^{18}F-FDG PET/CT parameters as therapy response predictors in patients with diffuse large B-cell lymphoma: A single centre experience

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Abstract

Objective: The aim of this study is to determine the importance of different fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET/CT) semi-quantitative and quantitative parameters, as well as various clinical and demographic parameters, in predicting disease outcomes and response to therapy in patients with diffuse large B-cell lymphoma (DLBCL). **Subjects and Methods:** The study included 64 patients diagnosed with DLBCL who underwent ^{18}F-FDG PET/CT imaging between January 2020 and April 2023. Each patient underwent both an initial ^{18}F-FDG PET/CT and an interim ^{18}F-FDG PET/CT after 2 or 4 cycles of chemotherapy. The Deauville score (DS) was calculated for each patient. Progression-free survival (PFS) was defined as the time from the date of diagnosis to the first appearance of metabolic or morphological progression of pre-existing lesions and/or the appearance of new lesions detected on interim ^{18}F-FDG PET/CT or follow-up radiological imaging, as well as in cases of death due to the underlying disease or until the end of the clinical follow-up period. **Results:** Among the clinical-demographic parameters analyzed, the only significant predictive factor was the international prognostic index (IPI) score, categorized by group. Of the ^{18}F-FDG PET/CT parameters examined, DS showed strong statistical significance in both univariate and multivariate analyses. While maximum standardized uptake value (SUVmax) and peak SUV (SUVpeak) were statistically significant in the univariate analysis. Progression-free survival was longer in patients with an IPI ≤2 and DS ≤3, compared to those with higher IPI and DS. **Conclusions:** The results of this study showed that the early metabolic response to therapy assessed on the basis of interim ^{18}F-FDG PET/CT is a significant independent predictive factor for disease outcome in patients with DLBCL.

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Introduction

Diffuse large B-cell lymphoma (DLBCL), the most prevalent subtype of non-Hodgkin lymphoma (NHL) accounts for 31% of NHL cases in Western countries, and 37% of all global B-cell tumors [1]. Since 2011, the annual mortality rate for DLBCL has risen by more than 3.5% each year, making it the most prevalent aggressive lymphoma in adults [2, 3].

At the beginning of DLBCL, the International Prognostic Index (IPI) was important for predicting outcomes and deciding on treatments, as it was created to assess risk in aggressive lymphomas before the use of rituximab [4]. The IPI takes into account five clinical criteria: age of the patient, lymphoma stage, Eastern Cooperative Oncology Group (ECOG) score, LDH values, and number of extranodal lesions [4].

Over time, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) in combination with computed tomography (CT) has become an essential method for assessing lymphoma at the time of diagnosis and is now regarded as the standard approach [5]. Because of its high sensitivity in identifying both nodal and extranodal manifestations of lymphoma, ^{18}F-FDG PET/CT is highly recommended for staging patients with DLBCL [6]. Using ^{18}F-FDG PET/CT, it is possible to determine the initial stage of the disease, as well as predict the effectiveness of therapy on control ^{18}F-FDG PET/CT imaging after two or four cycles of chemotherapy [7].

According to the Lugano classification, the Deauville five-point scale (DS) is the recommended method for assessing treatment response using ^{18}F-FDG PET/CT [8]. In 2009, DS was introduced to meet the growing need for simple and reproducible ^{18}F-FDG PET/CT

interpretation in the setting of early response assessment [9]. By visually comparing the ^{18}F-FDG uptake in lesions to that in the reference regions, such as the mediastinal blood pool and liver, the scale categorizes residual tissue from 1 to 5 [5].

One of the important features of ^{18}F-FDG PET/CT is the determination of semi-quantitative and quantitative parameters: maximum and peak standardized uptake value (SUVmax and SUVpeak); total lesion glycolysis (TLG); metabolic tumor volume (MTV). High SUV values are generally associated with more aggressive types of lymphoma [10].

The aim of this study is to determine the importance of different ^{18}F-FDG PET/CT semi-quantitative and quantitative parameters, as well as various clinical and demographic parameters, in predicting disease outcomes and response to therapy in patients with DLBCL.

Subjects and Methods

Patients

The study included patients diagnosed with DLBCL who underwent ^{18}F-FDG PET/CT imaging between January 2020 and April 2023. Inclusion criteria were: patients who had pathohistologically confirmed DLBCL; without any therapy before initial ^{18}F-FDG PET/CT imaging; underwent initial ^{18}F-FDG PET/CT scan and control one after 2 or 4 cycles of chemotherapy; 18 years of age or older; without another malignant disease; with complete clinical and biochemical records. The criteria for exclusion from the study were patients who received chemotherapy, radiotherapy, or surgical resection before the initial ^{18}F-FDG PET/CT scan; patients in whom no interim ^{18}F-FDG PET/CT imaging was performed; patients who were lost to follow-up. Finally, a total of 64 patients were enrolled in this study. The mean follow-up period was 15.7 months. Clinical and demographic data (age, sex, Ann Arbor staging, IPI score, LDH level, and extranodal involvement) were obtained from the medical records.

This study was conducted in accordance with the 1964 Helsinki declaration for ethical standards. The approval of the ethics committee was obtained by the ethics committee of the University Clinical Center of Serbia. Written informed consent was obtained from each patient included in the study.

^{18}F-FDG PET/CT imaging procedure and data acquisition

All patients underwent ^{18}F-FDG PET/CT examinations on a 64-slice Biograph True64 PET/CT hybrid scanner (Siemens Medical Solutions USA Inc, Malvern, PA, USA). The patients fasted for a minimum of 6 hours before the intravenous application of FDG (5.5MBq/kg of body weight). Before applying ^{18}F-FDG, glycemia was measured in each patient. If the glycemia was above 11mmol/L, the scan was postponed until regulation. This was followed by a rest period of at least 60 minutes from the application of the radiopharmaceutical until the beginning of the acquisition. The patients were first subjected to a low-dose multidetector CT imaging, which was used for attenuation correction and topographical localization. This examination was performed without the application of intravenous contrast agent, with the following CT parameters: voltage 120kV, current strength 45mAs, slice thickness 5mm, pitch 1.5, and rotation time of 0.5s. The PET acquisition followed immediately after that. The acquisition of 3D PET was carried out in the standard "whole-body" modality, from the base of the skull to the proximal third of the femur, pulses were collected from 6-7 bed positions (depending on the height of the patient) for three minutes each.

Qualitative and quantitative ^{18}F-FDG PET/CT analysis

After the low-dose multidetector CT and PET acquisition, the data were reconstructed using the standard statistical reconstruction method (ordered subsets expectation maximization-OSEM), and the obtained data were analyzed on a SYNGO workstation (Syngo 2008B, Siemens, Medical Systems, Erlangen, Germany). When interpreting the findings, individual PET and CT images were analyzed, and then fused PET/CT images were created, along with a rotating view in 3D mode (maximum intensity projection). The images were first analyzed qualitatively, in the form of visual interpretations, and then the following ^{18}F-FDG PET/CT semi-quantitative and quantitative parameters of the most metabolically active lesion were assessed: SUVmax, SUVpeak, MTV, and TLG.

Interim treatment response evaluation

In all patients included in the study, an interim ^{18}F-FDG PET/CT examination was performed under the same conditions as the initial ^{18}F-FDG PET/CT scan. The interim ^{18}F-FDG PET/CT scan was used to assess the morphological and metabolic response to therapy. Deauville five-point scale was calculated for each patient. The DS comprises 5 categories, which are defined as: score 1-no uptake above background; score 2-residual uptake not exceeding mediastinal uptake; score 3-residual uptake above mediastinal but not exceeding liver uptake; score 4-residual uptake above liver uptake; and score 5-residual uptake markedly above liver uptake or new lesions.

Follow-up assessment

In all patients included in the study, follow-up was conducted through clinical reports. Progression-free survival (PFS) was defined as the time from the date of diagnosis (data obtained from medical records) to the date of the first appearance of metabolic or morphological progression of initial lesions and/or the appearance of new lesions detected on interim ^{18}F-FDG PET/CT or follow-up radiological imaging, or death due to the underlying disease, or until the end of the clinical follow-up period. The maximum follow-up period was 18 months.

Statistical analysis

The methods of descriptive and analytical statistics were used in the statistical analysis. A database of patients included in the study was created in the Excel program. Regarding clinical-demographic parameters, all patients were ca-

tegorized into 2 groups: sex (male/female), age (≤60 and >60), Ann Arbor stage (≤2 and >2), IPI score (≤2 and >2), and LDH (normal/abnormal). For each semi-quantitative and quantitative ^{18}F-FDG PET/CT parameter, the median was calculated, based on which value the patients were divided into two groups: SUVmax (≤13.4 and >13.4), SUVpeak (≤10.2 and >10.2), MTV (≤9.8 and >9.8), and TLG (≤43.2 and >43.2) on initial ^{18}F-FDG PET/CT, as well as DS on interim ^{18}F-FDG PET/CT (≤3 and >3).

Examination of the association between the clinical-demographic parameters, semi-quantitative and quantitative ^{18}F-FDG PET/CT parameters with PFS was performed using Cox regression univariate and multivariate analysis. In determining the difference in PFS between different groups of patients, survival curves were constructed using the Kaplan-Meier method.

All statistical analyses were conducted using the EZR software. All values of P<0.05 were considered statistically significant.

Results

Patient characteristics

The clinical and demographic characteristics of 64 patients included in the study are presented in Table 1. The mean age of the patients was 53.8 (range, 20-84).

Initial ^{18}F-FDG PET/CT Imaging

The initial ^{18}F-FDG PET/CT scan revealed pathological accumulation of 18F-FDG in all patients (Figure 1). The most common localizations of intense pathological accumulation of ^{18}F-FDG were the supradiaphragmatic and infradiaphragmatic lymph nodes, followed by the spleen, bones and tonsils, muscles, lungs, and prostate. The site of the most metabolically active lesion was determined based on the SUVmax value (Table 2).

In subsequent analyses, additional semi-quantitative and quantitative parameters (SUVpeak, MTV, TLG) of the most active lesions were assessed. Based on the median values of these parameters, patients were categorized into two groups: those with values equal to or below the median, and those with values above the median for each respective parameter (Table 3).

Interim ^{18}F-FDG PET/CT imaging

All patients included in the study underwent an interim ^{18}F-FDG PET/CT scan after 2 or 4 cycles of chemotherapy (Figure 2). In each patient, the DS value was determined, after which the patients were categorized into two groups based on the value (DS ≤3 and >3). A total of 31 patients had DS ≤3 (DS 1, 2, or 3), while 33 patients had DS >3 (DS 4 or 5) (Table 3).

Univariate and multivariate analysis

Cox regression analysis was used to examine the relationship between clinical-demographic parameters (sex, age, Ann Arbor stage, IPI score, localization, extranodal involvement and LDH) and ^{18}F-FDG PET/CT semi-quantitative and

Table 1. *Demographic and clinical characteristics of the 64 patients with DLBCL.*

Parameter		Number of patients	Percentage (%)
Sex	Female	31	48.4
	Male	33	51.6
Age	(x̄±SD) 53.8±18.1		
	≤60	32	50
	>60	32	50
Ann Arbor	≤2	27	42.2
	>2	37	57.8
IPI	≤2	28	43.8
	>2	36	56.2
Extranodal involvement	Yes	46	71.9
	No	18	28.1
LDH	Normal	24	37.5
	Abnormal	40	62.5

DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, LDH: lactate dehydrogenase

Table 2. *Localization of the most metabolically active lesion based on the SUVmax value in 64 patients with DLBCL.*

The location of the most metabolically intensive lesion	Number of patients	Percentage (%)
Lymph nodes	**46**	**71.9**
Head and neck	6	9.4
Mediastinum	20	31.3
Axial	2	3.1
Abdomina/inguinal	18	28.1
Extranodal	**18**	**28.1**
Spleen	5	7.8
Bone	4	6.2
Tonsils	3	4.7
Muscle	3	4.7
Lungs	2	3.1
Prostate	1	1.6

DLBCL: Diffuse large B-cell lymphoma

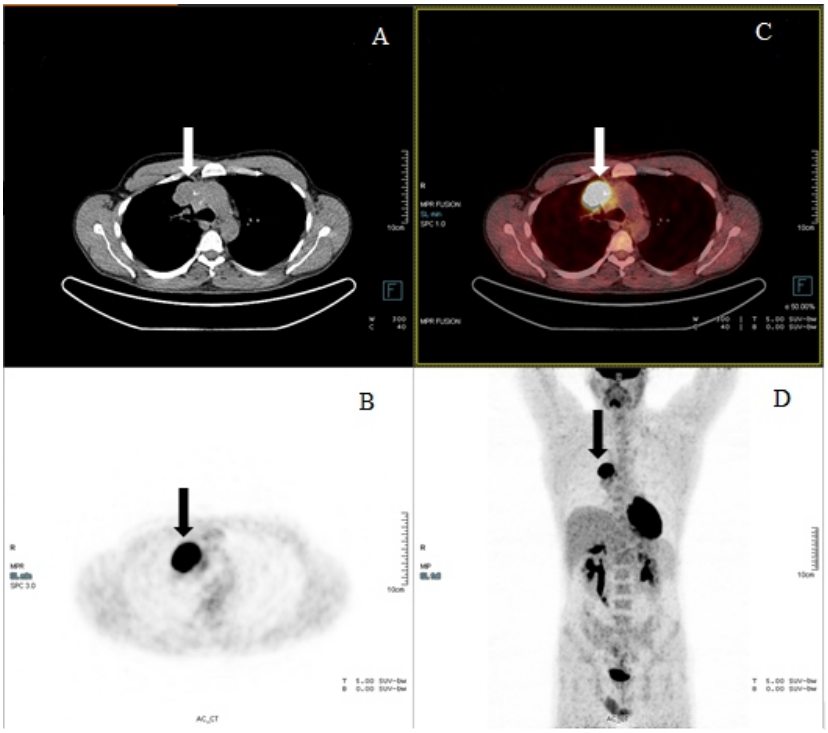

Figure 1. Initial ^{18}F-FDG PET/CT scan in a patient with DLBCL; axial section on non-contrast, low-dose CT (A); PET (B); fusion PET/CT (C) and maximum intensity projection (MIP) (D); in which arrows point to a change in the mediastinum with intensively increased ^{18}F-FDG accumulation, representing active disease.

Table 3. *Categorization of 64 DLBCL patients based on median values of semi-quantitative and quantitative parameters at initial and interim ^{18}F-FDG PET/CT examination.*

^{18}F-FDG PET/CT parameter		Number of patients	Percentage (%)
SUVmax	Med (min-max) 13.4 (4-46.7)		
	≤13.4	33	51.6
	>13.4	31	48.4
SUVpeak	Med (min-max) 10.2 (2.6-39)		
	≤10.2	32	50
	>10.2	32	50
MTV	Med (min-max) 9.8 (2.1-1168.7)		
	≤9.8	32	50
	>9.8	32	50
TLG	Med (min-max) 43.2 (6.1-1560.2)		
	≤43.2	32	50
	>43.2	32	50
DS	≤3	31	48.4
	>3	33	51.6

DLBCL: Diffuse large B-cell lymphoma, ^{18}F-FDG: fluorine-18-fluorodeoxyglucose, PET: Positron Emission Tomography, SUV: Standardized Uptake Value, MTV: Metabolic Tumor Volume, TLG: Total Lesion Glycolysis, DS: Deauville score

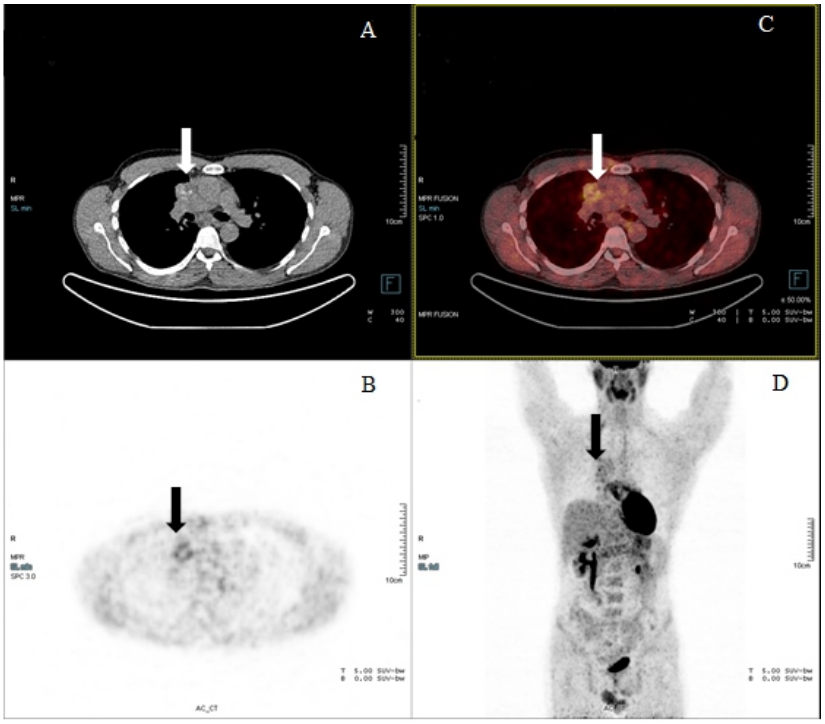

Figure 2. Interim ^{18}F-FDG PET/CT scan in a patient with DLBCL, axial section on non-contrast, low-dose CT (A); PET (B); fusion PET/CT (C) and MIP (D); In which arrows point to a change in the mediastinum with moderately increased ^{18}F-FDG accumulation, with metabolic and morphological regression compared to the initial ^{18}F-FDG PET/CT; DS 3 (shown in Figure 1).

quantitative parameters (SUVmax, SUVpeak, MTV, and TLG of the most active lesions and DS) with PFS in DLBCL patients.

In the univariate analysis, the association between clinical-demographic parameters and PFS in patients with DLBCL was assessed. The effects of the individual IPI score and the IPI score grouped into two categories were analyzed (one group includes patients with an IPI ≤2, and the other consisted of patients with an IPI >2). The results showed that the grouped IPI score was significantly associated with disease progression. Patients with an IPI score of 1 or 2 had a longer PFS compared to those with an IPI score of 3, 4, or 5 (P= 0.003). In contrast, the individual IPI score, as well as other clinical and demographic parameters, did not show a statistically significant effect on PFS (P>0.05) (Table 4). Multivariate analysis also revealed no significant association between the clinical and demographic parameters and disease progression (P>0.05) (Table 5).

Univariate analysis was also used to examine the association between ^{18}F-FDG PET/CT parameters and disease progression in patients with DLBCL. The results showed that the SUVmax and SUVpeak parameters were significant predictors of disease progression (P=0.035 and P=0.043), as well as DS, which demonstrated a strong statistical association with disease progression (P<0.001). However, in the multivariate analysis, only DS remained strong statistically significant (P< 0.001), while SUVmax and SUVpeak lost their significance due to the dominance of DS. The MTV and TLG parameters were not statistically significant in either univariate or multivariate analysis. The results of univariate and multivariate analyses of ^{18}F-FDG PET/CT parameters in 64 patients with DLBCL can be found in Tables 6 and 7.

Analysis of differences in PFS

In the subsequent analysis, differences in PFS between groups of patients divided into groups based on IPI score and DS on interim ^{18}F-FDG PET/CT imaging were evaluated using Kaplan-Meier survival analysis and log-rank test. Disease progression was observed in 29 (45.3%) patients. The mean time to disease progression was 12.9 months. The mean time PFS in patients who had an IPI ≤2 was 16.7, and in patients who had an IPI >2 was 14.9 months. Progression-free survival was significantly longer in patients who had an IPI ≤2 compared to those who had an IPI >2 (Kaplan-Meier, log-rank test, P=0.003) (Figure 3). The mean time PFS in patients who had DS ≤3 was 17.8, while the mean survival time in patients with DS >3 was 13.6 months. PFS was significantly longer in patients with DS ≤3 (Kaplan-Meier, log-rank test, P< 0.001) (Figure 4).

Discussion

In this study, various clinical, demographic parameters, and ^{18}F-FDG PET/CT parameters, were analyzed to assess their influence on the therapy response and prediction on PFS in patients with DLBCL. The only significant factor among the clinical-demographic parameters was the IPI score, categorized by group. Of the ^{18}F-FDG PET/CT parameters, DS demonstrated strong statistical significance in both univariate and multivariate analyses while SUVmax and SUVpeak were found to be statistically significant only in univariate analysis. Progression-free survival was longer in patients with IPI≤2

Table 4. *Univariate analysis of demographic and clinical parameters of 64 patients with DLBCL.*

Parameter	P	HR	95.0% CI for Exp(B)	
			Lower	Upper
Sex	0.267	1.514	0.728	3.147
Age (by groups)	0.265	1.526	0.729	3.196
Age	0.264	1.525	0.728	3.195
Ann Arbor	0.150	1.325	0.903	1.944
Ann Arbor (by groups)	0.339	1.433	0.680	3.061
IPI	0.082	1.321	0.965	1.808
IPI (by groups)	0.003*	2.477	1.094	5.608
Localization	0.769	0.964	0.751	1.236
Extranodal involvement	0.767	0.884	0.392	1.996
LDH	0.155	1.808	0.799	4.090

DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, LDH: lactate dehydrogenase

Table 5. *Multivariate analysis of demographic and clinical parameters of 64 patients with DLBCL.*

Parameter	P	HR	95.0% CI for Exp(B)	
			Lower	Upper
Sex	0.488	1.310	0.610	2.813
Age	0.541	0.991	0.962	1.021
Ann Arbor	0.412	1.227	0.753	1.998
IPI	0.308	1.276	0.799	2.038
Extranodal involvement	0.637	1.264	0.477	3.350
LDH	0.178	1.778	0.770	4.105

DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, LDH: lactate dehydrogenase

Table 6. *Univariate analysis of ^{18}F-FDG PET/CT parameters of 64 patients with DLBCL.*

Parameter	P	HR	95.0% CI for Exp(B)	
			Lower	Upper
SUVmax	0.035*	1.029	1.002	1.056
SUVpeak	0.043*	1.033	1.001	1.066
MTV	0.647	1.000	0.998	1.001
TLG	0.271	0.999	0.997	1.001
DS	<0.001*	3.982	2.385	6.648

DLBCL: Diffuse large B-cell lymphoma, ^{18}F-FDG: fluorine-18-fluorodeoxyglucose, PET: Positron Emission Tomography, SUV: Standardized Uptake Value, MTV: Metabolic Tumor Volume, TLG: Total Lesion Glycolysis, DS: Deauville score

Table 7. *Multivariate analysis of ^{18}F-FDG PET/CT parameters of 64 patients with DLBCL.*

Parameter	P	HR	95.0% CI for Exp(B)	
			Lower	Upper
SUVmax	0.525	0.925	0.727	1.177
SUVpeak	0.351	1.151	0.856	1.547
MTV	0.918	0.998	0.997	1.000
TLG	0.119	0.996	0.991	1.001
DS	<0.001*	4.027	2.306	7.030

DLBCL: Diffuse large B-cell lymphoma, ^{18}F-FDG: fluorine-18-fluorodeoxyglucose, PET: Positron Emission Tomography, SUV: Standardized Uptake Value; MTV: Metabolic Tumor Volume, TLG: Total Lesion Glycolysis, DS: Deauville score

and DS ≤3 compared to those with higher IPI and DS.

The IPI score is an internationally recognized and widely used prognostic index in patients with DLBCL, typically assessed before the initiation of therapy [11, 12]. However, contradictory data exist in the literature, as some clinical studies suggest that while the IPI score can predict the prognosis in many DLBCL patients, patients with similar IPI scores often have differing long-term survival rates [13, 14]. Kwon et al. (2016) found that a higher IPI score was associated with significantly worse survival compared to IPI values of 1 and 2, which is consistent with the results of our study [15]. Additionally, in the univariate analysis, Ann Arbor stage, LDH, extranodal involvement and SUVmax values were predictive parameters for the disease in DLBCL patients, which is not in accordance with the results of our study. On the other hand, in the multivariate analysis, only the IPI showed prognostic statistical significance. The IPI is considered to retain its predictive significance when the score is 0 or 4-5, while it shows inconsistency in stratifying patients with intermediate scores, whose prognosis is often unclear and/or difficult to estimate, ranging from intermediate to poor prognostic predictions [16]. These findings suggest that other clinical parameters, the presence of comorbidities, and individual characteristics must also be considered when assessing response to chemotherapy and prognosis in DLBCL patients.

The results of our study indicate that patients with lower DS had a better prognosis and PFS. Several other studies have investigated the significance of DS, or the metabolic response to therapy, through interim ^{18}F-FDG PET/CT scans in patients with DLBCL. The Lugano criteria are used to assess

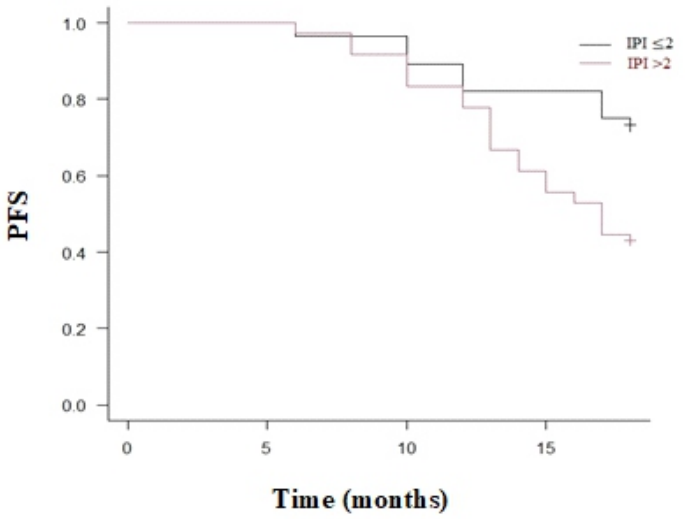

Figure 3. Kaplan-Meier survival analysis of PFS according to IPI (by groups). PFS: Progression-free survival; IPI: International prognostic ındex

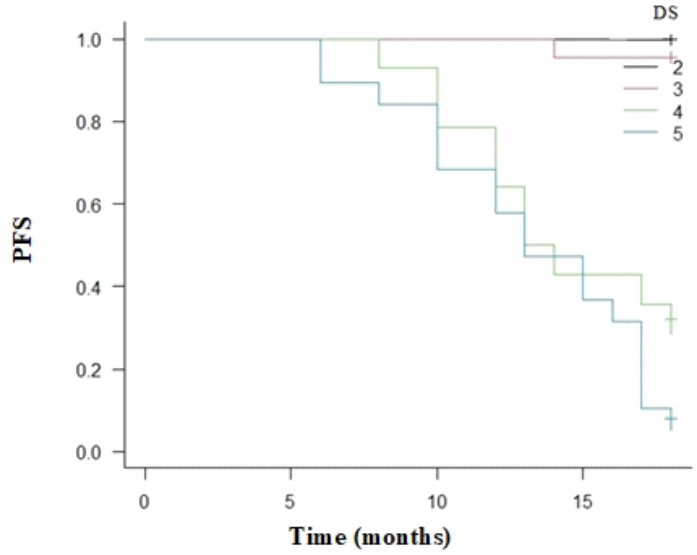

Figure 4. Kaplan-Meier survival analysis of PFS according to DS. PFS: Progression-free survival, DS: Deauville score

response to therapy based on DS, with a score ≤3 indicating a good metabolic response, while a DS of 4 or 5 is considered a poor metabolic response or metabolic progression [17]. Jin et al. (2021) demonstrated in their study that patients with DS ≤3 had a significantly longer PFS compared to those with DS >3 [18]. In line with these results, Allioux et al. (2021) reported significantly longer survival in patients who showed a good metabolic response to therapy (≤3), compared to those who had a poor metabolic response to therapy (DS 4 or 5) over a two-year period (P<0.0001). However, they also noted that no significant survival difference was observed between those with DS 4 and DS 5 [19]. One study found that the risk of disease progression, recurrence, and death within 2 years was significantly higher in patients who did not achieve a complete response (DS 4 or 5) compared to those who achieved a complete response (DS 1, 2, or 3) [20]. Poor interim treatment response is an indication for early clinical intervention, intensive treatment, or autologous stem cell transplantation [17]. Patients with a poor metabolic response to initial therapy have a higher risk of disease progression, relapse, and death due to the underlying disease. Therefore, with interim ^{18}F-FDG PET/CT examinations, determination DS and assessing metabolic response, it is possible to identify patients who have a greater chance of a worse prognosis of the disease, but also to find an adequate treatment strategy for them.

Other semi-quantitative and quantitative ^{18}F-FDG PET/CT parameters analyzed in our study did not demonstrate significant predictive value. Maximum SUV and SUVpeak showed statistical significance only in the univariate analysis, but their significance was lost after the inclusion of other semi-quantitative and quantitative ^{18}F-FDG PET/CT parameters. Data from literature are contradictory. Gallicchio et al. (2014) reported that higher SUVmax values were associated with a

better prognosis of the disease [21]. On the other hand, some studies show that higher SUVmax values are associated with worse prognosis [15, 16]. These conflicting results can be explained by several factors reported in the literature. High SUVmax values are generally associated with more aggressive types of lymphoma linked to faster progression and shorter survival [10]. However, some studies suggest that higher SUVmax values, indicating greater glycolytic activity, are associated with a better response to chemotherapy and longer survival [21].

In our study, MTV and TLG did not prove to be significant factors in the prediction of response to therapy, which is consistent with the results of other studies [12, 16, 21]. Possible explanation could be that the MTV and TLG parameters could underestimate the actual tumor burden due to necroses often present in large tumor masses, with absent accumulation of ^{18}F-FDG [12].

The main limitations of this study are related to the relatively small sample size and the fact that all patients from this study belonged to one center, so it is necessary to analyze, monitor and compare the results from more different institutions. A longer follow-up period is necessary to assess the predictive significance of all investigated parameters for the long-term prognosis of the disease. This study lays the foundation for further research to determine whether patients with DS ≤3, after 18 months, have successfully avoided disease progression, and for how long.

In conclusion, the results of this study indicate that the early metabolic response to therapy, assessed on the basis of interim ^{18}F-FDG PET/CT is a significant independent predictive factor of disease outcome in patients with DLBCL. The use of ^{18}F-FDG PET/CT during therapy helps in the early identification of patients at increased risk for disease progression, allowing for timely adjustments to the therapeutic approach.

The authors declare that they have no conflicts of interest.

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