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Relationship between spleen volume, spleen/liver SUVmax ratio, and percentage change and overall survival in patients undergoing immunotherapy

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ABSTRACT

Aims: This study aimed to investigate the pre- and post-treatment associations between spleen volume (SV), spleen/liver maximum standardized uptake value (SUVmax) ratio (SLR), and percent change (Δ) and overall survival (OS) in patients undergoing immunotherapy.

Methods: This retrospective study included 89 patients who underwent 18F FDG PET/CT imaging before immunotherapy (baseline) and during post-treatment at 3 and 6 months. SV, spleen SUVmax, and liver SUVmax parameters were determined based on PET/CT images. Patients' ages and date of mortality were recorded.

Results: In the present study, 52 (58.4%) were men, and the median OS was 17.7 (4-83) months. Furthermore, 63 out of 89 patients (70.8%) died during the study period. Baseline median SV value was 230 ml (47-1870). Baseline median SLR value was 0.80 (0.33-1.48). Median ΔSV1 at baseline and at 3 months post-treatment was -1.34 (-55.03-155.37). Percent change in SLR baseline and post-treatment (ΔSLR1) median was -0.52 (-48.39-121.02). Moreover, SLR1 had a sensitivity of 64.2% and specificity of 65.2% in detecting mortality with a cutoff value of >0.80. For a SLR1 value of ≤0.79, median OS was 29.5 months and 1-3-year survival was 87/37%. SLR1 and SLR3 were independent prognostic factors for OS (p=0.003 and p=0.004, respectively).

Conclusion: SV values before and at 3 months post-immunotherapy and SLR values before and at 6 months post-treatment were prognostic factors for OS. Higher SLR1 and SLR3 values from 18F FDG PET/CT before and at 6 months post-treatment were independent prognostic factors and associated with shorter OS.

Keywords: FDG PET/CT, immunotherapy, spleen volume, spleen/liver SUVmax ratio, overall survival

INTRODUCTION

In recent times, immunotherapy is considered one of the most important and promising therapeutic innovations. Antibodies that target programmed cell death protein-1 (α-PD-1) or programmed cell death ligand 1 (PD-L1) increase immunity against cancer cells by activating the T cells. Combined α-PD-1/PD-L1 is associated with increased treatment efficacy and may reduce treatment resistance (1-3). Immunotherapies are well known to lengthen progression-free survival (PFS) and overall survival (OS) in various tumor types.[4,5] Immunotherapy has recently become a routine or first-line systemic treatment option for treatment of some cancer types, and it is has found increasingly widespread use as a tumor treatment.[6,7] Therefore, early identification of patients who will respond to immunotherapy is important.

Numerous parameters have been used to predict treatment response in patients undergoing immunotherapy, and biochemical parameters, including neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and lactate dehydrogenase, may be used to predict response to treatment.[8,9] In addition, biomarkers such as many signal transducers and activators, RAS, mitogen-activated protein kinase, etc. have been shown to have potential predictive values in immunotherapy response.[10]

Studies in patients with non-small cell lung cancer (NSCLC) and malignant melanoma (MM) have reported that certain parameters such as bone marrow uptake, colon SUVmax, total lesion glycolysis and metabolic tumor volume obtained by fluorodeoxyglucose (18F) (FDG) positron emission tomography/computed tomography (PET/CT) can predict response to immunotherapy and serve as prognostic indicators.[11-15] Myeloid suppressor cells may support tumor progression, accumulate in the spleen, blood and peripheral lymphoid organs and lead to splenomegaly.[16,17] Immunotherapies are known to cause an increase in spleen size as a result of an increase in CD4+ lymphocytes, CD8+ lymphocytes and T cells in the spleen.[18] Splenic volume (SV)

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obtained by CT images may predict treatment response in patients on immunotherapy.[19] Previous studies suggested that SV change was not associated with treatment response.[20]

Moreover, splenic FDG uptake may be affected by various reasons.[21,22] However, liver FDG uptake is usually stable, and therefore, serves as a reference. Therefore, it is calculated by dividing the spleen SUVmax/liver SUVmax ratio (SLR) and previous studies suggested that the SLR value could predict treatment response in patients on immunotherapy.[23-25] It has been reported that those with lower baseline SLR have longer OS.[23] However, there are study showing the opposite.[26]

Our aim was to investigate the relationship between SV, SLR and percentage changes and OS pre- and post-immunotherapy.

METHODS

Study Design

Patients who underwent FDG PET/CT imaging before treatment and at 3 and/or 6 months after immunotherapy between October 2017 and November 2023 were retrospectively analyzed. All 89 patients in our study had baseline and 3-month PET/CT imaging available, but only 76 patients had 6-month PET/CT imaging. Patients with confirmed histopathologic diagnosis were included in the study. Patients with missing data, history of splenectomy (12 patients), splenic and liver disease (3 patients) and systemic infection (1 patient) were excluded. Age, gender, date of last follow-up visit and date of death were recorded for all patients. Our study was conducted in accordance with current laws and good clinical practice guidelines and with the approval of the Gazi Yaşargil Training and Research Hospital Non-Interventional Ethics Committee (Date: 07.06.2024, Decision No: 2024/101). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Image Evaluation

Spleen volume was calculated semi-automatically on the GE ADW4.7 workstation using images from PET/CT before immunotherapy and 3- and 6-months post-treatment. Spleen SUVmax and liver SUVmax values were obtained by drawing 30-mm volume-of-interests (VOIs) from fusion images of the spleen and liver at appropriate localizations. Spleen SUVmax value was divided by liver SUVmax to produce the spleen/liver SUVmax ratio (SLR) (**Figure 1**).[26] Furthermore, percentage change in spleen volume 1 and 2 (ΔSV1), and percentage change in spleen volume 1 and 3 (ΔSV3) were obtained. The percentage change in SLR1 and SLR2 (ΔSLR1) and the percentage change in SLR1 and SLR3 (ΔSLR3) were calculated as per the below formula.

ΔSV=(post-treatment spleen volume-spleen volume pre-treatment)/spleen volume pretreatment×100

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, USA) program was used to analyze the variables. Specificity and sensitivity rates of the relationship between the classification separated by the cutoff value calculated according to the variables and the actual classification were examined and shown by ROC (Receiver Operating Curve) curve analysis. Kaplan-Meier-log rank analysis was used to examine the effects of factors on survival and mortality. Univariate and multivariate cox regression analysis was utilized to quantify the effects of prognostic variables on survival and mortality using the Enter method. Multivariate cox regression analysis was performed on 76 patients after excluding missing data. Quantitative variables were presented as median (interquartile range) and mean±SD (standard deviation), while categorical variables were presented as n (%). Variables were analyzed at 95% confidence interval (CI) and $p<0.05$ was considered significant.

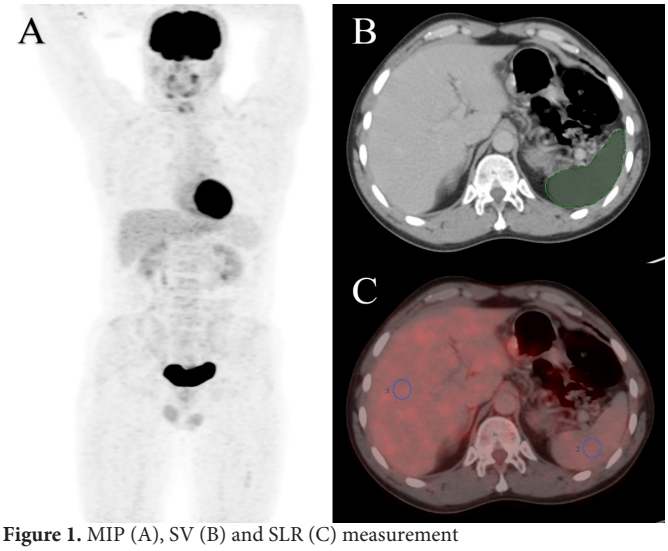

Figure 1. MIP (A), SV (B) and SLR (C) measurement

MIP: Maximum intensity projection, SV: Spleen volume, SLR: spleen-liver SUVmax ratio

RESULTS

Descriptive Parameters

In our study, 52 (58.4%) of 89 patients were male and the median age was 62 (23-91) years. Moreover, 30 patients had MM, 28 had renal cell adenocarcinoma (RCC), 17 had NSCLC, and 14 had other diseases (malignant mesothelioma, non-Hodgkin lymphoma, etc,); 44 (49.4%) patients underwent operation for the primary tumor. Furthermore, 76 patients received nivolumab, 9 received ipilimumab, and 3 received atezolizumab treatment. All 89 patients included in our study had baseline and 3-month PET/CT imaging and 76 patients also had 6-month PET/CT imaging. Of these 76 patients, 53 were exited and 23 were alive (**Table 1**).

Median SV1 value of the patients was 230 ml (47-1870). The median SLR1 value was 0.80 (0.33-1.48). The median ΔSV1 value was -1.34 (-55.03-155.37). The median ΔSLR1 value was -0.52 (-48.39-121.02). Other data are presented in **Table 1**.

ROC Curve Analysis

The specificity of the SLR1 cut-off value >0.80 in detecting mortality was 65.2% and its sensitivity was 64.2%, which was found to be statistically significant (AUC: 0.642±0.072, 95% CI: 0.502-0.783). The specificity of the SLR3 cutoff value >0.79 in detecting mortality was 65.2% and the sensitivity was 66%, which was found to be statistically significant (AUC: 0.655±0.065, 95% CI: 0.527-0.782) (**Figure 2, Table 2**).

Table 1. Descriptive parameters						
	Ex		Alive		Total	
	n	Median (min-max)	n	Median (min-max)	n	Median (min-max)
Age	63	64.00 (23.0-91.0)	26	53.50 (28.00-84.00)	89	62 (23-91)
SV1	63	230.05 (47.03-1870.32)	26	228.97 (54.39-594.00)	89	230.05 (47.03-1870.32)
SpleenSUVmax	63	1.97 (.91-4.55)	26	2.00 (1.25-4.60)	89	1.98 (.91-4.60)
LiverSUVmax	63	2.39 (1.33-5.62)	26	2.52 (1.71-5.12)	89	2.42 (1.33-5.62)
SV2	63	228.88 (21.97-3086.14)	26	244.02 (69.13-575.52)	89	232.84 (21.97-3086.14)
SpleenSUVmax2	63	1.84 (1.12-3.07)	26	2.00 (1.00-3.21)	89	1.86 (1.00-3.21)
LiverSUVmax2	63	2.15 (1.55-3.89)	26	2.37 (1.35-3.84)	89	2.25 (1.35-3.89)
SV3	53	230.08 (29.99-774.41)	23	224.25 (57.45-632.27)	76	228.83 (29.99-774.41)
SpleenSUVmax3	53	1.99 (.78-3.26)	23	1.97 (1.42-2.78)	76	1.98 (.78-3.26)
LiverSUVmax3	53	2.35 (1.51-4.21)	23	2.51 (1.80-3.33)	76	2.37 (1.51-4.21)
OS	63	14.47 (4-45)	26	42.88 (10-83)	89	17.77 (4-83)
ΔSV1	63	-3.43 (-55.03-155.37)	26	2.72 (-32.05-68.94)	89	-1.34 (-55.03-155.37)
SLR1	63	.82 (.33-1.48)	26	.76 (.58-1.29)	89	.80 (.33-1.48)
SLR2	63	.83 (.51-1.28)	26	.76 (.58-1.09)	89	.81 (.51-1.28)
SLR3	53	.83 (.39-1.16)	23	.78 (.64-1.02)	76	.82 (.39-1.16)
ΔSLR 1	63	-.42 (-48.39-121.02)	26	-1.80 (-31.56-25.03)	89	-.52 (-48.39-121.02)
ΔSLR 3	53	3.57 (-57.73-121.11)	23	1.82 (-27.96-21.91)	76	3.15 (-57.73-121.11)

SV: Spleen volume, OS: Overall survival, ΔSV: Spleen volume percentage change, SLR: Spleen/liver SUVmax ratio, ΔSLR: Spleen/liver SUVmax ratio percentage change, SUV: Standard uptake value, min: Minimum, max: Maximum

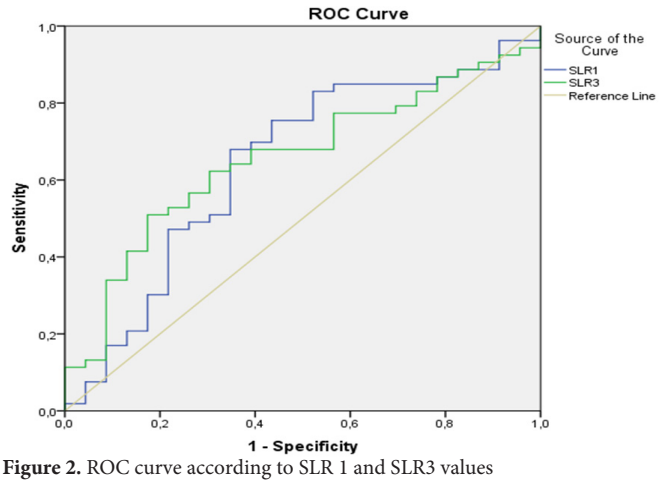

Figure 2. ROC curve according to SLR 1 and SLR3 values

ROC: Receiver operating characteristic, SLR: spleen-liver SUVmax ratio

Table 2. ROC analysis according to SLR 1 and SLR3 values in determining mortality					
	Area±SE	95% CI	Sensitivity	Specific	p
SLR1 >0.80	.642±.072	.502-.783	64.2%	65.2%	.042
SLR3 >0.79	.655±.065	.527-.782	66%	65.2%	.033

ROC: Receiver operating characteristic, SLR: Spleen/liver SUVmax ratio, SUV: Standard uptake value, SE: Standard error, CI: Confidence interval

Survey Analysis

Furthermore, 63 out of 89 patients (70.8%) died during the study period. SLR1 value ≤0.79 median OS 29.5 months and SLR1 value >0.79 median OS 13.4 months were found (p=0.003). SLR3 value ≤0.80 median OS 30.3 months and SLR1 value >0.80 SLR3 median OS 15.9 months were found (p=0.025) (Figure 3, Table 3).

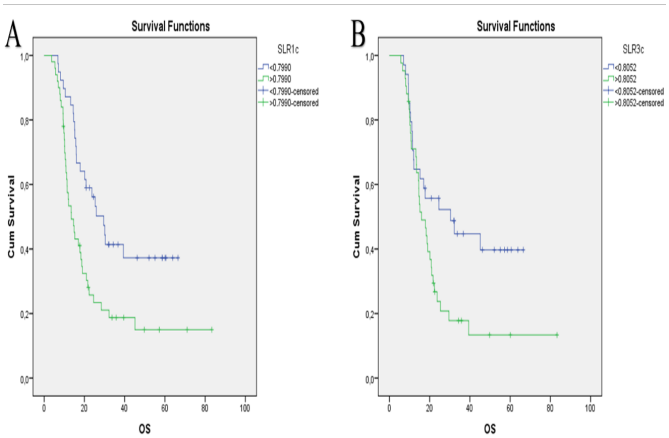

Figure 3. Kaplan-Meier survey analysis according to SLR1 (A) and SLR3 (B) values

SLR: Spleen/liver SUVmax ratio

Prognostic Factor

Univariate cox regression analysis found that SV1, SV2, SLR1, and SLR3 values were prognostic factors for OS (p=0.009, p=0.002, p=0.004, and p=0.027, respectively). Furthermore, multivariate cox regression analysis found that SLR1 and SLR3 values were prognostic factors for OS (p=0.003 and p=0.004, respectively) (Table 4).

Table 3. Kaplan Meier according to SLR 1 and SLR3 values 1-3 years survey analysis

		Mean±SE	95% CI	Median±SE	95% CI	1-3 years OS%	p
SLR1	≤0.79	36.9±3.9	29.1-44.6	29.5±4.4	20.9-38.2	87/37	.003
	>0.79	25.3±3.8	17.7-32.8	13.4±1.8	9.8-17.1	57.5/18.7	
SLR3	≤0.80	36.9±4.5	28.1-45.8	30.3±11.5	7.7-52.9	70.6/44.7	.025
	>0.80	25.4±3.9	17.6-33.2	15.9±2.3	11.4-20.5	71/17.8	
	Overall	33.6±3.6	26.5-40.8	18.2±2.6	13.0-23.4		

SLR: Spleen/liver SUVmax ratio, SUV: Standard uptake value, SE: Standard error, CI: Confidence interval, OS: Overall survival

Table 4. Univariate and multivariate cox regression

	Univariate cox				Multivariate cox			
	B	OR	95.0% CI	p	B	OR	95.0% CI	p
SV1	.002	1.002	1.001-1.004	.009	.0001	1.001	.994-1.008	.806
SV2	.002	1.002	1.001-1.003	.002	.001	1.001	.994-1.008	.739
SV3	.002	1.002	.999-1.004	.130				
SLR1	.764	2.147	1.280-3.601	.004	.882	2.416	1.355-4.307	.003
SLR2	1.788	5.978	.846-42.253	.073				
SLR3	.642	1.900	1.075-3.358	.027	.617	1.854	1.028-3.344	.004
ΔSLR 1	.001	1.001	.991-1.012	.814				
ΔSLR3	.011	1.011	.998-1.024	.085				

SV: Spleen Volume, SLR: Spleen/liver SUVmax ratio, ΔSLR: Spleen/liver SUVmax ratio percentage change, SUV: Standard uptake value, OR: Odds ratio, CI: Confidence interval

DISCUSSION

SV values pre-immunotherapy and at 3 months post-treatment and SLR values pre-immunotherapy and at 6 months post-treatment are prognostic factors for OS. Patients with a SLR1 value of >0.79 and SLR3 value of >0.80 on pretreatment and at 6 months post-treatment ^{18}F FDG PET/CT had shorter OS and these were independent prognostic factors for OS.

Previous studies on various malignancies (HCC, RCC, NSCL, etc.) reported baseline SV median value in patients undergoing immunotherapy 267-295, and there was no correlation between SV and OS and PFS.[27-31] Nevertheless, a study by Galland et al.,[32] which investigated 276 patients with NSCLC, reported the baseline SV cutoff value as 194 ml and that this value was prognostic factor for OS upon univariate cox analysis (p=0.001). Another study conducted on HCC patients found that patients with high SV who received immunotherapy had shorter OS (5.1 vs 18.1 months, p=0.013).[33] Furthermore, in 50 patients diagnosed with MM, who were undergoing immunotherapy, patients with low SV had better PFS compared to those with high SV, when the baseline SV cutoff was considered as 222 ml (30.6 and 11.2 months, p=0.021).[19] In the present study, SV1 median value was 230. Upon univariate cox regression analysis, SV1 value was a prognostic factor for OS (p=0.009), whereas as a result of multivariate cox regression analysis, SV1 was not an independent prognostic factor for OS (p=0.806).

Previous studies on SV and percentage change in SV after immunotherapy failed to find a relationship between treatment response, PFS and OS. Mo et al.[27] found that SV change (>20.05 cm^3) was prognostic factor for OS (p=0.01) in a study involving 240 patients diagnosed with HCC during immunotherapy. In another study of 45 patients with RCC treated with nivolumab, the median LV change was 10% and this was found to be prognostic factor for OS (p=0.048). It was also reported that change in SV was associated with PFS upon univariate cox regression analysis (p=0.04).[28] Galland et al.[32] found a median change of 4.4% in SV in 276 patients with NSCLC and determined that it was an independent prognostic factor for OS (p=0.001). In addition, post-treatment SV and ΔSV were associated with shorter PFS (p=0.02 and p=0.001, respectively).[32] Previous studies have found that patients with lower SV values after immunotherapy have longer OS.[30,31,33] Furthermore, patients with a median SV increase post-immunotherapy had longer PFS.[34,35] In our study, the median values of SV2, SV3, and ΔSV1 were 232, 228, and -1.34, respectively. Additionally, in the univariate cox regression analysis, SV2 was prognostic factor for OS (p=0.002), whereas in the multivariate cox regression analysis, it was not (p=0.739).

Seban[26] and Seban et al.[36] did not suggest baseline SLR median values as significant factors for survival in 2 different studies with patients diagnosed with MM on immunotherapy. Regardless, another study on 90 patients diagnosed with NSCLC on immunotherapy, reported the median value of baseline SLR as 0.81 and that high SLR was an independent prognostic factor (p=0.03).[37] It was reported that patients with high SLR who receive immunotherapy treatment were at a higher risk of mortality.[38,39] Wong et al.[40] reported in a study on 90 patients diagnosed with MM on ipilimumab that a median baseline SLR of 0.9 and higher baseline SLR (>1.1) were associated with worse PFS and OS (p=0.008 and

p=0.003, respectively). Furthermore, SLR value was prognostic factor for survival, as determined by multivariate analysis. Zhao et al.[41] reported in a study of 118 patients diagnosed with lymphoma that baseline SLR of >1.5 was considered prognostic factor for mortality in 83 patients with aggressive non-Hodgkin lymphoma. A study on 119 patients with MM who received mono- or combined immunotherapy reported that patients with lower baseline SLR values had significantly longer OS.[23] In the present study, SLR1 median value was 0.80, which was consistent with previous studies. Furthermore, the median SLR2 and SLR3 value was 0.81 and 0.82, respectively. Multivariate cox regression analysis found that SLR1 and SLR3 were prognostic factors for OS (p=0.003 and p=0.004, respectively). Additionally, consistent with previous studies, patients with higher SLR values (SLR1 >0.79 and SLR3 >0.80) had shorter OS. A comparison could not be made since the previous studies did not analyze the post-treatment SLR value.

Limitations

The heterogeneity of treatment and patient groups, small number of patients and retrospective design are the limitations of the study.

CONCLUSION

SV values before the treatment and at 3 months to post-immunotherapy and SLR values before the treatment and at 6 months post-immunotherapy were prognostic factors for OS. Patients with SLR1 values of >0.79 and SLR3 values of >0.80 on FDG PET/CT before the treatment and at 6 months post-treatment had shorter OS and these were independent prognostic factors for OS. Future, large-scale prospective studies are required to elucidate the relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yasargil Training and Research Hospital Non-interventional Ethics Committee (Date 07.06.2024, Decision No: 2024/101).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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