The Effect of Initial Fluorodeoxyglucose Uptake in the Liver and Spleen on Treatment Success and Prognosis Running Head: Initial Fdg Uptake in Liver and Spleen

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ABSTRACT

Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common and aggressive form of Non-Hodgkin Lymphomas. For many years, monoclonal antibody and multiple drug combination chemotherapies have been preferred in its treatment. In addition to the classifications such as International Prognostic Index (IPI), Revised International Prognostic Index (R-IPI) or The National Comprehensive Cancer Network- International Prognostic Index (NCCN-IPI) which predict prognosis and survival in DLBCL patients, many studies are conducted to find easier, cheaper, faster, applicable prognostic data. We aim to determine the relationship between the fluorodeoxyglucose (FDG) uptake in the liver and spleen and prognosis, treatment response, relapse and survival in patients with DLBCL.

Material and Method: Patients followed up between 2009-2019 were analyzed retrospectively. Age, gender, laboratory, PET / CT liver-spleen SUVmax, Ann Arbor stage, ECOG scale, presence of extranodal involvement, presence of B symptoms, IPI score, treatment responses, follow-up period, recurrence and overall survival were recorded.

Results: The median SUVmax of the liver was 3.87 (range: 2.04-19.70) and the median SUVmax of the spleen was 3.1 (range: 1.75-58.85). Based on the median figures of SUVmax, the patients were divided into two groups. The IPI score distribution between the low-high SUVmax groups did not differ significantly ($p > 0.05$) in terms of treatment response, recurrence and overall survival.

Keywords: diffuse large b cell lymphoma (dlbcl), pet / ct, suvmax fluorodeoxyglucose (fdg), prog- nostic factor.

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ABSTRACT

Introduction: Diffuse large B cell lymphoma (DLBCL) is the most common and aggressive form of Non-Hodgkin Lymphomas. For many years, monoclonal antibody and multiple drug combination chemotherapies have been preferred in its treatment. In addition to the classifications such as International Prognostic Index (IPI), Revised International Prognostic Index (R-IPI) or The National Comprehensive Cancer Network- International Prognostic Index (NCCN-IPI) which predict prognosis and survival in DLBCL patients, many studies are conducted to find easier, cheaper, faster, applicable prognostic data. We aim to determine the relationship between the fluorodeoxyglucose (FDG) uptake in the liver and spleen and prognosis, treatment response, relapse and survival in patients with DLBCL.

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Discussion: There is no study on initial liver and spleen SUVmax in the literature. In studies with the highest median tumor or total body SUVmax in DLBCL, as SUVmax increased; decreased progression-free survival, decreased treatment response, increased recurrence and poor prognosis were detected. In our study, there was no significant difference between liver and spleen SUVmax groups in terms of age, gender, clinical symptoms, IPI prognosis score, treatment response, recurrence and survival.

Keywords: diffuse large b cell lymphoma (dlbcl), pet / ct, suvmax fluorodeoxyglucose (fdg), prognostic factor.

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I. INTRODUCTION

Non-Hodgkin Lymphoma (NHL) ranks first among all hematological malignancies, although lymphomas accounts for only 3% of all cancers. DLBCL is a heterogeneous group of tumors consisting of large and transformed B cells (1). Its incidence increases with age; the median age of diagnosis is 64. It is more common in men and 55% of patients are male (2, 3). It may appear as de novo or may be histologically transformed from indolent lymphomas. The disease typically occurs as a fast-growing nodal or extranodal mass associated with systemic symptoms (4).

Clinical and demographic parameters such as age, gender, presence of B symptoms, areas of nodal and extranodal involvement, clinical stage and

serum lactate dehydrogenase (LDH) level have frequently been the subject of research in diffuse large B cell lymphomas. While these variables may affect survival independently of each other, the first most frequently used in predicting the prognosis calculated by evaluating a few parameters was defined after the first described in 1993. It is the "International Prognostic Index (IPI)" (5-7). Clinically, IPI or Revised IPI (R-IPI) scoring system is used to determine prognosis. These clinical parameters and IPI score are not always sufficient to determine the prognosis (8).

Instead of using fluoride-18 fluorodeoxyglucose positron emission tomography (F18-FDG PET) or computed tomography (CT) alone, the most useful method is FDG PET / CT (9-11). As an interim evaluation or at the end of treatment procedure to determine the final response ; FDG-PET / CT was found to be more sensitive than other conventional imaging methods due to its metabolic nature in revealing active tumor foci in residual masses after treatment and in predicting tumor's biological aggressiveness and prognosis (12).

We aim to determine the relationship between the FDG uptake in the liver and spleen and prognosis, treatment response, relapse and survival in patients with DLBCL. Initial liver and spleen FDG uptake SUVmax, as a new prognostic indicator, it was intended to be used as an early marker for the treatment resistance, relapse and survival.

II. MATERIAL AND METHOD

Patients followed up in our hematology clinic between 01.01.2009 - 01.01.2019 were retrospectively analysed. The data of 77 patients included in the study were obtained from the hospital electronic information management system and by scanning patient files.

Liver and spleen SUVmax on PET/CT, IPI scores of patients, gender and similar demographic data, leukocyte and neutrophil level at the time of diagnosis, presence of B symptoms were recorded. The treatment responses of the patients after 4 cycles of chemotherapy were examined with PET / CT and their responses were recorded according to the Lugano revised response criteria.

Statistical analysis: Average, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. Independent sample t test or Mann-Whitney U test was used in the analysis of quantitative independent data. In the analysis of qualitative independent data, chi-squared test, Fischer test was used when chi-squared test conditions were not met. Kaplan-Meier Logrank test was used in survival analysis. SPSS 22.0 program was used to analyse data. Ethics committee approval: Our study was approved by the Clinical Research Ethics Committee of our hospital on 26.04.2019 with the decision number 1810.

III. RESULTS

Seventy-seven (77) patients were analysed, 61% of whom was male and 39% was female. Male / female ratio was calculated as 1.56. Median incidence of age was 55 (range: 18-82). The presence of B symptoms was found to be 36.4%. According to the ECOG performance scale, 16.9% of patients were found to be at stage 2-4. According to the Ann Arbor staging system, 61% of the patients were found to be in advanced stages at the time of diagnosis. Extranodal involvement was observed in 55.8% of patients. According to the IPI score, 27% of patients were found in the risk group with low, 17% low-intermediate, 23% high-intermediate, and 10% high.

The median SUVmax was 3.87 (range: 2.04-19.70) for the liver and 3.1 (range: 1.75-58.85) for the spleen. After 4 cycles of R-CHOP treatment, 55.8% of patients had complete response, 36.4% partial response and 7.8% progression. Recurrence was observed in 5.2% of the patients after a response. During long-term follow-up, 22.1% of patients were found to be exitus. (Table 1.)

Patients were divided into two groups with liver median SUVmax: 3.87. The group with a median value of 3.87 and below and the group with a value higher than 3.87. Ages and genders of the patients did not differ significantly ($p > 0.05$) in

both groups. In the group with high liver SUVmax, the leukocyte and neutrophil values were significantly lower ($p < 0.05$) than the group with low SUVmax group. Among the liver SUVmax groups there was no significant difference ($p > 0.05$) in ECOG distribution and IPI, extranodal involvement, B symptom presence, treatment responses, recurrence, overall survival and mortality. (Tables 2 and 4)

When the relationship between low and high spleen SUVmax groups was examined, the group with a SUVmax of 3.1 and below is considered to be the group with low SUVmax and those with a value of higher than 3.1 are considered as the group with high SUVmax. The age and gender distribution of the patients did not differ significantly ($p > 0.05$) in the group with low spleen SUVmax and high spleen SUVmax. In addition, there was no significant difference ($p > 0.05$) between the two groups in terms of ECOG distribution, IPI score, presence of B symptoms, treatment responses, relapse, survival and mortality. (Tables 3 and 4)

IV. DISCUSSION

Diffuse large B cell lymphoma is the most common aggressive form of NHL (14). DLBCL is a highly heterogeneous disease and 30-40% of patients show progression and recurrence despite standard chemo-immunotherapy (15). Therefore, defining prognostic factors that can be easily and accurately classified into appropriate risk groups of patients with DLBCL is very important for disease management.

Although PET / CT staging is used widely in patients with DLBCL to evaluate early treatment response and to evaluate residual lesions with high sensitivity at the end of treatment, studies on SUVmax are very few (16-18). Based on the widespread usage of PET / CT in the management of DLBCL and with increasing evidence of the prognostic value of PET / CT parameters, SUVmax is the most studied parameter, partly due to its convenience and high repeatability (19).

In the literature, there are studies on SUVmax ratios in patients with hematological and solid organ malignancies, especially with DLBCL, but there is no study on liver and spleen SUVmax. Our study is the first in the literature in this context. In several studies, it has been shown that SUVmax is associated with survival before treatment in non-small cell lung cancer, oesophageal cancer, colorectal cancer and other solid tumors (20-22).

Huang et al. (23), in a retrospective study conducted in 2016, examined the relationship of FDG uptake involvement with clinico-pathological factors and prognosis in 140 new DLBCL patients. There was a significant difference between low and high SUVmax groups in terms of progression-free survival. In addition, Byun et al (24) and Hirose et al (25) found a significant relationship between SUVmax and IPI risk groups in their studies. In a study by Chihara et al. (26) in 2011, 110 new DLBCL patients were retrospectively analyzed; shorter overall survival and progression-free survival were detected, regardless of IPI, in the high SUVmax group. In addition, the high SUVmax was associated with a low complete response. In the retrospective study conducted by Miyazaki et al. (27) in 2012, it was found that the low SUVmax group in 50 newly diagnosed DLBCL patients showed a better prognosis than the high SUVmax group.

In our study, there was no significant difference between low and high liver and spleen SUVmax groups in terms of age, gender, clinical symptoms, IPI prognosis score, treatment response, recurrence and survival. In the literature, there is no study on liver and spleen SUVmax ratios. In studies with the highest median tumor or total body SUVmax in DLBCL, as SUVmax increased, decreased progression-free survival, decreased treatment response, increased recurrence and poor prognosis were detected. (23-27). When all studies were analyzed, it was observed that different values were used for the SUVmax threshold and those were quite high compared to our cut off values. In these studies we mentioned, a significant difference was observed between the low and high SUVmax groups depending on the high cut off values. Our threshold values have the lowest values compared to literature. The use of different threshold values may have affected the results of the study. A multicentre analysis is required to find the appropriate threshold. The

lower leukocyte and neutrophil values found in the group with high liver SUVmax may provide information about bone marrow involvement and may help with cytopenia prediction after chemotherapy; however, it should be said that a more detailed study is needed to support these comments.

In conclusion, our study is the first in the literature to examine the relationship between liver and spleen SUVmax and DLBCL prognosis and treatment. Although no significant difference was found among the disease parameters; we think that prospective studies with larger patient groups may yield different results.

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We respectfully remember all the colleagues we lost in the COVID-19 fight:

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No funding was received. None of the authors have disclosures relevant to this manuscript.

Conflict Of Interest

None to declare.

Informed Consent

An informed consent obtained from all of our patients to publish this study.

Author Contributions

All authors contributed to the editing of the manuscript. IS wrote the manuscript and made tables.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Table 1: Demographic Datas and Patient Characteristics

		Min-Max	Median	Mean.±s.d./n-%
Age		18.00 - 82.00	55.00	55 ± 14.78
Gender	Female			30 39.0%
	Male			47 61.0%
Liver SUVmax		2.04 - 19.70	3.87	4 ± 2.42
Spleen SUVmax		1.75 - 58.85	3.1	6 ± 8.17
Leukocyte		1.01 - 30.91	7.79	9 ± 4.79
Neutrophil		0.24 - 27.99	5.01	7 ± 4.66
Follow Up Period (Month)		5.33 - 97.07	28.88	35 ± 21.78
ECOG	0-1			64 83.1%
	2-4			13 16.9%
Stage	I			4 5.2%
	II			26 33.8%
	III			25 32.5%
	IV			22 28.6%
LDH	(-)			47 61.0%
	(+)			30 39.0%
IPI Score	Low			27 35.1%
	Low-intermediate			17 22.1%
	High			10 13.0%
	High-intermediate			23 29.9%
Presence of B Sypmtoms	(-)			49 63.6%
	(+)			28 36.4%
Extranodal Involvement	(-)			34 44.2%
	(+)			43 55.8%
Treatment Response	(-)			34 44.2%
	(+)			43 55.8%
	Partial Response			*28 36.4%*
	Progression			*6 7.8%*
	Complete Response			*43 55.8%*
Recurrence	(-)			73 94.8%
	(+)			4 5.2%
Exitus	(-)			60 77.9%
	(+)			17 22.1%

Table 2: Comparison of Liver SUVmax Subgroups

		Liver- High SUVmax Group		Liver- Low SUVmax Group		P
		Mean.±s.d./n-%	Median	Mean.±s.d./n-%	Median	
Age		52.0 ± 16.3	54.0	58.7 ± 12.4	56.5	0.087 [m]
Gender	Female	13 33.3%		17 43.6%		0.305 [X²]
	Male	26 66.7%		21 53.8%		
Liver SUVmax		3.1 ± 0.6	3.3	5.6 ± 2.9	4.4	***0.000*** [m]
Spleen SUVmax		4.0 ± 4.9	2.7	7.4 ± 10.4	3.7	***0.000*** [m]
Leukocyte		10.7 ± 5.6	10.3	7.7 ± 3.9	6.9	***0.002*** [m]
Neutrophil		8.3 ± 5.5	7.7	5.1 ± 3.4	4.3	***0.001*** [m]
Follow Up Period (Month)		36.6 ± 20.6	34.5	33.3 ± 23.2	24.7	0.338 [m]
ECOG	0-1	33 84.6%		31 79.5%		0.702 [X²]
	2-4	6 15.4%		7 17.9%		
Stage	I	3 7.7%		1 2.6%		0.499 [X²]
	II	15 38.5%		11 28.2%		
	III	12 30.8%		13 33.3%		
	IV	9 23.1%		13 33.3%		
LDH	(-)	23 59.0%		24 61.5%		0.707 [X²]
	(+)	16 41.0%		14 35.9%		
IPI Score	Low	15 38.5%		12 30.8%		0.143 [X²]
	Low-intermediate	11 28.2%		6 15.4%		
	High	2 5.1%		8 20.5%		
	High-intermediate	11 28.2%		12 30.8%		
Presence of B Symptoms	(-)	21 53.8%		28 71.8%		0.070 [X²]
	(+)	18 46.2%		10 25.6%		
Extranodal Involvement	(-)	20 51.3%		14 35.9%		0.202 [X²]
	(+)	19 48.7%		24 61.5%		
Treatment Response	(-)	20 51.3%		14 35.9%		0.202 [X²]
	(+)	19 48.7%		24 61.5%		
	Partial Response	*15* *38.5%*		*13* *33.3%*		
	Progression	*5* *12.8%*		*1* *2.6%*		
	Complete Response	*19* *48.7%*		*24* *61.5%*		
Recurrence	(-)	37 94.9%		36 92.3%		0.979 [X²]
	(+)	2 5.1%		2 5.1%		
Exitus	(-)	30 76.9%		30 76.9%		0.830 [X²]
	(+)	9 23.1%		8 20.5%		

[t] t test / [m] Mann-Whitney u test / [X²] Chi-Squared test (Fischer test)

Table 3: Comparison of Spleen SUVmax Subgroups

		Spleen- Low SUVmax Group		Spleen- High SUVmax Group		p	
		Mean.±s.d./n-%	Median	Mean.±s.d./n-%	Median		
Age		52.6 ± 16.1	53.5	57.1 ± 13.5	57.5	0.179	m
Gender	Female	13 33.3%		17 43.6%		0.842	X^2
	Male	21 53.8%		25 64.1%			
Liver SUVmax		3.7 ± 1.5	3.4	4.8 ± 2.9	4.3	***0.001***	m
Spleen SUVmax		2.5 ± 0.4	2.6	8.2 ± 10.3	4.3	***0.000***	m
Leukocyte		10.1 ± 5.6	9.3	8.2 ± 3.8	7.1	0.112	m
Neutrophil		7.5 ± 5.6	6.2	5.9 ± 3.6	4.7	0.210	m
Follow Up Period (Month)		34.9 ± 20.8	34.1	35.5 ± 22.8	25.6	0.950	m
ECOG	0-1	29 74.4%		34 87.2%		0.617	X^2
	2-4	5 12.8%		8 20.5%			
Stage	I	3 7.7%		1 2.6%		0.502	X^2
	II	16 41.0%		10 25.6%			
	III	8 20.5%		17 43.6%			
	IV	7 17.9%		14 35.9%			
LDH	(-)	22 56.4%		24 61.5%		0.184	X^2
	(+)	12 30.8%		18 46.2%			
IPI Score	Low	15 38.5%		12 30.8%		0.066	X^2
	Low-intermediate	9 23.1%		8 20.5%			
	High	2 5.1%		8 20.5%			
	High-intermediate	8 20.5%		14 35.9%			
Presence of B Symptoms	(-)	22 56.4%		26 66.7%		0.801	X^2
	(+)	12 30.8%		16 41.0%			
Extranodal Involvement	(-)	19 48.7%		15 38.5%		0.079	X^2
	(+)	15 38.5%		27 69.2%			
Treatment Response	(-)	17 43.6%		16 41.0%		0.298	X^2
	(+)	17 43.6%		26 66.7%			
	Partial Response	*15*	*38.5%*	*14*	*35.9%*		
	Progression	*2*	*5.1%*	*4*	*10.3%*		
	Compelete Response	*17*	*43,6%*	*26*	*66.7%*		
Recurrence	(-)	32 82.1%		40 %13		0.828	X^2
	(+)	2 5.1%		2 5.1%			
Exitus	(-)	26 66.7%		33 84.6%		0.827	X^2
	(+)	8 20.5%		9 23.1%			

[t] t test / [m] Mann-whitney u test / X^2 Chi-Squared test (Fischer test)

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Table 4: Comparison of Survival in Subgroups

	Predicted Survival (Month)	95% Confidence Interval	p
Liver- Low SUVmax Group	54.30	46.84-61.76	0.991
Liver- High SUVmax Group	75.43	62.30-88.57	
Spleen- Low SUVmax Group	53.56	45.24-61.89	0.838
Spleen- High SUVmax Group	76.03	64.00-88.06	

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