ratio*	0.856	0.186–3.943	0.841
SUVmean_M at baseline, ratio*	1.725	0.102–29.175	0.706
SUVmax_M at EoT, ratio*	0.983	0.216–4.469	0.982
SUVmean_M at EoT, ratio*	1.000	0.037–26.747	1.000
ΔSUVmax_M, ratio*	0.826	0.137–4.988	0.835
ΔSUVmean_M, ratio*	1.818	0.097–34.024	0.689
Variables	Multivariable Cox regression		
	Adjusted HR	95% CI	*P*
Sex (male vs. female)†	3.260	0.888–11.970	0.075
BMI at EoT, kg/m²*	1.240	1.032–1.490	0.021
β² microglobulin (elevated vs. normal)†	1.795	0.568–5.677	0.319
Sarcopenia at baseline (present vs. absent)†	5.051	1.453–17.562	0.011

*For continuous variables with reference units, an increase by 0.01 unit was considered when calculating HRs and 95% CIs with the Cox regression analysis, †For categorical variables with categories in parentheses, the former was compared with the latter (the reference) to calculate HRs and 95% CIs with the Cox regression analysis.
OS = overall survival, DLBCL = Diffuse large B-cell lymphoma, HR = hazard ratio, CI = confidence interval, BMI = body mass index, EoT = end-of-treatment, PS = performance status, LDH = lactate dehydrogenase, IPI = international prognostic index, SMI = skeletal muscle index, SUVmax_M = maximum standardized uptake value of muscle, SUVmean_M = mean standardized uptake value of muscle

cycles with dose reduction, and worse response to therapy were independent contributors to psoas muscle area loss. Bas et al. [21] also found that muscle mass declined after treatment in patients with Hodgkin's lymphoma. We assumed that malnutrition due to the tumor and antitumor therapy exacerbated muscle loss [22]. In addition, substantial limitations in physical muscle activity during the period of treatment also affect muscle mass.

Notably, the present study showed that SMI and glucose metabolism of muscle—as well as their changes—were positively correlated in patients with DLBCL at both baseline and end-of-treatment. Compared with non-sarcopenic patients, the SUVmax and SUVmean of muscle were lower in sarcopenic patients at both baseline and end-of-treatment, indicating that a reduction in glucose metabolism of muscle suggests an increased risk of sarcopenia. Even though the mechanism underlying the correlation between glucose metabolism of muscle and sarcopenia remains unclear, a similar phenomenon was observed in our previous studies [13,15]. Chu et al. [23] and Besutti et al. [24] found that skeletal muscle density evaluated using mean attenuation on CT was lower in sarcopenia than in non-sarcopenia. Thus, we assumed that the accumulation of intramuscular fat and water reduces muscle density and eventually decreases glucose metabolism.

Moreover, several studies have reported that sarcopenia

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is a poor prognostic factor in treatment-naïve patients with DLBCL [18,20,25]. For instance, Lucijanic et al. [20] found that muscle loss was significantly associated with worse clinical outcomes in patients newly diagnosed with DLBCL. Our study showed that sarcopenia at baseline was an independent risk factor for poorer OS, while sarcopenia at end-of-treatment was an independent risk factor for poorer PFS. The actual nutritional status of patients with tumors is influenced by many factors. Considering that sarcopenia before and after treatment has an impact on different survival analyses, it is necessary to evaluate its presence in patients with DLBCL at different stages of clinical management. In addition, the prognostic value of BMI in patients with DLBCL remains controversial. Camus et al. [26] and Lanic et al. [27] showed that a lower BMI was associated with poorer OS and PFS in DLBCL. Conversely, Iltar et al. [28] and Go et al. [29] reported that being underweight was not associated with poor survival in patients with DLBCL. In our series, BMI at both baseline and end-of-treatment had no prognostic impact on PFS, while BMI at end-of-treatment was an independent risk factor for OS. Additionally, our study showed that ΔBMI, a parameter revealing the decrease of body weight due to the progression of tumor cachexia or intolerance to chemotherapy [19], was an independent predictor for PFS. Moreover, this study demonstrated that female patients had a better PFS, probably related to a slower clearance rate and a longer serum elimination half-life of rituximab compared with male patients [30]. The survival advantage for female patients has been found in different kinds of tumors [31]. Our study also showed that the presence of B symptoms was a prognostic predictor for PFS in DLBCL, which was in line with previous studies [32]. Moreover, since the value of IPI in the prognostication of DLBCL patients has been significantly reduced in the era of rituximab [3], it was unable to predict PFS and OS in our study.

There are some limitations in this study. Firstly, the retrospective and single-center design might reduce the validity of our findings when extrapolated to other cohorts. Secondly, due to the retrospective nature of the study, we were unable to assess muscle function—including grip strength and gait speed—which is an important feature of sarcopenia. Additionally, the relationship between the metabolic response at the end-of-treatment PET/CT and either sarcopenia or muscle glucose metabolism was not analyzed due to the small sample of patients with stable and progressive disease. Moreover, we did not evaluate the development of sarcopenia and changes in glucose metabolism after treatment. Thus, prospective studies, including muscle functional measurements and body composition analyses during the entire treatment and follow-up process, are required and are placed on our research agenda. Despite these limitations, our results identified that sarcopenia was associated with glucose metabolism of muscle and that muscle loss worsens during the treatment period in patients with DLBCL.

In conclusion, sarcopenic patients had lower muscle glucometabolism, and the muscular and metabolic changes across treatment were positively correlated. Sarcopenia at both baseline and end-of-treatment was associated with a poorer prognosis of DLBCL.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Lei Jiang, Hui Yuan. Data curation: Xiaoyue Tan, Xiaolin Sun, Yang Chen, Fanghu Wang, Yuxiang Shang, Qing Zhang. Formal analysis: Xiaoyue Tan, Xiaolin Sun, Hui Yuan. Funding acquisition: Lei Jiang. Investigation: Xiaoyue Tan, Xiaolin Sun, Yang Chen, Fanghu Wang, Yuxiang Shang, Qing Zhang. Methodology: Xiaoyue Tan, Xiaolin Sun, Yang Chen, Fanghu Wang, Yuxiang Shang, Qing Zhang. Project administration: Xiaoyue Tan, Xiaolin Sun, Yang Chen, Fanghu Wang, Yuxiang Shang, Qing Zhang. Supervision: Lei Jiang, Hui Yuan. Validation: Lei Jiang, Hui Yuan. Writing—original draft: all authors. Writing—review & editing: all authors.

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