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Prostat Hacmi hem Prostat Kanserini hem de Gleason Skoru 7 veya Üzeri Olan Klinik Olarak Önemli Prostat Kanserini Öngörmede Tek Başına Güçlü Bir Araçtır

Prostate Volume Is a Strong Stand-Alone Tool in Predicting Both Prostate Cancer and Clinically Significant Prostate Cancer With a Gleason Score of 7 or Above

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ÖZ

GİRİŞ ve AMAÇ: *Prostat hacminin (PH), PSA dansitesinin (PSAD) ve serbest/total PSA oranının (s/tPSA) PSA değeri <10ng/mL ve 10.1-30 ng/mL olan hastalarda prostat kanseri ve klinik olarak anlamlı prostat kanserini öngörmedeki etkinliklerinin araştırılması amaçlanmıştır.*

YÖNTEM ve GEREÇLER: *Ocak 2015 - Haziran 2019 tarihleri arasında kliniğimizde transrektal ultrasonografi (TRUS) eşliğinde prostat biyopsisi yapılan 1682 hastanın verileri retrospektif olarak incelenmiştir. Klinik anlamlı PCa, Gleason skoru 7 veya üstü olarak tanımlanmıştır.*

BULGULAR: *Çalışmaya yaş, toplam-serbest PSA düzeyi ve TRUS ile hesaplanan prostat hacimleri bulunan 778 hasta dahil edilmiştir. PSA değeri <10ng/mL olan hastalar için hem PH hem de PSAD, PCa'nın bağımsız prediktörleri olarak bulunmuştur. Buna karşın, PSA >10ng/mL olan hastalar içinse sadece PH'nin PCa'nın bağımsız bir prediktörü olduğu bulunmuştur. ROC analizi, PSA <10ng/mL olan hastalarda PH için 51.5 cc bir kesme değeri ve PSA >10ng/mL olan hastalarda ise PH için 62.5 cc bir kesme değeri ortaya çıkarmıştır. ROC analizi, PSA <10ng/mL olan hastalarda PSAD için 0.099 kesme değerini ortaya çıkarmıştır. PSA <10ng/mL grubunda PV ve PSAD için önerilen kesme değerlerine göre, klinik olarak anlamlı kanseri olan ve olmayan hastalar arasında anlamlı bir fark varken, PSA >10ng/mL grubunda PV için önerilen kesme değerine göre anlamlı bir fark görülmemiştir.*

TARTIŞMA ve SONUÇ: *Prostat hacmi, PSA dansitesinin ve serbest/total PSA oranının bir adım önünde görülmektedir. Prostat hacmi, prostat biyopsisi için karar verme aşamasında aktif bir rol oynayabilir fakat bu sonuçlar yapılacak ileri çalışmalar ile doğrulanmalıdır.*

Anahtar Kelimeler: *Gleason skoru, Klinik anlamlı prostat kanseri, Prostat kanseri, Prostat Hacmi, PSA dansitesi, Serbest/total PSA oranı.*

ABSTRACT

GİRİŞ ve AMAÇ: *Prostat hacminin (PH), PSA dansitesinin (PSAD) ve serbest/total PSA oranının (s/tPSA) PSA değeri <10ng/mL ve 10.1-30 ng/mL olan hastalarda prostat kanseri ve klinik olarak anlamlı prostat kanserini öngörmedeki etkinliklerinin araştırılması amaçlanmıştır.*

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer in the world and is the second leading cause of cancer-related death in men (1). PCa usually proceeds insidiously, so patients are unlikely to get medical help at an early stage. Due to this feature of the disease, Prostate-specific antigen (PSA) is widely used worldwide for early detection of the disease. However, serum PSA levels can increase due to a rise in PSA production, an increase in vascular permeability, or due to disruption of tissue architecture. That's why both benign and malignant prostatic diseases can be associated with increased PSA serum levels. This difficulty in diagnosis due to the low specificity of PSA was tried to be over come in numerous studies with alternative parameters such as PSA density (PSAD), free PSA to total PSA ratio (f/tPSA), PSA velocity and age-referenced PSA. However contrary to these parameters, prostate volume has been evaluated for this purpose in a limited number of study.

These parameters were particularly investigated in patients in the gray zone which refers to the PSA interval between 4-10 ng/mL. However the population used to define the PSA gray zone was originally from Western countries. On the other hand, there are publications from Asian countries that the gray zone range may be higher for them due to the lower incidence of PCa (2, 3). Furthermore, chronic prostatitis has been reported to be a common cause of serum PSA elevation above 10 ng/mL in the Asian and Arab population of Kuwait, Egypt, Turkey and Singapore (4-7). Consequently, evaluating the effectiveness of above mentioned parameters in men with a PSA level of >10ng/mL is particularly pertinent to avoid unnecessary prostate biopsies.

In two patient groups with a PSA value < 10ng/mL and a PSA value between 10 and 30ng/mL, we aimed to investigate the effectiveness of PSAD and f/tPSA as well as PV in predicting prostate cancer and clinically significant prostate cancer and it was also aimed to determine the eligible cut-off values of these parameters in predicting prostate cancer and clinically significant prostate cancer.

MATERIALS AND METHODS

The data of 1682 men who underwent transrectal ultrasound (TRUS) guided prostate biopsy in our clinic between January 2015 and June 2019 were analyzed retrospectively. Having abnormal digital rectal examination (DRE) and/or serum PSA levels above 2.5 ng/mL formed our indication for prostate biopsy. Patients with PSA levels >30ng/mL (11 patients), aged <40 years (1 patient) or > 80 years (9 patients), with a history of 5alpha-reductase inhibitor therapy (58 patients) or any invasive therapy for BPH (36 patients) were excluded. Serum PSA levels were measured in ng/mL using the chemiluminescent microparticle immunoassay (CMIA) and all serum samples were drawn before any prostate manipulation including DRE, TRUS and biopsy. Two groups were formed according to whether PSA was lower or higher than 10 ng/mL. f/tPSA was calculated as the ratio of free PSA to total PSA, multiplied by 100. The pre-biopsy PV of the patients were calculated by measuring three dimensions of the prostate with TRUS, and using the ellipsoid formula (PV= height*width*length*0.52). In our clinic biopsy samples are routinely obtained as 12 cores and patients included in the study are those who have received at least 12 core biopsies. Histological evaluation divided each patient's prostate specimen into either cancerous (Prostate adenocarsinoma) or non-cancerous pathological cathegory (BPH and/or chronic prostatitis). Gleason score were classified as $\leq$6 and $\geq$7 in the cancer group. Clinical significant PCa was defined as Gleason score 7 or above. Patients who underwent multiple biopsies were included in the study according to the final biopsy result and the PSA and volume values of the last biopsy period.

The patients' age, total-free PSA value, pathology results and Gleason score were evaluated and the efficiency of PV, PSAD and f/tPSA in predicting PCa and clinically significant PCa, was investigated separately for the lower PSA and higher PSA groups.

Statistical analysis

The IBM SPSS software package version 21.0 (Statistical Package for Social Sciences™, Chicago, IL, USA) was used for statistical analysis and $p < 0.05$ was considered as significant. The Shapiro-Wilk test was used to evaluate the conformance of the data to the normal distribution curve. The continuous and categorical data were compared using the Mann-Whitney U-test and the chi-square test, respectively. The relationship of biopsy results with age, total-free PSA, PV, f/tPSA, PSAD and the Gleason score was investigated by a univariate analysis using the Mann-Whitney U and chi-square tests for the groups with PSA levels <10ng/mL and >10 ng/mL. Logistic regression multivariate analysis was performed to determine the independent predictive factors for malignant prostate biopsy results. The receiver operating characteristic (ROC) curve was employed to evaluate and compare the efficacy of PV, PSAD and f/tPSA for the diagnosis of PCa.

RESULTS

After applying the exclusion criteria, 778 patients with the available data of age, total-free PSA levels and PV calculated by TRUS were included the study. PCa was detected in 216 patients (27.7%) and the remaining 562 patients (72.3%) were diagnosed as BPH. Table 1 shows the clinical characteristics of patients. The PCa group was significantly older than the BPH group (p= <0.001). The differences in total PSA (tPSA), free PSA (fPSA), f/tPSA, PV, PSAD for patients with and without PCa were statistically significant (p= 0.003, p= 0.027, p= <0.001, p= <0.001, p= <0.001, respectively, Mann-Whitney U-test). Mean (±SD) and median (IQR) values of both groups were shown in Table 2.

For patients with a PSA value of <10 ng/mL there was no statistically significant difference between cancer and non-cancer groups for tPSA (p= 0.143). The mean value of fPSA, f/tPSA and PV were significantly lower in patients with PCa (p= 0.007, p <0.001 and p <0.001, respectively). The mean value of age and PSAD were significantly higher in patients with PCa (p= 0.021 and p <0.001, respectively). For patients with a PSA value of >10 ng/mL there were no statistically significant differences between cancer and non-cancer groups for age and tPSA (p= 0.056 and p= 0.291, respectively). The mean value of fPSA, f/tPSA and PV were significantly lower in patients with PCa that p values for all three parameters were <0.001. PSAD was significantly higher in patients with PCa (p= <0.001). Number of patients in each PSA group and mean (±SD) and median (IQR) values were shown in Table 3.

In patients with PSA <10ng/mL, area under curves (AUC) for PV, PSAD and f/tPSA were 0.749, 0.746 and 0.609, respectively and in patients with PSA >10ng/mL, those were 0.824, 0.805 and 0.697, respectively. According to this, for both PSA groups, the order of AUC values in predicting PCa was determined as PV > PSAD > f/tPSA (**Figure** 1- and Table 4).

Parameters with p value <0.001 in univariate analysis were then evaluated by multivariate analysis. According to multivariate analysis, both PV and PSAD were found to be independent predictors of PCa, unlike f/tPSA, for patients with PSA <10ng/mL. (p values= 0.003, <0.001 and 0.763). For patients with PSA> 10ng/mL only PV was found to be a significant predictor of PCa with p value <0.001 (Table 5).

Table 1. Clinical characteristics of patients.

	Age (years)	total PSA (ng/mL)	free PSA (ng/mL)	free/total PSA ratio	PV (cc)	PSAD (ng/mL/cc)	Biopsy results		
							PCa	BPH	Total
Mean ± SD	64.86 ± 7.346	8.79 ± 5.393	1.99 ± 1.559	0.23 ± 0.112	75.40 ± 52.849	0.16 ± 0.172	-	-	-
Median (IQR)	65 (60-70)	7,1 (5.21-10.28)	1,57 (1.06-2.37)	0,21 (0.15-0.30)	66 (44-95.25)	0,1 (0.07-0.17)			
n (%)	-						216 (27,7%)	562 (72,3%)	778 (100%)

PV: prostate volume, PSA: prostate specific antigen, PSAD: prostate specific antigen density, PCa: prostate cancer, BPH: benign prostate hyperplasia, SD: standard deviation, IQR: interquartile range.

Table 2. Comparison of patients' age, total PSA, free PSA, free/total PSA ratio, prostate volume and PSA density between prostate cancer and non-prostate cancer groups.

Parameters	Prostate cancer group (n=216)	Non-cancer group (n=562)	p value*
Age (years) Mean±SD Median (IQR)	66.31±7.158 66 (62-71)	64.31±7.348 64 (59-69)	**<0.001**
Total PSA (ng/mL) Mean±SD Median (IQR)	9.82±6.261 7.82 (5.62-11.61)	8.39±4.968 6.76 (5.09-9.85)	**0.003**
Free PSA (ng/mL) Mean±SD Median (IQR)	1.85±1.586 1.5 (0.97-2.13)	2.04±1.547 1.64 (1.1-2.45)	**0.027**
Free/Total PSA Mean±SD Median (IQR)	0.20±0.111 0.17 (0.13-0.25)	0.24±0.110 0.23 (0.17-0.31)	**<0.001**
Prostatevolume (cc) Mean±SD Median (IQR)	50.57±29.928 44.5 (32-62.75)	84.94±56.538 75.5 (53-103.25)	**<0.001**
PSAD (ng/mL/cc) Mean±SD Median (IQR)	0.26±0.252 0.18 (0.11-0.31)	0.12±0.105 0.09 (0.06-0.13)	**<0.001**

*Mann-Whitney U test.
PSA: prostates pecific antigen, PSAD: prostate specific antigen density.

We set cut-off values for parameters that are independent predictors, according to this for PV ROC analysis revealed a cut-off value of 51.5 cc in patients with PSA < 10 ng/mL and a cut-off value of 62.5 cc in patients with PSA > 10ng/mL. At the cut-off values of 51.5 and 62.5, the sensitivities and specifities were 75%, 62% and 78%, 73%, respectively. For PSAD ROC analysis revealed a cut-off value of 0.099 in patients with PSA < 10 ng/mL and a cut-off value of 0.19 cc in patients with PSA > 10ng/mL. At the cut-off values of 0.099 and 0.19, the sensitivities and specifities were 74%, 81% and 66%, 68%, respectively.

In patients with PSA <10 ng/mL, men with a PV of <51.5 cc were found to be an increased risk of having PCa with an odds ratio of 1.016

(CI: 1.005-1.026) when compared to those with a PV of > 51.5 cc. Similarly, in patients with PSA >10 ng/mL, men with a PV of < 62.5 cc were found to be an increased risk of having PCa with an odds ratio of 1.032 (CI: 1.015-1.049) when compared to those with a PV of > 62.5 cc. In patients with PSA <10 ng/mL, men with a PSAD of > 0.099 were found to be an increased risk of having PCa with an odds ratio of 0.001 (CI: 0.000-0.045) when compared to

those with a PSAD of <0.099 (Table 5, Table 6 and Table 7).

Table 3. Comprasion of patients' age, total PSA, free PSA, free/total PSA ratio, prostate volume and PSAD between cancer and non-cancer groups with PSA <10ng/mL and PSA>10ng/mL.

	PSA<10ng/mL (n= 569)			**PSA>10ng/mL** (n= 209)		
Parameters	**Biopsy result**		**p value**	**Biopsy result**		**p value**
	Cancer	**Non-cancer**		**Cancer**	**Non-cancer**	
Number of pateints n (%)	144 (25.4%)	425 (74.6%)		72 (34.5%)	137 (65.5%)	
Age (years) Mean±SD Median (IQR)	65.01±7,102 65 (61-69.75)	63.52±7.222 64 (59-68)	**0.021**	68.9±6.580 69 (65-73.75)	66.74±7.229 67 (62-72.5)	0.056
Total PSA (ng/mL) Mean±SD Median (IQR)	6.37±1.922 6.32 (5.08-7.83)	6.13±1.870 5.97 (4.71-7.43)	0.143	16.72±6.241 14.56 (11.6-21.4)	15.39±5.06 13.84(11.64-17.39)	0.291
Free PSA (ng/mL) Mean±SD Median (IQR)	1.37±0.873 1.25 (0.84-1.69)	1.51±0.734 1.4 (0.97-1.96)	**0.007**	281±2.164 2.23 (1.6-3.43)	3.66±2.163 3.15 (2.12-4.73)	**<0.001**
Free/Total PSA Mean±SD Median (IQR)	0.21±0,115 0.19 (0.14-0.28)	0.25±0.109 0.23 (0.17-0.31)	**<0.001**	0.16±0.091 0.15 (0.1-0.2)	0.239±0.115 0.23 (0.15-0.30)	**<0.001**
PV (cc) Mean±SD Median (IQR)	50.1±30.876 44 (30.25-61)	76.6±34.641 72 (52-96.5)	**<0.001**	51.53±28.122 45.5 (32.25-66)	110.77±92.498 96 (65.5-132.5)	**<0.001**
PSAD (ng/mL/cc) Mean±SD Median (IQR)	0.17±0.108 0.14 (0.09-0.23)	0.09±0.062 0.09 (0.06-0.11)	**<0.001**	0.447±0.344 0.33 (0.21-0.54)	0.20±0.159 0.15 (0.1-0.22)	**<0.001**

*Mann-Whitney U test.
PSA: prostate specific antigen, PSAD: prostate specific antigen density, PV: prostate volume.

Table 4. The AUCs for free/total PSA ratio, prostate volume and PSA density in predicting risk of prostate cancer stratified by PSA

	AUC	%95 CI	p value
PSA<10 ng/mL			
PV	0.749	0.703-0.795	**<0.001**
PSAD	0.746	0.696-0.796	**<0.001**
f/t PSA	0.609	0.555-0.663	**<0.001**
PSA>10 ng/mL			
PV	0.824	0.767-0.881	**<0.001**
PSAD	0.805	0.744-0.866	**<0.001**
f/t PSA	0.697	0.623-0.771	**<0.001**

AUC: area under curve, CI: confidence interval, f/t PSA: free/total PSA ratio,
PSA: prostate specific antigen, PSAD: prostate specific antigen density, PV: prostate volume.

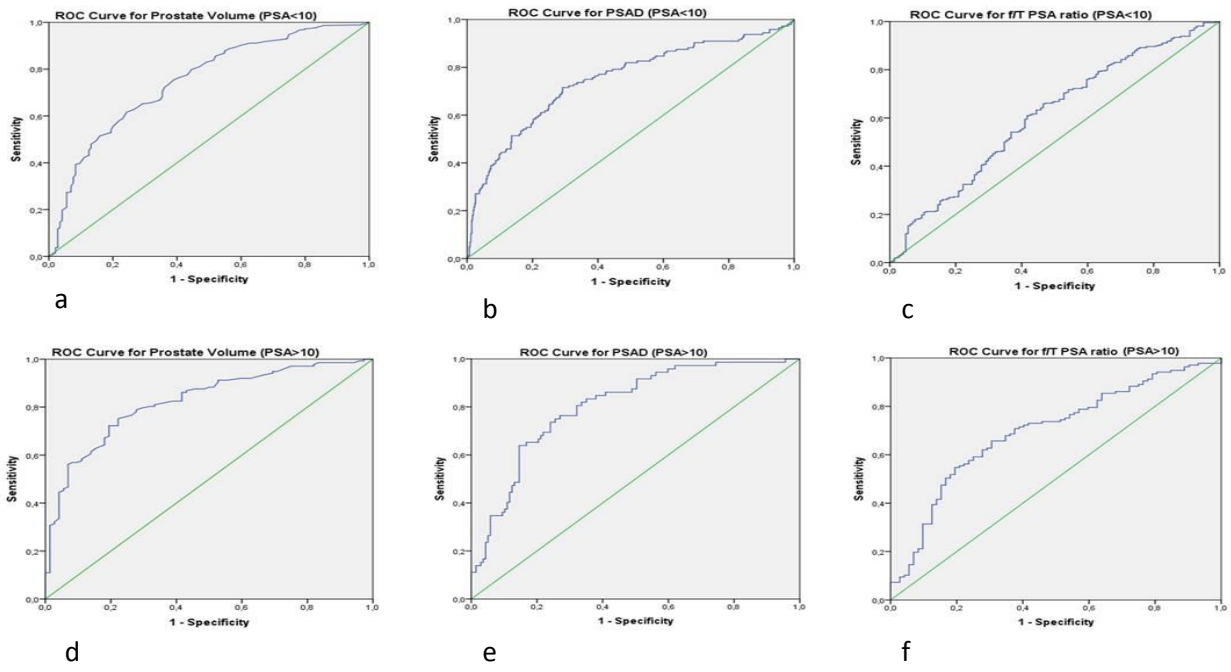

Figure 1. a. ROC Curve of Prostate Volume for PSA <10 ng/mL group. b. ROC Curve of PSA Density for PSA <10 ng/mL group. c. ROC Curve of free to total PSA ratio for PSA <10 ng/mL group. d. ROC Curve of Prostate Volume for PSA >10 ng/mL group. e. ROC Curve of PSA Density for PSA >10 ng/mL group. f. ROC Curve of free to total PSA ratio for PSA >10 ng/mL group.

Tablo 5. Multivarite analyses for patients with PSA<10 ng/mL and PSA>10ng/mL.

	PSA<10			PSA>10		
	OR	%95CI	p	OR	%95CI	p
PV	1.016	1.005-1.026	**0.003**	1.032	1.015-1.049	**<0.001**
PSAD	0.001	0.000-0.045	**<0.001**	0.405	0.054-3.048	0.380
f/t PSA	1.348	0.194-9.391	0.763	1.445	0.039-52.97	0.843

PSA: prostate specific antigen, PSAD: prostate specific antigen density
PV: prostate volume, OR: odds ratio, CI: confidence interval, f/t PSA: free/total PSA ratio.

According to the cut-off values given for PV and PSAD in patients with PSA <10ng/mL, a significant result was found between patients with and without clinically significant PCa whereas, no significant result was seen in patients with PSA >10 ng/mL according to cut-off values of that group. p values and patient numbers are shown in tables 6 and 7.

Tablo 6. Comparison of patients' biopsy results and Gleason scores according to the cut-off volue of prostate volume in the groups of PSA<10 ng/mL and PSA>10ng/mL.

	PSA < 10ng/mL			PSA > 10ng/mL		
Parameters	**PV**		**p value**	**PV**		**p value**
	<51.5 cc	**>51.5 cc**		**<62.5 cc**	**>62.5 cc**	
Number of patients n (%)	193 (33.9%)	376 (66.1%)		81 (38.7%)	128 (61.3%)	
Biopsy result **Cancer n (%)**	88 (45.6%)	56 (14.9%)	**<0.001**	52 (64.2%)	20 (27.8%)	**<0.001**
Non-cancer n (%)	105 (54.4%)	320 (85.1%)		29 (35.8%)	108 (84.4%)	
Gleason score **≤6** n (%)	53 (60.2%)	43 (76.8%)	**0.040**	29 (55.8%)	14 (69.9%)	
≥7 n (%)	35 (39.8%)	13 (23.2%)		23 (44.2%)	6 (30.1%)	0.270

Tablo 7. Comprasion of patients' biopsy results and Gleason scores according to the cut-off volue of PSAD in the groups of PSA<10 ng/mL and PSA>10ng/mL.

	PSA<10ng/mL			PSA>10ng/mL		
Parameters	**PSAD**		**p value**	**PSAD**		**p value**
	<0.099	**>0.099**		**<0.19**	**>0.19**	
Number of pateints n (%)	319 (56.1%)	250 (43.9%)		106 (50.7%)	103 (49.3%)	
Biopsy result **Cancer** n (%)	38 (11.9%)	106 (42.4%)	**<0.001**	14 (13.2%)	58 (56.3%)	**<0.001**
Non-cancer n (%)	281 (88.1%)	144 (57.6%)		92 (86.8%)	45 (43.7%)	
Gleason score **≤6** n (%)	31 (81.6%)	65 (61.3%)		11 (78.6%)	32 (55.2%)	
≥7 n (%)	7 (18.4%)	41 (38.7%)	**0.023**	3 (21.4%)	26 (44.8%)	0.109

DISCUSSION

Currently, the prostate cancer diagnostic pathway still puts more value on total PSA (tPSA) than on multifactorial individual risk stratification. Research on PSA derived markers and risk stratification tools has failed to translate into clinical practice. Whereas, although the determination of tPSA is recognized as the best diagnostic tool for the early detection of PCa, the specificity of tPSA is not sufficient. When PSA alone is used to predict the probability of PCa within the 4-10 ng/mL range, approximately 75% of all biopsies will be negative (8). Therefore, tPSA-associated parameters have been identified to reduce the number of unnecessary biopsies. Among these parameters, f/tPSA and PSAD are the most studied in the literature. In contrast to these two parameters, there are only a limited number of study in which prostate volume (PV) alone is used as a diagnostic tool in predicting PCa, although there are studies showing that PV is significantly lower in patients with PCa than patients without PCa (9, 10). Therefore, we considered PV alone as a parameter that could refine the interpretation of PSA in patients with suspected PCa.

Accordingly, all three parameters were significantly different in patients with and without cancer in both PSA groups (Table 3).

Moreover, regarding the AUC, PSAD and PV showed similar efficacy, but both performed better than f/tPSA (Table 4). In multivariate analysis, in patients with PSA <10ng/mL, unlike f/tPSA, PV and PSAD were found as independent predictors for positive biopsy results however in patients with PSA >10ng/mL, PV outperformed both PSAD and f/tPSA (Table 5). Although the superiority of PSAD over f/tPSA found in our study was similar to only a few studies (11-13), many studies have shown that these two parameters have similar efficacy (14-18). However, these studies were performed on patients with a PSA value in the gray zone. Similar to our study, Stephan et al. (19) showed that PSAD was superior to f/tPSA but this result was shown in patients with a PSA interval between 2 and 4 ng/mL. In accordance with these information, difference between the majority of the literature and the current study was attributed to the presence of patients with PSA <4ng/mL (n=62, 10.8%) in the PSA <10ng/mL group (n=569). The analysis of cut-off levels for PSAD revealed an important tendency that the higher the tPSA range, the higher the PSAD cut-off levels. Accordingly, the cut-off value for patients with PSA <10ng/mL was 0.099, whereas for patients with PSA >10ng/mL, it was 0.19. Stephan et al. (19) reported similar values of 0.1 and 0.19 for patients with PSA between 4-10 ng/mL and PSA between 10-20 ng/mL, respectively. These cut-off values are in contrast to most other studies which usually preferred PSAD cut-off levels around 0.15 (20-22) but for cut-off recommendations, the consideration of total PSA as affecting factors in PSAD probably would work best due to the tendency in our study.

When making distinction between PCa and BPH, actually the aim is to identify PCa which is of clinical significance. That's why, we also compared Gleason score according to clinical significance for cancer patients in both PSA groups for these cut-off values of PSAD. In the PSA <10ng/mL group, 7 of the 38 patients (18.4%) with a PSAD <0.099 had Gleason score ≥7, whereas 41 of 106 patients (38.7%) with a PSAD >0.099 had Gleason score ≥7 (p= 0.023, Table 7). In the PSA >10ng/mL group, there was no significant difference in Gleason score among cancer patients with PSAD less than 0.19 and PSAD higher than 0.19 (p=0.109, Table 7). This result is in line with another result of the current study that PSAD was not significant in multivariate analysis to predict PCa in patients with PSA >10ng/mL. San Francisco et al. (23) concluded that in active surveillance patients PSAD > 0.08 in the first re-biopsy, which was close to the value in our study, was an important predictor of subsequent progression. When we evaluate our own data together with this study, we think that PSAD <0.15, which is one of the criteria suggested by the European Association of Urology (EAU) guidelines for active surveillance, may be decreased with the new studies to be published. Although it has not been investigated in our study, in some studies, it was emphasized that the reference values of PSAD changed in different prostate volumes (19, 24, 25). We interpret that the fact which reference values for PSAD is dependent on PV, poses a disadvantage to PSAD versus PV in terms of being a diagnostic tool for predicting PCa.

In the current study, for both PSA groups, only the PV was an independent predictor for the detection of PCa. In the PSA <10ng/mL group, 88 of the 193 patients (45.6%) with a PV of <51.5 cc had cancer, whereas 320 of 376 patients (85.1%) with a PV of >51.5 cc had benign biopsy results. Similarly, in the PSA >10ng/mL group, 52 of 81 patients (64.2%) with a PV of <62.5 mL had cancer, while 108 of 128 patients (84.4%) with a PV of >62.5 mL

did not have cancer. In multivariate analysis, Erdoğan et al. (26) noted that PV as an independent predictor for PCa in patients with PSA levels 2.5-10 ng/mL and 10.1-30 ng/mL whereas f/tPSA and PSAD were not significant They reported that the cut-off values for PV were 43.5 cc and 61.5 cc in the PSA levels 2.5-10 ng/mL and 10.1-30 ng/mL, respectively. These cut-off values were relatively lower than those in our study. This result may be due to the difference in the mean PV values which were 63.8 and 75.4 in the study of Erdoğan et al. (26) and the current study, respectively. In another study, Kobayashi et al. (27) also reported that PV was a strong predictor of positive prostate biopsy results according to multivariate analysis in patients older than 70 years and using a cut-off of prostate volume <48 cc and <58 cc, 42.4% and 18.2% of specificities would be achieved with 90.2% and 95.3% of sensitivities retained, respectively, whereas PSAD was not. As a result of multivariate analysis, Shigemura et al. (28) showed that PV was a significant predictor for positive prostate biopsy, whereas PSAD was not. The results of these three studies (26-28) showing the superiority of PV to PSAD were similar to those of our PSA >10 ng/mL group, but differed from our PSA <10ng/mL group. Shigemura et al. (28) recommended 25 cc as the cut-off value for PV in patients with PSA <10ng/mL, but p values were 0.0497 and very close to the limit of significance. We interpret that this value, which is quite different from the 51.5 cc value given for the same patient group in our study, is due to the difference between the median values of PV between the two studies. (median values were 33.9 and 66 for Shigumura et al and our study, respectively.) On the other hand, we think that the fact that a remarkable majority of patients evaluated for suspicion of PCa would have a PV higher than 25 cc because of their possible advanced age, makes this cut-off value difficult to use in clinical practice. But ultimately, similar more studies aimed at investigating the efficacy of PV in predicting PCa are still needed to obtain more accurate cut-off values, such as for PSAD and f/tPSA.

There are studies reporting that the use of PV in risk calculators (RCs) increases predictive power for PCa. In Prostata Class (29), the Finne model (30), and the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator 3 (31), a higher prostate volume contributes to a lower likelihood of having prostate cancer. In contrast, Ankerst et al.'s analysis demonstrated PV to have only minor effect on risk assessment and they reported that prebiopsy imaging for the determination of PV is unnecessary in the assessment of PCa risk (32). With more data on PV, the importance of its place in RCs can be increased and more accurate estimates for the presence of PCa can be obtained. This situation may also increase the use of RCs that are still not systematically used in clinical practice. In addition Neves et al emphasized that considering these risk stratification tools were developed using cohorts with a median prostate volume between 30 and 50 cc, further analysis is needed to assess if there is benefit of using them in men with large prostates (over 100 cc in volume) (33).

For the cut-off values we recommend for PV, we also investigated whether there was a difference in Gleason scores according to clinical significance in patients with cancer, as we searched for PSAD. In the PSA <10ng/mL group, 53 of the 88 patients (60.2%) with a PV <51.5 cc had Gleason score ≥7, whereas 13 of 56 patients (23.2%) with a PV >51.5 cc had Gleason score ≥7 (p= 0.040, Table 5). As supporting our results, Chen et al. found that a tumor volume below 0.5 cc which is often considered a clinically insignificant PCa volume, was twice as frequent in large glands

greater than 50 cc (34). This finding also seems to be consistent with our report that the probability of clinically significant cancer in prostates over 51.5 cc was significantly less. In the PSA >10ng/mL group, there was no significant difference in Gleason scores among cancer patients with PV less than 62.5 cc and PV higher than 62.5 cc (p=0.270, Table 7). Contrary to our results, in the study of Erdoğan et al while there was a significant difference in Gleason scores according to clinically significant PCa in the PSA >10ng/mL group, no significant difference was found in the PSA <10ng/mL group (26). However, we emphasize that the fact that our results were found in patients with PSA <10ng/mL was more considerable for clinically significant PCa. At this point, PV alone may be a criterion for active surveillance in the future as a result of similar studies and new studies which aim to determine a cut-off value for PV to demonstrate progression in re-biopsies of patients under active surveillance as previously performed for PSAD, may be planned.

It is well established that PCa arises in about 80% from the peripheral zone (PZ), whereas BPH is caused by growth of the transitional zone (TZ) (35). It has been hypothesized that the BPH-related TZ enlargement could cause enough scarring and apoptosis of the epithelial cells in the PZ and thus significantly reducing the risk of developing PCa in the remaining epithelial glands. Arivazhagan et al. showed that there might be a relationship between increased PV and inflammatory events (36) and it is also known that PV increases with the advancing age of the patients [37]. These may be the causes of low diagnosis rates of PCa in high PVs in the present study.

In our study, f/tPSA was not significant in both PSA groups on multivariate analysis, and was behind both PSAD and PV in predicting PCa. This result where f/tPSA remains behind PV is similar to the two studies mentioned above (26, 27), whereas Bruno et al. found f/tPSA to be significant in multivariate analysis such as PV (38). In addition, another limitation of f/tPSA which was not the subject of our study but has been shown in other studies, is its insufficiency in discriminating between PCa and BPH in patients with large prostates where both diseases coexist (39). On the other hand, although PSAD and PV were superior to f/tPSA in the current study, it should be keep in mind that the need for TRUS is a limitation of PSAD and PV compared with f/tPSA in regard to time, cost and discomfort.

When evaluating parameters as diagnostic tools for PCa detection, the number of biopsy cores has been another subject of discussion. However, in the EAU guidelines, at least 8 systematic biopsies are recommended in prostates with a size of about 30 cc , 10 to 12 core biopsies are recommended in larger prostates and it is also mentioned that with > 12 cores not being significantly more conclusive. Thus, we aimed to minimize the errors due to sampling by including patients with at least 12 cores biopsy in our study. However, it is undeniable that in some patients we may have missed PCa and this may be considered as one of the limiting factors of our study. On the other hand, although Gorski et al showed that MR fusion and targeted prostate biopsies has minimized the number of sampling errors in enlarged prostate glands, the detection rate of PCa in the larger glands were lower than the smaller ones, consistent with our results (While the detection rate of PCa was 77% in a PV below 30 cc, it decreased to 34% for PVs greater than 55 cc.) (40).

Other limitations of the current study can be considered as its retrospective nature, potential insufficiencies in the PV measurements and Gleason score assessments due to the lack of radical prostatectomy specimens and finally it was not a population-based study as such it is

possible that our results overestimate the rate of PCa. However, no change in biopsy criteria and biopsy application in the time period of data collection as a single-center study and considering previous studies, relatively large sample size constitute the strength sides of our study. Furthermore, to the best of our knowledge, there are only four studies (26-28, 36) in which PV is used as a stand-alone tool to directly predict PCa. So, the present research is one of a limited number of studies evaluating the efficacy of PV in predicting PCa and has made a contribution to the literature by presenting that in the detection of PCa, PV is more effective than f/tPSA and as effective as PSAD in the gray zone and it is superior to other two parameters in the PSA >10 ng/mL group.

CONCLUSION

Our results demonstrate that PV has a great efficacy in predicting PCa in patients with PSA in the gray zone and higher PSA values (10-30 ng/mL). PV was also effective in predicting clinically significant PCa with a Gleason score 7 or above in the lower PSA group. So it is seen as one step ahead of the other two parameters (PSAD and f/tPSA).

We suggest that patients with a low PV should be evaluated more carefully for PCa and PV may play an active role in the decision making for prostate biopsy, such as PSAD and f/tPSA. Thus, with the contribution of using PV to other parameters, unnecessary biopsies and possible complications can be decreased.

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