Article

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The Relationship between the SUVmax Value Obtained in Ga-68 PSMA PET/CT and Lactate Dehydrogenase and Alkaline Phosphatase in Prostate Cancer

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Objectives: ALP and LDH are serum markers of prognostic importance in prostate cancer patients. PET/CT imaging with Ga-68 PSMA has played an important role in prostate cancer imaging in recent years. Our aim in this study was to evaluate the relationship and prognostic significance between SUVmax values obtained with Ga-68 PSMA PET/CT and LDH and ALP levels in prostate cancer patients.

Methods: We retrospectively evaluated 61 prostate cancer patients who had Ga-68 PSMA PET/CT imaging and who did not have a prostatectomy between 2019 and 2020. PSA, ALP and LDH levels were measured in all patients before or after imaging within a maximum of 28 days.

Results: The median age of the patients included in this study was 73 (range: 57–89) and all 61 patients were prostatic adenocarcinoma. 50 (82%) of the patients had distant metastasis in Ga-68 PSMA PET/CT. There was a significant positive correlation between serum LDH and PSA levels. There was a positive correlation between serum ALP and PSA levels. A negative correlation was found between ALP levels and prostate SUVmax.

Conclusions: While negative correlation was found between SUVmax and ALP levels, no correlation was found between LDH levels and SUVmax. High ALP levels were found to be related to metastasis rates and severity and high serum PSA levels.

Keywords: PSMA; PET/CT; bone metastasis; prostate cancer; alkaline phophatase; lactate dehydrogenase

Resumen

Objetivos: ALP y LDH son marcadores séricos de importancia pronóstica en pacientes con cáncer de próstata. Las imágenes de PET/CT con Ga-68 PSMA han jugado un papel importante en las imágenes de cáncer de próstata en los últimos años. Nuestro objetivo en este estudio fue evaluar la relación y la importancia pronóstica entre los valores de SUVmax obtenidos con Ga-68 PSMA PET/CT y los niveles de LDH y ALP en pacientes con cáncer de próstata.

Métodos: Evaluamos retrospectivamente a 61 pacientes con cáncer de próstata que se sometieron a imágenes de PET/CT con Ga-68 PSMA y que no se sometieron a prostatectomía entre 2019 y 2020. Los niveles de PSA, ALP y LDH se midieron en todos los pacientes antes o después de la obtención de imágenes en un plazo máximo de 28 días.

Resultados: La mediana de edad de los pacientes incluidos en este estudio fue de 73 (rango: 57–89) y los 61 pacientes eran adenocarcinoma de próstata. 50 (82%) de los pacientes tenían metástasis a distancia en Ga-68 PSMA PET/CT. Hubo una correlación positiva significativa entre los niveles séricos de LDH y PSA. Hubo una correlación positiva entre los niveles séricos de ALP y PSA. Se encontró una correlación negativa entre los niveles de ALP y el SUVmáx prostático.

Conclusiones: Si bien se encontró una correlación negativa entre los niveles de SUVmáx y ALP, no se encontró correlación entre los niveles de LDH y el SUVmáx. Se encontró que los niveles altos de ALP estaban relacionados con las tasas de metástasis y la gravedad y los niveles altos de PSA en suero.

Palabras Clave: PSMA; PET/CT; metástasis ósea; cancer de prostata; fosfatasa alcalina; lactato deshidrogenasa

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Introduction

Prostate cancer is the most frequently diagnosed cancer among men in 105 countries and is second leading cause of cancer death (1). Positron Emission Tomography/Computed Tomography (PET/CT) is a hybrid imaging method that demonstrates molecular processes of tissues as well as morphological imaging, providing superior diagnostic performance. PSMA Prostate-Specific Membrane Antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues and PSMA expression increases in prostate cancer patients (2). In recent years ^{68}Ga-PSMA PET/CT has been the standard assessment method for prostate cancer staging, evaluation of biochemical recurrence and treatment response (3).

Alkaline phosphatase (ALP) is one of the oldest known tumor marker and it primarily originating from the liver and bone. High levels of ALP in metastatic castration-resistant prostate cancer (mCRPC) patients, correlating with the spread of metastatic bone disease and it is a prognostic marker for overall survival (OS) (4). Although there is not enough correlation between PSA and ALP values in the evaluation of treatment responses, it is stated that the evaluation of the treatment response with ALP is more meaningful (4). ALP is often used as a prognostic marker of bone metastases. Although not certain, this is associated with increased bone turnover, osteoblastic activity and osteoid formation in the presence of bone metastasis. According to a meta-analysis, high serum ALP levels in patients with hormone-sensitive prostate cancer were associated with increased overall mortality and disease progression, but not associated with cancer-specific mortality (5). Similarly, according to Li *et al.* (6) ALP is not associated with cancer-specific mortality.

Lactate dehydrogenase is a marker showing tissue injury, inflammation, hemolysis, acute hepatitis, myocardial infarction, and has prognostic importance in prostate cancer as well as various solid and hematological cancers (7). Tumors often use anaerobic metabolism, and LDH, which controls the conversion of pyruvate to lactate, plays an important role in tumor metabolism (8). It is known issue that tumor cells consume lactate as energy source and therefore LDH plays a critical role in tumor growth and progression (9). Except for some tumors such as malignant lymphomas, LDH elevation is generally not observed in early-stage. However, LDH is a predictive factor for therapeutic effects or worsening symptoms (10). It is a known issue that increased LDH levels due to the Warburg effect, are associated with poor surveillance and faster recurrence in prostate cancer like other cancers such as head, neck, lung, and breast cancers (11). The reverse Warburg effect is mentioned in the studies conducted on this subject. According to this; it is stated that lactate produced by non-cancerous cells in the tumor microenvironment and is used by tumor cells. In a study on this topic, Goodwin *et al.* (12) have shown in mouse modeling sarcoma that lactate injection makes the tumor more vascular and causes proliferation despite normoxic conditions.

The aim of this study was to evaluate the relationship and prognostic significance between SUVmax values obtained with Ga-68 PSMA PET / CT and LDH and ALP.

Materials and Methods

We retrospectively evaluated 61 prostate cancer patients who had ^{68}Ga-PSMA PET/CT imaging and who did not have a prostatectomy between 2019 and 2020. Prostate specific antigen (PSA), ALP and LDH levels were measured in all patients before or after Ga-68-PSMA PET / CT within a maximum of 28 days. All patients were diagnosed with prostate cancer on the basis of transrectal biopsy. Region of interest were plotted around the prostate gland to calculate the maximum standardized uptake values (SUVmax). Patients whose LDH and / or ALP levels were not measured in the last 4 weeks with ^{68}Ga-PSMA PET / CT imaging were not included in the study. The histopathological and treatment data of the patients were obtained from the hospital information management system and our patient records. Overall survival (OS) was calculated from the date of diagnosis to the date of either last follow-up or death.

^{68}*Ga-PSMA Imaging Protocol*

Patients received an intravenous injection of 2 MBq/kg ^{68}Ga-PSMA 45-60 min before the imaging. ^{68}Ga-PSMA PET / CT imaging of all patients was performed with General Electric Discovery PET / CT 600 (GE Medical Systems, LLC, 3000 N. GRANDVIEW BLVD., WAUKESHA, WI., U.S.A.) device. Firstly, CT imaging was performed at 120 kV, 172 mAs, and axial slice thickness of 2.5 mm with a 16-section scanner for attenuation correction and anatomical correlation. PET imaging was performed in three dimensions, including cranium and feet, for approximately 3 minutes in each bed position. Using the iterative reconstruction method, CT and PET images were matched and fused into transaxial, coronal, and sagittal images. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing Workstation (AW Volume Share5 GE Medical Systems S.C.S, France). And then visual and semi-quantitative analysis was performed by nuclear medicine expert. The SUVmax computed by standard methods from the activity in the most intense voxel in the 3-D tumor region from the transaxial whole-body images.

Statistical Analyses

Statistical analyses were performed using the SPSS software version 23. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogrow-Smirnov/Shapiro-Wilk's test) to determine whether normally distributed. The Chi-square test or Fisher's exact test where appropriate, was used to com-

Table 1. Factors associated with SUVmax values of prostate and overall survival.

		Prostate SUVmax Levels		*p*
		< 11.5* n = 30 (49.1%)	≥ 11.5 n = (50.8%)	
Serum PSA	≤10	10 (33.3)	7 (22.6)	0.644
	10-20	5 (13.3)	5 (16.1)	
	>20	16 (53.3)	19 (61.3)	
Gleason score	≤6	5 (16.7)	4 (12.9)	0.619
	7	5 (16.7)	3 (9.7)	
	8-10	20 (66.7)	24 (77.4)	
Presence of metastasis in any tissue	Absent	5 (45.5)	6 (54.5)	0.785
	Present	25 (50.0)	25 (50.0)	
Presence of bone metastasis	Absent	9 (50.0)	9 (50.0)	0.934
	Present	21 (48.8)	22 (51.2)	
Presence of widespread bone metastasis	Absent	11 (42.3)	15 (57.7)	0. 355
	Present	19 (54.3)	16 (45.7)	
5 years Overall Survival		70%	73%	0.541

*Median prostate SUVmax: 11.5 (2-70.7). Presence of widespread bone metastasis: more than five bone metastases.

pare these proportions in different groups. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. Survival outcomes were characterized using the Kaplan-Meier method and were compared using log-rank tests. The prognostic significance of prostate SUVmax, LDH, and ALP was assessed by univariate analyses. A *p*-value of less than 0.05 was considered to show a statistically significant result.

Results

The median age of the patients included in this study was 73 (range: 57-89). All 61 patients were adenocarcinoma. Gleason score was 9 (4 + 5 or 5 + 4) and above at the time of primary diagnosis in 26 (42.6%) of the patients. Fifty (82%) of the patients had metastasis. There were bone and lymph node metastasis in 22 patients (44%), only bone metastasis in 13 patients (26%), visceral organ metastasis in 11 patients (22%), and only lymph node metastasis in 4 patients (8%),

Median prostate SUVmax was measured as 11.5 (2-70.7), and the median metastasis SUVmax was 17.4 (1.8-141). There was a statistically significant negative correlation between prostate SUVmax and ALP levels, while there was no statistically significant association between prostate SUVmax and LDH and serum PSA levels. In terms of overall survival, prostate SUVmax has not been identified as a prognostic factor. Table 1 shows the factors associated with prostate SUVmax and overall 5-year survival. No significant correlation was found between serum LDH and PSA levels ($p = 0.066$, r = 0.26). Also, no correlation was found between the prostate SUVmax value and LDH (p = 0.345). In terms of OS, LDH has not been identified as a prognostic factor. Table 2 shows the factors associated with LDH and overall 5-year survival. There was a positive correlation between serum ALP and serum PSA ($p = 0.001$, r = +0.43). However, a negative correlation was found between prostate SUVmax values and ALP ($p = 0.019$, r = -0.271). A significant correlation was found between high ALP (> 120 U / L, normal value: 30-120 U / L) values and serum PSA levels and metastasis rates ($p = 0.044$ and p = 0.039 respectively). Considering the presence of bone metastases alone; Although no statistically significant relationship was found between bone metastasis rates in patients with high ALP levels ($p = 0.052$), a statistically significant relationship was found with the presence of widespread bone metastasis ($p = 0.004$). In terms of OS, ALP has not been identified as a prognostic factor. Table 3 shows the factors associated with ALP and overall 5-year survival.

Survival Analysis

The median follow-up time of all patients was 17 (6-183) months. At the time of the last follow-up visit, 53 (86.9%) patients were alive, and 8 (13.1%) patients were dead. According to univariate analysis, LDH, ALP, and prostate SUVmax were not significant risk factors for OS ($p > 0.05$) (Fig. 1).

Discussion

In this study, we found that SUVmax and serum ALP levels were negatively correlated in prostate cancer patients, but no correlation was found between LDH and SUVmax levels. And also high ALP values were found to be related to metastasis rates and severity and high serum PSA values.

Table 2. Factors associated with LDH (Lactate Dehydrogenase) levels and overall survival.

		LDH Levels		*p*
		Normal* n = 27 (52.9%)	High n = 24 (47.1%)	
Serum PSA	≤10	10 (37.0)	4 (16.7)	0.262
	10-20	3 (11.1)	4 (16.7)	
	>20	14 (51.9)	16 (66.7)	
Gleason score	≤6	5 (18.5)	3 (1.5)	0.539
	7	2 (7.4)	4 (16.7)	
	8-10	20 (74.1)	17 (70.8)	
Presence of metastasis in any tissue	Absent	4 (57.1)	3 (42.9)	0.421
	Present	18 (40.9)	26 (59.1)	
Presence of bone metastasis	Absent	7 (58.3)	5 (41.7)	0.224
	Present	15 (38.5)	24 (61.5)	
Presence of widespread bone metastasis	Absent	11 (55)	9 (45)	0. 169
	Present	11 (35.5)	20 (64.5)	
5 years Overall Survival (%)		100%	63%	0.059

*Normal LDH: 135-225 U/L. Presence of widespread bone metastasis: more than five bone metastases.

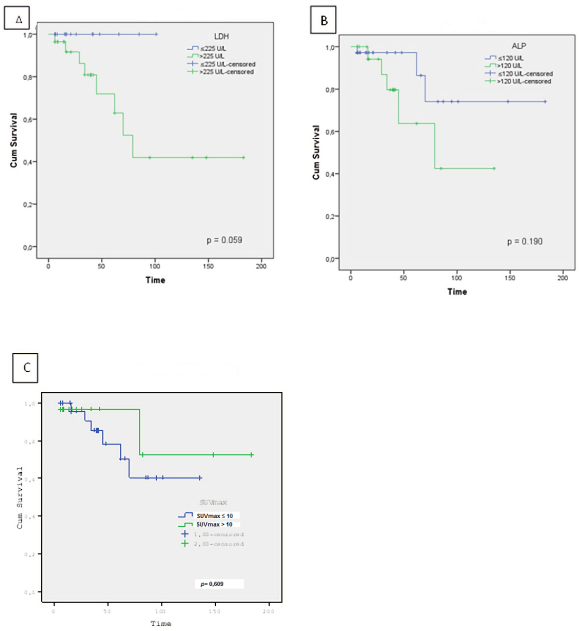


Fig. 1. Kaplan-Meier Analysis of Overall Survival for Prostate Cancer Patients. A) LDH U/L ≤ 225 versus > 225; B) ALP ≤ 120 U/L versus > 120 U/L; and C) SUVmax ≤ 10 versus >10. LDH= Lactate Dehydrogenase; ALP= Alkaline Phosphatase.

In prostate cancers, although it has a long survival when localized in the prostate gland, metastatic prostate cancers are often incurable despite intensive multimodal treatments. PET / CT with ^{68}Ga-PSMA is a non-invasive imaging method that evaluates PSMA expression which has prognostic significance (13). According to previous studies, ^{68}Ga-PSMA PET / CT is effective in showing the presence of tumors in the prostate and the SUVmax value of the prostate is related to the primary tumor grade (14, 15). ^{68}Ga-PSMA PET / CT can detect metastasis even even if PSA values are very low (16). However, according to the study of Budäus *et al.* (14), its effectiveness in showing lymph node metastasis may vary according to lymph node size. In our study, no statistically significant relationship was found between prostate SUVmax value and PSA levels, and Gleason scores. Also, there was no difference between the prostate SUVmax value and the rate of metastasis (in any organ or bone). Prostate SUVmax was not detected as a prognostic factor in survival analysis.

LDH and ALP are known to have prognostic significance in patients with prostate cancer (4, 17). Tumors often use anaerobic metabolism and LDH plays an important role in tumor metabolism, which controls the conversion of pyruvate to lactate. (8). While breast, colon, cervical, and liver cancers have increased glucose metabolism and uptake, prostate cancers become independent from glucose consumption and continue to grow with lactate, leading to anabolic pathways (18). This is probably why early-stage tumors usually do not have high LDH. It is used to evaluate treatment responses, and assess prognosis. According to the study of Naruse K *et al.* (19), high LDH is an excellent prognostic indicator in bone metastatic prostate cancers and they reported that high levels of LDH may be indicative of tissue damage in advanced cancers. Although not statistically significant, we found that the presence of bone metastases and the prevalence of bone metastases was higher in patients with high LDH levels (Table 3). In most studies, LDH is interpreted as a prognostic marker and its increase is shown as a risk for the progression of the disease (20). In our study, it was found that survival rates decreased significantly at high LDH levels (Figure 1). Although the data appear to be not statistically significant, considering the p-

Table 3. Factors associated with ALP (Alkaline Phosphatase) levels and overall survival.

		ALP Levels		*p*
		Normal* n = 36 (61%)	High n = 23 (39%)	
Serum PSA	≤10	13 (36.1)	2 (8.7)	**0.044**
	10-20	5 (13.9)	4 (17.4)	
	>20	18 (50.0)	17 (73.9)	
Gleason score	≤6	7 (19.4)	1 (4.3)	0.107
	7	6 (16.7)	2 (8.7)	
	8-10	23 (63.9)	20 (87.0)	
Presence of metastasis in any tissue	Absent	9 (90.0)	1 (10.0)	**0.039**
	Present	27 (55.1)	22 (44.9)	
Presence of bone metastasis	Absent	13 (81.3)	3 (18.8)	0.052
	Present	23 (53.5)	20 (46.5)	
Presence of widespread bone metastasis	Absent	20 (83.3)	4 (16.7)	**0.004**
	Present	16 (45.7)	19 (54.3)	
5 years Overall Survival (%)		86%	64%	0.190

*Normal ALP: 30-120 U/L, Presence of widespread bone metastasis: more than five bone metastases. Bold phrases: $p < 0.05$.

value (p = 0.059), this situation may be due to the number of patients. In our study, LDH values could not be determined as an indicator both in terms of prognosis and tumor aggressiveness.

Prostate cancers cause osteoblastic bone metastases by activating stromal cells in the bone microenvironment and stimulating the activity of osteoblasts (bone morphogenic proteins, sonic hedgehog, etc) (21). Basal ALP levels are prognostic markers for overall survival in metastatic castration-resistant prostate cancers. It is a more significant marker than PSA especially for bone metastases (22). It is also considered as an independent predictive marker for radioligand treatment responses with ^{177}Lu-PSMA (17). In our study, there was a significant relationship with ALP levels and the presence of metastasis in any organ, including bone. Although the relationship between ALP levels was not statistically significant in patients with bone metastasis alone, when the p-value was taken into account (p = 0.052), this situation may be related to the number of patients and suggest that the number of metastatic lesions may also be effective in these finding. Thus, the relationship between patients with widespread bone metastasis and ALP levels was found to be significant in our study. Also, considering all data, it was found that the rate of both bone and other organ metastases was lower in patients with normal ALP levels. Also, it was observed that high ALP values increased the likelihood of high serum PSA values. This makes us think that it is important to follow ALP levels in terms of metastasis during the follow-up of the patients. However, its prognostic significance for overall survival has not been demonstrated.

In our study, there was no statistical significance regarding prostate SUVmax, LDH and ALP levels, and 5-year survival of patients. However, this is thought to be due to the short follow-up period of the patients. And a series of more than 40% of Gleason ≥ 9 patients, and more than 80% metastatic is probably highly selected, and therefore difficult for any prognostic marker to discriminate between cases of better or worse prognosis. Also, another big limitation in our study was the insufficient number of patients, and ALP and LDH tests were not performed in some patients due to the retrospective nature of our study. Another limitation of the study was that the patient group was heterogeneous since it included patients who had previously received chemotherapy and / or radiotherapy. Another limitation of our study was that the causes of death were not included in our study and the cancer-specific mortality could not be calculated.

In conclusion, there was a negative correlation between SUVmax and ALP levels, but no correlation was found between LDH and SUVmax levels. And also high ALP values were found to be related to metastasis rates and severity and high serum PSA values.

Author Contributions

SAE, İŞ, BY, ÖUB, ZH—medical practices; SAE, İŞ, BY, ZH—concept; SAE, İŞ, BY, ZH—design; SAE, ÖUB, ZH—data collection or processing; SAE, İŞ, BY, ZH—analysisor interpretation; SAE, İŞ, BY, ÖUB, ZH—literature search; SAE, İŞ, BY, ZH—writing.

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Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interests

The authors declare no potential conflicts of interest.

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