Nucl Med Mol Imaging (2018) 52:216–223
https://doi.org/10.1007/s13139-017-0503-8

ORIGINAL ARTICLE

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Evaluating the Predictive Ability of Initial Staging F-18 FDG PET/CT for the Prognosis of Non-Hodgkin Malignant Lymphoma Patients Who Underwent Stem Cell Transplantation

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Received: 6 September 2017 / Revised: 24 October 2017 / Accepted: 30 October 2017 / Published online: 21 November 2017

Abstract
Objectives This study aimed to determine the value of clinical prognostic factors and semiquantitative metabolic parameters from initial staging fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) in non-Hodgkin lymphoma (NHL) patients treated with stem cell transplantation (SCT).
Methods A total of 39 malignant lymphoma patients who underwent initial staging F-18 FDG PET/CT were enrolled in this study. SUVmax, MTV_wb, and TLG_wb were measured during the initial staging PET/CT. Receiver operating characteristic curve (ROC) analysis was adopted to dichotomize continuous variables. Log-rank test and Cox proportional hazard regression analysis were used to evaluate disease-free survival (DFS) rate.
Results Among the 39 patients with malignant lymphoma, 17 (43.6%) had a relapse. For several clinical factors such as age, ECOG performance score, AMC/ALC score, stages, and revised International Prognostic Index score, differences between the two dichotomized groups were statistically insignificant. In univariate analysis, DFS estimates were 71.0 ± 7.8 months and 18.0 ± 5.9 months in high-SUVmax and low-SUVmax group, respectively ($P < 0.01$). For MTV_wb, DFS estimates were 46.6 ± 12.4 months and 69.1 ± 8.5 months in high-MTV_wb and low-MTV_wb group, respectively ($P = 0.12$). For TLG_wb, DFS estimates were 65.3 ± 7.5 months and 13.7 ± 8.6 months in high-TLG_wb and low-TLG_wb group, respectively ($P = 0.02$). In Cox proportional hazard regression analysis, only MTV_wb showed statistical significance (HR 3.01, 95% CI 1.04–8.74, $P = 0.04$).
Conclusion In NHL patients treated with SCT, the MTV_wb of initial staging F-18 FDG PET/CT was an independent prognostic factor.

Keywords F-18 FDG pet/Ct · Non-Hodgkin lymphoma · Stem cell transplantation · Metabolic parameters · Prognosis

Introduction

Since the establishment of combined rituximab chemotherapy complex, the survival rate and prognosis of malignant non-Hodgkin lymphoma (NHL) patients improved [1, 2]. However, some patients show poor treatment response or recurrence after the initial response. High-dose chemotherapy with hematopoietic stem cell transplantation (SCT) has been used as the standard treatment for recurrent malignant lymphoma, refractory malignant lymphoma, or some types of aggressive NHL [3–8]. Although allogeneic and autologous SCT are a promising treatment modality for relapsed or recurrent malignant lymphoma, these options are costly and have morbidity and mortality cases [9]. Therefore, predicting patient's treatment response can contribute to improved prognosis by enabling early changes to appropriate therapy. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) is a diagnostic

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imaging tool capable of qualitative or semi-quantitative analysis using imaging glucose metabolism in lesions and widely used in the diagnosing, staging, and treatment response evaluation of malignant tumors. Several studies exist on the effects of initial staging F-18 FDG PET/CT on the prognosis of patients with lymphoma [10–14]. In these studies, SUV representing glucose metabolism of malignant lymphoma was statistically and significantly correlated with patients' prognosis. Regarding the study for F-18 FDG PET/CT in predicting the prognosis of patients with malignant lymphoma who underwent SCT, most studies are designed to evaluate the role of initial staging F-18 FDG PET/CT performed after the salvage chemotherapy as prognostic factors for the outcome after SCT [15–23]. To the best of our knowledge, there was no study that investigated the correlation between metabolic parameters of initial staging F-18 FDG PET/CT and prognostic outcomes after a hematopoietic SCT. This study evaluated the prognostic value of initial staging F-18 FDG PET/CT assessed using semiquantitative metabolic parameters (SUVmax, whole body metabolic tumor volume (MTV_wb), and whole body total lesion glycolysis (TLG_wb) in patients with NHL undergoing hematopoietic SCT.

Materials and Methods

Patients

In this retrospective study, 39 malignant NHL patients who underwent autologous or allogenic SCT with frontline or second-line strategy at our institution were evaluated, from January 2007 to August 2014. Patients who underwent initial staging F-18 FDG PET/CT were enrolled, but patients who underwent resection or any kind of anticancer treatment for malignant lymphoma lesion before the initial staging F-18 FDG PET/CT were excluded. This retrospective study was approved by the institutional review board (IRB No. 16–0029). To evaluate the predictive ability of clinical and metabolic parameters, disease-free survival (DFS) was used as endpoint. DFS was defined as the number of months from the date of SCT to the date of recurrence, or the date of last follow-up in the patients without recurrence.

Image Acquisition

All patients fasted for >6 h before undergoing PET/CT, and the blood glucose level was <180 mg/dl (74–143 mg/dl). A whole-body scan from head to thigh was acquired 60 min following intravenous injection of 0.1–0.14 MBq/kg of F-18 FDG. PET/CT examinations were performed using a PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, WI, USA). The CT images were acquired using multidetector CT equipment with the standard protocol that consists of 140 kV, 60–80 mA, a tube rotation time of 0.4 s per rotation, a pitch of 0.984, and a section thickness 3.75 mm. Emission PET data were acquired for 2.5 or 3 min per bed. PET images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm with three iterations, 18 subsets, matrix size of 256 × 256, 50 cm transaxial field-of-view (FOV). PET images were then fused with CT images.

Image Analysis

Two nuclear medicine specialists independently reviewed the images, and discussed for equivocal findings to select true lesions. For semiquantitative analysis, all images were analyzed using PET VCAR on Advantage Workstation 4.6 (GE Medical System, Milwaukee, WI) by a nuclear physician. Physiologic uptake in kidney, urinary bladder, etc. was carefully excluded. SUVmax was measured within a designated region of interest (ROI) and defined as the highest SUV of pixel. MTV was determined by measuring the volume of the lesion above the 2.5 SUV value and the TLG was determined by the MTV × SUVmean [24]. MTV_wb and TLG_wb were calculated as the summation of individual MTV and TLG within the field of image (Fig. 1).

Clinical Prognostic Factors

Clinical staging of malignant lymphoma followed the Ann Arbor staging [25]. Imaging studies including the initial staging CT and F-18 FDG PET/CT and pathologic findings from the bone marrow biopsy of the hip were used to establish the clinical stage. If typical findings on the F-18 FDG PET/CT or positive results on the bone marrow biopsy were observed, patients were regarded as having bone marrow involvement. The revised International Prognostic Index (R-IPI) score was calculated using the patient's age, Lactate dehydrogenase (LDH) level, stage, extra-nodal lesion status, and performance status at the time of diagnosis. The absolute monocyte/lymphocyte count prognostic score (AMC/ALC score) was determined based on the number of neutrophils and lymphocytes in the blood at the time of diagnosis [26].

Recurrence Assessment

The follow-up duration was at least 2 years after hematopoietic SCT (median follow-up duration: 34 months). All patients were regularly followed every 3 or 6 months. During the follow-up period, physical examination, blood chemistries, and contrast-enhanced CT were used for surveillance. The recurrence of NHL was mostly confirmed through histologic examination. If suspected recurrent lesions were observed in the area where assessment for biopsy is difficult, recurrence was determined only based on the finding of F-18 FDG PET/CT or interval image finding.

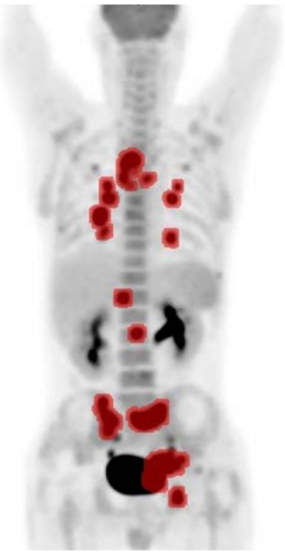

Fig. 1 Representative MIP image for segmentation from a patient with multifocal bone marrow and nodal lymphoma involvement lesions

Statistical Analysis

Medcalc statistical software version 14.12.0 (Medcalc software bvba, Ostend, Belgium: 2014) was used for statistical analysis. For the univariate analysis, the semi-quantitative metabolic parameters such as SUVmax, MTV_wb, and TLG_wb and clinical prognostic factors such as clinical staging, R-IPI, and AMC/ALC score were grouped into dichotomized variables by optimal cut-off value using the receiver operating characteristic (ROC) curve analysis. Kaplan–Meier survival analysis and log-rank test were used to compare the recurrence rates between groups, and *P*-value <0.2 was considered significant. Analysis for multicollinearity between independent variables was performed using the statistical software package SPSS 18.0 (SPSS Inc.,Chicago, IL).

Cox proportional hazard regression analysis was used for multivariate analysis and *P*-value <0.05 was considered statistically significant.

Results

Patients' Characteristics

A total of 39 patients were included in this study and the mean age was 50.3 years, consisting of 20 men and 19 women (Table 1). The mean follow-up duration was 39.5 ± 10.4 months, and 17 patients (43.6%) had relapsed. Among the NHL patients, diffuse large B-cell lymphoma (DLBCL) was commonly found in 23 patients and followed by peripheral T-cell lymphoma (*n* = 5), extranodal NK −/T-cell lymphoma (*n* = 3), follicular lymphoma (n = 3), anaplastic large cell lymphoma (*n* = 2), marginal zone B-cell lymphoma (*n* = 1), mantle cell lymphoma (n = 1), and angioimmunoblastic T-cell lymphoma (n = 1) (Table 2). In cases of DLBCL, the first-line of chemotherapy consists of cyclophosphamide, doxorubicin (Adriamycin), vincristine, and prednisone (CHOP) with or without rituximab, an anti-CD-20 antibody (RCHOP). The second-lines are dexamethasone/cisplatin/cytararbine (DHAP), etoposide/methylprednisolone/cytarabine/cisplatin (ESHAP), gemcitabine/dexamethasone/cisplatin (GDP), gemcitabine/oxlaliplatin (GemOx), and ifosfamide/carboplatin/etoposide (ICE). For the other types of NHL, chemotherapeutic regimen prior to SCT followed the National Comprehensive Cancer Network (NCCN) guideline for treatment.

Table 1 Patient characteristics

Characteristic (*n* = 39)	No. (%) of patients
Age	
Median, y	50.3 ± 5.5
Sex	
Male	20 (51%)
Female	19 (49%)
Transplantation type	
Allogenic	2 (5%)
Autologous	37 (95%)
Therapy type	
Frontline	30 (77%)
Salvage (second-line)	9 (23%)
Performance status	
ECOG 0–1	37 (95%)
ECOG >1	2 (5%)
Ann Arbor stage	
I–II	8 (21%)
III–IV	31 (79%)
R-IPI score	
Good, very good	19 (49%)
Poor	20 (51%)
Pretreatment SUVmax	
Low (≦8.2)	8 (21%)
High (>8.2)	31 (79%)
Pretreatment MTV	
Low (≦673)	25 (64%)
High (>673)	14 (36%)
Pretreatment TLG	
Low (≦81)	3 (8%)
High (>81)	36 (92%)

R-IPI, revised international prognostic index; SUV max, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis

Table 2 Pathologic classification

Classification (n = 39)	No. (%) of patients
Diffuse large B-cell lymphoma	23 (59.0%)
Peripheral T-cell lymphoma	5 (12.8%)
Extranodal NK−/T-cell lymphoma	3 (7.7%)
Follicular lymphoma	3 (7.7%)
Anaplastic large-cell lymphoma	2 (5.1%)
Marginal zone B-cell lymphoma	1 (2.6%)
Mantle cell lymphoma	1 (2.6%)
Angioimmunoblastic T-cell lymphoma	1 (2.6%)

Prognostic Evaluation of Clinical Parameters

The age at diagnosis was divided into two groups: elderly group (≧60 years) and young group (<60 years). DFS was 48.0 ± 13.5 months (95% CI, 21.5–74.5) in the elderly group and 62.6 ± 8.1 months (95% CI, 46.7–78.6) in the young group, and no statistically significant difference was observed between the two groups (P = 0.67). The ECOG performance score was divided into two groups: high group (≧1) and low group (=0), with DFS of 55.5 ± 11.8 months (95% CI, 32.3–78.7) in high group and 61.0 ± 8.7 months (95% CI, 44.0–78.0) in low group, and no statistically significant difference was observed between the two groups (P = 0.99). The AMC/ALC score was divided into two groups: high-risk group (AMC ≧0.63 × 109/L and ALC ≦1.0 × 109/L) and low-risk group, with DFS of 62.3 ± 94 months (95% CI, 43.9–80.6) and 48.7 ± 9.2 months (95% CI, 30.7–66.7) in high- and low-risk groups, respectively, and no statistically significant difference was observed between the two groups (P = 0.99). The stage was divided into two groups: high (III–IV) and low (I–II), with DFS of 63.2 ± 8.0 months (95% CI,47.4–79.0) and 53.9 ± 16.3 months (95% CI, 21.9–85.9) in high- and low-stage groups, respectively, and no statistically significant difference was observed between the two groups (P = 0.53). The revised IPI score was divided into two groups: high- (poor) and low-risk groups (very good and good), with DFS of 66.9 ± 10.2 months (95% CI, 46.8–86.9) and 53.2 ± 9.7 months (95% CI, 34.2–72.2) in high- and low-risk groups, respectively, and no statistically significant difference was observed between the two groups (P = 0.44) (Fig. 2).

Prognostic Evaluation of Metabolic Parameters on F-18 FDG PET/CT

The optimal cutoff of SUVmax, MTV_wb, and TLG_wb obtained using the ROC curve analysis was 8.2, 673 cm^3, and 81, respectively (Table 3). Using these cutoff values, PET/CT parameters were dichotomized. DFS was 71.0 ± 7.8 months (95% CI, 55.7–86.4) in patients with high SUVmax (>8.2) and 18.0 ± 5.9 months (95% CI, 6.5–29.5) in patients with low SUVmax, and a statistically significant difference was observed between the two groups (P < 0.01). The optimal cutoff of MTV_wb obtained using the ROC curve analysis was 673 cm^3. The MTV_wb at initial staging FDG-PET/CT was divided into two groups: high (>673 cm^3) and low MTV_wb groups. DFS was 46.6 ± 12.4 months (95% CI, 22.3–71.0) in patients with high MTV_wb (>673 cm^3) and 69.1 ± 8.5 months (95% CI, 52.4–85.8) in patients with low MTV_wb. A statistically significant difference was observed between the two groups (P = 0.12). Regarding TLG_wb, DFS was 65.3 ± 7.5 months (95% CI, 50.7–80.0) in patients with high TLG_wb (>81) and 13.7 ± 8.6 months (95% CI, 0–30.5) in patients with low TLG_wb group, and a statistically significant difference was observed between the two groups (P = 0.02) (Fig. 3).

Cox proportional hazards regression analysis was performed for multivariate analysis using the SUVmax, MTV_wb, and TLG of initial staging F-18 FDG PET/CT, which showed significant differences between the groups in log-rank test. The analysis showed that SUVmax (HR, 0.38; 95% CI, 0.08–1.94 P = 0.25), MTV_wb (HR, 3.01; 95% CI, 1.04–8.74; P = 0.04), TLG (HR, 0.32; 95% CI, 0.09–1.05; P = 0.32). MTV_wb was statistically significant different in Cox proportional hazards regression analysis (Table 4).

Discussion

Hematopoietic SCT is a promising therapeutic tool for recurrent or relapsed malignant lymphoma or some types of aggressive NHL [3, 4, 6, 7]. Almost all studies for the prognostic role of F-18 FDG PET/CT in SCT were approximately recurrent or relapsed malignant lymphoma, and these studies used the qualitative analysis or metabolic parameters using the semi-quantitative analysis on the pre-SCT and post-SCT F-18 FDG PET/CT [18–22]. In their studies, researchers concluded that FDG uptake of lesions were significantly correlated with the clinical outcomes of patients with malignant lymphoma who underwent SCT. This study aimed to evaluate the prognostic role of metabolic parameters for the initial staging F-18 FDG PET/CT in NHL patients who underwent SCT as the frontline or second-line strategy.

This study showed that only MTV was a statistically significant prognostic factor among metabolic parameters (SUVmax_rep, MTV, and TLG) of F-18 FDG PET/CT. This result is different from other studies in that SUVmax on initial staging F-18 FDG PET/CT was a significant prognostic factor [27–29]. However, the difference of enrolled patients' characteristics and treatment modality was incomparable. These patients were clinically high-risk groups or recurrent or relapsed patients with candidates for SCT as the frontline or second-line strategy.

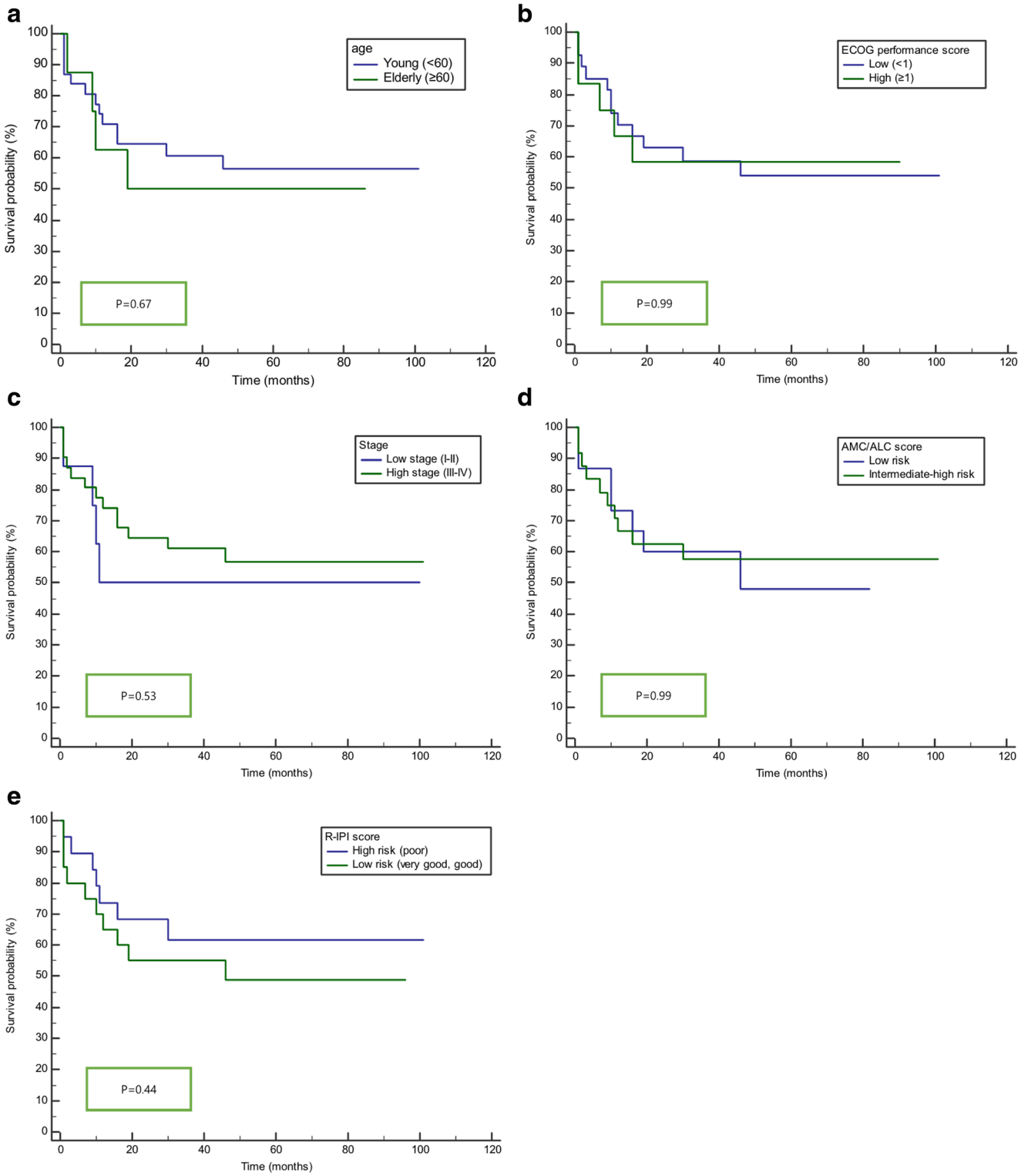

Fig. 2 Kaplan–Meier survival curves for disease-free survival related to clinical prognostic factors in patients with SCT. (a) Age; (b) ECOG performance score; (c) stage; (d) AMC/ALC score; (e) R-IPI score

Regarding the correlation between lesional SUVmax and clinical outcome of patients with aggressive malignant lymphoma, a few studies showed different results. Hwang et al. revealed that no significant correlation was observed between lesional SUVmax and patients' survival outcome in patients with aggressive NHL patients among their study population [30]. Yi et al.'s study also showed that although patients with higher SUVmax showed inferior overall survival than those

Table 3 ROC analysis for metabolic parameters to select cutoff value

Parameters	Optimal cutoff value	AUC (95% CI)	*P* value
SUVmax	8.2	0.697 (0.529~0.833)	0.0289
MTV (cm^3)	673	0.553 (0.386~0.712)	0.6018
TLG	81	0.521 (0.356–0.684)	0.8283

Table 4 Cox proportional hazard regression analysis of recurrence in lymphoma patients with stem cell transplantation

	HR	95% CI	P
Pretreatment SUV	0.38	0.08–1.94	0.25
Pretreatment MTV_wb	3.01	1.04–8.74	0.04
Pretreatment TLG	0.32	0.09–1.05	0.32

with lower SUVmax, the difference was not statistically significant [31]. Contrary to Hwang et al. and Yi et al.'s results, other researchers showed that lesional SUVmax was a significant prognostic factor in patients with T-cell lymphoma, a subtype of aggressive NHL [32, 33]. Unlike those studies, this study enrolled patients with various subtypes of NHL and different treatment modality. This difference might be the reason why the prognostic role of lesional SUVmax is different depending on each study. In addition, measurement of SUV from a single ROI, which does not represent the overall tumor profile, can be the other reason for the different results especially in aggressive NHL.

Similar explanations might be applicable to the IPI result in this study, which was not correlated with the patients' outcome. IPI has been an important tool in predicting outcomes of patients with aggressive NHL based on the number of negative prognostic factors present at the time of diagnosis [34]. However, an effective new treatment modality can affect the clinical significance of these prognostic markers. In fact, according to analysis of

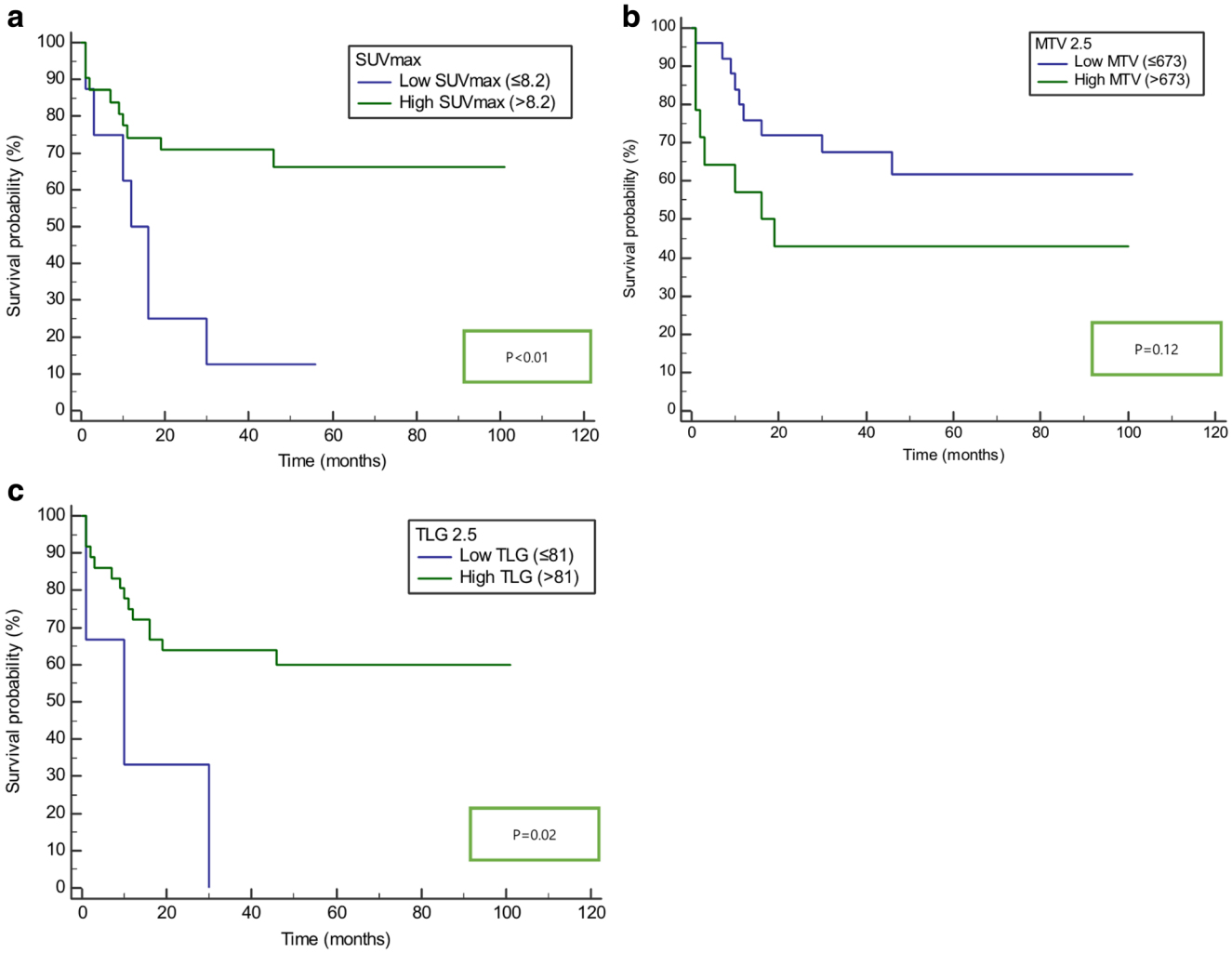

Fig. 3 Kaplan–Meier survival curves for disease-free survival related to metabolic parameters of F-18 FDG PET/CT in patients with SCT. (a) SUVmax of initial staging FDG PET/CT; (b) MTV_wb of initial staging FDG PET/CT; (c) TLG_wb of initial staging FDG PET/CT

PARMA trial, IPI was highly correlated with OS in the conventional chemotherapy arm, but was not a significant prognostic factor in the transplant arm [35].

TLG_wb as a prognostic factor was insignificantly correlated with patients' outcome and is calculated as the summation of each lesional MTV multiplied by its SUVmean. Although this parameter reflects metabolically active tumor volume, glucose metabolism of each tumor lesion can also affect the TLG value. This result might be due to the relationship between TLG and SUV of the tumor.

In this study, only MTV was a prognostic factor. Many studies revealed that tumor bulk of malignant lymphoma is one of the prognostic factors [36–39]. Therefore, we believe that measured MTV based on the cutoff value of SUV 2.5 can reflect the tumor size as a prognostic factor on the initial staging F-18 FDG PET/CT for NHL patients who are scheduled for hematopoietic SCT. Although the MTV was not measured by various cutoff values, the tumor from physiologic activity could be delineated at this cutoff value. Application of measured MTV using various cutoff values for larger patient cohorts might be warranted. Deauville criteria can be used for the evaluation of therapeutic response and prognosis. Although Deauville criteria might be reproducible, this criteria does not represent the volumetric aspect of tumor.

However, this study has several limitations. This is not a prospective study; thus, it is subject to the inherent limitations of retrospective data. In addition, the subtypes of NHL and treatment strategy, i.e., heterogeneous frontline and second-line strategies, in enrolled patients were heterogeneous. This situation might affect the results of the outcome. Therefore, further controlled prospective studies with larger population are necessary.

Conclusion

The results of this study show that MTV_wb of initial staging F-18 FDG PET/CT has a prognostic role in the aggressive and high-risk NHL patients who are scheduled for SCT as the frontline or second-line strategy. For SCT as the frontline or second-line strategy, patients with high MTV_wb might be classified as a group with poor outcomes. Therefore, appropriate therapeutic plans are necessary.

Acknowledgements The authors thank D Kang, staff of our department for her help during this study.

Compliance with Ethical Standards

Conflict of Interest Yun Soo Park, Seok Mo Lee, Ji Sun Park, Sang Kyun Bae, Hye-Kyung Shim, Won-Sik Lee, Sang-Min Lee declare that they have no conflict of interest.

Ethical Statement The study was approved by the Institutional Review Board of Inje University Busan Paik Hospital (IRB No. 16–0029) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent The institutional review board waived the need to obtain informed consent for this retrospective study.

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