ORIGINAL RESEARCH

Is There Any Correlation Between De Ritis Ratio and Prostate Cancer in Males Who Underwent Transrectal Prostate Biopsy?

Transrektal Prostat Biyopsisi Yapılan Erkeklerde De Ritis Oranı ile Prostat Kanseri Arasında Herhangi Bir İlişki Var Mı?

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Abstract

Objective: This study aims to evaluate the diagnostic value of the De Ritis ratio (DRR) in predicting prostate cancer (PCa) and clinically significant prostate cancer (csPCa) in biopsy-naive patients with suspected PCa.

Method: We retrospectively reviewed medical records of 282 male patients who underwent transrectal ultrasound-guided prostate needle biopsy (PNB) between January 2015 and July 2019. Demographic and clinical characteristics of the patients including digital rectal examination findings, preoperative prostate-specific antigene (PSA), aspartate aminotransferase levels, alanine aminotransferase levels, prostate volume, comorbidities and pathological findings of the PNB specimens were noted in detail for each patient. The study cohort was divided into two groups according to the histopathological results of PNB specimens (group 1: patients with benign histopathology, group 2: patients with PCa). The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of PSA, PSA density and DRR in predicting PCa.

Results: The median age of the participants was 64 (59-69) years. While 71.6% (n=202) of the participants were in group 1, 28.4% (n=80) of them were in group 2. The median DRR value of group 1 was 1.08 (range: 0.89-1.32), and the median DRR value of group 2 was determined as 1.19 (range: 0.95-1.56), and the median DRR value of group 2 was found to be statistically significantly higher than that of group 1 (p=0.013). Statistically significant but a weak positive correlation was observed between PCa in PNB specimens and DRR (r=0.149, p=0.012), while there was no statistically significant correlation between csPCa in PNB specimens and DRR (r=0.002, p=0.983). The ROC curve analysis showed that the cut-off value of DRR for the presence of PCa in PNB specimens was 1.125 and

Öz

Amaç: Bu çalışma, prostat kanseri şüphesi olan biyopsi olmamış hastalarda prostat kanseri ve klinik anlamlı prostat kanserini öngörmede De Ritis oranının (DRR) tanısal değerini değerlendirmeyi amaçlamaktadır.

Yöntem: Ocak 2015 ile Temmuz 2019 arasında transrektal ultrason eşliğinde prostat iğne biyopsisi (TRUS-Bx) yapılan 282 erkek hastanın tıbbi kayıtlarını retrospektif olarak inceledik. Hastaların parmakla rektal muayene bulguları, biyopsi öncesi prostat spesifik antijen (PSA), aspartat aminotransferaz ve alanin aminotransferaz düzeyleri, prostat hacmi, komorbiditeleri ve TRUS-Bx örneklerine ait patolojik bulgularını içeren demografik ve klinik özellikler her hasta için ayrıntılı olarak not edildi. Çalışma grubu, TRUS-Bx örneklerinin histopatolojik sonuçlarına göre iki gruba ayrıldı (grup 1: benign patolojili hastalar, grup 2: prostat kanseri hastaları). Prostat kanserini öngörmede PSA, PSA dansitesi ve De Ritis oranının tanısal performansını değerlendirmek için ROC eğrisi analizi yapıldı.

Bulgular: Hastaların ortanca yaşı 64 (59-69) yıl idi. Hastaların %71,6'sı (n=202) grup 1'de, %28,4'ü (n=80) grup 2'de yer aldı. Grup 1'deki DRR'nin ortanca değeri 1,08 (aralık: 0,89-1,32) ve grup 2'nin ortanca DRR değeri 1,19 (aralık: 0,95-1,56) olarak belirlendi. Grup 2 DRR medyan değeri grup 1'den istatistiksel olarak anlamlı olarak daha yüksek bulundu (p=0,013). TRUS-Bx örneklerinde prostat kanseri ile DRR arasında istatistiksel olarak anlamlı ancak zayıf bir pozitif korelasyon gözlendi (r=0,149, p=0,012). Buna karşın TRUS-Bx örneklerindeki klinik anlamlı prostat kanseri ile DRR arasında istatistiksel olarak anlamlı bir korelasyon yoktu (r=0,002, p=0,983). ROC eğrisi analizi, TRUS-Bx örneklerinde prostat kanseri varlığı için DRR'nin eşik değerinin 1,125 olduğunu gösterdi ve eğri altındaki alan 0,595 (%95 güven aralığı=0,518-0,672, p=0,013) idi.

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the area under curve was 0.595 (95% confidence interval=0.518-0.672, p=0.013) for the presence of PCa in PNB specimens.

Conclusion: This study suggests that DRR had restricted diagnostic importance in predicting PCa in biopsy-naive patients who underwent transrectal PNB.

Keywords: Alanine aminotransferase, aspartate aminotransferase, De Ritis ratio, prostate cancer

Öz

Sonuç: Bu çalışma, De Ritis oranının, transrektal prostat biyopsisi uygulanan biyopsi-naive hastalarda prostat kanserini öngörmede kısıtlı bir tanısal değeri olduğunu göstermektedir.

Anahtar kelimeler: Alanin aminotransferaz, aspartat aminotransferaz, De Ritis oranı, prostat kanseri

Introduction

Prostate cancer (PCa) is the 2nd most common form of cancer in men worldwide with an estimated 1,276,106 new cases and 358,989 deaths per year (1). Age-standardized incidence and mortality rates are 29.3 and 7.6, respectively (per 100,000) (1). Although prostate-specific antigen (PSA) is organ specific, not PCa specific, it is still the most important biomarker in the diagnosis and follow-up process of PCa. Different serum and urine biomarkers and ratios based on PSA such as PSA density (PSAD), PSA velocity, PSA doubling time, PCa antigen 3, (-2) pro-PSA isoform, and kallikrein-like peptidase 2 were investigated for diagnostic value in PCa diagnosis and follow-up (2). In recent years, multiparametric magnetic resonance imaging-guided fusion prostate biopsy has been recommended for the evaluation of any patient who has a suspicion of PCa with or without a history of negative prior prostate needle biopsy (PNB) (2-4). However, nearly 12% of clinically significant (cs) PCa would also be missed by fusion PNB techniques (5). Therefore, new biomarkers and imaging techniques are still needed in the PCa diagnosis process.

Attention to the various serum markers like aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] has recently increased in the urooncologic field in terms of their predictive and prognostic value in several malignancies. De Ritis ratio (DRR), which is calculated by dividing AST to ALT, was firstly described as a diagnostic marker for viral hepatitis and then its prognostic value in several malignancies including urologic malignancies was investigated (6-8). Recently, Ha et al. (9) reported that DRR had a predictive value in detection of csPCa in patients who had a negative PNB history. Moreover, higher DRR values could accompany worsened pathological outcomes and higher biochemical recurrence ratios in patients with localized PCa (10).

The current study aims to evaluate the diagnostic value of DRR in predicting PCa and csPCa in biopsy-naive patients

with suspected PCa [elevated and/or rising PSA and/or abnormal findings at digital rectal examination (DRE)] as primary outcomes. In addition, the present study aimed to compare the predictive value of DRR in addition to well-known parameters which are associated with PCa such as PSA, PSAD and suspicious DRE findings as secondary outcomes.

Materials and Methods

Study Population

We retrospectively reviewed the medical records of 1,497 male patients who underwent transrectal ultrasound (TRUS)-guided PNB in the University of Health Sciences Turkey, Bağcılar Training and Research Hospital, Department of Urology between January 2015 and July 2019. The study was approved by the local Institutional Ethics Committee (IRB no: 2020.06.2.02.086). All steps of the study were planned and conducted following the principles of the Declaration of Helsinki. A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Demographic and clinical characteristics of the patients including DRE findings, preoperative PSA, AST, and ALT levels, prostate volume and PSAD, comorbidities, smoking and alcohol consumption status, and pathological findings of the PNB specimens were noted in detail for each patient. Serum AST and ALT levels, which were evaluated 1 to 4 weeks before the PNB, were obtained from the medical records of the patients. The DRR was calculated using the following formula, as previously described: the ratio of AST-to-ALT (6).

Patients who had high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation, who had a medical history of prostate operation, who had any other malignancy history, those using any drug potentially influence serum AST or ALT levels, and those with missing

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clinical data were excluded. Patients with chronic liver diseases (hepatitis, liver cirrhosis, hepatitis B virus or hepatitis C virus carriers, etc.) were also excluded. Finally, a total of 282 patients who met the inclusion criteria were included in this study. The study cohort was divided into two groups according to the histopathological results of PNB specimens (group 1: patients with benign histopathology, group 2: patients with PCa).

Prostate Needle Biopsy Procedure and Pathological Evaluation

All PNB procedures were performed transrectally in a lateral decubitus position. A single dose of oral quinolone prophylaxis and rectal enema was administered to all patients in the morning of the PNB procedure. The perianal area was prepped with 10% of povidone-iodine. Periprostatic local anesthesia (2% lidocaine, 10 mL) was applied to all patients. 12-core systematic PNB samples were taken in accordance with the European Association of Urology guidelines on PCa recommendations (2). Additional biopsies were taken if necessary (e.g. for the hypo/hyper-echoic lesions on ultrasonography).

An experienced uropathologist from our institute evaluated the PNB specimens in accordance with the 2014 International Society of Urologic Pathology criteria (11). CsPCa in PNB specimens was defined according to the Epstein criteria (12). Patients in group 2 were further subclassified as csPCa and clinically non-significant PCa (nsPCa) and compared statistically in terms of DRR levels and other parameters associated with PCa.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of the quantitative data was analyzed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed in median and interquartile range, while categorical variables were expressed in number and frequency. The Pearson chi-square and Fisher's Exact tests were used to compare qualitative data. Correlation coefficient and statistical significance for the relationships between DRE, PSA, PSAD, DRR, and PCa and csPCa were calculated with the Spearman's correlation analysis. A two-tailed $p < 0.05$ was considered as statistically significant.

The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of PSA, PSAD and DRR in predicting PCa. The optimal cut-off value of DRR was determined to evaluate its diagnostic

scanning performance [sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)] for predicting PCa.

Results

The median age of the participants was 64 (59-69) years. Suspicious DRE findings were observed in 64 (22.7%) patients. The median PSA and PSAD levels were 6.44 (4.47-10.60) ng/mL and 0.13 (0.09-0.22) ng/mL^2, respectively (Table 1). The median DRR level was 1.12 (0.90-1.36). PCa was detected in 80 (28.4%) patients and 69 (24.5%) of them were csPCa (Table 1). The demographic and clinical characteristics of the participants are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the participants			
		median (IQR)	n, %
Age (year)		64 (59-69)	-
DRE	Benign	-	218 (77.3%)
	Suspicious	-	64 (22.7%)
PSA (ng/mL)		6.44 (4.47-10.60)	-
Prostate volume (mL)		48 (35-70)	-
PSA density (ng/mL^2)		0.13 (0.09-0.22)	-
AST (U/L)		21.25 (17.60-26.00)	-
ALT (U/L)		18.70 (14.00-26.00)	-
De Ritis ratio		1.12 (0.90-1.36)	-
DM (yes)		-	57 (20.2%)
HT (yes)		-	108 (38.3%)
CAD (yes)		-	41 (14.5%)
COPD (yes)		-	15 (5.3%)
CVD (yes)		-	10 (3.5%)
Smoking (yes)		-	155 (55.0%)
Alcohol (yes)		-	45 (16.0%)
PI-RADS	PI-RADS 1	-	29 (34.9%)
	PI-RADS 2	-	18 (21.7%)
	PI-RADS 3	-	15 (18.1%)
	PI-RADS 4	-	14 (16.9%)
	PI-RADS 5	-	7 (8.4%)
Pathology	Benign	-	202 (71.6%)
	Prostate cancer	-	80 (28.4%)
csPCa (yes)		-	69 (24.5%)

IQR: Interquartile range, DRE: Digital rectal examination, PSA: Prostate-specific antigen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, PI-RADS: Prostate imaging-reporting and data system, csPCa: Clinically significant prostate cancer

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The patients in group 2 were statistically significantly older than the patients in group 1 (p<0.001). The frequency of abnormal DRE findings was higher in group 2 when compared to group 1 (p<0.001). PSA levels, PSAD and DRR were statistically significantly higher in group 2 when compared to group 1 (p<0.001, for PSA and PSAD, p=0.013 for DRR) (Table 2). There was no statistically significant difference between the patients with csPCa and nsPCa when they were compared according to DRR levels (p=0.983). There were no statistically significant differences between the groups in terms of comorbidities except hypertension frequency (p>0.05, for each, p=0.045 for hypertension) (Table 2).

In correlation analysis, it was observed that there were statistically significant correlations in varying degrees between DRE findings, PSA levels and PSA density and PCa and csPCa in PNB specimens (Table 3). Statistically significant but a weak positive correlation was observed between PCa in PNB specimens and DRR (r=0.149, p=0.012), while there was no statistically significant correlation between csPCa in PNB specimens and DRR (r=0.002, p=0.983) (Table 3).

The ROC curve analysis showed that the cut-off value of DRR for the presence of PCa and csPCa in PNB specimens was 1.125, for both. The area under curve (AUC) was 0.595 [95% confidence interval (CI)=0.518-0.672, p=0.013] for the presence of PCa in PNB specimens, and the AUC was 0.502 (95% CI=0.318-0.686, p=0.983) for the presence of csPCa in PNB specimens (Figure 1a, b). The DRR cut-off value (1.125) had a sensitivity of 60.0% and 60.9%, and a specificity of 54.5% and 45.5% for predicting the presence of PCa and csPCa in PNB specimens, respectively. The PPV was 34.3% and NPV was 77.5% for predicting the presence of PCa in PNB specimens. The PPV was 87.5% and NPV was 15.6% for predicting the presence of csPCa in PNB specimens.

Discussion

In this retrospective study, we assessed the diagnostic value of DRR in biopsy-naive patients with suspected PCa. In addition, we also investigated the diagnostic importance of DRR in discriminating PCa and csPCa and compared it with well-known parameters that were associated with PCa such as PSA, PSAD, and DRE findings. According to

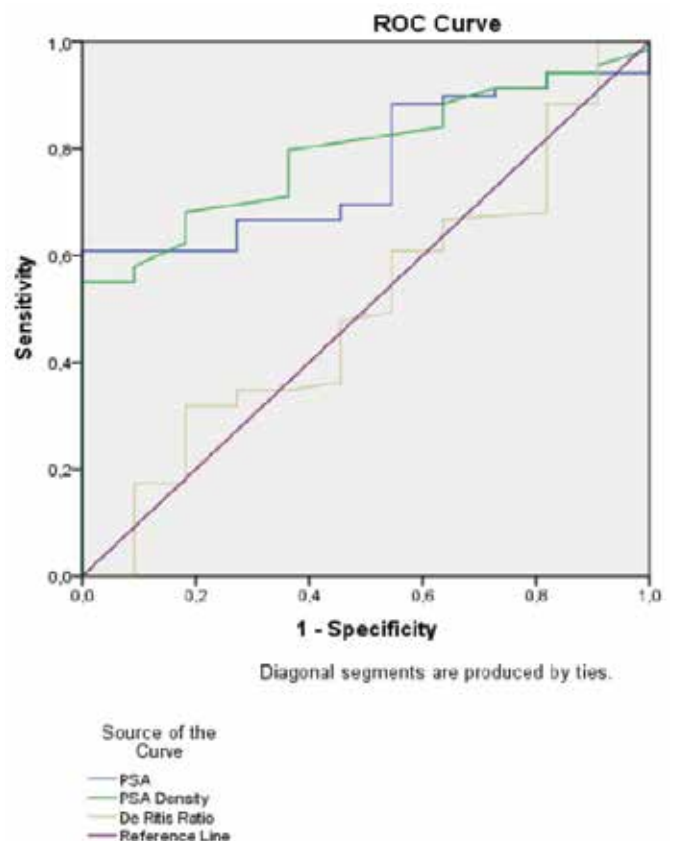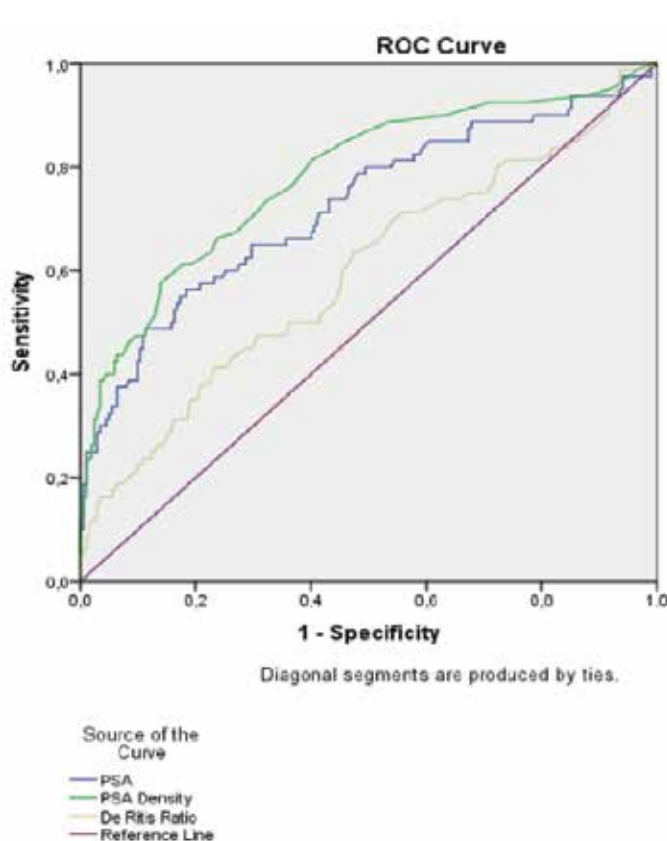### Table 2. Comparisons of the groups in terms of demographic and clinical data

Variables median (IQR)		Group 1 (benign) (n=202, 71.6%)		Group 2 (prostate cancer) (n=80, 28.4%)		
		n, %	median (IQR)	n, %	p	
Age (year)		63 (58-68)	-	68 (63-73)	-	a<0.001*
DRE	Benign	-	174 (86.1%)	-	44 (55.0%)	b<0.001*
	Suspicious	-	28 (13.9%)	-	36 (45.0%)	
PSA (ng/mL)		5.71 (4.18-8.26)	-	10.30 (6.01-32.27)		a<0.001*
Prostate volume (mL)		50.00 (38.00-75.00)	-	45.00 (30.00-60.00)	-	a0.005*
PSA Density (ng/mL^2)		0.11 (0.08-0.16)	-	0.23 (0.14-0.87)	-	a<0.001*
De Ritis ratio		1.08 (0.89-1.32)	-	1.19 (0.95-1.56)	-	a0.013*
DM (yes)		-	42 (20.8%)	-	15 (18.8%)	b0.700
HT (yes)		-	70 (34.7%)	-	38 (47.5%)	b0.045*
CAD (yes)		-	26 (12.9%)	-	15 (18.8%)	b0.207
COPD (yes)		-	8 (4.0%)	-	7 (8.8%)	c0.139
CVD (yes)		-	7 (3.5%)	-	3 (3.8%)	c1.000
Smoking (yes)		-	113 (55.9%)	-	42 (52.5%)	b0.601
Alcohol (yes)		-	32 (15.8%)	-	13 (16.3%)	b0.933

aMann-Whitney U test, bPearson chi-square test, cFisher's Exact test, *p<0.05, IQR: Interquartile range, DRE: Digital rectal examination, PSA: Prostate-specific antigen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease

Table 3. Correlation of suspicious DRE, PSA, PSA density and DRR with histopathology

	Suspicious DRE		PSA (ng/mL)		PSA density (ng/mL^2)		De Ritis ratio	
	r	p	r	p	r	p	r	p
PCa in PNB specimens	0.335**	<0.001	0.352**	<0.001	0.439**	<0.001	0.149*	0.012
csPCa in PNB specimens⁹	0.288**	0.010	0.318**	0.004	0.350**	0.001	0.002	0.983

DRE: Digital rectal examination, PSA: Prostate-specific antigen, DRR: De Ritis ratio, PNB: Prostate needle biopsy, csPCa: Clinically significant prostate cancer

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Figure 1a. ROC curve in predicting prostate cancer by De Ritis ratio

ROC: Receiver operating characteristic

Figure 1b. ROC curve in predicting clinically significant prostate cancer by De Ritis ratio

ROC: Receiver operating characteristic

our study results, higher DRR levels were associated with PCa in PNB specimens. However, no significant difference was observed between the patients with csPCa and nsPCa in terms of DRR levels. Moreover, a weak correlation was observed between PCa in PNB specimens and DRR, while no correlation was observed between csPCa in PNB specimens and DRR. In light of these outcomes, our study suggests that DRR restricted diagnostic importance in predicting PCa in biopsy-naive patients who underwent transrectal PNB. Moreover, it is insufficient in discriminating csPCa and nsPCa.

It is well-known that tumor cells need adenosine triphosphate (ATP) as energy to grow rapidly (13). Glycolysis increases in cancer cells to produce sufficient ATP (13). It has been shown that the cytosolic nicotinamide adenine dinucleotide hydride/nicotinamide adenine dinucleotide (NADH/NAD) is required for the maintenance of glycolysis. AST is one of the important components of the malate-aspartate shuttle pathway that allows NADH/NAD conversion (14). Also, while AST is commonly produced in different tissue types such as the skeletal muscle,

kidney, heart, and brain, ALT is considered as more liver-specific (15). Based on these two hypotheses, many studies investigating the relationship between DRR and urogenital cancers have been published (16-20). In a recently published meta-analysis, it was emphasized that DRR was a prognostic marker in solid tumors, and it was reported that it was inversely related to overall survival (OS), recurrence free survival, and cancer specific survival (CSS) in all tumors (21). Similarly, in the systematic review and meta-analysis examining the relationship between urogenital cancers and DRR, they reported that pretreatment DRR was a significant predictor for OS, CSS, and progression-free survival in urological cancers (22).

Although many studies have been conducted to evaluate the relationship between PCa and DRR, only few studies have focused on the relationship between pre-biopsy DRR values and PCa diagnosis (10,23-25). Zhou et al. (24) reported higher DRR values in PCa patients than in the benign prostate hyperplasia group in a recent retrospective study involving 404 patients who underwent PNB. They also reported that, according to the multivariate analysis results, the increase

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in DRR values increased the risk of PCa incidence, but they did not find a relationship between the risk groups of PCa and DRR (24). In another study, Ha et al. (9) reported that the DRR levels were higher in patients with PCa in the second biopsy compared to benign pathologies but they did not find a statistically significant difference. However, they reported that DRR was effective in detecting csPCa.

Study Limitations

Nonetheless, there are some limitations to this study. First, retrospective design of the study may have precluded the elimination of unknown confounders. Second, many patients were excluded from the study due to missing data. Finally, our sample size is low for PCa, which is known to be seen at a high rate in the society. However, the main strengths of this study are that it is one of the rare studies of the clinical use of DRR value for detecting PCa following PNB in biopsy naive males. Owing to the strength of the ROC analysis used in our study, we believe that the results of this study are valuable and clinically relevant.

Conclusion

In light of these outcomes, our study suggests that DRR has restricted diagnostic importance in predicting PCa in biopsy-naive patients undergoing transrectal PNB. Moreover, it is insufficient in discriminating csPCa and nsPCa. Although it appears to be a limited diagnostic test in our study results, we think that its joint use with risk factors related to PCa may be valuable for clinicians.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Ethics Committee (IRB no: 2020.06.2.02.086).

Informed Consent: A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Authorship Contributions

Concept: Y.Ş., M.Y., A.S., A.Y.M., İ.H., Design: Y.Ş., M.Y., A.S., A.Y.M., İ.H., Data Collection or Processing: Y.F., Y.Ş., Analysis or Interpretation: A.Ç., M.Y., Writing: A.Y.M., A.S., M.Y., Y.Ş., Y.F., A.Ç., İ.H.

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